



November 25, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2014-N-1051, Modified Risk Tobacco Product Applications: Applications for 10 Products Submitted by Swedish Match North America, Inc.

The undersigned organizations submit these comments in response to the announcement for public comment of a modified risk tobacco product application by Swedish Match North America, Inc. (“Swedish Match” or “the company”) for 10 tobacco products.¹

The Swedish Match application presents evidence to FDA that support the proposition that Swedish smokers who switch entirely to snus derive individual health benefits. Swedish Match also provides evidence indicating that the high prevalence of snus usage among men in Sweden has contributed to a lower frequency of tobacco-related disease and mortality than is found in comparable populations with higher cigarette smoking rates. This information suggests that if Swedish Match presents convincing evidence that being permitted to make a modified risk claim would lead smokers that would not otherwise quit smoking to switch completely to one of these Swedish snus products, without leading to significant use among youth, such an application would deserve serious consideration.

However, as discussed at length in Part I below, the modified risk application submitted by Swedish Match in its current form must be denied by FDA because it is legally defective under federal law. Although Swedish Match seeks a modified risk order under Section 911 of the Food, Drug & Cosmetic Act (FDCA), as amended by the Family Smoking Prevention and Tobacco Control Act (“Tobacco Control Act” or “TCA”), Swedish Match does not propose to make a claim concerning the relative risk for the listed snus products. Instead, it seeks to have FDA revise the statutorily-required warning labels for its products. Section 911 does not give FDA the authority to revise warning labels. Rather, such authority is conferred by Section 205 of the Tobacco Control Act, which sets forth the procedures and substantive requirements for

¹ 79 Fed. Reg. 51183 (August 27, 2014).

such a revision. Section 205 establishes a different regulatory process and different regulatory standards for revising smokeless warning labels and Swedish Match has complied with neither.

Moreover, even if Swedish Match had invoked FDA’s authority under Section 205, the warning label changes sought by the company are contrary to the text, structure and legislative history of the Tobacco Control Act. The specific changes requested seek to convert a statutory warning into a statement mandated by the government that the product poses less risk than another tobacco product and does so without providing any meaningful warning about the actual risk posed by these products.

Therefore, as a matter of law, the pending application should be denied and should not be referred to the Tobacco Products Scientific Advisory Committee, unless the application is modified to bring it into compliance with federal law. In light of the legal deficiencies in the application, consideration of the application by the Tobacco Products Scientific Advisory Committee in its present form would be pointless.

If Swedish Match does not believe that the current statutorily mandated warning label accurately characterizes the health risk posed by the specific products covered by its application, it does have a legally authorized pathway to address this concern: it may file a petition with the FDA asking FDA to initiate a proceeding under Section 205 of the Tobacco Control Act to revise the warning label requirements for these products, a group of products that Swedish Match describes as having a proven lower risk of disease than other smokeless tobacco products on the market.

In the event that FDA determines that Swedish Match’s application does not violate federal law, the agency should then consider the discussion in Part II of these comments, which addresses the appropriate standards to be applied to a legally valid modified risk application, as well as various empirical issues material to FDA’s evaluation of the Swedish Match application.

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I. THE SWEDISH MATCH APPLICATION IS LEGALLY DEFECTIVE BECAUSE THE MODIFIED RISK PROVISIONS OF THE TOBACCO CONTROL ACT CANNOT BE USED TO ADJUST THE TEXT OF THE STATUTORY SMOKELESS WARNING LABELS

Swedish Match seeks to use a modified risk application to change the statutory warning labels that apply to ten of its snus smokeless tobacco products. The company asks FDA to eliminate two of the four smokeless warnings, and to change the text of a third. However, federal law permits changes in smokeless warning statements only through the notice-and-comment rulemaking process set out in Section 205 of the Tobacco Control Act. Swedish Match has not requested the required rulemaking, nor has FDA initiated one. Swedish Match’s attempt to use the modified risk provisions of the statute to alter the warning labels is contrary to the text, structure and legislative history of the Tobacco Control Act.

A. The Application Improperly Seeks to Use a Modified Risk Application Under Section 911 to Adjust the Statutory Warning Labels

Although it purports to apply for a modified risk order under Section 911, which was added to the Food, Drug & Cosmetic Act by the TCA (“Section 911”), the Swedish Match application seeks only to change the warning label regime that applies to ten identified Swedish Match snus products. However, Section 911 does not authorize FDA to eliminate or modify the statutory warning labels; such changes to the warning statement requirements can be made only through, and in compliance with, Section 205.

Section 204 of the Tobacco Control Act, which amended Section 3 of the Comprehensive Smokeless Tobacco Health Education Act of 1986 (the “CSTHEA”), sets out the current mandatory health warnings for all smokeless tobacco products:

WARNING: This product can cause mouth cancer.

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

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

WARNING: Smokeless tobacco is addictive.

In Section 205(a) of the TCA, Congress added a new subsection (d) to Section 3 of the CSTHEA. The new subsection reads:

AUTHORITY TO REVISE WARNING LABEL STATEMENTS. The Secretary may, by a rulemaking conducted under section 553 of title 5, United States Code, adjust the format, type size, and text of any of the label requirements, require color graphics to accompany the text, increase the label area from 30 percent up to 50 percent of the front and rear panels of the package, or establish the format, type size, and text of any other disclosures required under the Federal Food, Drug and Cosmetic Act, if the Secretary finds that such a change would promote greater public understanding of the risks associated with the use of smokeless tobacco products.

Thus, in the TCA Congress specifically prescribed the process for revising what the government requires sellers to tell consumers about smokeless tobacco.

Based on evidence from the use of snus products in Sweden, Swedish Match asks FDA to exempt the listed snus products sold in the U.S. from two of the mandatory warnings altogether – those that concern mouth cancer and gum disease and tooth loss. Having asked FDA to eliminate all of the warning labels that set out any specific health risks, Swedish Match also requests that, for these products, FDA approve a change in the third warning— from “WARNING: This product is not a safe alternative to cigarettes”—to “WARNING: No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes.”

Swedish Match seeks to dramatically alter the governmentally prescribed message with respect to its snus products, but does not satisfy the requirements of Section 205(a) for either the two warnings it seeks to eliminate entirely for its products or for the warning it proposes to convert into an explicitly favorable comparison to cigarettes.

First, Swedish Match does not ask FDA to conduct a notice-and-comment rulemaking, nor does the Federal Register notice of August 27, 2014, purport to commence such a rulemaking. Second, the application does not invoke, nor purport to meet, the statutory standard for adjustment of the warning labels: *i.e.*, that the adjustment “would promote greater public understanding of the risks associated with the use of smokeless tobacco products.” Indeed, if the current warnings were deleted as proposed by Swedish Match and not replaced with warnings setting forth clearly the known health risks of these snus products, the consumer would not be

informed of any specific health effects of these products and would only be told that they are “addictive.”

Swedish Match instead seeks changes to the warnings through Section 911 of the TCA. Section 911 establishes the conditions under which FDA may issue an order allowing a company to make a claim of modified risk about its product. The company has conflated two separate sections of the TCA that address distinct types of statements about tobacco products. Section 911 does not permit the type of relief that Swedish Match seeks, and Section 205 does not provide the tools necessary to address the issues that must be addressed in Section 911.

The distinctions between Sections 205 and 911 are plain from the statutory text. Section 205 concerns warning labels prepared and required by the government to appear on smokeless tobacco packaging. If, as Swedish Match argues, the scientific evidence indicates that the current statutory warnings as to oral cancer, and as to gum disease and tooth loss, are inaccurate as to the Swedish Match snus products sold in the United States, then it would be appropriate for the company to seek an adjustment in those warnings by requesting a rulemaking under Section 205(a). FDA would then consider whether such an adjustment meets the Section 205(a) standard, i.e., that it “would promote greater public understanding of the risks associated with the use of smokeless tobacco products.”

Whether the text is that prescribed by the statute in Section 204, or as may be revised by FDA under Section 205, the warnings require manufacturers to convey the government’s messages to consumers to inform them about the risks of smokeless tobacco products. In contrast, Section 911 sets out the regulatory process and standards by which a manufacturer can seek to make a modified risk claim about its tobacco product. A modified risk claim, if approved by FDA under Section 911, is a statement, separate from the statutory health warning, prepared by the manufacturer representing that the tobacco product presents a lower risk or is less harmful than another tobacco product, or that the product contains a reduced level of a harmful substance, or is free of such a substance. Section 911(b)(2)(A)(i). A permissible modified risk statement is that of the manufacturer, permitted by the government. It is not a statement conveying the government’s messages to inform consumers about the health risks of the products, nor is it a substitute for the government health warning.

The congressional findings explaining the need for the modified risk provisions further confirm the intent of Congress that modified risk claims are those made by the manufacturer, not those of the government. Thus, finding #42 states: “*Permitting manufacturers to make unsubstantiated statements concerning modified risk tobacco products, whether express or implied, even if accompanied by disclaimers would be detrimental to the public health.*” Section 2(42) (emphasis added).

Thus, what constitutes a modified risk claim, and the standards for permitting such a claim, are distinct from the procedures and standards governing changes to the statutory

warnings under Section 205. Nothing in Section 205 suggests that Section 911 can be used to bypass the rules and procedures set out to revise the statutory warnings.

B. The Text and Legislative History of Section 205 Further Underscore the Statutory Distinction Between Modified Risk Claims and Required Warning Labels.

The TCA addresses the requirements for modified risk claims separately and distinctly from warning labels and provides different statutory requirements for each.

1. The Text of Section 205 is Consistent with the Distinction Between Modified Risk Claims and Required Warning Labels

Section 205(a) gives FDA the authority, after Notice and Comment Rulemaking, to make adjustments to the statutory warnings in order to enhance the impact and effective communication of messages conveying the health risks of smokeless tobacco products. There is nothing in the text of section 205 that indicates that warning label changes can be made through the modified risk provisions of the TCA.

Thus, for example, Section 205(a) gives FDA the authority to *increase* the area occupied by the warnings; no authority is given to *decrease* it. The text gives FDA authority to revise the warnings to enhance public understanding of the “*risks* associated with the use of smokeless tobacco products” (emphasis added). Indeed, the language of modified risk Swedish Match seeks to add – “No tobacco product is safe, but this product presents substantially lower risk to health than cigarettes” – is not a “warning” at all, but rather a recommendation for use. The text of Section 205(a) therefore is entirely consistent with the statutory distinction between modified risk claims and adjustments to the required warning labels.

2. The Legislative History of the TCA and the History of Congressional Consideration of Smokeless Tobacco Warnings Provide No Support for the Use of the Modified Risk Provisions to Alter the Text of the Required Warning Labels

Nothing in the legislative history of the TCA, nor in congressional consideration of smokeless tobacco warnings more generally, indicates that Congress intended the modified risk provisions of the statute to be used to modify the smokeless warnings to convey messages that some tobacco products pose less risk than other tobacco products.

The text of three of the four current statutory smokeless tobacco warnings, including the warning “This product is not a safe alternative to cigarettes,” originated with Section 3 of the CSTHEA, under which the Federal Trade Commission had authority over enforcement of the smokeless tobacco warnings. Section 204 of the TCA amended Section 3 of the CSTHEA to add a fourth warning about the addictiveness of smokeless tobacco, and to specify the format for the

warnings on packaging and advertisements. Section 205 of the TCA provided for adjustments of the warnings through an FDA notice-and-comment rulemaking.

While Congress was considering comprehensive tobacco control legislation for more than a decade before enactment of the TCA, on numerous occasions it received testimony from proponents of smokeless tobacco contending that such products cause less harm to health than cigarettes and urging revisions to the smokeless warnings to communicate that view. However, rather than adopting this recommendation, Congress opted in the TCA to retain the “no safe alternative” warning, recognizing the importance of providing affirmative scientific information about the health effects of smokeless products to better inform consumers, and rejected proposals to replace the warning to include language of modified risk.

The operative text of Sections 204 and 205 of the TCA closely parallels the analogous provisions in S. 1415, the 1998 tobacco control legislation introduced by Senator John McCain (R-Ariz.). The 1998 Senate Commerce, Science, and Transportation Committee report on S. 1415 stated that the purpose of defining the warning label format was to provide “new *more emphatic* warnings for smokeless tobacco labels, packaging and advertising.”² Section 204 of the TCA only slightly modified Section 303 of S. 1415, including increasing the area that the warning must occupy on smokeless tobacco packaging from 25 percent to 30 percent, thus making the warnings even more noticeable than proposed in S. 1415.

Section 205 was based on Section 304 of S. 1415. Notably, Section 205 gives FDA authority to increase the warning label area on the package from 30 percent to 50 percent, and to accompany the text with color graphics, authority not expressly given in S. 1415. Thus, the enacted statutory language is stronger than its predecessor legislation, which itself was described by a Senate Committee as providing for “more emphatic” warnings.

During the period of congressional consideration of comprehensive tobacco control legislation following the 1998 McCain bill and leading to the enactment of the TCA in 2009, there were extensive hearings at which Members of Congress, smokeless tobacco-sponsored researchers, industry representatives, and others testified and submitted voluminous evidence about the issue of smokeless tobacco as a reduced risk product. On numerous occasions, witnesses at congressional hearings and Members of Congress urged changes in the statutory warnings.

On June 3, 2003, two different House Committees held hearings on the issue of the warning statements. The House Committee on Energy and Commerce convened a hearing on the subject, “Can Tobacco Cure Smoking? A Review of Tobacco Harm Reduction.”³ Smokeless tobacco was the central focus of this hearing. In his opening statement, Rep. Cliff Stearns (R-

² S. Rep. No. 105-180 (May 1, 1998), at 36 (emphasis added).

³ “Can Tobacco Cure Smoking? A Review of Tobacco Harm Reduction,” Hearings before House Committee on Energy and Commerce, No. 108-31 (June 3, 2003).

Fl.), Chairman of the Subcommittee on Commerce, Trade and Consumer Protection, claimed “there is an increasing amount of research suggesting that some tobacco products are less harmful than others,” suggesting that for smokers “who can’t seem to quit smoking, switching to a less hazardous product could save lives.”⁴ Several witnesses, including Dr. Brad Rodu, a researcher supported by the smokeless tobacco industry, and Richard Verheij, Chairman of U.S. Smokeless Tobacco, testified in support of smokeless tobacco as a harm reduction product. The proposal to alter the smokeless tobacco warnings to make a modified risk claim was specifically discussed during the hearing, with Rep. Gene Green (D-Tx.) opposing the idea because:

These warnings all send the same message. Smokeless tobacco is hazardous to your health. For the FTC to consider a label effectively promoting smokeless tobacco as a lower risk alternative to cigarette smoking, however, sends a very different message. . . Not only is this message mixed. It also is based on questionable science.⁵

On the same day, the House Committee on Government Reform convened a hearing on a similar topic, “Potential Reduced Exposure/Risk Tobacco Products: An Examination of the Possible Public Health Impact and Regulatory Challenges,” which included testimony from the National Cancer Institute, the Institute of Medicine, the FTC and smokeless tobacco and cigarette industry executives.⁶ During that hearing, Richard Verheij of UST again testified, raising the question, “what obligation does the Federal Government and the public health community have to communicate to adult smokers who are not quitting that . . . smokeless tobacco is significantly less harmful?”⁷ Dr. Dorothy Hatsukami of the University of Minnesota Medical School cautioned the Committee that even though “individuals may show a reduction in tobacco toxin exposure...if more people start tobacco use or fewer people quit because they perceive these alternative products as safer, the total net harm may be increased.”⁸

Congressional consideration of smokeless tobacco as a harm reduction product continued in 2007 during a Senate hearing on S. 625, the tobacco control bill introduced in the 110th Congress to give FDA authority to regulate tobacco.⁹ That hearing featured specific testimony objecting to a larger warning label stating “This product is not a safe alternative to cigarettes,” because it does not inform smokers “that smokeless tobacco products pose fewer morbidity and mortality risks than cigarettes.”¹⁰ Indeed, the hearing record contains a proposal by two of the witnesses that the current warning be replaced with a warning similar to that Swedish Match now

⁴ *Id.* at 2.

⁵ *Id.* at 29.

⁶ “Potential Reduced Exposure/Risk Tobacco Products: An Examination of the Possible Public Health Impact and Regulatory Challenges,” Hearings before the House Committee on Government Reform (June 3, 2003).

⁷ *Id.* at 315.

⁸ *Id.* at 126.

⁹ “The Need for FDA Regulation of Tobacco,” Hearings before the Senate Committee on Health, Education, Labor and Pensions (February 27, 2007).

¹⁰ *Id.* at 129 (written testimony of Bill Godshall).

seeks for its snus products: “Warning: Smokeless tobacco use has risks, but cigarette smoking is far more dangerous.”¹¹

Several months later, the issue was addressed again in a House hearing on “The Family Smoking Prevention and Tobacco Control Act.”¹² For example, then-Rep. Buyer (R-Ind.) endorsed the idea of “moving people from cigarettes to smokeless tobacco as a harm reduction strategy.”¹³ In response to a question from Rep. Buyer about whether smokeless tobacco should be considered a safer alternative to smoking, Professor Richard Bonnie of the University of Virginia School of Law expressed skepticism about the idea that a regulatory agency should “be in the position of basically announcing to the public that our overall goal is to encourage people to use a smokeless tobacco, as an example.”¹⁴

Thus, throughout years of consideration of various proposals to regulate tobacco, Congress heard vigorous debate on the issue of whether smokeless tobacco should be promoted as a safer product than cigarettes and whether the smokeless tobacco warnings should communicate a reduced risk message. Specific proposals were made to alter the smokeless tobacco warnings to communicate the message now sought by Swedish Match.

Years of congressional consideration culminated in final consideration of the bill that became the TCA. In the House, that bill was H.R. 1256, sponsored by Rep. Henry Waxman (D-CA.). Rep. Buyer offered a substitute amendment to the underlying bill that he entitled the “Youth Prevention and Tobacco Harm Reduction Act.”¹⁵ The Buyer substitute would have altered the smokeless tobacco warning labels to delete the current warning that the smokeless tobacco product “is not a safe alternative to cigarettes” and to substitute this language: “WARNING: This product has significantly lower risks for diseases associated with cigarettes,”¹⁶ language substantially similar to that now sought by Swedish Match. Indeed, during the Floor debate, Rep. Buyer specifically referred to Swedish snus as an example of a reduced risk product.¹⁷

Rep. Waxman opposed the Buyer substitute on the Floor of the House and argued strongly against its revision of the smokeless tobacco warning labels:

There’s no evidence to support this approach. He is basing his assumption that current smokers will use smokeless tobacco to quit, but there’s no evidence to support this

¹¹ *Id.* at 148 (article by Rodu/Godshall).

¹² “The Family Smoking Prevention and Tobacco Control Act,” Hearings before the House Subcommittee on Health of the Committee on Energy and Commerce (October 3, 2007).

¹³ *Id.* at 26-27.

¹⁴ *Id.* at 52.

¹⁵ 155 Cong. Rec. H4344 (April 1, 2009).

¹⁶ *Id.* at H4357.

¹⁷ *Id.* at H4366.

assumption. . . Rather than have smokers quit, it’s just as likely that smokeless tobacco can be used to introduce youth to tobacco use and to discourage smokers from quitting.¹⁸

On April 2, 2009, the Buyer substitute was rejected by the House by a 284-142 margin.¹⁹

During Senate consideration of S. 1247, the Senate version of the TCA that mirrored H.R. 1256, Senator Richard Burr (R-NC) offered a substitute amendment (S. Amend. 1246) that would have deleted the then-existing smokeless tobacco warnings and substituted only two statutory warnings – that “Smokeless tobacco is addictive” and that it is “lower risk than cigarettes.”²⁰ The Senate rejected the Burr substitute by a vote of 60-36.²¹

Therefore, after a decade of consideration that included extensive debate about smokeless tobacco as a “harm reduction” product and the impact of the long-time statutory warning that smokeless tobacco “is not a safe alternative to cigarettes,” both the House and the Senate rejected legislation that would have mandated warning text nearly indistinguishable from that sought by Swedish Match.

Instead, Congress reaffirmed the existing warning and, in adding Section 911 to the new Chapter IX of the FDCA, established separate rules and rigorous standards to govern modified risk claims sought to be made by manufacturers. The history of congressional consideration of harm reduction, and the specific legislative history of Section 205, support the distinction between modified risk claims and required warning labels; nothing in the historical material suggests that Congress intended the warning labels to be revised through the provisions specifically designed to address proposed claims of modified risk.²²

Congress regarded both warning labels and requirements for modified risk claims to be important elements of the statute. It therefore established distinct requirements for both such

¹⁸ *Id.* at H4368.

¹⁹ 155 Cong. Rec. H4412 (April 2, 2009).

²⁰ 155 Cong. Rec. S6092 (June 3, 2009).

²¹ 155 Cong. Rec. S6347 (June 9, 2009).

²² As FDA is aware, R.J. Reynolds Tobacco Company and its smokeless tobacco subsidiary have filed a Citizen Petition with FDA asking the agency to initiate a rulemaking under Section 205(a) to adjust the statutory warning “This product is not a safe alternative to cigarettes.” The Reynolds petition seeks to change this warning, with respect to all smokeless products, to read: “WARNING: No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes.” The language sought by Reynolds for all smokeless products is identical to the language sought by Swedish Match for its snus products. As explained in our comments on the Reynolds petition, the petition should be denied because, like the Swedish Match application, it improperly conflates Sections 911 and 205 of the TCA. *See* Comments on Petition of R.J. Reynolds Tobacco Company for Rulemaking to Adjust Statutory Smokeless Tobacco Warning filed by Campaign for Tobacco-Free Kids, et al., Docket No. FDA-2011-P-0573 (November 16, 2012). *See also* Comments of Campaign for Tobacco-Free Kids, et al., Docket No. FDA-2012-N-1032-0001, Smokeless Tobacco Product Warning Statements (April 1, 2013). If Reynolds, or Swedish Match, seeks authorization to market a modified risk product, the legally appropriate course is to file a proper application for a modified risk order, which identifies the specific claim they wish to make (as opposed to improperly seeking to convert a warning label into a statement of reduced risk) and advances the evidence necessary to show that they meet the standards of Section 911. Swedish Match has invoked Section 911, but has failed to identify a legally allowable modified risk claim for FDA’s consideration.

elements. Congress did not intend for modified risk claims to substitute for warning labels but rather recognized that it was important for consumers to be adequately informed about the risks of a product even if a manufacturer could meet the requirements for making a claim that the product presents a lower risk than smoking cigarettes. It also provided under section 205 a mechanism for a manufacturer of a product that claimed the warning labels do not accurately describe its products to petition FDA for a change of the government mandated information manufacturers are required to disclose.

C. Swedish Match’s Assertion that Modified Risk Products Are Exempt from the TCA Provisions on Smokeless Warning Labels Has No Basis in the Text or Structure of the Statute

In a document submitted to FDA,²³ but not made part of its publicly available application, Swedish Match argued that products determined by FDA to be modified risk products under Section 911 are exempt from the statutory warning labels mandated by Section 204 and from the language in Section 205 governing adjustments to those labels. According to Swedish Match, once its snus products are found to meet the standards of Section 911, it need not make an application under Section 205 for a rulemaking to adjust the warning labels. The Swedish Match argument rests on a series of erroneous premises that yields an interpretation of the Tobacco Control Act divorced from the statute’s text, structure, and purposes.

First, Swedish Match asserts that only products that are “customarily marketed” tobacco products are subject to the statutory warning labels and further asserts that since modified risk products are, by definition, not “customarily marketed,” they are not subject to the warning labels. Swedish Match incorporates the term “customarily marketed” from *Sottera, Inc. v. FDA*, 627 F.3d 891 (D.C. Cir. 2010), but gives the term a meaning and a purpose that differs from the one applied by the *Sottera* court and that conflicts with the FDCA.

In *Sottera*, the Court invalidated FDA’s attempt to regulate electronic cigarettes as drugs or devices under Chapter V of the FDCA, finding that the agency “lacks FDCA drug/device authority to regulate all tobacco products marketed without claims of therapeutic effect, and that e-cigarettes are “tobacco products” “customarily marketed” because the nicotine in them is “derived” from tobacco. 627 F.3d at 895. Thus, the Court distinguished between (i) products for which therapeutic claims are made (which therefore are regulated by FDA as drugs or devices and that therefore were excluded from the definition of “tobacco products” under section 101 of the Tobacco Control Act) and (ii) “customarily marketed” tobacco products—that is, products otherwise meeting the definition of tobacco products for which no therapeutic claims are made—which are regulated as “tobacco products” under Chapter IX of the FDCA. Under *Sottera*, a product made or derived from tobacco is “customarily marketed” unless a therapeutic claim is made for it. Under the statute a claim of modified risk does not qualify as a “therapeutic

²³ The Swedish Match legal analysis (“FDA Authority Under Section 911 of the Tobacco Control Act: Revisions to Smokeless Warning Label Statements”) is submitted as Exhibit A to these comments.

claim” because it does not indicate that the product is “intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease.” *See* 21 U.S.C. §321(g)(1)(B). The *Sottera* District Court opinion expressly rejected the FDA’s contention that a manufacturer’s claims that its electronic cigarettes were “healthier alternatives” to cigarettes subjected them to regulation as drugs or devices, finding that such claims made a product “fall within the plain meaning of ‘modified risk tobacco product’” subject to regulation as a “tobacco product” under the TCA.²⁴ Thus, contrary to Swedish Match’s contention, modified risk tobacco products are still “customarily marketed” tobacco products subject to the provisions of Chapter IX of the FDCA. Swedish Match notes that Section 911(k) of the FDCA expressly exempts modified risk products from regulation as foods, drugs, or devices under Chapters IV or V of the FDCA so that they won’t be subject to dual regulation, but ignores the fact that Section 911 does not exempt modified risk tobacco products from the CSTHEA.

Moreover, the Tobacco Control Act itself declares unequivocally that “modified risk tobacco products for which an order has been issued in accordance with section 911, shall be regulated by the Secretary under [the Tobacco Control Act] and shall not be subject to the provisions of chapter V [i.e., the drug regulation provisions of the FDCA].” Sec. 901(a). Thus, Swedish Match’s argument that modified risk tobacco products should be regulated as something other than tobacco products conflicts directly with the statute.

Second, Swedish Match contends that it would be “nonsensical” for Congress to have required modified risk products to carry the warnings in the CSTHEA, that the CSTHEA was “preempted” by the TCA, and that therefore a decision by FDA that a product is a modified risk product somehow supersedes the requirements of Section 205. In fact, the TCA does not “preempt” the CSTHEA; rather, the TCA amends the CSTHEA to give the FDA power to change the content of the required smokeless warning statements. Indeed, Congress established a new regulatory regime for modified risk products in Section 911 and amended the required warnings for all smokeless products, but did not mention the CSTHEA or smokeless warnings in Section 911, let alone exempt smokeless products subject to Section 911 from the smokeless warnings. That is strong evidence that Congress saw no conflict or inconsistency between these provisions.

Moreover, there is nothing “nonsensical” about requiring the warning labels set forth in Sections 204 and 205 to be affixed to modified risk products. The fact that a product may pose less of a risk of certain diseases than another does not eliminate the need for FDA directed warning labels setting forth factually the health effects of the use of that product. What harms a product causes and whether a product poses less of a risk than other products are factually distinct elements, as Congress recognized by having two separate and distinct sections governing these issues.

²⁴ *Smoking Everywhere, Inc. and Sottera, Inc. v. FDA*, 680 F.Supp.2d 62, 75 (D.D.C.), *aff’d*, 627 F.3d 891 (D.C. Cir. 2010).

Third, Swedish Match suggests that, because a modified risk order would only apply to the specific products that were the subject of the Section 911 application, it would be “unnecessary, and indeed irrational” for the manufacturer to separately file a petition seeking a warning change under Section 205 because a rule adjusting the warning would necessarily apply to all smokeless products, even though the science supported only a claim of lesser risk for the specific modified risk products. Swedish Match incorrectly assumes that a rulemaking under the Administrative Procedure Act (“APA”), authorized by Section 205 of the TCA, must change the warnings for all smokeless products. The APA defines a “rule” in relevant part as “the whole or part of an agency statement of general or *particular applicability* and future effect” 5 U.S.C. §551(4) (emphasis added). The 1947 Attorney General’s Manual on the APA, cited repeatedly by the U.S. Supreme Court in interpreting the APA,²⁵ states, “Of particular importance is the fact that ‘rule’ includes agency statements not only of general applicability but also those of particular applicability applying either to a class *or to a single person.*”²⁶ Neither the TCA (including the amendments to the CSTHEA) nor the APA supports the Swedish Match premise that a rulemaking to adjust the warning labels under Section 205 must necessarily modify the warnings for all smokeless products.

Finally, Swedish Match suggests that FDA has discretion to ignore the amended Section 3(a) of the CSTHEA and change the statutory warnings through Section 911. Swedish Match characterizes this as an exercise of prosecutorial discretion permitted under *Heckler v. Chaney*, 470 U.S. 821 (1985). Swedish Match is wrong. In *Heckler v. Chaney*, the Supreme Court reaffirmed that an agency’s discretionary decision whether or not to pursue enforcement actions is presumptively unreviewable. That case and its holding do not apply here. Contrary to its statement, Swedish Match does not ask FDA “not to enforce . . . the labeling requirements established under Section 3(a)(1)” of the CSTHEA. Rather, Swedish Match wants FDA to take affirmative action to change the current warning regime for its snus products. The company wants FDA to ignore the regulatory mechanism that Congress prescribed for considering such a change, and to grant the relief it seeks under a different section of the statute (Section 911) that gives FDA no authority to take such action.²⁷ By enacting Sections 205 and 911 side by side in the TCA, Congress gave FDA clear direction as to how the agency can change smokeless warnings and how it may review and approve modified risk tobacco products, respectively. Any

²⁵ See *Bowen v. Georgetown Univ. Hosp.*, 488 U.S. 204, 218 (J. Scalia, concurring) and cases cited therein.

²⁶ Thus, for example, agencies have issued rules affecting specifically identified Airbus helicopter models (79 Fed. Reg. 48,707 (Aug. 18, 2014) (FAA) and a single power plant (71 Fed. Reg. 53,631 (Sept. 12, 2006) (EPA).

²⁷ See, e.g., *Natural Resources Def. Council, Inc. v. FDA*, 872 F.Supp.2d 318, 331-32 (S.D.N.Y. 2012) (finding that an FDA decision whether to initiate withdrawal proceedings was subject to judicial review because it was not an enforcement action), *rev’d on other grounds*, 760 F.3d 151 (2d Cir. 2014). Moreover, FDA’s June 2010 guidance regarding its enforcement of the smokeless warning rotation plan, which Swedish Match cites as precedent, is wholly inapposite. In that guidance, FDA reaffirmed that smokeless sellers must submit the rotation plan by the statutory deadline. However, because the transfer of authority to oversee such warning rotation plans from the FTC to the FDA was ongoing, FDA was not yet in a position to approve those plans. Because FDA was not in a position to meet its obligation by the deadline, the agency clarified that during the transition period, it would not enforce the requirement of the CSTHEA that all such plans be approved by the agency by the statutory deadline.

decision by FDA not to follow the separate requirements of Sections 205 and 911 would conflict with the statutory scheme.

At bottom, Swedish Match asks FDA to implement the TCA in a way that would violate the statute. Congress enacted the TCA with both the new Section 911 added to the FDCA, and Sections 204 and 205 concerning the smokeless warning labels. Those sections prescribe different regulatory processes with different substantive standards. Nothing in Section 205, or in the structure of the TCA, would preclude Swedish Match from filing *both* an application under Section 911, with a properly identified modified risk claim that it, not the government, proposes to make to consumers, including a specification of how the claim will be communicated in the labeling and advertising of the product, *and* a request for a rulemaking under Section 205 to adjust the statutory warning labels if the company is prepared to demonstrate that such an adjustment would promote greater public understanding of the risks associated with snus products in light of the modified risk claim it has specified in its Section 911 application. But Congress did not give FDA the authority to adjust the statutory warnings through a modified risk application under Section 911, and thereby ignore the process in Section 205 required to amend the smokeless warning labels.

D. The Application, on its Face, Demonstrates that the Changes in the Warnings Sought by the Applicant Would Not Meet the Requirements of Section 205.

In considering whether to make changes to the text of warning labels for smokeless tobacco products, FDA is directed by the statute to do so if it “finds that such a change would promote greater public understanding of the risks associated with the use of smokeless tobacco products.” The changes in the text of the warning labels sought by this application would eliminate any warning with regard to the health consequences of using the product other than a warning that the product is addictive and a general reference to the fact that “no tobacco product is safe.”

However, the application itself concedes that there are specific health risks related to the use of the product. For example, the application states that “maternal snus use has been reported to be associated with increased stillbirth and neonatal apnea as compared with tobacco non-users” and concludes that “Swedish snus is contraindicated during pregnancy. . . and lacta[tion].”²⁸ In addition, quoting the findings of the Swedish National Board of Health and Welfare, the application also references scientific literature “indicating that snus may increase the risk of pancreatic cancer.”²⁹ It also references studies concluding that snus users experience a higher risk of squamous cell esophageal cancer than non-users, although the risk level was significantly lower than that for smokers.³⁰ Furthermore, the data in the application supports the conclusion that the likelihood of fatal myocardial infarction is higher for snus users than for non-

²⁸ Application at 548-50. See also Application at 415-16, 443-50.

²⁹ Application at 99.

³⁰ Application at 414-15.

tobacco users.³¹ In addition, the application notes that a “specific, well-recognized mucosal reaction is associated with use of snus,” resulting in oral mucosal lesions.³²

Given these conclusions, although the evidence cited in the application might support some changes in the language of the warnings, the elimination of any reference to the adverse health effects of the product other than a reference to addictiveness would be misleading and would not “promote greater public understanding of the risks” of using the product.

Perhaps most significantly, the proposed changes in the warning labels fail to inform consumers that “the health risks among dual users [of snus and cigarettes] appear similar to those among exclusive smokers.”³³ Without an explicit statement that dual use of snus and cigarettes fails to confer a health benefit compared to continued use of cigarettes, any language in a warning stating that use of the product has a lower risk than smoking would be misleading and would not “promote greater public understanding of the risks” of using the product.

In addition, the failure of Swedish Match in its proposal to include language informing users about the fact that the health risk is reduced only if snus is used by smokers or individuals who would otherwise be smoking cigarettes AND is used instead of smoking is a critical failure.

Were FDA to consider changes in the warning labels, it would have to devise alternative warnings that meet the statutory requirements. The changes proposed in this application fail to do so.

FDA need not decide whether it is possible to have a health warning that could include a reference to comparative harm — in addition to conveying a clear warning of a specific disease risk — because that is not what Swedish Match has proposed. As we have noted, the changes in the warning labels sought by Swedish Match fail to provide adequate warning of the dangers presented by the product. Rather than promote public understanding of such risks, the proposed change would obscure them.

II. CONSIDERATIONS RELATED TO FDA’S EVALUATION OF THE APPLICATION’S IMPACT ON THE INDIVIDUAL USER AND THE POPULATION AS A WHOLE

In Part I of these comments, the undersigned argued that the application is legally defective and that it is inappropriate for the changes proposed in the warning labels for these products to be considered as modified risk claims under Section 911. This portion of these

³¹ Application at 453-54, Table 6-3. See Hatsukami, D. and Stepanov, I., “Establishing product standards for smokeless tobacco,” (February 2014) (Exhibit B).

³² Application at 435-39.

³³ Application at 466. See also Table 6-3, which indicates highly elevated disease risk for dual users compared both to exclusive snus users and non-tobacco users.

comments is designed to inform FDA’s consideration of this application under two alternative hypotheses. First, if FDA, contrary to the arguments in Part I, proceeds to consider such changes as modified risk claims, the following portion of these comments should guide FDA’s consideration of this application. Second, these comments would be relevant if FDA agrees that the applicant’s proposal to make changes in the warning label for these products is an improper use of the authority granted under section 911, but nevertheless uses this application as an opportunity to elucidate the requirements of section 911 and further describe the elements that would properly constitute a modified risk claim.

A. The Requirements of Section 911

Applications to make modified risk claims are governed by section 911 of the Food, Drug and Cosmetic Act as amended by the Family Smoking Prevention and Tobacco Control Act of 2009. In enacting the Tobacco Control Act, Congress found that “unless tobacco products that purport to reduce the risks to the public of tobacco use actually reduce such risks, those products can cause substantial harm to the public health.” Sec. 2(37). Congress also found that “the dangers of products sold or distributed as modified risk tobacco products that do not in fact reduce risk are so high that FDA must ensure that statements about modified risk products are complete, accurate, and relate to the overall disease risk of the product.” Sec. 2(40). In order to accomplish these goals, Congress required that manufacturers “must demonstrate that such products. . . meet a series of rigorous criteria, and will benefit the health of the population as whole” before a product making modified risk claims can be marketed. Sec. 2(36).

Under the Tobacco Control Act, a “modified risk tobacco product” is defined as a tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products. A product is “sold or distributed” for such a use if, in relevant part,

- (1) [its] label, labeling, or advertising, either implicitly or explicitly [represents] that
 - (i) the tobacco product presents a lower risk of tobacco-related disease or is less harmful than one or more other commercially marketed tobacco products;
 - (ii) the tobacco product or its smoke contains a reduced level of a substance or presents a reduced exposure to a substance; or
 - (iii) the tobacco product or its smoke does not contain or is free of a substance, or
- (3) . . .the tobacco product manufacturer has taken any action directed to consumers through the media or otherwise, other than by means of the label, labeling, or advertising. . .that would be reasonably expected to result in consumers believing that the tobacco product or its smoke may present a lower risk of disease or is less harmful than

one or more commercially marketed tobacco products, or presents a reduced exposure to, or does not contain or its free of, a substance or substances.

A tobacco product is a “modified risk tobacco product” if and only if FDA has granted an application for its marketing in connection with a specified modified risk claim. In the absence of a specific modified risk claim, a product cannot be a modified risk tobacco product; moreover, even if a modified risk application has been granted with regard to a given claim, the product cannot be marketed with any other modified risk claim unless an application has been granted with regard to that claim as well. Thus, the grant of an application is tied both to a specific product and to a specific claim and the grant of an application to make one claim does not permit the manufacturer to market its product with any other claim. Thus, a modified risk product is nothing more or less than a product as to which FDA has granted an application for the making of a modified risk claim under section 911.

The requirements for the granting of an application under section 911 to make a modified risk claim are set forth under section 911(1) and (2). An application must meet both prongs of the requirement. Under Section 911 (1) and (2), the applicant must demonstrate that the product, *as actually used by consumers*, will

Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and

Benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.

The statutory requirement that the applicant must demonstrate that the standards are met with regard to the product as it is actually used by consumers, means that the applicant must submit evidence not only about the properties of the product itself, but also about the way consumers use the product. For example, a product that might significantly reduce harm and the risk of tobacco-related disease to individual tobacco users if used by consumers while they totally abstain from combusted tobacco products might not significantly reduce harm and the risk of tobacco-related disease to individual users if they continue to use combusted tobacco products as well.

Moreover, the statute makes it clear that there are two distinct elements that an applicant must demonstrate. First, it must establish that marketing the product with the modified risk claim will significantly reduce harm and risk of tobacco-related disease to individual users. Even if that element is satisfied, however, an applicant must also demonstrate that the marketing of the product with the modified risk claim will 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.

B. Evaluating Whether the Product, As Actually Used by Consumers, Will Significantly Reduce Harm and the Risk Of Tobacco-Related Disease to Individuals.

1. Determining that the Products at Issue Are Identical to Products Sold in Scandinavia.

Several elements are relevant in evaluating whether a product, as actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individuals. In this case, Swedish Match relies heavily on epidemiological evidence from Sweden to support its assertion that the products at issue will significantly reduce harm and the risk of tobacco-related disease to individuals. Swedish Match asserts that the products at issue in this application are identical to products marketed for many years in Sweden and for a shorter time in Norway and that the epidemiological evidence from Sweden and Norway is therefore relevant to this evaluation. If the products are in fact identical, this experience may well be relevant but not dispositive. However, because information concerning harmful or potentially harmful constituents in the product submitted to FDA has been redacted from the application, a public commenter cannot conclusively evaluate the truth of the claim that the products are identical. The Campaign for Tobacco-Free Kids has filed a Freedom of Information Act request for this information, arguing that the information is not a trade secret since information purporting to describe the levels of harmful constituents has been disclosed in publications by authors associated with the applicant. Our request was denied and is currently on appeal. We reiterate the request and call upon the applicant to release this information. The epidemiological evidence from Scandinavia is relevant only if the products are in fact identical. In evaluating the relevance of such epidemiological evidence FDA should first make a threshold determination that the products that are the subject of this application are identical to the Scandinavian products.

In addition to physical identity, the storage of the product in the process of manufacture, distribution and sale must also be identical. Ensuring that the product is handled through identical procedures is important because refrigeration of the product is essential to ensure that the formation of TSNAs is inhibited. Failure to refrigerate the product up to the point where it is sold to consumers may result in the formation of highly toxic constituents. Thus, it is not sufficient to determine that the product as manufactured is identical to the Scandinavian product; the product must also be subject to same procedures for handling through the distribution and sales process as well. In this connection, Swedish Match's contention that "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" is inconsistent with its own practice in the handling and distribution of the product and is erroneous.³⁴

³⁴ Swedish Match MRTP Application at 333.

2. Relevance of Scandinavian Epidemiological Evidence.

Swedish Match relies heavily on epidemiological evidence from Scandinavia where snus has been widely used for many decades. According to the applicant, the Swedish and Norwegian evidence demonstrates that Swedish snus, as manufactured by Swedish Match, is significantly less harmful than cigarettes and that consumers' switching from cigarettes to snus has benefited the public health in those countries.³⁵

Because Swedish snus has been widely used in Sweden for many years and because the applicant's product represents the vast majority of smokeless tobacco used in Sweden for many years, there exists a large data set for the evaluation of the health effects of this product in comparison with the health effects of cigarettes in Sweden. This experience has made possible the kind of "long, intensive and robust observational studies of actual health outcomes" referred to in the Institute of Medicine's 2012 report on *Scientific Standards for Studies on Modified Risk Tobacco Products*. It is important to note, however, that this experience exists only with respect to health outcomes in Scandinavia involving the use of Swedish snus itself. This experience most certainly does not demonstrate such outcomes for any other smokeless tobacco product, including products denominated "snus" and sold by other manufacturers in the United States.

- a. The Swedish epidemiological evidence indicates that the use of Swedish snus increases the risk of fatal disease and some forms of cancer relative to the risk experienced by non-users of tobacco.

Professors Dorothy Hatsukami and Irina Stepanov of the University of Minnesota have recently completed a study (previously submitted to FDA and attached as Exhibit B to these comments) regarding the desirability of establishing product standards for smokeless tobacco, which study has been communicated to FDA. That study, which contrasted the data regarding the health effects of the use of smokeless products in the United States with the data regarding the health effects of the use of Swedish snus in Scandinavia, concluded that "[M]eta-analysis show that U.S. smokeless tobacco users are at increased risk of oral cancer [compared to non-tobacco users] whereas smokeless tobacco users in Scandinavian countries experience minimal increased oral cancer risk."³⁶ Moreover, quoting from one such meta-analysis, they concluded that "in general, the available epidemiological studies indicate an increased risk of oral cancer [compared to non-tobacco users] for use of smokeless tobacco in the USA, whereas results of studies in the Nordic countries do not support such association."³⁷

Professors Hatsukami and Stepanov cautioned that meta-analysis reported "evidence of moderate increase in risk of fatal myocardial infarction and fatal stroke" resulting from the use of

³⁵ *Id* at 85.

³⁶ Hatsukami and Stepanov at 29.

³⁷ *Id*, quoting from Boffetta, P, et al., "Smokeless tobacco and cancer," *The Lancet Oncology* 9(7):667-75, July 2008, <http://www.ncbi.nlm.nih.gov/pubmed/18598931>.

Swedish snus in Scandinavia and that “two other studies conducted in Sweden would suggest an increased risk in fatal heart disease.”³⁸

In addition, as noted in Professor Hatsukami and Stepanov’s report, some studies indicate that the use of Swedish snus in Sweden increases the risk of esophageal and pancreatic cancer compared to the risk experienced by non-tobacco users.³⁹

Furthermore, the Swedish Match application itself states that the product creates an elevated risk of fetal damage compared to the risk experienced by non-tobacco users and recommends that the Swedish snus not be used by pregnant women.⁴⁰

Despite these health risks resulting from the use of Swedish snus, the changes in the warning labels proposed in this application would eliminate any reference to negative health effects except for the statement that the product is addictive. Thus, even if Swedish Match were to submit a legally proper request for a rulemaking under Section 205, it is doubtful that the company’s proposed warning labels could meet the standard under that section that the proposed revisions to the text of the warning labels “promote greater public understanding of the risks associated with the use of smokeless tobacco products.”

- b. The epidemiological evidence from Sweden relates specifically to the product sold in Sweden only. Smokeless products sold in the United States do cause oral cancer and gum disease.

The data cited in Professor Hatsukami’s and Professor Stepanov’s report support the conclusion that while the use of Swedish snus did not increase the risk of oral cancer in Scandinavia compared to non-tobacco use, the smokeless products sold in the United States did increase the risk of oral cancer among users in the United States compared to non-tobacco use.⁴¹ Thus, whatever conclusion might be drawn from the epidemiological evidence regarding the effect of Swedish snus on users in Scandinavia is not generalizable to other smokeless tobacco products and particularly not to the use of other smokeless tobacco products in the United States, including products sold by other companies as “snus” in the United States.

As with any epidemiological evidence, comparing the results of studies in different countries does not take into account the general disease burden of the country and other

³⁸ *Id.* at 31, quoting from Boffetta, P & Straif, K, “Use of smokeless tobacco and risk of myocardial infarction and stroke: systematic review with meta-analysis,” *BMJ*, 339: b3060, 2009, <http://www.ncbi.nlm.nih.gov/pubmed/19690343>; Arefalk, G, et al., “Smokeless tobacco (snus) and risk of heart failure: results from two Swedish cohorts,” *European Journal of Preventive Cardiology* 19(5):1120-27, 2012, <http://www.ncbi.nlm.nih.gov/pubmed/21828223>.

³⁹ *Id.* at 29. Boffetta 2009, *supra*. International Agency for Research on Cancer (IARC), *Smokeless tobacco and some tobacco-specific N-nitrosamines*, IARC monographs on the evaluation of carcinogenic risks to humans, vol. 89, Lyon, France: World Health Organization, IARC, 2007, <http://monographs.iarc.fr/ENG/Monographs/vol89/mono89.pdf>.

⁴⁰ Swedish Match MRTP Application at 549-550.

⁴¹ Hatsukami and Stepanov, *supra*, at 28-29.

sociocultural, environmental and health-related factors (such as access to health care). Such factors may account for some difference in the risk ratio from the use of a product by one population versus that from the use of the same product by a different population. Thus, the risk posed by Swedish snus to individuals in Scandinavia is not necessarily identical to the risk posed by the same product to individuals in the United States.

3. Evidence Concerning the Levels of Harmful and Potential Harmful Constituents in the Products.

As noted above, although the applicant has provided FDA with evidence of the levels of harmful and potentially harmful constituents in the products that are the subject of the application, some information concerning these constituents has been redacted from the information made publicly available. Thus, it is not possible, based on information available in the redacted application itself, for a public commenter to reach firm conclusions regarding the relative toxicity or carcinogenicity of the products. However, considerable information regarding the levels of many of the principal harmful constituents in Swedish snus has been made public in articles published by scientists employed by the applicant and the data presented in the application is consistent with the publicly available data.⁴² Moreover, Professors Hatsukami and Stepanov, in the preparation of their study of various smokeless tobacco products, have conducted an independent analysis of the levels of various harmful constituents in Swedish snus and many of the leading brands of smokeless tobacco sold in the United States. The results of their analysis are presented in the study recently presented to FDA.⁴³ These results show substantially lower levels of NNN and NNK, the principal tobacco-specific nitrosamines in smokeless tobacco, and substantially lower levels of PAHs in Swedish snus compared to smokeless products sold in the United States. Some of the most popular smokeless products sold in the United States had levels of these harmful constituents that were far above the levels in Swedish snus.

These conclusions provide plausible explanations for the epidemiological results discussed above. When levels of the principal carcinogens are sharply reduced, it is not surprising that disease outcomes improve.

Moreover, these conclusions are consistent with results that would be expected from manufacturing and distribution practices associated with Swedish snus. The choice of tobacco blends used in a product, the choice of curing methods, the avoidance of tobacco sheet, the pasteurization of the tobacco, and the refrigeration of the product before it is sold to the consumer all would be expected to result in a product with lower levels of NNN, NNK, and PAHs. Moreover, substantial reductions in the levels of these harmful constituents would be expected to reduce the disease risk presented by the product.

⁴² Swedish Match MRTP Application at 514-545.

⁴³ Hatsukami and Stepanov, *supra*, at 10-24.

4. Relevance of the Gothia-Tek Standard.

The application makes substantial reference to the Gothia-Tek standard, the standard used since the late 1990s to govern the manufacture of Swedish snus. We understand that the Gothia-Tek standard includes both manufacturing and handling processes and maximum permissible levels of identified harmful constituents. It is also our understanding that the Gothia-Tek standard has evolved over time and become more stringent, so that the levels of harmful constituents in Swedish snus today are lower than levels of harmful constituents in the same products in prior years.

As noted above, the redaction of information regarding actual constituent levels in the products that are the subject of the application makes it impossible for commenters to evaluate the assertions made in the application about the contents of the product. It is important, however, for FDA to evaluate this information and to ensure that the contents of the product comport with the general descriptions of the product available to the public.

If an evolving Gothia-Tek standard has indeed continued to become more stringent with regard to both manufacturing process and constituent content, it would not be surprising to find that the application of such a standard has resulted in a reduction in disease risk from products manufactured in accordance with the standard.

5. Importance of Determining How the Product Will Actually Be Used by Consumers.

The Tobacco Control Act requires that FDA's evaluation both of the risk to the individual and the risk to the population as a whole must take account of the way the product is "actually used by consumers." Whether the product will "significantly reduce harm and the risk of tobacco-related disease to individual tobacco users" may depend on the way the product is "actually used by consumers" and in evaluating the applicability of the Swedish experience on the marketing of the product in the United States much may depend on whether the product will "actually be used" in the United States in the same manner as it was "actually used" in Sweden.

The application demonstrates clearly that the historical and cultural background of tobacco use in Scandinavia is quite different from that in the United States. In Sweden, snus has been widely available and widely used for many years; by contrast, the product has had virtually no presence in the United States market. Swedish snus differs substantially from smokeless tobacco products that have been sold in the United States; it also differs substantially from the products advertised as "snus" that have been on the market in the United States.⁴⁴ Other forms of smokeless tobacco popular in the United States have never been marketed in Sweden.

⁴⁴ Even those products marketed as "snus" in the United States by other companies have had a very small presence in the United States market for tobacco products.

Moreover, the entire market for tobacco products in Sweden differs from the United States market because Sweden permits no advertising of tobacco products—cigarettes or snus. Thus, advertising plays no role in the establishment of consumer preferences in Sweden. This difference may well account for differences in the way snus is used in Sweden as compared to how it would be used in the United States.

A substantial body of evidence supports the proposition that health benefits to an individual from quitting smoking occur only if the individual completely quits smoking. Merely reducing the level of smoking or smoking cigarettes and using other tobacco products concurrently does not eliminate the health risk.⁴⁵ The Swedish Match application itself states that “the health risks among dual users [of snus and cigarettes] appear to be similar to those among exclusive smokers.”⁴⁶ Thus, while snus might “significantly reduce harm and the risk of tobacco-related disease” *if an individual quits smoking altogether and takes up snus instead*, it might not do so for an individual who continues to smoke at the same time as he takes up snus. It is critical to determine whether the data on the Swedish experience differentiates between users who switch completely from cigarettes to snus and those who take up snus without completely giving up cigarettes. In addition, it would be critical to determine whether, in the United States, where tobacco products are advertised, the same pattern of use can be assumed to occur. This pattern of use must also be carefully tracked in post-market surveillance.

The Swedish Match application purports to show a relatively low level of dual use of snus and cigarettes in Sweden. In the United States, where cigarettes are advertised and where the history of smokeless tobacco use has been quite different, the prevalence of dual use of smokeless tobacco and cigarettes has historically been higher.⁴⁷

Because of the critical difference in health outcomes for those who completely quit smoking when they take up snus and those who use cigarettes and snus concurrently, it is essential that any modified risk claims for snus include clear and understandable statements to consumers advising them that any health benefits depend upon their switching entirely away from cigarettes. Moreover, because of the difference in the disease risk presented by Swedish snus and that presented by other smokeless tobacco products, any such claims should make it

⁴⁵ U.S. Department of Health and Human Services (HHS), *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease*, U.S. Centers for Disease Control and Prevention (CDC), Office of Smoking and Health (OSH), 2010, at 9. HHS, *Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General*, CDC, OSH, 2012, at 22, <http://www.surgeongeneral.gov/library/reports/preventing-youth-tobacco-use/index.html>.

⁴⁶ Application at 466.

⁴⁷ Lund, KE, McNeill, A, & Scheffels, J, “The use of snus for quitting smoking compared with medicinal products,” *Nicotine & Tobacco Research* 12(8):817-22, August 2010, <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2910876/pdf/ntq105.pdf>. Tomar, S, Alpert, HR, & Connolly, GN, “Patterns of Dual Use of Cigarettes and Smokeless Tobacco Among US Males: Findings from National Surveys,” *Tobacco Control* 19:104-109, 2010, <http://tobaccocontrol.bmj.com/content/19/2/104.full.pdf+html>. Agaku, IT, et al., “Use of Conventional and Novel Smokeless Tobacco Products Among US Adolescents,” *Pediatrics* 132(3):e578-86, September 2013, <http://pediatrics.aappublications.org/content/early/2013/07/31/peds.2013-0843.full.pdf>.

clear that health benefits depend on consumers not using other smokeless products as well. Failure to provide such information could mislead consumers into believing that dual use of snus and other tobacco products would confer a health benefit when in fact it would not.

C. Importance of Determining if a Modified Risk Marketing Order for the Product Will Benefit the Population as a Whole.

In order to obtain a modified risk marketing order, the applicant must also demonstrate that the issuance of such an order would “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.” Demonstrating such a benefit requires a prediction of the effect of the proposed claim on consumer behavior. Assuming that an individual who smokes cigarettes or uses another smokeless tobacco product and switches to Swedish snus as a result of the modified risk claim receives a significant health benefit, such benefits would be offset by (1) individuals who might otherwise have quit smoking or using other smokeless tobacco products engaging in dual use as a result of the claims; (2) individuals who have never used tobacco products initiating with snus as a result of the claims; and (3) individuals who have quit using tobacco products re-initiating with snus as a result of the claims. Thus, it becomes necessary to predict the effect of such claims on each potential group. One potentially significant effect should also be considered. In addition to considering the benefits from smokers who otherwise would not have quit switching completely to Swedish snus, there would also likely be a population-wide benefit from users of other smokeless tobacco products switching to Swedish snus. While this population is much smaller than that of smokers, the prospect of a complete switch to Swedish snus might be higher.

In making these predictions, the Swedish experience is of limited value. As noted above, the historic widespread prevalence of snus in Sweden makes uncertain the extent to which product choices made by Swedes would be similar to product choices made by Americans exposed to modified risk claims for Swedish snus. Moreover, the presence of pervasive advertising for cigarettes in the United States (and, to a lesser extent, advertising for other smokeless products) affects the consumer behavior of Americans; by contrast, the absence of all such advertising in Sweden creates a very different atmosphere for consumer choice. Finally, since other smokeless products have no market in Sweden, there is no way of predicting the likelihood of a switch from such products to Swedish snus on the basis of Swedish data.

In addition, the presence of e-cigarettes in the market—a factor too recent to be fully reflected in the Swedish experience—will influence the likely effect of modified risk claims for Swedish snus in the United States market.

For all these reasons, a determination of the effect of such claims in the United States must depend principally on studies of consumer perception and consumer behavior in the United States. In doing such studies, several issues should be considered.

1. The effects of the specific claims to be made must be considered. The language of any specific claim and the method by which it is to be disseminated must be studied. The effect of a statement that “this product, if used exclusively instead of cigarettes or other smokeless tobacco products, presents a lower health risk than the use of such other products” might be very different from the effect of a statement that “this product presents a lower health risk than cigarettes.” Moreover, the means by which a modified risk claim is disseminated would also be relevant in such an analysis. A claim made in a major advertising campaign in numerous media outlets might well have a different effect from a claim made by posting signs at the point of sale. Both the message and the means of delivery must be considered.

2. Any claim should include sufficient information to avoid misleading consumers. Because the benefits of switching from cigarettes or other smokeless tobacco products to Swedish snus accrue only to the extent that consumers who otherwise would not quit switch to this product exclusively, any modified risk claim should clearly and explicitly communicate this message to the public.

3. Swedish snus presents a very different health risk to an individual than that presented by other smokeless tobacco products. No modified risk claim should be permitted if it raises the possibility that consumers will draw the conclusion that claims made for Swedish snus are applicable to other smokeless tobacco products, including those marketed as “snus” products. Studies of consumer perception and consumer behavior should specifically address this important distinction.

4. Claims should be considered in light of the population they are designed to target. The population as to which a modified risk claim should be addressed is existing users of cigarettes, other combusted tobacco products, or other smokeless tobacco products. The effectiveness with which such a claim is targeted to this population may affect the appropriateness of granting the application. Thus, the applicant should present not only the text of the claim but a program for its dissemination. A program that effectively limits dissemination to current smokers and users of tobacco products is more likely to benefit the health of the population as a whole than a program that reaches non-users of tobacco products as well. Similarly, a program that is likely to reach a substantial youth market is less likely to benefit the public health. In any event, consideration of any modified risk claim should take into account the population most likely to encounter the claim.

D. Analysis of Consumer Behavior and Smokeless Tobacco Products

Swedish Match submitted an enormous amount of data regarding the Scandinavian experience. It is incumbent upon FDA to perform a complete and thorough analysis of Swedish Match’s submission with respect to transferability. In order for the Swedish experience to be

relevant in considering population level effects, Swedish Match must demonstrate a likelihood that the use of the product by consumers in the United States would be comparable to its use in Sweden. As noted by Swedish Match, data related specifically to snus use in the United States are limited due to the very low use rate. Most of the relevant data in the U.S. assess consumer behavior with respect to the broad smokeless tobacco category that includes snus, dry and moist tobacco and chewing tobacco. We believe that the available evidence in the U.S. relating to consumer behavior patterns with smokeless tobacco products demonstrate that the Swedish experience with snus is unlikely to be replicated in the U.S.

1. Would a Modified Risk Claim Result in Increased Smoking Cessation or an Increase in Dual Use?

While the Swedish experience with snus indicates that switching from cigarettes to snus is more common than switching from snus to cigarettes, in the U.S., there is no strong evidence that smokers switch from cigarettes to smokeless tobacco products. One U.S. longitudinal study found that few male smokers stopped smoking and switched to smokeless tobacco (0.3 percent in one year) and few former smokers turned to smokeless tobacco (1.7 percent).⁴⁸ Instead, smokeless tobacco users were more likely to switch to cigarettes. The study concluded that “smokeless tobacco is less useful for quitting smoking among U.S. smokers because in all likelihood they would quit smokeless tobacco before they quit cigarettes.”⁴⁹ Another longitudinal study of adolescent and young adult males who were smokers at baseline but did not use smokeless tobacco found that at four-year follow-up less than one percent (0.8 percent) switched to smokeless tobacco and 3.6 percent continued to smoke and became smokeless tobacco users as well.⁵⁰

The question of whether smokers who take up smokeless tobacco switch completely and abstain from smoking entirely or whether they use both products concurrently (dual use) has extremely important health consequences. As noted above, there is strong evidence that merely reducing smoking, as opposed to completely abstaining from it, does not reduce the disease risk associated with smoking.⁵¹ As also noted, the Swedish Match application itself states that “the health risks among dual users appear to be similar to those among exclusive smokers.”⁵² Thus, the question of how smokers who take up a smokeless tobacco product will actually use that product (i.e., whether they would use it exclusively while abstaining from smoking or whether

⁴⁸ Zhu, S-H, et al., “Quitting Cigarettes Completely or Switching to Smokeless: Do U.S. Data Replicate the Swedish Results?,” *Tobacco Control* 18:82-87, 2009.

⁴⁹ *Id* at 86.

⁵⁰ Tomar, S, “Is use of smokeless tobacco a risk factor for cigarette smoking? The U.S. experience,” *Nicotine & Tobacco Research* 5(4):561-569, August 2003, <http://www.ncbi.nlm.nih.gov/pubmed/12959794>.

⁵¹ HHS, *Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General*, 2012, at 22, http://www.cdc.gov/tobacco/data_statistics/sgr/2012/index.htm; HHS, *How Tobacco Smoke Causes Disease: A Report of the Surgeon General*, 2010, at 9, http://www.cdc.gov/tobacco/data_statistics/sgr/2010/index.htm.

⁵² Application at 466.

they would use both products concurrently) is critical in evaluating any potential benefit to health that might result from approval of a modified risk application.

Unlike the Swedish evidence, the evidence in the U.S. does not indicate that smokers would switch to exclusive smokeless tobacco use (i.e., the evidence does not demonstrate that smokers who take up smokeless tobacco would abstain from smoking cigarettes). In fact, the evidence suggests that smokers in the U.S. use smokeless tobacco products in conjunction with smoking, particularly in places where smoking is prohibited, rather than switching entirely. One U.S. study that examined perceptions of snus use found that snus was widely perceived as a temporary replacement and not a complete substitution for cigarettes.⁵³ A study that assessed smokers who were also using smokeless tobacco in the U.S. found that these “dual users” were using smokeless tobacco to maintain their cigarette addiction and not to help them quit smoking.⁵⁴ One study that assessed smokers’ receptivity to using either a smokeless tobacco product or a nicotine replacement product as a substitute for cigarettes had similar findings.⁵⁵ These findings are not that surprising given that in the U.S., many new smokeless tobacco products are being marketed as a way to get a nicotine fix when smokers cannot smoke. Such marketing discourages smokers from taking the one step that is sure to protect their health, which is to quit smoking entirely.

A longitudinal study of young adults in the U.S. found an increase in rates of dual use from 2009-2010 to 2011, as new smokeless tobacco products, including General Snus, and e-cigarettes became available and were promoted more widely.⁵⁶ Among young adults who were current tobacco users, 30 percent were dual users (cigarette smokers who also use one or more other tobacco products). Alarming, dual users in this study reported nearly the same levels of smoking as cigarette-only users (8.73 cigarettes per day versus 9.20 cigarettes per day), which suggests that the use of other tobacco products does not act as a substitute for cigarette smoking or decrease the number of cigarettes smoked per day among young adults.⁵⁷

Results from the Minnesota Adult Tobacco Survey show a significant increase in the prevalence of smokeless tobacco use and smokers using smokeless tobacco between 2007 and 2010.⁵⁸ Smokeless tobacco use among smokers doubled, whereas no similar increase was

⁵³ Bahreinifar, S, Sheon, NM, & Ling, PM, “Is snus the same as dip? Smokers’ perceptions of new smokeless tobacco advertising,” *Tobacco Control* 22:84-90, 2013, <http://tobaccocontrol.bmj.com/content/22/2/84>.

⁵⁴ McClave-Regan, AK & Berkowitz, J, “Smokers who are also using smokeless tobacco products in the US: a national assessment of characteristics, behaviours and beliefs of ‘dual users’,” *Tobacco Control* 20:239-242, 2011, <http://www.ncbi.nlm.nih.gov/pubmed/21172853>.

⁵⁵ O’Connor, RJ, et al., “US smokers’ reactions to a brief trial of oral nicotine products,” *Harm Reduction Journal* 8:1-10, 2011, <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3032705/pdf/1477-7517-8-1.pdf>.

⁵⁶ Rath, JM, et al., “Patterns of Tobacco Use and Dual Use in US Young Adults: The Missing Link between Youth Prevention and Adult Cessation,” *Journal of Environmental and Public Health* 2012(679134):1-9, 2012, <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3361253/pdf/JEPH2012-679134.pdf>.

⁵⁷ *Id.*

⁵⁸ Boyle, R, et al., “Concurrent Use of Cigarettes and Smokeless Tobacco in Minnesota,” *Journal of Environmental and Public Health*, (2012).

observed among former smokers or never smokers.⁵⁹ These results indicate that the increase in smokeless tobacco use was largely due to current smokers using smokeless tobacco concurrently, not to smokers switching to smokeless tobacco.

Dual use has become particularly common among young smokers. From 2002 to 2007, more than half (52.8 percent) of youth aged 12 to 17 who used smokeless tobacco in the past month also reported past month cigarette smoking.⁶⁰ An analysis of data from four large U.S. nationally representative surveys found that “the prevalence of daily smoking is very high among male students in middle school and high school who use smokeless tobacco.”⁶¹ For 12th grade males, the prevalence of smoking one-half pack of cigarettes or more per day was nearly five times greater among smokeless tobacco users than non-users.⁶²

Dual use of smokeless tobacco and cigarettes is concerning because it may prolong duration of smoking. Dual users are less likely to quit than are exclusive smokers or exclusive smokeless tobacco users.⁶³ Moreover, as one study concluded, “Because the health risks associated with cigarettes and ST are different in some respects, and because their effects may be additive if not synergistic, the concomitant use of cigarettes and ST may increase the risk of tobacco-attributable death and disease relative to use of either product alone.”⁶⁴

2. How Likely Are Those Who Initiate Tobacco Use with Smokeless Tobacco to Become Smokers?

Data on smokeless tobacco use in the U.S. suggest that smokeless tobacco products act as a gateway to smoking. As noted previously, the longitudinal study by Zhu, *et al.*, found that it was more likely for smokeless tobacco users to switch to cigarettes than for smokers to switch to smokeless tobacco. According to a review of the research, “the preponderance of evidence suggests that ST use is a predictor of cigarette smoking in the United States.”⁶⁵ Other studies have shown that the use of smokeless tobacco is associated with future smoking, particularly for young people. Severson, *et al.*, followed a cohort of adolescent boys in grades seven and nine

⁵⁹ *Id.*

⁶⁰ Substance Abuse and Mental Health Services Administration (SAMHSA), *The NSDUH Report: Smokeless Tobacco Use, Initiation, and Relationship to Cigarette Smoking: 2002 to 2007*, Rockville, MD: Office of Applied Studies, March 5, 2009, at 5.

⁶¹ Tomar, SL, “Patterns of Dual Use of Cigarettes and Smokeless Tobacco among U.S. Males: Findings from National Surveys,” *Tobacco Control* 19:104-109, 2010.

⁶² *Id.* at 105.

⁶³ Klesges, RC, *et al.*, “Tobacco Use Harm Reduction, Elimination, and Escalation in a Large Military Cohort,” *American Journal of Public Health* 100(12):2487-2492, December 2010, at 2490 (“Importantly, dual users were less likely to become tobacco abstinent than were smokers or smokeless tobacco users”); Wetter, D, *et al.*, “Concomitant Use of Cigarettes and Smokeless Tobacco: Prevalence, Correlates, and Predictors of Tobacco Cessation,” *Preventive Medicine* 34:638-648, 2002, (“Concomitant users were significantly less likely to quit using tobacco over the course of 4 years than were users of cigarettes or ST.”).

⁶⁴ Wetter, D, *et al.*, “Concomitant Use of Cigarettes and Smokeless Tobacco: Prevalence, Correlates, and Predictors of Tobacco Cessation,” *Preventive Medicine* 34:638-648, 2002.

⁶⁵ Tomar, SL, *et al.*, “Is Smokeless Tobacco Use an Appropriate Public Health Strategy for Reducing Societal Harm?,” *International Journal of Environmental Research and Public Health* 6:10-24, 2009, at 16.

who were smokeless tobacco-only users for two years. They found that initiation of weekly smoking in grades nine and eleven was significantly associated with baseline smokeless tobacco use, even after controlling for other risk factors.⁶⁶ The odds of being a weekly smoker after two years were more than 2.5 times greater for smokeless tobacco users than nonusers.⁶⁷ More than half (57.3 percent) of smokeless tobacco users later reported smoking cigarettes.⁶⁸ A recent survey of adolescents and young adults who had ever used tobacco found that those who initiated any tobacco use with smokeless tobacco (or any other non-combustible product) had higher odds of using multiple tobacco products than those who initiated with a combustible product.⁶⁹

In a military cohort study of almost 8,000 young adult male Air Force recruits who had not smoked in the past year, both current and former smokeless tobacco users were more than twice as likely as never users to begin smoking.⁷⁰ A 2002 study found that “snuff use may be a gateway form of nicotine dosing among males in the United States that may lead to subsequent cigarette smoking.”⁷¹ The study found that “the prevalence of smoking was substantially higher among men who had quit using snuff than among those who had never used snuff, suggesting that more than 40% of men who had been snuff users continued or initiated smoking.”⁷²

A longitudinal study of adolescent and young adult males found males who were smokeless tobacco users at baseline were significantly more likely than those who had never used these products to become cigarette smokers during the four-year follow-up period. Specifically, a quarter (25.5 percent) of males who were regular smokeless tobacco users at baseline but not smokers had switched to smoking at four-year follow-up.⁷³

In this connection, the Swedish Match application states that the current warning label text is more likely to discourage non-users to initiate snus use than the text urged by Swedish Match.⁷⁴

⁶⁶ Severson, H, et al., “Use of smokeless tobacco is a risk factor for cigarette smoking,” *Nicotine and Tobacco Research* 9(12):1331-1337, December 2007.

⁶⁷ *Id.* at 1335.

⁶⁸ *Id.* at 1334.

⁶⁹ Soneji, S, Sargent, J, & Tanski, S, “Multiple tobacco product use among US adolescents and young adults,” *Tobacco Control*, 2014, [Epub ahead of print], <http://www.ncbi.nlm.nih.gov/pubmed/25361744>.

⁷⁰ Haddock, CK, et al., “Evidence that smokeless tobacco use is a gateway for smoking initiation in young adult males,” *Preventive Medicine* 32:262-267, 2001.

⁷¹ Tomar, S, “Snuff Use and Smoking in U.S. Men: Implications for Harm Reduction,” *American Journal of Preventive Medicine* 23(3):143-149, October 2002.

⁷² *Id.*

⁷³ Tomar, S, “Is use of smokeless tobacco a risk factor for cigarette smoking? The U.S. experience,” *Nicotine & Tobacco Research* 5(4):561-569, August 2003, <http://www.ncbi.nlm.nih.gov/pubmed/12959794>. See also, Tomar, SL, “Smokeless tobacco use is a significant predictor of smoking when appropriately modeled,” *Nicotine & Tobacco Research* 5(4):571-573, August 2003, <http://www.ncbi.nlm.nih.gov/pubmed/12959795>.

⁷⁴ Application at 694.

3. Would a Modified Risk Claim Promote Smoking Cessation?

Though Swedish Match presented much evidence of the success of Swedish male smokers to quit with snus, there is not sufficient evidence in the U.S. on the impact of smokeless tobacco in helping smokers quit to support an inference that there would be a similar effect in the U.S. In fact, the 2008 Update of the U.S. Public Health Service Clinical Practice Guidelines regarding tobacco cessation concluded, “the use of smokeless tobacco products is not a safe alternative to smoking, nor is there evidence to suggest that it is effective in helping smokers quit.”⁷⁵

Moreover, evidence from the U.S. shows that U.S. smokers do not prefer smokeless tobacco, even snus, to quit smoking. A 2009 study based on data from the California Tobacco Survey showed that the majority of daily smokers were not interested in switching their cigarettes for smokeless tobacco. In fact, 87 percent of smokers said they were “definitely not” or “probably not” open to the idea of replacing their cigarettes with smokeless tobacco, compared to only 12.7 percent of the smokers who reported that they “definitely” or “probably” would consider it.⁷⁶ A national cross-sectional study of current and former smokers found that just “7.8% of respondents reported that they tried to quit smoking by switching to chewing tobacco, snuff, or snus; an additional 5.8% considered it but never tried, and most never considered it.”⁷⁷ A study of dual users found that three-quarters of dual users did not believe that smokeless tobacco products could help them quit smoking and the majority of them reported using smokeless tobacco at times when they were not able to smoke rather than as a cessation aid.⁷⁸ One study that reported that a majority of smokeless users (53 percent) used smokeless tobacco to cut down on the amount they smoke, found that those who used these products were no more likely to stop using cigarettes compared to those smokers who did not use smokeless tobacco.⁷⁹

Other evidence suggests that smokers in the U.S. prefer to use pharmaceutical nicotine products to quit over smokeless tobacco products. One study described previously that assessed smokers’ receptivity to using either a smokeless tobacco product or a nicotine replacement product as a substitute for cigarettes found that of the various substitutes offered, smokers were more willing to use a nicotine replacement product over a tobacco product and this was true even

⁷⁵ Fiore, MC, et al., *Treating Tobacco Use and Dependence: 2008 Update*, U.S. Public Health Service Clinical Practice Guideline, May 2008, http://www.surgeongeneral.gov/tobacco/treating_tobacco_use08.pdf.

⁷⁶ Timberlake, D, “Are smokers receptive to using smokeless tobacco as a substitute?” *Preventive Medicine* 49(2-3):229-32, 2009, <http://www.ncbi.nlm.nih.gov/pubmed/19631684>

⁷⁷ Popova, L & Ling, PM, “Alternative Tobacco Product Use and Smoking Cessation: A National Study,” *American Journal of Public Health* 103(5):923-930, May 2013, <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3661190/pdf/nihms456593.pdf>.

⁷⁸ McClave-Regan, AK & Berkowitz, J, “Smokers who are also using smokeless tobacco products in the US: a national assessment of characteristics, behaviours and beliefs of ‘dual users’,” *Tobacco Control* 20:239-242, 2011.

⁷⁹ Kasza, KA, et al., “Cigarette Smokers’ Use of Unconventional Tobacco Products and Associations With Quitting Activity: Findings From the ITC-4 U.S. Cohort,” *Nicotine & Tobacco Research* 16(6):672-681, June 2014, <http://www.ncbi.nlm.nih.gov/pubmed/24376276>.

though the smokeless tobacco and nicotine replacement products were provided at no cost.⁸⁰ Another study that examined smokers' preferences for medicinal nicotine versus smokeless tobacco found a statistically significant preference for medicinal nicotine and that the preference for medicinal nicotine held across many population groups (men, women, smokeless tobacco users and users of NRT gum).⁸¹

In addition to the consumer behavior data, there are many reasons why the Swedish experience may be inapplicable to the United States. In fact, according to one study, “[m]any have cautioned that the Swedish results could be a country-specific phenomenon due to unique historical and cultural factors associated with snus use.”⁸² For example, as noted previously, Sweden does not permit advertising of tobacco products in broadcast media, though internet and some point-of-sale advertising are allowed. On the contrary, in the U.S., there is a huge amount of advertising for tobacco products, particularly cigarettes. In 2011 alone, tobacco companies spent \$8.4 billion to market cigarettes. Tobacco companies spent an additional \$451.7 million on smokeless tobacco marketing that same year.⁸³ The level of industry spending to ensure that cigarettes are advertised heavily, displayed prominently, and priced cheaply is a significant factor present in the U.S. but not in Sweden militating against a replication of the Swedish experience in the U.S., particularly as to the likelihood that cigarette smokers will quit smoking for smokeless tobacco.

Another major consideration is that the popular smokeless tobacco products in the U.S. are traditional moist snuff, not snus. Snus has virtually no presence in the U.S. market. While the snus sales in the U.S. have grown over time, its share of the market for smokeless tobacco products in 2011 was just 3.7 percent (compared to 91.9 percent, for traditional moist snuff products).⁸⁴ Prevalence of snus use is very low among adults and youth. In 2012, current snus use was 0.8 percent among middle school students and 2.5 percent among high school students.⁸⁵

⁸⁰ O'Connor, RJ, et al., “US smokers’ reactions to a brief trial of oral nicotine products,” *Harm Reduction Journal* 8:1-10, 2011, <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3032705/pdf/1477-7517-8-1.pdf>.

⁸¹ Shiffman, S, et al., “Smokers' Preferences for Medicinal Nicotine vs Smokeless Tobacco,” *American Journal of Health Behavior* 31(5):462-472, September/October 2007, <http://www.ncbi.nlm.nih.gov/pubmed/17555377>.

⁸² Zhu, S-H, et al., “Quitting Cigarettes Completely or Switching to Smokeless: Do U.S. Data Replicate the Swedish Results?,” *Tobacco Control* 18: 82-87, 2009.

⁸³ U.S. Federal Trade Commission (FTC), *Cigarette Report for 2011*, 2013, <http://www.ftc.gov/os/2013/05/130521cigarettereport.pdf>. See also, FTC, *Smokeless Tobacco Report for 2011*, 2013, <http://www.ftc.gov/os/2013/05/130521smokelesstobaccoreport.pdf>. [Data for top 5 manufacturers only.]

⁸⁴ Delnevo, CD, et al., “Examining market trends in the United States smokeless tobacco use: 2005–2011,” *Tobacco Control* 23(2):107-12, 2014, <http://www.ncbi.nlm.nih.gov/pubmed/23117999>. This study examines convenience store sales.

⁸⁵ CDC, “Tobacco Product Use Among Middle and High School Students — United States, 2011 and 2012,” *MMWR* 62(45):893-897, November 15, 2013, <http://www.cdc.gov/mmwr/pdf/wk/mm6245.pdf>.

Only 5.4 percent of U.S. adults had ever used snus in 2012-2013 and among current snus users, only 11.3 percent report using the product every day.⁸⁶

Lastly, given these circumstances, it is improbable that any word of mouth movement that promotes snus use could be established among U.S. smokers. In a submission to the Tobacco Product Scientific Advisory Committee, Swedish Match's Rutqvist attributes part of the success of snus in Sweden to word of mouth: "neighbor talking to neighbor, family members sharing experiences."⁸⁷ But in the United States, since most Americans do not like snus products, any message about snus delivered or shared between smokers would likely be negative.

E. Analysis of the Swedish Match Premarket Consumer Perception Study⁸⁸

In support of its application, Swedish Match conducted a Premarket Consumer Perception Research Study. The company's stated goal was to "assess the effect and comprehension of the company's proposed MRTP labels on the public."⁸⁹

According to a report by the Institute of Medicine, a Modified Risk Tobacco Product (MRTP) would ideally "be sufficiently reinforcing so as to attract smokers away from conventional cigarettes but not encourage the widespread dependent use of the product by individuals who were previously nonusers or who would have quit smoking."⁹⁰

The central issue for FDA therefore is whether an MRTP could make claims that encourage smokers to switch away from cigarettes in significant numbers, without (1) encouraging use by those who otherwise would have quit tobacco completely and without (2) encouraging uptake by nonsmokers, especially adolescents or those who have already successfully quit cigarette smoking.

To encourage use of its snus products as an MRTP, Swedish Match proposes removing current mandated warnings on smokeless products that the product "can cause mouth cancer," "can cause gum disease and tooth loss," and "is not a safe alternative to cigarettes." In place of the last warning, the company tested two alternatives: "No tobacco product is safe, but this product presents a substantially lower risk to health than cigarettes" or the same warning without the word "substantially." (For convenience, we will refer to these two tested statements as "the

⁸⁶ CDC, "Tobacco Product Use Among Adults — United States, 2012–2013," *MMWR* 63(25):542-547, June 27, 2014, <http://www.cdc.gov/mmwr/pdf/wk/mm6325.pdf>.

⁸⁷ Rutqvist, LE, "The Swedish Experience," Submission to FDA Tobacco Product Scientific Advisory Committee Meeting, January 18-20, 2012, <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM293256.pdf>.

⁸⁸ The following analysis of the consumer perception study benefited considerably from the input of Dan Romer, Ph.D., Director of the Adolescent Communication Institute of the Annenberg Public Policy Center, University of Pennsylvania.

⁸⁹ Swedish Match MRTP Application at 121.

⁹⁰ Institute of Medicine, *Scientific standards for studies on Modified Risk Tobacco Products*, Washington, DC: The National Academies Press, 2012, at 225.

modified risk warnings.”)⁹¹ Swedish Match also proposes a change to the current warning that “Smokeless tobacco is addictive,” by seeking a warning label stating that, “This product is addictive.” Thus, they propose retaining two warnings on these products, one on addiction potential and one comparing Snus to cigarettes.

The Consumer Perception Study exposed a large sample of current and former tobacco users, as well as non-users, to one of the existing warnings or to one of the alternative warnings comparing the risk to cigarettes. As discussed below, the findings, within the limits of a single exposure to only one of the warnings, indicate that a modest number of current tobacco users were more likely to say that they would use snus based on the modified warning label. However, the study also raises concerns about the impact of the modified risk warnings on non-users, particularly young people. The study indicates that the modified risk warning did not encourage “use of snus” among current non-tobacco users, but those non-users did report that the modified risk warning would *discourage* their purchase of snus *less than* those exposed to the existing warnings. Thus, there was some evidence that the modified warning would be less of a deterrent to purchasing snus among current non-users. The modified risk warning had similar effects among former smokers.

As discussed below, in evaluating the study FDA must carefully consider a number of factors relating to the study itself as well as the stated results.

1. Consumer Perception Study Design and Methods

- a. Research Stages

In evaluating consumer perception of modified risk claims, IOM recommends three research stages for premarket research: (1) Formative focus groups to help determine the most accurate and easily comprehended message; (2) Additional focus groups to assess how the messages that were developed in phase one are received by consumers; and (3) Message testing research to test the effects of verbal and non-verbal messages on consumer perception. Swedish Match conducted a substantial survey to test its alternate label, and the documents indicate that the survey process included routine pre-testing of the questionnaire for clarity prior to fielding. However, Swedish Match does not provide any evidence that it conducted formative research to help determine messages that were both accurate and easy for consumers to comprehend. As discussed earlier, the application would benefit from the consideration of other messages besides the two they ultimately tested, which differed by just a single word.

- b. Study Stimulus

A central principle of this type of consumer perception research is that both the actual language of any specific claim and the method by which it is to be disseminated must be studied.

⁹¹ However, as noted above, the modified risk language Swedish Match seeks should not properly be regarded as a “warning” at all.

As discussed previously, this application concerns a change to the government-required product warning label rather than the identification of a specific modified risk claim Swedish Match seeks to communicate to consumers. In addition, inconsistencies in the study materials provided by Swedish Match raise questions about whether the warning label presented to consumers in the research study is indeed the same label the company is requesting FDA apply to the products under review.

Swedish Match proposes two specific warning labels for the snus products covered by this application. As detailed in text and, for the risk warning, in the sample product labels, the proposed text would read as follows:

“WARNING: This product is addictive.”

“WARNING: No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes.”⁹²

Appendix A to the research report⁹³ provides images of the “Warning Label Stimulus” provided to survey respondents. For the addiction warning, the study included an image of general snus products featuring the current warning label (“WARNING: Smokeless tobacco is addictive.”). For the new substantially lower/lower risk warning, the stimulus provided to survey respondents included an image of general snus products featuring one of the following labels:

“No tobacco product is safe, but this product presents a substantially lower risk to health than cigarettes.”

“No tobacco product is safe, but this product presents a lower risk to health than cigarettes.”

Thus, the representation of the label presented in the study omits the word “WARNING,” even though it is included in the proposed label. In addition, the materials reveal a slight wording variation between the proposed label and the version presented to consumers (lower risks to health vs. a lower risk to health).

The application does not appear to address the inconsistency or provide any explanation for the difference in the protocol text⁹⁴ and the warning label stimulus presented to consumers.

In addition to testing the precise message that will be presented to consumers, a thorough examination would consider both the message and all means of delivery, including labeling, packaging and marketing.

⁹² Swedish Match MRTP Application 344-353.

⁹³ MRTP Warning Label Evaluation 590-596.

⁹⁴ Swedish Match Premarket Consumer Perception Survey Protocol 56-67.

As noted by Swedish Match, any advertising for the snus products will necessarily carry warnings identical to those shown on the product label.⁹⁵ Even if there are no plans to revise any marketing statements or materials, the prominent presence of the new warning label in advertising will still interact with the message and can influence consumer perceptions and behavior.

For example, some of the marketing material for General Snus includes messages that could promote the use of snus as a bridge product to be used when and where other tobacco products are not allowed. A 2014 e-mail promotion said, “Take it all in. Tobacco shouldn't interrupt your experiences, it should enhance them. General Snus delivers premium tobacco satisfaction anytime, anywhere, pushing any experience forward without ever holding you back.”⁹⁶

Similarly, a magazine advertisement pairs a close up of a billiards table with a crowd of people in the background with the following text: “Tobacco satisfaction was meant to be enjoyed in life's moments – not around them. As the only authentic Swedish snus made and imported from Sweden, General Snus features a blend of 22 premium tobaccos that delivers superior flavor and discreet tobacco pleasure wherever you are. And wherever you're going.”⁹⁷ A direct mail piece emphasizing the “discreet” nature of snus noted that, “without the confines of traditional tobacco products, you have the freedom to enjoy General Snus anywhere you please.”⁹⁸

c. Exposure to the Warnings

It is important to note that the findings of this premarket study must be interpreted within the limits of *a single exposure to only one of the warnings*. To get a clear picture of the impact of a proposed label change or claim, consumer testing should involve repeated exposure to the proposed MRTP and its marketing to understand how consumers will perceive, process and react to this information. Indeed, the draft guidance from FDA encourages applicants to “use methods that assess the impact of repeated exposure to labels and advertising on consumer perceptions.”⁹⁹

d. Research Sample

According to IOM, perceptions of and intentions to use a given MRTP are also likely to differ by age group. Thus, IOM noted that it is “critical that studies include participants in the following age groups: children (≤ 12 years old), adolescents (13–17 years old), young or emerging adults (18–25 years old), adults (≥ 25 years old).”¹⁰⁰ As noted by IOM, “adolescents’

⁹⁵ Swedish Match MRTP Application 344-345.

⁹⁶ Trinkets and Trash, <http://www.trinketsandtrash.org/detail.php?artifactid=9033&page=1>.

⁹⁷ Trinkets and Trash, <http://www.trinketsandtrash.org/detail.php?artifactid=7618&page=1>.

⁹⁸ Trinkets and Trash, <http://www.trinketsandtrash.org/detail.php?artifactid=7418&page=1>.

⁹⁹ FDA guidance at 26.

¹⁰⁰ Institute of Medicine at 174.

perceptions of the risks and benefits of cigarette smoking play an important role in adolescents' decisions to smoke. Given that adolescence is a period of heightened vulnerability for the initiation of tobacco use, it is particularly important to evaluate whether adolescents accurately understand the purported benefits of an MRTP. Of particular importance are adolescents' perceptions of the risks and benefits of using the product, and whether they intend to initiate tobacco use with the MRTP rather than a traditional tobacco product because they believe the latter is a "safe" alternative."¹⁰¹

The Swedish Match Consumer Perception Study included adults age 18 to 64, leaving out the critical subgroup of adolescents. Each year, about 535,000 kids age 12-17 use smokeless tobacco for the first time.¹⁰² This demographic group is likely to try Snus and, from a public health perspective, it is critical to understand their perceptions of the revised warning label.

2. Consumer Perception Study Findings: Impact on Tobacco Use Behaviors among Current Tobacco Users
 - a. Impact on Likelihood to Use and Motivation to Purchase Snus by Current Tobacco Users.

The survey findings, within the limits of a single exposure to only one of the warnings, show that a modest number of current tobacco users were more likely to say that they would use snus based on the modified warning label.

Just over one in ten tobacco users (11 percent) exposed to the "substantially lower risk" label said they were extremely likely to use snus based on the information on the label, compared to 8-9 percent of tobacco users exposed to the current labels.¹⁰³

Of those both likely and extremely likely to use snus based on the label (top 2 box), tobacco users exposed to the "substantially lower risk" label were significantly more likely to say they would use snus (20 percent) compared to those seeing the current warnings (12-14 percent).¹⁰⁴

Among current tobacco users exposed to the proposed "substantially lower risk" warning, 27 percent said that they would "not at all be likely to use snus" based on the information on the warning label. This is significantly less compared to tobacco users exposed to the current labels (33-40 percent).¹⁰⁵

¹⁰¹ *Id.* at 165.

¹⁰² Substance Abuse and Mental Health Services Administration (SAMHSA), Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health (NSDUH), 2013, <http://www.samhsa.gov/data/NSDUH/2013SummNatFindDefTables/DefTabs/NSDUH-DefTabsSect4peTabs1to16-2013.htm#tab4.10a>.

¹⁰³ MRTP Warning Label Evaluation at 61.

¹⁰⁴ *Id.*

¹⁰⁵ *Id.*

Just 9 percent of tobacco users exposed to the proposed “substantially lower risk” warning said that the warning “definitely would motivate me to purchase snus.” This is slightly more compared to users exposed to the current labels (5-7 percent).¹⁰⁶

Of those both motivated and definitely motivated to purchase snus based on the label (top 2 box), tobacco users exposed to the “substantially lower risk” label were significantly more likely to say they would be motivated to purchase snus (17 percent) compared to those seeing the current claims (8-11 percent).¹⁰⁷

Just 11 percent of tobacco users exposed to the proposed “substantially lower risk” warning said that the warning “definitely would discourage me from purchasing snus.” This is significantly less compared to users exposed to the current labels (22-36 percent).¹⁰⁸

Overall, the survey findings show that a very modest number of current tobacco users would be more likely to use or purchase snus based on the modified warning label. The number of current tobacco users likely to use or purchase snus was about 6-9 percentage points higher among those exposed to the modified label over those exposed to the current labels. As discussed below, a certain percentage of these likely users indicate that they would be dual users of snus and cigarettes.

b. Likelihood of Dual Use among Current Tobacco Users.

Dual use is of particular concern because the potential benefits of using Swedish snus would only be fully realized if smokers switch *completely*. The Swedish Match application itself states that “the health risks among dual users appear to be similar to those among exclusive smokers.”¹⁰⁹ The consumer perception study found that dual use of cigarettes and snus is more likely among current smokers exposed to the modified risk warnings than among those exposed to the current warnings. Among current smokers reporting that they were likely or extremely likely to use snus, nearly one quarter (24 percent) of those exposed to the “substantially lower risk” label reported that they were either likely or extremely likely to use *both snus and cigarettes*.¹¹⁰ This was significantly higher than the likelihood of dual use reported by those exposed to the current addiction or mouth cancer warning (16 percent each), and higher, although not significantly higher, than those exposed to the current gum disease or not a safe alternative warnings (17 percent each).¹¹¹

Among current smokers likely to use both snus and cigarettes, 36 percent exposed to the “substantially lower risk” label said that the use of snus would reduce their cigarette usage and

¹⁰⁶ *Id.* at 71.

¹⁰⁷ *Id.*

¹⁰⁸ *Id.*

¹⁰⁹ Application at 466.

¹¹⁰ *Id.* at 62.

¹¹¹ *Id.*

29 percent said that they would try to use snus to quit. Another 27 percent indicated that they would use snus in addition to cigarettes, but it would not impact their current cigarette use. These findings among those exposed to the “substantially lower risk” label were not significantly different than those exposed to the current warnings.¹¹²

Overall, the survey findings assessing the likelihood of dual use are concerning, given that the data show that dual use of cigarettes and snus is more likely among current smokers exposed to the modified risk warnings than among those exposed to the current warnings.

c. Impact on Likelihood to Use and Motivation to Purchase Snus by Imminent Quitters or Reducers.

IOM notes that, as part of the minimum standards, smoking behavior should be characterized through an assessment of the frequency, timing, and duration of prior quit attempts. Instead of using specific information about prior quit attempts to help categorize smokers, the survey analysis broadly categorizes “imminent quitters or reducers” as current, daily tobacco users who report that they “definitely,” “most likely,” or “possibly” will attempt to quit *or* reduce their tobacco use in the next month.¹¹³

Therefore, this category encompasses a significant majority of tobacco users surveyed. For example, it would include 67 percent of all current cigarette smokers as “likely to quit” even though just 20 percent say that they “definitely will attempt to quit” in the next month. Another 18 percent say they “most likely will attempt to quit” and a 29 percent plurality “possibly will attempt to quit.”¹¹⁴ Also included are 76 percent of smokers categorized as “likely to reduce” smoking in the next month, even though just 26 percent indicate that they “definitely will attempt to reduce,” 22 percent “most likely will attempt to reduce” and 28 percent “possibly will attempt to reduce.”¹¹⁵

Combining the vast majority of tobacco users together as “imminent quitters or reducers” makes it impossible to assess the reactions among those *most* motivated to make a quit attempt. Survey results among the key subgroup of those indicating that they definitely or most likely to quit were not made available in the report. The study also does not address the degree to which users *who might otherwise have quit tobacco entirely* would use these snus products instead of quitting.

The survey findings, within the limits of a single exposure to only one of the warnings, show that a modest number of imminent quitters or reducers were more likely to say that they would use snus based on the modified warning label. As discussed, this category includes the

¹¹² *Id.* at 63.

¹¹³ *Id.* at 240.

¹¹⁴ *Id.* at 56.

¹¹⁵ *Id.* at 57.

majority of all tobacco users, so it is not surprising that the results among this group are consistent with the results already discussed among current users.

Just over one in ten imminent quitters or reducers (11 percent) exposed to the “substantially lower risk” label said they were extremely likely to use snus based on the information on the label, compared to 9-10 percent of tobacco users exposed to the current labels.¹¹⁶

Of those both likely and extremely likely to use snus based on the label (top 2 box), imminent quitters or reducers exposed to the “substantially lower risk” label were significantly more likely to say they would use snus (21 percent) compared to those seeing the current claims (14-15 percent).¹¹⁷

Among imminent quitters or reducers exposed to the proposed “substantially lower risk” warning, 25 percent said that they would “not at all be likely to use snus” based on the information on the warning label. This is significantly less compared to imminent quitters or reducers exposed to the current labels (34-40 percent).¹¹⁸

Just 9 percent of imminent quitters or reducers exposed to the proposed “substantially lower risk” warning said that the warning “definitely would motivate me to purchase snus.” This is slightly more compared to users exposed to the current labels (5-8 percent).¹¹⁹

Of those both motivated and definitely motivated to purchase snus based on the label (top 2 box), imminent quitters or reducers exposed to the “substantially lower risk” label were significantly more likely to say they would be motivated to purchase snus (18 percent) compared to those seeing the current claims (9-12 percent).¹²⁰

Just 12 percent of imminent quitters or reducers exposed to the proposed “substantially lower risk” warning said that the warning “definitely would discourage me from purchasing snus.” This is significantly less compared to imminent quitters or reducers exposed to the current labels (24-38 percent).¹²¹

Dual use is of particular concern among those motivated to quit or reduce because, as stated previously, the potential benefits of using Swedish snus would only be fully realized if smokers switch *completely*. The consumer perception study found that dual use of cigarettes and snus is more likely among imminent quitters or reducers exposed to the modified risk warnings than among those exposed to the current warnings. Among imminent quitters or reducers reporting that they were likely or extremely likely to use snus, one quarter (25 percent) of those

¹¹⁶ *Id.* at 249.

¹¹⁷ *Id.*

¹¹⁸ *Id.*

¹¹⁹ *Id.* at 259.

¹²⁰ *Id.*

¹²¹ *Id.*

exposed to the “substantially lower risk” label reported that they were either likely or extremely likely to use *both snus and cigarettes*. This was higher than the likelihood of dual use reported by those exposed to the current warnings (16-19 percent).¹²²

Among imminent quitters or reducers likely to use both snus and cigarettes, 36 percent exposed to the “substantially lower risk” label said that the use of snus would reduce their cigarette usage and 32 percent said that they would try to use snus to quit. Another 26 percent indicated that they would use snus in addition to cigarettes, but it would not impact their current cigarette use. These findings among those exposed to the “substantially lower risk” label were not significantly different than those exposed to the current warnings.¹²³

Overall, because the analysis of the reactions of “imminent quitters or reducers” included the vast majority of tobacco users, we cannot assess the impact of the warning labels on the critical subgroup of those smokers *most* motivated to make a quit attempt. And, importantly, the results do not address the degree to which users *who might otherwise have quit tobacco entirely* would use these snus products instead of quitting.

3. Consumer Perception Study Findings: Impact of Label on Tobacco Use Initiation Behavior among Non-Users

It is critical to establish the degree to which those who would have never used tobacco products would be open to using tobacco when exposed to a modified risk claim. To increase the likelihood of a positive public health outcome, pre-market studies should show that the warning labels continue to discourage purchase and use of tobacco products among non-users (especially younger consumers including adolescents).

The survey findings, within the limits of a single exposure to only one of the warnings, tended to show that non-users of tobacco were more inclined to try and purchase snus when exposed to the modified than the current warnings. This pattern was especially evident among those exposed to the *substantially* reduced risk warning.

The modified risk warnings did not appear to encourage “use of snus” among current non-tobacco users. However, non-users did report that the modified risk warning would *discourage* their purchase and use of Snus *less than* those exposed to the existing warnings.

Among current non-users exposed to the proposed “substantially lower risk” warning, 57 percent said that they would “not at all be likely to use snus” based on the information on the warning label. This is significantly less compared to non-users exposed to the current labels (63-71 percent).¹²⁴

¹²² *Id.* at 250.

¹²³ *Id.* at 251.

¹²⁴ *Id.* at 113.

Similarly, just 37 percent of non-users exposed to the proposed “substantially lower risk” warning said that the warning “definitely would discourage me from purchasing snus.” This is significantly less compared to non-users exposed to the current labels (52-70 percent).¹²⁵

Thus, there was some evidence that the modified warning would be less of a deterrent to purchase and use of snus among current non-tobacco users.

4. Consumer Perception Study Findings: Impact of Label on Tobacco Use Behavior among Former Users

Former tobacco users are a very important audience in the consumer perception study. The availability and marketing of MRTPs may convince those who have successfully quit smoking or other tobacco use that they can resume use with little or no harm, thus leading to relapse. Even if the MRTP were minimally harmful, MRTP claims could draw former users back into nicotine addiction and lead them back to the products they were using before they quit.

The study indicates that the modified risk warning had similar effects among former tobacco users as it did among non-users: the new warnings did not encourage “use of snus” among former tobacco users, but they did report that the modified risk warning would discourage their purchase of snus *less than* those exposed to the existing warnings.

Among former users exposed to the proposed “substantially lower risk” warning, 61 percent said that they would “not at all be likely to use snus” based on the information on the warning label. This is less compared to former users exposed to most of the current labels (69-81 percent), with the exception of the current addiction label (60 percent).¹²⁶

Similarly, just 34 percent of former users exposed to the proposed “substantially lower risk” warning said that the warning “definitely would discourage me from purchasing snus.” This is significantly less compared to former users exposed to the current labels (56-74 percent), again with the exception of the addiction label (42 percent).¹²⁷

In other words, there was evidence that the modified warning would be less of a deterrent to purchasing snus among former tobacco users than the warnings that would be removed from the products under the proposal by Swedish Match.

¹²⁵ *Id.* at 114.

¹²⁶ *Id.* at 157.

¹²⁷ *Id.* at 158.

5. Consumer Perception Study Findings: Impact of Label Change on Consumer Understanding and Perceptions

a. Ease of Understanding

About half of all respondents (52 percent) said that the “substantially lower risk” label was “very easy” to understand. This is significantly lower than those reporting that the current warning labels were very easy to understand (65-76 percent). It should be noted that asking people whether claims were easy to understand can sometimes incorporate a bias – people may not wish to signal that they have difficulty with comprehension. Nevertheless, compared to current labels, respondents were significantly less likely to indicate that the proposed lower risk labels were easy to understand.¹²⁸

The pattern was similar among key subgroups including current tobacco users, non-users, former users and non-users age 18-24. Among the younger non-users, 44 percent said that the “substantially lower risk” label was “very easy” to understand, significantly lower than those reporting that the current warning labels were very easy to understand (56-75 percent).¹²⁹

b. Clarity of Meaning

Compared to current labels, respondents were significantly less likely to indicate that the meaning of the proposed lower risk labels was clear. Less than half of all respondents (44 percent) said that the meaning of the “substantially lower risk” label was “very clear.” This is significantly lower than those reporting that the meanings of the current warning labels were very clear (60-79 percent).¹³⁰ Among younger non-users age 18-24, less than one-third (32 percent) said that the meaning of the “substantially lower risk” label was “very clear,” significantly lower than those reporting that the current the meanings of the current warning labels were very clear (50-69 percent).¹³¹

c. Believability

Respondents rated the modified risk warning as less believable than the existing warnings. One-quarter (25 percent) of respondents rated the “substantially lower risk” label as “extremely believable,” significantly lower than those giving the current warning labels the highest mark for believability (53-62 percent). The same is true for those rating the labels very or extremely believable (top 2 box). In that instance, 39 percent of those seeing the “substantially lower risk” label rated it as very or extremely believable, significantly lower than the current warning labels (68-77 percent).¹³²

¹²⁸ *Id.* at 13.

¹²⁹ *Id.* at 551.

¹³⁰ *Id.* at 14.

¹³¹ *Id.* at 552.

¹³² *Id.* at 17.

d. Perception of Risk

Risk perceptions for snus were consistent with what one would expect after respondents were exposed to the warning labels: those exposed to a modified, lower risk warning as opposed to a current risk warning rated snus as less risky to health in an absolute sense¹³³ and also compared to cigarettes.¹³⁴

While there is evidence that the modified warnings can give consumers a more accurate perception of risk relative to cigarettes, the modified warnings also have the potential to undermine the perception of harm relative to the most desired health outcome of quitting tobacco altogether. Among all respondents (prior to exposure to any warning label), 45 percent said that compared to not using ANY tobacco at all, using snus would be much more harmful to their health. Another 27 percent said that compared to not using ANY tobacco at all, using snus would be only somewhat harmful to their health, for a total of 72 percent indicating that snus would be more harmful than using no tobacco product at all. One quarter (25 percent) did not know.¹³⁵

After exposure to the warning labels, fewer respondents had no opinion and 78 percent of those seeing the “substantially lower risk” label rated snus use as much more harmful (35 percent) or somewhat more harmful (43 percent) compared to not using ANY tobacco at all. This is a significantly lower percentage than that of respondents exposed to the three warnings Swedish Match seeks to remove as part of this application (81-87 percent more harmful, including a majority saying that snus use would be much more harmful to health compared to not using any tobacco at all).¹³⁶

There was a similar trend among imminent quitters and reducers, especially as it relates to the perception that snus is much more harmful than quitting ALL tobacco. Prior to the exposure to any label, 43 percent of imminent quitters and reducers said that using snus would be “much more harmful” to their health compared to not using ANY tobacco at all.¹³⁷

After exposure to the warning labels, just 28 percent of those seeing the “substantially lower risk” label rated snus use as much more harmful compared to not using ANY tobacco at all. This is a significantly lower percentage than that of respondents exposed to the three warnings Swedish Match seeks to remove as part of this application (51-60 percent much more harmful compared to not using any tobacco at all).¹³⁸

¹³³ *Id.* at 19.

¹³⁴ *Id.* at 21.

¹³⁵ *Id.* at 29.

¹³⁶ *Id.* at 30.

¹³⁷ *Id.* at 272.

¹³⁸ *Id.* at 273.

IOM notes that it would be informative for studies to investigate how perceptions are linked to product use by the consumer. However, we could not identify any reported analyses on the relation between risk perceptions and purchase consideration, making it difficult to assess the effects of these differences.

This is particularly important as it relates to young people. Perception of risk, while not the sole factor, is related to tobacco use among young people. Indeed, analysis of the Monitoring the Future survey of 8th, 10th and 12th grade students has shown perceived risk “to be an important determinant of trends for many forms of substance use, including cigarette use . . .”¹³⁹ Thus, changes in perceptions of risk could impact initiation and make tobacco users of those who otherwise would be tobacco-free.

In addition, we did not identify any analyses reporting the relation between believability and risk perception. Swedish Match interprets the lower risk perceptions attached to the modified warnings as a sign that the warning educated consumers about the lower risk of snus compared to cigarettes. However, it would be helpful to understand the relation between believability of the modified warnings and risk perception. If those who expressed belief in the warnings were also more likely to report less risk associated with snus, this would support that conclusion that the modified warnings enhanced understanding of the risks. However, if believability is unrelated to risk perception, then the educational value of the warnings is called into question.

Finally, the study cannot help us determine how consumers would evaluate snus if exposed to both of the proposed labels (the addiction label and the substantially lower risk label) together. While it is true that only one label will appear at a time, both labels would be present in the marketplace and either could appear on marketing or advertising material. Only exposing consumers to one warning is useful for isolating the effects of specific warnings, but it does not tell us how the warning system will work as a whole when all of the warnings are present.

6. Conclusion

The results of the study summarized above suggest that, within the limits of a single exposure to only one of the warnings, the modified warning would reduce risk perceptions for snus compared to current warnings, even though the modified warnings are consistently rated as less clear and less believable. However, the study report does not provide a clear picture of whether a sufficient number of current cigarette smokers would *completely* replace cigarette use with snus or whether current non-smokers, especially adolescents and young adults, would start using snus. Indeed, there were no data collected from adolescents, and there was some evidence that the modified warning would be less of a deterrent to purchasing snus among current non-users, including former smokers.

¹³⁹ University of Michigan, Monitoring the Future, “Teen smoking continues to decline in 2013,” Press Release, December 18, 2013, http://www.monitoringthefuture.org/pressreleases/13cigrp_complete.pdf.

Given the critical distinction between smokers who give up smoking entirely when they switch to Swedish snus and those who use both products concurrently, any modified risk claim should include language informing consumers that they will experience a health benefit from switching only if they abstain completely from smoking. FDA should not approve a modified risk claim that fails to make this point clearly.

It does not appear that Swedish Match ever tested a modified risk message that included such a distinction. Indeed, it does not appear that Swedish Match ever tested any modified risk message other than the change in the warning label proposed in its application and a version of that message with one word omitted. In considering a modified risk application, FDA should consider whether the totality of the claim and the warnings convey, as effectively as possible, a true description of the risks and benefits of using the product. FDA should not approve a modified risk claim that fails to meet this criterion. The absence of any reference in the Swedish Match application to the importance of abstaining from smoking in order to achieve a health benefit from switching to snus is a serious omission. Moreover, the Swedish Match application fails to convey with sufficient clarity the message that the claim made for this product could not be made for any other smokeless tobacco product.

CONCLUSION

The Swedish Match modified risk application should be denied as legally defective on its face. FDA should reject Swedish Match's effort to evade the congressionally mandated administrative procedure by which FDA may consider the relief that Swedish Match seeks, should not refer the application to the Tobacco Product Scientific Advisory Committee, and should not give it further consideration absent changes to bring it into compliance with the law.

Respectfully submitted,

Campaign for Tobacco-Free Kids

Tobacco Control Legal Consortium

EXHIBIT A.

**FDA Authority Under Section 911 of the Tobacco Control Act:
Revisions to Smokeless Warning Label Statements**

**FDA Authority Under Section 911 of the Tobacco Control Act:
Revisions to Smokeless Warning Label Statements**

Swedish Match North America Inc. (“SMNA”) intends to submit an application for a modified risk tobacco product (“MRTP”) under Section 911 of the Federal Food, Drug, and Cosmetic Act (“FDCA”), as amended by the Family Smoking Prevention and Tobacco Control Act (“Tobacco Control Act”). In advance of the submission, SMNA requested and held two meetings with representatives of the Center for Tobacco Products (“CTP”) regarding the form and content of the proposed MRTP application, including SMNA’s intention to seek a modified risk order permitting the use of labeling that would not carry, or that would otherwise amend, certain warning label statements currently mandated for smokeless tobacco products under Section 3 of the Comprehensive Smokeless Tobacco Health Education Act of 1986 (“CSTHEA”). In the second of the two meetings, representatives from the FDA’s Office of Chief Counsel requested that SMNA provide additional information regarding CTP’s authority to modify the currently-mandated smokeless tobacco product warning label statements pursuant to Section 911 of the FDCA. The requested information is set forth herein, and the key findings may be summarized as follows: (1) FDA has historically engaged in “claim-based” regulation, and possesses the authority to impose different label requirements on the same product depending on the claims made by the manufacturer; (2) the courts have confirmed that this claims-based method of regulation applies to tobacco as well, as “customarily marketed” tobacco products are subject to title IX of the FDCA, while tobacco products that are not “customarily marketed” may be subject to regulation under different titles of the FDCA (i.e., the drug/device provisions of title V); (3) consistent with this demarcation, “customarily marketed” smokeless tobacco products should be subject to CSTHEA, while smokeless tobacco products that qualify as modified risk tobacco products should not (as they are not “customarily marketed”); (4) failure to distinguish between “customarily marketed” smokeless tobacco products and modified risk smokeless tobacco products in this way will undermine Section 911 and render modified risk labeling incomprehensible and misbranded.

FDA Regulates Labeling Based on the Nature of the Claims Made for a Product, and May Impose Different Labeling Requirements for the Same Product Accordingly.

As reflected in the language of the FDCA, the Agency has long imposed distinct labeling requirements on articles subject to its jurisdiction based on the “intended use” of the product, as determined through a review of the claims the manufacturer seeks to make on the label and labeling. For example, an article may meet the definition of both “dietary supplement” and “drug” under the FDCA, but the article will only be subject to one set of labeling requirements depending on the intended use of the article.¹ Specifically, the label and labeling of an article marketed as a “dietary supplement” are subject to chapter IV (Food) of the FDCA, while the label and labeling of a “drug” are subject to chapter V (Drugs and Devices). Similarly, the FDCA makes clear that an article that meets the definition of “tobacco product” will not be subject to the provisions of chapter IX (Tobacco Products) if the article otherwise meets the statutory definition of “drug” or “device,” acknowledging that an article may indeed fall within more than one regulatory category under the FDCA, but should only be subject to regulation

¹ See FDCA § 201(g)(1) and (ff).

under one of those categories.² In describing this distinction, the U.S. Court of Appeals for the District of Columbia Circuit noted in *Sottera, Inc. v. FDA* that the FDCA, as amended by the Tobacco Control Act, establishes that the FDA “cannot regulate customarily marketed tobacco products under the FDCA’s drug/device provisions, that it can regulate tobacco products marketed for therapeutic purposes under those provisions, and that it can regulate customarily marketed tobacco products under the Tobacco Act.”³

Modified Risk Tobacco Products Are Not, By Definition, Customarily Marketed Tobacco Products. As acknowledged by the court in the *Sottera* decision, the labeling requirements applicable to a particular tobacco product depend in large part on whether the tobacco product is “customarily marketed.” Consistent with this principle, smokeless tobacco products that are “customarily marketed” should be, and are, required to carry the warning label statements mandated under Section 3 of CSTHEA. Further, any changes to these warning label statements accomplished pursuant to Section 3(d) of CSTHEA would, by law, apply to *all* customarily marketed smokeless tobacco products – CSTHEA would not permit the alteration of the warning label statements for a single product. This process is reflected in the Citizen Petition filed on July 28, 2011 by R.J. Reynolds Tobacco Company and American Snuff Company (the “RJR Petition”)⁴, which seeks an amendment to the warning label statements under Section 3(d) of CSTHEA applicable to *all* smokeless tobacco products, and is supported by scientific evidence drawn from research on several varieties of smokeless tobacco products. In contrast, a smokeless tobacco product that meets the definition of “modified risk tobacco product” is, by virtue of meeting that definition, not a “customarily marketed” smokeless tobacco and should not be treated as such with respect to the labeling requirements of CSTHEA. An FDA order issued under Section 911 of the FDCA would be limited to *that single tobacco product*, and would be based on scientific evidence drawn from research conducted by the applicant on *that single tobacco product*. More to the point, the labeling permitted by FDA under a modified risk order would be limited to *that single tobacco product*. It would be unnecessary, and indeed irrational, for an applicant under Section 911 to separately file a petition (along the lines of the RJR Petition) seeking a change to the CSTHEA warning label statements based on scientific evidence relevant to a single smokeless tobacco product, when the successful outcome of the petition would result in revisions to the warning label statements for *all* customarily marketed smokeless tobacco products.

Section 911 of the FDCA Provides FDA With Unfettered Authority to Direct the Scope and Content of Modified Risk Labeling. In its terms and intent, the FDCA provides FDA with the authority to control all aspects of the label and labeling for a modified risk tobacco product, obviating the need to independently impose historical – and potentially misleading – labeling obligations set forth in other Sections of the FDCA or CSTHEA. First, one of the Congressional findings supporting passage of the Tobacco Control Act emphasized FDA’s unsurpassed ability to “evaluate the scientific studies supporting the claims about the safety or products, and to evaluate the impact of labels, labeling, and advertising on consumer behavior in order to reduce the risk of harm and promote understanding of the impact of the product on

² See *id.* at § 201(rr).

³ *Sottera, Inc. v. FDA*, (D.C. Cir. 2010)

⁴ Docket No. FDA-2011-P-0573

health.”⁵ Consistent with that finding, one of the enumerated purposes of the Tobacco Control Act is to provide FDA with “new and flexible enforcement authority to ensure that there is effective oversight of the tobacco industry’s efforts to develop, introduce, and promote less harmful tobacco products.”⁶ Such flexibility flows, in part, from the fact that the Tobacco Control Act revised CSTHEA to explicitly confirm that the latter statute is preempted by the former, thus manifesting Congress’ intent that the provisions of the Tobacco Control Act, including Section 911, will supersede any conflicting or inconsistent requirements imposed under CSTHEA.⁷ In Section 911 itself, FDA must ensure that “any advertising and labeling concerning modified risk tobacco products enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation to all of the diseases and health-related conditions associated with the use of tobacco products.”⁸ Further, FDA is empowered to impose other label and advertising disclosures on a modified risk tobacco product, whether or not those disclosures are first proposed by the applicant.⁹ Finally, Section 911 makes clear that modified risk products subject to an order under that section will not be subject to the FDCA titles that govern foods, drugs, and devices, and, as such, will not be required to carry the labeling that may otherwise have been required under those titles in the statute.¹⁰ In sum, accounting for the purpose of the Tobacco Control Act, its express preemption over CSTHEA, and the extensive labeling provisions set forth in Section 911 itself, it would be nonsensical (and contrary to Congressional intent) to require products subject to a modified risk order under Section 911 to also carry the label warnings mandated by CSTHEA.

Imposition of CSTHEA Requirements on Modified Risk Tobacco Products Would Potentially Render Some or All of Those Products Misbranded Under the FDCA. As noted above, Section 911 obligates FDA to ensure that the general public is able to comprehend the modified risk information set forth on the label and labeling of a modified risk tobacco product. Further, a tobacco product shall be deemed misbranded, and thus unlawful, if its labeling or advertising is false or misleading in any particular.¹¹ If FDA is unable to regulate the label and labeling of modified risk tobacco products exclusively under Section 911, it is inevitable that the public may be confused and misled by the application of the CSTHEA warning statements on modified risk labeling. For instance, Section 911 contemplates that a modified risk tobacco product may carry labeling stating that the tobacco product “presents a lower risk of tobacco-related disease or is less harmful than one or more other commercially marketed tobacco products.”¹² A manufacturer of a smokeless tobacco product may therefore seek a modified risk order, supported by scientific evidence, permitting it to claim that the

⁵ Tobacco Control Act § 2(44).

⁶ *Id.* at § 3(4).

⁷ *Id.* at § 205(b) (amending Section 7(a) of CSTHEA).

⁸ FDCA § 911(h)(1).

⁹ *See id.* at § 911(h)(3)(A); 911(h)(5).

¹⁰ *See id.* at § 911(k).

¹¹ *See id.* at § 903(a)(1); 903(a)(7)(A).

¹² *Id.* at § 911(b)(2)(A)(i)(I).

tobacco product presents lower risks to health than cigarettes (a commercially marketed tobacco product). However, if FDA were to issue the requested order in accordance with the criteria set forth in Section 911(g)(1), but the applicant were to remain obligated to comply with Section 3 of CSTHEA, the label would also carry the statement “WARNING: This product is not a safe alternative to cigarettes.” Such a label would contain health-related statements that directly contradict one another, and would therefore be incomprehensible to the public. Moreover, as FDA may only issue an order under Section 911 if the applicant has “demonstrated that such [modified risk] tobacco product, as it is actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users,”¹³ the warning label statement cited above would be false (and misleading) as applied to that particular tobacco product. For that reason, and to preserve the flexibility afforded by Congress to FDA in reviewing and approving less harmful tobacco products, FDA must conclude that a tobacco product subject to a modified risk order is not subject to CSTHEA, much as it would not be subject to the labeling requirements set forth in titles IV and V of the FDCA.

Even if FDA Does Not Believe It Possesses the Legal Authority to Amend CSTHEA Statements Under Section 911, It Possesses the Discretionary Authority to do so. In *Heckler v. Chaney*, the Supreme Court held that an agency’s decision not to take prosecutorial or enforcement action “is a decision generally committed to an agency’s absolute discretion,” unless Congress “has indicated an intent to circumscribe agency enforcement discretion, and has provided meaningful standards for defining the limits of that discretion.”¹⁴ Applying this principle, the Court found that the enforcement provisions of the FDCA do not restrict FDA’s discretion to enforce the requirements of the Act, explaining that though “[t]he section on criminal sanctions states baldly that any person who violates the Act’s substantive prohibitions ‘shall be imprisoned . . . or fined,’” there is no indication “that this statement mandates criminal prosecution of every violator of the Act,” particularly given that such language is “commonly found in the criminal provisions of Title 18 of the United States Code.”¹⁵ The enforcement provision of the CSTHEA is analogous to the FDCA criminal sanctions provision at issue in *Chaney*. Section 5 of the CSTHEA states that “Any person who is found to violate any provision of section 3 or 4(a) shall be guilty of a misdemeanor and shall on conviction thereof be subject to a fine of not more than \$10,000.” Like the FDCA, the CSTHEA provides only that a violator “shall be” punished in the manner described; thus like the FDCA, the CSTHEA does not circumscribe FDA’s authority to exercise discretion in enforcing the requirements established by the Act. It is therefore well within FDA’s decision-making authority not to enforce elements of the CSTHEA, including the labeling requirements established under Section 3(a)(1). FDA has in fact already exercised its discretion not to enforce one of the CSTHEA’s provisions. In a guidance posted in the Federal Register on June 8, 2010, FDA wrote that “At this time, as an exercise of enforcement discretion, FDA does not intend to commence or recommend enforcement of the requirement that a smokeless tobacco manufacturer, distributor, importer, or

¹³ *Id.* at § 911(g)(1)(A).

¹⁴ *Heckler v. Chaney*, 470 U.S. 821, 831, 834 (1985).

¹⁵ *Id.* at 835.

retailer must have an FDA-approved rotational warning plan,” as required by § 3(b)(3) of the CSTHEA.¹⁶

* * * *

As documented above, law, policy, and practical considerations compel the conclusion that FDA must regulate the labeling of modified risk tobacco products exclusively under Section 911 of the FDCA, and, consistent with that conclusion, FDA may impose reasonable and accurate warning label statements on a modified risk smokeless tobacco products pursuant to its authority under Section 911. Stated differently, FDA has the authority to, pursuant to a modified risk order issued under Section 911, allow a manufacturer of a smokeless tobacco product to deviate from the requirements of Section 3 of CSTHEA.

¹⁶ 75 Fed. Reg. 32,481, 32,482 (June 8, 2010).

EXHIBIT B.

Establishing product standards for smokeless tobacco

Establishing product standards for smokeless tobacco

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February 2014

INTRODUCTION

The Family Smoking Prevention and Tobacco Control (FSPTC) Act (the Act), which was signed into law in June of 2009, amended the Food Drug and Cosmetic Act to give FDA authority to establish product standards for tobacco products, including cigarettes and smokeless tobacco. Section 907 of the Act authorizes the FDA to establish product standards that “shall include provisions that are appropriate for the protection of the public health.” Such product standards may include “provisions, where appropriate...for the reduction or elimination of [] constituents, including smoke constituents, or harmful components of the product.” (Sec. 907(a)(4)(A)(ii), 21 USC 387g(a)(4)(A)(ii)).

The Act also directed FDA to establish a list of harmful and potentially harmful constituents (“HPHC”) in tobacco products. Pursuant to this authority, FDA promulgated a list of harmful and potentially harmful constituents in cigarettes and smokeless tobacco products.¹ Among the designated HPHC in smokeless tobacco products were the tobacco specific nitrosamines (TSNA), *N'*-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), and polycyclic aromatic hydrocarbons (PAH) such as benzo[*a*]pyrene (BaP). This memorandum proposes that FDA issue a product standard establishing maximum permissible levels of NNN and NNK in smokeless tobacco products and consider standards for other HPHCs because the issuance of such standards would be appropriate for the protection of the public health. Reducing harmful contaminants such as TSNA and PAH in non-combusted tobacco products is both technologically achievable and likely to benefit public health. These constituents are carcinogens that are likely the most harmful constituents in the product.

Human epidemiological studies have demonstrated a dose-response association between TSNA and PAH intake, as assessed by corresponding biomarker levels, and increased risk for lung and esophageal cancer among smokers; this dose-response relationship is likely to be generalizable to smokeless tobacco users. Countries in which smokeless tobacco products containing high levels of TSNA and other HPHC are marketed experience higher rates of oral tobacco-related morbidity and mortality than countries with lower levels of these carcinogens in tobacco products.² The level of these harmful constituents in oral tobacco products sold in the United States (and worldwide) varies substantially and may not even be consistent in different samples of the same brands.^{3,4} Many of the most popular US smokeless tobacco products contain high levels of these constituents. Consumers who use these products are thereby exposed to unnecessarily high levels of these constituents and therefore are placed at higher risk of tobacco-related disease. Variations in constituent levels are due to growing and manufacturing processes that are easily correctable. This fact is demonstrated by the presence of brands in the US and foreign markets with far lower levels. In view of the dangers to health posed by TSNA and PAH in smokeless tobacco products and the existence of feasible methods for reduction in TSNA and PAH levels, FDA should establish product standards for smokeless tobacco products that incorporate a maximum level of such constituents. The following provides the scientific evidence to support such standards.

OVERVIEW OF MAJOR CARCINOGENS AND TOXICANTS IN SMOKELESS TOBACCO PRODUCTS

Smokeless tobacco is associated with a range of adverse health effects and is classified by the International Agency for Research on Cancer (IARC) as carcinogenic to humans (Group 1).⁵ Tobacco is chemically complex and contains thousands of chemical substances.⁶ These include many toxicants and more than 30 potential or known carcinogens which are believed to be responsible for the carcinogenic effects associated with the use of smokeless tobacco.^{5,7-9} NNN and NNK are likely causative agents for cancers of the oral cavity, esophagus, and pancreas in smokeless tobacco users, and are classified as human carcinogens by the International Agency for Research on Cancer (IARC).¹⁰⁻¹² Because of their high carcinogenic potency in combination with the abundance in, and specificity to, tobacco products, NNN and NNK are widely accepted as central to the carcinogenicity of smokeless tobacco.⁵ NNN and NNK were the first tobacco constituents targeted for regulation by the WHO Framework Convention on Tobacco Control.¹³ PAH, metals, and volatile organic compounds are among other important carcinogens and toxicants present in smokeless tobacco products. Many PAH are potent carcinogens or toxicants in laboratory animals,¹⁴ and BaP – the prototypic PAH – is classified as a human carcinogen by IARC.^{14,15} The metals arsenic, nickel, beryllium, cadmium, and chromium are human carcinogens¹⁶ and are present in varying amounts in smokeless tobacco,¹⁷ depending on the composition and industrial contamination of the soil in which tobacco is grown.^{18,19} Certain volatile organic compounds can be introduced as contaminants during tobacco processing: varying amounts of formaldehyde, acetaldehyde, acrolein and crotonaldehyde have been measured in different smokeless tobacco products.^{7,8}

Among the carcinogenic and toxic constituents present in smokeless tobacco products, TSNA and PAH are perfectly positioned as targets for the immediate development and implementation of regulatory measures. First of all, TSNA and some PAH are potent carcinogens. TSNA targets organs that are most strongly associated with smokeless tobacco carcinogenesis, such as oral cavity, esophagus and pancreas,^{5,10} while PAH act as topical carcinogens and induce tumors at the point of contact.¹⁴ Second, as described below, the factors that contribute to TSNA and PAH formation in tobacco products are well understood. These factors are modifiable, and the extremely low levels of TSNA and PAH in some smokeless tobacco products, including some brands produced by the major US tobacco manufacturers, demonstrate that the technology is readily available to reduce TSNA and PAH levels in all smokeless tobacco products. Despite this knowledge and available technologies, the majority of smokeless tobacco products on the US market contain unjustifiably high amounts of TSNA and are contaminated with unjustifiably high levels of PAH.^{8,20} It is evident that the issuance of a product standard establishing maximum levels for these constituents in smokeless tobacco is necessary to protect the public health.

TOBACCO-SPECIFIC *N*-NITROSAMINES (TSNA)

Smokeless tobacco users are exposed to TSNA at levels that are 100-1,000-fold higher than those from other major sources of nitrosamines consumed by humans, such as cured meat and beer.²¹ TSNA are virtually absent in green tobacco plant and are formed from tobacco-specific alkaloids during curing and processing.^{22,23} TSNA are found only in tobacco products.^{5,10}

Particular attention is being paid to TSNA because of the compelling evidence of their contribution to tobacco-related carcinogenesis and the human data available on these constituents.

Factors contributing to TSNA formation in tobacco

Factors that determine the yields of TSNA in processed tobacco have been extensively studied and are well understood. These factors include tobacco type, its nitrate and nitrite content, cultivation and harvesting practices, processing techniques, and storage conditions.^{5,24-}

²⁹ Practical methods exist to produce smokeless tobacco products with far lower TSNA content than that in most smokeless tobacco products in the United States.

Factors that can influence the level of TSNA in tobacco are outlined below.

Tobacco type and nitrate content. It has been shown that TSNA levels are higher in Burley than in Bright tobacco, regardless of the curing method.^{26,30,31} Overall, the effectiveness of nicotine conversion to nornicotine, nitrate content, as well as the ability to lose water rapidly (thus limiting the formation of nitrite from nitrate) are among the main characteristics affecting the formation of TSNA in a particular tobacco variety.^{30,32} It has also been shown that higher

levels of nicotine and other alkaloids in tobacco may lead to the formation of high amount of TSNA during processing; for instance high levels of tobacco alkaloids in the species *Nicotiana Rustica* are believed to contribute to the extremely high levels of TSNA in Sudanese toombak.³³⁻

³⁵ Based on such findings agricultural practices that increase nitrate and alkaloid concentrations in the tobacco leaves favor TSNA formation.⁵ However, TSNA levels in tobacco leaf correlate more strongly with nitrite than with alkaloid content.³⁶

Cultivation, harvesting, and processing techniques. During cultivation, tobacco leaf becomes contaminated with soil bacteria and agricultural chemicals which become part of the subsequent transformations taking place during tobacco processing. For instance, bacteria which actively proliferate on tobacco leaves during the curing process³⁷ convert nitrate to nitrite which in turn can react with tobacco alkaloids to form TSNA. It has been shown that such measures as cleaning fermentation equipment prior to use and “seeding” the fermentation process with bacteria not capable of converting nitrate to nitrite can prevent increases in nitrite levels and substantially reduce TSNA levels in tobacco.³⁸

Tobacco curing techniques also significantly affect TSNA yields in the final product. There are four major types of tobacco curing: sun-curing, air-curing, flue-curing, and fire-curing. Sun- and air-curing occur naturally, by placing harvested tobacco leaves uncovered under the sun or in well-ventilated barns, respectively. Flue-curing and fire-curing take place in enclosed barns where tobacco is exposed to heat from an external source or directly to smoke from burning hardwood, respectively.⁵ Curing of tobacco leads to disruption of the plant cell membranes; this process exposes cell contents to microorganisms that produce nitrite that can further react with alkaloids to form TSNA.³⁹ It is likely that during flue- and fire-curing, additional amounts of TSNA are formed from the reaction of tobacco alkaloids with combustion gases such as nitrogen oxides.⁵ For instance, flue-curing of Bright tobacco produces a three-fold increase in TSNA yield as compared to air-curing of the same tobacco.⁵ Furthermore, TSNA concentrations increase as temperature increases during flue-curing.⁴⁰

Removal of heating with propane as part of the curing process has been shown to lead to substantial reductions in TSNA yields.^{28,41}

Relative humidity is another important factor that contributes to the formation of TSNA in tobacco during its processing.^{5,39} For instance, high continuous relative humidity during the entire curing process produces higher TSNA levels than in drier conditions.³⁹ A suggested approach to reduce nitrite and TSNA levels in tobacco would be to apply a well-controlled uniform air-flow during tobacco curing. This approach increases the rate and amount of moisture loss from the tobacco, and also reduces possible gas-phase reactions between alkaloids and gaseous nitric oxides.^{5,39}

Pasteurization of tobacco can remove bacteria that are capable of converting nitrate to nitrite and therefore is an effective approach to prevent the formation of high TSNA yields.⁴² Such pasteurization of air-cured tobacco is used in the manufacturing of Swedish snus, and presumably in the U.S. in manufacturing of relatively newer products that are also called snus and in dissolvable tobacco. It was shown that both Swedish and US snus products contain much lower levels of nitrite and TSNA than traditional US moist snuff made with fermented fire-cured tobacco.⁸

Storage conditions. Prolonged storage of processed tobacco can lead to further accumulation of TSNA, particularly at elevated temperatures and humidity.^{29,39} Furthermore, prolonged storage at ambient room temperature of manufactured smokeless tobacco products can also lead to the formation of additional amounts of TSNA.⁴³ This is because all the agents

necessary for the formation of TSNA – nitrate, nitrite, bacteria, and tobacco alkaloids – are present in smokeless tobacco products that are distributed to consumers. It should be noted that levels of nitrite and TSNA do not increase during long-term storage of Swedish snus.⁴⁴

In summary, there is large body of data on the mechanism of TSNA formation in tobacco and on factors that modify TSNA yields. Research conducted by both independent academic researchers and the tobacco industry laboratories clearly demonstrates that the levels of TSNA in smokeless tobacco products can be effectively controlled by judicious selection of tobacco types and careful management of tobacco processing and storage procedures. This conclusion is further supported by the evidence of the large variation of TSNA levels across various smokeless tobacco products, both internationally and within the US, as described in the following sections. Thus, if FDA established a product standard for TSNA, manufacturers of smokeless tobacco products would be able to meet it.

Global diversity of TSNA levels in smokeless tobacco products

The levels of TSNA vary dramatically – by several orders of magnitude – among products sold in different parts of the world, reflecting geographic differences in the use of different tobacco types, processing techniques, and product formulations.^{4,5,20,35,45-47} For instance, the highest levels of TSNA ever measured in a tobacco product have been reported for Sudanese toombak; the concentration of NNN in some samples of this product was as high as 3,080 µg/g, and NNK content as high as 7,870 µg/g tobacco dry weight.^{34,35,48} On the other hand, the sum of NNN and NNK levels in Swedish and US snus are around or below 1 µg/g tobacco dry weight.^{4,8,49} A wide range of TSNA levels was reported for products marketed in India: NNN

ranged from 0.09µg/g to 76.9 µg/g, and NNK ranged from 0.09µg/g to 28.4 µg/g, in tobacco-containing products.⁴⁶ This extensive range is due to the striking variety of smokeless tobacco formulations available in India.⁵⁰

There are well recognized differences in the adverse health outcomes resulting from use of products that differ in TSNA content.⁵ Smokeless products used in India and Sudan, as well as snuff that was produced in the US in the past, have been strongly associated with the risk of head and neck cancer.^{5,48,51} However, lower risks have been found in more recent studies in the U.S. and very limited evidence of oral cancer risk exists for the use of Swedish snus^{5,52,53} (see below for more detailed information).

TSNA levels in US products

There is a wide variation in TSNA levels among various smokeless tobacco products on US market. These variations are observed among various brands, with the same manufacturers producing both high- and low-TSNA products,^{8,20} as well as within the same brand when products are purchased in different locations⁴ or at different times.⁵⁴ These observations suggest that in the absence of established standards for NNN and NNK content, the levels of these carcinogens will continue to vary significantly in US smokeless tobacco products and that US consumers of smokeless tobacco products will continue to be exposed to highly variable levels of TSNAs.

Variation in TSNA levels across various US-manufactured smokeless brands. A recent survey of seven types of smokeless tobacco products which did not include moist snuff, the most

popular and most studied US smokeless tobacco product type, reported a more than 400-fold range of NNN levels in the tested products: from 0.07 µg/g in novel dissolvable tobacco products to 31.3 µg/g in a dental dry snuff.⁵⁵ Levels of NNK in that study also ranged widely, from 0.05 µg/g to 14.6 µg/g in the same products. An earlier survey that was focused on moist snuff alone, showed an 18-fold variation in TSNA content among 39 top-selling brands, with the levels of NNN ranging from 2.2 to 42.6 µg/g and levels of NNK ranging from 0.38 to 9.9 µg/g product.²⁰

The low levels of TSNA in the new oral “spit-free” and dissolvable smokeless tobacco products have been also demonstrated in a study which analyzed 117 samples of these products.⁴ In that study, NNN ranged from 0.09 µg/g in dissolvable pellets Ariva to 0.62 µg/g in Camel Snus, and NNK ranged from 0.06 µg/g in dissolvable pellets Stonewall to 0.31 µg/g in Camel Snus and dissolvable Camel Sticks. Thus, considerable variation of TSNA levels has been observed even in this low-TSNA category.

As can be seen from the wide range of TSNA levels across US smokeless product and the relatively low levels in some newer products, technologies to reduce TSNA levels in tobacco products not only exist, but also are utilized by the US manufacturers. Similar technologies can be applied in the manufacture of all U.S. smokeless tobacco brands.

Variations in TSNA levels are observed for different products that are manufactured by the same company. Certain variability of constituent levels in smokeless tobacco brands produced by different manufacturers can be expected due to potential differences in the

sources of product ingredients and other materials and potential discrepancies in technologies that are available to a given company for product manufacturing. Therefore, comparison of various brands produced by the same manufacturer can provide insights into the TSNA levels that are already being achieved by a given company and how TSNA levels in various brands compare to this achievable minimum. In our laboratory, we routinely analyze tobacco products for various chemical constituents, including TSNA. We have examined multiple samples of a few smokeless products, all produced by the same company and purchased and analyzed in our laboratory in the same year. Such examination was performed for the products purchased in 2010 and 2011. The analyses have been carried out by the validated method routinely applied in our laboratory.^{4,8,56} Brand differences in TSNA levels are evident from the results summarized in Figure 1 (results from 2010) and Figure 2 (results from 2011). For both manufacturers, conventional moist snuff brands that hold the majority of the U.S. smokeless tobacco market share contain much higher levels of NNN and NNK than newer products, such as snus and dissolvable tobacco. The reasons for these differences have been discussed earlier in this paper. Altogether, data presented in Figures 1 and 2 demonstrate that each of the examined manufacturers possesses technologies to reduce the highest TSNA levels found in their analyzed products by 6-fold to 30-fold.

In addition to brand differences within the same manufacturer, variations in NNN and NNK levels among different styles within the same brand are also commonly found. For instance, analysis of 40 top-selling varieties of moist snuff purchased in 2004 showed that NNN and NNK content in different styles of Skoal brand varied roughly 10-fold: NNN ranged from 4.5

to 42.5µg/g product, and NNK from 0.75 to 9.9 µg/g product.²⁰ Significant variation within brands is also seen from our recent analyses (Figures 1-2). Furthermore, as was shown in a study of a few popular moist snuff brands purchased in 1994, differences in NNN and NNK content can be found even within specific product variety, when samples are purchased in different locations (Table 1).³ In our recent studies on newer smokeless products, we also observed variations in NNN and NNK levels in samples of Camel Snus and Marlboro Snus purchased in different U.S. regions.⁴

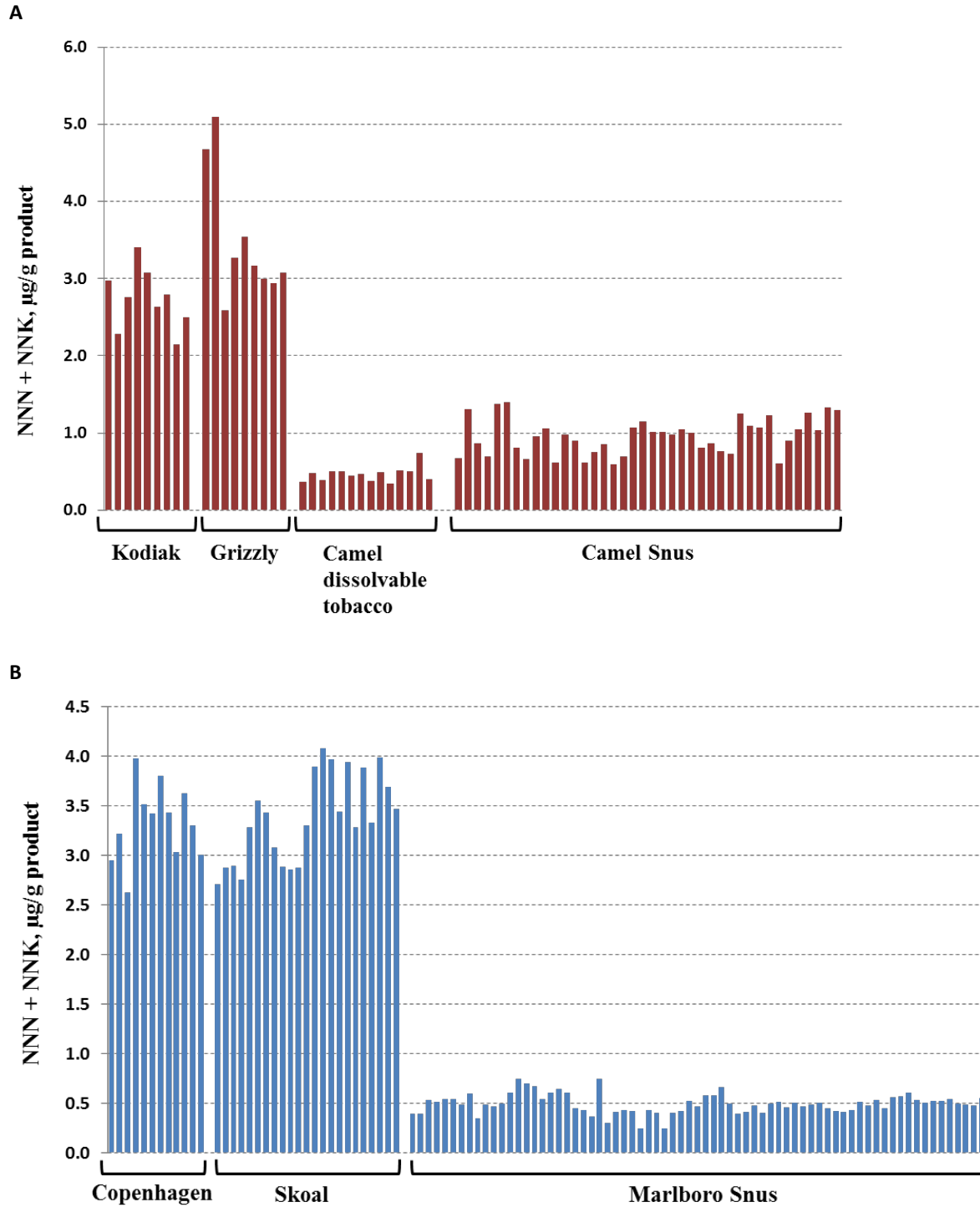


Figure 1. Sum of NNN and NNK measured in 2010 in selected brands manufactured by (A) RJ Reynolds and (B) Altria. Each bar represents individual sample. Each brand combines various styles and flavors. Results for novel products (dissolvable tobacco and snus) have been previously published⁴; data for conventional products are new.

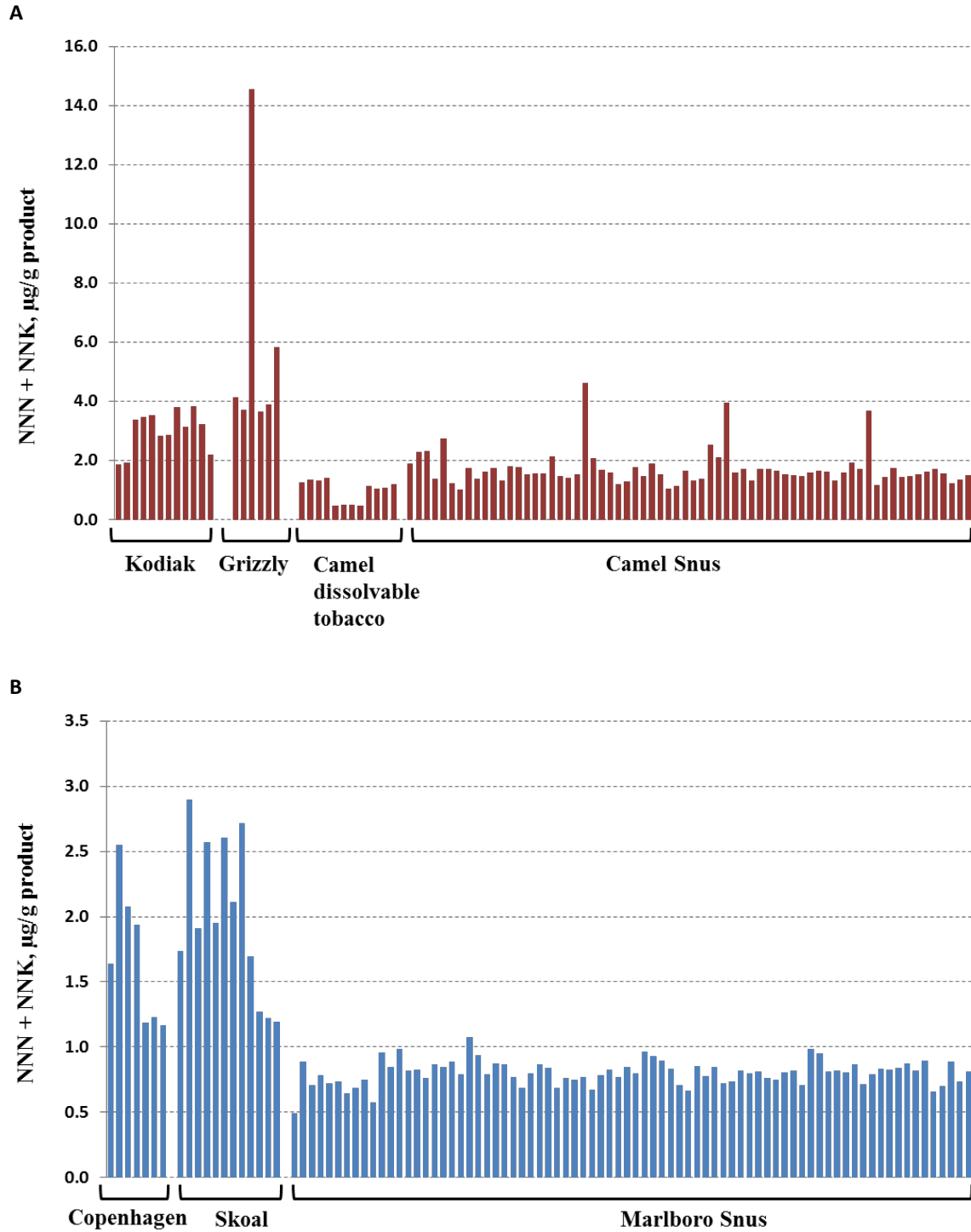


Figure 2. Sum of NNN and NNK measured in 2011 in selected brands manufactured by (A) RJ Reynolds and (B) Altria. Each bar represents individual sample. Each brand combines various styles and flavors. Results for newer products (dissolvable tobacco and snus) are published⁵⁶ data for conventional products are new.

Table 1. NNN and NNK in samples of U.S. moist snuff brands purchased in different locations ^a

Snuff brand	TSNA	Locations					
		1	2	3	4	5	6
Copenhagen	NNN	7.93	7.86	10.78	9.60	9.72	6.47
	NNK	1.45	1.55	3.20	1.46	2.05	1.61
Skoal Fine Cut Wintergreen	NNN	6.05	7.07	10.21	8.34	8.94	8.48
	NNK	1.21	1.09	1.47	1.11	1.29	1.31
Kodiak Wintergreen	NNN	6.27	5.84	4.63	5.99	7.03	8.05
	NNK	0.84	0.37	0.53	0.49	0.42	0.62
Skoal Bandits Straight	NNN	6.33	5.29	5.15	5.77	5.02	3.00
	NNK	0.83	0.81	0.93	1.43	0.95	0.53

^a Levels are in $\mu\text{g/g}$ dry weight; modified from³.

Temporal variation in US products. TSNA levels had declined in some U.S. smokeless tobacco products between 1980s and early 1990s.⁵⁷ A recent report analyzing available data on 3 unidentified brands asserted that TSNA levels continued to decline in U.S. smokeless tobacco products between 1997 and 2005.³⁸ Our independent analysis did not support the conclusion of the latter study. We analyzed literature published after 1992, and identified specific smokeless brands for which TSNA levels have been reported repeatedly in different years. Table 2 summarizes our findings combined with the data from our laboratory for the same products.

Table 2. NNN and NNK levels in selected brands between 1994 and 2011.

Brand	Year ^a	TSNA, µg/g dry weight ^b	
		NNN	NNK
Copenhagen	1994	8.73	1.89
	2004	8.41	2.03
	2006-2007	4.75	1.28
	2010-2011	5.77	1.69
Skoal Original Fine Cut Wintergreen	1994	8.18	1.25
	2004	18.02	4.36
	2006-2007	4.69	1.24
	2010-2011	3.32	1.05
Kodiak Wintergreen	1994	6.30	0.55
	2004	14.57	3.67
	2006-2007	4.76	1.18
	2010-2011	4.86	0.92
Hawken Wintergreen	1994	3.07	0.23
	2004	4.41	1.04
	2006-2007	2.85	0.90
	2010-2011	3.09	0.84

^a Sources of data: 1994³, 2004²⁰, 2006-2007⁵⁸, 2010-2011 (unpublished data from our laboratory).

^b Dry weight data for 2004 were calculated from the reported wet weight data and moisture content for corresponding brands²⁰

As can be seen from the data presented in Table 2, changes in NNN and NNK levels in these popular brands represent *variation* rather than *continuous decline*. While NNN levels for 3 out of 4 products are lower in the 2010-2011 sample as compared to 1994, the levels of NNK are generally not changed, or even increased in some products. Furthermore, high NNN and NNK levels in Skoal and Kodiak products analyzed in 2004 suggest that, in the absence of established standards for these carcinogens, a highly contaminated batch can appear on the market at any time.

Another important observation, which was made in our laboratory, is that TSNA levels in newer products, such as snus and dissolvable tobacco, have increased in recent years. Comparison of data obtained for Camel and Marlboro smokeless products between 2010 and 2011 showed an increase of NNN and NNK levels for most of products, except for Camel Sticks (Figure 3). This increase is most likely due to changes in the composition or processing of tobacco used in the manufacturing of these products. Importantly, the sum of NNN and NNK in the most recent addition to the this market – Marlboro Sticks and Skoal Sticks, which were not available in 2010 – is around 3 µg/g product; this is comparable to the amounts found in conventional moist snuff (Figures 1-2). Our most recent analyses (unpublished data) show that most recent versions of these products continue to contain TSNA at levels found in 2011. These findings once again indicate that establishing standards for NNN and NNK levels in smokeless products is needed in order to prevent such unnecessary variations in the levels of these carcinogens in products on U.S. market.

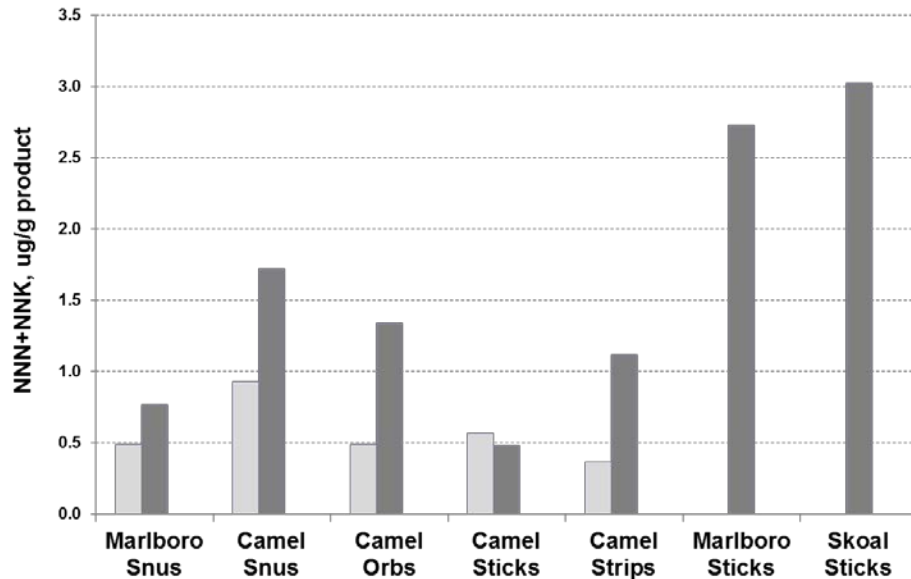


Figure 3. Sum of NNN and NNK in Marlboro and Camel novel smokeless tobacco products purchased and analyzed in: 2010⁴ and 2011⁵⁶.

TSNA reduction in smokeless tobacco products can be readily achieved

Smokeless tobacco products with high levels of TSNA are likely to present a higher risk of cancer to their users (see below for more details). Despite this fact, however, although practical methods exist to limit the levels of TSNA to very low quantities, smokeless tobacco products with far higher levels of TSNA continue to be sold in the United States. Establishment of a product standard setting maximum levels of TSNA is therefore necessary to protect the public health. The presented overview of TSNA formation in tobacco can be summarized in the following statements: (1) nitrosamine formation can be readily controlled during tobacco processing and product manufacturing; (2) there is a wide range of TSNA levels across products worldwide, with higher contaminated products being clearly associated with higher risk of cancer; (3) there are products on U.S. market, including those produced by the major U.S.

tobacco manufacturers, that contain very low TSNA levels; these data indicate that technologies are available for the manufacturing of low-TSNA products. Given the available data on TSNA carcinogenicity and the available technology to reduce levels of these carcinogens in processed tobacco, allowing manufacture of products with high TSNA levels is unacceptable.

POLYCYCLIC AROMATIC HYDROCARBONS

PAH include an extensive range of chemicals with a wide spectrum of toxicity and always occur as mixtures. At least 23 different PAH have been detected in smokeless tobacco products.^{8,15} Of these, ten PAH have been classified by IARC as established, probable, or possible human carcinogens: benzo[*a*]pyrene; dibenz[*a,h*]anthracene; benzo[*b*]fluoranthene, benzo[*j*]fluoranthene, benzo[*k*]fluoranthene, dibenzo[*a,i*]pyrene, indeno[1,2,3-*cd*]pyrene, 5-methylchrysene, naphthalene, and benz[*a*]anthracene.¹⁴ Furthermore, even though human toxicity data for other PAH found in smokeless products, such as acenaphthylene, phenanthrene, anthracene, fluoranthene, and pyrene, are not available, animal studies suggest a range of negative effects, including pulmonary, endocrine, and liver toxicity, as well as co-carcinogenicity.⁵⁹

PAH are formed during incomplete combustion of organic matter and only traces of PAH can be found in raw tobacco leaf, with air pollution being the potential source. Therefore, PAH levels in smokeless tobacco products, which are used without combustion, are directly influenced by the tobacco processing and manufacturing technologies. Indeed, products made with air-cured or pasteurized tobaccos contain very low, or even undetectable, levels of PAH; in contrast, the levels of PAH are high in products made with tobacco that is fire-cured – a process

that directly exposes tobacco to the smoke generated by burning hardwoods. For instance, the levels BaP vary from non-detectable in Swedish snus and some newer US smokeless products, to 102 ng/g dry weight in the U.S. moist snuff.⁸ Table 5 illustrates the variability in levels of PAH in smokeless tobacco products marketed in the U.S. It is clear that amounts of PAH can be reduced achieved by eliminating or reducing the use of fire-cured tobaccos.

Table 5. Levels of polycyclic aromatic hydrocarbons in some U.S. smokeless tobacco products^a

Sample content	PAH ^b , ng / g dry weight									
	Phenanthrene	Anthracene	Fluoranthene	Pyrene	BaA	BbF+BjF	BkF	BeP	BaP	Total PAH
Traditional moist Snuff										
Skoal Long Cut Straight	4250	712	1180	1020	149	76	15	45	53	10900
Copenhagen Snuff	4960	784	1650	1420	220	278	26	102	60	12700
Kodiak Wintergreen	8660	1440	2540	2250	328	139	37	89	86	20200
Grizzly Snuff	4230	835	975	1090	154	61	16	35	40	10100
Kayak Long Cut Straight	4170	651	989	1070	139	48	11	31	30	10200
Timber Wolf Fine Cut Natural	5970	1100	1940	1640	244	127	22	60	70	14600
Red Seal Natural	5670	976	1800	1580	229	105	21	49	69	13900
Longhorn Long Cut Wintergreen	3890	935	1000	1140	188	70	17	40	45	8670
Hawken Long Cut Wintergreen	58	8.6	45	46	5.3	7.4	LOQ ^c	LOQ	13	1250
Novel spit-free tobacco pouches										
Marlboro Snus Rich	13.5	LOQ	9.0	9.0	1.7	LOQ	LOQ	LOQ	LOQ	901.0
Marlboro Snus Peppermint	9.4	LOQ	5.6	6.0	1.1	LOQ	LOD ^d	LOQ	LOQ	1257
Camel Snus Original	68.0	6.9	60.1	46.5	5.9	38.8	3.1	23.2	15.2	1428
Camel Snus Frost	68.7	6.9	60.5	46.3	5.4	31.5	3.1	21.5	14.9	1363

^a Adopted from Stepanov et al.¹⁵

^b Abbreviations: BaA, benz[*a*]anthracene; BbF, benzo[*b*]fluoranthene; BjF, benzo[*j*]fluoranthene; BkF, benzo[*k*]fluoranthene; BeP, benzo[*e*]pyrene; BaP, benzo[*a*]pyrene; total PAH, sum of 23 PAH measured in the study¹⁵.

^c LOQ – detected, but below the limit of quantitation

^d LOD – below the limit of detection (signal to noise ratio is less than 3 for quantitation ion).

HUMAN EFFECTS: EVIDENCE TO SUPPORT THE REDUCTION OF TSNA AND OTHER

CONSTITUENTS

Limited human studies exist on the effects of reducing specific harmful and potentially harmful constituents in smokeless tobacco products. Most of the studies to date have been focused on TSNA and specifically on NNK. The available evidence suggests that reducing TSNA in smokeless tobacco products would benefit the public health.

Biomarkers of exposure

Few studies have examined the differences in exposures from various brands of smokeless tobacco products and the effects from switching from a brand with high TSNA to a brand with lower TSNA levels. The existing studies have focused on biomarkers for NNK. NNK is metabolized to 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) that undergoes glucuronidation resulting in [4(methylnitrosamine)-1-(3-pyridyl)-but-1-yl]- β -O-D-glucosiduronic acid (NNAL-gluc). These two urinary metabolites of NNK (total NNAL) are accepted biomarkers of NNK uptake.⁶⁰ In one cross-sectional comparison of tobacco users who used or were asked to use different brands of smokeless tobacco, total NNAL levels were generally related to the levels of TSNA found in the product (see Figure 4). Although there are many limitations to the data presented in this figure (e.g., small sample size, participants from various studies with different goals, etc.), the figure illustrates that the measured level of NNAL is directly dependent on the level of NNK in the product a consumer uses.

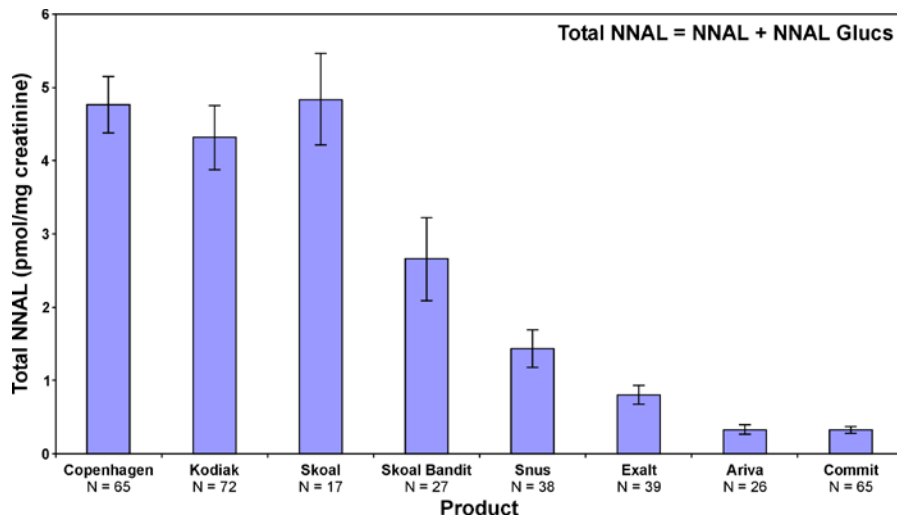


Figure 4. Total NNAL concentrations in urine: users of different brands of non-combusted oral tobacco products. Reproduced from Hatsukami et al.⁶¹

Ultimately, if product standards that reduce harmful constituent levels in smokeless tobacco products are imposed, there would be a significant reduction in uptake of the targeted toxicants, such as NNK. In a smokeless tobacco switching study, smokeless tobacco users using conventional U.S. brands of smokeless tobacco were switched to General Snus (contained in 1 gram pouches), a Swedish Match tobacco product that has lower TSNA levels than U.S. conventional smokeless tobacco brands, or to nicotine patch for four weeks.⁶² Figure 5 shows the results from this study. Smokeless tobacco users experienced a significant and substantial reduction in total NNAL levels when switched to a lower TSNA smokeless tobacco product. No differences were observed in number of tins used during conventional smokeless tobacco product use and when switched to the suns product. Compared to baseline (6193 ng/ml [95% CI: 4579, 7807]), urinary cotinine levels decreased at week 2 (4465 ng/ml [95% CI: 3127, 5803]), but increased to levels that were similar to baseline at week 4 (5926 ng/ml [95% CI: 4415, 7437]). Therefore, the approximately 50% relative decrease in total NNAL levels in those who

used snus for 4 weeks was not a result of decreased smokeless tobacco use. These results support the conclusion that reducing harm constituents can lead to a substantial reduction in exposure to these constituents.

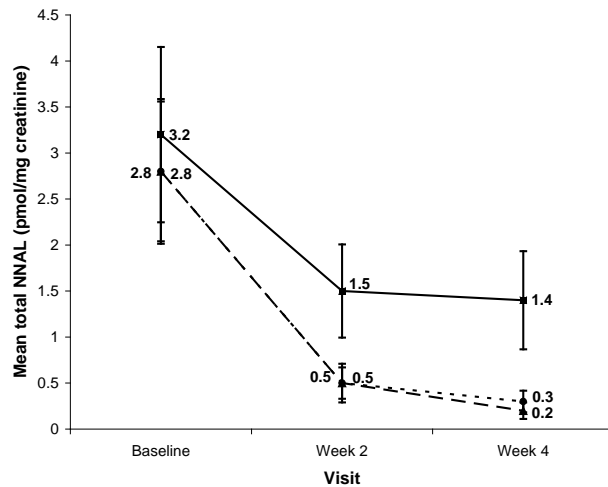


Figure 5. The observed mean and 95% CI of total NNAL per mg creatinine (NNAL plus NNAL-Gluc per mg creatinine) in urine of smokeless tobacco users assigned to nicotine patch versus snus groups over visits. Data analyzed for non-biochemically verified (NBCV) and biochemically verified (BCV) nicotine patch subjects. Square marker and solid line, snus group (N=19); triangle marker and long dash line, NBCV nicotine patch group (N= 22); circle marker and short dash line, BCV nicotine patch group (N=15). Reproduced from Hatsukami et al., 2004.⁶²

Effects on health

Biomarker levels and risk for cancer

To date, neither clinical studies nor epidemiological or longitudinal studies have been conducted on the effects of smokeless tobacco with differing levels of toxicants on risk for disease. However, several studies in cigarette smokers showed a dose response relationship between levels of biomarkers related to exposure to carcinogens and cancer risks. Although these studies were focused on cigarette smokers, it is not unreasonable to extrapolate these

results to smokeless tobacco users. Three studies examined the relationship between carcinogen biomarker levels and subsequent development of lung cancer. In all three studies, biological samples were collected several years prior to the diagnosis of lung cancer. Church *et al.* conducted a case-control study, randomly selecting participants enrolled in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (100 lung cancer cases and 100 controls).⁶³ All participants smoked at initial screening prior to any diagnosis of cancer. During this screening, biological samples were obtained. These samples were analyzed for serum total NNAL, cotinine and r-1,t-2,3,c-4-tetrahydroxy-1,2,3,4-tetrahydrophenanthrene (PheT, a biomarker of PAH exposure and metabolic activation). Total NNAL was the sole biomarker that was significantly related to lung cancer risk, even after adjusting for potential confounders (odds ratio, 1.6 per unit SD increase; 95% CI: 1.1-2.3). Similarly Yuan and his colleagues using a longitudinal cohort of Chinese cigarette smokers conducted a nested case control study of 246 cases of incident lung cancer and 245 matched controls.⁶⁴ Again, urinary levels of total NNAL were significantly related to risk of lung cancer in a dose-dependent manner. Those in the second and third highest tertile for total NNAL levels were at 1.4 (95% CI: 0.9-2.4) and 2.1 (95% CI: 1.3-3.5) higher risk for lung cancer than the first tertile, after adjusting for confounding factors. Similar dose response relationship was observed for cotinine. In the third epidemiological study related to this topic, Yuan *et al.* examined the relationship between levels of PheT, total NNAL and cotinine with lung cancer in a sample larger than prior studies.⁶⁵ In a nested case control study of 476 cases of lung cancer and of matched controls extracted from a large longitudinal cohort of Chinese cigarette smoking men from Shanghai, China

(Shanghai Cohort Study), urinary PheT, cotinine and total NNAL were higher in cases than controls and independently related to lung cancer risk.

In another study, the dose-response relationship between level of exposure to NNN and risk for esophageal cancer was explored.⁶⁶ A number of studies have demonstrated that NNN is a potent carcinogen, including the development of esophageal tumors in rats.⁶⁷ Human exposure to NNN is measured via quantification of unchanged NNN and its detoxification product NNN-pyridine-*N*-glucuronide in urine. In this study, urine samples were collected before a diagnosis of esophageal cancer in 77 smokers; 223 smokers without a diagnosis of cancer served as matched controls. These smokers were obtained from the Shanghai Cohort Study described above. The results showed odds ratio of esophageal cancer for the second and third tertiles of total NNN were 4.0 (95% CI: 1.3-12.7) and 17.0 (95% CI: 4.0-72.8), compared to the first tertile after adjusting for urinary total NNAL, total cotinine, smoking frequency and duration, and alcohol consumption.

In summary, the data from the epidemiological studies indicate that TSNA and PAH in cigarette smoke are associated with increased risk for lung or esophageal cancer in a dose-related manner. These findings would suggest that reducing these constituents is likely to lead to a decreased risk for cancer, not only in cigarettes but also smokeless tobacco products. Data comparing conventional smokeless tobacco users with smokers show considerably higher levels of total NNN (as well as other TSNA biomarkers such as total NAT and NAB⁶⁸) and total NNAL^{68,69} in smokeless tobacco users. Although the existing epidemiological studies have focused on the relationship between total NNAL levels and lung cancer and no relationship was

observed between total NNAL and esophageal cancer,⁶⁶ the combination of NNK and NNN has produced oral tumors in animals⁷⁰ and possibly in human smokeless tobacco users.⁷¹⁻⁷³ Hemoglobin adducts of both NNN and NNK have been found in the red blood cells of smokeless tobacco users.⁷⁴⁻⁷⁶ This finding indicates that NNN and NNK undergo metabolic activation in smokeless tobacco users – a process that also results in DNA adduct formation and can lead to DNA mutations.⁷⁷ That is, if DNA adducts (covalent bonding of metabolically activated carcinogen with DNA) persist, miscoding may occur during DNA replication, leading to mutations of the DNA sequence. These mutations can lead to cellular changes associated with cancer.⁷⁷ One study found a dose-response relationship between total NNAL as well as cotinine and the presence of oral leukoplakia, considered to be a precursor lesion to oral cancer.⁷⁸ Of final note, NNK administration has been observed in animals to lead to pancreatic cancers,⁷⁹ which are elevated among smokeless tobacco users compared to nonusers.^{5,80}

Country-specific incidence of disease among smokeless tobacco users

Another way to determine if reduction in toxicants might be associated with reduced disease risk is to examine the incidence of smokeless tobacco-related disease across countries that market products that differ in levels of harmful constituents. Most epidemiological studies on the effects of smokeless tobacco on disease risk have been conducted in the United States, Scandinavia or India. Data from India or Southeast Asia will not be described because of the great diversity of products from that area and the addition of other constituents such as areca nut, which by itself is carcinogenic. Generally, in India smokeless tobacco users compared to non-users appear to have higher risk for oral cancer (OR 5.1, 95% CI: 4.3–6.0)²¹ and esophageal

cancer (OR 3.7, 95% CI: 1.6–8.4)⁸¹ than observed in studies conducted in the U.S. and Sweden. The higher risks may be due to the higher levels of NNK and NNN found in some of their most popular products (see previous section). Table 3 summarizes the results from meta-analysis of cohort and case-control studies conducted in U.S. and Scandinavian countries. Comparing these two countries may be informative because in Scandinavia, particularly in Sweden, the smokeless tobacco products generally tend to be lower in harmful constituents compared to the smokeless tobacco products sold in the U.S. because of the standards imposed by the government and by the tobacco manufacturers (see section on Gøthiatek standards).

It should be noted that several of these reviews were conducted with support from tobacco companies;^{82,83} nonetheless these reviews were generally very thorough. There are many caveats in interpreting these results including small sample sizes of cases, the variability of the types of smokeless tobacco used within countries (particularly the U.S.) and the changes in smokeless tobacco products over time, the lack of information on actual exposures to carcinogens, the limited classification of smokeless tobacco use, and not controlling for all relevant confounding factors.^{49,84,85} Furthermore, direct comparisons in risk ratio across countries do not take into account the general disease burden of the country and other sociocultural, environmental and health related factors (such as access to care). Nonetheless, based on their meta-analysis on effects of smokeless tobacco on cancer risk, there appears to be a tendency of overall increased risk among smokeless tobacco users in the U.S. compared to the Scandinavian countries. Lee and Hamling stated that, *“Unlike the corresponding results for the USA, where meta-analysis estimates for cancer risk are predominantly greater than 1.0, the*

estimates for snuff as used in Scandinavia are as often below 1.0 as above 1.0” (see Table 31 and 34 of paper).⁸³ More specifically, meta-analysis shows that U.S. smokeless tobacco users are at increased risk for oral cancer whereas smokeless tobacco users in Scandinavian countries experience minimal increased oral cancer risk. Boffetta et al. concluded from their meta-analysis that, *“In general, the available epidemiological studies indicate an increased risk of oral cancer for use of smokeless tobacco in the USA, whereas results of studies in the Nordic countries do not support such association.”*²¹ (emphasis added) They further stated, *“Products historically consumed in the USA had, on average, higher nitrosamine content than those used in northern Europe, although the amount nitrosamines (and other carcinogens) in the products used by the study participants (in these studies) cannot be specified.”* (emphasis added)

On the other hand, with regards to esophageal and pancreatic cancers, the evidence is conflicting and less clear. Boffetta et al. stated that available evidence *“points to a causal association, mainly based on the studies from Nordic countries.”*²¹ Sponsiello-Wang et al. also commented *that* *“while no increased risk (for pancreatic cancer) is demonstrated in studies in North America, ...there is some evidence of an increased risk in studies in Sweden and Norway...”*⁸² However, in a more recent analysis of the studies conducted in Scandinavia, Lee⁸⁶ found at most a suggestive increase in risk for esophageal cancer (RR/OR 1.1, 95% CI: 0.9-1.3 in the whole population of smokeless tobacco users and RR/OR 1.9, 95% CI: 1.0-3.7 in smokeless tobacco users who were never smokers) and inconclusive risk for pancreatic cancer (RR/OR 1.2 95% CI: 0.7- 2.2 in the whole population and RR/OR 1.6, 95% CI: 0.8-3.3 in never smokers).

Table 3. Relative risks associated with smokeless tobacco use

Outcome	Country/region	Type of smokeless tobacco	Relative risk	Reference
Oral cancer	United States	Chew or snuff	2.6 (1.3-5.2)	Boffetta et al. ²¹
			1.7 (1.2-2.3) ^{a,c}	Lee & Hamling ⁸³
			3.3 (1.8-6.3) ^{b,c}	Lee & Hamling ⁸³
	Scandinavia	Snus Snuff/Snus	1.0 (0.7-1.3)	Boffetta et al. ²¹
			1.0 (0.7-1.4) ^a	Lee & Hamling ⁸³
			1.0 (0.7-1.5) ^b	Lee & Hamling ⁸³
Larynx	United States	Chew or snuff	2.0 (1.2-3.5) ^a	Lee & Hamling ⁸³
	Scandinavia	Snuff/Snus	0.9 (0.5-1.5) ^a	Lee & Hamling ⁸³
Esophageal cancer	United States	Smokeless tobacco [†]	1.2 (0.1-13)	Boffetta et al. ²¹
		Chew or snuff	1.9 (0.8-4.2) ^{a,b}	Lee & Hamling ⁸³
	Scandinavia	Snus	1.6 (1.1-2.4)	Boffetta et al. ²¹
	Scandinavia	Snuff/Snus	1.1 (0.9-1.3) ^a 1.9 (1.0-3.7) ^b	Lee & Hamling ⁸³ Lee & Hamling ⁸³
Pancreatic cancer	United States	Chew or snuff	1.4 (0.7-2.7)	Boffetta et al. ²¹
			1.0 (0.5-1.9) ^a	Lee & Hamling ⁸³
			1.1 (0.4-2.7) ^b	Lee & Hamling ⁸³
	North America	Chew or snuff	1.0 (0.5-2.0) ^b	Sponsiello-Wang et al. ⁸²
			1.0 (0.5-2.0) ^b	Sponsiello-Wang et al. ⁸²
	Scandinavia	Snus	1.8 (1.3-2.5) 1.2 (0.7-2.2) ^a 1.6 (0.8-3.3) ^b 1.6 (0.8-3.3) ^b	Boffetta et al. ²¹ Lee & Hamling ⁸³ Lee & Hamling ⁸³ Sponsiello-Wang et al. ⁸²
Heart disease or myocardial infarction (predominantly fatal)	United States	Chew and snuff	1.1 (1.0-1.3) ^d	Lee ⁸⁷
	Sweden	Snuff	1.1 (0.8-1.4) ^d	Lee ⁸⁷
Fatal myocardial infarction	United States	Chew or snuff	1.1 (1.0-1.2)	Boffetta & Straif ⁸⁸
	Sweden	Snuff	1.3 (1.1-1.5)	Boffetta & Straif ⁸⁸
Stroke (predominantly fatal)	United States	Chew and snuff	1.4 (1.2-1.7) ^d	Lee ⁸⁷
	Sweden	Snuff	1.2 (0.8-1.7) ^d	Lee ⁸⁷
Fatal stroke	United States	Chew or snuff	1.4 (1.2-1.6)	Boffetta & Straif ⁸⁸
	Sweden	Snuff	1.3 (0.9-1.7)	Boffetta & Straif ⁸⁸

^aMeta-analysis with smoking adjusted; ^bMeta-analysis among ST users who were never smokers; ^cStudies published since 1990 show no increase in oropharyngeal cancer risk; ^dMeta analysis among ST users who never smoked or near equivalent, random effects analysis.

Note: The work of Lee and Hamling was funded by the European smokeless Tobacco Council, which represents the interest of smokeless tobacco manufacturers and distributors as well as tobacco trade association.

With regard to the meta-analysis conducted on smokeless tobacco use and cardiovascular disease (see Table 3 for results), modest differences in risks for cardiovascular disease between countries depend on whether or not fatal heart disease is combined with non-fatal heart disease. Lee⁸⁷ stated, “*the overall evidence on use of snuff taken from a substantial number of studies in Sweden does not demonstrate any increase in the risk for CID (circulatory disease).*” He further stated, “*the evidence of a possible effect of smokeless tobacco as used in the US is more compelling.*” In a more recent analysis, Lee⁸⁶ continued to state that in studies conducted in Scandinavia no increased risk is observed for heart disease (RR/OR 1.0, 95% CI: 0.9-1.1 in the whole population of smokeless tobacco users and RR/OR 1.0, 95% CI: 0.9-1.1 in smokeless tobacco users who were never smokers) or stroke (RR/OR 1.1, 95% CI: 1.0 – 1.2 for the whole population and RR/OR 1.1, 95% CI: 1.0 -1.2 for the never smokers) when fatal and non-fatal cases are combined and maintained that there is no logical reason not to combine these cases.

On the other hand, Boffetta and Straif⁸⁸ reported evidence of “moderate increase in risk of fatal myocardial infarction and fatal stroke, whereas it does not provide evidence of a difference in effect of products consumed in North America compared with northern Europe.” Two other studies conducted in Sweden would suggest an increase risk in fatal heart disease. Hansson et al. more recently conducted a meta-analysis of prospective cohort studies conducted only in Sweden.⁸⁹ They found that current snus use was not associated with acute myocardial infarction (AMI), however, immediate (typically within 24 hours) fatality from AMI was modestly increased among snus users compared to non-users (OR 1.3, 95% CI: 1.0-1.7). In

another recent study conducted with two independent Swedish prospective cohorts, Arefalk et al.⁹⁰ found an increased risk of heart failure among a population of elderly men who were current snus users compared to non-users of snus (HR 2.1, 95% CI: 1.0-4.2) and among current users compared to never tobacco using male construction workers (HR 1.3, 95% CI: 1.0 – 1.6). Therefore, across the various studies, fatal heart disease and stroke appear to be associated with smokeless tobacco use and most likely no differences are observed across countries.

In summary, the results seem to indicate that smokeless tobacco users in North American countries have a higher risk for oral cancer than never users but no such evidence is observed in Scandinavian countries. This greater risk in North America was observed predominantly in earlier studies, possibly because products manufactured during these times had higher TSNA levels.⁸⁴ Other smokeless tobacco related diseases and fatality from these diseases appear to be similar across countries.

The data from these studies support the conclusion that a reduction in TSNA levels and possibly other harmful constituents in smokeless tobacco is likely to reduce the risk of oral cancer. The limited and sometimes conflicting data on other disease risk from the use of smokeless tobacco products in Scandinavian countries, although insufficient by itself to support a firm conclusion that such a reduction in TSNA levels and other toxicants would reduce the risk of other diseases, do not refute the conclusion that implementation of a product standard for TSNA in smokeless tobacco products would likely benefit the public health.

PROPOSED AND EXISTING STANDARDS FOR SMOKELESS TOBACCO:

World Health Organization

The World Health Organization Study Group on Tobacco Product Regulation¹³ has recommended the following product standards for smokeless tobacco: concentrations of NNN plus NNK should be limited to 2 µg/g dry weight and benzo[*a*]pyrene should be limited to 5 ng/g dry weight. Furthermore, they recommended that the *“regulation of the distribution and sale of smokeless tobacco products should include a requirement for affixation of the date by which the product must be sold and returned to the manufacturer and a requirement for refrigeration of the product before sale in order to limit the increase in the concentration of nitrosamines that occurs over time of storage.”* As an initial step, this group focused on TSNA and PAH because these constituents might explain the diversity in cancer risks observed across different regions of the world as a result of smokeless tobacco use. The limits recommended were considered to be achievable through use of tobacco with low nitrate content, pasteurization-like process that destroys bacteria that is associated with the formation of nitrosamines, alteration in curing methods (e.g., elimination of wood-smoke curing) and reduction of the aging process. While several different metrics for regulation were considered (per typical dose used, per gram as sold, per gram of residual weight, per gram nicotine), per gram dry weight was considered to have the greatest strength and least limitations including being a long-established standardized method for assessing smokeless tobacco constituents and not being affected by pattern of use, variation in moisture content of the products and manipulation of (free) nicotine content. In order to prevent misleading consumers and

potential consumers about the harms associated with smokeless tobacco use that might accompany this regulatory strategy, TobReg recommended that any regulatory approach *“prohibit use of the results of the proposed testing in marketing or other communications with the consuming public including product labeling.”* TobReg also recommended that *“manufacturers be prohibited from making statements that a brand has met government regulatory standards or from publicizing the relative ranking of brands by testing level.”* Surveillance of any of these activities as well as consumer perception, understanding and behaviors associated with this regulatory strategy was also recommended.

Gothiatek® Standard

In Sweden, the largest manufacturer of smokeless tobacco, Swedish Match, has developed and implemented the GothiaTek® standard. Products standards for Swedish snus evolved over time. In 1971, snus came under the jurisdiction of the Swedish Food Act and became regulated as a food product. Coming under this Act led to stricter hygienic requirements and restrictions on the range of allowed ingredients, additives, and containers, all of which must be food grade. In 1982, a newly built factory for manufacturing snus led to modernization of manufacturing process leading to more quality control over the product (e.g., pH stability through use of sodium carbonate, microbial growth containment). Standards for routine production began in the 1980s. Swedish Match had bought the state-owned company in the 1990s and in 2000, GothiaTek® standards were announced on the company website.⁴²

Currently the GothiaTek® standards include *“maximum permitted levels for undesirable substances, raw material quality requirements, manufacturing process requirements, and*

consumer product information requirements.” Table 5 shows the current limits and the averages levels that have been achieved with Swedish Match moist snuff products. Because of variations of water content between products, a standardized water content of 50 % has been used.

As described by Rutqvist et al.,⁴² manufacturing standards include criteria for selecting raw materials (e.g., non-genetically modified tobacco, low nitrosamine raw tobacco [*N. tabacum*] and approved food and tobacco additives under the National Food Act). In addition, requirements for manufacturing are similar to those proposed by TobReg and include air- or sun-cured tobacco, heat treatment (pasteurization) and production in a closed system and highly controlled process to avoid contamination and introduction of foreign objects.

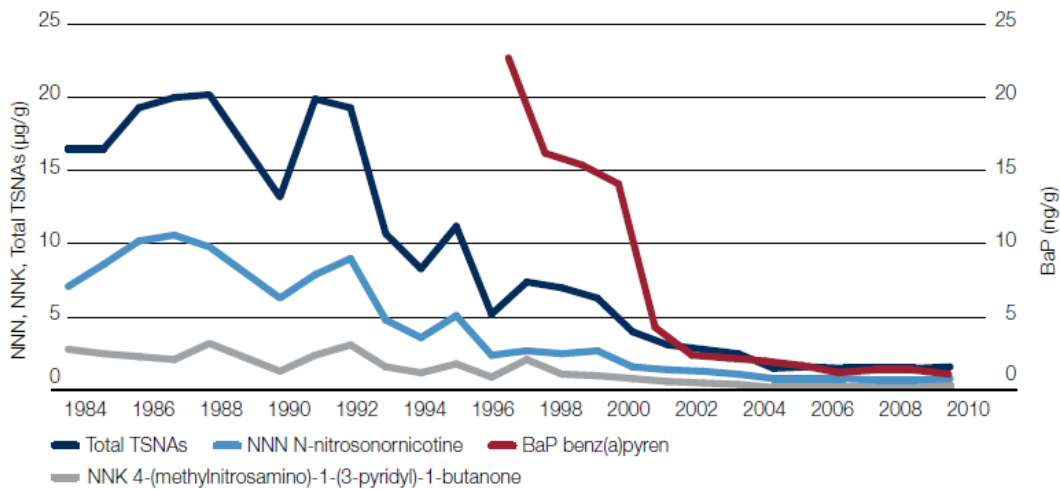
Table 5. The Gothiatek® Standard limits and the average contents of Swedish snus analyzed in 2012 are based on moist snus. Because of variations of water content between products, a standardized water content of 50 % has been used (<http://www.swedishmatch.com/en/Snus-and-health/GOTHIATEK/GOTHIATEK-standard/>; downloaded February 2104).

Component	Limit	Content 2012
Nitrite (mg/kg)	3.5	1.0 (<0.5 - 1.9)
NNN +NNK (mg/kg)	1.0	0.4 (0.3 - 0.6)
NDMA (µg/kg)	5.0	<0.3 (<0.3 - 0.4)
B(a)P (µg/kg)	2.5	0.4 (<0.3 - 1.0)
Agrochemicals	According to the Swedish Match Agrochemical Management Program	Below Swedish Match internal limits
Cadmium (mg/kg)	0.5	0.2 (0.1 - 0.3)
Lead (mg/kg)	1.0	0.1 (<0.04 - 0.2)
Arsenic (mg/kg)	0.25	<0.05 (<0.05 - 0.11)
Nickel (mg/kg)	2.25	0.7 (0.3 - 1.0)
Chromium (mg/kg)	1.5	0.3 (0.1 - 0.6)

Sanitation requirements are imposed throughout the process of packaging, cleaning equipment, product testing and shipping. Finally, consumer product information requirements include labeling on packages to include best before date, storage conditions and declaration of ingredients in accordance to labeling required for processed foods. A public website is available with brand specific information and information on snus and health effects. The Swedish Food Agency oversees the manufacture, chemistry of the product and compliance to content declaration.

In their conclusion, Rutqvist *et al.* (employed by Swedish Match) stated *“The GothiaTek® standard reflects the toxicological science and production techniques of the 1990s; the toxicant levels achieved today in routine production are lower, or much lower, than the MLs (maximum limits) defined by the GothiaTek® Standard. ... These circumstances (improved techniques for chemical analysis and improved scientific base for formal toxicological risk assessment) suggest that it is now appropriate to revisit the MLs according to GothiaTek as well as the selection of regulated constituents. The standards should be updated based on a modern risks assessment approach.”* Figure 6 demonstrates the significant reduction of harmful constituents that has occurred over time (reproduced from Rutqvist *et al.*⁴²).

Average levels of NNN (N'-nitrososornicotine), NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone), total TSNA's, and B(a)P (dry weight) in Swedish Match's snus products 1984–2009 (data based on internal Swedish Match documentation)



In light of the findings that products currently marketed in Sweden have levels of toxicants substantially below those called for in the Gothiatek® standards, in establishing U.S. product standards for smokeless tobacco products, at a minimum FDA should adopt standards at least as stringent as the toxicant levels that Swedish products currently contain.

Assessment of incremental lifetime cancer risk

Ayo-Yusuf and Connolly⁹¹ undertook an assessment of incremental lifetime cancer risk associated with exposure to select constituents in smokeless tobacco products. They applied a known toxicological assessment formula: Incremental lifetime cancer risk = $ADE_{\text{lifetime}} \times CPF$, where ADE_{lifetime} represented lifetime average daily oral exposure (mg/kg body weight per day) and CPF indicates cancer potency factor (mg/kg body weight/day). It was assumed that

smokeless tobacco users use 10 grams of dry weight of product and weigh on average 70 kg. $ADE_{lifetime}$ was estimated as ADE x number of years of snuffing (30 years was selected) divided by average lifetime (70 years was selected). Based on their analyses, the authors concluded that all smokeless tobacco products, including those meeting the GothiaTek® standards carry an “unacceptable” cancer risk as assessed by the US Environmental Protection Agency’s benchmark of acceptable risk of $<10E-6$. They proposed a level equivalent to 2 ng/g (0.002 $\mu\text{g/g}$) for TSNA and 1 ng/g for cadmium is necessary for an acceptable risk. (See Table 6 for table excerpted from article).

Table 6. Cancer risk of broad types of smokeless tobacco products for which comparable data is available

Smokeless tobacco type	Median pH	Category	Median concentration (ng/g) and cancer risk estimates*				
			TSNA	BaP	Cadmium	Lead	Total
Swedish snus (n=2)	7.4	Level	2309	3.68	980	238	
		Risk estimate	$1.2 \times 10E-3$	$9.0 \times 10E-8$	$1.7 \times 10E-4$	$1.8 \times 10E-8$	$1.4 \times 10E-3$
Low-moisture snuff (n=6)	9.5	Level	2025	34	320	659	
		Risk estimate	$1.1 \times 10E-3$	$8.2 \times 10E-7$	$5.4 \times 10E-5$	$4.8 \times 10E-8$	$1.2 \times 10E-3$
US-style chewing tobacco (n=2)	5.4	Level	2013	BDL	503	333	
		Risk estimate	$1.1 \times 10E-3$	--	$8.5 \times 10E-5$	$2.5 \times 10E-8$	$1.2 \times 10E-4$
Indian chew (Manikchand Gutka)†	8.3	Level	797	276	BDL	NQ	
		Risk estimate	$4.3 \times 10E-4$	$8.8 \times 10E-6$	--	--	†
US loose moist snuff (n=15)	7.5	Level	11675	140	933	340	
		Risk estimate	$6.4 \times 10E-3$	$3.4 \times 10E-6$	$1.6 \times 10E-4$	$2.5 \times 10E-8$	$6.6 \times 10E-3$
US pouch moist snuff (n=4)	7.6	Level	11667	70	1018	394	
		Risk estimate	$6.4 \times 10E-3$	$1.7 \times 10E-6$	$1.9 \times 10E-4$	$2.9 \times 10E-8$	$6.6 \times 10E-3$
Medicinal Nicotine gum (Nicorette)	9.3	Level	BDL	1.72	NQ	NQ	
		Risk estimate	--	$3.6 \times 10E-9$	--	--	$3.6 \times 10E-9$

* Based on data from *Rickert et al.*⁹² and the constituent reduced percentage transfer assumptions (sensitivity analysis).
 † Contains areca nut for which the carcinogen data is not provided, so that the risk estimate is likely to be grossly underestimated.
 BaP, benzo[*a*]pyrene; BDL, below detection limit; NO, below the limit of quantification; TSNA, tobacco specific nitrosamine.
 Reproduced from Ayo-Yusuf and Connolly⁹¹.

Although the ultimate goal would be to reduce harmful constituents to levels recommended by the authors, Table 7 demonstrates that the current smokeless tobacco products sold the U.S. exceeds even the maximum levels required in the GothiaTek® standard for some constituents (e.g, TSNA and benzo[*a*]pyrene) but not others.

Table 7. Content (calculated for dry weight) of trace-level substances, regulated by the GothiaTek Standard, in contemporary smokeless tobacco types

Trace-level substance	Gothiatek Standard (12)	U.S. moist snuff fine-cut 2008 (69)	U.S. moist snuff long-cut 2008 (69)
Nitrite, ppm	7	n.a.	n.a.
Total TSNA, ppm	10	10.5 - 13.7	8.8 - 14.6
NDMA, ppb	10	n.a.	n.a.
B[<i>a</i>]P, ppb	20	71 - 82	33 - 80
Cd, ppm	1	0.94 - 1.03	0.81 - 1.00
Pb, ppm	2	0.4	0.3 - 0.4
As, ppm	0.5	0.3 - 0.4	0.2 - 0.4
Ni, ppm	4.5	1.3 - 1.4	1.2 - 1.4
Cr, ppm	3	1.2 - 1.3	0.8 - 1.1

Reproduced from Klus et al.⁹³

CONCLUSION AND RECOMMENDATION:

- Significant variability of harmful and potentially harmful constituents in smokeless tobacco in products sold in the U.S.A. currently exists.
- Tobacco product manufacturers currently have the capability to reduce these constituents substantially using well established methods. For example, reducing nitrate content in the soil, using specific types of tobacco leaves, pasteurizing their

products, requiring refrigeration of the product are all measures that can be taken to reduce levels of important toxicants and carcinogens.

- The tobacco-specific nitrosamines NNN and NNK, the representative polycyclic aromatic hydrocarbon benzo[*a*]pyrene, and metals such as cadmium and arsenic are potent carcinogens in laboratory animals. Furthermore, formal evaluation of these constituents by the IARC provided sufficient evidence of their carcinogenicity in humans.
- There is strong evidence that higher constituent levels in smokeless tobacco products lead to higher constituent intake.
- There is strong evidence to demonstrate that higher levels of some of these carcinogens is associated with greater cancer risk (total NNAL for lung cancer and leukoplakia (pre-cancerous lesions), total NNN for esophageal cancer, PAH for lung cancer) in humans.
- Furthermore, the risk for oral cancer among snus users in Sweden is not higher than the risks among never users of tobacco products. Whereas in the U.S. the rates of oral cancer among smokeless tobacco users are higher than never tobacco users. While the reason for these differences are not fully understood, it is possible that lower levels of carcinogenic constituents in the Swedish snus compared to products sold in the U.S. may account for these differences.
- A precedent has already been established for setting product standards on smokeless tobacco products. Swedish snus products are under the National Food Act and are regulated as a food product. The major smokeless tobacco company in Sweden, Swedish

Match, uses the “GothiaTek® standard” which has established limits on TSNA, PAH, and metals.

- The World Health Organization’s Tobacco Regulation Study Group has made recommendations reductions in NNK plus NNN to 2 µg/g dry weight and benzo[*a*]pyrene to be limited to 5 ng/g dry weight.

In light of these findings and supportive evidence, **it is recommended that the U.S. Food and Drug Administration establish product standards for smokeless tobacco products. The standards should be at a minimum the standards proposed by WHO TobReg (which include reduction in NNK plus NNN and BaP) and below the GothiaTek® standards.**

Additional recommendations related to products standards include:

- Product labeling that includes best used-by date, disposal of expired products and recommendations for refrigeration of the products.
- No marketing or media campaigns related to the establishment of product standards by the tobacco companies.
- Surveillance to determine consumer perception and response to smokeless tobacco products and any marketing, media or publicity associated with performance standards.

Even with reduced levels of toxicants, smokeless tobacco still remains a hazardous product.

Users of lower nitrosamine products may still be at increased risk for pancreatic cancer, fatal cardiovascular diseases and oral pathologies (i.e., gum recession and leukoplakia).

Furthermore, there is an increased risk of fetal toxicity associated with the use of snus.²

Therefore, the following educational efforts are recommended:

- Graphic warning labels on smokeless tobacco use that describe the addiction potential and health consequences of smokeless tobacco use.
- Educational media campaigns aimed at reducing the uptake and continued use of these products and their potential health effects.

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