October 30, 2020

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
SWEDISH MATCH USA, INC.
Two James Center
1021 East Cary Street, Suite 1600
Richmond, VA 23219
Phone: 804-787-5100
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FOOD AND DRUG ADMINISTRATION
CENTER FOR TOBACCO PRODUCTS
Document Control Center
Building 71, Room G335
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

SUBJECT: PERIODIC REPORT for STN PM0000012

Dear Sir or Madam:

Swedish Match USA, Inc. ("Swedish Match" or "we") writes in regard to FDA's Marketing Order PM0000012 for General Portion Original Large ("PM0000012"), included below as **Attachment A.2020-PM0000012**.

Per requirements under section 910(f) of the FD&C Act, we are submitting a Postmarket Annual Report ("Report") for PM0000012 beginning October 2016 so that FDA may determine whether continued marketing of the tobacco product is appropriate for the protection of public health or whether there are or may be grounds for withdrawing or temporarily suspending the Marketing Order.

Periodic Report for the following tobacco product:

STN	PM0000012
Tobacco Product Name	General Portion White Large
Applicant	Swedish Match
Date of Report	10/30/2020
Reporting Period	10/1/2019 – 9/30/2020
Marketing Order Status USA	In market date is 4/6/2016
Marketing Status Outside USA	Commercially distributed in Sweden. No sales in EU member states. All other sales as governing law permits.

We set forth below our response to each Agency request enumerated in the Marketing Order. As directed by FDA, we are providing this single submission in response to the Marketing Order.

Swedish Match submits this Report with the confidence that continued marketing of the tobacco product is appropriate for the protection of public health.

Swedish Match submits that this submission and the information we are supplying in connection with this Report, are trade secret, proprietary information that is protected under state and federal law from public disclosure. This information should therefore be handled in accordance with the security procedures adopted by FDA in connection with enforcement of the FD&C Act.

If further information is required, please contact us.

Sincerely yours,

(b)(6)

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

Document Reference:

Kasza, K.A., et al. 2017. Tobacco-Product Use by Adults and Youth in the United States in 2013 and 2014. New England Journal of Medicine. 376(4); 342-353.

Document Attachments:

Attachment A.2020-PM0000012 – Marketing Order PM0000016
Attachment 2A1.2020-PM0000011,PM0000012,PM0000014,PM0000016 and PM0000017 – FDA's 6/1/2018 Correspondence
Attachment 2A2.2020-PM0000011,PM0000012,PM0000014,PM0000016 and PM0000017 – Internal Research Studies
Attachment 2B.2020-PM0000011,PM0000012,PM0000014,PM0000016 and PM0000017 – Full Text Articles of New Publications
Attachment 2C.2020-PM0000012 – Summary of Consumer Contacts (Adverse Experiences)
Attachment 2D.2020-PM0000012 – Summary of Sales and Distribution Data
Attachment 4A.2020-PM0000012 – Summary of Manufacturing Deviations
Attachment 5A.2020-PM0000011,PM0000012,PM0000014,PM0000016 and PM0000017 – Full Color Copies of Advertising
Attachment 6A.2020-PM0000012 – Full Color Copies of Revised Labeling

Document Table:

Table 2.b. Summary of publications not previously reported.

Swedish Match Reply to Section III. Periodic Reporting Information Request:

The information requested in the Marketing Order, Periodic Reporting, is reproduced below in bold type followed by Swedish Match's reply.

III.1. A single submission with a cover letter that includes the following text in your subject line PERIODIC REPORT FOR STN: PM0000012. The cover letter should include the STN and corresponding name, applicant name, date of report, reporting period, and marketing order status outside the United States.

Swedish Match Reply to III.1. for PM0000012:

Please see cover letter above.

III.2. A summary of how the tobacco product continues to be appropriate for the protection of the public health which includes:

a. A status report of ongoing studies and a summary of completed studies about the tobacco product conducted by, or on behalf of, the applicant;

b. A summary of significant findings on publications not previously reported and include full articles. Any new scientific data (published or otherwise) should also be reported on the likelihood of product use by current users of tobacco products within the same tobacco product category, current users of tobacco products in other tobacco product categories, former users of any tobacco product, and youth and young adults;

c. A summary of adverse experiences with this tobacco product reported to you, providing a listing and analysis (accompanied by a statement of any changes to the reference risk information and a summary of important risks, including the nature, frequency, and potential risk factors) of all adverse experiences including those serious and unexpected adverse experiences reported previously.

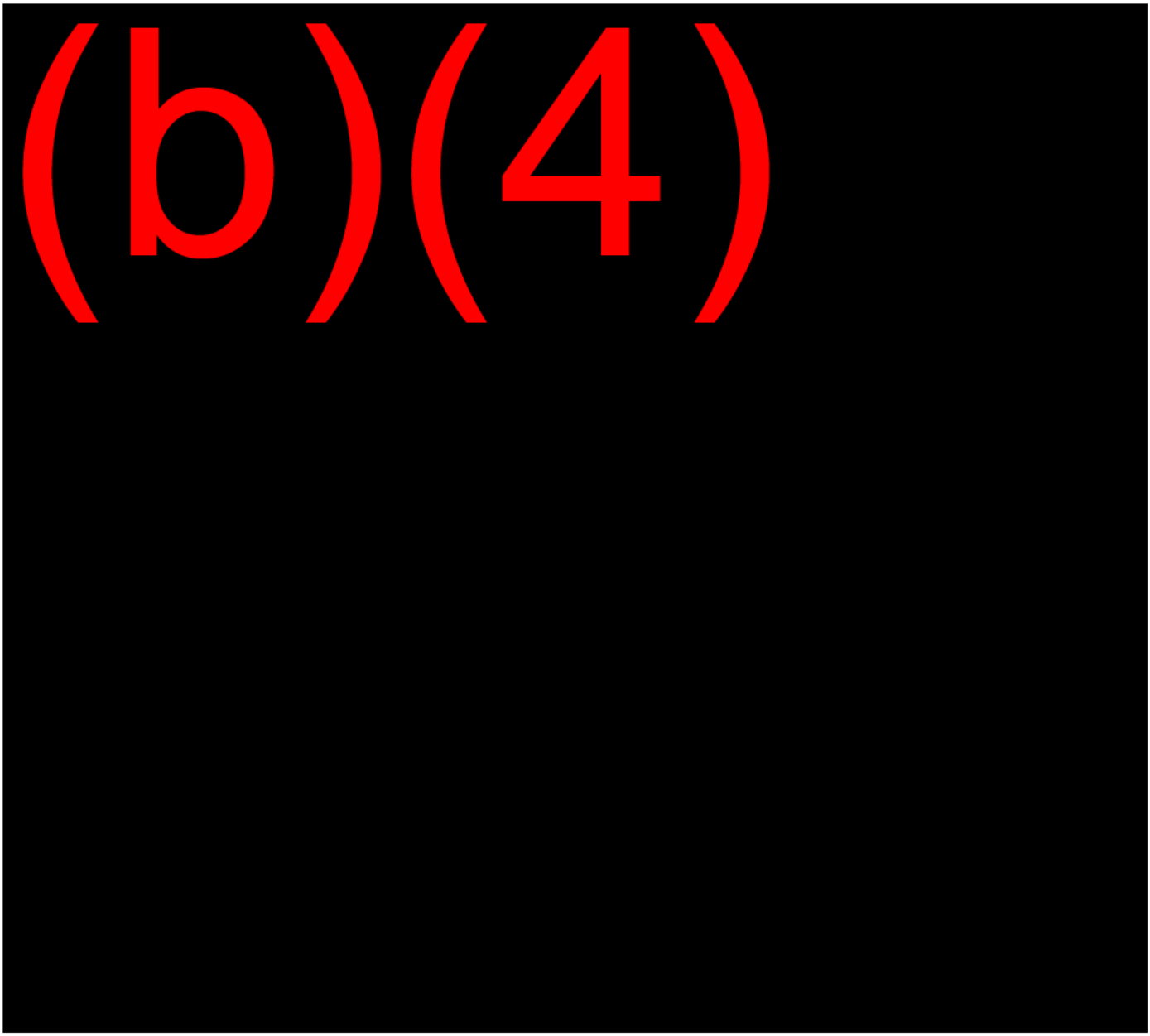
d. A summary of sales and distribution of the tobacco product: Total U.S. sales reported in dollars, units, and volume with breakdowns by US census region, major retail markets, and channels in which the product is sold (e.g., convenience stores, food and drug markets, big box retailers, internet/online sales, tobacco specialty shops);

e. Data on current product users. Data should be collected about new users, current users, those who have switched tobacco products, and multiple product users. The results should be broken down by key demographic variables including age, gender, and race/ethnicity. Also, any change in the intended target market for the product should be reported. The data described above may include sales data and post-marketing analysis.

Swedish Match Reply to III.2.a. for PM0000012:

Swedish Match asserts this report for the period October 1, 2019 – September 30, 2020, contains appropriate scientific evidence and, to the extent possible, addresses the recommendations made by FDA in its June 1, 2018, correspondence. The attached research reports, containing information as requested by FDA, allow for a complete and substantive review of PM0000012 and demonstrate that the tobacco product continues to be appropriate for the protection of public health

While this research did not include actual use behavior of snus users by demographic, we assert that data obtained from the recent PATH study may serve as a suitable surrogate for this actual use behavior. In PATH Wave 1, among adults 18 and older (see Kasza et al., 2017: Table 2[1] for percentages of current use and 95% confidence intervals), the prevalence of:



[1] https://www.nejm.org/doi/full/10.1056/nejmsa1607538

Swedish Match Reply to III.2.b. for PM0000012:

Swedish Match is supplying a summary of publications not previously reported (see Table 2.b. below). Full text articles are available in **Attachment 2B.2020-PM0000011,PM0000012,PM0000014, PM0000016 and PM0000017**. Swedish Match conducted a literature search of PubMed and Google Scholar using "snus" and "snus 2019" and "snus 2020" to access a general outline of peer reviewed Swedish snus-focused articles published in 2019 and 2020. Criteria for labeling articles as "not relevant" included articles not in English, articles using only U.S. snus (e.g. Camel Snus), and articles only mentioning snus in passing while not using snus in its research design. These "not relevant" articles are not attached.

144 **Table 2.b. Summary of publications not previously reported.**

Item#	Publication Citation and Summary
1.	Araghi, M., Galanti, M.R., Lundberg, M., Liu, Z., Ye, W., Lager, A., Engström, G., Alfredsson, L., Knutsson, A., Norberg, M., Wennberg, P., Lagerros, Y.T., Bellocco, R., Pedersen, N.L., Östergren, P-O, & Magnusson, C., No association between moist oral snuff (snus) use and oral cancer: pooled analysis of nine prospective observational studies, *Scandinavian Journal of Public Health,* 1–8, retrieved from • The study used pooled individual data from the Swedish Collaboration on Health Effects of Snus Use to assess the association between snus use and oral cancer in 418,369 male participants from nine cohort studies that were followed up for oral cancer incidence. • The study used 9,201,647 person-years of observation and found that 628 men developed oral cancer: when compared to never-snus use, ever-snus use was not associated with oral cancer (adjusted HR 0.90, 95% CI: 0.74, 1.09) and there were no clear trends in risk with duration or intensity of snus use, "although lower intensity use (⩽ 4 cans/week) was associated with a reduced risk (HR 0.65, 95% CI: 0.45, 0.94)." Snus use was not associated with oral cancer among never smokers (HR 0.87, 95% CI: 0.57, 1.32). • The study concluded that "Swedish snus use does not appear to be implicated in the development of oral cancer in men."
2.	Meier, E., Lindgren, B.R., Anderson, A., Reisinger, S.A., Norton, K.J., Jensen, J., Strayer, L., Dick, L., Tang, M.,, Chen, M., Carmella, S.G., Hecht, S.S., Murphy, S.E., Yang, J., Stepanov, I., O'Connor, R.J., Shields, P.G., and Hatsukami, D.K. (2020): A Randomized Clinical Trial of Snus Examining the Effect of Complete Versus Partial Cigarette Substitution on Smoking-Related Behaviors, and Biomarkers of Exposure. *Nicotine & Tobacco Research*, Volume 22, Issue 4, April 2020, Pages 473–481, retrieved from https://doi.org/10.1093/ntr/ntz055. • 8-week multi-site study assessing whether instructions to switch to snus is more effective in reducing cigarette use than ad lib use of snus and cigarettes. Smokers "reported greater reductions in cigarettes per day (ps < .001), using more snus pouches per day (p = .02), and more smoke-free days (CS median = 14.5, PS and UB medians = 0, p < .001). In addition, results demonstrated reductions in carbon monoxide (p < .001), total nicotine equivalents (p = .02), and four out of five measured volatile organic compounds (ps < .01) over time among the CS group." • They concluded that instructions to completely switch from cigarettes to snus resulted in the greatest reduction in cigarette use and exposure to harmful constituents.
3.	Pillitteri, J.L., Shiffman, S., Sembower, M.A., Polster, M.R., and Curtin, G.M. (2020): Assessing comprehension and perceptions of modified-risk information for snus among adult current cigarette smokers, former tobacco users, and never tobacco users, *Addictive Behaviors Reports* Volume 11, June 2020, 100254, retrieved from https://doi.org/10.1016/j.abrep.2020.100254 • Study assessed comprehension and perceptions of modified-risk information regarding snus in 3,922 adult cigarette smokers, former tobacco users, and never tobacco users. Participants viewed an advertisement about switching completely to snus and then answered questions regarding the modified-risk information and perceived risks of snus relative to cigarettes and other smokeless tobacco products. • Results indicated that "most respondents…understood that snus presents less risk than cigarettes but is not completely safe…Majorities understood snus is addictive…, quitting

	all tobacco is the best option for smokers…, and non-users of tobacco should not use snus." • The study concluded that "the modified-risk information, conveying that snus presents less risk than cigarettes but is not completely safe, was understood by majorities of respondents. Differential risk beliefs across diseases suggest responses were shaped not only by the modified-risk information, but also by intuitions and pre-existing beliefs about tobacco products."
4.	Wackowski, O. A., O'Conner, R.J., and Pearson, J.L. (2020): Smokers' Exposure to Perceived Modified Risk Claims for E-Cigarettes, Snus, and Smokeless Tobacco in the United States. *Nicotine & Tobacco Research*, ntaa159, retrieved from https://doi.org/10.1093/ntr/ntaa159. • Assessment of Wave 3 of the US-based Population Assessment of Tobacco and Health (PATH) study question which asks smokers if they had seen any e-cigarettes, snus, or other smokeless tobacco (SLT) products that claim to be "less harmful" in the past 12 months as well as their likelihood of using products with these claims in the next 30 days. • Results indicate that significantly fewer smokers saw snus (5.1%) or other SLT (5.6%) with "less harmful" claims compared with e-cigarettes (29.1%). The abstract states that for "each product, the prevalence of MRTP claim exposure was higher among smokers who perceived the product to be less harmful than smoking, who currently used the product, and who had higher rates of tobacco advertising exposure at the point of sale. Among smokers who noticed products with "less harmful" claims, about one-quarter said they would use them in the future (24%–27%)."

Swedish Match Reply to III.2.c. for PM0000012:

Swedish Match did not receive any reports of serious or unexpected adverse experiences, as defined on page 3 of the Marketing Order for PM0000012, relative to this tobacco product for the reporting period October 1, 2019 – September 30, 2020. There have been no changes to the reference risk information as was described in the PMTA.

We are supplying a summary of consumer contacts (all other reported adverse experiences) relative to this tobacco product for the reporting period October 1, 2019 – September 30, 2020, in **Attachment 2C.2020-PM0000012**.

Swedish Match Reply to III.2.d. for PM0000012:

Swedish Match is supplying a summary of sales and distribution data for the reporting period October 1, 2019 – September 30, 2020, in **Attachment 2D.2020-PM0000012**. This information includes total U.S. sales reported in dollars and units (i.e., number of cans), and volume (i.e., net weight multiplied by units) with breakdowns by US census region and retail markets and channels in which the product is sold (e.g., convenience stores, food and drug markets, big box retailers).

Swedish Match Reply to III.2.e. for PM0000012:

Other than the research (provided above at III.2.a) and sales and distribution data (provided above at III.2.d.) supplied in attachments referenced above, there is no current product user data for the reporting period October 1, 2019 – September 30, 2020, for PM0000012. Likewise, there has been no

change in the intended target market for this product for the reporting period October 1, 2019 – September 30, 2020.

III.3. A description of each change made to the manufacturing, facilities or controls during the reporting period, including:

a. A comparison of each change to what was described in the PMTA;

b. The rationale for making each change; and

c. A certification that the reported change did not result in any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of the tobacco product; the basis for concluding that each change did not result in any modification to the final product.

Swedish Match Reply to III.3. for PM0000012:

There has been no change to the manufacturing, facilities or controls during the reporting period October 1, 2019 – September 30, 2020, for PM0000012.

III.4. A summary of all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution and indicate a deviation that may affect the characteristics of the final product.

Swedish Match Reply to III.4. for PM0000012:

Swedish Match is supplying a summary of all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution and indicated any deviation(s) that may affect the characteristics of the final product for the reporting period October 1, 2019 – September 30, 2020, in **Attachment 4A.2020-PM0000012**. This product had no manufacturing deviations for the reporting period October 1, 2019 – September 30, 2020.

III.5. Full-color copies of all advertising for the tobacco product that has not been previously submitted, along with the original date the advertisements were first disseminated and the date the advertisements were discontinued; and

Swedish Match Reply to III.5. for PM0000012:

Swedish Match is supplying full-color copies of all advertising for this tobacco product, for the reporting period October 1, 2019 – September 30, 2020, in **Attachment 5A.2020-PM0000011,PM0000012, PM0000014,PM0000016 and PM0000017**. First disseminated and discontinuation dates are indicated next to the advertisement. Advertisements are still in market unless a discontinuation date is indicated.

III.6. In all annual reports, include a description of any or all labeling changes and submit revised full color final printed labeling.

a. The labeling should include all the panels, be presented in the actual size and color with legible text.

b. For the first annual report only, submit all final printed labeling (actual labeling for each required warning distributed with the product); include labels, inserts/onserts,

instructions, and other accompanying information or materials for this product.

Swedish Match Reply to III.6. for PM0000012:

In conjunction with this Report for the period October 1, 2019 – September 30, 2020, we are supplying copies of the revised top and side label final print proofs which include dimensions, Pantone[2] color numbers, and legible text **(see Attachment 6A.2020-PM0000012.)**

As this is the fifth annual report for this product, we are not required to submit actual physical labels for this product (as required in II.6.b., above).

[2] The Pantone Matching System (Pantone or PMS) is a standardized color reproduction system used in the printing industry for the faithful selection, articulation and reproduction of consistent, accurate color anywhere in the world. The tool organizes color standards through a proprietary numbering system.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Tobacco Products
10903 New Hampshire Avenue
Silver Spring, MD 20993

MARKETING ORDER

Swedish Match North America, Inc.
Attention: Gerard Roerty, Jr., Vice President, General Counsel & Secretary
Two James Center
1021 East Cary Street, Suite 1600
Richmond, VA 23219
via Certified Mail

FDA Submission Tracking Number (STN): PM0000012

Dear Mr. Roerty:

The Food and Drug Administration (FDA) completed the review of your Premarket Tobacco Product Application (PMTA) submitted under section 910(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for the following tobacco product:

Applicant:	Swedish Match North America, Inc.
Tobacco Product Name:[1]	General Portion Original Large
Tobacco Product Category:	Smokeless Tobacco
Tobacco Product Sub-Category:	Portioned Snus
Package Type:	Plastic Can
Package Quantity:	24.0 g
Characterizing Flavor:	None
Portion Count:	24 pouches
Portion Mass:	1000 mg
Portion Length:	33 mm
Portion Width:	18 mm
Portion Thickness:	6 mm
Tobacco Cut Size:[2]	(b)(4) [redacted]

Based on our review of your PMTA, we find permitting the new tobacco product specified above to be marketed is appropriate for the protection of public health, and that you have met the other requirements of section 910(c) of the FD&C Act. Under the provisions of section 910, you may introduce or deliver for introduction into interstate commerce the new tobacco product specified above with the enclosed labeling.

[1] Brand/sub-brand or other commercial name used in commercial distribution
[2] The applicant provided fraction scale weight buckets to characterize the tobacco cut size. Therefore, the tobacco cut size cannot be represented with a single value and corresponding range limit.

RECORD RETENTION

Under section 910(f) of the FD&C Act, we are requiring in this order that you retain the records listed below for a period of not less than 4 years from the date of distribution of the last batch of the new tobacco product specified above. These records must be legible, in the English language, and available for inspection and copying by officers or employees duly designated by the Secretary, upon request:

- PMTA submitted prior to product order
- Postmarket reports/postmarket status reports submitted to FDA, including adverse experiences and all relevant documentation associated with the experience
- Correspondence with FDA pertaining to authorized product
- Nonclinical or clinical study documentation including:
    - study protocols (including statistical analysis plan);
    - amendments showing the dates and reasons for each protocol revision;
    - Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approvals;
    - Informed consent forms;
    - Correspondence with study monitors/investigators/contract research organizations/sponsors/IRB/IEC;
    - Investigator financial disclosure statements;
    - Progress reports;
    - Monitoring reports;
    - Adverse experience reports;
    - Case report forms/subject diaries/medical records/laboratory reports;
    - Subject data line listings/observations records;
    - Test article accountability records;
    - Study results/protocol summaries/study reports; and
    - Certifications and amendments to certifications.
- Records pertaining to the manufacture, in process and release testing, process (including any changes to the process, facility, or controls), packaging, and storage of product
- Records pertaining to the sale, marketing, distribution, or other disposition of the product
- Specimens of all labeling, labels, inserts/onserts, instru.ctions, and other accompanying information
- Hazard analysis

POSTMARKET REPORTS

I. Serious and Unexpected Adverse Experiences Reporting

Under section 910(f) of the FD&C Act, we are requiring in this order that you report to the FDA all adverse experiences that are both serious and unexpected and your analysis of the association between the adverse experience and the tobacco product **within 15 calendar days** after the report is received by you. These experiences may become known to you through a response to a customer complaint, request, or suggestion made as a result of an adverse experience, tobacco product defect, or failure reported to you; or identified in the literature or media. Your information should be submitted with a cover letter that includes the following text in the subject line: **SERIOUS UNEXPECTED ADVERSE EXPERIENCE REPORT for STN PM0000012**.

For purposes of reporting under this order, serious adverse experience means an adverse experience that results in any of the following outcomes:

- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- Any other adverse experience that, based upon appropriate medical judgment, may jeopardize the health of a person and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

For purposes of reporting under this order, unexpected adverse experience means an adverse experience occurring in one or more persons in which the nature, severity, or frequency of the experience is not consistent with:

- The known or foreseeable risks associated with the use or exposure to the tobacco product as described in the PMTA and other relevant sources of information, such as postmarket reports and studies;
- The expected natural progression of any underlying disease, disorder, or condition of the persons(s) experiencing the adverse experience and the person's predisposing risk factor profile for the adverse experience; or
- The results of nonclinical laboratory studies.

II. Manufacturing Deviations

You should promptly investigate all manufacturing deviations, including but not limited to those associated with processing, testing, packing, labeling, storage, holding and distribution. For products that have been distributed, if the deviation may negatively impact public health, you must promptly identify and report that deviation to the Center for Tobacco Products. See instructions below for submitting your regulatory correspondence.

III. Periodic Reporting

Under section 910(f) of the FD&C Act, we are requiring in this order that you submit, on an annual basis, beginning October 2016, unless otherwise notified, the following information in a postmarketing annual report to help FDA determine whether continued marketing of your tobacco product is appropriate for the protection of public health or whether there are or may be grounds for withdrawing or temporarily suspending such order. For the 12- month reporting period, the report must include:

1. A single submission with a cover letter that includes the following text in your subject line: **PERIODIC REPORT for STN PM0000012**. The cover letter should include the STN and corresponding tobacco product name, applicant name, date of report, reporting period, and marketing order status outside the United States.
2. A summary of how the tobacco product continues to be appropriate for the protection of the public health which includes:
    a. A status report of ongoing studies and a summary of completed studies about the tobacco product conducted by, or on behalf of, the applicant;

   b. A summary of significant findings on publications not previously reported and include full articles. Any new scientific data (published or otherwise) should also be reported on the likelihood of product use by current users of tobacco products within the same tobacco product category, current users of tobacco products in other tobacco product categories, former users of any tobacco product, and youth and young adults;
   c. A summary of adverse experiences with this tobacco product reported to you, providing a listing and analysis (accompanied by a statement of any changes to the reference risk information and a summary of important risks, including the nature, frequency, and potential risk factors) of all adverse experiences including those serious and unexpected adverse experiences reported previously.
   d. A summary of sales and distribution of the tobacco product: Total U.S. sales reported in dollars, units, and volume with breakdowns by US census region, major retail markets, and channels in which the product is sold (e.g., convenience stores, food and drug markets, big box retailers, internet/online sales, tobacco specialty shops);
   e. Data on current product users. Data should be collected about new users, current users, those who have switched tobacco products, and multiple product users. The results should be broken down by key demographic variables including age, gender, and race/ethnicity. Also, any change in the intended target market for the product should be reported. The data described above may include sales data and post-marketing analysis.
3. A description of each change made to the manufacturing, facilities or controls during the reporting period, including:
   a. A comparison of each change to what was described in the PMTA;
   b. The rationale for making each change; and
   c. A certification that the reported change did not result in any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of the tobacco product; the basis for concluding that each change did not result in any modification to the final product.
4. A summary of all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution and indicate a deviation that may affect the characteristics of the final product.
5. Full-color copies of all advertising for the tobacco product that has not been previously submitted, along with the original date the advertisements were first disseminated and the date the advertisements were discontinued; and
6. In all annual reports, include a description of any or all labeling changes and submit revised full color final printed labeling.
   a. The labeling should include all the panels, be presented in the actual size and color with legible text.
   b. For the first annual report only, submit all final printed labeling (actual labeling for each required warning distributed with the product); include labels, inserts/onserts, instructions, and other accompanying information or materials for this product.

In accordance with 40 CFR 1506.6, we will make your environmental assessment publicly available.

This order authorizing the marketing of this new tobacco product does not mean FDA "approved" the new tobacco product specified above; therefore, you may not make any express or implied statement or representation directed to consumers that conveys, or misleads or would mislead consumers into believing, among other things, that the new tobacco product specified above is "approved" by FDA. See Section 301(tt) of the FD&C Act. This marketing order is subject to withdrawal or temporary suspension under section 910(d) of the FD&C Act.

We remind you that all regulated tobacco products, including the new tobacco product specified above, are subject to the requirements of Chapter IX of the FD&C Act and its regulations. These requirements currently include, but are not limited to, annual registration, listing of products, listing of ingredients, reporting of harmful and potentially harmful constituents, and payment of user fees. There are also packaging, labeling, and advertising requirements with which you must comply. It is your responsibility to ensure the tobacco product specified above complies with all applicable statutory and regulatory requirements. FDA will monitor your compliance with these applicable statutes and regulations.

If you discontinue the manufacture, preparation, compounding or processing for commercial distribution this tobacco product and later decide to reintroduce the product into the market, please contact the Office of Science to discuss if additional information is necessary.

For more information on your responsibilities under the FD&C Act, we encourage you to visit our website at http://www.fda.gov/TobaccoProducts. You may also obtain information by contacting FDA's Center for Tobacco Products at 1-877-CTP-1373, AskCTP@fda.hhs.gov, or SmallBiz.Tobacco@fda.hhs.gov.

We remind you all regulatory correspondence can be submitted via the FDA Electronic Submission Gateway (http://www.fda.gov/esg) using eSubmitter or by mail to:

Food and Drug Administration
Center for Tobacco Products
Document Control Center
Building 71, Room G335
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

We are unable to accept regulatory submissions by electronic mail.

If you have questions, you may contact Asia Brown, MHSA, Regulatory Health Project Manager, at (240) 402-3833.

Sincerely,

Digitally signed by David Ashley -S
Date: 2015.11.10 06:00:57 -05'00'

David L. Ashley, Ph.D.
RADM, US Public Health Service
Director
Office of Science
Center for Tobacco Products

Enclosure

General Portion Original Large Labeling

U.S. FOOD & DRUG ADMINISTRATION

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

June 01, 2018

GENERAL CORRESPONDENCE

Swedish Match North America, Inc.
Attention: Gerard Roerty, Jr., Vice President, General Counsel & Secretary
Two James Center
1021 East Cary Street, Suite 1600
Richmond, VA 23219

FDA Submission Tracking Numbers (STN(s)): MULTIPLE STNs, See Below

Dear Mr. Roerty:

Please refer to your Postmarket Periodic reports for the Premarket Tobacco Applications (PMTAs) received on October 27, 2017 and November 22, 2017, submitted under section 910(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for the following tobacco products:

Periodic Report STN	STN	TOBACCO PRODUCT NAME
TC0003310	PM0000010	General Loose
TC0003024	PM0000017	General Wintergreen Portion White Large
TC0003025	PM0000011	General Dry Mint Portion Original Mini
TC0003026	PM0000012	General Portion Original Large
TC0003028	PM0000014	General Mint Portion White Large
TC0003030	PM0000016	General Portion White Large

Based on our review of your 2017 Periodic reports, we have identified the following issues for which we believe additional information or clarification will be helpful to FDA in performing a complete substantive review of **subsequent** Periodic Reports.

1. For all products, you submitted summary information on the Snus Health Evaluation Survey and the 2017 Snus Category Market Research Online Community Panel. It appears that these two studies are ongoing. The Snus Health Evaluation study appears to be comprised of tobacco users and non-users, however details on the study population are not provided. In subsequent post-market Periodic reports, clearly indicate for all studies if they are ongoing or complete. Including details on the sample populations for all studies along with summary information by key demographic variables such as tobacco use status, age, and gender would assist FDA in evaluating the study.

2. For all products, you submitted summary information about the 2015 & 2016 Tobacco Market Tracker Study and the 2016 Snus Brand Tracker Study. On slide 2 of the PowerPoint slide deck you indicate that the Snus Brand Tracker was conducted between April and September 2016, and terminated on January 1, 2017. However, slide 16 suggests that data was collected for this

study from 2014 through 2016, presenting conflicting information. The Snus Brand Tracker Study was not mentioned in the previous post-market report for these products. The information provided also suggests that this study contains information specific to the General Snus brand and General Snus products. In order to assess the potential impact of these products on public health, it is important for FDA to review information from studies that have been completed about the products. In your next Periodic report, clarify the dates that referenced studies were completed. In addition, we recommend you provide complete summaries of all study data for completed studies relevant to these tobacco products to assist FDA evaluation of the study.

3. For all of the products you provide a table of publications identified through a literature search. In this post-market report 23 publications were identified. However, 2 of 23 publications in the table did not include complete information (citations #13 and 16). In subsequent reports, include a complete citation for the publications identified including full title, author names, publications date, and publisher so that FDA can easily identify the referenced publication.

4. For all products, you submitted information on the likelihood of snus use among various tobacco user groups via publications and data from the Snus Health Evaluation Survey and the Market Tracker Study. For the Market Tracker Study, it would be important to know if there was a change in snus use among never users of tobacco products. Additionally, the graphs provided in the summary PowerPoint slide deck pertaining to the Snus Health Evaluation Survey do not include denominators for each survey question or confidence intervals for the estimates. In subsequent reports, provide summary information including point estimates, confidence intervals, and denominators which will allow FDA to fully evaluate the study data.

5. For all products, you provided sales data for each product specific to this post-market review including a summary of total US distribution by units (cans and pounds) and dollars, by US census region, retail markets and channels. For all products, you also provide crosstab survey data from the 2015 & 2016 Market Tracker Study, and summary data from the 2017 Snus Health Evaluation Survey, the 2017 Snus Category Market Research Online Community Study, the Snus Brand Tracker Study, and the 2015 & 2016 Tobacco Market Tracker Study. The survey information does not provide direct information about the tobacco products specific to this post-market review.

   On the September 7, 2017 teleconference FDA recommended you provide data separated by product along with a summary of the prevalence of your product's use by key demographic variables (e.g., tobacco use status, age, gender). In this report, you state that there is not current product user data for the specific products associated with this review, yet the summary information provided about the Snus Brand Tracker and the Snus Market Research Online Community Studies suggest that information on user of the products associated with this report has been collected. In subsequent reports, we recommend that you provide complete summaries for studies relevant to the products associated with this review, including product use information by tobacco use status, age, and gender so the FDA can fully evaluate the study information.

Page 3,TC0003310, TC0003024-TC0003026, TC0003028, TC0003030

We remind you that all regulatory correspondence can be submitted via the FDA Electronic Submission Gateway (www.fda.gov/esg) using eSubmitter or mailed to :

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Silver Spring, MD 20993-0002

We are unable to accept regulatory submissions by electronic mail.

If you have any questions, please contact Shireen Ahmad, MS, Regulatory Health Project Manager, at (240) 402 – 0435 or at Shireen.Ahmad@fda.hhs.gov.

Sincerely,

Iilun C. Murphy -S
2018.06.01 13:12:30 -04'00'

Iilun Murphy, M.D.
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Consumer Insights

CATEGORY: SNUS

BRAND: GENERAL

2019 – 2020 Annual Report

CONSUMER INSIGHTS

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Scandinavian Journal of Public Health, 1–8

ORIGINAL ARTICLE

No association between moist oral snuff (snus) use and oral cancer: pooled analysis of nine prospective observational studies

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Abstract

Aims: Worldwide, smokeless-tobacco use is a major risk factor for oral cancer. Evidence regarding the particular association between Swedish snus use and oral cancer is, however, less clear. We used pooled individual data from the Swedish Collaboration on Health Effects of Snus Use to assess the association between snus use and oral cancer. *Methods:* A total of 418,369 male participants from nine cohort studies were followed up for oral cancer incidence through linkage to health registers. We used shared frailty models with random effects at the study level, to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) adjusted for confounding factors. *Results:* During 9,201,647 person-years of observation, 628 men developed oral cancer. Compared to never-snus use, ever-snus use was not associated with oral cancer (adjusted HR 0.90, 95% CI: 0.74, 1.09). There were no clear trends in risk with duration or intensity of snus use, although lower intensity use (≤ 4 cans/week) was associated with a reduced risk (HR 0.65, 95% CI: 0.45, 0.94). Snus use was not associated with oral cancer among never smokers (HR 0.87, 95% CI: 0.57, 1.32). ***Conclusions:*** **Swedish snus use does not appear to be implicated in the development of oral cancer in men.**

Keywords: *Oral cancer, incidence, smokeless tobacco, snus*

Background

In 2012, 529,500 new cases of cancers of the oral cavity and pharynx, and more than 300,000 deaths were reported worldwide [1]. Oral cancers are predominantly squamous cell carcinomas of the lip or oral cavity. Its incidence varies greatly worldwide, with low rates in most Western countries while being among the most common cancers on the Indian subcontinent and in other parts of Asia [1]. Tobacco and alcohol consumption and human papillomavirus (HPV)-infections are established risk factors for oral cancer [2].

Smokeless tobacco is not burned and can be used orally or nasally. Oral smokeless-tobacco products are sucked or chewed. Snuff is a general term for finely cut or powdered, sometimes flavoured tobacco, which can be prepared as moist or dry snuff (this

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latter can be inhaled through nasal passages) [3]. Smokeless-tobacco products contain nicotine and other alkaloids in addition to carcinogens such as nitrosamines, nitrosoamino acids, aldehydes and metals, but in varying doses depending, for example, on manufacturing methods and brands [3, 4]. Globally, a wide variety of different smokeless-tobacco products are used. Chewing tobacco is common throughout much of Southeast Asia and the Western Pacific, while in Sweden moist oral snuff, also known as snus, is the main product used [3]. Because of this variation, the global interpretation of epidemiological studies on health effects of smokeless tobacco use is complicated.

Results from four meta-analyses [3, 5–7] indicates that any type of smokeless tobacco (chewing or snuff) is significantly associated with an increased risk of oral cancer in the USA and South Asia. The International Agency for Research on Cancer (IARC), in 2007, hence concluded that there is strong evidence that smokeless tobacco causes cancer of the oral cavity [8]. The relationship between use of the Swedish snus and oral cancer is, however, less clear [9–15].

In 2018, 18% of Swedish men and 4% of Swedish women and 25% of Norwegian men and 14% of Norwegian women, were daily snus users [16, 17]. Snus use has been proposed as a smoking cessation aid, thus, it is important to fully understand the contribution of snus use to cancer incidence. The Swedish Collaboration on Health Effects of Snus Use (SCHESU) consists of a group of Swedish investigators, who have conducted prospective studies where data on snus use has been collected. The SCHESU has previously investigated the impact of snus use on multiple health outcomes such as pancreatic cancer [18], colorectal cancer [19], diabetes [20] and Parkinson's disease [21]. The present SCHESU involves data from nine Swedish cohort studies [9, 22–29], of which only one [9] had published data on snus use and oral cancer. We here take advantage of this large pooling project to investigate the impact of snus use on oral-cancer risk.

Materials and method

Contributing studies and data collection

We used data from nine prospective cohort studies, including participants of varying ages, recruited at different time periods from diverse geographic regions across Sweden. Exclusion criteria were age less than 18 years, missing information on body mass index (BMI) or tobacco, or being diagnosed with oral cancer, or death prior to study enrolment. Of the included studies, five were population-based [22, 23, 26–28], two were occupational cohorts [9, 29], one included participants in a charity-walk [24], and one was a twin study [25]. The cohorts are described in detail in Table I. Details on study design and data collection procedures of the individual studies have been reported elsewhere [9, 22–29]. Since snus use is rare in women, the study was restricted to men [16].

Information on tobacco use was collected at baseline using self-administrated questionnaires in seven studies [22–24, 26–29] and by a structured phone interview and personal interviews by nurses in two studies [9, 25]. All studies contributed information on current snus use and seven [9, 23–25, 27–29] on former snus use while amount and duration of snus use was available from seven [9, 22–25, 28, 29] and six studies [9, 23–25, 28, 29], respectively. Detailed information on snus use assessment across studies has been summarized in Table II. Information on height and weight, whether it was self-reported or measured by health professionals, was collected in all studies. Moreover, information on educational level and alcohol consumption was available and retrieved from all studies, except one [9]. Each cohort member contributed person-time from the date of entering into the study until the date of oral cancer diagnosis, death, or the end of the study, whichever came first. The Swedish National Cancer Register, established in 1958 and shown to be 98% complete, has coded malignant tumours according to the seventh revision of International Classification of Diseases (ICD7) [30]. In this study, we used the ICD7 codes 140, 141, 143 and 144 to identify incident cases of oral cancer (not including cancers of the salivary glands, pharynx, or larynx). Linkages were performed using the personal identity, a unique national identifier assigned to all Swedish residents. The specific studies were approved by their respective regional ethical vetting boards, and approval for the pooling project was granted by the Stockholm Regional Ethical Review Board (registration number 2009/971-31/3).

Statistical analyses

Smoking and snus use were categorized into never, former and current use (where non-current snus use was treated as never-use in the studies that did not have information on former snus use). These data were collected at baseline and no follow-up data on tobacco-use habits were available. Snus use (excluding former use) was further, where possible (see also Table II), categorized according to amount consumed per week ($\leqslant$ 4 cans, 5–6 cans, $\geqslant$ 7 cans) and duration ($\leqslant$ 4 years, 5–9 years, 10–14 years, 15-19 years, $\geqslant$ 20 years) of use. Such information for smoking status

Table I. Baseline characteristics of study participants in the Swedish Collaboration of Health Effects of Snus Use.

Study	Population	Data collection	Period of recruitment	Current snus users at baseline (%)	Last follow-up with register data	Male participants (*n*)	Person years of follow-up (*n*)	Mean age at recruitment (years)	Cases (*n*)
Construction Worker Cohort (CWC) [9]	Construction workers, national	Questionnaire	1978–1993	26	2013	273,604	7,696,573	34	475
Malmö diet and Cancer Study (MDCS) [21]	Population-based, Malmö City	Questionnaire	1991–1996	7	2013	11,208	193,165	59	47
Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) [22]	Population-based, Norrbotten and Västerbotten Counties	Questionnaire	1986–2004	23	2008	4472	55,843	49	3
National March Cohort (NMC) [23]	Participants in a charity walk, national	Questionnaire	1997	10	2010	13,289	168,374	53	12
Screening Across the Lifespan Twin Study (SALT) [24]	Twins born in Sweden between 1926,1958, national	Structured telephone interview	1998–2002	15	2010	17,909	173,595	56	41
Scania Public Health Cohort (Scania_PHC) [25]	Population-based, Scania County	Questionnaire	1999	20	2008	5835	52,783	48	4
Stockholm Public Health Cohort (Sthlm_PHC) [26]	Population-based, Stockholm County	Questionnaire	2002–2010	18	2011	37,780	180,018	49	8
Västerbotten Intervention Programme (VIP) [27]	Population-based, Västerbotten County	Questionnaire	1992–2013	27	2013	47,172	582,232	47	36
Work, Lipids and Fibrinogen Study (WOLF) [28]	Employees, Västernorrland, Jämtland, and Stockholm Counties	Questionnaire	1992–1997	23	2009	7100	99,064	42	2
All studies			1978–2013	24	2008–2013	418,369	9,201,647	40	628

Table II. Snus habit assessment across included cohorts.

	Construction Worker Cohort (CWC) [9]	Malmö diet and Cancer Study (MDCS) [21]	Determinants in Cardiovascular Disease (MONICA) [22]	National March Cohort (NMC) [23]	Screening Across the Lifespan Twin Study (SALT) [24]	Scania Public Health Cohort (Scania_PHC) [25]	Stockholm Public Health Cohort (Sthlm_ PHC) [26]w	Västerbotten Intervention Programme (VIP) [27]	Work, Lipids and Fibrinogen Study (WOLF) [28]
Information at baseline									
Current snus use	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
If yes, please record the exact question asked	'Have you tried snus? "yes" or "no"' At 'what age? . . . . years of age' 'For how many years did you use snus?'	'Do you use snus? "yes" or "no"' 'How many packages of snus do you consume every week?'	'Do you use snus? "yes" or "no"' '. . .packs per week'	'Have you taken snuff regularly (at least once a week during more than six months)? "yes"' or "no"'	'Do you use snus regularly and/or occasionally? "yes" or "no"'	'Do you use snus? "yes" or "no"'	'Do you currently use snus? "yes" or "no"'	'Have you ever used snus? "Yes, I use snus, . . . box per week"'	'Are you a current snuff user? "yes" or "no"'
Information about start-point of snus use	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes
If yes, please record the exact question asked	At 'what age? . . . . years of age'	-	'For how many years have you been using snus?'	'How old were you when you began snus use regularly'	'How old were you when you first start using snus?'			'Age of starting of snus. . .'	'Years of snus use'
Does 'Ever used' defined as current plus former use	Yes	Only current	Yes	Yes	Yes	Only current	Yes	Yes	Yes
Do any of the studies distinguish between daily and occasional use of snus use?	No	No	No	No	Yes	No	No	No	No
Former snus use	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes
If yes, define how former use was defined	'Not use of any tobacco 5 or more years prior to data of baseline data collection'	-	'I used to but not now'	'Tins per week during different ages in life'	'Not use snus currently'		'Not current users'	'I used to use snus'	'I am not current snus user'
Average amount of snus use	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
If yes, please record the exact question(s) asked	'Snus use in grams per day. . .'	'Pack of snus per week. . .'	'How much snus do you use per week?'	'Number of tins per week'	'Number of packs per week'			'Yes, I use snus, . . .box per week'	'number of packs per week'

was not available. Never-users of snus constituted the reference group.

Shared frailty models (gamma distributed) with random effects at the study level were used to estimate hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) of oral cancer in relation to tobacco use, using time from baseline to end of follow-up as the time scale. The shared frailty model is an extension of the Cox proportional hazards model and accounts for between study correlation by incorporating shared random effects [31]. Participants were followed from baseline until index date of oral cancer diagnosis, date of death, or end of follow-up, whichever came first. In addition to the inherent adjustment for age, all models were adjusted for BMI, calculated as body weight in (kilograms) by the height (in metres) squared and used as a continuous variable, and smoking (where possible, categorized as never, former or current smoking) [32]. The underlying assumption of proportional hazards was tested using Schoenfeld's global test. Stata statistical software (Version 13.1, Stata Corporation, and College Station, TX, USA) was used for all analyses.

We conducted a sensitivity analysis according to the following scenarios: (a) excluding the Construction Workers Cohort, since this cohort constituted 61.5% of the total sample size; (b) restriction to never smokers, as an alternative approach to control for the potential confounding effect of tobacco smoking; (c) adjusting for alcohol consumption ((grams/week), low, medium and high (in tertiles)) [33] and educational level ($\leqslant$ 9 (compulsory), 10–11 (secondary or high school) and $\geqslant$ 12 years (university or above) of education) [34] in the subset of studies where this information was available; (d) excluding cohorts [22, 26] with no available information on former snus use, thus enabling correct classification of former snus use.

Results

After exclusions of 14,625 subjects, including those being under 18 years old (n = 6697), missing information on BMI (n = 2125), missing information on tobacco variables (n = 5705), having a prior history of colorectal cancer (n = 87), or a death date before entry (n = 11), 418,369 men constituted the analytical sample yielding 9,201,647 person-years of observation (Figure 1). Characteristics of the participants from the various cohorts included in the collaboration are shown in Table I. Period of recruitment and duration of follow-up ranged from 1978 to 2013 and from 5 to 35 years, respectively. The mean age at entry was 40 years (range 18–99). A total of 628 incident cases of oral cancer occurred during follow-up.

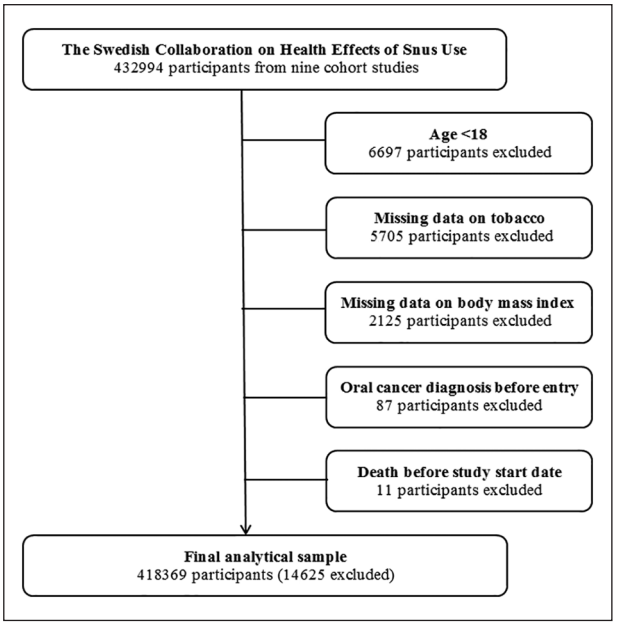

Figure 1. Derivation of the analytical sample.

At time of entry, 30% of study participants had ever used snus.

The main analyses including the full analytical sample, adjusting for smoking status and BMI did not support any association between ever-snus use and oral cancer (HR 0.90, 95% CI: 0.74, 1.09, compares ever- to never-snus users). The current users of snus had a statistically non-significant 21% lower risk of oral cancer than the never users (HR 0.79, 95% CI: 0.63, 1.00). Additionally, there was no clear trend with duration; while lower intensity use ($\leqslant$ 4 cans/week) was associated with a reduced risk (HR 0.65, 95% CI: 0.45, 0.94) (Table III).

Sensitivity analyses

Table IV presents the results from sensitivity analyses. Excluding the Construction Workers Cohort, the HR for oral cancer in current snus users was 0.79 (95% CI: 0.46, 1.37) after adjustment for BMI and smoking status. Snus use was furthermore not associated with oral-cancer risk in analysis restricted to never smokers (HR 0.93, 95% CI: 0.59, 1.44). The results from other sensitivity analyses scenarios including adjustment for educational level and alcohol consumption, and excluding cohorts with no information on former snus use were generally similar to the overall findings.

Discussion

This large pooling project, including nine prospective cohort studies and 628 incident cases, does not

support the notion that use of Swedish snus increases the risk for oral cancer among men. Indeed, current users had a seemingly reduced such risk which, however, is difficult to interpret in light of lacking dose-response relationships and biological rationale. Our results contrast convincing evidence of an increased risk of oral cancer with use of other types of oral smokeless tobacco, including those commonly used in the USA, India, Pakistan and Sudan, but are in line with most studies from the Nordic Countries.

Table III. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) for oral cancer in relation to snus use (n = 418,369).

Use of snus at baseline	Number of cases	HR[a]	95% CI	HR[b]	95% CI
Never-users[c]	485	Ref.		Ref.	
Ever-users	143	0.89	(0.73, 1.07)	0.90	(0.74, 1.09)
Former users	51	1.20	(0.89, 1.60)	1.20	(0.89, 1.61)
Current users	92	0.77	(0.62, 0.97)	0.79	(0.63, 1.00)
Amount (cans/week)[d]					
⩽ 4	31	0.71	(0.49, 1.02)	0.65	(0.45, 0.94)
5–6	29	0.77	(0.53, 1.13)	0.83	(0.56, 1.21)
⩾ 7	30	0.83	(0.57, 1.22)	0.97	(0.66, 1.41)
Duration (years)[e]					
⩽ 4	13	0.64	(0.36, 1.11)	0.67	(0.38, 1.17)
5–9	20	0.80	(0.50, 1.26)	0.86	(0.54, 1.35)
10–14	19	0.83	(0.52, 1.32)	0.86	(0.54, 1.37)
15–19	8	0.57	(0.28, 1.16)	0.60	(0.29, 1.21)
⩾ 20	30	0.99	(0.68, 1.44)	0.97	(0.67, 1.42)

[a] Hazard ratio estimates were adjusted for attained age.
[b]Hazard ratio estimates were adjusted for attained age, smoking (never, former and current) and body mass index.
[c]Never users of snus.
[d]Among current snus users only. The information was only available for following studies: CWC, MDCS, MONICA, NMC, SALT, VIP, and WOLF.
[e]Among current snus users only. The information was only available for following studies: CWC, MONICA, NMC, SALT, VIP, and WOLF.

In a previous report from the Swedish Construction Workers Cohort [9] from 279,897 male in 1978–1992 with follow-up until 2004 with 248 cases of oral cancer, snus users had a relative risk of oral cancer of 0.8 (95% CI: 0.4, 1.7) after restriction to never smokers. This result was replicated in the current study with complete follow-up until end of 2013 with total 475 cases of oral cancer during 35 years of follow-up (HR 1.0, 95% CI: 0.6, 1.7). In a cohort study by Boffetta and colleagues [10], snus use was not associated with oral cancer (RR 1.10, 95% CI: 0.50, 2.41) after adjusting for age and smoking. Similarly, two case-control studies by Rosenquist and colleagues [11] (odds ratio (OR) for ever-snus use 0.7, 95% CI: 0.3, 1.3) and Schildt and colleagues [12] (OR for current snus use 0.7, 95% CI: 0.4, 1.2) found no increased risk for development of oral cancer associated with the use of Swedish snus.

In contrast, results from an additional Swedish cohort [13] showed an elevated risk for ever daily use of snus compared to never daily use of snus controlling for smoking (HR 3.1, 95% CI: 1.5, 6.6) based on 11 exposed cases. Among never-smokers in the cohort, the HR for ever daily use of snus was 2.3 (95% CI: 0.7, 8.3) [13]. In a another small Swedish study [14] among men with snus-induced lesions, a relative risk of 2.3 (95% CI: 0.5, 6.7) was reported in relation to snus use, but none of the cancers had developed at the site of the lesions. In a case-control study [15], the OR for cancers of the oral cavity, pharynx and oesophagus combined in relation to current snus use was 1.0 (95% CI: 0.7, 1.6). In the subgroup of never-smokers, the OR for ever-users of snus was, however, 4.7 (95% CI: 1.6, 13.8).

The reason for the discrepancy between these findings is unknown, but all studies but the Construction Workers Cohort were based on small

Table IV. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) of oral cancer in relation to snus use from sensitivity analyses (n = 418,369).

Type of analysis	n	Use of snus at baseline				
		Ever users	Former users		Current users	
		HR[a] (95% CI)	n	HR[a] (95% CI)	n	HR[a] (95% CI)
Excluding Construction Workers Cohort	31	0.96 (0.63, 1.48)	15	1.27 (0.72, 2.26)	16	0.79 (0.46, 1.37)
Restriction to never smokers[b]	28	0.87 (0.57, 1.32)	3	0.58 (0.18, 1.83)	25	0.93 (0.59, 1.44)
Controlling for additional potential confounders[c]	31	0.95 (0.61, 1.49)	15	1.26 (0.70, 2.28)	16	0.78 (0.44, 1.38)
Excluding cohorts[d] with no information on former snus use	142	0.97 (0.79, 1.18)	51	1.26 (0.93, 1.71)	91	0.86 (0.67, 1.09)

[a]Adjusted for attained age, smoking (never, former and current) and body mass index.
[b]The reference is never users of any tobacco.
[c]Additional adjustment for alcohol consumption, and educational level, among the studies where this information was available (MONICA, NMC, SALT, Scania_PHC, Sthlm_PHC, VIP and WOLF).
[d]MDCS and Scania_PHC.

numbers. Furthermore, studies were concerned with different subsites of the head and neck cancers (e.g. oral cavity, nasopharynx/paranasal sinuses, oropharynx, hypopharynx and larynx). It is possible that snus use is associated with cancers of the hypopharynx and larynx, where saliva (and hence carcinogens from snus) tends to accumulate, but not with cancers of the oral cavity. Differential and insufficient control for confounding factors, in particularly of smoking, may also explain inconsistencies in study results. In fact, residual confounding by smoking may also explain the seemingly reduced risk among current snus users from our analysis including smokers. This is since dual smokers and snus users smoke less on average than exclusive smokers, and since we could only adjust for smoking status categorized as never, former or current. Our analysis restricted to never-smokers, supporting a null association, is less likely to be biased from confounding by smoking dose. This may be the reason behind the seemingly reduced risk among current smokers in our sample, while the analysis restricted to never-smokers, supporting a null association, is likely to have eliminated residual confounding by smoking dose.

The present study has several strengths, including its large sample size, and a diverse study population. Additionally, its prospective design minimizes recall and selection bias, often afflicting retrospective studies. In addition to control for confounding by smoking, with two approaches, that is multivariate modelling, and restriction of the study population to never-smokers – we had the opportunity to further control for educational level and alcohol, and again the main findings did not change. The study also has several limitations. The main limitation is that the information on smoking and snus use was self-reported and only assessed at baseline. This may produce biased estimates of the association between snus use and oral cancer as a result of measurement error (true effect of snus use cannot be retrieved due to behaviour changes during long-period follow-up). A recent Swedish study showed that 70% of snus users at baseline and 55% of smokers continued their tobacco use habit after 10 years, which indicates that using snus is a more stable habit than is smoking [35]. Moreover, snus was found to be the most stable form of tobacco use among a cohort of 3407 men and women over 13 years of follow-up [36]. We were unable to control for all potentially confounding factors, including for example, HPV infections and occupational exposures (e.g. wood dust or nickel) [2]. Finally, we could not address the association between snus use and oral cancer among women because of their low prevalence of use.

Our findings, from the largest sample to date, do not support a role of Swedish snus use in the development of oral cancer in men. Risk from Swedish snus is clearly less than from smokeless tobacco products used in North America and South Asia, but this does not imply that snus is harmless. As long as the knowledge of the health effects of long-term use of snus is limited, recommendation to use snus as smoking cessation support is questionable.

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Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Assessing comprehension and perceptions of modified-risk information for snus among adult current cigarette smokers, former tobacco users, and never tobacco users

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ABSTRACT

Introduction: Snus, a low nitrosamine smokeless tobacco product, presents less risks to health than cigarettes. Effectively communicating such risk information could facilitate smokers switching completely to snus, thereby benefiting public health.

Methods: This study assessed comprehension and perceptions of modified-risk information regarding snus. Adult cigarette smokers, former tobacco users, and never tobacco users (N = 3,922) from a US internet panel viewed an advertisement stating that smokers who switched completely to snus could greatly reduce risk of lung cancer, respiratory disease, heart disease, and oral cancer. Respondents answered questions regarding the modified-risk information and rated perceived risks of snus relative to cigarettes and other smokeless tobacco products.

Results: Across the four diseases mentioned in the advertisement, most respondents (49.7%–68.6%, across tobacco user groups) understood that snus presents less risk than cigarettes but is not completely safe. Some indicated snus presents the same risk as cigarettes; this was highest for oral cancer (33.7%–42.02%) and lowest for lung cancer (15.4%–23.1%) and respiratory disease (15.6%–23.4%). Majorities understood snus is addictive (77.7%–87.9%), quitting all tobacco is the best option for smokers (83.6%–93.1%), and non-users of tobacco should not use snus (80.4%–87.8%). Only 2.1%–5.8% indicated smokers would receive a health benefit if they continued to smoke while using snus.

Conclusions: The modified-risk information, conveying that snus presents less risk than cigarettes but is not completely safe, was understood by majorities of respondents. Differential risk beliefs across diseases suggest responses were shaped not only by the modified-risk information, but also by intuitions and pre-existing beliefs about tobacco products.

1. Introduction

A continuum of risk exists for tobacco products, with non-combustible products such as smokeless tobacco (SLT)[1] posing less risks to health than combustible cigarettes (Levy et al., 2004; Nutt et al., 2014; Zeller, 2013). Using snus, an SLT product with low levels of tobacco-specific nitrosamines, poses less health risks than smoking, and complete switching from cigarettes to snus is associated with demonstrated decreases in morbidity and mortality due to lung cancer, respiratory disease, heart disease, and oral cancer compared to continued smoking (Lee, 2013; Levy et al., 2004; US Department of Health and Human Services, 2014).

The lower risks of SLT and snus are, however, not well understood by the general public, with multiple studies indicating that most people incorrectly perceive SLT and snus to be as harmful or more harmful than cigarettes (Czoli, Fong, Mays, & Hammond, 2017; Feirman, Donaldson, Parascandola, Snyder, & Tworek, 2018; Fong et al., 2019; Kaufman, Mays, Koblitz, & Portnoy, 2014; Kiviniemi & Kozlowski,

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[1] **Abbreviations**FDA: Food and Drug Administration; MRTP: modified-risk tobacco product; MRTPA: modified-risk tobacco product application; NRT: nicotine replacement therapy; SLT: smokeless tobacco; US: United States

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2015; Wackowski, Ray, & Stapleton, 2019). Misperceptions about SLT and snus are likely influenced by intuitive theories of how particular health harms arise. Compared to cigarettes, SLT and snus are often viewed as being more likely to cause oral cancer, equally likely to cause heart disease, and less likely to cause lung cancer (Choi, Fabian, Mottey, Corbett, & Forster, 2012; Lund & Scheffels, 2014; Pepper, Emery, Ribisl, Rini, & Brewer, 2015; Wray, Jupka, Berman, Zellin, & Vijaykumar, 2012), presumably because SLT comes in contact with the mouth, and not the lungs. People who correctly believe SLT and snus are less harmful than cigarettes are more likely to use those products (Bernat, Ferrer, Margolis, & Blake, 2017; Fong et al., 2019; Kaufman et al., 2014; Wackowski & Delnevo, 2016), suggesting that such misperceptions—regardless of the source—may prevent smokers from switching to SLT and snus.

Education about the relative harms associated with different tobacco products has the potential to correct misperceptions (Borland, Li, & Cummings, 2012). Communicating relative risk information to consumers can improve understanding and support changes in tobacco use that are expected to reduce health risks (Wackowski, O'Connor, et al., 2016b), such as switching completely to snus in lieu of continuing to smoke.

The Family Smoking Prevention and Tobacco Control Act (2009), which gave the US Food and Drug Administration (FDA) regulatory authority over tobacco products, provided that tobacco companies could apply for authorization to communicate accurate relative risk information to the public, through the modified-risk tobacco product application (US Department of Health and Human Services, 2012). As part of such an MRTPA, a modified-risk communication or advertisement is proposed, and consumer risk perceptions are assessed following exposure to the communication. It must be demonstrated that consumers—regardless of their experience with tobacco—understand key concepts in the communication that bear on the MRTPA's potential impact on public health; for example, that quitting is the best option for cigarette smokers, that a modified-risk tobacco product (MRTP) is less risky than cigarette smoking but not completely safe, and that non-users of tobacco should not start using tobacco. The latter two concepts exemplify messages that need to be understood by non-tobacco users, as well as by current tobacco users.

As part of the evidence submitted to the FDA in support of an MRTPA for Camel Snus, the current study assessed comprehension and risk perceptions among US adults—including current cigarette smokers (who could benefit from switching to snus) and non-users of tobacco (i.e., former and never tobacco users, who could be harmed by initiating snus)—following exposure to an advertisement that included modified-risk information. The objectives were to assess comprehension of the MRTP messages and compare risk perceptions both across tobacco products and for diseases mentioned in the advertisement. While differences across tobacco user groups were not the focus of the analyses, the sample did include respondents with diverse tobacco use status to ensure representation of the entire population.

2. Methods

2.1. Sample

Participants were US adults drawn from the Research Now[2] national consumer panel, a demographically diverse online panel of three million individuals. Adults ages 18 and older who were legally eligible to purchase tobacco where they lived were surveyed in June and July of 2015. Quota sampling was implemented to ensure representation across key demographic groups (i.e., gender, age, race/ethnicity, education level, and geographic region) in each of three distinct tobacco user groups—current cigarette smokers (n = 896), former tobacco users (n = 1,526), and never tobacco users (n = 1,500). The data were weighted to match the US population on those demographic variables using the Annual Social and Economic Supplement to the Current Population Survey (March 2014) and the Tobacco Use Supplement to the Current Population Survey (TUS-CPS; January 2011).

Assessment of tobacco use history included not only cigarettes, but the full range of tobacco products. Current cigarette smokers were defined as those who smoked at least 100 cigarettes in their lifetime (Bondy, Victor, & Diemert, 2009) and smoked cigarettes "every day" or "some days" at the time of the survey. Former tobacco users had been established users of one or more tobacco products (i.e., used at least 100 times in their lifetime) but did not use any tobacco at the time of the survey. Never tobacco users reported never using any tobacco product, even once or twice.

In accordance with the Code of Federal Regulations 45 Part 46.101.b, which dictates that survey research that is anonymous or does not solicit subject-identified sensitive information that could harm participants is considered exempt (US Department of Health and Human Services, 2017), the study was not reviewed by an institutional review board.

2.2. Procedures

Panelists who responded to online invitations were assessed for demographic characteristics and tobacco use history. Participants were then shown an advertisement for Camel Snus that included modified-risk information, general information about the product and its use, and balancing information intended to communicate that less risk does not mean no risk and to caution against use by unintended populations (Supplemental Fig. 1). The advertisement included three color images that appeared one above the other on the same screen. The bottom fifth of each image included one of four government-mandated warning labels for SLT (US Food and Drug Administration, 2018a), which were randomly rotated. See Supplemental Table 1 for the information in the advertisement.

2.3. Measures

Following exposure to the advertisement, respondents were asked a series of questions (Supplemental Table 2) largely adapted from published literature (Haddock, Lando, Klesges, Peterson, & Scarinci, 2004; O'Connor et al., 2005; Peiper, Stone, van Zyl, & Rodu, 2010). The first four questions assessed comprehension of the modified-risk information. This was followed by questions on risk perceptions, which included both direct and indirect approaches to assess the absolute and relative risks of snus, as some research suggests that these different approaches may produce dissimilar results (Popova & Ling, 2013; Wackowski, Bover Manderski, & Delnevo, 2016). First, participants were asked a direct comparison question (Popova & Ling, 2013; Wackowski et al., 2016) about the health risks of snus relative to cigarettes; this question asked respondents to characterize the risk associated with snus as (a) the same risk as continuing to smoke, (b) less risk than continuing to smoke, (c) no health risk at all, or (d) I don't know. These assessments were made separately for the four diseases (lung cancer, respiratory disease, heart disease, and oral cancer) mentioned in the advertisement. Respondents were instructed to answer these initial risk perception questions based on what the advertisement communicated. The next questions asked for quantitative ratings of the absolute risks for snus, cigarettes, and other SLT products, respectively, on a 1–7 scale, for each of the four diseases, as well as for "generally poorer health" and "addictiveness," based on respondents' beliefs, allowing for an indirect comparison of relative risk (Wackowski et al., 2016). A subsequent question asked whether snus reduces the risk of other smoking-related diseases not mentioned in the advertisement (yes/no), and the last two questions asked respondents to identify the

[2] In 2017, Research Now merged with Survey Sampling International (SSI) to form Research Now SSI, which was renamed Dynata in 2019.

true statement (from two oppositely worded statements) about (1) the safety of snus compared to nicotine replacement therapy (NRT) and (2) the safety of snus compared to quitting tobacco entirely. Following completion of the questions, the Newest Vital Sign health literacy test (Weiss et al., 2005) was administered.

Comprehension and direct comparison questions appeared directly below the advertisement (on the same screen), so that respondents could scroll between the questions and the advertisement. This follows the practice recommended by the FDA for assessing comprehension of consumer drug labels (US Department of Health and Human Services, 2010), which focuses on documenting what consumers understand upon viewing the label, rather than what they recall or how the label changed their beliefs.

2.4. Data analyses

The analyses are primarily descriptive. Comparisons focus on differences in risk perceptions of different tobacco products and diseases, rather than differences among the tobacco user groups; however, broad trends across the three tobacco user groups are described. Where comparisons were made, tests of significance were done using an alpha level of $p < 0.05$. Analyses were conducted using SAS 9.4. Percentages are weighted, and Ns represent unweighted counts.

3. Results

3.1. Sample demographics

Table 1 presents the weighted demographic characteristics of the sample. Overall, 65.6% of respondents were non-Hispanic White and 11.6% were non-Hispanic Black; 35.3% of the sample had limited health literacy. Among current cigarette smokers, 78.7% smoked every day and 21.3% smoked some days; 7.3% reported dual/poly use of cigarettes, snus, and/or SLT. Among former tobacco users, 91.2% reported past use of cigarettes, 3.7% had used snus, and 13.7% had used SLT.

3.2. Assessment of absolute risk perceptions, and indirect assessment of relative risks

Fig. 1 displays the tobacco user groups' ratings—based on respondents' beliefs—of the impact of snus, other SLT products, and cigarettes on the risk of developing the four diseases mentioned in the advertisement (i.e., lung cancer, respiratory disease, heart disease, and oral cancer). The mean risk ratings assigned by current cigarette smokers, and former and never tobacco users for each disease were similar. Across each of these groups, mean risk ratings for cigarettes were always the highest and generally near the top of the scale (designated as "substantial risk"); risk ratings for snus for each of the four diseases were always significantly lower than those for cigarettes and other SLT (p's < 0.0001; see Supplemental Table 3); and all risk ratings were approximately at or above the midpoint of the 1–7 scale. Even the lowest mean risk rating for snus for any disease (respiratory disease risk rating of current smokers, 3.9) reflected an expectation of substantial risk. The risk ratings for oral cancer were consistently the highest (p's < 0.0001 [see Supplemental Table 4] compared to other diseases; range = 5.6–5.8).

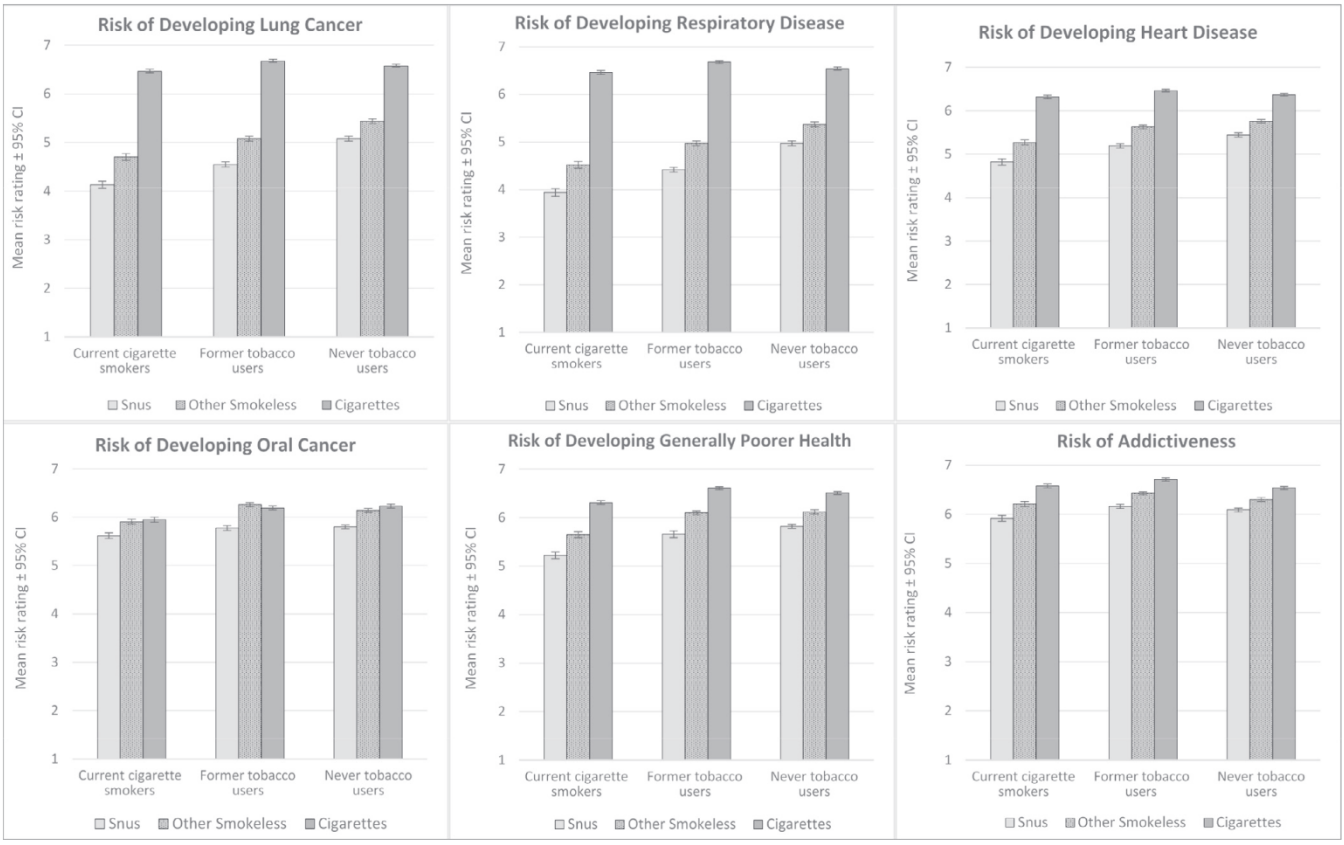
As seen in Fig. 1, the patterns noted above for risk perceptions of the three products (i.e., snus, SLT, and cigarettes) were similar across the three tobacco user groups for each disease. Within each of the groups, and for each of the risks, all between product comparisons were highly significant (p's < 0.0001; see Supplemental Table 5). The one exception was in evaluation of oral cancer risk of SLT compared to cigarettes, where current cigarette smokers evaluated those risks as similar ($p = 0.50$), former tobacco users thought SLT carried more risk than smoking ($p < 0.05$), and never tobacco users thought SLT carried less risk ($p < 0.003$), but these variations were small. As seen in Fig. 1, the patterns across products were highly similar across tobacco user groups for the other diseases and risks.

3.3. Direct assessment of relative risk perceptions

Respondents were asked to characterize the health risks presented

Table 1
Demographic characteristics of the sample.

	Total Sample (N = 3,922)	Current Cigarette Smokers (n = 896)	Former Tobacco Users (n = 1,526)	Never Tobacco Users (n = 1,500)
Gender				
Male	46.8%	54.0%	56.0%	40.4%
Female	53.2%	46.0%	44.0%	59.6%
Age (years)				
18–24	7.3%	5.5%	2.8%	10.1%
25–30	15.7%	16.4%	9.9%	18.7%
31–50	33.6%	38.1%	31.7%	33.8%
51 and older	43.4%	40.0%	55.6%	37.4%
Race/Ethnicity				
Non-Hispanic White	65.6%	76.4%	73.8%	59.1%
Hispanic or Latino	14.9%	7.4%	11.3%	18.4%
Non-Hispanic Black	11.6%	11.4%	8.8%	13.1%
Non-Hispanic Asian or other race	7.9%	4.8%	6.1%	9.4%
Education				
High school or less	41.7%	62.2%	37.3%	40.2%
Some college	28.9%	31.2%	28.5%	28.6%
Bachelor's degree or more	29.4%	6.6%	34.2%	31.2%
Health Literacy				
Adequate literacy	64.7%	56.7%	70.3%	63.2%
Limited literacy	35.3%	43.3%	29.7%	36.8%
Geographic Region				
Northeast	18.3%	15.3%	18.0%	19.0%
Midwest	21.2%	25.5%	21.8%	20.0%
South	36.9%	41.6%	36.0%	36.6%
West	23.6%	17.7%	24.2%	24.4%



Note: Non-overlapping error bars indicate statistically reliable (significant) differences. For all ratings other than addictiveness ratings, the scale was anchored by 1 = "no risk" and 7 = "substantial risk". For addictiveness ratings, the scale was anchored by 1 = "not at all addictive" and 7 = "extremely addictive".

Fig. 1. Ratings (1–7 scale) of the health risks of snus, other smokeless tobacco products, and cigarettes across the three tobacco user groups.

by snus as the same as cigarettes, less than cigarettes, or having no risk at all—separately for each of the four diseases—based on information communicated in the advertisement (Fig. 2). Approximately 60% of respondents in each of the three tobacco user groups indicated that, compared to cigarettes, snus presented less risk of lung cancer, respiratory disease, and heart disease; the percentages that offered the same assessment of less risk were significantly lower for oral cancer (p's < 0.0001; see Supplemental Table 6). The modified-risk information was not recognized or accepted by some respondents, with 15.4%–26.9% in each of the three groups reporting that snus and cigarettes presented the same risk for lung cancer, respiratory disease, and heart disease. The risk reduction for snus was most often doubted for oral cancer, with 33.7%–42.0% indicating that snus presented the same risk for oral cancer as cigarettes.

For each disease, < 13% in each tobacco user group reported that snus presented no risk at all (this figure was significantly lower for oral cancer [range = 1.5%–3.3%] across the three groups; p's < 0.0004 compared to the other three diseases [see Supplemental Table 7]). Similarly, for each disease respectively, approximately 10% did not know how to characterize the risk of snus compared to cigarettes. Respondents giving "don't know" answers were most often never tobacco users, less often former tobacco users, and least often current cigarette smokers, suggesting such answers increased with decreasing engagement with tobacco products.

3.3.1. Differential risk perception ratings by disease

The advertisement mentioned reduced risk for four diseases, and although the advertisement did not explicitly distinguish the risk reductions by disease, respondents appeared to do so in their risk ratings. In the indirect assessment of risk (Fig. 1), respondents in each of the three tobacco user groups consistently rated the risk of oral cancer with snus higher (p's < 0.0001; range of risk ratings = 5.6–5.8; see Supplemental Table 4) than that of the respiratory conditions (lung cancer = 4.1–5.1; respiratory disease = 3.9–5.0), with heart disease intermediate (range = 4.8–5.4). While respondents rated the risk of snus lower than that of cigarettes and other SLT for all four diseases (all p's < 0.0001), the comparison was much narrower for oral cancer than for the other three diseases. In each of the three tobacco user groups, the highest risk ratings were given for cigarette smoking for all diseases except oral cancer, where other SLT was rated similarly to cigarette smoking (Fig. 1).

Respondents also differentially assessed the risk of oral cancer with snus as greater than the risk of the other three diseases in the direct measure of relative risk (Fig. 2 provides risk estimates by tobacco user group, from which overall estimates are determined). Across all three tobacco user groups, 36.1% believed the risk of oral cancer with snus use was the same as that associated with continuing to smoke cigarettes; this was significantly higher than risks assigned for the other three diseases (20.1% for lung cancer, 20.4% for respiratory disease, and 24.3% for heart disease; p's < 0.0001 [see Supplemental Table 8]). Further, about 8.0% believed that snus presented no risk at all for lung cancer and respiratory disease, respectively, while only 2.5% perceived no risk for oral cancer (p's < 0.0001; see Supplemental Table 9).

3.4. Risk perceptions for diseases not included in the modified-risk advertisement

To assess whether respondents generalized the modified-risk information to other diseases, respondents were asked about the risk

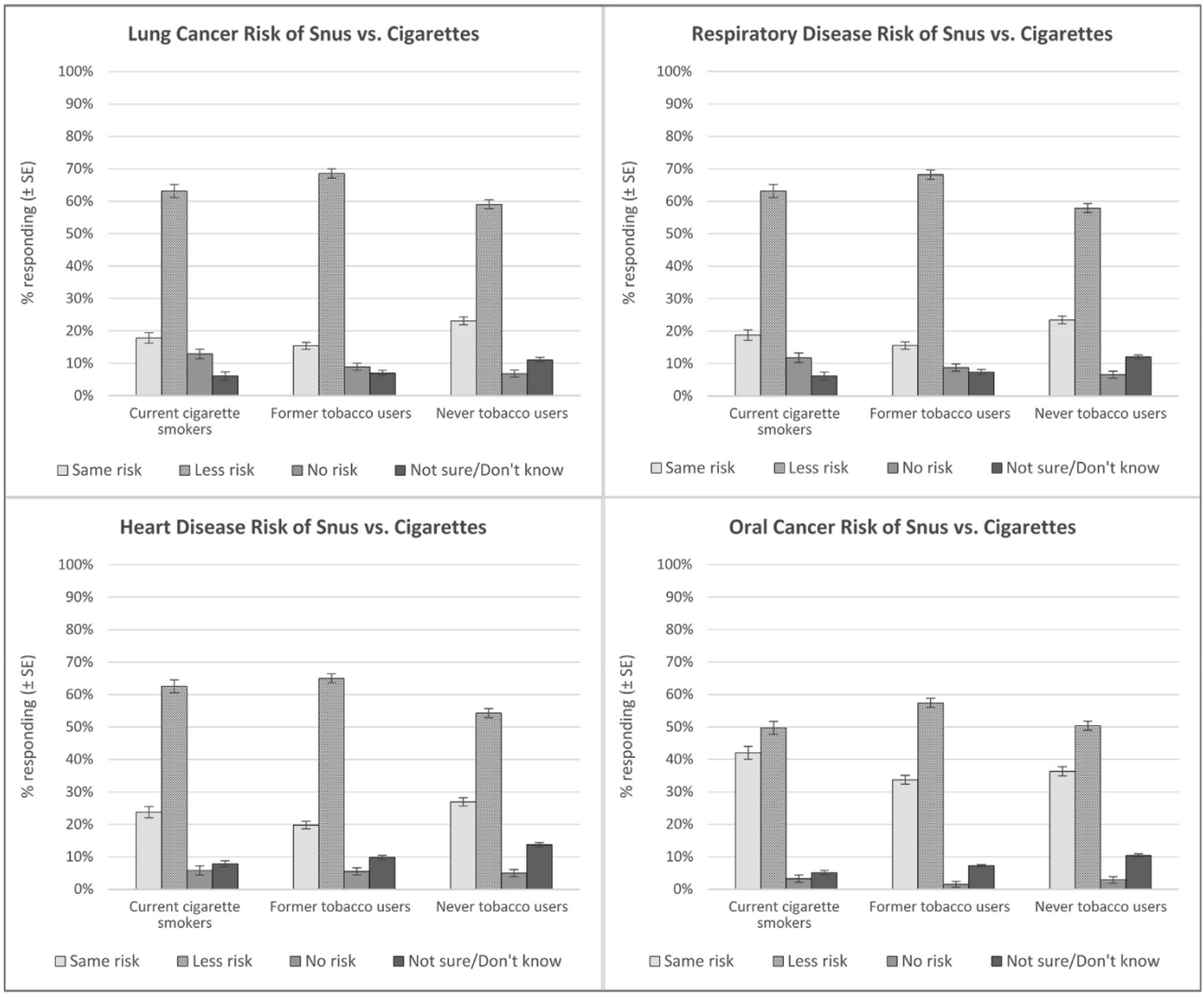


Fig. 2. Perceptions of the health risks of snus relative to continuing to smoke cigarettes across the three tobacco user groups.

reduction potential of snus for diseases "not mentioned in the advertisement." Across the three tobacco user groups, 14.5%–22.2% reported that snus reduces the risk of other smoking-related diseases not discussed in the advertisement, 32.1%–38.4% disagreed, but a plurality (45.7%–52.0%) were unsure (Table 2).

Respondents were also asked—based on their beliefs—to rate (1–7 scale) the impact of snus, cigarettes, and other SLT on the risk of developing "generally poorer health." Fig. 1 shows that for each of the three tobacco user groups, respectively, the mean risk ratings for snus were lower than those for cigarettes and other SLT (p's $<$ 0.0001; see Supplemental Table 10). The risk ratings indicate respondents thought snus carried greater risk for generally poorer health than for lung cancer, respiratory disease, and heart disease (p's $<$ 0.0001; see Supplemental Table 11); the risk was seen as closest to that for oral cancer, though generally slightly lower.

3.5. Perceptions of the addictiveness of snus, cigarettes, and other smokeless tobacco

Respondents' risk ratings for the addictiveness of snus were very high, ranging from 5.92 to 6.16 on the 7-point scale, which was higher than the risk ratings for the four diseases (p's $<$ 0.0001; Fig. 1 [see Supplemental Table 12]). In all three tobacco user groups, snus was perceived—based on respondents' beliefs—as less addictive than cigarettes and other SLT products; the product differences were small but reliable (p's $<$ 0.0001; see Supplemental Table 13).

Addictiveness of snus was also assessed by asking "Is Camel Snus, which contains nicotine, addictive?", mirroring statements made in the modified-risk advertising. Understanding that snus is addictive is important for all three tobacco user groups, and majorities in each group (77.7%–87.9%) responded that snus is addictive, though never tobacco users were most likely to answer incorrectly (8.3%) or to say they did not know if snus is addictive (14.0%; Table 2).

3.6. Comprehension of information about reducing health risks

There was good comprehension in the specific tobacco user group(s) for whom particular information is most germane. As shown in Table 3, a majority of current cigarette smokers (80.9%) understood that smokers should "stop smoking completely and use Camel Snus instead" to receive a health benefit, while few indicated that snus should be used while continuing to smoke (5.8%). Similarly, a large majority of current cigarette smokers (90.9%) correctly understood that "quitting is the best choice for a smoker who is concerned about health risks from smoking", with small proportions indicating the wrong answer (3.7%) or unsure of the correct response (5.4%) (Table 2). Finally, 70.0% of current cigarette smokers and 73.9% of former tobacco users correctly responded that "Camel Snus is NOT a safer alternative than quitting tobacco entirely"; 20.1% and 13.6%, respectively, answered incorrectly (Table 4).

Table 2
Comprehension of the information about using Camel Snus for current cigarette smokers (n = 896), and former (n = 1,526) and never (n = 1,500) tobacco users.

"Does Camel Snus reduce the risk of other smoking-related diseases that are not discussed in the ad?"

	Yes	No	Don't know/Not sure
	% (95% CI)	% (95% CI)	% (95% CI)
Current cigarette smokers	22.2% (18.8%–25.6%)	32.1% (28.4%–35.8%)	45.7% (41.8%–49.7%)
Former tobacco users	17.1% (14.9%–19.3%)	30.9% (28.3%–33.5%)	52.0% (49.2%–54.8%)
Never tobacco users	14.5% (12.5%–16.5%)	38.4% (35.6%–41.1%)	47.1% (44.3%–49.9%)

"Is Camel Snus, which contains nicotine, addictive?"

	Yes	No	Don't know/Not sure
	% (95% CI)	% (95% CI)	% (95% CI)
Current cigarette smokers	85.6% (82.9%–88.4%)	3.6% (2.2%–5.0%)	10.8% (8.3%–13.3%)
Former tobacco users	87.9% (86.0%–89.9%)	2.7% (1.8%–3.7%)	9.3% (7.6%–11.0%)
Never tobacco users	77.7% (75.3%–80.1%)	8.3% (6.6%–9.9%)	14.0% (12.0%–16.0%)

"Is quitting the best choice for a smoker who is concerned about the health risks from smoking?"

	Yes	No	Don't know/Not sure
	% (95% CI)	% (95% CI)	% (95% CI)
Current cigarette smokers	90.9% (88.6%–93.3%)	3.7% (2.3%–5.2%)	5.4% (3.5%–7.2%)
Former tobacco users	93.1% (91.6%–94.6%)	3.8% (2.7%–4.9%)	3.2% (2.1%–4.2%)
Never tobacco users	83.6% (81.5%–85.8%)	8.6% (7.0%–10.2%)	7.8% (6.2%–9.4%)

"Should adults who do not use or who have quit using tobacco products start using Camel Snus?"

	Yes	No	Don't know/Not sure
	% (95% CI)	% (95% CI)	% (95% CI)
Current cigarette smokers	7.6% (5.4%–9.8%)	80.4% (77.1%–83.7%)	12.0% (9.3%–14.7%)
Former tobacco users	3.9% (2.8%–5.0%)	87.8% (85.9%–89.8%)	8.3% (6.6%–9.9%)
Never tobacco users	4.6% (3.4%–5.8%)	82.7% (80.5%–84.9%)	12.7% (10.8%–14.6%)

3.7. Comprehension of other information in the modified-risk advertisement

A majority of current cigarette smokers (67.4%) correctly endorsed the statement "Camel Snus is NOT a safer alternative than products that are used to quit tobacco such as gum, patches, and lozenges", while approximately equal proportions gave an incorrect answer (15.4%) or indicated they did not know the answer (17.2%) (Table 4).

Respondents were asked, "Should adults who do not use or who have quit using tobacco products start using Camel Snus?". Large majorities of never and former tobacco users (the two groups for whom this information is most relevant) responded correctly (82.7% and 87.8%, respectively), while few answered incorrectly (4.6% and 3.9%) (Table 2).

Table 3
Comprehension of the information about receiving a health benefit with Camel Snus for current cigarette smokers (n = 896), and former (n = 1,526) and never (n = 1,500) tobacco users.

"According to the ad, what do smokers need to do in order to receive a health benefit from using Camel Snus?"

	Stop smoking completely and use Camel Snus instead	Continue to smoke but use Camel Snus as well	Don't know/Not sure
	% (95% CI)	% (95% CI)	% (95% CI)
Current cigarette smokers	80.9% (77.8%–84.1%)	5.8% (3.8%–7.8%)	13.3% (10.6%–15.9%)
Former tobacco users	85.2% (83.2%–87.3%)	2.1% (1.4%–2.9%)	12.6% (10.7%–14.5%)
Never tobacco users	74.7% (72.2%–77.2%)	3.5% (2.4%–4.6%)	21.8% (19.5%–24.2%)

3.8. Comprehension among respondents with limited health literacy

Results were examined by health literacy status for the six comprehension questions (data not shown). Compared to those with adequate health literacy, respondents with limited health literacy typically showed lower comprehension of the information and were consistently more likely to answer, "don't know" (odds ratios ranging from 1.8 to 5.1; p's < 0.0001 [see Supplemental Table 14]). Limited health literacy respondents answered "don't know" 24.2% of the time versus 9.6% of the time for respondents with adequate health literacy ($p < 0.0001$; see Supplemental Table 15). Across questions, limited health literacy respondents were more likely to respond, "don't know" (averaging 24.2% of the time) than to respond incorrectly (12.0%).

4. Discussion

This study assessed comprehension and risk perceptions after exposure to modified-risk information about Camel Snus, a low nitrosamine SLT product that presents less risk of disease than cigarettes. Although, as expected, comprehension scores were not perfect, strong majorities of current cigarette smokers, and former and never tobacco users understood the various modified-risk and balancing information. The information that smokers who switch completely from cigarettes to snus may greatly reduce their risk of lung cancer, respiratory disease, heart disease, and oral cancer was understood by a majority of respondents in each tobacco user group, with average risk ratings being lower for snus relative to cigarettes and other SLT products (Fig. 1). The three tobacco user groups showed very similar patterns of responses across the different tobacco products and diseases.

Absolute risk ratings for snus consistently averaged above the midpoint of the 7-point scale, implying perception of considerable risk. Respondents understood that snus presents less risk than cigarettes, but still presents some risk and is not completely safe. Very few considered snus to be without risk (Fig. 2).

Respondents generally *underestimated* the degree of risk reduction that smokers might gain from switching completely to snus. Experts have assessed that snus use presents about 90% less risk than cigarette smoking (Levy et al., 2004). However, respondents' absolute risk ratings implied very modest reductions compared to cigarette smoking, thus understating the actual risk reduction, particularly for lung cancer and respiratory disease. Given the explicit statement in the modified-risk information that switching completely from cigarettes to snus reduces the risk of the four diseases, it was striking that, across the four diseases, between one-fifth and one-third of respondents in the various tobacco users groups believed that—based on the information provided—snus presented the *same* risk as continuing to smoke. Respondents

Table 4
Comprehension of the information about Camel Snus as a safer alternative for current cigarette smokers (n = 896), and former (n = 1,526) and never (n = 1,500) tobacco users for the true/false questions.

"Which of the following statements is true?"

	Camel Snus is a safer alternative than quitting tobacco entirely. % (95% CI)	Camel Snus is NOT a safer alternative than quitting tobacco entirely. % (95% CI)	Don't know / Not sure % (95% CI)
Current cigarette smokers	20.1% (17.0%–23.2%)	70.0% (66.5%–73.6%)	9.8% (7.5%–12.2%)
Former tobacco users	13.6% (11.5%–15.6%)	73.9% (71.3%–76.5%)	12.5% (10.6%–14.5%)
Never tobacco users	12.0% (10.1%–13.8%)	69.1% (66.5%–71.7%)	18.9% (16.7%–21.2%)

"Which of the following statements is true?"

	Camel Snus is a safer alternative than products that used to quit tobacco such as gum, patches, and lozenges. % (95% CI)	Camel Snus is NOT a safer alternative than products that used to quit tobacco such as gum, patches, and lozenges. % (95% CI)	Don't know/Not sure % (95% CI)
Current cigarette smokers	15.4% (12.5%–18.2%)	67.4% (63.8%–71.1%)	17.2% (14.3%–20.1%)
Former tobacco users	10.5% (8.7%–12.3%)	66.0% (63.3%–68.7%)	23.5% (21.1%–25.9%)
Never tobacco users	10.4% (8.7%–12.1%)	61.9% (59.2%–64.6%)	27.7% (25.2%–30.2%)

likely formulated their responses not only on what they read and understood from the advertisement, but also on their pre-existing beliefs regarding risks of tobacco products, as many people believe SLT products are as harmful as smoking (Fong et al., 2019; Kaufman et al., 2014; Kiviniemi & Kozlowski, 2015; Liu et al., 2015; Regan, Dube, & Arrazola, 2012; Wackowski et al., 2019; Wray et al., 2012).

The results also suggested that respondents made distinctions among the four diseases, even though the modified-risk information claimed risk reduction for each disease without distinguishing among them or providing comparative or quantitative information. Intuitively, people believe that because SLT comes in contact with the mouth, its effects on oral cancer must be greater than on respiratory disease (Choi et al., 2012; Pepper et al., 2015). Conversely, people think of smoking as affecting the lungs, neglecting the fact that smoke passes through the mouth, making cigarette smoking a high risk for oral cancer (US Department of Health and Human Services, 2014). The pattern of results suggests that respondents applied their own beliefs and insufficient understanding of disease, and not just their understanding of the information provided, to assess absolute risks and relative risks.

Thus, the results are consistent with documented public misperceptions about SLT. Given these views, the skepticism with which reduced-risk information is received (Borland, Li, & Cummings, 2012; Fix et al., 2017), and the fact that the source of the information in this study was an advertisement from a tobacco company (which consumers believe to be less credible than health professionals and other trusted sources of health information [Byrne, Guillory, Mathios, Avery, & Hart, 2012; Owusu, Weaver, Yang, Ashley, & Popova, 2019]), it is understandable that some respondents continued to believe that snus was as harmful as cigarettes. Modified-risk information may need repetition and endorsement from multiple authoritative sources to become more persuasive and believable to consumers—and to overcome widely held misperceptions—in order to change beliefs and to support changes in tobacco use behaviors.

Consumers hold similar misperceptions about NRT, believing it to be unsafe (Bansal, Cummings, Hyland, & Giovino, 2004; Ferguson et al., 2011; Heavner, Rosenberg, & Phillips, 2009; Shiffman, Ferguson, Rohay, & Gitchell, 2008). Such misperceptions may have influenced respondents' uncertainty about whether snus is safer than those medications.

Some respondents (29.3%) in this study did not provide the correct answer or did not know that switching to snus is *not* a safer alternative to quitting tobacco. This may have been because the statement to which they were responding was a negation, which may have made answering a true/false question confusing. Notably, the findings from this study demonstrate that even after exposure to the modified-risk information, large majorities understood that snus should not be used by those who are not already using tobacco. Respondents also understood the statements that quitting smoking is the best choice for smokers, and that snus is addictive.

Generally, comprehension of the modified-risk and balancing information was good across the three tobacco user groups, and there was good comprehension in the groups for whom particular information is most relevant (e.g., current smokers understood that quitting is the best option). Respondents with limited health literacy typically showed lower comprehension, being particularly likely to give "don't know" responses. This is consistent with other studies that have repeatedly demonstrated an association between limited health literacy and lower comprehension of consumer communications, including prescription and over-the-counter drug labels (Davis et al., 2006; Raymond, Dalebout, & Camp, 2002; Wolf, Davis, Tilson, Bass, & Parker, 2006) and FDA risk communications (McCormack, Craig Lefebvre, Bann, Taylor, & Rausch, 2016; Shiffman, Gerlach, Sembower, & Rohay, 2011). The advertisement communicated a substantial amount of information, which can complicate communications, particularly in a single, brief exposure. Repeated and prolonged exposure, or expression of the modified-risk information in different ways from different sources may improve comprehension among those with limited health literacy.

The results of this study indicate that modified-risk and balancing information can be effectively communicated, without promoting misconceptions such as a belief that snus is completely safe. This suggests that such information could help motivate cigarette smokers to switch to snus, while avoiding attracting non-users of tobacco. Indeed, a companion study also exposed a range of US adults to this modified-risk information and found that interest in snus, and projected use of snus,

was greatest among current smokers who could benefit by switching to snus, with low rates of likely use among those who might be harmed by adopting snus (Gerlach, Shiffman, Battista, Polster, & Curtin, 2019).

4.1. Study strengths

This study had considerable strengths. The sample was large, diverse, weighted to match the demographic characteristics of US adults, and included individuals with a range of tobacco use states. The study used questions drawn from the published literature, and evaluated perceived risks using both direct and indirect assessments, with consistent, convergent results. In addition, the study's findings were replicated in two very similar executions of this study (US Food and Drug Administration, 2018b).

4.2. Study limitations

This study also had limitations, including the fact that the sample was drawn from an online panel, and thus may not be fully representative of the US population. The advertisement was evaluated online, as an on-screen display in a research context; such methods are often used to evaluate communications (Sullivan & O'Donoghue, 2015), and there is little reason to think results would not generalize to other media. The current study assessed a particular set of modified-risk information; other information might perform differently. However, two studies testing slightly different modified-risk information with the same methods yielded very similar results (US Food and Drug Administration, 2018b), suggesting that the findings are relatively robust to such variations in the information.

The study measured the effects of a single exposure of the modified-risk advertising, as opposed to the effects of multiple advertising exposures over time in the real world. It is possible that repeated exposure over time would lead to improved understanding of the absolute and relative health risks of snus and cigarettes (Borland et al., 2012). The advertisement communicated a great deal of presumably new information about snus and its risk-reduction potential relative to continued smoking. Nonetheless, the results indicate good comprehension of the modified-risk information.

4.3. Conclusions

Across a broad sample that included representatives of three different tobacco user groups, respondents demonstrated good understanding and application of the modified-risk information and did not develop misperceptions that snus is completely safe. Balanced information about reduced risk may support smokers taking action to reduce the harm from cigarette smoking.

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Contributors

MP and GC designed the study; MP was responsible for data collection; MP, MS, and SS had contributing roles during the analysis of data; all authors had a role in interpreting the data, writing the manuscript, and approving the paper for publication.

Credit authorship contribution statement

Janine L. Pillitteri: Writing - original draft, Writing - review & editing. **Saul Shiffman:** Validation, Formal analysis, Writing - review & editing. **Mark A. Sembower:** Formal analysis, Visualization. **Michael R. Polster:** Methodology, Investigation, Data curation. **Geoffrey M. Curtin:** Conceptualization, Supervision, Writing - review & editing.

Declaration of Competing Interest

Dr. Curtin is employed by RAI Services Company, a wholly owned subsidiary of Reynolds American Inc., whose operating companies market smokeless tobacco products including Camel Snus. Drs. Shiffman and Pillitteri and Mr. Sembower are employees of PinneyAssociates, Inc. PinneyAssociates provides consulting services on smoking cessation and tobacco harm reduction (including smokeless tobacco and vapor products, but not combustible cigarettes) to RAI Services Company, a subsidiary of Reynolds American Inc., now a subsidiary of British American Tobacco. Dr. Shiffman also owns an interest in intellectual property for a novel nicotine medication that has neither been developed nor commercialized. Dr. Polster is employed by NAXION, which provides consulting and research services to RAI Services Company.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.abrep.2020.100254.

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Original investigation

A Randomized Clinical Trial of Snus Examining the Effect of Complete Versus Partial Cigarette Substitution on Smoking-Related Behaviors, and Biomarkers of Exposure

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Abstract

Introduction: This 8-week multisite, randomized controlled trial of snus examined the differential effects of instructions on (1) snus use, (2) smoking and smoking-related measures, and (3) exposure to tobacco-related constituents.

Method: US adult daily cigarette smokers (n = 150; 43.3% female; $Median_{age}$ = 43.5) were recruited from Minneapolis, Minnesota; Columbus and Coshocton, Ohio; and Buffalo, New York. Following a 1-week sampling phase of snus, participants who used at least 7 pouches were randomized to either (1) partial substitution (PS; "use snus as you like with your cigarettes"), (2) complete substitution (CS; "avoid cigarettes"), or (3) usual brand cigarettes (UB). Analyses included between-group analyses (eg, PS vs. CS) using Wilcoxon rank sum test of cigarettes per day and snus pouches per day, and a linear mixed model (biomarkers).

Results: Compared to the PS and UB groups, smokers assigned to CS reported greater reductions in cigarettes per day (ps < .001), using more snus pouches per day (p = .02), and more smoke-free days (CS median = 14.5, PS and UB medians = 0, p < .001). In addition, results demonstrated reductions in carbon monoxide (p < .001), total nicotine equivalents (p = .02), and four out of five measured volatile organic compounds (ps < .01) over time among the CS group. Exposure to *N'*-nitrosonornicotine increased by trial end only among the PS group (p < .04). Phenanthrene tetraol increased among all groups by trial end (p = .02) with no difference between groups.

Conclusions: Instructions to completely switch from cigarettes to snus resulted in the greatest reduction in cigarettes and exposure to harmful constituents.

Implications: Directly instructing smokers to switch completely to snus, rather than using *ad libitum* (with no instructions to avoid cigarettes), is necessary for reductions in smoking and subsequent exposure to harmful constituents.

Introduction

Snus, a smokeless tobacco product with purportedly lower levels of tobacco-specific nitrosamines, results in substantially lower exposure to harmful constituents compared to cigarettes. Thus, switching from cigarettes to snus completely could reduce smoking-related death and disease.[1–4] For example, Sweden observed a significant reduction in tobacco-related disease over the past several decades as more smokers switched to snus.[2] A recent review of Swedish cohorts found that many smokers who switched to snus have similar risks of cancer and cardiovascular disease as smokers who quit tobacco altogether.[5,6] Given the introduction of snus in the United States, it is important to examine potential ways to optimize any beneficial effects and minimize any negative impacts when smokers are considering snus as an alternative nicotine product.

Instructions for use will likely influence the extent of snus uptake, smoking behaviors, and potentially subsequent health effects. In research examining switching from cigarettes to snus, instructions for use have varied from partial to complete substitution, and from prescribed minimum product use to *ad libitum* use (use as you like).[7] Results from these studies suggest that smokers can successfully reduce smoking with snus; however, complete substitution is rare, particularly when smokers are not instructed to stop smoking cigarettes.[7–9] However, no study to the best of our knowledge has randomized participants to and directly compared the effects of instructions for use on smokers' exposure to harmful constituents. Such data are important for informing regulatory decisions.

This study measured the effects of instructions for complete versus partial substitution of snus for cigarettes, on (1) snus use, (2) smoking and smoking-related factors, and (3) level of exposure to nicotine- and tobacco-related harmful constituents. In addition, patterns of cigarette and snus use over time were examined.

Methods

Participants

Smokers were recruited from Minneapolis, Minnesota; Columbus and Coshocton, Ohio, and Buffalo, New York between May 2013 and August 2016. Internet and local media advertisements read: "Smokers who want to try a new oral tobacco product are needed for a research study that may reduce their exposure to harmful tobacco smoke." Interested smokers who called the respective study site, were informed about the study, and were initially screened for eligibility over the telephone. Eligibility criteria included (1) at least 18 years of age, (2) smoking at least 5 cigarettes/day (CPD) for the past year, (3) no regular use of other nicotine/tobacco products (eg, ≤9 days/month), (4) good physical and mental health (eg, no unstable or untreated medical or psychiatric conditions), (5) not planning to quit smoking in the next 3 months, and (6) no chronic conditions affecting results of biochemical analyses (eg, liver disease). Participants were excluded if they were or had (1) a serious quit attempt in the past 3 months, (2) current or recent (<3 months) alcohol or drug abuse problems, (3) currently using nicotine replacement or other cessation methods, or (4) pregnant, planning to become pregnant, or breastfeeding. Each site's institutional review board approved this study (Clinicaltrials.gov #NCT01867242).

Design

The groups in this study were combined from two studies (study A and B) with similar designs, one of which also examined groups of e-cigarette use (study B) not included in this study. The only differences between the two study designs were the instructions for use and amount of monetary compensation (described later).

Orientation, Screening, and Sampling Phase (Week −3)

Potentially eligible participants were invited to an orientation visit during which they completed informed consent and further screening for medical and tobacco use history. Demographic and self-report measures of smoking-related variables were completed. Vitals and carbon monoxide (CO) were assessed, and pregnancy tests were conducted on women of childbearing potential. Smoking status was confirmed with exhaled CO at least 10 ppm (tested in the clinic); if CO was less than 10 ppm, then NicAlert test = level 6.

Next, eligible participants began the sampling phase. Participants chose two of three snus flavors to smell—Winterchill, Frost, or Robust—in blinded tins for 30 seconds. Participants sampled the product for a timed 5-minute period. After each sampling, they completed several questionnaires about the product (not reported here). Participants drank water and ate a saltine cracker to cleanse their palate between samplings.

Participants chose their preferred flavor and were provided four tins containing 15 pouches each to sample over the next week. Participants were told "Some people like snus and use a lot, others do not like it and don't use it. Use the product as you wish over the next week. Most people get the maximum effect if they keep the pouch in their mouth for at least 30 minutes." They were also instructed on how to complete daily automated phone calls regarding the previous day's tobacco use and scheduled for their second appointment 1 week (±3 days) later.

Sampling Phase, Week −2

After 1 week, participants returned to the clinic with snus tins and unused snus pouches. Tobacco use over the past week was assessed and participants completed self-report questionnaires. Participants who used at least seven snus pouches (based on potential use of one pouch per day) and continued to smoke were eligible to enter the clinical trial. These criteria were withheld from participants to ensure an unbiased willingness to use snus.

Clinical Trial Phase

Following the sampling week, participants attended a total of 8 visits over 10 weeks including 2 baseline weeks (weeks −1 and 0). During the baseline weeks, they smoked as usual, provided first morning urine samples, and completed daily phone diaries of tobacco use.

At week 0, participants were randomized to 1 of the 5 conditions for 8 weeks: (1) smoking usual brand cigarette control (UB); (2) complete substitution—*ad libitum* snus use (ie, "stop smoking cigarettes and use only snus; use the snus whenever you like; use enough snus to satisfy your cravings for cigarettes"); (3) complete substitution—specific instructions for snus use (ie, those smoking ≤20 CPD were instructed to use ≥8 snus pouches per day [SPD], and ≥20 CPD were instructed to use ≥12 SPD); (4) partial substitution—*ad libitum* snus use (ie, "use snus whenever you like instead of a cigarette; smoke as many or as few cigarettes as you want"); and (5) partial substitution—specific instructions (similar snus dosing as complete substitution—specific instructions group). Mid-study, conditions (3) and (5) were eliminated to increase recruitment numbers. For data analyses, instructions for use and study (A or B) were entered as covariates and groups were combined based on substitution instructions (complete

vs. partial substitution). This article reports on three groups: UB, partial substitution (PS), and complete substitution (CS).

At each following visit, daily phone diaries were reviewed, CO was measured, all tins and unused snus were collected and counted, and participants completed self-report measures. At each visit, all groups engaged in sessions in which compliance to product use instructions were discussed. For those in the CS groups who were unable to completely switch, participants problem-solved ways to foster complete switching. At week 8, all subjects were strongly encouraged to stop using all tobacco products and coached on setting a quit date.

Compensation

In study A, participants could earn up to $585. Participants received compensation for transportation ($5 per visit), clinic visits ($40 including a follow-up visit), daily diary completion (up to $150), protocol compliance ($290; including avoiding cigarettes for those in the CS groups), and two follow-up phone calls ($10). In study B, total compensation increased to $750. Specifically, participants received $25 per clinic visit and an additional "bonus" $25 for urine samples, protocol compliance (eg, avoiding cigarettes for those in the CS groups), and daily diary completion.

Products

Participants chose from Winterchill, Frost Large, and Robust flavored Camel Snus (Reynolds American Inc, Winston-Salem, NC) with 2.5–2.6 mg free nicotine per pouch, according to our analyses. Participants indicating the dose was too strong were switched to a small pouch Frost or Mellow, which contains 1.5-mg nicotine per pouch. All snus were provided free to participants.

Measures

Demographics and Tobacco Use

Demographic and tobacco use variables were collected for eligibility and potential moderators. Participants reported cigarette, snus, and other nicotine-containing product use via daily automated phone calls. The following tobacco use variables were assessed at clinic visits: CPD and SPD, and nicotine dependence via the Fagerström Test for Nicotine Dependence (FTND).[10] FTND total scores were used (range 0–10) with higher scores indicating greater dependence. The 20-item Center for Epidemiological Studies-Depression (CES-D) scale[11] was completed at baseline and week 8 to assess eligibility and monitor depressive symptoms.

Additional Measures Not Included

Additional measures assessing tobacco-related variables, evaluation of snus, psychiatric and medical variables, and perceived health risks were completed, but not reported here. At each visit, participants' blood pressure, heart rate, and oxygen saturation were measured.

Biomarker Analyses

Biomarkers included (1) urinary total nicotine equivalents (total nicotine + total cotinine + total 3′hydroxycotinine; TNEs),[12] (2) exhaled CO, (3) urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides (total NNAL) and *N*′-nitrosonornicotine (NNN), (4) urinary phenanthrene tetraol (PheT; a proxy for carcinogenic polycyclic aromatic hydrocarbons), and (5) urinary metabolites of volatile organic compounds (VOCs)—2-cyanoethylmercapturic acid (CEMA) for acrylonitrile, 3-hydroxypropylmercapturic acid (3-HPMA) for acrolein, 3-hydroxy-1-methylpropylmercapturic acid (HMPMA) for crotonaldehyde, 2-hydroxypropylmercapturic acid (2-HPMA) for propylene oxide, and *N*-acetyl-*S*-(2-carbamoylmethyl)-L-cysteine (AAMA) for acrylamide. These biomarkers come from an empirically informed panel of biomarkers for examining tobacco carcinogen and toxicant uptake for the purposes of tobacco product evaluation and cancer prevention.[13,14] See Supplementary Table 1 for a description of these biomarkers and example health effects.

Participants provided exhaled CO using a Bedfont Smokerlyzer. TNE, tobacco-specific nitrosamines, and mercapturic acids were analyzed using liquid chromatography–mass spectrometry.[15–19] PheT was analyzed by gas chromatography–tandem mass spectrometry.[16] Biomarker analysis was conducted as described in our previous work for NNAL,[16] NNN,[23] PheT,[16] 3-HPMA,[17] HMPMA,[17] CEMA,[17] 2-HPMA,[20] and AAMA.[20] Validation procedures from previously published work were used for each biomarker (TNE, creatinine[21]; NNAL, PheT, 3-HPMA, HMPMA, and CEMA[22]; NNN[23]; 2-HPMA[18]). Urinary creatinine concentrations were analyzed using a colorimetric microplate assay (CRE34-K01; Eagle Bioscience, Amherst, NH). All biomarker analyses were adjusted for creatinine to account for urine dilution variability between participants.

CO was collected weekly. Urinary TNEs were analyzed at baseline (week -1, 0) and weeks 4 and 8. All other biomarkers were analyzed at week 0, 4, and 8. TNEs at week –1 and 0 were averaged to create a baseline TNE measurement.

Data Analysis

Baseline demographics were summarized using median, range, frequency, and percent. Biomarkers below the limit of quantitation were imputed as 50% the limit of quantitation (samples below limit of quantitation = 15/371 (4%) for NNN, 3/495 (0.6%) for NNAL, and 0/396 (0%) across all MA biomarkers). No other data imputation procedures were conducted. All biomarkers were log-transformed and reported as geometric means. Chi-square and Wilcoxon rank sum tests were used to compare baseline demographic and tobacco use history variables between groups. All analyses were performed according to the intent-to-treat principle.

Poisson regression with repeated measures using generalized estimating equations was used to evaluate CPD and SPD between weeks from baseline until week 8. These endpoints were modeled via the logarithmic link function. The optimal variance–covariance structure was autoregressive for CPD and independent for SPD determined by the quasi-likelihood under independence model criterion.[24] A linear mixed model was used to compare study groups and timepoints when analyzing the biomarkers.[25] To model the within-subject effect, the optimal variance–covariance matrix was selected for each biomarker based on the Akaike and Bayesian information criteria. The following analytic approach was used for all the repeated measures analyses. First step: unadjusted model including the group indicator, week, and their interaction. If the interaction p value was greater than .1, the interaction term was dropped. Second step: adjusted model that included a preselected set of baseline covariates in addition to the group and week. If the interaction p value was less than .1, the three study groups were analyzed separately with an adjusted model including the week and the preselected covariates (baseline sex, race [white/nonwhite], age, employment [part/full time vs. other], FTND, CES-D, TNE, *ad libitum*/instructions, study A or B, and use of other combusted tobacco. Using a stepdown selection procedure to obtain the most parsimonious model, only significant covariates (p value < .05) were retained. Group and week indicators always remained in the model. The coefficients from the regression models are exponentiated

to represent the estimated ratio (95% CI) of CPD, SPD, and biomarkers in their original scale for every one unit per level increase in the covariates. Linear mixed models and generalized estimating equation models treat occasional missing observations or missed visit as missing at random. The frequent dropouts in this study were compared between groups in a separate analysis using a chi-square test.

Between-group analyses (PS vs. CS) of CPD and SPD at each week were conducted using Wilcoxon rank sum test. Paired *t* tests were conducted to determine when patterns of use stabilized by examining mean change scores in CPD and SPD from week to week. Days with no cigarette smoking were summarized by study group as the median percent of smoke-free days over the entire study period, the frequency of smoke-free weeks, and the percent of smokers that had at least one smoke-free day. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC). Final analyses were considered statistically significant with *p* less than .05.

Results

Participant Characteristics

Of the 1806 individuals who were phone screened (792 of these participants responded to a study advertisement that also included e-cigarette groups not reported here), 435 consented, and 150 were eligible to be randomized to the clinical trial. The most common reasons for ineligibility were nonmedical reasons (*n* = 85; eg, other tobacco use), medically ineligible (*n* = 51), lost to follow-up during baseline (*n* = 49), insufficient snus use during the sampling phase (*n* = 33), and personal reasons (*n* = 14; eg, too busy). Only three participants withdrew from the study due to reporting disliking the product during sampling. Fifty participants were randomized to e-cigarette conditions not reported here.

Table 1 shows baseline demographic information and tobacco use history of randomized participants across groups. Participants were primarily white (68.0%), with 43.3% female and a median age of 43.5 years. Nicotine dependence differed between groups at baseline; participants in the CS group (FTND median = 3.0) were more dependent on tobacco than the other two groups. Most participants chose Winterchill or Frost-flavored snus (69.2%–78.1%). There were no significant differences in dropout rates between groups following randomization (dropouts: CS, *n* = 24, 50%; PS, *n* = 16, 30.2%; UB, *n* = 8, 36.4%; *p* > .05). Most dropouts occurred by week 4 (week 1 [*n* = 15, 31.3%], week 2 [*n* = 8, 16.7%], week 3 [*n* = 7, 14.6%], week 4 [*n* = 7, 14.6%], week 6 [*n* = 3, 6.3%], and week 8 [*n* = 8, 16.7%]).

Table 1. Demographics Across Use Groups

Variable	Total (*N* = 150)	Complete substitution (*N* = 64)	Partial substitution (*N* = 60)	Usual brand (*N* = 26)	*p* value[a]
Study site, *N* (%)					
UMN	45 (30.0)	17 (26.6)	20 (33.3)	8 (30.8)	
OSU/Coshocton Clinic	84 (56.0)	37 (57.8)	33 (55.0)	14 (53.9)	.92
Roswell	21 (14.0)	10 (15.6)	7 (11.7)	4 (15.4)	
Age, median (min/max)	43.5 (18/83)	42.5 (18/83)	42.0 (18/64)	47.0 (23/68)	.38
Sex, Female, *N* (%)	65 (43.3)	28 (43.8)	24 (40.0)	13 (50.0)	.69
Race, *N* (%)					
White	102 (68.0)	44 (68.8)	43 (71.7)	15 (57.7)	
Black	43 (28.7)	16 (25.0)	16 (26.7)	11 (42.3)	.30[b]
Other	5 (3.3)	4 (6.3)	1 (1.7)	0 (0.0)	
Education, *N* (%)					
Eighth grade or less	1 (0.7)	1 (1.6)	0 (0.0)	0 (0.0)	
Some high school	13 (8.7)	7 (10.9)	5 (8.3)	1 (3.9)	
High school	44 (29.3)	17 (26.6)	20 (33.3)	7 (26.9)	—
Some college	70 (46.7)	26 (40.6)	28 (46.7)	16 (61.5)	
College grad	17 (11.3)	10 (15.6)	6 (10.0)	1 (3.9)	
Graduate/professional	5 (3.3)	3 (4.7)	1 (1.7)	1 (3.9)	
Education, *N* (%)					
High school/less	58 (38.7)	25 (39.1)	25 (41.7)	8 (30.8)	.63
Some college/more	92 (61.3)	39 (60.9)	35 (58.3)	18 (69.2)	
Income, *N* (%)					
Less than $30,000	97 (64.7)	42 (65.6)	39 (65.0)	16 (61.5)	.93
More than $30,000	53 (35.3)	22 (34.4)	21 (35.0)	10 (38.5)	
Current Employment, full/part-time, *N* (%)	55 (36.7)	26 (40.6)	17 (28.3)	12 (46.2)	.20
FTND total score, median (min/max)	3.0 (0/7)	3.0 (2/6)	3.0 (0/7)	3.0 (1/6)	.02[c]
CES-D (depression), median (min/max)	6.0 (0/34)	8.0 (0/34)	6.0 (0/19)	6.0 (0/24)	.07
Flavor, Winterchill/Frost, *N* (%)	104 (75.9)	50 (78.1)	45 (75.0)	9/13 (69.2)	.77
Baseline cigarettes/day, median (range)		14.0 (4.3/34.4)	11.7 (6.0/39.9)	12.1 (5.6/31.5)	.77
Baseline TNE nmol/mg creatinine, median (range)		58.3 (18.5/383.1)	55.9 (0.04/307.3)	65.7 (5.4/152.4)	.52
Dropout, *N* (%)	48 (32.0%)	24 (50.0%)	16 (30.2%)	8 (36.4%)	.12

CES-D = Center for Epidemiologic Studies Depression scale; FTND = Fagerström Test for Nicotine Dependence; OSU = The Ohio State University; TNE = total nicotine equivalents; UMN = University of Minnesota.

[a]The *p* values were derived from the chi-square test or the Wilcoxon rank sum test.

[b]This *p* value compares whites and blacks only.

[c]Participants assigned to Complete Substitution had higher FTND scores than the other groups.

Tobacco Use

Average CPD and SPD between groups and across weeks are shown in Figure 1. For CPD, a significant interaction emerged between week and study group ($p < .001$). Thus, the three groups were analyzed separately. The CS group reported significant reductions in CPD at each week compared to week 0 (CPD week 1:0 = 0.31, week 2:0 = 0.22, week 3:0 = 0.23, week 4:0 = 0.16, week 6:0 = 0.10, week 8:0 = 0.12; *ps* < .001); however, many smokers did not avoid cigarettes completely despite being incentivized and instructed to do so. The PS group reported a smaller but significant reduction in CPD at each week (except week 4) compared to week 0 (CPD week 1:0 = 0.92, $p = .004$; week 2:0 = 0.90, $p = .03$; week 3:0 = 0.90, $p = .04$; week 6:0 = 0.88, $p = .005$; week 8:0 = 0.86, $p = .002$). The UB group's CPD remained consistent throughout the trial, except for weeks 1 and 3, during which they reported a slight reduction compared to week 0 (CPD week 1:0 = 0.92, $p = .02$; week 3:0 = 0.91, $p = .02$).

No significant interaction emerged between week and study group for SPD. Over the 8-week study, the CS group used, on average, 36% more SPD than the PS group (SPD CS:PS ratio = 1.36, $p = .02$). For all snus groups, average SPD were significantly lower at week 1 (SPD week 1:8 = 0.78, $p = .002$) than week 8, but increased at week 2 to a similar amount used at week 8 (SPD week 2:8 = 0.99, $p = .84$), remaining consistent throughout the trial (*ps* > .05).

Between-week differences of SPD and CPD patterns among PS and CS groups are shown in Supplementary Tables 2 and 3. Stabilization of SPD occurred within 2 weeks among the PS and CS groups evidenced by significant increases in SPD from week 1 to 2 (PS $Mean_{change}$ = 0.88 SPD, $p = .001$; CS $Mean_{change}$ = 1.03 SPD, $p = .009$). Week-to-week changes in SPD were nonsignificant after week 2 (except for a slight drop at week 6 that eventually rebounded). Likewise, stabilization of CPD occurred within 2 weeks among CS group evidenced by significant decreases in CPD from week 0 to 1 ($Mean_{change}$ = −10.89 CPD, $p < .001$), week 1–2 ($Mean_{change}$ = −1.30 CPD, $p = .008$), and subsequent nonsignificant between week changes. However, stabilization of CPD occurred within the first week among the PS group evidenced by significant decreases in CPD from week 0 to 1 ($Mean_{change}$ = −1.23 CPD, $p = .002$), and nonsignificant changes from subsequent week to week. These patterns sustained when analyses were repeated among only participants who completed the entire trial.

Smoke-Free Days

Smoke-free days throughout the trial are shown in Supplementary Table 4. Over the 8-week study (~56 days), smokers in the CS group reported more smoke-free days (median = 14.5, range 0–61 days) than those in the PS and UB groups (PS and UB medians = 0, χ^2 (2, $N = 150$) = 52.8, $p < .001$).

When examining weeks with 100% smoke-free days, 80 weeks were identified, with 77 among the CS group and 3 among the PS group (all from one person). More smokers reported at least one smoke-free day, with the greatest number among the CS group (n = 34/48, 70.8%), followed by the PS group (n = 5/53, 9.4%), and the UB group (n = 2/22, 9.1%, $p < .001$; assuming those who dropped returned to smoking).

Supplementary Table 4 shows smoke-free weeks verified by a CO reading of less than or equal to 6 ppm among participants in the CS group. Among those who self-reported a smoke-free week, 84.4% were CO-verified (all weeks range = 66.7%–100%).

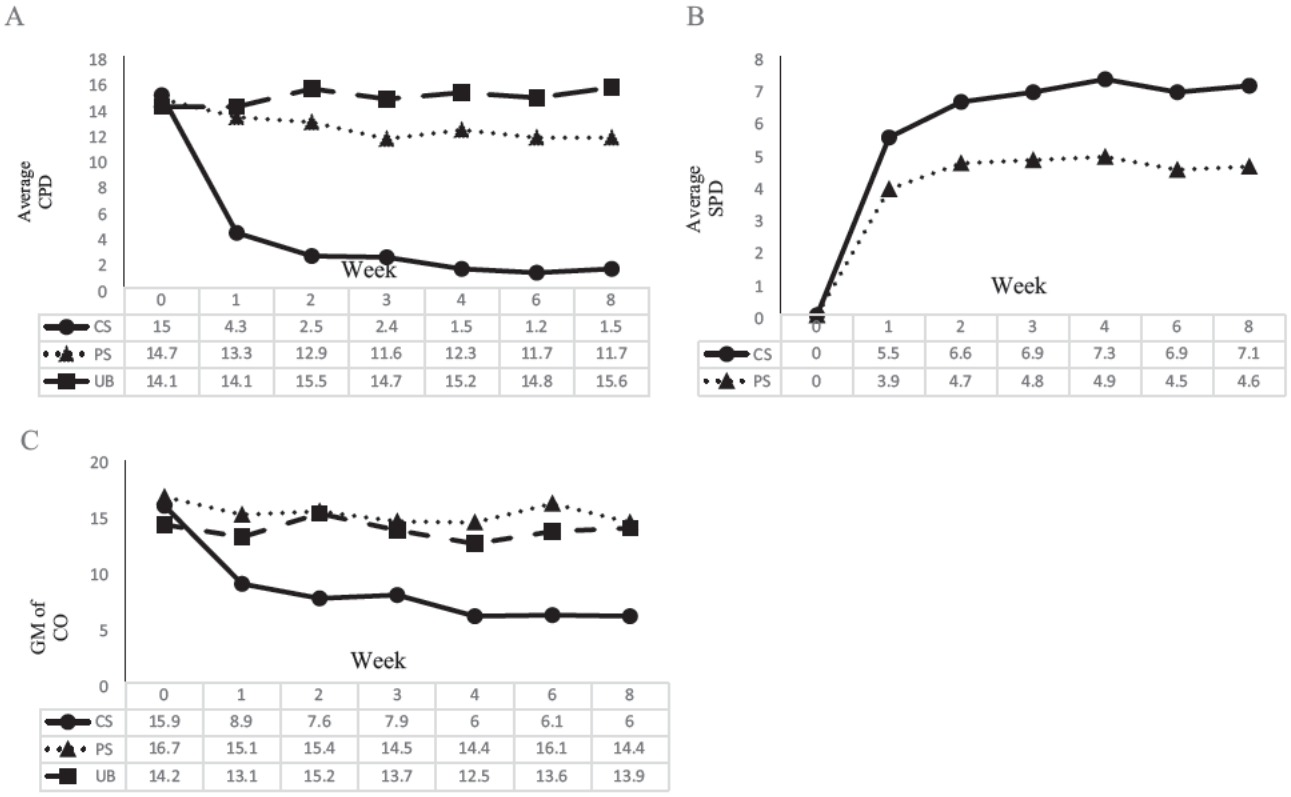

Figure 1. (A) Average CPD, (B) average SPD, and (C) exhaled CO by tobacco use group. CO = carbon monoxide; CPD = cigarettes per day; CS = complete substitution; GM = geometric mean; SPD = snus per day; PS = partial substitution; UB = usual brand.

Biomarkers

CO levels by group are shown in Figure 1. Table 2 shows geometric means and medians for the other biomarkers.

Carbon Monoxide

An interaction between week and study group emerged ($p < .001$). As a result, the three groups were analyzed separately. The CS group demonstrated significant decreases in CO throughout the trial compared to baseline ($ps < .001$). Compared to week 0, CO reduced by 45% by week 1 and 64% by week 8. The PS group demonstrated no significant changes in CO until week 8 (CO week 8:0 = 0.84, $p = .03$) and the UB group demonstrated no significant changes throughout the trial ($ps > .05$).

The stabilization of CO in the CS group occurred by week 2, as only weeks 0 (CO week 0:8 = 2.76, $p < .001$) and 1 (CO week 1:8 = 1.51, $p = .007$) were significantly different from week 8. Among the PS group, stabilization of CO occurred by week 1; only week 0 was significantly different from week 8 (CO week 0:8 = 1.17, $p = .046$).

Nicotine and Tobacco-Specific Nitrosamine

Significant interactions emerged between study group and week for urinary TNE ($p = .02$) and NNN ($p = .04$). Among the CS group, TNE levels decreased significantly from baseline to week 4 (ratio = 0.71, $p = .01$), but were nonsignificant from baseline to week 8 (ratio = 0.77, $p = .06$). Levels of TNE among the PS group showed a slight increase from baseline to week 4 that became statistically significant by week 8 (TNE baseline:4 = 1.17, $p = .11$; TNE baseline:8 = 1.22, $p = .047$). Levels of TNE among the UB group remained relatively unchanged ($ps > .05$). Levels of NNN remained the same for the CS ($ps > .05$) and UB groups ($ps > .05$) but increased by 75% among the PS group by the end of the trial (NNN week 0:4 = 1.50, $p = .07$; NNN week 0:8 = 1.75, $p = .01$). No interactions between week and study group emerged for NNAL ($p = .18$). Levels of NNAL remained the same across the trial and between study groups ($ps > .05$).

Phenanthrene Tetraol

No interaction between week and study group emerged ($p > .05$) for levels of PheT. Overall, there was a nonsignificant decrease in levels of PheT from week 0 to week 4 (PheT week 0:4 = 0.89, $p = .06$), followed by an increase from week 0 to week 8 (PheT week 0:8 = 1.17, $p = .02$). There were no differences between groups ($ps > .05$).

Volatile Organic Compounds

There were significant interactions between study group and week for CEMA ($p < .001$), 3-HPMA ($p = .003$), AAMA ($p < .001$), HMPMA ($p = .001$), but not 2-HPMA ($p > .05$). Levels of CEMA, 3-HPMA, AAMA, and HMPMA showed similar interactions patterns. Namely, levels of these biomarkers remained similar to baseline at weeks 4 and 8 among the PS and UB groups ($ps > .05$), with one exception for AAMA (ie, UB AAMA week 0:4 = 0.67, $p = .03$), but significantly lower levels of these biomarkers at weeks 4 and 8 among the CS group ($ps < .05$). Levels of 2-HPMA did not differ throughout the trial, nor between groups ($ps > .05$).

Discussion

Smokers instructed to completely substitute snus for their cigarettes reported smoking fewer CPD, using more SPD, experiencing more smoke-free days, and demonstrated reductions in some biomarkers of exposure levels (ie, TNE, CEMA, 3-HPMA, AAMA, and HMPMA). Although smokers who were instructed to use snus *ad libitum* demonstrated some reductions in reported CPD, most of their biomarkers of exposure levels did not differ from baseline and the UB group, and levels of TNE and NNN increased by the trial's end (suggesting an overall increase in tobacco exposure from snus).

These results indicate potential harm reduction can only be realized if smokers are instructed to stop smoking and completely switch to snus; partial reduction in smoking has minimal effects on biomarkers of exposure. Previous research has shown reductions in VOCs even when participants dual use[26]; however, this previous study observed larger reductions in CPD than observed in the current study (potentially due to the previous study's (1) higher CPD eligibility requirements, (2) research staff lit each cigarette for participants in a confined setting, and (3) participants were only able to smoke between 7 AM and 11 PM and every 32 minutes).

On the other hand, snus products are not free from risks. Levels of total NNAL did not decrease because of complete switching. Results from previous studies are mixed as to whether switching to snus lowers exposure to NNK, as some studies show reductions in urinary total NNAL[26,27] whereas other do not.[8] More importantly, smokers who used both cigarettes and snus (PS) demonstrated increases in NNN in this study. Slight increases in PheT were seen in this study, which is unlike previous studies that observed decreases in PheT levels even when smokers continued to use cigarettes.[26,28]

Patterns of use appeared to stabilize in 2–4 weeks. Snus use and CO largely stabilized by week 2. Similarly, many biomarkers of VOC exposure, with elimination half-lives conducive for a shorter clinical trial,[29,30] reached stabilization by week 4. Other biomarker levels continued to change from weeks 4 to 8 (eg, TNE, PheT).

This study has several limitations. First, smokers in the CS group were provided monetary bonuses for avoiding cigarettes, limiting real-world applications; however, this incentive allowed for better estimates of the maximal changes in biomarkers of exposure because of complete switching. Second, we combined two studies for analyses, one of which involved e-cigarettes; however, we statistically controlled for study A and B. Third, dropout rates ranged from 30% to 50%, with the highest rates among the CS group, potentially limiting generalizability. The dropout rates also might indicate that complete substitution with snus may be difficult to achieve for many smokers. A recent review of the literature showed that switching completely from cigarettes to smokeless tobacco is rare (0%–1.4% of adults).[31] Furthermore, although many smokers tried snus in efforts to cut back on cigarettes, uptake of snus is still relatively low.[32] Fourth, only smokers uninterested in quitting, who used at least seven pouches during the sampling phase, were eligible to enter the clinical trial. Then again, this procedure reflects consumers who are interested in continuing to use snus. Fifth, results of our own constituent analyses of snus products showed reductions in levels of NNN and NNK from 2013 to 2015. However, these reductions would not likely change the direction of the results as both complete and partial substitution groups experienced similar changes and we controlled for study group (A or B).

In summary, completely switching to snus seemingly reduces smokers' exposure to some harmful constituents (ie, acrolein, crotonaldehyde, acrylonitrile, acrylamide), but not all (NNK, propylene oxide, phenanthrene), whereas partial substitution increases exposure to nicotine and NNN. This finding suggests snus would be a modified risk product only if complete switching occurred. However, the uptake of this product and the success for complete switching may be low and therefore the public health benefit of snus as a modified risk product may be modest.

Table 2. Biomarkers Summary Statistics by Week and Study Group

Biomarker	Week	Study Group	*N*	GM (95% CI)	Median (Range)	*p* value[a]
GM TNE nmol/mg[b]	Baseline	UB	22	61.5 (44.8 to 84.5)	65.7 (5.4/152.4)	
		PS	53	48.3 (34.5 to 67.8)	55.9 (0.04/307.3)	.52
		CS	48	57.5 (48.9 to 67.6)	58.3 (18.5/383.1)	
	4	UB	15	52.3 (34.5 to 79.3)	55.1 (7.6/132.8)	
		PS	42	61.9 (47.3 to 81.0)	64.2 (1.6/257.7)	.09
		CS	26	42.2 (31.1 to 57.3)	44.8 (8.8/125.5)	
	8	UB	16	63.4 (42.7 to 94.0)	62.4 (8.0/167.8)	
		PS	39	65.0 (53.1 to 79.4)	68.5 (13.4/196.1)	.30
		CS	24	46.7 (32.5 to 67.0)	54.7 (4.7/178.6)	
GM NNAL pmol/mg creatinine	Baseline	UB	22	1.14 (0.65 to 2.00)	1.25 (0.02/9.48)	
		PS	53	1.06 (0.80 to 1.41)	1.14 (0.02/7.91)	.51
		CS	47	1.31 (1.03 to 1.66)	1.52 (0.07/5.28)	
	4	UB	15	1.29 (0.78 to 2.15)	1.17 (0.17/6.81)	
		PS	42	1.29 (1.02 to 1.64)	1.35 (0.20/8.73)	.94
		CS	26	1.15 (0.85 to 1.57)	1.39 (0.20/3.42)	
	8	UB	16	1.38 (0.91 to 2.08)	1.22 (0.22/5.66)	
		PS	39	1.27 (1.01 to 1.61)	1.14 (0.31/4.85)	.56
		CS	24	1.43 (1.07 to 1.91)	1.47 (0.33/4.30)	
GM NNN pmol/mg creatinine	Baseline	UB	22	0.022 (0.012 to 0.038)	0.030 (0.002/0.178)	
		PS	52	0.026 (0.017 to 0.039)	0.024 (0.001/1.527)	.89
		CS	45	0.027 (0.018 to 0.039)	0.027 (0.002/0.570)	
	4	UB	15	0.017 (0.008 to 0.036)	0.016 (0.002/0.291)	
		PS	41	0.044 (0.028 to 0.068)	0.046 (0.002/4.258)	.02
		CS	26	0.020 (0.012 to 0.036)	0.020 (0.002/0.187)	
	8	UB	16	0.023 (0.013 to 0.040)	0.030 (0.004/0.096)	
		PS	38	0.048 (0.029 to 0.080)	0.041 (0.003/11.187)	.18
		CS	24	0.025 (0.014 to 0.045)	0.027 (0.001/0.325)	
GM PheT pmol/mg creatinine	Baseline	UB	18	2.10 (1.58 to 2.81)	2.37 (0.63/4.39)	
		PS	46	2.15 (1.76 to 2.62)	2.13 (0.46/9.37)	.97
		CS	39	2.20 (1.81 to 2.67)	2.23 (0.72/7.16)	
	4	UB	15	1.79 (1.17 to 2.74)	2.11 (0.55/5.62)	
		PS	42	2.06 (1.66 to 2.55)	2.30 (0.28/6.57)	.62
		CS	26	1.76 (1.30 to 2.39)	1.81 (0.31/9.28)	
	8	UB	16	2.16 (1.48 to 3.13)	2.60 (0.58/5.45)	
		PS	38	2.58 (2.07 to 3.22)	2.71 (0.82/11.77)	.83
		CS	24	2.51 (1.79 to 3.53)	2.18 (0.75/18.42)	
GM CEMA pmol/mg creatinine	Baseline	UB	19	499.9 (311.9 to 801.2)	491.3 (46.2/2576.7)	
		PS	47	453.0 (335.6 to 611.5)	484.9 (2.9/1963.6)	.99
		CS	39	478.8 (381.8 to 600.5)	458.5 (99.8/2440.2)	
	4	UB	15	463.2 (313.6 to 684.2)	424.6 (140.9/1950.9)	
		PS	42	511.4 (396.8 to 659.0)	554.8 (30.1/2212.8)	.001
		CS	26	188.6 (112.5 to 316.0)	195.7 (13.9/4321.4)	
	8	UB	15	594.6 (441.9 to 800.0)	648.3 (225.1/1657.9)	
		PS	38	483.8 (365.0 to 657.5)	671.5 (41.8/2223.9)	.03
		CS	24	248.1 (142.7 to 431.2)	282.5 (21.9/2243.4)	
GM 2-HPMA pmol/mg creatinine	Baseline	UB	19	551.6 (386.4 to 787.3)	613.8 (171.7/2037.3)	
		PS	47	567.8 (471.2 to 684.2)	627.3 (153.0/1893.6)	.44
		CS	39	453.7 (351.2 to 586.1)	427.4 (73.6/2117.6)	
	4	UB	15	557.7 (350.7 to 887.1)	635.9 (171.6/4502.3)	
		PS	42	511.4 (383.5 to 682.0)	492.1 (30.1/3734.9)	.28
		CS	26	391.4 (265.2 to 577.7)	438.9 (92.3/6047.9)	
	8	UB	15	722.7 (465.3 to 1122.5)	522.9 (158.1/4302.6)	
		PS	38	589.2 (466.6 to 744.0)	609.6 (89.0/2026.2)	.60
		CS	24	500.5 (347.4 to 721.0)	580.6 (72.4/2311.6)	
GM 3-HPMA pmol/mg creatinine	Baseline	UB	19	5328.6 (3625.1 to 7832.7)	3902.3 (1495.4/33160.4)	
		PS	47	4240.9 (3459.5 to 5198.8)	4578.5 (815.2/17377.9)	.76
		CS	39	4482.9 (3650.3 to 5505.4)	4795.6 (994.4/20286.4)	
	4	UB	15	4098.5 (3070.5 to 5470.7)	4135.6 (1710.6/12307.4)	
		PS	42	5297.3 (4179.9 to 6713.4)	4959.8 (562.3/30538.1)	.002
		CS	26	2381.6 (1584.5 to 3579.8)	2245.7 (292.3/24270.9)	
	8	UB	15	4869.4 (3160.5 to 7502.2)	4798.2 (1091.9/16617.0)	
		PS	38	5269.5 (4071.3 to 6820.4)	5760.5 (615.8/18301.2)	.04

Table 2. Continued

Biomarker	Week	Study Group	*N*	GM (95% CI)	Median (Range)	*p* value[a]
		CS	24	3151.8 (2207.7 to 4499.5)	2856.5 (997.0/26281.5)	
GM AAMA pmol/mg creatinine	Baseline	UB	19	540.7 (358.8 to 814.7)	469.5 (99.4/2599.4)	
		PS	46	531.0 (419.9 to 671.4)	519.0 (45.8/3209.4)	.56
		CS	39	607.8 (509.8 to 724.8)	619.0 (232.3/1963.6)	
	4	UB	14	389.1 (280.7 to 539.4)	378.1 (159.0/1118.5)	
		PS	42	624.7 (499.1 to 781.8)	659.9 (50.5/2814.4)	.001
		CS	26	337.1 (237.4 to 478.8)	357.3 (25.8/2679.1)	
	8	UB	15	553.3 (393.3 to 778.6)	569.4 (194.8/1495.4)	
		PS	38	591.3 (480.4 to 727.8)	673.9 (145.6/2407.8)	.04
		CS	24	382.4 (281.7 to 519.0)	381.4 (88.5/1543.5)	
GM HMPMA pmol/mg creatinine	Baseline	UB	19	4620.3 (3197.5 to 6676.2)	4086.8 (1618.7/21661.2)	
		PS	47	3916.8 (3224.2 to 4758.2)	4326.6 (599.7/12709.7)	.90
		CS	39	4041.6 (3335.1 to 4897.8)	3871.2 (1331.9/10702.6)	
	4	UB	15	3765.3 (2674.5 to 5300.9)	3735.1 (990.1/9744.7)	
		PS	42	4894.1 (3940.1 to 6078.9)	4814.7 (776.7/22123.5)	.001
		CS	26	2072.2 (1417.0 to 3030.4)	1361.7 (520.8/11613.8)	
	8	UB	15	4365.6 (3013.6 to 6324.2)	4693.1 (1193.2/10319.0)	
		PS	38	4449.0 (3493.9 to 5665.1)	4689.9 (604.3/12362.2)	.19
		CS	24	3116.4 (2179.2 to 4456.6)	2506.0 (650.7/17596.4)	

CEMA = 2-cyanoethylmercapturic acid; CS = complete substitution; GM = geometric mean; HMPMA = 3-hydroxy-1-methylpropylmercapturic acid; HPMA = hydroxypropylmercapturic acid; PS = partial substitution; PheT = phenanthrene tetraol; TNE = total nicotine equivalent; NNN = *N′*-nitrosonornicotine; UB = usual brand.

[a]The *p* value is derived from the nonparametric Kruskal–Wallis test.

[b]TNE at baseline is the average of week 91 and 00.

Supplementary Material

Supplementary data are available at *Nicotine and Tobacco Research* online.

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Declarations of Interest

RO'C is a member of the FDA Tobacco Products Scientific Advisory Committee. PGS serves or has served as an expert witness in tobacco company litigation on behalf of plaintiffs.

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Brief Report

Smokers' Exposure to Perceived Modified Risk Claims for E-Cigarettes, Snus, and Smokeless Tobacco in the United States

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Abstract

Introduction: Based on arguments for harm reduction and health benefits, tobacco companies in the United States can apply for regulatory authorization to make "modified risk tobacco product" (MRTP) marketing claims. The impact of future MRTP claims may depend on whether they are noticed, believed, and lead to smokers switching products. This study provides baseline data about smokers' exposure to perceived MRTP claims ahead of any MRTP authorizations.

Aims and Methods: We analyzed measures from Wave 3 of the US-based Population Assessment of Tobacco and Health (PATH) study which asked smokers to indicate if they had seen any e-cigarettes, snus, or other smokeless tobacco (SLT) products that claim to be "less harmful" in the past 12 months, and their likelihood of using products with these claims in the next 30 days.

Results: Significantly fewer smokers noted having seen snus (5.1%) or other SLT (5.6%) with "less harmful" claims compared with e-cigarettes (29.1%). For each product, the prevalence of MRTP claim exposure was higher among smokers who perceived the product to be less harmful than smoking, who currently used the product, and who had higher rates of tobacco advertising exposure at the point of sale. Among smokers who noticed products with "less harmful" claims, about one-quarter said they would use them in the future (24%–27%).

Conclusions: Ahead of any Food & Drug Administration (FDA) authorization for MRTP claims, some smokers already perceive exposure to "less harmful" claims for e-cigarettes, but few do for SLT. MRTP claims may motivate some smokers to use these products.

Implications: This study provides new baseline data about smokers' perceived exposure to MRTP claims in the United States ahead of any regulatory claim authorization. Using data from Wave 3 of the US PATH study, we found that some smokers already perceive exposure to "less harmful" claims for e-cigarettes (29%), but few do for SLT (5%–6%). Among smokers who noticed products with "less harmful" claims, about one-quarter said they would use them in the future (24%–27%), suggesting MRTP claims may motivate some smokers to use products described as "less harmful."

Introduction

There is a growing recognition that different tobacco products pose different levels of risk and fall along a "continuum of risk."[1,2] Though not harmless, moist snuff smokeless tobacco, snus (a low nitrosamine type of moist snuff), and e-cigarettes pose significantly fewer health risks to individual users than cigarettes.[2–5] Thus, switching to these products may offer the potential for *harm reduction* for smokers who are unable or unwilling to quit nicotine. However, research indicates that consumers' perceptions about the comparative risks of tobacco products are often inconsistent with the continuum of risk. Many believe smokeless tobacco (SLT) and e-cigarettes are as harmful or more harmful than tobacco cigarettes.[6–8] As such, many tobacco control professionals have called for more accurate communication about the risks of such products relative to cigarettes.[8–10] Smokers may be receptive to such communications, with about half reporting they would be interested in using a tobacco product that claimed to be less harmful than other tobacco products.[11,12]

In the United States, tobacco companies are not permitted to make these types of comparative or "modified risk tobacco product" (MRTP) claims in their marketing or product labeling without authorization from the Food & Drug Administration (FDA). To date, applications from five brands, including a reduced-nicotine cigarette (22nd century), an electronic heated tobacco product (IQOS), and three SLT products (General Snus, Camel Snus, Copenhagen, Denmark) have been submitted. In October 2019, the FDA issued the first modified risk order to Swedish Match authorizing a claim that "Using General Snus instead of cigarettes puts you at lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis."[13] In July 2020, FDA authorized an exposure modification claim for IQOS, which states that switching completely from cigarettes to IQOS can "significantly reduces your body's exposure to harmful or potentially harmful chemicals."[14]

The potential impact of MRTP claims on population health may in part depend on whether smokers are exposed to these claims, perceive them to be salient and truthful,[15–17] and are motivated to try and completely switch to these products. This study provides baseline data about smokers' reported exposure to and potential behavioral response to MRTP claims for snus, other SLT, and e-cigarettes in the context of a regulatory landscape when no such claims had been authorized but ahead of several potential MRTP claim authorizations.

Methods

We analyzed data from the publicly available Wave 3 adult dataset of the Population Assessment of Tobacco and Health (PATH) study. The PATH study is a household-based, nationally representative, longitudinal cohort study of adults (ages 18+) and youth (12–17 years). The study uses audio computer-assisted self-interviews (ACASI) available in English and Spanish to collect self-reported information on tobacco use patterns and associated health behaviors. Recruitment for the Wave 1 cohort employed a stratified address-based, area-probability sampling design—Wave 1 methods details are published elsewhere.[18] Wave 3 data were collected from October 2015 through October 2016 and included responses from 28 148 adults, with an unweighted response rate of 78%. This analysis is limited to responses from 9013 current established smokers in the sample (ie, those who have used 100 cigarettes in their lifetime and now report smoking cigarettes some days or every day), the primary intended audience for nicotine harm reduction products/messages.

Measures

Primary measures included those about respondents' reported exposure to perceived MRTP claims and likelihood to use the products with these claims. Specifically, we examined responses to three questions that asked respondents to indicate whether, in the past 12 months, they had seen "any e-cigarettes or other electronic nicotine products that claim to be less harmful?," "any snus products that claim to be less harmful?," and "any smokeless tobacco products (such as dip, spit or chew) that claim to be less harmful?" Provided response options were "yes" and "no." Those who responded "yes" were asked a follow-up question about likelihood of using that product: "How likely is it that you will use one of these [e-cigarettes or other electronic nicotine products; snus products; smokeless tobacco products (such as dip, spit or chew)] that claim to be less harmful in the next 30 days?" Response options were dichotomized as very/somewhat likely or very/somewhat unlikely during analysis. These measures were asked for the first time on Wave 3.

Covariates included demographics and variables related to tobacco use, perceived product harmfulness relative to cigarettes, and exposure to tobacco marketing (see Supplementary Table S1). Current users of e-cigarettes, snus pouches, and other SLT were defined as those who reported using these products some days or every day. Harm perception measures asked whether using each product type was less harmful, about the same or more harmful than smoking cigarettes (dichotomized as "less harmful" versus "same or more harmful" during analysis). As an indicator of exposure to tobacco marketing, we included a question that asked participants "In the past 30 days, have you noticed tobacco ads or promotions on store windows or inside stores where tobacco is sold? (Yes/No)." We also included parallel product-specific marketing exposure measures that asked participants to indicate if they had received any discounts or coupons for e-cigarettes, snus pouches, and other SLT.

Analyses

We used PATH Wave 3 single wave survey weights (as recommended in the PATH User Guide)[19] to generate prevalence estimates and adjusted odds ratios (AORs) of reported exposure to perceived e-cigarette, snus, and SLT MRTP claims and likelihood of using one of these products. The weighting procedures adjusted for oversampling and nonresponse, yielding nationally representative estimates of the noninstitutionalized, adult civilian US population in 2015–2016. Individuals missing the outcomes or covariates included in a table were excluded from those analyses. We developed multivariable logistic regression models for exposure to a perceived MRTP claim and use likelihood for each of the three products, adjusting for participants' sociodemographic and non-cigarette tobacco use characteristics. We also included as covariates PATH measures from the Global Appraisal of Individual Needs–Short Screener (GAIN-SS) that assess internalizing mental health related problems (eg, symptoms of anxiety and depression) and externalizing problems (eg, lying and violent behavior). Model 1 (claim exposure) also adjusted for engagement with product marketing (eg, receiving coupons). We collapsed variable levels when sample sizes for that variable and the outcome restricted analyses (eg, race). All analyses were conducted in Stata/SE version 16.0.

Results

Exposure to Perceived MRTP Claims

Overall, 29.3% of current smokers indicated having seen e-cigarettes claiming to be "less harmful" while significantly fewer reported having seen snus (5.1%) or other SLT (5.6%) with such claims (Supplementary Table S1).

The odds of noticing e-cigarette MRTP claims did not differ by sex for e-cigarettes but were significantly higher among males versus females for snus (AOR = 1.4) and other SLT (AOR = 1.2) (Supplementary Table S1). For all three products, the prevalence of noticing MRTP claims was highest among the 18–24- and 25–34-year age groups. The odds of claim exposure were lower among black versus white smokers for e-cigarettes, but higher among black versus white smokers for snus and other SLT. The odds of noticing e-cigarette MRTP claims were lower for those with less education, but those with less education had higher odds of noticing snus and SLT claims. Odds of noticing e-cigarette claims were also higher among those with high levels of externalizing symptoms (AOR = 1.3).

For each product type, the odds of exposure to perceived MRTP claims for that product were significantly higher among product users versus nonusers (e-cigarettes, AOR = 1.3; snus, AOR = 1.6; other SLT, AOR = 1.4). In terms of risk perceptions, the prevalence of claim exposure was also significantly higher among those who perceived the product to be "less harmful" than smoking compared with "as or more harmful" for each product type (e-cigarettes, 34.4% versus 27.9%; snus, 10.2% versus 4.7%; other SLT, 11.4% versus 5.2%). Claim exposure was also significantly higher among smokers who reported exposure to tobacco advertising at the point of sale in the past 12 months versus those who did not (e-cigarettes, AOR = 2.1; snus, AOR = 1.6; other SLT, AOR = 1.9). Receiving product-specific discounts or coupons was also associated with greater odds for noticing MRTP claims for e-cigarettes and SLT (AOR = 2.1).

Product Use Likelihood

Among smokers who reported noticing MRTP claims for e-cigarettes, snus, and other SLT, the percentage who indicated they would likely use these "less harmful" products was similar—e-cigarettes (25.1%), snus (27.6%), and other SLT (25.7%) (Supplementary Table S2). Use likelihood did not significantly vary by age or race/ethnicity and was significantly higher for males versus females for snus only (AOR = 2.2). The reported prevalence and odds of likelihood of using snus (AOR = 2.7) and other SLT (AOR = 3.1) with "less harmful" claims were significantly higher among lesbian, gay or bi-sexual (LGB) smokers versus straight smokers.

Not surprisingly the prevalence and odds of being "likely to use" one of these products were higher among current smokers who already used these products, with the highest likelihood reported for e-cigarettes (AOR = 8.1), followed by snus (AOR = 2.3). Among smokers who noticed a claim, the prevalence of "likely to use" responses for each product was also significantly higher among those smokers who thought the product was less harmful than smoking versus equally or more harmful than smoking.

Discussion

This study of adult smokers in the United States found that, prior to any FDA authorization for the use of MRTP claims, few reported exposure to "less harmful" claims for snus or other SLT products, while almost 30% of smokers reported seeing such claims for e-cigarettes. Among smokers who did notice such claims, the proportion who said they would likely use these "less harmful" e-cigarettes, snus, or other smokeless products was similar (25%–28%).

This study also found that modified risk claim exposure was more prevalent among those with perceptions that those products are less harmful than smoking. As a cross-sectional study, it is not clear if these lower harm perceptions may have been influenced by MRTP message exposure, or if existing lower harm perceptions about these products made respondents more attuned to messages perceived as consistent with their existing beliefs. However, we found that over a quarter of smokers who do *not* believe e-cigarettes are less harmful still reported seeing e-cigarettes claiming to be "less harmful." This suggests these reported exposures cannot be fully explained by existing beliefs.

The difference in exposure to perceived MRTP claims for e-cigarettes versus snus and other SLT products may potentially be due in part to differences in their marketing. Previous analyses of e-cigarette marketing sources have documented their (unauthorized) use of implied and explicit modified risk messages.[20,21] However, participants may have also considered messages from nonindustry sources in their responses, such as friends, social media posts, or the press, which has notably focused more on e-cigarettes than SLT.[22,23] In contrast, smokers' low existing exposure to "less harmful" claims for snus and other SLT are consistent with a general lack of awareness about the relative harms of these products compared with cigarettes.[6,7]

Ultimately, smokers' potential for tobacco harm reduction depends on whether they completely switch to lower harm products. We found that some smokers exposed to less harmful messages for e-cigarettes, snus, and other SLT were also interested in using these products in the future. Given that most of these smokers were already co-using cigarettes and the alternative product, it is important that future MRTP communications make clear that harm reduction is conditional on complete product switching, not dual product use.[24]

Study limitations include reliance on a self-reported measure of claim exposure which may have been interpreted in variable ways, including communication from nonindustry sources. Analyses were also limited to current smokers. Future research should also consider claim exposure among nonsmokers (including young adults and former smokers) and, importantly, whether this translates into product uptake among these groups.

In conclusion, this baseline study found that smokers in the United States more frequently report exposure to modified risk claims for e-cigarettes than for snus or SLT, prior to any FDA authorization for such claims. Exposure to such claims may motivate some smokers to use these lower harm products. Future research should continue to examine perceived exposure to MRTP messages as the US tobacco regulatory landscape and MRTP marketing evolves.

Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, are available online at https://academic.oup.com/ntr.

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Declaration of Interests

The authors declare no conflict of interest. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding organizations.

Authors' Contributions

OAW obtained funding for the study and led writing of the manuscript. JP led data analysis and contributed to data interpretation, manuscript writing, and editing. RJO contributed to data analysis planning and manuscript writing and editing. All authors approved the final manuscript.

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Summary of Consumer Contacts (Adverse Experiences)

Product	General Portion Original Large
SKU Number	4880
FDA Tracking Number	PM0000012
Reporting Period	October 1, 2019 to September 30, 2020

Product	General Portion Original Large
SKU Number	4880
FDA Tracking Number	PM0000012
Reporting Period	October 1, 2019 to September 30, 2020

(b)(4)

Product: General Portions Original Large
SKU Number: 4880
FDA Tracking Number: PM0000012
Reporting Period: 10/1/2019 to 9/30/2020

Summary of Total US Distribution (Cans) by US Census Region and Retail Markets and Channels (Units)

Summary of Total US Distribution (Lbs) by US Census Region and Retail Markets and Channels (Volume)

Summary of Total US Sales by US Census Region and Retail Markets and Channels (US Dollars)

Summary of All Manufacuring Deviations

Product:	General Portion Original Large
SKU Number:	4880
FDA Tracking number:	PM0000012
Reporting Period:	October 1, 2019 to September 30, 2020

Deviation Number	Type of Manufacturing Deviation	Production Date (YYYY-MM-DD)	Description of Deviation	Design Feature	Deviation May Affect the Characteristics of the Final Product (Yes/No)	Product With Deviation Distributed at Retail Level (Yes/No)
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	Justification; why product that reached retail would not affect public health
---	No manufacturing deviations to report.

--- = Not applicable.