

February 6-7, 2019
Meeting of the Tobacco Products Scientific
Advisory Committee (TPSAC)

Modified Risk Tobacco Product Application (MRTPA)
MR0000108
U.S. Smokeless Tobacco Company LLC

Office of Science
Center for Tobacco Products
Food and Drug Administration

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Memorandum

To:	Members, Tobacco Products Scientific Advisory Committee (TPSAC)
From:	Matthew R. Holman, Ph.D., Director, Office of Science, Center for Tobacco Products, United States Food and Drug Administration
Subject:	Overview of the FDA Briefing Document for February 6-7, 2019 discussion of U.S. Smokeless Tobacco Company LLC MRTPAs for its Copenhagen Snuff Fine Cut moist snuff tobacco product (FDA Submission Tracking Number MR0000108)

Introduction

We would like to thank the TPSAC members in advance for their efforts to provide recommendations to FDA on the Modified Risk Tobacco Product Application (MRTPA) submitted by U.S. Smokeless Tobacco Company LLC (USSTC).

On March 20, 2018, FDA received an MRTPA from USSTC, which states that USSTC is seeking orders under Section 911(g)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for its Copenhagen® Snuff Fine Cut tobacco product. See Appendix A for additional information on the statutory requirements for Modified Risk Tobacco Products (MRTPs).

The applicant describes Copenhagen Snuff Fine Cut as a loose, non-portioned, fine cut moist snuff smokeless tobacco product. The applicant states that a pinch of the product is intended to be placed into the mouth between the cheek or lip and gum. The user typically holds the product in the mouth, expectorates the “juice” produced during use, and removes the product from the mouth after use. Some users swallow the “juice” produced during use instead of spitting (Section 3.2 of the MRTPA).

FDA evaluates all information and statements on the proposed label, labeling, and advertising submitted by the applicant as part of the agency’s scientific review. As part of its evaluation of the MRTPA, FDA is reviewing the following modified risk claim: “IF YOU SMOKE, CONSIDER THIS: Switching completely to this product from cigarettes reduces risk of lung cancer.” In addition to determining whether the proposed modified risk claim is scientifically accurate and consumers understand it, FDA must assess, when determining whether to issue an order, whether the product, as it is actually used, will reduce the risk to individual users of the tobacco product and benefit the population as a whole, taking into account both tobacco users and non-users.

As described below, the focus of the TPSAC meeting will be the evidence related to the modified risk claim and relative health risks of the product, consumer understanding and perceptions of the modified risk claim, and the impact of a modified risk marketing order on product use.

Draft Topics for TPSAC Discussion

FDA is reviewing the scientific information submitted in the MRTPA to determine whether the statutory requirements for authorization provided in Section 911 of the FD&C Act have been met. The evidence submitted by the applicant includes data from chemical analyses of the product; toxicological evidence; a study of consumer understanding, perception, and behavioral intentions; a pharmacokinetic study of the product's abuse liability and subjective effects; epidemiological evidence; and other scientific information. FDA is also reviewing public comments submitted in accordance with Section 911(e).

FDA intends to raise the following matters for discussion with TPSAC.

Evidence related to the modified risk claim and relative health risks of the product

The proposed label and advertising submitted in the MRTPA contains the modified risk claim: "IF YOU SMOKE, CONSIDER THIS: Switching completely to this product from cigarettes reduces risk of lung cancer." FDA will present the nonclinical, clinical, and epidemiological evidence used to assess the scientific accuracy of this statement. TPSAC will be asked to discuss the extent to which the proposed modified risk claim is scientifically accurate.

Consumer understanding and perceptions of the label, labeling, and advertising

The applicant submitted sample label and advertisements for Copenhagen Snuff Fine Cut with the proposed modified risk claim. An online study was conducted to test consumer understanding and perceptions of the proposed modified risk claim. FDA will present results from the consumer study and will ask TPSAC to discuss potential implications of the proposed modified risk claim on consumer understanding and perceptions.

Likelihood of use of the proposed MRTP

FDA will present data from several observational studies to describe characteristics of smokeless tobacco users, patterns of use among users of Copenhagen products, and transitions from cigarette smoking to exclusive use of smokeless tobacco. FDA will also present pharmacokinetic and subjective effects data from the applicant's clinical study that was used to evaluate abuse liability. In addition, FDA will present results from the applicant's consumer study to assess the likelihood that cigarette users will switch to Copenhagen Snuff Fine Cut when presented with modified risk information. TPSAC will be asked to discuss the potential users and use behaviors with respect to the proposed modified risk tobacco product.

The following sections provide a summary and assessment of the evidence provided in the MRTPA relevant to the foregoing topics. For a list of all research studies and data submitted by the applicant, please see Appendix B.

Preliminary FDA Review Findings

I. RELATIVE HEALTH RISKS TO INDIVIDUALS

This section describes and assesses the evidence submitted related to the relative health risks of Copenhagen Snuff Fine Cut to individuals. The constituent profile of the product is presented followed by nonclinical, clinical, and epidemiological evidence of potential health risks associated with use of the product.

A. Harmful and Potentially Harmful Constituents (HPHCs)

HPHCs are chemical constituents in a tobacco product or in tobacco smoke that are, or potentially are, inhaled, ingested, or absorbed into the body, including as an aerosol (vapor) or any other emission; and cause or have the potential to cause direct or indirect harm to users or non-users of tobacco products (including with respect to five disease outcomes: cancer, cardiovascular disease, respiratory effects, developmental or reproductive effects, and addiction).

The FDA identified 93 HPHCs in tobacco and tobacco smoke, a list of which is published in the Federal Register (77 FR 20034). Subsequently, FDA identified an abbreviated list of these HPHCs in its Draft Guidance on Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the FD&C Act,ⁱ nine of which are present in smokeless tobacco.

The applicant reported levels of nine HPHCs in Copenhagen Snuff Fine Cut as well as the pH and total moisture of the product. A summary of the HPHC data was submitted for Copenhagen Snuff Fine Cut on an “as is” (or wet weight) basis and “dry weight basis” (DWB) based on seven replicates performed for each of five lots. Both “as is” and “dry weight basis” data are needed to facilitate comparison with cigarette data, which is reported “as is”, and other smokeless data, which may be reported as “dry weight basis” (“as is” data is shown in Table 1).

Table 1: HPHCs in Copenhagen Snuff Fine Cut - Five Lots Combined (Source: MRTPA Section 7.1)

Constituent	Units	Mean Values “As-Is” (Std Dev)	SD/Mean x100
Nicotine (Total)	mg/g	12.5 (0.228)	1.8
Nicotine (Free)	mg/g	3.92 (0.278)	7.1
Cadmium	ng/g	700 (150)	21.4
Arsenic	ng/g	106 (12.0)	11.3
Benzo[a]pyrene	ng/g	53.3 (12.3)	23.1
Acetaldehyde	µg/g	2.87 (1.56)	54.4
Crotonaldehyde	µg/g	BLOQ	N/A
Formaldehyde	µg/g	0.721 (0.105)	14.6
NNN	ng/g	1746 (73.8)	4.2
NNK	ng/g	472 (88.3)	18.7

BLOQ=Below Limits of Quantitation; N/A= Not applicable

ⁱThis draft guidance is available for public comment. Once finalized, it will represent the Agency’s current thinking on the topics therein.

HPHCs in Copenhagen Snuff Fine Cut Compared to Cigarettes

The combustion involved in cigarette smoking generally contributes to a higher number of HPHCs, including carcinogens, in cigarettes than in smokeless tobacco. For example, aromatic amines, volatile hydrocarbons, carbonyls, carbon monoxide, hydrogen cyanide, hydrazine, phenols, heterocyclic aromatic amines, and epoxides found in cigarettes may not be present in smokeless tobacco. Of the 93 HPHCs identified by FDA, 65 were shown to be present in tobacco and 91 were shown to be present in mainstream cigarette smoke.

The applicant did not provide a direct side-by-side comparison of the HPHC levels in Copenhagen Snuff Fine Cut with any specific comparator cigarette product(s). Because Copenhagen Snuff Fine Cut is non-portioned and cigarettes are portioned products, FDA compared the levels of HPHCs between the two types of tobacco products based on potential daily intake (i.e., one tin per day (34.02 g) compared to a “heavy smoking” level of 20 cigarettes per day [CPD]^{1,2}). Section 3.2 of the MRTPA shows that one tin per day (34.02 g) represents the 90th percentile of use for the Copenhagen Snuff Fine Cut product, which has been described as the “health-protective” level for chemical exposure evaluations.³⁻⁵ Data for International Organization for Standardization (ISO) and Canadian Intense (CI) mainstream cigarette smoke yields are based on reported HPHC levels in the top 50 selling U.S. cigarettes according to an FDA-CDC collaborative study.⁶⁻⁸

Compared to the potential daily intake calculated from the mean published values for ISO/CI smoking of combustible cigarette products, there were relative decreases in the potential daily intake of some HPHCs (i.e., acetaldehyde, formaldehyde), and relative increases (~325-5,700-fold) in arsenic, benzo[a]pyrene (B[a]P), cadmium, n-nitrosonorcinine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), and nicotine for the Copenhagen Snuff Fine Cut product.

It is important to note that differences in portal of entry effects, differences in extraction rates, differences in toxicant absorption and distribution through the body, and differences in metabolism can affect the toxicity of HPHCs introduced through different routes of exposure. Differences in user exposure routes between cigarettes and Copenhagen Snuff Fine Cut can affect the overall toxicity of the HPHCs present in Copenhagen Snuff Fine Cut relative to cigarettes. Therefore, it is unclear how relative differences in HPHC intake levels between Copenhagen Snuff Fine Cut and cigarette smoke translate into differences in exposure levels and, ultimately, disease risk. Differences in health risk between Copenhagen Snuff Fine Cut and cigarettes are discussed in the nonclinical, clinical, and epidemiological summaries in Section I.B.

HPHCs in Copenhagen Snuff Fine Cut Compared to Other Smokeless Tobacco

The overall differences in HPHCs among smokeless tobacco products are influenced by factors such as tobacco growing conditions, tobacco type, curing conditions, storage conditions, and moisture content. In general, moist snuff primarily comprises dark air-cured (which typically includes burley tobacco) and dark fire-cured tobacco that has been fermented and has a moisture content typically near 50%. Swedish snus typically consists of low-nitrosamine tobacco that has been air-cured, moistened, ground, and heat-treated. Dry snuff consists of fermented or pasteurized fire-cured tobacco and has a moisture content less than 10%. Loose leaf is generally made from air-cured, cigar-leaf tobacco and has moisture

levels higher than 15%. Smokeless tobacco products containing fired-cured tobacco produce higher levels of polycyclic aromatic hydrocarbons (PAHs) (e.g., B[a]P) while elevated moisture content can impact NNN and NNK levels.⁹⁻¹¹ In general, the levels of tobacco-specific nitrosamines (TSNAs), specifically NNN, in moist snuff have trended downward since 2004.¹¹

Table 2 shows HPHC levels of Copenhagen Snuff Fine Cut compared to other marketed moist snuff, dry snuff, loose leaf, and Swedish snus smokeless tobacco products.

According to the published literature, some HPHC levels for Copenhagen Snuff Fine Cut are similar to those of other currently marketed smokeless tobacco products. However, Copenhagen Snuff Fine Cut has increased levels of the following HPHCs:

- Acetaldehyde (85% higher than dry snuff)¹²
- Arsenic (9%-122% higher than moist snuff, dry snuff, and loose leaf)¹²
- B[a]P (90%-3,243% higher than moist snuff, dry snuff, and loose leaf)¹²⁻¹⁴
- Cadmium (46%-165% higher than moist snuff, dry snuff, loose leaf, and Swedish snus)¹¹⁻¹⁴
- NNN (113%-427% higher than loose leaf and Swedish snus)¹¹⁻¹⁴
- NNK (98%-349% higher than loose leaf and Swedish snus)¹²⁻¹⁴
- Total nicotine (4%-102% higher than other moist snuff, loose leaf, and Swedish snus)¹¹⁻¹⁴
- Free nicotine (460%-9,700% higher than dry snuff and loose leaf)^{12,14}

Table 2. HPHCs in Copenhagen Snuff Fine Cut Compared to Other Smokeless Tobacco Products by Product Category* (Data Sources: Ammann et al.¹¹; Borgerding, et al.¹²; Stepanov et al.¹⁴; Swedish Match 2014 MRTPAs)

Constituent	Unit	Copenhagen Snuff Fine Cut Mean Quantity (5 lots combined)	Moist Snuff Mean Quantity	% Difference	Dry Snuff Mean Quantity	% Difference	Loose Leaf Mean Quantity	% Difference	Swedish Snus Mean Quantity	% Difference
Acetaldehyde	µg/g	6.3	35.7	↓ 82	3.4	↑ 85	N/A	N/A	21.6	↓ 71
Arsenic [†]	ng/g	233	214	↑ 9	179	↑ 30	105	↑ 122	N/A	N/A
Benzo[a]pyrene	ng/g	117	61.6	↑ 90	30.5	↑ 284	3.5	↑ 3,243	N/A	N/A
Cadmium [†]	ng/g	1537	1052	↑ 46	879	↑ 75	599	↑ 157	579	↑ 165
Crotonaldehyde	µg/g	N/A	2.98	N/A	13.33	N/A	N/A	N/A	N/A	N/A
Formaldehyde [†]	µg/g	1.58	8.43	↓ 81	3.18	↓ 50	N/A	N/A	15.7	↓ 90
NNN	ng/g	3825	4058	↓ 6	5535	↓ 31	1798	↑ 113	726	↑ 427
NNK	ng/g	1034	1394	↓ 26	2522	↓ 59	523	↑ 98	230	↑ 349
Total Nicotine	mg/g	12.5	12	↑ 4	15.8	↓ 21	6.2	↑ 102	8.71	↑ 44
Free Nicotine	mg/g	3.92	4.2	↓ 7	0.7	↑ 460	0.04	↑ 9,700	5.65	↓ 31

*Data in table are reported on a “dry weight basis” (DWB) except for total and free nicotine, which are reported “as is” (wet weight basis). Carbonyl data for moist snuff and dry snuff are from Stepanov et al.¹⁴; TNSAs, metals, and nicotine data for moist snuff, dry snuff, and loose leaf are from Borgerding et al.¹²; Swedish snus levels are reported as an average of data from Swedish Match 2014 MRTP applications.

[†] The values provided indicate that potential exposure to this HPHC is less than the EPA IRIS non-cancer RfD (arsenic: 0.0003 mg/kg/day; cadmium: 0.0005 mg/kg/day; formaldehyde: 0.2 mg/kg/day).

Permeation Enhancers

Furthermore, potential permeation enhancers that may influence exposure to HPHCs are incorporated into the product. Some of the ingredients used in Copenhagen Snuff Fine Cut are known dermal permeation enhancers.^{15- 20} Although there are structural differences between the human skin and buccal mucosa, various compounds commonly used as permeation enhancers for transdermal uptake have also been shown to function as absorption promoters across the buccal mucosa.²¹⁻²³ For example, chemical permeation enhancers such as terpenes cross the buccal mucosa by various mechanisms, such as enhanced partitioning coefficient of chemicals and increased membrane permeability.²⁴ The presence of these potential permeation enhancers may increase the absorption of the HPHCs, and therefore increase their associated toxicities. The potential for increased exposure due to the presence of permeation enhancers was not addressed in the application.

B. Evidence of Potential Health Risks

The applicant submitted nonclinical, clinical, and epidemiological evidence to describe the potential health risks of Copenhagen Snuff Fine Cut, including evidence related to the proposed modified risk

claim (IF YOU SMOKE, CONSIDER THIS: Switching completely to this product from cigarettes reduces risk of lung cancer.”). The nonclinical and clinical evidence relies heavily on published literature. For epidemiological evidence of health risks and comparisons to other tobacco product use, the applicant relies on its own analyses of longitudinal studies as well as published literature. While some of the evidence submitted is product-specific (i.e., data collected on Copenhagen Snuff Fine Cut), most submitted evidence relies on data from the product category of moist snuff or smokeless tobacco.

Nonclinical Evidence

To support its MRTPA, the applicant provided over 100 nonclinical study references from scientific literature. Of these, 59 were related to the applicant’s claim regarding lung cancer. The applicant provided published literature that it suggests addresses long-term exposure,²⁵⁻³¹ genotoxicity,³²⁻⁴³ carcinogenicity,^{25-29,32,44-54} modulating carcinogenicity,^{25-29,33,46-67} immunotoxicology,^{26,68,69} inflammation,⁷⁰⁻⁸³ oral toxicity and dental issues,⁸⁴⁻¹¹⁰ cardiovascular effects,^{25,31,111} and reproductive/developmental toxicities^{31,112-117} associated with the use of Copenhagen Snuff Fine Cut. Of these publications, one uses Copenhagen Snuff Fine Cut specifically, and five use a product labeled as “Copenhagen Snuff”. It is unclear whether “Copenhagen Snuff” is the same as the Copenhagen Snuff Fine Cut under review or another Copenhagen product. The remainder of the references used a variety of commercial brand smokeless tobacco products (defined and undefined) or research tobacco products. Such studies did not directly test the potential of Copenhagen Snuff Fine Cut to induce toxicities that may then be compared to never use, other smokeless tobacco products, or cigarettes. Additionally, most of the submitted studies did not provide a direct comparison among smokeless product categories or a comparison of smokeless tobacco to cigarette smoke, with few exceptions.

Lung Cancer Risk

Nonclinical studies have found an association between arsenic, B[a]P, formaldehyde, NNN and NNK and lung cancer (see Table 3). Assuming 100% extraction of the listed constituents in the candidate smokeless tobacco product, there is an increase in the potential daily oral intake of lung carcinogens, including arsenic, B[a]P, NNN, and NNK, with the Copenhagen Snuff Fine Cut product compared to the corresponding levels under both ISO and CI smoking regimens for a composite of combustible cigarette products on the market. However, due to variables such as route of exposure (i.e., oral vs. inhalation), extraction profile of different HPHCs from the product, absorption of HPHCs through the buccal mucosa, and others, the net exposure from HPHCs due to use of Copenhagen Snuff Fine Cut may be lower than exposure to these same HPHCs from cigarette smoking. The applicant did not provide any information specific to its product that would allow calculation of user exposure and the resulting comparative lung cancer risk. Additionally, published manuscripts provided by the applicant either do not relate to the assessment of lung cancer risk, do not use Copenhagen Snuff Fine Cut, or have issues that prevent the extrapolation of the data to this product and the assessment of lung cancer risk.

Other Health Risks

The HPHCs found in Copenhagen Snuff Fine Cut are known carcinogens in a variety of tissues, developmental and reproductive toxicants, cardiovascular toxicants, and immunotoxicants. The toxicological hazards associated with these HPHCs are described in Table 3.

Table 3. Toxicological Hazards of Selected HPHCs Relevant to the MRTPA

Constituent	Toxicological Hazard
Arsenic	<ul style="list-style-type: none"> Group 1 human carcinogen as determined by IARC and EPA IRIS based on data regarding liver, kidney, bladder, and skin cancer in human populations with oral exposure^{118,119} Potent lung carcinogen by oral route of exposure¹²⁰⁻¹³⁴ Chronic oral exposure is associated with systemic toxicities, including neurological,¹³⁵⁻¹⁴⁴ hematological,^{137,141,144-151} gastrointestinal,^{145,146,148-150,152-157} hepatic,^{145,149,154,155,157} renal,^{145,146,148-150,154-156} respiratory,^{146,149,150,154,155,158} and cardiovascular^{148-152,154,158}
B[a]P	<ul style="list-style-type: none"> Group 1 human carcinogen as designated by IARC¹⁵⁹ Oral exposure may induce lung carcinogenesis¹⁶⁰⁻¹⁶² Oral exposure associated with developmental, reproductive, and immunological effects in animals¹⁶³ Human and epidemiological studies involving exposure to polycyclic aromatic hydrocarbon (PAH) mixtures have shown association with adverse birth outcomes, neurobehavioral effects, and decreased fertility¹⁶³
Cadmium	<ul style="list-style-type: none"> Group 1 human carcinogen as designated by IARC¹⁶⁴ Associated with numerous non-cancer health effects¹⁶⁴⁻¹⁶⁷ Genotoxic, carcinogenic, reproductive, cardiovascular, and neurologic effects associated with oral exposure in humans¹⁶⁵⁻¹⁶⁷
Formaldehyde	<ul style="list-style-type: none"> Group 1 human carcinogen as designated by IARC¹⁶⁸ Several studies have shown significant positive associations between formaldehyde and cancers in the oral cavity, pharynx, lung, brain, pancreas, and blood¹⁶⁸ Results are inconsistent via oral exposure¹⁶⁸
NNN/NNK	<ul style="list-style-type: none"> Group 1 human carcinogens as designated by IARC (NNN and NNK)¹⁶⁹ Sufficient nonclinical data to determine that NNN and NNK may promote a variety of cancer endpoints, including lung, nasal cavity, oral, pancreas, and liver^{49,63,170-173}

Based on nonclinical data alone, it is difficult to determine how varying levels of HPHCs between Copenhagen Snuff Fine Cut and other tobacco products impact risk of disease in humans. Differences in portal of entry effects, toxicant absorption and distribution through the body, and metabolism can affect the toxicity of HPHCs introduced through different routes of exposure. For example, because smokeless tobacco is not combusted and is not inhaled, it triggers different physiological processes that may lead to differences in toxicity compared to cigarettes.

Clinical Evidence

The applicant did not provide studies assessing biomarkers of exposure among users of Copenhagen Snuff Fine Cut but did summarize published studies comparing smokeless tobacco users to non-users and cigarette smokers. The applicant noted that publications have shown that smokeless tobacco users may have exposure to nicotine or TSNA's comparable to or higher than smokers.¹⁷⁴⁻¹⁷⁶ The applicant also suggested that blood cadmium and urinary arsenic were not elevated among smokeless tobacco users compared to non-users.^{176,178}

The applicant also did not submit studies on biomarkers of potential harm associated with the candidate product. Alternatively, the applicant referenced cross-sectional studies analyzing biomarkers of potential harm in smokeless tobacco users compared to cigarette smokers and non-tobacco users.^{177,178} These studies identified three distinct biomarkers that differentiate between tobacco use groups.

Findings of significantly higher levels of these biomarkers suggest that smokers have an elevated inflammation and immune response compared to smokeless tobacco users. No significant differences in inflammatory response were observed between smokeless tobacco users and non-tobacco users.

Epidemiological Evidence

No long-term epidemiological data are available pertaining to the use of Copenhagen Snuff Fine Cut in particular. Instead, the applicant summarized evidence from the published literature and conducted original analyses of Federal datasets of the health risks associated with smokeless tobacco use to draw inferences regarding the risk for tobacco-related diseases related to Copenhagen Snuff Fine Cut. The applicant states this published data is relevant to the product under review because: (1) moist smokeless tobacco was the primary form of smokeless tobacco used in the U.S. at the time of these studies; (2) USSTC products generally, and specifically Copenhagen Snuff Fine Cut, held large market shares at the time of the studies; and (3) the product has not changed since the time of the studies, with the exception of a decrease in TSNA.

Figure 1 presents the market share volume of USSTC in the moist smokeless tobacco and chewing tobacco product categories, along with relevant studies of the health effects of smokeless tobacco products from 1972 to 2011. USSTC appears to account for the majority of market share of moist smokeless tobacco prior to 1985, and according to data provided by the applicant in MRTPA Appendix 2-3-2, USSTC products accounted for between 70-90% of the total moist smokeless tobacco market from 1985 to 2005 and between 55-68% of the market from 2005 to 2016 (Figure 2). According to Figure 2, Copenhagen Snuff Fine Cut accounted for between 37-44% of the total moist smokeless tobacco market share from 1985 to 1996 and a lower percentage (between 19-36%) from 1997 to 2006.

Figure 1. USSTC Volume within Moist Smokeless Tobacco (MST) and Chewing Tobacco Category (1972-2011) and Study Periods of Prospective Studies of the Health Effects of Smokeless Tobacco Products (Source: MRTPA Section 2.3)

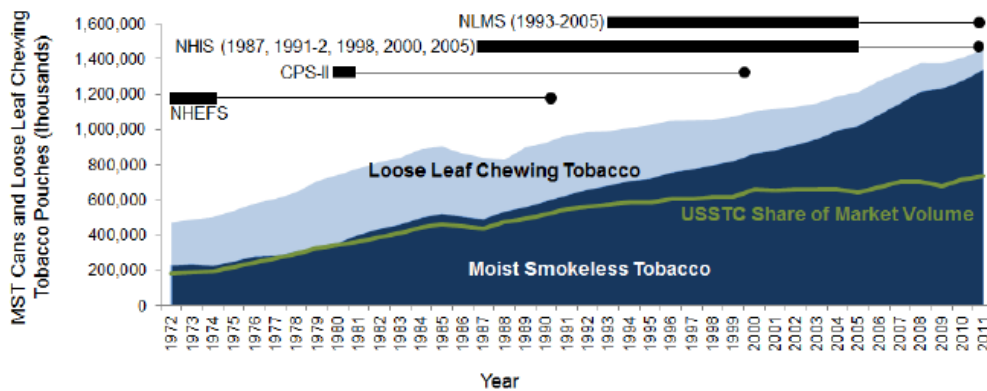
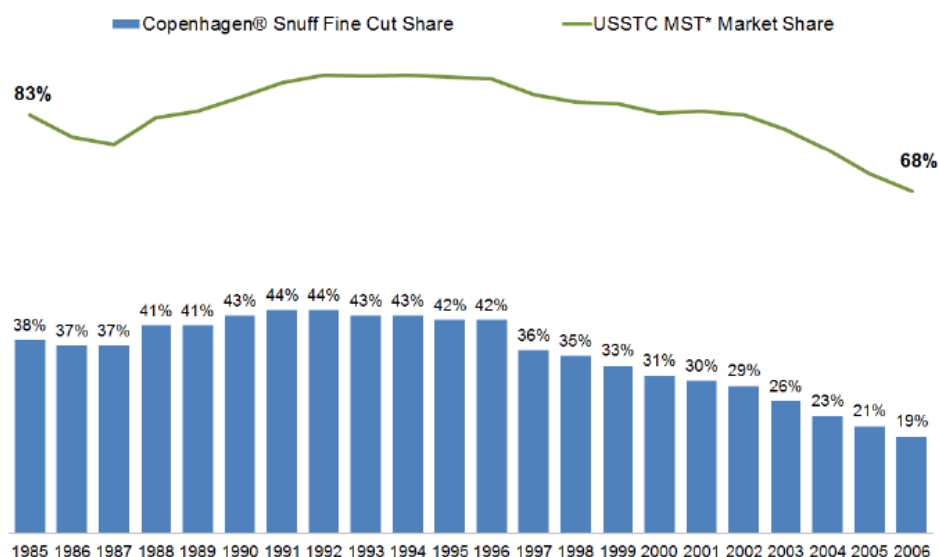


Figure 2. Contribution of Copenhagen Snuff Fine Cut to USSTC's Market Share, 1985-2016 (Source: MRTPA Section 2.3)



The use of epidemiological evidence from the published scientific literature to support a regulatory submission has several implications. The peer-reviewed and published studies presented in the application on the health risks of U.S. smokeless tobacco products reflect the products that were on the market and being used by study participants at the time the studies were conducted, and are not necessarily the same product that is the subject of this application. However, the market data presented above indicate that the candidate product accounted for between nearly 20-45% of the moist smokeless tobacco market in the time periods studied (1985-2005), and there is some evidence to suggest that harmful TSNA levels may have been higher in the time period of the published studies than in Copenhagen Snuff Fine Cut.

Data Sources

National Health Interview Survey (NHIS) and National Longitudinal Mortality Study (NLMS)

The National Health Interview Survey (NHIS) is a nationally representative, cross-sectional household interview survey of the amount, distribution and effects of illness and disability collected by the U.S. Census Bureau for the National Center for Health Statistics (NCHS), which is part of the Centers for Disease Control and Prevention (CDC). In MRTPA Section 7-4-1-3, the applicant provides analyses of NHIS data from 1986-2009, which NCHS linked to death record certificates from the National Death Index with vital status follow-up through December 31, 2011.

The National Longitudinal Mortality Study (NLMS) is based on data from the Current Population Surveys (February 1978, April 1980, August 1980, December 1980, September 1985), Annual Social and Economic Supplements (March 1973-March 2011) and a subset of the 1980 Census combined with death certificate information to identify mortality status and cause of death. In MRTPA Section 7-4-1-3,

the applicant states that it used the NLMS public use file, which is based on the 1993-2005 Current Population Survey Tobacco Use Supplements (CPS-TUS) and five years of follow-up for each respondent.

For most of the health risks and comparisons, the applicant relied on a combination of the applicant's own analyses of linked mortality data from the NHIS and NLMS as well as the published literature.

In the applicant's linked mortality analyses, the applicant adjusts for gender, race, age, education, family income, tobacco use, and health status in both NHIS and NLMS. The applicant also adjusts for body mass index (BMI) in the NHIS analyses, but this information was not available in NLMS. CPD was available in the NHIS analyses but not the NLMS analyses. Adjusting for health status could lead to possible over-adjustment,¹⁷⁹ since poor health status could be a direct effect of tobacco use.

Additionally, in both the published literature and the linked mortality analyses, the data available do not always present direct statistical comparisons to address the comparisons described below. Although not always a proxy for statistical significance,¹⁸⁰ FDA examined the magnitude of ratio measurements and notes where confidence intervals overlap or do not overlap. Furthermore, it is important to note that overlapping confidence intervals or lack of significance is not proof that the two groups are the same; other factors such as power and sample size can affect the width of a confidence interval.¹⁸¹

Although no formal power analysis was run, the number of smokeless tobacco users and deaths among smokeless tobacco users in the linked mortality analyses is relatively small. For example, an examination of lung cancer deaths among smokeless users reveals that there were just three deaths from lung cancer in NLMS and eight deaths from lung cancer in NHIS. Some authors suggest that a sample size of at least 10 events per variable in the smallest group is desirable.^{182,183}

Published Scientific Literature

In addition to analysis of observational studies, the applicant included epidemiological evidence from published studies of patterns of smokeless tobacco use and associated health risks. While most of the evidence presented was submitted by the applicant, additional peer-reviewed studies, omitted from the applicant's literature review or published after that review was conducted, are included. The estimates from these more recent studies are generally consistent with the summary risk estimates produced from published meta-analyses.

Several general considerations regarding the epidemiological evidence are presented below. The information on disease risks pertains to smokeless tobacco products generally—including products referred to in the literature as chewing tobacco, snuff, dip, or spit; the applicant did not present, nor is FDA aware of, long-term epidemiological studies pertaining to Copenhagen Snuff Fine Cut. In addition, much of the available U.S. evidence on smokeless tobacco and disease risk relies on three cohorts: First National Health and Nutrition Examination Survey (NHANES-I) Epidemiologic Follow-up Study (NHEFS),¹⁸⁸ the Cancer Prevention Study (CPS)-I, and CPS-II.^{184,187} Finally, other than adverse pregnancy outcomes, the available literature generally focuses on the health effects studied in male smokeless tobacco users.

Lung Cancer

Smokeless Tobacco Use Compared to Never Use

MRTPA Section 6.1.3.1 examines the cancer risks associated with smokeless tobacco use compared to never use, and MRTPA Section 6.1.2.1 also presents lung cancer estimates in smokeless tobacco users compared to never users. The applicant's linked mortality analysis of the public-use NLMS dataset found slightly elevated but non-significant hazard ratios for lung cancer in current smokeless tobacco users compared to never users. However, the magnitude of these hazard ratios (HR: 2.98, 95% CI: 0.91-9.76; see Table 4) were lower than the applicant's linked mortality estimate (NLMS) for current smokers compared to never users. It should be noted that in the NLMS dataset, all three lung cancer deaths among smokeless tobacco users occurred in females, and the applicant gives an HR among females of 7.09, 95%CI=1.93-26.07.

Table 4. Linked Mortality Analysis Hazard Ratios for Mortality from Lung Cancer and Non-Lung Cancer Endpoints from Neoplasms of the Trachea, Bronchus and Lung in Continued Smokers, Former Smokers, Complete Switchers and Continued Smokeless Tobacco Users (Data Source: MRTPA Section 6.1)

	Lung Cancer (MRTPA Table 6.1-22 and Table 6.1-7)		All-Cause Mortality (MRTPA Table 6.1-22)		All-Cancer Mortality (MRTPA Table 6.1-21)		Mortality from Diseases of the Heart (MRTPA Table 6.1-21)	
	NLMS Hazard Ratio (Confidence Interval)	NHIS	NLMS	NHIS	NLMS	NHIS	NLMS	NHIS
Current smokers who had never used ST (continued smokers) compared to never tobacco users	11.522 (8.740-15.190)	not reported	1.878 (1.744-2.023)	2.130 (2.048-2.215)*	2.880 (2.520-3.291)	2.951 (2.726-3.195)*	1.613 (1.404-1.853)	1.951 (1.812-2.100)
Former smokers who had never used ST (former smokers) compared to never tobacco users	5.650 (4.329-7.376)	not reported	1.416 (1.334-1.505)	1.301 (1.255-1.348)	1.953 (1.733-2.201)	1.577 (1.458-1.705)	1.162 (1.042-1.296)	1.161 (1.084-1.243)
Former smokers who currently used ST (complete switchers) compared to never tobacco users	5.341 (2.035-14.016)	not reported	1.317 (0.963-1.802)	1.331 (1.093-1.619)*	2.040 (1.173-3.548)	1.572 (1.098-2.250)*	0.828 (0.461-1.488)	1.471 (1.049-2.063)
Current ST users who had never smoked cigarettes (continued ST users)	2.979 (0.910-9.756)	not reported	0.815 (0.593-1.120)	1.110 (0.959-1.285)	0.805 (0.385-1.682)	1.079 (0.741-1.471)	1.073 (0.656-1.754)	

In the published literature, Lee and Hamling's systematic review restricted to studies of smokeless tobacco users who never smoked found that smokeless tobacco users had an elevated but non-significant association for lung cancer mortality (relative risk [RR]=1.79 95%CI=0.91-3.51, n=3).¹⁸⁵ Lee and Hamling's results were consistent with Boffetta and colleagues, who reported an elevated but non-significant association for lung cancer mortality among exclusive ever U.S. smokeless tobacco users (RR=1.8, 95%CI=0.9-3.5, n=3 studies) compared to never users of tobacco.¹⁸⁶ As the applicant notes, the

results of the individual cohort studies examining the risk of lung cancer mortality in smokeless tobacco users compared to non-users are mixed. Henley and colleagues¹⁸⁷ found no association in CPS-I, and no association was found among males in the NHANES I 20-year follow-up (NHEFS).¹⁸⁸ However, an association was found in CPS-II¹⁸⁷ and the Agricultural Health Study,¹⁸⁹ and three deaths were found among females in NHEFS (HR: 9.1, 95%CI=1.1-75.4).¹⁸⁸ As this study only measured smokeless tobacco use at one time point, we cannot rule out that these women later transitioned to cigarette smoking; Accortt and colleagues suggest that the results could be due to outcomes experienced by a small number of subjects having large sample weights.¹⁸⁸

Smokeless Tobacco Use Compared to Cigarettes

MRTPA Section 6.1.2.1 examines the health risks associated with smokeless tobacco use compared to cigarette smoking. In the applicant's linked mortality analysis, the hazard ratio for lung cancer mortality in current cigarette (never smokeless tobacco) users compared to never tobacco users in NLMS was significantly elevated (HR: 11.52, 95%CI=8.74-15.19). This is slightly lower than the mortality risk estimates for U.S. smokers compared to never smokers based on findings from the CPS-II and presented in the 2014 U.S. Surgeon General's Report.¹⁹⁰ According to CPS-II, among current smokers, the relative risk for lung cancer mortality is 23.26 among males and 12.69 among females.

However, the linked mortality analysis and CPS-II risk estimates for lung cancer mortality from cigarettes compared to never smokers are both higher than the hazard ratios among smokeless users compared to never users from the linked mortality analyses and systematic reviews discussed above and in Table 4.

No direct comparison between mortality risks for current smokeless tobacco compared to current cigarette smokers was presented in the application, and FDA is not aware of existing publications that directly compare risks for lung cancer among smokeless-only users vs. cigarette-only smokers.

Switching from Cigarettes to Smokeless Tobacco Use

MRTPA Section 6.1.4.1 examines the health risks associated with switching from cigarette smoking to smokeless tobacco use. The applicant's NLMS analyses for lung cancer mortality show that the hazard ratios were lower in NLMS for complete switchers and quitters compared to never users than for continued smokers compared to never users; however, the confidence intervals overlapped (complete switchers: HR=5.34, 95%CI=2.04-14.02; quitters: HR=5.65, 95%CI=4.33-7.38); continued smokers: HR=11.52, 95%CI=8.74-15.19) (see Table 4).

A study published by Henley et al.¹⁸⁴ relied on CPS-II cohort participants to estimate mortality risks for male former exclusive cigarette smokers who switched to exclusive U.S. smokeless tobacco products at the time of or after quitting exclusive cigarette smoking (i.e., "switchers"). To our knowledge, this is the only study that examined disease risk associated with sequential product use (details on this study are provided in Appendix C).¹⁸⁴

In Henley et al.,¹⁸⁴ after twenty years of follow-up, men who switched completely from cigarettes to smokeless tobacco experienced a significantly greater risk of dying from lung cancer compared to those who quit all tobacco (HR=1.46, 95%CI: 1.24-1.73), after accounting for smoking exposure and other factors. Switchers also had higher rates of death from lung cancer than never users (HR=5.61; CI not

provided). In interpreting these results, the study authors noted findings from a 10-year follow-up study of a small subset of CPS-II participants that found that switchers were somewhat more likely to relapse smoking than quitters, although the percentage that relapsed in both groups was small.¹⁸⁴ It was also noted that switchers had started at somewhat earlier ages and stopped smoking at somewhat older ages than quitters, although the analyses adjusted for smoking history.¹⁸⁴ Compared to former smokers who quit using tobacco entirely, switchers tended to be less educated and more likely to work in blue-collar employment. While the analyses adjusted for these and other factors, the possibility of residual confounding could not be ruled out in explaining part or all the observed findings. Exposure misclassification may have occurred since tobacco use was only ascertained at baseline. Henley and colleagues did not compare risks among switchers to risks among continuing smokers,¹⁸⁴ which would have provided additional relevant evidence to evaluate the MRTPA (see Table 5).

Table 5. Study Results for CPS-II from Henley et al.¹⁸⁴ and Thun et al.¹⁹¹

Disease Endpoint	CPS-II Henley et al. ¹⁸⁴		CPS-II (1982-1988) Thun et al. ¹⁹¹ & FDA analyses	
	Switchers vs Quit All Tobacco (HR, 95%CI)	Switchers vs Never Tobacco Users (HR) ^a	Former Smokers vs Current Smokers* (Thun et al. 2013) RR (95%CI)	Current Smokers vs Former Smokers [^] Inverse of RR
Lung cancer	1.46 (1.24-1.73)	5.61	0.20 (0.17-0.23)	5.00 (=1/0.20)
COPD	1.31 (0.96-1.78)	3.24	0.31 (0.24-0.39)	3.23
Oral cancer	2.56 (1.15-5.69)	^b	Not reported	--
Coronary heart disease	1.13 (1.00-1.29)	1.28	0.67 (0.63-0.72)	1.49
Stroke	1.24 (1.01-1.53)	1.34	0.49 (0.41-0.59)	2.04
All-cause mortality	1.08 (1.01-1.15)	^b	0.53 (0.51-0.55)	1.89

^a Numerical values for 95% confidence intervals (CIs) were not reported for estimates of switchers versus never tobacco users in Henley et al.,¹⁸⁴ Figure 1; results were statistically significant for each of the four disease endpoints based on the vertical line corresponding to the 95%CI for each RR in Figure 1 not including 1.0.^b Results were not reported for risks of fatal oral cancer or all-cause mortality among switchers compared to never tobacco users in Henley et al.¹⁸⁴* The RRs reported from Thun et al.¹⁹¹ are based on CPS-II males who quit smoking at age 40-49 years & who had quit ≥ 2 years prior to the survey date. Henley et al.,¹⁸⁴ Table 2 reports the age at quit smoking for CPS-II males to be 41.6 years for those who quit entirely and 42.9 years for those who switched from smoking to exclusive smokeless tobacco use.[^] RR for current smokers vs former smokers was calculated as $= 1/\text{RR}$ former smokers vs current smokers

Among cigarette smokers, Thun and colleagues reported on the relative risk of lung cancer mortality among former cigarette smokers versus current smokers from CPS-II.¹⁹¹ To provide additional information to evaluate the applications, FDA conducted an original analysis to assess the magnitude of the disease-specific relative risks by tobacco use status relying on former cigarette smokers as the referent category. This evidence is also relevant to the application because the proposed modified risk claim communicates to smokers, who may respond by switching to Copenhagen Snuff Fine Cut, continuing to smoke cigarettes, or quitting all tobacco, but who cannot become never tobacco users. In a paper published by Thun and colleagues, the authors estimated mortality relative risks for selected smoking-related diseases in former smokers (vs. current smokers) by age at cessation for CPS-II participants from 1982 to 1988.¹⁹¹ Here, we report the Thun et al.¹⁹¹ estimates for males who quit smoking at ages 40-49 years, since that range includes the median age at quitting smoking for participants of the Henley et al. switching analysis.¹⁸⁴ Table 5 summarizes the data from Thun and colleagues by disease endpoint (second column). FDA calculated the inverse of the relative risks (column 3) to make former smokers the

referent. Doing so facilitates comparisons to the relative risks for switchers (vs. former smokers) from Henley et al.¹⁸⁴

While the evidence presented in Thun et al.¹⁹¹ and Henley et al.¹⁸⁴ suggests that the greatest health benefits are achieved by quitting all tobacco, relative to quitters, lung cancer risk among men who completely switched from cigarettes to smokeless tobacco was substantially lower than the risk among continuing smokers, particularly among men who continued smoking for at least ten additional years.^{184,191}

Dual Use of Cigarettes and Smokeless Tobacco

MRTPA Section 6.1.5 examines the health risks associated with using the product in conjunction with other tobacco products, specifically cigarettes. The applicant presents the hazard ratios for both dual users compared to never users and dual users compared to current smokers. In NLMS, the hazard ratios were similarly elevated (based on confidence interval overlap) for dual users compared to never users (HR=11.46, 95%CI=3.31-39.64) and for current smokers compared to never users (HR=11.52, 95%CI=8.74-15.19). When comparing dual users to current smokers, no significant differences were seen in NLMS (HR=1.19, 95%CI=0.35-4.09) or the NHIS restricted use data (HR=1.06, 95%CI=0.57-1.97).

MRTPA Section 6.1.5 cites two analyses that examined the association between incident lung disease¹⁹² and lung cancer mortality¹⁸⁸ using NHEFS data. For lung cancer, mortality risks were similarly elevated (based on confidence interval overlap) for dual users (ever smokeless tobacco and current smokers, HR=33.9, 95%CI=8.0-143.7) and current exclusive smokers (HR=24.7, 95%CI=8.3-73.5, respectively) where the common referent group was non-tobacco users.¹⁸⁸

Analyses of the Agricultural Health Study show that lung cancer risks for ever U.S. smokeless tobacco users who currently smoked were lower than the risks of lung cancer among exclusive smokers (HR=0.50, 95%CI=0.27-0.92, n=14 cases).¹⁸⁹

Related to dual use behaviors is the potential for smokers to cut back on cigarettes and use smokeless tobacco but without completely quitting smoking. Health outcomes associated with this use pattern were not addressed by the applicant.

Epidemiological studies evaluating disease risk associated with reductions in smoking intensity have been inconsistent. For example, some studies have observed significant reductions in lung cancer risk associated with >50% reduction in CPD.^{193,194} However, other studies did not observe a change in disease or mortality risk with reduction in smoking intensity.¹⁹⁵⁻¹⁹⁸ The lack of consistent findings may be due, in part, to variations in definitions of smoking reduction, differences in the dose-response relationship by disease endpoint, and the potential for smoking compensation among self-reported reducers across published studies.

Moist Snuff Compared to Other Smokeless Tobacco Product Use

MRTPA Section 6.1.2.2 reviews evidence from the published literature examining mortality outcomes in chewing tobacco users compared to never users and snuff users compared to never users.^{187,199} No linked mortality analyses completed by the applicant assessing risks by sub-types of smokeless users are

presented. The only study to examine the risk of death from lung cancer by smokeless subtype was conducted by Henley and colleagues.¹⁸⁷ In CPS-II, two lung cancer deaths among current snuff users (HR=2.08, 95%CI=0.51-8.46) and 12 deaths among current chew users (HR=1.97, 95%CI=1.10-3.54) were observed.¹⁸⁷ Swedish snus has not been associated with lung cancer.¹⁸⁶

Other Health Risks

The applicant's linked mortality analysis showed no significant differences between smokeless tobacco users and non-users. Hazard ratios for select linked mortality analyses in current smokeless users compared to never users and cigarette smokers compared to never users are presented in Table 4. In general, the magnitude of the point estimates was lower for smokeless users than cigarette smokers, and the point estimates for switchers and quitters generally fell between smokeless users and cigarette users. However, as discussed above, the number of deaths among smokeless tobacco users is small; for all cause-mortality there were fewer than 50 deaths among current smokeless tobacco users who never smoked, and the sample may be underpowered to detect a difference.

In the literature, the 2012 IARC monograph "Personal Habits and Indoor Combustions" concluded that there was sufficient evidence to indicate the carcinogenicity of smokeless tobacco in humans and further stated that smokeless tobacco causes oral cancer, esophageal cancer and pancreatic cancer.¹⁵⁹ One meta-analysis reports an association between smokeless tobacco and fatal myocardial infarction and stroke,²⁰⁰ and data on all-cause mortality from individual studies are mixed.^{187 188,199} Lastly, while there is relatively little information on smokeless tobacco use among U.S. women, several studies from Sweden have found an association between smokeless tobacco use and adverse pregnancy outcomes.²⁰¹⁻²⁰³ With regard to the literature on switchers and dual users, similar to the lung cancer results, Henley et al.¹⁸⁴ found that, compared to quitters, switchers had higher rates of death from heart disease, oral cancer, stroke and all causes, but that the magnitudes of the point estimates were generally lower than those for current smokers (see Table 5).

Two studies found no evidence of differences in disease risk in snuff users compared to chew users.^{187,199} However, epidemiological studies have observed differences in risks associated with U.S. smokeless tobacco product use compared with Swedish snus product use,^{185,204,205-207} which may be due to the generally lower levels of HPHCs, such as TSNAs, found in Swedish snus products.

C. Summary and Conclusions

Relative Health Risks

The applicant tested its proposed MRTP for nine HPHCs that have previously been identified by FDA as present in smokeless tobacco products. The evidence provided by the applicant, coupled with information from the published literature, suggests that Copenhagen Snuff Fine Cut has higher levels of some HPHCs (arsenic, B[a]P, cadmium, nicotine) and lower levels of other HPHCs (acetaldehyde, formaldehyde, NNN, NNK) than the average of other moist snuff products. Additionally, Copenhagen Snuff Fine Cut has elevated levels of some HPHCs (nicotine, arsenic, B[a]P, cadmium) compared to dry snuff as well as several HPHCs (nicotine, arsenic, B[a]P, cadmium, NNN, NNK) compared to loose leaf tobacco products. As compared to Swedish snus products, Copenhagen Snuff Fine Cut has higher levels of cadmium, NNN, NNK, and nicotine. In comparison to cigarettes, Copenhagen Snuff Fine Cut has higher

potential daily intake levels of several HPHCs (arsenic, B[a]P, cadmium, NNN, NNK, nicotine) and lower levels of other HPHCs (acetaldehyde, crotonaldehyde, formaldehyde) than mainstream cigarette smoke. Oral exposure to the HPHCs found in Copenhagen Snuff Fine Cut are associated with cancer, developmental and reproductive effects, cardiovascular effects, and immunological effects. The HPHCs that are elevated in Copenhagen Snuff Fine Cut compared to the average of other tobacco products are carcinogenic and are also associated with neurological, hematological, gastrointestinal, hepatic, renal, respiratory, and cardiovascular toxicities. However, a number of variables such as route of exposure, portal of entry effects, differences in toxicant absorption and distribution through the body, and differences in metabolism, make it difficult to determine the effect of relative differences in HPHCs on disease risk specifically as compared to cigarettes. No nonclinical studies were conducted to test the potential of Copenhagen Snuff Fine Cut, specifically, to induce toxicities that may then be compared to never use, other smokeless tobacco products, or cigarettes.

While no long-term epidemiological studies pertaining specifically to Copenhagen Snuff Fine Cut exist, observational studies and published literature provide epidemiological evidence on the health effects associated with smokeless tobacco. Similar to findings in the published literature, the applicant's linked mortality analysis of the restricted-access NHIS and public-use NLMS datasets found slightly elevated but non-significant associations between current smokeless tobacco use (compared to never use) and lung cancer among never smokers.¹⁸⁵⁻¹⁸⁹ While evidence presented in Thun et al.¹⁹¹ and Henley et al.¹⁸⁴ suggests that the greatest health benefits are achieved by quitting all tobacco, lung cancer risk among men who completely switched from cigarettes to smokeless tobacco was substantially lower than the risk among continuing smokers, particularly among men who continued smoking for at least ten additional years.

The applicant's linked mortality analysis showed no significant differences between smokeless tobacco users and non-users for all-cause mortality, all malignant neoplasms or specific malignant neoplasms, mortality due to heart disease or Alzheimer's disease, diabetes mellitus, influenza, pneumonia or nephritis/nephrosis. Other studies report an association between smokeless tobacco use and all-cause mortality, fatal myocardial infarction and stroke, oral cancer, prostate cancer, pancreatic cancer, and adverse pregnancy outcomes. Indeed, the 2012 IARC monograph concluded there was sufficient evidence in humans to indicate the carcinogenicity of smokeless tobacco and further stated that smokeless tobacco causes oral cancer, esophageal cancer and pancreatic cancer.

In the linked mortality analyses, exclusive cigarette smokers (compared to never users) have higher rates of all-cause mortality and all-cancer mortality than smokeless tobacco users (compared to never users). Evidence from U.S. studies suggests that health risks for dual users are generally similar to the risks for exclusive smokers. Evidence on risks associated with cutting back on cigarettes without complete cessation, while limited, generally has not indicated a significantly decreased risk of death or disease from smoking reduction compared with continued cigarette smoking unless smokers cut back substantially on their smoking. Furthermore, results from epidemiologic studies suggest different cancer risk between U.S. smokeless tobacco and Swedish snus.¹⁸⁶ The differences seen in the epidemiologic literature may be due to the lower level of nitrosamines and other HPHCs in Swedish snus than in U.S. smokeless tobacco products, and as mentioned above, the HPHC levels in Copenhagen Snuff Fine Cut are higher than those seen in Swedish snus.

Scientific Accuracy of Modified Risk Claim

Despite the higher levels of certain HPHCs in Copenhagen Snuff Fine Cut compared to cigarette smoke, epidemiological evidence demonstrates that risks of lung cancer are substantially elevated among exclusive cigarette smokers (compared with never users) and risks are elevated but much lower among former smokers who switched to smokeless tobacco at the time of or after quitting exclusive cigarette smoking (i.e., “switchers”) (compared to never tobacco users). Evidence presented in Thun et al.¹⁹¹ and Henley et al.¹⁸⁴ suggests that, although the greatest health benefits are achieved by quitting all tobacco, lung cancer risk among men who completely switched from cigarettes to smokeless tobacco was substantially lower than the risk among continuing smokers. Furthermore, although arsenic, B[a]P, NNN, and NNK have been noted to potentially cause lung cancer from oral exposure in nonclinical animal models, lung cancer has not been conclusively linked to exclusive smokeless tobacco use in epidemiological studies, and in individual studies that did show an association, the magnitude of risk was lower than that seen among cigarette smokers. Although the epidemiological evidence is not product-specific, Copenhagen Snuff Fine Cut constituted a significant proportion of the moist smokeless tobacco market during the time periods studied. Based on the evidence described above, the proposed modified risk claim “IF YOU SMOKE, CONSIDER THIS: Switching completely to this product from cigarettes reduces risk of lung cancer” appears to be scientifically accurate.

In addition to determining whether the proposed modified risk claim is scientifically accurate and understandable to consumers, FDA must assess, when determining whether to issue an order, whether the product, as it is actually used, will reduce the risk to individual users of the tobacco product and benefit the population as a whole, taking into account both tobacco users and non-users. An assessment of consumer understanding and perceptions, as well as the potential impact of the proposed claim on use behavior, is described below.

II. CONSUMER UNDERSTANDING AND PERCEPTIONS

This section describes consumer perceptions of smokeless tobacco without modified risk information, presents the applicant’s proposed communication of the modified risk claim through the product’s label, labeling, and advertising, and assesses the applicant’s Claim Comprehension and Intentions (CCI) Study conducted to evaluate understanding of the proposed modified risk claim and the effect of the statement on risk perceptions of Copenhagen Snuff Fine Cut.

A. U.S. Consumers’ Perceptions of Smokeless Tobacco Risk

Almost all U.S. tobacco users and non-users perceive smokeless tobacco as harmful. In 2012-2013, 93% of U.S. smokeless tobacco users perceived smokeless tobacco as harmful and 90% perceived it as addictive.²⁰⁸ A study including youth and young adults found that 37% of respondents reported that smokeless tobacco use causes lung cancer (37%) even though lung cancer has not been conclusively linked to exclusive smokeless tobacco use.²⁰⁹ Tobacco users generally believe that smokeless tobacco is less harmful and addictive than do non-users.^{208, 210}

Several nationally representative surveys ask U.S. adults to rate the harm of using smokeless tobacco relative to smoking cigarettes and show that most U.S. adults (74-90%) rate smokeless tobacco as equally or more harmful than cigarettes or other combusted products.²¹¹⁻²¹⁴ These studies also find that a minority of U.S. adults (7-12%) rate smokeless tobacco as less harmful than cigarettes or other

combusted products. In these studies, up to one-fifth responded “don’t know.” Results were similar in a nationally representative study of youth.²¹⁵ Several studies also found that, compared to non-users, tobacco users are more likely to believe that smokeless tobacco is less harmful than cigarettes,^{210,211,213,216} though one study did not find this difference.²¹²

B. Label, Labeling, and Advertising

The applicant submitted a single modified risk claim: “IF YOU SMOKE, CONSIDER THIS: Switching completely to this product from cigarettes reduces risk of lung cancer.” The applicant submitted two qualitative studies that informed the development of this claim. These studies examined adult male consumers’ perceptions and expectancies regarding smokeless tobacco and identified modified risk language that the participants perceived as clear, relevant, and credible. The applicant provided the following sample label, labeling, and advertising (LLA) materials that contain this modified risk claim (all proposed LLA can be found in MRTPA Section 4.1):



Figure 3. Sample advertising submitted by USSTC (Source: MRTPA Appendix 4.1)

- Print advertisement (see MRTPA Appendix 4.1-1)
- Direct mail advertisement (see MRTPA Appendices 4.1-2 and 4.1-3)
- Email advertisement (see MRTPA Appendix 4.1-4)
- Website pop-up screen (see MRTPA Appendix 4.1-5)
- Promotional card (see MRTPA Appendices 4.1-6 and 4.1-7)
- Bottom can label (see Figure 3)
- Point of sale materials (see Figure 3)

Possible formats of the point of sale materials include a sign placed behind the checkout counter and within 48” of where smokeless products are sold, as an outward facing sign on the entry door of retail stores; and/or a sign placed in the parking lot of retail stores.

USSTC stated that its marketing and advertising plans have features that will reduce the risk of youth uptake (i.e., advertising and promotion will be targeted directly at adults). These plans include advertising in periodicals with predominantly adult readership, maintaining age-restricted brand websites, and using an age-verified consumer database for marketing communications, among other

strategies. FDA notes, however, that the applicant's planned advertising and promotions include non-targeted marketing techniques that may expose youth non-users to advertisements containing modified risk information (e.g., display outside retail outlets, behind the checkout counter).

C. USSTC Study of Consumer Understanding & Perceptions

Purpose

The applicant submitted a quantitative study examining consumer comprehension of the proposed modified risk claim and the effects of the claim on behavioral intentions and risk perceptions regarding Copenhagen Snuff. The study used a quasi-experimental, pretest-posttest design where consumers were assigned to one of two study conditions: viewing an advertisement with the modified risk claim (test) or without it (control). The applicant describes four study objectives: (1) to describe the percentage of participants assigned to the test condition who correctly comprehended the modified risk claim; (2) to measure changes in behavioral intentions (i.e., intentions to try, intentions to use, intentions to quit smoking, intentions to quit tobacco, intentions to dual use, intentions to switch) following exposure to an advertisement for Copenhagen Snuff (see Section III for results); (3) to compare participants' risk perceptions of Copenhagen Snuff to their risk perceptions of other types of tobacco products, nicotine replacement therapy (NRT), and quitting; and (4) to examine the distribution of participants' risk perceptions of Copenhagen Snuff in terms of risk for specific diseases and health outcomes, as well as poor health outcomes generally, both before and after viewing an advertisement for Copenhagen Snuff.

Methods

The applicant generally assigned participants to conditions randomly, but also considered quotas in assignment to balance demographic variables between conditions and across tobacco user groups. While the applicant describes the study design as quasi-experimental, most participants were randomly assigned to a condition. When quotas for a specific condition were met, participants were placed into a condition without random assignment. For any given participant, if the quota for his/her particular demographic characteristics was full in one condition, the participant would be assigned to the other condition. If the quota in the other condition was full as well, the participant would be released. The study was conducted entirely online. Participants completed a pretest, viewed the advertisement for as long as they wanted, and then completed a posttest. Each posttest question screen provided a link to the advertisement, allowing participants to revisit the advertisement as many times as they wished while completing the posttest. The product shown in these advertisements was named Copenhagen Snuff, rather than Copenhagen Snuff Fine Cut. Participants were randomized to view advertisements containing one of the four Surgeon General's warnings for smokeless tobacco. There was no manipulation check to determine whether participants saw and paid attention to the advertisement or, in the test condition, to the modified risk claim.

Measures

Risk perceptions

The pretest and posttest survey instruments included measures of risk perceptions. Risk perceptions assessed included risk to total health as well as for specific diseases including mouth cancer, lung cancer, heart disease/heart attack, nicotine addiction, and discolored teeth/decay. With three exceptions, the

applicant provided evidence of validity, either in a validation study it sponsored or by citing the PATH Study.

Claim comprehension and believability

At posttest, participants assigned to the test condition also responded to measures assessing comprehension and believability of the modified risk claim. Comprehension was assessed via a single measure that asked participants: "Please look at this ad again. Regardless of what you believe to be true, please answer the question based on the information shown in this ad. Based only on the information shown in this ad, smokers who switch completely from cigarettes to Copenhagen Snuff:" Participants completed this statement by selecting one of the following response options: Increase the risk of lung cancer, Reduce the risk of lung cancer, Eliminate the risk of lung cancer, or Do not know. Claim believability was assessed via a single measure wherein participants assigned to the test condition were asked the extent to which they agreed with the statement, "This ad is believable." Participants responded to this question using a 5-point scale with the following response options: Strongly disagree, Disagree, Neither disagree nor agree, Agree, or Strongly agree. The applicant did not provide reliability or validity information for either the claim comprehension measure or the believability measure, and these measures were not included in the measure validation study (PBI-Val-Study) submitted by the applicant.

Sample

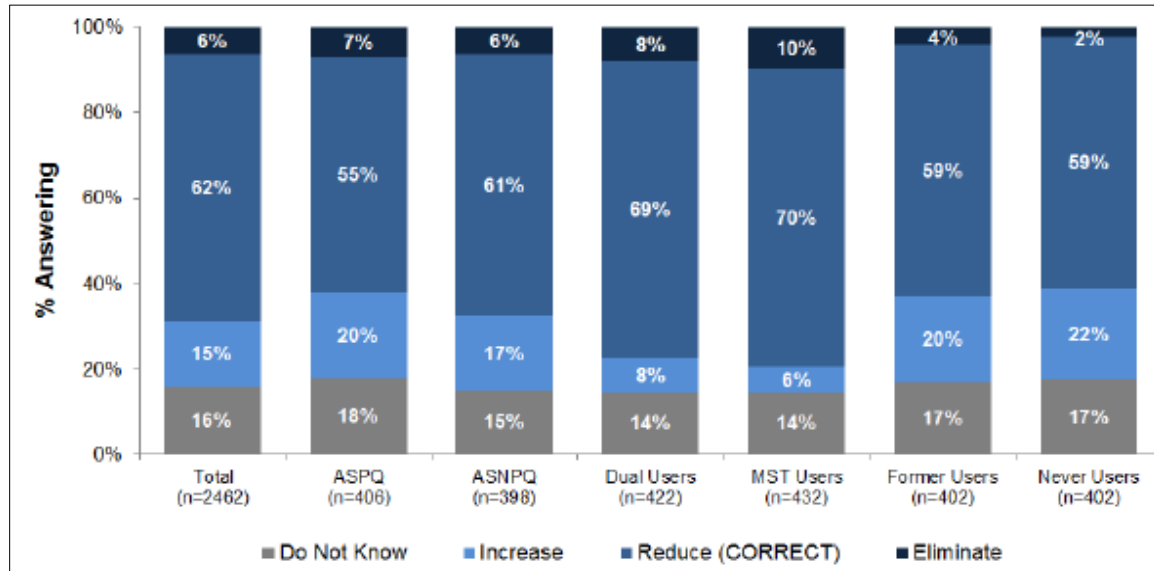
Participants were recruited via mall intercept, telephone solicitation, or email solicitation. A quota sampling approach was used, with quotas derived from PATH Wave 1. The study employed a non-probability sample of 5,871 adult participants, composed of a main study sample of 4,927 participants and a separate oversample of 944 young adult participants. Participants in the main sample were categorized to one of the following tobacco user subgroups: adult smokers planning to quit (ASPQ), adult smokers not planning to quit (ASNPQ), dual users, moist smokeless tobacco users, former users, and never users. The oversample of young adults included participants of the minimum legal age to purchase tobacco up to age 24. These participants were categorized to one of two tobacco user subgroups: tobacco users and tobacco non-users.

Findings

Comprehension

A majority of consumers who viewed the proposed modified risk claim were able to correctly answer a multiple-choice question assessing comprehension of its meaning (see Figure 4). This was true across all tobacco user subgroups, as well as among consumers with low health literacy: 55-70% were able to correctly respond that the claim stated that smokers who completely switch from cigarettes to Copenhagen Snuff would reduce their risk of lung cancer. A relatively small proportion of consumers – approximately 6% – misinterpreted the claim to mean that switching to Copenhagen Snuff would *eliminate* the risk of lung cancer. Among young adults, approximately 61% of tobacco users and 57% of tobacco non-users answered the claim comprehension question correctly.

Figure 4. Comprehension of Proposed Modified Risk Claim (Source: MRTPA Section 2.3)



Question: Based only on the information shown in this ad, smokers who switch completely from cigarettes to Copenhagen Snuff... **Response Options:** Increase the risk of lung cancer. Reduce the risk of lung cancer. Eliminate the risk of lung cancer. Do not know.

ASPQ=adult smokers planning to quit; ASNPQ=adult smokers not planning to quit; MST=moist smokeless tobacco

Believability

Claim believability was variable across user groups. On a scale of 1-5, mean believability scores were lowest among young adult tobacco non-users (mean=2.63), and highest among dual users of moist snuff and cigarettes (mean=3.74).

Risk Perceptions

The applicant examined consumers' perceptions of risk associated with using half a can of Copenhagen Snuff daily. The applicant compared these perceptions with consumers' perceptions of the risks associated with smoking 15 cigarettes daily, using half a can of other smokeless products daily, using NRT, quitting all tobacco, and never using tobacco products. Mean risk perception scores for these behaviors at posttest are shown in Table 6. While these means were provided without tests of statistical significance, the magnitude of differences between means in the test and control conditions appears small.

Table 6. Mean Risk Perception Scores¹ at Posttest, by Tobacco User Group and Study Condition
(Source: MRTPA Section 7.3.2)

	ASPQ ²		ASNPQ ³		Dual Users		MST ⁴ Users		Former Users		Never Users	
	Test (n=406)	Control (n=401)	Test (n=398)	Control (n=403)	Test (n=422)	Control (n=418)	Test (n=432)	Control (n=439)	Test (n=402)	Control (n=404)	Test (n=402)	Control (n=400)
Using half a can of Copenhagen Snuff daily	5.18	5.16	4.97	5.08	4.29	4.46	4.30	4.37	5.85	6.08	6.11	6.03
Smoking 15 cigarettes daily	5.62	5.54	5.11	5.29	4.87	4.94	5.27	5.17	6.23	6.25	6.45	6.32
Using half a can of other dip/snuff daily	5.15	5.14	5.00	5.10	4.26	4.47	4.35	4.30	5.86	6.04	6.05	6.03
Using NRT	3.93	3.55	3.46	3.65	3.17	3.50	3.09	3.56	3.88	4.21	4.14	4.37
Completely quitting all tobacco use	2.58	2.41	2.34	2.49	2.40	2.28	2.07	2.31	2.13	2.20	2.16	2.59
Never using tobacco products	2.44	2.16	2.28	2.16	2.00	1.88	1.84	1.94	1.88	1.78	1.82	2.13

¹Risk perception scores are expressed on a 7-point scale: 1=Not at all risky, 2=Slightly risky, 3=Somewhat risky, 4=Moderately risky, 5=Risky, 6=Very risky, 7=Extremely risky.

²ASPQ=Adult smokers planning to quit

³ASNPQ=Adult smokers not planning to quit

⁴MST=Moist smokeless tobacco

The applicant's study found no effects of the modified risk claim on risk perceptions among the populations most likely to receive a health benefit from switching – namely, smokers and dual users of moist snuff and cigarettes. After viewing an advertisement with the modified risk claim, 26% of smokers not planning to quit, 29% of smokers planning to quit, and 35% of dual users of moist snuff and cigarettes perceived using half a can of Copenhagen Snuff daily as less risky than smoking 15 cigarettes a day. Among these three tobacco user groups, viewing the advertisement with, rather than without, the proposed claim did not significantly reduce perceptions of health risks from using Copenhagen Snuff daily, including for overall health risk, lung cancer, or other specific diseases. These results suggest that a single occasion of online exposure to the ad with the claim was not effective at changing risk perceptions among the populations most likely to receive a health benefit from complete switching to Copenhagen Snuff Fine Cut (i.e., combusted cigarette smokers, dual users of combusted cigarettes and smokeless tobacco).

The proposed claim also had few effects on risk perceptions of Copenhagen Snuff among other tobacco user groups, including former tobacco users, never users, young adult tobacco users, and young adult tobacco non-users. After viewing the advertisement with the proposed claim, 24-35% of the people in these user groups perceived using half a can of Copenhagen Snuff daily to be less risky overall than smoking 15 CPD. In the study's main analyses of risk perceptions, viewing the advertisement with, rather

than without, the proposed claim only significantly affected risk perceptions in one group: among young adult non-users of tobacco, viewing the proposed claim decreased perceptions of overall health risk from using Copenhagen Snuff. While statistically significant, the magnitude of this decrease was small, with a decrease in the mean risk score of 1.1 points on a 100-point scale.

In terms of risk perceptions of Copenhagen Snuff compared to other products within the same product class, the majority of participants assigned to the test condition perceived Copenhagen Snuff and other dip/snuff products as posing an equal risk to health at posttest. This was true across all tobacco user groups, among young adults, among those with low health literacy, and among those with adequate health literacy. Among dual users and moist smokeless tobacco users—populations of great interest when considering the potential health effects of product switching within the product class—66% and 75%, respectively, perceived Copenhagen Snuff and other dip/snuff products as posing an equal risk to health, while 15% and 9%, respectively, perceived Copenhagen Snuff as more risky to health than other dip/snuff products at posttest. Fourteen percent of dual users and 13% of moist smokeless tobacco users assigned to the test condition perceived Copenhagen Snuff to be less risky to health than other dip/snuff products at posttest.

In addition to the main study analyses, the applicant provided an additional post-hoc analysis (Table 7) showing that, among those who viewed the advertisement with the proposed claim, a significantly greater proportion of young adult non-users of tobacco and former users reported decreased perceptions of lung cancer risk from using Copenhagen Snuff compared to their counterparts who saw the same advertisement without the proposed claim. The main study analyses examining lung cancer risk perceptions, which were more methodologically robust than the post-hoc analysis, did not show statistically significant results. The post-hoc analysis also showed that a significantly greater proportion of young adult non-users of tobacco who viewed the advertisement with the proposed claim reported decreased risk perceptions of overall health risk from using Copenhagen Snuff compared to their counterparts who saw the same advertisement without the proposed claim. This result is consistent with the more robust main study analyses of risk perceptions. Taken together, these results suggest that the claim may slightly reduce risk perceptions among young adult non-users, who are more susceptible to tobacco marketing and more likely to initiate tobacco product use.

Table 7. Proportion of Participants for whom Risk Perceptions Decreased after Viewing the Advertisement for Copenhagen Snuff (Source: MRTPA Section 7.3.2.9)

Health Outcome	Condition	ASPQ	ASNPQ	Dual Users	MST Users	Former Users	Never Users	LA-24 Users	LA-24 Nonusers
Negatively impacts health	Control	23%	19%	20%	22%	12%	11%	19%	11%
	Test	21%	23%	24%	20%	17%	17%	19%	20% ¹
Mouth cancer	Control	19%	19%	23%	19%	15%	14%	21%	13%
	Test	22%	20%	25%	23%	16%	18%	22%	20%
Lung cancer	Control	19%	20%	20%	15%	11%	14%	18%	15%
	Test	21%	24%	21%	21%	19% ¹	19%	21%	22% ¹
Heart disease/heart attack	Control	18%	18%	22%	22%	13%	13%	21%	17%
	Test	21%	25%	23%	24%	19%	16%	22%	22%
Nicotine addiction	Control	21%	17%	19%	21%	12%	11%	20%	12%
	Test	19%	16%	20%	17%	13%	16%	19%	18%
Discolored teeth or decay	Control	20%	17%	21%	21%	11%	13%	18%	14%
	Test	19%	17%	23%	20%	15%	18%	22%	17%

Note. ASPQ = Adult Smokers Planning to Quit; ASNPQ = Adult Smokers Not Planning to Quit; MST = Moist Smokeless Tobacco; LA: Legal age to purchase.

¹ Bold font indicates a statistically significant difference between the Control and Test conditions based on a chi-square test using Bonferroni-adjusted $\alpha = 0.05/6 = 0.008$.

After viewing an advertisement with the proposed modified risk claim, the majority of consumers correctly perceived using half a can of Copenhagen Snuff daily as more harmful than never using tobacco products (range: 60-80%) and completely quitting all tobacco use (range: 59-78%). Also, after viewing the proposed claim, roughly half of consumers correctly perceived using half a can of Copenhagen Snuff as more harmful than using NRT, though a substantial minority – roughly a third – perceived using Copenhagen Snuff and NRT as equally risky. These findings suggest that, even after exposure to the proposed claim, consumers understand that using Copenhagen Snuff poses risks to health.

The applicant did not assess how consumers perceive the health risks associated with partially switching from combusted cigarettes to Copenhagen Snuff. The applicant's proposed claim specifies that smokers can obtain the stated health benefit by switching completely to Copenhagen Snuff, but neither the claim nor the LLA materials describe the health effects of partial switching. This is important, as partial switching and long-term dual use are common use patterns, as described in more detail in Section IV.

D. Summary and Conclusions

Almost all U.S. tobacco users and non-users perceive smokeless tobacco and snus as harmful, with over one-third of youth and young adults surveyed reporting that smokeless tobacco use causes lung cancer. Studies have also found that a large majority of U.S. adults and youth rate smokeless tobacco as equally or more harmful than cigarettes or other combusted products. The applicant states that its proposed modified risk claim is intended to change adult smokers' perceptions of Copenhagen Snuff Fine Cut in an effort to get consumers to switch completely from cigarettes to Copenhagen Snuff Fine Cut. The applicant is proposing to include the claim "IF YOU SMOKE, CONSIDER THIS: Switching completely to this product from cigarettes reduces risk of lung cancer" on Copenhagen Snuff Fine Cut advertisements and product labels, including on its website, direct mail, point of sale advertisements, email, and the bottom of Copenhagen Snuff Fine Cut cans.

The applicant conducted an online study of adult tobacco users and non-users to assess comprehension of the proposed claim and impact of the claim on risk perceptions. A majority of participants, including those with low literacy, correctly responded that the claim stated that smokers who completely switch from cigarettes to Copenhagen Snuff would reduce their risk of lung cancer. In general, the applicant's research showed that the modified risk claim did not significantly change consumers' risk perceptions regarding use of Copenhagen Snuff, either in absolute terms or relative to the risks posed by smoking cigarettes, using other smokeless tobacco products, using NRT, quitting all tobacco use, or never using tobacco products. This was true across all tobacco user groups, including adult smokers not planning to quit, adult smokers planning to quit, moist snuff tobacco users, dual users of moist snuff and cigarettes, former tobacco users, and never tobacco users. These null results appear valid, as the study used acceptable measures of risk perceptions and appeared to have adequate statistical power to detect small effect sizes. Study findings also suggest that, even after exposure to the proposed claim, consumers understand that using Copenhagen Snuff poses risks to health. The applicant did not assess how consumers perceive the health risks associated with partially switching from combusted cigarettes to Copenhagen Snuff Fine Cut.

The applicant did not submit data or analyses of how its proposed claim may affect youth perceptions of Copenhagen Snuff Fine Cut. The applicant did, however, oversample young adults in the CCI Study and analyzed their results separately. At this time, FDA does not have sufficient information to know whether the claim's effects among youth would be different than those observed among young adults.

III. LIKELIHOOD OF USE AND IMPACTS TO THE POPULATION

This section uses observational studies and the applicant's clinical study to describe patterns of use of Copenhagen products and smokeless tobacco in the absence of modified risk information. The section then presents and assesses findings from the applicant's CCI Study designed to examine changes in intentions to use Copenhagen Snuff Fine Cut when participants are presented with the proposed modified risk claim.

A. Use of Smokeless Tobacco without Modified Risk Information

Data Sources

Population Assessment of Tobacco and Health (PATH) Study

The PATH Study is a large, nationally representative longitudinal study of tobacco use and health among adults and youths in the U.S. Wave 1 data collection was conducted from September 12, 2013 to December 14, 2014; Wave 2 interviews were conducted approximately one year later from October 23, 2014 to October 30, 2015.

Altria Client Services (ALCS) Tracking Study

The ALCS Tracking Study is an ongoing, nationally representative, mixed mode survey used to measure tobacco use prevalence among adult respondents. The ALCS Tracking survey enrolls approximately 2,400 adults per month, and the data provided in this application relies on 24 months of data prior to August 2017. The ALCS tracking study also includes information on smokeless tobacco form (loose fine-cut, loose-long cut, pouch) and brand. This application included respondents who reported using both

the Copenhagen brand as their regular brand and “Fine Cut” as their regular form (referred to as “Copenhagen Fine Cut”).

Claim Comprehension and Intentions Study (CCI)

The applicant conducted a quasi-experimental study examining consumer comprehension of the proposed modified risk claim and the effects of the claim on behavioral intentions and risk perceptions regarding Copenhagen Snuff. The study methods are described in more detail in Section II.C.

The CCI Study employed pretest and posttest survey instruments that included measures of behavioral intentions. Behavioral intentions assessed include intentions to try, use, dual use, and switch to Copenhagen Snuff; intentions to purchase Copenhagen Snuff; intentions to quit smoking; and intentions to quit all tobacco. With three exceptions, the applicant provided evidence of validity, either in a validation study it sponsored or by citing the PATH Study. For the measures of intentions to smoke cigarettes, intentions to use other nicotine products, and one measure of intentions to purchase, the applicant did not provide validity information; however, these measures had face validity and did not raise concerns.

In the population model submitted by the applicant, behavioral intentions inputs derived from the CCI Study are used as proxies for likelihood of use.

Altria Client Services LLC (ACS) Clinical Study

The applicant conducted a 7-day, within-subject laboratory study that compared the nicotine pharmacokinetics and subjective effects of a test moist snuff tobacco product “produced to the identical specifications as for the Copenhagen Original Fine Cut Snuff product marketed on or before February 2007” (referred to as “test moist snuff product” below) with participants’ usual brand of cigarettes and Nicorette Fresh Mint nicotine polacrilex gum (4 mg).

Participants in this study were 24 smokers (≥ 10 menthol or non-menthol CPD for at least 1 year) aged 21-65 years who were non-daily users of “original,” “natural,” “regular,” or similarly flavored moist snuff tobacco products (≥ 20 uses during lifetime, but not used every day in previous 30 days) with no use of Nicorette Fresh Mint gum in the previous 3 months.

Stage 1: Participants were randomized to the sequence of products they would receive on Days 1-3. On each day, participants received one of the three study products, and they were permitted to use the product *ad libitum* for 4 hours. Craving was assessed with the Questionnaire on Smoking Urges-Brief (QSU-B) within 5 minutes before use and immediately after the 4-hour *ad libitum* use period. Other subjective effects were assessed with a Modified Cigarette Evaluation Questionnaire (mCEQ) immediately following the *ad libitum* use period. Stage 1 was followed by a 1-day washout period on Day 4.

Stage 2: Participants were randomized to the sequence of products they would receive on Days 5-7. They received one of the three study products and were instructed to use the product under prescribed use conditions. Venous blood samples were collected for plasma nicotine analysis at 5 minutes prior to prescribed use of each product and 5, 7.5, 10, 15, 20, 25, 30, 35, 40, 50, 60, 120, and 180 minutes after the onset of prescribed use. Craving and withdrawal were assessed with the Tobacco/Nicotine

Withdrawal questionnaire 5 minutes prior to product use and 5, 15, 30, and 60 minutes after the onset of product use. Other subjective effects were also assessed 5, 15, 30, and 60 minutes after the onset of product use with the Direct Effects of Product questionnaire.

Data from this study provide evidence of how the abuse liability of the test moist snuff product compares to the abuse liability of cigarettes and an FDA-approved cessation aid in cigarette smokers following brief periods of exposure to the study products.

Current Use of Smokeless Tobacco/Copenhagen

In 2017, approximately 2.1% of U.S. adults were current users of any smokeless tobacco product, with prevalence higher among males (4.0%) than females (0.2%).²¹⁹ From 2002 to 2014, prevalence of past 30-day smokeless tobacco use increased slightly for adults aged 18-25 years (4.8% to 5.6%) and remained stable for adults aged >26 years (3.2% to 3.0%).²¹⁷ In Wave I of the PATH Study, prevalence of any smokeless tobacco was 2.9% (2.7-3.1) and use of non-pouched snus smokeless tobacco was more common among males, non-Hispanic whites, adults living in nonurban areas, and adults aged 25-49 years.²¹⁸ According to the applicant, 1.9% of adult current established users (defined as: “has ever used the product fairly regularly and now uses every day or some days”) aged 18-24 years used Copenhagen Snuff as their last brand used or usual brand, compared to 9.4% of adult established users aged 25 and older. In the PATH Study, Copenhagen Snuff users used moist smokeless tobacco an average of 28.0 days (CI: 26.9-29.1) in the past month, and in the ALCS Tracking Study, Copenhagen Fine Cut users used moist smokeless tobacco 26.3 days in the past month. In the PATH Study, 20% (12.0-31.5) of Copenhagen Snuff users used cigarettes in the past 30 days, and in the ALCS Tracking study, 19% of Copenhagen Fine Cut users used cigarettes in the past 30 days.

Current use of smokeless tobacco among youth is relatively low (high school students 5.5% [CI: 4.2-7.0], middle school students 1.9% [CI:1.5-2.4]).²¹⁹ Data from Monitoring the Future 2015 found that 1.7% of 12th graders reported first using smokeless tobacco in 12th grade, and 2.6% of 12th graders first reported using smokeless tobacco in 11th grade.²²⁰ Some studies have suggested that youth who use smokeless tobacco products may be more likely to initiate tobacco products that present higher levels of individual risk (i.e., combustible cigarettes),²²¹⁻²²⁶ while other studies in youth and young adults have found no association.²²⁷⁻²²⁹ Copenhagen (no sub-brands specified) was a common brand used by youth users in the National Survey on Drug Use and Health (NSDUH), but the applicant’s analysis of PATH Wave 1 Study data found that only 1.5% of 12-17-year-old past 30-day non-light smokeless tobacco users (those who reported using smokeless tobacco more than ten times in their lifetime and last used smokeless tobacco within the past 30 days) used a “Copenhagen Snuff” product as the type of Copenhagen brand usually or most recently used. When expanding the analysis to any Copenhagen product, FDA found that 40.8% (CI: 32.8%-49.3%) of 12-17-year-old past 30-day non-light users reported Copenhagen as their usual or most recent brand used.

Transitions from Cigarette Smoking to Exclusive Smokeless Tobacco Use

Under current real-world conditions (i.e., in the absence of a modified risk claim), observational studies from the peer-reviewed literature have examined transitions from cigarette smoking to exclusive smokeless tobacco use. For example, Tam and colleagues published a systematic review that examined the proportion of tobacco users and non-users who transition between four tobacco use states over

time: never use, exclusive smokeless use, exclusive smoking, and dual use.²²⁵ In this study, authors reported that the proportion of adult users demonstrating switching behaviors from exclusive smoking to exclusive smokeless tobacco use was low (0%-1.4%), with transitions from exclusive smoking to dual use of cigarettes and smokeless tobacco being slightly more common (0.1%-3.2%).²²⁵ Compared to rates of switching from exclusive smoking to exclusive smokeless tobacco use, transitions from exclusive smokeless tobacco use to exclusive smoking also appeared to be more common (0.9%-26.6%), although significant variability in these estimates exists, and other studies have found similar proportions of users moving from exclusive smokeless tobacco to cigarette smoking as from cigarette smoking to exclusive smokeless tobacco.²³⁰ Additionally, published analyses from the National Adult Tobacco Survey (NATS) found that among recent former cigarette smokers (quit smoking within the past year), complete switching from cigarette smoking to smokeless tobacco in the past year was low (4.6% in 2012-2013, 4.5% in 2013-2014).²³¹ Similarly, data from the 2010-2011 Tobacco Use Supplement of the Current Population Survey (TUS-CPS) found that quitting one form of tobacco and switching to the other was infrequent (1.2% for cigarettes to smokeless tobacco vs. 1.4% from smokeless tobacco to cigarettes).²³⁰

Dual Use of Smokeless Tobacco/Copenhagen Snuff Fine Cut and Cigarettes

Nineteen percent (CI not given) of past 30-day “Copenhagen Fine Cut” consumers in the ALCS Tracking Study and 20% (95%CI=12-31%) of past 30-day “Copenhagen Snuff” users in the PATH Study reported past 30-day use of cigarettes. These estimates for the percent of past 30-day cigarette use in Copenhagen users are lower than the percent of overall moist smokeless tobacco users (total category) who used cigarettes in the past 30 days (30% [CI not given] in the ALCS tracking study), 40% (95%CI=36-43%) in the PATH Study. In the PATH Study, dual Copenhagen Snuff users report smoking 11.0 cigarettes (95%CI=5.6-16.3) on days they smoked cigarettes, and the total number of cigarettes smoked on days cigarettes were smoked in the overall moist smokeless tobacco group was 16.2 (95%CI=13.7-18.7); however, the number of cigarettes smoked by non-smokeless tobacco users was not presented for comparison, nor was the number of days cigarettes were smoked among moist smokeless tobacco or non-moist smokeless tobacco smokers.

In MRTPA Section 6.3.5, the applicant states that it expects some period of multiple tobacco product use to occur, “even among adult smokers who are committed to transitioning to exclusive use of the candidate product.” The applicant notes that data from longitudinal studies show that more male dual users switch to exclusive smokeless tobacco (17.4%)^{225,232} compared to exclusive smokers switching to exclusive smokeless tobacco use (1.4%).^{225,232} However, the applicant fails to note that in that same study showing that 17.4% of male dual users switched to exclusive smokeless use,^{225,232} 27.0% switched from dual use to exclusive cigarette smoking and an additional 44.3% remained dual users over a 4-year follow-up period. Zhu and colleagues also found that there was more movement from dual use to smokeless tobacco than from exclusive cigarettes to smokeless tobacco;²³³ however, like Wetter et al. 2002,²³² they found that a higher percentage of dual users switched to cigarettes (37.0% [23.2-53.4%]) than to smokeless tobacco (4.9% [0.9-23.1%]), and nearly half of dual users remained dual users at 1-year follow-up (45.0% [29.7-61.3%]).²³³

Pharmacokinetic and Subjective Effects

In the absence of data on the long-term usage patterns of a tobacco product, abuse liability data collected under conditions of brief exposure, including nicotine pharmacokinetic and subjective effects

data, can help predict likelihood of product use. Nicotine is the primary addictive constituent of tobacco products.²³⁴⁻²³⁷ Therefore, exposure to nicotine is an important factor to consider when evaluating the abuse liability of a tobacco product. In addition to the amount of nicotine absorbed from a tobacco product, the speed at which it is absorbed may also affect abuse liability. Research suggests that the rate of increase in plasma drug concentration influences abuse liability, such that a faster rate of increase results in greater abuse liability.²³⁸⁻²⁴⁰ Furthermore, self-reported subjective effects, such as drug “liking”, have face validity and are some of the most sensitive and reliable measures of abuse liability.²⁴¹

In USSTC’s ACS Clinical Study, the applicant compared the nicotine pharmacokinetics and subjective effects of the test moist snuff product with participants’ usual brand of cigarettes and an FDA-approved cessation aid in cigarette smokers.

Peak plasma nicotine concentration (C_{max}) was not significantly different between the test moist snuff product and usual brand cigarette conditions, but it was higher in the test moist snuff product condition than the nicotine gum condition. Area under the curve from 0 to 180 minutes ($AUC_{0-180min}$) was significantly higher in the test moist snuff product condition relative to the usual brand cigarette and Nicorette gum conditions. Thus, overall exposure to nicotine was higher following one prescribed administration of the test moist snuff product relative to one prescribed administration of Nicorette gum or participants’ usual brand cigarettes. Plasma nicotine data reported in the scientific literature were comparable to those observed in the clinical study.^{242,243}

The rate of increase in plasma nicotine concentration as expressed by the median time to peak plasma nicotine concentration (T_{max}) was much longer in the test moist snuff (30.5 minutes) and Nicorette gum (37.5 minutes) conditions than the usual brand cigarette condition (7.5 minutes). Therefore, nicotine was absorbed more rapidly from usual brand cigarettes than from Nicorette gum or the test moist snuff product. Taken together, these plasma nicotine data suggest that the test moist snuff product may have lower abuse potential than usual brand cigarettes and similar or greater abuse potential than Nicorette gum. However, abuse liability is not determined based solely on plasma nicotine data.

Differences in some subjective effects measures were also reported between study conditions. For example, the pre-product-use visual analog scale (VAS) score of “urges to smoke” on the Tobacco/Nicotine Withdrawal questionnaire showed a non-significant trend with greater suppression of smoking urges following usual brand cigarette smoking relative to use of the test moist snuff product. In addition, maximum VAS scores for the question, “Is the product pleasant right now?” on the Direct Effects of Product questionnaire administered during prescribed use were significantly lower for the test moist snuff product and Nicorette gum than usual brand cigarettes. In general, the largest differences in subjective effects ratings were observed between the usual brand cigarette condition and the other two study conditions, such that subjective effects ratings were often significantly higher for cigarettes than the test moist snuff product or Nicorette gum on questionnaires administered during prescribed use and *ad libitum* use. Differences in subjective effects were less robust between the test moist snuff product and Nicorette gum, such that subjective effects ratings were often higher (but not statistically significantly higher) for the test moist snuff product than Nicorette gum, or ratings were similar for these two products. Taken together, the subjective effects data from this study suggest that the abuse potential of the test moist snuff product is lower than that for usual brand cigarettes and similar to or higher than the abuse potential of Nicorette gum among cigarette smokers who are non-daily users of

smokeless tobacco under conditions of brief exposure. Although limited, evidence from the scientific literature supports the findings from the ACS Clinical Study.^{243,244}

Evidence from the ACS clinical study suggests that the abuse liability of the test moist snuff product may be lower than that of usual brand cigarettes and higher than that of Nicorette gum in cigarette smokers, and these findings suggest that exclusive cigarette smokers may be unlikely to switch to exclusive use of Copenhagen Snuff Fine Cut. However, several study limitations should be noted. First, participants in this study were exposed to the study tobacco products under controlled conditions for a very brief duration. No abuse liability outcomes of the test moist snuff product were measured following extended use (i.e., weeks or months of use) in participants' natural environments. Thus, it is unclear whether the abuse liability outcomes associated with the test moist snuff product would change under such conditions. Second, measures of dependence were not evaluated in the ACS Clinical Study. Third, participants in this study were cigarette smokers (≥ 10 CPD) with previous experience using moist snuff tobacco products (≥ 20 uses during lifetime, but not used every day in the previous 30 days). Therefore, it is unclear how results from this study would generalize to daily smokeless tobacco users, nonsmokers, former smokers, or smokers with no history of moist snuff use.

B. Potential Impact of Modified Risk Claim on Intentions to Use

The applicant's CCI Study assessed the effect of the proposed modified risk claim on consumers' intentions to use Copenhagen Snuff. The product shown in the tested advertisements was named Copenhagen Snuff, rather than Copenhagen Snuff Fine Cut.

Current Tobacco Users

The applicant assessed behavioral intentions to try, use, dual use, and switch to Copenhagen Snuff; quit smoking; and quit all tobacco via a series of analyses of covariance (ANCOVAs) that assessed differences in behavioral intentions after consumers viewed an advertisement either with or without the proposed claim (Table 8). Intentions to use Copenhagen Snuff were higher among adult smokers not planning to quit who viewed the advertisement with the claim compared to those who viewed the advertisement without the claim. However, intentions to try, dual use, and switch to Copenhagen Snuff did not differ significantly between those who viewed the advertisement with vs. without the claim. This makes the increase in intentions to use among this group difficult to interpret, as it is unclear how such use would occur if not in the context of trying, dual using, or switching to Copenhagen Snuff.

Table 8. Composite Scores (unadjusted means) of Responses Related to Candidate Product Trial, Use, or Switching among Current Tobacco Users (Source: MRTPA Section 2.3)

Group	Condition	Intention ¹					
		Intent to Try		Intent to Use		Intent to Switch	
		Pre	Post	Pre	Post	Pre	Post
ASPQ ²	Control (n = 401)	2.43	2.30	2.31	2.20	2.19	2.11
	Test (n = 406)	2.40	2.36	2.29	2.25	2.16	2.11
ASNPQ ³	Control (n = 403)	2.54	2.46	2.41	2.31	2.08	2.06
	Test (n = 398)	2.49	2.48	2.32	2.34*	2.02	2.09
MST ⁴ users	Control (n = 341)	4.36	4.35	4.27	4.18	Not asked since already using MST products	
	Test (n = 356)	4.49	4.37	4.22	4.16		
Dual Users	Control (n = 337)	4.51	4.38	4.22	4.13	3.33	3.27
	Test (n = 336)	4.59	4.54	4.43	4.32	3.51	3.51

¹ Values represent the unadjusted average score of responses to statements or questions related to trial or use of the candidate product before (pre) or after (post) reading an advertisement containing the proposed modified risk claim language (Test) or reading and advertisement without the proposed claim language (Control). Participants assigned their agreement on a scale of 1-6 (6=Strongly Agree, 5=Agree, 4=Somewhat Agree, 3=Somewhat Disagree, 2=Disagree, 1=Strongly Disagree) to the following: Trial - I am open to trying Copenhagen[®] Snuff in the next 30 days; Based on what you know about Copenhagen[®] Snuff, how likely or unlikely are you to try Copenhagen[®] Snuff?; Based on what you know about Copenhagen[®] Snuff, how likely or unlikely are you to try Copenhagen[®] Snuff if one of your best friends were to offer Copenhagen[®] Snuff to you?; Use - I would consider using Copenhagen[®] Snuff more than once. I expect to use Copenhagen[®] Snuff. It is likely that I will regularly use Copenhagen[®] Snuff in the next 6 months. Copenhagen[®] Snuff will be my regular brand of snuff/dip/smokeless tobacco in the next 30 days. Switch - I plan to gradually switch from regular cigarettes to a Copenhagen[®] Snuff. I plan on Copenhagen[®] Snuff as a complete replacement for regular cigarettes. I intend on switching from cigarettes to Copenhagen[®] Snuff in the next six months.

² ASPQ = Adult Smokers Planning to Quit

³ ASNPQ = Adult Smokers Not Planning to Quit

⁴ MST = Moist Smokeless Tobacco

*Statistically significant greater change (pre – post) in intention in the Test Condition relative to the Control Condition after exposure to the claim. (ANCOVA - After Bonferroni adjustment, *p*-values < 0.008 were considered to be statistically significant.)

Among other tobacco user groups that could potentially benefit by completely switching to Copenhagen Snuff, the CCI Study found no evidence that the proposed claim would promote switching. Findings from the study show that the modified risk claim did not significantly increase intentions to try, use, switch to, or dual use Copenhagen Snuff among smokers planning to quit, dual users of moist snuff and cigarettes, or young adult tobacco users. Of particular interest is the claim's null effect on intentions to switch to Copenhagen Snuff among current dual users of moist snuff and cigarettes. Dual users are perhaps the subpopulation where a net positive public health impact may be most realistically achievable. Dual users would likely receive a health benefit by complete switching, and, as they are already smokeless tobacco users, they may generally be more willing to use Copenhagen Snuff.

In addition, there was no evidence that the modified risk claim would affect smokers' intentions to quit smoking cigarettes or tobacco users' intentions to quit all tobacco. In terms of intentions to quit

smoking, among tobacco user groups currently using cigarettes (smokers planning to quit, smokers not planning to quit, dual users of moist snuff and cigarettes, and young adult tobacco users), viewing the advertisement with vs. without the claim did not significantly increase or decrease intentions to quit smoking. Similarly, null effects of the claim were also found for intentions to quit all tobacco among user groups currently using tobacco (smokers planning to quit, smokers not planning to quit, dual users of moist snuff and cigarettes, moist snuff users, and young adult tobacco users).

Non-users of Tobacco

In addition, there was little evidence that the modified risk claim increased intentions to use Copenhagen Snuff among non-users of tobacco, including former users, never smokers, and young adult non-users of tobacco products. Among these user groups, the applicant's research found no statistically significant differences in intentions to try or use Copenhagen Snuff based on whether the advertisement did or did not include the proposed claim (Table 9).

Table 9. Unadjusted Mean Composite Scores for Intentions to Try and Intentions to Use Copenhagen Snuff among Adult Non-users of Tobacco (Source: MRTPA Section 2.3)

Group	Condition	Intentions to Try ¹			Intentions to Use ²		
		Pretest	Posttest	p-value ⁴	Pretest	Posttest	p-value
Never users	Test (n=402)	1.3	1.2	0.358	1.3	1.2	0.126
	Control (n=400)	1.4	1.3		1.3	1.3	
Former users	Test (n=402)	1.4	1.3	0.758	1.3	1.3	0.215
	Control (n=404)	1.3	1.3		1.3	1.2	
Non-users LA-24 ³	Test (n=401)	1.5	1.4	0.774	1.4	1.4	0.422
	Control (n=403)	1.4	1.4		1.3	1.3	

¹Intentions to try was a composite measure of mean ratings from three items: (1) I am open to trying Copenhagen Snuff in the next 30 days; (2) Based on what you know about Copenhagen Snuff, how likely or unlikely are you to try Copenhagen Snuff; (3) Based on what you know about Copenhagen Snuff, how likely or unlikely are you to try Copenhagen Snuff if one of your best friends were to offer Copenhagen Snuff to you? Each question was asked before and after viewing the advertisement for the candidate product. The first item was measured on a six-point scale, ranging from Strongly disagree to Strongly agree. The other two items were also measured on a 6-point scale, ranging from Definitely Not to Definitely.

²Intentions to use was a composite measure of mean ratings from four items: (1) I would consider using Copenhagen Snuff more than once; (2) I expect to use Copenhagen Snuff; (3) It is likely that I will regularly use Copenhagen Snuff in the next six months; and (4) Copenhagen Snuff will be my regular brand of snuff/dip/smokeless tobacco in the next 30 days. All four items were measured on a six-point scale, ranging from Strongly disagree to Strongly agree.

³Non-users LA-24=Non-users of tobacco of the minimum legal age to purchase tobacco in their jurisdiction of residence up to age 24.

⁴After Bonferroni adjustment, p-values < 0.008 were considered to be statistically significant.

C. Population Modeling

MRTPA Section 6.5 presents the applicant's ALCS Cohort Model modeling approach and a quantitative assessment of the potential population health impact of a marketing order for Copenhagen Snuff Fine Cut. The modeling approach incorporates a compartmental model to represent transitions between tobacco-use states. The product categories in the model are cigarettes and moist smokeless tobacco. Results for moist smokeless tobacco are then scaled by Copenhagen Snuff Fine Cut's market share of this product category to produce specific estimates for the candidate product. This quantitative assessment looks specifically at the U.S. male population, given that males represent the overwhelming majority of U.S. smokeless tobacco users. Transition probabilities between these states come from values presented in studies cited in a review by Tam and colleagues.²²⁵ The effect of the proposed modified risk claim on tobacco use behavior is estimated based on findings from the CCI Study (see Section III.B). The model uses mortality data derived from the Kaiser Permanente Medical Care Program Study. The applicant calculated the excess relative risk (ERR) of smokeless tobacco use compared to cigarette smoking using Cox proportional hazards models applied to National Health Interview Survey – Linked Mortality Files (NHIS-LMF) data (6.5.6.1). The applicant estimated the ERR of current smokeless tobacco users compared to that of current cigarette smokers to be 0.09 and the ERR of former smokeless tobacco users compared to that of former cigarette smokers to be 0.04. MRTPA Section 7.4.2 provides additional information about the model.

Applicant's Findings

The applicant presents results in terms of comparisons between the Base Case scenario (includes existing tobacco product use behaviors for cigarettes and moist smokeless tobacco products) and the Master Case, a particular version of the Modified Case scenario (includes behaviors for cigarettes and moist smokeless tobacco products with the proposed claim) that represents what the applicant thinks are the most likely estimates for each of the transition probabilities.

Using the single cohort approach with a cohort of one million males, the applicant finds that there would be a difference of 1,120 survivors (95% Credible Interval = 958, 1301) at age 73 years between the Master Case scenario and the Base Case scenario. The difference between the two scenarios in terms of person-years lived would be 32,856 years.

The applicant performed sensitivity analyses for seven important tobacco use transitions. In each case, the applicant changed the probability of that transition to its value in the Master Case while keeping all other transition probabilities at their values in the Base Case scenario. The applicant found that the transition producing the greatest benefit was cigarette smokers switching to exclusive moist smokeless tobacco use with a difference of 425 additional survivors at age 73 compared to the Base Case (95% Credible Interval = 366, 489), followed by non-smokers who would otherwise initiate smoking initiating moist smokeless tobacco use instead (393 additional survivors, 95% Credible Interval = 343, 442) and cigarette smokers transitioning to dual cigarette and moist smokeless tobacco use (282 additional survivors, 95% Credible Interval = 210, 363). The transition producing a significant detriment was cigarette smokers who would have otherwise quit smoking switching to moist smokeless tobacco use (63 fewer survivors, 95% Credible Interval = 26, 99).

The applicant performed similar sensitivity analyses for the same seven transitions in which it allowed the percent change in the transition probabilities between the Base Case and Modified Case scenarios to vary from 0 to twice the value used in the Master Case scenario. Results were similar to those in the previous sensitivity analyses, although the credible intervals were wider.

The applicant then implemented a time-staggered, multiple cohort approach to extend the results from the single cohort model to the U.S. native-born male population over time. The applicant estimated that there would be 93,323 more survivors between the ages of 0 and 84 years in this population in the Master Case scenario compared to the Base Case scenario in 2075, 60 years after potential authorization of the modified risk claim.

The applicant then scaled this estimate by Copenhagen Snuff Fine Cut's current market share of 8% (6.5, 7.6) to estimate the effect of the modified risk claim for the specific candidate product. The applicant estimated that authorization of the proposed claim for Copenhagen Snuff Fine Cut would result in 7,500 additional survivors in the U.S. native-born male population after a follow-up period of 60 years.

Assessment of the Applicant's Approach

The applicant presents a population modeling approach to assess the potential effect of authorization of a modified risk claim for Copenhagen Snuff Fine Cut. The modeling approach uses a compartmental model that includes transitions between tobacco use states. The tobacco product use categories included in the model are cigarettes and moist smokeless tobacco. Tobacco use states in the model include never, current, former, and dual use of these products. Key data inputs in the model are summarized in Table 10.

The compartmental model includes relevant tobacco use transitions for the population. Data inputs include results from the scientific literature and publicly available national health survey data linked for mortality follow-up. Specific evaluation of the analysis of NHIS-LMF and CCI Study data is discussed in other sections of the review of the application.

The applicant estimated use transition probabilities using inputs derived from the CCI Study. Specifically, use transition probabilities were estimated using the relative percent difference in responses to composite measures of intentions to use, dual use, switch, and purchase Copenhagen Snuff from pretest to posttest between the test and control conditions among male participants only. The CCI Study report did not provide analyses separately for male participants, and it is therefore not known whether the relative percent differences used to estimate transition probabilities represent statistically significant differences. However, both the moist smokeless tobacco and dual user groups in the CCI Study were approximately 96% male. As analyses were performed separately for these groups, these analyses provide some information regarding behavioral intentions among males. The CCI Study showed that the proposed modified risk claim did not significantly affect behavioral intentions, with the exception of a small but statistically significant increase in intentions to use among adult smokers not planning to quit. As previously noted, this finding is difficult to interpret given the absence of significant differences in intentions to try, dual use, or switch to Copenhagen Snuff among adult smokers not planning to quit. The CCI Study did not find any other statistically significant differences in behavioral intentions between the test and control conditions, including among the predominately male moist smokeless tobacco and dual user groups. Therefore, the relative percent differences used in the model to estimate use

transitions are likely derived from non-statistically significant findings and are unlikely to represent true “differences.” We therefore do not expect use transitions to substantially differ from those already observed in the U.S. population. We also note that behavioral intentions measures are imperfect predictors of actual future behaviors. In particular, participants who have not tried the product may be unable to accurately predict whether they will use it regularly or switch to it completely.

Table 10. Key Data Inputs in Population Model (Data Source: MRTPA Section 6.5.6)

Data Input	Source	Value
Excess Relative Risk (ERR)	National Health Interview Survey - Linked Mortality Files data (NHIS public-use data from 1987, 1991, 1992, 1998, 2000, and 2005 linked to the National Death Index for mortality follow-up through the end of 2011)	Cox proportional hazards models were used to estimate hazard ratios, which were used to calculate ERRs. The ERR for smokeless tobacco users compared to cigarette smokers was 0.09 for current users and 0.04 for former users.
Transition probabilities between tobacco use states	Three of the six studies (Wetter et al., ²³² Tomar, ²²² and Zhu et al. ²³³) included in the systematic review of transitions between smokeless tobacco and cigarette use by Tam et al. ²²⁵	Transition probabilities for adolescent males in the Base Case were obtained from Tomar ²²² and are given in MRTPA Table 7.4.2-17. Probabilities for adult males were obtained from Wetter et al. ²³² and Zhu et al. ²³³
Effect of authorization of proposed modified risk claim on transition probabilities	Altria Client Services (ALCS) Claim Comprehension and Intentions (CCI) Study	MRTPA Table 7.4.2-20 presents the relative percentage change of likelihood of product use for Test Groups (shown the proposed claim) and Control Groups (not shown the claim) for various tobacco use groups and intended behaviors.

D. Summary and Conclusions

In the absence of modified risk information, the prevalence of smokeless tobacco products is 2.3%, with use more common among those who are male, non-Hispanic white, adults living in nonurban areas, and adults aged 25-49 years.²⁴⁵ Current use of smokeless tobacco among youth is relatively low.²¹⁹ In terms of patterns of use, the PATH Study and ALCS Tracking Study found that Copenhagen users report using moist smokeless tobacco on 26.3-28 days in the past month and that approximately 20% of Copenhagen users also used cigarettes in the past 30 days. Several studies have found that switching from exclusive smoking to exclusive smokeless tobacco use among adults is low.^{225,230,231}

Pharmacokinetic and subjective effects data from the applicant’s ACS Clinical Study suggest that the abuse potential of the tested smokeless tobacco product among smokers is less than that of cigarettes and similar to or greater than that of an FDA-approved cessation aid. Although more nicotine is likely to be delivered by the tested smokeless tobacco product than some cigarettes and FDA-approved cessation aids, the rate of nicotine absorption from the tested smokeless tobacco product is slower than that of cigarettes and comparable to that of some FDA-approved cessation aids. Furthermore, subjective effects ratings for the tested moist snuff product were typically lower than those for cigarettes. Given the lower abuse liability of the tested smokeless tobacco product, these data suggest that exclusive cigarette smokers may be unlikely to switch to exclusive use of Copenhagen Snuff Fine Cut.

The applicant's research found little evidence that the proposed modified risk claim would increase use of the product among consumers who may benefit from switching to the product or among those who may be harmed by initiating tobacco use with the product. Overall, adding the modified risk claim to the advertisement did not significantly change consumers' behavioral intentions to try, use, dual use, or switch to Copenhagen Snuff; quit smoking cigarettes; or quit using all tobacco. These findings were consistent across all tobacco user groups tested. The null results appear credible, as the study used acceptable measures of behavioral intentions and appeared to have adequate statistical power to detect small effect sizes. While self-reported behavioral intentions are an imperfect predictor of actual future behavior, the applicant's research provides little evidence that the proposed claim would increase use of the product among adult consumers.

The applicant did not submit data or analyses of how its proposed claim may affect youth intentions to use Copenhagen Snuff Fine Cut. The applicant did, however, oversample young adults in the CCI Study and analyzed their results separately. In the scientific literature, evidence regarding the effect of modified risk information on youth is sparse. We identified one study of sufficient methodological quality that assessed the effect of modified and relative risk information on youth. El-Toukhy and colleagues found that the provision of modified risk information to youth resulted in a small, statistically significant reduction in risk perceptions, but did not affect susceptibility to using the product.²⁴⁶ At this time, FDA does not have sufficient information to know whether the claim's effects among youth would be different than those observed among young adults.

The applicant presented results from a computational model that estimated a relatively small net population health benefit from market authorization of the proposed modified risk claim. The applicant projected that there would be approximately 7,500 additional survivors in the U.S. native-born male population 60 years following authorization of the claim. However, results are dependent on inputs for health risks from NHIS-linked mortality data and consumer behavior from the CCI Study.

Appendix A: Statutory Requirements for Modified Risk Tobacco Products (MRTPs) and Overview of FDA Review Process

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

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

Before an MRTP can be introduced into interstate commerce, an order from FDA under Section 911(g) must be issued and in effect with respect to the tobacco product, and if the proposed modified risk tobacco product is also a new tobacco product, it must comply with the premarket review requirements under section 910(a)(2).

To request a Section 911(g) order from FDA, a person must file a modified risk tobacco product application (MRTPA) under Section 911(d). The MRTPA should include, among other things, information about the various aspects of the tobacco product as well as information to enable FDA to assess the impacts of the proposed MRTP on individual health outcomes and population-level outcomes, such as initiation or cessation of tobacco product use. In March 2012, FDA published a draft guidance for public comment, entitled “Modified Risk Tobacco Product Applications,” which discusses the submission of applications for an MRTP under Section 911 of the FD&C Act and considerations regarding studies and analyses to include in an MRTPA (<https://www.congress.gov/111/plaws/publ31/PLAW-111publ31.pdf>).

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

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

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

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

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

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

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

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

- Issuance of the exposure modification order is expected to benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products.

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

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

Once an MRTPA is submitted, FDA performs preliminary administrative reviews to determine whether to accept and file it. In general, after filing an application, FDA begins substantive scientific review. As part of this scientific review, FDA will seek and consider public comments on the application as well as recommendations from the FDA Tobacco Products Scientific Advisory Committee (TPSAC). FDA intends to review and act on a complete MRTPA within 360 days of FDA filing an application. An order authorizing an MRTP refers to a specific product, not an entire class of tobacco products (e.g., all smokeless products).

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

Appendix B: Tabulated Index of USSTC Research Studies and Data Submitted in MRTPA (Source: MRTPA Section 2.3)

Area	Study type	Title	MRTPA Section
Health Risks of the Tobacco Product: Section 911(g)(4)(A) Key Findings Summarized in MRTPA Section 6.1	Secondary Analysis	Health Risks – Literature Summary	7.5.6-1 and 7.5.6-2
	Secondary Analysis	Smokeless Tobacco Mortality Risks: Analyses of Two Contemporary Nationally Representative Longitudinal Mortality Studies	7.4.1
	Chemical Analysis	HPHC Levels in Copenhagen® Snuff Fine Cut	7.1
Effect of Marketing on Consumer Understanding and Perceptions: Section 911(h)(1) Key Findings Summarized in MRTPA Section 6.2	Secondary Analysis	Perceptions – Literature Summary	7.5.7-1 and 7.5.7-2
	Adult Human Studies	Qualitative Study to Support Claims Language Development for Moist Smokeless Tobacco (CS01 Claims Qualitative Study)	7.3.3
	Adult Human Studies	Qualitative Study to Explore Modified Risk Communications Bundles for Moist Smokeless Tobacco	7.3.3
	Adult Human Studies	ALCS-CMI-17-20-MST-Claim Comprehension and Intentions Study for Product Currently Marketed as Copenhagen® Snuff (CCI)	7.3.2
Effect on Tobacco Use Behavior Among Current Tobacco Users Key Findings Summarized in MRTPA Section 6.3	Secondary Analysis	Behavior – Users Literature Summary	7.5.2-1 and 7.5.2-2
	Adult Human Studies	ALCS-CMI-17-20-MST-Claim Comprehension and Intentions Study for Product Currently Marketed as Copenhagen® Snuff (CCI)	7.3.2
	Adult Human Studies	ALCS-RS-17-02-MST – Pharmacokinetic Study with Subjective Effects	7.3.1
Effect on Tobacco Use Behavior among Non-users: Section 911(g)(4)(C) Key Findings Summarized in MRTPA Section 6.4	Secondary Analysis	Behavior – Non-users Literature Summary	7.4.3-1 and 7.5.3-2
	Secondary Analysis	National Surveys	3.2
	Adult Human Studies	Qualitative Study to Explore Modified Risk Communications Bundles for Moist Smokeless Tobacco	7.3.3

Effect on the Population as a Whole: Section 911(g)(1)(B) Key Findings Summarized in MRTPA Section 6.5	Modeling	Population Model Development, Input Parameters, and Outcomes	7.4.2
Postmarket Surveillance: Section 911(g)(1)(B) Proposed Program Described in Section 8.1	Adult Human Secondary Analysis	Proposed program of study Adverse Event Summary	8.1 7.4.3

Appendix B: Summary of Study Characteristics for Henley et al.¹⁸⁴

Study Characteristic	Description
Study population	Male participants of Cancer Prevention Study (CPS)-II cohort. At baseline, reported to be: - former exclusive cigarette smokers (previously smoked cigarettes and no other product) - current smokeless tobacco users who began doing so at time of or after quitting smoking (i.e., “switchers”) - never users of any tobacco
Study period	1982-2002; 20 years of follow up
Age at baseline	≥30 years
Study size (approximate)	112,000 former exclusive cigarette smokers (i.e. quit all tobacco use) 4,000 current exclusive smokeless tobacco users who previously smoked cigarettes (i.e., “switchers”) 112,000 never users of tobacco (includes cigarettes, smokeless tobacco, cigars, pipes)
Smokeless tobacco type	Smokeless tobacco, chewing tobacco, snuff
Exposure ascertainment	Tobacco use status ascertained from questionnaire completed at baseline. Full cohort was not re-interviewed for potential changes in tobacco use status over time.
Mortality Outcome (ICD-9)	Lung cancer (162), oral cancer (140-149), COPD (490-492, 496), coronary heart disease (410-414), stroke (430-438), all causes
Outcome ascertainment	-From 1982-88, through personal inquiries from volunteers of American Cancer Society and reported deaths verified by death certificate -From 1988-2002, through automated linkage with the National Death Index
Measure	Hazard ratio (HR) for switchers versus: 1) quit all tobacco use, 2) never tobacco users
Adjustment factors	Age, number of cigarettes formerly smoked per day, number of years smoked cigarettes, age at which participant quit smoking, race, educational level, BMI, exercise level, consumption of: alcohol, fat, fruit/vegetables, aspirin intake, employment type, employment status

References

- ¹ Wilson D, Wakefield M, Owen N, Roberts L. Characteristics of heavy smokers. *J Prev Med.* 1992 May 1;21(3):311-9.
- ² Jamal A, Phillips E, Gentzke AS, et al. Current Cigarette Smoking Among Adults — United States, 2016. *MMWR Morb Mortal Wkly Rep* 2018;67:53–59..
- ³ U.S. Environmental Protection Agency. Guidelines for Exposure Assessment. Federal Register 57(104):22888-22938. 1992 May 29. Available from: https://www.epa.gov/sites/production/files/2014-11/documents/guidelines_exp_assessment.pdf.
- ⁴ National Research Council. Science and decisions: advancing risk assessment. Washington, DC: National Academies Press; 2009 Mar 24.
- ⁵ National Research Council. Exposure Science in the 21st century: a vision and a strategy. Washington, DC: National Academies Press; 2012 Oct 12.
- ⁶ Pazo DY, Moliere F, Sampson MM, et al. Mainstream smoke levels of volatile organic compounds in 50 US Domestic cigarette brands smoked with the ISO and Canadian intense protocols. *Nicotine Tob Res.* 2016 Apr 25;18(9):1886-94.
- ⁷ Counts ME, Hsu FS, Tewes FJ. Development of a commercial cigarette “market map” comparison methodology for evaluating new or non-conventional cigarettes. *Regul Toxicol Pharmacol.* 2006 Dec 1;46(3):225-42.
- ⁸ Bodnar JA, Morgan WT, Murphy PA, Ogden MW. Mainstream smoke chemistry analysis of samples from the 2009 US cigarette market. *Regul Toxicol Pharmacol.* 2012 Oct 1;64(1):35-42.
- ⁹ McAdam KG, Faizi A, Kimpton H, Porter A, Rodu B. Polycyclic aromatic hydrocarbons in US and Swedish smokeless tobacco products. *Chem Cent J.* 2013 Dec 1;7(1):151.
- ¹⁰ Djordjevic MV, Brunnemann KD, Hoffmann D. Identification and analysis of a nicotine-derived N-nitrosamino acid and other nitrosamino acids in tobacco. *Carcinogenesis.* 1989 Sep 1;10(9):1725-31.
- ¹¹ Ammann JR, Lovejoy KS, Walters MJ, Holman MR. A survey of N'-nitrosonornicotine (NNN) and total water content in select smokeless tobacco products purchased in the United States in 2015. *J Agric Food Chem.* 2016 May 18;64(21):4400-6.
- ¹² Borgerding MF, Bodnar JA, Curtin GM, Swauger JE. The chemical composition of smokeless tobacco: a survey of products sold in the United States in 2006 and 2007. *Regul Toxicol Pharmacol.* 2012 Dec 1;64(3):367-87.
- ¹³ Song MA, Marian C, Brasky TM, Reisinger S, Djordjevic M, Shields PG. Chemical and toxicological characteristics of conventional and low-TSNA moist snuff tobacco products. *Toxicol Lett.* 2016 Mar 14;245:68-77.

¹⁴ Stepanov I, Jensen J, Hatsukami D, Hecht SS. New and traditional smokeless tobacco: comparison of toxicant and carcinogen levels. *Nicotine Tob Res.* 2008 Dec 1;10(12):1773-82.

(b) (4)



²¹ Lesch CA, Squier CA, Cruchley A, Williams DM, Speight P. The permeability of human oral mucosa and skin to water. *J Dent Res.* 1989 Sep;68(9):1345-9.

²² Squier CA. Penetration of nicotine and nitrosornicotine across porcine oral mucosa. *J Appl Toxicol.* 1986 Apr;6(2):123-8.

²³ Squier CA, Hall BK. The permeability of skin and oral mucosa to water and horseradish peroxidase as related to the thickness of the permeability barrier. *Journal of Invest Dermatol.* 1985 Mar 1;84(3):176-9.

²⁴ Hassan N, Ahad A, Ali M, Ali J. Chemical permeation enhancers for transbuccal drug delivery. *Expert Opin Drug Deliv.* 2010 Jan 1;7(1):97-112.

²⁵ Homburger F, Hsueh SS, Russfield AB, Laird CW, Van Dongen CG. Absence of carcinogenic effects of chronic feeding of snuff in inbred Syrian hamsters. *Toxicol Appl Pharmacol.* 1976 Mar 1;35(3):515-21.

²⁶ Johansson SL, Hirsch JM, Larsson PA, Saidi J, Osterdahl BG. Lack of promoting ability of snuff in rats initiated with 4-nitroquinoline-N-oxide. *IARC Sci Publ.* 1991(105):507-9.

²⁷ Johansson SL, Hirsch JM, Johnson DR. Effect of repeated oral administration of tobacco snuff on natural killer-cell activity in the rat. *Arch Oral Biol.* 1991 Jan 1;36(6):473-6.

- ²⁸ Johansson SL, Hirsch JM, Larsson PA, Saidi J, Österdahl BG. Snuff-induced carcinogenesis: effect of snuff in rats initiated with 4-nitroquinoline N-oxide. *Cancer Res.* 1989 Jun 1;49(11):3063-9.
- ²⁹ Johansson SL, Hirsch JM, Larsson PA, Saidi J, Osterdahl BG. Lack of promoting ability of snuff in rats initiated with 4-nitroquinoline-N-oxide. *IARC Sci Publ.* 1991(105):507-9.
- ³⁰ Theophilus EH, Hayes JR, Ayres PH, et al. Toxicological evaluation of smokeless tobacco: 2-year chronic toxicity and carcinogenicity feeding study in Wistar Han rats. *Exp Toxicol Pathol.* 2015 Oct 1;67(10):539-50.
- ³¹ Theophilus EH, Hayes JR, Potts RJ, Ayres PH, Williams CD, Garner CD. Toxicological evaluation of smokeless tobacco: 90-day rodent feeding studies. *Exp Toxicol Pathol.* 2012 Jan 1;64(1-2):15-24.
- ³² Barley RD, Pollock S, Shallow MC, Peters E, Lam EW. Tobacco-related-compound-induced nitrosative stress injury in the hamster cheek pouch. *J Dent Res.* 2004 Dec;83(12):903-8.
- ³³ Coppe JP, Boysen M, Sun CH, et al. A role for fibroblasts in mediating the effects of tobacco-induced epithelial cell growth and invasion. *Mol Cancer Res.* 2008 Jul 1;6(7):1085-98.
- ³⁴ Guttenplan JB. Mutagenic activity in smokeless tobacco products sold in the USA. *Carcinogenesis.* 1987 May 1;8(5):741-3.
- ³⁵ Guttenplan JB. Mutagenic activity in smokeless tobacco products sold in the USA. *Carcinogenesis.* 1987 May 1;8(5):741-3.
- ³⁶ Rickert WS, Joza PJ, Trivedi AH, Momin RA, Wagstaff WG, Lauterbach JH. Chemical and toxicological characterization of commercial smokeless tobacco products available on the Canadian market. *Regul Toxicol Pharmacol.* 2009 Mar 1;53(2):121-33.
- ³⁷ Rickert WS, Wright WG, Trivedi AH, Momin RA, Lauterbach JH. A comparative study of the mutagenicity of various types of tobacco products. *Regul Toxicol Pharmacol.* 2007 Aug 1;48(3):320-30.
- ³⁸ Shirnamé-Moré L. Forward mutation of *S. typhimurium* by smokeless tobacco extracts. *Mutat Res.* 1991 Jan 1;259(1):37-42.
- ³⁹ Shirnamé-Moré L. Smokeless tobacco extracts mutate human cells. *Carcinogenesis.* 1991 May 1;12(5):927-30.
- ⁴⁰ Smith RA, Lawson T, Johansson SL. Detection of DNA adducts by 32P postlabeling following chronic exposure of rats to snuff. *Cancer Lett.* 1997 Dec 16;121(1):11-7.
- ⁴¹ Stamm SC, Zhong BZ, Whong WZ, Ong T. Mutagenicity of coal-dust and smokeless-tobacco extracts in *Salmonella typhimurium* strains with differing levels of O-acetyltransferase activities. *Mutat Res.* 1994 Jun 1;321(4):253-64.
- ⁴² Tucker JD, Ong TM. Induction of sister chromatid exchanges by coal dust and tobacco snuff extracts in human peripheral lymphocytes. *Environ Mutagen.* 1985;7(3):313-24.

- ⁴³ Whong WZ, Ames RG, Ong TM. Mutagenicity of tobacco snuff: possible health implications for coal miners. *J Toxicol Environ Health A*. 1984 Jan 1;14(4):491-6.
- ⁴⁴ Alonge OK, Ashrafi SH, Colvard MD. Mitochondrial volume densities in the smokeless tobacco-treated hamster cheek pouch epithelium. *Oral Dis*. 2003 May;9(3):138-43.
- ⁴⁵ Ashrafi S, Das A, Worowongvasu R, Mehdinejad B, Waterhouse J. A light, transmission and scanning electron microscope study of snuff-treated hamster cheek pouch epithelium. *Scanning Microsc*. 1992;6(1):183-193; discussion 193-194.
- ⁴⁶ Brunnemann KD, Rivenson A, Adams JD, Hecht SS, Hoffmann D. A study of snuff carcinogenesis. *IARC Sci Publ*. 1987(84):456-9.
- ⁴⁷ Chen SY. Effects of smokeless tobacco on the buccal mucosa of HMT rats. *J Oral Pathol Med*. 1989 Feb;18(2):108-12.
- ⁴⁸ Colvard MD, Ashrafi SH, Alonge OK, Cordell GA. Smokeless tobacco-induced lamellar body abnormalities. *Oral Dis*. 2006 May;12(3):343-8.
- ⁴⁹ Hecht SS, Rivenson A, Braley J, DiBello J, Adams JD, Hoffmann D. Induction of oral cavity tumors in F344 rats by tobacco-specific nitrosamines and snuff. *Cancer Res*. 1986 Aug 1;46(8):4162-6.
- ⁵⁰ Murrah VA, Gilchrist EP, Moyer MP. Morphologic and growth effects of tobacco-associated chemical carcinogens and smokeless tobacco extracts on human oral epithelial cells in culture. *Oral Surg Oral Med Oral Pathol*. 1993 Mar 1;75(3):323-32.
- ⁵¹ Peacock Jr EE, Brawley BW. An evaluation of snuff and tobacco in the production of mouth cancer. *Plast Reconstr Surg*. 1959 Jun 1;23(6):628-35.
- ⁵² Peacock Jr EE, Greenberg BG, Brawley BW. The effect of snuff and tobacco on the production of oral carcinoma: An experimental and epidemiological study. *Ann Surg*. 1960 Apr;151(4):542.
- ⁵³ Schwartz JL, Brunnemann KD, Adami AJ, et al. Brand specific responses to smokeless tobacco in a rat lip canal model. *J Oral Pathol Med*. 2010 Jul;39(6):453-9.
- ⁵⁴ Shklar G, Niukian K, Hassan M, Herbosa EG. Effects of smokeless tobacco and snuff on oral mucosa of experimental animals. *J Oral Maxillofac Surg*. 1985 Feb 1;43(2):80-6.
- ⁵⁵ Jenson HB, Baillargeon J, Heard P, Moyer MP. Effects of smokeless tobacco and tumor promoters on cell population growth and apoptosis of B lymphocytes infected with Epstein–Barr virus types 1 and 2. *Toxicol Appl Pharmacol*. 1999 Oct 15;160(2):171-82.

- ⁵⁶ Jenson HB, Heard P, Moyer MP. Evaluation of the effect of smokeless tobacco purified products and extracts on latent Epstein–Barr virus. *Toxicology*. 1999 Mar 1;133(1):35-42.
- ⁵⁷ Müns G, Vishwanatha JK, Rubinstein I. Effects of smokeless tobacco on chemically transformed hamster oral keratinocytes: role of angiotensin I-converting enzyme. *Carcinogenesis*. 1994 Jul 1;15(7):1325-7.
- ⁵⁸ Oh JS, Cherrick HM, Park NH. Effect of snuff extract on the replication and synthesis of viral DNA and proteins in cells infected with herpes simplex virus. *J Oral Maxillofac Surg*. 1990 Apr 1;48(4):373-9.
- ⁵⁹ Park NH, Akoto-Amanfu E, Paik DI. Smokeless tobacco carcinogenesis: The role of viral and other factors. *CA Cancer J Clin*. 1988 Jul;38(4):248-56.
- ⁶⁰ Park NH, Herbosa EG, Niukian K, Shklar G. Combined effect of herpes simplex virus and tobacco on the histopathologic changes in lips of mice. *Oral Surg Oral Med Oral Pathol*. 1985 Feb 1;59(2):154-8.
- ⁶¹ Park NH, Herbosa EG, Sapp JP. Effect of tar condensate from smoking tobacco and water-extract of snuff on the oral mucosa of mice with latent herpes simplex virus. *Arch Oral Biol*. 1987 Jan 1;32(1):47-53.
- ⁶² Park NH, Sapp JP, Herbosa EG. Oral cancer induced in hamsters with herpes simplex infection and simulated snuff dipping. *Oral Surg Oral Med Oral Pathol*. 1986 Aug 1;62(2):164-8.
- ⁶³ Prokopczyk G, Adams JD, LaVoie EJ, Hoffmann D. Effect of snuff and nicotine on DNA methylation by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. *Carcinogenesis*. 1987 Oct 1;8(10):1395-7.
- ⁶⁴ Rubinstein I. Smokeless tobacco potentiates VIP-induced DNA synthesis and inactivates NEP 24.11 in oral keratinocytes. *Am J Physiol Cell Physiol*. 2000 Feb 1;278(2):C391-6.
- ⁶⁵ Stich JE, Li KK, Chun YS, Weiss R, Park NH. Effect of smokeless tobacco on the replication of herpes simplex virus in vitro and on production of viral lesions in hamster cheek pouch. *Arch Oral Biol*. 1987 Jan 1;32(4):291-6.
- ⁶⁶ Summerlin DJ, Dunipace A, Potter R. Histologic effects of smokeless tobacco and alcohol on the pouch mucosa and organs of the Syrian hamster. *J Oral Pathol Med*. 1992 Mar;21(3):105-8.
- ⁶⁷ Wang Y, Rotem E, Andriani F, Garlick JA. Smokeless tobacco extracts modulate keratinocyte and fibroblast growth in organotypic culture. *J of Dent Res*. 2001 Sep;80(9):1862-6.
- ⁶⁸ Antoniades D, Niukian K, Schwartz J, Shklar G. Effects of smokeless tobacco on the immune system of Syrian hamsters. *J Oral Med*. 1984;39(3):136-41.
- ⁶⁹ Lindemann RA, Park NH. Inhibition of human lymphokine-activated killer activity by smokeless tobacco (snuff) extract. *Arch Oral Biol*. 1988 Jan 1;33(5):317-21.
- ⁷⁰ Arimilli S, Damratoski BE, Bombick B, Borgerding MF, Prasad GL. Evaluation of cytotoxicity of different tobacco product preparations. *Regul Toxicol Pharmacol*. 2012 Dec 1;64(3):350-60.

- ⁷¹ Arimilli S, Damratoski BE, Prasad GL. Combustible and non-combustible tobacco product preparations differentially regulate human peripheral blood mononuclear cell functions. *Toxicol In Vitro*. 2013 Sep 1;27(6):1992-2004.
- ⁷² Bernzweig E, Payne JB, Reinhardt RA, Dyer JK, Patil KD. Nicotine and smokeless tobacco effects on gingival and peripheral blood mononuclear cells. *J Clin Pedodontol*. 1998 Mar;25(3):246-52.
- ⁷³ Chan WS, Chowdhry S, Chang T, Kew RR. Initial characterization of the complement activating compounds in extracts of smokeless tobacco. *Immunobiology*. 1999 Sep 1;201(1):64-73.
- ⁷⁴ Chang T, Chowdhry S, Budhu P, Kew RR. Smokeless tobacco extracts activate complement in vitro: A potential pathogenic mechanism for initiating inflammation of the oral mucosa. *Clin Immunol Immunopathol*. 1998 Jun 1;87(3):223-9.
- ⁷⁵ Goud SN, Zhang L, Kaplan AM. Immunostimulatory potential of smokeless tobacco extract in in vitro cultures of murine lymphoid tissues. *Immunopharmacology*. 1993 Mar 1;25(2):95-105.
- ⁷⁶ Hassoun EA, Bagchi D, Bagchi M, Stohs SJ. Effect of vitamin E succinate on smokeless tobacco-induced production of nitric oxide by rat peritoneal macrophages and J774A. 1 macrophage cells in culture. *Free Radic Biol Med*. 1995 Mar 1;18(3):577-83.
- ⁷⁷ Johnson RR. Ammonia technology conference minutes. Brown and Williamson. 1989 Jun;12.
- ⁷⁸ Payne JB, Johnson GK, Reinhardt RA, Maze CR, Dyer JK, Patil KD. Smokeless tobacco effects on monocyte secretion of PGE2 and IL-1 β . *J Peridontol*. 1994 Oct;65(10):937-41.
- ⁷⁹ Petro TM. Modulation of IL-12 p35 and p40 promoter activity by smokeless tobacco extract is associated with an effect upon activation of NF- κ B but not IRF transcription factors. *Int Immunopharmacol*. 2003 May 1;3(5):735-45.
- ⁸⁰ Petro TM, Anderson LL, Gowler JS, Liu XJ, Schwartzbach SD. Smokeless tobacco extract decreases IL-12 production from LPS-stimulated but increases IL-12 from IFN- γ -stimulated macrophages. *Int Immunopharmacol*. 2002 Feb 1;2(2-3):345-55.
- ⁸¹ Petro TM, Schwartzbach SD, Zhang S. Smokeless tobacco and nicotine bring about excessive cytokine responses of murine memory T-cells. *Int Immunopharmacol*. 1999 Mar 15;21(2):103-14.
- ⁸² Petro TM, Zhang S. The effect of smokeless tobacco extract on murine T cell cytokine production. *Immunopharmacology*. 1997 Apr 1;36(1):17-26.
- ⁸³ Vishwanatha JK, Swinney R, Banerjee AG. Modulation of annexin I and cyclooxygenase-2 in smokeless tobacco-induced inflammation and oral cancer. *Mol Cell Biochem*. 2003 Jun 1;248(1-2):67-75.

- ⁸⁴ Andersson G, Wahlin A, Bratthall G. The effect of Swedish and American smokeless tobacco extract on periodontal ligament fibroblasts in vitro. *Swed Dent J*. 2006;30(3):89-97.
- ⁸⁵ Rubinstein I. Smokeless tobacco potentiates VIP-induced DNA synthesis and inactivates NEP 24.11 in oral keratinocytes. *Am J Physiol Cell Physiol*. 2000 Feb 1;278(2):C391-6.
- ⁸⁶ Bagchi M, Bagchi D, Stohs SJ. In vitro effects of a smokeless tobacco extract on the production of reactive oxygen species by human oral epidermal cells and rat hepatic mitochondria and microsomes, and peritoneal macrophages. *Arch Environ Contam Toxicol*. 1996 Mar 1;30(3):418-22.
- ⁸⁷ Bagchi M, Balmoori J, Bagchi D, Ray SD, Kuszynski C, Stohs SJ. Smokeless tobacco, oxidative stress, apoptosis, and antioxidants in human oral keratinocytes. *Free Radic Biol Med*. 1999 Apr 1;26(7-8):992-1000.
- ⁸⁸ Bagchi M, Kuszynski C, Patterson EB, et al. In vitro free radical production in human oral keratinocytes induced by smokeless tobacco extract. *In Vitro Toxicol*. 1997;10(2):263-74.
- ⁸⁹ Bagchi M, Kuszynski CA, Balmoori J, Joshi SS, Stohs SJ, Bagchi D. Protective effects of antioxidants against smokeless tobacco-induced oxidative stress and modulation of Bcl-2 and p53 genes in human oral keratinocytes. *Free Rad Res*. 2001 Jan 1;35(2):181-94.
- ⁹⁰ Falkler Jr WA, Zimmerman ML, Martin SA, Hall ER. The effect of smokeless-tobacco extracts on the growth of oral bacteria of the genus *Streptococcus*. *Arch Oral Biol*. 1987 Jan 1;32(3):221-3.
- ⁹¹ Furie MB, Raffanella JA, Gergel EI, Lisinski TJ, Horb LD. Extracts of smokeless tobacco induce pro-inflammatory changes in cultured human vascular endothelial cells. *Immunopharmacology*. 2000 Apr 1;47(1):13-23.
- ⁹² Galvin RJ, Ramp WK, Lenz LG. Smokeless tobacco contains a nonnicotine inhibitor of bone metabolism. *Toxicol Appl Pharmacol*. 1988 Sep 15;95(2):292-300.
- ⁹³ Gao H, Prasad GL, Zacharias W. Differential cell-specific cytotoxic responses of oral cavity cells to tobacco preparations. *Toxicol In Vitro*. 2013 Feb 1;27(1):282-91.
- ⁹⁴ Gao XP, Akhter SR, Ikezaki H, Hong D, Rubinstein I. Dexamethasone attenuates acute macromolecular efflux increase evoked by smokeless tobacco extract. *J Appl Physiol*. 1999 Aug 1;87(2):619-25.
- ⁹⁵ Gao XP, Suzuki H, Olopade CO, Pakhlevaniants S, Rubinstein I. Angiotensin-converting enzyme and neutral endopeptidase modulate smokeless tobacco-induced increase in macromolecular efflux from the oral mucosa in vivo. *J Lab Clin Med*. 1997 Oct 1;130(4):395-400.
- ⁹⁶ Gao XP, Suzuki H, Olopade CO, Pakhlevaniants S, Rubinstein I. Purified ACE attenuates smokeless tobacco-induced increase in macromolecular efflux from the oral mucosa. *J Appl Physiol*. 1997 Jul 1;83(1):74-81.
- ⁹⁷ Gao XP, Vishwanatha JK, Conlon JM, Olopade CO, Rubinstein I. Mechanisms of smokeless tobacco-induced oral mucosa inflammation: role of bradykinin. *J Immunol*. 1996 Nov 15;157(10):4624-33.

- ⁹⁸ Henderson JS, Johnson RB. The effects of smokeless tobacco extract on bone nodule formation and mineralization by chick osteoblasts in vitro. *Arch Oral Biol.* 1995 Jul 1;40(7):615-21.
- ⁹⁹ Huckabee KD, Barnes RT, Williams AG, Fan WL, Downey HF. Effects of snuff on regional blood flow to the cheek and tongue of anesthetized dogs. *Oral Surg Oral Med Oral Pathol.* 1993 Dec 1;76(6):729-35.
- ¹⁰⁰ Joyce AR, Hawkins W, Fariss MW, Sengupta TK. Role of plasma membrane disruption in reference moist smokeless tobacco-induced cell death. *Toxicol Lett.* 2010 Oct 5;198(2):191-9.
- ¹⁰¹ Lenz LG, Ramp WK, Galvin RJ, Pierce Jr WM. Inhibition of cell metabolism by a smokeless tobacco extract: tissue and species specificity. *Proc Soc Exp Biol Med.* 1992 Feb;199(2):211-7.
- ¹⁰² Lombard C, Farthing D, Sun J, Fariss MW, McKallip RJ. Reference moist smokeless tobacco-induced apoptosis in human monocytes/macrophages cell line MM6. *Int Immunopharmacol.* 2010 Sep 1;10(9):1029-40.
- ¹⁰³ Mangipudy RS, Vishwanatha JK. Role of nitric oxide in the induction of apoptosis by smokeless tobacco extract. *Mol Cell Biochem.* 1999 Oct 1;200(1-2):51-7.
- ¹⁰⁴ Mitchell C, Joyce AR, Piper JT, McKallip RJ, Fariss MW. Role of oxidative stress and MAPK signaling in reference moist smokeless tobacco-induced HOK-16B cell death. *Toxicol Lett.* 2010 May 19;195(1):23-30.
- ¹⁰⁵ Rubinstein I, Gao XP, Pakhlevaniants S, Oda D. Smokeless tobacco-exposed oral keratinocytes increase macromolecular efflux from the in situ oral mucosa. *Am J Physiol Regul Integr Comp Physiol* 1998 Jan 1;274(1):R104-11.
- ¹⁰⁶ Rubinstein I, Pedersen GW. Bacillus species are present in chewing tobacco sold in the United States and evoke plasma exudation from the oral mucosa. *Clin Diagn Lab Immunol.* 2002 Sep 1;9(5):1057-60.
- ¹⁰⁷ Sells Galvin RJ, Ramp WK, Lenz LG. Comparison of the effects of smokeless tobacco extract with the effects of prolyl hydroxylase inhibitors on collagenous and noncollagenous protein synthesis by osteoblasts. *Connect Tissue Res.* 1991 Jan 1;26(3):217-29.
- ¹⁰⁸ Suzuki H, Gao XP, Olopade CO, Jaffe HA, Pakhlevaniants S, Rubinstein I. Aqueous smokeless tobacco extract impairs endothelium-dependent vasodilation in the oral mucosa. *J Appl Physiol.* 1996 Jul 1;81(1):225-31.
- ¹⁰⁹ Tobey NA, Schreiner VJ, Readling RD, Orlando RC. The acute effects of smokeless tobacco on transport and barrier function of buccal mucosa. *J Dent Res.* 1988 Nov;67(11):1414-21.
- ¹¹⁰ Galvin RJ, Ramp WK, Lenz LG, Pierce Jr WM. Smokeless tobacco contains an inhibitor of prolyl hydroxylase activity. *Toxicol Lett.* 1992 Sep 1;62(2-3):301-10.
- ¹¹¹ Squires Jr WG, Brandon TA, Zinkgraf S, et al. Hemodynamic effects of oral smokeless tobacco in dogs and young adults. *Prev Med.* 1984 Mar 1;13(2):195-206.

- ¹¹² Paulson RB, Shanfeld J, Dean J, Mullet D, Fernandez M, Paulson JO. Alcohol and smokeless tobacco effects on the CD-1 mouse fetus. *J Craniofac Genet Dev Biol.* 1992;12(2):107-17.
- ¹¹³ Paulson RB, Shanfeld J, Mullet D, Cole J, Paulson JO. Prenatal smokeless tobacco effects on the rat fetus. *J Craniofac Genet Dev Biol.* 1994;14(1):16-25.
- ¹¹⁴ Paulson R, Shanfeld J, Sachs L, Price T, Paulson J. Effect of smokeless tobacco on the development of the CD-1 mouse fetus. *Teratology.* 1989 Nov;40(5):483-94.
- ¹¹⁵ Paulson RB, Shanfeld J, Prause L, Iranpour S, Paulson JO. Pre-and post-conceptional tobacco effects on the CD-1 mouse fetus. *J Craniofac Genet Dev Biol.* 1991;11(1):48-58.
- ¹¹⁶ Paulson RB, Shanfeld J, Vorhees CV, Cole J, Sweazy A, Paulson JO. Behavioral effects of smokeless tobacco on the neonate and young Sprague Dawley rat. *Teratology.* 1994 Apr;49(4):293-305.
- ¹¹⁷ Paulson RB, Shanfeld J, Vorhees CV, et al. Behavioral effects of prenatally administered smokeless tobacco on rat offspring. *Neurotoxicol Teratol.* 1993 May 1;15(3):183-92.
- ¹¹⁸ U.S. Environmental Protection Agency, National Center for Environmental Assessment. Integrated Risk Information System (IRIS) chemical assessment summary: arsenic, inorganic; CASRN 7440-38-2. 1988 Feb 10. Available from: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0278_summary.pdf
- ¹¹⁹ IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. IARC monographs on the evaluation of carcinogenic risks to humans. Ingested nitrate and nitrite, and cyanobacterial peptide toxins. *IARC Monogr Eval Carcinog Risks Hum.* 2010;94:v.
- ¹²⁰ Bergoglio RM. Mortalidad por cáncer en zonas de aguas arsenicales de la Provincia de Córdoba, República Argentina. *Prensa Méd Argent.* 1964;51:994-8.
- ¹²¹ Biagini RE, Rivero M, Salvador M, Córdoba S. Hidroarsenicismo crónico y cáncer de pulmón. *Arch Argent Dermatol.* 1978;28:151-58.
- ¹²² Chen CJ, Chuang YC, You SL, Lin TM, Wu HY. A retrospective study on malignant neoplasms of bladder, lung and liver in blackfoot disease endemic area in Taiwan. *Br J Cancer.* 1986 Mar;53(3):399.
- ¹²³ Chen CJ, Chuang YC, Lin TM, Wu HY. Malignant neoplasms among residents of a blackfoot disease-endemic area in Taiwan: high-arsenic artesian well water and cancers. *Cancer Res.* 1985 Nov 1;45(11 Part 2):5895-9.
- ¹²⁴ Chen CJ, Kuo TL, Wu MM. Arsenic and cancers. *Lancet.* 1988 Feb 20;331(8582):414-5.
- ¹²⁵ Chen CJ, Wang CJ. Ecological correlation between arsenic level in well water and age-adjusted mortality from malignant neoplasms. *Cancer Res.* 1990 Sep 1;50(17):5470-4.

- ¹²⁶ Chen CJ, Wu MM, Lee SS, Wang JD, Cheng SH, Wu HY. Atherogenicity and carcinogenicity of high-arsenic artesian well water. Multiple risk factors and related malignant neoplasms of blackfoot disease. *Arterioscler Thromb Vasc Biol.* 1988 Sep 1;8(5):452-60.
- ¹²⁷ Goldman AL. Lung cancer in Bowen's disease. *Am Rev Respir Dis.* 1973 Nov;108(5):1205-7.
- ¹²⁸ Guo HR. Arsenic level in drinking water and mortality of lung cancer (Taiwan). *Cancer Causes Control.* 2004 Mar 1;15(2):171-7.
- ¹²⁹ Heddle R, Bryant GD. Small cell lung carcinoma and Bowen's disease 40 years after arsenic ingestion. *Chest.* 1983 Dec 1;84(6):776-7.
- ¹³⁰ Lühtrath H. The consequences of chronic arsenic poisoning among Moselle wine growers. *J Cancer Res Clin Oncol.* 1983 Feb 1;105(2):173-82.
- ¹³¹ Putila JJ, Guo NL. Association of arsenic exposure with lung cancer incidence rates in the United States. *PloS One.* 2011 Oct 7;6(10):e25886.
- ¹³² Robson AO, Jelliffe AM. Medicinal arsenic poisoning and lung cancer. *BMJ.* 1963 Jul 27;2(5351):207.
- ¹³³ Smith AH, Hopenhayn-Rich C, Bates MN, et al. Cancer risks from arsenic in drinking water. *Environ Health Perspect.* 1992 Jul;97:259-67.
- ¹³⁴ Smith AH, Steinmaus CM. Health effects of arsenic and chromium in drinking water: recent human findings. *Annu Rev Public Health.* 2009 Apr 21;30:107-22.
- ¹³⁵ Barton EN, Gilbert DT, Raju K, Morgan OS. Arsenic: The forgotten poison? *West Indian Med J.* 1992 Mar;41(1):36-8.
- ¹³⁶ Goddard MJ, Tanhehco JL, Dau PC. Chronic arsenic poisoning masquerading as Landry-Guillain-Barré syndrome. *Electromyogr Clin Neurophysiol.* 1992 Sep;32(9):419-23.
- ¹³⁷ Guha Mazumder D, De B, Santra A, et al. Clinical manifestations of chronic arsenic toxicity, its natural history and therapy: experience of study in West Bengal, India. Paper presented at: Proceedings of the International Conference on Arsenic Pollution of Groundwater in Bangladesh: Causes, Effects and Remedies, Dhaka, Bangladesh, 1988 Feb 8-12.
- ¹³⁸ Hauptert TA, Wiersma JH, Goldring JM. Health effects of ingesting arsenic-contaminated groundwater. *Wis Med J.* 1996 Feb;95(2):100-4.
- ¹³⁹ Hindmarsh JT, McLetchle OR, Heffernan LP, et al. Electromyographic abnormalities in chronic environmental arsenicalism. *J Anal Toxicol.* 1977 Nov 1;1(6):270-6.

- ¹⁴⁰ Huang YZ, Qian XC, Wang GQ, et al. Endemic chronic arsenism in Xinjiang. *Chin Med J*. 1985 Mar;98(3):219.
- ¹⁴¹ Sass U, Grosshans E, Simonart JM. Chronic arsenicism: Criminal poisoning or drug-intoxication? *Dermatology*. 1993;186(4):303-5.
- ¹⁴² Silver AS, Wainman PL. Chronic arsenic poisoning following use of an asthma remedy. *JAMA*. 1952 Oct 11;150(6):584-5.
- ¹⁴³ Szuler IM, Williams CN, Hindmarsh JT, Park-Dincsoy H. Massive variceal hemorrhage secondary to presinusoidal portal hypertension due to arsenic poisoning. *Can Med Assoc J*. 1979 Jan 20;120(2):168.
- ¹⁴⁴ Tay CH, Seah CS. Arsenic poisoning from anti-asthmatic herbal preparations. *Med J Aust*. 1975 Sep;2(11):424-8.
- ¹⁴⁵ Armstrong CW, Stroube RB, Rubio T, Siudyla EA, Miller GB. Outbreak of fatal arsenic poisoning caused by contaminated drinking water. *Arch Environ Health*. 1984 Jul 1;39(4):276-9.
- ¹⁴⁶ Fincher RM, Koerker RM. Long-term survival in acute arsenic encephalopathy. Follow-up using newer measures of electrophysiologic parameters. *Am J Med*. 1987 Mar 1;82(3):549-52.
- ¹⁴⁷ Glazener FS, Ellis JG, Johnson PK. Electrocardiographic findings with arsenic poisoning. *Calif Med*. 1968 Aug;109(2):158.
- ¹⁴⁸ Lugo G, Cassady G, Palmisano P. Acute maternal arsenic intoxication with neonatal death. *Am J Dis Child*. 1969 Mar 1;117(3):328-30.
- ¹⁴⁹ Mizuta N, Mizuta M, Ito F, et al. An outbreak of acute arsenic poisoning caused by arsenic contaminated soy-sauce: A clinical report of 220 cases. *Bull Yamaguchi Med Sch*. 1956 Dec 31;4(2):131-49.
- ¹⁵⁰ Moore MM, Harrington-Brock K, Doerr CL. Genotoxicity of arsenic and its methylated metabolites. *Environ. Geochem. Health*. 1994;16:191-8.
- ¹⁵¹ Prasad GR, Rossi NF. Arsenic intoxication associated with tubulointerstitial nephritis. *American Journal of Kidney Diseases*. 1995 Aug 1;26(2):373-6.
- ¹⁵² Cullen NM, Wolf LR, St Clair D. Pediatric arsenic ingestion. *Am J Emerg Med*. 1995 Jul 1;13(4):432-5.
- ¹⁵³ Franzblau A, Lilis R. Acute arsenic intoxication from environmental arsenic exposure. *Arch Environ Health*. 1989 Dec 1;44(6):385-90.
- ¹⁵⁴ Levin-Scherz JK, Patrick JD, Weber FH, Garabedian C. Acute arsenic ingestion. *Ann Emerg Med*. 1987 Jun 1;16(6):702-4.
- ¹⁵⁵ Quatrehomme G, Ricq O, Lapalus PH, Jacomet Y, Ollier A. Acute arsenic intoxication: forensic and toxicologic aspects (an observation). *J Forensic Sci*. 1992 Jul 1;37(4):1163-71.

- ¹⁵⁶ Goebel HH, Schmidt PF, Bohl J, Tettenborn B, Krämer G, Gutmann L. Polyneuropathy due to acute arsenic intoxication: biopsy studies. *J Neuropathol Exp Neurol*. 1990 Mar 1;49(2):137-49.
- ¹⁵⁷ Kamijo Y, Soma K, Asari Y, Ohwada T. Survival after massive arsenic poisoning self-treated by high fluid intake. *J Toxicol Clin Toxicol*. 1998 Jan 1;36(1-2):27-9.
- ¹⁵⁸ Civantos DP, Rodriguez AL, Aguado-Borruey JM, Narvaez JA. Fulminant malignant arrhythmia and multiorgan failure in acute arsenic poisoning. *Chest*. 1995 Dec 1;108(6):1774-5.
- ¹⁵⁹ International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Personal habits and indoor combustions. 2012; vol. 100E. Available from: <https://monographs.iarc.fr/iarc-monographs-on-the-evaluation-of-carcinogenic-risks-to-humans-17/>
- ¹⁶⁰ Hakura A, Sonoda J, Tsutsui Y, et al. Toxicity profile of benzo [a] pyrene in the MaleLacZTransgenic Mouse (MutaMouse) following oral administration for 5 consecutive days. *Regul Toxicol Pharmacol*. 1998 Jun 1;27(3):273-9.
- ¹⁶¹ Stoner GD, Greisiger EA, Schut HA, et al. A comparison of the lung adenoma response in strain A/J mice after intraperitoneal and oral administration of carcinogens. *Toxicol Appl Pharmacol*. 1984 Feb 1;72(2):313-23.
- ¹⁶² Wattenberg LW, Leong JL. Inhibition of the carcinogenic action of benzo (a) pyrene by flavones. *Cancer Res*. 1970 Jul 1;30(7):1922-5.
- ¹⁶³ U.S. Environmental Protection Agency. Integrated Risk Information System (IRIS) assessments: Benzo[a]pyrene (BaP); CASRN 50-32-8. Available from: https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=136
- ¹⁶⁴ International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Cadmium and cadmium compounds. 2012; vol. 100C. Available from: <https://monographs.iarc.fr/iarc-monographs-on-the-evaluation-of-carcinogenic-risks-to-humans-19/>
- ¹⁶⁵ International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry. 1993; vol. 58. Available from: <https://monographs.iarc.fr/iarc-monographs-on-the-evaluation-of-carcinogenic-risks-to-humans-63/>
- ¹⁶⁶ U.S. Department of Health and Human Services, Agency for Toxic Substance and Disease Registry (ATSDR). Toxic substances portal: cadmium (CAS ID# 7440-43-9). Available from: <https://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=15>
- ¹⁶⁷ Navas-Acien A, Selvin E, Sharrett AR, Calderon-Aranda E, Silbergeld E, Guallar E. Lead, cadmium, smoking, and increased risk of peripheral arterial disease. *Circulation*. 2004 Jun 29;109(25):3196-201.

¹⁶⁸ International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Formaldehyde. 2012; vol. 100F. Available from: <https://monographs.iarc.fr/iarc-monographs-on-the-evaluation-of-carcinogenic-risks-to-humans-16/>

¹⁶⁹ International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Smokeless tobacco and some tobacco-specific N-nitrosamines. 2007; vol. 89. Available from: <https://monographs.iarc.fr/iarc-monographs-on-the-evaluation-of-carcinogenic-risks-to-humans-32/>

¹⁷⁰ Padma PR, Lalitha VS, Amonkar AJ, Bhide SV. Carcinogenicity studies on the two tobacco-specific N-nitrosamines, N'-nitrosoanabasin and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. Carcinogenesis. 1989 Nov 1;10(11):1997-2002.

¹⁷¹ Rivenson A, Hoffmann D, Prokopczyk B, Amin S, Hecht SS. Induction of lung and exocrine pancreas tumors in F344 rats by tobacco-specific and Areca-derived N-nitrosamines. Cancer Res. 1988 Dec 1;48(23):6912-7.

¹⁷² Hecht SS, Young R, Maeura Y. Comparative carcinogenicity in F344 rats and Syrian golden hamsters of N'-nitrosoanabasin and N'-nitrosoanabasin-1-N-oxide. Cancer Lett. 1983 Oct 1;20(3):333-40.

¹⁷³ Hoffmann D, Raineri R, Hecht SS, Maronpot R, Wynder EL. A study of tobacco carcinogenesis. XIV. Effects of N'-nitrosoanabasin and N'-nitrosoanabasin in rats. J Natl Cancer Inst. 1975 Oct 1;55(4):977-81.

¹⁷⁴ Carmella SG, Han S, Fristad A, Yang Y, Hecht SS. Analysis of total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) in human urine. Cancer Epidemiol Biomarkers Prev. 2003 Nov 1;12(11):1257-61.

¹⁷⁵ Stepanov I, Hecht SS. Tobacco-specific nitrosamines and their pyridine-N-glucuronides in the urine of smokers and smokeless tobacco users. Cancer Epidemiol Biomarkers Prev. 2005 Apr 1;14(4):885-91.

¹⁷⁶ Rostron BL, Chang CM, van Bommel DM, Xia Y, Blount BC. Nicotine and toxicant exposure among US smokeless tobacco users: results from 1999 to 2012 national health and nutrition examination survey data. Cancer Epidemiol Biomarkers Prev. 2015 Nov 18. 24(12): 1829-37.

¹⁷⁷ Nordskog BK, Brown BG, Marano KM, Campbell LR, Jones BA, Borgerding MF. Study of cardiovascular disease biomarkers among tobacco consumers, part 2: biomarkers of biological effect. Inhal Toxicol. 2015 Feb 23;27(3):157-66.

¹⁷⁸ Prasad GL, Jones BA, Chen P, Gregg EO. A cross-sectional study of biomarkers of exposure and effect in smokers and moist snuff consumers. Clin Chem Lab Med. 2016 Apr 1;54(4):633-42.

¹⁷⁹ Ford ES, Greenlund KJ, Hong Y. Ideal cardiovascular health and mortality from all causes and diseases of the circulatory system among adults in the United States. Circulation. 125(8): 987-995.

¹⁸⁰ Schenker N, Gentleman JF. On judging the significance of differences by examining the overlap between confidence intervals. Am Stat. 2001 Aug 1;55(3):182-6.

- ¹⁸¹ Jewell NP. Statistics for epidemiology. Boca Raton, FL: Chapman & Hall; 2004.
- ¹⁸² Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol*. 1996 Dec 1;49(12):1373-9.
- ¹⁸³ Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996 Feb 29;15(4):361-87.
- ¹⁸⁴ Henley SJ, Connell CJ, Richter P, et al. Tobacco-related disease mortality among men who switched from cigarettes to spit tobacco. *Tob Control*. 2007 Feb 1;16(1):22-8.
- ¹⁸⁵ Lee PN, Hamling J. Systematic review of the relation between smokeless tobacco and cancer in Europe and North America. *BMC Med*. 2009 Dec;7(1):36.
- ¹⁸⁶ Boffetta P, Hecht S, Gray N, Gupta P, Straif K. Smokeless tobacco and cancer. *Lancet Oncol*. 2008 Jul 1;9(7):667-75.
- ¹⁸⁷ Henley SJ, Thun MJ, Connell C, Calle EE. Two large prospective studies of mortality among men who use snuff or chewing tobacco (United States). *Cancer Causes Control*. 2005 May 1;16(4):347-58.
- ¹⁸⁸ Accortt NA, Waterbor JW, Beall C, Howard G. Chronic disease mortality in a cohort of smokeless tobacco users. *Am J Epidemiol*. 2002 Oct 15;156(8):730-7.
- ¹⁸⁹ Andreotti G, Freedman ND, Silverman DT, Lerro CC, Koutros S, Hartge P, Alavanja MC, Sandler DP, Freeman LB. Tobacco use and cancer risk in the Agricultural Health Study. *Cancer Epidemiol Biomarkers Prev*. 2017 May 1;26(5):769-78.
- ¹⁹⁰ U.S. Department of Health and Human Services. The health consequences of smoking—50 years of progress: A report of the Surgeon General. Atlanta, GA: Centers for Disease Control and Prevention; 2014.
- ¹⁹¹ Thun MJ, Carter BD, Feskanich D, et al. 50-year trends in smoking-related mortality in the United States. *N Engl J Med*. 2013 Jan 24;368(4):351-64.
- ¹⁹² Accortt NA, Waterbor JW, Beall C, Howard G. Cancer incidence among a cohort of smokeless tobacco users (United States). *Cancer Causes Control*. 2005 Nov 1;16(9):1107-15.
- ¹⁹³ Godtfredsen NS, Prescott E, Osler M. Effect of smoking reduction on lung cancer risk. *JAMA*. 2005 Sep 28;294(12):1505-10.
- ¹⁹⁴ Song YM, Sung J, Cho HJ. Reduction and cessation of cigarette smoking and risk of cancer: a cohort study of Korean men. *J Clinical Oncol*. 2008 Nov 1;26(31):5101-6.

- ¹⁹⁵ Godtfredsen NS, Holst C, Prescott E, Vestbo J, Osler M. Smoking reduction, smoking cessation, and mortality: a 16-year follow-up of 19,732 men and women from The Copenhagen Centre for Prospective Population Studies. *Am J Epidemiol*. 2002 Dec 1;156(11):994-1001.
- ¹⁹⁶ Godtfredsen NS, Osler M, Vestbo J, Andersen I, Prescott E. Smoking reduction, smoking cessation, and incidence of fatal and non-fatal myocardial infarction in Denmark 1976–1998: a pooled cohort study. *J Epidemiol Community Health*. 2003 Jun 1;57(6):412-6.
- ¹⁹⁷ Tverdal A, Bjartveit K. Health consequences of reduced daily cigarette consumption. *Tob Control*. 2006 Dec 1;15(6):472-80.
- ¹⁹⁸ Hart C, Gruer L, Bauld L. Does smoking reduction in midlife reduce mortality risk? Results of 2 long-term prospective cohort studies of men and women in Scotland. *Am J Epidemiol*. 2013 Jul 3;178(5):770-9.
- ¹⁹⁹ Timberlake DS, Nikitin D, Johnson NJ, Altekruse SF. A longitudinal study of smokeless tobacco use and mortality in the United States. *Int J Cancer*. 2017 Jul 15;141(2):264-70.
- ²⁰⁰ Boffetta P, Straif K. Use of smokeless tobacco and risk of myocardial infarction and stroke: systematic review with meta-analysis. *BMJ*. 2009 Aug 19;339:b3060.
- ²⁰¹ England LJ, Levine RJ, Mills JL, Klebanoff MA, Kai FY, Cnattingius S. Adverse pregnancy outcomes in snuff users. *Am J Obstet Gynecol*. 2003 Oct 1;189(4):939-43.
- ²⁰² Wikström AK, Cnattingius S, Galanti MR, Kieler H, Stephansson O. Effect of Swedish snuff (snus) on preterm birth. *BJOG*. 2010 Jul 1;117(8):1005-10.
- ²⁰³ Baba S, Wikström AK, Stephansson O, Cnattingius S. Influence of smoking and snuff cessation on risk of preterm birth. *Eu J Epidemiol*. 2012 Apr 1;27(4):297-304.
- ²⁰⁴ Lee PN, Hamling J. Systematic review of the relation between smokeless tobacco and cancer in Europe and North America. *BMC Med*. 2009 Dec;7(1):36.
- ²⁰⁵ Lee PN, Hamling J. Systematic review of the relation between smokeless tobacco and cancer in Europe and North America. *BMC Med*. 2009 Dec;7(1):36.
- ²⁰⁶ Boffetta P, Straif K. Use of smokeless tobacco and risk of myocardial infarction and stroke: systematic review with meta-analysis. *BMJ*. 2009 Aug 19;339:b3060.
- ²⁰⁷ Rostron BL, Chang JT, Anic GM, Tanwar M, Chang CM, Corey CG. Smokeless tobacco use and circulatory disease risk: a systematic review and meta-analysis. *Open Heart*. 2018 Oct 1;5(2):e000846.
- ²⁰⁸ Agaku IT, Singh T, Rolle IV, Ayo-Yusuf OA. Exposure and response to current text-only smokeless tobacco health warnings among smokeless tobacco users aged ≥ 18 years, United States, 2012–2013. *Prev Med*. 2016 Jun 1;87:200-6.

²⁰⁹ Adkison SE, Bansal-Travers M, Smith DM, O'Connor RJ, Hyland AJ. Impact of smokeless tobacco packaging on perceptions and beliefs among youth, young adults, and adults in the US: findings from an internet-based cross-sectional survey. *Harm Reduct J*. 2014 Dec;11(1):2.

²¹⁰ Kaufman AR, Mays D, Koblitz AR, Portnoy DB. Judgments, awareness, and the use of snus among adults in the United States. *Nicotine Tob Res*. 2014 Aug 6;16(10):1404-8.

²¹¹ Borland R, Cooper J, McNeill A, O'Connor R, Cummings KM. Trends in beliefs about the harmfulness and use of stop-smoking medications and smokeless tobacco products among cigarettes smokers: Findings from the ITC four-country survey. *Harm Reduct J*. 2011 Dec;8(1):21.

²¹² Kiviniemi MT, Kozlowski LT. Deficiencies in public understanding about tobacco harm reduction: results from a United States national survey. *Harm Reduct J*. 2015 Dec;12(1):21.

²¹³ Richardson A, Pearson J, Xiao H, Stalgaitis C, Vallone D. Prevalence, harm perceptions, and reasons for using noncombustible tobacco products among current and former smokers. *Am J Public Health*. 2014 Aug;104(8):1437-44.

²¹⁴ Wackowski OA, Delnevo CD. Young adults' risk perceptions of various tobacco products relative to cigarettes: results from the National Young Adult Health Survey. *Health Educ Behav*. 2016 Jun;43(3):328-36.

²¹⁵ Persoskie A, O'Brien EK, Nguyen AB, Tworek C. Measuring youth beliefs about the harms of e-cigarettes and smokeless tobacco compared to cigarettes. *Addict Behav*. 2017 Jul 31;70:7-13.

²¹⁶ Capella ML, Taylor CR, Kees J. Tobacco harm reduction advertising in the presence of a government-mandated warning. *J Consum Aff*. 2012 Jun;46(2):235-59.

²¹⁷ Substance Abuse and Mental Health Services Administration (SAMHSA). Behavioral health trends in the United States: results from the 2014 National Survey on Drug Use and Health (HHS Publication No. SMA 15-4927). Rockville, MD: U.S. Department of Health and Human Services, SAMHSA Center for Behavioral Health Statistics and Quality; 2015. Available from <https://www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.pdf>

²¹⁸ Cheng YC, Rostron BL, Day HR, et al. Patterns of use of smokeless tobacco in US adults, 2013–2014. *Am J Public Health*. 2017 Sep;107(9):1508-14.

²¹⁹ Wang TW, Gentzke A, Sharapova S, Cullen KA, Ambrose BK, Jamal A. Tobacco product use among middle and high school students—United States, 2011–2017. *MMWR Morb Mortal Wkly Rep*. 2018 Jun 8;67(22):629.

²²⁰ Miech RA, J. L., O'Malley PM, Bachman JG, Schulenberg JE. Monitoring the Future national survey results on drug use, 1975–2015: Volume I, secondary school students. Ann Arbor, MI: University of Michigan Institute for Social Research; 2016.

- ²²¹ Haddock CK, Vander Weg M, DeBon M, et al. Evidence that smokeless tobacco use is a gateway for smoking initiation in young adult males. *Prev Med*. 2001 Mar 1;32(3):262-7.
- ²²² Tomar SL. Is use of smokeless tobacco a risk factor for cigarette smoking? The US experience. *Nicotine Tob Res*. 2003 Jul 1;5(4):561-9.
- ²²³ Severson HH, Forrester KK, Biglan A. Use of smokeless tobacco is a risk factor for cigarette smoking. *Nicotine Tob Res*. 2007 Dec 1;9(12):1331-7.
- ²²⁴ Soneji S, Sargent JD, Tanski SE, Primack BA. Associations between initial water pipe tobacco smoking and snus use and subsequent cigarette smoking: results from a longitudinal study of US adolescents and young adults. *JAMA Pediatr*. 2015 Feb 1;169(2):129-36.
- ²²⁵ Tam J, Day HR, Rostron BL, Apelberg BJ. A systematic review of transitions between cigarette and smokeless tobacco product use in the United States. *BMC Public Health*. 2015 Dec;15(1):258.
- ²²⁶ Watkins SL, Glantz SA, Chaffee BW. Association of noncigarette tobacco product use with future cigarette smoking among youth in the population assessment of tobacco and health (PATH) study, 2013-2015. *JAMA Pediatr*. 2018 Feb 1;172(2):181-7.
- ²²⁷ Kozlowski LT, O'Connor RJ, Quinio Edwards B, Flaherty BP. Most smokeless tobacco use is not a causal gateway to cigarettes: using order of product use to evaluate causation in a national US sample. *Addiction*. 2003 Aug;98(8):1077-85.
- ²²⁸ O'Connor RJ, Kozlowski LT, Flaherty BP, Edwards BQ. Most smokeless tobacco use does not cause cigarette smoking: results from the 2000 National Household Survey on Drug Abuse. *Addict Behav*. 2005 Feb 28;30(2):325-36.
- ²²⁹ Timberlake DS, Huh J, Lakon CM. Use of propensity score matching in evaluating smokeless tobacco as a gateway to smoking. *Nicotine Tob Res*. 2009 Mar 23;11(4):455-62.
- ²³⁰ Chang JT, Levy DT, Meza R. Trends and factors related to smokeless tobacco use in the United States. *Nicotine Tob Res*. 2016 Mar 19;18(8):1740-8.
- ²³¹ Anic GM, Holder-Hayes E, Ambrose BK, et al. E-cigarette and smokeless tobacco use and switching among smokers: findings from the National Adult Tobacco Survey. *Am J Prev Med*. 2018 Apr 1;54(4):539-51.
- ²³² Wetter DW, McClure JB, de Moor C, et al. Concomitant use of cigarettes and smokeless tobacco: prevalence, correlates, and predictors of tobacco cessation. *Prev Med*. 2002 Jun 1;34(6):638-48.
- ²³³ Zhu SH, Wang JB, Hartman A, et al. Quitting cigarettes completely or switching to smokeless: do US data replicate the swedish results?. *Tob Control*. 2009 Jan 23;tc-2008.

- ²³⁴ Benowitz NL. Nicotine addiction. *N Engl J Med*. 2010 Jun 17;362(24):2295-303.
- ²³⁵ Henningfield JE, Fant RV, Tomar SL. Smokeless tobacco: an addicting drug. *Adv Dent Res*. 1997 Sep;11(3):330-5.
- ²³⁶ Stolerman IP, Jarvis MJ. The scientific case that nicotine is addictive. *Psychopharmacol*. 1995 Jan 1;117(1):2-10.
- ²³⁷ US Department of Health and Human Services. The health consequences of smoking: nicotine addiction. A Report of the Surgeon General. Rockville, MD: Public Health Service, Centers for Disease Control, Center for Health Promotion and Education, Office on Smoking and Health; 1988. Available from: <https://profiles.nlm.nih.gov/ps/access/nnbbzd.pdf>
- ²³⁸ Abreu ME, Bigelow GE, Fleisher L, Walsh SL. Effect of intravenous injection speed on responses to cocaine and hydromorphone in humans. *Psychopharmacol*. 2001 Feb 1;154(1):76-84.
- ²³⁹ De Wit H, Bodker B, Ambre J. Rate of increase of plasma drug level influences subjective response in humans. *Psychopharmacol*. 1992 Jun 1;107(2-3):352-8.
- ²⁴⁰ De Wit H, Dudish S, Ambre J. Subjective and behavioral effects of diazepam depend on its rate of onset. *Psychopharmacol*. 1993 Sep 1;112(2-3):324-30.
- ²⁴¹ Carter LP, Griffiths RR. Principles of laboratory assessment of drug abuse liability and implications for clinical development. *Drug Alcohol Depend*. 2009 Dec 1;105:S14-25.
- ²⁴² Benowitz NL, Porchet H, Sheiner L, Jacob P. Nicotine absorption and cardiovascular effects with smokeless tobacco use: comparison with cigarettes and nicotine gum. *Clin Pharmacol Ther*. 1988 Jul 1;44(1):23-8.
- ²⁴³ Kotlyar M, Mendoza-Baumgart MI, Li ZZ, et al. Nicotine pharmacokinetics and subjective effects of three potential reduced exposure products, moist snuff and nicotine lozenge. *Tob Control*. 2007 Apr 1;16(2):138-42.
- ²⁴⁴ Blank MD, Eissenberg T. Evaluating oral noncombustible potential-reduced exposure products for smokers. *Nicotine Tob Res*. 2010 Feb 16;12(4):336-43.
- ²⁴⁵ Phillips E, Wang TW, Husten CG, et al. Tobacco product use among adults—United States, 2015. *MMWR Morb Mortal Wkly Rep*. 2017 Nov 10;66(44):1209.
- ²⁴⁶ El-Toukhy S, Baig SA, Jeong M, Byron MJ, Ribisl KM, Brewer NT. Impact of modified risk tobacco product claims on beliefs of US adults and adolescents. *Tob Control*. 2018 Nov 1;27(Suppl 1):s62-9.