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2.4 Glossary

1-HOP	1-hydroxypyrene
1-OH-Naph	1-hydroxynaphthalene
1-OH-Phen	1-hydroxyphenanthrene
2-OH-Fluor	2-hydroxyfluorene
2-OH-Naph	2-hydroxynaphthalene
2-OH-Phen	2-hydroxyphenanthrene
3-HPMA	3-(hydroxypropyl)mercapturic acid
3-OH-Fluor	3-hydroxyfluorene
3-OH-Phen	3-hydroxyphenanthrene
4-ABP	4-aminobiphenyl
4-OH-Phen	4-hydroxyphenanthrene
9-OH-Fluor	9-hydroxyfluorene
AA	Aortic aneurysm
ACS	American Cancer Society
AE	Adverse event
AMI	Acute myocardial infarction
ARIC	Atherosclerosis Risk in Communities
As	Arsenic
ASC	American Snuff Company
ATC	Adult Tobacco Consumer
ATS	American Thoracic Society
AUC	Area under the concentration versus time curve
B[a]P	Benzo[a]pyrene
BDL	Below (unreported) Detection Limit
BQL	Below (unreported) Quantitation Limit
CAN SPAM ACT	Controlling the Assault of Non-Solicited Pornography and Marketing Act
CAS	Complete Artificial Saliva
ccf	Hundred Cubic Feet
Cd	Cadmium
CD	Cross Direction
CDC	U.S. Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CEMA	2-cyanoethylmercapturic acid
CFR	Code of Federal Regulations
CFU	Colony Forming Units
CHD	Coronary heart disease
CHO	Chinese Hamster Ovary
CI	Confidence interval
CITES	Convention on International Trade in Endangered Species
CL	Confidence Level / Confidence Limit
C_{max}	Peak plasma nicotine exposure
CO	Carbon monoxide
Co	Cobalt
CO_2	Carbon dioxide
CO_2e	Carbon dioxide equivalents
COPD	Chronic Obstructive Pulmonary Disease

CORESTA	Cooperation Centre for Scientific Research Relative to Tobacco
CPD	Cigarettes per day
CPS-I	American Cancer Society's Cancer Prevention Study I
CPS-II	American Cancer Society's Cancer Prevention Study II
CRP	CORESTA Reference Product
CSC	Cigarette Smoke Condensate
CSR	Clinical study report
CSTHEA	Comprehensive Smokeless Tobacco Health Education Act of 1986
CTP	FDA Center for Tobacco Products
CVD	Cardiovascular disease
DBahA	Dibenz[a,h]anthracene
DHBMA	Dihydroxybutylmercapturic acid
DMBA	Dimethylbenz[a]anthracene
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DPM	Dynamic Population Model
EA	Environmental Assessment
ECG	Electrocardiogram
ECO	Expired carbon monoxide
ELL-PSS	Eurofins Lancaster Laboratories-Professional Scientific Services
ENVIRON	ENVIRON International Corporation
EPA	Environmental Protection Agency
ERR	Excessive relative risk
ESA	Endangered Species Act
ETS	Environmental tobacco smoke
EU	European Union
F	Female
F&L	Fiedler and Lundgren
FCC	Food Chemicals Codex
FDA	U.S. Food and Drug Administration
FDCA	Federal Food, Drug and Cosmetic Act
FEMA	Flavor and Extract Manufacturers Association
FGS	Final Ground Snus
FLT	Fluoranthene
FTC	Federal Trade Commission
FTND	Fagerström Test for Nicotine Dependence
FTND-ST	Fagerström Test for Nicotine Dependence—Smokeless Tobacco
g	Gram
GC-MS	Gas chromatography-mass spectrometry
GCP	Good Clinical Practice
GHG	Greenhouse Gas
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GRAS	Generally Recognized as Safe
HACCP	Hazard Analysis and Critical Control Point
HAH	Halogenated Aromatic Hydrocarbon
HAN	Wistar Hannover rats
HCI	Health Canada intense

HEMA	2-hydroxyethyl mercapturic acid
Hg	Mercury
HMPMA	3-hydroxy-1-methylpropylmercapturic acid
HMT	Harwell Mouth Tumor
HPB	4-hydroxy-1-(3-pyridyl)-1-butanone
HpCDD	1,2,3,4,6,7,8-hepta-chlorodibenzo-p-dioxin
HpCDF	1,2,3,4,6,7,8-hepta-chlorodibenzofuran
HPHC	Harmful and Potentially Harmful Constituents
HR	Hazard ratio
HSV	Herpes simplex virus
HSV-1	Herpes simplex virus-1
HSV-2	Herpes simplex virus-2
HxCDD	1,2,3,6,7,8-hexa-chlorodibenzo-p-dioxin
HxCDF	1,2,3,4,7,8-hexa-chlorodibenzofuran
IARC	International Agency for Research on Cancer
IC_{50}	Inhibitory Concentration, 50%
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
IFP	Individual Finished Pouch
IHD	Ischemic heart disease
IMS	Ingredient Mixing & Storage
INS-GAS	Gastrin transgenic
IOM	Institute of Medicine
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent-to-treat
IVRS	Interactive voice response system
KS	King size
kWh	Kilowatt Hour
KY	Kentucky
LCQ	Leicester Cough Questionnaire
LOAEL	Lowest Observed Adverse Effect Level
LOC	Level of Concern
LOQ	Limit of Quantification
LSRO	Life Sciences Research Organization
LULUCF	Land use, land-use change, and forestry
M	Male
MCDA	Multi-criteria decision analysis
MD	Machine Direction
mg	Milligram
MHBMA	Mmonohydroxybutenylmercapturic acid
MI	Myocardial infarction
mL	Maximum Level
MLE	Mouth-level exposure
MLY	Mouse lymphoma cell
mm	Millimeter
MMRM	Mixed model with repeated measures

MN	Micronucleus
MNWS	Minnesota Nicotine Withdrawal Scale
MPSS	Mood and Physical Symptoms Scales
MRH	Maximum relative harm
MRTP	Modified Risk Tobacco Product
MRTPA	Modified Risk Tobacco Product Application
MSC	Moist snuff consumers
MSW	Municipal Solid Waste
MTD	Maximum Tolerated Dose
MUL	Maximum use level
N	Number of subjects
NAB	N-nitrosoanabasine
NAT	N-nitrosoanatabine
NCI	National Cancer Institute
NCSU	North Carolina State University
NDELA	N-nitrosodiethanolamine
ng	Nanogram
NHANES	National Health and Nutrition Examination Survey
NHEFS	NHANES I Epidemiologic Follow-up Study
NIH	National Institutes of Health
NIR	Near infra-red
NK	Natural killer
NMOR	N-nitrosomorpholine
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNK	4-[methylnitrosamino]-1-[3-pyridyl]-1-butanone
NNN	N-nitrosonornicotine
NP	Naphthalene
NRT	Nicotine replacement therapy
NRU	Neutral red uptake
NT	Nicotine tartrate
NTBM	National Tobacco Behavior Monitor
NVS	Newest Vital Sign
OCDD	1,2,3,4,5,6,7,8-octa-chlorodibenzo-p-dioxin
OECD	Organization for Economic Cooperation and Development
OR	Odds ratio
OTC	Over-the-Counter
P30D	Past 30 day
P7D	Past 7 day
PAD	Peripheral artery disease
PAH	Polycyclic aromatic hydrocarbon
PATH	Population Assessment of Tobacco and Health Study
Pb	Lead
PDM	Product Data Management
PeCDF	2,3,4,7,8-penta-chlorodibenzofuran
PHE	Phenanthrene
PHI	Public Health Impact
PI	Principal Investigator
PID	Personal Identification Number

PMTA	Premarket Tobacco Application
POTWs	Publicly Owned Treatment Works
ppm	Parts per million
PREP	Potential reduced exposure tobacco product
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient Reported Outcomes
R&D	Research and Development
RAIS	RAI Services Company
RCP	United Kingdom's Royal College of Physicians
RJRT	R.J. Reynolds Tobacco Company
RR	Relative risk
SAE	Serious adverse event
SALLS	Swedish Annual Level-of-Living Survey
SALT	Screening Across the Lifespan Twin Study
SAP	Statistical Analysis Plan
SAU	Snus-after-use
SCD	Sudden cardiac death
SCE	Sister Chromatid Exchange
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SCQoL	Smoking Cessation Quality of Life Questionnaire
SD	Standard deviation
Se	Selenium
SE	Substantial Equivalence
SGRQ	St. George's Respiratory Questionnaire
SKU	Stock-Keeping Unit
SMNA	Swedish Match North American, Inc.
SOP	Standard operating procedure
SOT	Society of Toxicology
SPCC	Spill Prevention, Control, and Countermeasure
ST	Smokeless tobacco
TAPS	Teenage Attitudes and Practices Survey
TCA	Family Smoking Prevention and Tobacco Control Act
TD	Transverse Direction
TDP	Tobacco derived product
Tg	Teragrams
T_{max}	Time to attainment of peak concentration
TPIP	Tobacco Product Integrity Plan
TPL	Technical Project Lead
TPM	Total Particular Matter
TPSAC	Tobacco Products Scientific Advisory Committee
TRI	Toxic Release Inventory
TS	Tobacco smoke
TSNA	Tobacco-specific nitrosamine
TTB	Department of the Treasury Alcohol and Tobacco Tax and Trade Bureau
TTM	Total Tobacco Migration Tracker
U.S.C.	United States Code
U.S.P.-NF	United States Pharmacopeia-National Formulary
UB	Usual brand

UPS	United Parcel Service
US	United States
USDA	U.S. Department of Agriculture
USDHEW	United State Department of Health, Education and Welfare
USDHHS	US Department of Health and Human Services
USP	U.S. Pharmacopeial Convention
VOC	Volatile organic compounds
WHO	World Health Organization
WT	Wild-type
WTPM	Wet Total Particulate Matter
wwb	Wet weight basis
YIU	Yield-in-use

2.5 Summary of Application

2.5.1 Introduction

R.J. Reynolds Tobacco Company ("RJRT") requests that the U.S. Food and Drug Administration ("FDA") issue orders authorizing RJRT to advertise each of its Camel Snus styles (Frost, Frost Large, Winterchill, Robust, Mellow, and Mint, collectively, "Camel Snus") as a modified risk tobacco product ("MRTP") pursuant to Section 911 of The Family Smoking Prevention and Tobacco Control Act ("the TCA"). RJRT proposes three different modified risk advertising executions for each of the six Camel Snus styles and is requesting a total of eighteen (18) MRTP orders.

In accordance with Section 911(g)(1) of the TCA, FDA shall issue an MRTP order only if the product, as actually used by consumers, will "significantly reduce harm and the risk of tobacco-related disease to individual tobacco users" and also "benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products" (TCA Section 911(g)(1)). In this Application, RJRT submits a wide body of scientific studies and data applicable to Camel Snus (product design and composition, comparative harmful and potentially harmful constituents (HPHC) chemistry, comparative preclinical toxicology, epidemiology, human clinical studies, comprehension and perceptions studies of the proposed modified risk advertising, likelihood of use studies and population-level modeling) demonstrating that individual smokers who switch completely from smoking cigarettes to using Camel Snus will reduce their risk for lung cancer, oral cancer, respiratory disease and heart disease compared to continued smoking and, if sufficient numbers of smokers switch to Camel Snus, there will be a net public health benefit.

2.5.2 Camel Snus satisfies the statutory requirements for commercial marketing as an MRTP

RJRT believes that the scientific information and data presented in this Application fully satisfy the statutory standard under TCA Section 911(g). The results of the studies and data presented in this Application make a compelling scientific case that smokers who switch completely from smoking cigarettes to using Camel Snus will reduce their risk for lung cancer, oral cancer, respiratory disease and heart disease compared to continued smoking.

First, data from U.S. and Swedish epidemiological studies are highly relevant to comparing estimated health risks for individuals who switch completely from smoking cigarettes to using Camel Snus. U.S. and Swedish epidemiological studies of cigarette smokers report significantly elevated health risks for a wide range of cancers, non-neoplastic respiratory disease (COPD), cardiovascular diseases, and other adverse health effects. In contrast, U.S. and Swedish epidemiological studies of smokeless tobacco ("ST") users report substantially lower health risks. Although the epidemiological studies of smokeless tobacco users are categorical, and not specific to any particular smokeless tobacco product, the lower health risk estimates reported are applicable to users of Camel Snus for two principal reasons: 1) Camel Snus toxicant content

is comparable to, or less than, the historical U.S. and Swedish smokeless tobacco products on which the epidemiological studies are based, and 2) Camel Snus usage patterns suggest lower levels of toxicant exposure compared to the historical patterns reflected in U.S. and Swedish epidemiology. Collectively, the results of U.S. and Swedish epidemiological studies provide clear and consistent evidence that the health risks from use of smokeless tobacco products, including Camel Snus, are less than the health risks from smoking. While no tobacco product is safe and devoid of all risk when used, tobacco products that do not burn tobacco during use present less risk for lung cancer, oral cancer, respiratory disease and heart disease than do tobacco products that burn tobacco during use (*e.g.*, traditional cigarettes).

Second, the body of RJRT-sponsored and external published research specific to Camel Snus submitted with this Application shows that, compared to cigarettes, all brand styles of Camel Snus (a) present a reduced toxicant profile in comparative product analyses, (b) produce lower toxic effects in preclinical *in vitro* and *in vivo* studies, and (c) are associated with reduced exposure to combustion-related HPHCs (*i.e.*, toxicants formed from burning tobacco during smoking) in human clinical studies. The dose-response principle, which is fundamental to the discipline of toxicology, suggests that the lower disease risks observed in smokeless tobacco users is due to their comparatively lower exposure to cigarette smoke toxicants. The findings from comparative chemical analyses of Camel Snus with cigarettes and other smokeless tobacco products are consistent with findings from *in vitro* and *in vivo* toxicology evaluations, human biomarkers studies and epidemiological studies presented in this Application. These complementary lines of evidence provide a coherent scientific basis for the designation of Camel Snus as an MRTP that will reduce lung cancer, oral cancer, respiratory disease, and heart disease risk for smokers who switch completely from smoking cigarettes to exclusive use of Camel Snus.

Third, results of extensive empirically-informed statistical modeling for population-level health impact shows that MRTP orders for Camel Snus with the proposed modified risk advertising is likely to yield net benefits to population health, substantially increasing survival in the population based on projected likelihoods of use among tobacco users and non-users, and an MRTP order is very unlikely to result in net harm on population health. In fact, only a small portion of current smokers would need to switch completely to Camel Snus to cause a significant decrease in population-level mortality.

2.5.3 Organization of submission materials

RJRT has organized this Application into sections that are intended to follow the criteria for FDA assessment of an MRTP application set forth in Section 911(d) of the TCA and FDA's Draft Guidance for Modified Risk Tobacco Product Applications.

Section 1 – This section contains cover letters for each of the six (6) Camel Snus Products that are the subject of this Application. RJRT proposes three different modified risk advertising executions for each of the six Camel Snus styles (Frost, Frost Large, Winterchill, Robust, Mellow, and Mint) and is requesting a total of eighteen (18) MRTP orders.

Section 2 – This section contains a summary of the scientific rationale for the health benefits of switching completely from smoking cigarettes to using Camel Snus and why it is appropriate for FDA to issue MRTP orders with respect to the six Camel Snus styles that are the subject of this Application. This section also contains a summary of the health risk information and scientific data submitted in this Application with respect to Camel Snus.

Section 3 – This section provides descriptive information regarding the six Camel Snus products, including their features and designs, formulations, ingredients, manufacturing processes, and conditions for use, and it includes information regarding how consumers actually use the products.

Section 4 – This section contains a description of how RJRT intends to communicate the proposed Camel Snus modified risk advertising executions to the public and provides copies of draft modified risk advertising materials (*e.g.*, print advertising, direct mail, e-mail, a branded website, and direct consumer engagement brochures) that have been developed at the time of filing this Application.

Section 5 – This section contains environmental assessments under 21 CFR 25.40 for each proposed advertising execution for each of the six Camel Snus styles that are the subject of this Application.

Section 6 – This section contains a summary of all the research findings related to Camel Snus (both favorable and unfavorable). This section is organized according to the following key areas: Health Risks of the Tobacco Product; Comprehension and Perceptions of Proposed Modified Risk Advertising among Tobacco Users and Non-Users; Likelihood of Use Studies among Tobacco Users and Non-Users; and Effects on the Health of the Population as a Whole. This section also contains a tabulated index of all studies and analyses submitted in support of this Application.

Section 7 – This section contains the supporting documents, research reports, electronic data sets, data dictionaries and other documents relating to research findings referenced in this Application. The supporting documents and data files are organized by study type and include: product analyses; non-clinical studies; human studies; secondary data analysis and modeling; and other documents related to research on Camel Snus.

Section 8 – This section contains a foreign language certification for any documents that have been translated into English.

Section 9 – This section contains a description of RJRT's proposed post-market surveillance program for the six Camel Snus products that are the subject of this Application.

2.5.4 RJRT's Guiding Principles and Beliefs

RJRT is committed to addressing the issues regarding the use of and harm associated with tobacco products in an open and objective manner. RJRT features its Guiding Principles and

Beliefs prominently on its corporate website (RJRT Website 2017). These Guiding Principles and Beliefs include, among others:

- Cigarette smoking is a leading preventable cause of death.
- Quitting cigarette smoking significantly decreases the risk for lung cancer, heart disease, chronic bronchitis, emphysema and other serious diseases and conditions.
- No tobacco product has been shown to be safe or risk-free, but the type of tobacco product used, how long it is used, and the frequency and amount of use significantly affect the risk of serious diseases.
- The best course of action for tobacco consumers concerned about their health is to quit.
- Cigarette smokers who don't quit altogether should have access to a range of tobacco and nicotine products that may lower their health risks.
- Minors should never use tobacco products, and adults who don't use tobacco or have quit tobacco should not start.
- Cigarette smokers should avoid exposing youth and nonsmokers to secondhand smoke.
- Reducing disease and death associated with cigarette smoking is in the best interest of not only adult tobacco consumers, but society as well. The best way for smokers to achieve these risk reductions is to quit. Smokers who don't want to quit tobacco altogether should consider switching to tobacco products that may present less risk to their health.

2.5.5 Harm reduction and MRTPs are important parts of sound public health policy to reduce the burden of disease and death caused by cigarette smoking

Section 911 of the TCA represents the federal government's recognition that there may be tobacco products that, when appropriately marketed, could significantly reduce the burden of disease and death from using tobacco products. Issuing MRTP orders represent FDA's opportunity to reduce the harm to the public caused by tobacco use (TPSAC Meeting, April 9, 2016, Tr. at 16-17). Because FDA serves as the regulatory gatekeeper standing between consumers and the companies seeking to make claims about their products, it has immense harm reduction responsibility and should evaluate MRTP applications in the context of this responsibility.

The TCA recognizes the health impact of tobacco products in our society and the right of manufacturers to communicate the absolute and relative risks of specific tobacco products. FDA's mission to reduce the harms caused by tobacco products includes issuing orders authorizing manufacturers to make modified risk claims about tobacco products when they are appropriately supported by scientific data. Fulfillment of FDA's mission includes ensuring that

"consumers are better informed . . . relating to the health . . . or safety of [the MRTP]." TCA Section 3(6).

Although it is indisputable that quitting is the only safe alternative to using any tobacco product, many smokers do not stop smoking cigarettes, and are unwilling to use (or have been unsuccessful in using) nicotine replacement therapies or non-nicotine smoking cessation medications to stop smoking. If smokers were adequately informed, on a sustained and repeated basis, about the comparatively lower risk of smoking-related diseases, it is likely that some smokers will switch to a modified risk tobacco product that presents less risk for smoking-related diseases.

RJRT believes that adult tobacco consumers have a right to be fully and accurately informed about the risks of serious diseases, the significant differences in the comparative risks of different tobacco and nicotine-based products and the benefits of quitting. Governments, public health officials, tobacco manufacturers and others share a responsibility to provide adult tobacco consumers with accurate information about the comparative risks associated with the use of different tobacco and nicotine products. This information should be based on sound science.

Within the public health and tobacco control communities, harm reduction as a public health policy has been debated extensively. And, it has been posited that smokers have a right, a "human right," to receive accurate information about the comparative risks of tobacco and nicotine products. It has been suggested that avoiding, or objecting to, the fair presentation of information on effective harm reduction products to smokers in order to allow them to make an informed choice to reduce health risk can represent a violation of a human right – the right to information. The necessary conditions for protecting public health are not met by restricting accurate information on MRTPs (Kozlowski 2002).

Key principles of public health ethics—individual rights, health literacy, and personal autonomy (making decisions for oneself)—with respect to providing the public with differential risk information regarding different types of tobacco products are discussed extensively in Kozlowski and Sweanor 2016. In that article, the authors argue that "omitting key health relevant information" represents a kind of quarantine of health-relevant information that "effectively blindfolds [consumers] and impairs their making informed personal choices":

> "As with disease quarantines, the coercive effects of quarantining information on differential risks needs to be justified, not merely by fears of net negative public health effects, but by convincing evidence that such measures are actually warranted, that public health overall is in imminent danger and that danger is sufficient to override principles of individual autonomy. . . Moral psychological issues that treat all tobacco/nicotine products similarly may also be influencing the reluctance to inform on differential risks. In countries where tobacco/nicotine products are legally sold and also differ greatly in disease risks compared to cigarettes (e.g., smokeless tobacco and vape), science-based, comprehensible, and actionable health information (consistent with

health literacy principles) on differential risks should be available and only reconsidered if it is established that this information is causing losses to population health overall."

(Kozlowski and Sweanor 2016).

RJRT agrees that tobacco products should be regulated in a manner that is designed to achieve significant and measurable reductions in the risks and adverse health effects associated with tobacco use. FDA should enhance the information available to adult tobacco consumers to permit them to make informed choices, and encourage the development of tobacco and nicotine products with lower risks than existing cigarettes. Further, RJRT recognizes that Section 911 of the TCA provides for the communication of such information in the form of modified risk advertising for a specific tobacco product when authorized by the Agency.

2.5.6 Scientific consensus for the tobacco product risk continuum

According to the U.S. Surgeon General, combustible tobacco products by far have the greatest adverse impact on public health (USDHHS 2014). Because cigarettes undergo combustion processes when used as intended, smokers are exposed by inhalation to substantial quantities of products of incomplete combustion from the burning of cigarettes, as well as other substances in cigarettes that transfer from tobacco to smoke. Because smokeless products do not undergo combustion during use, users of smokeless tobacco products are not exposed to tar, carbon monoxide, or other products of incomplete tobacco combustion. In addition, smokeless tobacco users are exposed to much lower quantities of combustion-related products, *i.e.,* to whatever combustion-related products, if any, remain from the curing of the tobacco in smokeless tobacco products or from natural environmental sources (as with food). These differences in exposure, as well as differences in routes of exposure (inhalation vs. oral absorption), result in significantly lower risk profiles for smokeless tobacco users as compared with cigarette smokers, as demonstrated in many epidemiological studies (s*ee* Section 2.8 and Section 2.9).

Public-health researchers have described this differentiation in risk through a construct called a "continuum of risk," with combustible tobacco products on one end and smokeless tobacco and nicotine products on the other (Zeller *et al.* 2009). Smokeless tobacco products are not safe, but "there is no scientific doubt that manufactured smokeless tobacco products in the U.S. (and notably, low-nitrosamine Swedish snus) are dramatically less dangerous than cigarettes to life-long users of each product." (Kozlowski and Sweanor 2016). As stated by the United Kingdom's Royal College of Physicians ("RCP"), "it is very clear that, for most of the major health effects of tobacco, smoking is many times more dangerous than ST [smokeless tobacco] use" (RCP 2007, p. 156).

It is against this tobacco "continuum of risk" harm reduction backdrop that RJRT set out to develop proposed modified risk advertising executions to communicate accurately a harm reduction message that smokers who switch completely from cigarettes to using Camel Snus will reduce their risks of lung cancer, oral cancer, respiratory disease and heart disease, compared to continued smoking.

2.5.7 Modified risk messaging and smoker misperceptions

In developing modified risk advertising, RJRT was acutely aware of the prevailing public misperception that use of smokeless tobacco, including snus, is at least as harmful as cigarette smoking. Studies that have evaluated consumer perceptions show that, contrary to the consensus in the public health and tobacco control communities, the public (including consumers) believes – erroneously – that smokeless tobacco products are as harmful as, or more harmful than, cigarettes (Fong *et al.* 2016; Kaufman *et al.* 2014; Kiviniemi and Kozlowski 2015; Liu *et al.* 2015; Regan *et al.* 2012; Wray *et al.* 2012), especially for oral cancer (Choi *et al.* 2012; Pepper *et al.* 2015). Given this prevailing view, and the skepticism with which reduced risk information is received (Borland *et al.* 2012), modified risk advertising will need repetition and endorsement from multiple credible sources to become more persuasive and believable to consumers, so as to change their beliefs and to support changes in tobacco use behavior.

Although the data are limited, some published reports and an RJRT-sponsored study suggest that exposure to modified risk information with respect to potential health benefits of switching to Camel Snus as compared to continued smoking may influence smokers' perceptions in and interest in snus (Borland *et al.* 2012; Meier *et al.* 2016; Choi *et al.* 2017; CSD1010 CSR). The data also suggest that modified risk messaging will need to be repeated over time and not contradicted by messages from public health agencies such as FDA, in order to overcome deeply ingrained smokeless tobacco attitudes and beliefs and misperceptions. In a recent nationwide smoking cessation trial of smokers not interested in quitting smoking, abstinence measures were assessed among smokers who were randomized to receive free samples of Camel Snus versus not (Carpenter 2016). Subjects randomized to the Camel Snus group were provided free samples of Camel Snus and all subjects were advised to quit all tobacco products. In addition, subjects were provided with a limited description of the potential health benefits of the study product ("new potentially safer tobacco product" and "some evidence suggests that the product we will be testing could be safer than conventional cigarettes"), but were not explicitly given the name of the test product and were not provided any details about the medical evidence supporting the health benefits of switching to Camel Snus. Although there were no differences in abstinence in the Camel Snus group compared to the control group and smokers in the Camel snus group were less likely to make any quit attempt, 16% of smokers were regularly using Camel Snus at the end of 12 months. This study illustrates that the perception of a potential health benefit of Camel Snus compared to continued smoking may be an important determinant of snus use and potential substitution for cigarettes.

RJRT recognizes that existing statutory warnings and public health messages with respect to smokeless tobacco products may undermine the credibility of modified risk advertising even if FDA issues an MRTP order. In the event that modified risk advertising does not encourage substantial numbers of smokers to switch to Camel Snus, RJRT has designed the proposed Camel Snus modified risk advertising materials to further educate smokers about the risks of cigarette smoking, in more detail than the statutory warning labels, and is optimistic that, over time, the effect of MRTP advertising may decrease consumer misperception that using

smokeless tobacco is the same as or more risky than smoking cigarettes. Indeed, education about relative risks of smokeless tobacco and snus versus smoking (in the form of Camel Snus modified risk advertising) has the potential to mitigate the prevailing misperceptions about relative risk of smokeless tobacco versus cigarettes.

In a small multinational sample, the effects of education about the relative harms of smokeless tobacco versus smoking were assessed using a four-page fact sheet (and, in the U.S., a face-to-face power-point presentation) (Borland *et al.* 2012). The educational intervention resulted in modest increases in correct perceptions of smokeless tobacco's harm relative to smoking, and these were accompanied by increased interest among smokers in trying smokeless tobacco. Similar effects were observed for education about NRT. However, many smokers expressed skepticism of the facts presented, the increases in correct understanding were modest, and the majority of smokers in most countries were still misinformed (U.S. smokers' correct responses rose from 7% to 27%), underscoring the limitations of single exposures to information, and the need for more compelling and ongoing education.

A larger improvement in understanding of relative risks is possible, and is suggested by data on changes over time in particular countries (Borland *et al.* 2011). In the U.K., the proportion of smokers recognizing that smokeless tobacco is less harmful than smoking increased from 25% to 40% from 2002 to 2009. However, the proportion of U.S. smokers reporting a belief that smokeless tobacco is less harmful than smoking did not significantly change over this period, with five of six smokers reporting misperceptions. The authors attribute the improvement in understanding to the efforts in the U.K. to educate smokers about the safety of NRT and nicotine as alternatives to smoking. These results suggest the potential for education to improve U.S. smokers' understanding of the relative risks of non-combustible nicotine sources compared to smoking.

RJRT believes that the worst case scenario should FDA issue MRTP orders for Camel Snus is that smokers will not switch to Camel Snus in significant numbers, but will have increased opportunities to learn more about the risks of continuing to smoke. The proposed modified risk advertising reinforces the current health warnings on Camel Snus packaging and more generally public health messages about the health risks and addictive nature of smokeless tobacco products and cigarettes.

2.5.8 Consensus conclusions regarding comparative health risks of cigarette smoking and smokeless tobacco use, including snus, for the individual user

The gross disparity in health risks presented by smokeless tobacco use, including snus, compared with cigarette smoking has been widely discussed within the scientific, medical, public health and regulatory communities and in published reports summarized in this Application (*see* Section 2.8, Section 2.9.1 and Section 6.1). While some researchers have expressed uncertainty over the difficulties in predicting population-level effects of modified risk advertising in the U.S., virtually none question the substantially lower health risks to individual users associated with smokeless tobacco use. The following public-health organizations and public-health advocates have considered the data on smokeless tobacco products, including

snus, and concluded that smokeless tobacco use presents substantially less risk than smoking cigarettes:

- Smokeless tobacco information provided on the American Cancer Society's website poses the question "How do the risks of using smokeless tobacco compare with cigarette smoking?" And supplies the answer that "smokeless tobacco products are less lethal than cigarettes (ACS 2017).

- Though not safe, there is no scientific doubt that manufactured smokeless tobacco products in the U.S. (and notably, low-nitrosamine Swedish snus) are dramatically less dangerous than cigarettes to life-long users of each product (Kozlowski and Sweanor 2016).

- An expert panel convened by the Independent Scientific Committee on Drugs developed a multi-criteria decision analysis (MCDA) model of the relative importance of different types of harm related to the use of nicotine-containing products, including cigarettes, snus, other smokeless tobacco products, and NRTs. Basing their opinions of relative harm on 14 separate and differently weighted criteria, 7 representing "harms to self" and 7 representing "harms to others," the panel provided a ranking of relative harm for 12 different nicotine-containing products. Cigarettes were assigned maximum "harm scores" for 12 of the 14 criteria, were considered most harmful overall, and were assigned a score of 100% of maximum relative harm (MRH). Snus was assigned an MRH value of 5%, and NRTs a value of 2% (Nutt *et al.* 2014).

- Current director of CTP, Mr. Mitchell Zeller, has acknowledged that smokeless tobacco products pose less risk to the individual user compared with cigarettes. Mr. Zeller has stated on a number of occasions that a continuum of risk exists among nicotine-delivering products, with associated toxicities varying dramatically, with conventional cigarettes at one end of the spectrum, and at the other end, products, including smokeless tobacco products, that pose less harm to the individual (Zeller 2013).

- The Strategic Dialogue on Tobacco Harm Reduction Group, a collection of researchers and public-health advocates, met in 2009 to discuss issues pertaining to tobacco harm reduction. Among the Group's findings were that a continuum of risk exists among tobacco products and that: "Cigarette smoking is undoubtedly a more hazardous nicotine delivery system than various forms of noncombustible tobacco products" (Zeller *et al.* 2009).

- In their 2008 evaluation of the differential health risks of smoking versus smokeless tobacco use, scientists at the Life Sciences Research Organization ("LSRO") concluded that smokeless tobacco use carries reduced risk for smoking-related diseases compared with cigarette smoking, and in many cases results in no increased risk compared with non-users of tobacco (LSRO 2008).

- The 2008 report from the Scientific Committee on Emerging and Newly Identified Health Risks ("SCENIHR") noted first that there is no evidence that smokeless tobacco is associated with any major health hazard that is not associated with smoking. Next, there was no consistent evidence that any smokeless tobacco product, including snus, causes any of the major smoking-related respiratory diseases in the EU—lung cancer, COPD and pneumonia (SCENIHR 2008). In regards to cardiovascular diseases, the SCENIHR report proposed a conservative estimate that switching from cigarette smoking to snus could reduce cardiovascular mortality by at least 50%. The report concluded that overall, in relation to the risks of the major smoking-related diseases, with the exception of use in pregnancy, "[smokeless tobacco products] are clearly less hazardous, and in relation to respiratory and cardiovascular disease substantially less hazardous, than cigarette smoking" (SCENIHR 2008, p. 114).

- The WHO Study Group on Tobacco Product Regulation (WHO 2008) stated in a 2008 report that "there is little question that, in general, smokeless tobacco products are less harmful than combusted products such as cigarettes; however, whether smokeless tobacco products contribute to continuation or reduction of the global tobacco epidemic depends in part on their nature, how their health effects are communicated, how they are marketed and how they are used." Each of these considerations itemized by the WHO study group fall fully within the scope of the MRTP paradigm, intended as it is to ensure that anticipated benefits to the public health will be fully realized. A major conclusion of the report was that "users of smokeless tobacco products generally have lower risks for tobacco-related morbidity and mortality than users of combustible tobacco products such as cigarettes" (WHO 2008).

- A comprehensive 2007 review of 16 primary studies of snus use in Sweden was conducted by the New Zealand Ministry of Health (Broadstock 2007). The review concluded that the available evidence suggested that the harm of using snus relative to non-tobacco use was significantly less than found for smoking with respect to cancers of the head, neck and gastro-intestinal region, and for cardiovascular disease events. The author further concluded that while some studies were not sufficiently powered to detect small increases in risks compared to no tobacco use, the results suggested that snus use does not lead to significant risks for these diseases (Broadstock 2007).

- Dorothy Hatsukami reviewed the changing spectrum of smokeless tobacco products in recent decades and commented that "[e]xcepting nicotine pharmaceuticals, of the various currently available potential reduced exposure products (PREPs) that may result in actual harm reduction, smokeless tobacco products have the greatest potential to reduce risk for disease if smokers completely switch from cigarettes to these products." And "[u]nlike cigarette smoking, smokeless tobacco use has not been linked to many of the smoking-related cancers or to pulmonary disease" (Hatsukami *et al.* 2007b).

- In 2007, the Royal College of Physicians (RCP) reviewed the available data to provide an evaluation of the health effects of smokeless tobacco compared with cigarettes. The

subsequent published report provided an extensive analysis of key issues surrounding tobacco use and nicotine addiction, including a review of the risk profile of smokeless tobacco products, and the health effects of smokeless tobacco compared with cigarette smoking. The report concluded that "it is very clear that, for most of the major health effects of tobacco, smoking is many times more dangerous than smokeless tobacco use" (RCP 2007).

- A panel of experts on tobacco use and health, including Jonathan Samet, former Chair of FDA's Tobacco Products Scientific Advisory Committee, estimated that total mortality risk among users of low-nitrosamine ST products is less than 10% of the risk associated with smoking (Levy *et al.* 2004). The publication presented the results of a modified Delphi evaluation of the risks of low-nitrosamine smokeless tobacco (such as snus) compared with conventional cigarettes, based on responses from a nine-member panel of tobacco epidemiologists. Four health risk mortality endpoints were considered: premature total mortality, lung cancer, heart disease, and oral cancer. Within this panel of experts, there was a consensus that low-nitrosamine smokeless tobacco products such as snus are less hazardous than conventional cigarette smoking by a wide margin. The panel estimated that for the individual tobacco user, snus risk for total mortality was 90-95% lower, for oral cancer was 70-85% lower, for heart disease 90% lower, and for lung cancer, 96-98% lower than risks from cigarette smoking (Levy *et al.* 2004).

- Neal Benowitz, a long-time nicotine and tobacco researcher and former member of the Tobacco Products Scientific Advisory Committee of the FDA, stated in 2003 that, "It is clear, however, that the use of smokeless tobacco is much less hazardous than cigarette smoking" (Benowitz 2003; *see also* Benowitz 2011).

- In 2002, the Royal College of Physicians concluded: "As a way of using nicotine, the consumption of non-combustible tobacco is of the order of 10—1,000 times less hazardous than smoking, depending on the product" (RCP 2002, p. 5).

In summary, the consensus conclusions of public health organizations and leading tobacco control experts are that use of smokeless tobacco, including snus, is associated with far less risk for all smoking-associated diseases compared with cigarette smoking. These conclusions also consistently support RJRT's Application generally that individuals who switch from cigarette smoking to exclusive use of Camel Snus will greatly reduce their risk of lung cancer, oral cancer, respiratory disease and heart disease compared with continued cigarette smoking.

2.6 Proposed Modified Risk Advertising Executions

2.6.1 Modified risk execution #1

Smokers who **switch completely** from cigarettes to Camel SNUS can significantly reduce their risk of lung cancer, oral cancer, respiratory disease, and heart disease

2.6.2 Modified risk execution #2

Smokers who **SWITCH COMPLETELY** from cigarettes to Camel SNUS greatly reduce their risk of lung cancer, oral cancer, respiratory disease, and heart disease

2.6.3 Modified risk execution #3

Smokers who **SWITCH COMPLETELY** from cigarettes to Camel SNUS can greatly reduce their risk of lung cancer and respiratory disease

2.7 Description of Camel Snus Products

2.7.1 Historical background for Camel Snus development

Snus is an oral smokeless tobacco that has been used in Sweden since the early 1800s and is sold both as loose tobacco and as tobacco portioned in fleece pouches. Snus has historically used finely ground tobaccos that undergo a two-step process: (1) a heat treatment process in the presence of water and sodium chloride; and (2) a cooking process which incorporates the addition of a pH-modifying solution. The primary differences between snus and the various types of moist snuff tobacco products traditionally sold in the United States are (1) the tobacco types used and (2) manufacturing processes used to produce the final product. Specifically, snus manufacturing uses tobaccos processed via heat treatment, rather than via fermentation. Both of these tobacco processing methods, heat treatment and fermentation, are used in order to improve the taste and/or to minimize the potential for microbial activity, but it is generally accepted that heat treatment (along with selection of tobaccos) has the greater impact on lowering quantities of harmful and potentially harmful constituents ("HPHCs") when compared to other forms of smokeless tobacco which use the fermentation process.

2.7.2 Current Camel Snus products that are the subject of this MRTP Application

The six Camel Snus tobacco products that are the subject of this MRTP Application are all portioned pouched smokeless tobacco products within the snus sub-category. All six Camel Snus brand styles are manufactured using a very similar process as other snus products sold in various markets. All six Camel Snus products are portioned, pouched products and use a (b) (4) base blend of tobaccos. (b) (4)
(b) (4)
(b) (4) . These unique sub-brand blends are then pouched in a porous fleece material and packaged in metal tins to make the finished product.

2.7.3 List of Camel Snus products that are the subject of this MRTP Application

	Brand	Sub-brand[1]	Product Weight (per portion)	Pouches (per package)
1.	Camel	Camel Snus Frost	600 mg	15
2.	Camel	Camel Snus Mint	600 mg	15
3.	Camel	Camel Snus Mellow	600 mg	15
4.	Camel	Camel Snus Frost Large	1000 mg	15
5.	Camel	Camel Snus Winterchill	1000 mg	15
6.	Camel	Camel Snus Robust	1000 mg	15

The full descriptive information, including design and construction, specifications, formulation, ingredients, components and manufacturing processes for each of these Camel Snus products is provided in Section 3.1 and Section 3.2.

2.8 Scientific Rationale for the Potential Benefits of Camel Snus

The results of RJRT's studies on Camel Snus, when combined with the body of epidemiological studies, human clinical studies, preclinical toxicology studies, and chemistry studies of smokeless tobacco and health, provide a sound scientific basis to conclude that, for individuals who are current cigarette smokers, switching completely from smoking cigarettes to Camel Snus will significantly reduce those individuals' risk for lung cancer, respiratory disease, coronary heart disease, and oral cancer. The following provides a detailed review of the scientific rationale for the benefits of Camel Snus. In particular, the following will be discussed:

- Epidemiological studies of U.S. and Swedish smokeless tobacco usage provide clear and consistent evidence of reduced individual disease risk compared to cigarette smoking and are appropriate for estimating disease risks to individual users of Camel Snus.
- RJRT-sponsored clinical and preclinical studies of Camel Snus and external studies of Camel Snus and other U.S. smokeless tobacco products support reduced individual disease risks compared to cigarette smoking.
- Marketing Camel Snus as an MRTP will benefit the health of the population as a whole.

These concordant lines of evidence provide compelling support for both individual and population benefits of switching from cigarette smoking to Camel Snus.

[1] RJRT refers to these subbrands as "brand styles," "varieties," "variants," or "flavor variants" in the text of this Application.

2.8.1 Epidemiological studies of U.S. and Swedish smokeless tobacco usage provide clear and consistent evidence of reduced individual disease risk compared to cigarette smoking

The results of U.S. and Swedish epidemiological studies provide clear and consistent evidence that the health risks from use of smokeless tobacco products, including Camel Snus, are less than the health risks from smoking. While no tobacco product is safe and devoid of all risk when used, tobacco products that do not burn tobacco during use present less risk for lung cancer, oral cancer, respiratory disease and heart disease (Section 6.1.1) than do tobacco products that burn tobacco during use (*e.g.*, traditional cigarettes).

FDA has previously indicated "that it is not necessary for epidemiological studies used to support an MRTPA to focus solely on each specific, uniquely identified product that is the subject of the application. However, in applying this evidence to support an MRTPA for a specific product," RJRT "should provide evidence demonstrating how the product under study and the product that is the subject of the application are comparable in terms of characteristics that may influence disease risk. This may include, but is not limited to, differences in product design, product chemistry, package type and size, portion size, labeling, flavor, exposure to HPHCs, and factors that may influence product use behavior" (FDA 2014).

The following sections provide the scientific rationale for the relevance of published epidemiological studies of both U.S. and Swedish smokeless tobacco users for estimating health risks to individuals who use Camel Snus, rather than smoking, in support of the proposed modified risk advertising submitted in this Application. The data reviewed in the sections below demonstrate that the smokeless tobacco products whose health risks are determined in U.S and Swedish epidemiological studies share basic characteristics with Camel Snus in terms of product design, toxicant content and manner of use. In specific regard to potential health effects, Camel Snus toxicant content is comparable to, or less than, historical U.S. and Swedish smokeless tobacco products on which the epidemiological studies are based. Differences in the amounts of product used per day and manner of use of Camel Snus compared with historical U.S. and Swedish products likewise indicate a lower level of exposure to HPHCs. Therefore epidemiological studies of U.S. and Swedish smokeless tobacco users either provide viable estimates of the health risks associated with using Camel Snus as compared to cigarette smoking, or more likely, overstate those risks.

2.8.2 Epidemiological studies of U.S. smokeless tobacco users are appropriate for estimating disease risks to individual users of Camel Snus

Smokeless tobacco products have been commercially available and in use for many decades in the United States. Available observational epidemiological studies of U.S. smokeless tobacco users are representative of the smokeless tobacco products used by study participants, the participants' use behaviors, and the associated health outcomes that are observed at the time of the study. No existing epidemiological study of U.S. smokeless tobacco users reflects the health effects of any single product or single use behavior. In addition, health outcomes observed in studies that have evaluated the use of products over long periods of time – for

example, the American Cancer Society's Cancer Prevention Studies (CPS-I and CPS-II), reflect an aggregate exposure and risk associated with a range of smokeless tobacco products and use patterns. This aggregate exposure incorporates the natural variation (for example, different products and use patterns) that occurs among and within users, as well as the evolving composition of U.S. smokeless tobacco products over time. With few exceptions, those epidemiological studies, conducted among U.S. population cohorts, have found the risks associated with U.S. smokeless tobacco products, including products with higher levels of toxicants than current market smokeless tobacco products, to be significantly lower than the risks from cigarette smoking.

Smokeless tobacco products, including products that preceded commercial manufacture, have been used in the United States for hundreds of years. In that time, smokeless tobacco products have varied in composition and in toxicant content. In the most recent decades, the toxicant content of U.S. smokeless tobacco products has declined significantly, most notable with regard to TSNA content. Camel Snus styles are U.S. smokeless tobacco products. The Camel Snus styles that are the subject of this Application have much lower toxicant content than U.S. smokeless tobacco products from both the near and distant past. Camel Snus products are also lower in toxicant content than many other smokeless tobacco products sold in the U.S. today (*e.g.*, Borgida *et al.* 2015; *see also*, Section 6.1.5). The relative health risks associated with Camel Snus use, as compared to cigarette smoking, are provided by existing U.S. epidemiological studies of tobacco users. These studies provide valuable insight into the relative health risks from using Camel Snus as compared to cigarette smoking because toxicant exposure when using Camel Snus styles is comparable to, or less than, such exposure from other smokeless tobacco products in use prior to, and during the time course of U.S. epidemiological studies. Toxicant exposure from smokeless tobacco products, including Camel Snus styles is driven by two principal factors: (1) the toxicant content of the tobacco product and (2) the manner of use (*i.e.,* quantity, duration, frequency). Camel Snus toxicant content is generally lower than the U.S. smokeless tobacco products that have been in use for much of the last century (*i.e.,* the products used in the available epidemiological studies of U.S. smokeless tobacco users). A comparable manner of use also exists for Camel Snus styles and historical U.S. smokeless tobacco products, with use of Camel Snus quantities (*i.e.*, grams of tobacco per day) that are generally less than has been historically observed for other smokeless tobacco products (see below for additional discussion of use behavior).

The sections of this Application that follow estimate the time periods of smokeless tobacco use represented by the U.S. epidemiological studies, review available data regarding the toxicant content of smokeless tobacco products that were available for use by the participants in those studies and examine the typical tobacco use behaviors representative of those time periods. Collectively, available toxicant and product use information demonstrate that available epidemiological studies of U.S. smokeless tobacco users represent a range of products that, as used, present less risk for lung cancer, oral cancer, respiratory disease and heart disease than cigarette smoking. Given the general consistency in toxicant content and manner of use between Camel Snus and the smokeless tobacco products used in those studies, the available epidemiological studies of U.S. smokeless tobacco users are relevant to demonstrate the

reduced risk of Camel Snus, and support the conclusion that smokers who switch completely to Camel Snus will reduce their risk for lung cancer, oral cancer, respiratory disease and heart disease.

2.8.2.1 Epidemiological data for U.S. smokeless tobacco users reflect use of U.S. smokeless products available during the past 100 years

In order to determine estimated time periods for smokeless tobacco product use that correspond to risk estimates reported in U.S. epidemiological studies, the following calculations are presented as examples. In U.S. Cancer Prevention Study I (CPS-I) study participants were enrolled from 1959 through 1960 and followed until 1972. The median age at enrollment for the cohort of "current" smokeless tobacco users was 62 years (Henley *et al.* 2005, p. 349). No data were obtained for age at smokeless tobacco initiation among this group, but reports suggest that the typical age for smokeless tobacco use initiation during the time frame for smokeless tobacco users included in CPS-I was from 12 to 18 years (Schroeder *et al.* 1987; Glover *et al.* 1989). Assuming smokeless tobacco initiation at age 15 would mean that the individuals who were followed in this study used smokeless tobacco products purchased from approximately 1912 through 1972, a period of approximately 60 years. Similarly, the earliest of the studies cited in the meta-analysis of Lee and Hamling (2009a) was a study reported by Broders (1920). The average patient age was 57 years, meaning that smokeless tobacco initiation could have occurred in the late 19th century.

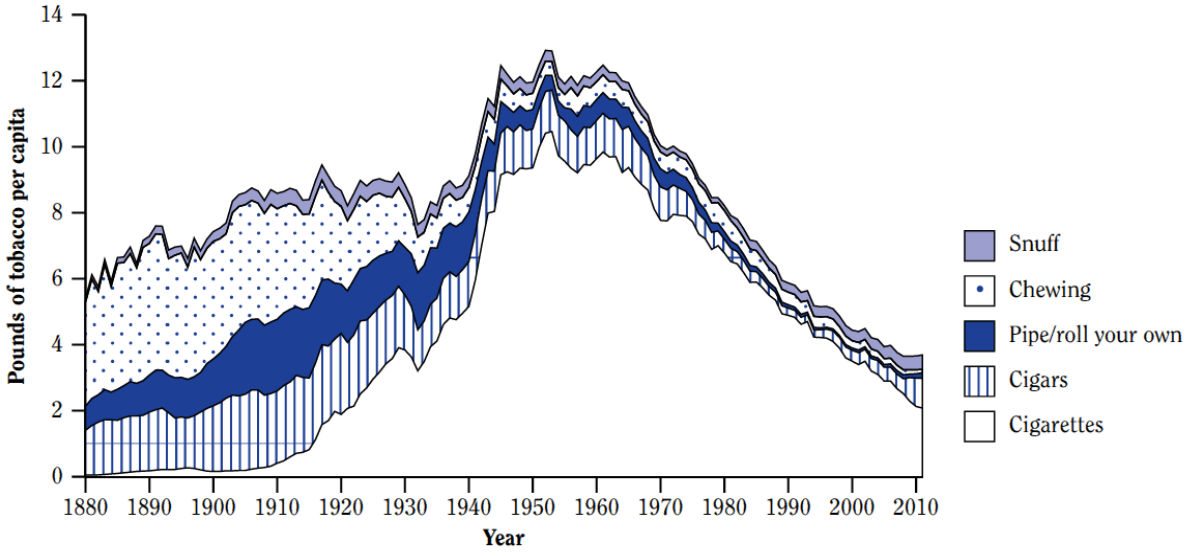
The most recent of the U.S. epidemiological studies cited in the meta-analysis of Lee and Hamling (2009a) was that of Hassan *et al.* (2007). This study enrolled participants from 2000 through 2006. Although the specific ages of the smokeless tobacco users in the study were not provided, participants ranged in age from younger than 40 years to more than 70 years. Thus, the smokeless products used during the span of years encompassed by epidemiological studies of U.S. smokeless tobacco users surveyed by Lee and Hamling begins with products in use during the late part of the 19th century, and ends with the products in contemporary use. When considered collectively, it is clear that available epidemiological studies of U.S. smokeless tobacco users incorporate the range of smokeless tobacco products and tobacco product use patterns from the past hundred years. The general product characteristics, toxicant profile and product use patterns associated with Camel Snus (*see* below) fall within the range of smokeless tobacco products used in these studies. As such, these epidemiological studies are relevant to determinations regarding individual risks associated with the use of Camel Snus as compared to cigarette smoking.

2.8.2.2 The types and composition of smokeless tobacco products reflected in the results of published U.S. epidemiological studies represent a range of smokeless products; studies that report individual or collective risks from these products are relevant for estimating Camel Snus risks

The smokeless tobacco products whose health risks are documented in U.S. epidemiological studies of smokeless tobacco users are not of a single type, but rather several different product types that differ in their content and composition. The predominant types are loose leaf

chewing tobacco and loose moist snuff. These products, along with some lesser-used products such as dry snuff, have dominated the U.S. smokeless tobacco marketplace for the past hundred years as illustrated in Figure 2.8.2-1. Dry snuff has constituted only a small fraction of the overall U.S. smokeless tobacco market, has distinct differences (*e.g.*, composition and processing) from chewing tobacco and moist snuff products, including Camel Snus, and will therefore not be further discussed in this section due to lack of relevance. It should be noted that dry snuff possesses relatively high levels of TSNAs compared with other forms of U.S. smokeless tobacco (*see* Table 2.8.2-2) and epidemiological studies have reported significantly elevated risks for oral cancer associated with use of this product (Rodu and Jansson 2004). The inclusion of dry snuff users in epidemiological studies or summary analyses that did not account for product type would therefore likely inflate the overall risks from "smokeless tobacco" use.

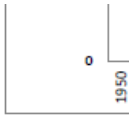
Figure 2.8.2-1: Per capita consumption of different forms of tobacco in the United States, 1880-2011 (from USDHHS 2014, p. 705)



Source: U.S. Department of Treasury 2012.

As demonstrated in Figure 2.8.2-2, chewing tobacco remained the dominant form of smokeless tobacco until the mid-1990s, when snuff sales exceeded those of chewing tobacco:

Figure 2.8.2-2: U.S. sales of chewing tobacco and snuff 1950-2002



Data provided in IARC 2007b on smokeless tobacco use (p. 99). Note that some types of fine-cut smokeless tobacco that were classified as "chewing tobacco" prior to 1981 were subsequently classified as "moist/fine-cut snuff." This accounts for the abrupt changes observed from 1981-1982 (IARC 1985, p. 57).

Because of the range of smokeless tobacco products used in the U.S. in earlier decades, U.S. epidemiological studies reflect risks to users of the range of products available to users included in the studies. Accordingly, as differences in the composition of smokeless tobacco products exist, it is important to understand the general characteristics of each type of smokeless tobacco product (USDHHS 1986), including typical manner of use and type of packaging. This information is provided in Table 2.8.2-1 below.

Table 2.8.2-1: Characteristics of traditional smokeless tobacco products (from USDHHS 1986, p. 6)

Product	Description	How Used	Packaging*
CHEWING TOBACCO			
Loose leaf	Made from air-cured, cigar leaf tobaccos of Pennsylvania and Wisconsin. Consists of stripped and processed tobacco leaves. The leaves are stemmed, cut, or granulated and are loosely packed to form small strips of shredded tobacco. Most brands are sweetened and flavored with licorice.	A piece of tobacco, ¾ to 1 inch in diameter, is tucked between the gum and jaw, usually to the back of the mouth.	Pouch, typically 3 ounces. A few brands market a 1.5-ounce pouch.
Plug	Made from enriched tobacco leaves (Burley and bright tobacco and cigar tobacco) or fragments wrapped in fine tobacco and pressed into bricks. May be firm (less than 15 percent moisture) or moist (15 percent or greater moisture). Most plug tobacco is sweetened and flavored with licorice.	Chewed or held in the cheek or lower lip. May be held in the mouth for several hours.	A compressed brick or flat block wrapped inside natural tobacco leaves. Packaged in clear plastic. Packages range from 7 to 13 ounces. Also sold by the piece.
Twist	Handmade of dark, air-cured leaf tobacco treated with a tarlike tobacco leaf extract and twisted into strands that are dried. Majority is sold without flavoring and sweeteners.	Similar to plug.	A pliable but dry rope. Sold by the piece, packaged in plastic bags. No standard weight. Sold in small (approximately 1-2 ounces) and larger sizes based on the number of leaves in the twist.
SNUFF			
Moist	Made from air-cured and fire-cured tobacco. Consists of tobacco stems and leaves that are processed into fine particles or strips. Some products are flavored. Has a moisture content of up to 50 percent.	A small amount ("pinch" or "dip") is placed between the lip or cheek and gum and is typically held for 30 minutes or longer per pinch.	Cans and plastic containers, typically 1.2 ounces.

Product	Description	How Used	Packaging*
Dry	Most dry snuff is made from fire-cured tobaccos of Kentucky and Tennessee. After initial curing the tobacco is fermented further and processed into a dry powdered form. Products vary in strength and flavoring. Generally has a moisture content of less than 10 percent.	Same as moist snuff. May also be sniffed.	Metal cans or glass containers, vary from 1.15 to 7 ounces per container.

* Product weight (includes moisture).

In addition to the general characteristics of smokeless tobacco products described in the table above, manufacturers distinguished their products in a variety of ways, by blending several types of tobacco, adding different levels or proportions of sweeteners and flavorings such as honey, sugar, molasses and licorice, and using different manufacturing processes; product composition was often determined by the availability of tobacco types and by regional customs and preferences. Thus, even within categories of smokeless tobacco, considerable variation in composition existed.

Many epidemiological studies, such as CPS-I, do not provide data on either specific use or comparative health effects of individual types of smokeless products. A number of others, including several examined in the 2009 meta-analysis conducted by Lee and Hamling (Lee and Hamling 2009a), reported separately on risks associated with chewing tobacco, moist snuff, and uncategorized smokeless tobacco. Among those studies was CPS-II, where the majority (74%) of the 2488 exclusive smokeless tobacco users reported current use of chewing tobacco only; another 14% used snuff only, and 12% used both chewing tobacco and moist snuff (Henley *et al.* 2005) (*see* discussion below).

As presented in a 1989 publication by Djordjevic and co-workers (Djordjevic *et al.* 1989) (Table 2.8.2-2), there are differences in composition and processing of chewing and snuff tobacco, and those differences can result in differences in product chemistry as illustrated in the table below.

Table 2.8.2-2: Tobacco-specific *N*-nitrosamine (TSNA) content in smokeless tobacco (from Djordjevic *et al.* 1989)

Product type	Sample	Moisture (%)	pH	TSNA content (µg/g dry wt)				
				NAT	NAB	NNN	NNK	Total
Chewing tobacco	KY 1S1	18.8	6.3	1.0	0.04	2.4	0.17	3.6
	A	18.6	6.3	0.7	0.02	1.5	0.11	2.3

Product type	Sample	Moisture (%)	pH	TSNA content (µg/g dry wt)				
				NAT	NAB	NNN	NNK	Total
Moist snuff	KY 1S3	58.7	7.7	7.4	0.51	10.9	0.82	19.6
	A	51.0	7.9	9.8	0.42	13.8	0.93	25.0
	B	57.0	7.5	7.3	0.51	8.5	0.76	17.1
	C	49.0	8.6	12.6	0.55	10.2	0.59	24.0
	D	21.5	6.6	1.0	0.21	4.7	0.34	6.3
	E	53.3	8.6	3.2	0.19	5.1	0.63	9.1
Dry snuff	KY 1S2	10.0	6.5	32.7	3.22	81.3	20.30	137.5
	A	12.0	5.8	12.6	0.52	10.6	0.88	24.6
	B	12.9	6.1	11.2	0.56	35.2	3.71	50.6
	C	15.5	63	11.3	0.54	33.6	3.53	48.9

Table 2.8.2-2 illustrates levels of 4 TSNAs in three different smokeless product categories. The commercial tobacco products (loose leaf chewing tobacco sample "A", moist snuff samples "A" through "E" and dry snuff samples "A" through "C") were purchased on the open market in Westchester County, NY in 1987 and 1988. Kentucky (KY) reference moist snuff (1S3), dry snuff (1S2) and loose leaf chewing tobacco (1S1) samples were obtained from the Tobacco and Health Research Institute, University of Kentucky, Lexington, KY. The lowest levels of TSNAs were detected in chewing tobacco, with higher levels in moist snuff, and highest levels in dry snuff. Higher levels of TSNAs in moist snuff compared with chewing tobacco have been reported in multiple studies (Brunnemann *et al.* 1985; Chamberlain *et al.* 1988; Brunnemann and Hoffmann 1991). As noted before, the levels of these toxicants reflect different tobacco selection and manufacturing processes, with the higher levels of TSNAs in moist and dry snuff a likely result of fermentation of tobaccos used in those products.

In spite of differences in type and composition, moist snuff and chewing tobacco present similarly low health risks. In 1985, IARC concluded that there was sufficient evidence that oral use of snuffs of the types commonly used in North America and Western Europe is carcinogenic to humans, but only limited evidence for the carcinogenicity of chewing tobacco (IARC 1985). These conclusions, however, were based on limited studies that did not distinguish between moist and dry snuff, and for which concurrent smoking habits often were not recorded. The meta-analysis of cancer and smokeless tobacco use conducted by Lee and Hamling contained several U.S. studies that reported individual risk values associated with snuff use, with use of chewing tobacco, and with unspecified smokeless tobacco (Lee and Hamling 2009a). Among the referenced studies that provided comparative risks associated with each of the three tobacco product categories, no consistent difference in risk among the various smokeless tobacco products was observed, regardless of disease endpoint. As an illustration (Figure 2.8.2-3), the five cited U.S. studies of "oropharyngeal cancer" containing risk estimates from use of all three product types, using the same population cohort, showed two studies with higher risks attributed to snuff and three studies with higher risks attributed to chewing tobacco.

Figure 2.8.2-3: Comparative risks of oropharyngeal cancer from chewing tobacco, snuff, and nonspecified smokeless tobacco

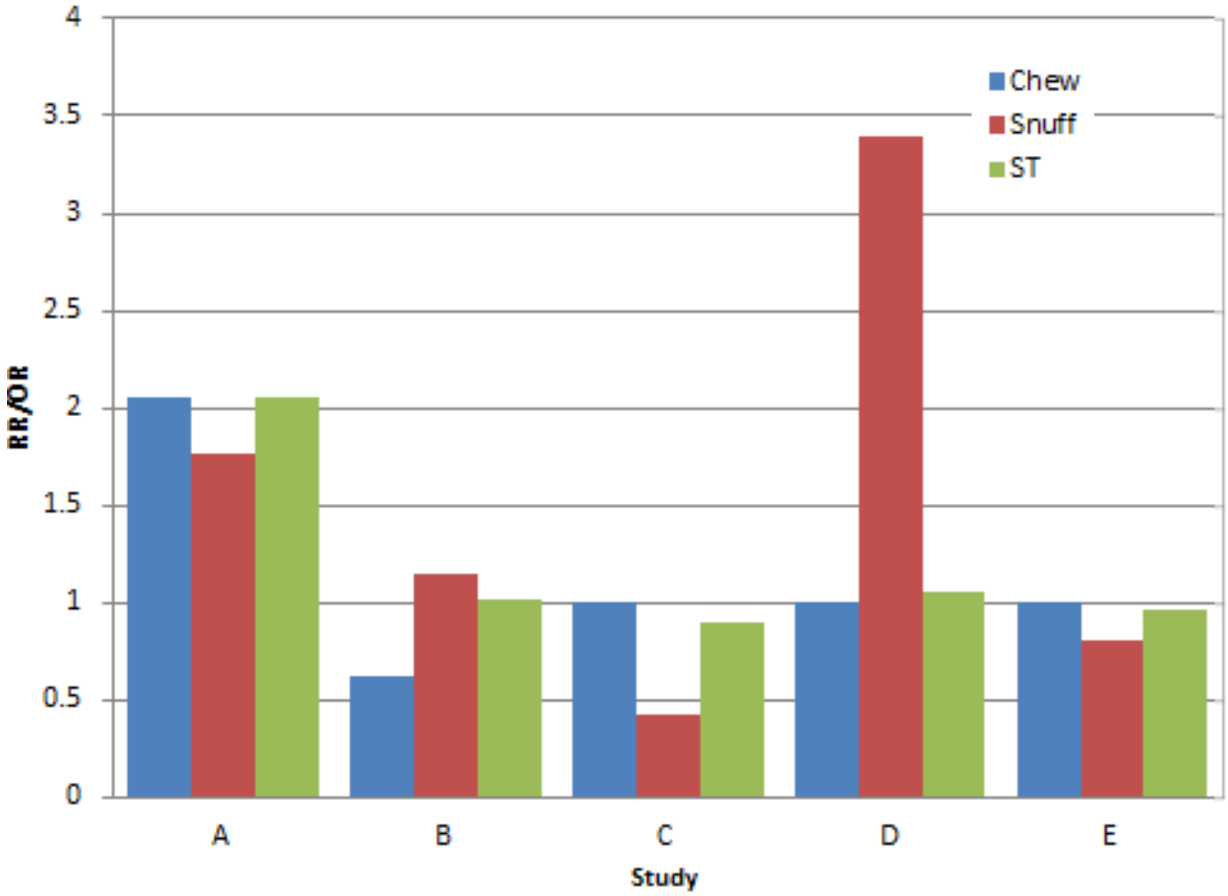


Chart compares risks (RR/OR) determined in U.S. studies of smokeless tobacco use and oropharyngeal cancer as reported in the meta-analysis of Lee and Hamling 2009a; studies from left to right: "A"- Broders 1920; "B"- Wynder and Stellman 1977; "C"- Wynder *et al.* 1983; "D"- Spitz *et al.* 1988; "E"- Mashberg *et al.* 1993. "Chew"- chewing tobacco; "Snuff"- moist or dry snuff; "ST"- smokeless tobacco type not specified

Likewise, the findings of Henley *et al.* 2005, using data from CPS-II in which the majority (74%) of the 2488 men who reported current use of spit tobacco used chewing tobacco only, another 14% used snuff only, and 12% used both products, indicated no consistent or substantial differences between mortality risks from chewing tobacco compared with snuff for all causes combined, all cardiovascular disease, coronary heart disease or lung cancer (Figure 2.8.2-4).

Figure 2.8.2-4: Comparative mortality risks from use of chewing tobacco (chew/never snuff), snuff (snuff/never chew), or combined usage (chew and snuff) – CPS-II data

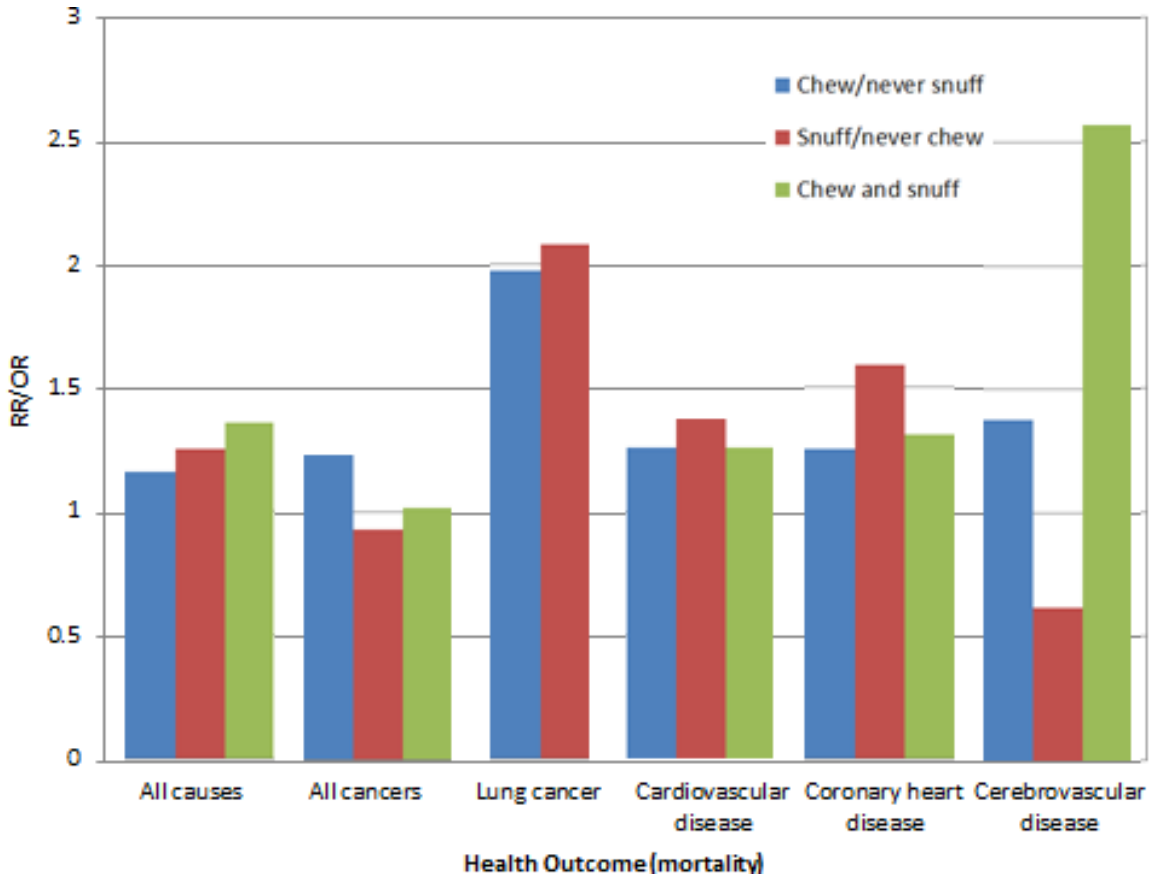


Chart created using data from CPS-II; (Henley *et al.* 2005, Table 4)

Thus, the studies providing risk estimates for all three tobacco product categories (chew, snuff, both chew and snuff) illustrate two important points. First, all tobacco product types displayed low to insignificant increases in risks of mortality from all causes, all cancers, lung cancer, cardiovascular disease, coronary heart disease and cerebrovascular disease. Second, there were no consistent differences in risks presented by the use of chewing tobacco, moist snuff, or both products. These data highlight the low levels of risk associated with use of U.S. smokeless tobacco and the fact that differences in the levels of specific constituents in different forms of smokeless tobacco products (*i.e.*, chewing tobacco vs snuff) do not translate into consistent differences in estimated disease risk, at least as reported in the body of U.S. epidemiological data. These findings add further weight to the relevance of U.S. epidemiological studies to estimate individual health risks associated with Camel Snus, since, as described in Section 2.8.2.4, Section 2.8.2.5, and Section 2.8.2.6, Camel Snus composition and usage patterns fall within the range of U.S. smokeless tobacco products for which established risk estimates are available.

2.8.2.3 U.S. smokeless tobacco products have evolved over the course of decades to lower levels of many harmful and potentially harmful constituents, and Camel Snus continues that evolution

Toxicant levels in U.S. smokeless tobacco have been reported since approximately the 1970s, when analytical techniques capable of detecting known or suspected toxic substances were developed and implemented for smokeless tobacco products. The isolation of NNN from tobacco and cigarette smoke in the early 1970s led to studies of nitrosamines in smokeless tobacco. In 1975, Hecht *et al.* reported NNN levels in samples of "fine-cut" chewing tobacco (reclassified in 1981 as moist snuff) and "snuff" (Hecht *et al.* 1975). TSNAs, particularly NNN and NNK, were initially the only recognized carcinogens in smokeless tobacco, although trace amounts of polycyclic aromatic hydrocarbons (PAHs) and metals were also thought to be present. Subsequent years saw a series of studies, mostly from scientists at the American Health Foundation, reporting the finding of additional nitrosamines as well as other carcinogens such as PAHs and polonium 210, in smokeless tobacco (USDHHS 1986). Nonetheless, focus remained on TSNAs, considered by many to be the major contributors to the potential carcinogenicity of chewing tobacco and snuff (Brunnemann and Hoffmann 1992; NCI 2016**;** Stepanov and Hatsukami 2016). Beginning about 1980, and continuing for at least a decade, substantial reductions in the levels of TSNAs in U.S. smokeless tobacco products were achieved. Individual product brands were generally not provided in published studies of TSNAs, and thus it is not possible to track data for individual brands. However, analytical data from Djordjevic *et al.* 1993 for two "leading U.S. snuff brands" that accounted for 84% of the U.S. market in 1992 indicate that TSNA content was reduced by 70-90% from 1980 to 1992 in these major brands (Table 2.8.2-3; Figure 2.8.2-5).

These changes likely came about through elimination of nitrate-rich tobacco components as well as changes in processing, each of which can lead to major reductions in TSNAs (Brunnemann and Hoffmann 1992). Other investigators have likewise noted reductions in TSNA levels in U.S. smokeless tobacco products over time (*e.g.*, Rodu and Jansson 2004; Hatsukami *et al.* 2007b).

Table 2.8.2-3: Reductions in select TSNAs in two leading U.S. snuff brands, 1980-1992 (from Djordjevic *et al.* 1993, p. 499)

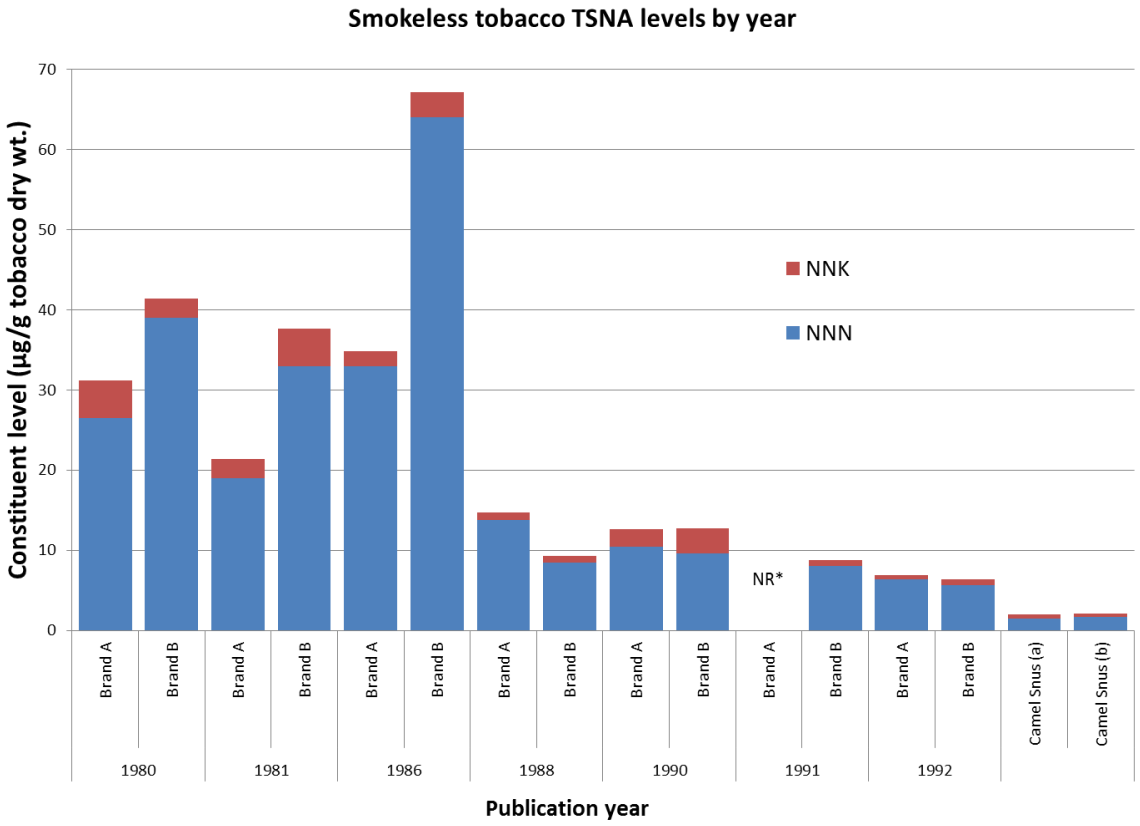
Brand	Year	Tobacco-specific *N*-nitrosamines (µg/g)			Nicotine (%)
		NNN	NNK	NAT*	
USA (A)	1980	26.5	4.65	22.7	2.34
	1981	19.0	2.4	19.8	2.20
	1986	33.0	1.8	44.0	2.07
	1988	13.8	0.93	10.2	1.99
	1990	10.4	2.20	9.8	2.04
	1992	6.4	0.50	3.6	1.71
Reduction 1980-92 (%)		75.8	89.0	84.1	
USA (B)	1980	39.0	2.4	44.0	2.4
	1981	33.0	4.6	41.9	2.7
	1986	64.0	3.1	215	3.07
	1988	8.5	0.76	7.8	2.61
	1990	9.6	3.1	7.9	2.17
	1991	8.0	0.8	6.0	2.1
	1992	5.7	0.7	3.9	2.2
Reduction 1980-92 (%)		85.4	70.8	91.1	

* NAT contains 5-10% NAB.
All values are based on dry weight.

Reductions in TSNAs have also been documented through biomarker data for U.S. smokeless tobacco users monitored over time (*see* Section 6.1.2). Using NHANES data, Rostron and co-workers reported that cotinine concentrations for smokers and smokeless tobacco users were relatively constant over the period 1999 through 2012 (Rostron *et al.* 2015). In smokers, urinary NNAL levels were likewise generally unchanged over the years 2007 to 2012 (the period for which these data were available). In contrast, mean urinary NNAL levels for smokeless tobacco users declined dramatically between 2007 and 2012, from a 2007-2008 geometric mean of 1013.7 pg/mg creatinine to a 2011-2012 mean of 328.6 pg/mg creatinine. The 2007 levels were approximately 3-fold higher than those found for smokers, whereas by 2012, the levels were similar to those found for smokers. Given that serum cotinine levels did not change over this period, the data suggest that the reduction seen in urinary NNAL in smokeless tobacco users reflects a reduction in TSNAs in smokeless products overall, a transition among smokeless tobacco users toward products with lower levels of these constituents, such as snus, or some combination.

Levels of TSNAs in Camel Snus products have likewise been determined and reported in a number of studies, with publications beginning shortly after the introduction of Camel Snus to the U.S. market (*e.g.*, Hatsukami *et al.* 2007b; Stepanov *et al.* 2008a; Borgerding *et al.* 2012) and in internal RJRT studies submitted as part of this Application (*see* Section 6.1.5). These data, when compared with historical data and displayed in Figure 2.8.2-5, illustrate the substantially lower levels of NNN and NNK in Camel Snus compared with historical moist snuff products. The lower TSNA levels in Camel Snus reflect the selection of low-nitrosamine tobaccos and the lack of any fermentation step during Camel Snus processing.

Figure 2.8.2-5: Reductions in select TSNAs in two leading U.S. moist snuff brands, 1980-1992 compared with contemporary Camel Snus



Brand A and Brand B values for moist snuff samples from 1980-1992 obtained from Djordjevic *et al.* 1993; Camel Snus (a), mean of published values for Camel Snus brand styles included in this Application – *see* Table 6.1.5-7; Camel Snus (b), mean of values for all Camel Snus brand styles determined by internal RJRT studies – *see* Table 6.1.5-15. Camel Snus values reported on an "as-is" basis were converted to dry weight based on 32% moisture content.
*NR: not reported

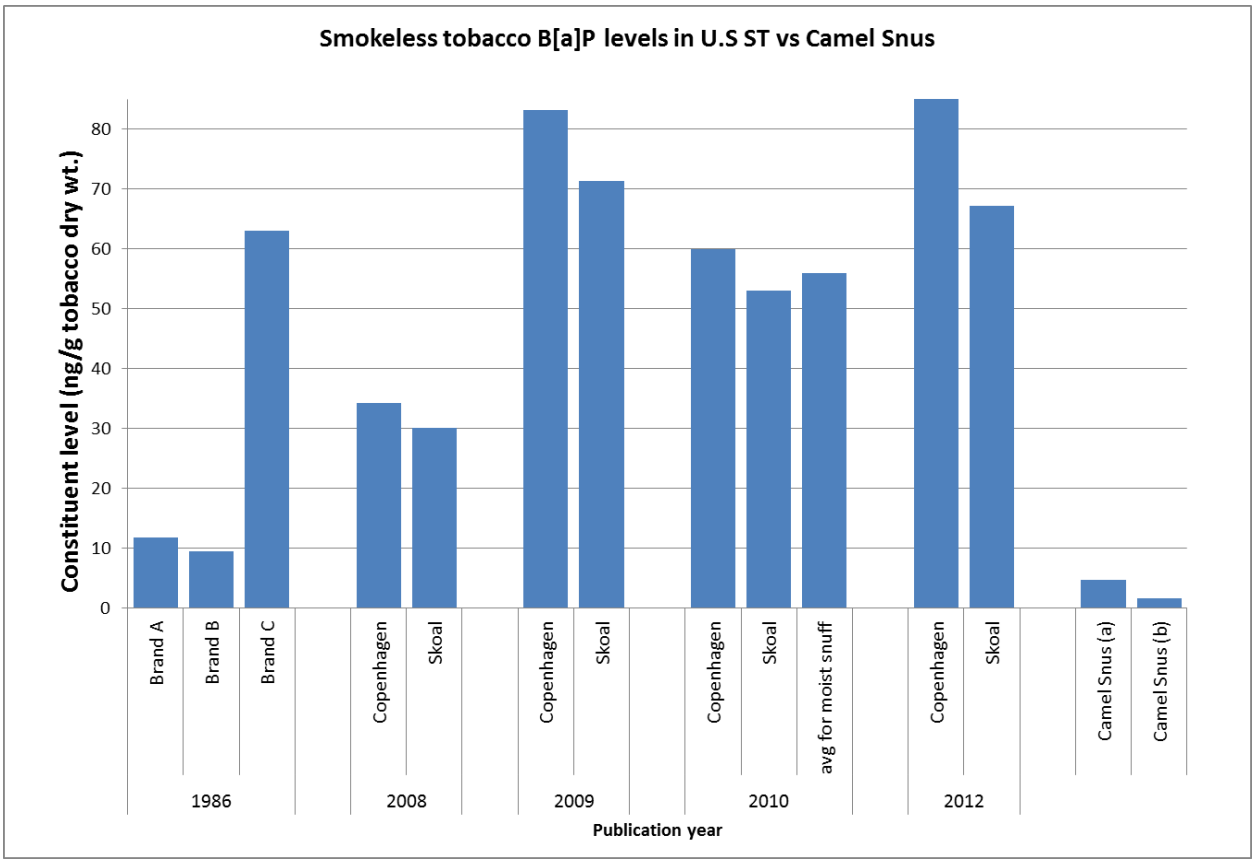
Levels of other smokeless tobacco product toxicants have also been reported for multiple years. For example, published data on PAHs in smokeless tobacco suggest that levels are and have

been variable, likely depending on the amounts of fire-cured tobaccos included in each formulation (McAdam *et al.* 2013). Data on the five most popular U.S. moist snuff brands (specific brands not identified) marketed in 1984-85 indicate levels of B[a]P, the only PAH in tobacco and tobacco smoke classified as a Group 1 carcinogen by IARC, ranged from <0.10 to 63 ng/g (Hoffmann *et al.* 1986). In 2005, moist snuff accounted for more than 80% of total sales of smokeless tobacco (Stepanov *et al.* 2010). During this same period, the moist snuff brands Copenhagen (introduced in 1822) and Skoal (introduced in 1934) accounted for 80% or more of the U.S. snuff market. B[a]P levels for these two market-leading moist snuff brands have been included in reports published in the years 2008 through 2012 (Stepanov *et al.* 2008a; Stepanov *et al.* 2010; Borgerding *et al.* 2012; Rickert *et al.* 2009). B[a]P levels as reported in these publications indicate little change in the B[a]P levels in traditional moist snuff products over at least the past several decades (Figure 2.8.2-6). While traditional moist snuff products have not seen reductions in the levels of PAHs to parallel the reductions in TSNAs in those products, newer smokeless tobacco products, such as snus, have lower levels of these toxicants.

The level of B[a]P has been determined in varieties of Camel Snus and reported in several publications and in RJRT internal studies submitted as part of this Application (Stepanov *et al.* 2010; Borgerding *et al.* 2012; RJR internal studies (*see* Section 6.1.5)). These data, displayed in Figure 2.8.2-6 below, illustrate the substantially lower levels of B[a]P in Camel Snus compared with historical moist snuff products. (b) (4)

. McAdam *et al.* 2013 observed in their analysis of PAHs that good correlations were obtained between B[a]P and all the other PAHs except naphthalene, 1-methylnaphthalene and 2-methylnaphthalene, providing evidence for the first time that even though not fully validated, B[a]P can be used as a reasonable marker for PAHs in smokeless tobacco products.

Figure 2.8.2-6: Levels of B[a]P in major brands of U.S. moist snuff, 1987-2012 compared with contemporary Camel Snus



1986 values for moist snuff from Hoffmann *et al.* 1986; 2008 values from Stepanov *et al.* 2008a; 2009 values from Rickert *et al.* 2009; 2010 values from Stepanov *et al.* 2010; 2012 values from Borgerding *et al.* 2012; Camel Snus (a), mean of published values for Camel Snus brand styles included in this Application – *see* Table 6.1.5-7; Camel Snus (b), mean of values for all Camel Snus brand styles determined by internal RJRT studies- see Table 6.1.5-15. Camel Snus values reported on an "as-is" basis were converted to dry weight based on (b) (4) . Some values were below the analytical method limit of quantitation (LOQ). In those cases, the LOQ was used to calculate the means.

Levels of other smokeless tobacco HPHCs (*e.g.*, formaldehyde, acetaldehyde, crotonaldehyde, arsenic), required for reporting in smokeless tobacco by FDA beginning in 2012, are not often reported in older literature. However, based on available data, Camel Snus exhibits similar or lower levels of these toxicants compared to historical smokeless tobacco products (Hoffmann *et al.* 1986; Hoffmann *et al.* 1987; Stepanov *et al.* 2008a; Borgerding *et al.* 2012). As an example, Hoffmann and co-workers determined levels of a number of toxicants, including several that would later be classified as HPHCs, in a 1987 study of the five most popular moist snuff brands on the U.S. market in 1985-86 (Hoffmann *et al.* 1987). Compared with those historical products, Camel Snus exhibits substantially lower levels (see Table 6.1.5-15; mean values of all six Camel

Snus styles[2]) of acetaldehyde (2.27 vs 5.04 µg/g), crotonaldehyde (0.91 vs 1.48 µg/g), formaldehyde (1.59 vs 13.28 µg/g), cadmium (585 vs 1212 ng/g) and B[a]P (1.57 vs 15.14 ng/g).

Other toxicants have likewise been reduced over time. The U.S. EPA banned the use of maleic hydrazide diethanolamine, a chemical treatment used during tobacco growing, resulting in a reduction in the level of the carcinogen *N*-nitrosodiethanolamine (NDELA) from 6,840 to 94 ppb in snuff, and from 224 to 74 ppb in chewing tobacco; the concentration of another carcinogen, *N*-nitrosomorpholine (NMOR), in one snuff brand fell from 690 ppb in 1981 to a nondetectable level by 1990 following the elimination of traces of morpholine present in the packaging material (Brunnemann and Hoffmann 1992). Cadmium values for moist and dry snuff have remained constant for more than two decades, while lead values in moist snuff have dropped substantially (Borgerding *et al.* 2012).

While the table, graphs and discussion above illustrate the substantial changes in smokeless tobacco product composition since 1980, many of the smokeless tobacco products whose health effects are reflected in U.S. epidemiological studies, particularly the products of long-term smokeless tobacco users, predate those for which toxicant information is available. It is noteworthy that the decline in U.S. smokeless tobacco toxicant levels began only after methods were developed to monitor those toxicants. It is reasonable, therefore, to conclude that toxicant levels of those earliest products were likely higher than products for which measured toxicant levels are available, and most certainly higher than their more contemporary counterparts, such as Camel Snus. For example, it was reported in a 1987 study that during the entire prior decade (1977-1987), there was no indication of a decrease in the concentration of any TSNAs in snuff (Hoffmann *et al.* 1987). The same authors remarked that this observation reflected continued application of the conventional production methods for snuff in the United States during that time period, at least as they relate to the formation of the carcinogenic nitrosamines (Hoffmann *et al.* 1987).

More recently, improvements in sanitation and bacterial control practices, implemented beginning in 2005, have resulted in decreases in the TSNA content of commercial moist snuff manufactured after that time. Using three different moist snuff brands, Fisher *et al.* 2012 showed that high TSNA levels observed after tobacco blend fermentation [a process in the production of moist snuff that can contribute to TSNA formation in those products] in the years 1997 through 2004 had been substantially lowered by 2005, and have remained relatively constant since (Fisher *et al.* 2012). Alternative interpretations of TSNA data published since the early 1990s proposed that these decreases in TSNA content more likely reflect variability rather than a continuous decline (Stepanov and Hatsukami 2016). Stepanov and Hatsukami (2016) also reported substantial differences among the same smokeless tobacco brands over time, different styles within the same brand, significant variation within the same brands, and within specific product varieties when samples were purchased in different locations. Nonetheless, the

[2]For comparisons, Camel Snus values reported in Table 6.1.5-15 on an "as-is" basis were converted to a dry weight basis based on (b) (4) .

available data indicate substantially higher levels of toxicants in 1980 and previous years compared to contemporary smokeless tobacco products, including Camel Snus.

In summary, documented levels of NNN, NNK, B[a]P, and likely many other toxicants, were substantially higher in the historical smokeless tobacco products whose use and health risks are reflected in U.S. epidemiological data. Contemporary smokeless tobacco products contain essentially the same spectrum of constituents as in historical products; however, the levels of many of these toxicants have been reduced significantly in recent decades, with lowest levels found in contemporary snus products such as Camel Snus. Because Camel Snus has levels of toxicants well below the toxicant levels in historical smokeless tobacco products, U.S. epidemiological studies are relevant to evaluate whether Camel Snus presents lower risk for lung cancer, oral cancer, respiratory disease and heart disease than cigarette smoking.

2.8.2.4 All Camel Snus styles are low-nitrosamine products designed, formulated, and manufactured in the same manner as other contemporary Swedish-style snus

As described in Section 2.7 and Sections 3.1 – 3.2 of this Application, Camel Snus is a moist snuff tobacco product that is also Swedish-style snus. It was designed and developed in Sweden using the same elements of product design (*e.g.*, the same tobacco types), the same basic formulation and the same production methods (*e.g.*, heat treatment, rather than fermentation of the tobaccos) as other snus manufactured in Sweden. In 2006, RJRT issued product specifications and product quality standards to a manufacturer of Swedish snus (Fiedler and Lundgren (F&L)), located in Malmo, Sweden, for the manufacture of Camel Snus Frost for initial testing. Camel Snus was created using a (b) (4) [redacted]. Commercial production of Camel Snus began in April 2006 for lead market launch in the U.S. Products were air-shipped from Sweden prior to distribution to U.S. markets. Commercial production in Sweden continued through April 2007. During 2006, RJRT obtained (b) (4) [redacted] (b) (4) [redacted] the production of Camel Snus in Winston-Salem, NC. Commercial U.S. production of Camel Snus began in Winston-Salem in June 2007. The product has been made there continuously since that time.

Contemporary Swedish-style snus products, including Camel Snus, incorporate manufacturing changes and improvements that have been developed over decades, which result in modern smokeless tobacco products with lower levels of HPHCs and a high degree of quality control compared with smokeless tobacco products on the market in the 1970s – 1990s, and almost certainly as compared to products prior to the 1970s.

2.8.2.5 Historical usage patterns of smokeless tobacco products reflected in U.S. smokeless epidemiological studies suggest higher levels of toxicant exposures compared to use of contemporary products, including Camel Snus

The extent of exposures to toxicants in smokeless tobacco is determined by several factors, but primarily, the toxicant content of the product and the manner in which that product is used by the individual. The discussion above has demonstrated that compared with historical smokeless tobacco products represented in U.S. epidemiological studies, contemporary smokeless tobacco products, including Camel Snus, contain similar types of toxicants, many present at lower levels than for historical products for which direct measurement comparisons can be made.

Detailed information on product use patterns from individual epidemiological studies is generally not available. However, there is scientific literature that describes tobacco use behaviors characteristic of the years and types of products reflected in U.S. epidemiological studies. Because there is substantial variation in smokeless tobacco use behaviors among individuals, these "typical" values should be interpreted as rough averages.

A 1981 study by Glover and co-workers (Glover *et al.* 1981) described differences in use of chewing tobacco (the dominant form of smokeless tobacco until approximately 1996; *see* Figure 2.8.2-2) and "dipping tobacco" (moist snuff). A "quid," "pinch" or "dip" is a small portion of any smokeless tobacco which is held in the mouth for dipping (snuff) or chewing (leaf or plug). Some persons keep a quid in place 24 hours a day. This same study reported the average user of chewing tobacco consumes 85 g per week or slightly more than 12 grams/day. Greer and co-workers reported that the average exposure duration among teen-age users ranged from 53 to 177 minutes per day (Greer and Poulson 1983). The 1985 IARC Monograph addressing smokeless tobacco use cited studies reporting that moderate chewers experienced exposure durations of up to 200 minutes per day, and more for heavy chewers. Moist snuff consumers used on average 1.5 tins (tin size 1.2 oz. or 34 g) per week (51 g total) or approximately 7.3 grams/day; many users had initiated their use before age 10 and had used snuff for 40 years (IARC 1985).

More detailed information on smokeless tobacco product use behaviors was provided in a 1988 study by Hatsukami and co-workers (Hatsukami *et al.* 1988). Study results indicated that on average, moist snuff users took 6.3 dips per day, with each dip on average consisting of approximately 2 grams of tobacco, which was held in the mouth approximately 40 minutes. Thus, the average consumer used approximately 12 grams per day with a total duration of usage per day of 250 minutes or 4.2 hours. Each of these observed values exhibited considerable variability among the individual study participants. Thus, individual exposure to HPHCs depended on the amount of product taken in a "pinch," the number of dips taken per day and the time each dip was held in the mouth. Other studies observed smokeless tobacco product usage behaviors generally in agreement with those reported by Hatsukami *et al.* (1988) with the number of dips per day of non-portioned smokeless tobacco products ranging between 6 – 10, with a dip duration lasting from 39 – 71 minutes (Hatsukami *et al.* 1991; Oliver

et al. 2013; Lemmonds *et al.* 2005). Combining the data on pinch size and dips per day suggests a range for daily consumption of loose moist snuff to be on the order of 6 – 20 grams per day.

Regarding the relationship between usage behaviors and nicotine and likely other toxicant exposures, data has shown a stronger correlation with frequency and duration of smokeless tobacco product use than with the amount of tobacco used (Hatsukami *et al.* 1988; Lemmonds *et al.* 2005).

Data on Camel Snus usage have been reported in a number of published studies (*e.g.*, Blank and Eissenberg 2010; O'Connor *et al.* 2011; Hatsukami *et al.* 2011; Caraway and Chen 2013; Ogden *et al.* 2015a; Hatsukami *et al.* 2016), as well as in internal clinical studies conducted by RJRT (*see* Section 6.1.2.3; Table 3.5.2-1). Considering usage only of products in 0.6 g and 1.0 g pouch sizes (the product sizes submitted in this Application), pouches used per day among exclusive Camel Snus users ranged from 3.8 – 6.4, while dual users of Camel Snus and cigarettes consumed lower amounts (2.2 – 6.0 pouches) (*see* Table 3.5.2-1). For example, a published clinical study of mouth-level exposure to tobacco constituents among adult Camel Snus users in the United States (Caraway and Chen 2013) indicated that overall mean (± standard deviation) Camel Snus consumption among exclusive users was 5.4 (± 3.7) pouches per day. However, dual users of Camel Snus and cigarettes (49% of the study subjects) consumed only 2.8 (± 1.2) pouches per day. Most (88.7%) subjects in this study reported using one pouch at a time, while 11.3% reported using two or more pouches simultaneously; 26% of participants kept Camel Snus in their mouth for less than 10 minutes, 47% of participants kept Camel Snus in their mouth for between 10 and 30 minutes, and 26% of participants kept Camel Snus in their mouth for greater than 30 minutes. Converting the above consumption data from pouches per day to amount of tobacco per day using the nominal pouch weight of 0.6 g of the study products results in usage of approximately 3.24 grams per day for exclusive users. Internal RJRT clinical studies indicate similar amounts of Camel Snus used per day among exclusive users, ranging from 2.28 – 3.84 grams/day (Table 3.5.2-1), and lower usage among dual users (1.44 – 3.30 grams/day).

RJRT has also conducted studies of tobacco use behaviors, including behaviors of current Camel Snus users, using survey data from the RAIS National Tobacco Behavior Monitor, and confirmed by RJRT's Consumer Brand Tracker and in some instances, by the NIH/FDA-sponsored PATH study (*see* Section 3.5). Data from these analyses demonstrate that adult users of Camel Snus are similar to other contemporary smokeless tobacco users, including patterns of tobacco use and frequency and rate of use of smokeless tobacco. Greater than 90% of Camel Snus users are dual/poly users of other combustible and/or non-combustible tobacco products. Most (~85%) Camel Snus consumers use the product less than daily with a mean frequency of use of 2 – 3 days/week, and at a rate of 3 – 4 pouches per day. Usage data for historical smokeless tobacco products and Camel Snus are summarized in Table 2.8.2-4 below.

Table 2.8.2-4: Patterns of smokeless tobacco use: historical products and Camel Snus

Smokeless Tobacco Usage Metric	Smokeless Tobacco product	Value	Data Source
Average # of uses per day			
	Historical smokeless tobacco products	6 – 7.2 dips	A,B,C
	Camel Snus	3.8 – 6.4 pouches (excl.)	D
	Camel Snus	2.2 – 6.0 pouches (dual)	D
Average portion size			
	Historical smokeless tobacco products	~2.0 grams (a "pinch")	A
	Camel Snus	0.6 – 1.0 grams (1 pouch)	D
Average amount used per day			
	Historical smokeless tobacco products	7.3 – 20 grams	A, E, F
	Camel Snus	3.24 – 5.30 grams (excl.)	D
	Camel Snus	1.44 – 5.80 grams (dual)	D
Average duration per use			
	Historical smokeless tobacco products	~40 min – ~70 min	A,B,C
	Camel Snus	~ 30 min	G
Average total time of use per day			
	Historical smokeless tobacco products	0 – 24 h	E
	Historical smokeless tobacco products	53 – 423 min	A,C,F,H
	Camel Snus	84 – 150 min	G

Data sources: A, Hatsukami *et al.* 1988; B, Hatsukami *et al.* 1991; C, Lemmonds *et al.* 2005; D, Table 3.5.2-1; E, Glover *et al.* 1981; F, IARC 1985; G, Caraway and Chen 2013; H, Greer and Poulson 1983.
"excl."- exclusive users of Camel Snus; "dual"- dual users of Camel Snus and cigarettes

In addition to smokeless tobacco usage patterns described above, data indicate that both nicotine uptake and the extraction of TSNAs are higher from loose snuff than from portion packed snuff (Andersson *et al.* 1994; Ahlbom *et al.* 1997). Similarly, Rodu and Jansson 2004 noted that TSNA levels in more contemporary, traditional American non-pouched moist snuff products ranged from 7.3 to 12.3 ppm, which is lower than historical levels, but that three American pouched moist snuff products had TSNA levels from about 5 to 7 ppm, and thus lower than those found in loose moist snuff (Rodu and Jansson 2004).

In summary, use behavior of smokeless tobacco products generally is, and has been, highly variable, whether portioned or not. However, overall comparisons of usage behaviors between Camel Snus users and users of other smokeless tobacco products that are represented in historical U.S. epidemiological studies suggest usage patterns that would result in similar or lower levels of exposures among Camel Snus users.

2.8.2.6 The health risks presented Camel Snus users are reasonably estimated, or overestimated, by existing epidemiological studies of U.S. smokeless tobacco users based on Camel Snus's similar or lower toxicant profile and similar tobacco use patterns among smokeless tobacco users

As discussed above in Section 2.8.2.4, Camel Snus is a U.S. moist snuff product with many characteristics, both in composition and manner of use, that are shared with historical U.S. smokeless tobacco products. U.S. smokeless tobacco epidemiological studies provide clear evidence that smokeless tobacco presents substantially lower risk than that associated with cigarette smoking (*see* Section 6.1.1).

To date, no clinical, epidemiological or longitudinal study has specifically investigated the possible differential health effects of smokeless tobacco products containing different levels of toxicants (Stepanov and Hatsukami 2016). In the absence of such studies, Stepanov and Hatsukami suggested examining the incidence of smokeless tobacco-related disease across countries that market products that differ in the levels of these harmful constituents. For example, the question, "Do higher levels of toxicants account for higher oral cancer risk for smokeless tobacco users in India compared to smokeless tobacco users in Sweden?" might be investigated. The authors also suggested that perhaps observations about changes in smokeless tobacco product constituent levels over time could be equally informative. As an example, the authors noted the finding of a strong association between smokeless tobacco use (most likely, dry snuff) and oral cancer by Winn *et al.* 1981 (RR= 4.2, 95% CI: 2.6 – 6.7) compared to results from a more contemporary cohort that found a statistically non-significant elevation in oral cancer risk (OR = 2.88; 95% CI: 0.68 – 12.25) in individuals who reported 10 or more years of smokeless tobacco use (Zhou *et al.* 2013). The U.S. Surgeon General and other authors have stated that it is likely that current smokeless tobacco users have less risk than users of four or five decades ago (Rodu and Jansson 2004; USDHHS 2010). The time period for smokeless tobacco use covered by U.S. epidemiological studies has spanned a century or more, and represented many smokeless tobacco products with different toxicant levels and manners of use, resulting in toxicant exposures that were likely higher than in more recent cohorts.

In summary, individual health risks associated with Camel Snus use are reasonably approximated, or possibly overestimated, by existing epidemiological studies of U.S. smokeless tobacco users. The key evidence supporting this conclusion is:

1) the toxicant levels in Camel Snus are similar to, or lower than, levels observed in U.S. smokeless tobacco products that have been in use for much of the last century (*i.e.,* the products used in the available epidemiological studies among U.S. smokeless tobacco users).

2) tobacco use patterns observed with Camel Snus equate to either similar or possibly lower toxicant exposures compared to what has been historically observed.

3) the studies include U.S. smokeless tobacco users, incorporating characteristics relevant to the population of current and future U.S. Camel Snus users.

2.8.3 Swedish epidemiological data are relevant for estimating individual disease risk for users of Camel Snus

There is a significant body of epidemiological data that estimates the risks to individual Swedish-style snus users for tobacco-related diseases. The relevance of epidemiological studies of Swedish snus users in estimating tobacco-related disease risks to individual Camel Snus users is evident from a detailed consideration of the composition and use patterns of Swedish snus products represented in those studies.

FDA has previously stated that epidemiological studies on the health risks of Swedish snus may be relevant to support an MRTPA for Camel Snus products, provided that evidence is presented demonstrating that Camel Snus products are comparable to the products represented in such studies in terms of the characteristics that may influence disease risk (FDA 2014). Evidence is presented in this section in the same manner as presented for U.S. studies. Results of epidemiological studies among users of snus in Sweden are consistent with results from comparable studies of U.S. smokeless tobacco. As such, epidemiological studies of Swedish snus users inform and confirm the substantially lower health risks for exclusive Camel Snus use compared with smoking, and thus support the proposed modified risk advertising in this Application.

Contemporary Swedish smokeless tobacco products share similar levels of toxicants and manners of use with Camel Snus. It is important to note, however, that contemporary Swedish snus products were not in use during the conduct of available epidemiological studies conducted in Sweden. Rather, historical snus products used in Sweden for decades are the basis for health risks reported in published epidemiological studies of Swedish smokeless tobacco users. In a manner parallel to the review of U.S. smokeless tobacco epidemiology in Section 2.8.2, the following sections review the time periods of smokeless tobacco use represented in Swedish studies and consider: the types of smokeless tobacco products in use during those periods, the levels of toxicants present in the products and the manner of product use. The characteristics of Camel Snus are compared to the results of that assessment and provide support for the relevance of Swedish epidemiological data in estimating the health risks from Camel Snus use compared to cigarette smoking. Epidemiological studies of Swedish snus users inform and confirm the substantially lower health risks for exclusive Camel Snus use compared with smoking, and thus support the proposed modified risk advertising in this Application.

Strengthening the relevance of Swedish epidemiology for evaluating Camel Snus risk is the fact that differences in risk between smokers and smokeless tobacco users in Sweden mirror those reported for these respective groups of U.S. tobacco users. As an illustration, data from the Swedish prospective cohort study of Nilsson *et al.* 2001 and U.S. CPS-II data reported in several

studies serve as an appropriate comparison, as both study designs, ages of the participants, cigarettes smoked per day (cpd) (in CPS-II, male smokers averaged 25.4 cpd), and other characteristics of the studies and their participants were most similar.

These studies collectively show similar levels of risks for smoking-related diseases for Swedish smokers as compared with U.S. smokers. At least two broad conclusions may be drawn from these findings. First, the Swedish smoking population is similar to the U.S. smoking population in regard to their smoking behaviors as well as their susceptibility to and degree of risk for smoking-related diseases. Second, given similar levels of exposure (cpd), Swedish cigarettes present a similar level of risk to smokers as do U.S. cigarettes. Taken together, these data indicate that an individual U.S. smoker may experience the same magnitude of risk reduction after exclusive adoption of Camel Snus as has been seen for decades among Swedish smokers who switched to snus use.

Table 2.8.2-5: Comparison of relative risks for smoking-related diseases between U.S. and Swedish male smokers

	Swedish smokers		U.S. smokers	
	Relative risk (95% CI)	**Exposure cigarettes/day**	**Relative risk (95% CI)**	**Exposure cigarettes/day**
Lung cancer	20.6 (13.5 – 31.4)	16 – 25	23.2 (19.3 – 27.9)[a]	25.4[d]
	25.8 (13.9 – 48.1)	>25	21.3 (17.1 – 25.6)[b]	25.4
COPD	8.46 (5.15 – 13.9)	8 – 15	9.65 (7.00 – 13.30)[c]	25.4
	15.9 (9.34 – 30.0)	16 – 25	10.8 (8.4 – 13.9)[b]	25.4
Oral cancer	2.24 (0.96 – 5.24)	8 – 15	NR	25.4
	6.84 (3.33 – 14.1)	16 – 25	8.1 (5.7 – 11.7)[b]	25.4
Coronary heart disease	1.70 (1.46 – 1.97)	16 – 25	1.94 (1.80 – 2.08)[c]	25.4
	2.01 (1.48 – 2.74)	>25	1.9 (1.8 – 2.1)[b]	25.4

Risks for Swedish smokers were obtained from Nilsson *et al.* 2001; risks for U.S. smokers were obtained from CPS-II data reported in: a) Thun *et al.* 1995; b) Thun *et al.* 2000; c) USDHHS 1989; d) CPS-II male smokers used an average of 25.4 cigarettes per day. NR = not reported.

Swedish epidemiological studies thus provide important information on the risks for many tobacco-related diseases. However, the studies have provided limited, if any, specific information regarding the individual snus products used by study participants. Rather, study participants used the marketed snus products available to them during and prior to the study periods of interest. As such, results from epidemiological studies among Swedish-style snus users collectively represent both the different product types (*e.g.,* loose and pouched products) and different brands of snus used by the individuals enrolled in the study. During the studies, it is possible that some individuals switched snus brand or type, switched from smoking to snus uses or varied the manner in which they used tobacco products.

This section summarizes literature and data on historical Swedish snus products and use behavior characteristics that would best correlate with the periods of smokeless tobacco use represented in relevant epidemiological studies. As described below, Swedish epidemiological studies collectively represent a range of products, rather than a single product, with toxicant content and associated product use characteristics that have consistently proven to be far less harmful than cigarette smoking. Camel Snus product characteristics, toxicant content and manner of use fall within that range of Swedish snus products in the Swedish epidemiological literature.

2.8.3.1 Swedish epidemiological studies represent snus products in use from the 1930s to contemporary time periods

The period of Swedish snus use assessed in epidemiological studies of Swedish snus users is estimated to span the years from the mid-1930s to approximately 2007. This estimate is based on available snus use data obtained from each Swedish epidemiological study cited in the Ramboll Environ systematic review (Ramboll Environ 2016). Generally, Swedish epidemiological studies report demographic data including calendar years of recruitment, duration of follow-up, ages of participants, duration of snus use and age at time of health assessments. Age of snus initiation was not provided in any of the cited epidemiological studies, but was estimated to be approximately 20 – 25 years (Ramström and Foulds 2006; Andersson *et al.* 1994), although some studies report higher ages of initiation for some users due to snus use as an aid in smoking cessation (Huhtasaari *et al.* 1999; Ramström 2000). Based on the information contained in the Swedish epidemiological studies, it is likely that snus use assessed in those studies could have started as early as the mid-1930s (or earlier in some cases) and included use as recently as 2007. Three representative examples of major Swedish epidemiological studies where information supports this estimated range for product use are summarized below.

First, Bolinder *et al.* 1994 examined the possible association between snus use and cardiovascular mortality using data from one of the most significant cohorts applicable to Swedish snus research, the Swedish Construction Industry's Organization for Working Environment, Safety and Health Cohort. The epidemiological studies based on this cohort collected data on snus use over the 24-year period from 1969 – 1993, but reflect the cumulative risk of snus use that most likely began decades earlier. Bolinder *et al.* 1994 used data collected from medical checkups conducted from 1971 – 1974, and included three groups of study participants, stratified by age (<35 years, 35 – 54 years, and 55 – 65 years). Members of the oldest cohort who initiated snus use at age 20 would have done so as early as 1935, with some using snus at least until the close of the follow-up period in 1985.

As a second example, Arefalk *et al.* (2011) examined the possible association between snus use and hospitalization for heart failure. One of the study cohorts, the Uppsala Longitudinal Study of Adult Men, consisted of men who were 50 years old in 1970 – 1973. The cohort was revisited in 1991 – 1995 when participants were approximately age 71. Subjects were then followed until 2002. Members of this cohort who initiated snus use at age 20 would have done so around

1945, with members of the cohort using snus at least until the close of the follow-up period in 2002.

Finally, the study of Nordenvall *et al.* 2013, the most recent of the Swedish epidemiological studies cited in the Ramboll Environ systematic review (Ramboll Environ 2016), followed study subjects until 2007. Thus, it is important to recognize that Swedish epidemiological studies represent the use of products formulated and used as early as the 1930s and as recently as 2007.

2.8.3.2 The types of smokeless tobacco products reflected in the results of published Swedish epidemiological studies represent a range of "Swedish snus" products

Given the time periods of snus use associated with the epidemiological studies discussed in the previous section and reviewed in Section 6.1.1., it is not surprising that the Swedish snus products used during those studies changed and evolved. Snus products in the 1950s and earlier decades were made by a number of different manufacturers, yet all used recipes and production techniques similar to those employed during the 1800s (Rutqvist *et al.* 2011). As late as the 1960s, Swedish snus continued to be manufactured using many of the same processes and formulations as in the 1800s, albeit with slightly higher heat treatment temperatures to decrease problems related to microbial contamination, a then-unrecognized source of tobacco-specific nitrosamines. Products were packaged as loose snus, typically in 50 g containers. Pouched snus products (typically 1 g portion size) were introduced in the mid-1970s, where upon both loose snus and pouched styles became popular. Since 1970, a trend towards greater use of pouched snus has been evident, with ~75% loose snus use in 1992 (Andersson *et al.* 1994) falling to 41% in 2009 (Digard *et al.* 2009).

Quality problems, coupled with the inclusion of snus under the jurisdiction of the Swedish Food Act in 1971, prompted the introduction of more modern snus manufacturing facilities with additional quality assurance and quality control initiatives successively introduced from the 1970s through the 1990s. The routine monitoring of the chemical properties of snus was greatly expanded during those years. Assays of tobacco-specific nitrosamines (TSNAs) were introduced in 1984 and extensive, annual chemical testing of all snus brands started in 1988.

Thus, Swedish snus products and manner of use changed significantly during the time period of interest. Improvements in tobacco heat treatment and manufacturing quality control resulted in reduced product toxicant levels (*see* additional discussion in the next section). A trend toward pouched vs. loose snus products resulted in a different manner of use compared to products produced decades earlier. Long-term snus users would likely have used all of these products over the years. It is these users whose health outcomes are documented in Swedish epidemiological studies.

To emphasize the changing nature of Swedish smokeless tobacco over time, Ahlbom *et al.* 1997 noted that "… 'Snuff' is not really a homogeneous concept, even if referring to Swedish moist snuff, since there are differences between both loose snuff and portion-packed snuff, and between different types of loose snuff. These differences concern both levels of nitrosamines

and nicotine, and pH" (Ahlbom *et al.* 1997). Thus, the Swedish epidemiological studies cited in the Ramboll Environ systematic review (Ramboll Environ 2016) and discussed in other sections of the Application certainly represent use of a relatively broad spectrum of products of varying design and composition, all considered to be "Swedish snus" and treated as such in epidemiological studies.

2.8.3.3 The trend for Swedish snus products over several decades has been toward lower levels of toxicants

Limited data exist regarding constituents in Swedish snus prior to the late 1970s. The discussion in this section focuses on TSNAs and PAHs, two classes of carcinogens most frequently measured in smokeless tobacco. Much attention in the scientific literature has been paid to tobacco-specific nitrosamines (TSNAs), once the only known carcinogenic substances in snuff (Hoffmann and Adams 1981). TSNAs are now considered significant carcinogens in tobacco and tobacco smoke (Österdahl *et al.* 2004) and central to the carcinogenic potential of smokeless tobacco (Stepanov and Hatsukami 2016). A major source of TSNA formation in some types of smokeless tobacco is the fermentation of tobacco during the manufacturing process. For example, tobacco fermentation is common for U.S. moist snuff products; however, it is not for the tobaccos in loose leaf products. Similarly, the tobaccos in Camel Snus are not fermented.

Some reports state that before the early 1980s, fermentation was also a part of Swedish snus manufacture before a switch to a non-fermentation method using a heat treatment process (Ramström 2000; Rosenquist *et al.* 2005), while others claim that this view is erroneous (ENVIRON 2010; ENVIRON 2013). Regardless, according to Österdahl *et al.* 2004, TSNA levels in Swedish snus decreased beginning sometime in the 1980s, from 7.3 µg/g wet weight (for a product with a 50% moisture content) in 1983 to 4.4 µg/g in 1992.

Österdahl *et al.* 2004 reported results from a survey of 23 different 2002 market samples from 8 manufacturers in Sweden revealing a similarly low level and narrow range of total TSNAs (0.15 – 3.0 µg/g wet weight; 55% moisture content). The authors noted that during the past two decades (1984 – 2004) moist snuff products (snus) on the Swedish market had exhibited a decrease in TSNAs of approximately 85%. This magnitude of reduction would indicate that TSNA levels were between 1 and 20 µg/g wet weight for products in the Swedish market prior to 1984. TSNA levels in Swedish market samples from 1983 to 2002 are illustrated in the table below (Table 2.8.3-1 below; adapted from Österdahl *et al.* 2004).

Table 2.8.3-1: Levels of tobacco-specific N-nitrosamines in moist snuff on the Swedish market in 1983 – 2002[a] (from Österdahl *et al.* 2004)

				Tobacco-specific *N*-nitrosamine content (µg/g)				
Sample	Country of Origin	Year	No. of brands[b]	NNN	NNK	NAT	NAB	Total
Moist snuff	Sweden	1983	16 (32)	3.8	0.80	2.5	0.17	7.3
		1986	18 (34)	4.3	0.75	2.9	–[c]	8.0
		1992	20 (20)	1.9	0.64	1.9	–	4.4
		2001	10 (10)	0.53	0.22	0.35	0.03	1.1
		2002	23 (27)	0.49	0.19	0.32	0.03	1.0

[a] All values are based on wet weight.
[b] Number in parentheses is the number of samples analyzed.
[c] NAB content is included in the figure for NAT.

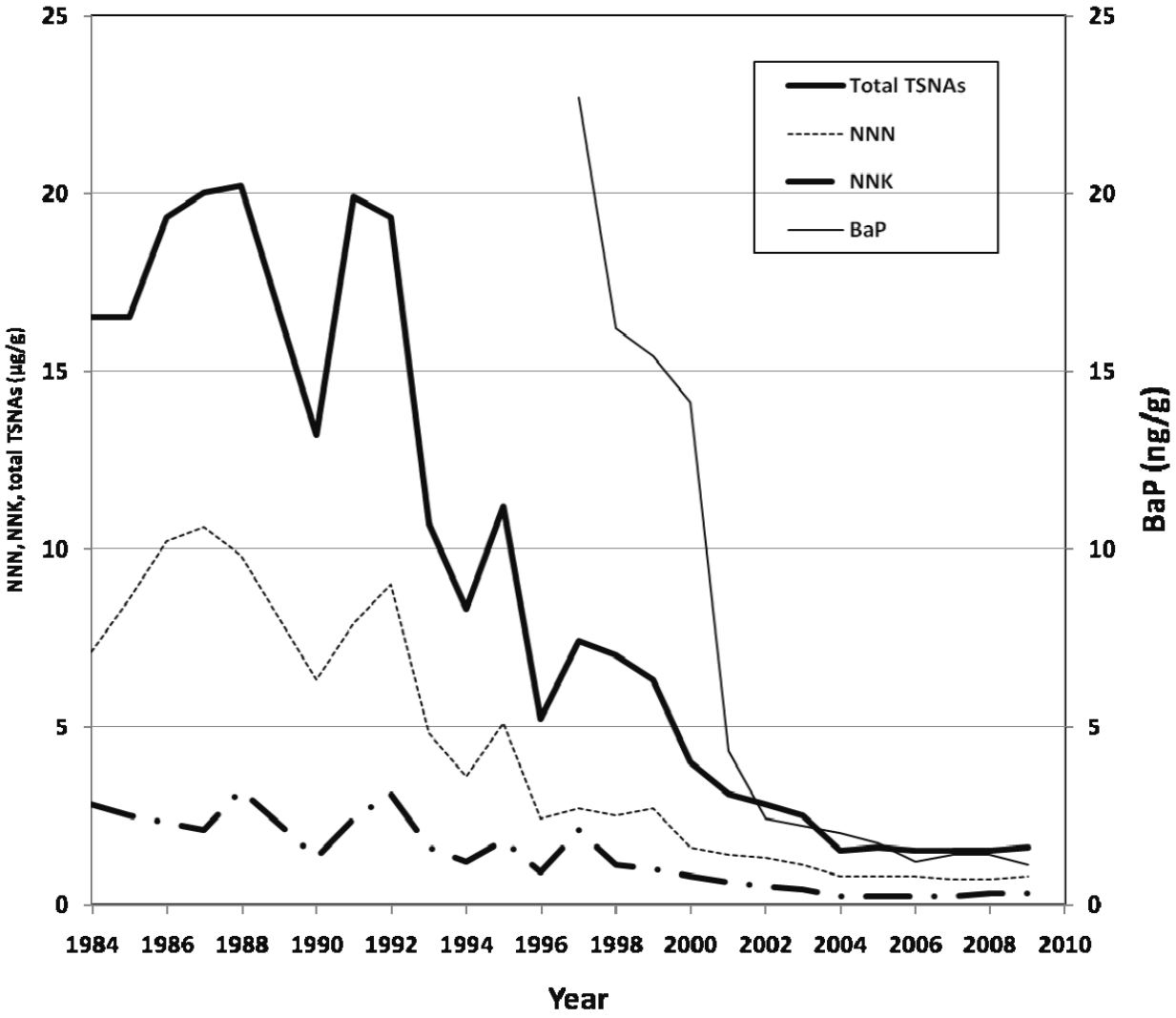
A 1983 publication reported that mean levels of volatile *N*-nitrosamines in Swedish snuff products sampled in 1982 were 92% lower than products from 1979 (Österdahl and Slorach 1983). The authors proposed that the dramatic reductions observed were likely due to better control of nitrosamine-forming bacterial content in the products. Thus, available data consistently indicate that nitrosamine levels in Swedish snus products have decreased over time and that the levels present in products used during the time course of Swedish epidemiological studies were considerably greater than in products available in Sweden today. Additionally, the data indicate that the levels present in products used during the time course of Swedish epidemiological studies were considerable greater than Camel Snus styles.

Polycyclic aromatic hydrocarbons, including the IARC Group 1 carcinogen B[a]P, have also been reported in smokeless tobacco products in Sweden (Stepanov *et al.* 2008a; Stepanov *et al.* 2010; McAdam *et al.* 2013). PAHs do not occur naturally in plant material, and where present, are due to contamination from combustion residue. In some types of smokeless tobacco, most PAHs originate from the use of fire-cured tobaccos, with the levels of PAHs generally tracking with the proportion of fire-cured tobaccos included in tobacco blends (McAdam *et al.* 2013). Although PAHs occur as complex mixtures of numerous individual PAH constituents, it has been recently shown that B[a]P can be used as a reliable surrogate marker for many PAHs that are found in smokeless tobacco (McAdam *et al.* 2013). Awareness PAHs in smokeless tobacco gained attention with mention in the 1985 IARC report on smokeless tobacco, followed by reports of more detailed analysis (Hoffmann *et al.* 1986) in subsequent publications. During the 1990s, fire-cured tobaccos were phased out of Swedish snus. As a result, levels of B[*a*]P in finished snus products decreased from around 25 ng/g to less than 2 – 3 ng/g dry weight (Rutqvist *et al.* 2011). Therefore prior to the 1990s, Swedish snus products contained higher levels of B[a]P and likely higher levels of many other PAHs.

Data presented in the figure below illustrate the reductions in the levels of total TSNAs, NNN, NNK, and B[a]P (Figure 2.8.3-1; adapted from Rutqvist *et al.* 2011) that have been reported for Swedish snus products. Swedish snus TSNA and PAH data indicate higher levels in products

prior to 1980 with a gradual lowering of levels to those found presently in contemporary snus products.

Figure 2.8.3-1: Average levels of NNN (N'-nitrosonornicotine), NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone), and total TSNAs, and B[a]P (dry weight) in Swedish Match's snus products 1984 – 2009 (from Rutqvist *et al.* 2011; data based on internal Swedish Match documentation)



Data regarding other potentially harmful constituents (such as aldehydes, metals, radionuclides) in Swedish smokeless tobacco products from prior decades are generally not available. However it is possible that improvements in tobacco growing, curing and processing, together with a greater awareness of the toxic constituents present in smokeless tobacco have led to lower current levels. What is clear is the fact that the levels of TNSAs and B[a]P present in Swedish snus in the past have been greatly reduced. For example, Johansson *et al.* 2005 remarked that the composition of snuff (snus) has changed substantially over the years since the Construction Worker cohort was first formed and that smokeless tobacco on the Swedish

market now is practically free from nitrosamines. They further comment that this change in the composition of snuff could imply that the results from the construction worker study (indicating an increased risk of CVD death) are no longer applicable.

2.8.3.4 All Camel Snus styles are contemporary, low-nitrosamine, Swedish-style snus products and exhibit lower levels of toxicants compared with historical Swedish snus products

As previously described in Section 2.8.2.4, and in greater detail in Section 3.1 – 3.2 of this Application, all Camel Snus styles are Swedish-style snus products manufactured with the same types of tobaccos and processes used in Sweden today. TSNAs are among the few constituents in snus products that have been tracked over several decades. According to a 2008 study, TSNAs have become a reference group of carcinogens in smokeless tobacco products, with their levels to some degree defining the degree of potential health risk (Stepanov *et al.* 2008a).

Comparison of TSNA levels in Swedish snus products since 1980 shows (1) that toxicant levels found in Camel Snus are comparable to other snus products today and (2) that toxicant levels in Swedish snus have declined since 1980. As summarized in Table 2.8.3-2 and illustrated in Figure 2.8.3-2, combined levels of NNN and NNK in Swedish snus market samples have ranged from 5050 to 680 ng/g wet weight beginning in 1980 through 2016.

Table 2.8.3-2: Camel Snus vs. other Swedish-style Snus: contemporary and historical TSNA data

		NNN ng/g	NNK ng/g	NNN+NNK ng/g	Data Source
Swedish Snus 1980	avg of 4 brands	3195	772	3967	1
Swedish Snus 1983	avg of 16 brands	3800	800	4600	2
Swedish Snus 1986	avg of 18 brands	4300	750	5050	2
Swedish Snus 1992	avg of 20 brands	1900	640	2540	2
Swedish Snus 2001	avg of 10 brands	530	220	750	2
Swedish Snus 2002	avg of 23 brands	490	190	680	2
General Snus 2002		1200	280	1480	3
General Snus 2003		780	75	855	3
Swedish Snus 2006-7*	avg of 5 brands	736*	275*	1011	4
General Snus 2006-7*		855*	239*	1094	5
Camel Snus (a)	published values	1010	370	1380	6
Camel Snus (b)	internal RJRT studies	1130	332	1462	6

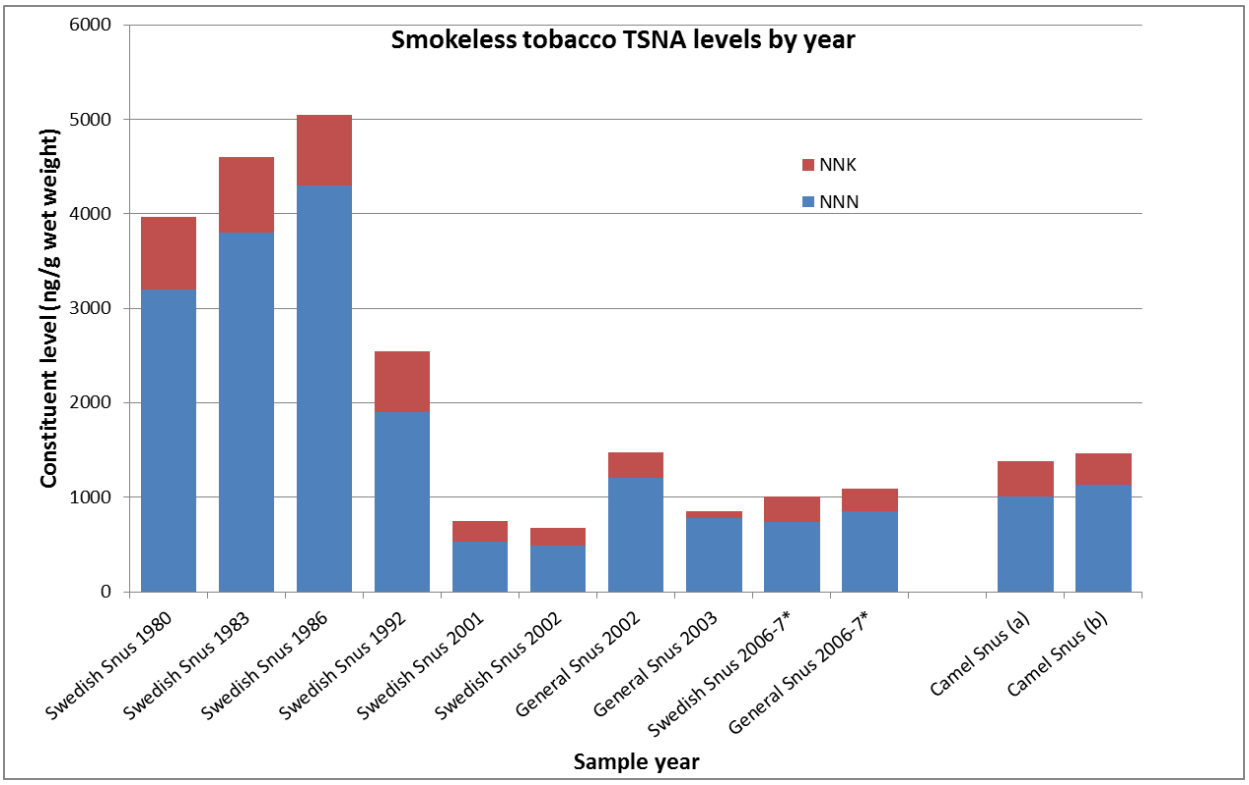
Notes: All values are ng/g wet weight of product. Values marked with an asterisk are calculated from dry weight data, adjusted for the reported moisture content of the product. Years indicate the years in which market samples were obtained. Sources of data are as follows: 1) Hoffmann and Adams 1981; 2) Österdahl *et al.* 2004; 3) Stepanov

et al. 2006; 4) Borgerding *et al.* 2012; 5) Stepanov *et al.* 2008a; 6) Camel Snus (a), mean of published values for Camel Snus brand styles included in this Application – *see* Table 6.1.5–7; Camel Snus (b), mean of values for all Camel Snus brand styles determined in internal RJRT studies – *see* Table 6.1.5-15.

The exact snus products and usage patterns represented by the cohorts included in the epidemiological studies cited in Section 6.1.1 are not precisely known. However, as discussed in Section 2.8.3.1 and Section 2.8.3.2, it is likely that the majority of snus products in use and evaluated by those studies possessed characteristics resembling the oldest products. It is the health risks associated with the use of these products that underlie the values reported in the existing studies for risk to individual snus users.

Based on NNN and NNK levels in the table above, Camel Snus and contemporary Swedish snus contain comparable levels of these toxicants, but with substantially reduced levels compared to the earlier products represented in Swedish epidemiological studies. A comparable level of total TSNAs was also reported in 2008 by Stepanov *et al.* (Stepanov *et al.* 2008a), although in that study the TSNA content of the Swedish snus (General) sample was greater than found for Camel Snus. Figure 2.8.3-2 illustrates the substantial differences between older and contemporary snus products, including Camel Snus.

Figure 2.8.3-2: Reductions in select TSNAs in Swedish Snus, 1980 – 2007, and comparison with Camel Snus



Notes: Combined NNN and NNK values for Swedish Snus and Camel Snus by year. Bars indicated with an asterisk in the legend are values derived from dry weight data, adjusted for moisture content. Camel Snus (a), mean of published values for Camel Snus brand styles included in this Application – *see* Table 6.1.5-5; Camel Snus (b), mean of values for all Camel Snus brand styles determined in internal RJRT studies – *see* Table 6.1.5-15.

Thus, Camel Snus contains low levels of toxicants consistent with other contemporary snus products. As with U.S. smokeless tobacco products, "Swedish snus" does not refer to a single, homogeneous product with a fixed toxicant content. Rather, Swedish snus products have evolved from products with much higher toxicant levels as reflected in the health outcomes of Swedish epidemiological studies to the much lower nitrosamine content products currently marketed.

2.8.3.5 Historical usage patterns of Swedish snus suggest higher levels of toxicant exposure, and potentially higher health risks, compared to use of contemporary pouched Swedish-style snus, including Camel Snus

In general, health risks of tobacco products vary depending on the toxicant content of the product and the manner of product use. Available information indicates that snus usage behaviors were quite variable during the time periods corresponding to Swedish snus epidemiological studies. Prior to the mid-1970s, snus was sold as loose ground tobacco and used as a 1 – 2 g "pinch." In the mid-1970s, 1 g portion-packed pouches were introduced. Both styles continued to be used, with an increasing trend toward pouches. Andersson and co-workers reported that as of 1994, 73% of Swedish snus consumers used only loose snus, 13% only pouched snus, and 14% used both types (Andersson *et al.* 1994). Two separate estimates for the amount of smokeless tobacco used by smokeless tobacco consumers surveyed in the large Swedish Construction Workers cohort (>5000 subjects; estimated period of use spanning the 1950s to 1990s) indicate weekly smokeless tobacco usage of approximately 150 g (Arefalk *et al.* 2011; Hergens *et al.* 2008). According to studies cited by IARC 1985, it was estimated that snuff users in Sweden used snuff 10 hours per day in 1978 and had been using snuff for 22 years. The estimated amount of snuff used per day for an average user was about 15 g. Average use was estimated to be approximately 100 g per week and 5.4 kg per year per user. Other data indicate use by Swedish males of 100 g per week in 1980 (Österdahl and Slorach 1983), 111 g per week in 1983 (Österdahl and Slorach 1984), 140 g per week in 1996 (Ramström 2000).

Differences between loose snus users and users of pouched snus have been noted for both product usage pattern as well as toxicant exposure (Andersson *et al.* 1994). On average, 15 g per day of loose snus was used compared to 9 g per day for pouched snus. Results from a more detailed study of 22 loose snus users, 23 pouched snus users and 9 users of chewing tobacco found that the average age was similar for loose snus (38.8 years) and pouched snus (40.8) users. The time that tobacco was kept in the mouth per day was also similar for loose and pouched products (12.3 – 13.1 hrs). However, the average amount of tobacco used was higher when using loose snus (20.8 g/day) than pouches (14.4 g/day), consistent with other data. The duration of habitual use was also greater for loose snus users (14.5 years) as compared to pouch users (7.4 years) (Table 2.8.3-3).

Table 2.8.3-3: Age distribution and consumption data for snus users and chewers (average ± SD and (range))

Users of smokeless tobacco	Mean age (years)	Amount/day (grams)	Time/day (hours)	Duration (years)
Portion-bag snus	40.8 ± 8.7 (21 – 57)	14.4 ± 7.1 (5.8 – 32.8)	13.1 ± 3.1 (8.0 – 20.0)	7.4 ± 6.6 (3.5 – 35.0)
Loose snus	38.8 ± 13.8 (22 – 75)	20.8 ± 15.5 (6.7 – 82.4)	12.3 ± 3.6 (6.0 – 16.0)	14.5 ± 6.3 (5.0 – 29.0)
Chewing tobacco	50.4 ± 9.6 (38 – 68)	7.2 ± 4.0 (1.9 – 12.7)	13.0 ± 4.0 (7.5 – 17.0)	9.5 ± 6.7 (3.0 – 24.0)

(Table adapted from Andersson *et al.* 1994, p. 163)

Differences relevant to estimating toxicant exposure were also noted. Higher fractions and amounts of nicotine and TSNAs were extracted from loose compared with pouched snus (Table 2.8.3-4).

Table 2.8.3-4: Amount of nicotine and TSNA extracted during 24 h (average ± SD and (range))

Category of Smokeless tobacco product	Extracted nicotine (mg/24 hours)	Degree of nicotine extraction (%)	Extracted TSNA (µg/24 hours)	Degree of TSNA extraction (%)	Saliva cotinine (ng/ml)	Systemic dose (mg/24 hours)
Portion-bag snus	47.6 ± 31.4 (12.3 – 164.4)	37.4 ± 17.6 (10.3 – 74.7)	44.5 ± 25.7 (10.7 – 120.3)	55.7 ± 20.5 (23.7 – 84.2)	342.9± 180.8 (113.4 – 612.2)	34.5 ± 23.1 (12.3 – 87.6)
Loose snus	94.7 ± 67.9 (18.5 – 274.3)	49.1 ± 17.2 (12.7 – 81.7)	125.3 ± 115.5 (19.6 – 403.8)	64.1 ± 16.4 (35.2 – 403.8)	326.6 ± 135.6 (116.2 – 589.1)	35.6 ± 18.6 (9.3 – 74.3)

(Table adapted from Andersson *et al.* 1994, p. 165)

More recent data describing Swedish snus product usage behaviors were reported in a study based on a 2007 – 2008 telephone survey of 2555 male and 359 female snus users in Sweden (Digard *et al.* 2009). The survey found that the majority of smokeless tobacco consumers used either pouched or loose snus exclusively. Only 12.6% used both snus and combustible tobacco products. The average daily smokeless tobacco usage was 11 – 12 g for pouched snus and 29 – 32 g for loose snus. Typical duration of use for each pouch or portion was 60 – 70 minutes. Approximately 59% of smokeless tobacco consumers used pouched products, while 41% used loose products. This usage pattern represents a substantial shift from periods as recent as the 1990s, where almost 75% of snus users used only loose snus (Andersson *et al.* 1994). Most (89.2%) users of pouched snus used one pouch at a time, although a small fraction used two (9.9%) or more (0.9%) at a time. Thus, contemporary Swedish snus consumers use approximately 80 – 200 g per week, depending on whether loose or pouched snus is used. Consistent with that finding, a 2008 study of the Swedish Construction Workers cohort by

Hergens *et al.* 2008 reported that the mean amount of smokeless tobacco used by current snuff users (ages <35 to 55+ years) was 23 g/day (161 g per week).

Thus, earlier time periods of snus use covered by epidemiological studies would reflect the collective risks of higher proportions of loose snus users, greater amounts of loose snus product used per day, and greater extraction of nicotine and TSNAs from those products. The data indicate that the trend since 1970 has been toward products and usage characteristics that present lower risk potential.

Both historical and more recent levels of snus usage in Sweden contrast with that of Camel snus usage, which is much lower. For example, in a 2013 cross-sectional study, subjects who used only Camel Snus (no use of other tobacco products) used on average 5.4 pouches (0.6 g style) per day (Caraway and Chen 2013). Using the nominal pouch weight of 0.6 g, weekly usage is estimated to be ~23 g. Other studies of tobacco use behaviors conducted by RJRT, using survey data from the RAIS National Tobacco Behavior Monitor, RJRT's Consumer Brand Tracker, or the NIH/FDA-sponsored PATH study (*see* Section 3.5), demonstrate that adult users of Camel Snus share characteristics with other contemporary U.S. smokeless tobacco users, including patterns of tobacco use and frequency and rate of use of smokeless tobacco. For example, greater than 90% of current Camel Snus users are dual/poly users of other combustible and/or non-combustible tobacco products. Most (~85%) Camel Snus consumers use the product less than daily with a mean frequency of use of 2 – 3 days/week, and at a rate of 3 – 4 pouches per day. These levels of usage are considerably lower than those reported in historical Swedish epidemiological studies.

Recently, Stepanov has remarked that aside from differences in the levels of potentially harmful constituents, differences in portion sizes between products such as Camel Snus and other snus products such as General could lead to higher exposure levels from traditional snus products (Stepanov *et al.* 2008a). Camel Snus data do not support that premise, with similar levels of NNK and NNN exposure among users of different Camel Snus pouch sizes (Hatsukami *et al.* 2016; Section 2.9.1.2.9).

In summary, analysis of historical usage patterns of Swedish snus from all available sources (Swedish epidemiological studies, reported product usage studies and other sources) indicates more intense usage patterns for both historical and contemporary Swedish snus as compared with Camel Snus styles. Higher levels of toxicant exposure and potentially greater health risks were also found for historical Swedish snus use as compared to Camel Snus use.

2.8.3.6 The level of health risk presented to Camel Snus users is reasonably estimated or overestimated by the existing epidemiological literature regarding Swedish Snus use

In summary, Camel Snus products share many key characteristics with other Swedish-style snus products. The discussion presented above illustrates that the snus products represented in the published epidemiology of Swedish smokeless tobacco users are not that of a single, homogeneous product. Those snus products did not contain the levels of toxicants found in

contemporary Swedish-style snus products, including Camel Snus, which are much lower. Notwithstanding the fact that the U.S. and Sweden are two different, Westernized populations, Swedish epidemiological data are relevant to U.S. users of Camel Snus given that: the toxicant levels in Camel Snus are lower than historical Swedish products, Camel Snus tobacco use patterns are similar, or lower, compared to Swedish snus and levels of toxicant exposure are reduced for Camel Snus compared to snus products used by subjects participating in epidemiological studies.

Thus, Swedish epidemiological studies present a reasonable indication, and possibly an overestimate, of health risks to individual Camel Snus users. As with U.S. studies, epidemiological findings among the Swedish population consistently demonstrate reduced risk for smokeless tobacco (snus) compared with cigarette smoking. The body of Swedish epidemiology presented as evidence for reduced harm to individual snus users is both relevant and sufficient to support the conclusion that smokers who switch completely from cigarette smoking to Camel Snus will significantly reduce their risks for lung cancer, oral cancer, heart disease and respiratory disease.

2.9 Summary of Health Risk Information and Scientific Data

2.9.1 Human studies

No single class of evidence in itself is sufficient to support an MRTP application (IOM 2012). Rather, a portfolio of evidence, with an emphasis on studies in humans, is required for the justification of a modified risk claim. According to FDA Draft Guidance, studies conducted with human subjects and appropriate for an MRTPA include epidemiological studies, clinical investigations, consumer perception studies, actual use studies and other studies that involve humans actually consuming or interacting with the product. Human studies provide FDA with information critical for determining what effect the product may have on the health of individuals and on the population as a whole if the product is commercially marketed as an MRTP (FDA MRTPA Draft Guidance 2012). The following sections summarize the results of human studies, both relevant published studies as well as those conducted or contracted by RJRT, that collectively support the position that exclusive use of Camel Snus presents lower risks to health compared with cigarette smoking.

2.9.1.1 Epidemiological studies

2.9.1.1.1 Cigarette smoking elevates risk for many diseases, but epidemiological data shows that switching completely to smokeless tobacco, including Camel snus, will significantly reduce harm and the risk of tobacco-related lung cancer, oral cancer, respiratory disease and heart disease to individual tobacco users

According to the Institute of Medicine, observational epidemiological studies play a critical role in the evaluation of MRTPs (IOM 2012). Supportive epidemiology should provide “clear and consistent evidence of reduction in disease risk (*e.g.*, cancer, cardiovascular disease, chronic

obstructive pulmonary disease) or intermediate endpoint thereof," and "no significant evidence of offsetting increased risk for other diseases" should be found (IOM 2012). Similarly, FDA's MRTP Draft Guidance states that "human studies [including epidemiological studies] provide FDA with information critical for determining what effect the product may have on the health of individuals and on the population as a whole if the product is commercially marketed as an MRTP" (FDA MRTPA Draft Guidance 2012, p. 24).

The following subsection summarizes the epidemiological data that show clear and consistent evidence for a reduction in risk for lung cancer, oral cancer, respiratory disease and heart disease among ST users, including users of Camel Snus, compared with cigarette smokers. Although this Application is limited to claims of reduced risk for these four health conditions, the data also show lower risks for virtually all smoking-related diseases, confirming that no offsetting health risks are associated with use of ST products, including Camel Snus.

Data from both U.S. and Swedish epidemiological studies (Section 6.1.1) are relevant and central in estimating the anticipated health risks to tobacco users who currently use or will switch to Camel Snus if commercially marketed as an MRTP and for comparison to health risks estimated for U.S. smokers. U.S. data is of greater importance in such a comparison, since such data incorporates, by default, the innate characteristics of U.S. tobacco consumers in terms demographics, socioeconomic status, genetics and patterns of cigarette smoking and/or smokeless tobacco use. Epidemiological studies of U.S. smokers report significantly elevated risks for a wide range of cancers, non-neoplastic respiratory disease (COPD), cardiovascular diseases, and other adverse health effects. CDC reports that the greatest adverse U.S. population health impact of cigarette smoking is currently attributed to lung cancer (131,000 annual deaths), cardiovascular and metabolic diseases (161,000 annual deaths), and COPD (101,000 annual deaths) (USDHHS 2014, p. 660). Cigarette smoking-related deaths from oral cancer have been reported to be ~4900 annually (CDC 2011).

Substantially lower health risks are reported in studies of U.S. and Swedish smokeless tobacco products. RJRT believes that the lower health risk estimates reported in studies of U.S. and Swedish smokeless tobacco products as compared to the risks reported for U.S. cigarette smokers apply to Camel Snus based upon product toxicant content and exposure profiles for users of Camel Snus and historical U.S. and Swedish smokeless tobacco products (Section 2.9.1.2 (exposure), Section 2.9.5 (toxicant content), Section 6.1.2 (exposure), and Section 6.1.5 (toxicant content)). Specifically, Camel Snus toxicant content is comparable to, or less than, U.S. and Swedish smokeless tobacco products (Section 6.1.5) and the typical amount per day and manner of use for Camel Snus is comparable to, or less than their historical counterparts (Section 2.8.2.5). Therefore, RJRT believes that U.S. and Swedish smokeless tobacco epidemiology either provides viable estimates of the health risks from using Camel Snus or possibly overestimates those risks.

The following provides a summary and discussion of data that demonstrate cigarette smoking substantially elevates risk for many diseases, but epidemiological data shows that switching

A systematic, critical review of pertinent U.S. and Swedish epidemiological literature on the risks of lung and oral cancers, respiratory disease, and cardiovascular disease, specifically coronary heart disease, among users of snus and other smokeless tobacco products compared with cigarette smokers and never or non-users of tobacco products was conducted by Ramboll Environ (Ramboll Environ 2016). Forty-four relevant primary epidemiological studies of U.S. and Swedish tobacco users were identified through this systematic review. In addition, a number of reviews and meta-analyses of available studies regarding these and other health outcomes were considered.

Lung cancer: Cigarette smoking is overwhelmingly the strongest risk factor for lung cancer. The respiratory tract is much more sensitive to toxicant exposure than the gastrointestinal tract, and portal of entry effects from irritating HPHCs can produce respiratory toxicity that has much more severe consequences than the oral irritation caused by the use of snus. Inhaled cigarette smoke creates a situation in which carcinogenic smoke constituents can directly contact the cells that line the respiratory tract, putting the lung at risk of neoplasms in a way that oral tobacco use does not. Epidemiological studies show that there is little to no evidence that lung cancer risk is associated with snus use based on Scandinavian studies. FDA's TPL Review of the Swedish Match North America MRTPA recently concluded that "the observed relative risks reported by the individual studies and the summary estimates from the two meta-analyses suggest that the use of Swedish snus does not have a significant effect on the risk of lung cancer" (SMNA MRTPA TPL Review, p. 50). The ST studies conducted in the U.S. that suggest a possible association between lung cancer and ST use (*e.g.*, Accortt *et al.* 2005; Henley *et al.* 2005) are limited by factors that include potentially inadequate exposure assessments, which might have led to misclassification. Meta-analyses of U.S. and Scandinavian studies (Lee and Hamling 2009a; Boffetta *et al.* 2008) have found no statistically significant elevation in lung cancer risk among ST users.

Oral cancer: Numerous epidemiological studies provide consistent evidence that cigarette smokers experience a higher incidence of or mortality from cancers of the oral cavity than do lifetime nonsmokers. The average risk among persons who currently smoke and have smoked only cigarettes is approximately 10-fold higher in men compared with lifetime nonsmokers [both higher and lower estimates of risk have been reported; *see e.g.,* Figure 2.9.1-1 and Figure 2.9.1-2]. Incidence and mortality rates increase with the number of cigarettes smoked per day and decrease with years since smoking cessation. Together, smoking and alcohol account for most cases in the United States and elsewhere (USDHHS 2004). In contrast, the epidemiological data for U.S. populations have reported inconsistent results regarding associations between oral cancer and ST use. Despite the strong associations presented in some older case-control studies, methodological problems in most of the case-control studies and in the cohort studies preclude conclusive judgment (*see* Ramboll Environ 2016). The methodologically strongest U.S. study in this group (Zhou *et al.* 2013), suggests a positive association may exist between ST use and squamous cell carcinoma of the head and neck, but the association was not statistically significant for oral cancer, and one study is an insufficient basis for reaching a causal conclusion. Overall, Scandinavian studies of oral cancer risk and snus use suggest, somewhat inconsistently, that snus use may likewise be associated with elevated risk for certain head and neck cancers

significant for oral cancer, and one study is an insufficient basis for reaching a causal conclusion. Overall, Scandinavian studies of oral cancer risk and snus use suggest, somewhat inconsistently, that snus use may likewise be associated with elevated risk for certain head and neck cancers (Lewin *et al.* 1998; Roosaar *et al.* 2008) and squamous cell oral cancers (Schildt *et al.* 1998), with case-control studies showing statistically significant associations, but cohort studies generally not reporting elevated risks of oral cancer among snus users. The strongest evidence suggesting an effect of ST and snus use on oral cancer risk comes from older studies or from cohort studies that included exposure to products that likely had higher levels of nitrosamines and other constituents than are typically found in more modern products, especially snus. In contrast, where data were available in these studies, risks for oral cancer were significantly increased among current cigarette smokers.

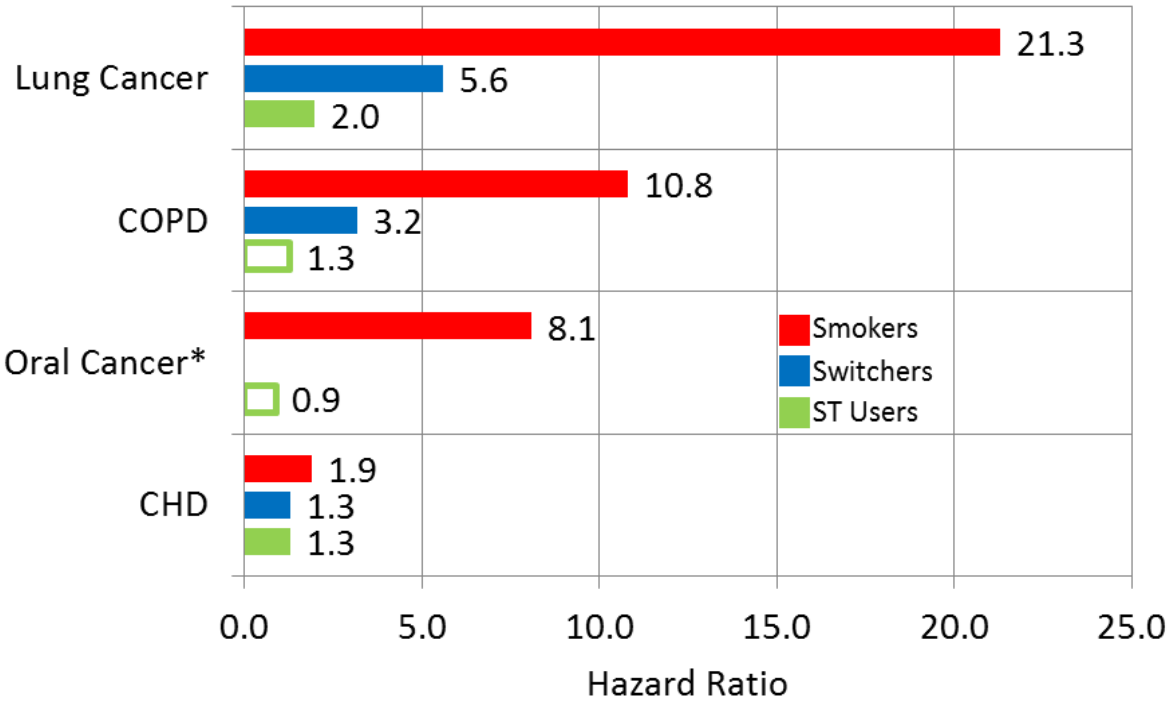
Respiratory disease: As found with lung cancer, epidemiological studies confirm that cigarette smoking is overwhelmingly the strongest risk factor for respiratory disease. In contrast, there has been no clear demonstration of an increased risk for respiratory disease among U.S. or Swedish users of smokeless tobacco. FDA's TPL Review of the Swedish Match North America MRTPA recently concluded that large "population studies confirm minimal, if any, increase in risk of respiratory disease related to use of [snus]" (SMNA MRTPA TPL Review, p. 51). Although there are harmful and potentially harmful constituents (HPHCs) found in ST products, none have been linked to the development of chronic lung disease unless inhaled (SMNA MRTPA TPL Review, p. 50). Since the tar of cigarette smoke is the primary source of toxins, snus [including Camel Snus] is much less likely to be a significant risk factor for COPD or other respiratory diseases (SMNA MRTPA TPL Review, p. 51).

Coronary heart disease: Epidemiological studies provide no clear or consistent evidence of an association between ST use and coronary heart disease (heart disease) mortality or incidence (*see* Section 6.1.1.3). Studies reporting positive associations assessed tobacco products in use decades ago, and it is likely that the constituents of the ST products used at that time differed from those found in modern products (*see* Section 2.8.2.2). Results from the study with the shortest follow-up and whose methods were least likely to be substantially impacted by misclassification of product use (Hansson *et al.* 2009) indicate no association between snus use and CHD hospitalization and deaths. In contrast to the conflicting results for ST, the evidence for a positive association between smoking and risk of CHD is clear and consistent, with approximately a two-fold risk of CHD/IHD incidence or mortality for current smokers, compared to never tobacco users. Thus, from the available evidence, it is clear that smoking carries a greater risk of CHD/IHD compared to exclusive ST use.

Results from the systematic, critical review of the relevant epidemiological literature on the risks of oral and lung cancers, respiratory disease, and cardiovascular diseases, specifically coronary heart disease, among users of snus and other smokeless tobacco products compared with cigarette smokers and never or non-users of tobacco products provide evidence to support the modified risk claim that switching from cigarette smoking to the exclusive use of Camel Snus will reduce the risk for these noted health outcomes. The figure below provides a

Results from the systematic, critical review of the relevant epidemiological literature on the risks of oral and lung cancers, respiratory disease, and cardiovascular diseases, specifically coronary heart disease, among users of snus and other smokeless tobacco products compared with cigarette smokers and never or non-users of tobacco products provide evidence to support the modified risk claim that switching from cigarette smoking to the exclusive use of Camel Snus will reduce the risk for these noted health outcomes (Ramboll Environ 2016). Figure 2.9.1-1 below provides a representative comparison of risks for the aforementioned health outcomes among smokers, ST users, and switchers from smoking to exclusive ST use.

Figure 2.9.1-1: Disease-specific mortality risk estimates based on Cancer Prevention Study-II (CPS-II) data for male U.S. cigarette smokers, smokers that switch completely to smokeless tobacco use, and smokeless tobacco users



Notes: Data obtained from Thun *et al.* 2000, Henley *et al.* 2007, and Henley *et al.* 2005. Solid bars represent significant differences compared to never users of tobacco, while open bars represent no difference.
* No value reported for switchers. Value for cigarette smokers includes all cancers of the "upper aerodigestive tract," including lip, oral cavity, pharynx, esophagus and larynx (Thun *et al.* 2000). Value for smokeless tobacco users includes only cancers of the lip, oral cavity, and pharynx; the corresponding value for cancers of the lip, oral cavity, and pharynx for cigarette smokers, based on CDC's SAMMEC analysis of CPS-II data, is 10.9 (CDC SAMMEC 2011).

Other health outcomes: In addition to the four diseases that are specific to the proposed modified risk advertising in this Application, a number of other diseases and conditions, malignant and non-malignant, are associated to varying degrees with cigarette smoking. Several of these other diseases have been investigated with respect to ST use as well (*see* Section 6.1.1.4). Meta-analyses of ST use and cancer risks conducted by Lee and Hamling 2009a

provided data from combined studies of U.S. and Scandinavian smokeless tobacco users as well as risks analyzed separately from U.S. and Scandinavian studies. The authors concluded that the study results "show no indication of an increased risk of cancer for snuff, as used in Scandinavia" ... "A weak but significant association with prostate cancer, based on limited data from U.S. studies, [but requiring] more confirmatory evidence. Reports of significant associations with pancreatic and esophageal cancer in an earlier review (citing Boffetta *et al.* 2008) are not confirmed..." and finally that "Risk from smokeless tobacco products as used in North America and Europe is clearly very much less than that from smoking, and is not evident at all in Scandinavia."

Besides coronary heart disease discussed above (*also see* Section 6.1.1.3), the epidemiological literature has considered other cardiovascular outcomes (*i.e.,* all cardiovascular disease (CVD), myocardial infarction (MI), stroke, blood pressure and hypertension) among smokers and ST users. Most such studies have been conducted in Sweden, with a few conducted among U.S. ST users.

Evidence regarding a relationship between ST use and CVD is mixed. Some U.S. studies suggest a positive association, but imprecision in the definitions of both exposure and outcome make interpretation difficult. Some Swedish data also suggests a positive association between snus use and CVD. However, adequate exposure assessment of ST usage is lacking in all of the studies discussed and the differing definitions of "cardiovascular disease" used in each study complicate conclusions that can be drawn from this body of literature (*see* Ramboll Environ 2016). These results contrast with the clear evidence for an elevated risk for all cardiovascular diseases among smokers.

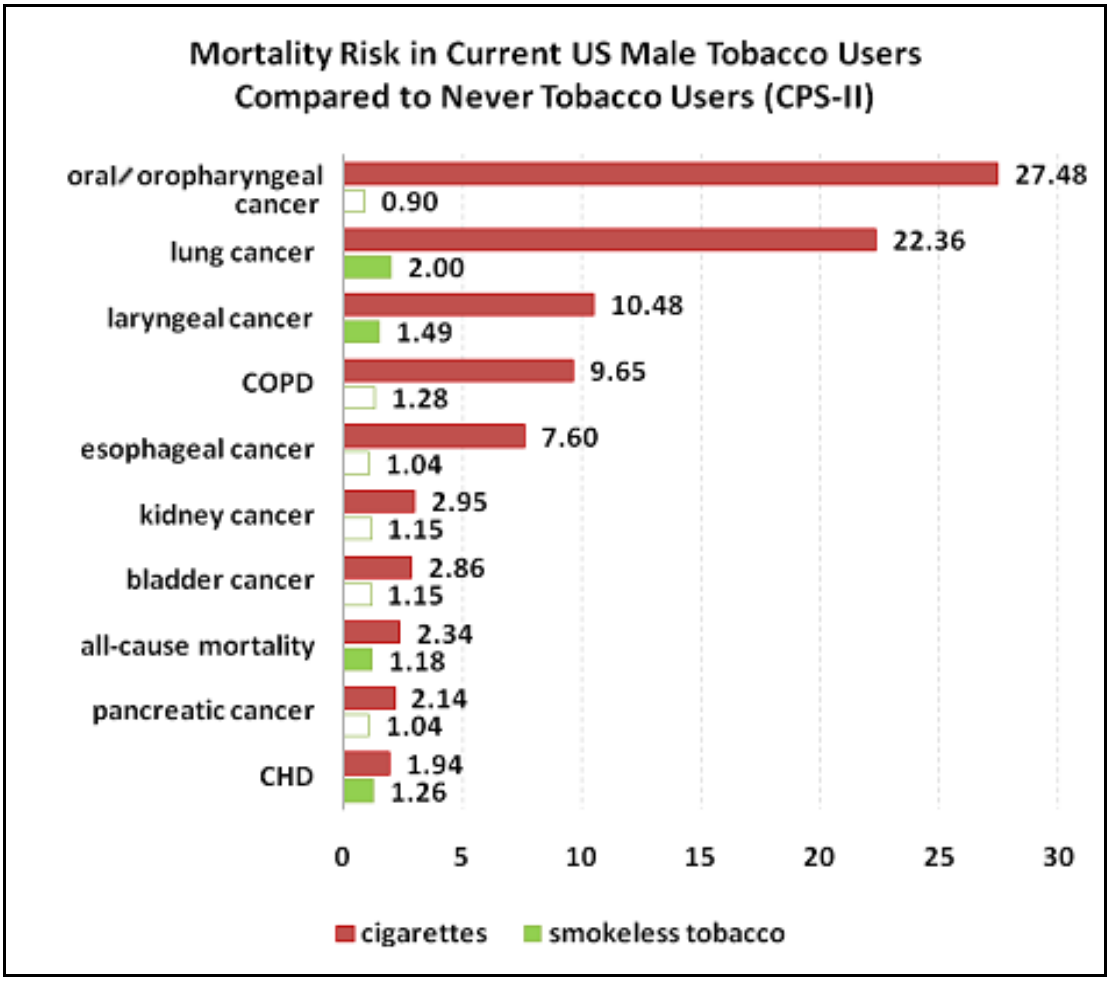
The evidence for an association between ST use and MI is also mixed, and interpretation is likewise complicated by imprecision in case definitions, exposure measures, and outcomes. A single U.S. study (Yatsuya *et al.* 2010), which examined MI as part of a larger group of cardiovascular outcomes, found a slightly elevated risk of CVD associated with ST use among current, but not former, chewing tobacco and snuff users. Using ST in addition to smoking was not associated with any additional risk of cardiovascular disease. Unfortunately, the design of this study did not allow a direct comparison between ST use and cigarette smoking as cardiovascular risk factors. Among Swedish studies, the available evidence points to a possible association between current snus use and elevated risk of fatal MI; no association is seen with non-fatal MI. Although the evidence for elevated risk of MI among snus users in Swedish studies is mixed, studies that assessed cigarette smoking in the same study group showed a significantly elevated risk of MI among current smokers.

Results from large, population-based U.S. cohort studies and pooled analysis of Swedish cohort studies suggest an association between stroke mortality and ever having used snus, especially among current users. The evidence for an association between stroke incidence and U.S. ST use, although positive, is not as well supported. In contrast, there is unequivocal evidence that cigarette smoking increases risk for stroke.

although positive, is not as well supported. In contrast, there is unequivocal evidence that cigarette smoking increases risk for stroke.

The following chart illustrates the magnitude of the differences in risk of major health hazards faced by users of cigarettes and those faced by users of ST, including Camel Snus; it shows relative risk estimates from the U.S. Surgeon General, which are based on the American Cancer Society's CPS-II cohort and hazard ratios from Henley *et al.* 2005:

Figure 2.9.1-2: Disease-specific mortality risk estimates in current male tobacco users compared to never tobacco users based on CPS-II data



Sources: USDHHS 1989 for cigarette data (RR) and Henley *et al.* 2005 for smokeless tobacco data (HR); filled bars represent statistically increased risk versus never tobacco users, while empty bars represent no statistically significant difference from never-tobacco users.
COPD: chronic obstructive pulmonary disease; CHD: coronary heart disease

Among other diseases and adverse conditions that have been examined with respect to tobacco use, there is evidence that snus use during pregnancy is associated with a modest reduction in average birth weight, and an increased risk of preterm delivery and preeclampsia (England *et al.* 2003; England *et al.* 2010; *see* Section 2.9.1.1.3). Cigarette smoking before and during pregnancy is a significant cause of maternal, fetal, and infant morbidity and mortality

other hand, smoking is inversely associated with risk for pre-eclampsia, possibly mediated by CO.

The detailed review of the epidemiology of health effects of ST use presented above, and in the numerous cited studies, reviews and meta-analyses, confirms that use of Camel Snus products presents a far lower overall health risk to the individual user than does cigarette smoking. Collectively, the data provide unequivocal support for the proposed advertising executions for Camel Snus indicating that smokers who switch to exclusive use of Camel Snus will lower their risks for lung cancer, oral cancer, respiratory disease and heart disease.

2.9.1.1.2 Dual use of cigarettes and smokeless tobacco is not associated with unique or increased disease risks, which are not anticipated or observed from cigarette smoking alone

RJRT's proposed advertising executions specify that current smokers should switch completely from smoking to using Camel Snus to reduce their risk of lung cancer, oral cancer, respiratory disease and heart disease. However, there is likely a period during which smokers may engage in dual use of cigarettes and Camel Snus products. Thus, it is important to consider evidence on tobacco-related harm associated with the dual use of cigarettes and smokeless tobacco products (*see* Section 6.1.1.6). Few studies have focused specifically on the prevalence of, or the health consequences associated with, dual use; however, relevant data are often found within studies examining the health effects associated with smokeless tobacco use. The possibility of unique or increased risk for diseases among dual users has been considered in two recent reviews.

The first considered 17 separate studies (4 from the U.S. and 13 from Europe, primarily from Sweden) that addressed dual use in some format (Frost-Pineda *et al.* 2010). The authors concluded that the evidence is sufficient and clear that there are no unique health risks (either qualitative or quantitative) associated with dual use of cigarettes and smokeless tobacco products, which are not anticipated or observed from exclusive use of one of these products. Endpoints in these studies included various cancers and cardiovascular diseases. Furthermore, some data indicate that the risks of dual use are lower than those of exclusive smoking, most likely due to reduced smoking.

The second study, a systematic review that identified 51 separate relative risk estimates from Scandinavian studies, likewise found little evidence of any special risk from dual use (Lee 2014). An exception was risk for gestational hypertension (pre-eclampsia), which is reduced in exclusive smokers (*see* Section 6.1.1.8). This study also found evidence that dual use results in attenuated risks among dual users compared with exclusive smokers, with 32 of the 51 estimates showing at least somewhat reduced risks. The best explanation for lower risks reported in some studies of dual use is lower cigarette consumption among dual users (reduced by an estimated 26%; Lee 2014).

2.9.1.1.3 Smokeless tobacco use by specific sub-populations presents no unique disease risks to individual users that would not also be presented by cigarette smoking

Cigarette smoking is a cause of many adverse health effects across all groups of smokers in the U.S., including females, pregnant females, adolescents, and various ethnic populations. Disparities in the prevalence and patterns of cigarette smoking, as well as the incidence and outcomes of smoking-related diseases among population subgroups are widely reported, but the underlying reasons are numerous and complex. Smokeless tobacco use also varies considerably across various groups, with ST use prevalence determined by the same complexity of factors as smoking, although not with the same distribution profile. An examination of the available literature revealed that cigarette smoking results in high risks for many diseases, and those risks depend overwhelmingly on exposures to smoking-related toxicants, rather than any inherent unique susceptibility in specific groups (*e.g.*, USDHHS 1998; Patel *et al.* 2016). Differences in smoking-related risk noted across various population subgroups can thus be largely, if not totally, explained by differences in smoking patterns and individual behaviors.

Although data are limited and somewhat indirect, ST use appears to present no unique risks to adolescents, females, and members of various ethnic/racial groups. Thus, the risks to health reported in epidemiological studies of more diverse populations, although largely composed of male ST users, should be generally applicable to all groups of users. RJRT is not aware of a biological rationale for differences in ST risks among individuals who use the products comparably (*see* SMNA MRTPA TPL Review, p. 37). A number of adverse health outcomes from ST use among pregnant females have been described, although the number and severity of those outcomes, with the exception of pre-eclampsia, whose risk is lowered by smoking, are lower than with cigarette smoking. Pregnant women should not use any tobacco products. However, it should be noted that some practitioners may recommend nicotine replacement therapy (NRT), with a risk profile similar to that of smokeless tobacco, for female smokers during pregnancy (Forest 2010).

2.9.1.1.4 Smokeless tobacco use presents health risks more comparable to those risks associated with use of approved smoking cessation products than with cigarette smoking

Available data provide consistent evidence that Camel Snus and other U.S. and Swedish ST products present substantially lower health risks for lung cancer, oral cancer, respiratory disease and heart disease compared to cigarette smoking. While ST products, including Camel Snus, contain low levels of tobacco combustion products and lower levels of many other tobacco toxicants compared to cigarettes, they do contain higher levels of several toxicants (such as TSNAs) compared with medicinal nicotine products. Medicinal nicotine is not considered to pose a risk for lung cancer or other cancers, and cardiovascular risks associated with NRT use are considered slight. The relative harms of cigarettes, smokeless tobacco and smoking cessation therapies are best viewed within the continuum of risk (Zeller *et al.* 2009). As estimated by Levy *et al.* 2004 and Nutt *et al.* 2014, smokeless tobacco, including Camel Snus, is

on the least toxic end of this continuum, with estimated harm at most, only 5-10% that of smoking, with NRT presenting slightly lower risks.

2.9.1.1.5 Smokeless tobacco use produces no environmental tobacco smoke, reducing health risks for both tobacco and non-tobacco users

Non-tobacco users experience no increase in health risks associated with the use of smokeless tobacco, since ST products, including Camel Snus, produce no second-hand smoke. This contrasts sharply with the potential risks that may be associated with ETS exposure for smokers and nonsmokers alike. According to the American Cancer Society, the American Heart Association, and the American Lung Association, secondhand tobacco smoke contributes to risk for heart disease, lung cancer, and other diseases and adverse conditions (*see* respective websites).

2.9.1.2 Clinical studies

Clinical studies provide important information for the evaluation of a proposed MRTP. FDA recommends that applicants conduct human studies to "assess the full range of the human health risks related to the use of the tobacco product, including exposure to tobacco-related compounds (*e.g.*, biomarkers of exposure) and health outcomes (*e.g.*, disease incidence or mortality)" (FDA MRTPA Draft Guidance 2012, p. 25). FDA also recommends that applicants submit data relevant to any health risks associated with switching to a proposed MRTP as compared to using an FDA-approved tobacco cessation medication (FDA MRTPA Draft Guidance 2012). Although exposure reduction is distinct from risk reduction, biomarkers and other clinical measures can serve as potential indicators of tobacco-related disease risk (*see* Hatsukami *et al.* 2009; IOM 2012, p. 80). Given the latency between tobacco exposure and disease development, clinical data provide useful information over a relatively short time frame and enable direct comparisons between Camel Snus and combustible cigarettes.

Accordingly, this Application includes data from eight RJRT-sponsored clinical studies of Camel Snus that investigate product use behaviors, biomarkers of exposure and other health-related endpoints. RJRT's clinical studies of Camel Snus are based on various designs, including: (a) cross-sectional evaluation of natural adopters of Camel Snus, (b) randomized controlled trials of product switching (ambulatory and confined) and (c) a randomized trial of smokers with an intent to quit smoking, who were switched to either Camel Snus or a nicotine replacement therapy (NRT) product to assess smoking cessation rates.

Depending upon study objectives, subjects included exclusive Camel Snus users, dual users of Camel Snus and cigarettes, product switchers (*e.g.*, cigarette smoking to Camel Snus use), users of other smokeless tobacco products and non-users of tobacco. Study endpoints included biomarkers of exposure and effect, nicotine pharmacokinetics measures, tobacco product use metrics and safety profiles. Biomarkers of exposure and effect relevant to tobacco use were assessed in biological matrices such as blood, urine and expired breath.

Biomarkers of exposure measure actual exposure to constituents of tobacco (IOM 2012) as opposed to chemical analyses which provide information about specific characteristics of a tobacco product, such as HPHC content, but cannot predict actual exposures in product users. Exposure to constituents present in a tobacco product or tobacco smoke is the result of multiple factors, including the manner of use (*e.g.*, inhalation *vs.* placement of tobacco in the mouth), product use behaviors (*e.g.*, cigarette puffing behavior or time smokeless tobacco held in mouth), the chemical composition of the smoke or tobacco product and the route(s) of exposure.

The following sections summarize relevant information from the eight RJRT-sponsored clinical studies, as well as from the published literature and provide useful short-term information regarding the relative risks of lung cancer, oral cancer, respiratory disease and heart disease risks presented by Camel Snus compared with cigarette smoking. Additional, more detailed discussion of clinical studies that compare Camel Snus use and cigarette smoking is found in Section 6.1.2 and supporting documents to that section.

2.9.1.2.1 Exclusive Camel Snus use results in reduced exposure to combustion-related toxicants compared with cigarette smoking

The body of RJRT-sponsored and external published clinical research specific to Camel Snus shows that, compared with cigarette smoking, exclusive Camel Snus use results in less exposure to combustion-related toxicants (*i.e.*, toxicants formed from burning tobacco during smoking). Two RJRT-sponsored clinical studies, one of smokers switched from their usual brand of cigarette to Camel Snus (CSD0901) and another of natural adopters of Camel Snus (CSD0904), as well as a published study of smokers switched to Camel Snus (Kotlyar *et al.* 2011), measured levels of combustion-related toxicant biomarkers in exclusive users of Camel Snus and exclusive cigarette smokers.

All RJRT-sponsored studies, as well as other published research, uniformly show lower biomarker levels in exclusive Camel Snus users than in exclusive cigarette smokers for aromatic amines, carbon monoxide, carbonyl compounds, hydrogen cyanide, mutagens, other volatile organic compounds and the PAHs phenanthrene and fluorene. Biomarker levels comparable to those in cigarette smokers were observed in some studies for pyrene and naphthalene (*see* Table 2.9.1-1). Naphthalene and pyrene, however, are not tobacco-specific and can be affected by environmental exposures or genetics (*see, e.g.*, Chang *et al.* 2016, Gregg *et al.* 2013). The utility of the pyrene biomarker, 1-hydroxypyrene, in tobacco studies has been questioned due to confounding exposure from alternative sources (*see, e.g.*, Hecht *et al.* 2004, St. Helen *et al.* 2012, USDHHS 2010). It is also important to note that changes in product use rate occurred when subjects in study CSD0904 were confined to clinic. While Camel Snus user groups used nominally more product during clinical confinement, cigarette smoker groups smoked fewer cigarettes (due to fewer opportunities to smoke because of required study procedures and access to designated smoking areas), thus reducing the magnitude of exposure differences found between smoker and non-smoker subject groups to some extent (*see* Table 2.9.1-4). As

such, biomarker exposure differences found between smokers and Camel Snus users in study CSD0904 would be expected to be even greater for samples taken without clinical confinement.

Consistent with published reports that compare toxicant exposures from use of smokeless tobacco and from smoking (*see, e.g.*, Chang *et al.* 2016, pp. 16-18), the biomarker results summarized in Table 2.9.1-1 show clearly that cigarette smokers who switch completely to Camel Snus can significantly reduce their exposure to combustion-related toxicants found in cigarette smoke. Such findings are not surprising, given that toxicants and carcinogens produced during combustion, including carbon monoxide, PAHs and many VOCs, are absent or greatly reduced in the Camel Snus products when compared to cigarette smoke (*see* Section 6.1.5).

Table 2.9.1-1: Biomarker studies of combustion-related toxicant exposure from exclusive Camel Snus use compared to exclusive cigarette use

				Relative Toxicant Exposure[a]		
Study	**Measurement Type**	**Sample Matrix**	**Study Design**	**Camel Snus < Cigarettes**	**Camel Snus ≈ Cigarettes**	**Camel Snus > Cigarettes**
CSD0901	Aromatic Amines[b]	24-hr Urine	Switching (confinement)	X		
CSD0901	PAHs[c]	24-hr Urine	Switching (confinement)	X		
CSD0901	PAHs[d]	24-hr Urine	Switching (confinement)		X	
CSD0901	Carbonyls[e]	24-hr Urine	Switching (confinement)	X		
CSD0901	Thiocyanate[f]	24-hr Urine, Plasma	Switching (confinement)	X		
CSD0901	Organic Compounds[g]	24-hr Urine	Switching (confinement)	X		
CSD0901	Mutagens[h]	24-hr Urine	Switching (confinement)	X		
CSD0901	Carbon Monoxide[i]	Blood, Breath	Switching (confinement)	X		
CSD0904	Aromatic Amines[b]	24-hr Urine	Cross-sectional (natural adopters)	X		
CSD0904	PAHs[j]	24-hr Urine	Cross-sectional (natural adopters)	X		
CSD0904	PAHs[k]	24-hr Urine	Cross-sectional (natural adopters)		X	
CSD0904	Carbonyls[e]	24-hr Urine	Cross-sectional (natural adopters)	X		
CSD0904	Thiocyanate[f]	24-hr Urine, Blood	Cross-sectional (natural adopters)	X		
CSD0904	Organic Compounds[l]	24-hr Urine	Cross-sectional (natural adopters)	X		
CSD0904	Mutagens[m]	24-hr Urine	Cross-sectional (natural adopters)	X		
CSD0904	Carbon Monoxide[i]	Blood, Breath	Cross-sectional (natural adopters)	X		
CSD0904	Hemoglobin Adducts[n]	Blood	Cross-sectional (natural adopters)	X		
Kotlyar *et al.* 2011	Carbon Monoxide	Breath	Switching (ambulatory)	X[o]		

[a] An "X" in either the "Camel Snus < Cigarettes" or "Camel Snus > Cigarettes" columns indicates a statistically significant difference between Camel Snus and cigarette biomarker results, with Camel Snus less than or greater than cigarettes, respectively. An "X" in the "Camel Snus ≈ Cigarettes" column indicates that no statistically significant difference was observed between Camel Snus and cigarette biomarker results.

[b] *o*-toluidine, 2-aminonaphthalene, 3-aminobiphenyl and 4-aminobiphenyl
[c] 1- and 2-OH-naphthalene, 2 OH-fluorene and 1-, 2-, 3-, 4- and 9-OH-phenanthrene
[d] 1-OH-pyrene
[e] Acrolein and crotonaldehyde
[f] Biomarker of hydrogen cyanide exposure
[g] Acrylonitrile, acrylamide, 1,3-butadiene, benzene and ethylene oxide
[h] Compounds that are mutagenic in the Ames assay (strain YG1024)
[i] Exhaled breath carbon monoxide and blood carboxyhemoglobin
[j] 2-OH-fluorene and phenanthrene equivalents (*see* RDM PC 2016 274-a)
[k] Naphthalene equivalents and 1-OH-pyrene (*see* RDM PC 2016 274-a)
[l] Includes biomarker measurements for acrylamide, 1,3-butadiene and benzene
[m] Compounds that are mutagenic in the Ames assay (strains TA98 and YG1024)
[n] 4-aminobiphenyl hemoglobin adducts in blood
[o] Some dual use of cigarettes and Camel Snus occurred during the study. As reported, 9.1% of subjects smoked on average more than 3 cigarettes per day.

2.9.1.2.2 Exclusive Camel Snus use results in either similar or reduced exposure to toxicants in tobacco (TSNAs) when compared with cigarette smoking

While many of the toxicants present in cigarette smoke are formed when tobacco is burned during smoking, some toxicants present in tobacco (*e.g.*, TSNAs) are transferred directly from tobacco to smoke. RJRT-sponsored and other external clinical study data show that exclusive Camel Snus use results in either similar or reduced exposure to toxicants present in tobacco when compared to exclusive cigarette smoking. NNK and NNN, the most-studied TSNAs, are classified as Group 1 carcinogens by IARC and are considered to be important drivers of cancer risk associated with tobacco use (*see, e.g.*, Hecht *et al.* 2015). NNAL, the primary metabolite of NNK, is a tobacco-specific biomarker (Chang *et al.* 2016). Levels of NNAL in the urine of cigarette smokers are associated with lung cancer risk in a dose-dependent manner (*see* USDHHS 2010, Yuan *et al.* 2011a, Yuan *et al.* 2014). Two RJRT-sponsored studies (CSD0901 and CSD0904), and several studies in the published literature (Blank and Eissenberg 2010, Hatsukami *et al.* 2016, Kotlyar *et al.* 2011), provide comparisons of TSNA biomarkers measured in the urine of exclusive users of Camel Snus and exclusive cigarette smokers.

An RJRT-sponsored study of Camel Snus adopters (CSD0904) found urinary levels of NNN, NAT, NAB and NNAL to be similar between exclusive Camel Snus users and cigarette smokers. However, opportunities to smoke while in-clinic were limited by study procedures and requirements to smoke inside a designated area. As such, these levels reflect less exposure from cigarettes than would be expected when smoking *ad libitum* outside the clinic. Camel Snus users used consistent amounts of product both before and during clinical confinement. Therefore, these results likely under-represent differences in exposure between the two groups (*see* Table 2.9.1-4). Randomized product-switching studies conducted by RJRT and others, however, show reduced levels of some TSNA biomarkers in smokers switched to exclusive Camel Snus use (CSD0901, Kotlyar *et al.* 2011). Unlike other U.S. smokeless tobacco products, where users are exposed to greater amounts of TSNAs than cigarette smokers (*see, e.g.*, Table 2.9.1-12), use of Camel Snus does not increase TSNA exposure compared to cigarette smoking.

The TSNA biomarker results summarized below in Table 2.9.1-2 demonstrate that exclusive Camel Snus users exhibit reduced or similar levels of these compounds when compared with cigarette smokers. Because Camel Snus is consumed orally, exclusive use of Camel Snus eliminates the direct exposure of lung tissues to toxicants, thereby mitigating some of the potentially harmful effects of those compounds experienced by cigarette smokers. When considered collectively, the data in Section 2.9.1.2.1 and Section 2.9.1.2.2 show that smokers who switch completely to Camel Snus can reduce their exposure to combustion-related tobacco toxicants without simultaneously increasing their exposure to toxicants present in tobacco (TSNAs).

Table 2.9.1-2: Biomarker studies of TSNA exposure from exclusive Camel Snus use compared to exclusive cigarette use

				Relative TSNA Exposure[a]		
Study	**Measurement Type**	**Sample Matrix**	**Study Design**	**Camel Snus < Cigarettes**	**Camel Snus ≈ Cigarettes**	**Camel Snus > Cigarettes**
CSD0901	Total TSNAs	24-hr Urine	Switching (confinement)	X		
CSD0901	NNN, NAT, NAB	24-hr Urine	Switching (confinement)	X		
CSD0901	NNAL	24-hr Urine	Switching (confinement)		X	
CSD0904	NNN, NAT, NAB, NNAL	24-hr Urine	Cross-sectional (natural adopters)		X[b]	
Blank and Eissenberg 2010	Total NNAL[c]	Urine	Switching (ambulatory)		X	
Hatsukami *et al.* 2016	NNN, NNAL	Urine	Switching (ambulatory)		X[d]	
Kotlyar *et al.* 2011	NNAL	Urine	Switching (ambulatory)	X[e]		
Kotlyar *et al.* 2011	NNN	Urine	Switching (ambulatory)		X[e]	

[a] An "X" in either the "Camel Snus < Cigarettes" or "Camel Snus > Cigarettes" columns indicates a statistically significant difference between Camel Snus and cigarette biomarker results, with Camel Snus less than or greater than cigarettes, respectively. An "X" in the "Camel Snus ≈ Cigarettes" column indicates that no statistically significant difference was observed between Camel Snus and cigarette biomarker results.

[b] Differences in exposure were minimized due to altered product use rates during clinical confinement)

[c] The sum of unconjugated NNAL and NNAL-glucuronide

[d] Statistical significance information not provided for NNN. However, evaluation of data provided suggests no significant difference.

[e] Some dual use of cigarettes and Camel Snus occurred during the study. As reported, 9.1% of subjects smoked on average more than 3 cigarettes per day.

2.9.1.2.3 Exclusive Camel Snus use results in either similar or reduced exposure to nicotine compared with cigarette smoking

Exclusive Camel Snus use results in either similar or reduced exposure to nicotine when compared with exclusive cigarette smoking. Two RJRT-sponsored studies (CSD0901, CSD0904), as well as three studies in the published literature (Hatsukami *et al.* 2016, Kotlyar *et al.* 2011, Cobb *et al.* 2010), have examined biomarkers of nicotine exposure in exclusive Camel Snus users (product switchers and natural product adopters) compared with exclusive cigarette smokers. Recently, the Surgeon General has asserted the biological plausibility of a relationship between nicotine and negative cardiovascular effects, noting that short-term nicotine exposure can elevate heart rate and blood pressure (USDHHS 2016). However, epidemiological data do not suggest that nicotine exposure from non-combustible tobacco products leads to cardiovascular disease.

Studies of smokers who switched to Camel Snus uniformly show reductions in urinary total nicotine equivalents, plasma nicotine and plasma cotinine (*see, e.g.*, CSD0901, Hatsukami *et al.* 2016, Kotlyar *et al.* 2011). An RJRT study of Camel Snus adopters (CSD0904), found equivalent levels of urinary total nicotine equivalents and blood cotinine in exclusive Camel Snus users compared to exclusive cigarette smokers, but reported lower levels of blood nicotine for Camel Snus users. There are no biomarker data suggesting that Camel Snus users are exposed to higher levels of nicotine than cigarette smokers. The biomarker data for exclusive Camel Snus users and exclusive cigarette smokers are summarized in Table 2.9.1-3.

Table 2.9.1-3: Biomarker studies of nicotine exposure from exclusive Camel Snus use compared to exclusive cigarette use

				Relative Nicotine Exposure[a]		
Study	**Measurement Type**	**Sample Matrix**	**Study Design**	**Camel Snus < Cigarettes**	**Camel Snus ≈ Cigarettes**	**Camel Snus > Cigarettes**
CSD0901	Total Nicotine Equivalents[b]	24-hr Urine	Switching (confinement)	X		
CSD0901	Nicotine	Plasma	Switching (confinement)	X		
CSD0901	Cotinine	Plasma	Switching (confinement)	X		
CSD0901	Total Nicotine Equivalents[b]	Feces	Switching (confinement)		X	
CSD0904	Total Nicotine Equivalents[b]	24-hr Urine	Cross-sectional (natural adopters)		X	
CSD0904	Nicotine	Blood	Cross-sectional (natural adopters)	X		
CSD0904	Cotinine	Blood	Cross-sectional (natural adopters)		X	
Cobb *et al*. 2010	Nicotine	Plasma	Single Use[c]	X		
Hatsukami *et al.* 2016	Total Nicotine Equivalents[d]	Urine	Switching (ambulatory)	X		
Hatsukami *et al.* 2016	Total Cotinine	Urine	Switching (ambulatory)	X		
Kotlyar *et al.* 2011	Cotinine	Urine	Switching (ambulatory)	X[e]		

[a] An "X" in either the "Camel Snus < Cigarettes" or "Camel Snus > Cigarettes" columns indicates a statistically significant difference between Camel Snus and cigarette biomarker results, with Camel Snus less than or greater than cigarettes, respectively. An "X" in the "Camel Snus ≈ Cigarettes" column indicates that no statistically significant difference was observed between Camel Snus and cigarette biomarker results.

[b] Unconjugated nicotine and the 9 metabolites were converted to molar unconjugated nicotine equivalents and summed.

[c] Product used twice during a single clinical session

[d] The sum of total nicotine, total cotinine and total 3'hydroxycotinine

[e] Some dual use of cigarettes and Camel Snus occurred during the study. As reported, 9.1% of subjects smoked on average more than 3 cigarettes per day.

2.9.1.2.4 Dual-users of cigarettes and Camel Snus smoke fewer cigarettes per day than exclusive cigarette smokers

Dual users of cigarettes and Camel Snus smoke significantly fewer cigarettes per day than do exclusive cigarette smokers. Exposure to many combustion-related and tobacco toxicants can be reduced following reductions in CPD, either alone (*see*, *e.g.*, Theophilus *et al.* 2015) or in combination with dual use of other smokeless tobacco products (*see*, *e.g.*, Sarkar *et al.* 2010). Such reductions are significant, given the established relationship between risk/severity of adverse health outcomes and duration/level of exposure to these toxicants in tobacco smoke (*see* USDHHS 2010).

Dual users of Camel Snus and cigarettes in the study of natural product adopters (CSD0904) smoked fewer cigarettes per day compared with exclusive cigarette smokers, showing differences of up to 25% (*see* Table 2.9.1-4). These data are directionally consistent with descriptive survey data compiled by RJRT and based on a National Tobacco Behavior Monitor (NTBM), as well as RJRT's Consumer Brand Tracker and NIH/FDA's PATH study. The NTBM data (survey period from Q1 2013 to Q1 2016) estimate the mean rate of cigarette use to be lower among those who report using both cigarettes and Camel Snus (11.8 cigarettes/day) when compared to exclusive cigarette smokers (12.9 cigarettes/day) (Camel Snus Product Use Final Report). By the last survey quarter, the predicted difference in cigarette use rate among exclusive users and those who use both cigarettes and snus increased from approximately 1 to approximately 5 cigarettes per day, with greater use observed for exclusive cigarette smokers.

It is noteworthy that the survey product use rates are reported only for days that products were used (*i.e.,* not averaged across use and non-use days) and that dual users of Camel Snus and cigarettes smoked on fewer days (4.8 days/week) than exclusive smokers (5.9 days/week). It is also important to note that, while mean cigarette use rates changed during clinical confinement, exclusive cigarette smokers smoked more cigarettes than dual users of Camel Snus and cigarettes under both pre-clinic and in-clinic use conditions.

Table 2.9.1-4: Study CSD0904 Product Use Rates of Natural Tobacco Product Adopters*

User Group	Time Point	Pouches/Day		Cigarettes/Day	
		(Mean ± SD)	Min, Max	(Mean ± SD)	Min, Max
Exclusive Cigarettes	Pre-Clinic Use	--	--	18 ± 7 cigarettes	(6, 47)
	In-Clinic Use	--	--	12 ± 4 cigarettes	(4, 27)
Dual Use (Camel Snus + Cigarettes)	Pre-Clinic Use	2 ± 2 pouches	(1, 12)	15 ± 8 cigarettes	(4, 43)
	In-Clinic Use	2 ± 2 pouches	(0, 12)	9 ± 4 cigarettes	(0, 21)
Exclusive Camel Snus	Pre-Clinic Use	4 ± 2 pouches	(1, 8)	--	--
	In-Clinic Use	5 ± 3 pouches	(1, 15)	--	--

* Cigarette use rates changed during the in-clinic portion of the study. Smokers smoked 5-6 fewer cigarettes per day (*see* discussion in Section 2.9.1.2.4).

2.9.1.2.5 Dual use of Camel Snus and cigarettes can reduce exposure to combustion-related toxicants, dependent on the number of cigarettes smoked per day

Dual use of Camel Snus and cigarettes can reduce exposure to combustion-related toxicants compared with exclusive cigarette smoking, dependent on the number of cigarettes smoked per day. Combustion-related toxicants (*e.g.*, carbon monoxide, PAHs, VOCs) are formed primarily during smoking, are generally not present in tobacco, and are known or suspected to cause cancer or toxic effects (Chang *et al.* 2016). Several studies have compared biomarkers of combustion-related toxicant exposure in dual users of Camel Snus and cigarettes with biomarkers from exclusive cigarette smokers. One RJRT-sponsored study examined natural adopters of both Camel Snus and cigarettes (CSD0904), while others evaluated subjects switched partially from cigarettes to Camel Snus (CSD0901, CSD0905, HSD0702). One study from the literature also evaluated subjects switched partially from cigarettes to Camel Snus (Burris *et al.* 2014).

An RJRT-sponsored randomized product switching study, in which subjects confined to clinic reduced their usual-brand smoking by 60%, found that biomarkers in urine, blood and breath were significantly reduced across all examined toxicant categories (CSD0901). Similar results were reported in other studies of smokers switched partially to Camel Snus (CSD0905, HSD0702). A study of natural product adopters, including dual users of both Camel Snus and cigarettes (CSD0904), found more limited differences in those dual users compared with exclusive cigarette smokers. However, significantly lower biomarker levels for thiocyanate, urine mutagenicity and carbon monoxide were reported. It is important to note that mean product use rates among these natural product adopters changed during clinical confinement, with cigarette smokers smoking 5-6 fewer cigarettes per day. This decrease in cigarettes smoked per day was likely due to more limited opportunities to smoke because of study procedures and requirements to smoke inside a designated area (*see* Section 2.9.1.2.4).

The biomarker data summarized in Table 2.9.1-5 show that dual users of Camel Snus and cigarettes can reduce exposure to many combustion-related toxicants compared with exclusive cigarette smokers. It is noteworthy that the dual users enrolled in clinical study CSD0904 exhibited several statistically significant biomarker reductions, despite smoking nearly as many cigarettes (mean 15 per day) as the comparator group of exclusive cigarette smokers (mean 18 per day) during a 24-h in-clinic confinement (*see* Table 2.9.1-4). These results indicate that significant reductions in exposure to combustion-related toxicants are achievable, even for smokers who do not completely switch to Camel Snus. However, the greatest reductions in exposure will result from switching completely to Camel Snus and discontinuing all cigarette smoking.

Table 2.9.1-5: Biomarker studies of combustion-related toxicant exposure from dual use* of Camel Snus and cigarettes compared to exclusive cigarette use

				Relative Toxicant Exposure[a]		
Study[a]	Measurement Type	Sample Matrix	Study Design	Dual Use < Cigarettes	Dual Use ≈ Cigarettes	Dual Use > Cigarettes
CSD0901	Aromatic Amines[b]	24-hr Urine	Switching (confinement)	X[c]		
CSD0901	PAHs[d]	24-hr Urine	Switching (confinement)	X[c]		
CSD0901	PAHs[e]	24-hr Urine	Switching (confinement)		X[c]	
CSD0901	Carbonyls[f]	24-hr Urine	Switching (confinement)	X[c]		
CSD0901	Thiocyanate[g]	24-hr Urine, Plasma	Switching (confinement)	X[c]		
CSD0901	Organic Compounds[h]	24-hr Urine	Switching (confinement)	X[c]		
CSD0901	Mutagens[i]	24-hr Urine	Switching (confinement)	X[c]		
CSD0901	Carbon Monoxide[j]	Blood, Breath	Switching (confinement)	X[c]		
CSD0904	Aromatic Amines[b]	24-hr Urine	Cross-sectional (natural adopters)		X	
CSD0904	PAHs[k]	24-hr Urine	Cross-sectional (natural adopters)		X	
CSD0904	Carbonyls[f]	24-hr Urine	Cross-sectional (natural adopters)		X	
CSD0904	Thiocyanate[g]	24-hr Urine, Blood	Cross-sectional (natural adopters)	X[l]		
CSD0904	Organic Compounds[m]	24-hr Urine	Cross-sectional (natural adopters)		X	
CSD0904	Mutagens[n]	24-hr Urine	Cross-sectional (natural adopters)	X		
CSD0904	Carbon Monoxide[j]	Blood, Breath	Cross-sectional (natural adopters)	X		
CSD0904	Hemoglobin Adducts[o]	Blood	Cross-sectional (natural adopters)		X	
CSD0905	Aromatic Amines[b]	24-hr Urine	Switching (ambulatory)	X		
CSD0905	PAHs[p]	24-hr Urine	Switching (ambulatory)	X		
CSD0905	PAHs[q]	24-hr Urine	Switching (ambulatory)		X	
CSD0905	Carbonyls[f]	24-hr Urine	Switching (ambulatory)	X		
CSD0905	Thiocyanate[g]	24-hr Urine	Switching (ambulatory)	X		
CSD0905	Organic Compounds[h]	24-hr Urine	Switching (ambulatory)	X		
CSD0905	Carbon Monoxide[j]	Blood, Breath	Switching (ambulatory)	X		
HSD0702[r]	Aromatic Amines[b]	24-hr Urine	Switching (ambulatory)	X		
HSD0702[r]	PAHs[s]	24-hr Urine	Switching (ambulatory)	X		
HSD0702[r]	PAHs[t]	24-hr Urine	Switching (ambulatory)		X	
HSD0702[r]	Carbonyls[d]	24-hr Urine	Switching (ambulatory)	X		
HSD0702[r]	Organic Compounds[m]	24-hr Urine	Switching (ambulatory)	X[u]		
HSD0702[r]	Mutagens[n]	24-hr Urine	Switching (ambulatory)	X		
HSD0702[r]	Carbon Monoxide[v]	Blood	Switching (ambulatory)	X		
HSD0702	Hemoglobin Adducts[o]	Blood	Switching (ambulatory)		X	
Burris *et al.* 2014	Carbon Monoxide	Breath	Switching (ambulatory)		X	

* Concurrent use of Camel Snus and cigarettes

[a] An "X" in either the "Camel Snus < Cigarettes" or "Camel Snus > Cigarettes" columns indicates a statistically significant difference between Camel Snus and cigarette biomarker results, with Camel Snus less than or greater than cigarettes, respectively. An "X" in the "Camel Snus ≈ Cigarettes" column indicates that no statistically significant difference was observed between Camel Snus and cigarette biomarker results.
[b] *o*-toluidine, 2-aminonaphthalene, 3-aminobiphenyl and 4-aminobiphenyl
[c] Subjects were allowed to smoke up to 40% of their usual number of cigarettes per day.
[d] 1- and 2-OH-naphthalene; 2-OH-fluorene and 1-, 2-, 3-, 4- and 9-OH-phenanthrene
[e] 1-OH-pyrene
[f] Acrolein and crotonaldehyde
[g] Biomarker of hydrogen cyanide exposure
[h] Acrylonitrile; acrylamide; 1,3-butadiene; benzene and ethylene oxide
[i] Compounds that are mutagenic in the Ames assay (strain YG1024)
[j] Exhaled breath carbon monoxide, blood carboxyhemoglobin
[k] 1-OH-pyrene, 2-OH-fluorene, phenanthrene equivalents, naphthalene equivalents (*see* RDM PC 2016 274-a)
[l] Weighted values were significantly lower in dual users compared with cigarette smokers. Unweighted values were reduced, but did not reach statistical significance.
[m] Acrylamide; 1,3-butadiene and benzene
[n] Includes measurement of compounds that are mutagenic in the Ames assay (strains TA98 and YG1024)
[o] Includes measurement of 4-aminobiphenyl hemoglobin adducts in blood
[p] 1-OH-napthalene, 2-OH-napthalene, 2-OH-fluorene
[q] 1-, 2-, 3-, 4- and 9-OH-phenanthrene; 1-OH-pyrene
[r] Subject compliance with assigned study product was less than 100%, making estimates relevant to dual use.
[s] 2-naphthol, 2-OH-fluorene, 1-/9-OH-phenanthrene, 2-/3-OH-phenanthrene
[t] 1-naphthol, 1-OH-pyrene
[u] Although one metabolite of 1,3-butadiene (DHBMA) was not significantly reduced; a second, more specific marker (MHBMA) was statistically significantly reduced at both Week 12 and Week 24.
[v] Blood carboxyhemoglobin

2.9.1.2.6 Dual use of Camel Snus and cigarettes can reduce exposure to toxicants in tobacco (TSNAs), depending upon the number of cigarettes smoked per day

Dual users of Camel Snus and cigarettes can reduce their exposure to tobacco toxicants (TSNAs) compared with exclusive cigarette smokers, depending on the number of cigarettes smoked per day. As discussed above in Section 2.9.1.2.2, TSNAs are considered to be drivers of cancer risk associated with tobacco use. RJRT-sponsored clinical studies discussed in the previous sections (CSD0901, CSD0904, CSD0905, HSD0702), as well as one published study (Hatsukami *et al.* 2016), have accordingly examined urinary biomarkers of tobacco-related toxicants in dual users of Camel Snus and cigarettes. Study designs included smokers switched partially to Camel Snus while in confinement or under ambulatory conditions, as well as cross-sectional study of Camel Snus and cigarette natural adopters.

An RJRT-sponsored cross-sectional study including natural adopters of both Camel Snus and cigarettes (CSD0904) found urinary levels of NNN, NAT, NAB and NNAL to be similar between those dual users and cigarette smokers. Three randomized product-switching studies show reduced levels of some TSNA biomarkers in smokers switched partially to Camel Snus use (CSD0901, CSD0905, HSD0702), while one product-switching (smoking cessation) study reported no differences (Hatsukami *et al.* 2016). There are no biomarker data to suggest that dual users of Camel Snus and cigarettes exhibit higher levels of urinary TSNAs than cigarette smokers.

The TSNA biomarker results summarized below in Table 2.9.1-6 show that dual users of Camel Snus and cigarettes exhibit similar or reduced levels of these compounds when compared with exclusive cigarette smokers. When considered collectively, the data in Section 2.9.1.2.5 and Section 2.9.1.2.6 show that smokers who switch partially to Camel Snus can reduce their exposure to both combustion-related toxicants and toxicants transferred from tobacco to smoke. However, the greatest reductions in exposure will result from switching completely to Camel Snus and discontinuing all cigarette smoking.

Table 2.9.1-6: Biomarker Studies of TSNA exposure from dual use[*] of Camel Snus and cigarettes compared to exclusive cigarette use

				Relative TSNA Exposure[a]		
Study	Measurement Type	Sample Matrix	Study Design	Dual Use < Cigarettes	Dual Use ≈ Cigarettes	Dual Use > Cigarettes
CSD0901[b]	NAT, NAB, NNAL	24-hour Urine	Switching (confinement)	X		
CSD0901[b]	NNN	24-hour Urine	Switching (confinement)		X	
CSD0904	NNN, NAT, NAB, NNAL	24-hour Urine	Cross-sectional (natural adopters)		X	
CSD0905	Total TSNAs	24-hour Urine	Switching (ambulatory)		X	
CSD0905	NNN, NAT	24-hour Urine	Switching (ambulatory)		X	
CSD0905	NAB, NNAL	24-hour Urine	Switching (ambulatory)	X[c]		
HSD0702[d]	Total NNAL[e]	24-hour Urine	Switching (ambulatory)	X		
Hatsukami *et al.* 2016	NNN, NNAL	Urine	Switching (ambulatory)		X[f]	

[*] Concurrent use of Camel Snus and cigarettes

[a] An "X" in either the "Dual Use < Cigarettes" or "Dual Use > Cigarettes" columns indicates a statistically significant difference between Dual Use and cigarette biomarker results, with Dual Use less than or greater than cigarettes, respectively. An "X" in the "Dual Use ≈ Cigarettes" column indicates that no statistically significant difference was observed between Dual Use and cigarette biomarker results.

[b] Subjects were allowed to smoke up to 40% of their usual number of cigarettes per day.

[c] Statistical significance was nominal (p = 0.07) for NNAL.

[d] Subject compliance with assigned study product was less than 100%, making estimates relevant to dual use.

[e] The sum of unconjugated NNAL and NNAL-glucuronide

[f] Statistical significance information not provided; evaluation of data provided suggests no significant difference.

2.9.1.2.7 Dual use of Camel Snus and cigarettes results in either similar or reduced exposure to nicotine, depending upon the number of cigarettes smoked per day

Dual use of Camel Snus and cigarettes results in either similar or reduced exposure to nicotine compared with exclusive cigarette smokers, depending on the number of cigarettes smoked per day. Four RJRT-sponsored studies (CSD0901, CSD0904, CSD0905, HSD0702), as well as one external study (Hatsukami *et al.* 2016), have examined biomarkers of nicotine exposure in dual users of Camel Snus and cigarettes compared with exclusive cigarette smokers. Study designs included smokers switched partially to Camel Snus while in confinement or ambulatory, as well as recruited natural adopters of both Camel Snus and cigarettes.

A study of smokers confined to clinic and instructed to reduce their cigarettes per day by at least 60% reported significant reductions in all urine and plasma nicotine biomarkers (CSD0901). Other studies of smokers switched partially to Camel Snus (CSD0905, HSD0702, Hatsukami *et al.* 2016), as well as a cross-sectional investigation of natural adopters of both Camel Snus and cigarettes (CSD0904), have reported comparable levels of nicotine biomarkers for both dual users and exclusive cigarette smokers. One ambulatory clinical study (CSD0905) of users switched partially to Camel Snus showed a small but significant increase from baseline in serum cotinine levels at a single time point, but this increase was not mirrored in 24-hour urine total nicotine equivalents.

Overall, the data summarized in Table 2.9.1-7 demonstrate that dual users of Camel Snus and cigarettes experience similar or reduced exposure to nicotine when compared to exclusive cigarette smokers. Collectively, these results indicate that smokers who switch partially to Camel Snus experience generally similar, or reduced, exposure to nicotine while simultaneously reducing exposure to combustion-related toxicants and toxicants transferred from tobacco to smoke. The greatest reductions in exposure will result from switching completely to Camel Snus and discontinuing all cigarette smoking.

Table 2.9.1-7: Biomarker studies of nicotine exposure from dual use* of Camel Snus and cigarettes compared to exclusive cigarette use

				Relative Nicotine Exposure[a]		
Study	**Measurement Type**	**Sample Matrix**	**Study Design**	**Dual Use < Cigarettes**	**Dual Use ≈ Cigarettes**	**Dual Use > Cigarettes**
CSD0901[b]	Total Nicotine Equivalents[c]	24-hr Urine	Switching (confinement)	X		
CSD0901[b]	Nicotine	Plasma	Switching (confinement)	X		
CSD0901[b]	Cotinine	Plasma	Switching (confinement)	X		
CSD0901[b]	Total Nicotine Equivalents[c]	Feces	Switching (confinement)		X	
CSD0904	Total Nicotine Equivalents[c]	24-hr Urine	Cross-sectional (natural adopters)		X	
CSD0904	Nicotine	Blood	Cross-sectional (natural adopters)		X	
CSD0904	Cotinine	Blood	Cross-sectional (natural adopters)		X	
CSD0905	Total Nicotine Equivalents[c]	24-hr Urine	Switching (ambulatory)		X	
CSD0905	Cotinine	Serum	Switching (ambulatory)		X	
HSD0702[d]	Total Nicotine Equivalents[c]	24-hr Urine	Switching (ambulatory)		X	
HSD0702[d]	Cotinine – Week 12	Serum	Switching (ambulatory)		X	
HSD0702[d]	Cotinine – Week 24	Serum	Switching (ambulatory)			X[e]
Hatsukami *et al.* 2016	Total Nicotine Equivalents[f]	Urine	Switching (ambulatory)		X[g]	
Hatsukami *et al.* 2016	Total Cotinine	Urine	Switching (ambulatory)		X[g]	

* Concurrent use of Camel Snus and cigarettes

[a] An "X" in either the "Dual Use < Cigarettes" or "Dual Use > Cigarettes" columns indicates a statistically significant difference between Dual Use and cigarette biomarker results, with Dual Use less than or greater than cigarettes, respectively. An "X" in the "Dual Use ≈ Cigarettes" column indicates that no statistically significant difference was observed between Dual Use and cigarette biomarker results.

[b] Subjects were allowed to smoke up to 40% of their usual number of cigarettes per day.

[c] Unconjugated nicotine and the 9 metabolites were converted to molar unconjugated nicotine equivalents and summed.

[d] Subject compliance with assigned study product was less than 100%, making estimates relevant to dual use.

[e] A statistically significant increase (1.59 nmol/L to 2.09 nmol/L) was observed at Week 24 compared with Baseline.

[f] The sum of total nicotine, total cotinine and total 3'hydroxycotinine

[g] Statistical significance information not provided; evaluation of data provided suggests no significant difference.

2.9.1.2.8 Camel Snus use results in exposure to only a fraction of the toxicants and nicotine present in the tobacco

Camel Snus use results in exposure to only a fraction of the toxicants and nicotine present in the tobacco because Camel Snus pouches are not ingested during use. Rather, Camel Snus users place the pouch between their upper lip and gum, and discard the pouch after a period of use. RJRT-sponsored clinical studies of actual product use by natural adopters and by product switchers have included chemical analysis of compounds present in Camel Snus pouches before and after use. The differences in those quantities provide estimates of the amounts of tobacco-related toxicants and nicotine depleted from the pouch during use, *i.e.*, the "mouth-level" exposure (MLE) experienced when using Camel Snus. MLE is an estimate of maximum potential exposure to a toxicant or nicotine. The MLE data from RJRT-sponsored clinical studies show that Camel Snus users are exposed to only a fraction of the tobacco-related toxicants present initially in Camel Snus pouches (*see* Table 2.9.1-8, Table 2.9.1-9 and Table 2.9.1-10).

TSNAs were analyzed in used Camel Snus pouches in studies CSD0804, CSD0904, CSD0905 and HSD0702. For TSNAs, mean quantities of up to 40% were removed from the Camel Snus pouch during product use. For B[a]P, mean quantities of up to 29% were removed during product use (CSD0804). Nicotine MLE was assessed in studies CSD0804, CSD0901, CSD0904, CSD0905, CSD0914 and HSD0702. Mean nicotine quantities of up to 37% were removed during product use. Trace metals were analyzed in clinical studies CSD0804 and CSD0905, but the data were inconclusive because of limitations of the analytical methodology applied.

Table 2.9.1-8: Mouth-level exposure (MLE) studies of external TSNA exposure for exclusive Camel Snus users and dual users[*] of Camel Snus and cigarettes

Study	Study Design	Product Use Condition	MLE (ng/pouch)[a]	% Removed from Pouch[b]
NNN				
CSD0804	Cross-sectional	Camel Snus	97.1 (92.7)	23.1 (22.1)
CSD0904	Cross-sectional	Camel Snus (pre-clinic)	225.7 (199.5)	40.7 (36.7)
CSD0904	Cross-sectional	Dual Use (pre-clinic)	166.9 (220.8)	28.7 (35.4)
CSD0905	Switching	Dual Use	78.4 (50.2)	18.6 (11.9)
HSD0702[c]	Switching	Dual Use[d]	41 (52)	17.2 (21.5)
NNK				
CSD0804	Cross-sectional	Camel Snus	37.5 (28.2)	29.9 (20.6)
CSD0904	Cross-sectional	Camel Snus (pre-clinic)	73.6 (62.3)	40.4 (34.0)
CSD0904	Cross-sectional	Dual Use (pre-clinic)	52.8 (58.4)	26.5 (26.1)
CSD0905	Switching	Dual Use	18.1 (19.1)	13.4 (13.9)
HSD0702[c]	Switching	Dual Use[d]	5 (21)	7.1 (38.3)
NAT				
CSD0804	Cross-sectional	Camel Snus	34.1 (57.4)	15.6 (26.2)
CSD0904	Cross-sectional	Camel Snus (pre-clinic)	37.2 (112.2)	17.4 (52.7)
CSD0904	Cross-sectional	Dual Use (pre-clinic)	-11.9 (200.3)[e]	-7.6 (99.2)[e]
CSD0905	Switching	Dual Use	10.7 (38.8)	5.2 (19.5)
HSD0702[c]	Switching	Dual Use[d]	4 (47)	2.1 (27.9)

Study	Study Design	Product Use Condition	MLE (ng/pouch)[a]	% Removed from Pouch[b]
NAB				
CSD0804	Cross-sectional	Camel Snus	2.8 (11.7)	9.5 (40.4)
CSD0904	Cross-sectional	Camel Snus (pre-clinic)	-1.8 (29.8)[e]	-6.6 (99.1)[e]
CSD0904	Cross-sectional	Dual Use (pre-clinic)	-15.0 (64.4)[e]	-52.3 (219.2)[e]
CSD0905	Switching	Dual Use	-3.6 (7.5)[e]	-14.7 (30.5)[e]

* Concurrent use of Camel Snus and cigarettes
[a] Mean (standard deviation)
[b] Mean (standard deviation)
[c] Subject compliance with assigned study product was less than 100%, making estimates relevant to dual use.
[d] 24-week use results
[e] Negative values may be due to differences between the unused snus products and the products actually used by the subjects or an artifact of variability of the analytical method used (*see* CSD0904, CSD0905).

Table 2.9.1-9: Mouth-level exposure (MLE) studies of external B[a]P exposure for exclusive Camel Snus users and dual users* of Camel Snus and cigarettes

Study	Study Design	Product Use Condition	B[a]P MLE (ng/pouch)[a]	% B[a]P Removed From Pouch[b]
CSD0804	Cross-sectional	Camel Snus	0.2 (0.1)	29.0 (13.8)
CSD0905	Switching	Dual Use	0.0 (0.1)	-6.6 (13.8)[c]

* Concurrent use of Camel Snus and cigarettes
[a] Mean (standard deviation)
[b] Mean (standard deviation)
[c] Negative values may be due to differences between the unused snus products and the products actually used by the subjects (*see* CSD0904) or an artifact of variability of the analytical method used (*see* CSD0905).

Table 2.9.1-10: Mouth-level exposure (MLE) studies of external nicotine exposure for exclusive Camel Snus users and dual users* of Camel Snus and cigarettes

Study	Study Design	Product Use Condition	Nicotine MLE (mg/pouch)[a]	% Nicotine Removed From Pouch[b]
CSD0804	Cross-sectional	Camel Snus	2.8 (1.7)	39.2 (23.0)
CSD0901	Switching	Camel Snus[c]	2.7 (1.2)	39.7
CSD0901	Switching	Dual Use[c]	2.7 (1.3)	39.3
CSD0904	Cross-sectional	Camel Snus (pre-clinic)	1.9 (1.6)	38.5 (30.9)
CSD0904	Cross-sectional	Dual Use (pre-clinic)	1.1 (1.7)	21.3 (33.7)
CSD0904	Cross-sectional	Camel Snus (in-clinic)	1.8 (1.6)	35.7 (31.7)
CSD0904	Cross-sectional	Dual Use (in-clinic)	1.0 (1.5)	20.0 (28.1)
CSD0905	Switching	Dual Use	1.6 (1.1)	22.2 (14.7)
CSD0914	Single Use	Camel Snus	2.3 (1.6)	31.7 (22.8)
HSD0702[d]	Switching	Dual Use[e]	1.8 (1.1)	32.4 (20.7)

* Concurrent use of Camel Snus and cigarettes
[a] Mean (standard deviation)
[b] Mean (standard deviation). When standard deviation is not shown, the mean value was calculated from means of mouth-level nicotine and nicotine remaining in used Camel Snus pouches.
[c] Day 5 use results
[d] Subject compliance with assigned study product was less than 100%, making estimates relevant to dual use.
[e] 24-week use results

2.9.1.2.9 Use of different Camel Snus pouch sizes results in similar exposure to nicotine and TSNAs

Camel Snus users are exposed to similar levels of nicotine and TSNAs, regardless of Camel Snus pouch size. Four RJRT-sponsored clinical studies of 0.4 g and 0.6 g Camel Snus styles (CSD0901, CSD0904, CSD0905 and HSD0702) and one external study of primarily 1.0 g Camel Snus styles (Hatsukami *et al.* 2016) have evaluated nicotine and TSNA exposure. To compare urinary biomarker results from the different studies in order to assess potential exposure differences due to Camel Snus pouch size, selected biomarker results from RJRT-sponsored studies were converted (*see* RDM PC 2016 175-a) to the units reported by Hatsukami *et al.* 2016. Based on the biomarker endpoints reported in that study, total cotinine, total nicotine equivalents, total NNAL and total NNN results were transformed.

Similar nicotine and TSNA biomarker levels were observed for all Camel Snus pouch sizes (*see* Table 2.9.1-11 and Table 2.9.1-12). No trends associated with Camel Snus pouch size were evident, with mean biomarker levels for users of 0.4 g and 1.0 g products falling largely within the range observed for users of 0.6 g products. The consistency of these biomarker results across various studies suggests that Camel Snus pouch size is not a principal driver of exposure to nicotine and toxicants.

Table 2.9.1-11: Urinary nicotine biomarkers by exclusive or dual Camel Snus use*

Study	Study Design	Camel Snus Pouch Size (g)	Duration of Use (weeks)	Total Nicotine Equivalents (nmol/mL)			Total Cotinine (ng/mL)		
				Mean	SD	N	Mean	SD	N
Exclusive Camel Snus Use									
CSD0901	Switching	0.6	1	30.0	30.2	30	1974	2099	30
CSD0904[a]	Cross-sectional	0.6	24+	41.9	49.3	50	2417	2338	50
Hatsukami *et al.* 2016[b]	Switching	1.0	4	35.6	31.0	53	2152	2005	53
Dual Use									
HSD0702[c,d]	Switching	0.4	24	43.0	16.8	29	3054	1421	29
CSD0901	Switching	0.6	1	40.9	21.1	29	2564	1397	29
CSD0904[a]	Cross-sectional	0.6	24+	65.5	53.6	50	3866	2937	50
CSD0905	Switching	0.6	4	76.2	50.9	33	4065	2704	33
Hatsukami *et al.* 2016[b]	Switching	1.0	4	55.7	43.0	100	3079	2398	100

* Concurrent use of Camel Snus and cigarettes

[a] One subject in the Camel Snus group and one subject in the Dual Use group used 1.0 g pouch size products.

[b] Some participants who experienced adverse effects from use of 1.0 g pouch size products were provided 0.6 g pouch size products.

[c] Intent-to-treat subject group. Similar results were observed for the per-protocol subject group.

[d] Subject compliance with assigned study product was less than 100%, making estimates relevant to dual use.

Table 2.9.1-12: Urinary TSNA biomarkers by exclusive or dual Camel Snus use[*]

Study	Study Design	Camel Snus Pouch Size (g)	Duration of Use (weeks)	Total NNAL[a] (pmol/mg creatinine)			Total NNN[b] (pmol/mg creatinine)		
				Mean	SD	N	Mean	SD	N
Exclusive Camel Snus Use									
CSD0901	Switching	0.6	1	1.39	0.85	30	0.07	0.17	30
CSD0904[c]	Cross-sectional	0.6	24+	1.64	2.31	50	0.04	0.04	50
Hatsukami *et al.* 2016[d]	Switching	1.0	4	1.34	1.42	52	0.06	0.07	18
Dual Use (Concurrent Camel Snus and Cigarettes)									
HSD0702[e,f]	Switching	0.4	24	1.72	0.99	28	NA[g]	NA[g]	NA[g]
CSD0901	Switching	0.6	1	1.83	1.11	29	0.13	0.26	29
CSD0904[a]	Cross-sectional	0.6	24+	1.60	1.31	50	0.05	0.04	50
CSD0905	Switching	0.6	4	4.23	2.59	33	0.15	0.11	33
Hatsukami *et al.* 2016	Switching	1.0	4	1.55	1.67	96	0.11	0.10	23

[*] Concurrent use of Camel Snus and cigarettes
[a] The sum of unconjugated NNAL and NNAL-glucuronide
[b] The sum of unconjugated NNN and NNN-glucuronide
[c] One subject in the Camel Snus group and one subject in the Dual Use group used 1.0 g pouch size products.
[d] Some participants who experienced adverse effects from use of 1.0 g pouch size products were provided 0.6 g pouch size products.
[e] Intent-to-treat subject group. Similar results were observed for the per-protocol subject group.
[f] Subject compliance with assigned study product was less than 100%, making estimates relevant to dual use.
[g] Not applicable

2.9.1.2.10 Reduced tobacco toxicant exposure profiles for Camel Snus users compared with cigarette smokers are generally consistent with results for other U.S. smokeless tobacco users

Reduced toxicant exposure profiles for Camel Snus users compared with cigarette smokers are generally consistent with results for other U.S. smokeless tobacco users. Numerous clinical studies, including cross-sectional and randomized product-switching studies sponsored by RJRT and others, as well as large nationally-representative studies (NHANES), have reported biomarker data on exposures in smokeless tobacco users and cigarette smokers.

Clinical studies uniformly show lower levels of many combustion-related toxicant biomarkers for smokeless tobacco users compared with cigarette smokers. Consistently reduced biomarkers include aromatic amines, carbon monoxide, carbonyl compounds, hydrogen cyanide, mutagens and various other organic compounds. Most polycyclic aromatic hydrocarbon (PAH) biomarkers are also consistently reduced in smokeless tobacco users, though similar levels have been reported in some studies for particular PAHs (*see* Benowitz *et al.* 1989, reporting similar levels of 1-hydroxypyrene and total hydroxyphenanthrenes; Naufal *et al.* 2011, reporting similar levels of 9-hydroxyfluorene and 1-hydroxyphenanthrene). The utility of 1-hydroxypyrene in tobacco studies has been questioned, in particular, due to confounding

exposure from alternative sources (*see, e.g.*, Hecht *et al.* 2004, St. Helen *et al.* 2012, USDHHS 2010). The only combustion-related toxicant biomarkers reported to be higher in smokeless tobacco users are some halogenated aromatic hydrocarbons (HAHs) (Naufal *et al.* 2011), and these results may be confounded due to enhanced metabolic clearance of these compounds in cigarette smokers (*see* Jain and Wang 2011). Biomarker data summarized in Table 2.9.1-13 demonstrate that smokeless tobacco use, like Camel Snus use, reduces exposure to combustion-related toxicants compared with exclusive cigarette smoking.

Smokeless tobacco users can experience greater exposure to some tobacco-related toxicants (TSNAs) when compared with cigarette smokers (*see* Table 2.9.1-14), as illustrated by NHANES biomarker data (*see, e.g.*, Naufal *et al.* 2011, Rostron *et al.* 2015). In contrast, some heavy metal biomarkers are consistently lower in smokeless tobacco users (*e.g.*, cadmium; *see, e.g.*, Marano *et al.* 2012b, Naufal *et al.* 2011, Prasad *et al.* 2016, Rostron *et al.* 2015), while others differ between studies (*e.g.*, lead) or are similar to cigarette smokers (*e.g.*, arsenic; *see, e.g.*, Naufal *et al.* 2011, Rostron *et al.* 2015). Heavy metal biomarker data for smokeless tobacco users compared to cigarette smokers are summarized in Table 2.9.1-15.

Clinical studies of smokeless tobacco users show that they experience similar or increased exposure to nicotine when compared to cigarette smokers (*see* Table 2.9.1-16). Due to first-pass liver metabolism of orally-ingested nicotine, cotinine biomarker levels may overestimate actual nicotine exposure from use of smokeless tobacco (*see, e.g.*, Ebbert *et al*. 2004; Henningfield *et al*. 2017).

Overall, the data summarized in Table 2.9.1-13, Table 2.9.1-14, Table 2.9.1-15 and Table 2.9.1-16 demonstrate that reduced toxicant profiles in smokeless tobacco users are generally consistent with results for Camel Snus users compared with cigarette smokers. Despite potential increased exposure to nicotine or TSNAs for smokeless tobacco users compared to cigarette smokers, reduced combustion-related toxicant exposure profiles are still observed in smokeless tobacco users that are, overall, comparable to those seen in users of Camel Snus.

Table 2.9.1-13: Biomarker studies of combustion-related tobacco toxicants in exclusive smokeless tobacco[*] users compared to exclusive Cigarette Smokers

Study	Measurement Type	Sample Matrix	Study Design	Relative Toxicant Exposure[a]		
				ST < Cigarettes	ST ≈ Cigarettes	ST > Cigarettes
CSD0904	Aromatic Amines[b]	24-hr Urine	Cross-sectional (natural adopters)	X		
CSD0904	PAHs[c]	24-hr Urine	Cross-sectional (natural adopters)	X		
CSD0904	PAHs[d]	24-hr Urine	Cross-sectional (natural adopters)		X	
CSD0904	Carbonyls[e]	24-hr Urine	Cross-sectional (natural adopters)	X		
CSD0904	Thiocyanate[f]	24-hr Urine, Blood	Cross-sectional (natural adopters)	X		
CSD0904	Organic Compounds[g]	24-hr Urine	Cross-sectional (natural adopters)	X		
CSD0904	Mutagens[h]	24-hr Urine	Cross-sectional (natural adopters)	X		
CSD0904	Carbon Monoxide[i]	Breath, Blood	Cross-sectional (natural adopters)	X		
CSD0904	Hemoglobin Adducts[j]	Blood	Cross-sectional (natural adopters)	X		
Benowitz *et al.* 1989	Mutagens[k]	Urine	Crossover (confinement)	X		
Benowitz *et al.* 2012	PAHs[l]	Urine	Cross-sectional (natural adopters)	X		
Benowitz *et al.* 2012	PAHs[m]	Urine	Cross-sectional (natural adopters)		X	
Campbell *et al.* 2015	Carbon Monoxide[n]	Blood	Cross-sectional (natural adopters)	X		
Campbell *et al.* 2015	PAHs[o]	Spot Urine	Cross-sectional (natural adopters)	X		
Campbell *et al.* 2015	Organic Compounds[p]	Spot Urine	Cross-sectional (natural adopters)	X		
Campbell *et al.* 2015	Carbonyls[e]	Spot Urine	Cross-sectional (natural adopters)	X		
Campbell *et al.* 2015	Aromatic Amines[q]	Spot Urine	Cross-sectional (natural adopters)	X		
Naufal *et al.* 2011	Organic Compounds[r]	Blood	NHANES (1999 to 2008)	X		
Naufal *et al.* 2011	HAHs	Urine	NHANES (1999 to 2008)		X[s]	X[s]
Naufal *et al.* 2011	PAHs[t]	Urine	NHANES (1999 to 2008)	X		
Naufal *et al.* 2011	PAHs[u]	Urine	NHANES (1999 to 2008)		X	
Prasad *et al.* 2016	HCN	Blood	Cross-sectional (natural adopters)	X		
Prasad *et al.* 2016	PAHs[v]	24-hr Urine	Cross-sectional (natural adopters)	X		
Prasad *et al.* 2016	Aromatic Amines[w]	24-hr Urine	Cross-sectional (natural adopters)	X		
Prasad *et al.* 2016	Organic Compounds[x]	24-hr Urine	Cross-sectional (natural adopters)	X		
Rostron *et al.* 2015	Acrylonitrile (CYMA)	Urine	NHANES (1999 to 2012)	X		

[*] Camel Snus results are excluded from this table.

[a] An "X" in either the "ST < Cigarettes" or "ST > Cigarettes" columns indicates a statistically significant difference between smokeless tobacco and cigarette biomarker results, with smokeless tobacco less than or greater than cigarettes, respectively. An "X" in the "ST ≈ Cigarettes" column indicates that no statistically significant difference was observed between smokeless tobacco and cigarette biomarker results.

[b] *o*-toluidine, 2-aminonaphthalene, 3-aminobiphenyl and 4-aminobiphenyl

[c] 1-OH-pyrene, 2-OH-fluorene and naphthalene equivalents (*see* RDM PC 2016 274-a)
[d] Phenanthrene equivalents (*see* RDM PC 2016 274-a)
[e] Acrolein and crotonaldehyde
[f] Biomarker of hydrogen cyanide exposure
[g] Acrylamide; 1,3-butadiene and benzene
[h] Compounds that are mutagenic in the Ames assay (strain YG1024)
[i] Exhaled breath carbon monoxide and blood carboxyhemoglobin
[j] 4-aminobiphenyl hemoglobin adducts in blood
[k] Statistical comparison of smokeless tobacco products to cigarettes was not reported. The number of revertant colonies/5 mL reported for cigarettes was approximately 6-fold that reported for oral snuff and 3-fold that reported for chewing tobacco.
[l] 2-naphthol, sum of hydroxyfluorenes
[m] 1-hydroxypyrene, sum of hydroxyphenanthrenes
[n] Blood carboxyhemoglobin
[o] 1-OH-pyrene
[p] Benzene; 1,3-butadiene and acrylamide
[q] *o*-Toluidine, 2-aminonaphthalene, 3-aminobiphenyl and 4-aminobiphenyl
[r] Acrylamide (AA/GA adducts), benzene, toluene, ethylbenzene, xylene and styrene
[s] Levels of halogenated aromatic hydrocarbons (polychlorinated dibenzo-p-dioxins and dibenzofurans) in users of smokeless tobacco were higher than or comparable to those reported in smokers.
[t] 2-OH-naphthalene, 1-OH-naphthalene, 4-OH-phenanthrene, 3-OH-phenanthrene, 2-OH-phenanthrene, 3-OH-fluorene, 2-OH-fluorene and 1-OH-pyrene
[u] 9-OH-fluorene and 1-OH-phenanthrene
[v] 1- and 9-OH-phenanthrene, 1-OH-pyrene, 1-napthol, 2- and 3-OH-phenanthrene, 2-OH-fluorene and 2-naphthol
[w] 2-aminonaphthalene, 4-aminobiphenyl and *o*-toluidine were significantly lower in users of smokeless tobacco. Levels of 3-aminobiphenyl were significantly lower in smokers compared to users of smokeless tobacco and to non-users of tobacco.

Table 2.9.1-14: Biomarker studies of TSNA exposure from exclusive smokeless tobacco* use compared to exclusive cigarette smokers

Study	Measurement Type	Sample Matrix	Study Design	Relative TSNA Exposure[a]		
				ST < Cigarettes	ST ≈ Cigarettes	ST > Cigarettes
CSD0904	NNN, NAT, NAB, NNAL	24-hr Urine	Cross Sectional (natural adopters)			X
Benowitz *et al.* 2012	NNAL-T[b]	Urine	Cross-sectional (natural adopters)			X
Benowitz *et al.* 2012	NNN-T[c]	Urine	Cross-sectional (natural adopters)		X	
Campbell *et al.* 2015	NNAL-T	Urine	Cross-sectional (natural adopters)			X
Hatsukami *et al.* 2004a	NNAL-T	Urine	Switching (baseline values)		X	
Hatsukami *et al.* 2007b	NNAL-T	Urine	Composite[d]		X	X
Hecht *et al.* 2007	NNAL-T	Urine	Cross-sectional (six studies)[e]			X
Kresty *et al.* 1996	NNAL-Gluc, NNAL	Urine	Cross-sectional (natural adopters)		X	
Naufal *et al.* 2011	NNAL-T	Urine	NHANES (1999 to 2008)			X
Prasad *et al.* 2016	NNAL-T	24-hr Urine	Cross-sectional (natural adopters)			X
Rostron *et al.* 2015	NNAL-T	Urine	NHANES (1999 to 2012)			X
Stepanov and Hecht 2005	NNN, NAT, NAB, NNAL	Urine	Cross-sectional (natural adopters)			X

* Camel Snus results excluded from this table.

[a] An "X" in either the "ST < Cigarettes" or "ST > Cigarettes" columns indicates a statistically significant difference between smokeless tobacco and cigarette biomarker results, with smokeless tobacco less than or greater than cigarettes, respectively. An "X" in the "ST ≈ Cigarettes" column indicates that no statistically significant difference was observed between smokeless tobacco and cigarette biomarker results.

[b] The sum of unconjugated NNAL and NNAL-glucuronide

[c] The sum of unconjugated NNN and NNN-glucuronide

[d] Composite data from multiple studies, including natural adopters of smokeless tobacco and smokers switched to smokeless tobacco. Use of more conventional smokeless tobacco products (Copenhagen, Kodiak, Skoal) resulted in higher total NNAL concentrations in urine compared with cigarette use, while others (Skoal Bandit) resulted urinary total NNAL levels comparable to cigarette smoking.

Table 2.9.1-15: Biomarker studies of metal exposure from exclusive smokeless tobacco* use compared to exclusive cigarette use

Study	Measurement Type	Sample Matrix	Study Design	Relative Metal Exposure[a]		
				ST < Cigarettes	ST ≈ Cigarettes	ST > Cigarettes
Marano *et al.* 2012b	Cadmium	Blood/Urine	NHANES (1999 to 2006)	X		
Naufal *et al.* 2011	Cadmium	Blood	NHANES (1999 to 2008)	X		
Naufal *et al.* 2011	Cadmium	Urine	NHANES (1999 to 2008)	X		
Naufal *et al.* 2011	Lead	Blood	NHANES (1999 to 2008)	X		
Naufal *et al.* 2011	Lead	Urine	NHANES (1999 to 2008)		X	
Naufal *et al.* 2011	Cobalt	Urine	NHANES (1999 to 2008)		X	
Naufal *et al.* 2011	Arsenic	Urine	NHANES (1999 to 2008)		X	
Naufal *et al.* 2011	Selenium	Blood	NHANES (1999 to 2008)		X	
Naufal *et al.* 2011	Mercury	Blood	NHANES (1999 to 2008)		X	
Naufal *et al.* 2011	Mercury	Urine	NHANES (1999 to 2008)		X	
Prasad *et al.* 2016	Cadmium	Urine	Cross-sectional (natural adopters)	X		
Prasad *et al.* 2016	Chromium	Urine	Cross-sectional (natural adopters)		X	
Prasad *et al.* 2016	Nickel	Urine	Cross-sectional (natural adopters)		X	
Prasad *et al.* 2016	Tin	Urine	Cross-sectional (natural adopters)		X	
Prasad *et al.* 2016	Selenium	Urine	Cross-sectional (natural adopters)		X	
Rostron *et al.* 2015	Total Arsenic	Urine	NHANES (1999 to 2012)		X	
Rostron *et al.* 2015	Cadmium	Blood	NHANES (1999 to 2012)	X		
Rostron *et al.* 2015	Lead	Blood	NHANES (1999 to 2012)		X	
Rostron *et al.* 2015	Total Mercury	Blood	NHANES (1999 to 2012)		X	

* Camel Snus results excluded from this table.

[a] An "X" in either the "ST < Cigarettes" or "ST > Cigarettes" columns indicates a statistically significant difference between smokeless tobacco and cigarette biomarker results, with smokeless tobacco less than or greater than cigarettes, respectively. An "X" in the "ST ≈ Cigarettes" column indicates that no statistically significant difference was observed between smokeless tobacco and cigarette biomarker results.

Table 2.9.1-16: Biomarker studies of nicotine exposure from exclusive smokeless tobacco* use compared to exclusive cigarette use

				Relative Nicotine Exposure[a]		
Study	**Measurement Type**	**Sample Matrix**	**Study Design**	**ST < Cigarettes**	**ST ≈ Cigarettes**	**ST > Cigarettes**
CSD0904	Total Nicotine Equivalents[b]	24-hr Urine	Cross-sectional (natural adopters)			X
CSD0904	Nicotine	Blood	Cross-sectional (natural adopters)			X
CSD0904	Cotinine	Blood	Cross-sectional (natural adopters)			X
Benowitz *et al.* 1988	Nicotine C_{max}	Blood	Single Use		X	
Benowitz *et al.* 1988	Nicotine AUC	Blood	Single Use			X
Benowitz *et al.* 1989	Nicotine AUC	Plasma	Switching (confinement)		X	
Benowitz *et al.* 1989	Cotinine AUC	Plasma	Switching (confinement)		X	
Benowitz *et al.* 1989	Nicotine C_{max}	Plasma	Switching (confinement)		X	
Benowitz *et al.* 1989	Cotinine C_{max}	Plasma	Switching (confinement)		X	
Benowitz *et al.* 1989	Nicotine	24-hr Urine	Switching (confinement)		X	
Benowitz *et al.* 2012	Trans-3'hydroxycotinine (3HC)	Plasma	Cross-sectional (natural adopters)		X	
Benowitz *et al.* 2012	Cotinine, Cotinine +3HC	Plasma	Cross-sectional (natural adopters)			X
Benowitz *et al.* 2012	Nicotine Equivalents[c]	Urine	Cross-sectional (natural adopters)		X	
Campbell *et al.* 2015	NicEq[b] (ages 26-31)	Urine	Cross-sectional (natural adopters)		X	
Campbell *et al.* 2015	NicEq[b] (ages 32-37)	Urine	Cross-sectional (natural adopters)		X	
Campbell *et al.* 2015	NicEq[b] (ages 38-42)	Urine	Cross-sectional (natural adopters)		X	
Campbell *et al.* 2015	NicEq[b] (ages 44-49)	Urine	Cross-sectional (natural adopters)			X
Campbell *et al.* 2015	Nicotine	Serum	Cross-sectional (natural adopters)		X	
Campbell *et al.* 2015	Cotinine (ages 26-31)	Serum	Cross-sectional (natural adopters)		X	
Campbell *et al.* 2015	Cotinine (ages 32-37)	Serum	Cross-sectional (natural adopters)		X	
Campbell *et al.* 2015	Cotinine (ages 38-43)	Serum	Cross-sectional (natural adopters)			X
Campbell *et al.* 2015	Cotinine (ages 44-49)	Serum	Cross-sectional (natural adopters)			X
Hecht *et al.* 2007	Total Cotinine[d]	Urine	Cross-sectional (natural adopters)			X
Holiday *et al.* 1995	Cotinine	Serum	Randomized Controlled Trial		X	
Jacob *et al.* 1993	Nicotine	24-hr Urine	Cross-sectional (natural adopters)		X	
Jacob *et al.* 1993	Cotinine	24-hr Urine	Cross-sectional (natural adopters)		X	
Naufal *et al.* 2011	Cotinine	Serum	NHANES (1999 to 2008)			X
Prasad *et al.* 2016	Nicotine	Plasma	Cross-sectional (natural adopters)		X	
Prasad *et al.* 2016	Cotinine	Plasma	Cross-sectional (natural adopters)		X	
Prasad *et al.* 2016	Total Nicotine Equivalents[b]	24-hr Urine	Cross-sectional (natural adopters)			X
Rostron *et al.* 2015	Cotinine	Serum	NHANES (1999 to 2012)			X

* Camel Snus results excluded from this table.

[a] An "X" in either the "ST < Cigarettes" or "ST > Cigarettes" columns indicates a statistically significant difference between smokeless tobacco and cigarette biomarker results, with smokeless tobacco less than or greater than cigarettes, respectively. An "X" in the "ST ≈ Cigarettes" column indicates that no

statistically significant difference was observed between smokeless tobacco and cigarette biomarker results.
[b] Unconjugated nicotine and the 9 metabolites were converted to molar unconjugated nicotine equivalents and summed.
[c] The sum of nicotine and its metabolites
[d] The sum of unconjugated cotinine and cotinine-glucuronide

2.9.1.2.11 Smoking one cigarette results in significantly greater and more rapid nicotine exposure than when using one Camel Snus pouch

Smoking a cigarette results in significantly greater and more rapid nicotine exposure than when using a pouch of Camel Snus. It is accepted that nicotine has a prominent role in the abuse liability of tobacco products (USDHHS 2014) and that clinical pharmacokinetic measures of nicotine, along with other information, provide a means for evaluating the abuse liability of a tobacco product. FDA thus recommends that applicants submit human studies "to assess the abuse liability and potential for misuse of the product as compared to other tobacco products on the market" (FDA MRTPA Draft Guidance 2012).

RJRT-sponsored pharmacokinetic studies of Camel Snus users and cigarette smokers show that smoking a single cigarette results in greater nicotine exposure over time (AUC), a greater peak plasma nicotine exposure (C_{max}) and a peak plasma exposure that occurs significantly more quickly (T_{max}) than with the use of a single Camel Snus pouch (*see* CSD0905, CSD0914, CSD1101).

The results of RJRT-sponsored studies of clinical pharmacokinetic measures of nicotine during Camel Snus use are summarized below in Table 2.9.1-17 and are consistent with other systemic exposure data regarding nicotine and its metabolites taken from each of the switching, single-use and cross sectional studies presented in this Application (*see* Table 2.9.1-3). Although these pharmacokinetic data suggest that Camel Snus exhibits significantly reduced abuse liability compared to cigarettes, Camel Snus nicotine delivery is on par with or can exceed that of approved smoking cessation products (*see* Cobb *et al.* 2010 and discussion in Henningfield *et al.* 2017). Thus, Camel Snus is expected to benefit smokers who are concerned about the risks of smoking, but who find medicinal NRT products unacceptable and will continue to use some form of tobacco product. While the ultimate population impact of Camel Snus as an MRTP will depend on factors beyond abuse liability, an evaluation by PinneyAssociates concluded that Camel Snus appears to fall in the general "midrange" for a viable harm reduction product (Henningfield *et al.* 2017).

Additional discussion of the abuse liability of Camel Snus relative to cigarettes, including a more detailed discussion of the quantitative and qualitative data produced by studies conducted by RJRT and others, is found in Section 2.9.2, Section 6.1.6 and Henningfield *et al.* 2017.

Table 2.9.1-17: Pharmacokinetic studies of nicotine from exclusive Camel Snus use compared to exclusive cigarette use

				Relative Nicotine Exposure[a,b]		
Study	**Measurement Type**	**Sample Matrix**	**Study Design**	**Camel Snus < Cigarettes**	**Camel Snus ≈ Cigarettes**	**Camel Snus > Cigarettes**
CSD0905	Nicotine C_{max}	Serum	Single Use	X		
CSD0905	Nicotine AUC_{0-90}	Serum	Single Use	X		
CSD0905	Nicotine T_{max}	Serum	Single Use			X
CSD0914	Nicotine C_{max}	Serum	Single Use	X		
CSD0914	Nicotine AUC_{0-180}	Serum	Single Use	X		
CSD0914	Nicotine T_{max}	Serum	Single Use			X
CSD1101	Nicotine C_{max}	Serum	Single Use	X		
CSD1101	Nicotine AUC_{0-180}	Serum	Single Use	X		
CSD1101	Nicotine T_{max}	Serum	Single Use			X

*Data are based upon exclusive single use of either Camel Snus or usual brand (UB) cigarette during a clinic visit.

[a] An "X" in either the "Camel Snus < Cigarettes" or "Camel Snus > Cigarettes" columns indicates a statistically significant difference between Camel Snus and cigarette pharmacokinetic results, with Camel Snus less than or greater than cigarettes, respectively. An "X" in the "Camel Snus ≈ Cigarettes" column indicates that no statistically significant difference was observed between Camel Snus and cigarette pharmacokinetic results.

[b] For T_{max} measurements, marks are indicative of relative time to reach T_{max} and do not indicate greater relative exposure.

2.9.1.2.12 Camel Snus use impacts fewer biomarkers of effect than cigarette smoking

When compared to non-users of tobacco, far fewer biomarkers of effect (*i.e.*, biomarkers of potential harm, short-term markers that may indicate long-term consequences such as cancer, cardiovascular, or pulmonary diseases) are altered by the exclusive use of Camel Snus than are affected by cigarette smoking. Two RJRT-sponsored clinical studies have evaluated biomarkers of effect in users and non-users of tobacco, both with the goal of assessing biomarkers of cardiovascular disease risk. The first study, a cross-sectional evaluation of natural product adopters, compared biomarkers from exclusive Camel Snus users, exclusive cigarette smokers, dual users of Camel Snus and cigarettes and non-users of tobacco (CSD0904). The second study evaluated biomarkers in smokers switched partially to Camel Snus and also compared those smokers at baseline (*i.e.*, as exclusive cigarette smokers) to non-users of tobacco (HSD0702).

Both RJRT-sponsored clinical studies reported results that are generally consistent with the published literature for smokers and found significant reductions in markers of oxidative stress and inflammation for exclusive users of Camel Snus. The cross-sectional study of 90 different biomarkers of effect found that 30 were statistically significantly different in smokers compared with non-users of tobacco, with 23 markers higher and 7 markers lower in smokers. By contrast, for exclusive users of Camel Snus compared to non-tobacco users, only 7 biomarkers were increased and none were decreased. The randomized switching study found similar results for cigarette smokers, with 9 of 21 biomarkers reported to be statistically significantly higher than in non-users of tobacco.

Consistent with published reports that compare biomarkers of effect in smokeless tobacco users with biomarkers in cigarette smokers (*see, e.g.*, Frost-Pineda *et al.* 2011, Nordskog *et al.* 2015), the results summarized in Table 2.9.1-18 show that far fewer biomarkers of effect are altered by the exclusive use of Camel Snus than are affected by cigarette smoking. Inflammation and oxidative stress are reduced in Camel Snus users relative to cigarette smokers. These results are consistent with potentially reduced risk of adverse health effects from the use of Camel Snus compared with cigarette smoking, including cancers, pulmonary disease and cardiovascular disease.

Table 2.9.1-18: Biomarkers of effect in cigarette smokers, Camel Snus users and non-users of tobacco

Biomarker	Cigarettes *vs.* Non-Tobacco	Camel Snus *vs.* Non-Tobacco	Camel Snus *vs.* Cigarettes	Dual Use *vs.* Cigarettes
Nitric Oxide Pathway (Blood)				
ADMA	↑[a]			
SDMA	↑[a]			↑[a]
Homocysteine	↑[a] ↑[b]	↑[a]		
L-citrulline	↑[a]		↓[a]	

Biomarker	Cigarettes *vs.* Non-Tobacco	Camel Snus *vs.* Non-Tobacco	Camel Snus *vs.* Cigarettes	Dual Use *vs.* Cigarettes
Inflammation (Blood)				
α-2-macroglobulin	↓[a]			
BDNF	↑[a]		↓[a]	
CRP				↓[a]
Eotaxin-1	↑[a]			
Ferritin	↑[a]	↑[a]		↓[a]
Folate	↓[a]			
Haptoglobin			↓[a]	↓[a]
IL-1 receptor antagonist	↓[a]			
IL-1 receptor antagonist (excl. extreme values)	↓[a]			
IL-3	↓[a]			
IL-12 subunit P70			↓[a]	
ICAM1	↑[a] ↑[b]	↑[a]	↓[a]	↓[b]
MMP-9	↑[a]		↓[a]	
Stem cell factor		↑[a]		
RANTES	↑[a]			
TIMP-1	↑[a]			
TNFβ			↓[a]	
VEGF	↑[a]	↑[a]		
VDBP				↓[a]
Lipids and Lipoproteins (Blood)				
Apo B				↓[a]
Lp[a]	↓[a]			
VLDL-C	↑[a]			
Hematology (Blood)				
Hematocrit	↑[a] ↑[b]		↑[a]	
Hemoglobin	↑[a] ↑[b]			
MCH	↑[a]			
MCV	↑[a]		↓[a]	
RBCs				↓[a]
WBCs	↑[a] ↑[b]			↓[bc]
Monocytes	↑[a]			
Neutrophils	↑[a]			
Miscellaneous (Blood)				
Hemoglobin A1c	↓[a]			↑[bd]
Oxidative Stress (24hr Urine)				
8,12-iso-iPF$_{2\alpha}$-VI	↑[b]			↓[bd]
iPF$_{2\alpha}$-III	↑[a] ↑[b]		↓[a]	↓[bd]
iPF$_{2\alpha}$-VI	↑[a] ↑[b]	↑[a]		
iPF$_{2\alpha}$-VI (excl. extreme values)	↑[a]	↑[a]		
DNA Damage (Blood)				
SCE	↑[b]	--	--	↑[bc]
All Categories				
Totals	**25↑ 7↓**	**7↑**	**1↑ 9↓**	**3↑ 10↓**

"↑" and "↓" indicate that biomarker levels were statistically significantly increased, or decreased, respectively, in the first group as compared to the second group.

[a] Results from CSD0904

[b] Results from HSD0702

[c] Statistically significant difference observed at Week 12 only.

[d] Statistically significant difference observed at Week 24 only.

2.9.1.2.13 Smoking cessation rates at 6 or 12 months are comparable for participants using Camel Snus or an FDA-approved smoking cessation product

RJRT is not seeking authorization from FDA to market Camel Snus as a smoking cessation product. However, in evaluating the benefit to health of individuals and of the population as a whole, "FDA must take into account [. . . .] the risks and benefits to persons from the use of the modified risk tobacco product compared to the use of smoking cessation drug or device products approved by FDA to treat nicotine dependents" (FDA MRTPA Draft Guidance 2012).

This Application therefore includes the available clinical data comparing Camel Snus to FDA-approved smoking cessation products. One RJRT-sponsored clinical study, as well as several studies from the literature (Hatsukami *et al.* 2011; Kotlyar *et al.* 2011; Hatsukami *et al.* 2016), have evaluated the relative effectiveness (*i.e.*, resulting smoking cessation rates) of Camel Snus and nicotine replacement therapies (NRT) for the treatment of nicotine dependence. The results of these studies are summarized below and described fully in Section 6.1.2.

The available data suggest that smoking cessation rates at 6 or 12 months for subjects using Camel Snus are comparable to those observed for an approved smoking cessation product. RJRT conducted a randomized clinical trial to compare smoking cessation rates between smokers administered either Nicorette 4 mg lozenges or Camel Snus (*see* CSD1010). Continuous cessation rates at 6 and 12 months were low (1.4% for Camel Snus, 0.9% for lozenges) and no statistical differences were observed between study products at either time point for any of the cessation criteria defined in the study protocol (*see* Table 2.9.1-19).

Two exploratory endpoints were added later to re-classify treatment failures who quit by Month 9 and these new endpoints did show some minor statistical differences (5.5% for Camel Snus, 10.8% for lozenges). It is important to note, however, that the study design was not optimized to assess single-point abstinence at later months and as such, these two endpoints provide an incomplete look at late-onset abstinence.

Published external studies comparing Camel Snus to approved cessation products at shorter intervals also show comparable relative potential for promoting cigarette abstinence (*see* Hatsukami *et al.* 2011; Kotlyar *et al.* 2011; Hatsukami *et al.* 2016). Thus, concordant with the pharmacokinetic data and assessment of Camel Snus abuse liability presented by Henningfield *et al.* 2017, Camel Snus is expected to benefit smokers who are concerned about the risks of smoking, but who find medicinal NRT products unacceptable and will continue to use some form of tobacco product.

Table 2.9.1-19: Study CSD1010 smoking cessation rates (% [95% CI]) at 6 and 12 months

Endpoint	Cohort	Time Point:	
		Month 6	Month 12
R1	Camel Snus (with risk info)*	2.3 (0.3, 4.3)	1.4 (0.0, 2.9)
	Camel Snus (no risk info)	2.3 (0.3, 4.3)	1.4 (0.0, 2.9)
	Nicorette Lozenge	2.3 (0.3, 4.4)	0.9 (0.0, 2.2)
R2	Camel Snus (with risk info)*	5.0 (2.1, 8.0)	2.8 (0.6, 4.9)
	Camel Snus (no risk info)	6.9 (3.5, 10.2)	2.8 (0.6, 4.9)
	Nicorette Lozenge	6.1 (2.9, 9.3)	3.8 (1.2, 6.3)
R3	Camel Snus (with risk info)*	6.0 (2.8, 9.1)	3.2 (0.9, 5.6)
	Camel Snus (no risk info)	8.3 (4.6, 11.9)	4.1 (1.5, 6.8)
	Nicorette Lozenge	8.0 (4.3, 11.6)	5.2 (2.2, 8.1)
R4	Camel Snus (with risk info)*	5.0 (2.1, 8.0)	2.8 (0.6, 4.9)
	Camel Snus (no risk info)	5.0 (2.1, 8.0)	2.3 (0.3, 4.3)
	Nicorette Lozenge	7.0 (3.6, 10.5)	5.2 (2.2, 8.1)
R5A	Camel Snus (with risk info)*	--	5.5 (2.5, 8.5)
	Camel Snus (no risk info)	--	5.5 (2.5, 8.5)
	Nicorette Lozenge	--	**10.3 (6.2, 14.4)**
R5B	Camel Snus (with risk info)*	--	5.5 (2.5, 8.5)
	Camel Snus (no risk info)	--	5.5 (2.5, 8.5)
	Nicorette Lozenge	--	**10.8 (6.6, 15.0)**

* "with risk info" indicates that smokers were informed of the benefits of smoking cessation and the relative risks of smoking cigarettes *vs*. smokeless tobacco product use.
** Bold indicates a statistical difference between the Nicorette cohort and the combined Camel Snus cohorts.
R1 = The subject has not smoked following the quit date (day after Visit 1).
R2 = The subject has not smoked in any two consecutive weeks following the quit date.
R3 = The subject has not smoked in any two consecutive weeks following a two-week grace period after the quit date.
R4 = The subject has not smoked within the past 7 days following a two-week grace period after the quit date.
R5A = The subject has not smoked since Month 9. Exploratory non-optimized endpoint.
R5B = The subject has not smoked in any two weeks since Month 9. Exploratory non-optimized endpoint.

2.9.1.2.14 The safety profile of Camel Snus is comparable to NRT

Clinical studies show that Camel Snus, like NRT, is generally well tolerated. Among those randomized to the Nicorette Lozenge or Camel Snus, there were a similar number of subjects reporting adverse events (AEs) across groups (*see* CSD1010). A similar proportion of subjects from each group discontinued due to AEs. Three serious adverse events (SAEs) were reported during the course of the study, but none were related to the use of the study product. Most AEs were mild, did not result in study discontinuation and were common effects of nicotine use (*e.g.*, nausea, dyspepsia). A total of 108 subjects (16.6%) reported at least one adverse event, with a similar number of subjects reporting adverse events across groups. The most frequently observed AEs were: nausea (18 subjects), upper respiratory tract infection (9 subjects),

dyspepsia (8 subjects) and sinusitis (4 subjects). These results are consistent with an external study that compared the safety profiles of Camel Snus and NRT (Hatsukami *et al.* 2016).

Mild to moderate AEs that were associated with Camel Snus in other clinical studies included headache, nausea, throat irritation/burn, mouth burn, indigestion/heartburn/stomach discomfort and hiccups. These AEs generally resolve quickly after product use and are similar to the AEs reported in clinical trials of NRT (Stead *et al.* 2012).

2.9.1.2.15 Clinical data are consistent with reduced individual disease risk observed in epidemiological studies of smokeless tobacco users

Exposure to constituents present in a tobacco product or tobacco smoke is the result of multiple factors, including the manner of use (*e.g.*, inhalation *vs.* placement of tobacco in the mouth), product use behaviors (*e.g.*, cigarette puffing behavior or time smokeless tobacco held in mouth), the chemical composition of the smoke or tobacco product and the route(s) of exposure. Biomarkers of exposure incorporate the net effect of all of these factors and measure actual exposure to constituents of tobacco and tobacco smoke. The clinical data presented in this Application (both RJRT-sponsored clinical studies and those conducted by others and reported in the literature) demonstrate that use of Camel Snus reduces exposure to toxicants as compared to cigarette smoking, particularly those toxicants formed during tobacco combustion.

Reduced toxicant exposures observed include compounds that have important biological significance because most have been designated as carcinogens (IARC) and HPHCs (FDA) associated with cancer, respiratory disease and cardiovascular disease. Reduced exposure to such toxicants is consistent with reduced individual disease risk observed in epidemiological studies of U.S. smokeless tobacco users as compared with cigarette smokers. Further, these clinical data are consistent with reduced individual disease risk observed in epidemiological studies of snus users as compared to cigarette smokers conducted in Sweden. The available clinical data indicate that significant reductions in exposure to combustion-related toxicants are achievable, even for smokers who do not completely switch to Camel Snus. However, the greatest reductions in exposure will result from switching completely to Camel Snus and discontinuing all cigarette smoking.

2.9.1.3 Actual product use

TCA Section 911(d)(6) requires that applications for modified risk tobacco products include data and information "on how consumers actually use the tobacco product." Section 3.5 of this Application describes the available data and information on how consumers actually use Camel Snus, including: (1) the number of units (pouches) of Camel Snus consumed per day and (2) concurrent use of Camel Snus with other products containing nicotine or tobacco (FDA MRTPA Draft Guidance 2012, pp. 14-15). The data and information presented apply to each of the six Camel Snus styles in this Application, *i.e.*, Camel Snus Frost, Camel Snus Frost Large, Camel Snus Mellow, Camel Snus Mint, Camel Snus Robust and Camel Snus Winterchill.

Section 3.5.2 of this Application presents information on how consumers actually use Camel Snus in terms of the number of pouches consumed (used) per day. Published studies and RJRT's clinical studies show that consumers of Camel Snus generally report using between 2 and 6 pouches per day. In addition, data from the literature and RJRT's clinical studies suggest that smokers are able to achieve substantial reductions in cigarette use at these Camel Snus use rates (*see* Section 3.5.2 and Table 3.5.2-1).

In addition to published literature and RJRT's clinical studies, RJRT conducted descriptive analyses of survey data from the National Tobacco Behavior Monitor (NTBM), RJRT's Consumer Brand Tracker (Brand Tracker) and NIH/FDA's Population Assessment of Tobacco and Health Study (PATH). Collectively, data from all three surveys indicate that the use rate for Camel Snus is generally similar to that for other smokeless tobacco products, with the mean use rate among current users of Camel Snus being approximately 3 uses per day on days used. In addition, analyses from these surveys indicate that use frequency (days/week) for Camel Snus is generally similar to that for other smokeless tobacco products, with the mean use frequency among current users of Camel Snus being about 2 to 4 days per week (*see* Section 3.5.2.2).

Section 3.5.3 of this Application describes the available data on concurrent use of Camel Snus and other products that contain nicotine or tobacco. Descriptive analyses based on data from NTBM indicate that the vast majority of users of Camel Snus, non-Camel snus, portioned moist snuff, loose leaf chew and loose moist snuff are dual/poly users of other combustible and/or non-combustible tobacco products (Table 3.5.2-6; Camel Snus Product Use Report).

Based on data from NTBM and Brand Tracker, cigarette use rates for exclusive cigarette smokers were compared to users of both cigarettes and Camel Snus. Data from NTBM (survey period from Q1 2013 to Q1 2016) show that smokers who are exclusive cigarette smokers report a mean use rate of 12.9 cigarettes per day, compared to a lower mean use rate of 11.8 cigarettes per day for smokers who use both cigarettes and Camel Snus. By the last survey quarter, the predicted difference in cigarette use rate among exclusive users and those who use both cigarettes and snus increased from approximately 1 to approximately 5 cigarettes per day, with greater use observed for exclusive cigarette smokers. Similarly, data from Brand Tracker show that exclusive cigarette smokers report a mean use rate of 13.3 cigarettes per day, compared to a lower mean use rate of 12.4 cigarettes per day for smokers who use both cigarettes and Camel Snus (*see* Table 3.5.3-2; Camel Snus Product Use Report).

In addition, information from a clinical study of Camel Snus adopters (CSD0904, sponsored by RJRT) indicates that dual users of Camel Snus and cigarettes reported smoking fewer cigarettes per day compared to exclusive cigarette smokers, with reductions of up to 25%. Thus, analyses of data from RJRT's clinical study of natural Camel Snus adopters, as well as survey data from NTBM and Brand Tracker, show that current users of both cigarettes and Camel Snus report a lower cigarette use rate than exclusive cigarette smokers.

With respect to use frequency (*i.e.*, number of days smoked during the past week), data from both NTBM and Brand Tracker indicate that current users of both cigarettes and Camel Snus

report a lower cigarette use frequency (days smoked during the past week) than exclusive cigarette smokers (s*ee* Section 3.5.3.2.2).

2.9.2 Abuse liability of Camel Snus products

FDA recommends that applicants submit human studies "to assess the abuse liability and potential for misuse of the product as compared to other tobacco products on the market" (FDA MRTPA Draft Guidance 2012, p. 19). In the context of tobacco products, *abuse liability* refers to the risk that use of a tobacco product will lead to psychological and/or physiological dependence, along with persistent product usage behaviors, development of tolerance and impeded ability to discontinue product use (FDA MRTPA Draft Guidance 2012). It is accepted that nicotine has a prominent role in the abuse liability of tobacco products (USDHHS 2014). It is also recognized that the manner of product use (*i.e.,* inhalation during smoking *vs.* buccal absorption during oral use) and the product's formulation substantially determine its effects and abuse liability. Thus, tobacco and other nicotine products vary widely in their abuse liability. Part of evaluating an MRTPA is determining the proposed modified-risk product's abuse liability relative to other tobacco products (*e.g.,* cigarettes). If the candidate MRTP is intended to reduce cigarette smoking, some of its characteristics and effects that contribute to abuse liability must remain sufficient for it to adequately substitute for the reinforcing effects of cigarettes.

Important product and clinical data related to the abuse potential of Camel Snus include its nicotine content and buffering, pharmacokinetic measures of nicotine exposure (*i.e.,* peak plasma concentrations [C_{max}] and time to peak plasma concentration [T_{max}]), as well as systemic measures such as biomarkers of exposure to nicotine and its metabolites. Accordingly, the study data summarized in this Application specifically address nicotine exposure resulting from the use of Camel Snus, as compared to exposure from cigarette smoking. Additional discussion of the abuse liability of Camel Snus relative to cigarettes, including a discussion of published literature as well as quantitative and qualitative data produced by studies conducted by RJRT and others, is found in Section 6.1.6 and Henningfield *et al.* 2017.

Henningfield *et al.* 2017, in their abuse liability assessment of the six Camel Snus products that are the subject of this Application, support the designation of all six products as MRTPs. After review of available data, the authors conclude that, based on the abuse liability profile of Camel Snus, it will serve as an acceptable and beneficial MRTP. This designation reflects the fact that the abuse liability of Camel Snus is substantially less than that of traditional cigarettes and likely higher than that of FDA-approved over-the-counter nicotine replacement therapy (NRT) medications. Thus, Camel Snus is expected to benefit smokers who are concerned about the risks of smoking, but find medicinal NRT products unacceptable and who will continue to use some form of tobacco product. While the ultimate population impact of Camel Snus as an MRTP will depend on factors beyond abuse liability, Camel Snus appears to fall in the general "midrange" of nicotine product abuse liability, consistent with a potential to serve as a viable harm reduction product (*see* non-specific product discussion and illustrative graph in Niaura 2016). A midrange harm reduction product is one that manifests low to moderate abuse liability

and acceptability to current smokers, while also providing a substantial potential to reduce the risks that attend cigarette smoking.

2.9.3 *In vitro* toxicology studies

In vitro toxicology testing is established as an integral component of FDA regulatory oversight across most of its historically-regulated product sectors. Non-clinical *in vitro* testing provides qualitative and quantitative information on potential adverse effects of products with test methods that offer a very high degree of control over experimental conditions. FDA has appropriately stated that *in vitro* toxicology testing can provide useful information to address the known and potential toxicities of tobacco products, and thus has utility in evaluation of the range of toxicities of a potential MRTP as compared to other tobacco products on the market (FDA 2012a, p. 24).

A substantial extant body of published literature on tobacco-related genotoxicity and cytotoxicity is available to provide a context for comparisons among products. These two manifestations of toxicity are particularly appropriate in comparisons of a conventional tobacco product and a candidate MRTP, since both genetic toxicity and cytotoxicity are believed to have a role in the etiology of many serious smoking-related diseases, including lung and oral cancer, cardiovascular disease and chronic respiratory diseases such as COPD. Test systems that measure structural changes to the genetic material (*e.g.,* the mammalian cell micronucleus and sister-chromatid exchange assays), and those that evaluate the induction of mutations in target genes (*e.g.,* the Ames bacterial mutagenesis assay) have proven to be particularly reliable in providing evidence for the genotoxic properties of cigarette smoke that are believed to be a primary mechanism of cancer initiation. *In vitro* cytotoxicity tests that assess the relative potency of different tobacco products to kill mammalian cells under specified exposure conditions provide information on processes that have an etiologic role in cancer initiation, tumor promotion, cardiovascular disease, and respiratory diseases such as COPD (Rock and Kono 2008; USDHHS 2010). Thus a battery of *in vitro* genotoxicity and cytotoxicity assessments can provide data having relevance to disease processes that occur among tobacco-using human populations to serve as a basis for comparisons within and among different tobacco product categories. The rationale for the selection of the testing performed in support of this Application is further detailed in Section 6.1.3.1, and Section 6.1.3.4.1, Section 6.1.3.4.2, Section 6.1.3.4.3, Section 6.1.3.4.4 and Section 6.1.3.4.5.

2.9.3.1 Extracts of smokeless tobacco and Camel Snus show reduced biological activity when compared with cigarette smoke

A body of peer-reviewed, published research has previously addressed the genetic toxicity and cytotoxicity of smokeless tobacco product extracts and cigarette smoke. These studies are reviewed in some detail in Section 6.1.3.2 and Section 6.1.3.3 of this Application. This extant literature is very consistent in demonstrating that extracts of smokeless tobacco products such as traditional U.S. chewing tobacco, moist snuff and Swedish-style snus are markedly less mutagenic, clastogenic and cytotoxic than are preparations of the particulate/droplet phase of cigarette smoke. Whereas the diverse published studies vary in their in extraction and testing

conditions, the reported relative genotoxicity and cytotoxicity of smokeless tobacco is consistent and clear, and has generally been reported to be on the order of 10% or less of that of cigarette smoke tested similarly (Rickert *et al.* 2009).

Newer test methods currently under development and refinement have demonstrated additional genotoxic and cytotoxic properties for the gas/vapor phase of cigarette smoke. These methods employ exposure systems that allow testing of the whole smoke aerosol or the gas/vapor phase of smoke separated by filtration to characterize the toxicological properties of reactive gas/vapor constituents that comprise the predominant mass fraction of cigarette smoke (Thorne and Adamson 2013). Recent studies of this sort demonstrate that the majority (~65%) of the cytotoxicity induced by the whole smoke aerosol is attributable to the gas/vapor phase (Thorne *et al.* 2015b). These recent findings indicate that the difference between the dramatically lower toxicologic properties of smokeless tobacco products and the higher toxicity of combusted tobacco products is in all likelihood even greater than has been historically reported in the published literature from testing conducted with solutions prepared from only the cigarette smoke particulate material.

Whereas scores of published papers have reported on *in vitro* toxicology testing of cigarette smoke or smokeless tobacco extracts (reviewed by Johnson *et al.* 2009), relatively few have reported findings for concurrently-tested smokeless tobacco and cigarette products such as those that are presented and discussed herein for Camel Snus. Table 2.9.3-1 below briefly summarizes the findings of such published work to date.

Table 2.9.3-1: Published *in vitro* assessments consistently show ST products to be less genotoxic and cytotoxic than cigarette smoke

Study	ST Test Article	Study Type	ST < cigarettes	ST = cigarettes	ST > cigarettes
Rickert *et al.* 2007[1]	4 U.S. brands moist snuff	Ames *Salmonella* mutagenesis, TA100+S9	X		
Rickert *et al.* 2009[2,3]	19 brands US moist snuffs, 6 brands dry snuff, 2 brands Swedish snus, 2 brands US chewing tobacco	Ames *Salmonella* mutagenesis	X		
		Mammalian cell micronuclei	X		
		Mammalian cell cytotoxicity	X		
Laytragoon-Lewin *et al.* 2011	Swedish snus	Primary human endothelial cells and fibroblasts:	X		
		Inhibition of DNA synthesis	X		
		Phenotypic abnormalities Cytotoxicity	X		
Benowitz *et al.* 1989	U.S. smokeless tobacco: Copenhagen, Skoal Bandits-Wintergreen and Hawken-Wintergreen	Urinary mutagens, YG1024 +S9; US smokeless users vs. smokers	X		
Curvall *et al.* 1987	Swedish moist snuff	Urinary mutagens, TA98 +S9; Swedish moist snuff users vs. smokers	X		

[1] Rickert *et al.* (2007) evaluated a wide variety of smokeless and combustible tobacco products. Only those products that are representative of U.S. smokeless and cigarette products are discussed in this Application.

[2] Rickert *et al.* (2009) also evaluated an Indian-style gutkha chewing tobacco product that is markedly different from US smokeless products; those results are not summarized or discussed herein.

[3] Rickert *et al.* (2009) did not report results of direct comparisons of the tested smokeless tobacco products with cigarettes in concurrently-performed assays. The authors did, however, state in regard to their findings for the smokeless tobacco products and for cigarettes in prior work in their laboratory that "the results were only a small fraction (less than 10%) of those observed for extracts of mainstream cigarette smoke condensate."

2.9.3.2 Camel Snus extracts are less cytotoxic, genotoxic and mutagenic than cigarette smoke

A series of studies sponsored by RJRT that provide *in vitro* mutagenicity (Ames tests), chromosome damage (mammalian cell micronucleus and sister chromatid exchanges) and cytotoxicity (neutral red uptake assay) data specific to the subject Camel Snus products is presented in Section 6.1.3.5 and Section 6.1.3.6. These studies compared the biological activities of Camel Snus to those of the smoke of the leading U.S. 85mm non-menthol and menthol cigarette brands and Kentucky Reference cigarettes, as well as to other U.S. smokeless products and Swedish snus products.

Overall, these studies demonstrated that the bacterial mutagenicity of Camel Snus extracts in the Ames *Salmonella* test system are similar to or lower than those of the other tested smokeless products, and statistically-significantly lower than those of concurrently-tested cigarette smoke extracts. Exceptions to this overall trend were observed for 1) Ames bacterial strains TA1535 and TA102, which have historically been found to be unresponsive to cigarette smoke extracts, and 2) sporadic instances of statistical similarity between Camel Snus and cigarette mutagenic responses, when expressed as mean slopes of dose-response curves (discussed further in Section 6.1.3.5). The nominal mutagenicity responses that were observed for Camel Snus were in all instances judged to lack biological significance, as discussed in Section 6.1.3.4.1 since they did not induce revertant bacterial colony counts in excess of the characteristic normal ranges for spontaneous revertants in any of the *Salmonella* tester strains, both in the presence or absence of an exogenous rat liver S9 metabolic activation mixture.

Genotoxic effects manifested as changes at the chromosome level of mammalian cells (induction of sister chromatid exchanges and micronuclei) were found to be significantly lower for Camel Snus than for cigarette smoke extracts, as detailed in Section 6.1.3.4 and Section 6.1.3.5. Camel Snus was also found to be comparable or lower in these activities than other Reference and commercial U.S. smokeless products tested concurrently, both in the presence or absence of rat liver S9.

All of the tested Camel Snus brand styles exhibited consistent and highly significantly lower cytotoxicity than did the smoke of leading U.S. brands of menthol and non-menthol cigarettes tested concurrently, as detailed in Section 6.1.3.6. The essential findings of this entire series of *in vitro* studies on Camel Snus are summarized in Table 2.9.3-2 below:

Table 2.9.3-2: *In vitro* mutagenicity, cytotoxicity, and genotoxicity studies of Camel Snus compared to cigarettes

			Relative Specific Activity				
Study[a]	**Study Type[b]**	**Strain or Cell Type[c]**	**Camel Snus Lower Than Cigarettes[d]**	**Camel Snus Equal to Cigarettes[e]**	**Camel Snus Greater Than Cigarettes[f]**	**Sample Matrix[g]**	**Basis of Comparison**
M194A-GLP	Ames *Salmonella* mutagenicity	TA102		X[h]		CAS-extract; TPM	Revertants/Pouch 'as-is' vs. Revertants/Cigarette
		TA1535		X[i,j]			
		TA98	X[j]				
		TA100	X[j]				
		TA1537	X[j]				
M97	Ames *Salmonella* mutagenicity	TA102			X[h]	DMSO-extract; TPM	Revertants/µg Nicotine
		TA98	X				
		TA100	X				
		TA1537	X				
		TA1535		X[i,j]			
M194B-GLP	NRU (cytotoxicity)	CHO cells	X			CAS-extract; TPM	Pouch 'as-is'/mL medium vs. Cigarettes/mL medium
M100 NRU	NRU (cytotoxicity)	CHO cells	X			DMSO-extract; TPM	µg Nicotine/mL medium
M100 MN	MN (genotoxicity)		X				% Micronucleated Cells/(µg Nicotine/mL medium)
M125	SCE (genotoxicity)	CHO cells	X			DMSO-extract; TPM	(# SCE/Cell)/(µg Nicotine/mL medium)

[a] M194A-GLP Final Study Report: Determination of Mutagenic Response of Camel Snus and Other Tobacco Products (July 17, 2014); M97 Report Toxicology of Smokeless Tobacco Products: Bacterial Reverse Mutagenicity (R3: December 15, 2009); M194B-GLP Final Report: Determination of Cytotoxic Response of Camel

Snus and Other Tobacco Products (July 15, 2014); M100 Report Toxicology of Smokeless Tobacco Products: Neutral Red Uptake Cytotoxicity (R2: December 17, 2009); M100 Report Toxicology of Smokeless Tobacco Products: *In Vitro* Micronucleus Assay (R2: December 17, 2009); M125 Report Sister Chromatid Exchange Assays of Smokeless Tobacco Samples (February 4, 2011).

[b] Ames *Salmonella*/Microsome Mutagenicity (Ames) assay; Neutral Red Uptake (NRU) assay; Micronucleus (MN) assay; Sister Chromatid Exchange (SCE) assay. All six Camel Snus product variants were evaluated in studies M194A and M194B. Camel Snus Frost, (b) (4) (b) (4) , was evaluated in the experimental studies M97, M100 and M125.

[c] Bacterial strain or mammalian cell type used. All assays were performed both with and without an induced rat liver S9 metabolizing mixture.

[d] A designation in this column indicates that the Camel Snus and cigarette findings are statistically significantly different, and that the Camel Snus findings were lower than those of cigarette smoke.

[e] A designation in this column indicates that the Camel Snus and cigarette findings were not statistically significantly different. Note however, that for Ames test dose response slope comparisons the Camel Snus means are directionally less than those of cigarettes (unless otherwise noted).

[f] A designation in this column indicates that the Camel Snus and cigarette findings are statistically significantly different, and that the Camel Snus mean Ames dose-response slope is greater than the cigarette mean slope.

[g] Smokeless tobacco tests used Complete Artificial Saliva (CAS) and/or dimethyl sulfoxide (DMSO) solvents; all cigarette tests used cigarette smoke Total Particular Matter (TPM) in DMSO solvent.

[h] Based on p-values; Camel Snus produced some mean slope values greater than cigarettes in TA102, a strain which typically does not respond to cigarette smoke particulate material. All mean colony counts for Camel Snus treatments were within normal revertant background ranges, and were judged not to have biological relevance, as discussed in the text.

[i] Neither Camel Snus nor the cigarette produced positive mean slope values in TA1535, so based on p-values, their responses were statistically similar.

[j] Sporadic instances of positive mean slope values for Camel Snus that did not differ statistically from that of cigarettes were observed for comparisons of different Camel Snus flavors, major brand cigarettes, S9 activation conditions and smoking protocols (ISO or HCI). However, since all Camel Snus responses represented revertant colony counts that were a.) within the laboratory's acceptable ranges for background revertant colony counts and b.) less than a two-fold elevation in counts relative to concurrent solvent controls, these responses were not considered to represent biologically-relevant mutagenicity.

2.9.3.3 *In vitro* data are consistent with reduced individual disease risks observed in U.S. epidemiological studies of smokeless tobacco users relative to cigarette smokers

Whereas there is a scientific consensus that the *in vitro* genotoxicity and cytotoxicity of a tested material generally cannot in isolation be extrapolated directly into a quantitative prediction of human disease risk, such studies complement information from the disciplines of chemistry, *in vivo* toxicology, clinical studies and epidemiology to provide a weight of scientific evidence that, if consistent, is sufficient to characterize human disease risks.

The significantly lower *in vitro* toxicity of smokeless tobacco products relative to tobacco smoke has been consistently reported in the peer-reviewed scientific literature. The series of *in vitro* studies of Camel Snus that are included and described in this Application are consistent with that body of independently-performed work, with broadly similar smokeless tobacco products, in demonstrating that Camel Snus manifests significantly lower genotoxic and cytotoxic properties than does cigarette smoke. Further, these *in vitro* findings strongly concur with the considerable body of epidemiological studies of U.S. populations that show significantly lower risks for a number of serious diseases; including lung cancer, oral cancer and serious respiratory diseases; among users of U.S. smokeless tobacco products relative to U.S. smokers. The significantly lower *in vitro* toxicity of Camel Snus is also consistent with epidemiological evidence from Swedish populations with a longer history of use of similar Swedish snus products. These population studies have clearly demonstrated that smokeless tobacco products convey far lower risks of lung cancer, oral cancer and serious respiratory diseases than does cigarette smoking.

Taken together with the weight of evidence from comparative product analyses, *in vivo* toxicology, and human clinical studies that is presented elsewhere in this Application, the *in vitro* toxicology evidence is consistent with an expectation that Camel Snus presents significantly lower risks of cancer and serious respiratory diseases to smokers who switch to Camel Snus and discontinue smoking.

2.9.4 *In vivo s*tudies

Scientific studies using laboratory animals are key scientific components of FDA oversight across most of its regulated product sectors. Whereas both FDA and regulated product manufacturers support ongoing effort to reduce, replace and refine (the ‘3 Rs’) the use of living animals in nonclinical safety assessments, at the present time such studies continue to serve an important role in regulatory science as a link between the information generated by laboratory chemical and *in vitro* toxicology studies and by human clinical and epidemiological investigations.

2.9.4.1 Smokeless tobacco exhibits some carcinogenic potential in laboratory animals, but it is lower than that of cigarette smoke

The repeated application of cigarette smoke condensates to the skin of laboratory mice has been demonstrated in over 60 years of research and testing to reliably produce very significant increases in benign and malignant tumors in treated dermal areas. The dermal epithelium represents an experimental target tissue having certain fundamental characteristics in common with common sites of elevated cancer occurrence in human smokers, such as the epithelia of the oral mucosa and respiratory tract. Experimental studies with the mouse "skin painting" technique have clearly demonstrated that cigarette smoke condensate may act as a weak tumor initiator, a potent tumor promoter, or a complete carcinogen, with sufficient net potency to consistently produce one or multiple malignant tumors in 50% or more of treated mice in as few as six months of treatment in susceptible, tumor-initiated mouse strains. Cigarette smoke condensates are therefore regarded to be demonstrably carcinogenic in this test system, based on a cumulative body of evidence developed in multiple, independent laboratories.

Repeated topical applications of smokeless tobacco and its extracts to the oral mucosal epithelium of rodents, usually rats, has similarly been used to evaluate the potential of smokeless tobacco to induce or promote oral cancers. These published evaluations of smokeless tobacco in the oral cavity of experimental animals, whether by repeated insertions into the buccal pouch, swabbing, surgical implantation or other means to achieve long-term exposures, have been found to produce oral epithelial tumors only sporadically and inconsistently in studies conducted by several independent groups worldwide. These studies, discussed in more detail in Section 6.1.4.2, support a general conclusion that *in vivo* evaluations of smokeless tobacco or its extracts provide no consistent evidence of oral carcinogenicity by smokeless tobacco or its extracts.

This body of experimental smokeless tobacco evidence from the aforementioned topical oral epithelial exposure procedures is complemented by published reports of data from subchronic and chronic feeding studies that have evaluated any potential of smokeless tobacco or its extracts to cause systemic effects, target organ toxicity, or cancers at other sites in addition to the point of contact or treatment. This method of administration is the predominant technique used by the National Toxicology Program in its chronic toxicity and carcinogenicity bioassay studies, and achieves high levels of exposure of the animals' oral cavity to smokeless tobacco and its constituents, as well as systemic exposures of other organs and organ systems. Several chronic feeding studies of snuff or other smokeless tobacco in rats, mice and hamsters have been reported and published, and all have reported a few signs of moderate toxicity consequent to the high experimental dosing, but none have reported prominent manifestations of irreversible toxicity in any organ or system, and none have demonstrated increases in tumors in any tissue site.

In contrast to these subchronic and chronic smokeless tobacco findings, subchronic and chronic cigarette smoke inhalation studies in laboratory rodents have been found to reliably produce substantial, adverse histopathologic changes in the respiratory tract, significant elevations in

indices of inflammation, oxidative stress, compromised respiratory function and other adverse outcomes that resemble some of the clinical observations reported in chronic smokers.

Chronic cigarette smoke inhalation studies in laboratory animals have proven to be a generally unreliable and inconsistent experimental model for the development of lung cancers of the kinds that occur with elevated frequency among chronic smokers. For this reason, chronic cigarette smoke inhalation bioassays have not proven to be a practical and useful means to compare the complete carcinogenicity of one cigarette to that of another. Whereas the respiratory tract epithelial hyperplastic, metaplastic and inflammatory changes induced by cigarette smoke in laboratory animals only infrequently progress to attain a malignant neoplastic character, the *in vivo* carcinogenicity of cigarette smoke has been amply demonstrated with the mouse skin painting technique, as discussed above.

Considered together, this diverse body of published evidence from a variety of *in vivo* laboratory models is consistent with the following conclusions:

- Smoke condensates prepared from cigarettes are clearly and significantly carcinogenic to experimental animals, while smokeless tobacco and its extracts exhibit little or no carcinogenic activity when tested for extended durations up to the lifetime of laboratory animals.

- Other, non-neoplastic manifestations of the toxicity of cigarette smoke and solutions of its condensates have been consistently reported to be more extensive and severe when compared to those reported for animals treated for similar durations with smokeless tobacco or its extracts.

2.9.4.2 Camel Snus tobacco blend exhibits low systemic toxicity when ingested by laboratory animals

RJRT sponsored a series of *in vivo* studies on the tobacco blend of the Camel Snus products that are the subject of this Application. These *in vivo* studies, itemized in Table 2.9.4-1 below, when considered together with product analyses, *in vitro* toxicology studies, human clinical investigations and the other scientific evidence presented elsewhere in this Application, provide strong and consistent evidence that Camel Snus exhibits significantly reduced toxicity and carcinogenicity relative to cigarettes.

Table 2.9.4-1: Index of RJRT studies discussed in Section 6.1.4.2

Reference	Title	Tested Tobacco Blend; Relevance to Camel Snus Flavor Styles[a]
TOX209	Two Week Investigational Study of the Palatability of Smokeless Tobacco Blend and Extract Formulated in NTP-2000 Diets for Rats	Frost, Frost Large, Mellow, Mint, Robust, Winterchill
TOX210	Two Week Investigational Study of the Palatability of Smokeless Tobacco Blend and Extract Formulated in NTP-2000 Diets for Mice	
TOX213	Two Week Repeat Investigational Study of the Palatability of Smokeless Tobacco Blend and Extract Formulated in NTP-2000 Diets for Mice at Higher Doses	
CN49730C	28-Day Repeated Dose Toxicity Study of Tobacco Blend and Aqueous Tobacco Extract in Wistar Han Rats	
CN49730D	28-Day Repeated Dose Toxicity Study of Tobacco Blend and Aqueous Tobacco Extract in CD-1 Mice	
CN49730E	90-Day Repeated Dose Subchronic Toxicity Study of Tobacco Blend and Aqueous Tobacco Extract in Wistar Han Rats	
CN49730F	90-Day Repeated Dose Subchronic Toxicity Study of Tobacco Blend and Aqueous Tobacco Extract in CD-1 Mice	
CN49730G Final Toxicity Report	2-Year Chronic Toxicity/ Carcinogenicity Feeding Study of Tobacco Blend and Aqueous Tobacco Extract in Wistar Han Rats: 12-Month Repeated Dose Chronic Toxicity Study	
CN49730G Final Carcinogenicity Report	2-Year Chronic Toxicity/Carcinogenicity Feeding Study of Tobacco Blend and Aqueous Tobacco Extract in Wistar Han Rats: 2-Year Carcinogenicity Study	

[a] (
b
)
(

The *in vivo* studies of Camel Snus summarized in this Section include several preliminary investigations intended to guide the design and analysis of longer-term studies to ensure that the dosing regimens are appropriate and optimized to provide the most informative data. These preliminary investigative studies are:

- Two Week Investigational Study of the Palatability of Smokeless Tobacco Blend and Extract Formulated in NTP-2000 Diets for Rats (TOX209)
- Two Week Investigational Study of the Palatability of Smokeless Tobacco Blend and Extract Formulated in NTP-2000 Diets for Mice (TOX210)

- Two Week Repeat Investigational Study of the Palatability of Smokeless Tobacco Blend and Extract Formulated in NTP-2000 Diets for Mice at Higher Doses (TOX213)

These preliminary shorter-term studies, described more fully in Section 6.1.4.3, are not discussed in this summary of results, as their findings were relevant only to the selection of dosing schedules employed in the subchronic and chronic bioassays.

After completing the preliminary investigational studies, RJRT sponsored a series of 28-day and 90-day repeated dose subchronic oral studies of Camel Snus in both rats and mice. These 28- and 90-day subchronic studies entailed the addition of the Camel Snus tobacco blend or an aqueous extract of that blend to the animals' laboratory diets, and served to further refine the chronic study dosing regimen and to identify potential target organs, clinical chemistry and general toxicology endpoints likely to be most informative in the subsequent chronic bioassays. These studies were performed in accordance to applicable provisions of Good Laboratory Practices requirements, and included:

- 28-Day Repeated Dose Toxicity Study of Tobacco Blend and Aqueous Tobacco Extract in Wistar Han Rats (CN49730C Final Report)

- 28-Day Repeated Dose Toxicity Study of Tobacco Blend and Aqueous Tobacco Extract in CD-1 Mice (CN49730D Final Report)

- 90-Day Repeated Dose Subchronic Toxicity Study of Tobacco Blend and Aqueous Tobacco Extract in Wistar Han Rats (CN49730E Amended Final Report)

- 90-Day Repeated Dose Toxicity Study of Tobacco Blend and Aqueous Tobacco Extract in CD-1 Mice (CN49730F Amended Final Report)

The findings of these subchronic feeding studies confirmed that the Camel Snus tobacco blend and extract were reasonably well-tolerated by mice and rats at dosage levels sufficiently high to meet or exceed systemic nicotine exposures that are experienced by smokeless tobacco users. No significant clinical toxicity or microscopic histopathology was evident in animals subchronically dosed with Camel Snus. These findings are in sharp contrast to the numerous histopathologic and inflammatory changes in the respiratory tract that are observed consistently in subchronic rat and mouse cigarette smoke inhalation studies of similar duration.

RJRT sponsored a 2-year, GLP-compliant chronic toxicology/carcinogenesis bioassay of Camel Snus in male and female Wistar Hannover rats to identify any systemic or target organ toxicity or carcinogenesis resulting from chronic daily dietary exposures to three dose levels of the Camel Snus tobacco blend or an aqueous extract of that tobacco blend. Rats were selected for the chronic studies since the preliminary subchronic work had identified the rat to be a more sensitive species than the mouse in terms of demonstrating effects from the Camel Snus blend and extract. Control groups received normal laboratory diet or diet supplemented with nicotine tartrate at levels approximating those contained in the three Camel Snus dosage levels. The dietary supplementations with Camel Snus blend and extract were adjusted throughout the

study to maintain a consistent range of nicotine dosages that spanned or exceeded those typical of smokeless tobacco consumers, and nicotine and cotinine biomarker findings confirmed that target dosages were satisfactorily attained. The general toxicology arm of the study proceeded through study termination at the 1-year time points, whereas the chronic carcinogenicity arm of the study continued on to study termination at the 2-year time point, approximating the normal lifespan of the animals. The two concurrent arms of this study are described in separate final reports:

- 2-Year Chronic Toxicology/Carcinogenicity Feeding Study of Tobacco Blend and Aqueous Tobacco Extract in Wistar Han Rats: 12 Month Repeated Dose Chronic Toxicity Study (CN49730G Final Toxicity Report)

- 2-Year Chronic Toxicity/Carcinogenicity Feeding Study of Tobacco Blend and Aqueous Tobacco Extract in Wistar Han Rats: 2-Year Carcinogenicity Study (CN49730G Final Carcinogenicity Report)

The 1-year toxicology component of this chronic *in vivo* bioassay produced anticipated general toxicity findings, including decreased feed consumption and body weights; these changes were also observed in rats receiving nicotine alone. Together with periodic plasma nicotine and cotinine biomarker determinations, these general findings documented the appropriateness of the selected low, middle and high doses used in the study. Neither comprehensive clinical chemistry nor ophthalmic, hematologic, gross and microscopic histopathologic evaluations revealed any significant, treatment-related toxicology findings in any organs or tissues of animals of either sex. Findings from the oral cavity and digestive tract that were the primary points of contact and absorption of the tested Camel Snus blend and extract were entirely normal in gross examination and microscopic histopathology, and were indistinguishable from those of control animals that had received the normal diet. The study findings indicated that neither the Camel Snus tobacco blend nor its extract exhibit significant toxicity in any organ or system, including tissues of the oral, respiratory and cardiovascular systems that are prominent sites for development of serious chronic diseases caused by smoking. These findings are in stark contrast to the severe respiratory tract histopathologic and inflammatory changes, as well as small numbers of tumors, that have been reported in chronic rodent cigarette smoke inhalation studies of similar duration.

2.9.4.3 Camel Snus tobacco blend exhibits minimal, if any, carcinogenic potential when ingested by laboratory animals

The 2-year carcinogenicity component of Study CN49730G further demonstrated than the chronic dietary administration of the Camel Snus tobacco blend or an aqueous extract of that blend resulted in some general, nonspecific findings typical of long-term dosing with any test article, but no significant increases in mortality, functional impairment, histopathologic changes or tumors at any site; including the oral, respiratory, cardiovascular and excretory organs that are primary target tissues for major smoking-related chronic diseases in humans. Statistically-significant increases in tumor incidence were observed at two sites, and statistically-significant decreases in tumor incidence were observed at three sites. None of these tumor sites represent

organs or tissues that have been identified as primary targets for either smokeless tobacco or cigarettes smoke carcinogenesis in humans. No gross or microscopic histopathologic evidence of precancerous changes were observed at these tumor sites in the 1-year chronic toxicity evaluations, and the tumor morphologies and incidences were all within the historical ranges of spontaneous tumors for aging rats of this strain. These tumor findings were therefore judged to be unrelated to dietary administration of Camel Snus and not indicative of any tumorigenic potential for the Camel Snus tobacco blend or its extract.

The essential findings of the RJRT series of *in vivo* studies on Camel Snus are briefly summarized in Table 2.9.4-2 below, along with the findings of representative published studies of cigarette smoke and cigarette smoke condensates to provide points of contrast and comparison. These published, peer-reviewed studies of cigarette smoke have used subchronic and chronic dosing/exposure regimens or topical applications of similar duration as the Camel Snus studies presented in this Application. It is acknowledged that fundamental differences in dosing and exposure methods are necessary in smokeless and combustible tobacco research (*i.e.,* oral feeding, smoke inhalation, topical skin and topical oral cavity applications). Whereas these differences constrain certain direct comparisons of relative toxicity and carcinogenicity under matched conditions in a given bioassay platform, the markedly lower toxicity and carcinogenicity of Camel Snus and other U.S. smokeless products relative to cigarettes is clearly evident and consistent across all studies of diverse designs.

Table 2.9.4-2: Summary findings of subchronic and chronic *in vivo* oral dosing studies of Camel Snus compared to inhalation and topical dosing studies of cigarette smoke

Studies Compared	Endpoints Evaluated	Changes Observed	
		Camel Snus	Cigarette Smoke
<u>90-day Subchronic Studies</u> Oral Camel Snus administration[a] *vs.* Cigarette smoke inhalation[b]	General toxicology	Reduced feed consumption and body weight	Reduced feed consumption and body weight
	Biomarkers of exposure	Elevated nicotine, cotinine	Elevated nicotine, cotinine, carboxyhemoglobin
	Physiologic measurements	No changes observed in ophthalmologic measures, clinical chemistry, urinalysis, or hematology	Elevated inflammatory cytokines and indices of oxidative stress; adverse lipid profiles; degraded respiratory function
	Principal organs showing effects	None identified	Heart, respiratory tract (nasal turbinates, larynx, trachea, lung)
	Gross pathology	No treatment-related, gross pathologic changes observed in any organ	Cardiomegaly and increased lung weights are seen in most subchronic cigarette smoke inhalation studies
	Microscopic histopathology	No treatment-related, microscopic histopathologic changes observed in any organ	Extensive respiratory tract histopathology observed, *e.g.*, epithelial hyperplasia, metaplasia, dysplasia and keratinization; loss of ciliated epithelium, inflammatory cell influx, goblet cell hyperplasia, and pathologic remodeling of bronchoalveolar tissues

Studies Compared	Endpoints Evaluated	Changes Observed	
		Camel Snus	Cigarette Smoke
Chronic Studies Oral Toxicity/Carcinogenesis Bioassays of Camel Snus[c] *vs.* Topical Carcinogenesis Bioassays of Cigarette Smoke Condensates[d]	General toxicology	Reduced feed consumption and body weight	Progression and growth of malignant tumors accompanied by significant body weight loss and increased morbidity and mortality
	Principal organs showing effects	None identified	Dermal epithelium
	Gross pathology	No gross pathologic changes were observed	Multiple neoplastic masses observed in treated skin area
	Microscopic histopathology	No microscopic histopathologic changes observed	Acanthosis, hyperkeratosis, multiple benign papillomas and malignant squamous cell carcinomas observed in treated skin

[a] Theophilus *et al.* 2012 is a representative example of such studies. This is a peer-reviewed, published report for study CN49730E, which is also submitted with this Application. The subchronic and chronic rat oral feeding studies of the Camel Snus tobacco blend and an aqueous extract prepared from that blend, summarized here and discussed in detail in Section 6.1.4, achieve high levels of exposure of potential target organs, including the oral cavity, digestive tract and other systemic organs and tissues. This route of exposure resembles the manner in which humans are exposed to this and other oral smokeless tobacco products, and accompanying nicotine biomarker measurements confirmed that the exposures resulted in systemic nicotine exposures resembling and exceeding those typically reported for smokeless tobacco users.

[b] Higuchi *et al.* 2004 is a representative example of a contemporary subchronic cigarette smoke inhalation study in rats. Numerous other published, independently-performed studies have produced similar findings (*e.g.,* Heck *et al.* 2002).

[c] Theophilus *et al.* 2015 is a representative example of such studies. This is a peer-reviewed, published report for study CN49730G, submitted with this Application. The Camel Snus tobacco blend or an extract of that blend were administered at 3 doses in the diet of rats for 1 year in a toxicity evaluation and for 2 years in a carcinogenesis bioassay. No treatment-related toxicologic or histopathologic changes were observed in any of the animals of either sex. Statistically-significant increases or decreases in tumors were observed at a few tissue sites among the Camel Snus-exposed groups, but these occurrences were not dose-related and did not occur in organs analogous to those that have been identified as primary targets for either smokeless tobacco or cigarettes smoke carcinogenesis in humans. The tumor morphologies and incidences were within the historical ranges of spontaneous tumors in the rat strain used, and were therefore judged to be incidental and unrelated to the treatment with Camel Snus or its extract.

[d] Meckley *et al.* 2004. A representative example of a contemporary mouse skin painting tumor promotion bioassay in SENCAR mice. Numerous other, independently-performed bioassays have reported similar findings (*e.g.* NTP 1996; Gaworski *et al.* 1999).

2.9.4.4 *In vivo* data are consistent with reduced individual disease risk observed in U.S. epidemiological studies of smokeless tobacco users

Smoke inhalation studies in laboratory animals produce an array of inflammatory and histopathologic changes that, while largely reversible, are similar to certain of the effects of smoking that are believed to play a role in the etiology of serious chronic diseases such as lung and oral cancers and COPD. Cigarette smoke exposure also produces elevated systemic inflammation beyond the respiratory tract, as evidenced by increases in inflammatory signaling molecules, oxidative stress biomarkers and adverse hematologic and lipid changes that are believed to be significant etiologic contributors to cardiovascular conditions that are exacerbated by smoking.

Whereas smoke inhalation studies in laboratory animals have not proven to be reliable models for the development of the kinds of lung cancers that occur among chronic smokers, a considerable, cumulative body of evidence developed from other kinds of *in vivo* laboratory studies has abundantly documented the carcinogenic properties of cigarette smoke condensates. In contrast, smokeless tobacco and its extracts have not demonstrated consistent evidence of carcinogenicity in independently-performed studies of diverse designs. A few epithelial tumors have been seen in some studies performed with surgical implantation of smokeless tobacco in the oral cavity of rats. These tumors occurred in low numbers and have been reported only sporadically in the published literature.

Thus, when considered together as a body of evidence, extant published *in vivo* studies have demonstrated that smoke or smoke condensates prepared from combustible cigarettes are clearly carcinogenic in certain laboratory animal systems, whereas smokeless tobacco or its extracts exhibit a very low or statistically-insignificant capacity to induce or promote oral or other cancers in animals. The body of published *in vivo* smokeless tobacco studies (*see* Section 6.1.4.2), and the *in vivo* experimental evidence specific to Camel Snus that is summarized here and presented in greater detail in Section 6.1.4.3, is likewise very consistent with the abundant epidemiological evidence developed from users of broadly similar U.S. and Scandinavian smokeless tobacco products. That evidence, considered together with the findings from product chemistry, *in vitro* toxicology, clinical studies and other scientific disciplines that are described in this Application, demonstrates that smokers who switch completely from cigarette smoking to Camel Snus will reduce their risks for lung and oral cancers and serious respiratory diseases that are caused by smoking.

2.9.5 Product analyses (chemistry studies)

The FDA's MRTPA Draft Guidance recommends providing the results of product chemistry testing in an MRTPA. The draft guidance (FDA MRTPA Draft Guidance 2012) states:

> "Product analyses regarding the chemistry and engineering of the product may be used to verify and validate the information submitted regarding the formulation of the

product. In addition, product analyses will facilitate FDA's understanding of the product, the potential for exposure to harmful or potentially harmful constituents from use of the product, and provide context for evaluating other data submitted in an MRTPA."

Accordingly, RJRT has conducted chemical analyses of Camel Snus, as well as analyses of the smoke of U.S. cigarettes and other U.S. smokeless tobacco products. The findings of these analyses are summarized and presented in Section 6.1.5.3 of this Application, and are discussed in the context of the chemical composition of smokeless tobacco products that have been used historically in the U.S., along with the associated health risks that have been reported in the U.S. epidemiological studies that are presented and discussed in Section 2.8.1 and its subsections.

It is well understood that, whereas product chemistry provides information about a tobacco product, such analyses do not provide information about actual exposure to any given compound during product use. Other data, particularly data produced from exposure biomarkers studies that sample biological matrices such as urine, blood and exhaled breath, offer the best means to assess actual exposure to the chemicals that are measured in product analyses (Chang *et al.* 2016).

Product chemistry studies of Camel Snus, U.S. cigarettes and other U.S. smokeless tobacco products conducted or sponsored by RJRT are itemized in Table 2.9.5-1. In addition to these studies, other independently conducted analyses of Camel Snus reported in the scientific literature are summarized in Section 6.5.1 of this Application. RJRT study findings are in good general agreement with those from published reports conducted in other laboratories.

Table 2.9.5-1: RJRT chemistry studies

Reference	Title	Products Tested
RDM JAB 2016,306	Summary of 2014 and 2015 Cigarette Market Surveys	45 commercial U.S. cigarette brand styles in 2014 and 50 commercial U.S. cigarette brand styles in 2015
RDM JAB 2016,281	Summary of 2014 and 2015 Smokeless Market Surveys	43 commercial U.S. smokeless tobacco products (including Camel Snus Frost, Camel Snus Frost Large, Camel Snus Mellow, Camel Snus Mint, Camel Snus Robust, Camel Snus Winterchill) in 2014 and 50 commercial U.S. smokeless tobacco products (including Camel Snus Frost, Camel Snus Frost Large, Camel Snus Mellow, Camel Snus Mint, Camel Snus Robust, Camel Snus Winterchill) in 2015

Reference	Title	Products Tested
RDM JMR 2016,235	Analytical Testing of Camel Snus Products	Camel Snus Frost, Camel Snus Frost Large, Camel Snus Mellow, Camel Snus Mint, Camel Snus Robust, Camel Snus Winterchill sampled quarterly
LSI 2014 113	Determination of Smokeless Tobacco HPHC Values for Camel Snus and Other Tobacco Products – M195-GLP	7 commercial U.S. snus brands (including Camel Snus Frost, Camel Snus Frost Large, Camel Snus Mellow, Camel Snus Mint, Camel Snus Robust, Camel Snus Winterchill), 4 commercial Swedish snus brands, and 2 leading U.S. cigarette brands
LSI 2016 097	Characterization of Tobacco-Minor Alkaloids – M273	8 commercial U.S. snus brands (including Camel Snus Frost, Camel Snus Frost Large, Camel Snus Mellow, Camel Snus Mint, Camel Snus Robust, Camel Snus Winterchill), 3 commercial U.S. dry snuff brands, 3 commercial U.S. moist snuff brands, CORESTA Reference Product (CRP1 reference snus)

2.9.5.1 Cigarette smoke is far more chemically complex than smokeless tobacco and contains many more FDA-designated and reportable HPHCs

Cigarette smoke contains many constituents that are associated with the induction or promotion of cancers or other serious diseases caused by cigarette smoking. Various classes of HPHCs in cigarette smoke, including gases (*e.g.*, carbon monoxide), polycyclic aromatic hydrocarbons (*e.g.,* benzo[a]pyrene), aromatic amines (*e.g.,* 4-aminobiphenyl), reactive carbonyls (*e.g.,* acrolein, crotonaldehyde, formaldehyde) and volatile organic compounds (*e.g.,* benzene, isoprene, 1,3-butadiene) have been reported at quantifiable and substantially higher levels in cigarette smoke than in smokeless tobacco products.

FDA recommends that applicants conduct product analyses to determine levels of harmful and potentially harmful constituents (HPHC), including smoke constituent and tobacco analyses, as appropriate to the product that is the subject of an MRTPA. The FDA has identified 93 HPHCs (FDA 2012c) and currently mandates testing and reporting of an abbreviated list of HPHCs in cigarette smoke (18 HPHCs) and smokeless tobacco (9 HPHCs) (FDA 2012b). The tobacco and cigarette mainstream smoke HPHCs specified by FDA represent several chemical classes, and include nicotine and tobacco alkaloids, carbon monoxide, tobacco-specific nitrosamines (TSNAs), polycyclic aromatic hydrocarbons (PAHs), volatile organic compounds (VOCs), aromatic amines, and metals. The initial criterion for HPHC designation was the availability of evidence that a tobacco or smoke constituent is a carcinogen, a respiratory toxicant, a cardiovascular toxicant, a reproductive or developmental toxicant or addictive. This classification scheme reflects a broad scientific agreement that several major classes of chemicals present in tobacco, and several additional classes of chemicals found in tobacco smoke are toxic in some respect,

and/or carcinogenic (USDHHS 2010). The abbreviated list of HPHCs for which reporting is required also reflects the availability of adequate, reproducible analytical methods for only a subset of the 93 FDA-listed HPHCs that permit meaningful comparisons among different products. Table 2.9.5-2 lists the HPHCs that are currently specified by FDA for reporting.

Table 2.9.5-2: The abbreviated list of harmful and potentially harmful constituents (HPHC) in cigarette smoke and smokeless tobacco that are specified by FDA for mandatory reporting

HPHCs in Cigarette Smoke	HPHCs in Smokeless Tobacco
Acetaldehyde	Acetaldehyde
Acrolein	Arsenic
Acrylonitrile	Benzo[a]pyrene
4-Aminobiphenyl	Cadmium
1-Aminonaphthalene	Crotonaldehyde
2-Aminonaphthalene	Formaldehyde
Ammonia	Nicotine (total and free)
Benzene	NNK*
Benzo[a]pyrene	NNN**
1,3-Butadiene	
Carbon monoxide	
Crotonaldehyde	
Formaldehyde	
Isoprene	
Nicotine (total)	
NNK*	
NNN**	
Toluene	

*4-(methynitrosamino)-1-(3-pyridy1)-1-butanone
** N'-nitrosonornicotine

2.9.5.2 Camel Snus tobacco is not burned during use, so Camel Snus users are not exposed to tar or other products of incomplete tobacco combustion formed during smoking

When conducting product chemistry analyses, cigarette smoke chemistry is often initially characterized in terms of mainstream smoke yields of tar, nicotine and carbon monoxide. Direct

product chemistry comparisons between Camel Snus and U.S. cigarettes are not possible for tar and other combustion products present in cigarette smoke (*e.g.,* carbon monoxide) because those substances are formed from burning tobacco. Tar (a defined quantity consisting of thousands of compounds) and carbon monoxide (a principal component of tobacco smoke) are formed during cigarette smoking via incomplete combustion of tobacco present in the product.

As would be expected, since no tobacco is burned when using Camel Snus, users of the product are not exposed to tar, carbon monoxide or other products of incomplete tobacco combustion. Direct evidence of this fact is provided by biomarker results from clinical studies. Specifically, differences in carboxyhemoglobin (a biomarker of carbon monoxide exposure) and urine mutagenicity (a biomarker which integrates response from many different constituents present in tar) demonstrate that smokers who switch exclusively to Camel Snus use are not exposed to these substances. For example, in study CSD0904, carboxyhemoglobin and urine mutagenicity biomarker results for Camel Snus product adopters were, respectively, no different than and less than results for non-tobacco users (Table 6.1.2-32).

2.9.5.3 Camel Snus contains lower levels of some HPHCs and greater amounts of others relative to tobacco smoke

Differences in HPHC results are observed between Camel Snus and cigarettes, with levels of some HPHCs greater than, and others less than, the levels found in cigarette smoke. Comparisons of Camel Snus and cigarette product chemistry show a clear delineation between results for constituents that originate primarily in cured tobacco leaf (As, Cd, nicotine, NNN, NNK) and those that originate primarily in the processes that occur during cigarette smoke formation, *i.e.*, during the burning of tobacco (acetaldehyde, B[a]P, crotonaldehyde, formaldehyde). Table 2.9.5-3 summarizes a comparison of HPHCs present in Camel Snus and cigarette smoke (presented in greater detail in Section 6.1.5 as Table 6.1.5-19).

Table 2.9.5-3: Comparison of HPHCs in Camel Snus (per pouch, as-is) and mainstream smoke from U.S. cigarettes (per cigarette)

Constituent	Camel Snus Less than Cigarette Smoke[1]	Camel Snus Greater than Cigarette Smoke[2]
Acetaldehyde	X	
Arsenic		X
B[a]P	X	
Cadmium		X
Crotonaldehyde	X	
Formaldehyde	X	
Nicotine		X
NNK		X
NNN		X

Abbreviations: B[a]P = Benzo[a]pyrene; NNN= N'-nitrosonornicotine; NNK= 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone

[1] An 'X' in this column denotes constituents that are found at lower levels in Camel Snus than are found in the smoke of U.S. cigarettes.

[2] An 'X' in this column denotes constituents that are found at higher levels in Camel Snus than are found in the smoke of U.S. cigarettes.

2.9.5.4 Greater amounts of HPHCs (nicotine, TSNAs and metals) in Camel Snus compared to cigarette smoke are not predictive of consumers' exposures

As discussed briefly above, and in more detail in Section 6.1.5 and Section 6.1.2, product chemistry data are not a measure of actual toxicant exposure when consumers use a tobacco product. The chemical analyses of Camel Snus presented in this Application show Camel Snus to contain higher levels of some HPHCs than are found in mainstream cigarette smoke produced by standardized laboratory smoking regimens. Specifically, metals derived from the soil (arsenic, cadmium), nicotine and TNSAs that are formed during tobacco curing processes (NNN, NNK) are greater in Camel Snus than in cigarette smoke. Such differences between Camel Snus and cigarette smoke must be considered in the context of the actual exposures to these constituents experienced by users of Camel Snus, as presented in Section 6.1.2.

Tobacco users are exposed to a fraction of the metals initially present in cigarettes or smokeless tobacco, including Camel Snus. Metals found in cured tobacco leaf are not transferred efficiently into cigarette smoke and have also been shown to transfer partially, if at all, from Camel Snus during product use (Caraway and Chen 2013). Additionally, published population surveys show that urinary excretion of metals by smokeless tobacco users is lower than or, in a few instances, similar to those of cigarette smokers, but are not higher than those of cigarette smokers (Naufal *et al.* 2011; see also discussion of other exposure biomarkers studies in Section 6.1.2).

Similarly, Camel Snus users are exposed to only a fraction of the TSNAs and nicotine present in Camel Snus under actual conditions of use (*see*, *e.g.*, Table 2.9.1-8, Table 2.9.1-9 and Table 2.9.1-10). Consistent with these findings, biomarker results demonstrate that Camel Snus users are exposed to similar, or reduced, levels of TNSAs (*see*, *e.g.*, Table 2.9.1-2 and Table 2.9.1-6) and nicotine (*see*, *e.g.*, Table 2.9.1-3 and Table 2.9.1-7) compared to cigarette smokers. Camel Snus users are not exposed to higher levels of nicotine or TSNAs than cigarette smokers.

2.9.5.5 Camel Snus contains comparable or lower levels of HPHCs relative to other smokeless tobacco products sold in the United States

Certain types of smokeless tobacco products such as moist snuff and dry snuff contain higher levels of some HPHCs (*e.g.*, TSNAs and B[a]P) than do other smokeless tobacco products, including Camel Snus. Observed differences in smokeless tobacco HPHC content are driven by several factors, including selection of the tobaccos used in a product and the manner in which those tobaccos are cured and processed, *i.e.*, via fermentation, heat-treatment or with exposure to smoke during fire-curing.

As described in detail in Section 6.1.5, product chemistry data for Camel Snus and other U.S. smokeless tobacco products has been extensively reported in the scientific literature. RJRT has also conducted unpublished studies of these products. While available data were generated in a number of different analytical testing laboratories using varied analytical testing methodology, all results are in general agreement and show that Camel Snus has lower levels of TSNAs, B[a]P and other HPHCs than are found in many other U.S. smokeless tobacco products.

Based on available product chemistry data, Table 2.9.5-4 summarizes the percentage of U.S. smokeless tobacco products containing greater HPHC levels than Camel Snus (per gram tobacco, as-is basis). For example, 97% of U.S. smokeless tobacco products contained greater amounts of B[a]P than Camel Snus styles, on average. (b) (4) Depending on the particular tobacco constituent, from 43% to 97% of the U.S. smokeless tobacco products tested contained greater amounts of the HPHC than Camel Snus styles, on average. Comparisons of Camel Snus product chemistry with products in other smokeless tobacco subcategories (*i.e.*, moist snuff, dry snuff, loose leaf) are summarized in Table 6.1.5-26.

Table 2.9.5-4: Percentage of U.S. smokeless tobacco products tested containing greater HPHC levels than Camel Snus (per gram tobacco, as-is basis)

Tobacco Constituent	Mean (Min., Max.)[a]
Nicotine (mg/g)	82 (79, 85)
Acetaldehyde (ng/g)	59 (54, 61)
Crotonaldehyde (ng/g)	92 (90, 93)
Formaldehyde (ng/g)	43 (30, 79)
Arsenic (ng/g)	94 (94, 94)
Cadmium (ng/g)	89 (87, 96)
NNN (ng/g)	75 (60, 87)
NNK (ng/g)	57 (49, 66)
B[a]P (ng/g)	97 (97, 97)

[a] Mean and range of mean values (minimum, maximum) for all six Camel Snus styles (Frost, Mellow, Mint, Frost Large, Robust, Winterchill). Comparisons to individual Camel Snus styles are summarized in Table 6.1.5-25.

2.9.5.6 Product chemistry data are only partially concordant with the findings of *in vitro* biology, *in vivo* biology, exposure biomarker and epidemiological studies

In vitro biology, *in vivo* biology, exposure biomarker and epidemiological studies consistently demonstrate less biological activity, less exposure to toxicants and less risk for smoking-related diseases when using smokeless tobacco products, including Camel Snus, as compared to cigarettes. The product chemistry results presented in this Application show that Camel Snus contains lower levels of some HPHCs and greater amounts of others relative to tobacco smoke. Thus as reported, product chemistry results are not fully predictive of observed biological activity differences, toxicant exposure differences and differences in observed smoking-related risks for Camel Snus as compared to cigarette smoking. This lack of full concordance is likely due to the limited number of HPHCs common to both product types and available for comparison, as well as differences in manner of product use. Comparisons of the nine HPHCs common to both Camel Snus and cigarettes do not fully reflect the many other toxicants present in cigarette smoke that are lower or absent in Camel Snus.

2.10 Summary of Consumer Testing Studies of the Proposed Modified Risk Advertising

In addition to requiring that a modified risk tobacco product, as actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users, the TCA requires that a modified risk tobacco product will benefit the health of the population as a whole, taking into account both users and non-users of tobacco products (TCA Section 911(h)(1)). Assessing the impact on the health of the population as a whole requires an understanding of how sub-populations, including both tobacco users and non-users, will comprehend and apply the proposed modified risk information, in particular the effect of the proposed modified risk information on tobacco use behaviors. FDA's MRTPA Draft Guidance states that applications must contain evidence to show that the advertising and labeling concerning modified risk products enable the public to comprehend the information concerning

modified risk, as well as the relative significance of that information within the context of total health and in relation to all of the diseases and health-related conditions associated with the use of tobacco products (FDA MRTPA Draft Guidance 2012, pp. 5, 20, 26; TCA Section 911(h)(1)).

Therefore, in accordance with the TCA and FDA's MRTPA Draft Guidance, RJRT conducted comprehension and perceptions studies to evaluate consumers' understanding and application of the information provided in each of RJRT's three proposed modified risk advertising executions. The three comprehension and perceptions studies, summarized in detail in Section 6.2, assessed adults' understanding of advertising that presented risk reduction information, and also conveyed important information aimed to mitigate potential unintended consequences of modified risk messaging. RJRT's studies show that the proposed advertising will be successful in communicating reduced risk information to consumers while avoiding over-generalization of the risk messaging, which in turn would be expected to mitigate any potential for the advertising to deter tobacco quitting or promote tobacco initiation. RJRT's studies also find no indication that consumers will be misled by the proposed modified risk advertising. Overall, the results of RJRT's three comprehension and perceptions studies demonstrate that consumers will have a good understanding of the key message that Camel Snus presents less risk than cigarette smoking, but still presents some health risks and is not completely safe.

Modified risk tobacco products provide a potential health benefit to those who switch completely to them from tobacco products that pose a greater risk to health. To evaluate how the proposed modified risk advertising is likely to affect consumers' behavior, RJRT conducted three likelihood of use studies to determine whether the proposed modified risk advertising for Camel Snus would appeal to those for whom it would provide a reduced health risk (*i.e.*, current cigarette smokers); and, importantly, whether such advertising would have unintended consequences by differentially attracting those for whom use would not be beneficial (*i.e.,* non-smokers and smokers expecting to quit). The three likelihood of use studies also assessed, among those who were likely to use Camel Snus, their intended pattern of use (*i.e.*, switch completely, use in addition to other tobacco products, or use instead of quitting). Consistent with the understanding of messages demonstrated in the comprehension and perceptions studies, the three likelihood of use studies, summarized in detail in Section 6.3, show that overall interest in Camel Snus was greatest among current smokers, especially among those not expecting to quit, for whom switching to Camel Snus would confer a health benefit. Likelihood of use was consistently higher among current smokers, who stand to benefit from switching to Camel Snus, than among those not currently using tobacco or smoking, who could be harmed by Camel Snus.

Findings from the likelihood of use studies serve as one source of input to statistical modeling of the effects that introducing the proposed modified risk advertising for Camel Snus is likely to have on population health. Extensive modeling, summarized below in Section 6.4, demonstrates that, under a wide range of assumptions about the behavior of populations, an MRTP order for Camel Snus is likely to result in a population benefit of reduced mortality, and very unlikely to result in harm to the population as a whole. The comprehension and

perceptions studies, the likelihood of use studies, and the statistical modeling are summarized below.

2.11 Effect of the Modified Risk Messaging on Comprehension and Perceptions

In support of this Application, RJRT conducted three comprehension and perceptions studies – one for each of the three proposed modified risk advertising executions - to assess whether consumers understood and applied the modified risk information.

As background to these new data, the published literature on the perception of risk among the population with regard to smokeless tobacco products in general and snus in particular is summarized below. Understanding where the population has been historically in its level knowledge and beliefs with respect to the risks of smokeless tobacco products provides an important context for understanding the consumer testing findings with regard to the proposed Camel Snus modified risk advertising.

2.11.1 Published literature on perceptions of risk of smokeless tobacco and snus

As context for evaluating the results from RJRT's comprehension and perceptions studies, it is useful to examine what the existing published literature indicates about individuals' perceptions of the risks of smokeless tobacco products, including snus, and about how these perceptions are affected by education about those risks. Multiple studies have examined individuals' perceptions of the risk associated with using various tobacco products, including smokeless tobacco and snus, and the relative harmfulness of these products in relation to cigarettes. Studies of the general U.S. adult population suggest that very few adults (generally less than 10%) believe that smokeless tobacco and snus are less harmful to their health than cigarettes; the overwhelming majority of U.S. adults incorrectly believe smokeless tobacco and snus to be either just as harmful or more harmful than traditional cigarettes (Fong *et al.* 2016; Kaufman *et al.* 2014; Kiviniemi and Kozlowski 2015; Regan *et al.* 2012). The most recent and most comprehensive study of individuals' perceptions of risk associated with tobacco product use was based on responses from a representative sample of over 32,000 U.S. adults participating in the PATH study (Fong *et al.* 2016). Fong and colleagues found that only 9% of adults believed smokeless tobacco was less harmful than smoking, while 28% believed smokeless tobacco products were *more* harmful than smoking (the most of any tobacco product); the majority (64%) believed smokeless tobacco was as harmful as smoking.

Consumer misperceptions of the relative harms due to use of smokeless tobacco and snus are pervasive. Misperceptions are prominent among young adults, an important population sub-group with the highest rates of adult tobacco use (Choi and Forster 2013; Wackowski and Delnevo 2016), high school seniors (Tomar and Hatsukami 2007), college students (Berg *et al.* 2014; Smith *et al.* 2007), and young adults entering military service (Haddock *et al.* 2004). These misperceptions are not limited to youth or to the general population, as they are also seen among tobacco control professionals (Biener *et al.* 2014), health professionals (England *et al.* 2014; van Zyl *et al.* 2013), and university faculty (Peiper *et al.* 2010). Similar misperceptions are also prevalent outside the U.S., where they are observed among current and former smokers

(Borland *et al.* 2011; Heavner *et al.* 2009; Lund and Scheffels 2014a; Wikmans and Ramström 2010), youth (Overland *et al.* 2008), healthcare professionals (Moysidou *et al.* 2016), and tobacco retailers (Heavner *et al.* 2010).

As is the case with the general public, current and former smokers also appear to be misinformed about the relative risk of smokeless tobacco (Pepper *et al.* 2015; Popova and Ling 2013; Richardson *et al.* 2014). The International Tobacco Control Four-Country (ITC-4) Survey found that, among U.S. cigarette smokers who are aware of smokeless tobacco products, relatively few (fewer than 13%) believe that any smokeless tobacco products are less harmful than cigarettes (Borland *et al.* 2011; O'Connor *et al.* 2005a; O'Connor *et al.* 2007).

While misperceptions about the risk of smokeless tobacco and snus relative to smoking are widespread, they are also modulated by individuals' intuitive theories of how particular health harms arise. Thus, compared to cigarettes, smokeless tobacco and snus are often viewed as being more likely to cause oral cancer, equally likely to cause heart disease, and less likely to cause lung cancer (Choi *et al.* 2012; Pepper *et al.* 2015; Wray *et al.* 2012). Focus group research suggests that such beliefs are attributable to the products' mode of nicotine delivery – because smokeless tobacco and snus come into constant and direct contact with oral tissue, these products are perceived as likely to cause oral cancer (Choi *et al.* 2012; Liu *et al.* 2015). Lack of control over nicotine delivery has also been cited in qualitative research as a reason for greater perceived harm associated with smokeless tobacco use (Choi *et al.* 2012; Sami *et al.* 2012).

Beliefs about the relative harms of smokeless tobacco products are related to use of the products, with those perceiving smokeless tobacco and snus to be less harmful than cigarettes being more likely to use these products (Fong *et al.* 2016; Kaufman *et al.* 2014; O'Connor *et al.* 2007; Richardson *et al.* 2014; Wackowski and Delnevo 2016). For example, Fong and colleagues (Fong *et al.* 2016) reported that, among those familiar with snus, belief that snus was less harmful than smoking (compared to believing the risk was the same) was associated with a 150% increase in the odds of actually using snus, while belief that snus was more harmful than smoking reduced the odds of using snus by 60%. These analyses suggest that education about relative harms might encourage switching from smoking to use of smokeless tobacco and snus.

Indeed, education about relative risks of smokeless tobacco and snus versus smoking has the potential to mitigate the observed misperceptions about relative risk. In a small multinational sample, the effects of education about the relative harms of smokeless tobacco versus smoking were assessed using a four-page fact sheet (and, in the U.S., a face-to-face power-point presentation) (Borland *et al.* 2012). The educational intervention resulted in modest increases in correct perceptions of smokeless tobacco's harm relative to smoking, and these were accompanied by increased interest among smokers in trying smokeless tobacco. Similar effects were observed for education about NRT. However, many smokers expressed skepticism of the facts presented, the increases in correct understanding were modest, and the majority of smokers in most countries were still misinformed (U.S. smokers' correct responses rose from 7% to 27%), underscoring the limitations of single exposures to information, and the need for more compelling and ongoing education.

A larger improvement in understanding of relative risks is possible, and is suggested by data on changes over time in particular countries (Borland *et al.* 2011). In the U.K., the proportion of smokers recognizing that smokeless tobacco is less harmful than smoking increased from 25% to 40% from 2002 to 2009. However, the proportion of U.S. smokers reporting a belief that smokeless tobacco is less harmful than smoking did not significantly change over this period, with five of six smokers reporting misperceptions. The authors attribute the improvement in understanding to the efforts in the U.K. to educate smokers about the safety of NRT and nicotine as alternatives to smoking. These results suggest the potential for education to improve U.S. smokers' understanding of the relative risks of non-combustible nicotine sources compared to smoking.

2.11.1.1 Comprehension and perceptions studies among tobacco users and non-users

RJRT's proposed modified risk advertising communicates the message that switching completely to Camel Snus from cigarette smoking can reduce the risk of serious chronic diseases (lung cancer, oral cancer, respiratory disease, heart disease), while also communicating several other key messages, such as the message that persons who do not use tobacco should not use Camel Snus. In accordance with the TCA and FDA's MRTPA Draft Guidance, RJRT conducted three comprehension and perceptions studies, one for each of the three proposed modified risk advertising executions, to assess the effects of the proposed modified risk advertising for Camel Snus on current tobacco users' and non-users' (both former users and never users) understanding and application of the modified risk information (USDHHS 2012; TCA Section 911(h)(1)).

RJRT's comprehension and perceptions studies were designed to determine whether consumers sufficiently understand the modified risk advertising and appropriately apply the modified risk messaging within the context of total health and in relation to all of the diseases and health-related conditions associated with the use of tobacco products, as demonstrated by perceptions of risk. Specifically, these studies assessed whether consumers understand that Camel Snus carries less risk than smoking for particular diseases, while at the same time understanding that this reduction in risk does not imply that Camel Snus has no risk at all, or that it reduces the risk of all tobacco-related diseases. To place the reduced risk of Camel Snus in an appropriate context, consumers' understanding of the risk of Camel Snus was assessed relative to several comparators. Consumers were expected to understand that quitting all tobacco use is the best and safest option, and also to understand how the risk of Camel Snus compares to that of nicotine-based smoking cessation medications and quitting all tobacco use completely. Because the proposed modified risk claims are product-specific, consumers were expected to understand that the proposed modified risk advertising would not apply to other products in the same category (in this case, smokeless tobacco products other than Camel Snus).

Besides shaping risk perceptions appropriately, the proposed modified risk advertisements also aim to convey other information that can help consumers understand the appropriate use of Camel Snus. Important messages include: (1) individuals who do not already use tobacco should

not initiate use of Camel Snus, (2) Camel Snus should not be used by minors or pregnant women, (3) Camel Snus is addictive, and (4) Camel Snus is best used as a complete substitute for smoking, not as a supplement to it.

To test consumer comprehension of the proposed modified risk messaging, RJRT conducted a total of three comprehension and perceptions studies, one for each proposed modified risk advertising execution. These studies are summarized in this section, presented in more detail in Section 6.2, and all study documents (study protocols, study reports, and raw data) are submitted with this Application in Section 7.

2.11.2 Comprehension and perceptions study objectives

The comprehension and perceptions studies were intended to assess consumer understanding of the following messages, or communication objectives:

- Smokers switching completely to Camel Snus can reduce the risk of certain smoking-related diseases enumerated in the proposed advertisements
- Camel Snus still carries health risks (even for diseases where risk is reduced)
- Camel Snus does not reduce the risk of all other smoking-related diseases
- Camel Snus does not eliminate all risk to overall health
- The proposed modified risk advertising executions for Camel Snus do not apply to other smokeless tobacco products
- Camel Snus is not a safer alternative to nicotine-based smoking cessation medications
- Camel Snus is not a safer alternative to quitting tobacco use completely
- Quitting smoking is the best choice for smokers
- Camel Snus is addictive
- Those who do not use tobacco products should not use Camel Snus

2.11.2.1 Findings from the comprehension and perceptions studies

Each of the three proposed modified risk advertising executions for Camel Snus was independently tested for consumer comprehension and perceptions. Large samples (N=8,404; execution 1; N=4,924, execution 2; and, N=4,906, execution 3) were recruited for each of the three studies. The samples included current, former, and never tobacco users who were exposed to the proposed modified risk advertisement, and then answered a series of questions regarding the content (messaging) of the advertisement, the absolute and relative risks associated with using Camel Snus, and the appropriate use of the product to receive a health

benefit (*i.e.,* complete switching from cigarettes to Camel Snus). Relative risk questions also assessed respondents' perceptions of the risks of smoking, use of smokeless tobacco products other than Camel Snus, nicotine-based smoking cessation medications, and quitting all tobacco use completely.

Although the three executions differ in several ways, as described in Section 4.2, they share many common messages and communication objectives, and were assessed using similar methods on samples recruited from the same online panels. Accordingly, one would expect the resulting consumer responses to be similar – and they were. The results were quite consistent across the three studies, suggesting that the findings are robust and reliable. In the summary that follows, the findings across studies are discussed. Where numerical findings are given as a range, they represent the range of values obtained across studies. Detailed descriptions of the results for each of the three studies are reported in Section 6.2 and in the individual study reports submitted with this Application (Camel SNUS Modified Risk Messaging: Comprehension and Perceptions among Tobacco Users and Non-Users – *First Execution of Consumer Testing* – Amended Final Report; Camel SNUS Modified Risk Messaging: Comprehension and Perceptions among Tobacco Users and Non-Users – *Second Execution of Consumer Testing* – Amended Final Report; Camel SNUS Modified Risk Messaging: Comprehension and Perceptions among Tobacco Users and Non-Users – *Third Execution of Consumer Testing* – Amended Final Report).

Across all three executions and studies, respondents demonstrated sufficient understanding of the key messages in the proposed modified risk advertisements. Respondents exposed to the proposed modified risk advertisements understood that switching completely to Camel Snus carries less risk than cigarette smoking for particular diseases named in the advertisements, but also understood that *reduced* risk did not mean *no* risk. Respondents did not overgeneralize the modified risk messaging to conditions that were not addressed in the advertisements, nor did they believe that the claims applied equally to all smokeless tobacco products. They understood that using Camel Snus was not safer than quitting smoking, and that people who were not already using tobacco should not use Camel Snus. They understood that Camel Snus is addictive, and most understood that smokers should switch completely to Camel Snus to realize the risk reduction benefit.

Comprehension and perceptions of the modified risk advertising were tested in important sub-groups defined by tobacco use, and results showed that key messages were understood by the sub-groups to which they were most relevant. For example, almost all current tobacco users, as well as the subset of current tobacco users likely to quit (*i.e.,* potential quitters) understood the message that quitting smoking is the best option for smokers concerned about health risks. These results suggest that the proposed modified risk advertising will not deter smokers from quitting, and that switching to Camel Snus will not be seen as a substitute for quitting. Few current tobacco users thought Camel Snus would lower the risk of tobacco-related diseases if they continued smoking. Further, few of those who were not current tobacco users thought Camel Snus should be used by non-users of tobacco. Thus, the proposed modified risk advertising appropriately communicated risk reduction, while avoiding communicating

messages that could potentially undermine the population health benefit of marketing Camel Snus with modified risk advertising.

2.11.2.1.1 Respondents understood that switching to Camel Snus reduces their risk of tobacco-related diseases compared to smoking, and did not mistakenly believe that there is no risk associated with using Camel Snus

All three proposed modified risk advertising executions claimed reduced risk of lung cancer and respiratory disease, and the results were consistent in showing consumer understanding. The message that switching completely from smoking cigarettes to using Camel Snus reduces the risk of lung cancer and respiratory disease was understood by a majority of respondents. Roughly 60% or more indicated that Camel Snus carried less risk (but still some risk) for these diseases, and respondents' average ratings of disease risk were consistently lower for Camel Snus relative to cigarette smoking. Importantly, no more than 10% of respondents in any of the three studies believed that Camel Snus presented *no* risk of lung cancer or respiratory disease. Thus, respondents understood that a reduction in *relative* risk did not imply a complete *absence* of risk; they did not exaggerate the reduction in risk claimed by the advertisements. Indeed, the opposite was observed, with 15-20% of respondents (across the three executions) responding that Camel Snus carried the same risk of lung cancer and respiratory disease as smoking, despite the reduced risk claims for these lung diseases. Further, respondents' quantitative ratings of expected risk from Camel Snus compared to cigarette smoking suggested that they underestimated the likely magnitude of reduction in risk of these conditions from switching to Camel Snus. This misperception may be due to intransigent pre-existing beliefs about the harmfulness of smokeless tobacco (including snus and Camel Snus) that have been demonstrated to be resistant to change (Borland *et al.* 2012), and may reflect respondents' reluctance to believe claims made in tobacco company advertisements, as discussed in Section 6.2.

The proposed modified risk advertising in Executions 1 and 2 also claimed reduced risk of heart disease and oral cancer. Execution 3 did not. In response to executions 1 and 2, respondents – particularly ever tobacco users (current users, former users, and experimenters) who perhaps have thought more about the harms of tobacco – distinguished among the four diseases claimed to be reduced in the proposed advertisements, making discriminations among the diseases that were not made in the advertisements themselves. These respondents assumed that Camel Snus would yield greater reduction in risk of respiratory conditions (lung cancer and respiratory disease) than heart disease and oral cancer, where a higher percentage perceived that Camel Snus might carry no risk (8-14%); in terms of oral cancer, a higher percentage of respondents perceived that Camel Snus might carry the same risk as smoking (31-36%). Their response to claims about heart disease were intermediate. This corresponds to the public's intuitive understanding of risk from smoking and oral tobacco products (Choi *et al.* 2012; Liu *et al.* 2015), and indicates that the responses were infused with respondents' own pre-existing beliefs (perceptions), even though respondents were asked to respond to questions by expressing what they understood from the advertisement they had seen (comprehension).

Thus, the test reflected the impact of pre-existing beliefs and perceptions – and the persuasive effect of the advertisement – as much as comprehension of the messages.

As expected, consumers did not find a single exposure to a tobacco company advertisement entirely persuasive regarding reduced risk of Camel Snus compared with cigarettes. In general, consumers are inherently skeptical of claims made in advertising (Carman *et al.* 2010; Langan 2015), and assume the advertiser has an interest in making claims for their product. Consumers also consider the trustworthiness of the source in considering the believability of a claim (Schmidt *et al.* 2016), with tobacco companies being highly mistrusted compared to other sources of information; this, in turn, detracts from the believability of any modified risk claim made by a tobacco company (Byrne *et al.* 2012; Harris Interactive 2013). It is therefore not surprising that a single exposure to a tobacco company advertisement did not persuade some respondents regarding the reduced risk associated with switching completely from smoking cigarettes to using Camel Snus. Additionally, U.S. government-mandated smokeless tobacco health warnings that were prominently placed on the proposed advertisements may have made the modified risk claims less credible. Importantly, while persistent misperceptions that Camel Snus is as harmful as smoking may limit the potential population health benefit of Camel Snus, such misperceptions do not present any risk of increasing harm to the public health.

2.11.2.1.2 Respondents did not overgeneralize the claimed risk reduction to other diseases and understood that using Camel Snus could harm overall health

The comprehension and perceptions studies also tested for potential generalization of the proposed modified risk advertising for Camel Snus to other diseases that were not mentioned in the advertisements, and to overall health. Respondents were asked whether Camel Snus reduced the risk of diseases not discussed in the advertisements, and only 15-17% of the respondents considered this to be true. The most frequent response – given by about half of the respondents in each study sample (48-53%) – stated they did not know or were unsure of the correct response, which is reasonable given that this risk was not addressed in the advertisements. This indicates that respondents understood the specificity of the proposed modified risk advertising, and did not necessarily apply the reduced risk messages to diseases for which risk reduction was not claimed.

Respondents also understood that, despite claims of reduced risk for specific diseases, Camel Snus carried considerable risk of harming health. Overall, respondents rated the risk of poorer health as substantial (*i.e.*, 5.5-5.8 on a 7-point scale), and higher than the risk of all the claimed diseases except oral cancer (which, as noted above, participants believed to be the least reduced by Camel Snus). This finding held across the sub-groups studied. Thus, respondents understood that the claims for reduction in risk of specific diseases compared to smoking did not obviate the risk that use of Camel Snus could result in generally poorer health.

2.11.2.1.3 Respondents understood that Camel Snus is addictive

The proposed modified risk advertisements contain the statement that Camel Snus is addictive. This addiction warning was also expressed in the government-mandated rotating warning label

statements, seen by one-fourth of the respondents. Respondents understood that Camel Snus is addictive, as 82% agreed with the statement across the three proposed advertising executions; only 5-7% disagreed, and the remaining respondents were not sure. Consistent with these findings, respondents rated the addictiveness of Camel Snus quite high, at 5.9-6.1 on the 7-point scale, which was only about a half point lower than the addictiveness of cigarette smoking. Recognition that Camel Snus is addictive was evident among both current tobacco users and non-users.

2.11.2.1.4 Respondents did not believe that the risk reduction applies to other tobacco products

The comprehension and perceptions studies also tested for potential generalization of the proposed modified risk advertising for Camel Snus to other products in the same tobacco category (*i.e.,* smokeless tobacco products other than Camel Snus) that do not currently have authorized modified risk claims. In quantitative ratings, respondents consistently rated the risk of other smokeless tobacco products as modestly higher than Camel Snus, suggesting that respondents would not globally generalize the claims to all smokeless tobacco products. The risk ratings for smokeless tobacco products other than Camel Snus were generally lower than those assigned to cigarette smoking, which represents a reasonable inference.

2.11.2.1.5 Respondents understood that Camel Snus is not safer than nicotine replacement smoking cessation products

Another aspect of understanding how respondents assessed the relative risk of Camel Snus was to compare its risks to those of nicotine replacement products, which are approved by FDA as safe and effective for smoking cessation. This comparison was not made in the proposed advertisements, but respondents were asked whether the statement "Camel Snus is NOT a safer alternative than products that are used to quit tobacco such as gum, patches, and lozenges" was true or false. Most respondents (62-68%) understood that this was true, although 20-27% of potential quitters indicated it was false.

2.11.2.1.6 Respondents understood that those who do not use tobacco should not use Camel Snus

A concern about modified risk claims is that such claims may unintentionally encourage use by people who are not currently using tobacco, which could add risk rather than reduce it, and thus reduce the overall population health benefit. Following exposure to the proposed modified risk advertising, very few respondents (5-6%) in the overall sample believed that non-users of tobacco should use Camel Snus. The percentage who believed Camel Snus should be used by non-tobacco users was highest among experimenters, who may have seen Camel Snus use as preferable to initiating smoking. Even among experimenters, most understood that Camel Snus was not to be used by non-users of tobacco. The message was also well understood among the non-users themselves, both former and never tobacco users, with only 3-6% giving an incorrect response. Thus, the proposed modified risk advertising, along with the explicit

statement that non-users of tobacco should not use Camel Snus, did not lead respondents to believe Camel Snus should be used by those who do not currently use tobacco.

2.11.2.1.7 Respondents understood that switching completely from cigarettes to Camel Snus is necessary to reduce disease risk

The proposed modified risk advertisements stress that smokers must switch completely to Camel Snus to reduce their risk of disease: "Smokers who **switch completely** from cigarettes to Camel Snus can significantly reduce their risk of lung cancer, oral cancer, respiratory disease, and health diseases" and "Smokers who **SWITCH COMPLETELY** from cigarettes to Camel Snus can greatly reduce their risk of lung cancer, oral cancer, respiratory disease, and heart disease."[3] Respondents were shown the proposed advertisements and then asked to indicate what cigarette smokers should do in order to benefit from using Camel Snus. Across all three studies, roughly three-quarters understood that smokers should stop smoking completely and use Camel Snus instead. In execution 1, where respondents could endorse an option of reducing their smoking by half, 10% endorsed this option, but only 3% thought smokers could benefit without changing their smoking. In executions 2 and 3, where respondents were not provided a reduction option, very few (3-4%) believed that using Camel Snus while continuing to smoke cigarettes would deliver health benefits.

2.11.2.1.8 Respondents understood that quitting smoking is the best choice for smokers

From a health perspective, cigarette smokers who switch completely to Camel Snus are likely to reduce their risk of smoking-related diseases, but the greatest benefit and risk reduction comes from quitting tobacco use altogether. Accordingly, the proposed advertisements explicitly communicated that quitting is preferred to switching to Camel Snus. Strong majorities understood that quitting is the best choice for smokers; importantly, this was true among current tobacco users (89-91%), including those who were planning to quit (91-93%).

Less clear results were obtained when respondents were asked whether Camel Snus was "NOT a safer alternative to quitting tobacco entirely," which was endorsed by 69-71% of the sample. On balance, the data indicate that respondents, including current tobacco users considering quitting, understood that quitting tobacco use is preferable to switching to Camel Snus.

2.11.2.1.9 Special population groups understood the modified risk messaging

In addition to testing comprehension and perceptions in sub-groups defined by smoking status, the studies also examined performance in sub-groups defined by demographics and health literacy. The responses of White males were examined because this is the demographic group currently most likely to use smokeless tobacco (USDHHS 2014). Responses among White males were very similar to those of the sample as a whole.

[3] Proposed modified risk advertising in execution 3: "Smokers who **SWITCH COMPLETELY** from cigarettes to Camel SNUS can greatly reduce their risk of lung cancer and respiratory disease."

The responses of ethnic minority (*i.e.*, non-White) individuals were also examined. Ethnic minority responses were generally similar to those of the sample as a whole, but with a greater tendency towards incorrect and "I don't know" responses. This likely reflects the fact that individuals in some ethnic minority groups were more likely to be assessed as having limited health literacy (IOM 2004; Kutner *et al.* 2006; Rudd 2007). Indeed, as expected, individuals with limited health literacy generally scored lower on most of the assessments. By definition, such individuals have more difficulty reading material and extracting meaning (IOM 2004), and typically perform less well on tests of comprehension (Davis *et al.* 2006; Raymond *et al.* 2002; Shiffman *et al.* 2011; Wolf *et al.* 2006). Although individuals with limited health literacy were more likely to answer questions incorrectly, in every case they were more likely to respond "I don't know" than to provide an incorrect answer. As just one example (in execution 1), only 9% of limited health literacy respondents thought that Camel Snus had no risk at all for lung cancer (the same as the sample as a whole), but 17% said they did not know or were not sure. Perhaps more than those with stronger literacy skills, individuals with limited health literacy may need multiple communications from multiple sources to effectively convey the intended messages.

2.11.2.2 Conclusions from the comprehension and perceptions studies

The proposed Camel Snus advertisements conveying modified risk messaging and educating about risk reduction were generally well understood by consumers across the three executions of the studies. The advertisements communicated that Camel Snus had lower risk of certain diseases, but respondents did not develop a misperception that it had no risk at all. Indeed, respondents tended to *under*estimate the degree of risk reduction that cigarette smokers might expect from switching completely from smoking to Camel Snus. Also, respondents did not overgeneralize the modified risk messages – they did not apply them to diseases not specifically cited in the advertisements, or to their general health – and did not apply them to smokeless tobacco products other than Camel Snus. They understood that Camel Snus is addictive. Current tobacco users, including those intending to quit, understood that quitting was the best option, and non-tobacco users – both former users and never users – understood that non-users should not use Camel Snus. In sum, the proposed advertisements communicated conservative risk reduction messaging, and did not promote misconceptions that might lead to inappropriate use of Camel Snus or lead to unintended effects that would reduce the population benefit of having smokers switch completely to Camel Snus.

2.12 Effect of the Modified Risk Messaging on Tobacco Use Behaviors

In support of this Application, RJRT conducted three likelihood of use studies – one for each of the three proposed modified risk advertising executions – to assess how the use of Camel Snus might be affected by the proposed modified risk advertising. Regulatory consideration of a Camel Snus MRTP order may also be informed by existing literature on the use of snus and other smokeless tobacco products.

2.12.1 Published literature on snus use

Much of the evidence regarding patterns of use of snus and other smokeless tobacco products is from other countries (not the U.S.), where the use of these products is more common and where use experience has lasted, in some instances, for decades. The broadest understanding of the use and impacts of smokeless tobacco products can be gained by examining what is known about the likelihood to use these products, both within the U.S. and in other countries where their use is more wide-spread and longer in duration. Therefore, the published literature on the population's use of smokeless tobacco products, including snus, was examined and is discussed below to provide background and context for the data presented.

The history of snus use in countries such as Sweden and Norway suggests that snus can serve as a product that can keep people from using or continuing to use cigarettes. The experience in these countries with regard to effects on younger individuals is mixed, but mostly suggests that snus does not appreciably promote cigarette smoking uptake. Snus use in Sweden and Norway has increased, suggesting that it can have enough appeal to draw those who are or might become smokers toward a less harmful product. In the U.S., snus has a relatively short history, but studies that have examined snus specifically have not found it to appreciably promote smoking initiation among youth or reduce cigarette quitting among adult smokers.

2.12.1.1 Published literature on prevalence of snus and smokeless tobacco use outside the U.S.

In countries such as Sweden and Norway, the use of smokeless tobacco is predominated by snus use (Leon *et al.* 2016), which has a long cultural history in those countries. In Sweden, the prevalence of ever use of tobacco products (assessed between 1998 and 2002) among adults aged 42-64 years in the Swedish Twin Registry (n=31,213) was 63% for cigarettes and 15.8% for snus (Furberg *et al.* 2006); prevalence of current use of cigarettes was 23.7% and snus was 9.9%. Differences were seen by gender, in that men were less likely to smoke than women (21.6% versus 25.6%) but were more likely to use snus (19.1% versus 1.5%). In Norway, the prevalence of snus use in 2012 was 20% among adult males (aged 16-74) and 6% among adult females (Norwegian Institute of Public Health 2014). Rates of daily cigarette smoking were similar for males and females (16%), with an additional 11% of males and 9% of females smoking occasionally.

Although Sweden and Norway are different culturally and demographically from the U.S., the history of snus use in these countries provides important information regarding patterns of use, including use with other tobacco products – especially cigarettes – and use among youth that can be informative for the U.S. The experiences in these countries suggest that it is at least possible for snus to be adopted by large fractions of the tobacco-using population.

2.12.1.2 Published literature on the relationship between use of snus and cigarette smoking outside the U.S.

One concern about modified risk tobacco products is that new initiates to tobacco who adopt the alternative product might thereby be caused to progress to cigarette smoking. This is referred to in the literature as the "gateway effect" (Kozlowski *et al.* 2003; Lee 2015), which proposes that adoption of one tobacco product (snus or smokeless tobacco) can lead to an increased probability of subsequent use of another, more harmful, tobacco product (cigarettes).

To examine the possible effects of snus on cigarette smoking, data from a nationally representative sample of males in Sweden were examined over an 8-year period (Stenbeck *et al.* 2009). For both the younger cohort (16-44 years old) and older cohort (45-84 years old) (overall N=2,156), use of snus was associated with *lower* likelihood of continuing to smoke, although the association was statistically significant only for the younger cohort. The odds of becoming a smoker were significantly lower for baseline snus users than nonusers (OR=0.52; 0.33-0.80). That is, the net trend was the reverse of the hypothesized gateway effect. The authors concluded that, among Swedish males, snus more often serves as a way *out* of smoking than a way *into* smoking.

A similar reverse-gateway effect was reported in two additional studies in Sweden (Ramström and Foulds 2006; Furberg *et al.* 2005). In the first study (Ramström and Foulds 2006) the odds of initiating daily cigarette smoking were lower among those who had started their tobacco product use with snus compared with those who had not used snus (OR=0.28; 0.22-0.36). In the Swedish Twin Study (N=14,424), regular or occasional use of snus among males was associated with decreased odds of starting to smoke cigarettes compared to males who did not use snus (OR=0.2; 0.2-0.3) (Furberg *et al.* 2005).

Several studies in Sweden and Norway examined the use of snus and cigarette smoking among youth. In a cohort of youth (N=2,938) in Sweden, followed from age 11 to age 18, among those who initiated tobacco use, 11.2% initiated tobacco use with snus (compared to 69.5% initiating with cigarettes and 19.3% starting both products in the same year) (Galanti *et al.* 2008). This study also found that youth who started tobacco use with snus were less likely than those who started with cigarettes (19.5% versus 33.1%), or started with both products (19.5% versus 38.2%), to be current smokers at age 18. Another study also suggested a reverse-gateway effect. A cohort of 16-year-old males in Norway (N=1,395) was followed from 2001 to 2004, and assessed for smoking and snus use (Grøtvedt *et al.* 2013). Those who used snus exclusively at baseline were not more likely to become a smoker at follow-up (OR=0.86; 0.4-1.8) compared to those who did not use any tobacco at baseline. Baseline smokers were significantly more likely to remain a smoker at follow-up (OR=13.31; 8.2-21.6) compared to those who had not used any tobacco at baseline.

However, in another cohort (N=649) of Swedish youth followed from age 12 to age 18 researchers reported that ever having used snus at baseline (age 12) was associated with greater odds of being a cigarette smoker at follow-up (age 18) (OR=3.43; 1.78-6.62) (Joffer *et al.* 2014). In this study, 23% of never-users of snus were smokers 5 years later, compared to 54%

of those who had use snus at baseline, implying an incremental gateway risk of 31%. Other researchers (Lund and Scheffels 2014b) examined the association between snus use and smoking uptake among youth in Norway and found that youth who began using snus before age 16 had increased odds of ever smoking compared to those who initiated snus use after age 16 (OR=3.06; 1.98-4.76). Prevalence of current cigarette smoking among early snus users (22.9%) did not differ from than among those who had never used snus (29.6%); that is, there was no indication of a gateway effect. Among those who used snus after age 16, current smoking rates were *lower* (5.9%), indicating a *reverse*-gateway effect.

Taken as a whole, this literature suggests that there is no gateway effect to smoking among individuals who initiate snus use. One study (Joffer *et al.* 2014) suggested that snus users were more likely to later take up cigarette smoking. However, this could be because the individuals who initiate snus might be the same ones who are also interested in taking up smoking. That is, the association may not be causal. Importantly, most studies did not find any increased likelihood of taking up cigarette smoking among snus users, and several studies found the opposite effect, a reverse-gateway effect in which snus users were less likely to subsequently take up smoking, suggesting (but not proving) that snus use may divert vulnerable individuals from initiating cigarette smoking.

In addition to concerns expressed about gateway effects, concerns have also been expressed regarding dual use of snus and cigarettes, and whether that reduces quitting or, alternatively, whether it reduces harm by leading to eventual quitting of smoking altogether. It is therefore important to assess usage patterns among those who have and have not used either or both products. Two studies examined this issue in Sweden (Ramström and Foulds 2006; Rodu *et al.* 2002). Among primary smokers (those who began their tobacco use with cigarettes), 88% of those who started using snus quit smoking compared to 56% of smokers who had never used snus (OR=5.7; 4.9-8.1) (Ramström and Foulds 2006), suggesting that starting snus may have led to discontinuation of smoking. Among primary snus users (those who started their tobacco use with snus) who later started smoking, 74% stopped smoking (56% returned to exclusive daily snus use, 18% quit all tobacco use). The odds of being a daily cigarette smoker were significantly higher for daily smokers who had no history of daily snus use compared to smokers with a history of daily snus use (OR=4.4), again suggesting that snus may lead to discontinuation of cigarette smoking. In another study of males in Northern Sweden who used snus (Rodu *et al.* 2002), former smokers and never smokers consumed significantly more snus packages daily (0.41 and 0.44, respectively) than males who used both cigarettes and snus (0.25 packages). The dual product users also consumed significantly fewer cigarettes per day (10.8) than current smokers who had stopped using snus (15.1 cigarettes per day) and current smokers who had never used snus (16.0 cigarettes per day). Therefore, according to these two studies, dual use among males in Sweden led some to quit smoking altogether, some to return to snus use only, and, among those who continued dual use (1.5% of the population in Ramström and Foulds 2006), to a reduction in the amount of cigarettes they consumed. Overall, these studies suggest that the use of snus – whether prior to, following, or concomitantly with smoking – has positive effects on smoking (*i.e.,* more quitting, lower cigarette consumption).

2.12.1.3 Conclusions from the published literature outside the U.S.

In Sweden and Norway, where snus use is more common than in the U.S., adult males are most likely to use snus and are also less likely to smoke cigarettes. Patterns of snus and cigarette use among youth suggest that use of snus was more often associated with reduced rather than increased cigarette smoking, a finding inconsistent with gateway effects.

2.12.1.4 Published literature on the prevalence of snus and smokeless tobacco use in the U.S.

Snus, as a type of smokeless tobacco product, has only been available in the U.S. since 2006. As such, information on its use in the published literature is limited[4], although information on other types of smokeless tobacco use with longer experience in the U.S. market is available.

In 2012, the prevalence of smokeless tobacco use (defined as snuff or chewing tobacco use) among adults in the U.S. was 3.6% (USDHHS 2014). Males were significantly more likely than females to use smokeless tobacco (males: 7.1%; females: 0.4%); and, among males, use was more common among younger males (ages 18-25: 10.5%) than older males (ages 45-64: 5.0%; ages 65+: 2.7%). Among 2,067 adults in an online panel who were surveyed in 2013, 5.2% had ever tried snus and less than 1% were currently using snus (Kaufman *et al.* 2014), the same as the rate of trial reported by others (McMillen *et al.* 2012). As with smokeless tobacco use in general, snus users tended to be male and younger.

Among a sample of college students in 2010, 1.4% were current snus users (Wolfson *et al.* 2014), the same rate reported from the 2009-2010 National Adult Tobacco Survey (NATS) (King *et al.* 2012). Among young adults (ages 18-29) in the 2012-2013 NATS, 2.2% were current snus users (Mays *et al.* 2016).

In 2015, the prevalence of past-30-day use of smokeless tobacco (defined as chewing tobacco, snuff, or dip) among students in grades 9-12 was 7.3% (6.1%-8.6%) and varied by gender (males: 11.9%; females: 2.3%) (Kann *et al.* 2016). In 2011, past-30-day use of snus was 1.9% (1.5%-2.4%) among middle and high school students in the U.S., and snus use was higher among males (3.2%) compared to females (0.7%) (Agaku *et al.* 2013). Among 8,472 teens in grades 6-12 surveyed in Texas in 2009, 7.1% had ever tried snus, and those who tried snus were significantly more likely (p's<0.001) than those who did not try snus to be male (76.6%) (Loukas *et al.* 2012).

2.12.1.5 Published literature on the relationship between use of smokeless tobacco or snus and cigarette smoking among youth

The concern about smokeless tobacco or snus use leading to uptake of cigarette smoking (among youth predominantly) or continued smoking (among adults and youth) has been examined in some U.S. studies. Given that snus is relatively new to the U.S. market, many of the

[4] Data on Camel Snus use in the U.S. from RJRT surveys are included in Section 3.5.

studies do not include snus in the category of smokeless tobacco products. It is not known whether snus follows the same dynamics as other smokeless tobacco products.

Data from the 1989 and 1993 Teenage Attitudes and Practices Survey (TAPS) on smokeless tobacco use among 3,996 respondents (ages 11-19 at baseline) found that among males who had used smokeless tobacco regularly at baseline, 24% had initiated cigarette smoking by follow-up, compared to 8% of those not using smokeless tobacco at baseline (OR=3.45; 1.84-6.47) (Tomar 2003). The proportion of males who stopped smoking completely by follow-up did not differ between those who had ever regularly used smokeless tobacco (20.5% had quit smoking) and those had never used smokeless tobacco (26.3% had quit smoking). In a separate study (Severson *et al.* 2007) among 2,935 males in grades 7 and 9, those who used smokeless tobacco had increased odds for cigarette smoking initiation than did those who had not used smokeless tobacco (OR=2.55; 1.45-4.47).

The association between use of cigarettes and snus in the U.S. was examined among a youth cohort (ages 12-16 at baseline; N=2,184) who were followed up for eight years (Taylor *et al.* 2015). Among youth who were not smoking cigarettes at baseline but had tried snus (n=145), there was an increased odds of becoming a current smoker at follow-up compared to those who had not tried snus at baseline (OR=1.79; 1.01-3.14). In this study, there was no association between snus use (current or ever use) and the amount of cigarettes consumed among the smokers at follow-up.

One potential confounding factor in studies examining the sequence of smokeless use and cigarette smoking initiation is that the individuals who take up smokeless tobacco may already be predisposed to initiate smoking. Further analysis of the TAPS data (O'Connor *et al.* 2003) that included only males (ages 12-18) who had never used or experimented with cigarettes, and who had known psychosocial predictors of smoking initiation (*e.g.,* poor school performance) – attempting to control for the predisposition to smoke – found no significant association between smokeless tobacco use and smoking initiation, similar to another study (Timberlake *et al.* 2009), which matched snus users and non-users by propensity scores.

Another study – also analyzing data from 3,284 current smokers from the National Longitudinal Study of Adolescent Health (1994-1996) – found no association between dual use of cigarettes and smokeless tobacco (compared to cigarette use only) and future rates of cigarette smoking (O'Hegarty *et al.* 2012).

In another study (Rodu and Cole 2010) the prevalence of ever or current cigarette smoking among 5,564 U.S. males (ages 16-17) who had initiated with smokeless tobacco was half the rate of those who initiated tobacco use with cigarettes, indicating a reverse-gateway effect.

The National Longitudinal Study of Adolescent Health provides data on use transitions among a cohort of youth (N=20,774; grades 7-12 at baseline in 1995) who were followed into young adulthood (2008-2009) (Kaufman *et al.* 2015). Probabilities of transitioning between smokeless tobacco and cigarettes were examined. White males (the predominant users of smokeless tobacco) who had used smokeless tobacco at baseline had a 6.5% chance of using cigarettes –

either as a cigarette only user (1.3%) or a dual user (5.2%) – over a one-year period. In contrast, individuals who initially had used neither smokeless tobacco nor cigarettes had a 7.8% probability of cigarette smoking over a one-year period (7.3% cigarettes only and 0.5% dual use). This study suggests that smokeless tobacco use is not associated with a greater probability of transitioning to cigarette smoking among youth. Indeed, the figures imply a reverse-gateway effect.

Although some individual studies report evidence consistent with a gateway effect, as a whole the literature on smokeless tobacco use and cigarette smoking in the U.S. suggests that there is little support for concerns regarding the potential "gateway effect" leading from smokeless tobacco use to more harmful use of cigarettes. In fact, some studies in the U.S. as well as other countries with longer experience with snus suggest that snus may keep those who are predisposed to trying tobacco products from using cigarettes, thereby providing a net public health benefit.

2.12.1.6 Published literature on the relationship between use of smokeless tobacco or snus and cigarette smoking among adults

It is also important to understand the effect of snus on adult smokers, as they are the intended audience for the proposed modified risk advertising. Three studies examined the association between smokeless tobacco use and cigarette smoking among adults (Rodu and Cole 2010; O'Connor *et al.* 2005b; Kozlowski *et al.* 2003). These national studies found that small proportions (one-tenth to one-third) of smoking initiation among adults could possibly be attributable to use of smokeless tobacco as the majority of those who initiated cigarette smoking did so prior to or coincident with use of smokeless tobacco. A study of U.S. Air Force recruits found an increased odds of smoking initiation (OR=2.33; 1.84-2.94) among current smokeless tobacco users compared to non-users, and also among former smokeless tobacco users compared to never users (OR=2.27; 1.64-3.15) (Haddock *et al.* 2001). It is possible that there are differences between the national samples and the military cohort that account for the different conclusions. Particularly important may be the prohibition of any smoking during military training, which might have resulted in use of smokeless tobacco as a default product until cigarette use was again permitted, leading to what can be viewed as gateway but might actually be an artifact of the controlled environment.

Other published studies have examined whether use of smokeless tobacco might promote abstinence from smoking. Examination of a one-year follow-up of 15,056 U.S. adults between 2002 and 2003 from the Tobacco Use Supplement to the Current Population Survey found that, among males who were cigarette only smokers in 2002, 0.3% had switched completely to smokeless tobacco by 2003. Among males who only used smokeless tobacco in 2002, 35.0% had quit all tobacco use by 2003. Among males who used both cigarettes and smokeless tobacco in 2002, 4.9% used only smokeless tobacco in 2003 and another 13.1% used neither product (Zhu *et al.* 2009). The same patterns were seen for females, although far fewer used smokeless tobacco. Those females who did use smokeless tobacco in 2002 were significantly more likely to have quit all tobacco than females who only smoked cigarettes (47.3% vs. 12.3%;

p<0.01). This study suggests that transitioning to smokeless tobacco can result in complete abstinence from cigarette smoking and that smokeless tobacco users can completely quit all tobacco at fairly significant rates (35.0% for males, 47.3% for females).

2.12.1.7 Published literature on interventional studies to assess use of smokeless tobacco or snus and smoking cessation among adults

In addition to observational studies on the relationship between cigarette smoking and the use of smokeless tobacco, other studies have experimentally intervened to encourage switching from cigarette smoking to smokeless tobacco[5]. One study compared quit attempts among 1,236 U.S. smokers not motivated to quit smoking who were randomized to receive a 6-week supply of free snus (along with brief information about why it might be safer than cigarettes) (n=626) or not (Carpenter *et al.* 2016). Among the group that received snus, those who were current, frequent snus users were more likely to try to quit (RR=2.24; 1.30-3.86) and to succeed in quitting (RR=2.21; 1.18-4.13) than those who never used snus.

In a randomized clinical trial among smokers interested in switching from cigarettes in order to reduce harm, those who were randomized to switch to snus were about equally as likely as those randomized to switch to nicotine gum to have a 7-day complete avoidance of smoking (21.9% and 24.6%, respectively) (Hatsukami *et al.* 2016). At the 26-week follow-up, 6.0% of gum users were using only gum and 14.9% of snus users were using only snus (p<0.006). Since this was a study among smokers interested in switching to a less harmful product (*i.e.*, not interested in quitting all tobacco or nicotine use), these results suggest that snus can serve as an alternative product among those interested in switching.

Another study found that providing information to smokers on the lower risk of smokeless tobacco compared to cigarettes led to significant increases in interest in trying smokeless tobacco (Borland *et al.* 2012). These findings further support the clinical trial data, and suggest the need for clear messages for smokers regarding the relative risks of smokeless tobacco (snus) and cigarettes.

2.12.1.8 Conclusions from the published literature in the U.S.

The prevalence of smokeless tobacco use in the U.S. is low, and estimates of snus use specifically mirror the historical rates of smokeless tobacco use among adults and youth, which are low and concentrated among males. The effect of smokeless tobacco on smoking among youth in the U.S. is mixed, but predominantly it has little impact on cigarette smoking uptake. In the few studies that accounted for other known predictors of cigarette smoking, there was no additional impact of smokeless tobacco use on smoking initiation (*i.e.*, no gateway effect).

[5] One RJRT-sponsored clinical study (CSD1010 CSR) was a multicenter, randomized, open-label study to compare smoking cessation rates with Camel Snus, with and without health-related smokeless tobacco relative risk information provided on a single occasion, and Nicorette® nicotine lozenges. All subjects in both Camel Snus study groups as well as the lozenge group reduced cigarette consumption. Declines in smoking urges and withdrawal symptoms were similar across all groups.

Among adults, snus may be an acceptable alternative for some smokers, especially those interested in switching and those who are aware of the relative harms compared to cigarettes. Regardless, smokeless tobacco and snus do not appear to increase the overall rate of cigarette use among U.S. adults or youth.

2.12.2 Likelihood of use studies among tobacco users and non-users

RJRT conducted studies to assess consumer responses, with respect to likelihood of use of Camel Snus, for each of the three proposed modified risk advertising executions. In a randomized design, the studies assessed U.S. adults' interest in using Camel Snus after seeing either the proposed modified risk advertisement or a control advertisement; the latter, constructed for this study, resembled the proposed modified risk advertisement but did not include modified risk information or other cautions or warnings regarding snus, except for the statutorily-mandated warning label statements that were included on both the test and control advertisements. The aim of the three likelihood of use studies was to estimate the appeal of Camel Snus and proposed modified risk advertising in relevant sub-populations, particularly contrasting appeal and likely use in the target sub-groups (current smokers and tobacco users, especially those not expecting to quit) and off-target sub-groups (former and never users of tobacco, and those current users expecting to quit.)

The studies exposed current users, former users, and never users of tobacco products (including current smokers, former smokers and never smokers) to the proposed Camel Snus advertisements containing modified risk messaging as well as several cautionary statements about the use of snus stressing the importance of quitting and not starting tobacco use (*e.g.,* an addiction warning, a warning against use by non-tobacco-users). For contrast, a parallel group of respondents (by random assignment) was exposed to a control advertisement (created for the purpose of the study) that did not contain modified risk messaging. After viewing the advertisements (test or control), respondents rated their interest in trying Camel Snus, and an empirically derived algorithm was used to transform these ratings into projected probabilities of actually purchasing Camel Snus for personal use. Among current smokers, additional questions identified respondents who were potential quitters to assess appeal to this off-target group compared to the appeal to the target group of smokers who were not likely to quit. Analyses focused on contrasting the interest and projected use in target and off-target groups, overall, and as well as in response to the proposed modified risk advertisements.

Thus, the likelihood of use studies provide insight into the appeal of Camel Snus with modified risk messaging in target and off-target groups. The estimates, in turn, serve as useful inputs into modeling of population health under various scenarios and assumptions, helping to estimate the 'net' impact of Camel Snus as an MRTP on population health (Section 6.4).

2.12.2.1 Findings from the likelihood of use studies

This section summarizes the results across the three likelihood of use studies, each of which evaluated one of the proposed modified risk advertising executions. The results were largely consistent across the studies, and so are described collectively with results sometimes given as

the range across studies. Detailed descriptions of the results for each study execution are reported in Section 6.3.

Large samples (over 30,000 in aggregate) were recruited for the three studies. The studies were sized to detect (at 80% power) changes in projected use of Camel Snus with versus without modified risk messaging, by as little as 1%. Post-hoc power analyses showed that the sample size was large enough to detect even small effects in almost every analysis. For these studies, respondents rated their interest in purchasing Camel Snus for personal trial, on a 1-10 scale, ranging from "Definitely would not purchase" to "Definitely would purchase." Because stated intent to purchase does not always translate into actual purchase, and does so differently for different sub-groups, the ratings collected were also used to project likelihood of purchase, based on an algorithm empirically derived from studies of the introduction of new cigarette brands. Thus, the arbitrarily scaled 1-10 ratings were translated into projected likelihoods that the groups of interest would actually purchase Camel Snus, which are relevant inputs to models of population health impact.

Analyses were done for various samples, designated by tobacco use history (current, former, and never tobacco users) as well as by smoking history (current, former, and never cigarette smokers). Among current smokers, potential quitters were identified through a series of standard questions to identify those likely to quit. Sub-analyses were also done among white males, who are most likely to use smokeless tobacco products, and among young adults, whose tobacco use may be more flexible and thus responsive to the proposed modified risk advertising for Camel Snus.

Exposure to the proposed modified risk advertisements modestly increased current smokers' interest in Camel Snus. Importantly, the proposed advertisements differentially increased interest among current smokers, and not among never smokers or former smokers, whose interest was much lower and not increased by exposure to the modified risk advertising. The proposed modified risk advertisements did not differentially appeal to smokers who were likely to quit; smokers likely to quit expressed less interest in using Camel Snus than did smokers who were not likely to quit, and their interest was not increased among those who viewed the modified risk advertising. These findings suggest that advertising modified risk, as proposed, does not attract interest from individuals whose risk might be increased by using Camel Snus (never smokers, former smokers, and smokers likely to quit).

To achieve maximum risk reduction by switching to Camel Snus, smokers should completely eliminate smoking and use Camel Snus instead. To this end, the proposed modified risk advertisements emphasize switching **completely** to Camel Snus (emphasis in the original). However, among the smokers with some interest in Camel Snus, about one-third anticipated using it to substitute for some, but not all of their smoking. This would be consistent with findings from the comprehension and perceptions study, execution 1, which suggested that some respondents expected health benefits from reducing smoking by half. In the likelihood of use studies, some smokers (20-27%) also indicated they would use Camel Snus in addition to

their current smoking. These respondents' intentions were not affected by exposure to the modified risk advertisement compared to the control advertisement.

Interest in Camel Snus was very low among former users of tobacco products (<1.5% projected use). One might be concerned that use of Camel Snus among former tobacco users might lead to those same users transitioning to other tobacco products with potentially greater risk (cigarettes). Former tobacco users who expressed any interest in Camel Snus were asked how likely they were to return to using other tobacco products that present greater risk. In each execution, the mean ratings of likely future use were lower among former tobacco users who were shown the proposed modified risk advertisements compared to those who were shown the control advertisement; this difference was statistically significant only in execution 1. These results suggest that the proposed modified risk advertising does not promote interest in progression from Camel Snus to tobacco products that present more risk.

There has been particular concern about a similar progression process among individuals who may initiate tobacco use with a modified risk tobacco product, such as Camel Snus. The concern is whether individuals who had not used tobacco, but start with Camel Snus might later be caused to switch to higher-risk products, such as cigarettes (*i.e.*, a "gateway" effect). To assess the likelihood of such progression, never tobacco users who expressed any interest in Camel Snus were asked about the likelihood of later switching to another tobacco product, such as cigarettes. In this group, seeing the proposed modified risk advertisements decreased the expected likelihood of then progressing to another tobacco product such as cigarettes; this difference was statistically significant only in execution 1. Thus, the proposed modified risk advertising did not seem to increase the likelihood of gateway effects.

Overall, the findings from the likelihood of use studies demonstrated that the proposed modified risk advertisements for Camel Snus attracted modest interest from the target for modified risk messaging – current smokers who were not planning to quit, the population most likely to benefit from switching to Camel Snus. At the same time, the proposed modified risk advertisements for Camel Snus did not increase appeal to off-target populations for whom using Camel Snus could increase risk (*i.e.,* former tobacco users, never tobacco users, or smokers planning to quit). This suggests that the proposed modified risk advertisements for Camel Snus are likely to result in an improvement in population health, and unlikely to harm population health.

2.12.2.1.1 Camel Snus with modified risk advertising appeals to current smokers and is likely to prompt switching

The intended population for Camel Snus modified risk advertising is current smokers who are not likely to quit, and who can reduce their risk by switching completely from smoking to Camel Snus. Accordingly, the studies assessed the appeal of Camel Snus and of the Camel Snus proposed modified risk advertising in this population.

The study data estimated that 5.8% to 8.2% (across executions) of current smokers would try Camel Snus after seeing the proposed advertisements with modified risk messaging.

Importantly, exposure to the proposed advertisements increased current smokers' likelihood of trying Camel Snus (relative to exposure to the control advertisement). The increase was modest (5.4% to 5.8%, 6.9% to 8.2%, and 6.9% to 8.0% in executions 1, 2, and 3, respectively), but statistically significant for executions 2 and 3. Moreover, the proposed modified risk advertising *differentially* increased interest among current smokers (compared to former smokers and never -users, whose data are presented below), significantly so for executions 2 and 3.

Among smokers who were not likely to quit and who saw a proposed Camel Snus advertisement with modified risk messaging, likelihood to purchase was estimated at 6.2%-8.7% (across executions). Importantly, rates among those who were likely to quit were significantly lower, at 3.9%-4.7%, as discussed below.

2.12.2.1.2 Camel Snus has comparatively lower appeal to current smokers who are planning to quit, and the proposed modified risk advertising did not increase that appeal

Camel Snus presents considerably less risk than smoking, but is not completely free of risks, and (as the proposed Camel Snus modified risk advertisements state) the best option for smokers is to quit. Thus, if Camel Snus modified risk advertising differentially appealed to current smokers who are already likely to quit, possibly delaying or deterring them from quitting, this could result in harm, and thus mitigate the population health benefit of harm reduction with Camel Snus. Therefore, the appeal of Camel Snus proposed modified risk advertising was assessed among current smokers who, by multiple criteria, were most likely to quit (*i.e.*, potential quitters).

Across the three likelihood of use studies, interest in Camel Snus was lower among those likely to quit (versus those not likely to quit), with projected purchase rates 40%-60% lower among the potential quitters. The proposed modified risk advertising did not increase interest among potential quitters, relative to those not likely to quit.

Although interest in Camel Snus was higher among current smokers who were not likely to quit, there was some projected trial (3.9%-4.7%) among current smokers who were likely to quit. Follow-up questioning showed that, in this group of potential quitters who expressed some level of interest in trying Camel Snus after seeing the proposed modified risk advertising, approximately one-half (48%, 51%, and 57% in executions 1, 2, and 3, respectively) envisioned using it to help them quit, suggesting it would not divert them from quitting smoking. The largest remaining fraction (20-36%) just wanted to try it out of curiosity, also suggesting it would be unlikely to deter quitting. In all three proposed advertising executions, the percentage of potential quitters who were interested in Camel Snus to help them quit smoking was higher among those exposed to the proposed modified risk advertisement than the control advertisement. The effect was significant for execution 3. Finally, the least common response from smokers likely to quit was wanting to try Camel Snus in order to use it in situations where smoking is not permitted (6-11%); this suggests use of Camel Snus to subvert smoking restrictions – which has been hypothesized to possibly deter quitting – is unlikely. Given that less than 5% of smokers likely to quit were projected to use Camel Snus, and that more than

three-quarters of this group wanted to use Camel Snus to help them to quit, or out of curiosity, the data suggest that the proposed modified risk advertising for Camel Snus would not likely deter quitting.

Thus, overall, the evidence suggests that the Camel Snus proposed modified risk advertising is unlikely to differentially appeal to current smokers who are intent on quitting, or to deter or delay them from quitting.

2.12.2.1.3 Current smokers not planning to quit who are interested in Camel Snus expect to use it to stop smoking, to reduce smoking, or to supplement smoking

To maximize the harm reduction benefit of Camel Snus, smokers should stop smoking completely, and the Camel Snus proposed modified risk advertisements emphasize this by stating that the harm reduction benefit accrues to those who switch completely from cigarettes to Camel Snus and use Camel Snus instead of cigarettes.[6] After exposure to these messages, smokers who did not intend to quit (the target for harm reduction with Camel Snus advertising) were asked how they would use Camel Snus. The optimal answer ("Instead of current tobacco [stop using current tobacco completely])" was given by 14%-22%. Another 30%-34% envisioned reducing (not stopping) their cigarette smoking, and using Camel Snus in place of *some* current tobacco use. This is consistent with findings from the comprehension and perceptions study, execution 1, which suggested that about 1 in 10 respondents believed they could achieve a health benefit from reducing their smoking by half. In the likelihood of use studies, 20%-23% envisioned adding Camel Snus to their current smoking, possibly increasing their tobacco exposure. One-quarter to one-third of respondents did not know how they might use Camel Snus, perhaps because the questions required considering a hypothetical, and the question was asked even of those with only very modest interest in Camel Snus.

2.12.2.1.4 Camel Snus has low appeal to never tobacco users, and the proposed modified risk advertising did not increase that appeal

While switching to Camel Snus will benefit current cigarette smokers by reducing their health risk, Camel Snus adds new risks if adopted by individuals who have not been tobacco users and are not likely otherwise to become tobacco users. Adoption of Camel Snus among never tobacco users would add greater risk if use of Camel Snus subsequently led to progression to smoking (*i.e.*, the hypothesized gateway effect) (Kozlowski *et al.* 2003; Lee 2015).

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[6] Execution 1: Smokers who **switch completely** from cigarettes to Camel SNUS can significantly reduce their risk of lung cancer, oral cancer, respiratory disease, and heart disease.
Execution 2: Smokers who **SWITCH COMPLETELY** from cigarettes to Camel SNUS can greatly reduce their risk of lung cancer, oral cancer, respiratory disease, and heart disease.
Execution 3: Smokers who **SWITCH COMPLETELY** from cigarettes to Camel SNUS can greatly reduce their risk of lung cancer and respiratory disease.

Ratings from respondents who had never used tobacco indicated very low interest in trying Camel Snus (an average rating of 1.4-1.7 on a 1-10 scale, and projected trial rate of 0.3%-0.4% across the three study executions). Further, exposure to the Camel Snus modified risk advertisements (compared to the control advertisements) did not increase this group's interest in trying Camel Snus.

Among individuals who have never used tobacco, some may be open to doing so, and may be quite likely to do so at a later time. The likelihood of use studies identified never tobacco users who were open to tobacco use by means of items that are used in the literature to assess 'susceptibility' to smoking (Pierce *et al.* 1996) – a predictor of subsequent smoking initiation – and then compared responses of those who (according to this measure) were or were not open to tobacco use. Although projected use of Camel Snus was very low among all never tobacco users, it was consistently lower (by 50-70%) among those not open to smoking – those *not* likely to initiate tobacco use – regardless whether they saw the Camel Snus proposed modified risk advertisements or the control advertisements. Results were similar among younger respondents (*e.g.*, ages 18-22 or 18-27), for whom tobacco initiation might be more likely as compared to older adults.

Thus, Camel Snus with modified risk advertising is unlikely to increase the likelihood that individuals who are not tobacco users will start using Camel Snus. For the few never tobacco users who are attracted to Camel Snus, it tends to be individuals who are susceptible to initiating smoking, for whom adoption of Camel Snus instead of smoking would represent a reduction in risk.

2.12.2.1.5 Camel Snus with modified risk advertising decreased the likelihood of progressing to smoking (gateway effects)

The findings above suggest that it is unlikely that individuals who had not previously used tobacco would adopt Camel Snus; this was especially true among individuals who were not likely to smoke. Adoption of Camel Snus by a never tobacco user would imply some increase in risk, but the risk would be much greater if use of Camel Snus resulted in subsequent progression to smoking, which carries much greater risks. Concern has been expressed about such gateway effects, although the literature suggests that the use of smokeless tobacco does not lead to subsequent smoking (Furberg *et al.* 2005; Kaufman *et al.* 2015; Kozlowski *et al.* 2003; O'Connor *et al.* 2003; Ramström and Foulds 2006; Stenbeck *et al.* 2009). In any case, the never tobacco users who indicated some level of interest in Camel Snus were asked to rate (on a 1-10 scale) how likely they would be to subsequently switch to another tobacco product with greater risk (such as cigarette smoking). Respondents rated this eventuality less likely (significantly so for execution 1) if they had been exposed to the Camel Snus proposed modified risk advertising. That is, the Camel Snus modified risk advertising does not appear to increase the risk of gateway progression to other tobacco use, in particular products that present greater health risk.

2.12.2.1.6 Camel Snus has low appeal to former tobacco users or former smokers, and the proposed modified risk advertising did not increase that appeal

As with individuals who never used tobacco, those who used it in the past but have since quit are not a target for Camel Snus modified risk advertising, as starting to use Camel Snus would increase rather than decrease their risk. The risk for former tobacco users would be particularly increased if using Camel Snus caused them to switch to a higher-risk product. These issues were evaluated in the likelihood of use studies by assessing the appeal of Camel Snus to former tobacco users, and by assessing the likelihood of subsequently switching to a higher-risk product among former tobacco users who expressed some level of interest in Camel Snus.

Former users of tobacco expressed little interest in trying Camel Snus (projected use ranged from 1.2% to 1.4% across the three studies), and exposure to the Camel Snus proposed modified risk advertisements (versus the control advertisements) did not increase their interest. Similar findings were obtained for former cigarette smokers, where projected use ranged from 1.9% to 2.1%, and in no case was increased by exposure to the modified risk advertisements. This suggests that the Camel Snus proposed modified risk advertising is not likely to incite return to tobacco use among former tobacco users or former smokers.

2.12.2.1.7 Camel Snus modified risk advertising reduced the expected likelihood of resuming smoking among former smokers

Among the minority of former tobacco users who expressed some level of interest in trying Camel Snus after seeing the proposed modified risk advertisements, their expected likelihood of then switching to another (possibly more harmful) tobacco product was modest (3.3-4.4 on a 1-10 scale, compared to 5.9-7.3 for current smokers). Those who were shown the proposed modified risk advertisements generally rated this likelihood lower (compared to those who were shown the control advertisements), and this difference was statistically significant in execution 1. This suggests that the proposed Camel Snus proposed modified risk advertisements would not promote resumption of smoking among former smokers who might adopt Camel Snus.

2.12.2.2 Conclusions from the likelihood of use studies

The net population health effect of the proposed modified risk advertising for Camel Snus depends heavily on who uses the product. Adoption by the key intended target population – current smokers, particularly those who are not potential quitters – would have favorable effects. Findings from RJRT's likelihood of use studies indicate that current smokers – especially those who were not deemed potential quitters – showed the highest projected use of Camel Snus, and their projected use was increased by exposure to the modified risk advertising, significantly and differentially so in executions 2 and 3.

The effect of exposure to the proposed modified risk advertisements (compared to the control advertisements) in promoting interest among current smokers was modest, but this should not be surprising. The factual messages in the proposed modified risk advertisements go against

pre-existing and deeply entrenched misconceptions about the risk of using smokeless tobacco. Multiple studies have shown that many smokers believe that using smokeless tobacco is as hazardous as, or more hazardous than, smoking (Fong *et al.* 2016; Kaufman *et al.* 2014; Kiviniemi and Kozlowski 2015; Regan *et al.* 2012). Indeed, although the Camel Snus proposed modified risk advertisements clearly states that Camel Snus may reduce the risk of certain diseases, substantial percentages of respondents in the comprehension and perception studies (as high as 37%; *see* Section 6.2) who saw the Camel Snus proposed modified risk advertisements still believed that using Camel Snus was as harmful as smoking. As beliefs about the risk of smokeless tobacco use influence its adoption (Fong *et al.* 2016; Kaufman *et al.* 2014; O'Connor *et al.* 2007; Richardson *et al.* 2014; Wackowski and Delnevo 2016), these misconceptions may limit adoption of Camel Snus. A single exposure to a product advertisement from a tobacco company may not be sufficient to change these misconceptions and thus promote switching from smoking to Camel Snus. Multiple exposures, and consistent messages from other, more trusted sources would likely also help convey the message and thus encourage smokers to switch to the less hazardous product.

The comparison between the effect of the test advertisements and the controls is also complicated by the fact that the test advertisements differed from the controls not just in its inclusion of messages about reduced risk with Camel Snus, but also in the inclusion of other cautionary messages. The proposed modified risk advertisements (but not the control advertisements) noted that "Camel Snus contains nicotine and is addictive," that "no tobacco product is safe," that "adults who do not use or have quit using tobacco products should not start," that "minors and pregnant women should never use tobacco products," and that "if you're a smoker concerned about the health risks from smoking, the best choice is to quit." These messages are appropriate to promote healthy choices, but may have reduced the differences between the proposed modified risk and control advertisements, because the control advertisements did not include these appropriate cautions about tobacco use, including use of Camel Snus. In any case, the proposed modified risk advertisements did in fact increase interest in Camel Snus among smokers, and even modest amounts of switching would be expected to confer a population health benefit.

Importantly, the benefit of smokers switching completely to Camel Snus needs to be weighed against the potential harm if the modified risk advertising increases adoption of Camel Snus by off-target populations – former and never tobacco users, and potential quitters. The data from the likelihood of use studies showed consistently that projected purchase rates were low among former and never smokers, and that the proposed modified risk advertisements did not differentially appeal to these groups. Across all three advertising executions, projected purchase among former smokers was 2.5 to 4 times lower than that among current smokers. For example, in execution 2, the rate among current smokers was 8.2% whereas the rate among former smokers was 1.9%. Projected purchase was 10-20 times lower among never smokers than among current smokers across the three executions. For example, in execution 3, projected purchase among current smokers was 8.0% whereas the rate among never smokers was 0.4%. Being exposed to the modified risk advertisements increased projected purchase among current smokers, but not among former and never smokers, especially for executions 2

and 3. Among current smokers, projected use of Camel Snus was consistently lower among the smokers who were likely to quit as compared to smokers who were unlikely to quit, and the proposed modified risk advertising did not differentially attract (or deter) this group. Even among the potential quitters who expressed some level of interest in trying Camel Snus, many anticipated using it to quit, rather than to perpetuate smoking, suggesting that Camel Snus is unlikely to divert smokers from quitting smoking.

Respondents in the likelihood of use studies expressed their interest in Camel Snus, or lack thereof, by numerical ratings on a 1-10 scale. To make these ratings more interpretable, they were transformed into figures for projected purchase of Camel Snus, and these were also analyzed, and yielded generally comparable, though not identical, results. The rates of use projected from the empirically derived algorithm (*see* Section 6.3) are likely to be higher than observed rates, because the algorithm used tends to overestimate use, and because it estimates trial, rather than persistent use (New Tobacco Product "Likelihood" Study: An Algorithm to Predict Usage of New Tobacco Products Prior to Market Launch – Methodological Report).

However, even if the estimated rates are overestimated, the important finding is that interest in Camel Snus is consistently highest among the intended audience that can most benefit from switching to Camel Snus, compared to audiences for whom Camel Snus is not intended, such as those who do not currently use tobacco (both never- and former users). This steep differential in interest suggests that the balance of benefit and harm implied by these figures is robust. Altogether, these data suggest that the benefit gained by smokers switching completely to Camel Snus is not likely to be offset by any harms due to adoption of Camel Snus by off-target groups, such as former or never smokers, or smokers who might otherwise quit.

Likelihood of use testing of the proposed Camel Snus modified risk advertisements suggests that Camel Snus modified risk advertising is likely to benefit the health of the U.S. population as a whole. A benefit is expected because the Camel Snus proposed modified risk advertising is likely to attract some current smokers to switch to Camel Snus, thus reducing their health risk. This benefit would be maximized if modified risk messaging were more persuasive, as might occur through repeated exposure and consistent messages from other, more trusted sources, and if smokers who switch to Camel Snus make a complete switch, stopping smoking altogether. Conversely, the Camel Snus proposed modified risk advertising does not seem to invite use by off-target populations that would trigger offsetting risks that might mitigate those benefits. Communicating reduced risk for Camel Snus did not increase appeal to individuals who are not currently using tobacco, including cigarettes (never or former users), or to tobacco users or cigarette smokers who are likely to quit. Thus, beneficial population health effects are likely, and harmful effects are unlikely, suggesting that a Camel Snus MRTP would provide a net benefit to the population as a whole.

The effect on overall population health is a function of the likely adoption of Camel Snus by different segments of the tobacco-user population. The likelihood of use studies summarized here provide empirical estimates of such adoption and of likely transitions among tobacco-use

states (non-use, smoking, and use of Camel Snus). These estimates provide useful input to formal statistical modeling to estimate the effect on population health. The results of such modeling using a Dynamic Population Model [DPM(+1)] to estimate the effect of a Camel Snus MRTP on mortality are described below.

2.13 Statistical Modeling of the Effects on the Health of the Population as a Whole

Under Section 911(g)(1) of TCA, the granting of an MRTP order is based on the expected effects of the order on the health of the population as a whole. Accordingly, a tobacco product proposed for an MRTP order must meet two criteria.

First, FDA must determine that the tobacco product, as actually used by consumers, will "significantly reduce harm and the risk of tobacco-related disease to individual tobacco users" (TCA Section 911(g)(1)(A); FDA MRTPA Draft Guidance 2012, p. 3). Accordingly, throughout this Application, RJRT presents a wide body of scientific studies and data applicable to Camel Snus (product design and composition, comparative harmful and potentially harmful constituents (HPHC) chemistry, comparative preclinical toxicology, epidemiology, and human clinical studies) that demonstrate that use of Camel Snus is associated with much less risk than smoking. Indeed, a panel of experts (Levy *et al*. 2004) estimated that snus was associated with 89% to 92% less risk than smoking.

Second, FDA must determine that the broader impact of a proposed MRTP "benefit[s] 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" (TCA Section 911(g)(1)(B); FDA MRTPA Draft Guidance 2012, p. 3). As described Section 6.3, RJRT collected data from both users and non-users of tobacco products in order to estimate their likelihood of using Camel Snus with the proposed modified risk advertising. These data, in turn, inform the expected effect of the MRTP and its proposed modified risk advertising on population health. That is, the impact of an MRTP on population health depends on its effect on the health of individuals using and not using various tobacco products and also on population changes in tobacco product use that may result from the introduction of the MRTP and its associated modified risk advertising.

Estimating this population health impact requires modeling. The expected effect of an MRTP order on population health must be assessed in a pre-market context, before the MRTP is marketed with modified risk advertising. Thus, the effects cannot be directly observed at the time an MRTP order is being considered but must be estimated through statistical modeling, taking into account likely changes in population tobacco use behaviors and their resulting effects on health.

This section summarizes the results of extensive empirically-informed statistical modeling, showing that an MRTP order for Camel Snus with the proposed modified risk advertising is likely to yield net benefits to population health, substantially increasing survival in the population. The model considers a single birth cohort of 1 million males, followed from age 13 years. In this single birth cohort, a Camel Snus MRTP with the proposed advertising is estimated to improve survival to age 72 by at least 5,000 lives. Further, tipping point analyses indicate that

only modest numbers of smokers who would otherwise have continued to smoke need to switch completely to Camel Snus to obtain a population health benefit. Switching by just 2% of smokers in each age interval of follow-up offsets estimates of potential harms from a Camel Snus MRTP order. Thus, the modeling described below indicates that Camel Snus is likely to yield very substantial net benefits to population health and very unlikely to result in net harm.

2.13.1 Statistical modeling and the Dynamic Population Modeler (+1)

Statistical modeling has been widely used to support regulatory decision-making in a variety of contexts, from housing and transportation, to the impact of health risk factors such as obesity and substance abuse (*e.g.*, National Academies of Sciences, Engineering, and Medicine 2016). Specifically applied to tobacco health policy, six statistical models have been designed to estimate the health effects of introducing an MRTP to a population (Apelberg *et al*. 2010; Levy *et al*. 2004; Mejia *et al*. 2010; Poland and Teischinger 2016; Vugrin *et al*. 2015; Weitkunat *et al*. 2015). These models have been able to evaluate the impact of a variety of tobacco use behaviors and their associated risks on health outcomes. However, there are important differences among the models that affect their ability to accurately estimate the impact of the availability of various tobacco products on population health. For example, the Apelberg *et al*. 2010 and Mejia *et al*. 2010 models are limited by the range of questions they can address because they do not allow smoking initiation and cessation rates to depend on age and incorporate only a very limited number of transitions between tobacco exposure states. The Poland and Teischinger 2016, Vugrin *et al*. 2015 and Weitkunat *et al*. 2015 models follow a cross-section of the population over time. However, this approach can also result in conceptual inconsistencies that lead to invalid results. The preferred statistical modeling approach follows a birth cohort over time to assess the effect of any regulatory health policy change on net population health (Bachand and Sulsky 2013).

The Dynamic Population Modeler (DPM) (+1), employed to assess the effects of the introduction of Camel Snus as an MRTP, is a fit-for-purpose statistical modeler designed to meet the recommendations regarding modeling specified in the FDA MRTPA Draft Guidance. The DPM(+1) estimates the impact of an MRTP on population health by comparing a base case involving cigarette smoking only, with its attendant effects on population health, to a counterfactual scenario that posits hypothetical alternative tobacco use scenarios envisioning some use of Camel Snus marketed with modified risk advertising. The DPM(+1) calculates a population health impact by projecting differences in the number of survivors between the base case and counterfactual scenario, estimating whether the availability of a Camel Snus MRTP with modified risk advertising increases or decreases projected survival in the population.

The DPM(+1) estimates the effect of an MRTP on a single birth cohort, modeling its behavior – and the health impact of that behavior – as the cohort ages. The primary analysis starts with a hypothetical birth cohort of individuals with no tobacco exposure at age 13, follows that cohort as it ages, distributes subsets of the cohort into tobacco-exposure categories (non-users, cigarette smokers, or Camel Snus users), and estimates the mortality rate in each category. The modeler contrasts two scenarios: (1) a base case in which the population may smoke and some

smokers may quit, modeling the current situation, and (2) a counterfactual scenario in which, in addition to smoking, some in the population may use Camel Snus with modified risk advertising. In this manner, the DPM(+1) estimates the effects that granting an MRTP order for Camel Snus would have on all-cause mortality in a tobacco naïve cohort of one million 13 year-old males. The outputs are expressed as the change in survival to age 72 among the cohort being modeled. These net effects on the population can be harmful (resulting in fewer people living past age 72) or beneficial (resulting in more people living past age 72), depending on the scenario.

The DPM(+1) can be used to assess a variety of different scenarios involving multiple different types of tobacco use transitions over time. To be maximally informative to regulatory decision-making regarding this Application, a 'Master' model was constructed to realistically assess the likely impact of a Camel Snus MRTP order. This Master model considers *all* potential harmful and beneficial transitions in tobacco use (except for *Relapse*, which is estimated separately), using empirically-derived estimates of the primary tobacco use transitions and conservative values for secondary tobacco use transitions (*i.e.*, transitions that result from a primary transition, described below), thus yielding an integrated estimate of the net population impact of a Camel Snus MRTP with modified risk advertising. To provide insight into the individual contributions of particular transitions in tobacco use behavior, the Master model is supplemented with Component analyses that consider the health impact in the cohort for each tobacco use transition individually. As discussed below, the analysis indicates that the biggest influence on the net impact of a Camel Snus MRTP is the percentage of adult continuing smokers who switch permanently to Camel Snus instead of continuing to smoke, and thus accrue a benefit in a reduced risk of mortality. With this in mind, the DPM(+1) was used to conduct tipping point analyses that consider what proportion of continuing smokers need to switch to Camel Snus permanently to counteract the effect of harmful tobacco use transitions, even when extreme assumptions are made about the likelihood of these harmful tobacco use transitions. An additional analysis considers how the effects on population health would vary depending on the degree of individual harm reduction achieved by switching completely from smoking to Camel Snus. Thus, the modeling exercise as a whole estimates the likely result of a Camel Snus MRTP with modified risk advertising and also considers the effects on population mortality of extreme scenarios, allowing for confidence in estimating the population impact of a Camel Snus MRTP order.

2.13.1.1 Simplifying assumptions incorporated into the DPM(+1) modeler

Like all modelers, the DPM(+1) makes some simplifying assumptions to help make tractable the challenge of quantifying and estimating the long-term, real-world impact of an MRTP's availability. It assumes that the health effects of tobacco use vary entirely with tobacco use status (cigarette smoking or not, using Camel Snus or not) and duration, but do not vary with the amount of smoking or quantity of Camel Snus used. The DPM(+1) considers dual use of Camel Snus along with smoking to have the same mortality risk as smoking alone, even though use of Camel Snus may be accompanied by reduced cigarette consumption (Ogden *et al.* 2015a; Ramström and Foulds 2006; Rodu *et al*. 2002). The DPM(+1) does not incorporate any effects of cigarette smoking or Camel Snus use on the health of others who may be exposed to

environmental tobacco smoke. The modeler only considers two modes of tobacco use – cigarette smoking and use of Camel Snus; no other tobacco product is considered. The analyses presented here also do not allow for a transition from Camel Snus to abstinence (individuals who adopt Camel Snus can transition to cigarette smoking but not to abstinence from all tobacco) because data on the rate of quitting Camel Snus are not available. This is a conservative assumption, as some Camel Snus users likely do transition to abstinence from all tobacco, which is beneficial. The analyses do not include the effects of individuals switching from other smokeless tobacco products to snus. To the extent that occurs and presents some decrease in risk, the population benefit would be underestimated. The analyses presented here are based on modeling male mortality data, but projections to U.S. cohorts are adjusted for the difference between male and female data on smoking and mortality. In any case, an analysis indicated that tipping points would be similar for males and females (Appendix H in Assessing the Population Health Effects of Camel Snus and its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler, Execution 1 Final Report; Assessing the Population Health Effects of Camel Snus and its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler, Execution 2 Final Report; Assessing the Population Health Effects of Camel Snus and its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler, Execution 3 Final Report).

2.13.1.2 Validating the DPM(+1)

The validity of modelers such as the DPM(+1) can be established by showing that they can retrospectively "predict" known population outcomes with accuracy. The DPM(+1) was validated in two ways. The base case model of smoking was validated by "predicting" the actual observed mortality in the U.S. population based on inputs about transitions in and out of smoking. The model used age-specific 1980 U.S. smoking initiation (Substance Abuse and Mental Health Services Administration 1999) and smoking cessation rates (Messer *et al*. 2007) to predict the 2006 U.S. life table (Arias 2010). The model-projected estimates were within 0.2% of the actual age-specific survival probabilities estimated using the U.S. life table for 2006, validating the DPM(+1) and showing that it can be well-validated with its base case assumptions.

To validate the modeling of the counterfactual scenario where people can adopt Camel Snus, the DPM(+1) was used to estimate mortality among males in Sweden, where snus has been widely adopted, and where detailed data on the use of snus are available (Lundqvist *et al*. 2009). Using the estimate that snus confers 11% of the risk of smoking (Levy *et al*. 2004), the model produced estimates of mortality that were within 0.3% of the actual age-specific survival probabilities estimated using the Swedish life table for 2006. This demonstrates that the DPM(+1) counterfactual scenario modeling is a valid tool that can be used to estimate the population-based health effects of Camel Snus as an MRTP.

2.13.1.3 Modeling the dynamics and health effects of cigarette smoking

To model the dynamics of smoking and its effects on mortality in the base case (with no Camel Snus MRTP), the modeler uses age-specific population estimates of smoking initiation and

cessation published by the Substance Abuse and Mental Health Services Administration (Substance Abuse and Mental Health Services Administration 1999). To model the effects of smoking on mortality, the modeler uses age-specific mortality rates for current, former, and never smokers derived from the Kaiser-Permanente Cohort Study data (Friedman *et al*. 1997), which uniquely estimates mortality rates by age, gender, duration of smoking, and duration of smoking cessation. Results from the DPM(+1) reflect uncertainty in the model inputs. Bayesian and Markov Chain Monte Carlo techniques are used to generate 10,000 sets of coefficients for a Poisson model of mortality rates. Uncertainty in estimates of smoking initiation and cessation and in the estimates of the excess relative risk (ERR) of cigarette smoking compared to Camel Snus is incorporated by allowing values to vary randomly around the literature-based values over 10,000 iterations of the model. The 95% Posterior Intervals (PIs) define a range in which the true number of survivors is likely to lie (Assessing the Population Health Effects of Camel Snus and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 1, Final Report; Assessing the Population Health Effects of Camel Snus and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 2, Final Report; Assessing the Population Health Effects of Camel Snus and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 3, Final Report).

2.13.2 DPM(+1) parameter specifications for assessing the population health impact of Camel Snus and MRTP advertising (the counterfactual scenario)

2.13.2.1 DPM(+1) modeler inputs

How the introduction of modified risk advertising for an MRTP such as Camel Snus will affect transitions in tobacco use behavior cannot be observed in advance. To provide an empirical basis for estimating these effects, RJRT conducted research with large groups of adults, including never users, former users, and current users of tobacco. These likelihood of use studies, described in Section 6.3, were used to derive empirically-based probabilities of tobacco use transitions if a Camel Snus MRTP with modified risk advertising were available. Using an algorithm based on prior research (New Tobacco Product 'Likelihood' Study: An Algorithm to Predict Usage of New Tobacco Products Prior to Market Launch), respondents' ratings of interest in purchasing Camel Snus for trial were converted into estimated probabilities of use, which are entered in the DPM(+1) to estimate the population impact of a Camel Snus MRTP.

The likelihood of use study findings are used to estimate primary tobacco use transitions among smokers and among non-users of tobacco. Secondary tobacco use transitions, however, in which individuals who use Camel Snus then progress to or return to cigarette smoking, could not be estimated from the likelihood of use data for two reasons. First, it requires respondents to speculate about two sequential hypotheticals (*e.g.*, first to estimate their likelihood of adopting Camel Snus, and then, without even having actually tried Camel Snus, to estimate the likelihood of another transition to smoking). Second, while respondents did provide estimates of the likelihood of this secondary transition, there was no validated model for converting these

likelihood ratings into projected probabilities of the actual tobacco use transition. Accordingly, for these secondary tobacco use transitions, values regarded as conservative (*i.e.*, unfavorable to population health) are used in the modeler. In each case, it is assumed that half the individuals who use Camel Snus will transition to smoking (see below).

2.13.2.1.1 The excess relative risk (ERR) of smoking compared to Camel Snus

To estimate the effect of an MRTP on the health of the population as a whole, one must estimate the degree of risk conferred by the MRTP compared to continued smoking. This estimate addresses the effect of the MRTP on individual risk. The modeled analyses use two estimates of the excess relative risk (ERR) of cigarette smoking compared to Camel Snus, both derived from a published expert consensus estimate for low-nitrosamine smokeless tobacco products (Levy *et al*. 2004). These experts estimated the ERR to be 0.11 for those ages 35-49 and 0.08 for those ages 50 and older (Levy *et al*. 2004). The DPM(+1) was run using each of these two estimates (*i.e.*, estimating that the mortality risk associated with using Camel Snus was either 89% or 92% less than that of smoking). As with smoking transitions and the effects of smoking on survival, it is considered that these estimates contain some uncertainty (a standard deviation of 1%, resulting in a range of roughly ±3%), which is incorporated into the 95% PIs associated with each projected estimate of survival (Assessing the Population Health Effects of Camel Snus and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 1, Final Report; Assessing the Population Health Effects of Camel Snus and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 2, Final Report; Assessing the Population Health Effects of Camel Snus and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 3, Final Report). A set of analyses was conducted to assess the sensitivity of the outcomes to the magnitude of the estimated ERRs. Specifically, these analyses assessed the maximum ERR value (*i.e.*, the smallest reduction in risk compared to smoking) at which the effects of a Camel Snus MRTP would be neutral in the population (*i.e.*, produce no net change in survival) given the expected tobacco use transitions when a Camel Snus MRTP with its modified risk advertising is introduced.

2.13.2.1.2 Modeling changes in population tobacco use

This section outlines the tobacco use transitions incorporated in the modeler, considering the likelihood of adoption of Camel Snus by various subgroups of individuals within the population. Table 2.13.2-1 identifies multiple possible transitions in tobacco use behaviors. The transitions in the counterfactual scenario are classified as harmful or beneficial to the affected individuals compared to the base case, in which the only transitions are between smoking and abstinence. Subsequent sections describe how the probability of each of these transitions is incorporated into the DPM(+1) using execution-specific, empirically-derived estimates and when performing analyses to estimate tipping points in population health effects. Each tobacco use transition is given a brief descriptor that is used in the discussion that follows. These descriptors are capitalized and set in *italic* font to identify their usage in this specific technical way.

Table 2.13.2-1: Tobacco use transitions

Transition Type	Description of Tobacco Use Transition	Descriptor	Health Impact: Benefit or Harm
Primary	Initiation with Camel Snus (instead of abstinence) by never users of tobacco who were *not* likely to initiate smoking	*Additional Initiation*	Harm
Secondary	--- Subsequent progression to smoking due to use of Camel Snus	*Gateway Effect*	Harm
Secondary	--- Subsequent cessation of Camel Snus‡		Benefit
Primary	Initiation with Camel Snus (instead of smoking) by never users of tobacco who *were* otherwise likely to initiate smoking	*Alternative Initiation*	Benefit
Secondary	--- Subsequent initiation of smoking due to use of Camel Snus	*Delayed Smoking*	Harm†
Secondary	--- Subsequent cessation of Camel Snus‡		Benefit
Primary	Adoption of Camel Snus (instead of smoking) by smokers who were *not* likely to quit	*Switching*	Benefit
Secondary	--- Subsequent return to smoking♦	*Resumed Smoking*	Harm†
Secondary	--- Subsequent cessation of Camel Snus‡		Benefit
Primary	Adoption of Camel Snus by smokers who were likely to quit, who either switch to Camel Snus instead of quitting¶ or who quit, then adopt Camel Snus*	*Diversion from Quitting*	Harm
Secondary	--- Subsequent relapse to smoking**	*Relapse*	Harm
Secondary	--- Subsequent cessation of Camel Snus‡		Benefit

--- Indicates a secondary transition among the population undergoing the primary transition immediately above.

‡ This secondary tobacco use transition is not considered in these analyses because no data are available to estimate the rate at which this transition would occur. This approach is conservative, as it does not consider health benefits that could accrue from quitting Camel Snus.

† This secondary transition is not net-harmful but rather reduces the benefit of the prior primary transition. For example, if a certain proportion of smokers *Switching* quickly go back to smoking (*Resumed Smoking*), this negates the benefit of *Switching* for that subset, yet they are no worse off than they were before trying Camel Snus.

♦These analyses treat smokers who initially switch to Camel Snus but then return to smoking as though they never use Camel Snus at all, rendering this secondary tobacco use transition neutral in effect (the affected individuals were smoking before the transition and are smoking after the transition). That is, a

return to smoking was treated as a reversal of *Switching*, discounting the estimated *Switching* rate. This is conservative, as it does not consider any benefit due to a limited period of use of Camel Snus versus continued smoking.

¶ These analyses do not consider the potential that adoption of Camel Snus might delay rather than completely deter smoking cessation. This is conservative, as it does not count any health benefit that would come from smoking cessation, even if cessation was delayed.

* Smokers who quit and then adopt Camel Snus are modeled as never having quit smoking, with no health benefit attributed to quitting. In essence, these analyses assume these smokers never quit, but adopt Camel Snus instead of quitting.

** The modeler cannot directly accommodate individuals who quit, adopt Camel Snus, and then *Relapse* to smoking within the same age interval. To model *Relapse*, the model was run with the likelihood of quitting reduced, which has roughly the same effect as having a certain proportion of quitters instead continuing to smoke. This is conservative, as it does not account for any benefit of a period of smoking abstinence or use of Camel Snus. To discern the impact of *Relapse*, survival in the counterfactual scenario of this run of the model is compared to survival in the counterfactual scenario of a corresponding run of the model that does not include this effect. The difference in estimates between these two runs of the model is then used to adjust the estimated survival in analyses meant to include *Relapse*.

Figure 2.13.2-1 and Figure 2.13.2-2 schematically and heuristically portray the tobacco use transitions that are considered in analyses described here. As shown in detail in Figure 2.13.2-1 (Initiation Flows), members of the cohort enter the process as non-tobacco users at age 13. The cohort consists of some members who are, by disposition, headed towards smoking. Some of these initiate smoking, as they would have in the base case where the Camel Snus MRTP is not available. Others initiate tobacco use instead with Camel Snus; this primary tobacco use transition is designated *Alternative Initiation*. Some individuals in the *Alternative Initiation* group may continue on to smoking, which is a secondary tobacco use transition designated as *Delayed Smoking*. *Delayed Smoking* is harmful because it reduces the benefit of *Alternative Initiation*, but is not harmful relative to the base case in which these individuals were destined to smoke in the absence of Camel Snus.

While some members of the cohort are headed to cigarette smoking, others are not headed to smoking, and some of these will remain non-users of tobacco, as they would have in the base case. Other individuals in this population take up Camel Snus, designated as *Additional Initiation*, initiation that would not have occurred but for the availability of Camel Snus as an MRTP, increasing their harm relative to the base case. Some among those in this *Additional Initiation* group may further proceed to smoking, designated as *Gateway Effect*, which would further increase their harm.

After initiation of cigarette smoking occurs (Figure 2.13.2-2, Continuation Flows), further tobacco use transitions can occur within each subsequent 5-year age interval. In any interval, some smokers are not headed towards quitting, and, indeed, some of these individuals do continue smoking, as they would have in the base case. Other smokers switch completely to using Camel Snus; this tobacco use transition, designated as *Switching*, is beneficial, as the harm of using Camel Snus is less than the harm from smoking. In these analyses, dual use is modeled as having no benefit – that is, it assumes dual users have the same risk as smokers, thus individuals engaging in dual use are simply considered continuing smokers. Some individuals in the *Switching* group may return to smoking (designated as *Resumed Smoking*).

Other smokers are headed towards quitting (*i.e.*, they would quit if the Camel Snus MRTP were not available), and, indeed, some do quit smoking. However, others adopt Camel Snus instead of quitting or adopt Camel Snus after a brief period of quitting, a tobacco use transition designated as *Diversion from Quitting*. This transition is harmful, as the risk of Camel Snus is higher than that of complete abstinence from tobacco. Some of those who undergo *Diversion from Quitting* may undergo *Relapse* to smoking, which exacerbates the harm because smoking is more harmful than using Camel Snus.

Figure 2.13.2-1: Schematic of the tobacco use transitions in the DPM(+1)

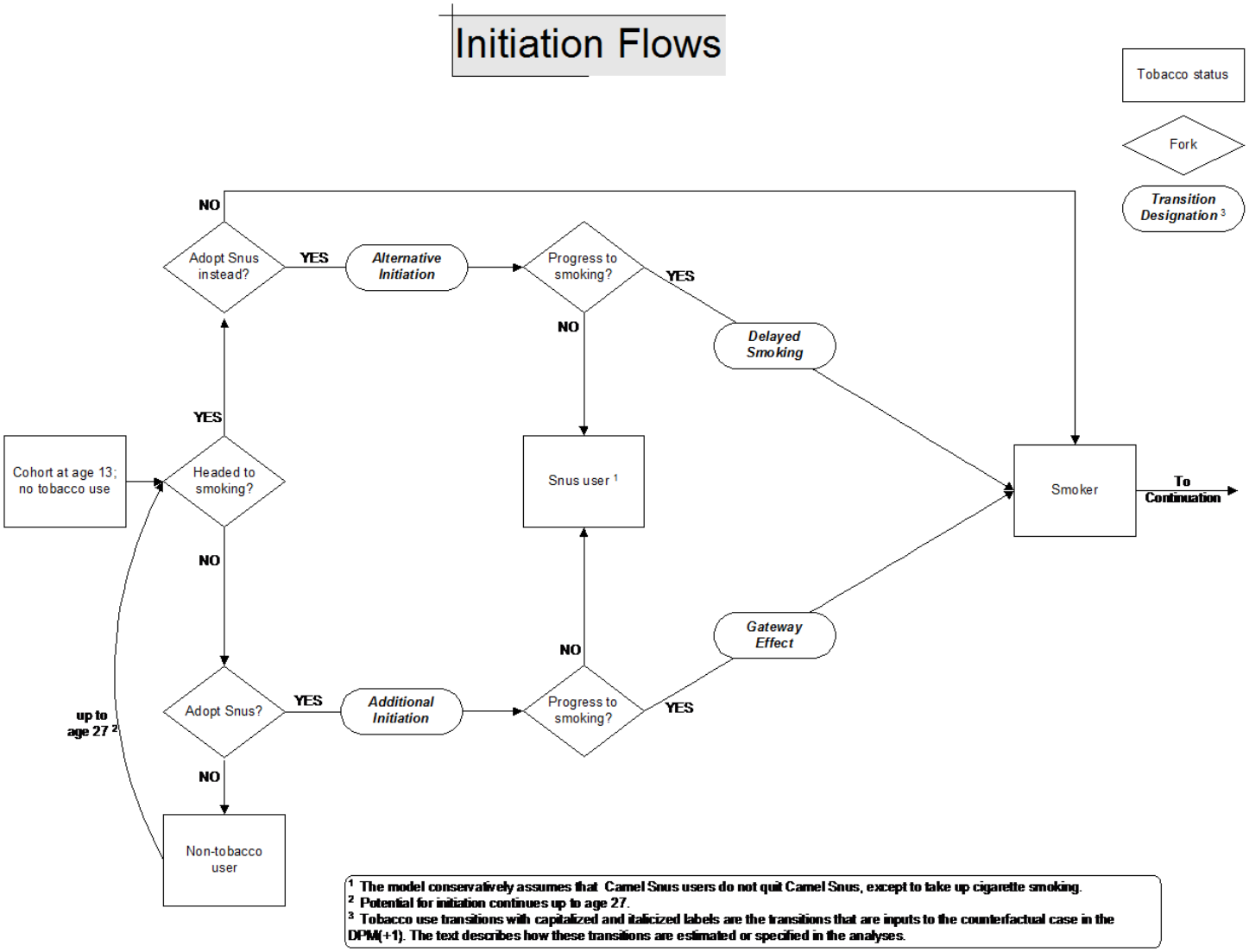
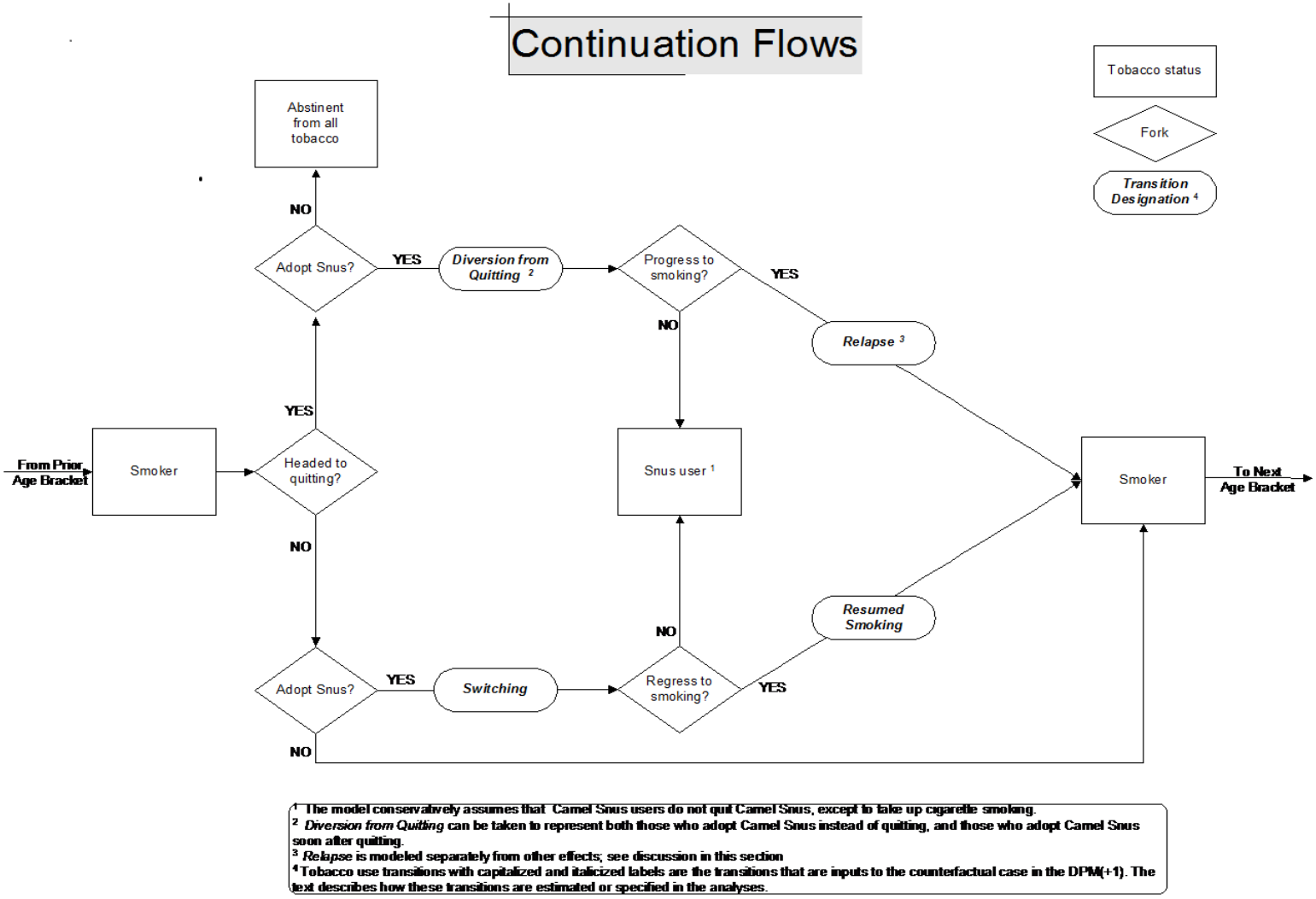


Figure 2.13.2-2: Schematic of the tobacco use transitions in the DPM(+1)



The next several sections describe the DPM(+1) inputs used for each of the tobacco use transitions shown in Table 2.13.2-1 and Figure 2.13.2-1 and Figure 2.13.2-2. As the DPM(+1) models the trajectory of a cohort that is initially not using tobacco, we begin with the tobacco use transitions shown in the Initiation Flows of Figure 2.13.2-1 to describe transitions that involve adoption of Camel Snus by individuals who are not smoking or using any tobacco and then describe the tobacco use transitions shown in the Continuation Flows in Figure 2.13.2-2, which occur among those who initiate smoking.

2.13.2.1.2.1 Initiation flows in the DPM(+1)

The statistical modeling considers the health effects of adoption of Camel Snus by individuals who had not previously used tobacco, that is, initiation with Camel Snus. The modeler considers two different pathways of initiation with Camel Snus, each with different implications for health.

Additional Initiation

Although Camel Snus presents less risk for lung cancer, oral cancer, respiratory disease and heart disease than cigarette smoking, it still carries some risk. Accordingly, an individual who otherwise would not have used tobacco but adopts Camel Snus use as a result of exposure to the MRTP advertising would consequently be harmed. The probability of such *Additional Initiation* is derived from responses in the likelihood of use studies among individuals who had not used tobacco and who were assessed as not susceptible to smoking based on standard measures (Pierce *et al*. 1996). Historical experience indicates that initiation is highly unlikely after age 26 (USDHHS 2012). Accordingly, the analysis uses estimated Camel Snus trial probabilities from respondents aged 18-27 and applies these transition probabilities to each of the first three 5-year age intervals in the model: 13-17, 18-22, and 23-27. Across all three executions of the likelihood of use studies, the estimated probability of this tobacco use transition was 0.3% in each age interval.

Gateway Effect

Individuals who engage in *Additional Initiation* incur the harm associated with Camel Snus. The adverse health effect is even greater for those who then subsequently progress to smoking (*i.e.*, a *Gateway Effect*) with its greater harms. As this secondary tobacco use transition cannot be estimated from the likelihood of use data, it is assigned a probability of 50% (*i.e.*, the model conservatively assumes that half of all individuals who engage in *Additional Initiation* progress to smoking). The *Gateway Effect* is estimated by having the affected individuals transition to smoking in the next age interval after they initiate with Camel Snus.

Alternative Initiation

While initiation of Camel Snus by someone who would not otherwise have used tobacco is harmful, adopting Camel Snus can be favorable if it is taken up by someone who otherwise would have smoked cigarettes (*i.e.*, *Alternative Initiation*), as it exposes them to a

comparatively lower risk than smoking. The probability of this tobacco use transition was estimated from the likelihood of use studies, where participants who were assessed to be susceptible to smoking (Pierce *et al*. 1996) rated their likelihood to try Camel Snus with modified risk advertising. Since tobacco initiation is highly unlikely after age 26 (USDHHS 2012), the model applies the likelihood of this transition estimated for ages 18-27 to each of the first three 5-year age intervals in the model: 13-17, 18-22, and 23-27. The probability of this transition in each age interval was estimated at 0.50%, 0.85%, 0.70%, respectively, in Executions 1, 2, and 3.

Delayed Smoking

Some individuals who take up Camel Snus instead of smoking (*i.e.*, *Alternative Initiation*) might nevertheless take up smoking later (*Delayed Smoking*). *Delayed Smoking* is harmful in that it diminishes the potential benefit of *Alternative Initiation* (keeping in mind that these individuals would have smoked in the base case). The probability of *Delayed Smoking*, a secondary tobacco use transition, cannot be estimated from the likelihood of use studies. It is modeled at 50% (*i.e.*, it is assumed that half of those who took up Camel Snus instead of smoking would subsequently progress to smoking anyway, thus diminishing the potential benefit of using Camel Snus instead of smoking).

2.13.2.1.2.2 Continuation flows in the DPM(+1)

The DPM(+1) incorporates empirically-derived rates of smoking initiation from population studies. Thus, over time, a proportion of the population initiates and adopts smoking. The expected effect of a smoker switching to Camel Snus depends on whether that smoker was or was not otherwise likely to quit smoking.

Switching

Among smokers who were not likely to quit smoking (*i.e.*, who otherwise would have continued smoking), adopting Camel Snus instead of continued smoking (*Switching*) confers a health benefit, since Camel Snus is less harmful than cigarette smoking. Smokers in the likelihood of use studies whose survey responses indicated that they were not likely to quit smoking were used to generate empirically-derived estimates of the *Switching* tobacco use transition. The likelihood of *Switching* was lower among older smokers, and age-specific rates are used in the DPM(+1) modeler; no *Switching* is permitted before age 18. The estimated transition probabilities differ somewhat among the three advertising executions tested, with probabilities ranging from 14.2%-16.5% among younger respondents to 1.7%-3.1% among those over the age of 62.

Resumed Smoking

Some smokers *Switching* to Camel Snus may eventually return to smoking. The likelihood of this secondary tobacco use transition, *Resumed Smoking*, cannot be reliably estimated from the likelihood of use studies. It is modeled as 50%; that is, it is assumed that 50% of the smokers

who adopt Camel Snus instead of continuing to smoke will return to smoking in the same age interval. In essence, *Resumed Smoking* is modeled by discounting 50% of the otherwise-expected benefit of *Switching*.

Diversion from Quitting

Unlike smokers who would otherwise continue smoking, smokers who switch to Camel Snus instead of quitting (*Diversion from Quitting*) would be harmed. *Diversion from Quitting* is estimated from the likelihood of use studies based on expressed interest in Camel Snus among those who were deemed likely to quit, based on their recent quitting behavior, expressed interest in quitting, and confidence that they could quit. The projected likelihood of use of Camel Snus among those smokers likely to quit was lower in older smokers, and age-specific probabilities are applied in the modeling. The projected probabilities of *Diversion from Quitting* vary somewhat across executions, though generally decline with age across executions, ranging from 1.6-2.2% in the oldest age interval and varying from 8.6%-20.0% in the 18-22 age interval.

Relapse

As stated above, smokers who undergo *Diversion from Quitting* who would otherwise have quit all tobacco use and instead adopt Camel Snus are harmed because they suffer the incremental risk of using Camel Snus compared to quitting tobacco use entirely. However, their residual health risk is still much lower than if they had continued smoking as long as they do not resume smoking. If some of these smokers subsequently return to smoking as a result of adopting Camel Snus (*Relapse*), this would increase their harm relative to quitting and remaining abstinent. The effect of *Relapse* after quitting cannot be directly modeled within the integrated DPM(+1) modeler and is instead estimated in separate analyses, comparing two counterfactual scenarios, and the results are then applied as an adjustment to model results (Appendix C in Assessing the Population Health Effects of Camel Snus and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 1, Final Report; Assessing the Population Health Effects of Camel Snus and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 2, Final Report; Assessing the Population Health Effects of Camel Snus and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 3, Final Report). Like other secondary tobacco use transitions, *Relapse* cannot be estimated from the likelihood of use studies but is instead assigned a high probability of 50%. The result is then used to adjust the expected impact on survival in analyses that include the *Relapse* effect.

2.13.3 Results of the modeling

This section summarizes the result of extensive statistical modeling with the DPM(+1) of the potential effects of a Camel Snus MRTP on population health (survival). The methods and results are presented in greater detail for each execution of the proposed modified risk advertising in Section 6.4 and in each of the reports submitted with this Application (Assessing the Population Health Effects of Camel Snus and Its Proposed Marketing as a Modified-Risk

Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 1, Final Report; Assessing the Population Health Effects of Camel Snus and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 2, Final Report; Assessing the Population Health Effects of Camel Snus and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 3, Final Report).

Table 2.13.3-1 shows the results from modeling the effects of a Camel Snus MRTP under two different estimates of the ERR across the three executions of the proposed modified risk advertising. The table shows the results of comprehensive analyses, which include all tobacco use transitions listed in Table 2.13.2-1 and Component analyses, which assess specific tobacco use transition probabilities. As a best estimate of the impact of a Camel Snus MRTP, a comprehensive Master model (adjusted for *Relapse* effects) considers a counterfactual scenario that includes all of the tobacco use transitions listed in Table 2.13.2-1. The Master model provides a global and summative sense of the overall population effects of the Camel Snus MRTP. However, the Master model does not provide a clear view of the impact of each of the individual transitions (*i.e.*, which transitions are most or least influential on the population health effect). In order to provide such insights, the DPM(+1) was used to analyze specific tobacco use transitions individually. These more limited Component analyses do not represent the full range of anticipated effects, but rather, by isolating the effect of particular tobacco use transitions, lend insight into the relative contribution of the individual transitions.

The entries in Table 2.13.3-1 are the expected change in survival to age 72 in a hypothetical single birth cohort of 1 million males who initially enter the age of risk for tobacco use at age 13. The mean estimated number of survivors is shown; the 95% PIs around these estimates are in the source reports (Assessing the Population Health Effects of Camel Snus and Its Proposed Marketing as a Modified- Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 1, Final Report; Assessing the Population Health Effects of Camel Snus and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 2, Final Report; Assessing the Population Health Effects of Camel Snus and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 3, Final Report.) The table shows the results for each of the three executions of the proposed modified risk advertising, each under the assumption of an ERR=0.11 and ERR=0.08, respectively.

As noted, Table 2.13.3-1 shows the expected effects on survival as they impact a hypothetical cohort of 1 million males, and we report this as the primary analysis. However, to better estimate the effect on a mixed-gender birth cohort, it is important to take account of the different effect of a Camel Snus MRTP on females, and to scale the size of the cohort from the arbitrary 1 million to the size and gender distribution of a U.S. birth cohort. DPM(+1) analyses of the Master model that used estimates of smoking and mortality for females, and used the transition probabilities from the likelihood of use studies estimated that the survival benefit for females was 19% less than that estimated for males (*i.e.*, 81% of male estimates). Population data show that, at the relevant ages, females comprise 51% of the population (and, accordingly,

males are 49%). Further, U.S. Census data show that the birth cohort born in 2005 (*i.e.*, those who will be 13 in 2018) actually contained 4.1 million individuals. To account for all of these facts, the estimates based on the cohort of 1 million males are scaled to the mixed-gender cohort by multiplying estimates for each tobacco use transition by ~3.7[7]. These scaled estimates, representing the projected effect on more realistic single birth cohort of 4.1 million individuals of mixed gender, are also reported (Table 2.13.3-2). (Note that the empirically-derived probabilities for primary transitions are drawn from samples of mixed gender in the likelihood of use studies, and thus do not take account of differential response by gender to Camel Snus or to the proposed modified risk advertisements.)

As shown in the tables, and as expected, the projected population impact varies across the three different executions of the modified risk advertising, and also by the value estimated for the ERR. Despite these variations, the results suggest substantial commonality across executions and ERR values. In discussing the modeling results in this section, ranges are provided; these indicate the ranges across the advertising executions and posited ERR values (and should not be mistaken for posterior intervals).

2.13.3.1 Master model

Across all three study executions and both ERR estimates derived from the literature (Levy *et al*. 2004), the Master model incorporating all beneficial and harmful tobacco use transitions (including *Relapse*) indicates that introduction of Camel Snus with modified risk advertising would yield substantial net population health benefits, increasing survival to age 72 by at least 5,000 people compared to the base case without a Camel Snus MRTP, in a male cohort of 1 million (Table 2.13.3-1). In the more realistic mixed-gender birth cohort of 4.1 million, the net population impact is to increase survival by at least 18,000 (Table 2.13.3-2).

These strongly favorable outcomes occur because smokers who would otherwise continue smoking can reap very substantial health benefits from *Switching* to Camel Snus instead. Based on published expert consensus estimates (Levy *et al*. 2004), it was estimated that *Switching* to Camel Snus would reduce smoking-related mortality risk by 89-92% (ERR=0.11 to 0.08). Further, continuing smokers have multiple opportunities to switch to Camel Snus as they age. Finally, the likelihood of use studies consistently indicate that the group that can most benefit from S*witching* to Camel Snus – smokers who are unlikely to quit – also shows more interest in using Camel Snus with modified risk advertising than non-smokers. Thus, as discussed in more detail below, the modeling indicates that the beneficial effects of *Switching* – switching to Camel Snus by smokers who would otherwise continue smoking – outweigh the harms that may accrue from harmful tobacco use transitions, such as the *Gateway Effect*. Accordingly, the Master model (scaled to a single mixed-gender birth cohort) that considers all possible tobacco use transitions, both harmful and beneficial, indicates that the effects of a Camel Snus MRTP are

[7] Simplifying the computation to account for differential effects by gender and for the size of the birth cohort, the figures in Table 2.13.3-2 can be derived by multiplying those in Table 2.13.3-1 by 3.70271 (4.1 {cohort scaling} * [0.49 {proportion male} +(0.51 {proportion female} * 0.81 {gender correction for mortality differential}]).

likely to be beneficial, reducing premature mortality for 18,000 or more individuals in a single birth cohort.

Table 2.13.3-1: Estimated changes in survival to age 72, compared to the base case without a Camel Snus MRTP, for the Master model and Component analyses, by execution and estimated ERR, for a birth cohort of 1 million males, followed from age 13 to age 72

	Execution 1		Execution 2		Execution 3	
	ERR=0.11	ERR=0.08	ERR=0.11	ERR=0.08	ERR=0.11	ERR=0.08
Master model††	5,751	6,196	6,819	7,374	6,318	6,824
Master model, with *Relapse*♦	5,035	5,445	5,675	6,175	5,310	5,768
Component analyses††						
Switching	11,864	12,476	13,925	14,639	12,953	13,614
Switching with *Resumed Smoking**	6,450	6,781	7,702	8,093	7,131	7,492
Diversion from Quitting	-318	-235	-529	-390	-453	-334
Diversion from Quitting with *Relapse**♦	-1,177	-1,135	-1,964	-1,892	-1,698	-1,637
Alternative Initiation	80	91	136	155	112	127
Alternative Initiation with *Delayed Smoking**	45	51	77	87	63	72
*Additional Initiation***	-205	-145	-205	-145	-205	-145
Additional Initiation with *Gateway Effect**,***	-415	-382	-415	-382	-415	-382

†† Refer to the tobacco use transitions in Table 2.13.2-1 where each tobacco use transition is described.

* Analyses that include secondary tobacco use transitions necessarily must also include their predicate primary transitions. The impact of the secondary transition can be estimated by the difference in survival between the model run with the secondary transition and the model run with only the predicate primary transition.

♦ The estimated change in survival in these model runs incorporates *Relapse* effects. As discussed in this section, *Relapse* in the same age interval cannot be fully incorporated into the DPM(+1), but its effects can be estimated by comparing two counterfactual scenarios. The reduction in projected survival due to *Relapse* is used to reduce the projected survival estimates in model runs that include *Relapse* compared to the same model run without *Relapse*. However, because the difference between the counterfactual scenario and the base case is not estimated directly for counterfactual scenarios incorporating *Relapse*, 95% PIs are not provided.

Table 2.13.3-2: Estimated changes in survival to age 72, compared to the base case without a Camel Snus MRTP, for the Master model and Component analyses, by execution and estimated ERR, scaled to a birth cohort of 4.1 million of mixed gender, followed from age 13 to age 72

	Execution 1		Execution 2		Execution 3	
	ERR=0.11	ERR=0.08	ERR=0.11	ERR=0.08	ERR=0.11	ERR=0.08
Master model††	21,294	22,942	25,249	27,304	23,394	25,267
Master model, with *Relapse*♦	18,643	20,161	21,013	22,864	19,661	21,357
Component analyses††						
Switching	43,929	46,195	51,560	54,204	47,961	50,409
Switching with *Resumed Smoking**	23,882	25,108	28,518	29,966	26,404	27,741
Diversion from Quitting	-1,177	-870	-1,959	-1,444	-1,677	-1,237
Diversion from Quitting with *Relapse**♦	-4,358	-4,203	-7,272	-7,006	-6,287	-6,061
Alternative Initiation	296	337	504	574	415	470
Alternative Initiation with *Delayed Smoking**	167	189	285	322	233	267
*Additional Initiation***	-759	-537	-759	-537	-759	-537
Additional Initiation with *Gateway Effect**,***	-1,537	-1,414	-1,537	-1,414	-1,537	-1,414

†† Refer to the tobacco use transitions in Table 2.13.2-1 where each tobacco use transition is described.

* Analyses that include secondary tobacco use transitions necessarily must also include their predicate primary transitions. The impact of the secondary transition can be estimated by the difference in survival between the model run with the secondary transition and the model run with only the predicate primary transition.

♦ The estimated change in survival in these model runs incorporates *Relapse* effects. As discussed in this section, *Relapse* in the same age interval cannot be fully incorporated into the DPM(+1), but its effects can be estimated by comparing two counterfactual scenarios. The reduction in projected survival due to *Relapse* is used to reduce the projected survival estimates in model runs that include *Relapse* compared to the same model run without *Relapse*. However, because the difference between the counterfactual scenario and the base case is not estimated directly for counterfactual scenarios incorporating *Relapse*, 95% PIs are not provided.

As seen in Table 2.13.3-1 and Table 2.13.3-2, the Master model yields substantial benefits in improved survival in a scenario that includes all anticipated risks, across the three executions and for both ERR estimates. The results for the most comprehensive model – the Master model including *Relapse* – differ somewhat across the three executions of the modified risk advertising (varying approximately ±13% from lowest to highest (Table 2.13.3-1 and Table 2.13.3-2), reflecting variations in consumer response to each of the modified risk advertisements used in the likelihood of use studies. The magnitude of population benefit is greatest for Execution 2, which also shows the greatest likelihood of both beneficial and harmful transitions. However, despite these numerical differences, the overall picture, and the policy conclusions it implies, is very similar across the three executions, which are projected to yield substantial benefits in improved population survival for at least 18,000 individuals in a single mixed-gender birth cohort.

2.13.3.1.1 Variations by study execution and by estimated ERR

The projected substantial net population benefit holds for both estimates of ERR (0.08 and 0.11). Compared to using the lower estimated ERR (0.08), using the higher (more conservative) estimate of the ERR of 0.11 results in approximately 9% reduced survival to age 72. This difference is less than the percentage difference between the two ERR estimates themselves; the survival benefit does not scale proportionately with variation in the ERR. Subsequent analyses, reported in Section 6.4, explicitly examine the sensitivity of the outcomes to variation in the estimated ERR. As the similarities in projected effect on survival across executions and ERR estimates seem greater than the differences, this section discusses the overall results, while noting where there are differences.

2.13.3.1.2 Sensitivity analyses for estimates of primary tobacco use transitions

In the Master model, estimates empirically-derived from the likelihood of use studies are used as assumptions about the probability of primary tobacco use transitions. As described in Section 6.4, these are projections based on self-reported interest in trying Camel Snus given by the likelihood of use study participants and the application of an algorithm to convert the rated interest to estimates of the probability of purchase for trial (New Tobacco Product 'Likelihood' Study: An Algorithm to Predict Usage of New Tobacco Products Prior to Market Launch). There is reason to think that these projections may overestimate the rate of transitions to use of Camel Snus (New Tobacco Product 'Likelihood' Study: An Algorithm to Predict Usage of New Tobacco Products Prior to Market Launch). However, logically, consistently overestimating use of Camel Snus is not expected to change the conclusion that Camel Snus has a net positive effect on population health (survival), although it would be expected to diminish the magnitude of the benefit. This is because adoption of Camel Snus is responsible for ***both*** the harms and the benefits in the model, with harms or benefits accruing depending on the population in question. So, if adoption of Camel Snus were lower than estimated, across the board, this would reduce both benefits and harms, proportionately, leaving unchanged the conclusion that a Camel Snus MRTP yields a population benefit, though reducing the magnitude of that benefit.

To test this, a variation of the Master model was run in which all of the empirically-derived estimates of primary tobacco use transitions (Table 2.13.2-1) were reduced by 75% (secondary tobacco use transitions, which do not derive from the likelihood of use studies, were not changed). As expected, the model with radically reduced projections of Camel Snus uptake yields less population benefit, with expected survival benefits shrinking by 73-74% (across study executions and ERR values), but, crucially, all of the analyses indicate a net positive (and statistically significant) population benefit, despite the dramatically discounted estimates of use of Camel Snus (Camel Snus Modified Risk Messaging: Likelihood of Use among Tobacco Users and Non-Users – First Execution of Consumer Testing – Amended Final Report; Camel Snus Modified Risk Messaging: Likelihood of Use among Tobacco Users and Non-Users – Second Execution of Consumer Testing – Amended Final Report; Camel Snus Modified Risk Messaging: Likelihood of Use among Tobacco Users and Non-Users – Third Execution of Consumer Testing – Amended Final Report). Thus, the conclusion that a Camel Snus MRTP is likely to benefit population health is robust to even extreme variations in the estimated appeal of Camel Snus, if, in fact, those variations are proportional.

2.13.3.2 Examining the effects of particular tobacco use transitions: Component analyses

The Master model integrates the effects of multiple tobacco use transitions (both harmful and beneficial) to estimate the effect on population health. To provide insight into the dynamics of this effect, Component analyses examined, in isolation, the effects of individual tobacco use transitions on survival. These are not meant to be realistic or integrative analyses, but rather analyses that are designed to enhance understanding of how particular tobacco use transitions might contribute to the net effect on population health. These analyses make clear that the greatest influence on the population impact of a Camel Snus MRTP is the percentage of smokers *Switching* to Camel Snus instead of continuing to smoke. Table 2.13.3-1 and Table 2.13.3-2 show the results of these Component analyses for Executions 1, 2, and 3.

2.13.3.2.1 Switching

Based on the expected rate of *Switching* (from the likelihood of use studies), this tobacco use transition on its own (*i.e.*, without considering any other transition, either beneficial or harmful) is expected to improve survival by more than 10,000 lives in a cohort of 1 million males, and by at least 44,000 in a more realistically-sized mixed-gender cohort of 4.1 million. Even considering that 50% of those *Switching* might return to smoking in the same age interval (*Resumed Smoking*), estimated benefits range from approximately 6,000-8,000 additional survivors in the 1 million-person cohort and 24,000-30,000 in the 4.1 million mixed-gender cohort by the time the birth cohort reaches age 72.

2.13.3.2.2 Additional initiation and gateway effect

In comparison to the benefit gained by smokers *Switching*, the negative effects of harmful tobacco use transitions (*e.g.*, *Gateway Effect*) are much smaller. For example, the expected adverse impact of *Additional Initiation* to tobacco use among young people who otherwise

would not have used tobacco is expected to decrease survival by 145-205 individuals (537-759 in the 4.1 million mixed-gender cohort). Even when positing that half of those who adopt Camel Snus go on to smoke (*Gateway Effect*), the expected reduction in survival would be less than 420 in the 1 million-person cohort (and less than 1,600 in the 4.1 million mixed-gender cohort). This is not to discount such potential adverse effects of a Camel Snus MRTP; strong efforts should be made to minimize such effects, but it is important to recognize that this adverse effect is very much offset by the much larger magnitude of expected beneficial effects from *Switching*, which are at least 10 times greater than the survival loss due to *Additional Initiation* and *Gateway Effect*.

2.13.3.2.3 Diversion from quitting

Similar to *Gateway Effect*, *Diversion from Quitting* among smokers otherwise expected to quit has adverse effects (ranging from 235-529 fewer survivors in the cohort of 1 million males and 870-1,959 in the mixed-gender cohort of 4.1 million). This adverse effect is much smaller than the beneficial effect of *Switching* among smokers who were not expected to quit. The largest adverse effect is attributable to *Relapse* to smoking among diverted quitters; that is, the effect of smokers who experience *Diversion from Quitting* (*i.e.*, take up Camel Snus instead of quitting), 50% of whom return to smoking (the adult equivalent of *Gateway Effect*). Such extreme levels of *Relapse* are projected to reduce survival by as much as 1,964 in the 1 million cohort and between 4,203 and 7,272 in the 4.1 million mixed-gender cohort. Nevertheless, this extreme adverse effect is estimated to be offset by the much larger beneficial effect of smokers *Switching* to Camel Snus instead of smoking.

2.13.3.3 Tipping point analyses

The Master model projects the most likely population effect of a Camel Snus MRTP based on empirically-derived assumptions, and it projects a substantial benefit to population health. Tipping point analyses address a different question: What percent of continuing smokers would need to switch to Camel Snus to offset expected – or even extreme – adverse effects of harmful tobacco use transitions? The results of tipping point analyses that include the empirically-derived estimates of harmful tobacco use transitions and a conservative (that is, exaggerated) estimate of *Relapse* are reassuring. Across the three study executions and considering the two different values of ERR, 2% or less of continuing smokers need to switch permanently to Camel Snus in each 5-year interval of follow-up to overcome multiple harmful tobacco use transitions (including *Diversion from Quitting* with *Relapse* and *Additional Initiation* with *Gateway Effect*). This estimate is based on persistent *Switching;* if 50% of those *Switching* do not switch persistently, but engage in *Resumed Smoking*, the tipping point would be doubled. In any case, tipping point analyses lend confidence that a Camel Snus MRTP would not yield population harm, and reinforces the indication that it is likely to result in a net benefit to population health.

Additional analyses assessed the tipping point with extreme assumptions about the harmful tobacco use transitions *Additional Initiation* and *Diversion from Quitting*. In contrast to models relying on empirically-derived or realistic model inputs, these tipping point analyses instead used extreme values to assess the question: How much *Switching* would be required to offset

even these extreme assumptions about harmful tobacco use transitions? Thus, these tipping point analyses explore the extreme boundaries of the model inputs, rather than relying on empirically-derived and thus more realistic input values.

One situation imagines a scenario in which adoption of Camel Snus by youth who were not otherwise destined to use tobacco (*i.e.*, *Additional Initiation*) is as high as smoking initiation. Even under this extreme assumption, the resulting projected harm would be reversed if 2.60% or 4.12% (for ERR=0.08 and 0.11, respectively) *Switching* occurs in each 5-year interval of follow-up among continuing smokers. Another analysis examines a scenario where the rate of *Additional Initiation* is 10 times as great as the rate projected from actual consumer data, and, further, that half then begin smoking (*i.e.*, *Gateway Effect*). Persistent *Switching* rates of 2.43% or 2.80% (for ERR=0.08 and 0.11, respectively) per 5-year age interval of follow-up are sufficient to offset these hypothetical extremes of harmful tobacco use transitions. Finally, the harms from a scenario in which half of all smokers intending to quit tobacco use completely instead adopt Camel Snus (*Diversion from Quitting*) are offset by persistent *Switching* at rates of 0.90% or 1.29% per 5-year age interval of follow-up (for ERR=0.08 and 0.11, respectively). Thus, tipping point analyses suggest that a Camel Snus MRTP with modified risk advertising is unlikely to yield net harm to the population even under extreme and unlikely scenarios.

2.13.3.3.1 Sensitivity testing for values of the ERR

The DPM(+1) modeler incorporated two estimates of the ERR for Camel Snus compared to smoking – 0.08 and 0.11 – derived from expert consensus about these comparative risks (Levy *et al*. 2004). These ERR values were modeled as having some uncertainty, which is incorporated in the PIs in the modeling. To further explore how the ERR value affects the estimated population impact of a Camel Snus MRTP in the context of the Master model, additional sensitivity analyses were conducted using a variant of the tipping point approach. That is, the question was: How high would the ERR need to be (*i.e.*, how small would the risk reduction associated with switching from cigarette smoking to Camel Snus have to be) to offset the expected population benefit of a Camel Snus MRTP?

The analyses of variations in ERR were based on the tobacco use transition probabilities from the Master model with empirically-based estimates of primary tobacco use transitions and unfavorable estimates of secondary tobacco use transitions (all estimated at 50%). Under these input assumptions, a range of ERR values was considered to identify the value of ERR at which the net population effect was near zero – *i.e.*, neither beneficial nor harmful. Thus, this identifies the point below which the Camel Snus MRTP would be projected to produce benefit. Across executions, this ERR value ranged from 0.46 to 0.48. That is, as long as use of Camel Snus presents less than 46%-48% of the risk of smoking, a Camel Snus MRTP is expected to have a net positive effect on population health. These values for the ERR are roughly 4-6 times higher than the expert consensus values for the ERR (0.08 or 0.11; Levy *et al*. 2004), indicating that there is substantial room for a higher-than-estimated ERR that would still result in a Camel Snus MRTP producing a net benefit to population health. This lends confidence that a Camel Snus MRTP with modified risk advertising is very likely to benefit population health.

2.13.3.4 Extrapolation of the modeling to a population-based U.S. cohort

The Master model and Component analyses discussed above consider the effect of a Camel Snus MRTP only on a single tobacco-naïve cohort of individuals entering their teen years when a Camel Snus MRTP first becomes available. However, this underestimates the potential effect of a Camel Snus MRTP on the full population, as it does not count the effects on other age cohorts in the population that may also use a Camel Snus MRTP when it becomes available. Notably, it does not assess the potential benefit to people who are already smoking at the time the MRTP with modified risk advertising is introduced and could benefit from *Switching* completely to Camel Snus. This section presents an extension of the analyses that extrapolates from a single birth cohort to estimate the effects in the multiple cohorts that make up the current U.S. population aged 13-72.

The DPM(+1) is designed to estimate the effect of an intervention on a single cohort that is followed over time to a certain end-point (in this case, from the age of tobacco initiation to age 72). Results from the DPM(+1) single cohort-based model runs were extrapolated to estimate effects in multiple cohorts representing the full population. The current population can be thought of as a series of birth cohorts, each of which has reached a different age at the time the Camel Snus MRTP becomes available. For these multiple cohort analyses, the introduction of the Camel Snus as an MRTP occurs at different ages for each birth cohort and affects current smokers in addition to never tobacco users. Thus, in aggregate, it aims to estimate the effect of introducing the MRTP to a population of mixed age (13-67 years) and smoking status. Consistent with the single-cohort analyses, the cohorts were grouped into 5-year age intervals, as shown in Table 2.13.3-3.

To assess the effect of introducing a Camel Snus MRTP into each cohort, the model posits that each age group reaches its index age with cigarettes available, but not a Camel Snus MRTP. Each age group then gains access to a Camel Snus MRTP at their "current" age – enabling transitions to Camel Snus as they enter the next 5-year age interval. (So, for example, individuals in the cohort now age 33-37 may initiate or quit smoking up to that age, and then may engage in *Switching* to Camel Snus starting at age 38.) The analyses are based on the estimated tobacco use transitions that make up the Master model (*i.e.*, representing empirically-estimated primary tobacco use transition probabilities and conservative estimates of secondary transitions, except for *Relapse*, which cannot be included in the Master model, as discussed previously). Separate analyses were run assuming an ERR=0.08 and 0.11.

This multiple cohort full population analysis applies the inputs used in the single-cohort analyses (*i.e.*, the 2000 mortality rates, the 2009 smoking initiation rates, the 2005-2008 smoking cessation rates) to multiple cohorts that may have different tobacco use and survival experiences. As such, this extrapolation should be taken only as a heuristic indication of the potential impact on these cohorts.

Table 2.13.3-3 shows the predicted effect on survival to age 72 for each of these 5-year age cohorts of mixed gender. The table shows that a Camel Snus MRTP would benefit survival for individuals in each of the 5-year age intervals at the time the Camel Snus MRTP is introduced.

The estimated magnitude of the benefit is greatest in the younger cohorts, which is expected since smokers in those age intervals have the shortest history of smoking, have the most time available to switch to Camel Snus, and gain the benefit from switching over a longer period of time. Indeed, in some of the older age intervals, many smokers will already have died before the Camel Snus MRTP is introduced. Thus, it is expected that younger individuals will reap the most benefit from the introduction of Camel Snus as an MRTP. Conversely, the benefits accruing to older individuals are realized sooner, as they are closer to age 72 (the age at which survival is tallied in the model).

Table 2.13.3-3: Estimated changes in survival* to age 72 for mixed-gender cohorts, sized to the U.S. population aged 13 to 67 at the time of the hypothetical Camel Snus MRTP introduction

Age when MRTP becomes available		Execution 1		Execution 2		Execution 3	
For initiation	For switching	ERR=0.11	ERR=0.08	ERR=0.11	ERR=0.08	ERR=0.11	ERR=0.08
13-17	18-22♦	107,289	115,336	126,963	137,034	117,729	126,889
18-22	18-22	91,591	98,053	113,964	122,647	108,509	116,586
23-27†	23-27	65,836	70,186	90,857	97,402	86,672	92,890
	28-32	41,157	43,742	56,773	60,638	54,126	57,839
	33-37	22,593	24,002	28,994	30,925	29,665	31,614
	38-42	12,051	12,785	15,584	16,548	16,334	17,312
	43-47	6,460	6,819	7,979	8,433	8,661	9,117
	48-52	3,001	3,163	3,836	4,055	4,104	4,315
	53-57	1,248	1,313	1,523	1,606	1,725	1,817
	58-62	501	520	530	549	645	684
	63-67*	89	89	106	106	106	115

*Based on the tobacco use transitions in the Master model (Table 2.13.2-1), without *Relapse*.
♦ This cohort cannot engage in *Switching* until it has initiated smoking, which can occur in the 13-17 age interval at the earliest. Hence, the first age for *Switching* is later than the age for initiation.
† Initiation is modeled as ceasing after age 27.
* This is the last age interval during which *Switching* can make a difference in the outcome (survival).

These analyses suggest that a Camel Snus MRTP would increase survival for individuals in each age interval. (Note that these estimates do not include the adverse effects of *Relapse*, which reduces the survival benefit by approximately 12%-16% [Table 2.13.3-2]).

While the figures from this full population extrapolation are not precise, together with the primary single-cohort model analyses, the multiple-cohort analysis further emphasizes the potential for a Camel Snus MRTP with the proposed modified risk advertising to provide substantial benefit to population health.

2.13.4 Limitations and strengths

In advance of actual in-market experience with an MRTP, modeling provides a means of estimating the likely impact of product availability and use on population health. Like all modelers, the DPM(+1) relies on simplifying assumptions about the dynamics of tobacco use and tobacco-related mortality. Importantly, wherever possible, model inputs were based on empirical data, and the model was validated against observed data on mortality in the U.S. (for the base case with only cigarettes available to the population) and Sweden[8] (for the counterfactual scenario with cigarettes and snus available to the population).

Many inputs to the DPM(+1) were based on the likelihood of use studies, which assessed interest in trying Camel Snus among various subgroups who viewed three different executions of the proposed modified risk advertising for Camel Snus. Self-reported likelihood of use ratings were translated into probabilities of trial using an empirically-validated algorithm (New Tobacco Product 'Likelihood' Study: An Algorithm to Predict Usage of New Tobacco Products Prior to Market Launch). It is likely that these projections overestimate the adoption of Camel Snus. However, greater use of Camel Snus enhances both benefits and harms, since both depend on use of Camel Snus, just in different exposure groups (*i.e.*, smokers versus non-smokers). Thus, an overall reduction in the estimated appeal of Camel Snus is unlikely to change the conclusion that the net effect of an MRTP is positive.

In another respect, estimates of use based on the likelihood of use studies may underestimate actual use of Camel Snus since the estimates were derived from a single exposure to a tobacco company advertisement with modified risk information that counters most smokers' pre-existing beliefs about the relative risk of smokeless tobacco compared with cigarettes (Fong *et al*. 2016; Kaufman *et al*. 2014; Kiviniemi and Kozlowski 2015). Repeated exposures to the information may increase interest in a reduced harm product. Testing of the information as part of a tobacco company advertisement may also have limited impact because consumers are skeptical of claims made in advertisements and are particularly suspicious of claims made by a tobacco company (Byrne *et al*. 2012; Harris Interactive 2013). Accurate information about reduced risk of Camel Snus compared to cigarette smoking from other, more acceptable authoritative sources, may increase the appeal of an MRTP, particularly to current smokers not intending to quit smoking.

The primary analyses are based on a single 13-year-old cohort of 1 million individuals and used smoking and mortality statistics for males. Separate analyses suggest that the survival benefit for females would be 19% lower than that for males. To assess the effect of introducing the Camel Snus MRTP in a mixed-gender cohort of 4.1 million individuals, the estimated benefit was reduced to account for this sex differential and adjusted to account for 51% females. However,

[8] This was done in a separate validation exercise (Bachand and Sulsky 2013). The modeling of Camel Snus MRTP effects does not use estimates from the Swedish population; it uses U.S.-based smoking mortality statistics, and the specified ERR values to model the effects of snus on mortality, and U.S.-based likelihood of use data to model tobacco use transitions.

the input estimates for the tobacco use transitions (whether empirically-derived or conservative values) were not differentiated by gender. Thus, the analyses do not take detailed account of gender differences. Importantly, analysis showed that tipping points were similar for males and females.

The modeling results presented here also benefit from considerable strengths. The DPM(+1) considers multiple transitions in smoking and Camel Snus use that could affect population health. The DPM(+1) modeler itself, and the inputs regarding tobacco use and its effects on survival, were validated against population data addressing the health effect of smoking (in the U.S.) and snus (in Sweden). The modeler incorporates conservative assumptions – for example, by not including the benefits of discontinuing Camel Snus – suggesting that the benefits may be greater than model output. Thus, the conclusion from the extensive modeling exercises – that a Camel Snus MRTP would yield substantial positive benefits to population health – is robust.

2.13.5 Conclusion: A Camel Snus MRTP with the proposed modified risk advertising is very likely to have substantial net positive effects on population health

Extensive modeling strongly indicates that a Camel Snus MRTP is highly likely to have substantial positive net effects on population health in terms of increased longevity to age 72. Scaling of the Master model – integrating the effects of all potentially harmful and beneficial tobacco use transitions for a single birth cohort of 4.1 million people entering their teen years at the time a Camel Snus MRTP is introduced with modified risk advertising – indicates that Camel Snus would improve survival to age 72 by at least 18,000. Extrapolating the model results to the full U.S. population of various ages and smoking status demonstrates improved survival for individuals in each age interval at the time the Camel Snus MRTP is introduced.

The projected net population health benefit was robust to variations in modeling assumptions. Model runs were conducted with an estimated reduction in mortality risk for a Camel Snus MRTP of 89-92%, compared to cigarette smoking, based on expert consensus regarding the relative risks (Levy *et al*. 2004). Sensitivity testing shows that even if the risk reduction were as low as about 50%, a Camel Snus MRTP with modified risk advertising would still yield a benefit to population health. Similarly, sensitivity testing shows that even if the uptake of Camel Snus were much lower than the empirically-derived estimates used in the modeling, across the board, a Camel Snus MRTP would still yield a population health benefit, albeit a more modest one. Tipping point analyses based on a Master model integrating empirically-derived estimates of all potential harmful and beneficial tobacco use transitions show that if fewer than 2% of continuing smokers switched persistently to Camel Snus in each 5-year period, a population benefit would be achieved. Even in tipping point analyses that assume very extreme scenarios of harmful tobacco use transitions (specifically, *Additional Initiation* and *Diversion from Quitting*), less than 4% of smokers would need to switch persistently to Camel Snus in each 5-year period to offset these extreme scenarios. Thus, extensive modeling suggests that making Camel Snus with modified risk advertising available is likely to produce a substantial net benefit to population health and is unlikely to result in net negative effects on population health.