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R.J. Reynolds Tobacco Company Briefing Materials

Briefing Materials for

Proposed Camel Snus Modified Risk Advertising

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Prepared by RAI Services Company on behalf of R.J. Reynolds Tobacco Company for the September 13-14, 2018 Tobacco Products Scientific Advisory Committee Meeting

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1 Introduction

R.J. Reynolds Tobacco Company ("RJRT") submitted modified risk tobacco product Applications ("MRTPAs") to the U.S. Food and Drug Administration ("FDA") in March 2017 under Section 911(g) of the Federal Food, Drug, and Cosmetic Act ("FD&C Act"), as amended by the Family Smoking Prevention and Tobacco Control Act ("TCA"), requesting modified risk marketing orders for six different Camel Snus products (Frost, Frost Large, Winterchill, Robust, Mellow, and Mint, collectively, "Camel Snus").

This briefing document presents a summary of the data and information included in the Camel Snus MRTPAs and highlights the key evidence making it appropriate for FDA to issue marketing orders permitting modified risk advertising with the following key claims:

Claim #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.

Claim #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.

Claim #3: Smokers who **SWITCH COMPLETELY** from cigarettes to Camel SNUS can greatly reduce their risk of lung cancer and respiratory disease.

According to the U.S. Surgeon General, combustible tobacco products by far have the greatest adverse impact on public health (USDHHS 2014). Because tobacco in cigarettes is burned and the resulting smoke inhaled, smokers are exposed to substantial quantities of combustion-related toxicants, as well as other substances that transfer directly from tobacco to smoke.

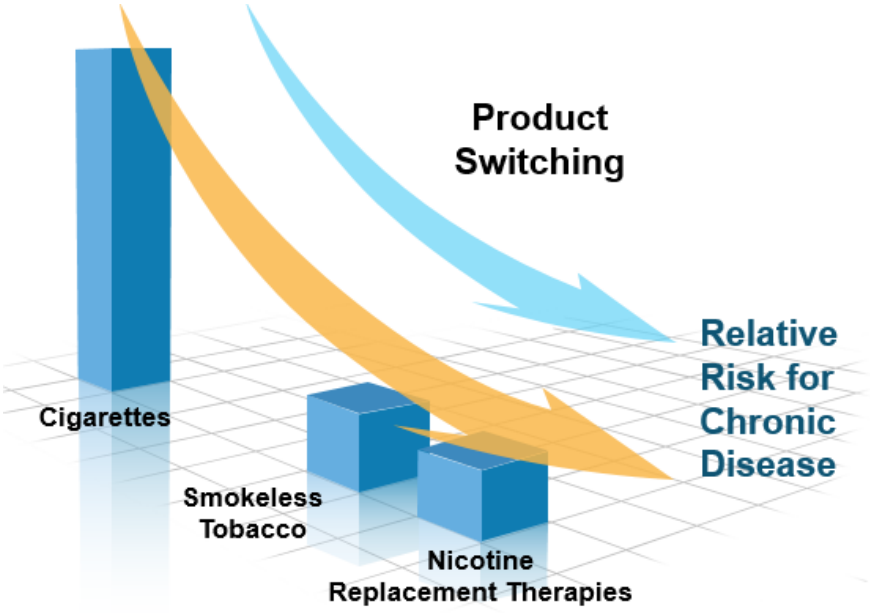
Camel Snus is a smokeless tobacco product that does not undergo combustion during use; therefore, users of Camel Snus are not exposed to tar, carbon monoxide, or other combustion-related toxicants that drive many of the individual disease risks associated with cigarette smoking.

These differences in toxicant exposure result in significantly lower disease risks for lung cancer, oral cancer, respiratory disease, and heart disease in Camel Snus users. Smokeless tobacco products are not safe – and the proposed advertisements communicate that to individuals – 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), and this includes Camel Snus.

Public-health experts conceptualize this risk differential along a "continuum of risk," placing cigarettes and other combustible products on the most harmful end of the risk continuum due to the increased risk from inhalation of smoke from burned tobacco, and noncombustible

products (i.e., smokeless tobacco and nicotine products and nicotine replacement therapies) on the other, least harmful end (Zeller *et al*. 2009).

1.1 The Tobacco and Nicotine Product Risk Continuum



Subchapter IX of the TCA includes provisions for modified risk tobacco products (Section 911), that represent the Federal Government's recognition that there may be tobacco products that, when appropriately marketed, could significantly reduce the burden of disease and death caused by tobacco use, and the need to communicate accurate relative risk information. Section 911 affords a pathway for manufacturers to communicate the absolute and relative risks of specific tobacco products with FDA serving as the regulatory gatekeeper.

Specifically, Section 911(g)(1) of the FD&C Act gives FDA the authority to issue an MRTP order if the agency determines that the product, as actually used by consumers, will:

A. significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and

B. 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.

RJRT's Applications demonstrate that the proposed modified risk claims, as presented in the submitted advertisements, are fully supported by epidemiological, preclinical, and clinical studies as contemplated in FDA's 2012 Draft Guidance in regard to Section 911 of the Tobacco Control Act.

Further, evidence from multiple sources shows that smokers are currently misinformed about the relative risks of cigarette smoking compared to use of non-combusted tobacco products like Camel Snus, believing the two to be equally harmful. If smokers were adequately informed about the substantially lower risks of lung cancer, oral cancer, heart disease, and respiratory disease when using Camel Snus exclusively, some smokers would be more likely to switch completely from cigarettes to Camel Snus. Such switching would significantly reduce harm and the risk of these smoking-related diseases to individual tobacco users, and would benefit public health.

2 Executive Summary

A robust body of U.S. and Swedish smokeless tobacco epidemiology studies provides a sound scientific basis to conclude that, for individuals who are current cigarette smokers, switching completely from smoking cigarettes to Camel Snus can significantly reduce those individuals' risk for lung cancer, oral cancer, respiratory disease, and heart disease. RJRT's testing of Camel Snus products encompassed a wide range of scientific studies using established methodologies for comparative assessment of tobacco products and associated health risks, including chemical analyses, preclinical toxicology and clinical studies. Results from these studies are consistent with the epidemiological findings, and together provide a sound scientific basis to conclude that, for individuals who are current cigarette smokers, switching completely from smoking cigarettes to Camel Snus can significantly reduce those individuals' risk for lung cancer, oral cancer, respiratory disease, and heart disease.

Behavioral studies demonstrate that the proposed modified risk messages are well understood. Specifically, it is understood that while Camel Snus presents less risk to a smoker who switches completely. Individuals also understand that because Camel Snus is a tobacco product, it still carries risk and is addictive.

The population health standard under which MRTP applications are considered requires that applications assess the overall impact on population health of the proposed communications. Thus, in addition to determining the potential benefit to the individual smoker, these Applications determine the potential impact of the proposed advertising on non-users of tobacco, who could be harmed if they adopted the product. In consumer studies, RJRT evaluated the likelihood of use of Camel Snus (with modified risk advertising) among former and never users of tobacco, as well as among current smokers.

These studies also demonstrated that, after seeing the modified risk messaging, current smokers who do not expect to quit smoking are most likely to use the product, while interest among non-tobacco-users is low. Population modeling to integrate and quantify the scientific and behavioral research applicable to Camel Snus with the proposed advertising shows that an FDA order permitting Camel Snus to be marketed as a modified risk tobacco product is likely to produce a substantial overall public health benefit.

2.1 History of Camel Snus

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.

Before developing Camel Snus in the mid-2000s, RJRT was aware of the epidemiology studies conducted in Sweden that showed a significant reduction in smoking and smoking-related disease had occurred due to snus use. Cigarette smoking rates and smoking-related disease rates in Swedish males are lower than those in any other European country, even though total overall tobacco consumption is comparable. This Swedish-based epidemiological evidence, often referred to as the "Swedish Experience," was a driving force behind RJRT's development of a snus product for the U.S. market.

To bring Swedish snus to the U.S., in 2006, RJRT issued product specifications and standards for the manufacture of Camel Snus Frost to Fiedler and Lundgren (F&L), a manufacturer of Swedish snus. Camel Snus was created using a Swedish tobacco blend, processed using a Swedish heat-treatment process and produced using the same production equipment as was used for the manufacturer's other Swedish snus products.

Camel Snus was made to the same specifications and standards as snus products for the Swedish market. Camel Snus was initially manufactured in Sweden and shipped to the U.S. In 2007, commercial production of Camel Snus moved to the U.S., using the same processing equipment and detailed specifications of snus processing procedures from Sweden. Today, all six Camel Snus products are manufactured using a process consistent with snus products sold in Sweden and other markets.

2.2 Description of Camel Snus Products

Snus commonly uses finely ground tobaccos that undergo a two-step process:

1. A heat treatment process in the presence of water and salt (sodium chloride); and

2. A cooking process which incorporates the addition of a pH-stabilizing solution.

The primary differences between snus and the various types of moist snuff tobacco products prevalent in the United States today are the tobacco types used and the manufacturing processes employed with those tobaccos. The tobaccos used in snus contain lower levels of toxicants than the tobaccos used in most other smokeless tobacco products, and the special heat-treatment steps employed in snus manufacturing further minimizes the quantities of those constituents in the final product.

It is generally accepted that heat treatment, along with selection of tobaccos, limits the levels of some harmful and potentially harmful constituents ("HPHCs"). Tobacco-specific nitrosamines (TSNAs) are formed from tobacco alkaloids during tobacco curing, fermentation, and aging.

Using heat treatment inhibits microbial growth and thereby minimizes further development of TSNAs in finished smokeless tobacco products.

Camel Snus differs from its Swedish origins only in its taste profile, which was formulated using flavors and humectants consistent with the taste preferences of American smokers.

All six Camel Snus products are portioned, pouched products and use a common base blend of tobaccos. The Camel Snus tobacco blend is finely milled, mixed with water and salt, and then heat treated. A sodium carbonate and sodium bicarbonate pH-stabilizing solution is added and followed by an additional heat treatment.

In order to create different flavors of Camel Snus, a humectant and flavoring ingredients are added to the processed common tobacco blend. These blends are then pouched in a porous fleece material, which is a dry-laid, non-woven material made from viscose fiber, and packaged in metal tins to make the finished product.

Table 2-1: Camel Snus products that are the subject of the MRTP Applications

	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

RJRT developed two different Camel Snus pouch sizes (600mg and 1000mg) to appeal to different consumer preferences. Some Camel Snus users prefer larger pouches and some prefer smaller pouches.

To make the product appealing to American smokers, the flavorings were adapted to the American palate using ingredients commonly used in existing smokeless tobacco products and those commonly used in foods.

2.3 Proposed Modified Risk Advertising

An MRTP application is not an application for authorization to market a particular product, but rather an application for authorization to communicate accurate information about the risks of a marketed tobacco product compared to other marketed tobacco products, i.e., the relative risk of Camel Snus compared to cigarettes.

RJRT's Applications include copies of all proposed modified risk advertising planned for Camel Snus, and are shown below in this section. Importantly, RJRT is seeking orders to use *these exact communications*, as proposed and submitted, and as tested in RJRT's MRTPA research program.

Specifically, RJRT is requesting that FDA issue an MRTP order allowing three different proposed advertising Executions to communicate the primary modified risk claim to adult smokers:

[1] RJRT refers to these sub-brands as "brand styles," "varieties," "variants," or "flavor variants" in the text of the applications.

Proposed Advertising 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.
Proposed Advertising 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.
Proposed Advertising Execution 3	Smokers who **SWITCH COMPLETELY** from cigarettes to Camel SNUS can greatly reduce their risk of lung cancer and respiratory disease.

The proposed advertising is intended for current adult smokers and emphasizes the need to switch completely from cigarette smoking to exclusive use of Camel Snus to realize the claimed health benefits.

The proposed advertising contains substantial balancing information to explain that individuals not already using tobacco should not start using Camel Snus, that minors and pregnant women should never use tobacco, that Camel Snus is addictive, and that quitting is the best choice for smokers concerned about health risks.

This health-related balancing information includes:

Proposed Advertising Execution 1 Balancing Information	NO TOBACCO PRODUCT IS SAFE However, smokers who use Camel SNUS **instead of** cigarettes can significantly reduce their health risks from smoking. Like all tobacco products, Camel SNUS contains nicotine and **is addictive**. Adults who do not use or have quit using tobacco products should not start. Minors and pregnant women should never use tobacco products. If you're a smoker concerned about the health risks from smoking, the best choice is to quit. A good place to begin is talking with a healthcare provider. But if you're not going to quit using tobacco products, you should think about switching to Camel SNUS.

Proposed Advertising Execution 2 Balancing Information	NO TOBACCO PRODUCT IS SAFE Like all tobacco products, Camel SNUS **contains nicotine** and **is addictive.** Adults who do not use or have quit using tobacco products should not start. **Minors and pregnant women should never use tobacco products.** If you're a smoker concerned about the health risks from smoking, the best choice is to quit. A good place to begin is talking with a healthcare provider. But if you're not going to quit using tobacco products, you should think about switching to Camel SNUS.
Proposed Advertising Execution 3 Balancing Information	NO TOBACCO PRODUCT IS SAFE Like all tobacco products, Camel SNUS **contains nicotine** and **is addictive.** Adults who do not use or have quit using tobacco products should not start. **Minors and pregnant women should never use tobacco products.** If you're a smoker concerned about the health risks from smoking, the best choice is to quit. A good place to begin is talking with a healthcare provider. But if you're not going to quit using tobacco products, you should think about switching to Camel SNUS.

These proposed messages were tested with both users and non-users of tobacco, who were of legal age to purchase tobacco, in order to assess the effect on these populations. RJRT's studies showed that the proposed modified risk messages and balancing information are well understood.

RJRT is *not* proposing any changes to the existing warning label statements on product packaging, labeling, or advertising. The labeling and advertising for Camel Snus styles currently contains one of the four warning label statements mandated by law, used in rotation. These four statutorily-mandated warnings are:

1. WARNING: This product can cause mouth cancer.
2. WARNING: This product can cause gum disease and tooth loss.
3. WARNING: This product is not a safe alternative to cigarettes.
4. WARNING: Smokeless tobacco is addictive.

Below are images of the three proposed print advertisements, each of which would be a trifold in a magazine:

Execution 1 Cover Page:

Execution 1 Interior Pages:

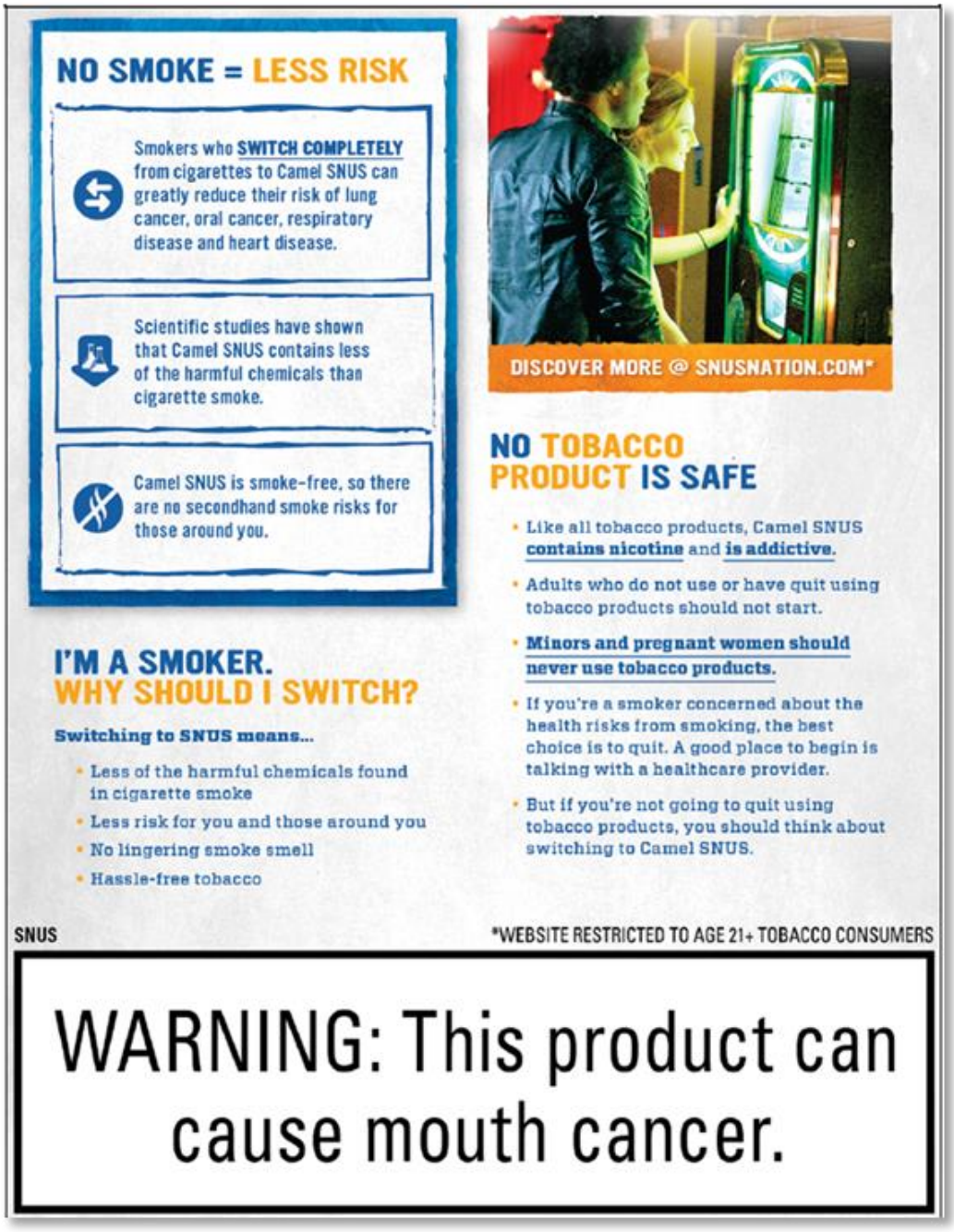
Execution 1 Interior Detail (Left):

Execution 1 Interior Detail (Right):

Execution 2 Cover Page:

Execution 2 Interior Detail (Left):

Execution 2 Interior Detail (Right):



Execution 3 Cover Page:

Execution 3 Interior Detail (Left):

Execution 3 Interior Detail (Right):

RJRT is seeking authorization to advertise Camel Snus with the specific content and images in the above print advertisements. If authorized by FDA, RJRT intends to communicate the modified risk messaging using five communication platforms: print advertising, direct mail, e-mail, a branded website, and direct consumer engagement. Each communication form would include all three panels of information shown above.

RJRT's Camel Snus MRTP proposed marketing plan is described in detail in Section 4 of the MRTPA.

2.4 Advertising Execution Development

RJRT developed the three proposed advertising Executions through an iterative process. A series of qualitative focus groups, as well as preliminary comprehension and perceptions research, was used to develop Advertising Execution 1.

During the April 2015 TPSAC meeting with Swedish Match, there was significant discussion regarding simplicity, reading level, and comprehension of comparative risk information. Some TPSAC members expressed concerns about the complexity of the word "significantly" in the context of advertising. RJRT carefully considered the TPSAC discussion and created proposed Advertising Execution 2, substituting the word "greatly" for "significantly."

In addition, Advertising Execution 2 simplified language throughout the proposed advertisement and emphasized health related balancing information text through the increased use of bolding, underlining, and capitalization. The table below shows key changes from proposed Advertising Execution 1 to proposed Advertising Execution 2.

Advertisement Section Heading	Proposed Advertising Execution 1	Proposed Advertising Execution 2
How do I use it? (Interior Left Page)	"Smokers who use Camel SNUS **instead of** cigarettes can significantly reduce their health risks from smoking."	"**Switch completely** from cigarettes to Camel SNUS."
No Smoke = Less Risk (Interior Right Page)	"**switch completely**"	"**SWITCH COMPLETELY**"
	"Scientific studies have shown that Camel SNUS contains fewer carcinogens than cigarette smoke."	"Scientific studies have shown that Camel SNUS contains less of the harmful chemicals found in cigarette smoke."
No Tobacco Product is Safe	"contains nicotine and **is addictive.**"	"**contains nicotine** and **is addictive.**"

Advertisement Section Heading	Proposed Advertising Execution 1	Proposed Advertising Execution 2
(Interior Right Page)	"minors and pregnant women should never use tobacco products."	"**Minors and pregnant women should never use tobacco products."**

In the April 2015 meeting, TPSAC members generally agreed that Swedish snus products, when used exclusively, conferred no risk of lung cancer or respiratory disease compared to never tobacco users. However, some TPSAC members expressed uncertainty regarding whether the evidence presented was strong enough to conclude that snus use confers no risk of heart disease or oral cancer.

RJRT took note of comments by TPSAC and FDA on the epidemiological evidence with respect to whether there was an association between using Swedish snus and oral cancer or heart disease. Importantly, RJRT is not asserting or communicating that Camel Snus confers *no* risk for these diseases. The modified risk information in Executions 1 and 2 asserts that switching to Camel Snus *reduces* individual risk for oral cancer and heart disease compared to continued smoking (i.e., relative risk). The validity of this assertion is established in the Applications.

Nevertheless, RJRT was cognizant of TPSAC's caution, and of consumers' existing misperceptions of the risks of oral smokeless tobacco. Accordingly, RJRT developed and tested proposed Advertising Execution 3, which is identical to Execution 2 in all respects but eliminates claims for reduced oral cancer and heart disease risk.

2.5 Modified Risk Marketing Order Statutory Requirements

Section 911(g)(1) of the FD&C Act gives FDA the authority to issue an MRTP order if the agency determines that the product, as actually used by consumers, will:

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

2. 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.

With respect to 911(g)(1)(A), the body of epidemiological studies, human clinical studies, preclinical toxicology studies, and chemistry studies of smokeless tobacco and health, provides a sound scientific basis to conclude: for individuals who are current cigarette smokers, switching completely from smoking cigarettes to Camel Snus will significantly reduce their risk for lung cancer, oral cancer, respiratory disease, and heart disease.

With respect to 911(g)(1)(B), the results of RJRT's testing of individuals' understanding and response to the proposed advertisements, which informed extensive statistical modeling, show

that changes in tobacco usage patterns likely to follow Camel Snus modified risk advertising are likely to produce a substantial overall population health benefit.

2.6 Camel Snus Satisfies the MRTPA Statutory Requirements

2.6.1 Camel Snus significantly reduces harm and the risk of tobacco-related disease to individual tobacco users

The evidence that switching to Camel Snus from cigarette smoking reduces the harm and smoking-related disease risks to individual tobacco users is compelling. U.S. and Swedish epidemiological studies show that cigarette smokers experience significantly elevated health risks for lung cancer, oral cancer, respiratory disease, and heart disease compared to non-tobacco users. By comparison, these same U.S. and Swedish epidemiological studies show that smokeless tobacco users experience substantially lower health risks for each of these diseases.

The epidemiological studies are based on historical tobacco products as a category and are not specific to any particular tobacco product or brand. However, the lower health risks reported are applicable to users of Camel Snus for two principal reasons:

1. Camel Snus toxicant content is less than that of the historical U.S. and Swedish smokeless tobacco products on which the epidemiological studies are based; and

2. Camel Snus usage patterns (e.g., quantities used and duration of daily use) are generally lower than the historical usage patterns reflected in U.S. and Swedish epidemiology, supporting the conclusion of lower toxicant exposure from Camel Snus.

Collectively, the results of U.S. and Swedish epidemiological studies provide clear and consistent evidence that the health risks from use of smokeless tobacco and snus products, including Camel Snus, are less than the health risks from smoking.

Product-specific evidence submitted with these Applications also shows that, compared to cigarettes, Camel Snus:

1. Presents a reduced toxicant chemistry profile;

2. Produces lower toxic effects in preclinical *in vitro* and *in vivo* studies; and

3. Is associated with reduced human exposure to combustion-related toxicants formed from burning tobacco that are believed to cause serious smoking-related diseases.

Alongside the epidemiology, these complementary lines of evidence provide a sound scientific basis for the conclusion that smokers who switch completely from smoking cigarettes to using Camel Snus will reduce their risks for lung cancer, oral cancer, respiratory disease, and heart disease, compared to continued smoking.

2.6.2 MRTP orders for Camel Snus will benefit the health of the population as a whole

The data submitted in RJRT's Applications demonstrate that a modified risk marketing order for Camel Snus will benefit the health of the population as a whole. Population impact depends on the balance of beneficial use (i.e., complete switching from smoking to Camel Snus) and potentially harmful use (e.g., uptake by non-users, reduced smoking cessation, etc.).

Behavioral studies assessing the "likelihood of use" of Camel Snus with modified risk advertising clearly showed that likely use was much greater among current smokers (specifically among those not expecting to quit) than among former and never tobacco users. Camel Snus is thus most likely to be used by those who could benefit from switching (i.e., current continuing smokers), and unlikely to be adopted by those who could be harmed (i.e., non-users of tobacco).

Integration of the results of these likelihoods of use findings among tobacco users and non-users provided a basis for estimating the population health impact of Camel Snus with modified risk advertising. These data were used as inputs to empirically-informed statistical modeling. Results indicate a likely substantial net benefit to population health, and a very low likelihood of net harm.

Only a small portion of current smokers would need to switch completely to Camel Snus to cause a significant decrease in population-level mortality. Over time, dynamic population modeling projects an estimated benefit of approximately 350,000-450,000 additional survivors to age 72 for the population as a whole. This reflects the expected number of smokers who would switch completely to Camel Snus.

2.6.3 Summary

In summary, a body of epidemiological evidence from both the U.S. and Sweden supports the conclusion that Camel Snus confers substantially less risk than smoking for lung cancer, oral cancer respiratory disease, and heart disease, and that smokers who switch completely to Camel Snus will reduce their risk of these diseases. The epidemiological data is supported by evidence from chemical product analyses, animal and *in vitro* studies, and human clinical biomarker studies of Camel Snus. These data establish the potential for Camel Snus to reduce individual risk to smokers, and validate the modified risk information in the proposed advertising.

Comprehension and perceptions studies demonstrate individuals understand, after exposure to the proposed modified risk advertisements, that Camel Snus has less risk than smoking, but still has risk. Upon exposure to the proposed advertisements, projected product use was far more likely among current smokers, especially those not expecting to quit, than among non-users of tobacco products. Extensive statistical modeling integrated these empirically-derived inputs and concluded that Camel Snus with modified risk advertising is likely to result in considerable population health benefit, and is unlikely to result in population harm.

3 Epidemiological, Clinical, and Preclinical Evidence

The proposed advertising for Camel Snus states that switching completely from smoking cigarettes to Camel Snus will significantly reduce individual disease risk for lung cancer, oral cancer, respiratory disease, and heart disease. These facts are supported by a compelling body of epidemiology on smokeless tobacco, including snus, and further supported by product-specific human clinical studies, preclinical toxicology studies, and chemistry studies of Camel Snus.

The following provides an overview of the scientific rationale presented in the MRTPAs for the benefits of Camel Snus for individual cigarette smokers:

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

- These U.S. and Swedish epidemiology studies are appropriate for estimating disease risks to individual users of Camel Snus. This is because the toxicant profile of Camel Snus is similar, or more favorable, compared to the smokeless tobaccos evaluated in those epidemiology studies. Further, Camel Snus exclusive usage patterns (e.g., quantities used and duration of daily use) are generally lower than that of historical smokeless tobacco products.

- RJRT-sponsored clinical and preclinical studies of Camel Snus, as well as external studies of Camel Snus and other U.S. smokeless tobacco products, are concordant with these epidemiological findings, and provide a sound basis of biological plausibility for reduced individual disease risks compared to cigarette smoking.

3.1 Epidemiological Studies of U.S. Smokeless Tobacco and Swedish Snus Usage Provide Clear and Consistent Evidence of Reduced Individual Disease Risk Compared to Cigarette Smoking

This section summarizes the large body of epidemiological data that demonstrate clear and consistent evidence for reductions in risk for lung cancer, oral cancer, respiratory disease, and heart disease among smokeless tobacco and snus users, compared with cigarette smokers.

RJRT is submitting claims of reduced risk for these four diseases. However, the epidemiological data also show lower risks for virtually all smoking-related diseases, confirming that no offsetting health risks are associated with the use of smokeless tobacco and snus products, including Camel Snus (*see* MRTPA Section 2.9 and MRTPA 6.1.1). These reductions in other health risks are consistent with the fact that, unlike cigarettes, use of Camel Snus does not expose users to substantial quantities of combustion-related toxicants by inhalation.

Epidemiological studies of U.S. smokers demonstrate significantly elevated risks for a wide range of cancers (e.g., lung cancer and oral cancer), non-neoplastic respiratory disease (e.g., chronic obstructive pulmonary disease (COPD)), cardiovascular diseases, and other adverse

health effects. The Centers for Disease Control and Prevention (CDC) reports that the greatest adverse U.S. population health impact of cigarette smoking is 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). Less well-appreciated is that cigarette smoking is also associated with approximately 4,900 deaths from oral cancer annually (CDC 2011).

In contrast, the risks for these diseases are greatly reduced for exclusive smokeless tobacco users, and for those who have switched from smoking to smokeless tobacco use. Because smokeless tobacco products do not undergo combustion during use, users of smokeless tobacco products are not exposed to tar, carbon monoxide, and the many other products of incomplete tobacco combustion.

These differences in exposure, as well as differences in routes of exposure during cigarette smoking and smokeless tobacco use (i.e., inhalation versus oral absorption), result in significantly lower risk profiles for smokeless tobacco users compared with cigarette smokers, as demonstrated in epidemiological findings (*see* MRTPA Section 2.8 and MRTPA Section 2.9).

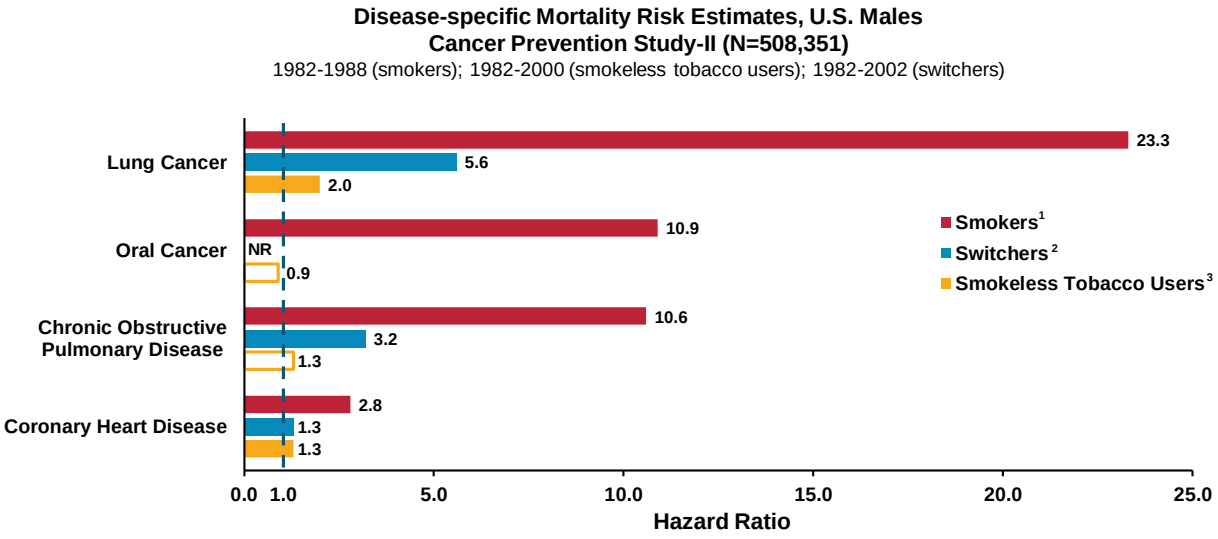
Figure 3-1 below provides a representative comparison of the risks for the four major diseases, which are the subject of the Camel Snus proposed modified risk advertising, derived from the American Cancer Society's Cancer Prevention Study II (CPS-II), one of the largest U.S. epidemiology studies. CPS-II gathered data from over one million participants, both men and women, in the U.S. Multiple analyses have computed the mortality risks of lung cancer, oral cancer, respiratory disease, and heart disease for smokers and for users of smokeless tobacco. Further, analyses of CPS-II have estimated risks associated with individuals who have switched from cigarette smoking to the use of smokeless tobacco (USDHHS 2014; Henley et al. 2005; Henley et al. 2007).

As shown in Figure 3-1, the risks of mortality, relative to never users of tobacco, from lung cancer, oral cancer, COPD, and coronary heart disease (CHD) for smokeless tobacco users, are substantially lower than for cigarette smokers. Cigarette smokers who switched to smokeless tobacco use ("switchers") also experience substantially lower risks.

These data demonstrate that the risk for lung cancer, oral cancer, COPD, and heart disease are all significantly reduced for smokeless tobacco users and switchers, compared to cigarette smokers. These data are consistent with the broader body of epidemiological evidence that confirms substantially reduced risk for these four diseases among smokeless tobacco users and switchers to smokeless tobacco use, relative to cigarette smokers.

Further discussion of relevant epidemiology studies is found in MRTPA Section 6.1.1 and supporting documents associated with that section.

Figure 3-1: U.S. Epidemiology Data Confirms Substantial Reductions in Risks for All Four Diseases



[1]USDHHS 2014; [2]Henley et al. 2007; [3]Henley et al. 2005
NR=Not Reported
Solid bars = statistically significantly different versus never users of tobacco
Open bars = not statistically significantly different versus never users of tobacco

3.1.1 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 any oral irritation caused by the use of smokeless tobacco, including 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. Further, regenerative cell division, which occurs in the repair processes that arise in respiratory tissues following multiple, daily cytotoxic insults that accompany cigarette smoking, inflicts a potent tumor-promoting effect on nascent tumors induced by these carcinogenic smoke constituents.

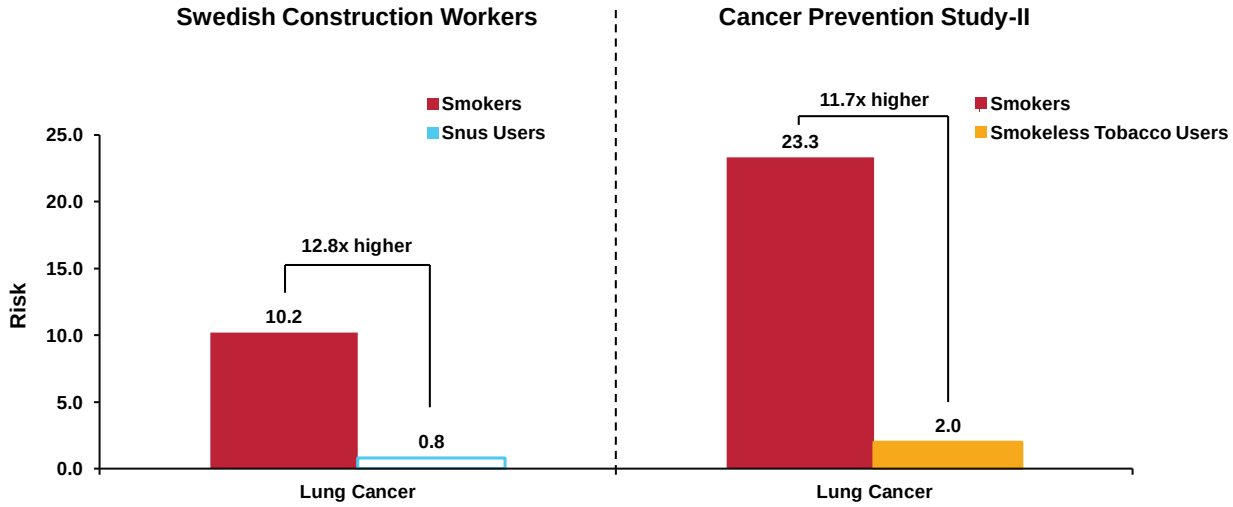
Compared with never users of tobacco, mortality risk estimates for lung cancer are approximately 23-times higher for cigarette smokers (USDHHS 2014; Figure 3-1; Figure 3-2). Some studies conducted in the U.S. suggest a possible association between lung cancer and smokeless tobacco use (e.g., Accortt et al. 2005; Henley et al. 2005), but are limited by methodological weaknesses, including potential inadequate exposure assessments and potential residual confounding due to smoking (e.g., Foulds and Ramström, 2006).

There is no evidence of an association of snus use with lung cancer based on the studies in Sweden and Norway (e.g., Figure 3-2). Two meta-analyses of combined U.S. and Scandinavian studies found no meaningful elevation in lung cancer risk among smokeless tobacco and snus users relative to never users, e.g., 0.96 (95% CI: 0.73-1.27) [eight risk estimates: Accortt et al. 2005; Boffetta et al. 2005; Doll and Hill 1952; Henley et al. 2005 (CPS-I and CPS-II); Luo et al. 2007; Williams and Horm 1977; Wynder and Stellman] and 1.2 (95% CI: 0.7-1.9) [four risk estimates: Boffetta et al. 2005; Henley et al. 2005 (CPS-I and CPS-II); Luo et al. 2007], respectively (Lee and Hamling 2009a; Boffetta et al. 2008). (See MRTPA Section 6.1.1.3.1.) Regardless, the evidence clearly demonstrates the risks of lung cancer for smokeless tobacco users are substantially reduced relative to cigarette smokers. An expert panel, reviewing similar studies (MRTPA Section 6.1.1.3.1), reported a 97% reduction in the risk of lung cancer from snus use compared with cigarette smoking (Levy et al. 2004).

FDA has previously reviewed the epidemiological data on snus and concluded that “there is no evidence of an association between snus and lung cancer” (FDA Briefing Document for 4-9-2015 SMNA TPSAC meeting; p. 25). And FDA’s Technical Project Lead (TPL) Review of the Swedish Match North America MRTPA 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 present analysis concurs with these prior FDA evaluations in concluding that there is little to no evidence that lung cancer risk is associated with snus use based on Scandinavian studies.

In any case, the key issue of the proposed modified risk statement for Camel Snus is the risk relative to smoking, not the absolute risk. The risks for lung cancer are much lower for smokeless tobacco users (as well as for switchers from cigarettes to smokeless tobacco) than for cigarette smokers (Figure 3-1; Figure 3-2). Therefore, switching from cigarette smoking to Camel Snus use will greatly and significantly reduce the risk of lung cancer.

Figure 3-2: U.S. and Swedish Epidemiology Data are Consistent: Lung Cancer



Henley et al. 2005; Luo et al. 2007; USDHHS 2014
Solid bars = statistically significantly different versus never users of tobacco
Open bars = not statistically significantly different versus never users of tobacco

3.1.2 Oral cancer

Consumers naturally associate oral tobacco use with oral cancer (Pepper et al. 2015), but may fail to appreciate the oral cancer risks associated with smoking, which exposes the oral cavity to the many carcinogens created by combustion. Numerous epidemiological studies provide clear and consistent evidence that cigarette smoking significantly increases both incidence of and mortality from cancers of the oral cavity. The average risk for male smokers is approximately 10-fold higher than lifetime nonsmokers (USDHHS 2014), although both higher and lower estimates of risk have been reported.

In contrast, and contrary to consumers' intuitions, the epidemiological data for U.S. populations have indicated inconsistent associations between smokeless tobacco use and oral cancer (*see* MRTPA Section 6.1.1.3.4). While older U.S. case-control studies, dating back to the 1970s, suggest an association between smokeless tobacco use and oral cancer relative to never users of tobacco, these older studies address the risk of different, higher-toxicant tobaccos, and suffer methodological limitations. Further, it is reasonable to anticipate that some level of residual risk persists from prior smoking in these studies.

Most studies in the last two decades, especially those that appropriately control for confounders (i.e., cigarette smoking and alcohol consumption), do not find statistically significant associations (*see* MRTPA Section 2.8.2.2 and MRTPA Section 6.1.1.3.4). This is demonstrated in meta-analyses.

No meaningful increase in oral cancer risk was observed in a meta-analysis restricted to U.S. studies that appropriately controlled for alcohol use and cigarette smoking, i.e., 1.04; (95% CI: 0.80-1.35) [six risk estimates: Henley et al. 2005 (CPS-I and CPS-II); Mashberg et al. 1993; Perry et al. 1993; Schwartz et al. 1998; Sterling et al. 1992] (Lee and Hamling 2009a). A previous meta-analysis reported an oral cancer risk estimate based on U.S. studies of 2.6 (95% CI: 1.3-5.2) [eight risk estimates: Blot et al. 1988; Brown et al. 1988; Henley et al. 2005 (CPS-I and CPS-II); Kabat et al. 1994; Mashberg et al. 1993; Stockwell et al. 1986; Winn et al. 1981]; however, this analysis was not restricted to those studies that controlled for alcohol use and cigarette smoking (Boffetta et al. 2008). Nonetheless, it is clear that the risk for oral cancer associated with smokeless tobacco use is much lower than for cigarette smoking.

Studies of snus users from Sweden and Norway generally do not indicate an increased risk of oral cancer for snus users relative to never tobacco users (*see* MRTPA Section 6.1.1.3.4). A meta-analysis of the studies from Sweden and Norway, appropriately controlling for alcohol use and cigarette smoking, similarly did not find a meaningful increase in risk of oral cancer, i.e., 1.10 (95% CI: 0.64-1.90) [four risk estimates: Boffetta et al. 2005; Lewin et al. 1998; Luo et al. 2007; Schildt et al. 1998] (Lee and Hamling 2009a). The meta-analysis conducted by Boffetta et al. (2008), similarly reported no increased risk of oral cancer with the same four studies. Including all U.S. and Swedish studies that controlled for alcohol use and cigarette smoking in the meta-analysis, the resulting risk estimate for oral cancer was 1.07 (95% CI: 0.84-1.37) [ten risk estimates: Henley et al. 2005 (CPS-I and CPS-II); Lewin et al. 1998; Mashberg et al. 1993; Perry et al. 1993; Roosaar et al. 2008; Rosenquist et al. 2005; Schildt et al. 1998; Schwartz et al. 1998; Sterling et al. 1992] (Lee and Hamling 2009a).

The body of evidence clearly demonstrates smokeless tobacco use confers much less risk of oral cancer than cigarette smoking, which is the key question, given the proposed modified risk claim emphasizing relative risk compared to cigarette smoking. Moreover, the Surgeon General has stated that the risks for oral cancer associated with smokeless tobacco use are lower than those associated with cigarette smoking (USDHHS 2014, p. 116).

Data representative of the body of epidemiological evidence comparing oral cancer mortality risks from cigarette smoking and smokeless tobacco use are presented in Figure 3-3 (i.e., data from CPS-II; Figure 3-1). Data for switchers are not available from CPS-II; however, data for switchers from Sweden are available (Schildt et al. 1998; Figure 3-4). These data clearly demonstrate reduced risk following switching from cigarette smoking to snus use.

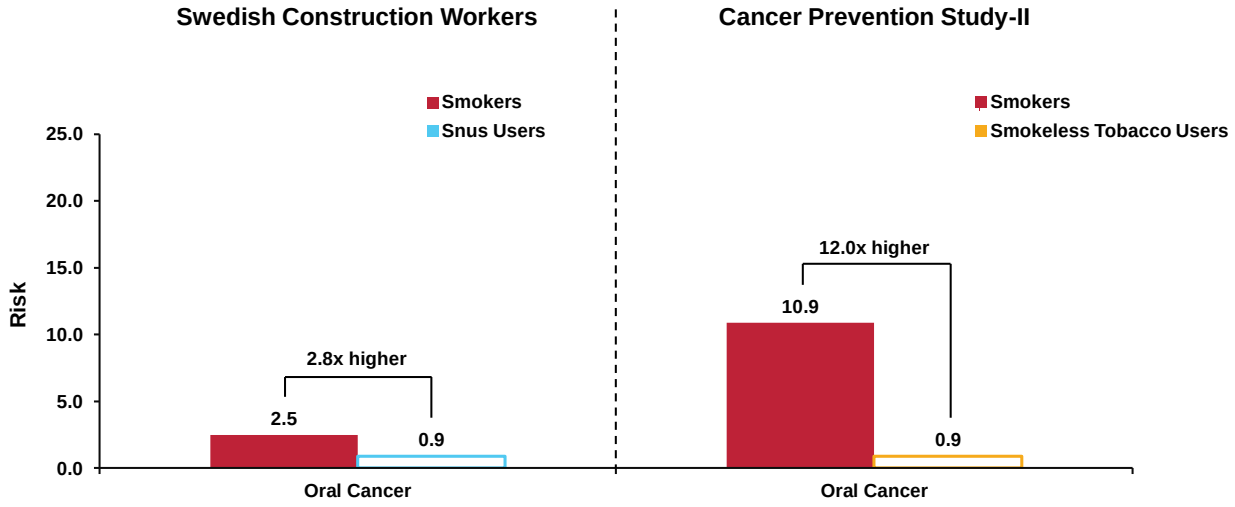
Figure 3-3, including further representative data from the Swedish Construction Workers Cohort, also demonstrates significant risk differentials in incident oral cancer risk between cigarette smoking and snus use, further confirming that snus presents substantially lower risk than cigarettes (Luo et al. 2007).

The epidemiological data clearly demonstrate that risks for oral cancer are consistently lower for smokeless tobacco and snus users than for cigarette smokers (Figure 3-1; Figure 3-3; Figure 3-4). (See MRTPA Section 6.1.1.3.4.) An expert panel reviewing similar studies reported a 79-

84% reduction in risk of oral cancer from snus use compared with cigarette smoking (Levy et al. 2004).

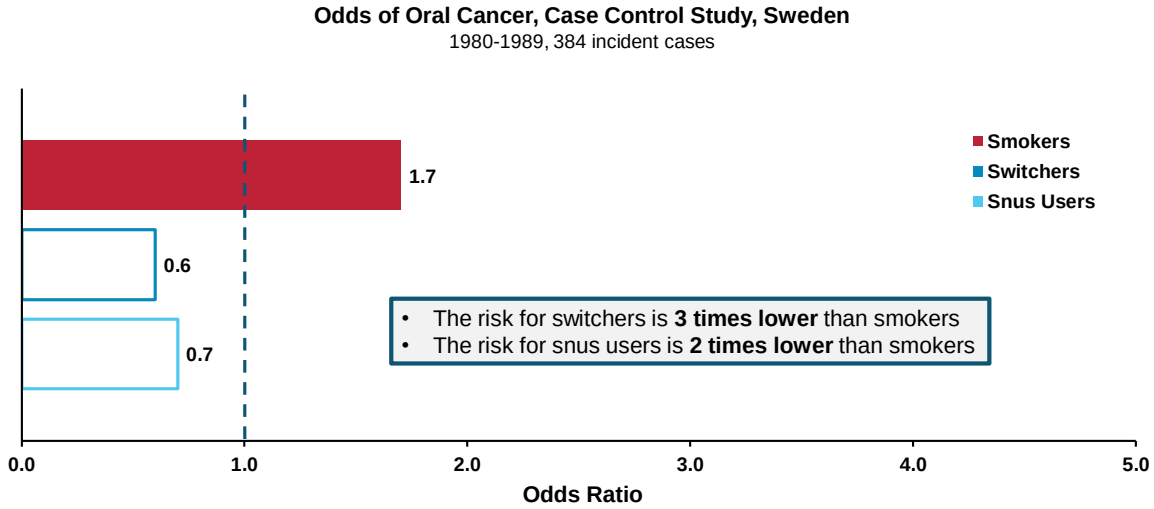
Therefore, based on the clear and consistent large body of epidemiological evidence, switching from cigarette smoking to Camel Snus use will greatly and significantly reduce the risk of oral cancer.

Figure 3-3: U.S. and Swedish Epidemiology Data are Consistent: Oral Cancer



Henley et al. 2005; Luo et al. 2007; USDHHS 2014
Solid bars = statistically significantly different versus never users of tobacco
Open bars = not statistically significantly different versus never users of tobacco

Figure 3-4: Swedish Epidemiology Data Confirm Substantial Reduction in Risk for Oral Cancer among Switchers



Schildt et al. 1998
Solid bars = statistically significantly different versus never users of tobacco
Open bars = not statistically significantly different versus never users of tobacco

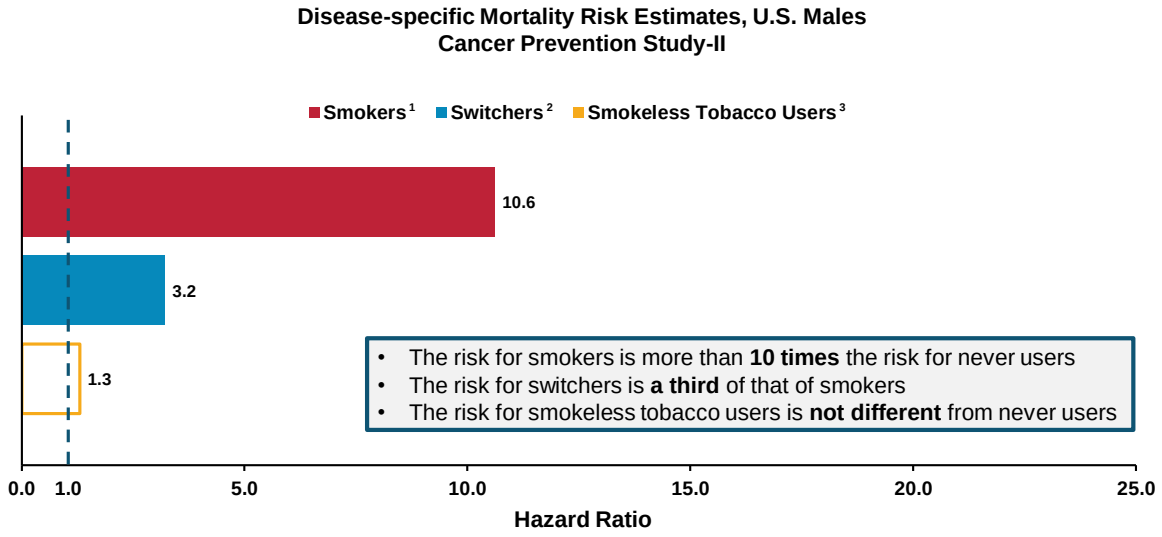
3.1.3 Respiratory disease

As with lung cancer, epidemiological studies confirm that cigarette smoking is overwhelmingly the strongest risk factor for respiratory disease; mortality risk for chronic obstructive pulmonary disease among cigarette smokers is more than 10-times that of never smokers (USDHHS 2014). In contrast, there has been no clear demonstration of an increased risk for respiratory disease among U.S. or Swedish users of smokeless tobacco or snus. Data, representative of the large body of epidemiological evidence confirming this fact, are presented in Figure 3-5 and Figure 3-1 (USDHHS 2014; Henley et al. 2005) (*see* MRTPA Section 6.1.1.3.2). Further, CPS-II data specifically show that switching from cigarette smoking to smokeless tobacco use markedly decreases the risk of COPD mortality, compared to cigarette smoking (Henley et al. 2007).

FDA's Technical Project Lead (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 smokeless tobacco products, none have been linked to the development of chronic lung disease unless inhaled (SMNA MRTPA TPL Review, p. 50). Because smokeless tobacco does not contain combustion-related toxicants, and avoids any inhalation route of exposure, snus is much less likely to be a significant risk factor for COPD or other respiratory diseases (SMNA MRTPA TPL Review, p. 51). (See MRTPA Section 6.1.1.3.2.)

Therefore, the use of smokeless tobacco or snus poses a far lesser risk for respiratory disease than smoking, and switching from cigarettes to smokeless tobacco use reduces the risk for respiratory disease. Consequently, switching from cigarette smoking to Camel Snus use will reduce the risk of respiratory disease.

Figure 3-5: U.S. Epidemiology Data Confirms Substantial Reduction in Risk for Respiratory Disease



[1]USDHHS 2014; [2]Henley et al. 2007; [3]Henley et al. 2005
Solid bars = statistically significantly different versus never users of tobacco
Open bars = not statistically significantly different versus never users of tobacco

3.1.4 Heart disease

The epidemiological evidence for a positive association between smoking and risk of coronary heart disease (CHD) is clear and consistent, with an approximate two to three-fold risk of CHD/ischemic heart disease (IHD) incidence and mortality for current smokers compared to never tobacco users (USDHHS 2014). Notably, the relative risks for heart disease among cigarette smokers are comparatively lower than those associated with the other noted disease outcomes, because of the numerous additional risk factors associated with this disease.

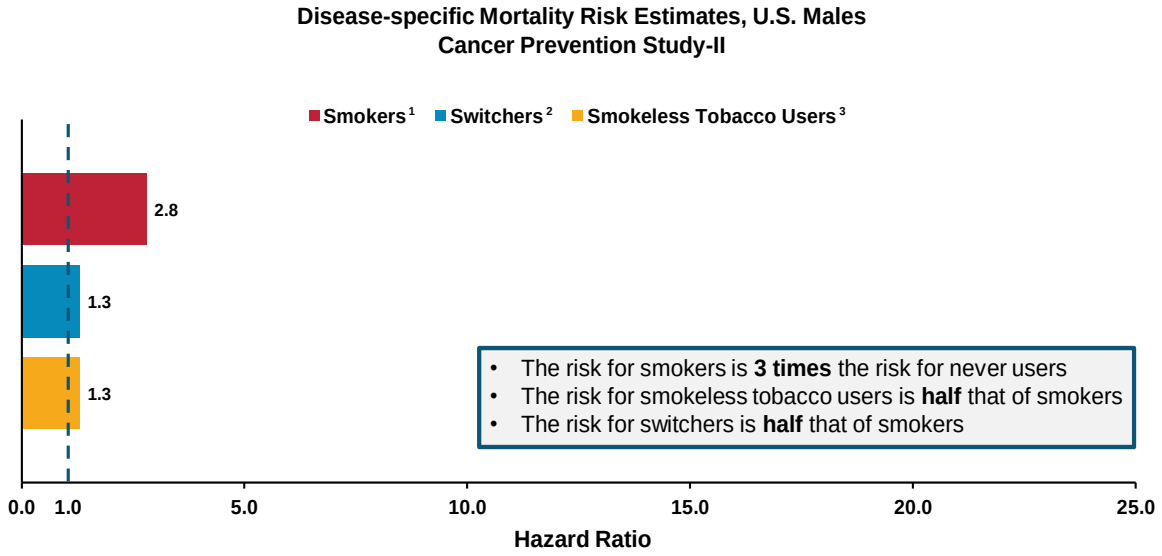
Based on the epidemiological data from the U.S. and Sweden, there is evidence of a marginal increase in heart disease (mortality and incidence) associated with smokeless tobacco use compared with never tobacco use, although the evidence is inconsistent – some studies show an association and some studies do not (*see* MRTPA Section 6.1.1.3.3).

However, it is clear that even if the use of smokeless tobacco, including snus, confers increased risk of heart disease relative to never tobacco use, that risk is lower than the risk from cigarette smoking (*see* MRTPA Section 6.1.1.3.3). An expert panel, reviewing similar studies (MRTPA Section 6.1.1.3.1), reported an 89% reduction in risk of heart disease from snus use compared with cigarette smoking (Levy et al. 2004). In addition, in a policy statement from the American Heart Association it was noted that although "smokeless tobacco products are not without harm…[c]ompared with cigarette smoking, the CV [cardiovascular] risk associated with ST use is markedly lower" (Piano 2010).

Data, representative of the body of epidemiological evidence (i.e., CPS-II; Figure 3-1; Figure 3-6), demonstrate the substantial risk differential between smokeless tobacco users and cigarette smokers for heart disease, with smokeless tobacco users having much less risk. Further, CPS-II data specifically show that switching from cigarette smoking to smokeless tobacco use markedly decreases the risk of heart disease mortality, compared to smoking.

Thus, the epidemiological evidence confirms that switching from cigarette smoking to Camel Snus use will greatly and significantly reduce the risk of heart disease.

Figure 3-6: U.S. Epidemiology Data Confirms Substantial Reduction in Risk for Heart Disease



[1]USDHHS 2014; [2]Henley et al. 2007; [3]Henley et al. 2005
Solid bars = statistically significantly different versus never users of tobacco

3.1.5 Summary of support for the proposed modified risk information

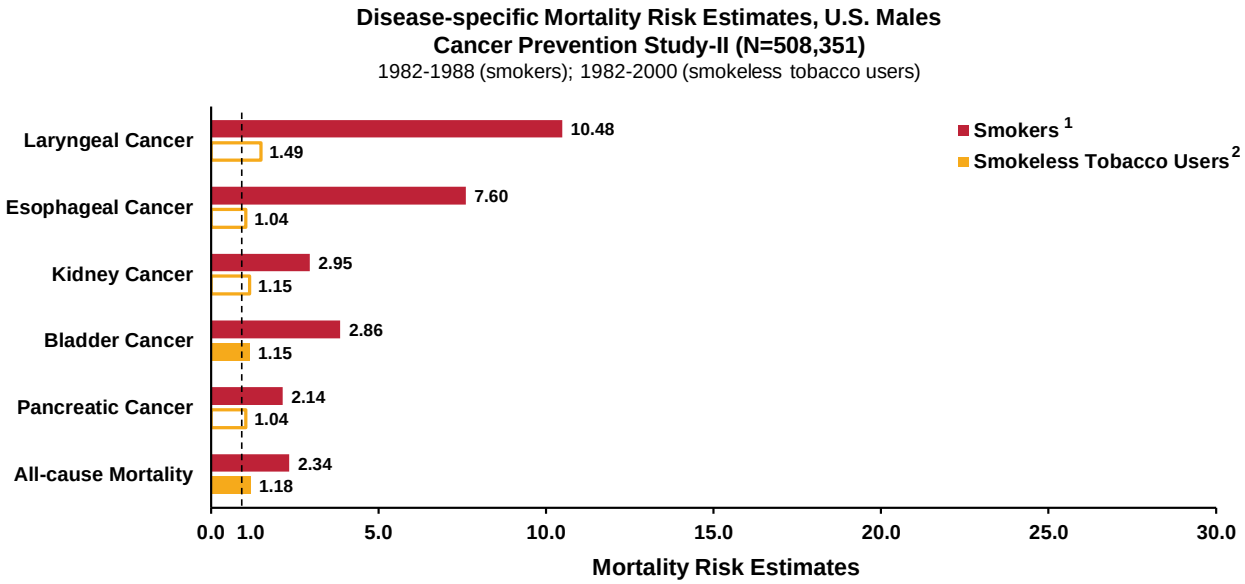
In summary, a substantial body of epidemiological evidence clearly and consistently confirms that the risks for lung cancer, oral cancer, respiratory disease, and heart disease are lower for users of smokeless tobacco, including snus, compared with cigarette smokers. Further, the evidence indicates that switching from cigarette smoking to smokeless tobacco use is also associated with reductions in risk for all four diseases, supporting scientifically the modified risk statements proposed under these Applications.

3.1.6 Other smoking related diseases

Reductions in risk for smokeless tobacco and snus users relative to cigarette smokers are not limited to the diseases of lung cancer, oral cancer, respiratory disease, and heart disease in the proposed modified risk advertising. Figure 3-7 illustrates that use of smokeless tobacco carries less risk than cigarette smoking for other major tobacco-related cancers, and for all-cause

mortality. It shows mortality risk estimates based on the American Cancer Society's CPS-II cohort.

Figure 3-7: U.S. Epidemiology Data Confirm Substantial Reductions in Risks for Other Diseases



[1]USDHHS 1989 (relative risk estimates)
[2]Henley et al. 2005 (hazard ratios)
Solid bars = significant difference versus never users of tobacco
Open bars = no significant difference versus never users of tobacco

The data presented in Figure 3-7, and in numerous cited studies, reviews, and meta-analyses in the Applications (*see* MRTPA Section 6.1.1.4), confirm that use of smokeless tobacco products, including snus, presents a far lower overall health risk to the individual user than cigarette smoking.

In total, these data show reductions in risk for diseases that are not part of the proposed modified risk statements. This means that reductions in risk for the claimed diseases (lung cancer, oral cancer, respiratory disease, and heart disease) are not offset by consideration of other diseases. There are reductions in all-cause mortality, and other outcomes, for smokeless tobacco use compared to cigarette smoking.

3.1.7 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 women, pregnant women, adolescents, and various racial and 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.

An examination of the available literature reveals 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 different population subgroups can thus be largely, if not totally, explained by differences in smoking patterns and individual behaviors.

Smokeless tobacco use also varies considerably across various groups, with smokeless tobacco use prevalence determined by the same numerous and complex factors, although not with the same distribution profile.

There is no evidence that smokeless tobacco use presents unique risks to adolescents, women, and members of various racial and ethnic subpopulations. Further, there is no plausible biological rationale to expect differences in risks among individuals who use smokeless tobacco products comparably, although data are limited and somewhat indirect (*see* SMNA MRTPA TPL Review, p. 37). Thus, the risks to health reported in epidemiological studies of more diverse populations, although largely composed of male smokeless tobacco users, should be generally applicable to all groups of users.

Pregnant women should never use any tobacco products, as is emphasized in the "No Tobacco Product is Safe" section of the proposed modified risk advertisements (specifically "Minors and pregnant women should never use any tobacco product"). A number of adverse health outcomes associated with smokeless tobacco use among pregnant women have been described. Pre-eclampsia is a singular exception because its risk is lower with increased smoking; the risk of pre-eclampsia is the same for smokeless tobacco users as it is for women who do not use tobacco. Outside this exception, the number and severity of the other adverse effects on pregnancy are lower or possibly the same with smokeless tobacco use and cigarette smoking (*see* MRTPA Section 2.9.1.1.3 and MRTPA Section 6.1.1.3).

3.1.8 Dual use of cigarettes and smokeless tobacco is not associated with unique or increased disease risks, but reflects the risks associated with cigarette smoking alone

RJRT's proposed modified risk advertising emphasizes that current smokers should switch completely from cigarette smoking to using Camel Snus in order to reduce their risk of lung cancer, oral cancer, respiratory disease, and heart disease. However, there may be a period during which smokers may engage in dual use of cigarettes and Camel Snus.

The possibility of unique, or increased, risk for diseases among dual users has been considered in two recent reviews. The first, which considered 17 separate studies addressing dual use (Frost-Pineda et al. 2010), concluded that the evidence is sufficient and clear that there are no unique health risks (either in the kinds of risks or the magnitude of risk) associated with dual

use of cigarettes and smokeless tobacco products, which are not anticipated or observed from exclusive use of one of the products used on its own.

The second study, a systematic review that identified 51 separate relative risk estimates from studies conducted in Sweden and Norway, likewise found no evidence of any special or increased risk from dual use (Lee 2014), with the exception of risk for gestational hypertension (pre-eclampsia), which is, paradoxically, reduced in exclusive smokers, as discussed above (*see* MRTPA Section 6.1.1.8).

3.2 Epidemiological Studies of U.S. and Swedish Smokeless Tobacco Users are Appropriate for Estimating Disease Risks to Individual Users of Camel Snus

Epidemiological studies are based on historical tobacco products as a category and are not specific to any particular tobacco product or brand. Thus, the epidemiological data are focused on the use of smokeless tobacco, generally, rather than Camel Snus specifically. Nevertheless, the epidemiological data apply to Camel Snus, and are valid for estimating the risks associated with Camel Snus compared to cigarette smoking.

FDA has recognized this issue, noting 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" (FDA 2014). FDA provided explicitly for use of more general epidemiological evidence, asking that "in applying this evidence to support an MRTPA for a specific product," the applicant "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). On that basis, the existing epidemiology clearly applies to Camel Snus.

Data from both the U.S. and Swedish epidemiological studies are relevant and central in estimating the anticipated health risks to individual cigarette smokers who switch to Camel Snus, as well as for comparison to health risks estimated for U.S. cigarette smokers. A key factor affecting the lower risk of smokeless tobacco use compared to cigarette smoking is the fact that the user of smokeless tobacco products is not inhaling combustion products, which are responsible for a large share of the health consequences of smoking (USDHHS 2010).

Further, among the range of smokeless tobacco products, the toxicant profile of Camel Snus is equal to, or more favorable than the profiles of smokeless tobacco and snus products whose effects are seen in the epidemiological data.

The health effects documented in the epidemiological data reflect exposures that occurred decades earlier. This is because of the long latency of tobacco-related diseases, i.e., disease occurs after many years of tobacco use. Thus, to understand the products that caused the outcomes documented in the epidemiology, one has to examine products in use decades earlier. As an example, the American Cancer Society's Cancer Prevention Studies (CPS-I and

CPS-II) recorded deaths occurring in 1972-2002. These deaths are attributable to tobacco use that may have occurred as far back as the early 20th century. Similarly, the Swedish epidemiological studies reflect smokeless tobacco usage as early as the mid-1930s.

Thus, evaluating the applicability of these epidemiological findings requires comparing the toxicant profile of Camel Snus to the products in use decades ago. Such analyses show that the historical smokeless tobaccos, which are the subject of the U.S. and Swedish epidemiology, contained higher levels of toxicants, including TSNAs, than current smokeless tobaccos, especially Camel Snus.

In fact, Camel Snus is lower in toxicant content even compared to many other smokeless tobacco products currently used in the U.S. (e.g., Borgida et al. 2015; *see* MRTPA Section 6.1.5) and comparable to the snus currently used in Sweden.

Another factor in evaluating the health effects of tobacco products is usage patterns, which affects the extent of toxicant exposure (*see* MRTPA Section 2.8.2.5 and MRTPA 2.8.3.5). Data indicate that the usage patterns displayed by Camel Snus users results in lower exposures (i.e., smaller amounts used, fewer usage occasions, shorter exposure times) than historical smokeless tobacco use, further reinforcing that the observed health effects of smokeless tobacco products reflected in the epidemiology studies may overstate – and certainly do not understate – the risks of Camel Snus.

Thus, the epidemiological evidence supports the conclusion that smokers who switch completely to Camel Snus will reduce their risk for lung cancer, oral cancer, respiratory disease, and heart disease.

3.2.1 Smokeless tobacco products in U.S. epidemiology studies had higher toxicant levels than Camel Snus

It is possible that data from the U.S. are more relevant than data from Sweden when determining the epidemiological relevance to Camel Snus, as such data incorporate the characteristics of U.S. tobacco consumers and their product usage patterns.

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. TSNAs, particularly NNN (*N*'-nitrosonornicotine) and NNK (4-(methynitrosamino)-1-(3-pyridyl)-1-butanone), were initially the only recognized carcinogens in smokeless tobacco; they are included on FDA's list of harmful and potentially harmful constituents (HPHCs), and have been designated by the International Agency on Research for Cancer (IARC) as carcinogenic to humans. NAB (*N*'-nitrosoanabasine) and NAT (*N*'-nitrosoanatabine) are additional TSNAs, though their health relevance is unknown.

Beginning in about 1980, and continuing for at least a decade, substantial reductions in the levels of TSNAs in U.S. smokeless tobacco products were achieved. Data from Djordjevic et al. 1993 for two "leading U.S. snuff brands," which 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 two major brands (Figure 3-8; Figure 3-3). 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. 2007). Thus, TSNA levels in current smokeless tobaccos are lower than those seen in the smokeless tobacco products that are evaluated in the epidemiology (*see* MRTPA Section 2.8.2.3).

Table 3-1: TSNAs in two leading U.S. snuff brands, 1980-1992 (from Djordjevic et al. **1993, p. 499)**

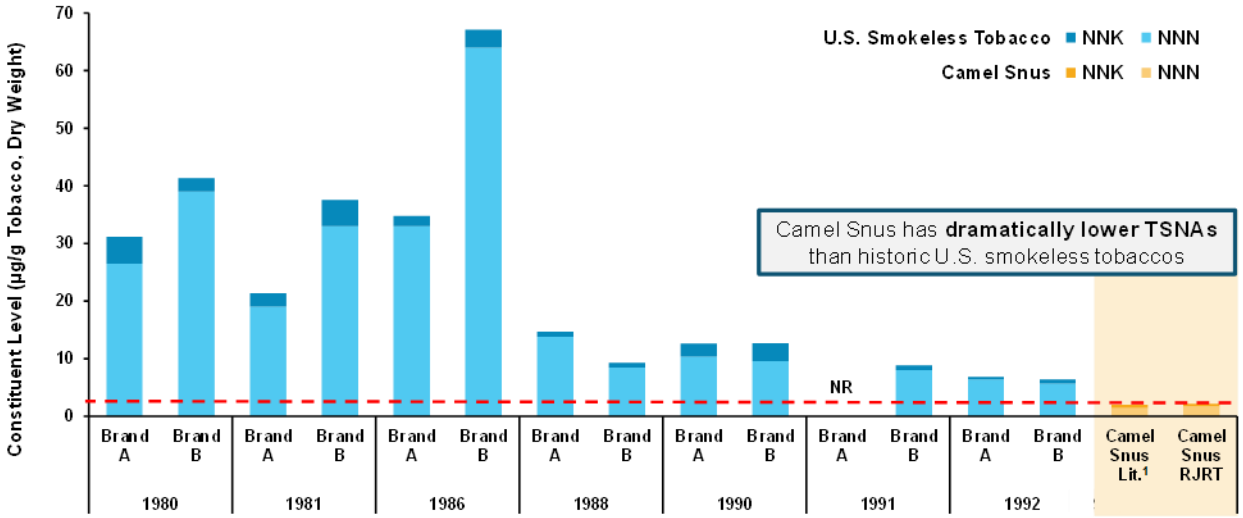
Brand	Year	Tobacco-specific *N*-nitrosamines (μg/g)			Nicotine (%)
		NNN	NNK	NAT*	
USA (Brand A)	1980	26.5	4.65	22.7	2.34
	1981	19.0	2.4	19.8	2.20
	1986	33.0	1.8	44.0	2.07
	1988	13.8	0.93	10.2	1.99
	1990	10.4	2.20	9.8	2.04
	1992	6.4	0.50	3.6	1.71
Reduction 1980-92 (%)		75.8	89.0	84.1	
USA (Brand B)	1980	39.0	2.4	44.0	2.4
	1981	33.0	4.6	41.9	2.7
	1986	64.0	3.1	215	3.1
	1988	8.5	0.76	7.8	2.6
	1990	9.6	3.1	7.9	2.2
	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.

Moreover, Camel Snus, in fact, has lower levels of TSNAs than the reduced levels found in other more contemporary smokeless tobacco products, as seen in Figure 3-8 (data from e.g., Hatsukami et al. 2007b; Stepanov et al. 2008; Borgerding et al. 2012 and internal RJRT studies [*see* MRTPA Section 6.1.5]).

These data, when compared with historical data and displayed in Figure 3-8, illustrate the substantially lower levels of NNN and NNK in Camel Snus compared with historical smokeless tobacco products. This is also true for other contemporary smokeless tobacco products (*see* MRTPA Section 6.1.5.3.1, Table 6.1.5-8 and Table 6.1.5-9).

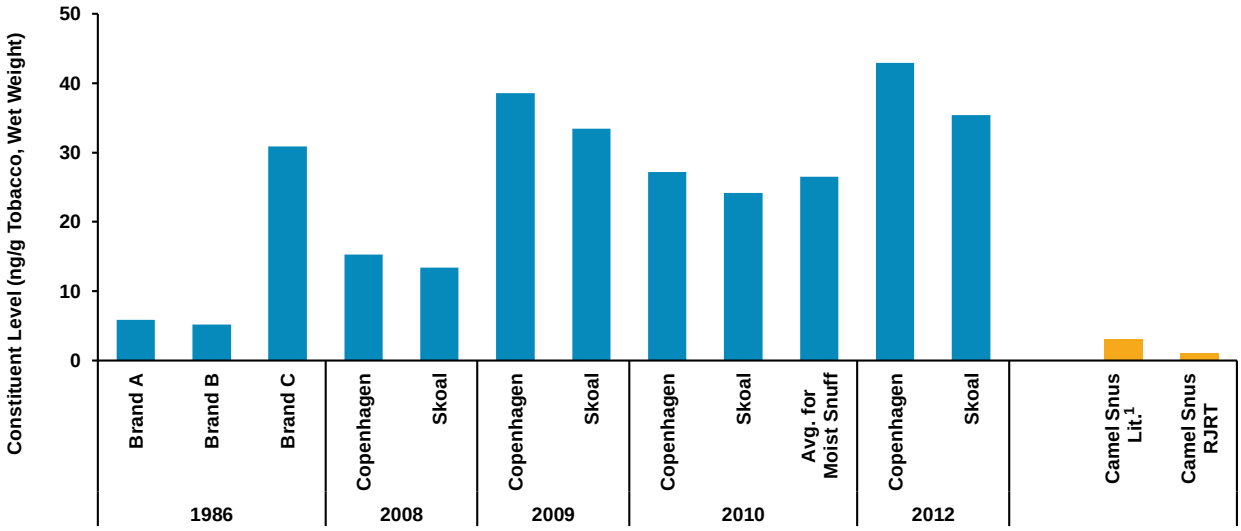
Figure 3-8: Camel Snus Has Lower Tobacco Specific Nitrosamines than U.S. Smokeless Tobacco Products Used in Epidemiology Studies



[1] Camel Snus Lit.: Hatsukami et al. 2015, 2017; Hecht et al. 2011; Lawler et al. 2013; Song et al. 2016, Stepanov et al. 2008, 2012, 2013, 2014; and others (mean of published values for Camel Snus brand styles – *see* MRTPA Table 6.1.5-7); Camel Snus RJRT: mean of values for all Camel Snus brand styles determined by internal RJRT studies – *see* MRTPA Table 6.1.5-15. Camel Snus values reported on an "as-is" basis were converted to dry weight based on 32% moisture content. U.S. smokeless data from Djordjevic et al. 1993; NR: not reported

Historical levels of other smokeless tobacco toxicants have also been reported (Hoffmann et al. 1986; Stepanov et al. 2008; Stepanov et al. 2010; Borgerding et al. 2012; Rickert et al. 2009). Benzo[a]pyrene (B[a]P) is the only PAH in tobacco products designated by IARC as carcinogenic to humans, and has been found to be a reliable marker of other PAHs in smokeless tobacco (McAdam et al. 2013). As seen in Figure 3-9, Camel Snus has substantially lower levels of B[a]P than historical, and contemporary, U.S. smokeless tobacco products (*see* MRTPA Section 2.8.2.3).

Figure 3-9: Camel Snus Has Lower B[a]P Levels than Smokeless Tobacco Products Used in U.S. Epidemiological Studies



1986 values (Brand A, B, C) from Hoffmann et al. 1986; 2008 values from Stepanov et al. 2008; 2009 values from Rickert et al. 2009; 2010 values from Stepanov et al. 2010; 2012 values from Borgerding et al. 2012. Published B[a]P values converted from dry weight to wet weight using moisture values reported in the publication.

[1]Camel Snus Published Literature: Borgerding et al. 2012; Caraway and Chen 2013; McAdam et al. 2015b; Moldoveanu and Gerardi 2013; Song et al. 2016; Stepanov et al. 2008, 2010; mean of published values for Camel Snus brand styles; *see* MRTPA Table 6.1.5-7.

Camel Snus RJRT: mean of values for all Camel Snus brand styles determined by internal RJRT studies; *see* MRTPA Table 6.1.5-15.

Levels of other smokeless tobacco HPHCs (e.g., formaldehyde, acetaldehyde, crotonaldehyde, arsenic), required by FDA for reporting in smokeless tobacco 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. 2008; Borgerding et al. 2012). (See MRTPA Section 2.8.2.3)

In summary, documented levels of NNN, NNK, B[a]P, and other toxicants (e.g., acetaldehyde, crotonaldehyde, formaldehyde, and cadmium) 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, but at reduced levels. And Camel Snus displays lower levels of toxicants even compared to other contemporary smokeless tobacco products (*see* MRTPA Section 2.8.2.3).

Thus, U.S. epidemiological studies are relevant to evaluating the risks of Camel Snus compared to smoking, and show that Camel Snus use presents lower risk for lung cancer, oral cancer, respiratory disease, and heart disease than cigarette smoking.

3.2.2 Historical usage patterns of smokeless tobacco products suggest higher levels of toxicant exposures compared to contemporary products, including Camel Snus

In considering how the risk of Camel Snus use relates to that of smokeless tobacco products used during the time period evaluated in historical epidemiology studies, it is also relevant to consider whether the extent of individuals' usage of the respective products is different, since an individual's usage pattern affects exposure to toxicants.

Although detailed information on product usage patterns from individual epidemiological studies is generally not available, there is scientific literature that describes typical tobacco use behaviors for 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.

Data are also available on usage patterns for Camel Snus, and specifically for the styles included in the Applications. Taken as a whole, the comparative data (*see* Table 3-2) show that usage of Camel Snus (e.g., amount of tobacco, duration of exposure) is generally less than that seen for historical products (*see* MRTPA Section 2.8.2.5).

Table 3-2: Consumption of Camel Snus is Generally Less than Historical Consumption of U.S. Smokeless Tobacco Products

Consumption Metric	Camel Snus (Exclusive Use)	Historical U.S. Smokeless Tobacco Products
Average amount used/day	3 – 5 g[8]	7 – 20 g[1,4,5]
Average portion size	0.6 – 1 g (1 pouch)[8]	~2 g (a "pinch")[1]
Average # of uses/day	4 – 6 pouches[8]	6 – 7 dips[1,2,3]
Average duration/use	~30 min[6]	~40 – ~70 min[1,2,3]
Average total time of use/day	84 – 150 min[6]	53 – 423 min[1,3,4,5,7]

[1]Hatsukami et al. 1988; [2]Hatsukami et al. 1991; [3]Lemmonds et al. 2005; [4]Glover et al. 1981; [5]IARC 1985; [6]Caraway and Chen 2013; [7]Greer and Poulson 1983; [8]RJRT internal studies

RJRT has also conducted studies of Camel Snus use behaviors using survey data from the RAIS National Tobacco Behavior Monitor (NTBM), which was confirmed by RJRT's Consumer Brand Tracker and, in some instances, by the NIH/FDA-sponsored Population Assessment of Tobacco and Health (PATH) study (*see* MRTPA Section 3.5). These studies show that exclusive Camel

Snus users use smaller portions, fewer times per day, for shorter periods, compared to historical patterns of U.S. smokeless tobacco use.

In summary, overall comparisons of usage behaviors between exclusive Camel Snus users and users of other smokeless tobacco products that are represented in U.S. epidemiological studies indicate usage patterns that would result in generally lower levels of toxicant exposure among exclusive Camel Snus users.

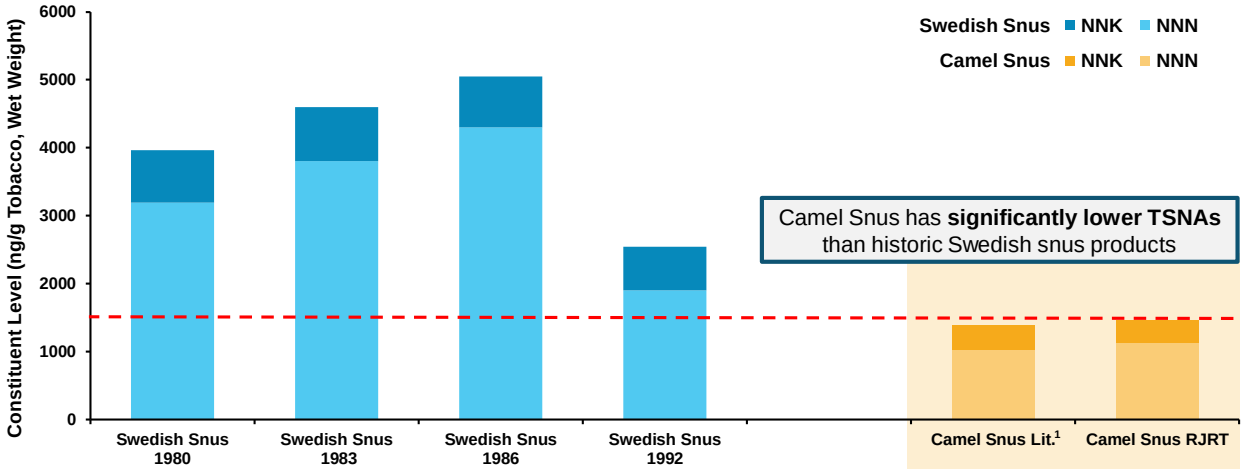
3.2.3 Snus products in Swedish epidemiology studies had higher toxicant levels than Camel Snus

As detailed in MRTPA Section 3.1, Camel Snus is Swedish snus. While it is recognized that the U.S. and Swedish populations are not identical, the Swedish epidemiology is nevertheless highly relevant because it includes the same product type and demonstrates consistency with the U.S. epidemiology. Further, just as in the U.S., the toxicant profiles of the products that were the subject of the Swedish epidemiology contained higher toxicant levels than Camel Snus, and the usage patterns (quantity, duration) were greater than are seen with Camel Snus (*see* MRTPA Section 2.8.3.5).

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 (MRTPA Section 6.1.1). Just as in the U.S., TSNA levels in Swedish snus decreased in the 1980s (Österdahl et al. 2004). Österdahl and colleagues 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%.

Comparison of TSNA levels in Swedish snus products since 1980 shows that levels of these toxicants found in Camel Snus are similar to other snus products today (*see* MRTPA Section 6.1.5.3.1 Table 6.1.5-8 and Table 6.1.5-9) and lower than toxicant levels in historical snus products, whose effects are reflected in the Swedish epidemiology. (See Figure 3-10.)

Figure 3-10: Camel Snus Has Lower Tobacco Specific Nitrosamines than Swedish Snus Products Used in Epidemiology Studies

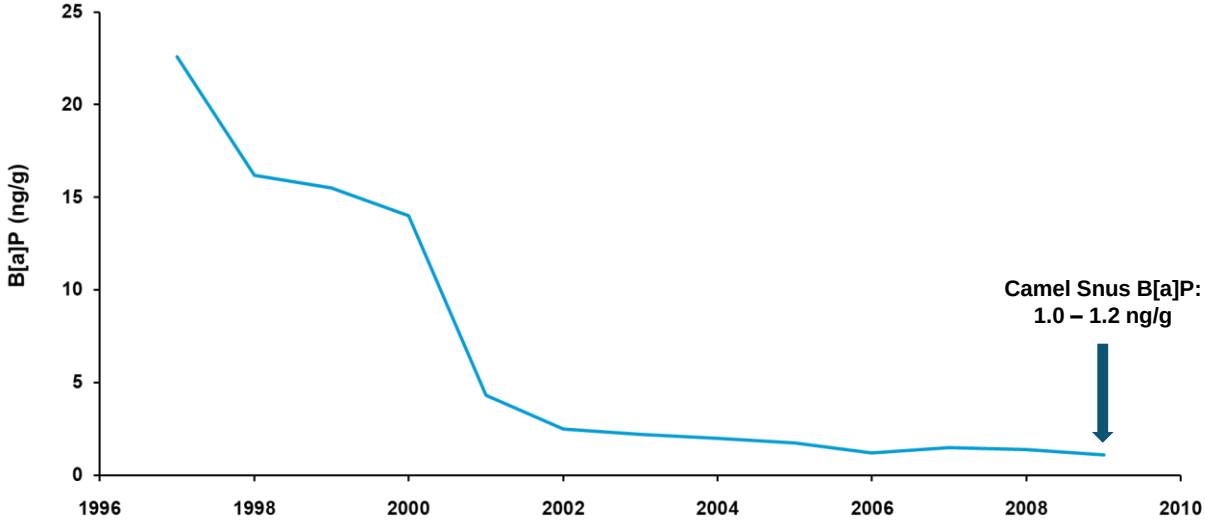


[1]Camel Snus Published Literature: Hatsukami et al. 2015, 2017; Hecht et al. 2011; Lawler et al. 2013; Song et al. 2016, Stepanov et al. 2008, 2012, 2013, 2014, and others; Camel Snus RJRT: mean of values for all Camel Snus brand styles determined by internal RJRT studies – *see* MRTPA Table 6.1.5-15.
Swedish Snus data from Österdahl et al. 2004.

There has also been a reduction in B[a]P in Swedish snus, due to changes in curing practices. 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 about 90% (Rutqvist et al. 2011; Figure 3-11).

Data for B[a]P are available since around 1997 (Figure 3-11); however, given this known phase-out of fire-cured tobaccos and concomitant reduction of B[a]P, it is reasonable to conclude that the products evaluated by the Swedish epidemiology contained higher levels of B[a]P, and likely higher levels of many other PAHs relative to today's Swedish snus (*see* MRTPA Section 2.8.3.3).

Figure 3-11: Camel Snus Has Lower B[a]P Levels than Swedish Snus Products Used in the Epidemiological Studies



3.2.4 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 snus products. The discussion presented above illustrates that the snus products represented in the published epidemiology of Swedish snus users are not that of a single, homogeneous product. Those historical snus products did not contain the much lower levels of toxicants found in contemporary Swedish-style snus products, including Camel Snus. Thus, just as in the U.S., the epidemiological data from Sweden apply to, and likely over-estimate, the risks of contemporary Swedish-style snus, including Camel Snus.

While there are differences between the U.S. and Sweden in cultures and populations, the countries are two Westernized nations, with similarities in socioeconomic and public health metrics. Thus, the Swedish epidemiology is relevant to the U.S.

Additionally, Swedish epidemiological data are relevant to U.S. users of Camel Snus given that:

- Camel Snus is designed, formulated, and manufactured in the same manner as other contemporary Swedish-style snus;
- The toxicant levels in Camel Snus are lower than historical Swedish products that are the subject of the epidemiological studies presented above;
- Usage of Camel Snus (*e.g.,* quantities and duration) is generally lower, compared to Swedish snus (MRTPA Section 2.8.3.5, Table 2.8.3-3); and
- Levels of toxicants are reduced for Camel Snus compared to snus products used by subjects participating in Swedish 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 substantially 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 confirm the conclusion that smokers who switch completely from cigarette smoking to Camel Snus will significantly reduce their risks for lung cancer, oral cancer, respiratory disease, and heart disease.

3.2.5 Summary of epidemiology

U.S. and Swedish epidemiological data are clear and consistent in showing that users of smokeless tobacco incur substantially lower risk than cigarette smokers for lung cancer, oral cancer, respiratory disease, and heart disease. This is substantiated by multiple studies in both countries. In both countries, the observed health effects of smokeless tobacco are attributable to historical smokeless tobaccos, which had higher levels of toxicants than contemporary smokeless tobacco products – and higher levels than Camel Snus. Thus, a large body of epidemiological evidence confirms that Camel Snus use confers less risk than cigarette smoking for lung cancer, oral cancer, respiratory disease, and heart disease, and that cigarette smokers who switch completely to Camel Snus can lower their risks for these diseases, as well as for all-cause mortality, and other diseases.

3.3 Clinical Studies

In contrast to epidemiological studies that provide results from years of product use and focus on disease and mortality as outcomes, clinical studies reflect data over a shorter time frame but enable direct comparisons of exposure between product types, such as Camel Snus and combustible cigarettes. 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), especially when considered alongside the epidemiological evidence presented in the MRTPAs.

RJRT sponsored eight clinical studies of Camel Snus, and several other researchers have also published clinical studies of Camel Snus. Study designs generally included:

1. Cross-sectional evaluation of non-users of tobacco or natural adopters of tobacco products, studying tobacco use under natural conditions; and

2. Randomized controlled trials of product switching (ambulatory and confined).

Depending upon the study design, subjects included natural adopters of various tobacco product types (e.g., exclusive Camel Snus users, exclusive smokers, dual users of Camel Snus and cigarettes, and non-users of tobacco) or included product switchers (e.g., smokers who were switched to Camel Snus use or a control group).

Study endpoints included biomarkers of exposure and effect, nicotine pharmacokinetic parameters, mouth-level exposure measures, tobacco product use metrics, and safety profiles. Biomarkers of exposure and effect relevant to tobacco use were assessed in biological matrices such as urine, blood, and expired breath.

Biomarkers of exposure measure actual exposure to constituents of tobacco or to constituents generated by combustion of tobacco (IOM 2012). In contrast, chemical analyses of products provide information about specific characteristics of a tobacco product, such as HPHC content, but cannot predict actual user exposure to constituents of tobacco (or tobacco smoke in the case of cigarettes). Many of the biomarkers employed measure exposure to HPHCs that have been designated as carcinogens, respiratory toxicants, and/or cardiovascular toxicants by FDA (77 Fed. Reg. 20,034).

Exposure to constituents from use of a tobacco product is the result of multiple factors, including whether or not the product is combusted, the manner of use (e.g., inhalation versus placement of tobacco in the mouth), product use behaviors (e.g., cigarette puffing behavior or time a smokeless tobacco is held in the mouth), and the chemical composition of the smoke or tobacco product.

The following sections summarize relevant information from the RJRT-sponsored clinical studies, as well as from the published literature, and provide useful information regarding exposure to constituents known to contribute to the risks of lung cancer, oral cancer, respiratory disease, and heart disease from Camel Snus use compared with cigarette smoking.

Further discussion of clinical studies that compared Camel Snus use and cigarette smoking is found in MRTPA Section 6.1.2 and supporting documents associated with that section.

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

The body of RJRT-sponsored and externally conducted and published clinical research specific to Camel Snus shows that, compared with cigarette smoking, exclusive Camel Snus use results in substantially reduced exposure to combustion-related toxicants (i.e., toxicants formed from burning tobacco during smoking) (Kotlyar et al. 2011, Blank and Eissenberg 2010, Hatsukami et al. 2016, Krautter et al. 2015, MRTPA Sections 2.9.1.2.1 and 2.9.1.2.2).

Two RJRT-sponsored clinical studies, one of individuals who had, on their own, adopted and used different types of tobacco products ("natural adopters"), including Camel Snus (CSD0904) and another of smokers switched from their usual brand of cigarette to Camel Snus or smoking abstinence (CSD0901), as well as a published study of smokers switched to Camel Snus (Kotlyar et al. 2011), compared levels of combustion-related toxicant biomarkers in exclusive users of Camel Snus and exclusive cigarette smokers.

All the studies, 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 (VOCs), and the PAHs phenanthrene and fluorene. A full list of combustion-related toxicant exposure results can be found in Table 3-3.

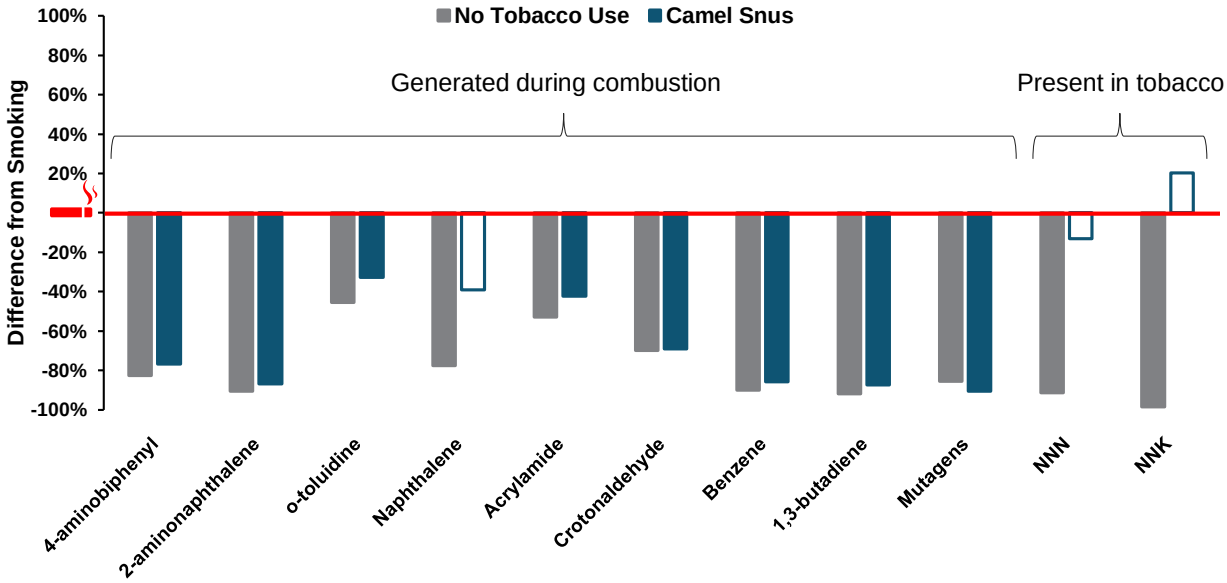
While most of the toxicants present in cigarette smoke are formed when tobacco is burned during smoking, some toxicants present in tobacco (e.g., TSNAs) are transferred directly from the tobacco to smoke and also are conveyed to users of smokeless tobacco. Data from RJRT-sponsored studies (CSD0904 and CSD0901) and data from other external clinical studies (Kotlyar et al. 2011, Blank and Eissenberg 2010, Hatsukami et al. 2016) show that exclusive Camel Snus use results in either similar or reduced exposure to such toxicants present in tobacco when compared to exclusive cigarette smoking (Table 3-4). These results are expected, given that both types of products contain tobacco and users of both products would be exposed to these constituents during use.

The constituents evaluated in the studies listed above also can be considered by disease relevance, as designated by FDA's established list of HPHCs. Established biomarkers exist for nearly 20 constituents included on the HPHC list of 93, and all but two of those are for constituents generated during combustion. Of the combustion-related constituents with established biomarkers, 14 are designated as carcinogens, six are designated as respiratory toxicants, and three are designated as cardiovascular toxicants, with some overlap because several constituents are associated with more than one disease type. Established biomarkers also exist for two additional constituents that are present in unburned tobacco, NNN and NNK, which are both designated as carcinogens. Assessing the totality of the exposures to these constituents can add to the epidemiological evidence for lung cancer, oral cancer, respiratory disease, and heart disease.

3.3.2 Exclusive Camel Snus users are generally exposed to lower levels of carcinogens than cigarette smokers

Results from a natural adopters study (CSD0904) show that, compared to smokers, exclusive Camel Snus users are exposed to lower amounts of carcinogens generated from the combustion of tobacco, including 2-aminonaphthalene, 4-aminobiphenyl, o-toluidine, acrylamide, benzene, 1,3-butadiene and crotonaldehyde. Of the carcinogen biomarkers related to combustion that were measured in this study, only naphthalene showed no statistically significant difference in Camel Snus users compared to smokers. (Figure 3-12). Importantly, the differences observed compared to smokers for the Camel Snus group are similar to the differences seen in the no tobacco use group (*see* MRTPA Section 2.9.1.2.1).

Figure 3-12: Natural Adopters of Camel Snus Are Generally Exposed to Lower Levels of Carcinogens than Smokers – Similar to Non-Tobacco Users

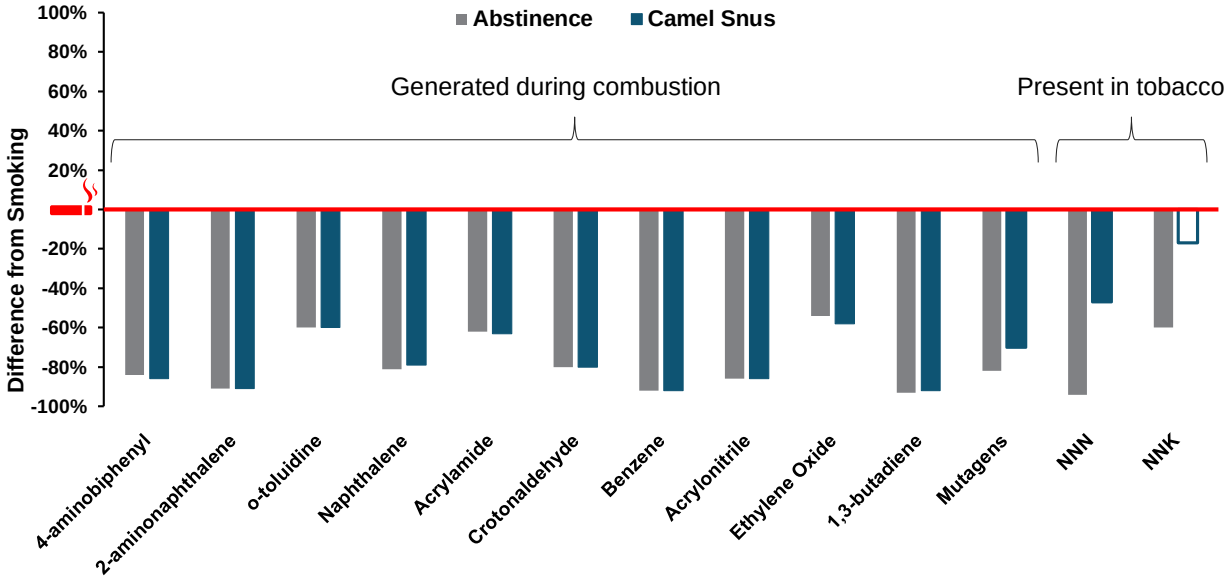


Red line indicates mean exclusive smoking values for each constituent
Solid bars = significant difference versus smoking
Open bars = no significant difference versus smoking
n=60, exclusive cigarette smokers; n=59 non-tobacco users; n=50 exclusive Camel Snus users

Results from the switching study (CSD0901) are similar. Five days of exclusive Camel Snus use reduced exposure to all measured combustion-related carcinogens compared to baseline smoking, and the results for the Camel Snus group were very similar to the abstinence group. Biomarkers of combustion-related carcinogens measured in this study included 2-aminonaphthalene, 4-aminobiphenyl, *o*-toluidine, acrylamide, benzene, 1,3-butadiene, naphthalene, crotonaldehyde, and ethylene oxide (Figure 3-13).

Further, measurement of the mutagenicity of participants' urine, which is considered a composite measure of many carcinogenic products of combustion, showed large differences similar to no tobacco use or abstinence in both the natural adopters and switching studies.

Figure 3-13: Switching to Camel Snus Results in Reduced Exposure to Carcinogens, Generally Similar to Abstinence



Red line indicates mean baseline smoking values for each constituent
Solid bars = significant difference versus smoking
Open bars = no significant difference versus smoking
n=25, smokers switched to abstinence; n=30 smokers switched to Camel Snus

Biomarkers also exist for two carcinogens present in unburned tobacco, NNN and NNK. Results indicate that exposure to these constituents was not statistically significantly higher in Camel Snus users (CSD0904) or switchers to Camel Snus (CSD0901) compared to cigarette smoking (*see* Figure 3-12, Figure 3-13, and MRTPA Section 2.9.1.2.2). Similar results were observed in studies by Hatsukami et al. (2016) and Blank and Eissenberg (2010, NNK only). In addition, results from both CSD0901 and Kotlyar et al. (2011) showed significant reductions in NNN exposure when smokers switched to Camel Snus.

Further, because Camel Snus is used 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.

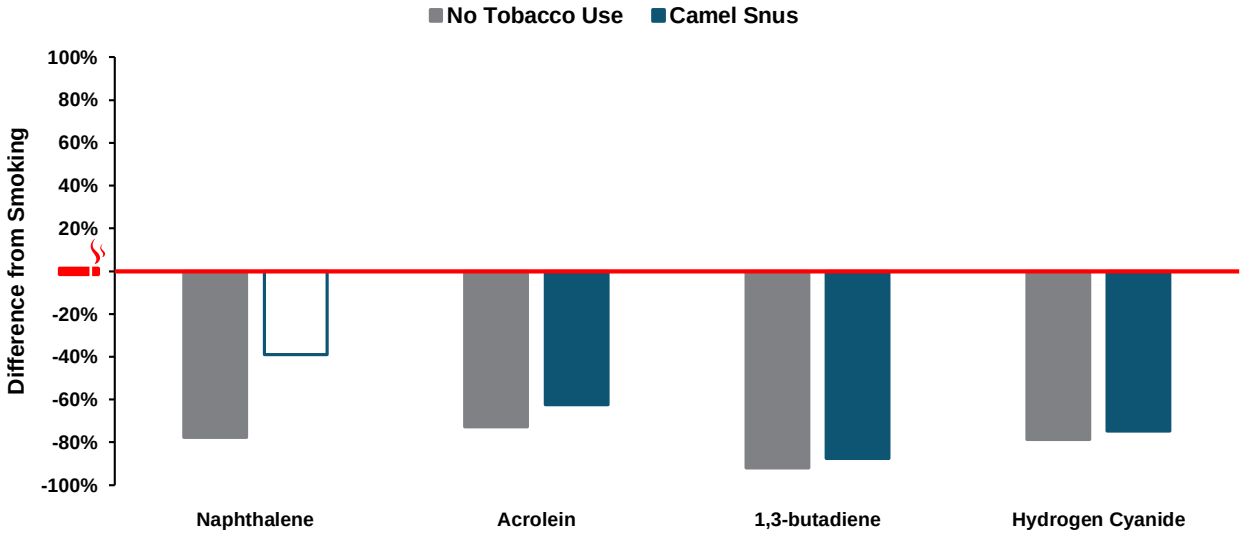
In sum, the results of exposure to all measured carcinogens demonstrate an overall reduction in exposure to carcinogens with Camel Snus use compared to smoking. These results are consistent with the epidemiological findings for reduced risk of lung cancer and oral cancer with use of smokeless tobacco products, such as Camel Snus, compared to smoking.

3.3.3 Exclusive Camel Snus users are exposed to lower levels of respiratory toxicants than cigarette smokers

Among the respiratory toxicants included on FDA's established list of HPHCs, biomarkers of exposure exist for six: acrolein, acrylonitrile, 1,3-butadiene, ethylene oxide, hydrogen cyanide, and naphthalene, all of which are generated during the combustion of tobacco. Four of these biomarkers were included in the natural adopters study and all six were included in the switching study.

Natural adopters of exclusive Camel Snus use showed lower exposure to acrolein, 1,3-butadiene, and hydrogen cyanide than exclusive smokers, and exposure levels were similar to the no tobacco use group. Naphthalene exposure was not statistically significantly different than smoking (Figure 3-14).

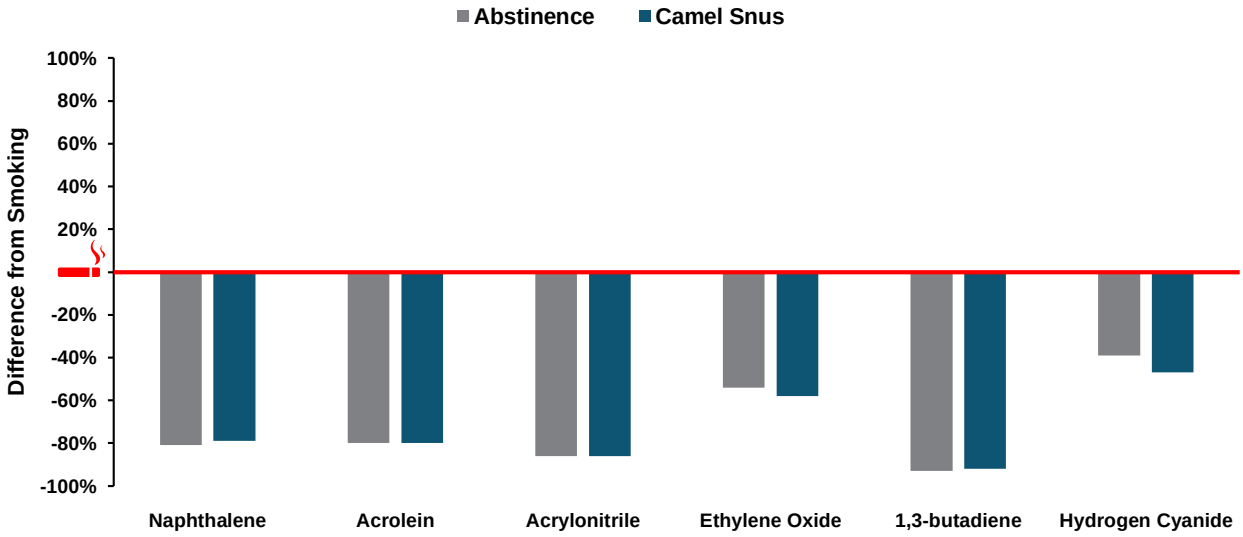
Figure 3-14: Natural Adopters of Camel Snus Are Exposed to Lower Levels of Respiratory Toxicants than Smokers – Similar to Non-Tobacco Users



Red line indicates mean exclusive smoking values for each constituent
Solid bars = significant difference versus smoking
Open bars = no significant difference versus smoking
n=60, exclusive cigarette smokers; n=59 non-tobacco users; n=50 exclusive Camel Snus users

Switchers to Camel Snus showed lower levels of all respiratory toxicants (including naphthalene), and the decreases in all were very similar to the abstinence group (Figure 3-15).

Figure 3-15: Switching to Camel Snus Results in Reduced Exposure to Respiratory Toxicants, Similar to Abstinence



Red line indicates mean exclusive smoking values for each constituent
Solid bars = significant difference versus smoking
Open bars = no significant difference versus smoking
n=25, smokers switched to abstinence; n=30 smokers switched to Camel Snus

Additionally, unlike smoking, direct exposure of these toxicants to respiratory tissues is eliminated with Camel Snus use. This difference in exposure provides another mechanism to potentially reduce the risk of respiratory-related conditions.

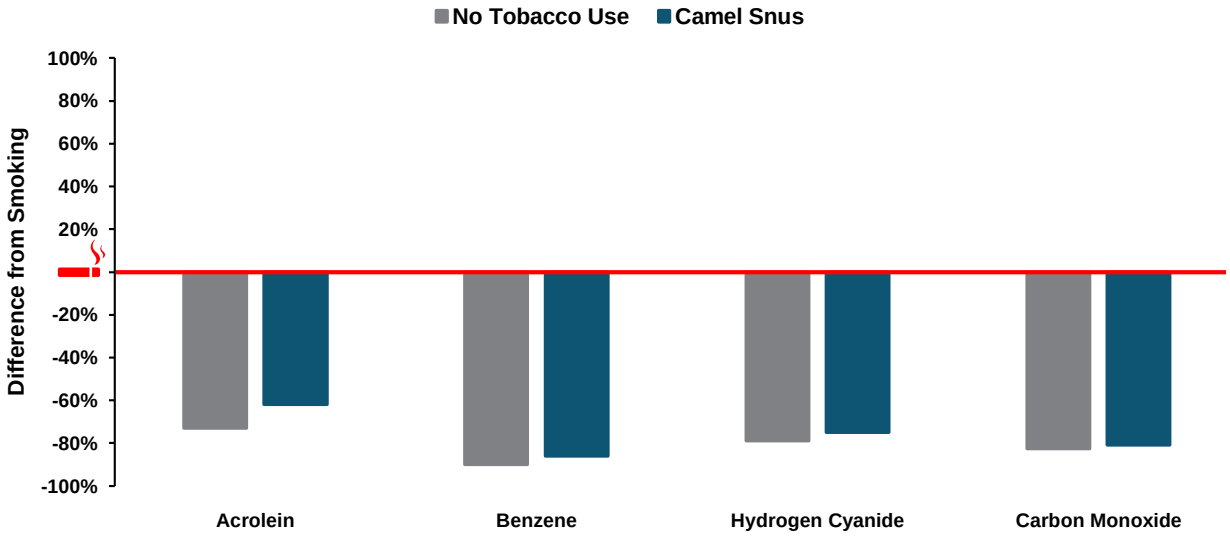
The totality of the results indicate that exclusive use of Camel Snus results in lower exposure to respiratory toxicants, and any remaining exposure is through the oral cavity, not through contact with respiratory tissues. These results are consistent with the epidemiological evidence for lower risk of respiratory disease for smokeless tobacco users of products like Camel Snus, compared to smokers.

3.3.4 Exclusive Camel Snus users are exposed to lower levels of cardiovascular toxicants than cigarette smokers

Among the cardiovascular toxicants included on FDA's established list of HPHCs, established biomarkers of exposure exist for three: acrolein, benzene, and hydrogen cyanide. A biomarker also exists for carbon monoxide, which is included with this list by virtue of its identification as a biomarker of cardiovascular disease risk from smoking by the U.S. Surgeon General (*see* Table 6.3, p. 392 in USDHHS 2010).

Natural adopters of exclusive Camel Snus use showed significantly lower exposure to all four constituents relative to exclusive smokers, and the levels of exposure were similar in magnitude to the no tobacco use group (Figure 3-16).

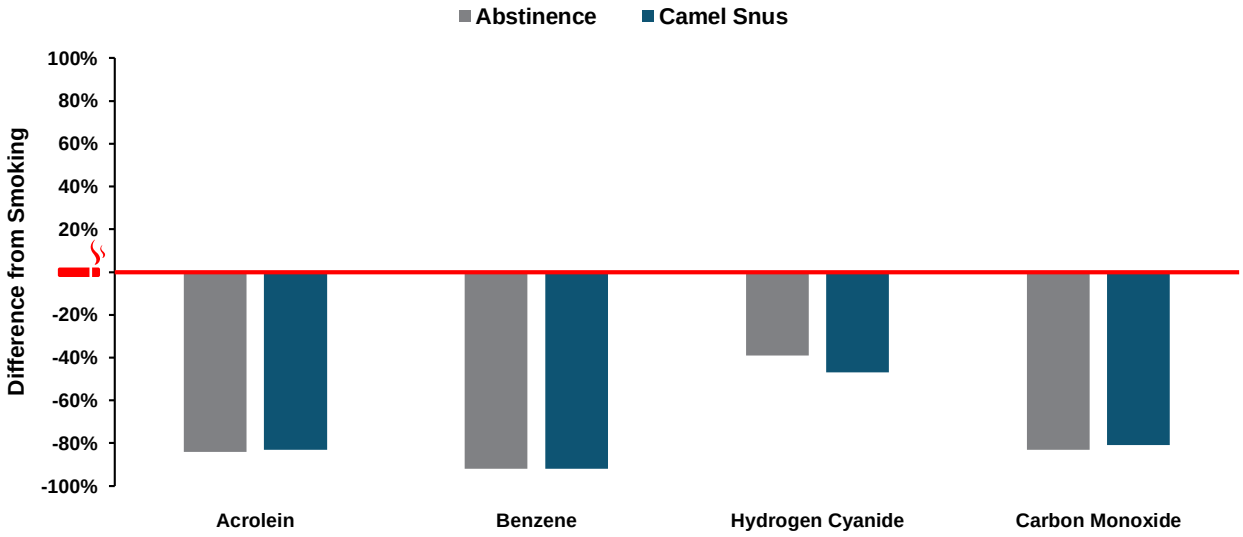
Figure 3-16: Natural Adopters of Camel Snus Are Exposed to Lower Levels of Cardiovascular Toxicants than Smokers – Similar to Non-Tobacco Users



Red line indicates mean exclusive smoking values for each constituent
Solid bars = significant difference versus smoking
Open bars = no significant difference versus smoking
n=60, exclusive cigarette smokers; n=59 non-tobacco users; n=50 exclusive Camel Snus users

Smokers who were switched to Camel Snus showed similar results; significant decreases in exposure were observed for all cardiovascular toxicants and the large, significant decreases were consistent with those observed for the abstinent group (Figure 3-17). Together the results indicate that exclusive use of Camel Snus results in lower exposure to cardiovascular toxicants, which is consistent with the epidemiology that shows lower risk of heart disease for users of smokeless tobacco, like Camel Snus, compared to smokers.

Figure 3-17: Switching to Camel Snus Results in Reduced Exposure to Cardiovascular Toxicants, Similar to Abstinence



Red line indicates mean exclusive smoking values for each constituent
Solid bars = significant difference versus smoking
Open bars = no significant difference versus smoking
n=25, smokers switched to abstinence; n=30 smokers switched to Camel Snus

3.3.5 Summary of exposure to toxicants from exclusive use of Camel Snus

When considered collectively, the data presented above and in MRTPA Sections 2.9.1.2.1 and 2.9.1.2.2 show that smokers who switch completely to Camel Snus reduce their exposure to toxicants that contribute to tobacco-related disease and therefore are likely to reduce their risk of lung cancer, oral cancer, respiratory disease, and heart disease. The reasons behind this are threefold:

1. The majority of toxicants that contribute to tobacco-related illness are formed during combustion, and Camel Snus is not combusted during use (*see* MRTPA Section 6.1.5);

2. Smokers who switch exclusively to Camel Snus eliminate their exposure to those combustion-related toxicants that are the major source of disease and do not simultaneously increase their exposure to the remaining toxicants present in tobacco; and

3. The route of exposure to the toxicants that are present in tobacco is different, and direct exposure to respiratory tissues is eliminated.

The development of lung cancer and oral cancer is likely to occur due to direct exposure of those organs/tissues to carcinogens. With respect to risk of lung cancer, many biomarkers of carcinogens are lower in exclusive Camel Snus users, and those that are at levels similar to smokers are absorbed by extraction in the mouth rather than by inhalation through the

respiratory tract. Specific to lung cancer, the great majority of the risk that attends smoking appears to arise from chronic exposures to smoke constituents other than TSNAs (e.g. Pankow et al. 2007).

A similar scenario is found for oral cancer. In smokers, the mouth and oral tissues are exposed to carcinogens, both from combustion and present initially in the tobacco, by direct contact with smoke. In contrast, Camel Snus users are exposed to only those carcinogens present in the tobacco, and only a fraction of what is initially present in the tobacco is extracted from the pouch during use. Consistent with these differences, the epidemiology shows far lower risk of oral cancer among U.S. smokeless tobacco users compared to smokers.

The totality of the data for overall exposure to carcinogens and the difference in route of exposure indicate a potential for reduction in risk for lung cancer and oral cancer, which is consistent with the epidemiological findings for users of smokeless tobacco, like Camel Snus, compared to smoking.

Exposures to respiratory and cardiovascular toxicants are generally decreased in exclusive users of Camel Snus compared to smokers. In addition, direct exposure to respiratory tissues does not occur because Camel Snus is used in the mouth. Overall, the reduction in exposures to these classes of toxicants supports the epidemiology that shows a lower risk of respiratory disease and heart disease for users of smokeless tobacco, like Camel Snus, compared to smokers.

Table 3-3: Biomarker studies of combustion-related toxicant exposure from exclusive Camel Snus use compared to exclusive cigarette use

				Relative Toxicant Exposure[a]		
Study	**Toxicant 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	Hydrogen Cyanide	24-hr Urine, Plasma	Switching (confinement)	X		

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

[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] Naphthalene, fluorine, and phenanthrene

[d] pyrene

[e] Acrolein and crotonaldehyde

[f] Acrylonitrile, acrylamide, 1,3-butadiene, benzene, and ethylene oxide

[g] Compounds that are mutagenic in the Ames assay (strain YG1024) include PAH, nitroarenes, aromatic amines
[h] Exhaled breath carbon monoxide and blood carboxyhemoglobin
[i] Fluorene and phenanthrene
[j] Naphthalene and pyrene
[k] Acrylamide, 1,3-butadiene and benzene
[l] Compounds that are mutagenic in the Ames assay (strains TA98 and YG1024) include PAH, nitroarenes, aromatic amines
[m] 4-aminobiphenyl hemoglobin adducts in blood
[n] 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.

Table 3-4: Biomarker studies of TSNA exposure from exclusive Camel Snus use compared to exclusive cigarette use

				Relative TSNA Exposure[a]		
Study	**Toxicant 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	NNK	24-hr Urine	Switching (confinement)		X	
CSD0904	NNN, NAT, NAB, NNK	24-hr Urine	Cross-sectional (natural adopters)		X[b]	
Blank and Eissenberg 2010	NNK[c]	Urine	Switching (ambulatory)		X	
Hatsukami et al. 2016	NNN, NNK	Urine	Switching (ambulatory)		X[d]	
Kotlyar et al. 2011	NNK	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.

3.3.6 Dual use of Camel Snus and cigarettes does not increase exposure to HPHCs

As clearly stated in the proposed modified risk advertising, smokers must switch completely to Camel Snus to achieve the health benefits. However, RJRT conducted several studies to address

the effect of dual use of Camel Snus and cigarettes on constituent exposures compared to exclusive smoking. Based on clinical study results, dual use of Camel Snus and cigarettes does not increase exposure and, indeed, may reduce exposure to combustion-related toxicants compared with exclusive cigarette smoking. Additionally, dual use does not increase exposure to toxicants present in tobacco, such as TSNAs.

Several studies have compared biomarkers of 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, and HSD0702) (*see* MRTPA Sections 2.9.1.2.5 and 2.9.1.2.6). Two studies from the literature also evaluated subjects switched partially from cigarettes to Camel Snus (Burris et al. 2014, Hatsukami et al. 2016). (See Table 3-5 for combustion-related biomarker results and Table 3-6 for TSNA results.)

The RJRT-sponsored study of natural product adopters included dual users of both Camel Snus and cigarettes (CSD0904), and found generally similar levels of constituent exposure in dual users compared with exclusive cigarette smokers. However, significantly lower levels of exposure were observed for carbon monoxide, hydrogen cyanide, and urine mutagenicity. 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-hour in-clinic confinement.

An RJRT-sponsored short-term product switching study (CSD0901) included a group of smokers who were randomized to reduce their usual-brand smoking by 60% and use Camel Snus while confined to a clinic. Study results showed exposure to combustion-related carcinogens, respiratory toxicants, and cardiovascular toxicants were significantly reduced 47-92%. Ambulatory studies of smokers switched partially to Camel Snus (i.e., used both Camel Snus and cigarettes) reported decreases of 12-38% in combustion-related toxicants compared to exclusive smoking, with most of the reductions being statistically significant (CSD0905, HSD0702).

Exposure to carcinogens present in tobacco either did not increase or showed small decreases with dual use during confinement. NNN was not significantly increased, and exposure to NNK showed a statistically significant 20% decrease. Two ambulatory product switching studies (CSD0905, Hatsukami et al. 2016) reported no differences in NNN or NNK exposure with dual use. A third ambulatory product switching study (HSD0702) reported a statistically significant 25% decrease in NNK exposure with dual use compared to exclusive smoking.

When considered collectively, the data presented above and in MRTPA Sections 2.9.1.2.5-2.9.1.2.6 demonstrate that smokers who partially switch to Camel Snus (i.e., engage in dual use) are exposed to similar or lower levels of tobacco combustion-related toxicants and toxicants transferred from tobacco to smoke, including carcinogens, respiratory toxicants, and

cardiovascular toxicants, than exclusive cigarette smokers. Importantly, there is no evidence for increased exposure to any toxicants measured. However, the greatest reductions in exposure and diseases risks will result from switching completely to Camel Snus, as emphasized in the proposed modified risk advertising.

Table 3-5: 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	Toxicant 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]		
CSD0904	Aromatic Amines[b]	24-hr Urine[b] Blood[o]	Cross-sectional (natural adopters)		X	
CSD0905	Aromatic Amines[b]	24-hr Urine	Switching (ambulatory)	X		
HSD0702[r]	Aromatic Amines[b]	24-hr Urine	Switching (ambulatory)	X		
HSD0702[r]	Aromatic Amines[o]	Blood[o]	Switching (ambulatory)		X	
Burris et al. 2014	Carbon Monoxide	Breath	Switching (ambulatory)		X	
CSD0901	Carbon Monoxide[j]	Blood, Breath	Switching (confinement)	X[c]		
CSD0904	Carbon Monoxide[j]	Blood, Breath	Cross-sectional (natural adopters)	X		
CSD0905	Carbon Monoxide[j]	Blood, Breath	Switching (ambulatory)	X		
HSD0702[r]	Carbon Monoxide[v]	Blood	Switching (ambulatory)	X		
HSD0702[r]	Carbonyls[d]	24-hr Urine	Switching (ambulatory)	X		
CSD0901	Carbonyls[f]	24-hr Urine	Switching (confinement)	X[c]		
CSD0904	Carbonyls[f]	24-hr Urine	Cross-sectional (natural adopters)		X	
CSD0905	Carbonyls[f]	24-hr Urine	Switching (ambulatory)	X		

				Relative Toxicant Exposure[a]		
Study	Toxicant Type	Sample Matrix	Study Design	Dual Use < Cigarettes	Dual Use ≈ Cigarettes	Dual Use > Cigarettes
CSD0901	Mutagens[i]	24-hr Urine	Switching (confinement)	X[c]		
CSD0904	Mutagens[n]	24-hr Urine	Cross-sectional (natural adopters)	X		
HSD0702[r]	Mutagens[n]	24-hr Urine	Switching (ambulatory)	X		
CSD0901	Organic Compounds[h]	24-hr Urine	Switching (confinement)	X[c]		
CSD0905	Organic Compounds[h]	24-hr Urine	Switching (ambulatory)	X		
CSD0904	Organic Compounds[m]	24-hr Urine	Cross-sectional (natural adopters)		X	
HSD0702[r]	Organic Compounds[m]	24-hr Urine	Switching (ambulatory)	X[u]		
CSD0901	PAHs[d]	24-hr Urine	Switching (confinement)	X[c]		
CSD0901	PAHs[e]	24-hr Urine	Switching (confinement)		X[c]	
CSD0904	PAHs[k]	24-hr Urine	Cross-sectional (natural adopters)		X	
CSD0905	PAHs[p]	24-hr Urine	Switching (ambulatory)	X		
CSD0905	PAHs[q]	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	
CSD0901	Hydrogen Cyanide[g]	24-hr Urine, Plasma	Switching (confinement)	X[c]		
CSD0904	Hydrogen Cyanide[g]	24-hr Urine, Blood	Cross-sectional (natural adopters)	X[l]		
CSD0905	Hydrogen Cyanide[g]	24-hr Urine	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] Naphthalene, fluorene, and phenanthrene
[e] Pyrene
[f] Acrolein and crotonaldehyde
[g] Thiocyanate
[h] Acrylonitrile; acrylamide; 1,3-butadiene; benzene and ethylene oxide
[i] Compounds that are mutagenic in the Ames assay (strain YG1024) include PAH, nitroarenes, aromatic amines
[j] Exhaled breath carbon monoxide, blood carboxyhemoglobin
[k] Pyrene, fluorene, phenanthrene and naphthalene
[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), e.g., PAH, nitroarenes, aromatic amines
[o] Includes measurement of 4-aminobiphenyl hemoglobin adducts in blood
[p] Naphthalene and fluorene
[q] Phenanthrene and pyrene
[r] Subject compliance with assigned study product was less than 100%, making estimates relevant to dual use.
[s] Naphthalene (2-naphthol), fluorene, and phenanthrene
[t] Naphthalene (1-naphthol) and 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

Table 3-6: Biomarker Studies of TSNA exposure from dual use* of Camel Snus and cigarettes compared to exclusive cigarette use

				Relative TSNA Exposure[a]		
Study	Toxicant Type	Sample Matrix	Study Design	Dual Use < Cigarettes	Dual Use ≈ Cigarettes	Dual Use > Cigarettes
CSD0901[b]	NAT, NAB, NNK	24-hour Urine	Switching (confinement)	X		
CSD0901[b]	NNN	24-hour Urine	Switching (confinement)		X	
CSD0904	NNN, NAT, NAB, NNK	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, NNK	24-hour Urine	Switching (ambulatory)	X[c]		
HSD0702[d]	NNK[e]	24-hour Urine	Switching (ambulatory)	X		
Hatsukami et al. 2016	NNN, NNK	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.

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

The foregoing sections addressed measures of users' exposures to HPHCs. This section summarizes data on biomarkers of effect, which concern the response of the user's body to such exposures. Whereas biomarkers of effect are potentially very informative for predicting potential longer-term risks from tobacco product use, their identification, measurement and interpretation are currently still evolving as subjects of scientific investigation. When compared

to non-users of tobacco, far fewer biomarkers of effect (i.e., biomarkers of potential harm, short-term markers that may index processes related to the development of long-term consequences such as cancer, respiratory disease, or heart disease) 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 (*see* MRTPA Section 2.9.1.2.12). 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. Camel Snus reduces proinflammatory effects, which are believed to play an etiologic role in cancer, respiratory, and heart and other cardiovascular diseases (USDHHS 2010).

Consistent with published reports that compare biomarkers of effect in smokeless tobacco users with cigarette smokers (*see*, e.g., Frost-Pineda et al. 2011, Nordskog et al. 2015), the results show that far fewer biomarkers of effect are altered by the exclusive use of Camel Snus than are affected by cigarette smoking.

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

Camel Snus is marketed in two pouch sizes, 600 mg and 1000 mg. To examine whether differences in toxicant exposures may occur based on pouch size, data is presented from a range of internal and external clinical studies. These studies show that Camel Snus users are exposed to similar levels of toxicants, including TSNAs, as well as other markers of tobacco use, like nicotine, regardless of whether they use 600 mg or 1000 mg Camel Snus pouch sizes (*see* MRTPA Section 2.9.1.2.9).

The effect of pouch size was explored in four RJRT-sponsored clinical studies of 400 mg (not the subject of the MRTPAs but useful for comparison) and 600 mg Camel Snus styles (CSD0901, CSD0904, CSD0905 and HSD0702). One external study of primarily 1000 mg Camel Snus styles (Hatsukami et al. 2016), has also evaluated nicotine and TSNA exposure. To compare urinary biomarker results from the different studies and assess potential exposure differences due to Camel Snus pouch size, biomarker results from RJRT-sponsored studies were converted to the units reported by Hatsukami et al. 2016. Based on the biomarker endpoints reported in Hatsukami et al. 2016, total cotinine, total nicotine equivalents, total NNAL and total NNN results were converted in this manner.

Similar nicotine and TSNA biomarker levels were observed for all Camel Snus pouch sizes (*see* Table 3-7 [nicotine, cotinine] and Table 3-8 [TSNAs]). No trends associated with Camel Snus pouch size were evident, with mean biomarker levels for users of 400 mg and 1000 mg products falling largely within the range observed for users of 600 mg 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. It is important to keep in mind that mouth-level exposure studies included in the MRTPAs (e.g., Caraway and Chen, 2013) demonstrate that much of the constituent content of the snus pouches, around 60-90%, is not extracted during use, so exposure is not proportional to the mass of a snus pouch.

Table 3-7: Urinary nicotine biomarkers by exclusive or dual Camel Snus use*

Study	Study Design	Camel Snus Pouch Size (mg)	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	600	1	30.0	30.2	30	1974	2099	30
CSD0904[a]	Cross-sectional	600	24+	41.9	49.3	50	2417	2338	50
Hatsukami et al. 2016[b]	Switching	1000	4	35.6	31.0	53	2152	2005	53
Dual Use									
HSD0702[c,d]	Switching	400	24	43.0	16.8	29	3054	1421	29
CSD0901	Switching	600	1	40.9	21.1	29	2564	1397	29
CSD0904[a]	Cross-sectional	600	24+	65.5	53.6	50	3866	2937	50
CSD0905	Switching	600	4	76.2	50.9	33	4065	2704	33
Hatsukami et al. 2016[b]	Switching	1000	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 1000 mg pouch size products.
[b] Some participants who experienced adverse effects from use of 1000 mg pouch size products were provided 600 mg 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 3-8: Urinary TSNA biomarkers by exclusive or dual Camel Snus use*

Study	Study Design	Camel Snus Pouch Size (mg)	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	600	1	1.39	0.85	30	0.07	0.17	30
CSD0904[c]	Cross-sectional	600	24+	1.64	2.31	50	0.04	0.04	50
Hatsukami et al. 2016[d]	Switching	1000	4	1.34	1.42	52	0.06	0.07	18
Dual Use (Concurrent Camel Snus and Cigarettes)									
HSD0702[e,f]	Switching	400	24	1.72	0.99	28	NA[g]	NA[g]	NA[g]
CSD0901	Switching	600	1	1.83	1.11	29	0.13	0.26	29
CSD0904[a]	Cross-sectional	600	24+	1.60	1.31	50	0.05	0.04	50
CSD0905	Switching	600	4	4.23	2.59	33	0.15	0.11	33
Hatsukami et al. 2016	Switching	1000	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 1000 mg pouch size products.
[d] Some participants who experienced adverse effects from use of 1000 mg pouch size products were provided 600 mg 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 analyzed.

3.3.9 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 is the result of multiple factors, including the manner of use (e.g., smoking versus oral tobacco use), product use behaviors (e.g.,, cigarette puffing behavior or time smokeless tobacco is held in the mouth), and the chemical composition of the smoke or tobacco product.

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 the MRTPAs (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 by FDA as HPHCs 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. The proposed modified risk messaging clearly communicates that smokers should switch completely.

3.4 Preclinical Studies

RJRT conducted a broad range of *in vivo* and *in vitro* preclinical scientific studies of Camel Snus. Such studies serve as a link between the chemistry of Camel Snus and the human clinical and epidemiological investigations. The *in vivo* and *in vitro* toxicology studies, when considered together with the other scientific evidence presented in the MRTPAs, provide strong and consistent evidence that Camel Snus exhibits significantly reduced toxicity and carcinogenicity relative to cigarettes.

3.4.1 *In vivo* studies

Scientific studies using laboratory animals are key scientific components of FDA oversight across most of its regulated product sectors. Though 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, 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 information captured in human clinical and epidemiological investigations.

RJRT sponsored a series of *in vivo* studies on the tobacco blend of Camel Snus. These *in vivo* studies, when considered together with the results of epidemiological, clinical, and *in vitro* studies, provide strong and consistent evidence that Camel Snus exhibits significantly reduced toxicity and carcinogenicity relative to cigarettes. Overall results are presented in Table 3-9 below and additional detail on these studies is available in Section 6.1.4 of the MRTPA.

Table 3-9: Overview of Findings from Subchronic and Chronic *In* Vivo Toxicity and Carcinogenicity Studies of Cigarettes and Camel Snus

Rodent Studies	Cigarette Smoke	Camel Snus	
Subchronic (90-day)	Significant histopathologic and inflammatory respiratory changes[1]	No significant organ or system toxicity	
Chronic	Significant malignant epidermal tumors[1]	1 year	No significant toxicity
		2 year	No significant tumor occurrences due to snus

[1]Historical data; literature review

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

Following a series of subchronic studies that identified optimum dosing, potential target organs, and the tolerability of Camel Snus in laboratory mice and rats, RJRT sponsored a 2-year, GLP-compliant chronic toxicology/carcinogenesis bioassay of Camel Snus in male and female Wistar Hannover rats receiving daily dietary exposures to three dose levels of the Camel Snus tobacco blend or an aqueous extract of that tobacco blend (Theophilus et al. 2015). This route of administration was chosen to provide high levels of exposure to the oral cavity, as well as systemically, for a dosing period approximating the animals' normal lifetime. Control groups received normal laboratory diet. Toxicokinetic evaluations confirmed that the animals' nicotine and cotinine biomarkers levels spanned or exceeded those typical of smokeless tobacco consumers, and confirmed that target dosages were satisfactorily attained. The general toxicology arm of the study proceeded through study termination at the 1-year time point, whereas the chronic carcinogenicity arm of the study continued on to study termination at the 2-year time point.

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 similar to those observed in rats receiving the Camel Snus test articles or nicotine alone in the 28-day and 90-day subchronic studies, indicating that this was an anticipated effect of nicotine rather than other components of Camel Snus and its extract.

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.

Similar findings of no effect were seen for the oral cavity and digestive tract, which were the primary points of contact and absorption of the tested Camel Snus blend and extract. These

were entirely normal in gross examination and microscopic histopathology, and were indistinguishable from those of control animals that had received the control 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 chronic rodent cigarette smoke inhalation studies of similar duration, which, as briefly reviewed and discussed in MRTPA Section 6.1.4 and references therein, have described severe respiratory tract histopathologic and inflammatory changes, as well as systemic inflammation and, in some studies, malignant tumors (Coggins 1998, 2007; Hecht 2005). These findings are consistent with the substantial respiratory and cardiovascular diseases risks that attend cigarette smoking, and, by comparison to the Camel Snus findings, support the conclusion that using Camel Snus carries less risk than smoking.

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

The 2-year carcinogenicity component of the chronic feeding study found 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. As expected, 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 findings were suggestive of carcinogenicity.

Similar to findings from the numerous chronic carcinogenicity studies conducted by the National Toxicology Program, a number of sporadic tumors were identified in a variety of tissues in the aging rats as they approached the end of their normal lifespan (~ 2 years) at study termination. Among these, three tumor types had significantly decreasing incidence trends (i.e., benign mammary gland adenomas in females receiving the tobacco blend, malignant skin basal cell carcinomas in females receiving the tobacco extract, and benign thyroid follicular cell adenomas for males receiving the tobacco extract). Statistically significant increasing tumor incidence trends were observed at two tissue sites in animals receiving the Camel Snus tobacco blend (i.e., malignant carcinomas of the uterus in females and malignant mesotheliomas of the epididymis in males).

None of these tumor sites represent organs or tissues that have been identified as primary targets for either smokeless tobacco or cigarette 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. The study pathologist therefore judged these trends of decreased and increased tumor findings 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.

Importantly, and as discussed more extensively in Section 6.1.4 of the MRTPA, these findings contrast starkly with the robust carcinogenic responses reported in multiple published studies of mice treated dermally with cigarette smoke condensates. Such treatments reliably produce a high incidence of multiple benign papillomas and malignant carcinomas in a dose-related manner, documenting the carcinogenicity of cigarette smoke condensates.

Experimental chronic cigarette smoke exposure studies in rodents have also produced severe inflammatory and histopathological changes in the respiratory tract tissues, as well as systemic inflammation, 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 caused or exacerbated by smoking (Coggins 1998, 2007; Hecht 2005). In other words, the findings indicate that cigarette smoke produced significant toxicity whereas Camel Snus extracts did not.

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

When considered together as a body of evidence, 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 and its extracts exhibit a very low or statistically insignificant capacity to induce or promote oral or other cancers in animals. Similarly, a considerable body of published literature documents severe respiratory tract histopathological and inflammatory changes consequent to cigarette smoke inhalation. In contrast, the Camel Snus tobacco blend and extract produced no adverse systemic or target organ effects following chronic, lifetime exposures of rats to dietary levels sufficient to produce nicotine biomarkers spanning and exceeding those of human smokeless tobacco consumers.

The body of published *in vivo* smokeless tobacco studies (*see* MRTPA Section 6.1.4.2), and the *in vivo* experimental evidence specific to Camel Snus, is very consistent with the abundant epidemiological evidence developed from users of broadly similar U.S. and Swedish and Norwegian smokeless tobacco products. That evidence, considered together with the findings from product chemistry, *in vitro* toxicology, clinical studies, and epidemiology that are described in the MRTPAs, establishes a sound basis of biological plausibility that smokers who switch completely from cigarette smoking to Camel Snus will reduce their risks for lung and oral cancers, respiratory diseases, and heart disease that are caused by smoking.

3.4.2 *In vitro* toxicology studies

In vitro toxicology testing is established as a component of FDA regulatory oversight across most of its historically-regulated product sectors. Preclinical *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, and thus has utility in evaluation of the inherent toxicity of a potential MRTP as compared to other tobacco products on the market (FDA 2012a, p. 24).

As reviewed and discussed in Section 6.1.3 of the MRTPA, a substantial 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 evaluate the induction of mutations in target genes (e.g., the Ames bacterial mutagenesis assay), and those that measure structural changes to the genetic material (e.g., the mammalian cell micronucleus and sister-chromatid exchange assays) 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 provides data relevant to disease processes that occur among users of different tobacco products, and thus are suitable as a basis for comparisons among different tobacco product categories. The rationale for the selection of the testing performed in support of this Application is further detailed in MRTPA Section 6.1.3.1, and Section 6.1.3.4.1, MRTPA 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.

3.4.2.1 Camel Snus extracts are less cytotoxic, mutagenic, and genotoxic 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 (mammalian cell neutral red uptake assay) data specific to the subject Camel Snus products is presented in MRTPA 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 from the market-leading U.S. 85 mm non-menthol and menthol cigarette brands and Kentucky reference cigarettes, a standard experimental comparator used by industry, regulatory, and academic researchers.

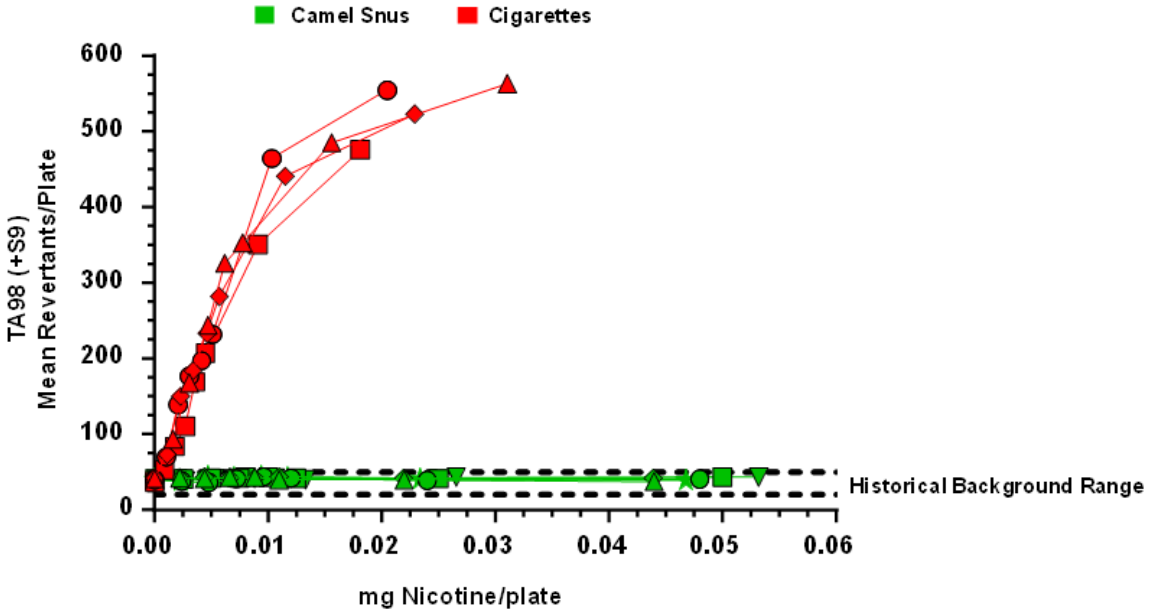
The studies consistently show less toxicity for Camel Snus extracts compared to cigarette smoke.

Five Ames Salmonella strains were employed in the mutagenicity assessments, each having been engineered to respond to different classes of chemicals. Overall, these studies

demonstrate that the bacterial mutagenicity of Camel Snus extracts in the Ames Salmonella test system are statistically-significantly lower than those of concurrently-tested cigarette smoke extracts. Any nominal mutagenicity responses that were observed for Camel Snus were judged to lack biological significance, as defined by FDA in its 2012 Guidance for genotoxicity testing of pharmaceuticals and discussed in MRTPA Section 6.1.3.4.1 since they did not induce revertant bacterial colony counts (i.e., mutations) in excess of the characteristic normal ranges for spontaneous revertants (mutations) in any of the Salmonella tester strains, both in the presence or absence of an exogenous rat liver S9 metabolic activation mixture.

Figure 3-18 below shows study results for one responsive Salmonella tester strain in the presence of S9, as an example. The red symbols denote the high mutagenic activity of the market-leading non-menthol and menthol cigarettes, smoked under the ISO (non-intense) and HCI (intense) regimens, and the green symbols denote the six Camel Snus product varieties that are the subjects of the Applications. The Camel Snus findings for all six varieties were within the normal ranges for spontaneous mutants in all five Ames Salmonella strains, indicating no detected mutagenic activity whatsoever.

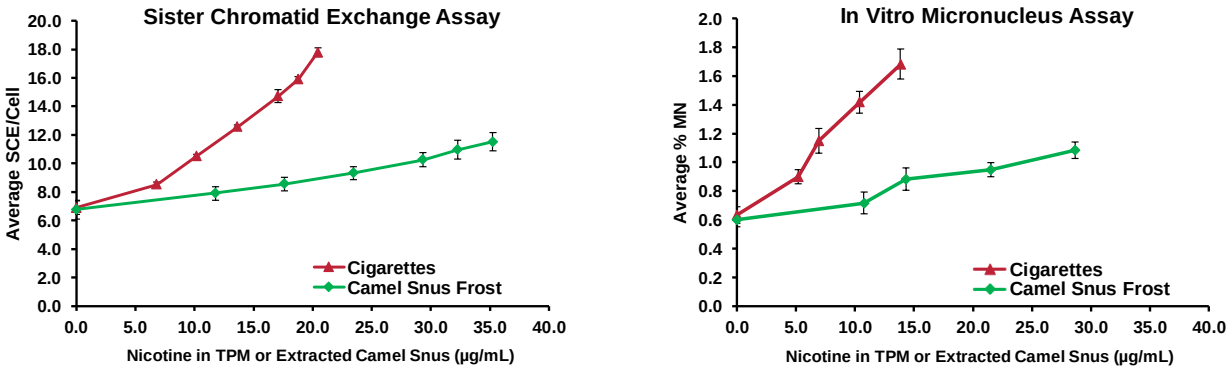
Figure 3-18: Results of the Bacterial Assay for DNA Damage at the Gene Level: Ames Assay (Mutagenicity)



One strain is shown as a representative of the Ames results.
All six Camel Snus variants were tested.
Dashed lines indicate the historical background range observed for this assay.
Cigarettes include the results of two commercial cigarette comparators smoked under ISO and Health Canada Intense machine smoking regimens.

A test of genotoxic effects manifested as changes at the chromosome level of mammalian cells (i.e., induction of sister chromatid exchanges and micronuclei) compared Camel Snus extracts to cigarette smoke, with the two products matched by nicotine levels to equate doses. These genotoxic effects were found to be significantly lower for Camel Snus than for cigarette smoke extracts, both in the presence and absence of S9 metabolic activation, as detailed in MRTPA Section 6.1.3.4 and Section 6.1.3.5 and the references cited therein. Published studies of other smokeless tobacco products have reported a similar, modest degree of genotoxic activity that contrasts markedly with the highly genotoxic character of cigarette smoke total particulate matter (TPM) (Johnson et al. 2009). (Figure 3-19)

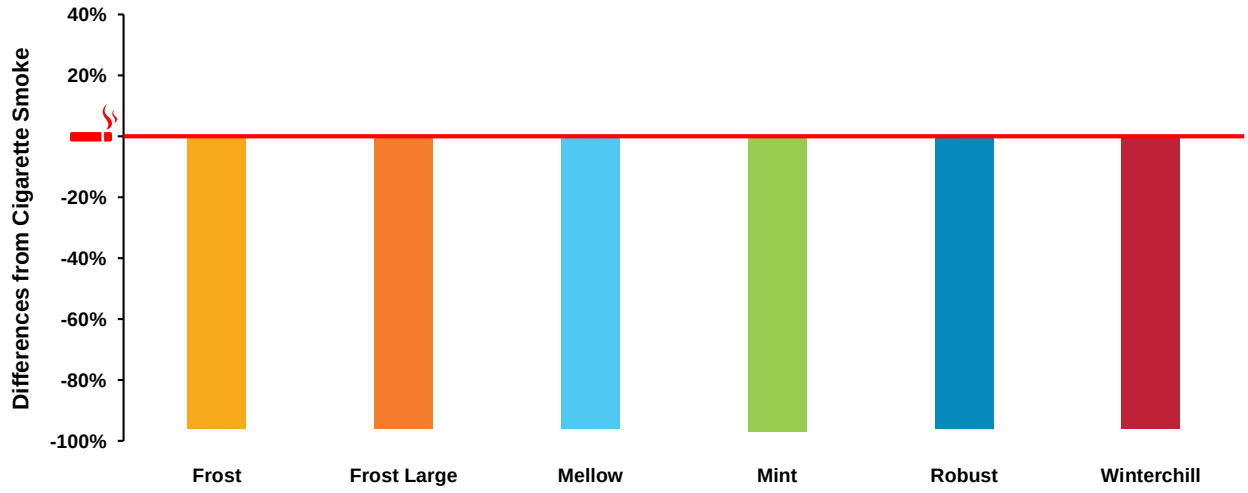
Figure 3-19: Results of Mammalian Cell Assays for DNA Damage at the Chromosomal Level



The Kentucky Reference cigarette 2R4F was the cigarette comparator, smoked under the ISO machine smoking regimen.

Another *in vitro* test examines the effect of Camel Snus extracts on cytotoxicity, which is an important, fundamental consideration in both lung and oral cancer promotion and in the development of respiratory diseases. All six of the tested Camel Snus brand styles that are the subjects of the MRTPAs exhibited significantly lower cytotoxicity than did the smoke of leading U.S. brands of menthol and non-menthol cigarettes tested concurrently in the sensitive mammalian cell Neutral Red Uptake assay, as detailed in MRTPA Section 6.1.3.6. A summary of the cytotoxicity results can be found in Figure 3-20, below:

Figure 3-20 Results of the Mammalian Cell Assay for Cytotoxicity: Neutral Red Assay



Horizontal red line indicates mean cytotoxicity values for cigarette smoke.
Colored bars represent the reduction in the respective cytotoxicity for the six Camel Snus varieties when compared with commercial cigarette comparators on the basis of respective nicotine content.

3.4.2.2 *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 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. In the case of Camel Snus compared to cigarettes, the findings are clear across the full spectrum of studies and methods, indicating that Camel Snus confers less biological activity and hence less risk than cigarette smoking. The *in vitro* data help provide biological explanation for the *in vivo* animal data and the human epidemiology findings that are consistent in showing less risk for Camel Snus compared to cigarettes.

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 the MRTPAs 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 effects than does cigarette smoke.

Further, these *in vitro* findings strongly concur with the findings from the chronic *in vivo* studies of Camel Snus, and in turn 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, respiratory disease, and heart disease – among users of U.S. smokeless tobacco products relative to U.S. smokers, and similar findings in Sweden.

The *in vitro* data, the *in vivo* data, and the human clinical data on Camel Snus are all consistent with, and support the population epidemiology studies that have clearly demonstrated that use of smokeless tobacco products, including Camel Snus, convey far lower risks of lung cancer, oral cancer, respiratory disease, and heart disease than does cigarette smoking.

3.5 Abuse Liability

3.5.1 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 versus 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 for it to adequately substitute for the reinforcing effects of cigarettes.

Product and clinical data related to the abuse liability of Camel Snus include its nicotine content and buffering, pharmacokinetic measures of nicotine exposure (i.e., peak blood concentrations [C_{max}] and time to peak concentration [T_{max}]), as well as systemic measures, such as biomarkers of exposure to nicotine and its metabolites. Accordingly, the study data summarized in the MRTPAs 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 MRTPA Section 6.1.6 and Henningfield et al. 2017.

After review of available data, Henningfield et al. 2017, in their abuse liability assessment of the six Camel Snus variants, conclude that, based on the abuse liability profile of Camel Snus, it will serve as an acceptable and beneficial MRTP. The scientific evidence indicates 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 (Henningfield et al. 2017; Cobb et al. 2010).

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 is acceptable to current smokers and manifests low to moderate abuse liability, while also providing a substantial potential to reduce the risks associated with cigarette smoking.

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

Smoking a cigarette results in significantly greater and more rapid nicotine exposure than 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.

In particular, delivering more nicotine (up to a point) and delivering it more quickly are associated with greater abuse liability. RJRT-sponsored pharmacokinetic studies of Camel Snus users and cigarette smokers show that smoking a single cigarette results in greater nicotine exposure over time (area under the concentration versus time curve, or AUC), a greater peak nicotine exposure (C_{max}) and a peak exposure that occurs significantly more quickly (T_{max}) than with the use of a single Camel Snus pouch (*see* MRTPA Section 2.9.1.2.11).

The results of RJRT-sponsored studies of clinical pharmacokinetic measures of nicotine during Camel Snus use are summarized below in Table 3-10 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 3-11).

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 MRTPA Section 2.9.2, MRTPA Section 6.1.6 and Henningfield et al. 2017.

Table 3-10: 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**
AUC – higher values indicate greater total nicotine exposure						
CSD0914	Nicotine AUC_{0-180}	Serum	Single Use	X		
CSD1101	Nicotine AUC_{0-180}	Serum	Single Use	X		
CSD0905	Nicotine AUC_{0-90}	Serum	Single Use	X		
C_{max} – higher values indicate higher peak nicotine concentration						
CSD0905	Nicotine C_{max}	Serum	Single Use	X		
CSD0914	Nicotine C_{max}	Serum	Single Use	X		
CSD1101	Nicotine C_{max}	Serum	Single Use	X		
T_{max} – higher values indicate slower nicotine delivery						
CSD0905	Nicotine T_{max}	Serum	Single Use			X
CSD0914	Nicotine T_{max}	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, "X" indicates relative time to reach T_{max} and does not indicate greater relative exposure to nicotine. AUC = area under the concentration versus time curve, reflecting total systemic nicotine exposure during the study interval.

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

The above studies concerned nicotine delivery from a single use of a cigarette compared to a single use of Camel Snus. There are also data about overall nicotine intake during ad libitum use of each product. 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.

Table 3-11: 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.

In sum, based on its acute as well as longer-term nicotine delivery characteristics, Camel Snus has lower abuse liability than cigarettes.

3.5.4 Appeal of Camel Snus increases over time when smokers are switched to dual use

Another important factor when considering abuse liability is the overall appeal of the product. To favorably impact public health by encouraging continuing smokers to switch to a modified risk product, the MRTP must have some appeal, an aspect of abuse liability that is often measured as product liking.

One clinical study, in which smokers were switched to dual use of cigarettes and Camel Snus (CSD0905), assessed product liking over the course of the study (Round et al. 2015). Smokers used their usual brand (UB) cigarettes ad libitum for the first week of the study and gradually reduced cigarettes per day over the next three weeks as they adopted Camel Snus. At the end of each week, product liking was assessed for both cigarettes and Camel Snus. At the end of the first week of dual use, Camel Snus ratings were significantly lower than UB cigarettes. However, by the end of week four, the appeal of Camel Snus was nearly as high as that of UB cigarettes and not statistically significantly different. These results show that smokers' liking of Camel Snus increases with increased usage and suggest that Camel Snus can be an acceptable product to smokers. This increased acceptability of Camel Snus over time among dual users suggests that their potential to complete their migration to exclusive snus use may be greater than would be evident from a single, initial trial of the product.

In summary, the abuse liability of Camel Snus is lower than that of cigarette smoking, but the product has appeal to smokers and is liked by smokers, indicating that it can be an adequate (but lower-risk) substitute for smoking for some smokers.

4 Comprehension and Perceptions Studies

4.1 Introduction

In addition to requiring that a modified risk tobacco product significantly reduce harm and the risk of tobacco-related disease to individual tobacco users, the TCA requires that a modified risk tobacco product 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)).

The TCA and FDA's MRTPA Draft Guidance state 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.

To address comprehension of the information in RJRT's proposed advertisements, RJRT conducted comprehension and perceptions studies to evaluate individuals' understanding 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 MRTPA 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 that modified risk messaging.

RJRT's studies show that after viewing the proposed modified risk advertising, individuals understood that Camel Snus was associated with less risk of the named diseases, while still recognizing that Camel Snus is not completely safe. Individuals also understood that Camel Snus contains nicotine and is addictive, that the best option for smokers is to quit smoking, and that non-users of tobacco should not use the product – all messages communicated in the advertisements. This balancing information mitigates the potential for the advertising to deter tobacco quitting or promote tobacco initiation.

4.2 Comprehension and Perceptions Studies

RJRT's comprehension and perceptions studies were designed to determine whether individuals sufficiently understand the key information covered in the modified risk advertising, and come away with appropriate perceptions of the risk of using Camel Snus relative to cigarette smoking. Specifically, these studies assessed whether individuals 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 equally reduces the risk of all tobacco-related diseases.

Individuals were also asked a number of additional questions to ensure that they did not come away from the advertisement with misconceptions that could cause potential adverse public health consequences. Specifically, the study assessed their understanding that quitting all tobacco use is the best and safest option, and also assessed individuals' understanding of 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, individuals were tested for their understanding of the relative risks of other smokeless tobacco products.

The study also assessed individuals' understanding of several balancing or cautionary statements included in the proposed modified risk advertisements, specifically that: individuals who do not already use tobacco should not start use of Camel Snus; Camel Snus is addictive; and Camel Snus should be used as a complete substitute for smoking, not as a supplement to it.

4.3 Comprehension and Perceptions Study Objectives

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

- Smokers switching completely to Camel Snus can reduce the risk of the smoking-related diseases identified in the proposed advertisements
- Camel Snus still carries health risks (even for diseases where risk is reduced)
- Camel Snus does not equally reduce the risk of all other smoking-related diseases
- Camel Snus does not eliminate all risk to overall health
- The proposed modified risk claims for Camel Snus do not necessarily 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

4.4 Methods

Each of the three proposed modified risk advertising Executions for Camel Snus was independently tested for individuals' comprehension and perceptions. Large samples (N=8,404; Execution 1; N=4,924, Execution 2; and, N=4,906, Execution 3) of US adults (≥ 18 years old, and legally eligible to purchase tobacco in their jurisdiction) were recruited from an online consumer research panel for each of the three studies. The samples were diverse and balanced and weighted to represent the U.S. adult population and included current, former, and never tobacco users. Respondents' health literacy was tested using the Newest Vital Sign (Weiss et al. 2005) test of health literacy, and 33-35% of respondents (across executions) were classified as demonstrating low-health literacy.

Data were collected online. Respondents were exposed to the proposed modified risk advertisement, and then answered a series of questions regarding the targeted messages contained in the advertisement. For each disease contained in the modified risk information, respondents rated the risk of cigarette smoking and, separately, the risk of using Camel Snus,

allowing for indirect assessment of relative risks. Respondents also directly compared the risk of Camel Snus compared to smoking for the diseases named in the modified risk information.

To assess their generalization of the modified risk information, respondents rated the risks of other smokeless tobacco products, and indicated whether they thought Camel Snus would also reduce the risk of other diseases not named in the advertisement. Respondents were asked about the risk of Camel Snus relative to that of nicotine-based smoking cessation medications and of quitting all tobacco use completely. Respondents were tested for their understanding of the optimal use of the product to receive a health benefit (i.e., complete switching from cigarettes to Camel Snus), and also for understanding of the cautionary statements.

These studies are summarized in this section, and presented in more detail in MRTPA Section 6.2.

4.5 Summary of Findings from the Comprehension and Perceptions Studies

Although the three advertising Executions use different language with respect to the modified risk claim, they share many common messages and communication objectives, and were assessed using similar methods on samples recruited from the same online panel.[2] Accordingly, the resulting individuals' responses were similar. The findings across studies are discussed below. Where numerical findings are given as a range, they represent the range of values obtained across the three studies.

Across all three proposed modified risk advertising Executions and studies, respondents demonstrated understanding of the key messages.

Respondents:

- Understood that switching completely to Camel Snus carries less risk than cigarette smoking for the diseases named in the advertisements, but also understood that reduced risk did not mean no risk;
- Did not overgeneralize the modified risk messaging to diseases that were not addressed in the advertisements or to other smokeless tobacco products;
- Understood that using Camel Snus was not safer than quitting smoking;
- Understood that people who were not already using tobacco should not use Camel Snus;
- Understood that Camel Snus is addictive; and
- Understood that smokers should switch completely to Camel Snus to realize the risk reduction benefit.

[2] Testing of Executions 2 and 3 occurred at the same time, and respondents were randomized to executions.

Comprehension and perceptions of the modified risk advertising were tested in important sub-groups defined by tobacco use and smoking (i.e., current, former, never), and results showed that key messages were understood by the sub-groups to which they were most relevant. For example, almost all current smokers, as well as the subset of current tobacco users likely to quit tobacco use (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 smokers thought Camel Snus would lower the risk of tobacco-related diseases if they continued smoking while using Camel Snus (5.8-14%). Further, very few of those who were not current tobacco users thought Camel Snus could be used by non-users of tobacco (4.3-5.5%).

Thus, the proposed modified risk advertising was associated with appropriate understanding of risk reduction, and avoided communicating messages that could potentially undermine the population health benefit (e.g., encourage initiation, discourage cessation) of marketing Camel Snus with modified risk advertising.

4.5.1 Respondents understood that Camel Snus reduces the 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 individuals' understanding. The lower risk of lung cancer and respiratory disease from use of Camel Snus, compared to smoking, 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.

A majority of the remaining respondents (15-20%, across the three Executions) believed that Camel Snus carried the same risk of lung cancer and respiratory disease as smoking, despite the reduced risk claims for these pulmonary diseases (and the factual basis for these claims). 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. Considering the lower end of the 1-7 point scale to be 'no risk,' the respondents' quantitative ratings of Camel Snus compared to smoking implied roughly a one-third risk reduction at most (for lung cancer and respiratory disease, smaller for heart disease and oral cancer). These implied risk reductions are much smaller than those derived from expert consensus (Levy et al. 2004; Nutt et al. 2014), which imply much higher levels of risk reduction.

Crucially, 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, and the absolute ratings for the

risk of Camel Snus for these diseases were well above the mid-point of the 7-point rating scale (i.e., 4). 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.

The proposed modified risk advertising for Executions 1 and 2 also claimed reduced risk of heart disease and oral cancer. In response to Executions 1 and 2, respondents indicated that they perceived the risk of Camel Snus for these diseases to be reduced, compared to cigarette smoking. Here, too, few respondents (2.5-5.5%, across Executions and diseases) believed that Camel Snus carried no risk for these diseases.

It was notable that, although the modified risk statement did not distinguish the degree of risk-reduction for the four diseases, respondents reported different risk perceptions for the different diseases. In particular, respondents assumed that Camel Snus would yield greater reduction in risk for respiratory conditions (lung cancer and respiratory disease) than for heart disease and oral cancer. This was especially the case for oral cancer, where about one third of participants believed Camel Snus carried the same risk as smoking (31-36% across the two Executions), even after exposure to a modified risk statement that indicated otherwise.

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. Thus, the responses reflected the impact of pre-existing beliefs and perceptions as well as comprehension of the messages.

Consumers may not have found 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). 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 (which include a warning about mouth cancer) 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.

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

All three comprehension and perceptions studies tested for potential generalization of each proposed modified risk advertisement 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. (Relevantly, epidemiological evidence suggests that this is true, e.g., for other cancers.)

The most frequent response – given by about half of the respondents (48-53% across the three Executions) – 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 Camel Snus for overall poorer health as substantial (i.e., 5.5-5.8 on the 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 key sub-groups (current, former, and never smokers). 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.

In sum, after viewing the proposed modified risk advertisements, respondents came away with reasonable beliefs about the risks of Camel Snus. They understood that Camel Snus carried less risk for the diseases claimed in the modified risk information, but understood that this did not mean there was no risk. They also did not overgeneralize the modified risk information to all other diseases, or to effects on health in general.

4.5.3 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. (It is notable that endorsing this implied a double negative: that it is true that is not safer, which may have been confusing to respondents.) Most respondents (62-68%) understood that this was true, although 20-27% (across the three Executions) of smokers who were potential quitters indicated it was false.

4.5.4 Respondents understood that Camel Snus is addictive

The proposed modified risk advertisements state that Camel Snus is addictive. This addiction warning was also expressed in the government-mandated rotating warning label statements, seen by a random one-fourth of the respondents. Respondents understood that Camel Snus is addictive, as 82% agreed with the statement across the three proposed advertising Executions and only 5-7% disagreed; 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.

4.5.5 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% across the three Executions) 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 (individuals who had used tobacco products but not reached the threshold to be considered established users), 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% across the three Executions 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.

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

From a health perspective, cigarette smokers who switch completely to Camel Snus will 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 to evaluate a negatively-worded statement, 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.

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

Respondents were shown the proposed advertisements and then asked to indicate what cigarette smokers should do in order to benefit from using Camel Snus. The proposed modified risk advertisements all stressed that smokers must switch completely to Camel Snus to reduce their risk of disease, but differed in the details of how that message was expressed:

- In Execution 1: “Smokers who **switch completely** from cigarettes to Camel Snus can significantly reduce their risk of lung cancer…” and "Smokers who use Camel Snus instead of cigarettes can significantly reduce their health risks from smoking."

- In Executions 2 and 3: “Smokers who **SWITCH COMPLETELY** from cigarettes to Camel Snus can greatly reduce their risk of lung cancer…” and a directive, "Switch completely from cigarettes to Camel Snus."

Across all three studies, roughly 75% 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 behavior.

In Executions 2 and 3, where respondents were not provided a reduction option, very few (3-4% across the two Executions) believed that using Camel Snus while continuing to smoke cigarettes would deliver health benefits.

4.5.8 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.

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).

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 exposures to the material and more communications from multiple sources to effectively convey the intended messages.

4.6 Strengths and Limitations

Like any study, these studies had both strengths and limitations. The samples were large, diverse, and sampled and weighted to match the demographic characteristics of U.S. adults. They included a demographically diverse population with varied tobacco use histories. They also included a substantial proportion of individuals with demonstrably limited health literacy. The samples were drawn from an opt-in online panel, but a majority of the U.S. population is online (Perrin et al. 2015) , and online panels can produce reasonable population estimates (Farrell 2010). Moreover, the sample was balanced and weighted to represent the demographic characteristics of the U.S. population.

One limitation is that the studies were conducted among adults who could legally purchase tobacco, and thus did not assess those under the legal age to purchase tobacco. However, tests of modified risk advertisements for Camel Snus among adults (18-65) and teens (14-17) showed comparable responses by adults and teens (Fix et al. 2017).

These studies assessed relative risk perceptions for Camel Snus compared to smoking in two different ways: a direct method where respondents directly indicated how the risks of Camel Snus compared to those of smoking, and an indirect method, where individuals separately gave quantitative ratings for each products' risks. The results across methods were consistent in demonstrating that respondents understood that Camel Snus had *less* risk, while also demonstrating that they did not come to believe that Camel Snus was without risk.

4.7 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 individuals 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 underestimate, based on the epidemiological evidence, 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. They understood that Camel Snus is addictive.

Current tobacco users, including those expecting 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.

5 Likelihood of Use Studies

5.1 Likelihood of Use Studies among Tobacco Users and Non-users after Exposure to the Modified Risk Messaging

As noted in the TCA and in FDA's MRTPA guidance, it is important to consider who is likely to use a modified risk product, and particularly to consider potential use by current smokers compared to those not currently using tobacco. Accordingly, RJRT conducted studies to understand the likelihood of use of Camel Snus in such key population subgroups following exposure to each of the proposed modified risk advertisements.

The aim of the three likelihood of use studies was to estimate the likely use of Camel Snus with proposed modified risk advertising in relevant sub-populations, particularly contrasting likely use in the target sub-group (current smokers, especially those not expecting to quit) and off-target sub-groups (former and never users of tobacco, and those current users expecting to quit.)

5.1.1 Methods of the likelihood of use studies

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 and seen below, resembled the proposed modified risk advertisement but did not include modified risk information *or* other cautions or warnings regarding snus (aside from the legally-mandated warnings). The warning label statements mandated by statute were included on both the test and control advertisements.

Control Advertisement Cover Page:

Control Advertisement Interior Pages:

Large samples (~11,000-14,000 for each Execution) were recruited for the three studies. The need for large samples was dictated by the need to produce estimates to inform statistical modeling, which required likelihood of use in various subpopulations, stratified by age. The samples comprised US adults (≥ 18 years old, legally eligible to purchase tobacco in their jurisdiction) recruited from an online consumer research panel. The samples were diverse and balanced and weighted to represent the U.S. adult population and included current, former, and never tobacco users.

After viewing the advertisements (test or control), 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." An empirically derived algorithm was used to transform these arbitrarily-scaled Likert ratings into projected probabilities of actually purchasing Camel Snus for personal use. The algorithm was developed in a separate longitudinal study that analyzed how questionnaire-expressed interest in a tobacco product related to actual purchase and use in the ensuing 9 months. This study used logistic regression to estimate the probability of use from such ratings, and from the respondent's demographics and tobacco-use status.

Among current smokers, additional questions identified respondents who were expecting to quit to assess appeal to this off-target group compared to the appeal to the target group of

smokers who were not expecting to quit. Among never users of tobacco, smoking susceptibility (Pierce et al. 1996) was assessed to differentiate those at risk to initiate smoking versus those not susceptible. 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.

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). 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.

These estimates also serve as empirical inputs into modeling of population health (*see* MRTPA Section 6 Statistical Modeling) under various scenarios and assumptions, helping to estimate the 'net' impact of Camel Snus as an MRTP on population health (*see* MRTPA Section 6.4).

In addition to assessing likelihood of use, the questionnaire included follow-up questions that asked those who indicated any interest in Camel Snus (scoring >1 on the 1-10 scale) about how and why they might use the product. These questions were considered more hypothetical, as they required more speculation on the part of the respondent, and, unlike the likelihood of use ratings, were not validated in any way.

5.1.2 Findings from the likelihood of use studies

The results were largely consistent across the three likelihood of use studies, and so are described collectively, with results sometimes given as the range across studies and Executions. Detailed descriptions of the results for each study Execution are reported in MRTPA Section 6.3.

Consistently, interest in Camel Snus and probability of use were much greater among current smokers (the intended target population for switching to Camel Snus) than among never or former tobacco users (not intended to use Camel Snus). In response to the modified risk advertisements, the projected use among current smokers was about 20 times greater than that among never users, and 4-7 times greater than among former users (current smokers: 6-8%; never tobacco users: 0.3-0.4%; former users: 1.2-1.4%). Importantly, the proposed advertisements (compared to the controls) differentially increased interest among current smokers, and not among never smokers or former smokers.

The proposed modified risk advertisements also did not differentially appeal to smokers who were expecting to quit; smokers expecting to quit expressed less interest in using Camel Snus than did smokers who were not expecting to quit, and their interest was not increased by seeing the modified risk advertising.

In a similar vein, among never users of tobacco (which included experimenters, who never established use), interest was higher among those susceptible to smoking, and very low among those not susceptible to take up smoking. 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).

Interest in Camel Snus was also 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, more speculatively, how likely they were to return to using other tobacco products that present greater risk. In each Execution, the mean ratings of likely future smoking were numerically lower among former tobacco users who were shown the proposed modified risk advertisements compared to those who were shown the control advertisement.

Similarly, never users who expressed any interest in Camel Snus were asked to speculate about the likelihood of later switching to another tobacco product, such as cigarettes (i.e., a potential "gateway" effect). In this group, seeing the proposed modified risk advertisements decreased the expected likelihood of then progressing to another tobacco product such as cigarettes. Thus, the proposed modified risk advertising is very unlikely to increase any risk of gateway effects.

Overall, the findings from the likelihood of use studies demonstrate that the proposed modified risk advertisements for Camel Snus attracted interest from the target for modified risk messaging – current smokers who were not expecting 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.

5.1.2.1 Camel Snus with modified risk advertising appeals most 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 5.8-8.2% (across Executions) of current smokers would try Camel Snus after seeing the proposed advertisements with modified risk messaging. This degree of projected use was consistently several times higher than that seen in former tobacco users and never tobacco users (See Section 5.1.2.4-5.1.2.5). Exposure to the proposed modified risk advertisements increased current smokers' likelihood of trying Camel Snus (relative to exposure to the control advertisement). The increase was modest (5.4-5.8%, 6.9-8.2%, and 6.9-8.0% 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; the difference was significant for Executions 2 and 3.

Among smokers who were not expecting 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 expecting to quit were significantly lower, at 3.9-4.7%, as discussed below.

5.1.2.2 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. 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 expecting to quit, possibly delaying or deterring them from quitting, this could result in harm. Therefore, the appeal of Camel Snus proposed modified risk advertising was assessed among current smokers who expected to quit in the succeeding 9 months (matching the 'window' for estimated use of Camel Snus).

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

Although interest in Camel Snus was higher among current smokers who were not expecting to quit, there was some projected trial (3.9-4.7%) among current smokers who were expecting to quit. In follow-up questioning, the potential quitters who expressed any level of interest in trying Camel Snus (>1 on the 1-10 scale) were asked to indicate the reason for their interest in Camel Snus. 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. In all three proposed advertising Executions, the percentage of potential quitters who were interested in Camel Snus to help them quit smoking was numerically higher among those exposed to the proposed modified risk advertisement than the control advertisement.

The largest remaining fraction (20-36%) said they were "just curious," which may also suggest it would be unlikely to deter quitting.

Finally, the least common reason smokers expecting to quit gave for interest in Camel Snus was 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. In any case, the overall proportion of this subpopulation considering this use was very low (<0.5%), suggesting 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 expecting to quit, or to deter them from quitting.

5.1.2.3 The majority of current smokers not expecting to quit who are interested in Camel Snus expect to use it to stop smoking or to reduce smoking, as opposed to supplement smoking

To maximize the harm reduction benefit of Camel Snus, smokers should switch completely to Camel Snus, and the Camel Snus proposed modified risk advertisements emphasize this by framing the harm reduction benefit as applying to those who switch completely from cigarettes to Camel Snus.

After exposure to these messages, smokers who did not expect to quit (the target for harm reduction with Camel Snus advertising) were asked how they envisioned using 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 necessarily stopping) their cigarette smoking, and using Camel Snus in place of some current tobacco use.

In the likelihood of use studies, 20-23% envisioned adding Camel Snus to their current smoking. Another 26-32% of respondents did not know how they might use Camel Snus, perhaps because the questions required considering a further hypothetical, and the question was asked even of those with only minimal interest in Camel Snus (i.e., any but the lowest rating on the 1-10 scale).

5.1.2.4 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., a gateway effect) (Kozlowski et al. 2003; Lee 2015).

Ratings from respondents who had never used tobacco indicated very low interest in trying Camel Snus (projected trial rate of 0.3-0.4% across the three study Executions). Further, exposure to the Camel Snus proposed 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 likely to do so at a later time. The likelihood of use studies used standard measures of 'susceptibility' to smoking (Pierce et al. 1996) – a predictor of subsequent smoking initiation – to identify subsets of never users who were or were not susceptible to smoking.

Although projected use of Camel Snus was very low among all never tobacco users, it was consistently lower (by 50-70%) among those not susceptible to smoking – those not likely to initiate tobacco use – regardless of 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 compared to older adults (i.e., those older than 27).

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. The few never tobacco users attracted to Camel Snus tend to be individuals who are susceptible to initiating smoking, for whom adoption of Camel Snus instead of smoking would represent a reduction in risk.

5.1.2.5 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 have never used tobacco, those who have 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.

Former users of tobacco expressed little interest in trying Camel Snus (projected use ranged from 1.2-1.4% 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 1.9-2.1%, and in no case was increased by exposure to the modified risk advertisements. It is possible that some of this group's interest in using Camel Snus derives from concerns about the risk of relapse to smoking.

In any case, the data suggest that the Camel Snus proposed modified risk advertising is not likely to result in a return to tobacco use among former tobacco users or former smokers.

5.1.3 Strengths and limitations

Like any study, these studies had both strengths and limitations. Strengths include large and diverse samples that were weighted to match the demographic characteristics of U.S. adults. The studies included demographically diverse populations with varied tobacco use histories. The samples were drawn from opt-in online panels, but a majority of U.S. individuals are online (Perrin and Duggan 2015), and online panels can produce reasonable population estimates (Farrell and Peterson 2010). Moreover, the samples were balanced and weighted to represent the demographic characteristics of the U.S. population.

One limitation is that the studies were conducted among adults who could legally purchase tobacco, and thus did not assess those under the legal age to purchase tobacco. However, data among young adults suggest that there was little interest in Camel Snus among those not using tobacco and modified risk information did not increase their interests. Tests of modified risk

advertisements for Camel Snus among adults (18-65) and teens (14-17) showed comparable responses by adults and teens (Fix et al. 2017). Moreover, the age of tobacco initiation has now shifted from teens to young adults (Perry *et al* 2018) who were included in the sample.

The studies relied on self-reported interest in purchasing Camel Snus after seeing an advertisement. While self-reported interest does not translate directly to actual purchase or use, the studies used an empirically-derived algorithm to project initial use rates. The algorithm also projects initial purchase, not long-term persistence, and it is likely there is considerable fall-off after initial trial (Carpenter et al. 2016). Thus, projected purchase rates over-estimate persistent use.

On the other hand, it is reasonable to expect that the consistent finding of greater use among current smokers, especially those not expecting to quit would be maintained, even if the overall usage is lower. Moreover, the trial rates projected here, based on the algorithm, are for usage over a 9-month period, and so likely underestimate usage over longer periods, such as the 5-year periods used in statistical modeling (below).

While the use of self-reported likelihood of use was validated as a predictor of actual use, some of the questions that asked respondents how or why they would use Camel Snus were more speculative. Thus, the projected rates of use for various subpopulations are likely more valid than are these less behavioral reports.

5.1.4 Conclusions from the likelihood of use studies

The net population health effect of the proposed modified risk advertising for Camel Snus depends on who uses the product. Adoption by the key intended target population – current smokers, particularly those who are not expecting to quit – would have favorable effects. Findings from the likelihood of use studies indicate that current smokers – especially those who were not expecting to quit – showed the highest projected use of Camel Snus, and their projected use was increased by exposure to the modified risk advertising.

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).

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 completely 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 cautionary messages that were not part of the control advertisement:

- "Camel Snus contains nicotine and is addictive;"
- "No tobacco product is safe;"
- "Adults who do not use or have quit using tobacco products should not start;"
- "Minors and pregnant women should never use tobacco products;" and
- "If you're a smoker concerned about the health risks from smoking, the best choice is to quit."

These messages may have reduced interest in Camel Snus when seeing the proposed modified risk advertisements. In any case, it is the likelihood of use after seeing the proposed modified risk advertising that is relevant to understanding its public health impact.

Importantly, the benefit of smokers switching 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 consistently show 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 use among current smokers was several times higher than among former smokers, and some 20 times higher than among never users of tobacco.

Being exposed to the proposed modified risk advertisements increased projected purchase among current smokers, but not among former and never smokers. Among current smokers, projected use of Camel Snus was consistently higher among the smokers who were expecting to continue smoking compared to smokers who were expecting to quit, and the proposed modified risk advertising did not differentially attract (or deter) those expecting to quit.

The rates of use estimated from the likelihood of use ratings were based on an empirical algorithm. It is possible that the estimates over-estimate use. 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 data is robust.

Altogether, these data suggest that the benefit gained through having continuing smokers switching 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. In the section that follows, this proposition is formally evaluated using statistical modeling of population effects, using the likelihood of use estimates as inputs, and integrating the expected benefits and harms to estimate the net impact on population health of Camel Snus with modified risk information.

6 Population Modeling

Under Section 911(g)(1)(B) of the TCA, the granting of a risk modification order is based on an expectation that advertising a tobacco product as modified-risk will benefit the health of the population as a whole, taking into account both tobacco users and non-users. Assessing the overall population health effect of a product and its proposed advertising requires the use of statistical modeling because the effect must be assessed prior to the order being granted. Such modeling integrates evidence on changes in tobacco use patterns that may occur in relevant subgroups of the population, and the ensuing effects of those changes on individuals' health to assess the overall effect on population health.

A considerable amount of epidemiological evidence demonstrates that the health risks associated with using snus are substantially reduced compared to cigarette smoking. Moreover, likelihood of use studies projected probabilities of use for Camel Snus with its proposed modified-risk advertising among relevant subgroups of the population (in particular, current smokers who are not likely to quit smoking (continuing smokers), tobacco non-users who are not susceptible to smoking, and current smokers who are likely to quit). Results from these studies show that those mostly likely to use Camel Snus are those most likely to benefit from its use (continuing smokers). Statistical modeling, which integrates the projected patterns of use for Camel Snus and its associated risks relative to cigarettes, provides an estimate of the effect on all-cause mortality for the population as a whole (as a surrogate for population health). Accordingly, modeling estimates based on an estimated risk reduction of 89% for the use of Camel Snus compared to smoking project substantial population health benefits – ranging from 350,000 to 450,000 additional survivors through age 72 – for the three advertising executions.

The Dynamic Population Modeler (DPM) (Bachand and Sulsky 2013; Bachand et al. 2018) was used to assess the overall population health effect likely to result from advertising Camel Snus as a modified-risk product. The modeling fully accounted for both the benefits and harms that may result from use of the product by tobacco users and non-users, and projected a substantial benefit for the full population (a population of mixed gender, age (13-67 years), and smoking states (e.g., current, former, and never smoking)). The favorable direction and substantial magnitude of that projected benefit provides a high level of confidence that the specific advertising detailed in Camel Snus MRTPAs will lead to an overall population health benefit. Confidence in a population health benefit is warranted based on a number of features specific to the modeling itself, including: (1) use of a model with demonstrated validity; (2) accounting of all harmful changes in tobacco use that may occur for Camel Snus; (3) heavy reliance on

empirically derived model inputs; and, (4) extensive sensitivity testing of those inputs that are primary to the projected benefit. The projected population health benefit for Camel Snus, as well as the aforementioned modeling features are discussed in detail in subsequent sections.

6.1 Population Health Benefit for Camel Snus with Modified Risk Advertising

The statistical model used to assess Camel Snus and its modified-risk advertising was designed to estimate the overall effect of an intervention on a single cohort that was followed over time to a certain end-point (e.g., from the age of tobacco initiation to age 72). For the Camel Snus modeling, this framework was adapted to estimate the effect of changes in tobacco use patterns that may result across multiple cohorts representing the full population (a population of mixed gender, age and smoking states).

The modeling for Camel Snus estimated the overall population health effect of the proposed advertising by following multiple cohorts over time – integrating evidence on transitions among tobacco use states and the health consequences of those changes. The model included a base case, or 'what currently is' scenario, in which individuals can either be smoking or abstinent from smoking. Age-specific changes in tobacco use patterns were based on empirical data for these transitions in the U.S. population and the impact of these usage patterns on mortality. The counterfactual, or 'what could be' scenario, built upon the base case by adding the possibility of transitioning to or from the use of Camel Snus. Estimates for these transitions were based largely on projections from likelihood of use testing, and the impact of these transitions on mortality was based on epidemiological data (for the health risks of using snus relative to smoking).

The modeling considered both beneficial transitions (such as switching from smoking to the use of Camel Snus by continuing smokers) and a full range of harmful transitions (such as initiation of snus use by individuals who would have otherwise remained abstinent, and the possibility that initiating the use of snus may cause some individuals to progress to smoking). For the Camel Snus modeling, birth cohorts were followed from their index age to age 72, with transitions in tobacco use states having the potential to occur every 5 years. By comparing the mortality projected in the ‘what could be’ scenario (expressed as the number of individuals surviving through age 72) to that for the ‘what currently is’ scenario, the model provided a quantitative estimate of the overall population health effect of advertising Camel Snus as a modified-risk product.

The multiple cohort analyses used for the Camel Snus modeling assessed the effect of the proposed advertising on the full population (modeled as a series of birth cohorts), with each cohort having reached a different index age at the time when the advertising was communicated. Specifically, each cohort had progressed to its current age under the ‘what currently is’ scenario, such that individuals (in that cohort) could be never smokers, current smokers or former smokers. The transitions to and from Camel Snus were then introduced at different index ages across the full population, and had the potential to affect both current smokers and tobacco non-users in the ‘what could be’ scenario. In the aggregate, these

multiple cohort analyses estimated the effect of advertising Camel Snus as a modified-risk product to the full population. Cohorts were grouped into 5-year age intervals.

Thus, the modeling posited that each age group had reached its index age with cigarettes available, but not Camel Snus. Each age group then gained access to Camel Snus and its advertising at that index age (current age), enabling transitions to the product as they entered the next 5-year age interval (e.g., individuals in the cohort ages 33-37 may have initiated or quit smoking up to that age, and then may have adopted Camel Snus starting at age 38). The multiple cohort analyses were based on empirical probabilities for primary changes in tobacco use patterns projected from likelihood of use testing, as well as conservative estimates for secondary harmful transitions (e.g., from Camel Snus use to smoking). Separate analyses were conducted based on excess relative risks (ERR) of 0.08 and 0.11 (ERRs of 0.08 and 0.11 equate to risk reductions of 92% and 89%, respectively, comparing the use of snus to smoking, based on estimates from Levy et al. 2004).

Table 6-1 presents the projected effects on survival (through age 72) for each of the 5-year age cohorts comprising the full population. The table shows that the changes in tobacco use patterns that may result from advertising Camel Snus as modified-risk would benefit survival for individuals in each of the 5-year cohorts, indexed by their age at the time that the advertising was communicated. The magnitude of the projected benefit is greatest for 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 accrue the benefit from switching from smoking to Camel Snus over a longer period of time. While some smokers in the older cohorts will have already died or incurred substantial risk from smoking before being informed of the lower risks for Camel Snus, benefits in these cohorts would be realized sooner as they are closer to age 72 (the age at which survival was tallied in the model).

As seen in Table 6-1, estimates from these analyses project a substantial survival benefit to result from advertising Camel Snus as a modified-risk product to a population of mixed gender, age (13-67 years) and smoking states. Using the more conservative ERR of 0.11 (89% risk reduction), the number of additional survivors to age 72 ranges from approximately 350,000 to 450,000 across the three executions of the modified-risk advertisement.

Table 6-1: Projected increases in the number of survivors through age 72 for multiple cohort analyses, sized to U.S. population

Birth cohorts, indexed by age when advertising communicated	Execution 1		Execution 2		Execution 3	
5-year intervals	**ERR=0.11**	**ERR=0.08**	**ERR=0.11**	**ERR=0.08**	**ERR=0.11**	**ERR=0.08**
13-17†♦	107,289	115,336	126,963	137,034	117,729	126,889
18-22†	91,591	98,053	113,964	122,647	108,509	116,586
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
Cumulative totals‡	**351,816**	**376,008**	**447,109**	**479,943**	**428,276**	**459,178**

♦ This cohort cannot engage in switching to Camel Snus until it has initiated smoking, which can occur in the 13-17 age interval at the earliest (the first age for switching is later than the age for initiation); thus, the earliest switching can occur is in the age 18-22 interval.
† These cohorts can initiate tobacco use with Camel Snus (initiation is modeled as occurring only up to age 27).
* This is the last age interval during which switching can affect the model outcome (survival, at the next interval).
‡ The secondary harmful transition of relapse cannot directly be modeled, but instead was assessed during sensitivity testing (testing indicated a reduction in the overall survival benefit of approximately 12-16%).

While the cumulative totals for the projected increases in additional survivors for the full population are substantial, statistical modeling is best suited for more general estimation of population trends and likelihoods – meaning that it is the direction and magnitude of the overall population estimate that is most informative. In this case, the magnitude of the projected survival benefit for Camel Snus provides strong evidence that the changes in tobacco use patterns that may result from the proposed advertising will benefit population health.

A number of features specific to the modeling itself provide high confidence for the substantial population health benefit projected for Camel Snus with modified-risk advertising. First, the model used for the analyses was validated by faithfully reproducing mortality statistics from the U.S. and Sweden. Second, the modeling accounted for all harmful changes in tobacco use that

may occur for Camel snus – including tobacco non-users initiating with snus and subsequently transitioning to smoking (gateway effect) and current smokers being diverted from quitting. Third, the modeling relies heavily on empirically derived model inputs, including transition probabilities to and from smoking, transition probabilities for the initiation and adoption of Camel Snus (from likelihood of use testing), and the mortality rates for those transitions. Finally, the modeling is supported by extensive sensitivity testing of the primary inputs (those with the greatest potential to affect the projected benefit). Each of these modeling features is discussed in greater detail below.

6.2 Multiple Cohort Analyses Based on Model with Demonstrated Validity

6.2.1 Validating the DPM

Models can be validated by evaluating their ability to retrospectively predict a known outcome. To that end, two validation assessments were conducted for the DPM (Bachand and Sulsky 2013) – one validating the base case for smoking (using U.S. data on smoking behavior and the impact of smoking on mortality), and the other validating the counterfactual for use of snus (using the same type data from Sweden). As described below, both successfully modeled actual population mortality to within less than 0.3% of the observed values. Jointly, these two validation assessments demonstrated the validity of the DPM and its assumptions to estimate all-cause mortality in a population transitioning from smoking to the use of snus. Thus, the model is appropriate for projecting the overall population health effects of advertising Camel Snus as a modified-risk product.

6.2.1.1 Validating the DPM base case for smoking

For the first validation, the model was used to predict mortality in the U.S. population, based on model inputs and assumptions about the dynamics of smoking behavior (without snus) and the impact of smoking on mortality. The model was used to estimate mortality in 2006 using age-specific 1980 U.S. smoking initiation (SAMHSA 1999) and smoking cessation (Messer et al. 2007) rates; the modeling results were compared to the 2006 U.S. life table for men (Arias 2010). Table 6-2 shows the results, with the number of survivors estimated by the model's base case being within 0.02% of the U.S. life table-based actual number of survivors. This demonstrates that estimates derived from the model very closely match the observed mortality experience of the U.S. population, validating the DPM and its assumptions for the base case.

Table 6-2: Number of survivors by age interval: 2006 U.S. life table versus model estimates (starting with 1,000,000 13-year-old male never tobacco users)

Age interval (years)	Survivors based on U.S. life table	Survivors based on model estimate
38-42*	957,654	957,100
43-47	940,866	939,200
48-52	915,745	914,300
53-57	880,470	879,800
58-62	832,268	832,000
63-67	764,922	765,600
68-72	674,217	674,300

*Age interval 38-42 is the first age group where all possible tobacco use transitions have occurred.

6.2.1.2 Validating the DPM counterfactual for smoking with snus availability

The second validation used Swedish data for the use of snus, and transitions between smoking and snus to predict mortality outcomes in Sweden. The model used empirically derived probabilities of transitioning among cigarettes, snus and dual use in Sweden (Lundqvist et al. 2009), with some adjustments (Bachand and Sulsky 2013). The model assessed survival using the assumption that the all-cause mortality risk of snus is reduced 89% compared to smoking (equating to an ERR of 0.11) (Levy et al. 2004).

Projections of survival from the model were compared to observed survival rates, based on the 2006 Swedish life table for men (Swedish Statistics 2012). As shown in Table 6-3, the number of survivors estimated by the model was within 0.3% of the Swedish life table-based number of survivors. This demonstrates that the DPM is a valid model that can be used to estimate the population health effects of a lower-risk tobacco product (snus).

Table 6-3: Number of survivors by age interval: 2006 Swedish life table versus model estimates (starting with 1,000,000 13-year-old male never tobacco users)

Age interval (years)	Survivors based on Swedish life table	Survivors based on model estimate
38-42*	980,999	979,274
43-47	972,889	970,010
48-52	959,782	957,276
53-57	936,838	935,677
58-62	902,590	902,104

Age interval (years)	Survivors based on Swedish life table	Survivors based on model estimate
63-67	846,884	847,362
68-72	764,275	762,582

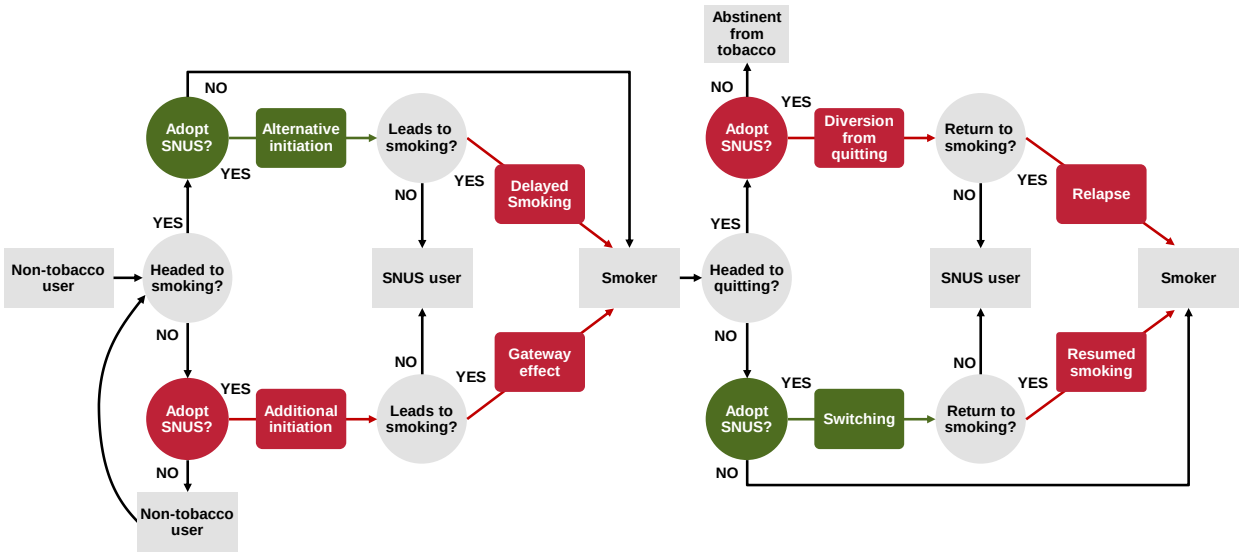
* Age interval 38-42 is first age group where all possible tobacco use transitions have occurred.

6.3 Modeling Accounts for All Potentially Harmful Changes from Camel Snus Use

DPM uses a cohort framework to contrast the projected number of survivors for two scenarios. Specifically, a 'what currently is' scenario, or simplified base case that only allows the use of cigarettes; and, a 'what could be' scenario, or counterfactual that allows the use of cigarettes and/or Camel Snus.

Figure 6-1 presents the tobacco use transitions accounted for in the modeling, considering the likelihood of adoption of Camel Snus by relevant subgroups of the population. The transitions in the 'what could be' scenario are classified as harmful or beneficial to the affected individuals compared to the 'what currently is' scenario (only transitions are between smoking and abstinence). As show in the figure, the modeling accounted for a wide range of use patterns among tobacco users and non-users, including those expected to benefit population survival (in green) and those that may be harmful to the population (in red).

Figure 6-1: Modeling Projects Net Population Health Effect



Each of the eight transitions is briefly summarized in Table 6-4, with each transition given a brief descriptor that will be used in the sub-sections that follow the table. The modeling includes two beneficial transitions (alternative initiation and the intended transition of switching) and six harmful transitions that may result from use of Camel Snus. Three of the

harmful use patterns are related to the initiation of snus use by tobacco non-users (left half of the schematic; additional initiation, gateway effect and delayed smoking), while the other three are related to the adoption of snus by smokers (right half of the schematic; diversion from quitting, relapse and resumed smoking). The harmful pattern of relapse could not be modeled directly, and was accounted for during sensitivity testing.

Table 6-4 distinguishes primary and secondary transitions in tobacco use. Primary transitions are those that involve a single change in tobacco use state (e.g., from abstinence to use of snus); probabilities for these transitions were estimated from likelihood of use testing conducted for Camel Snus with modified-risk advertising. Secondary transitions are those that involve a second transition, caused by the first (e.g., the initiation of snus causing a further transition to smoking - one that would not otherwise have occurred). These could not reasonably be estimated from likelihood of use testing (as they require imagining two counterfactuals, the second in response to the first), and were estimated conservatively at 50%.

Table 6-4: Tobacco use transitions accounted for in the Camel Snus modeling

Transition Type	Description of Tobacco Use Transition	Descriptor	Health Impact
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**

Transition Type	Description of Tobacco Use Transition	Descriptor	Health Impact
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 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, yet those individuals are no worse off than they were before using Camel Snus.
ˈThese analyses treat smokers who initially switch to Camel Snus but then return to smoking as though they never used Camel Snus at all, rendering this secondary 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 transition probability. This is conservative, as it does not consider any benefit due to a limited period of Camel Snus use 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. 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 are caused to 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 a counterfactual that includes relapse is compared to survival in a counterfactual that does not include that transition. The difference in estimates between the two counterfactuals is then used to adjust the estimated survival (in analyses meant to include relapse).

6.3.1 Transitions related to initiation of Camel Snus by tobacco non-users

The modeling considered the health effects of initiation of Camel Snus by individuals who had not previously used tobacco (initiation with Camel Snus). The model considered two different pathways of initiation – according to whether non-tobacco users were or were not susceptible to smoking – each with different implications for population health.

6.3.1.1 Additional initiation

Although Camel Snus presents substantially less risk to health than smoking, it still carries some risk. Thus, an individual who otherwise would not have used tobacco but initiates use of Camel Snus as a result of exposure to the proposed advertising could consequently be harmed. The probability of such additional initiation is derived from individuals' responses in the likelihood

of use testing – 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 (SGR 2012). Accordingly, the modeling used projected probabilities for initiation of Camel Snus from respondents ages 18-27, and applied these transition probabilities to each of the first three 5-year age intervals in the model (ages 13-17, 18-22 and 23-27). Across all three executions of the likelihood of use testing, the projected probability for this transition was 0.3% in each 5-year age interval.

6.3.1.2 Gateway effect

Individuals who engage in additional initiation incur the risk associated with using Camel Snus (compared to remaining abstinent). The harmful health effect is even greater for those who are thereby caused to then subsequently progress to smoking (gateway effect), with its increased risk. As this secondary harmful transition cannot be estimated from the likelihood of use testing, it was assigned a probability of 50% (modeling conservatively assumed that half of all individuals who engage in additional initiation would be caused to progress to smoking). The gateway effect was accounted for by transitioning the affected individuals to smoking in the next age interval after they had initiated use of Camel Snus.

6.3.1.3 Alternative initiation

While initiation of Camel Snus by someone who would not have otherwise used tobacco is potentially harmful, initiation of Camel Snus by individuals who otherwise would have smoked cigarettes (alternative initiation) can be beneficial, as it exposes those individuals to a comparatively lower risk than smoking. The probability of this transition was estimated from the likelihood of use testing, where participants who were assessed to be susceptible to smoking (Pierce et al. 1996) rated their likely use of Camel Snus in response to the proposed advertising. Since tobacco initiation is highly unlikely after age 26 (SGR 2012), the model applied the transition probability projected for ages 18-27 to each of the first three 5-year age intervals in the model (ages 13-17, 18-22 and 23-27). The probability of this transition in each age interval was projected to be 0.50%, 0.85%, 0.70%, respectively, for Advertising Executions 1, 2 and 3.

6.3.1.4 Delayed smoking

Some individuals who initiate Camel Snus instead of smoking (alternative initiation) might nevertheless transition to smoking (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 harmful transition, could not be estimated from the likelihood of use testing. Thus, it was assigned a probability of 50% (modeling conservatively assumed that half of those who initiated Camel Snus instead of smoking would subsequently progress to smoking anyway, thus diminishing the potential benefit of using Camel Snus instead of smoking).

6.3.2 Transitions related to adoption of Camel Snus by smokers

The statistical modeling considered the health effects of adoption of Camel Snus by individuals who had previously initiated smoking. The model considered two different pathways of adoption (whether that smoker was or was not otherwise likely to quit smoking), each with different implications for population health.

6.3.2.1 Switching (intended tobacco use transition of advertising)

Among smokers who were not likely to quit smoking (who otherwise would have continued to smoke), adopting Camel Snus instead of continuing to smoke (switching) confers a health benefit, since Camel Snus is substantially less harmful than cigarette smoking. Smokers in the likelihood of use testing whose survey responses indicated that they were not likely to quit smoking were used to generate empirical probabilities for switching (the intended behavior of the advertising). Probabilities for switching were higher among younger compared to older smokers, and age-specific rates were used for the modeling. The projected transition probabilities differed somewhat among the three advertising executions tested, with probabilities ranging from 14.2-16.5% among younger smokers to 1.7-3.1% among smokers over age 62.

6.3.2.2 Resumed smoking

Some continuing smokers who switch to Camel Snus may eventually return to smoking. The likelihood of this secondary harmful transition (resumed smoking) could not be reliably projected from the likelihood of use testing. Thus, it was assigned a probability of 50%; that is, it was assumed that 50% of the smokers who adopt Camel Snus instead of continuing to smoke would return to smoking in the same age interval.

6.3.2.3 Diversion from quitting

Unlike smokers who would otherwise continue smoking, smokers who switch to Camel Snus instead of quitting (diversion from quitting) could be harmed. Diversion from quitting was estimated from the likelihood of use testing based on projected use of 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 for Camel Snus among those smokers likely to quit was higher in younger smokers, and age-specific probabilities were applied in the modeling. The projected probabilities for diversion from quitting varied somewhat across advertising executions, varying from 8.6-20.0% in the youngest age interval and ranging from 1.6-2.2% in the oldest age interval.

6.3.2.4 Relapse

Smokers who would otherwise have quit all tobacco use and instead adopt Camel Snus (diversion from quitting) are potentially 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 are caused to subsequently return to smoking as a result of adopting Camel Snus (relapse), this would increase their risk relative to quitting and remaining abstinent. The effect of relapse after quitting could not be directly estimated within the model, and was instead estimated in separate analyses (comparing two counterfactuals); the results were then applied as an adjustment to model results. Like other secondary transitions, relapse could not be estimated from the likelihood of use testing but was instead assigned a conservative probability of 50%.

6.3.3 Simplifying assumptions adopted for the Camel Snus modeling

DPM makes some simplifying assumptions in order to address the challenges of assessing the long-term, real-world effect of changes in tobacco use patterns that may occur as a result of advertising Camel Snus as modified-risk. Survival estimates projected from the modeling were based on male mortality data, which were then adjusted for the difference between male and female data on smoking and mortality (See MRTPA Section 7 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, Appendix H; 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, Appendix H; 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, Appendix H).

The modeling assumed that the health effects of tobacco use varied entirely with tobacco use state (cigarette smoking or not, using Camel Snus or not) and duration, but did not vary with the amount of smoking or quantity of Camel Snus used. The modeler also only considered two states of tobacco use (cigarette smoking and use of Camel Snus); no other tobacco product was considered.

Also, consistent with data from epidemiological studies and from human biomarker data, the modeling considered dual use of Camel Snus along with cigarettes to have the same high mortality risk as continued smoking.

Finally, the current modeling did not allow for a transition from Camel Snus to abstinence (individuals who adopted Camel Snus could transition to cigarette smoking but not to abstinence from all tobacco), because data on the rate of quitting Camel Snus (as a modified-risk product) were not available. This is a conservative assumption, as some Camel Snus users are likely to transition to abstinence from all tobacco, which would be beneficial.

6.4 Modeling Relies Heavily on Empirically Derived Inputs

The modeling for Camel Snus was based on inputs that were empirically derived (*see* Table 6-5). Primary inputs included those for mortality (calculated for each 5-year age interval) and changes in tobacco usage patterns (allowed to occur at each age interval).

Table 6-5: Empirically Derived Model Inputs

	Model Inputs	Supporting Source Data
Mortality rates **Each 5-year interval (current age, duration of tobacco use, duration of quit)**	**Cigarette smoking**	**Kaiser-Permanente Cohort Study**
	Camel Snus use	**Levy et al. (2004) evidence synthesis (89% and 92% risk reduction)**
Transition probabilities **Changes in tobacco use may occur at each 5-year age interval**	**Cigarette smoking**	**U.S. initiation/cessation rates (NSDUH)**
	Camel Snus use	**Age-interval-specific probabilities from 'likelihood of use' testing**
	Camel Snus use to smoking	***Hypothetical* probabilities (50% of snus users)**

Mortality rates. Age-interval-specific all-cause mortality rates for current, former and never smokers were calculated using data from the Kaiser-Permanente Cohort Study (which provides mortality rates by age, gender, duration of smoking and duration of smoking cessation) (Friedman et al. 1997) and the 2000 U.S. Census (USNCHS 2000) (Bachand & Sulsky 2013). Results comparing the number of survivors in the 'what could be' (counterfactual) scenario and 'what currently is' (base case) scenario were projected through age 72, with estimates beyond this age becoming increasingly uninformative (as the number of survivors in both scenarios approached zero).

Excess relative risk of snus compared to smoking. Consensus estimates provided by Levy et al. (2004) were used for the expected reduction in all-cause mortality risk when switching from smoking to Camel Snus. These estimates were based on a review of the available published literature on the health risks for low-nitrosamine smokeless tobacco products, and suggested a reduction in risk of 89% (ages 35-49) and 92% (ages 50+) for snus compared cigarette smoking (uncertainty in the adjusted means for the estimated risk reductions was accounted for by modeling ERRs as left-truncated normal random variables; for example, using a mean of 0.08 and a standard deviation of 0.01, which ensured a range for the ERR of approximately 0.05–0.11). As previously noted, dual use of snus and cigarettes was assigned the same risk as continued smoking for all Camel Snus modeling - consistent with evidence that dual use of these products is unlikely to increase exposure to harmful chemicals (Section 4).

Transitions to/from smoking. The 'what currently is' (base case) scenario specified transition probabilities based on 2009 US cigarette smoking initiation rates (SAMHSA 2010a) and 2005–2008 smoking cessation rates (SAMHSA2010b). Uncertainty in initiation and cessation rates was accounted for by modeling the transition probabilities as truncated normal random variables, with means equal to the respective estimates and standard deviations equal to 0.01.

Transitions to/from Camel Snus. Transition probabilities for the 'what could be' scenario were derived from the likelihood of use testing conducted for Camel Snus with modified risk advertising; specifically, age-interval-specific probabilities for relevant subgroups of the population - including 'continuing smokers' (who are the intended audience for the advertising) and tobacco non-users. Transition probabilities from likelihood of use testing were previously summarized (Sections 7.4.1 and 7.4.2). An empirically derived algorithm - based on prior research – was used to convert respondents' ratings of intent to purchase Camel Snus into projected probabilities of use.

6.5 Extensive Sensitivity Testing Conducted for Primary Model Inputs

The substantial population health benefit projected for Camel Snus and its modified risk messaging – like projections from all models – is sensitive to the inputs used. Sensitivity testing was conducted to assess the impact of variations in the inputs on the modeling projections.

6.5.1 Sensitivity testing for changes in tobacco usage patterns

Sensitivity testing considered the possibility that the empirically derived projections for changes in tobacco use patterns that may result from the proposed advertising may overestimate the actual rates at which relevant subgroups of the population adopt Camel Snus. Consistently overestimating likely product use across the population would not be expected to change the overall conclusion from the modeling that Camel Snus with modified-risk advertising will lead to an overall population health benefit, although it would be expected to diminish the magnitude of the benefit. This is because adoption of Camel Snus is responsible for *both* the benefits and harms in the modeling, with the accrual of benefits or harms depending on the population subgroup in question.

To assess the impact of variations in the projected transition probabilities, all empirically derived estimates for the primary tobacco use transitions were reduced by 75% (secondary transitions, which do not derive from the likelihood of use testing, were not changed). Multiple cohort analyses using these drastically reduced projections of Camel Snus adoption indicated a reduced population benefit - with projected survival benefits diminished by 73-74% across advertising executions and ERR values (*e.g.*, for Advertising Execution 2 and based on the more conservative risk reduction of 89%, the modeling projected about 120,000 additional survivors). It bears mentioning that, prior to this sensitivity testing, the empirical projections for switching (from cigarettes to snus) had already been reduced by 50% to account for resumed smoking. Thus, this sensitivity analysis effectively considered the rate of switching to be only 12.5% (25% of 50%) of that projected from the likelihood of use testing. Nevertheless, all of the analyses indicated a substantial overall population health benefit for the population as a whole, despite the dramatically discounted projections for use of Camel Snus.

6.5.2 Sensitivity testing for values of the expected reduction in risk

The modeling used two empirical estimates for the expected reduction in risk for using snus compared to smoking (ERRs of 0.08 and 0.11). To assess the impact of variations for these estimates, sensitivity testing was conducted to determine how high the ERR would need to be (how small the risk reduction associated with using snus compared to cigarettes would have to be) to offset the projected survival benefit for Camel Snus. Using empirically derived probabilities for the primary tobacco use transitions and conservative probabilities for the secondary harmful transitions (all retained at 50% transitioning to smoking), a range of ERRs was assessed to identify the percent risk reduction at which the overall population health effect would be near zero (neither beneficial nor harmful); this identifies the point below which snus would be projected to produce a benefit.

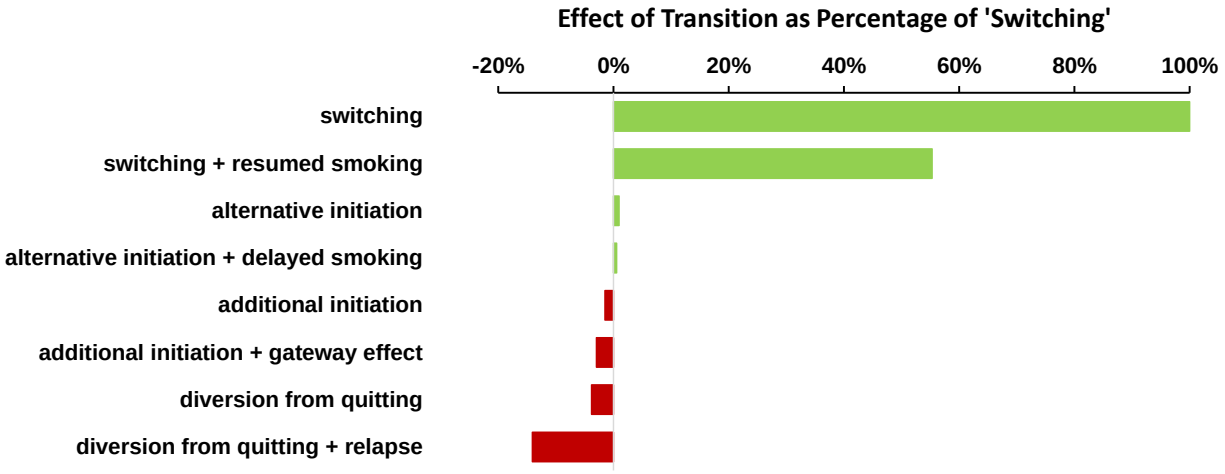
Across all advertising executions, the ERR that produced a near zero effect ranged from 0.46 to 0.48. Alternatively stated, as long as the risk reduction for Camel Snus compared to smoking was at least 53-55%, changes in tobacco use patterns that may occur for Camel Snus would be expected to have an overall beneficial effect on population health. These modeled values for the ERR are roughly 4-6 times higher than the expert consensus estimates used for the Camel Snus modeling (Levy *et al*. 2004), indicating that a substantially higher than estimated ERR would still result in a population health benefit. This lends confidence to the overall conclusion that Camel Snus with modified-risk advertising will benefit population health.

6.5.3 Identifying the most influential inputs

Sensitivity testing can also be used to identify the key variable(s) that influence the projected population health benefit for Camel Snus. Unlike the previously described multiple cohort analyses, this sensitivity testing focused on a single age-interval cohort – the cohort with the most opportunities to switch to and benefit from using Camel Snus (the one that enters the 'what could be' scenario at ages 13-17) – and examined the effects of individual tobacco use transitions on the projected survival benefit.

Figure 6-2 (based on Advertising Execution 2, and representative of results from the other two executions) presents the effects on population survival for each transition accounted for in the Camel Snus modeling; effects on survival are depicted as a percentage of the intended behavior of switching. These analyses make clear that the tobacco use transition with the greatest effect on the population survival was switching (by continuing smokers). The harmful (unintended) changes in tobacco use patterns – as projected by likelihood of use testing – had a much smaller effect on population health, due to their low probability of occurrence. This is the reason that the overall population health effect for Camel Snus with modified-risk advertising was projected to be beneficial.

Figure 6-2: Sensitivity Testing of Specific Behaviors (tobacco use transitions)



Thus, these analyses identified the proportion of continuing smokers who would switch to Camel Snus as the most important source of population benefit in the modeling. The projected rates of switching yield the population benefits described in section 6.1. Tipping point analyses reported in the Applications (*see* Sections 6.4.3.2, 6.4.6.2 and 6.4.9.2 for Advertising Executions 1, 2 and 3, respectively) identified the amount of switching that would be necessary to overcome even extreme hypotheticals for potentially harmful transitions. Estimates from these analyses indicated that generally low rates of switching (in each 5-year age interval) would be sufficient to offset the harms from the extreme transitions examined.

6.6 Limitations and Strengths

In advance of actual in-market experience with modified-risk tobacco product advertising (including post-marketing surveillance), statistical modeling provides the only means of assessing the overall population health effect of changes in tobacco use patterns likely to occur in relevant subgroups of the population, and the ensuing effects of those changes on individuals' health.

Primary inputs to the Camel Snus modeling included projected transition probabilities for product adoption by relevant subgroups of the population, which in turn were based on individuals' responses from likelihood of use testing. Self-reported likelihood of use ratings obtained in those studies were translated into probabilities of use according to an empirically derived algorithm.

A potential limitation to the modeling is that the projected probabilities for use of Camel Snus are unlikely to be exact, as they were based on trial use and thus may overestimate the persistent use needed to elicit changes in tobacco use patterns. Conversely, the algorithm-based projections may underestimate Camel Snus adoption, as they were based on product use in a relatively brief interval (9 months of follow-up after the baseline assessment), and the modeling was based on adoption of Camel Snus over a longer interval (5 years) that would

provide more opportunities for switching to snus (especially given a concerted advertising campaign directed to adult smokers).

Estimates from the likelihood of use studies may have also underestimated actual use of Camel Snus because they were derived from a single exposure to an advertisement with modified-risk information – one that countered 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). A more extended advertising campaign that provides relative risk information for Camel Snus may have a greater impact on product use.

In any case, sensitivity testing indicated that lower probabilities for Camel Snus adoption would still produce an overall population health benefit, and would be unlikely to produce population harm. This is because both the benefits and harms to the population as a whole depend on the use of Camel Snus – just in different subgroups of the population (e.g., continuing smokers compared to tobacco non-users). Thus, a consistent reduction in the estimated use of Camel Snus across the population subgroups is unlikely to change the conclusion that the overall effect of the modified-risk advertising will be beneficial.

Another potential limitation is that the primary analyses were based on single age-interval cohorts of 5 million individuals, and used smoking and mortality statistics for males. However, separate analyses suggested that the survival benefit for females was 19% lower than that for males, and projections were accordingly adjusted to account for a mixed-gender population. Nonetheless, the input estimates for the tobacco use transitions (whether empirically derived or conservative values) were not differentiated by gender – meaning the analyses do not take detailed account of gender differences.

The modeling for Camel Snus also benefits from considerable strengths, which in turn provide confidence in an overall population health benefit for the proposed modified-risk advertising. The model was validated against population data addressing the health effects of smoking (in the U.S.) and the adoption of snus (in Sweden). For both the base case (smoking) and counterfactual (use of snus), projected population mortality was modeled to within less than 0.3% of the values observed for the respective life-tables.

In addition, the modeling accounted for multiple transitions in smoking and snus adoption that could affect population health – including all of those that could potentially lead to population harm. Of the eight transitions accounted for in the model, six had the potential to harm overall population health (including initiation of Camel Snus by tobacco non-users who would have remained non-users, and subsequent transitioning to smoking; and, smokers who would have quitting smoking instead adopting Camel Snus).

To the extent possible, inputs for the transitions in smoking and adoption of snus were empirically derived. Transition rates for smoking were based on U.S. government survey data, and those for adoption of Camel Snus were based on empirically derived projections from likelihood of use testing. The modeling also incorporated conservative assumptions (e.g., by not

including the benefits of discontinuing use of Camel Snus), suggesting that the benefits may be greater than indicated by the overall population health estimate.

Finally, sensitivity and tipping point analyses showed that the overall population health benefit was projected across a range of assumptions and scenarios (*e.g.*, after reducing empirically derived projections for use of Camel Snus by 75%; or, reducing the estimated risk reduction for Camel Snus compared to smoking to 55%). Therefore, the overall conclusion from the extensive modeling conducted for Camel Snus – that the proposed modified-risk advertising will benefit the public health – is robust.

6.7 Modeling Predicts Camel Snus with Proposed Modified Risk Advertising Will Benefit Overall Population Health

The extensive modeling conducted for Camel Snus provides strong and consistent evidence that the proposed modified-risk advertising will yield an overall population health benefit. Based on multiple cohort modeling that integrated the effects of all potentially beneficial and harmful tobacco use transitions for the full population, it is projected that the proposed advertising would yield 350,000 to 450,000 additional survivors through age 72 (across executions, and based on the more conservative estimate for the reduction in risk for snus compared to smoking). A substantial population benefit would be retained even if adoption of Camel Snus is lower than projected, and even if the reduction in risk (compared to smoking) is less than estimated.

A number of features of the modeling approach adopted for the current analyses instill confidence in the projected population health benefit for Camel Snus with modified-risk advertising, including the use of a validated model, inclusion of all harmful changes in tobacco use that may occur for Camel Snus, the heavy reliance on empirically derived inputs, and the extensive sensitivity testing of those same inputs. Collectively, the evidence from empirically informed modeling consistently shows that changes in tobacco use patterns that may occur for Camel Snus with modified-risk advertising will yield an overall population health benefit, and will not lead to overall population harm.

7 Proposed Post-Market Surveillance Program

The data presented in the sections above indicate that Camel Snus with modified risk information is likely to benefit individual user and the population as a whole. The role of a post-market surveillance program (PMSP) is to continually evaluate how the product is used in the post-market environment, and particularly to collect information regarding any unanticipated and undesired events related to an MRTP once it is introduced to the market (FDA MRTPA Draft Guidance 2012, p. 29).

According to Section 911(i) of the TCA, final planning for the PMSP for an MRTP is determined in consultation with FDA at the time that FDA anticipates granting an MRTP order. However, RJRT has outlined the elements of a proposed PMSP in the MRTPAs. Importantly, results of all monitoring activities would, as mandated, be reported to FDA at least annually.

The following are activities and domains proposed for Camel Snus PMSP (*see* Table 7-1).

Table 7-1: Elements of the PMSP for Camel Snus under an MRTP Order

Assessment Elements	Monitoring Activities
(1) Manufacturing deviations	Document incident manufacturing deviations from product specifications
(2) Adverse event reports	Collect reports of adverse events associated with Camel Snus, both from consumer complaints reported to RJRT and from FDA adverse event reporting system. As part of monitoring for adverse effects, RJRT will also collect and summarize any incidents involving Camel Snus that are reported to poison control centers. The American Association of Poison Control Centers collects and reports data on incidents of concern (including ingestions by young children) for a full range of products.
(3) Report of all RJRT-sponsored scientific studies on Camel Snus	Report methods and results for all company-sponsored scientific studies (whether ongoing or completed) related to Camel Snus
(4) Scientific publications that include information about Camel Snus	Provide and summarize publications that relate to Camel Snus
(5) Sales and distribution data	Provide annual sales and distribution data for Camel Snus products

Assessment Elements	Monitoring Activities
(6) Surveys of US adults	RJRT will continue to conduct surveys of US adults to document who is using Camel Snus and how they are using it, as well as attitudes, beliefs, and perceptions related to Camel Snus and other tobacco products. Data will include reports from users of Camel Snus as well as data from a broader population of current, former, and never users of tobacco products. Current RJRT-sponsored surveys include the National Tobacco Behavior Monitor, which collects data from approximately 120,000 respondents per year, and the Total Tobacco Migration Tracker (TTM), which collects data, including detailed tobacco histories, on approximately 24,000 respondents per year RJRT will also analyze and report on Camel Snus-relevant data from publicly-available government-sponsored surveys of adults, including PATH, NSDUH, HINTS, and NATS. Data will include reports from users of Camel Snus as well as data from a broader population of current, former, and never users of tobacco products.
(7) Surveys of US youth	RJRT has long had a policy of not conducting surveys with youth below the age of legal tobacco purchase. However, the PMSP will monitor this population using data collected by government sources, including PATH, NSDUH, NYTS, and MTF. Data will include reports from users of Camel Snus as well as data from a broader population of current, former, and never users of tobacco products.
(8) Updated projections from the Dynamic Population Model	Inputs to the DPM model for the impact of Camel Snus on the population health will be updated as new data become available on who is using Camel Snus, and if new data emerge to update other inputs to the model. This will enable projections of the impact on population health to be revised if needed.

As indicated, these elements of a proposed PMSP for Camel Snus have been outlined in the MRTP Applications for Camel Snus, with the understanding that applicants granted a risk modification order must submit detailed protocols for required post-market surveillance for discussion with FDA and, ultimately for FDA concurrence. FDA may require or suggest alternative or additional surveillance activities or studies to those proposed here. In any case,

with FDA input, RJRT will field a robust program of post-market surveillance to keep FDA informed of developments in-market, and ensure that Camel Snus with modified risk information continues to benefit population health.

8 Conclusion

The evidence clearly shows that these Applications meet the requirements set out in Section 911 of the TCA: Camel Snus should receive clearance to be marketed as a product with reduced risk for lung cancer, oral cancer, respiratory disease, and heart disease, relative to cigarette smoking.

The epidemiology for both smokeless tobacco in the U.S. and for snus in Sweden provide strong evidence that Camel Snus is less risky than cigarettes. Clinical and preclinical studies further support decades of epidemiology, demonstrating reduced exposure and reduced toxicity, respectively. These multiple lines of evidence are in line with the broad public health consensus that smokeless tobacco is less risky than cigarettes.

Yet, despite this strong body of supportive science, consumers remain misinformed about the relative risks of snus compared to smoking. The proposed modified risk advertisements are intended to inform individuals – especially current smokers who expect to continue smoking – about the difference in risk between Camel Snus and smoking. In support of that goal, RJRT has developed advertisements that communicate that risk information accurately and simply, that include balancing information, and that directs smokers who are not going to quit to switch completely to Camel Snus. The advertisements were tested among both users and non-users of tobacco.

Though some individuals remain misinformed about the relative risks of Camel Snus versus smoking, the majority of those studied understood the reduced risk messaging and other key communication objectives, including the balancing information and other health related content. Importantly, people understood that use of Camel Snus, though incurring less risk than smoking, still carries risk.

Moreover, research showed that smokers who do not expect to quit were the most likely users of Camel Snus with modified risk information, in contrast to non-users of tobacco, likelihood of use was projected to be very low. That is, Camel Snus with modified risk advertising invites interest from those who can benefit from switching to Camel Snus, and not from those who could potentially be harmed.

Importantly, extensive modeling, taking account of empirical data on likely patterns of use, suggests that Camel Snus with modified risk advertising would yield a meaningful public health benefit, improving health outcomes for the population as a whole. Sensitivity testing showed that only a small percentage of smokers who would otherwise continue to smoke would need to switch completely to Camel Snus in order to realize a health benefit at the population level, even assuming conservative estimates of unintended consequences.

Should RJRT receive an MRTP order, there will be a thorough and responsible introduction of the proposed advertising to smokers. Changes resulting from the modified risk advertising will be monitored according to an authorized post-market surveillance plan.

Granting of an MRTP order for Camel Snus will measurably benefit population health.

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