6 SUMMARY OF ALL RESEARCH FINDINGS AND TABULATED INDEX OF ALL STUDIES

6.1 Health Risks of the Tobacco Product

This section provides a summary of research findings related to health risks associated with the use of Camel Snus compared to health risks associated with cigarette smoking, with emphasis on diseases that are specifically described in the proposed modified risk advertising executions for Camel Snus (lung cancer, oral cancer, respiratory disease, and coronary heart disease). Thus, this section summarizes a wide range of studies and study types that support the proposed modified risk claim that switching completely from smoking cigarettes to exclusive use of Camel Snus will result in a significant reduction in the risk of lung cancer, oral cancer, respiratory disease, and coronary heart disease.

As stated in the proposed advertising executions for Camel Snus, no tobacco product is safe, and quitting is the best choice for a smoker concerned about the health risks from smoking. However, many public health researchers and governmental agencies, including officials at FDA, agree that a "continuum of risk" exists among tobacco products, with combustible products (*e.g.*, cigarettes and cigars) at the upper end of the risk continuum and non-combustible tobacco products (*e.g.*, smokeless tobacco products) and nicotine replacement therapies on the lower end. FDA Director Mitch Zeller has stated that "Anyone who would ponder the endgame [for tobacco control efforts] must acknowledge that the continuum of risk exists and pursue strategies that are designed to drive consumers from the most deadly and dangerous to the least harmful forms of nicotine delivery" (Zeller 2013). The proposed modified risk advertising for Camel Snus is consistent with Director Zeller's stated goals and can be an important component of an effective tobacco harm reduction strategy.

Cigarette smoking results in an increased risk for developing many chronic diseases, largely due to the inhalation of toxic and carcinogenic byproducts of tobacco combustion. Cigarette smoking significantly increases the risk of developing cancers of the respiratory tract (oropharyngeal, laryngeal, and lung) and other cancers (*e.g.*, bladder, kidney, pancreatic); cardiovascular diseases (including coronary heart disease and cerebrovascular disease); and nonmalignant respiratory diseases (chronic bronchitis, emphysema, and chronic airway obstruction) (Thun *et al.* 2000; USDHHS 2004; USDHHS 2010; USDHHS 2014). In the U.S., the Surgeon General reports that cigarette smoking has its greatest adverse effects related to lung cancer, cardiovascular and metabolic diseases, and chronic obstructive pulmonary disease (COPD) (USDHHS 2014).

In contrast, use of the most prevalent forms of smokeless tobacco ("ST") in the U.S. and Sweden, including snus, is associated with substantially lower risks for smoking-related cancers and/or nonmalignant respiratory diseases (*e.g.*, Lee and Hamling 2009a; Lee and Hamling 2009b; Lee 2011; Lee 2013a). Indeed, there is a scientific consensus that ST users incur substantially lower health risks compared to cigarette smokers (*e.g.*, Levy *et al.* 2004; LSRO 2008; Broadstock 2007; SCENIHR 2008; RCP 2007; Zeller *et al.* 2009; Zeller 2013; Nutt *et al.* 2014). The FDA has also acknowledged that use of snus products offers the potential for lower

health risks compared with cigarette smoking. In the Technical Project Lead Review of Swedish Match North America's Premarket Tobacco Application for several snus products, FDA concluded that the products offer potential for reduction in risk for serious diseases associated with smoking, including cancer (oral esophageal, lung) and respiratory disease (PMTA (Premarket Tobacco Application) Technical Project Lead (TPL) Review, CTP, PM0000010-PM0000017, 11-03-2015, http://www.fda.gov/downloads/TobaccoProducts/Labeling/TobaccoProductReviewEvaluation/UCM472123.pdf). Like Camel Snus, the snus products that were the subject of the Swedish Match PMTA included tobaccos selected for low toxicant content that were processed via heat treatment, rather than fermentation.

TCA Section 911(g)(1) of the TCA specifies that an order shall be issued that a modified risk product may be commercially marketed only if it is demonstrated that use of the product will (a) significantly reduce harm and the risk of tobacco-related disease to individual users and (b) benefit the health of the population as a whole. This section of the Application summarizes research findings addressing the first requirement, and in doing so provides evidence that cigarette smokers who switch completely to Camel Snus will significantly reduce their harm and risk of tobacco-related disease compared to continued use of cigarettes.

Multiple lines of evidence have been evaluated to assess whether or not switching completely from cigarette smoking to exclusive use of Camel Snus will reduce the risk of lung cancer, oral cancer, coronary heart disease, and respiratory disease. These lines of evidence include: epidemiology data; human biomarkers data; preclinical toxicology data; and product analyses (*e.g.*, measurements of harmful and potentially harmful constituents (HPHCs) as required for reporting by the FDA (FDA 2012b)).

These lines of evidence are generally accepted and used by national and international agencies (*e.g.*, USDHHS 2004; IARC 2007b; Zeller *et al.* 2009) for demonstrating the potential for lower risk. They are also consistent with the Institute of Medicine's recommendations on "Methods for Studying Health Effects" described in the publication "Scientific Standards for Studies on Modified Risk Tobacco Products" (IOM 2012). Additionally, these lines of evidence are consistent with FDA recommendations for preparation of a modified risk tobacco product application (FDA MRTPA Draft Guidance 2012).

Research findings summarized in this section regarding the health risks associated with smokeless tobacco, including those from the use of Camel Snus, and with cigarette smoking, are consistent with differences in the manner of use and routes of exposure associated with the two types of tobacco products. Smokeless tobacco (non-combusted tobacco products, including snus) and cigarette smoke have very different toxicant profiles. When cigarettes are smoked, a mainstream smoke aerosol consisting of thousands of compounds, including many toxicants, is formed. Exposure to toxicants present in cigarette smoke occurs both orally and via inhalation. In contrast, smokeless tobacco does not generate combustion-related toxicants during use because the tobacco is not burned. As a result, users of ST products are not exposed to toxicants formed from tobacco combustion. ST users are exposed orally, however, to toxicants

that are present in the tobacco. Camel Snus tobaccos are selected for low toxicant content and the tobaccos are processed via heat treatment, rather than fermentation, which limit further formation of tobacco-related toxicants.

The research findings summarized in this section consistently reflect the differences in manner of use and routes of administration for Camel Snus and cigarettes. Differences in human biomarker data, preclinical *in vivo* and *in vitro* testing data, and comparative chemistry data are concordant with differences in epidemiological data for smokeless tobacco use as compared to cigarette smoking. Collectively, the data support the proposed modified risk advertising that switching completely from cigarette smoking to exclusive use of Camel Snus will result in a reduction in the risk of lung cancer, oral cancer, respiratory disease, and coronary heart disease.

6.1.1 Epidemiological Studies

The following sections provide discussion of the risks to individual users of combustible cigarettes and smokeless tobacco products based on a systematic review of the epidemiological literature among tobacco users to support the proposed modified risk advertising for Camel Snus (*see* Ramboll Environ 2016) as well as other sources including the 2014 U.S. Surgeon General's Report (USDHHS 2014). Additional review and discussion of relevant epidemiological literature is submitted with this Application and was previously presented to FDA in RJRT's Citizen Petition Appendix submitted on July 28, 2011 (FDA-2011-P-0573-0001).

6.1.1.1 Published epidemiological studies of smoking and smokeless tobacco use and determinations of risks for tobacco-related diseases

No long-term epidemiological data currently exist for specific, individual tobacco product brand styles sold in either Sweden or the U.S. today, including Camel Snus. However, as discussed in Section 2 of this Application, available epidemiological data describing the health risks from U.S. ST product use are relevant for estimating health risks to individual users of Camel Snus, and in concluding that Camel Snus presents lower health risks compared with cigarette smoking. Importantly, these studies reflect the effects of U.S. smokeless tobacco products as manufactured and sold several decades ago. Smokeless tobacco products have evolved since that time. Today, U.S. smokeless tobacco products contain lower levels of harmful or potentially harmful constituents than in the past, with levels in Camel Snus among the lowest. Since smokeless tobacco products available for use by tobacco users in U.S. smokeless epidemiology studies presented higher levels of toxicant exposures than Camel Snus (*see* Section 2.8.2), the health risks presented to a Camel Snus user are reasonably estimated, and more likely overestimated, by existing epidemiological studies of U.S. smokeless tobacco users.

Camel Snus brand styles are low-nitrosamine tobacco products designed, formulated, and manufactured in the same manner as other contemporary Swedish-style snus. As such, Swedish epidemiological findings are also relevant to support the proposed modified risk advertising for Camel Snus. As with U.S. studies, no Swedish brand-specific epidemiological data exist, and Swedish studies reflect the effects of smokeless tobacco products manufactured and sold

several decades ago. Swedish snus tobacco products have evolved since that time. Today, Swedish snus products contain lower levels of harmful or potentially harmful constituents than in the past. Since smokeless tobacco products available for use by tobacco users in Swedish smokeless epidemiology studies presented higher levels of toxicant exposures than Camel Snus, the health risks presented to a Camel Snus user are reasonably estimated, and more likely overestimated, by existing epidemiological studies of Swedish smokeless tobacco users.

Epidemiological studies that evaluate the health risks from ST use in the U.S. and Sweden are provided to support the modified risk claim that switching completely from cigarette smoking to exclusive Camel Snus use will significantly reduce one's health risks. Both U.S. and Swedish epidemiology studies provide insight into the relative risks from smokeless tobacco use versus cigarette smoking. While differences in the two subject populations may exist (*e.g.*, genetic, cultural), both countries are westernized nations that are largely comparable from socioeconomic and public health perspectives. In particular, in support of the proposed modified risk advertising for Camel Snus, the following research topic areas are summarized:

- the health risks associated with cigarette smoking, use of U.S. ST, and use of Swedish snus
- the health risks associated with switching from cigarettes to ST use
- the health risks associated with dual use of cigarettes and ST products

These data provide evidence to support the proposed modified risk advertising that complete switching to the exclusive use of Camel Snus from cigarette smoking will reduce the risk of lung cancer, oral cancer, respiratory disease, and coronary heart disease.

6.1.1.2 Health risks associated with cigarette smoking as determined by epidemiological studies of U.S. tobacco consumers

The U.S. Surgeon General has determined that cigarette smoking is causally associated with a variety of malignant and non-malignant diseases, as well as decreased health status based on a review of the epidemiological data (USDHHS 2014).

Table 6.1.1-1 and Table 6.1.1-2 below summarize data presented in the U.S. Surgeon General's 2014 Report (USDHHS 2014) regarding relative risks for adult mortality from cigarette smoking-related malignant and non-malignant diseases. The data are based on the first 6 years of follow-up of Cancer Prevention Study II (Thun *et al*. 1997) and have been used by the CDC for estimates of smoking-related morbidity and mortality in the U.S. The data demonstrate elevated levels of risk for many of these diseases, consistent with the Surgeon General's conclusions regarding health risks associated with cigarette smoking. Of note, some of the largest risk estimates can be observed for the four diseases specifically referenced in the proposed Camel Snus modified risk advertising executions: lung cancer; oral cancer; respiratory disease; and coronary heart disease.

Table 6.1.1-1: Relative risks for mortality from malignant neoplasms associated with current and former cigarette smoking in U.S. males and females aged ≥ 35 years (USDHHS 2014, p. 652)

	Males		Females	
Disease Category	**Current smoker**	**Former smoker**	**Current smoker**	**Former smoker**
Lip, Oral Cavity, Pharynx	10.89[a]	3.40	5.08	2.29
Esophagus	6.76	4.46	7.75	2.79
Stomach	1.96	1.47	1.36	1.32
Pancreas	2.31	1.15	2.25	1.55
Larynx	14.60	6.34	13.02	5.16
Lung	23.26	8.70	12.69	4.53
Uterine cervix	n/a[b]	n/a[b]	1.59	1.14
Kidney	2.72	1.73	1.29	1.05
Bladder	3.27	2.09	2.22	1.89
Leukemia	1.86	1.33	1.13	1.38

[a] values reported for relative risk. No confidence intervals provided.

[b] n/a = not applicable

Table 6.1.1-2: Relative risks for mortality from cardiovascular and respiratory diseases associated with current and former cigarette smoking in U.S. males and females aged ≥ 35 years (USDHHS 2014, p. 652)

	Males		Females	
Disease Category	**Current smoker**	**Former smoker**	**Current smoker**	**Former smoker**
Ischemic Heart Disease (age 35-64)	2.80[a]	1.64	3.08	1.32
Ischemic Heart Disease (age 65+)	1.51	1.21	1.60	1.20
Other Heart Disease	1.78	1.22	1.49	1.14
Cerebrovascular Disease (age 35-64)	3.27	1.04	4.00	1.30
Cerebrovascular Disease (age 65+)	1.63	1.04	1.49	1.03
Atherosclerosis	2.44	1.33	1.83	1.00
Aortic Aneurysm	6.21	3.07	7.07	2.07
Other arterial disease	2.07	1.01	2.17	1.12
Pneumonia, Influenza	1.75	1.36	2.17	1.10
Bronchitis, Emphysema	17.10	15.64	12.04	11.77
Chronic Airways Obstruction	10.58	6.80	13.08	6.78

[a] values reported for relative risk. No confidence intervals provided.

6.1.1.3 Health risks of oral and lung cancer, respiratory diseases and coronary heart disease among users of ST products, including snus, compared with cigarette smokers and never or non-users of tobacco products

In order to determine health risks associated with the use of ST products, including snus, RJRT contracted with Ramboll Environ to conduct and document a systematic, critical review of pertinent U.S. and Scandinavian epidemiological literature on the risks of lung and oral cancers, respiratory disease, and cardiovascular disease, specifically coronary heart disease, among users of snus and other ST products compared with cigarette smokers and never or non-users of tobacco products (Ramboll Environ 2016). The review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, documented in a detailed protocol contained within the report, that includes search and screening strategies, the criteria used to evaluate the quality of the individual studies, and the quality assurance/quality control procedures that were employed. Forty-four relevant primary epidemiological studies were identified through this systematic review. Results are discussed below by health outcome relative to the modified risk advertising proposed for Camel Snus.

6.1.1.3.1 Lung Cancer

Cigarette smoking is the major cause of lung cancer and lung cancer deaths in the U.S. (CDC 2016b). In contrast, reviews conducted and published by well-respected scientific and public health agencies have found no convincing evidence that ST use is a cause of lung cancer. For example, the 2008 report from the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) concluded that there is "inadequate evidence that smokeless tobacco products cause lung cancer" (SCENIHR 2008). In 2007, the International Agency for Research on Cancer ("IARC") published a monograph (IARC 2007b) on "the carcinogenic risks associated with the use of smokeless tobacco, including chewing tobacco and snuff" and concluded that "studies on cancers at other sites [including lung cancer] did not provide conclusive evidence of a relationship with smokeless tobacco use," citing four epidemiological studies that addressed this topic (Accortt *et al.* 2002; Boffetta *et al.* 2005; Henley *et al.* 2005; Williams and Horm 1977)[1]. The Royal College of Physicians reported in its 2007 review that "smokeless tobacco products have little or no effect on the risk of … lung cancer" (RCP 2007). And finally, the CDC does not list lung cancer among the adverse health effects attributed to smokeless tobacco use (CDC 2016c).

Of the individual publications considered in the Ramboll Environ systematic review (Ramboll Environ 2016), three drew upon data from U.S. populations (Accortt *et al.* 2002; Accortt *et al.* 2005; Henley *et al.* 2005) and four studies were conducted in Scandinavian populations (Boffetta *et al.* 2005; Bolinder *et al.* 1994; Luo *et al.* 2007; Nordenvall *et al.* 2013). These publications were determined by Ramboll Environ to be of adequate or fair quality for inclusion in their review. There is little to no evidence that lung cancer risk is associated with snus use based on the Scandinavian studies. In contrast, findings from these same studies indicated a statistically significant increased risk of lung cancer among current cigarette smokers. Some of the values for lung cancer risk and ST use reported in studies of the U.S. population are elevated, possibly suggesting a marginal association (*e.g.*, Accortt *et al.* 2002; Henley *et al.* 2005; *see* Ramboll Environ 2016). However, the reliability of these estimates is limited by several factors, including small numbers of cases. For example, data from NHANES I (Accortt *et al.* 2002) indicated a hazard ratio of 9.1 (95% CI: 1.1-75.4) among female ST users. But these results were based on only three cases, and there were no lung cancer deaths among male exclusive ST users in this study. In addition, Accortt *et al.* failed to show a dose-response, and had potentially inadequate exposure assessment, which might have led to smoking status misclassification. For example, some of those who were exclusive ST users at baseline may have become smokers during the course of the study period, and some of those who were former smokers at baseline may have been incorrectly categorized as users of only ST according to their status at enrollment. If this misclassification occurred, it could have resulted in the apparent elevated lung cancer risk among nominal exclusive ST users. Additional methodological limitations of these studies include possible information bias, and limited

[1] The Ramboll Environ systematic review included three of these four studies, but excluded the study published by Williams and Horm because its ST exposure group was not clearly restricted to exclusive users (Williams and Horm 1977; *see* Ramboll Environ 2016).

statistical power due to few cases of lung cancer and over-controlled regression models (Hosmer *et al.* 2013; Vittinghoff and McCulloch 2007).

Several high quality literature reviews and meta-analyses of epidemiological studies of lung cancer and ST use have been published in peer-reviewed journals. Colilla 2010 concluded that "the relationship between ST use and lung cancer appears tenuous at best", and pointed out that the sporadically observed association between ST use and lung cancer in individual studies may have been related to problems with exposure assessment and the likely misclassification of smokers as exclusive ST users. (Colilla 2010)

Meta-analyses provide a quantitative summary of findings between an exposure and an outcome and can increase power and examine uncertainties between suspected relationships. Lee and Hamling's meta-analysis (Lee and Hamling 2009a) found no statistically significant increase in lung cancer risk in never smokers who used ST in studies conducted in the U.S. (RR/OR=1.38, 95% CI: 0.72-2.64) or conducted in Scandinavia (RR/OR=0.82, 95% CI: 0.52-1.28). Results were not substantially different when studies that reported results in ST users after adjusting for smoking were included. The authors reported that there was "considerable heterogeneity" as a result of data from three publications- the high RR of 6.80 (1.60–28.5) in female never smokers in the National Health and Nutrition Examination Survey I (NHANES I) (Accortt *et al.* 2005), although the data was for female ST users and was based on only four cases; the significant increase of 1.77 (95% CI: 1.14–2.74) from Cancer Prevention Study II (CPS-II) (Henley *et al.* 2005), a value estimated by Lee and Hamling from data provided in the source; and the low RR of 0.70 (95% CI: 0.60–0.70) for the Swedish construction workers study (Luo *et al.* 2007), a value also estimated by Lee and Hamling that may have included smokers. The Ramboll Environ review included five of nine studies included by Lee and Hamling (Accortt *et al.* 2005; Henley *et al.* 2005; Boffetta *et al.* 2005; Luo *et al.* 2007). The remaining four studies (Doll and Hill 1952; Williams and Horm 1977; Wynder and Stellman 1977; Winn *et al.* 1982) failed to meet the inclusion criteria for that review (*see* Ramboll Environ 2016). A second meta-analysis that relied on a more limited body of the same literature (Boffetta *et al.* 2005; Henley *et al.* 2005; Luo *et al.* 2007) also did not observe a significantly elevated risk of lung cancer among ST users in studies conducted in the U.S. (RR=1.8, 95% CI: 0.9-3.5) or in studies conducted in Scandinavian countries (RR=0.8, 95% CI: 0.6-1.0) and reported that "[r]esults on lung cancer risk are inconclusive" (Boffetta *et al.* 2008). Lee and Hamling undertook an assessment of their review and meta-analysis process compared to that of Boffetta *et al.* (Lee and Hamling 2009b). Lee and Hamling concluded that they "cannot evaluate the lung cancer meta-analyses of Boffetta *et al.* due to their only providing four of the five individual RRs they used," but note that they "agree that an association has not been demonstrated" (Lee and Hamling 2009b). Differences between reviews in the material cited or emphasized can be expected as a result of differing scopes and other review parameters (Rosen and Suhami 2016). Findings and limitations reported in these review documents are consistent with the study design issues noted in the discussion of individual studies (*see* Ramboll Environ 2016 for additional discussion).

Taken together, the available epidemiological data indicate substantially elevated lung cancer risk associated with cigarette smoking, and little to no risk associated with ST use. These data provide strong support that switching completely from cigarette smoking to Camel Snus will reduce the risk of lung cancer.

6.1.1.3.2 Respiratory Disease

Emphysema, chronic bronchitis, and chronic airway obstruction are related pathological conditions that are commonly combined under the term "chronic obstructive pulmonary disease (COPD)," and are referred to in the proposed modified risk advertising for Camel Snus as "respiratory disease." COPD is characterized by pathophysiological inflammatory changes that result in airflow limitation and the destruction of essential tissue (*i.e.*, lung parenchyma). Cigarette smoking is the dominant cause of COPD, with high relative risk, and attributable risk around 79% (USDHHS 2014, p. 660). The incidence of COPD is highly associated with smoking history, and a strong dose-response relationship is consistently reported. Two U.S. studies were identified that address the potential association of ST use and COPD (Accortt *et al.* 2002; Henley *et al.* 2005). Results from these two studies fail to provide a consistent demonstration that ST use in the U.S. is associated with elevated risks for chronic respiratory diseases. In addition, two Swedish studies were identified that address the potential association of snus use and COPD (Bolinder *et al.* 1992; Roosaar *et al.* 2008). Similar to the studies of the U.S. population, these two studies provide no consistent evidence regarding an association between snus use in Sweden and the risk of respiratory diseases or symptoms. Bolinder *et al.* 1992 reported a higher prevalence of respiratory symptoms among ST users compared with never smokers, but an even greater prevalence of these symptoms among cigarette smokers; Bolinder *et al.* 1992 suggested that smokers faced more hazards for all respiratory symptoms and had worse health profiles compared with snus users. Finally, given what is known about the pathobiology of COPD, there is no known plausible mechanistic basis by which ST (including snus) use would meaningfully contribute to the development of COPD (Foulds *et al.* 2003; LSRO 2008). To date, no review has examined the question of ST use and COPD development (*see* Ramboll Environ 2016 for additional discussion), and no public health agency has suggested that ST use is a cause of respiratory disease.

Epidemiological data indicate substantially elevated risk of respiratory disease, including COPD, associated with smoking and no consistent evidence that ST use poses any risk of respiratory disease among exclusive ST users. These data provide strong support that switching completely from cigarette smoking to Camel Snus will reduce the risk of respiratory disease.

6.1.1.3.3 Coronary Heart Disease/Ischemic Heart Disease

The Ramboll Environ systematic review identified six cohort studies, two conducted in U.S. populations (Accortt *et al.* 2002; Henley *et al.* 2005) and four conducted in Swedish populations (Bolinder *et al.* 1994; Johansson *et al.* 2005; Haglund *et al.* 2007; Hansson *et al.* 2009), examining the association between ST use and ischemic heart disease (IHD) mortality or incidence. In some studies, the term coronary heart disease (CHD) is used instead of IHD; despite the difference in nomenclature, these two terms refer to the same outcome. For the

purposes of this discussion, the term "IHD" is used, except where the authors specifically investigate CHD. Across all studies, IHD was defined using the International Classification of Diseases, Eighth Revision (ICD-8) codes 410-414, ICD-9 codes 410-414, or ICD-10 codes I20-25 (*see* Ramboll Environ 2016 for additional discussion).

The literature identified provides no consistent demonstration of an association between ST use and IHD mortality or incidence. Of the six studies identified, only two studies (Bolinder *et al.* 1994; Henley *et al.* 2005) provide any indication of a positive association between ST use and IHD. Both of the studies reporting positive associations assessed tobacco use many years prior, and it is likely that the constituents of the ST products used at that time included substantially higher toxicant levels compared to those found in modern products, as discussed in Section 2.8 of this Application. Accortt *et al.* 2002 identified no association within their study, and ST users would have used these older products as well. Findings from all six studies were limited by their tobacco usage assessments, as tobacco usage was assessed either at baseline or once during follow up, and nothing is known about changes in habits that may have occurred during each study's respective follow-up period. Results from the study with the shortest follow-up and whose methods were least likely to be substantially impacted by misclassification (Hansson *et al.* 2009) indicate no association between snus use and IHD hospitalization and deaths.

In contrast to the conflicting results for ST, the evidence for a significantly elevated risk between smoking and risk of IHD was clear and consistent. All five studies identified in the Ramboll Environ systematic review that included exclusive smokers (Accortt *et al.* 2002; Bolinder *et al.* 1994; Haglund *et al.* 2007; Hansson *et al.* 2009; Johansson *et al.* 2005) reported approximately a two-fold risk of CHD/IHD incidence or mortality for current smokers, compared to never tobacco users. Thus, from the available evidence, it is clear that smoking carries substantially higher risk of CHD/IHD compared to exclusive ST use (*see* Ramboll Environ 2016 for additional discussion), and that switching completely from cigarette smoking to Camel Snus will reduce the risk of CHD/IHD.

6.1.1.3.4 Oral Cancer

The "oral cavity" is a heterogeneous tissue composed of a number of subsites. According to the World Health Organization (WHO), the oral cavity includes the lips, the inside lining of the lips and cheeks (buccal mucosa), the teeth, the gums, the front two-thirds of the tongue, the floor of the mouth below the tongue, the front, bony portion of the roof of the mouth (hard palate), and the area behind the wisdom teeth (retromolar trigone) (WHO 2005). The terms "oral cavity cancer" and "oral cancer" will be used synonymously in this Application. The oropharynx includes the base of the tongue (the back third of the tongue), the soft palate (the back part of the roof of the mouth), the tonsils, and the side and back wall of the throat. Studies that report tobacco use-related risks for cancer of the oral cavity and oropharynx have sometimes considered these sites separately. Other studies have combined these sites, and some have even included such unrelated sites as the larynx and esophagus. Cigarette smoking is a cause of cancers at all of these oral sites, and although the strength of the association varies by subsite, all exhibit high relative risks associated with current smoking (USDHHS 2014). For purposes of

this Application, “oral cancer” will refer to cancers occurring in either the oral cavity or oropharynx.

Eight published studies were identified in the Ramboll Environ systematic review (Ramboll Environ 2016) that reported on the association between ST use and risks of oral cancers in the U.S., though each study defined endpoints differently (Keller 1970; Zahm *et al.* 1992; Winn *et al.* 1984, Winn *et al.* 1981; Blot *el al.* 1988; Accortt *et al.* 2002; Accortt *et al.* 2005 [note: the two publications from Accortt and co-workers reported on data obtained from NHANES]; Henley *et al.* 2005; Zhou *et al.* 2013). Overall, the epidemiological data drawn from U.S. populations are inconsistent in the manners in which exposures are reported, anatomic sites are classified, and outcomes evaluated, and as a likely consequence, have resulted in inconsistent results regarding associations between oral cancer and ST use in the U.S. Despite some strong associations reported in older case-control studies (*e.g.*, Winn *et al.* 1981), methodological problems in most of the case-control studies as well as in the cohort studies (NHANES and CPS I and II) preclude a conclusive judgment regarding a causal association (*see* Ramboll Environ 2016 for discussion). The most recent of the eight cited studies (Zhou *et al.* 2013) suggests a positive association may exist between ST use and squamous cell carcinoma of the head and neck (combining cancers of the oral cavity, pharynx and larynx) using never-smokers as the referent group. When stratified by anatomic subsite, but including participants with a smoking history, fully adjusted estimates for oral cancer risk were elevated, but not statistically significant.

Estimates of an association between snus use and oral cancer in Swedish populations were presented in two case-control studies of Swedish populations that met the Ramboll Environ study inclusion criteria (Lewin *et al.* 1998, Schildt *et al.* 1998). Lewin *et al.* reported elevated risks for head and neck cancer (which included cancers of the oral cavity, pharynx, larynx, and esophagus) among ever (RR= 4.7 (95% CI: 1.6-13.8)), current (RR= 3.3 (95% CI: 0.8-12.0)), and former (RR= 10.5 (95% CI: 1.4-117.8)) users of snus compared with never-tobacco-users, but the total number of cases among those who had ever used snus but had never smoked was small (9), and as noted by the authors, the “precision was very low.” When comparisons included subjects with smoking exposures, no statistically significant elevation in risk for head and neck cancer among snus users was observed, regardless of age at start, duration of usage, or intensity of usage after adjustment for age, geographic region, smoking and alcohol use. After stratification of cases by anatomic subsite and the same adjustments, there was no statistically significant elevation in risk for oral cavity cancer compared with never users of snus. In contrast, relative risk for oral cancer among current smokers was substantially elevated and statistically significant (RR= 4.9 (95% CI: 2.6-9.2)), and even higher for those who smoked for 45 years or longer (RR= 6.3 (95% CI: 3.2-12.4)). Schildt *et al.* reported a small, non-statistically significant decrease in risk of squamous cell oral cancer among current snus users versus non-users (OR=0.7, 95% CI: 0.4-1.2), based on 19 cases and 23 controls within a population-based case-control study of 708 participants from 4 counties of Sweden. The risk was increased among former snus users compared to never smokers (OR=1.8, 95% CI: 0.9-3.5), but it was not statistically significant. Active smokers had a statistically significant increased risk of oral cancer compared to never tobacco users (OR=1.7, 95% CI: 1.1-2.6).

Cohort studies in Scandinavia (Luo *et al.* 2007; Roosaar *et al.* 2008) reported no statistically significantly elevated risk of oral cancers for exclusive snus users, but Roosaar *et al.* 2008 reported that compared to never daily use of snus, ever daily use of snus among never-smokers was associated with a non-statistically significant increased risk of combined oral and pharyngeal cancer (HR=2.3, 95% CI: 0.7-8.3) after adjusting for age, alcohol use, and area of residence. However, the small number of cases in this comparison (5) implies low statistical power and the possibility that the results suggesting a possible increase in risk occurred by chance. Overall, some Scandinavian studies of oral cancer risk and snus use suggest that Swedish snus could be associated with an elevated risk for head and neck cancers (Lewin *et al.* 1998, Roosaar *et al.* 2008) and squamous cell oral cancers (Schildt *et al.* 1998). In contrast, where data were available in these studies, risks for oral cancer were consistently and statistically significantly increased among current cigarette smokers.

Several high quality literature reviews (Colilla 2010; Critchley and Unal 2003; IARC 2007b; Lee 2011; Lee 2013a) and meta-analyses (Boffetta *et al.* 2008; Gross *et al.* 1995; Lee and Hamling 2009a; Rodu and Cole 2002; Weitkunat *et al.* 2007), as well as a pooled analysis of 11 U.S. case-control studies (Wyss *et al.* 2016), evaluating the association between ST use and oral cancers have been published in peer-reviewed journals or by public health agencies. These reviews have consistently highlighted the fact that although elevated risks are often reported, especially among nonsmokers, methodological issues, particularly low numbers of ST users or oral cancer cases, limit the ability of studies to unequivocally demonstrate a causal association between smokeless tobacco use and oral cancer. For example, in an invited commentary on the study of Wyss *et al.*, Freedman (2016) noted that in spite of the large sample size (6772 cases and 8375 controls), among never cigarettes smokers, only 44 cases and 62 controls had used snuff, and only 61 cases and 96 controls had used chewing tobacco. These low numbers precluded definitive assessments of dose response or the effects of cessation, two key metrics used in establishing causal associations. In addition, several reviews pointed out that the strongest evidence for an association between ST use and oral cancer was provided by older studies, in which ST products contained higher levels of TSNAs and other harmful and potentially harmful constituents compared with modern products (Colilla 2010; Critchley and Unal 2003; Lee and Hamling 2009a; Lee 2013a). And the pooled analysis by Wyss *et al.* (2016) found higher levels of risk associated with use of snuff, a fermented product, compared with non-fermented chewing tobacco. Overall, the authors of the reviews and meta-analyses identified the same study design issues noted in the Ramboll Environ review's discussion of individual studies (Ramboll Environ 2016) and arrived at similar conclusions. Despite the inconsistent definition of oral cancers and mixture of exposures captured in the "ST" category in the U.S. studies, there is suggestive evidence that risk of oral cancer is elevated among ST users, mostly driven by results of case-control studies, although the reported risks are substantially lower than the oral cancer risk estimates for cigarette smoking. Results from Scandinavian studies follow the same trend, with case-control studies showing statistically significant associations, while cohort studies generally have not reported elevated risks of oral cancer among snus users. The strongest evidence suggesting an effect of ST and snus use on oral cancer risk comes from older studies or cohort studies that included exposure to products that likely had higher levels of nitrosamines

and other constituents than are typically found in more modern products, especially snus, and particularly Camel Snus.

The available data thus provide support for lower risks for oral cancer among ST users compared with cigarette smokers, and that switching completely from cigarette smoking to Camel Snus will reduce the risk of oral cancer.

In conclusion, results from the studies included in the Ramboll Environ systematic, critical review of the relevant epidemiological literature on the risks of lung and oral cancers, respiratory disease, and cardiovascular diseases, specifically coronary heart disease, among users of snus and other ST products compared with cigarette smokers and never or non-users of tobacco products provide evidence to support the modified risk advertising that switching completely from cigarette smoking to the exclusive use of Camel Snus will significantly reduce the risk for these four health outcomes. The available data provide no consistent support for an increased risk associated with ST use for these health outcomes compared with non- or never-users of tobacco; and studies that indicate an increased risk suffered methodological flaws and/or reflected use of historic ST products having higher levels of potentially harmful constituents.

6.1.1.4 Health risks of other diseases among users of ST products, including snus, compared with cigarette smokers and never or non-users of tobacco products

The following presents a summary of research findings relevant to health risks of other diseases not specifically identified in the proposed modified risk advertising (*i.e.*, other than lung cancer, oral cancer, respiratory disease, and coronary heart disease) among users of ST, including snus, compared with cigarette smokers and never or non-users of tobacco products. These findings support the conclusions that there is no demonstrated increased risk of other diseases associated with switching completely from cigarette smoking to exclusive use of Camel Snus.

6.1.1.4.1 Other Cancers

The meta-analyses of Lee and Hamling 2009a provide quantitative data regarding the potential association between ST use, including snus, and other cancer endpoints including esophageal, stomach, pancreatic, prostate, bladder, kidney, and digestive system cancers, non-Hodgkins lymphoma, and all cancers combined. The meta-analyses were conducted combining studies of U.S. ST users and Scandinavian snus users and were also stratified by geography (the U.S. and Scandinavia). The authors concluded that the study results:

> "[S]show no indication of an increased risk of cancer for snuff, as used in Scandinavia ... A weak but significant association with prostate cancer, based on limited data from U.S. studies, requires more confirmatory evidence. Reports of significant associations with pancreatic and oesophageal cancer in an earlier review (Boffetta *et al.* 2008) are not confirmed .... Risk from ST products as used in North America and Europe is clearly very much less than that from smoking, and is not evident at all in Scandinavia." (Lee and Hamling 2009a).

A recent study of prostate cancer and tobacco use in Sweden found that a history of both smoking and snus use was associated with a slight increase in risk of total and prostate-cancer specific mortality (Wilson *et al.* 2016). The study did not examine possible associations with prostate cancer incidence, and thus the findings could be attributed to tobacco users not seeking timely diagnosis and treatment.

Lee and Hamling also compared the CPS-II-based smoking-related risk estimates (from USDHHS 1989) with their smoking-adjusted meta-analysis estimates for ST users (Table 6.1.1-3, adapted from Lee and Hamling 2009a). Their analysis led them to conclude that any cancer risk associated with the use of modern ST products, whether considering U.S. studies only, Scandinavian studies only, or all studies combined, is a small fraction of the risks incurred from smoking cigarettes.

Table 6.1.1-3: Relative risks/odds ratios (95% confidence intervals) for various smoking-related cancers associated with current cigarette smoking compared with smokeless tobacco use (adapted from Lee and Hamling 2009a)

	Cancer type				
	Esophagus	**Pancreas**	**Larynx**	**Bladder**	**Kidney**
Current smoking[a]	7.60 (3.81 – 15.17)	2.14 (1.62 – 2.82)	10.48 (3.61 – 30.43)	2.86 (1.85 – 4.44)	2.95 (1.92 – 4.54)
Any ST use (US studies)[b]	1.89 (0.84 – 4.25)	0.99 (0.51 – 1.91)	2.01 (1.15 – 3.51)	1.24 (0.83 – 1.85)	1.41 (0.64 – 3.10)
Any ST use (Scandinavian studies)[c]	1.10 (0.92 – 1.33)	1.20 (0.66 – 2.20)	0.90 (0.50 – 1.50)	0.83 (0.62 – 1.11)	0.72 (0.44 – 1.18)
Any ST use (U.S. + Scandinavian studies)[d]	1.13 (0.95 – 1.36)	1.07 (0.71 – 1.60)	1.34 (0.61 – 2.95)	0.95 (0.71 – 1.29)	1.09 (0.69 – 1.71)

[a] Relative risks for current smoking; U.S. males age 35+ (USDHHS 1989; Table 6, p. 150); derived from CPS-II data

[b] Relative risks for any ST use based on U.S. studies; smoking-adjusted data; results of meta-analysis (Lee and Hamling 2009a; Table 31, p. 41)

[c] Relative risks for any ST use based on Scandinavian studies; smoking-adjusted data; results of meta-analysis (Lee and Hamling 2009a; Table 32, p. 41)

[d] Relative risks for any ST use based on combined U.S. and Scandinavian studies; smoking-adjusted data; results of meta-analysis (Lee and Hamling 2009a; Table 30, p. 40)

6.1.1.4.2 Other Cardiovascular Diseases: Overview

Cardiovascular disease (CVD) includes diseases of the heart and/or vascular (blood vessel) system, including hypertension, ischemic heart disease (IHD; also commonly referred to as coronary heart disease, CHD), cerebrovascular disease, atherosclerosis, aortic aneurysm (AA), and peripheral artery disease (PAD). Clinical events that may result from these conditions

include stroke (for cerebrovascular disease) and myocardial infarction (MI, for IHD or CHD). Epidemiological studies typically rely on reported clinical events rather than diagnoses of their underlying conditions, since data on clinical events are more easily obtained.

The critical, systematic review of the epidemiological literature (*see* Ramboll Environ 2016) identified 33 studies that examined the association between use of ST and cardiovascular outcomes. Most of these studies were conducted in Sweden. The studies focused on the following cardiovascular system events: 1) "all CVD," which includes multiple and/or combined adverse cardiovascular events; 2) IHD/CHD; 3) MI; 4) blood pressure and hypertension; 5) stroke and cerebrovascular disease; and 6) changes in miscellaneous indicators of cardiovascular dysfunction, *e.g.*, flow mediated dilatation and heart rate variability. While some evidence for an increase in risk for these cardiovascular disease outcomes associated with ST use has been reported, the overall results suggesting an increase in risk are marginal and inconsistent. In contrast, the risks associated with smoking are consistent, strong, exhibit robust dose-response characteristics, and are higher than any suggested risks associated with ST use.

6.1.1.4.3 All Cardiovascular Disease

Two publications conducted in U.S. populations examined CVD mortality (Accortt *et al.* 2002; Henley *et al.* 2005). These analyses were based on data from NHANES I, NHANES I Epidemiologic Follow-up Study (NHEFS), and CPS-I and CPS-II. Yatsuya *et al.* 2010 examined the association between incident CVD and ST use using data from the Atherosclerosis Risk in Communities (ARIC) Study cohort. In spite of their methodological limitations (*see* Ramboll Environ 2016), results from CPS I and II and the ARIC study provide suggestions of an association between ST use and CVD. All identified studies provide a sufficient number of cases, lengthy follow-up periods, appropriate age ranges, and adequate adjustment for confounding, at least in the exposure groups with larger numbers of cases. However, they fall short in their assessment of ST usage and use of non-specific case definitions, and differ in their definitions of both exposure and outcomes. Non-differential misclassification of the exposure is a particular concern in the longest exposed groups in each cohort, because tobacco usage was only assessed early in the study period and nothing is known about changes in habits that may have occurred during follow up. Use of proxies to gather information about a portion of participants in the NHANES I and NHEFS study published by Accortt *et al.* may introduce information bias, particularly if proxy data were more commonly collected for cases and were more accurate or complete for certain exposure groups (including non-exposed) (Accortt *et al.* 2002).

Two publications using data from the Swedish Construction Workers cohort have examined CVD (Bolinder *et al.* 1994; Bolinder *et al.* 1992). Two additional Swedish studies were identified on this topic, one conducted among Swedish twins who participated in the Screening Across the Lifespan Twin Study (SALT) (Hansson *et al.* 2009) and one conducted in male residents of Uppsala county (Roosaar *et al.* 2008). The findings presented by Roosaar *et al.* 2008 and Hansson *et al.* 2009 point to no association between ST use and CVD while Bolinder *et al.*'s two analyses of the Construction Workers Study suggest a positive association (Bolinder *et al.* 1994, Bolinder *et al.* 1992). Evidence from Bolinder *et al.*'s first study, however, is particularly weak as

a result of its cross-sectional design (Bolinder *et al.* 1992). Findings from Bolinder *et al.* 1994; Hansson *et al.* 2009 and Roosaar *et al.* 2008 are strengthened by their prospective study designs. The Swedish studies, as with the U.S. studies, fall short in their exposure assessment of ST usage and differ in their definitions of "cardiovascular disease" outcomes. Non-differential misclassification of the exposure is a particular concern in the longest exposed groups in each cohort, because tobacco usage was only assessed early in the study period and nothing is known about changes in habits that may have occurred during follow up. Data available in these Swedish studies consistently indicate increased risk for CVD outcomes among current smokers, but such data also suffer from the aforementioned limitations.

Evidence regarding a relationship between ST use and CVD is therefore mixed. Two of the three large U.S. cohorts suggest a positive association, but employed non-specific definitions of both exposure and outcome. One of the three large Swedish cohorts reported a positive association between snus use and CVD. Adequate assessment of ST usage is lacking in all of the studies discussed and the differing definitions of "cardiovascular disease" used in each study complicate conclusions that can be drawn from this body of literature (*see* Ramboll Environ 2016). Although the evidence for elevated risk of CVD among ST users in both U.S. and Swedish studies is mixed, all of the above studies that also assessed cigarette smoking found higher CVD risks among current smokers.

6.1.1.4.4 Myocardial Infarction

The critical, systematic review identified four case-control studies, two prospective cohort studies, a pooled analysis, and a meta-analysis conducted in Swedish populations examining the association between ST use and myocardial infarction (Hergens *et al.* 2005; Huhtasaari *et al.* 1992; Huhtasaari *et al.* 1999; Janzon and Hedblad 2009; Wennberg *et al.* 2007). An additional prospective cohort study conducted in a U.S. population examined myocardial infarction as one of a larger group of CVD outcomes (Yatsuya *et al.* 2010) (*see* Ramboll Environ 2016). Overall, the evidence for an association between ST use and MI is mixed. The one available U.S. study (Yatsuya *et al.* 2010), which examined MI as part of a larger group of cardiovascular outcomes, found a slightly elevated risk of CVD associated with ST use among current (HR= 1.31 (95% CI: 1.06-1.61)), but not among former users of chewing tobacco and snuff. However, the study is limited by the failure to impose a specific case definition. Using ST in addition to smoking was not associated with any additional risk of cardiovascular disease. The design of this study also did not allow a direct comparison between ST use and cigarette smoking as cardiovascular risk factors.

Among Swedish studies, the available evidence suggests a possible association between current snus use and elevated risk of fatal, but not non-fatal MI. Five of the six available individual studies of Swedish populations found no association between snus use and risk of either non-fatal or fatal MI (Hergens *et al.* 2005; Huhtasaari *et al.* 1992; Huhtasaari *et al.* 1999; Janzon and Hedblad 2009; Wennberg *et al.* 2007), while one study, using data from the Swedish Construction Workers cohort, found a positive association with fatal, but not non-fatal MI (Hergens *et al.* 2007). In addition, a pooled analysis, which included many of the above cohorts

and previously unpublished data, found no elevated risk of nonfatal MI (Hansson *et al.* 2012); however, this same pooled analysis found that current snus users had a higher risk of fatality from MI within the first 24 hours ($p<0.05$; no risk estimate reported), and the 28-day case fatality risk from MI (referred to as acute myocardial infarction (AMI) by the study authors) was 1.28 (95% CI: 0.99-1.68). Results of the pooled analysis were similar when data from the Swedish Construction Worker cohort were excluded. Another meta-analysis that used a broader grouping of cardiovascular outcomes (Lee 2013a) found a slightly reduced risk of cardiovascular disease among current snus users, but a slightly higher risk of fatality from AMI/ischemic heart disease. Although the evidence for elevated risk of MI among snus users in Swedish studies is mixed, all four of the above studies that assessed cigarette smoking (Huhtasaari *et al.* 1992; Huhtasaari *et al.* 1999; Wennberg *et al.* 2007) showed a significantly elevated risk of MI among current smokers.

6.1.1.4.5 Cerebrovascular Disease (Stroke)

Two U.S. studies investigated the association of ST use with stroke outcomes, as part of their investigations into a broader association with cardiovascular disease (Accortt *et al.* 2002; Henley *et al.* 2005). Accortt and co-workers, using data from NHANES I, found no association of stroke with exclusive smokeless tobacco use in either male or female ST users age 45 years and older. However, the reliability of the results is limited by the relatively small size of the study sample. Mortality risk from cerebrovascular disease was found increased based on data from both CPS-I (HR= 1.46, 95% CI: 1.31-1.64) and CPS-II (HR= 1.40, 95% CI: 1.10-1.79) for current exclusive male users of "spit" tobacco (Henley *et al.*, 2005).

Six Swedish studies were identified that evaluated the risk of stroke/cerebrovascular disease in male snus users (Bolinder *et al.* 1994; Asplund 2003; Haglund *et al.* 2007; Hergens *et al.* 2008; Hansson *et al.* 2009; Janzon and Hedblad 2009) (*see* Ramboll Environ 2016). None of these studies found an overall significant association between snus use and cerebrovascular events, although after stratification by usage and stroke type, some evidence of a positive association was seen for fatal, but not nonfatal stroke (Hergens *et al.* 2008). A pooled analysis by Hansson *et al.* (Hansson *et al.* 2014), which included over 130,000 men with over 32,000 reporting current snus use, did not find a statistically significant elevated risk of mortality from stroke overall (HR= 1.04, 95% CI: 0.92-1.17), ischemic stroke (HR= 1.06, 95% CI: 0.91-1.23), hemorrhagic stroke (HR= 0.94, 95% CI: 0.73-1.22) or from unspecified stroke (HR= 1.10, 95% CI: 0.78-1.54). The findings of this study are of particular importance because of the statistical power achieved by the pooled sample, and the fact that the analysis drew from some of the cohorts included in the individual studies above. Compared to never tobacco users, the HR for overall stroke among current snus users was 1.01 (95% CI: 0.89–1.14, based on 291 exposed cases) and 0.88 (95% CI: 0.64–1.22, based on 39 exposed cases) among former snus users. Similar hazard ratios were observed after stratified analyses of individual types of stroke, duration and amount of snus use. The results were adjusted for BMI, year of diagnosis and socio-economic position; however, other potential confounders such as physical activity were not controlled, which might have resulted in some residual confounding in this analysis. In

contrast, available data in the Swedish studies consistently indicate increased risk of stroke among current cigarette smokers.

Results from two large meta-analyses of cohort studies did suggest an association between snus use and mortality from all types of stroke. Based on five of the six individual Swedish studies, Lee 2007 estimated the risk of mortality from all types of stroke among ever users of snus compared to never users to be 1.42 (95% CI: 1.29-1.57). On the basis of the studies conducted in the U.S. by Henley *et al.* 2005 and Accortt *et al.* 2002, Lee 2007 also concluded that the risk of stroke death for current ST users compared to never-users was 1.44 (95% CI: 1.3-1.60). There was no statistical evidence of heterogeneity in the studies included in this analysis (p =0.29). A later meta-analysis by Boffetta and Straif 2009 identified a non-statistically significant increased risk of mortality due to stroke of all types among ever-users of snus compared to never users, with the excess risk estimated to be around 19% (HR= 1.19, 95% CI: 0.97-1.47). For current snus users, the risk was 1.28 (95% CI: 1.00-1.64), while for former users, the risk was 0.93 (95% CI: 0.56-1.55). Unlike Lee 2007, Boffetta and Straif 2009 identified significant heterogeneity in the Swedish studies. Data from the U.S. cohorts, however, did not show any heterogeneity, and suggested that an elevated risk of mortality from any stroke exists for ST use compared to never users (HR= 1.39, 95% CI: 1.22-1.60).

On balance, while the evidence is not conclusive, results from large, population-based cohort studies and pooled analysis of these cohort studies support a small, but positive association of stroke mortality with ever having used snus, especially among current users. The evidence for an association with stroke incidence and ST is not as well supported.

Additional health conditions and ST use are addressed in the Ramboll Environ systematic review (Ramboll Environ 2016), and in RJRT's Citizen Petition Appendix.

In conclusion, the data presented above indicate that while some degree of risk associated with the use of smokeless tobacco, including snus, cannot be excluded in regards to diseases other than lung cancer, oral cancer, respiratory disease, and coronary heart disease, the risks are substantially lower than the risks associated with cigarette smoking. These findings thus support the proposed modified risk advertising by demonstrating no increased risk for diseases not identified in the proposed modified risk advertising, and demonstrate that switching completely from cigarette smoking to Camel Snus will reduce health risks to individual users.

6.1.1.5 Health risks associated with switching from cigarette smoking to exclusive use of smokeless tobacco

As the evidence presented thus far has demonstrated, smokeless tobacco products, like Camel Snus, present less risk for chronic diseases compared with cigarette smoking. The evidence presented supports the proposed modified risk advertising that switching completely from cigarette smoking to exclusive use of Camel Snus reduces the risk of lung cancer, oral cancer, respiratory disease, and cardiovascular disease. Additionally, specific data regarding risk reduction among individuals who switch from cigarette smoking to smokeless tobacco use are

relevant to support the proposed modified risk advertising. These epidemiological data are summarized below.

There are no available epidemiological data specifically evaluating health risks to U.S. smokers who switch to Camel Snus products. However, a search of the National Library of Medicine's PubMed database identified published epidemiological data from the American Cancer Society's CPS-II for cigarette smokers who switched from exclusive cigarette smoking to exclusive use of U.S. smokeless tobacco products in general (Henley *et al.* 2007). Although the ST products that were represented in this study are older products with likely higher toxicant levels compared with Camel Snus, the results nonetheless inform as to what levels of risk reduction might be achieved from complete switching.

Henley and co-workers selected a cohort of 116,000 men based on tobacco use information collected by questionnaire at enrollment indicating they were either former exclusive cigarette smokers and were no longer using any tobacco products ("quitters;" n=111,952) or who reported using "spit tobacco" (chewing tobacco and/or snuff) and had begun doing so at the time of or after they had quit exclusive cigarette use ("switchers;" n=4443). A secondary analysis included never-users of tobacco.

Mortality data on the cohort were tracked for 20 years (1982-2002), focusing on deaths from the following smoking-attributable diseases: lung cancer, respiratory disease (defined as bronchitis, chronic bronchitis, emphysema, and chronic airway obstruction in this study), coronary heart disease, and stroke. Comparisons were made among the three user group cohorts based on tobacco use patterns. Both quitters and switchers had smoked cigarettes for approximately 25 years, although switchers had a slightly longer smoking history (25.8 years vs. 23.2 years), and had begun smoking approximately 1 year earlier (Henley *et al.* 2007). Switchers had used smokeless tobacco for an average of 9.2 years, but could have been using smokeless tobacco for as little as 2 years. The authors noted that those who had switched from cigarettes to chewing tobacco experienced similar mortality risk as compared to those who switched to only snuff. The values in Table 6.1.1-4 reflect risks among "switchers" without specifying the type of smokeless tobacco.

Table 6.1.1-4 below shows that compared with those who quit tobacco use entirely, switchers had a risk of lung cancer mortality of 1.46 (95% CI: 1.24-1.73). When compared with never-users of tobacco, quitters had a residual risk of lung cancer mortality of 3.81 (no CI provided), and those who had switched to ST use had a residual risk of lung cancer mortality of 5.61 (no CI provided) compared with never-users of tobacco. The elevated relative risk of lung cancer in both those who quit tobacco use entirely and those who switched, compared to never users of tobacco most likely reflects the effects of prior smoking, since smoking-related risks continue to fall for many years after cessation (IARC 2007a, p. 79). The higher risks among switchers compared with quitters could be attributed in part to the facts that on average, switchers initiated smoking at an earlier age and quit smoking at a later age, were less educated and more often employed in blue-collar occupations, and had a less healthy diet. The risks found among switchers stand in stark contrast to the substantial risks for these diseases among

continuing smokers (risk values for current male smokers from USDHHS 2014). Although some residual risk among switchers was present, those who switched experienced a calculated 76% reduction in risk for lung cancer. Similar or greater reductions in risk for switchers from cigarettes to ST use were observed for mortality from COPD (69-81%), coronary heart disease (54%), and stroke (59%). Given the higher levels of toxicants in the historical ST products reflected in this study, the data suggest that similar or greater reductions would be observed with complete switching to Camel Snus.

Table 6.1.1-4: Relative risks/hazard ratios for lung cancer, respiratory disease (COPD), oral cancer and heart disease associated with either current cigarette smoking, with quitting, or with switching to U.S. ST products

	Lung cancer	COPD		Oral Cancer	Cardiovascular disease	
		(chronic airway obstruction)	(bronchitis; emphysema)		(Coronary Heart disease)	(Stroke)
Continuing smokers	23.26[ab]	10.58[ab]	17.1[ab]	10.89[ab]	2.80[ad]	3.27[ad]
Switchers (relative to never-users of tobacco)	5.6[ce]	3.24[ce]	3.24[ce]		1.28[ce]	1.34[ce]
Switchers (relative to quitters)	1.46 (1.24-1.73)[ce]	1.31 (0.96-1.78)[ce]	1.31 (0.96-1.78)[ce]		1.13 (1.00-1.29)[ce]	1.24 (1.01-1.53)[ce]
Quitters	8.70[ab] 3.81[ce]	6.80[ab] 2.49[ce]	15.64[ab] 2.49[ce]	3.40[ab]	1.64[ad]	1.04[ad]
% risk reduction for switchers (relative to continuing smokers)	76%[f]	69%[f]	81%[f]		54%[f]	59%[f]

[a] Data from USDHHS 2014; no confidence intervals provided

[b] Males age 35+

[c] Data from Henley *et al.* 2007

[d] Males age 35-64

[e] Males age 30+

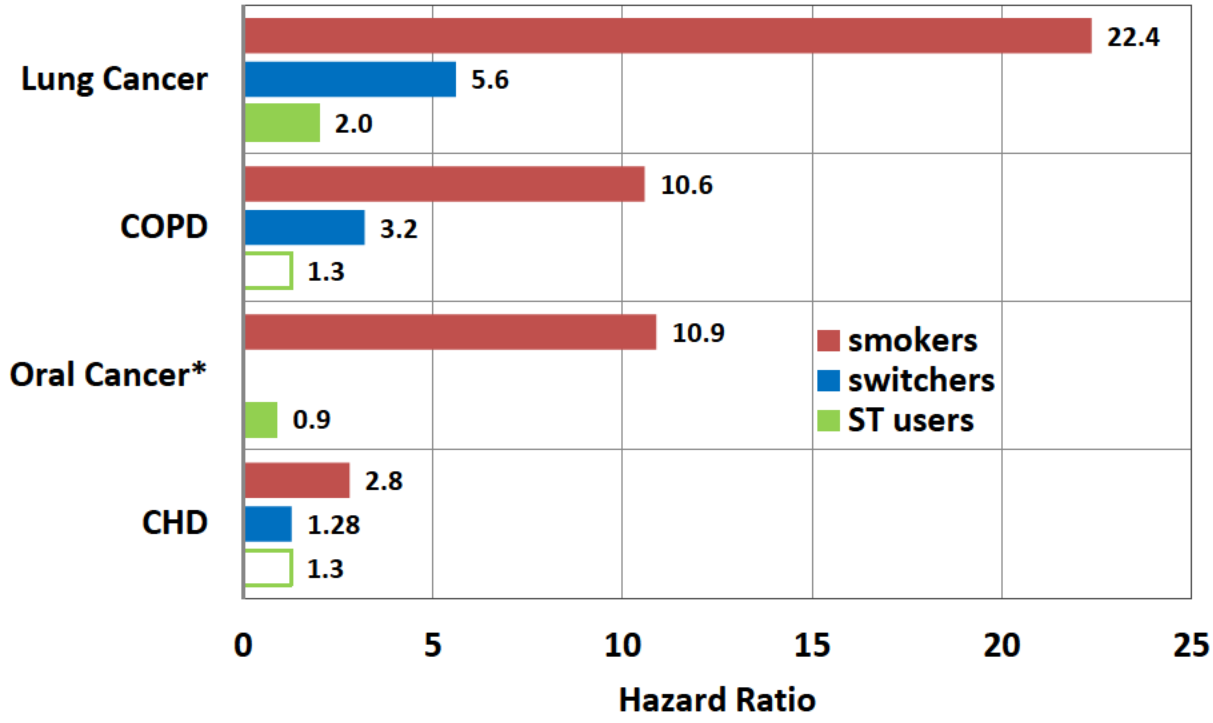
[f] Percent reductions calculated using the relative risk values for continuing smokers and for switchers relative to never-users of tobacco (*i.e.*, for lung cancer, (23.26-5.6)/23.26 = 76% reduction

No risk estimate for oral/oropharyngeal cancer among switchers was provided in this study, as the number of cases was small. However, the large difference between the risk estimates for oral/oropharyngeal cancer observed for smokers and ST users (Table 6.1.1-1), and the reduction in risk seen for the other diseases for which switching data are available indicates that switching completely from smoking to using Camel Snus products will similarly substantially reduce risk of oral/oropharyngeal cancer mortality.

It should be noted that the study by Henley and co-workers examined risks associated with the use of historical products, and not contemporary low nitrosamine snus products such as Camel Snus. As reviewed in Section 2, historical U.S. ST products have chemistry profiles that indicate higher levels of some toxic constituents compared to contemporary Camel Snus products, and a pattern of consumption that resulted in generally the same or likely higher exposures compared with use of Camel Snus. In addition, CPS-II, the source of data for all of the risk values reported above, was conducted among adult members of the U.S. population, and inherently incorporates the characteristics (*e.g.*, genetic, cultural, exposure to advertising, etc.) that may influence differences in health outcomes that may occur when comparing outcomes across populations residing in different countries. Therefore, the U.S. switching data are particularly relevant in estimating disease risk to U.S. smokers who switch from a cigarette smoking to Camel Snus. Given the higher levels of HPHCs in older US smokeless tobacco products, the results approximate, or possibly, overestimate the risk associated with switching from cigarette smoking to contemporary Camel Snus products.

Figure 6.1.1-1 graphically illustrates the differences in risks of mortality from four major smoking-related diseases among male cigarette smokers, males who switch completely from cigarette smoking to exclusive use of ST and male users of smokeless tobacco exclusively.

Figure 6.1.1-1: Disease mortality risk estimates based on CPS-II data for male U.S. cigarette smokers, male U.S. cigarette smokers that switch completely to ST use, and males U.S. ST users



Data obtained from USDHHS 2014 (smokers), Henley *et al.* 2007 (switchers), and Henley *et al.* 2005 (ST users). Solid bars represent significant differences compared to never users of tobacco, while open bars represent no difference.

* No value reported for switchers. Values for "oral cancer" among cigarette smokers and ST users include cancers of the lip, oral cavity, and pharynx.

Data regarding health risks to Swedish smokers who switched to snus likewise suggest lower health risks for switchers compared with continuing smokers, and because they document risks after changing from a combustible to a noncombustible tobacco product, are relevant in spite of sampling a different population. Five studies were identified among those collected in the Ramboll Environ systematic review that provided data for switchers (defined as former smokers who were now current exclusive snus users) (*see* Table 6.1.1-6 below). The 1998 study of Schildt and co-workers (Schildt *et al.* 1998) found that active snuff users who were former smokers had substantially lower risk than active smokers. Their risk for oral cancer was similar to those who had quit tobacco use entirely, and was not statistically significantly different than never users of tobacco. Four other studies, reviewed below, measured cardiovascular endpoints among switchers.

Based on data from the Swedish Annual Level-of-Living Survey (SALLS), Johansson and co-workers found a lower hazard ratio for coronary heart disease for men age 30-74 who were former smokers but now daily snuff users (switchers) than for either former smokers (quitters) or current smokers (Johansson *et al.* 2005). Hergens and co-workers assessed the risk of first-time myocardial infarction (MI) in males among various categories of tobacco use, stratifying results by whether the MI was nonfatal (patient still living 28 days after the MI) or fatal (patient dies within 28 days) (Hergens *et al.* 2005). For all cases combined, risk among switchers (former smokers, current snuff users) was not statistically higher (overlapping confidence intervals) compared with never snuff users who were former smokers (quitters). Both categories of snuff users had substantially lower risks compared with never snuff users who were current smokers. The same order of risk was found among nonfatal cases (quitters<switchers<current users), but risks were lowest (and not statistically significantly different from never users) among switchers in the category of fatal cases. Another study of tobacco use and both MI and sudden cardiac death (SCD) found similar results to those of Hergens and co-workers (Wennberg *et al.* 2007). Switchers (former smokers, current snuff users) and quitters had no statistically significant elevation in risk, compared with never-users of tobacco, for MI, fatal MI, SCD with survival times of <24 hours, and SCD with survival times of <1 hour, in contrast to current smokers, who exhibited statistically significant and substantially elevated risks for each of these endpoints. Finally, Hansson and co-workers' 2009 study of all cardiovascular disease, ischemic heart disease, and stroke among a cohort of Swedish twins participating in the Screening Across the Lifespan Twin Study (Hansson *et al.* 2009) found no statistically significant elevation in risks for any of these endpoints among former smokers who were current snus users, slightly elevated risks among former smokers, and highest risks (all statistically significantly different from never users) for current smokers.

Table 6.1.1-5: Health risks among switchers from cigarette smoking to use of Swedish Snus

Odds ratios (95% confidence intervals)

Study	Endpoint	Switchers	Quitters	Current smokers
Hansson *et al.*2009	IHD	1.22 (0.82-1.74)[a]	1.34 (1.10-1.64)	1.99 (1.59-2.50)
	All CVD	1.04 (0.78-1.39)	1.17 (1.00-1.38)	1.86 (1.56-2.22)
	Stroke	0.77 (0.46-1.29)	1.01 (0.78-1.30)	1.61 (1.22-2.13)
Hergens *et al.*2005	All MI	1.60 (1.10-2.20)	1.30 (1.10-1.60)	2.80 (2.30-3.40)
	Nonfatal MI	1.60 (1.10-2.20)	1.20 (0.98-1.50)	2.70 (2.20-3.30)
	Fatal MI 28 days	1.50 (0.69-3.20)	1.70 (1.60-2.60)	3.60 (2.40-5.20)
Johansson *et al.*2005	Coronary Heart Disease	1.18 (0.67-2.06)	1.47 (1.07-2.03)	2.30 (1.66-3.19)
Schildt *et al.*1998	Oral Cancer	0.6 (0.3-1.3)	0.9 (0.6-1.4)	1.7 (1.1-2.6)
Wennberg *et al.*2007	MI	1.25 (0.80-1.96)	1.18 (0.82-1.70)	2.60 (1.91-3.54)
	Fatal MI 28 days	1.24 (0.44-3.53)	1.02 (0.45-2.31)	3.53 (1.83-6.84)
	SCD <24hr	1.39 (0.44-4.42)	0.74 (0.28-1.97)	3.12 (1.53-6.33)
	SCD<1hr	2.67 (0.52-13.80)	0.35 (0.07-1.78)	4.54 (1.55-13.25)

[a]Odds ratio (95% confidence interval)

Health risks among switchers from cigarette smoking to snus use in Sweden have also been examined in a review by Lee (Lee 2013b). In addition to the five studies discussed above, Lee included a 1999 study of tobacco use and gastric cancer by Ye *et al.* (Ye *et al.* 1999), a study where switchers were defined as ever (rather than current) snus users who formerly smoked. As a consequence, "switchers" in this study could have quit snus use before quitting smoking. Continuing smokers incurred a significantly elevated risk of gastric cancer (OR= 2.00; 95% CI: 1.30-2.90), while no significantly elevated risks were observed for switchers (OR= 1.20; 95% CI: 0.80-1.90) or quitters (OR= 1.20; 95% CI: 0.90-1.80).

Collectively, the data from U.S. tobacco and Swedish users indicate that substantial reductions in risk for a number of smoking-related diseases were achieved by switching from cigarette smoking to exclusive use of traditional U.S. ST products and snus. These findings provide a sound scientific basis to support the conclusion that smokers who switch completely to Camel Snus will experience significant reductions in health risks compared to continuing smokers.

6.1.1.6 Health risks associated with dual use of cigarettes and smokeless tobacco

Although RJRT's proposed modified risk advertising executions specify that current smokers should switch completely from smoking to using Camel Snus to reduce their risks of smoking-related lung cancer, oral cancer, coronary heart disease, and respiratory disease, some smokers may engage, for a period of time, in dual use of cigarettes and Camel Snus products. Thus, it is important to consider evidence on tobacco use-related harm associated with the dual use of cigarettes and ST products, and to demonstrate no unintended or unanticipated consequences (*e.g.,* unique or synergistic risks) associated with this "dual use" behavior.

There is currently no established definition for the term "dual use," but it is generally considered the period of time during which people smoke cigarettes and use smokeless tobacco concurrently, but not simultaneously (Frost-Pineda *et al.* 2010). "Dual use" encompasses such behaviors as use of smokeless tobacco by smokers who do not intend to quit smoking during periods when they may not smoke, or use by smokers who wish to reduce tobacco use-related harms by reducing the number of cigarettes smoked per day. For smokers transitioning from exclusive smoking to exclusive smokeless tobacco use, it represents the time during which smokers smoke progressively fewer cigarettes, while substituting smokeless tobacco. Characterization of dual use in the available epidemiological literature, identified by a PubMed search, is often imprecise, but the literature reviewed below regarding health effects of dual use of cigarettes and smokeless tobacco is representative of the available data.

Few studies have focused specifically on the prevalence of, or the health consequences associated with dual use. Limited data from individual studies of U.S. and Swedish tobacco users suggest no unique health risks (either qualitative or quantitative) associated with dual use of cigarettes and smokeless tobacco products. Accortt and co-workers examined the 20-year lung cancer and all cancer mortality data obtained for a cohort of subjects from the U.S. NHANES I follow-up study (Accortt *et al.* 2002; Accortt *et al.* 2005). Numerically higher point estimates of lung cancer mortality risk among male dual users, defined as smokeless tobacco users and smokers, (HR= 22.6; 95% CI: 6.4-80.3) compared with male exclusive smokers (HR=

13.2; 95% CI: 4.5-38.2) were reported, but the findings were not statistically significantly different from one another (based on overlapping confidence intervals) and the confidence intervals were wide (Accortt *et al.* 2002). The higher risk estimate for dual users compared with smokers was partially attributed to a higher number of pack-years of smoking among the dual users compared to exclusive smokers (42.3 versus 35.1 mean pack-years, respectively), leading the authors to conclude that, "[t]he higher cigarette smoking dose, not the use of smokeless tobacco, is likely leading to the increased lung cancer mortality among combined [dual] users." The authors likewise concluded that there was no synergistic effect between cigarette smoking and smokeless tobacco use for any of the major cancers, as the "combined use of smokeless tobacco and cigarettes did not increase overall mortality beyond that expected from use of the individual products." (Accortt *et al.* 2002).

A lack of synergistic health effects among dual users can also be inferred from oral cancer risk data reported in studies by Winn *et al.* 1981 and Schildt *et al.* 1998. In a case-control study of U.S. female tobacco users, dual users of snuff and cigarettes were not at statistically significantly higher risk for oral cancer compared with either exclusive smokers or exclusive snuff users, the authors noting "no enhanced effect" for dual use (Winn *et al.* 1981). Likewise, no synergistic effects were observed in a case-control study of Swedish tobacco users, where active cigarette smoking compared to never use of tobacco was associated with a statistically significantly increased risk of oral cancer (OR=1.7, 95% CI: 1.1-2.6), and active dual use of moist snuff and cigarettes was not (OR=1.2, 95% CI: 0.6-2.4) (Schildt *et al.* 1998). While the estimated odds ratio for oral cancer among cigarette smokers was lower in this study than that observed in other studies (*e.g.*, CPS-II, which has a substantially larger sample population), the oral cancer risk associated with dual users was not increased compared to exclusive smokers, and was not significantly different from the risk among never users of tobacco.

U.S. and Swedish data reveal no statistically significant increase in CVD risk for dual users compared to exclusive cigarette smokers, and in some cases, no increased CVD mortality risk for dual users compared to never-users of tobacco. Based on national survey data, exclusive cigarette smoking was associated with an increased risk of ischemic heart disease (IHD), stroke, and/or all CVD; in contrast, dual use of cigarettes and smokeless tobacco was not associated with an increased risk of IHD compared with never-use of tobacco (Accortt *et al.* 2002, based on mortality data from NHANES I) and was not associated with an increased risk of all CVD, IHD or stroke (Hansson *et al.* 2009, based on incidence data from Swedish SALTS[2]). Haglund *et al.* 2007 examined incidence and mortality data from the Swedish Survey of Living Conditions, and reported an increased risk of IHD (both incidence and mortality) and stroke (incidence) associated with cigarette smoking. Dual use was associated with an increased risk of IHD and stroke incidence and mortality. The magnitude of risk was similar to that of smoking for IHD incidence and mortality and stroke incidence, but was higher than the risk from smoking for stroke mortality, although the risk estimate for stroke mortality was based on only 3 cases (Haglund *et al.* 2007). Specific to CHD, Johansson *et al.* 2005 reported similar disease risks among Swedish males (ages 30-74) who were daily dual users and daily cigarette smokers;

[2] The Screening Across the Lifespan Twin Study (SALTS) was a telephone interview conducted in a subset of males from the Swedish Twin Registry.

there was no indication of a synergistic effect of cigarette smoking and snuff use (Johansson *et al.* 2005). Finally, available studies show no increased risk of myocardial infarction (MI) among dual users of Swedish moist snuff and cigarettes, compared with exclusive smokers (Wennberg *et al.* 2007; Hergens *et al.* 2005; Huhtasaari *et al.* 1999). These findings were consistent with a recent meta-analysis by Lee 2007, which found "no indication of a multiplicative interaction between the effects of smoking and the possible effects of ST. Thus, the data did not indicate any special hazard in relation to the dual use of smoking and ST" (OR=1.01; 95% CI: 0.87-1.18).

Two reviews of published literature (Lee 2014; Frost-Pineda *et al.* 2010), analyzing data regarding dual use of ST and cigarettes, provide, if not a comprehensive survey of dual use health risk information, at least representative estimates of risks associated with dual use.

Frost-Pineda and co-workers (Frost-Pineda *et al.* 2010) identified 17 epidemiological studies containing data relevant for evaluating health effects associated with dual use, including 4 from the United States. U.S. data were supportive of no elevated risks among dual users compared with exclusive smokers for oral cancer (Winn *et al.* 1981), lung cancer (Accortt *et al.* 2002; Accortt *et al.* 2005), pancreatic cancer (Hassan *et al.* 2007), or ischemic heart disease (Accortt *et al.* 2002). Accortt *et al.* 2005 specifically noted that "no synergistic effect was observed between ST and cigarette smoking among male combined users for the major cancers." Swedish data likewise indicated no unusual elevations in risk among dual users for oral cancer (Schildt *et al.* 1998), esophageal and stomach cancer (Zendehdel *et al.* 2008), ischemic heart disease and stroke (Haglund *et al.* 2007; Johansson *et al.* 2005; Hansson *et al.* 2009), or myocardial infarction (Huhtasaari *et al.* 1992; Huhtasaari *et al.* 1999; Hergens *et al.* 2005; Wennberg *et al.* 2007). Frost-Pineda *et al.* concluded that "the evidence is sufficient and clear that there are no unique qualitative or quantitative risks associated with dual use of cigarettes and smokeless tobacco products, which are not anticipated or observed from single use of these products for the major health effects associated with smoking and smokeless tobacco." (Frost-Pineda *et al.* 2010). Indeed, the review pointed to two studies (Boffetta *et al.* 2005; Luo *et al.* 2007) suggesting that dual use results in reduced smoking, and consequently reduced smoking-related risks compared with exclusive smokers who do not use ST.

A 2013 systematic review of available literature conducted by Lee considered comparative risks among those who smoked and used snus (dual users), those who smoked but did not use snus (smokers), those who used snus only (snus users) and those who used no tobacco products (non-users) (Lee 2014). In this review of Swedish studies, a search of literature published through February 2013 identified 21 publications containing relevant data on Swedish participants described in prospective cohort, case-control, and cross-sectional studies. For a number of disease endpoints divided among cardiovascular diseases, cancers, conditions related to pregnancy, and chronic inflammatory diseases, relative risks/odds ratios were determined for snus use compared with never-use of tobacco, and for dual use compared with exclusive smoking. If the proportional increase in risk for snus users was greater in smokers than in non-smokers (or if the proportional risk increase in smokers was greater in snus users than in non-users of snus), such an interaction would be evidence of synergy between smoking and snus use. No such evidence of synergy was observed.

Based on a meta-analysis of seven studies, Lee 2014 found no increase in risks for ischemic heart disease, coronary heart disease or acute myocardial infarction in current exclusive snus users as compared to non-users of tobacco. Similarly, no additional risks for these diseases were observed among dual users compared with smokers. For cancers, four comparisons (oropharyngeal, esophageal, stomach, anal) showed evidence of higher than additive risks among dual users, but the values were not statistically significant. Five comparisons exhibited lower than additive values, but these findings were considered to be artefacts, related to higher calculated snus-related risks in never-smokers compared to risks in ever smokers. In particular, there was no evidence of enhanced risk for oral cancer among dual users. Results for respiratory mortality, total non-cancer mortality, and for overall cancer likewise showed no evidence of a synergistic interaction between cigarette smoking and snus use. Thus, the analysis of Lee 2014 was consistent with the earlier conclusions of Frost-Pineda *et al.* 2010 in finding little evidence of any special risk from dual use of snus and smoking for cancers or cardiovascular diseases.

Risks for several conditions related to pregnancy and birth outcomes (these topics are also discussed in RJRT's Citizen Petition Appendix submitted with this Application) were also examined in the study of Lee 2014 using data from the Swedish Medical Register. For pre-eclampsia, diabetes and antenatal bleeding, there was no statistically significant increase in risk associated with snus use alone, nor any additional risk from snus use among either smokers or ex-smokers. For very preterm birth, preterm birth, still births, small for gestational age, and neonatal apnea, there were small but significant increases in risk among exclusive snus users, but not among dual users. There was no evidence of synergy between smoking and snus use for these conditions. The only condition exhibiting a significant positive interaction (indicating an enhanced effect from dual use) was gestational hypertension, with an association with snus use present in smokers but not in nonsmokers. RJRT's proposed advertising executions for Camel Snus clearly state that minors and pregnant women should never use tobacco products.

The available studies discussed above consistently find no unique health risks (either qualitative or quantitative) associated with dual use of cigarettes and smokeless tobacco products, which are not anticipated or observed from cigarette smoking alone for the major health effects associated with smoking and smokeless tobacco. In fact, some studies examining the disease risks associated with dual use have suggested a possible reduction in risk compared to exclusive cigarette smoking (*e.g.*, Schildt *et al.* 1998, for oral cancer; Hansson *et al.* 2009 and Accortt *et al.* 2002, for CVD). This reduction would be consistent with studies indicating that dual use may reduce toxicant exposure (compared to exclusive smoking) due to a decrease in cigarette consumption (*see* Section 6.1.2). Nevertheless, the Camel Snus proposed advertising executions in this Application clearly specify that current smokers should switch completely from smoking cigarettes to using Camel Snus to reduce their risks of lung cancer, oral cancer, respiratory disease, and heart disease, and consumers understand this message (*see* Section 6.2).

6.1.1.7 Comparative health risks associated with smokeless tobacco and FDA-approved smoking cessation therapies

In evaluating the benefit to health of individuals and of the population as a whole under Section 911(g)(1) of the FD&C Act, FDA must take into account, among other things, the risks and benefits to persons from the use of the modified risk tobacco product compared to the use of smoking cessation drug or device products approved by FDA to treat nicotine dependence (FDA MRTPA Draft Guidance 2012). This section of the Application summarizes the available data on comparative health risks to individual users of ST, like Camel Snus, and products approved by the FDA used for smoking cessation and nicotine dependence. The discussion will focus on health risks to the individual from use of each type of product, and will not consider changes in overall population health from smoking cessation.

The health risks of ST, like Camel Snus, as determined from epidemiological studies have been discussed in Section 6.1.1, and are evaluated in clinical (Section 6.1.2), *in vivo* (Section 6.1.3.3), *in vitro* (Section 6.1.3.2), and chemistry (Section 6.1.3.1) studies. In addition, health risks among individuals who switch from cigarette smoking to use of ST, like Camel Snus, have been estimated (Section 6.1.1.4). Collectively, the findings from those studies constitute overwhelming evidence that the use of Camel Snus is far less hazardous than cigarette smoking.

FDA-approved smoking cessation products include nicotine-containing (chewing gums, lozenges, transdermal skin patches, and inhalers) and non-nicotine-containing (Chantix (varenicline tartrate) and Zyban (bupropion)) products. The health risks of these products are generally recognized as very low. In 2013, the FDA amended its required labeling for over-the-counter (OTC) nicotine-containing nicotine replacement therapy (NRT) products to acknowledge that the concomitant use of OTC NRT products with cigarettes or with other nicotine-containing products, as well as usage of these products for longer than 12 weeks, does not raise significant safety concerns (FDA 2013). In doing so, the FDA gives tacit acknowledgment that possible higher levels of nicotine exposures among users of multiple products was well as long-term use of NRT products pose low and acceptable health hazards relative to continued cigarette smoking.

6.1.1.7.1 Nicotine-Containing Replacement Therapies

NRTs, approved by the FDA in the mid-1980s, are designed to help people stop smoking by supplying controlled amounts of nicotine to ease the withdrawal symptoms associated with a quit attempt. There are currently three types of OTC nicotine-containing NRT products - nicotine gum, transdermal patch, and nicotine lozenges. Nicotine inhalers are available by prescription. NRT products either do not contain, or contain low levels, of carcinogens and harmful constituents found in cigarettes and other tobacco products, including ST products. In 2007, the Royal College of Physicians reviewed health risks associated with the use of medicinal nicotine (RCP 2007). Their review noted mild and transient local effects (*i.e.*, dyspepsia and gastrointestinal discomfort among nicotine gum users; throat or nose irritation and cough among nicotine inhaler users). Based on clinical trial and observational data, NRTs did not

increase the incidence of acute cardiovascular events or of sudden death in either the general population or in patients with pre-existing cardiovascular disease.

Animal models had suggested that nicotine could be associated with a number of pre- and postnatal health issues (reviewed in Forest 2010). However, little evidence has emerged that use of NRT during pregnancy results in major adverse events. A large trial of nicotine patch use among pregnant women smokers (the SNAP trial) found NRT no more effective than placebo in smoking cessation, but infants born to women in the NRT group had a higher 2-year survival without impairment (Cooper *et al.* 2014). Controversy remains around this topic, however, with some practitioners recommending NRT only when nonpharmacologic smoking cessation therapies have failed (Forest 2010).

Health risks associated with nicotine have also been examined in other contexts. A 2011 commentary by Shields regarding possible cancer risks from long-term NRT use noted that cell culture and laboratory experiments have shown that nicotine can enhance proliferation in lung, bladder, and other tumors, can decrease apoptosis, can enhance angiogenesis, and can promote metastasis (Shields 2011). However, as the commentary points out, long-term ST use is generally not associated with cancer risks, extrapolating human risks from animal and other models is problematic, and the risk-benefit of long-term NRT use is extremely favorable compared to continued smoking. Reviews that have considered cardiovascular effects of NRTs have likewise found that in spite of some short-term effects such as increased blood pressure and heart rate, NRTs are generally safe for use in smokers who want to quit, including those with stable cardiovascular disease (Sobieraj *et al.* 2013).

In April 2013, the FDA announced that prior labeling for OTC nicotine-containing NRTs be modified to permit concomitant use with other nicotine-containing products, including cigarettes, as well as usage of NRTs for longer than 12 weeks. In its review of studies that preceded the announcement, FDA determined that "that the concomitant use of OTC NRT products with cigarettes or with other nicotine-containing products does not raise significant safety concerns." Furthermore, the FDA noted that "since NRT products became available for OTC use, a number of studies have examined the use of NRT products over periods longer than 12 weeks. We [FDA] have reviewed the published literature on this longer-term use of NRT products and have not identified any safety risks associated with such use" (FDA 2013). A 5-year study of almost 6000 smokers in the Lung Health Study provided data that among the 1000 subjects still using nicotine gum after 1 year, no correlation was found between long-term gum use and cardiovascular events (Murray *et al.* 1996). In a follow-up study, 5-year use of NRT did not predict an increase in lung cancer, gastrointestinal cancer, or all cancers (Murray *et al.* 2009). Other studies of NRT use (Joseph *et al.* 2011; Newhouse *et al.* 2012), in which large numbers of participants used NRT products for 6 months to 1 year, reported few adverse events related to NRT use (FDA 2013).

In summary, nicotine-containing NRTs, although not completely risk-free, offer only slight risks of mild adverse health effects, even after extended periods of use.

6.1.1.7.2 Non-Nicotine Tobacco Cessation Medications

Two non-nicotine smoking cessation products, bupropion and varenicline, are currently approved for use in the U.S. Bupropion SR (marketed as Zyban, Wellbutrin, and under other trade names) was approved for the treatment of nicotine dependence in 1997 as the first non-nicotine-based therapy option, although it had been previously available for the treatment of depression. The drug inhibits the reuptake of norepinephrine and dopamine, but the mechanism by which it facilitates smoking cessation is not clear.

Health risks related to bupropion use include a dose-related risk for epileptic seizures and a risk for hypertension, regardless of pre-existing hypertension. Bupropion has been evaluated in multiple studies for cardiovascular effects (reviewed in Sobieraj *et al.* 2013), since drugs with similar chemical structure had displayed a propensity for certain adverse cardiac effects. No clinically important changes were observed in these studies. The drug has also been evaluated in smoking cessation trials among patients with existing cardiovascular disease. Although some unfavorable changes were recorded, events were rare and/or mild. In 2009, the FDA issued an alert requiring a new warning regarding a possible risk for certain behavioral changes such as hostility, depressed mood and suicidal thoughts among both bupropion and varenicline users. It has been noted that the low short-term risks from bupropion use (typically 12 weeks of therapy for smoking cessation) are outweighed by the lifetime benefit from smoking cessation (Sobieraj *et al.* 2013).

Varenicline (marketed as Chantix and under other trade names) was approved for use in smoking cessation therapies in 2006. The drug is a selective agonist of certain nicotinic acetylcholine receptors, and is thought to aid in smoking cessation by lessening nicotine withdrawal symptoms and inhibiting the surge of dopamine release that occurs during smoking, thus reducing the reinforcing effects of smoking.

In June 2011, FDA issued a safety communication warning that varenicline may be associated with a small increased risk for certain cardiovascular events in patients with cardiovascular disease, and called for the manufacturer to conduct an analysis of placebo-controlled trials. Two such analyses were conducted, the first (Singh *et al.* 2011) suggesting a slight increase in risk for any ischemic or arrhythmic adverse cardiovascular event. The second (Prochaska and Hilton 2012), which included more than 9000 patients, did not observe a significant difference in risk between varenicline users and controls. A follow-up commentary (Krebs and Sherman 2012) concluded that when all available trial results were considered, there was no significant increase in serious cardiovascular events in adult tobacco users who used varenicline for cessation compared with placebo.

Recently, a joint FDA advisory panel reviewed results of a new study of bupropion and varenicline and adverse neuropsychiatric risks, including suicidal thoughts, hostility and agitation. In spite of criticizing aspects of the study, a majority of panel members voted in favor of dropping the black box warning for neuropsychiatric risks instituted in 2009, stating that the new study provided adequate evidence that the risk/benefit of the drugs was favorable (FDA 2016).

In summary, use of bupropion and varenicline, the two non-nicotine smoking cessation therapies currently approved for use in smoking cessation in the U.S., result in extremely low levels of health risks, which are overshadowed by the benefits associated with smoking cessation.

6.1.1.7.3 Relative harms of smokeless tobacco products, smoking, and NRT

Smokeless tobacco products, like Camel Snus, are associated with a low level of health risk, which varies somewhat by the type of ST product, and by the disease under consideration. As discussed extensively in Section 6.1.1, epidemiological studies of U.S. and Swedish ST products show essentially no risk for lung cancer or non-malignant respiratory disease, and marginal, if any, risk for oral cancer or cardiovascular disease. To provide perspective on the comparative risks of cigarette smoking, ST, and NRT use, Levy *et al.* 2004 convened a nine-member expert panel to offer opinions regarding mortality risks from the use of low-nitrosamine ST products (such as Camel Snus). The expert panel reached the consensus that such products were substantially less hazardous than conventional cigarettes, with a mean total mortality estimate falling between 5% and 10% of the risk of smoking. Estimated risks for oral cancer, heart disease, and lung cancer for ST users was 15-30%, 10%, and 2-4% respectively compared with the risks from smoking.

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

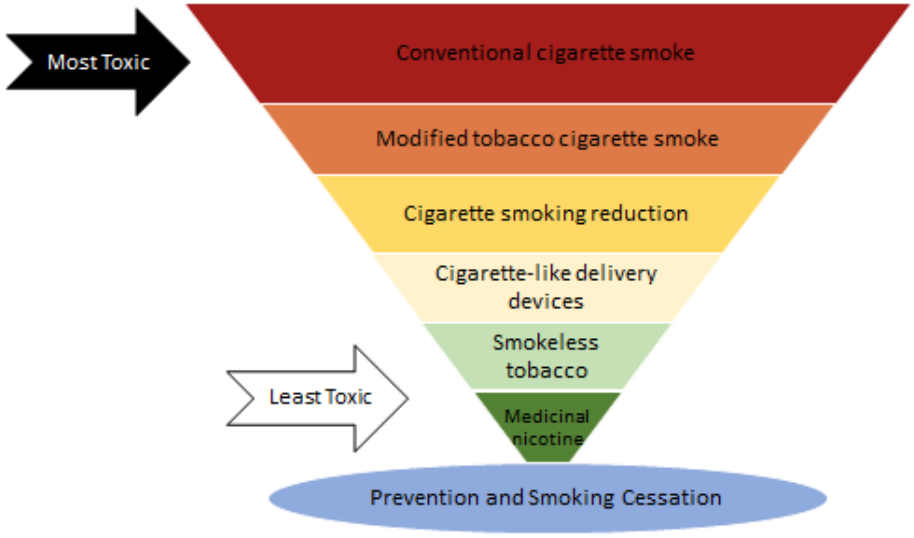
Thus, the health risks of ST, like Camel Snus, present only a fraction of the risk associated with cigarette smoking, and for health outcomes such as lung cancer and nonmalignant respiratory disease, pose no greater risk than NRT products.

6.1.1.7.4 The continuum of risk among nicotine-containing products

A concept often used in discussions of tobacco harm reduction strategies is one regarding what has come to be known as the "continuum of risk." This concept has been articulated in a number of publications (*i.e.*, Hatsukami *et al.* 2007a; Zeller *et al.* 2009; Nutt *et al.* 2014) and has been embraced by many public health experts who agree that moving tobacco users away from combustible tobacco products and toward the use of lower risk nicotine-containing noncombustible products is a viable and practical strategy for tobacco harm reduction. According to Zeller *et al.* 2009, "[t]here is a very pronounced continuum of risk depending upon how toxicants and nicotine, the major addictive substance in tobacco, are delivered. Cigarette

smoking is undoubtedly a more hazardous nicotine delivery system than various forms of non-combustible tobacco products for those who continue to use tobacco, which in turn are more hazardous than pharmaceutical nicotine products." Offering specific recommendations to smokers about this continuum of risk, Zeller asserts that "[o]n the continuum of risk, non-combustible tobacco products are more likely to reduce harm than a smoked form of tobacco for individuals who would otherwise be using conventional cigarettes," and that "if smokers who cannot or will not quit their dependence on nicotine switched completely to smokeless tobacco products, they would likely experience a reduction in tobacco-caused mortality and morbidity. The extent of this reduction is unknown. Nevertheless, these persons would not be risk-free, and their risk would be higher than if they switched to medicinal nicotine." An example of the continuum of risk is illustrated in Figure 6.1.1-2 below.

Figure 6.1.1-2:Continuum of risk associated with nicotine-containing products (adapted from Hatsukami *et al.* 2007a)



6.1.1.7.5 Conclusion

Available data provide consistent evidence that Camel Snus and other U.S. and Swedish ST products present substantially lower health risks compared to cigarette smoking. Compared with cigarettes, ST products, like Camel Snus, contain low levels of tobacco combustion products and lower levels of many other tobacco smoke toxicants, however they do contain higher levels of toxicants compared with medicinal nicotine products. Medicinal nicotine is not considered to pose a risk for lung cancer or other cancers, and cardiovascular risks associated with NRT use are considered slight. The relative harms of cigarettes, ST and smoking cessation therapies are best viewed within the continuum of risk, as discussed and illustrated above. As estimated by Levy *et al.* 2004 and Nutt *et al.* 2014, ST, like Camel Snus, is on the least toxic end

of this continuum, with estimated harm at most, only 5-10% that of smoking, with NRT carrying risks slightly lower.

6.1.1.8 Additional health risk information applicable to comparative health risks to sub-populations (*e.g.*, youth, pregnant women, ethnic groups)

Cigarette smoking is a cause of adverse health effects across all groups of smokers in the U.S., including females, pregnant females, adolescents, nonsmokers and various ethnic populations. Generally tracking with smoking prevalence, disparities in the incidence and outcomes of tobacco use-related diseases among population subgroups are widely reported, but the underlying reasons are complex, with multiple factors in play, including smoking behaviors, socioeconomic factors, diet, cultural traits, occupational exposures, genetic susceptibility, differences in treatment, responses to therapies, etc.

Smokeless tobacco use also varies considerably across various groups, with ST use prevalence determined by the same complex factors as smoking, although not with the same distribution profile as with smokers. Most of those factors are beyond the scope of this section, which focuses on individual health risks and not prevalence or behaviors. Health outcomes from smokeless tobacco use stratified by different population subgroups have not been well-studied due to the overall low prevalence of ST use in the U.S., and the low incidence of disease in ST users. The discussion that follows will focus on available representative data regarding comparative health effects to individuals in several population subgroups from smoking and ST use, assuming that such individual tobacco users experience the same levels of exposure.

RJRT believes that minors and pregnant women should never use tobacco products and adults who do not use or have quit using tobacco products should not start.

6.1.1.8.1 Health risks to population subgroups due to cigarette smoking

Overall: Higher rates of smoking compared to U.S. averages are reported among persons of low socioeconomic status, sexual minorities, low educational attainment, some racial/ethnic minority groups, those living with mental illness and substance use disorders, and across different regions of the country (USDHHS 2014; USDHHS 1998). Differences in the magnitude of smoking-related disease risk among U.S. racial/ethnic groups and by gender have been directly related to differences in patterns of smoking (Prizment *et al.* 2014; Patel *et al.* 2016; Huxley *et al.* 2012; Freedman *et al.* 2008; Thun *et al.* 2013).

Females, pregnant females, adolescents: A number of older epidemiological studies have reported differences in relative risks for various smoking-related diseases among female smokers compared with their male counterparts. However, more recent studies, and studies of more contemporary cohorts that better account for actual smoking and other exposures have found that equal cigarette smoke exposure equates to approximately equal smoking-related risks for lung cancer (Freedman *et al.* 2008; Thun *et al.* 2013), COPD, ischemic heart disease, any type of stroke, and for all causes (Thun *et al.* 2013).

Cigarette smoking before and during pregnancy is a significant cause of maternal, fetal, and infant morbidity and mortality (USDHHS 2014). It appears that tobacco combustion products (such as CO), and not nicotine, are largely responsible for reductions in birth weights among infants of smokers, since the magnitude of association is smaller for users of ST (studies reviewed in USDHHS 2014). On the other hand, smoking is inversely associated with risk for pre-eclampsia, possibly mediated by CO. These topics and others related to reproductive outcomes are further discussed in RJRT's Citizen Petition Appendix.

Cigarette smoking causes reduced lung function and impaired lung growth during childhood and adolescence, as well as wheezing severe enough to be diagnosed as asthma in susceptible individuals (USDHHS 2012). The acute effects of nicotine are well-documented and include transient increases in heart rate and blood pressure. However, no data have been identified that indicate unique harms leading to chronic smoking-related diseases occur in adolescent compared with adult smokers. RJRT believes, and states in its current advertising and proposed advertising executions for Camel Snus, that minors should never use tobacco products and adults who do not use or have quit using tobacco products should not start.

6.1.1.8.2 Health risks to population subgroups due to smokeless tobacco use

Compared with cigarette smoking, U.S. smokeless tobacco use is associated with a lower risk for adverse health effects among users, and also with fewer disease endpoints as discussed in prior sections of this Application. Due to the much smaller number of ST users (currently 3.4% of U.S. adults) compared with smokers (based on 2014 data, 16.8% of U.S. adults, but historically, as high as 43% in 1965), the literature on ST-related health risks stratified by population subgroups is limited. There is a striking distribution profile for prevalence of use for smokeless tobacco (Table 6.1.1-8). The prevalence of smokeless tobacco use is significantly higher among males as compared to females, and varies by race/ethnicity (Table 6.1.1-8). There are also distinct regional differences in ST use, ranging from 8.8% in Wyoming to 1.5% in Massachusetts, Delaware and Hawaii.

Table 6.1.1-6: Prevalence of current smokeless tobacco use among U.S. adults by population subgroup

Adults aged 18 years and older	3.4%
Males	6.7%
Females	0.3%
Non-Hispanic African Americans	1.2%
Non-Hispanic American Indians / Alaska Natives	7.1%
Non-Hispanic Asians	0.6%
Hispanics	0.9%
Non Hispanic Whites	4.6%

Values for 2014; from CDC website; accessed 10-20-2016 (CDC 2016d).

As with differences in smoking prevalence, the underlying reasons for the observed differences in ST use prevalence are complex and multifactorial.

Females: Due to the large disparity in ST use between men and women, the most robust results from epidemiological studies of ST use and health outcomes are restricted to male ST users, and no focused comparison of ST-related health risks for men compared to women has been published. Studies that included female ST users (i.e., Accortt *et al.* 2002; Winn *et al.* 1984; Blot *et al.* 1988; Accortt *et al.* 2005; Yatsuya *et al.* 2010; Janzon and Hedblad 2009) are discussed in the Ramboll Environ systematic review of relevant epidemiological studies (Ramboll Environ 2016) submitted with this Application. Taken together, the studies do not support a difference in risks between men and women for the health effects of ST use among individuals. Indirect evidence regarding possible differential health risks for males and females is also provided in studies reviewed above that indicate that smoking-related risks are overwhelmingly determined by levels of exposure, rather than to measurable inherent differences in susceptibility. Thus, female smokers who switch completely to Camel Snus would be expected to experience reductions in health risks similar to male smokers who switch to Camel Snus.

Pregnant females: RJRT's proposed advertising executions for Camel Snus clearly state that the product is not to be used during pregnancy. ST use during pregnancy has been associated with low birth weight, preterm births, stillbirths, and infants small for gestation age (Inamdar *et al.* 2015; Ratsch and Bogossian 2014). These topics and others related to reproductive outcomes are further discussed in RJRT's Citizen Petition Appendix.

Adolescents: The epidemiology of ST use and health outcomes already accounts for exposures at younger ages, even though those studies have focused on health outcomes occurring in adulthood (USDHHS 2012). As such, no differential chronic adverse effects on adolescents have been documented. RJRT supports the existing age restrictions on the sale of all tobacco products, including smokeless tobacco, and states in its proposed advertising executions that minors should never use tobacco products.

Nonsmokers: ST products produce no secondhand smoke and there is no evidence that non-tobacco users will experience any increase in health risks associated with the use of smokeless tobacco by others in their presence.

Other population subgroups: There is no robust evidence that when usage patterns are taken into account, ST presents any unique health risks to other specific population subgroups.

Conclusion: Cigarette smoking results in high risks for a multitude of tobacco-related diseases, and those risks depend overwhelmingly on exposures to smoking-related toxicants, rather than any inherent unique susceptibility in specific groups. Differences in smoking-related risk noted across various population subgroups can thus be largely, if not totally, explained by differences in smoking patterns and individual smoking behaviors.

Although data are limited and somewhat indirect, ST use appears to present no unique risks to any specific population subgroups, for example, adolescents, females, and members of various ethnic/racial groups. With the exception of reproductive health risks, any risks to diverse populations from Camel Snus use, although largely composed of male users, should mirror the health risks for all groups of users. And those risks are far lower than those associated with cigarette smoking. As such, encouraging smokers to switch completely to Camel Snus is expected to benefit all smokers in the U.S. population, including those among population sub-groups.