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An Assessment of Camel Snus Abuse Liability

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1 Executive Summary of Abuse Liability of Camel Snus

Abuse liability refers to the risk that use of a substance or product will lead to psychological and physiological dependence, along with persistent self-administration and impeded ability to discontinue use of the substance (Food and Drug Administration [FDA], 2010, 2012a).

Assessment of the abuse liability of a substance or product is accomplished by a variety of methods that may include *in vitro*, nonclinical and human participant studies of:

- where in the central nervous system (CNS) the substance acts,
- to what receptors it binds to determine the pharmacological site(s) of action
- direct and indirect effects on neurotransmitter systems associated with abuse potential
- animal and human behavioral pharmacology studies including discriminative and reinforcing effects
- human abuse potential studies including assessment of liked and positive effects, and its behavioral effects, such as reinforcement and production of pleasure
- physical dependence potential studies including assessment of tolerance and withdrawal
- patterns of self-administration of the substance, and
- epidemiological data.

Such lines of evidence are described and relied upon by the FDA Center for Tobacco Products (CTP) for evaluating tobacco products and by the FDA Center for Drug Evaluation and Research (CDER) for evaluating pharmaceutical products (FDA, 2010, 2012a, 2015).

The abuse liability of nicotine has been very well characterized, and it is accepted that nicotine has a prominent role in the abuse liability of tobacco products (FDA, 1995; United States Department of Health and Human Services [USDHHS], 1988, 2010, 2014). However, it is also recognized that the formulation of a product that contains nicotine substantially determines its effects and, thus, nicotine delivering products vary widely in their abuse liability – from the minimal abuse liability associated with FDA-approved transdermal nicotine patches to the high abuse liability associated with traditional cigarettes (FDA, 1995; USDHHS, 1988, 2010, 2014).

The 2012 Draft Guidance for Modified Risk Tobacco Product (MRTP) Applications mandates that the product proposed for authorization as an MRTP be evaluated for abuse liability. Such an evaluation would determine if use of the proposed product (i.e., Camel Snus in RJRT's MTRP Application) would contribute to reduced individual harm and public health risk if used in place of other tobacco products (e.g., cigarettes). This is similar in concept to assessing, for example, the relative carcinogenicity, cardiotoxicity, and oral disease risk of the two tobacco products, although available methods for assessment of abuse liability may reasonably be described as less quantitative than are measures of some other biological effects, and as having a subjective component that

may differ among individuals. However, there is one important difference – whereas adverse effects (e.g., carcinogenicity, cardiotoxicity, and oral disease risk) should be ideally reduced to the greatest possible extent, some of the effects that contribute to abuse liability must remain sufficient for a putative MRTP to adequately substitute for the reinforcing effects of traditional cigarette smoking that have been well-documented over time (FDA, 1995; USDHHS, 1988, 2010, 2014; also see discussion in Cobb et al., 2010; National Institute on Drug Abuse, 2016). Thus, an abuse liability assessment is relevant for assessing potential risks and benefits associated with Camel Snus being considered a MRTP. This rationale also keeps in mind that the FDA could reject authorization of a product for which the abuse liability was determined to pose an unacceptably high risk of causing, perpetuating, or expanding the population reach of dependence. There is no standard of what level of abuse liability would be acceptable for approval of a MRTP application, just as there is no absolute standard for how low the cancer-causing risk of a product should be to warrant authorization as a MRTP. This report evaluates the abuse liability of Camel Snus based on the 2012 FDA draft guidance, as well as FDA's guidance of 2010 and 2015 for assessing the abuse liability of other substances and formulations.

The abuse liability assessment of Camel Snus contained in this section addresses four key questions, and conclusions related to those questions are summarized below. More detailed analysis of published and unpublished literature is provided in subsequent sections and forms the basis for the conclusions below.

1. *What is the abuse liability of Camel Snus compared to traditional cigarettes and nicotine replacement therapy?*

   The abuse liability of Camel Snus is substantially less than that of traditional cigarettes and likely higher than that of FDA-approved over-the-counter nicotine replacement therapy (NRT) medications (i.e., gum, lozenge and transdermal patch). Thus, Camel Snus is expected to benefit some smokers who are concerned about the risks of smoking, but find medicinal NRT products unacceptable and who will continue to use some form of tobacco product. How many smokers actually adopt Camel Snus in place of cigarettes will likely be influenced by allowable labeling and communication, as well as by its physical characteristics.

   These conclusions are based on converging lines of evidence from laboratory studies, as well as clinical and epidemiological studies (a summary of such data is found in the main body of this report). In addition, these conclusions are consistent with and support a key premise of the 2014 Surgeon General's Report that "*Cigarettes carry the highest risk of addiction following initiation*…" (USDHHS, 2014, p.783). For example, the prevalence of use, risk of dependence following initiation of use, and severity of withdrawal are the highest for traditional cigarettes among all tobacco products. Conversely, prevalence, risk of dependence, and severity of withdrawal are generally lower for oral smokeless tobacco products. These differences are well established by epidemiological findings, and are consistent with

findings from relevant laboratory studies employing nonclinical and clinical models to assess product contents and emissions, as well as modes of use (i.e., inhalation as compared to oral/ buccal use).

The widely-accepted continuum of risk hierarchy of nicotine-delivering products places medicinal NRT products at the lowest level of risk and traditional cigarettes at the highest level of risk, with smokeless tobacco products closer to NRT than to cigarettes, as represented here:

Continuum of Risk*:* NRT < Oral Smokeless < Cigarettes and other Combustible Products

Similarly, Fagerström & Eissenberg (2012) and others (e.g., Niaura, 2016) have proposed an analogous continuum of abuse liability/dependence potential hierarchy that assigns rankings to different nicotine-delivering product classes based on the current understanding of their respective abuse liabilities. This hierarchy places medicinal nicotine products such as transdermal patches at the lowest level of abuse liability, conventional cigarettes at the highest level of abuse liability, and oral smokeless tobacco products at an intermediate ranking, closer to NRT than to cigarettes. Electronic nicotine delivery systems (ENDS), also known as electronic cigarettes are provisionally ranked higher in abuse liability than smokeless tobacco, while it is recognized that published evidence for this product category is presently less extensive than is available for the other nicotine-delivering products:

Continuum of Abuse Liability ("dependence potential")*:*

NRT < Oral Smokeless < Electronic Cigarettes < Cigarettes and other Combustible Products

Importantly, while this continuum emphasizes the general ranking of these four categories of products, it is likely that there are a range of levels of abuse liability within each category just as there is a range of toxicity for such products. For example, among NRT products there is some evidence to suggest that nicotine nasal spray is likely of higher abuse liability than other products (Schuh et al., 1997). Among oral smokeless tobacco products, the nicotine content and fraction of unionized nicotine can range from very low and of likely low potential to sustain dependence, to much higher levels which overwhelmingly dominate the United States (U.S.) market (Henningfield et al, 1995; Fant et al., 1999; Stanfill et al., 2011; Delnevo et al., 2014). Electronic Nicotine Delivery Systems likely occupy a broader band on the risk continuum, with insufficient information currently available to assign a more specific ranking for such products with confidence. Among combusted tobacco products, there is little doubt that conventional nicotine-containing tobacco cigarettes are of the highest abuse liability, with relatively little overall variation across brands. However, it is likely that other combusted products such as waterpipes, cigars, and pipes are lower in abuse potential than cigarettes (USDHHS, 1996; Henningfield et al., 1999).

2. *What is the abuse liability of Camel Snus compared to other forms of smokeless tobacco?*

Among smokeless tobacco products, the category known as “snus” is generally accepted as lowest in toxicant content and disease risk, although not necessarily lowest in abuse liability. For example, some typical low nitrosamine products in Sweden have pH levels above 8 and relatively high unionized nicotine levels (see data presented in Appendix A), and may exceed Camel Snus in estimated abuse liability. Camel Snus is on the lower end of the continuum of nicotine content and unionized nicotine content among oral smokeless tobacco brands. This does not ensure that its abuse liability is lower than market-leading brands in the U.S.; however, it is unlikely, based on this profile and its historical modest market penetration, that the abuse liability of Camel Snus exceeds that of currently marketed smokeless tobacco products. Furthermore, it is plausible that its abuse liability is lower than that of many popular traditional brands of oral smokeless tobacco, which are higher in nicotine concentration, pH, and unionized nicotine than Camel Snus.

The possibility that Camel Snus is actually lower in abuse liability than some nicotine-containing products is suggested by initial human studies (O’Connor et al., 2011; Blank & Eissenberg, 2010), while others suggest that Camel Snus abuse liability is similar to or exceeds the abuse liability of some very low nicotine-containing, low pH products (e.g., nicotine gum or lozenge, Ariva tobacco tablets; Cobb et al., 2010; Hatsukami et al., 2011; Kotlyar et al., 2011). Correspondingly, pharmacokinetic studies confirm that the speed of absorption and peak nicotine levels associated with Camel Snus are higher than what has been observed for some smokeless tobacco products, but lower than that of several market leading high nicotine content smokeless tobacco products (see). As shown in Appendix B, Camel Snus nicotine delivery is within the range of delivery per unit dose of oral and nasal nicotine replacement products.

Although prevalence of product use depends on many factors beyond abuse liability, the modest uptake of Camel Snus (despite active marketing for several years) also suggests that it is not a product of high abuse potential. That said, Camel Snus has a current market share of 79.4% (percent of snus pouches sold in United States in 2015) and that is much larger compared to other snus products including Swedish Match General snus (12.5%), Skoal snus (7.0%), and Marlboro snus (1.14%) (2015 U.S. market data reflecting shipments to retail (data collected by IRI/Capstone, processed and managed by MSAi). A greater market share for Camel Snus is consistent with a greater potential to have a positive impact on the public health and U.S. smokers as a substitute for cigarettes. When considering the foregoing estimates of market share, it is important to consider that that tobacco market is overwhelmingly dominated by traditional cigarettes. Thus, for example, when all

traditional cigarettes and snus categories are combined, the Camel Snus market share is 0.3% (RAI, Camel Snus Survey Data, Dec. 15, 2016, p.20

3. *Does the abuse liability of Camel Snus vary between product styles described in RJRT's MRTP Application?*

   No. The Camel Snus styles submitted for authorization as MRTPs in RJRT's Application do not likely differ in abuse liability given that they are pharmacologically equivalent, (b) (4) Further, biomarker data from several clinical studies in which participant groups used Camel Snus styles of different pouch sizes (0.4 g, 0.6 g and 1 g) indicate that nicotine and tobacco-specific N-nitrosamine (TSNA) exposures were similar for all Camel Snus styles studied.

4. *What are the implications of the abuse liability profile of Camel Snus with respect to its potential to function as an acceptable MRTP and thereby serve the public health goal of contributing to the reduction of combustible tobacco product use, as advocated by the 2014 Surgeon General's report?*

   The abuse liability profile of Camel Snus supports the conclusion that it will serve as an acceptable and beneficial MRTP. Camel Snus contains sufficient nicotine and is sufficiently buffered to match or exceed oral nicotine replacement medications in nicotine delivery and absorption speed and levels per unit, and this has been confirmed in pharmacokinetic studies (See Appendix B). The laboratory, clinical, and market data suggest that the abuse liability, while far lower than that of traditional cigarettes, will likely enable Camel Snus to serve as an acceptable alternative to cigarettes for some, and reach many people who find NRT products unacceptable or unhelpful. The population impact will also depend on factors beyond abuse liability (e.g., FDA-authorized claims and marketing, attractiveness of flavors and other product characteristics, as well as its pharmacological abuse liability). Camel Snus appears to fall in the general midrange of a viable harm reduction product as conceptualized by Niaura (2016) and Henningfield (2015b), and also described in this report.

2 Background

2.1 Defining Abuse Liability

In this report, we use the definition of abuse liability as presented by the FDA Center for Tobacco Products in its Draft Guidance for MRTP applications: "*Abuse liability is the likelihood that individuals will develop physical and/or psychological dependence on the tobacco product. Physical dependence is characterized by the development of tolerance to tobacco product use and/or the onset of withdrawal symptoms upon stopping use of the tobacco product. Psychological dependence is characterized by persistent tobacco-seeking and tobacco-use behaviors, impairment in behavioral control, craving, and*

inability to abstain consistently" (FDA, 2012a, p. 19). Note that 'psychological dependence' in this definition is equivalent to what the American Psychiatric Association (APA) refers to in the third and fourth revisions of its Diagnostic and Statistical Manual (DSM-III and DSM-IV) as 'dependence' and in its fifth revision (DSM-5) as 'substance use disorder' (APA, 1980, 1987, 1994), and what the World Health Organization (WHO) refers to as 'dependence' in the tenth edition of its International Classification of Diseases (ICD-10) (WHO, 1994). 'Physiological dependence' is the widely used scientific term (e.g., USDHHS, 1988; Carter et al., 2009; O'Brien, 2011) for what the APA and WHO refer to as 'withdrawal' in diagnostic manuals, because withdrawal symptoms are used clinically to determine if physiological dependence is present. In sum, abuse liability is a scientific term that refers to the risk that a substance or drug will be used repeatedly and often harmfully by people in order to experience central nervous system-mediated pleasurable effects (National Institute on Drug Abuse, Monographs 52, 89; WHO Expert Committee on Drug Dependence, 2003). Historically, and in the general literature, as well as in documents produced by the FDA, the Surgeon General, and the National Institute on Drug Abuse, the term abuse liability is often used interchangeably with 'abuse potential', 'addiction potential' and 'dependence'. See additional background below in the Insert Box on the next page titled "Background on Abuse Liability and Related Terminology by Different Organizations".

Background on Abuse Liability and Related Terminology by Different Organizations

Internationally, the World Health Organization (WHO) and other organizations have typically used the term 'dependence potential' to describe the properties of a substance that can lead to the disorder of 'dependence' as described in the WHO International Classification of Diseases (WHO, 1992, ICD 10). This use of the term 'dependence potential' is synonymous with what U.S. agencies and researchers refer to as 'abuse potential' and 'abuse liability'. Regardless of the term, the same types of methods of evaluation in laboratory and clinical studies are used to describe and quantify abuse liability. In the U.S., abuse liability and/or abuse potential emerged as the predominant terms used to describe the property of drugs that would contribute to their self-administration, often in the face of harm or legal sanction, regardless of whether there was evidence that physiological dependence was present. 'Dependence' became more synonymous with the state of physiological dependence that would lead to a withdrawal syndrome if drug administration was terminated. Such variation in terminology nationally and internationally is not uncommon in science and often reflects the prevailing concerns of a particular time. Thus, in the 1970's, the U.S. government and scientists were focusing heavily on drugs such as cocaine and other stimulants, hallucinogens, and marijuana, which were not understood to generally produce physiological dependence and withdrawal as did alcohol, opioids and sedatives.

Several lines of evidence are typically necessary to determine if a substance or product has sufficient abuse liability to merit special consideration among marketed products (e.g., Controlled Substances Act (CSA) Scheduling and labeling in the case of pharmaceutical products). A warning was required by the Family Smoking Prevention and Tobacco Control Act for cigarettes and smokeless tobacco products that included the word "addictive". The conclusion that these products were of sufficiently high abuse liability and physical dependence potential to merit such warnings was based on multiple lines of evidence. Tobacco products, along with alcoholic beverages, are by law exempt from certain other regulatory control mechanisms (e.g., placement in a CSA schedule) that apply to other products (Drug Enforcement Administration, Fact Sheet, Accessed December 9, 2016 at http://www.dea.gov/druginfo/concern_dextro.shtml; Controlled Substances Act, Part A, Section 802, No. 6 ("The term [controlled substance] does not include distilled spirits, wine, malt beverages, or tobacco, as those terms are defined or used in subtitle E of the Internal Revenue Code of 1986.") Accessed December 9, 2016 at: http://www.deadiversion.usdoj.gov/21cfr/21usc/802.htm).

At the FDA, evaluation of abuse liability occurs in the Center for Drug Evaluation and Research (CDER), and CDER uses the term "abuse potential". The FDA Center for Tobacco Products (CTP) determined that it would use the term "abuse liability". By either term, abuse liability assessment refers to the portfolio of scientific methods that can be used before a product is marketed to determine the risk that self-administration or consumption will lead to pharmacologically-based dependence. Such information is considered by regulatory authorities and policy makers, including the FDA, to determine whether there is sufficient concern to warrant special labeling and warnings, restrictions on marketing and availability, minimum age requirements for procurement, and, in the case of drugs, regulation or "scheduling" under the United States Controlled Substances Act. Although tobacco products are exempt from CSA scheduling, their abuse liability is a factor in restrictions on their marketing, access to minors, and in warnings and labeling.

As described by FDA, assessment of abuse liability is accomplished by a combination of laboratory studies that include chemistry studies, in vitro/ex vivo determinations of mechanisms of action, laboratory studies involving both animals and humans, and epidemiological findings characterizing use and dependence at the population level (FDA, 2010, 2012). These methods serve to guide drug regulation and development, as well as regulation of various substances with apparent potential to cause abuse or dependence, including tobacco and nicotine products (e.g., USDHHS, 1988; Schuster & Henningfield, 2003; Carter et al., 2009; FDA, 2010, 2015). These methods are also used internationally, including by the World Health Organization for its drug control and regulation efforts (e.g., Spillane & McAllister, 2002; Balster & Bigelow, 2003).

In the United States, the FDA and the National Institute on Drug Abuse (NIDA), along with the Drug Enforcement Administration (DEA), are charged with performing an abuse liability assessment of new drugs and substances to determine how they should be labeled and if they should be subject to control or scheduling under the 1970 CSA (DEA, 2016). Similarly, assessment of abuse liability is important in FDA tobacco product evaluation to help the FDA accomplish its statutory requirements to evaluate the relative risk that a product poses (e.g., compared to products in the same class or products claimed to be substantially equivalent), including the likelihood that use will increase initiation and dependence and impede cessation (FDA, 2010, 2012a). In the context of tobacco product regulation by FDA, including assessment of products for designation as modified risk tobacco products, the purpose of abuse liability assessment is to enable FDA to carry out its statutory requirements to determine the likely effect of the product on tobacco product initiation in non-users of tobacco, the likelihood that the product will be used or misused, and other potential issues as described in its 2012 draft guidance for MRTP applications, which also provided the FDA CTP's definition of abuse liability (see insert box on next page titled "Effect on Tobacco Use Behavior among Current Tobacco Users"). This role is generally consistent with FDA's Center for Drug Evaluation and Research definition of abuse potential as provided in its 2010 guidance on abuse potential assessment of drugs (FDA, 2010). Although the CTP and CDER guidance documents were drafted at different times and with a focus on tobacco by CTP and a focus on pharmaceutical products (including NRT products) by CDER, the difference in wording or terms is not assumed to represent a fundamental difference in FDA thinking. Moreover, the types of studies and data referred to in the CTP guidance are taken largely from the 2010 CDER guidance and other expert reviews (e.g. Schuster & Henningfield, 2003; Carter & Griffiths, 2009; Carter et al., 2009; Henningfield et al., 2011).

Effect on Tobacco Use Behavior among Current Tobacco Users

In order for FDA to assess the full impact that an MRTP and its marketing may have on population health under section 911(g)(1)(B) or 911(g)(2)(B)(iv) of the [Federal Food, Drug and Cosmetic Act] FD&C Act, an MRTPA should contain scientific evidence about the effect the product may have on tobacco use behavior among current tobacco users. This includes consideration of areas such as the expected rates of use of the tobacco product by current tobacco users, the use of the tobacco product in conjunction with other tobacco products, and the potential for abuse and misuse of the product. An application must provide evidence regarding whether the product and its marketing will increase or decrease the likelihood that existing users of tobacco products who would otherwise stop using such products would instead switch to the tobacco product that is the subject of the application. See section 911(g)(4)(B) of the FD&C Act.

To address the effect on behavior among current tobacco users, FDA recommends that applicants submit:

- Nonclinical and/or human studies to assess the abuse liability and the potential for misuse of the product as compared to other tobacco products on the market; and
- Human studies regarding actual use of the product and consumer perception of the product, including its labeling, marketing and advertising.

The scientific studies submitted by the applicant should inform FDA's evaluation of the tobacco product's impact on tobacco use behavior, including:

- The likelihood that current tobacco product users will start using the product;
- The likelihood that tobacco users who adopt the product will switch to or switch back to other tobacco products that present higher levels of individual health risk;
- The likelihood that consumers will use the product in conjunction with other tobacco products;
- The likelihood that users who may have otherwise quit using tobacco products will instead use the product; and
- The likelihood that consumers will use the product as intended or designed.

Footnote from FDA Guidance: Abuse liability is the likelihood that individuals will develop physical and/or psychological dependence on the tobacco product. Physical dependence is characterized by the development of tolerance to tobacco product use and/or the onset of withdrawal symptoms upon stopping use of the tobacco product. Psychological dependence is characterized by persistent tobacco-seeking and tobacco-use behaviors, impairment in behavioral control, craving, and inability to abstain consistently.

From FDA, 2012. Guidance for Industry: Modified Risk Tobacco Product Applications, Draft Guidance, page 4, lines 727-759.

Further, with regards to the definition of abuse liability it is important to understand that both 'psychological' and 'physiological' dependence involve parts of the nervous and endocrine systems, and both also involve mood and behavior. Traditionally, the primary measures of psychological dependence have been behavioral measures, whereas physiological dependence (withdrawal) is more readily assessed by a combination of behavioral and physiological measures (e.g., change in heart rate, pupil diameter, and muscle relaxation depending on the substance).

Among tobacco products, there has been far more research on traditional cigarettes than any other product type; however, all lines of evidence taken together have led the U.S. Surgeon General to conclude that among tobacco products, combustible products and cigarettes in particular carry the highest risk of dependence, morbidity, and premature mortality (USDHHS, 2014). Whereas cigars, waterpipes, and other combusted tobacco products have not been demonstrated to carry the same risks of addiction and other disease as traditional cigarettes, combustible products as a single category were differentiated from all other nicotine-containing products with respect to disease risk and public health impact. Such a categorization is consistent with the fact that substantial numbers of harmful and potentially harmful constituents are produced by the combustion of tobacco when smoked in any traditional manner.

Furthermore, many published scientific reviews have indicated that the risk of dependence and withdrawal, along with many other diseases, varies widely across nicotine delivering tobacco products, with the highest risks found for combustible products in general and traditional cigarettes in particular (e.g., USDHHS, 1988; Henningfield et al., 1997; WHO, 2006; , USDHHS, 2010; Fagerström & Eissenberg, 2012; USDHHS, 2014). The lowest risks are related to nicotine gum and transdermal patches, while smokeless tobacco products are thought to convey intermediate risk. In sum, evaluation of a product's abuse liability is important to FDA in MRTP applications in order to provide an empirical basis for estimating this category of risk as compared to traditional cigarettes.

2.2 Relationships Among Abuse Liability, Product Appeal, and Consumer Perception

The U.S. FDA, the WHO, and other regulatory organizations and experts recognize that many factors in addition to pharmacology determine how a product is used, its prevalence of use, the potential benefits of the product, and the risk that the product poses for dependence in the community or "real world" (WHO, 2007a, b, 2011; Henningfield et al., 2011; FDA, 2010, 2012a, 2015; European Commission Directorate-General for Health and Consumers, 2010). Such factors are referred to by terms including product 'attractiveness', 'consumer perception', 'appeal', and/or 'consumer appeal'. Further, the determinants of product appeal could include how it is consumed (e.g., inhaled versus oral), cost, accessibility, physical attractiveness, ease of use, taste and odor in the case of orally consumed products, governmental agency approved or

required claims and warnings, perceptions of risk versus benefit, and how the product is marketed.

Four decades of monitoring youth trends in tobacco, alcohol, and substance use in the U.S. by the Monitoring the Future Surveys has revealed that the most consistent determinants of prevalence of use and use-associated harm are perception of harm, cost, and availability (Johnston et al., 2015). This finding emphasizes that the use and harm associated with a product or substance is determined by many factors beyond its pharmacologically-based abuse liability. For example, the finding by the Population Assessment of Tobacco and Health (PATH) that "*Smokeless tobacco was the product that was more likely to be perceived as more harmful than cigarettes*…" suggests that improved education is needed to support the 2014 Surgeon General Report's goal of reducing combusted tobacco product use (Fong et al., 2016).

Of note is the observation that perceptions and beliefs, including misperceptions, are essential for informing regulation and some studies have examined these factors with respect to Camel Snus (e.g., Biener et al., 2014a, b; Delnevo et al., 2014; Smith et al., 2015a; Hatsukami et al., 2016b; Wackowski et al., 2016). Perceptions by cigarette smokers that smokeless tobacco is as harmful or even more harmful than smoking, likely reduces consideration of smokeless tobacco as a replacement for cigarettes (Sami et al., 2012). While studies that address the effects of claims, marketing, and advertising on perceptions are important to use in the community (FDA, 2012a, Section VI.A.3), they are beyond the scope of the present abuse liability assessment of Camel Snus.

2.3 Relationship Between Abuse Liability and Modified Risk

For a product designated as an MRTP to be an acceptable substitute for traditional cigarettes, the product must provide absorbable nicotine and sufficient satisfaction to sustain use in place of traditional cigarettes. That is, the product must have some level of abuse liability. In the case of snus products, the World Health Organization Tobacco Regulation Study Group (WHO TobReg) addressed this issue in its report titled "Contents and design features of tobacco products: their relationship to dependence potential and consumer appeal" (WHO, 2007b). As stated in the report: "*For the categories of oral smokeless products known as moist snuff, including snus, the design and method of use of the product require the pH of the product to be controlled with sufficient buffering material to enable nicotine to be free for absorption over the many minutes that the product may be kept in the mouth*" (WHO, 2007b, page 13). This quote suggests that for the product to "work", it needed to be manufactured to enable nicotine delivery. The report also made clear, however, that a regulatory goal was to reduce – and not increase – tobacco product abuse liability (referred to as 'dependence potential' in the report) and/or appeal.

The above quote from WHO is in contrast to the typical goals of regulators and product developers of pharmaceutical products under development for treatment of most

diseases (e.g., anxiety, insomnia, and pain). For such products, the goal is to minimize abuse liability to the lowest possible level, including minimal reinforcing, physiological dependence, and withdrawal-producing effects. In contrast, for drugs developed as agonist, or replacement, therapies for substance use disorders, the benefits of the drug may be related to its ability to sufficiently sustain physiological dependence to prevent the onset of withdrawal symptoms when use of the targeted dependence producing substance is discontinued.

Similarly, compliant use of the treatment product and use of the treatment product in place of the targeted dependence-producing substance may be enhanced by making the product sufficiently attractive and appealing and with sufficient abuse liability to sustain use by providing some degree of satisfaction. Thus, for example, the two most widely used and essential opioid dependence treatment medicines (buprenorphine and methadone) can sustain physiological dependence and prevent the onset of withdrawal symptoms when heroin use is discontinued, and they provide a degree of satisfaction that is adequate to sustain use by many people, although less than that provided by intravenous heroin (Preston & Bigelow, 1985; Johnson et al., 1995; Donny et al., 2002; Donny et al., 2005; Bell, 2014; Mattick et al., 2014). The result is that these medications are considered inadequate by some heroin users, while others find them to be acceptable alternatives to injectable opioids.

Similarly, NRT medicines (e.g., nicotine gum, lozenge, patch) are effective in providing withdrawal relief and aiding smoking cessation; however, their acceptability and ability to sustain compliant use over the weeks and months necessary to produce lasting smoking cessation in some smokers is constrained by their limited dose capacity and satisfying effects related to their abuse liability (Fant et al., 2009). Adding flavoring to nicotine gum and lozenges and attending to the organoleptic qualities (i.e., those involving the sense organs such as taste, smell, sight, and touch; Simon & Nicolelis, 2001; Meilgaard et al., 2006) that make oral products more satisfying to use has been considered important in expanding the use of the products and, hopefully, contributes to increased real world effectiveness.

In the context of putative harm reduction tobacco products, these issues have received extensive discussion, particularly as pertains to electronic nicotine delivery systems (ENDS). Among one of the more detailed models is that developed by Raymond Niaura and colleagues (2016; see Figure 1 below). The figure shows three dimensions that might be independently controlled: abuse liability, appeal, and harmfulness. The concept is that harmfulness should be reduced to the lowest feasible level; however, abuse liability and appeal should be at intermediate levels such that the products are sufficiently appealing and sufficiently capable of delivering nicotine and providing reinforcing effects to sustain self-administration in place of traditional cigarettes. This model has also been discussed in some detail in a submission to the FDA docket by the American Legacy Foundation, since renamed the Truth Initiative (Truth Initiative, 2015).

Figure 1. Three Dimension Model: Abuse Liability, Appeal, and Harmfulness (Niaura, 2016)

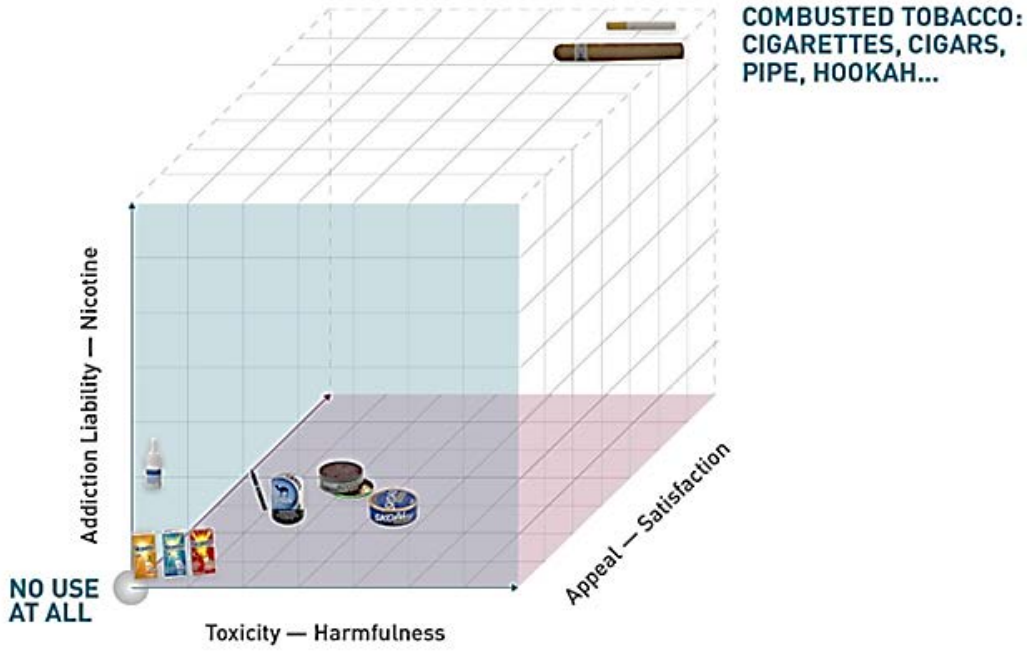


Figure 1 represents concepts and product design approaches related to toxicity, appeal, and addiction liability. These characteristics are not unique to tobacco products and were also relevant in the development of various forms and flavors of nicotine replacement medications. A specific flavor or potential organoleptic enhancing ingredient such as menthol or sugar, may increase satisfaction and appeal to some while it diminishes satisfaction and appeal for others; however, as is the case for nicotine gum or lozenge, the product market size and population reach is assumed to be expanded by a variety of forms and flavors.

A similar model for a discussion of pharmacokinetic and pharmacodynamic contributors to abuse liability was presented in a symposium of the College on Problems of Drug Dependence (CPDD) in 2015 (Henningfield, 2015a; see Figure 2 below).

Figure 2. Modeling Pharmacokinetic and Pharmacodynamic Contributors to Abuse Liability (Henningfield, 2015a)

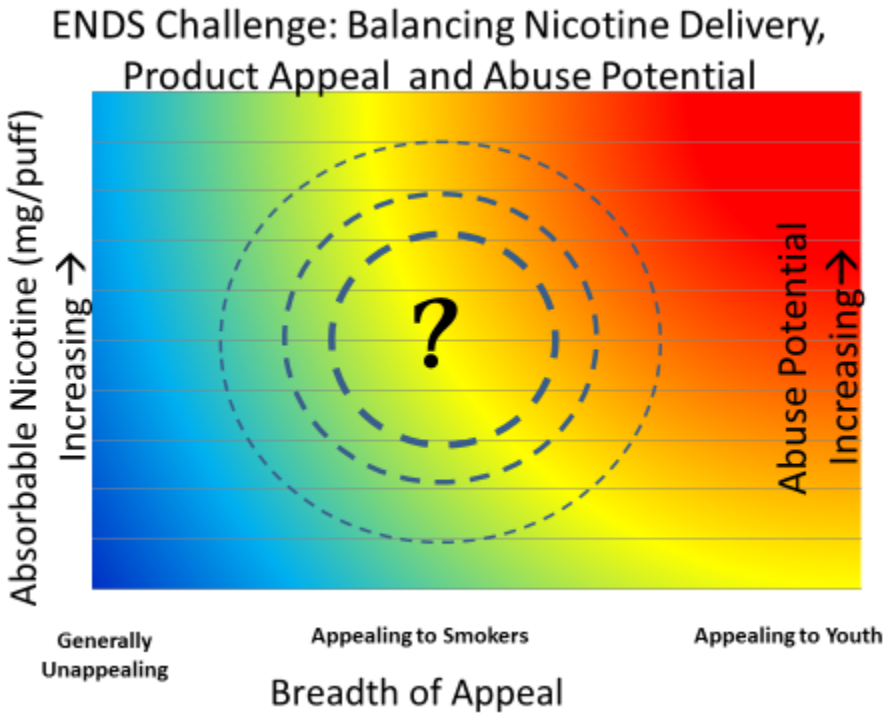


Figure 2 illustrates two concepts, the first being that abuse liability across a broad range of potentially dependence producing substances, drug products, and tobacco products is influenced by the pharmacokinetics and pharmacodynamics of the formulations and products. Thus, for example, for nicotine, opioids, and stimulants, smoked or intravenous administration produce the fastest and strongest effects and are associated with higher abuse liability than oral formulations. The second concept being that treatments for substance abuse disorders intended to serve as substitutes for abused and harmful substances must be able to sustain dependence and to retain some liability for abuse, although ideally at a lower level than that attributed to the primary substances of concern. In the context of treatment, such products are often referred to as “agonist therapies”. The approved agonist therapies include methadone and Suboxone (i.e., buprenorphine) for opioid dependence and NRT products for tobacco dependence, while oral pharmaceutical stimulants including methylphenidate and amphetamine are under evaluation by the National Institute on Drug Abuse for treating cocaine dependence (O’Brien, 2001; Negus & Henningfield, 2015). Oral smokeless tobacco products have long been used as substitutes for cigarettes for situations when cigarette smokers cannot smoke and as a means to achieve lasting cessation from smoking (Henningfield & Fagerström, 2001; Foulds et al. 2003; WHO, 2003; Swedish Match, 2014; WHO, 2015). In fact, such use of traditional Swedish snus by Swedish submariners who could not smoke, at least during submersion (i.e., “dives”), led to the development of nicotine gum as a medicinal substitute for cigarette smoking and for smoking cessation (Fagerström et al., 2008). The findings presented in this review

support the utility of Camel Snus as a viable, less harmful alternative form of tobacco product use compared to traditional cigarettes.

There is no scientific basis for a precise level of abuse liability and appeal that will enable an MRTP to work as a replacement product, yet not be overly attractive, reinforcing, dependence producing, or harmful to health. For example, studies of NRT products have shown that the oral dose range that relieves withdrawal in smokers is between 2 and 4 mg on a population basis (Herrera et al., 1995; Sachs, 1995; Shiffman, 2008; Stead et al., 2012), and although oral NRT products are not considered to have significant abuse liability (West et al., 2000; Houtsmuller et al., 2003; Hughes et al., 2004), some individuals continue to use them for months or years with little evidence of significant harm relative to continued smoking (Hajek et al., 1988; Shiffman et al. 2003a, b; Hajek et al., 2007).

To be useful and provide benefit to the user, non-combustible MRTPs must provide some level of consumer appeal and deliver enough nicotine to attenuate withdrawal in smokers, but not so much as to be locally toxic or aversive, maintain nicotine dependence at an unnaturally elevated level, or lead to initiation by non-tobacco users. This concept has been discussed by tobacco control leaders extensively since the 1990s (e.g., Warner et al., 1997; Henningfield & Slade, 1998; Warner et al., 1998). For example, Warner et al. 1997 (p. 1087) wrote:

> "*The avoidance of tobacco use is thus considered far more important than kicking an addiction to nicotine. For those, who cannot or will not stop using nicotine, might it not be prudent to offer an alternative to tobacco products, one that satisfies their addiction while dramatically reducing their risk of disease?"*

Of note is that the context of the quote is a focus on the potential for further development and promotion of novel noncombusted tobacco products, within the prevailing view that smokeless tobacco products were far more toxic than nicotine replacement products.

A recent submission to an FDA docket by the Truth Initiative (formerly *American Legacy Foundation)* also highlights similar views *(Electronic Cigarettes and the Public Health Workshop, Docket No. FDA-2014-N-1936, July 2, 2015*). The submission noted that a product intended to replace cigarettes must carry sufficient abuse liability to enable cigarette smokers to fully substitute the replacement product for cigarettes. As the Truth Initiative stated:

> "*It is also unclear whether severity of dependence on a cleaner form of nicotine is of as much public health concern if the degree of addiction/dependence is de-coupled from the toxicity in combusted products (i.e., a delivery system that increases addiction liability, but with cleaner nicotine delivery). The net public health benefits versus harms would need to be determined by the degree to which a more addictive*

clean delivery system can successfully compete with combusted tobacco. That is, the benefits of a product with high addiction liability and with minimal harm (associated with clean nicotine) would outweigh harms associated with combusted tobacco if that product strongly encouraged complete switching away from combusted products. This would contrast with a lower addiction liability product that resulted not in complete switching but rather prolonged dual use (a public health benefit if the comparison is to lethal cigarettes and not to placebo or nothing)."

In other words, the Truth Initiative also came to the conclusion that a product without sufficient abuse liability may not realize its potential health benefit, even if it is less harmful, because it would likely fail to find broad acceptance by smokers as a complete, long-term substitute for traditional cigarettes. Although the Truth Initiative submission to the FDA docket was in the context of making the case that there should be regulatory flexibility to allow for a range of levels of abuse liability of electronic nicotine delivery systems, the same core concept is relevant to oral smokeless tobacco products that are intended to be used as harm-reducing alternatives to traditional cigarettes.

It is important to note that no organization or leading tobacco control experts have defined precisely what the level and speed of nicotine delivery should be in a product intended to replace traditional cigarettes, nor what its abuse liability should be. Rather, experience in the tobacco product marketplace and the oral NRT marketplace have come to provide what may better be envisioned as boundaries with respect to tobacco. A clear example among NRT products is seen as nicotine content and dosing characteristics advanced on the basis of preliminary product testing in cigarette smoking cessation and substitution studies in the 1970s and 1980s (e.g., Ferno, 1973, 1977; Jarvis et al., 1982; Fagerström et al., 2008). This led to the findings guiding decisions such as the amount of nicotine and level of buffering necessary for an effective oral nicotine gum product, which were later extended to nicotine lozenge products. Specifically, the products need more than 1 mg of nicotine and to be buffered to a pH of approximately 8.0 to enable satisfactory absorption (note that this may be higher than required in oral smokeless tobacco products due to the fact that the gum base used for nicotine gum involves a polacrilex cation exchanger to slow the release of the nicotine). Variability among cigarette smokers in their nicotine tolerance led to the development of graduated doses of 2 and 4 mg nicotine gum and lozenge products. In contrast, the smokeless tobacco product marketplace includes a far broader range of products with respect to nicotine content and buffering and nicotine delivery characteristics. Camel Snus is consistent with that of other oral tobacco products in general, although in the mid-range of marketed products with respect to nicotine content per pouch or gram of tobacco, product pH, and unionized nicotine fraction. This is consistent with the summary of such products by the WHO TobReg, which stated:

"*For the categories of oral smokeless products known as moist snuff, including snus, the design and method of use of the product require the*

pH of the product to be controlled with sufficient buffering material to enable nicotine to be free for absorption over the many minutes that the product may be kept in the mouth" (WHO, Technical Report No. 945, 2007b).

In sum, over time, it may very well be that consumers and public health are best served by a variety of MRTPs that present less risk compared to traditional cigarettes but have varying degrees of abuse liability and appeal.

3 Assessment of the Abuse Liability of Camel Snus

3.1 Objectives of this report

The objective of this report review is to identify and critically evaluate research that examines the abuse liability of Camel Snus compared to other tobacco and nicotine products. The report includes a review of the literature as it relates to the abuse liability of smokeless tobacco products including Camel Snus. This report focuses on content areas that are designated as key components for evaluating the abuse potential of drugs in the FDA's 2010 Guidance for Industry on the Assessment of Abuse Potential of Drugs. These key content areas include chemistry, preclinical pharmacology, animal behavioral pharmacology, pharmacokinetics and pharmacodynamics, human laboratory studies, clinical trial data, and epidemiological data on product use. The primary goal of the report is to provide an overall assessment of Camel Snus' abuse liability as an aggregate of the research across these content areas. Specifically, this report is designed to answer four key questions related to the abuse liability of snus and related products, and these questions are addressed in the Executive Summary of the report:

1. What is the abuse liability of Camel Snus compared to traditional cigarettes and nicotine replacement therapy?
2. What is the abuse liability of Camel Snus compared to other forms of smokeless tobacco?
3. Does the abuse liability of Camel Snus vary between product styles described in RJRT's MRTP Application?
4. What are the implications of the abuse liability profile of Camel Snus for its potential to function as an acceptable MRTP and thereby serve the public health goal of contributing to the reduction of combustible tobacco product use as advocated by the 2014 Surgeon General's report?

3.2 Search Strategy

Evidence for the present literature review was obtained from a search of the PubMed and Google Scholar databases with publications dates up to 2016. Key search terms included: Camel Snus, abuse liability, abuse potential, reinforcement, addiction, nicotine delivery profile, self-administration, subjective, craving, reward, withdrawal, and/or

abstinence. Additionally, relevant studies conducted by R.J. Reynolds Tobacco Company (RJRT) were reviewed and included as supplemental evidence when appropriate.

3.3 Chemistry

3.3.1 Camel Snus overview

Snus is an oral smokeless tobacco that has been used in Sweden since the early 1800s and is sold both as loose tobacco and as tobacco portioned in fleece pouches. Snus has historically used finely ground tobaccos that undergo a heat treatment process in the presence of water, salt, and a pH-modifying solution. The primary differences between snus and the various types of moist snuff tobacco products traditionally sold in the U.S. are (1) the tobacco types used and (2) manufacturing processes used to produce the final product. Specifically, snus manufacturing uses tobaccos processed via heat treatment, rather than via fermentation. Both of these tobacco processing methods are used in order to improve the taste and/or to reduce microbial activity. Heat treatment generally results in lower quantities of harmful or potentially harmful constituents ("HPHCs"), most notably tobacco-specific nitrosamines, when compared to other forms of smokeless tobacco which use the fermentation process.

Camel Snus products were developed based upon a commercial snus tobacco blend manufactured and sold in Sweden, adapted for acceptability to U.S. smokers' palates. As described in Appendix C, Camel Snus styles are pouched products containing an identical blend of tobaccos, combined with water; a sodium carbonate/sodium bicarbonate buffering system; the (b) (4) ; a humectant to retain moisture; salt; and natural and artificial flavorings.

The methods of manufacture of Camel Snus have evolved from those that have themselves been evolving in Sweden for nearly a half century since the single portion form of snus was introduced by Swedish Match. In the 1970s, a convergence of public health concerns, consumer interest, and business interests led to increased development of less harmful tobacco products that would be acceptable alternatives to traditional cigarettes. Sweden's leading cigarette marketer, Swedish Match, invested heavily in research and development to provide products reduced in potentially harmful constituents, but with nicotine delivery sufficient to substantially satisfy the needs of many cigarette smokers. In 1999, Swedish Match focused its product development and marketing on snus and other oral nicotine products (Foulds & Furberg, 2008; Rutqvist et al., 2011). This contributed to the migration of many of Sweden's traditional cigarette smokers away from cigarettes to smokeless tobacco use over the last quarter of the 20th century. In turn, this led to Sweden's emergence by the 1990s as among the countries with the lowest per capita smoking rates by youth and adults in comparison to other developed countries with high per capita smoking rates in the mid-20th century. By the early 2000s, Sweden was distinguished as the first nation in modern history anywhere in the world to document a decline in lung cancer and several other cigarette

smoking associated diseases. This history has been described in some detail by Foulds and Ramström (2006), and described as “a harm reduction experiment in progress” by Henningfield and Fagerström (2001) (see also Foulds et al., 2003).

Key to the business and public health success was a core product that was sufficiently low in toxicants to provide a less harmful alternative to traditional cigarettes, but of sufficient nicotine delivery and associated abuse liability as to provide an acceptable alternative to cigarettes to a substantial fraction of cigarette smokers. Thus, as is the case with snuff products that continue to be made in the U.S. and elsewhere, the products were buffered to provide relatively reliable and predictable nicotine absorption. Swedish Match also developed methods of curing and making the products so as to be relatively low in potentially harmful constituents. Ingredients and constituents in addition to tobacco that may be important to enable Camel Snus to emerge as a viable alternative to cigarettes for many smokers in the U.S., as occurred in Sweden, are the focus of this portion of this review. Factors discussed include the nicotine content, buffering ingredients, minor alkaloids, acetaldehyde, flavors and other ingredients, among others.

3.3.2 Nicotine

Tobacco contains nicotine, and all common forms of tobacco involve the delivery of nicotine to the consumer. How products are made, including their constituents and ingredients, and how they are used influence the pharmacokinetic profiles that are characteristic of different types of tobacco products, and hence the profiles of effects that tobacco product consumers have come to enjoy and seek (USDHHS, 1988, 2010; Benowitz, 1990).

Traditional cigarettes produce a mildly acidic smoke, which upon inhalation delivers nicotine deep into the lung, where it is retained and absorbed for systemic distribution. Research has shown that among different tobacco product types, cigarette smoking produces the most rapid systemic delivery of nicotine due to the large surface area of the alveolar gas exchange regions. In contrast, the higher pH and alkaline nature of cigar tobacco and smoke largely reduces lung inhalation because of the relatively harsh (as compared to cigarette smoke) sensory properties of basic smoke constituents such as ammonia and nicotine. Furthermore, the alkaline nature of cigar smoke droplets results in higher levels of unionized nicotine that are readily absorbed through the oral mucosa, albeit much more slowly than is seen from deep lung inhalation.

Transmucosal Nicotine Absorption and Product pH – A Brief Primer

Absorption of nicotine through the lining of the mouth (the oral mucosa) is strongly influenced by the pH of the product and the saliva because the pH determines the fraction of the nicotine that is in its readily absorbable form, technically referred to as the unionized, or unprotonated form, or more commonly the “free” or “free-base” form. When in a charged form (ionized, protonated or “bound”), absorption through mucosa is very slow. In the unionized, more lipophilic form, nicotine can rapidly enter the systemic circulation, bypassing the gastrointestinal tract and first-pass metabolism in the liver that occurs with swallowed nicotine. Depending on swallowing rates, some fraction of the nicotine that is released from the product, be it nicotine gum or snus, is swallowed (Henningfield et al., 1990; Fant et al., 1999; Benowitz et al., 2009).

pH is a measure of proton concentration, and it is on a logarithmic scale, so that an increase of 1 point on the 1-14 point scale is equivalent to a 10-fold change in proton concentration. Alkaloid drugs, which are weak bases, have different dissociation constants (pKa values) that determine their degree of protonation/unprotonation under different solution pH conditions. The pKa of nicotine is 8.02, which means that at a pH of 8, approximately 50% of the nicotine is in the unprotonated or unionized form. These principles were critical in developing effective nicotine gum. Prototypes that were not buffered to increase their pH above 7.5 were essentially functioning as placebos. Adding sodium bicarbonate to nicotine gum provided a means of increasing unionized nicotine, because release of the sodium bicarbonate increased salivary pH to about 8 or more and increased the fraction of nicotine that became unionized and readily absorbable. A somewhat stronger buffer was used in an experimental gum prototype (Shiffman et al., 2009; JSR LLC, 2002 patent) to provide somewhat more rapid and more complete dissociation of the hydrogen ions and also reduce the degree to which recent consumption of acidic foods or beverages would impair nicotine absorption (see also Henningfield et al., 1990).

The snuff and snus category of oral smokeless tobacco products historically relied upon some sort of alkalinizing agent, such as potash or lime, to enable efficient absorption of nicotine (Rutqvist et al., 2011; Rutqvist, Fry & Lee, 2013). In the 20th century, more commonly seen buffering agents have included sodium and calcium carbonate, because they are mild, safe, and can positively contribute to the overall sensory and subjective experience (Andersson & Warfvinge, 2003). Note that saliva released from various glands into the oral cavity varies widely in pH, but has relatively little buffering capacity; thus the pH of the saliva in the mouth may be strongly influenced by foods, beverages, and buffers in products. For example, the sodium bicarbonate and/or carbonate contained in some nicotine gum products can produce salivary pH of approximately 8.0, but the small amount of buffer means that recent prior consumption of foods or beverages greatly reduces salivary pH and, therefore, nicotine absorption rate (Henningfield et al., 1990). Currently, there is a wide range of variation in pH levels across oral smokeless tobacco products in the U.S. and globally. Product reporting to FDA and CDC must include evaluations of pH along with the estimated unionized nicotine fraction levels of products.

Thus, is not surprising that, although traditional cigars have been used for decades as a means of reducing or quitting traditional cigarette smoking, it is not necessarily easy for cigarette smokers to make that transition (Russell, 1971; Turner et al., 1981; Jarvis, 1984; Pechacek et al., 1985). Among those who smoke both cigarettes and cigars, many inhale the smoke more than persons who are primary cigar smokers with little cigarette smoking experience (Jarvis, 1984; Ockene et al., 1987; Herling & Kozlowski, 1988). Furthermore, rate of daily use, dependence, and cigarette-like withdrawal appear overall substantially lower in cigar smokers as opposed to cigarette smokers, which is also indicative of a lower abuse liability of cigars (Henningfield et al., 1996; Baker et al., 2000).

The foregoing observations are relevant to the present assessment, as they demonstrate the importance of a consideration of a product's form, method of use and composition in evaluating its abuse liability. The parallels between cigars and oral smokeless tobacco products were described by Fant and Henningfield in the 1996 U.S. Cancer Control Monograph 9 as follows:

> "*Other research on withdrawal from cigars and smokeless tobacco confirms the similarities in withdrawal across nicotine delivery formulations. However, it appears that formulations which deliver nicotine more slowly (e.g., nicotine patch and smokeless tobacco), or in low daily doses (e.g., nicotine gum as typically used), result in weaker syndromes of abstinence-associated withdrawal. Discontinuation of smokeless tobacco results in less reliable and/or weaker syndromes of withdrawal than discontinuation of cigarette smoking…*"

Oral smokeless tobacco products include chewing tobacco products that generally are more acidic in nature than snuff and snus products, and therefore tend to produce slower and lower levels of nicotine absorption. Moist snuff and snus products, which are buffered to a slightly more alkaline range (typically pH 7-8, as discussed below, with some products above pH 8.0), have higher levels of unionized nicotine, which increases the speed and efficiency of oral nicotine absorption. This was described by the WHO TobReg as follows:

> "*The effect of tobacco pH on free nicotine levels has been well documented for smokeless tobacco products. For some oral tobacco products, such as shredded or twisted tobacco leaves intended for chewing, the typically low pH means that the products tend to deliver their available nicotine slowly as the product is chewed. For the categories of oral smokeless products known as moist snuff, including snus, the design and method of use of the product require the pH of the product to be controlled with sufficient buffering material to enable nicotine to be free for absorption over the many minutes that the product may be kept in the mouth."* (WHO, 2007b, p.13).

Contemporary moist snuff and snus products are used in relatively small portions when compared to chewing tobacco. Typically, a 0.5 to 2 g portion of moist snuff or snus is

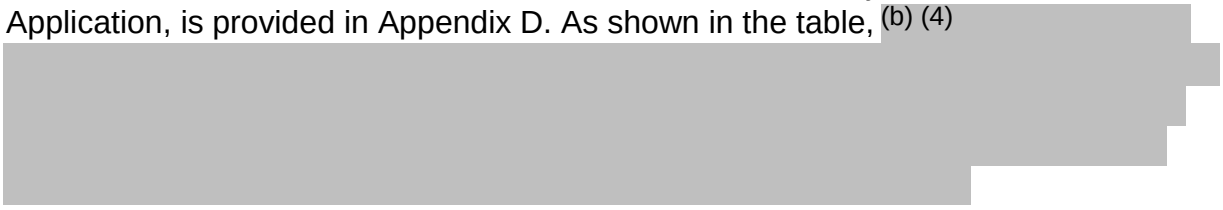
used, whereas a “chaw” of chewing tobacco may be much larger. For loose-packed moist snuff and snus products, a user-selected pinch (often referred to as a “dip”) of tobacco is placed in the mouth. Moist snuff and snus products are also sold pre-portioned or “pouched.” This form provides a consistent and convenient unit of use. Pouched snus products offer characteristic tobacco flavor and sensory notes that are common to other types of tobacco products, and a consistent and convenient usage experience that may have appeal to cigarette smokers who find their smoking to be an increasingly less convenient and less socially-tolerated choice if they wish to continue with tobacco use.

3.3.3 Nicotine levels in Camel Snus compared to other products in the U.S.

Appendix D lists the brand styles and basic characteristics of Camel Snus products that are the subject of RJRT’s MRTPA. Appendix D includes data on pouch size expressed by weight (grams), nicotine content in milligrams per gram, product pH, and the calculated amount of unionized nicotine expressed both as the percentage of the total nicotine content and as mg per gram of tobacco.

Variation in product size and flavor is predicted to increase the population reach of Camel Snus by providing alternatives to address variation in consumer preferences. Providing variations of a product is consistent with marketing experience across a wide range of consumer goods, including confectionary chewing gums and oral nicotine medications. For example, whereas a single flavor of “original” nicotine gum at only one dose (2 mg) was originally approved for prescription marketing in 1984, FDA agreed by 1991 that the 4 mg dosage was needed and then in 1998 FDA approved mint flavored nicotine gum to provide a flavor alternative (Callahan-Lyon, 2012; FDA, 2016). For the initial flavor variation approvals for nicotine gum and lozenge, FDA required the conduct of human abuse liability studies to determine if flavoring (i.e., mint) and the product form (i.e., a lozenge) would somehow increase pharmacological abuse liability. The studies confirmed that whereas flavors appeared likely to address consumer flavor preferences, and counter the distaste of many consumers for the “original” flavor, flavoring did not alter pharmacological abuse liability (Houtsmuller et al., 2002; Houtsmuller et al., 2003). Presently there are a variety of oral nicotine medication forms and flavors (including mint, citrus, and various branded flavors such as Fruit Chill®, White Ice Mint®, and Cinnamon Surge®) on the market with no evidence of differential abuse liability. Such variation across both flavor and product format is assumed to help address a broader range of consumer preferences than would a single product flavor or style variation.

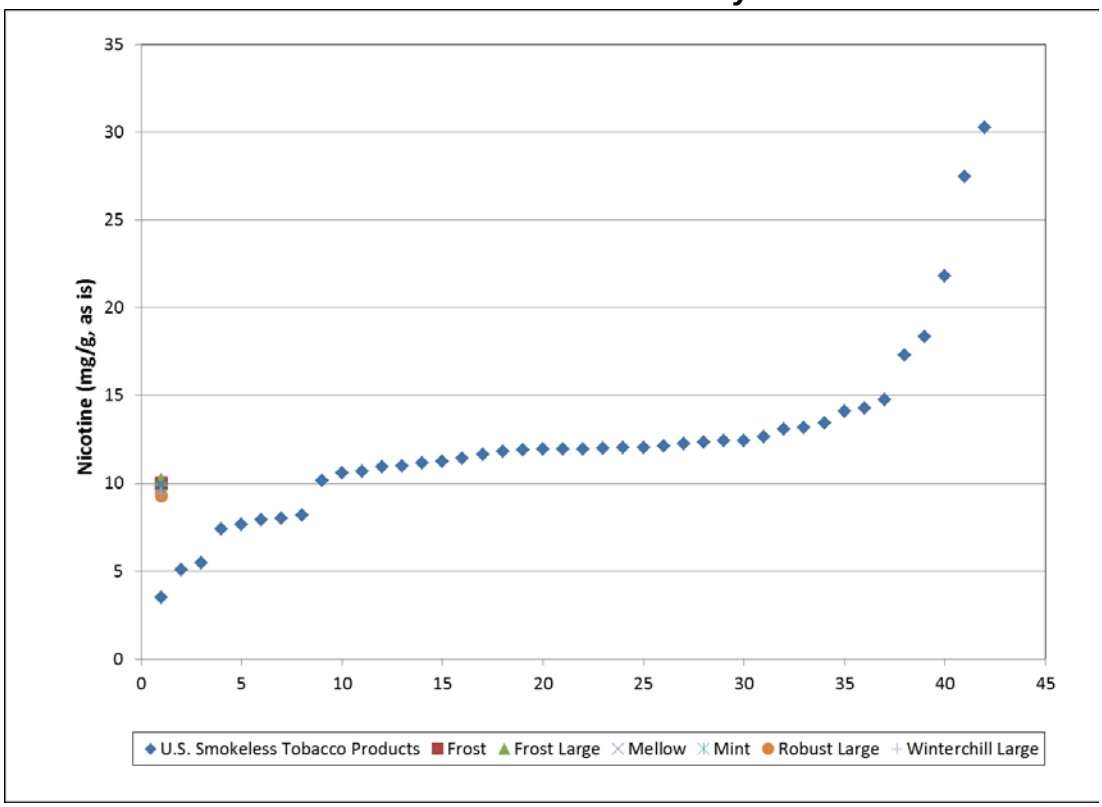
The unionized fraction of nicotine in six Camel Snus brand styles in RJRT’s MRTP Application, is provided in Appendix D. As shown in the table, (b) (4)



To provide a basis for comparison with the U.S. marketplace, Figures 3 – 6 (see below) show results from all Camel Snus styles and other smokeless tobacco products sampled from the U.S. market in 2014 and/or 2015. Forty-two unique products (moist snuff, dry snuff and loose leaf) were sampled in one of the two years. Additionally, all Camel Snus styles and 26 of the other smokeless tobacco products were sampled both years. The figures address comparisons of: nicotine content (Figure 3), tobacco pH (Figure 4), unionized nicotine (Figure 5), and unionized nicotine expressed in mg per gram of tobacco (Figure 6). The figures representing nicotine speciation were developed through the methods specified by the CDC that are based on the Henderson-Hasselbalch equation that calculates the state of association or dissociation of acids and bases under different pH conditions (Federal Register, 2009).

Figure 3 shows nicotine content of Camel Snus in relation to other U.S. smokeless tobacco products (moist snuff, dry snuff, loose leaf and snus). Please note that the term “as-is” in this and other figures indicates determinations and expressions of analyte levels from the finished product of commerce, whether pouched or loose, per gram of product weight. There are approximately 10 mg of nicotine per gram of tobacco in Camel Snus products and because Camel Snus is available in 0.6 and 1.0 gram sizes, this means that consumers can select products of about 6 or 10 mg nicotine content per pouch. Of note is that consumers have the choice of using multiple pouches should they desire stronger effects, and the option of removing the snus pouch after a short time should they desire more moderate effects.

Figure 3. Comparison of Nicotine (mg/g, as is) for Camel Snus Styles and U.S. Oral Smokeless Tobacco Products Surveyed in 2014-2015*

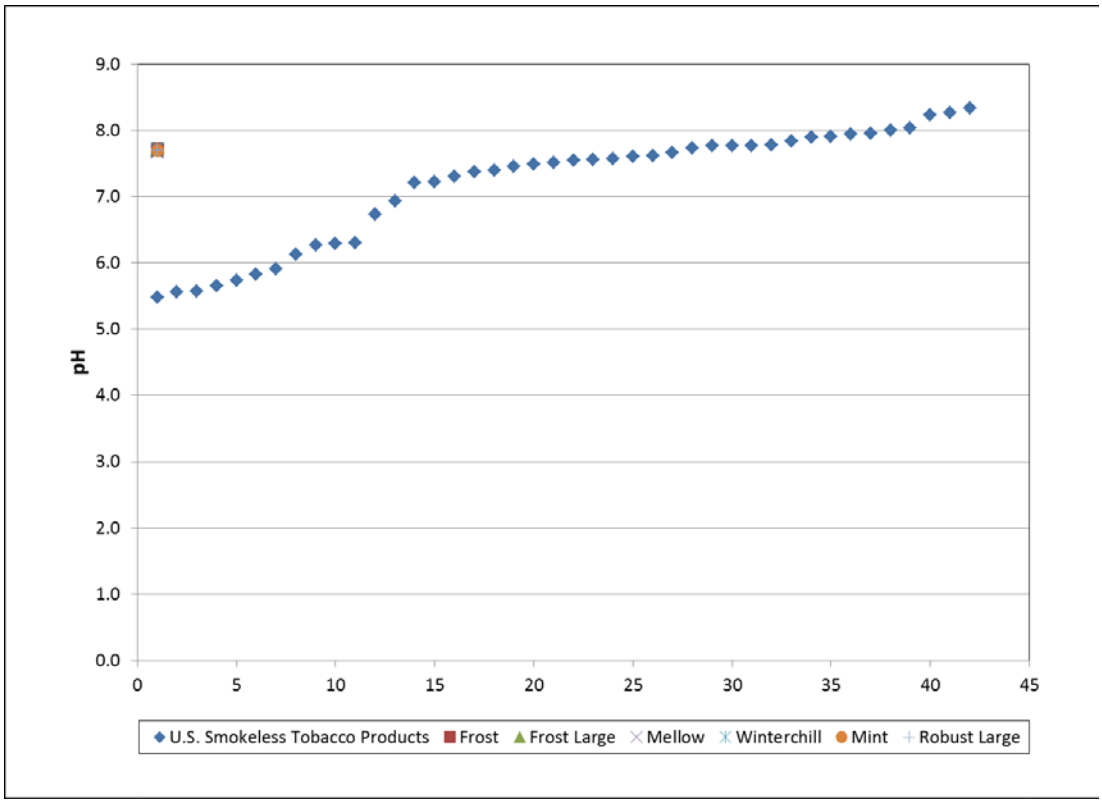


Data Sources provided by RJRT: Rowe, J., 2016. Analytical Testing of Camel Snus Products. RDM JMR 2016,235. Bodnar, J., 2016. Summary of 2014 and 2015 Smokeless Market Surveys. RDM JAB 2016,281. Labstat International ULC, 2014. Determination of Smokeless Tobacco HPHC Values for Camel Snus and Other Tobacco Products (M195-GLP. Labstat. 2014). ExternalCo LSI 2014,113.

*As determined by the CDC-specified method; Federal Register, 2009. Volume 74, Number 4, p. 712-719.

Figure 4 below shows the pH of Camel Snus in relation to other smokeless tobacco products surveyed from the U.S. market when determined according to procedures specified in the CDC method (USDHHS, 2009). As shown in the figure, Camel Snus' pH of 7.7 is very close to the median value of 7.6 that was determined for all other surveyed U.S. smokeless tobacco products. Whereas the product pH is a function of many factors, including the (b) (4) , the dominant factor in the finished product is the sodium carbonate/sodium bicarbonate buffer system used in all Camel Snus varieties, as discussed below.

Figure 4. pH of Camel Snus Styles and U.S. Oral Smokeless Tobacco Products Surveyed in 2014-2015*



Data Sources provided by RJRT: Rowe, J., 2016. Analytical Testing of Camel Snus Products. RDM JMR 2016,235. Bodnar, J., 2016. Summary of 2014 and 2015 Smokeless Market Surveys. RDM JAB 2016,281. Labstat International ULC, 2014. Determination of Smokeless Tobacco HPHC Values for Camel Snus and Other Tobacco Products (M195-GLP. Labstat. 2014). ExternalCo LSI 2014,113.

*As determined by the CDC-specified method; Federal Register, 2009. Volume 74, Number 4, p. 712-719.

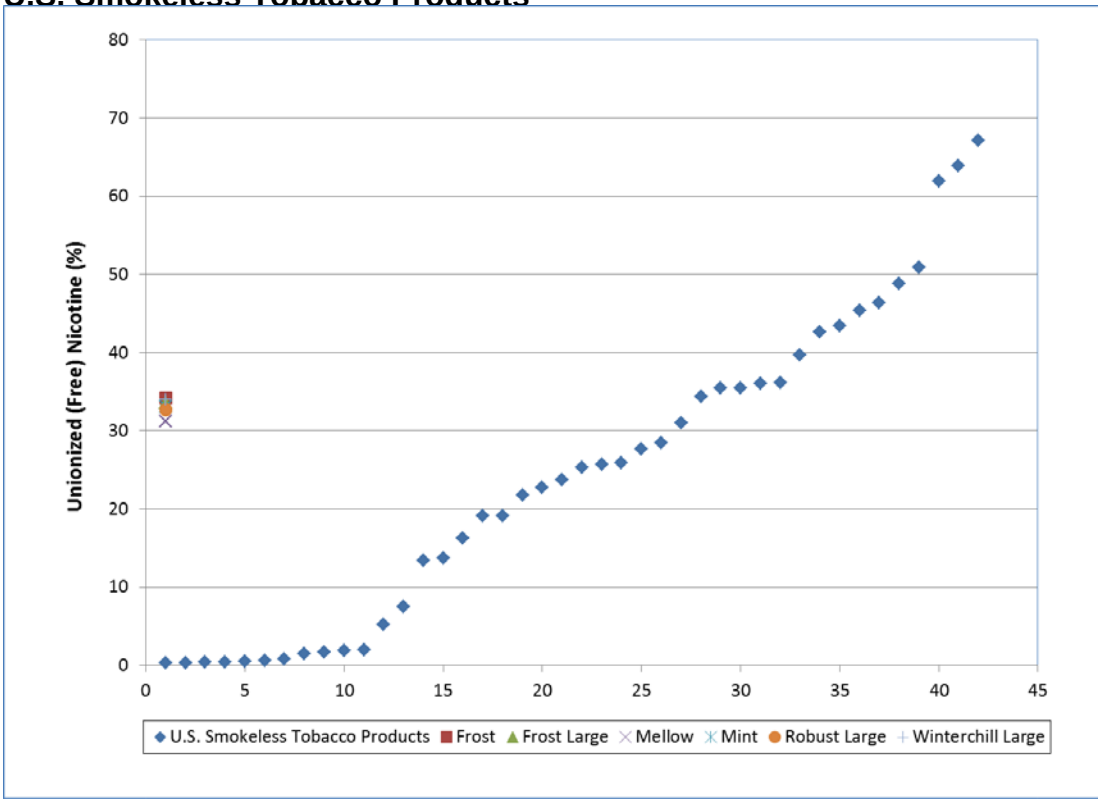
Figures 5 and 6 below, which include the same products as shown in Figures 3 and 4 above from the U.S. market, show that approximately 31 – 34% of Camel Snus' nicotine, or about 3.0 – 3.4 mg nicotine per gram, is unionized and therefore readily absorbable through the oral mucosa. Similarly, among the products whose data are shown in the figure, about one-third contain lower levels of unionized nicotine and about two-thirds of the products contain higher levels of unionized nicotine than Camel Snus. These characteristics, along with the nicotine content, provide the physiochemical basis for the predicted and observed moderate levels of speed of nicotine absorption and peak levels of nicotine found in the Camel Snus pharmacokinetic studies, as discussed in Section 3.6.

Actual nicotine absorption kinetics for Camel Snus would be expected to be influenced by the same factors that affect absorption from other oral nicotine delivering products, discussed elsewhere (Henningfield & Nemeth-Coslett, 1988; Benowitz et al., 2009). These factors include oral manipulation, buffering capacity of the product, individual

salivary volume and pH, and possibly prior consumption of foods or beverages. For example, the sodium bicarbonate and/or carbonate contained in some nicotine gum products can produce salivary pH of approximately 8.0, but the small amount of buffer means that recent prior consumption of foods or beverages greatly reduces salivary pH and, therefore, nicotine absorption rate (Henningfield et al., 1990).

The sodium carbonate/sodium bicarbonate buffer system employed in all Camel Snus products produces an initial local environment of around pH 7.7 when placed in the mouth. At this pH, approximately one-third of the nicotine released into the saliva will be unionized and available for absorption into systemic venous circulation. Over time, as the tobacco material becomes saturated by saliva and its nicotine is released in the oral cavity, the nicotine molecules will continue to dissociate their ions and this unionized nicotine will be absorbed via the oral mucosa, thus resulting in absorption rates and patterns as shown in pharmacokinetic studies (see Section 3.6). Thus, over time, an additional quantity of the total nicotine content of Camel Snus will eventually be absorbed, but more slowly than that which occurs during the first few minutes that the product is in the mouth, as the saliva equilibrates to its native pH. In addition, some fraction of nicotine will also be swallowed and undergo first pass metabolism in the liver, but will still lead to systemic absorption of approximately one-third or somewhat more of the swallowed nicotine (Westman et al., 2001; Benowitz et al., 2009). Once nicotine has passed into the systemic venous circulation, it is subject to the efficiently buffered and very tightly regulated pH of the blood (pH 7.35-7.45), and the pH of the product or at its local environment in the mouth becomes irrelevant. Once nicotine has entered the central venous compartment, its subsequent distribution and partitioning into other body compartments is anticipated to be similar to that for nicotine delivered from any other oral nicotine product such as gums and lozenges, whereas the introduction of nicotine by inhalation of cigarette smoke or nicotine aerosols favors its introduction into the arterial circulation, with significantly more rapid delivery of a nicotine bolus to the central nervous system.

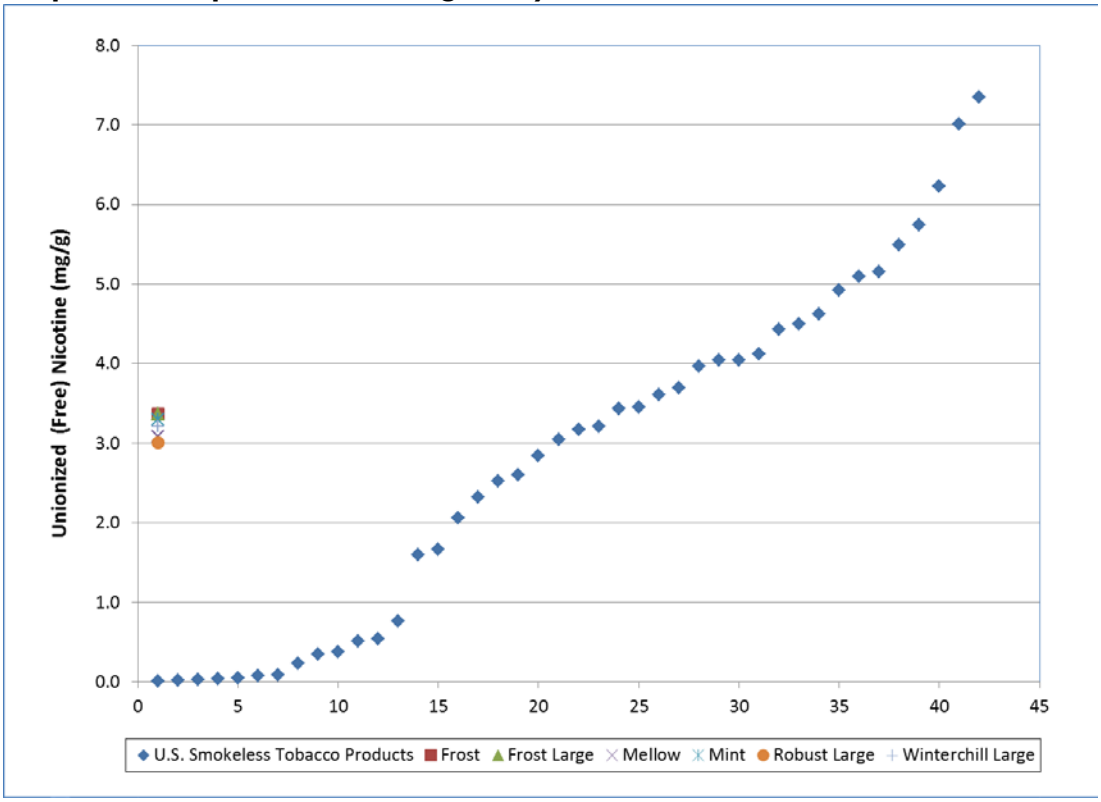
Figure 5. Unionized Fraction of Nicotine Calculated for Camel Snus and Other U.S. Smokeless Tobacco Products*



Data Sources provided by RJRT: Rowe, J., 2016. Analytical Testing of Camel Snus Products. RDM JMR 2016,235. Bodnar, J., 2016. Summary of 2014 and 2015 Smokeless Market Surveys. RDM JAB 2016,281. Labstat International ULC, 2014. Determination of Smokeless Tobacco HPHC Values for Camel Snus and Other Tobacco Products (M195-GLP. Labstat. 2014). ExternalCo LSI 2014,113.

*As determined by the CDC-specified method; Federal Register, 2009. Volume 74, Number 4, p. 712-719.

Figure 6. Comparison of Unionized (Free) Nicotine (mg/g, as is) for Camel Snus Styles and U.S. Oral Smokeless Tobacco Products Surveyed in 2014-2015 (based on pH values presented in Figure 4)*



Data Sources provided by RJRT: Rowe, J., 2016. Analytical Testing of Camel Snus Products. RDM JMR 2016,235. Bodnar, J., 2016. Summary of 2014 and 2015 Smokeless Market Surveys. RDM JAB 2016,281. Labstat International ULC, 2014. Determination of Smokeless Tobacco HPHC Values for Camel Snus and Other Tobacco Products (M195-GLP. Labstat. 2014). ExternalCo LSI 2014,113.

*As determined by the CDC-specified method; Federal Register, 2009. Volume 74, Number 4, p. 712-719.

3.3.4 Products outside of the U.S.

Stanfill and colleagues (2011) conducted a global evaluation of oral tobacco products to characterize total nicotine, unionized nicotine and TSNAs across products. This survey confirmed that many of the diverse smokeless tobacco products that are used elsewhere in the world, notably in Africa and south Asia, differ greatly from those that are used in the U.S. with respect to their composition and chemistry. Smokeless tobacco products that are markedly different from those that are used in the U.S. and Scandinavia provide little or no useful insight in regard to the individual or population level effects that may arise from the use of contemporary snus products or broadly similar conventional smokeless tobacco that has been historically used in the U.S.

3.3.5 Other constituents or ingredients that may contribute to abuse liability

Table 4 below shows the levels of each of three natural tobacco constituents (i.e., nornicotine, anabasine and acetaldehyde) that have been posited to have a potential to affect the abuse liability of tobacco products. These compounds were listed on this basis among the 93 constituents identified by FDA as harmful or potentially harmful constituents (HPHCs) in tobacco products (FDA, 2012b). For comparison, in addition to Camel Snus levels, Table 4 includes the levels of these constituents as measured in other U.S. commercial smokeless tobacco products, and in the smoke from U.S. cigarettes when smoked with two standardized machine smoking regimens.

Table 4. Comparison of Selected Harmful and Potentially Harmful Constituent Ranges for U.S. Smokeless Tobacco Products (expressed on a per gram, as is basis) and Cigarettes (expressed on a per cigarette basis)*

HPHC Constituent**	Camel Snus (all styles combined)	U.S. Smokeless Products	U.S. Cigarettes	
	(per gram)	(per gram)	ISO Smoking Regime (per cig)	Canadian Intense Smoking Regime (per cig)
Nicotine (mg)	9.3 – 10.2	3.5 – 32.6	0.1 – 2.1	1.4 – 4.2
Nornicotine (µg)	141 – 180	80 – 538	N/A***	N/A
Anabasine (µg)	50 – 58	25 – 104	N/A	N/A
Acetaldehyde (µg)	1.4 – 1.8	<1 – 10	81 – 892	1,267 – 2,381

*Data sources provided by RJRT: Rowe, J., 2016. Analytical Testing of Camel Snus Products. RDM JMR 2016,235. Bodnar, J., 2016. Summary of 2014 and 2015 Smokeless Market Surveys. RDM JAB 2016,281. Labstat International ULC, 2014. Determination of Smokeless Tobacco HPHC Values for Camel Snus and Other Tobacco Products (M195-GLP. Labstat. 2014). ExternalCo LSI 2014,113. Labstat International ULC, 2016. Characterization of Smokeless Tobacco - Minor Alkaloids (Project M273). ExternalCo LSI 2016,097. Bodnar, J., 2016. Summary of 2014 and 2015 Cigarette Market Surveys. RDM JAB 2016,252. ** Compounds include those designated as "AD" (addictive) on FDA's "Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Established List" (FED REG: 77 FR 20034). Tabulated values represent the minimum/maximum range of individual product means found for each group. Nornicotine and anabasine results from Labstat Project M273 are summarized for Camel Snus and other U.S. smokeless products. *** N/A= not available

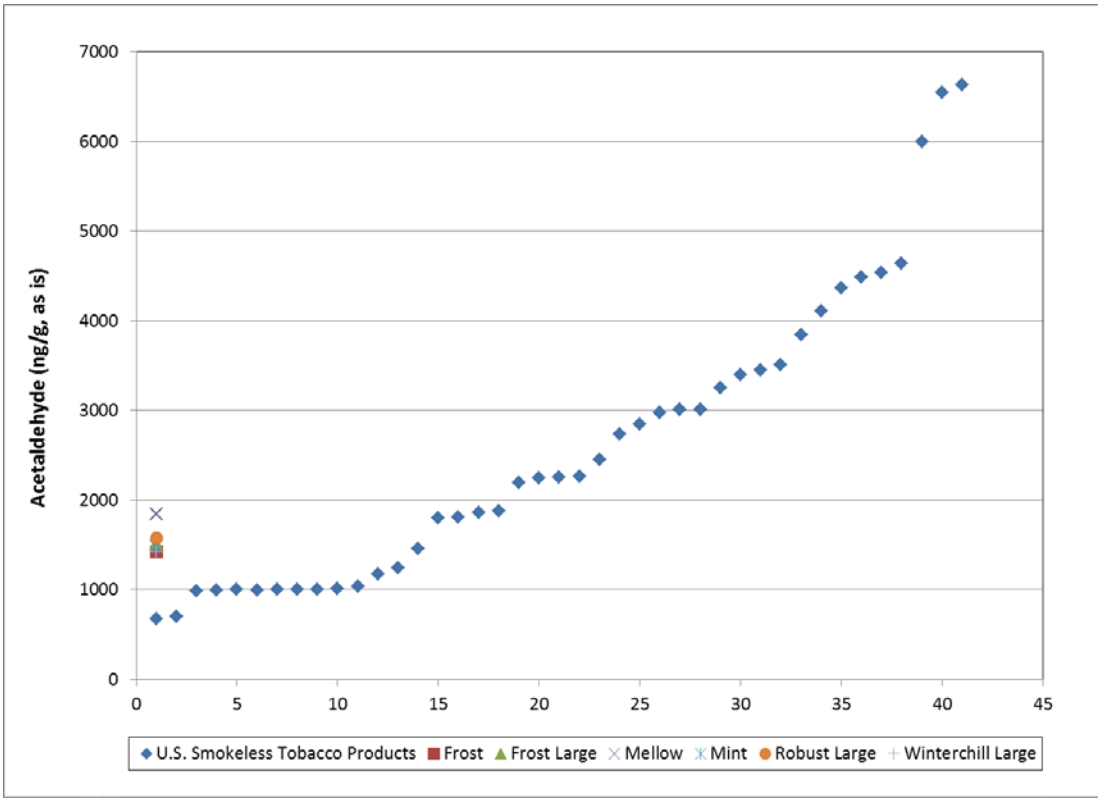
As indicated by these results, the levels of nornicotine, anabasine, and acetaldehyde in Camel Snus are within the range of other U.S. smokeless tobacco products and are substantially lower than those present in a number of the other comparator smokeless tobacco products. While recognizing the limitations of machine smoking, i.e., smoking machines are neither a measure of inherent smoking behavior variability nor a measure of actual smoker exposure, a comparison of machine-determined levels of acetaldehyde in cigarette smoke reveals an extreme difference in traditional cigarettes as compared to smokeless tobacco products such as Camel Snus.

As shown in Table 4, per the Canada Intense smoking regimen U.S. cigarettes yield milligram quantities of acetaldehyde and nicotine in mainstream smoke (specifically, 1.4 – 4.2 mg nicotine per cigarette and 1,267 – 2,381 µg acetaldehyde per cigarette). Calculation of the ratio for each cigarette brand style yields a mean acetaldehyde to nicotine ratio for all cigarette brand styles of 806:1 µg/mg based on Canadian Intense regimen smoke yields. When the mean acetaldehyde to nicotine ratio is calculated for U.S. cigarettes based upon ISO smoking regime data, the result is 705:1 µg/mg. By comparison, U.S. smokeless tobacco products average acetaldehyde to nicotine ratios are approximately 0.3:1, 0.7:1 and 0.1:1 µg/mg, respectively, for the moist snuff, loose leaf and dry snuff products evaluated. The Camel Snus acetaldehyde to nicotine ratio is approximately 0.2:1 µg/mg. This suggests that whatever contribution acetaldehyde may have on the reinforcing effects and abuse liability of traditional cigarettes, it is much lower, and likely negligible, with respect to Camel Snus.

Animal studies support this by showing that much higher levels of acetaldehyde (whether given intravenously or orally) are required to produce reinforcing effects alone or to enhance those produced by nicotine (Hoffman & Evans, 2013). Also for added perspective, but not necessarily addressing the specific potential impact of low levels of acetaldehyde on nicotine reinforcement, is the fact that acetaldehyde is present in many common foods (e.g., fresh fruits and yogurt), and at concentrations substantially higher than those in Camel Snus, yielding estimated daily dietary intake of 48 to 96 mg per person (Uebelacker & Lachenmeier, 2011). Acetaldehyde's inherent chemical reactivity, and its rapid metabolism by the aldehyde dehydrogenase enzymes that are found throughout the body (notably, in saliva; Sreerama et al., 1995), strongly suggest that the low quantities of acetaldehyde found in Camel Snus are extremely unlikely to affect its abuse liability through actions in the central nervous system.

To provide a basis for comparing Camel Snus with other U.S. smokeless tobacco products, the following five figures (Figures 7-11) provide measured levels of acetaldehyde, anabasine, and nornicotine. Note that the products depicted in Figure 7 (acetaldehyde) include the same products as are shown above in Figures 3 – 6, i.e., all Camel Snus styles and 42 smokeless tobacco products sampled from the U.S. market in either 2014 and/or 2015. The products shown in Figures 8 – 11 represent all Camel Snus styles (sampled either in 2013 or in 2016) compared to eight U.S. smokeless tobacco products (three moist snuff, three dry snuff and two snus) sampled in 2016.

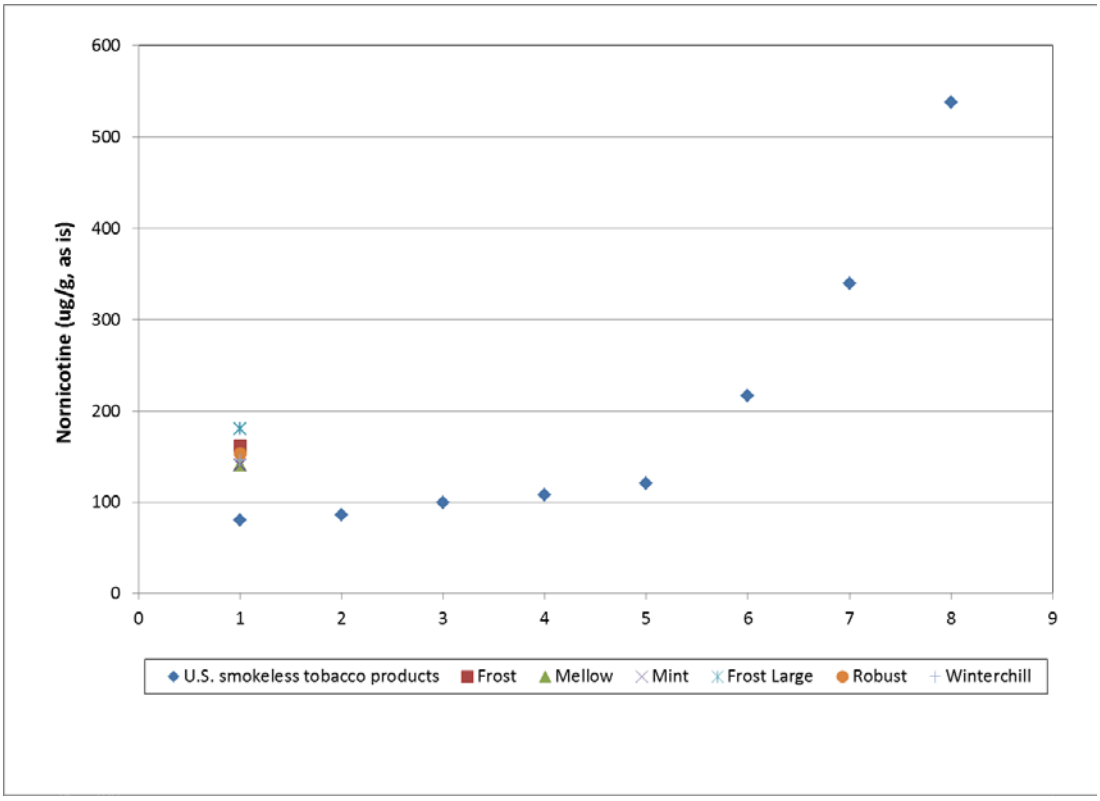
Figure 7. Comparison of Acetaldehyde (ng/g, as is) for Camel Snus Styles and U.S. Oral Smokeless Tobacco Products Surveyed in 2014-2015*



* Data Sources provided by RJRT: Rowe, J., 2016. Analytical Testing of Camel Snus Products. RDM JMR 2016,235. Bodnar, J., 2016. Summary of 2014 and 2015 Smokeless Market Surveys. RDM JAB 2016,281. Labstat International ULC, 2014. Determination of Smokeless Tobacco HPHC Values for Camel Snus and Other Tobacco Products (M195-GLP. Labstat. 2014). ExternalCo LSI 2014,113.

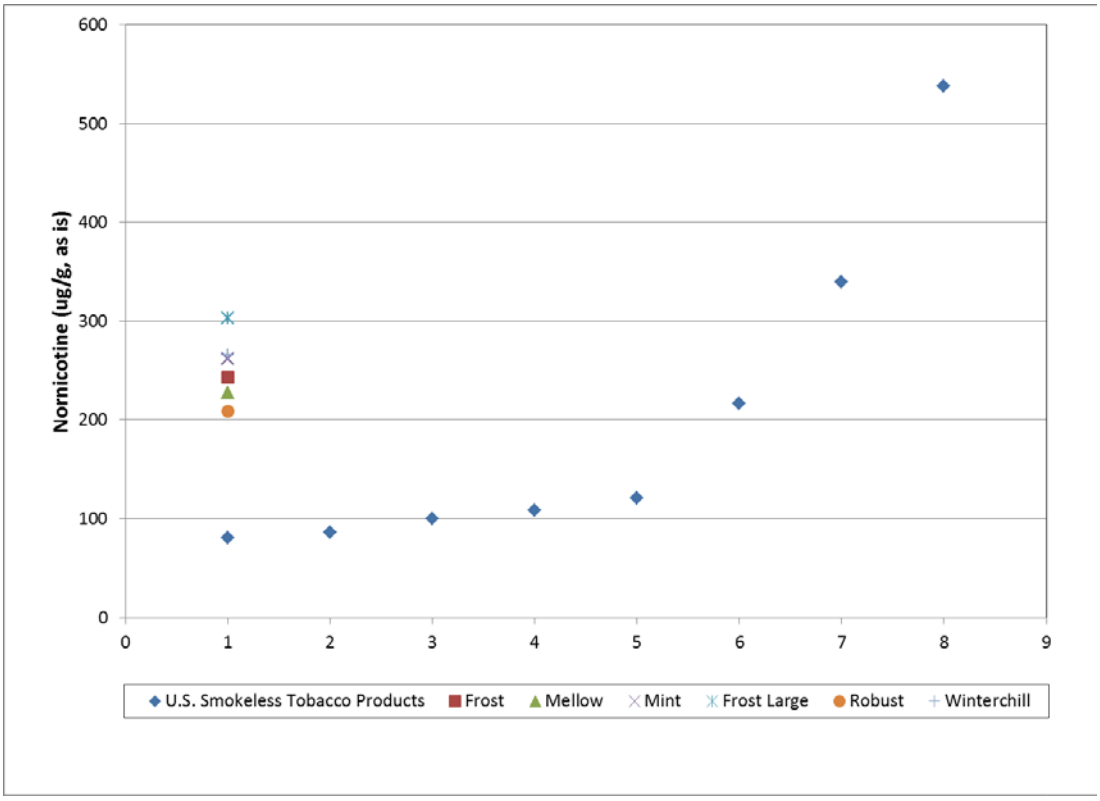
Figure 7 includes only those products having acetaldehyde values above the analytical method limit of quantitation (~1000 ng/g, as is). For scaling purposes, one smokeless tobacco product is not included (b) (4)

Figure 8. Comparison of Nornicotine (µg/g, as is) for Camel Snus Styles and Other U.S. Oral Smokeless Tobacco Products Sampled in 2016*



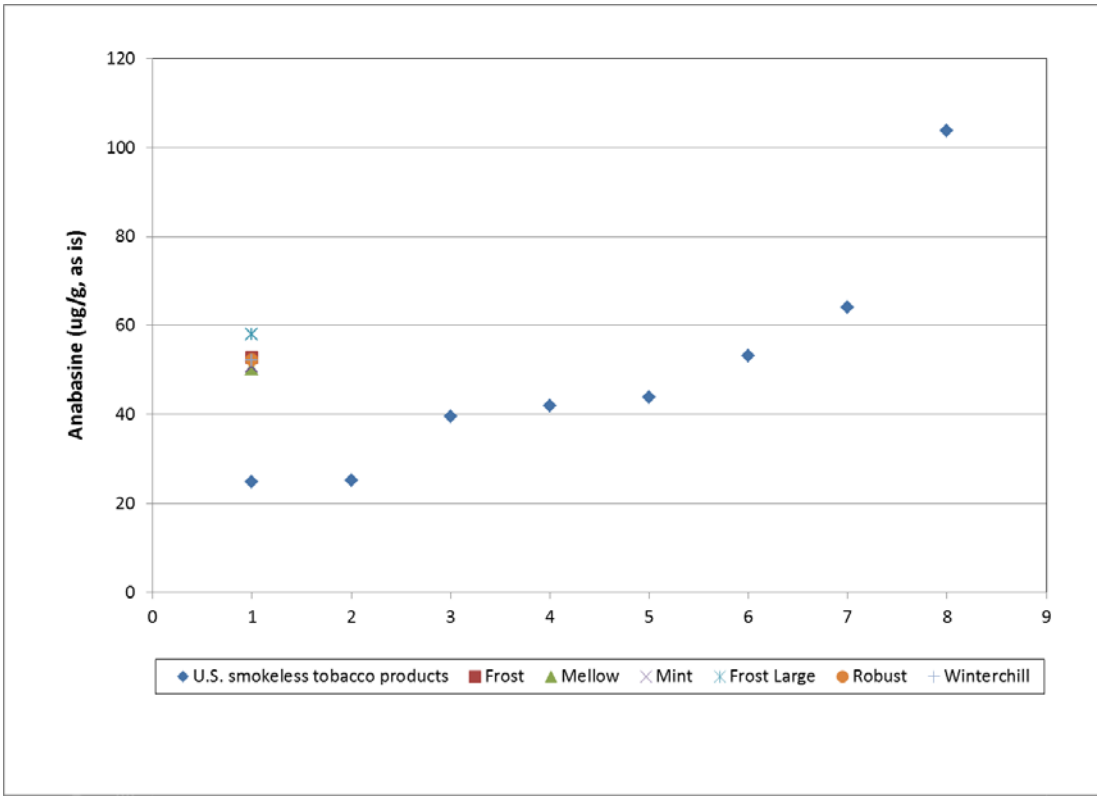
Notes: All products tested in a single laboratory in 2016. * Data Source: Labstat International ULC, 2016. Characterization of Smokeless Tobacco - Minor Alkaloids (Project M273). ExternalCo LSI 2016,097.

Figure 9. Comparison of Nornicotine (μg/g, as is) for Camel Snus Styles and Other U.S. Oral Smokeless Tobacco Products Sampled in 2016*



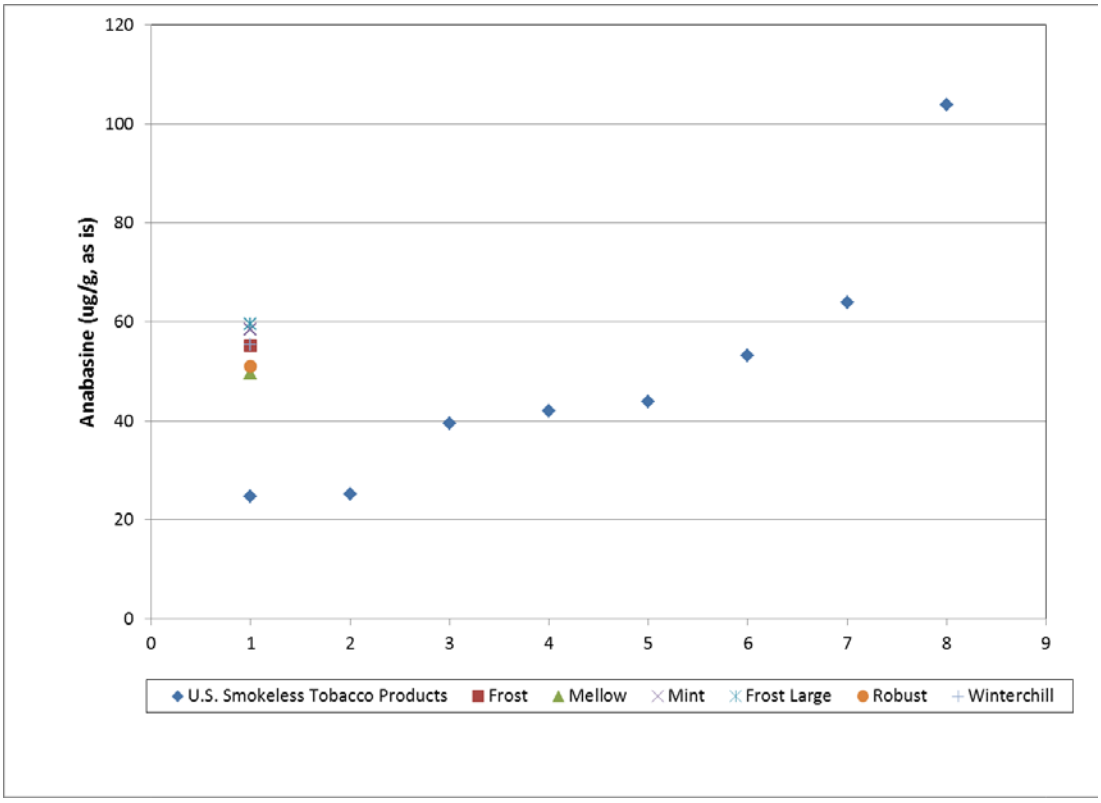
Notes: Camel Snus products were tested in 2013 and all other products in 2016. The testing was conducted in two different laboratories. * Data Sources provided by RJRT: Labstat International ULC, 2016. Characterization of Smokeless Tobacco - Minor Alkaloids (Project M273). ExternalCo LSI 2016,097. Rowe, J., 2016. Analytical Testing of Camel Snus Products. RDM JMR 2016,235.

Figure 10. Comparison of Anabasine (µg/g, as is) for Camel Snus Styles and Other U.S. Oral Smokeless Tobacco Products Sampled in 2016*



Notes: All products tested in a single laboratory in 2016. * Data Sources provided by RJRT: Labstat International ULC, 2016. Characterization of Smokeless Tobacco - Minor Alkaloids (Project M273). ExternalCo LSI 2016,097.

Figure 11. Comparison of Anabasine (µg/g, as is) for Camel Snus Styles and Other U.S. Oral Smokeless Tobacco Products Sampled in 2016*



Notes: Camel Snus products were tested in 2013 and all other products in 2016. The testing was conducted in two different laboratories. * Data Sources provided by RJRT: Labstat International ULC, 2016. Characterization of Smokeless Tobacco - Minor Alkaloids (Project M273). ExternalCo LSI 2016,097. Rowe, J., 2016. Analytical Testing of Camel Snus Products. RDM JMR 2016,235.

3.3.6 Other variables that may contribute to abuse liability and product appeal

For oral nicotine delivering products, a variety of factors, in addition to nicotine, may influence abuse liability, product appeal, and use, including potentially beneficial patterns of use such as use to quit or reducing smoking. The constellation of oral product attributes that include flavor, odor, appearance, and sensory feel, are together often referred to as the organoleptic properties of the product. The organoleptic properties of oral products are strongly determined by the ingredients used to make the product as well as manufacturing techniques that can make the product feel smooth and supple or loose and gritty (the former more typically being perceived as more pleasant than the latter) (Simon & Nicolelis, 2001; Meilgaard et al., 2006).

The importance of product form and organoleptics extends across tobacco and other nicotine products, as well as a wide range of consumer products whose net appeal is related to users' subjective impressions of palatability, convenience, overall acceptability, and sensory pleasure. Such products include manufactured foods, snacks, beverages, and over-the-counter pharmaceutical products such as throat

lozenges, cough syrup, and nicotine replacement medications (e.g., gum and lozenges), which come in different sizes, shapes, flavors, and textures.

Mint and fruit family flavors are prominently used among various oral medicinal products along with various sweeteners in an effort to produce an acceptable and generally pleasant experience that contributes to sufficient and compliant use. For example, Pepto-Bismol™ liquid and chewable tablets may be flavored as “original” or “cherry” and include saccharin as a sweetener. Rolaids™ and Tums™ include various mint and fruit family flavors and sweeteners including corn syrup. For FDA-approved nicotine gum and lozenge products for smoking cessation in the U.S. as well as for smoking reduction in the United Kingdom, flavors include those variously described as “fruit”, “citrus”, “mint” and “peppermint” with brand name descriptors including Fruit Chill™, White Ice Mint® and Cinnamon Surge™. A typical sweetener for nicotine gum is sucralose.

3.3.7 Lessons learned from flavor modification of nicotine gum and lozenge.

Within a few years of the marketing of the first nicotine replacement product, Nicorette® brand nicotine gum, it was evident that poor flavor and organoleptics, variously described as “aversive”, “hard”, “gritty” and “bad”, was a barrier to use beyond initial trial, a barrier to using the recommended nine or more units per day for smoking cessation, and a barrier to using the product long enough to quit smoking and stay off cigarettes (Fortmann et al., 1988; Henningfield & Stitzer, 1991; Jarvik & Henningfield, 1993; Rose, 1996; Houtsmuller et al., 2002). Switching the gum from a prescription drug product to an over-the-counter consumer product increased the interest of both those involved in commercialization and marketing of the product as well as those interested in maximizing its public health impact in improving the flavor and overall organoleptics.

The major initial advance was the application by the nicotine gum marketer, Smith Klein Beecham, for approval to market a mint flavored form of nicotine gum to provide an option that was believed would be more acceptable and pleasurable than the original flavor for many cigarette smokers. The FDA, however, was concerned that the mint flavoring would increase the abuse liability of the product and potentially foster misuse by young people. FDA required the sponsor to conduct an abuse liability study involving 18 to 21-year-old cigarette smokers as ethically acceptable proxies for adolescents compared to 22 to 55-year-old cigarette smokers. The study showed that mint did not increase the pharmacological abuse liability of the gum; however, the mint flavored gum was rated as more “palatable” and “sweet”, better “liked”, and less “bad” and “bitter” as compared to the original flavor nicotine gum, and it produced significantly stronger effects on craving reduction than the original flavor. A similarly designed study was later employed to assess the abuse liability of nicotine lozenge due to concerns of FDA that its mint flavor combined with physical resemblance to “candy lozenges”, less effortful use requirements, and somewhat higher release of nicotine as compared to nicotine gum would combine to produce increased abuse liability. The general finding of the study was that the subjective effects related to abuse liability were similar to those of

nicotine gum, although, apparently less appealing to the 18 to 21-year-old participants than to the 22 to 55-year-old participants.

These foregoing studies contributed to FDA's approval of Nicorette Mint® nicotine gum in 1998 and the Commit® lozenge in 2002 (FDA, 2016). Today there are many flavor variations of nicotine gum and lozenge, as discussed above, with the total market share of the flavor variations substantially higher than that of "original" flavor (FDA, 2016). Reynolds American Inc.'s subsidiary, Niconovum, markets nicotine gum in mint, cinnamon, and fruit, and mini-lozenges in mint flavor, not even offering a so-called "original" flavor.

Abuse of nicotine gum and lozenge and regular use or dependence among never tobacco users (adolescent or adult) is apparently at such low rates nationwide as to not be considered a public health problem of significance: it is not the focus of prevention campaigns by organizations addressing tobacco use and addiction, nor is it a focus of the FDA, such that the products are under consideration for removal from over the counter sale. To the contrary, nicotine gum and lozenge marketers view variations in ingredients and flavors as important to enhancing organoleptics, acceptance, pleasantness of use, and to sustain higher levels of use than expected if only "original" flavor were available. In addition, there has been little evidence of long term use of nicotine gum other than that reported for the purpose of sustaining tobacco use abstinence (Shiffman et al., 2003b; Gerlach et al., 2008).

Market data are not the same as clinical efficacy data, but limited studies suggest that flavored gum is preferred by those using nicotine gum to replace or quit smoking, and that there may be public health benefits of pleasantly flavored nicotine gum. For example, data from one controlled trial of Camel Snus (Hatsukami et al., 2016a) was closely examined in a separate publication to determine flavor preference among participants (Meier et al., 2016b). In this study, only one (0.5%) participant chose the original (unflavored) product and 78 (40.0%) chose mint, 69 (35.4%) fruit, and 47 (24.1%) the cinnamon-flavored varieties (Meier et al. 2016b).

A total of 607 adult cigarette smokers in Germany "who intended to cut down or give up smoking" were evaluated in two single blind studies of a newly introduced fruit flavored gum compared to other marketed flavored nicotine gum products in both 2 and 4 mg content strengths. The investigators' conclusions seemed reasonable, in light of their findings: "Product characteristics such as crunchiness, sweetness and flavor, appear to be crucial for the expectations that smokers have in the likelihood that any particular nicotine gum will help them quit smoking. Thus, improved organoleptic characteristics of nicotine gums may lead to higher compliance…." Pleasant or at least acceptable flavor non-nicotine containing confectionary gum may also contribute to beneficial health outcomes as demonstrated by an evaluation of the effects of various gum flavors in relieving negative affect associated with smoking cessation (Cohen et al., 2010).

The Swedish experience with smokeless tobacco products also suggests that factors that influence food product preferences and use may also influence oral tobacco product use and subjective effects that make the total experience more or less pleasurable, increasing the likelihood of using the product in place of cigarettes. For example, traditional Swedish snus products were used almost exclusively by men in Sweden in part due to physical attributes including flavors and textures, as well as perceived messiness of use requiring dipping the fingers into containers and placing "pinches" between gum and cheek. The development of relatively neat, clean, small and discretely usable pouches, in flavors considered more likely to be refreshing and pleasant, were important advances in extending the potential acceptability of the products to a broader range of men as well as women in Sweden. This also appears to be the case in the U.S. These designs may not necessarily appeal to persons seeking a product with a strong masculine image and in Sweden and the U.S., most snus users remain men with only relatively recent increases in use by women. These increases appear to be the result of heightened concerns about cigarette smoking and restrictions on cigarette smoking along with availability of products designed to be more acceptable to women.

3.3.8 Camel Snus

As discussed below, Camel Snus has several characteristics that may contribute in some way to use and product appeal (also commonly referred to as 'consumer appeal', 'attractiveness', and/or 'acceptability'). Although there is no generally agreed upon bright line distinction between abuse liability and consumer appeal, we follow the general approach of the 2009 Conference on Abuse Liability and Consumer Appeal of Tobacco Products: Science and Future Directions, which included leading experts in abuse liability assessment and consumer appeal. The conference steering committee and rapporteurs, Henningfield, Hatsukami, Zeller and Peters, co-authored a conference report based on presentations and discussion at the conference. A generally agreed upon convention for that conference has been followed in the present review. Specifically, 'abuse liability assessment', was used to distinguish the 'pharmacologically determined risk of abuse' from those factors affecting what was referred to as 'attractiveness', 'consumer appeal', and 'product appeal'. These factors included the following: the sensory characteristics of product including taste, smell, or other sensory effects; advertising and promotion efforts; image; cost; the target population; positioning among other products; and claims and warnings related to benefits and risks which can increase or decrease product appeal, respectively (Slovic, 2001; Rees et al., 2009; FDA, 2010).

A similar approach to differentiating pharmacological abuse liability and product appeal factors was taken by the European Union's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) in its 2010 report on Tobacco Product Addictiveness and Attractiveness. In that report, 'addictiveness' was distinguished from 'attractiveness' (European Commission Directorate-General for Health and Consumers, 2010). Ingredients that affected flavor and other organoleptic qualities were assumed to

be more related to attractiveness. Further, the SCENIHR report determined that there was a lack of evidence at that time connecting the role of additives to the initiation of smokeless tobacco use and subsequent dependence. The WHO TobReg has also discussed the mutual importance but distinctive contribution of abuse liability and product appeal factors emphasizing that both categories influence the likelihood that a product will be used, the risk of dependence, patterns of use and the difficulty of abstaining from the product (see WHO, 2007b).

Similarly, it is likely that a variety of factors will contribute to Camel Snus acceptability for use in general, as well as to adoption and use as an MRTP that smokers will switch to completely. Certain of these factors may also contribute to the acceptability of Camel Snus to existing users of other smokeless tobacco as well. For example, the product's pouched portioning is intended to provide convenience to the user and prevent the release of loose bits of tobacco in the mouth, as occurs with other loose moist snuff products. In addition, Camel Snus flavor varieties are intended to provide a broader appeal to the subjective taste preferences of diverse adult smokers than would be possible with a single flavor style. Various ingredients contribute to appeal, for example:

- Sucralose, a non-cariogenic sweetener, compliments the different characteristic flavor varieties of Camel Snus by providing a modest degree of sweetness that is similarly preferred by U.S. adults in many consumer products other than tobacco.
- The humectant propylene glycol is a functional ingredient in all Camel Snus products that acts in concert with a resilient sealing gasket on the lid of the container to maintain the moisture level in the packaged product.
- The salt levels in Camel Snus are lower than those of many Swedish snus products, which are higher than many U.S. consumers find to be palatable. Further, the lower salt content of Camel Snus contributes to its convenience of use, as it produces less salivation and reduces or eliminates the need to spit or swallow excessive volumes of induced saliva during product use. These moderate levels of salt are sufficient to maintain the shelf stability of the product, and eliminates the need for other preservative ingredients or refrigeration.

In summary, with regard to added ingredients, several may be viewed as contributing to the overall acceptability of Camel Snus, but it is only those ingredients that comprise the buffering system of the product, and resulting nicotine speciation, that would appear to have a potential to affect abuse liability in any meaningful way, as discussed in Section 3.3.3 above.

3.3.9 Discussion and Conclusions

Camel Snus contains sufficient total nicotine to enable use as a replacement for traditional cigarette smoking and to address any nicotine dependence that has been established in cigarette smokers who have interest in an alternative smokeless tobacco product. Six product style variants of Camel Snus are being submitted for designation

as MRTPs. These include two pouch sizes (600 mg and 1000 mg) and five flavors (Frost, Mint, Mellow, Winterchill, and Robust). (b) (4) (b) (4) (b) (4) with the tobacco blend comprising the major portion of the product and water as the second largest component. A buffering system comprising sodium carbonate and sodium bicarbonate is common to all Camel Snus flavor varieties to maintain the packaged product at approximately pH (b) (4) and with nicotine content ranging from (b) (4) (b) (4) mg per gram of tobacco. Thus, the total nicotine content is approximately 5.9 – 6.0 mg for the 0.6 g pouch size and 9.3 – 10.2 mg for the 1 g pouch size; unionized nicotine content is approximately 1.9 – 2.0 mg for the 0.6 g pouch size and 3.0 – 3.4 mg for the 1 g pouch size.

Study averages up to about 39% (range 20.0–39.7% in the studies reported in RJRT's MRTP Application; see Table 5 below) of the nicotine content of Camel Snus is extracted and systemically available during its use. As a point of comparison, approximately 50-60% of the nicotine in the 2 and 4 mg dose sizes of nicotine gum are typically absorbed under its specified conditions of usage (Benowitz, 2011). On the other hand, the total nicotine content and unionized fraction in Camel Snus is substantially less than that found in several of the popular smokeless tobacco brands currently sold in the U.S., which can exceed 10 mg per gram and are typically used in 2 g "pinches" (Hatsukami et al., 1988). Importantly, the unionized nicotine fraction allows for nicotine molecules to be very rapidly absorbed into venous blood through the oral mucosa, thus potentially contributing to initial subjective effects. Unionized nicotine is also thought to contribute to sensory impact (Wayne et al., 2004). Depending on the patterns of swallowing of the individual, some nicotine will be swallowed with only about one-third surviving first pass liver metabolism and then systemically absorbed. This is a substantially slower and less efficient process than occurs when nicotine delivered in smoke is inhaled into the lung. Thus, peak blood nicotine levels and the time to attainment peak levels are considerably lower and slower than those experienced by cigarette smokers. Camel Snus may, however, provide higher and faster levels of nicotine than are provided by 2 mg nicotine gum or lozenge or than by the Nicotrol® inhaler, but likely slower than provided by nasal nicotine (see Appendix B and also discussion of nicotine absorption kinetics and metabolism in Benowitz et al., 2009). It also likely leads to substantially lower and slower onset of nicotine effects than have been documented to occur with oral snuff that is buffered to higher pH levels (e.g., Fant et al., 1999). This and other aspects of the comparative nicotine delivery from Camel Snus, cigarettes, and NRT are further discussed in detail in the summary of published and unpublished clinical studies included in this review.

None of this is intended to imply that switching from inhaled cigarette smoke to Camel Snus will be easy, as it is well known that for many traditional cigarette smokers, even the transition to cigars and more recently, ENDS, is not easy. It is well understood that a variety of non-nicotine, sensory and behavioral factors contribute substantially to the persistence of smoking (Rose et al., 1996; 2010) and these subjective components of

human smoking behavior likely differ in their perceived importance to different smokers. For those smokers for whom the sensory and ritual behavioral elements of smoking are of higher importance than nicotine delivery, it might be anticipated that migration to a smokeless product would be more difficult.

It is likely that Camel Snus would be positioned somewhere near the center of the theoretical targets for an ideal and acceptable MRTP on the two diagrams (Niaura, 2016; Henningfield, 2015b) presented in the Background Section, near the ideal point of balance among abuse potential, acceptability and inherent risks. In contrast, nicotine gum would likely be located in the relatively lower abuse liability and lesser appealing quadrants of those charts, while also conveying the lowest risk to the user.

Other constituents with a theoretical potential to contribute to abuse liability (specifically, acetaldehyde, anabasine, and nornicotine) are relatively low compared to those reported for many products in a survey of diverse smokeless tobacco products in the U.S. market. These findings provide no basis for predicting that the abuse liability of Camel Snus would equal that of the higher nicotine content smokeless tobacco brands on the market, and present a reasonable basis for concluding that if there is any difference in abuse liability it is in the direction of lower abuse liability for Camel Snus relative to other U.S. smokeless tobacco products.

Available nicotine levels would appear to provide the basis for sufficient abuse liability and physiological dependence potential to enable the migration from cigarette smoking to Camel Snus, and thereby provide an acceptable cigarette alternative to a substantial fraction of traditional cigarette smokers. The varieties of Camel Snus product flavors and pouch sizes are intended to allow adult smokers/prospective switchers to choose the specific product that they find most acceptable. Such product variety is not predicted to alter pharmacological abuse liability, but as is the case with oral NRT and all manner of other products, it provides consumers with a choice that would be predicted to contribute to the population reach of the products.

3.4 Preclinical Pharmacology

3.4.1 Nicotine and Tobacco (not specific to Camel Snus)

As noted, the primary constituent found in snus that contributes to its abuse liability is nicotine. Nicotine has been studied extensively using a variety of preclinical pharmacological methods including receptor binding and brain imaging studies over the past several decades (e.g., USDHHS, 1988; Dani & Bertrand, 2007; Benowitz, 2008; Benowitz, 2009; USDHHS, 2010; De Biasi & Dani, 2011). Charged nicotine binds to the nicotinic acetylcholine receptor (nAChR) subtypes, including the alpha4-beta2 receptor subtype, which is proposed as the main receptor to mediate nicotine reinforcement and dependence (Benowitz, 2008; De Biasi & Dani, 2011).

3.4.2 Camel Snus

One recent study has examined the preclinical pharmacology of Camel Snus as it relates to abuse liability (Harris et al., 2015). In the study, the influence of nicotine alone and nicotine dose-equivalent concentrations of aqueous smokeless tobacco extracts on intracranial self-stimulation (ICSS) thresholds and binding affinities at various nAChR subtypes was examined in rats. The extracts were derived from Kodiak Wintergreen or Camel Snus Winterchill. There were no differences in ICSS effects or the binding affinities between nicotine alone and the extracts. The authors concluded that non-nicotine constituents found in Kodiak snuff and Camel Snus do not significantly contribute to the abuse liability of these products. However, the authors also noted that more research is needed to fully explore whether higher levels of these non-nicotine constituents could play a role in abuse liability.

3.4.3 Discussion and Conclusions

The preclinical pharmacology of nicotine is well elucidated and includes binding activity at the nAChR including the alpha4-beta2 receptor subtype, which is proposed as the main receptor to mediate nicotine reinforcement and dependence. However, there is limited research examining the effects of Camel Snus using preclinical pharmacology research methods. Research suggests that the primary determinants of Camel Snus abuse liability are nicotine and buffering agents that affect nicotine dosing capacity, speed of delivery, and absorption. Thus, the relative abuse liability of Camel Snus compared to traditional cigarettes, others smokeless tobacco products, and NRT medications is primarily related to the levels of nicotine that are delivered and the speed of nicotine delivery, as further discussed below.

3.5 Animal Behavioral Pharmacology

3.5.1 Nicotine and Tobacco (not specific to Camel Snus)

The importance of nicotine in tobacco use is well documented in basic research and clinical studies (cf. US DHHS, 1988; 2010; 2014), but the extent to which other tobacco constituents and tobacco product ingredients contribute to abuse liability is less clear, and perhaps best evaluated in animal studies including animal behavioral pharmacology research (Goodwin et al., 2015). For example, a 2016 editorial by Borland and Gartner (2016) addressed findings related to Camel Snus (Hatsukami et al. 2016a), and called into question the hypothesis that minor tobacco alkaloids have any meaningful role in the treatment of nicotine dependence. Instead, Borland and Gartner suggest that factors such as expectancies by consumers, cost, and marketing contribute to greater long term use of oral tobacco products as compared to nicotine replacement products which are generally used short term to quit smoking. While the observations of Borland and Gartner may be correct, it is also possible that minor tobacco alkaloids contribute to tobacco use in more subtle ways than nicotine and are thus less clear in cigarette smoking cessation studies where numerous factors may influence outcome, thus masking the specific effects of factors that may contribute but with less readily

discernable impact. Animal behavioral pharmacology studies have the potential to clarify the contribution of tobacco product constituents, ingredients, and other factors on tobacco use and effects that may be subtle but relevant for potential regulation (e.g., Donny et al., 2012; Harris et al., 2015).

Research supports the conclusion that nicotine functions as a reinforcer across a variety of behavioral models and across different animal species including non-human primates (O'Dell & Khroyan, 2009; Goodwin et al., 2015; Rupprecht et al., 2015). Some studies have found at least some reinforcing properties of non-nicotine tobacco product constituents (acetaldehyde, nornicotine, anabasine, and anatabine) across different behavioral paradigms (Takayama & Uyeno, 1985; Goldberg et al., 1989; Takadat al., 1989; Bardo et al., 1999; Dwoskin et al., 1999; Belluzzi et al., 2005; Cao et al., 2007; Clemens, et al., 2009; Harris et al., 2012; Brennan et al., 2013; Brennan et al., 2014; Caine et al., 2014; Mello et al., 2014; Brennan et al., 2015; Harris et al., 2015). However, findings have not been consistent across studies with some constituents not always functioning as reinforcers (e.g., anatabine), while others, such as acetaldehyde and nornicotine, reported to be more likely to function as reinforcers (Hoffman & Evans, 2013; Mello et al., 2014). Desai et al. (2016) evaluated the nicotine-like behavioral effects of nicotine, nornicotine, anabasine, anatabine, myosmine, and cotinine in squirrel monkeys trained to discriminate the alpha4-beta2 nAChR selective agonist (+)-epibatidine from saline, and found that all compounds tested, except cotinine, substituted fully or partially for (+)-epibatidine. The authors also reported that the relative potency of each compound to substitute for (+)-epibatidine was highly correlated with its binding affinity at the alph4-beta2 nAChR subtype, suggesting that the effects of these compounds were mediated by this receptor subtype. These findings provide additional support for the widely-held view that activation of the alph4-beta2 nAChR subtype is primarily responsible for the behavioral and reinforcing effects of nAChR agonists, including nicotine. The relative concentrations of these minor alkaloidal constituents of tobacco with respect to nicotine should be borne in mind in evaluating their potential to meaningfully contribute to any potential nicotinic receptor agonist effects, as discussed below.

Additional studies have explored behavioral outcomes in animals as it relates to key constituents found in tobacco products. For example, Harris et al. (2015) compared the effects of nicotine and the minor alkaloids nornicotine, anabasine, anatabine, mysomine, and cotinine on ICSS thresholds in rats. ICSS is used to evaluate the abuse liability of drugs, and drugs that decrease ICSS thresholds have higher abuse liability (i.e., are likely reinforcing), while those that increase ICSS thresholds are believed to be aversive, and thus have low abuse liability. The investigators found that of the compounds tested, only nicotine, nornicotine, and anabasine significantly reduced ICSS thresholds, suggesting that although less potent than nicotine, nornicotine and anabasine may also have abuse potential.

Additionally, some animal studies have found that pretreatment with specific tobacco constituents, including anatabine and anabasine, may interfere with or attenuate the discriminative stimulus and reinforcing effects of nicotine, suggesting that interactions at nAChRs or on dopaminergic signaling pathways may be responsible (Caine et al., 2014; Hall et al., 2014; Mello et al., 2014). For example, Caine et al. (2014) found that pretreatment with anabasine and anatabine on their own significantly reduced nicotine-appropriate responding in rats trained to discriminate nicotine, and pretreatment with anabasine, anatabine, and nornicotine on their own significantly reduced nicotine self-administration. Similarly, Hall et al. (2014) found that pretreatment with anabasine and anatabine on their own could reduce nicotine self-administration in rats. Mello et al. (2014) extended these findings in rodents by showing that pre-administration of anatabine significantly reduced nicotine self-administration in nonhuman primates.

Although progress has been made in understanding the behavioral and reinforcing effects of non-nicotine tobacco constituents in nonclinical studies, there is not a consensus on the role these constituents play in the abuse liability of different tobacco products. Often, the doses or concentrations of the constituents that have been tested greatly exceed typical exposure levels obtained from tobacco product use and/or have been administered by routes (e.g., subcutaneous, intravenous, intraperitoneal) that do not mimic product use. However, as noted above, several of these constituents (acetaldehyde, nornicotine, and anabasine) are considered to contribute to abuse liability according to FDA's established list of Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke (FDA, 2012b).

Recent research examining tobacco extracts in general, rather than specific constituents per se, have also reported variable findings with some showing comparable reinforcing properties of tobacco/tobacco extracts and nicotine alone (Harris et al., 2012; Brennan et al., 2013; Costello et al., 2014; Harris et al., 2015), and others reporting greater reinforcing effects of tobacco or tobacco extracts than nicotine alone (Brennan et al., 2014; Costello et al., 2014; Brennan et al., 2015). Explanations for this variability could include differences in methodology, such as the behavioral test administered or route of administration, or differences in the chemical constituents (Harris et al., 2015). Recent studies have highlighted the complexity and challenges inherent in determining the degree to which specific constituents contribute to the reinforcing properties of nicotine (Hogg, 2016; Smith et al., 2015b), as well as the importance in methodology (Khalki et al., 2013).

Recent reviews have discussed additional research that has documented the inhibition of the enzyme monoamine oxidase (MAO) by tobacco smoke constituents other than nicotine (van Amsterdam et al., 2006; Hogg, 2016). MAO serves to attenuate neural signaling by catecholamine and serotonin neurotransmitter molecules, including those involved in central reward pathways. A recently reported study in rats has also shown that MAO-inhibiting drugs enhance the reinforcing properties of low doses of nicotine (Smith et al., 2015b). MAO inhibition has also been associated with alcohol drinking

(van Amsterdam et al., 2006), consistent with experimental studies showing that the ethanol metabolite acetaldehyde reacts with tryptophan to produce the MAO-inhibiting beta carbolines harman and norharman.

MAO inhibiting drugs such as bupropion have been used therapeutically to treat mood disorders (Fava et al., 2005), and the therapeutic utility of bupropion in assisting smoking cessation is consistent with a possible role for cigarette smoke-induced MAO inhibition in the subjectively-perceived rewarding properties of smoking for some persons, which in turn may be viewed as possibly contributing to the abuse liability of cigarettes. It is noted that several cigarette smoke constituents, namely the acetaldehyde reaction products harman and norharman, and 2-naphthylamine, have been shown to manifest MAO inhibition in experimental rodent studies. These MAO-inhibitory smoke constituents are produced primarily by the combustion processes that occur during smoking, as opposed to a modest natural presence in cured leaf tobaccos, so it might be anticipated that smokeless tobacco would have a lower potential than smoked tobacco for any abuse liability that may derive from MAO inhibition. Whereas the current state of understanding is insufficient to definitively support a role for MAO inhibition as a contributor to either smoking or smokeless tobacco use (Hogg, 2016), it seems reasonable that Camel Snus is broadly similar to other smokeless tobacco products, and lower than cigarette smoking, with respect to any role that MAO-inhibiting constituents may have in the persistence of tobacco use.

3.5.2 Camel Snus

One of the most recent studies cited above that examined nicotine alone compared to tobacco extracts in a behavioral model included smokeless tobacco extracts from Kodiak Wintergreen (dip) and Camel Snus Winterchill (Harris et al., 2015). Acute subcutaneous injection of both extracts produced reinforcement-enhancing (ICSS threshold-decreasing) effects similar to those of nicotine alone at low to moderate nicotine doses, as well as similar reinforcement-attenuating/aversive (ICSS threshold-increasing) effects at high nicotine doses. Extracts and nicotine alone also had similar binding affinity at all nAChRs studied. Similarly, a separate study by the same research group found similar reinforcing efficacy between nicotine alone or extracts of Camel Snus or Kodiak smokeless tobacco (LeSage et al., 2016). While these findings require replication before any firm conclusions can be drawn, they are consistent with a provisional conclusion that minor tobacco alkaloids and other leaf constituents in Camel Snus do not appear to affect the reinforcing properties of nicotine in this animal model.

It may be informative to consider the relative quantities of nicotine and non-nicotine alkaloidal constituents of Camel Snus in order to evaluate their potential to meaningfully contribute to abuse liability. Nicotine is present in Camel Snus at levels approximately 1 to 2 orders of magnitude higher than those of the minor alkaloidal constituents, suggesting that any potential of the latter to modify the dominant role of nicotine in abuse liability is likely small. The levels of nicotine and these other alkaloidal

constituents are broadly similar to or lower than those of many other commercial products sampled from the U.S. market (see Figures 3 – 11).

3.5.3 Discussion and Conclusions

Similar to the body of work related to the preclinical pharmacology of nicotine, there is a large body of evidence supporting that nicotine is a reinforcer across different animal behavioral pharmacology paradigms. Nicotine is thus a key factor in the use and effects of Camel Snus. Animal behavioral pharmacology research to date does not imply a similarly robust role for minor tobacco alkaloids and other tobacco constituents in the use of oral smokeless tobacco in general or in Camel Snus in particular. The fact that potentially CNS-active nonnicotine constituents in Camel Snus are unlikely to contribute substantially to Camel Snus abuse potential is also consistent with the fact that such constituents are at generally lower levels than many other smokeless tobacco products surveyed from the U.S. marketplace (see Section 3.3, Chemistry). Any conclusions regarding the potential role of whole tobacco extracts and other tobacco constituents such as minor alkaloids are also limited by the relatively small body of research in this area as compared to research on nicotine, schedule of reinforcement, and potential conditioned stimuli. Thus, the relative abuse potential of Camel Snus compared to traditional cigarettes, other smokeless tobacco products, and/or NRT medications is primarily related to the levels of nicotine delivered and the speed of nicotine delivery, as further discussed in the section below.

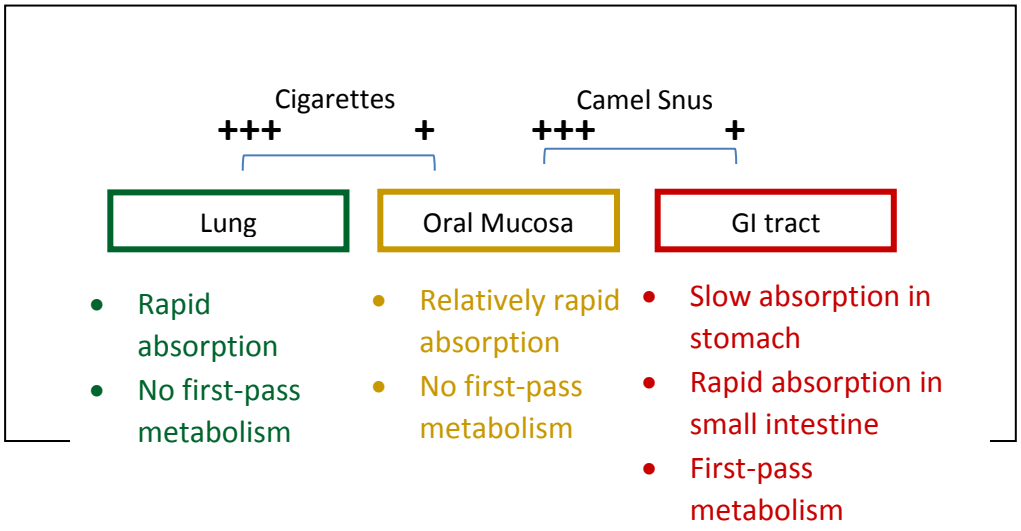
3.6 Pharmacokinetics and Pharmacodynamics

3.6.1 Nicotine and Tobacco (not specific to Camel Snus)

The pharmacology of tobacco use has been explored in depth over time and general principles of nicotine delivery, absorption, distribution, metabolism, and excretion are described elsewhere (Gritz et al., 1981; Benowitz, 1988; Benowitz et al., 1988; Benowitz, 1990; Henningfield & Keenan, 1993; Benowitz, 1997; Henningfield et al., 1997; Tomar & Henningfield, 1997; Fant et al., 1999; Henningfield & Fant, 1999; Benowitz, 2009; Benowitz et al., 2009).

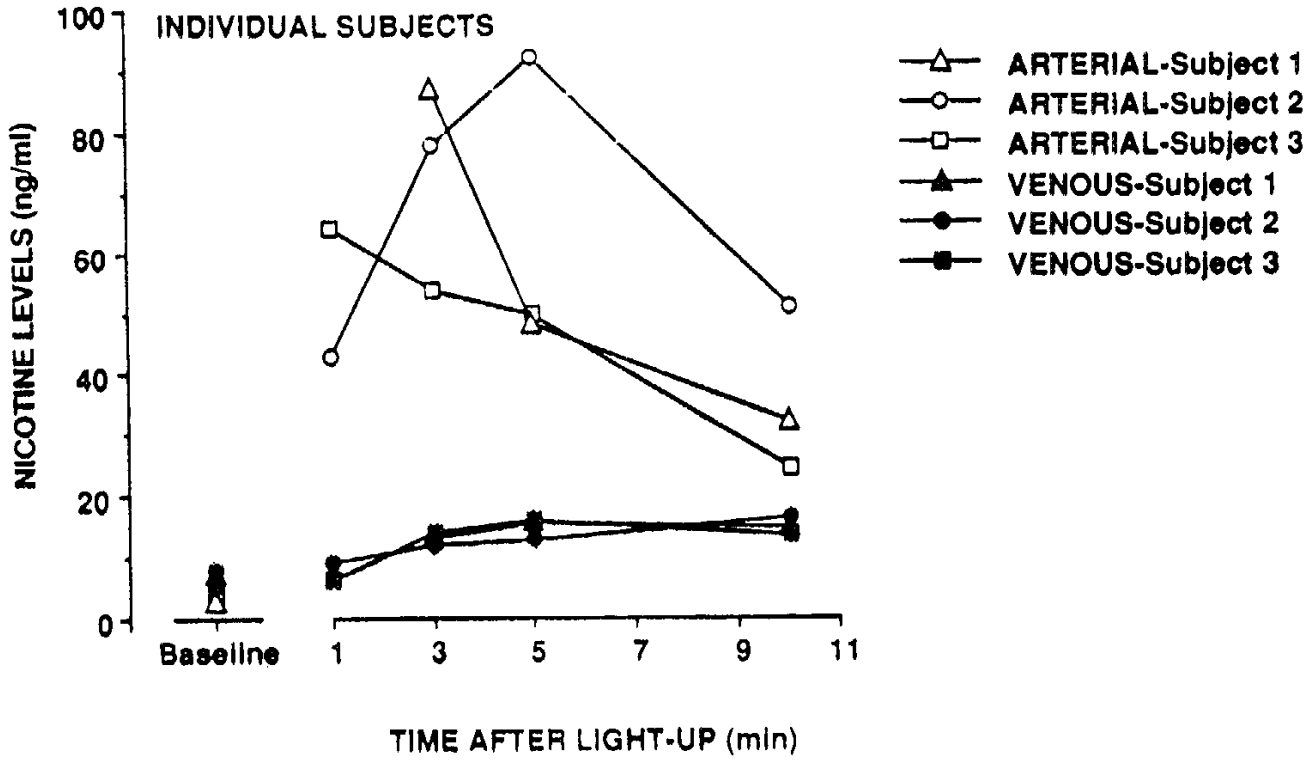
Nicotine derived from the inhalation of cigarette smoke is taken up very efficiently and, conveyed by freshly-oxygenated blood emerging from the pulmonary circulation, is rapidly introduced into the arterial blood volume for distribution throughout the body. A minor quantity of cigarette smoke nicotine is absorbed through the oral mucosa, albeit with relatively slower and less efficient uptake kinetics. The nicotine derived from Camel Snus and other smokeless tobacco products is primarily absorbed through the oral mucosa and introduced into the general venous circulation, with a minor quantity being swallowed with saliva and absorbed relatively slowly in the gastrointestinal tract. Such nicotine is subjected to first-pass metabolism in the liver, which has the effect of greatly reducing the quantities available for systemic distribution (see Figure 12).

Figure 12. Physiologic Characteristics of Nicotine Absorption from Cigarette Smoking and Smokeless Tobacco Use



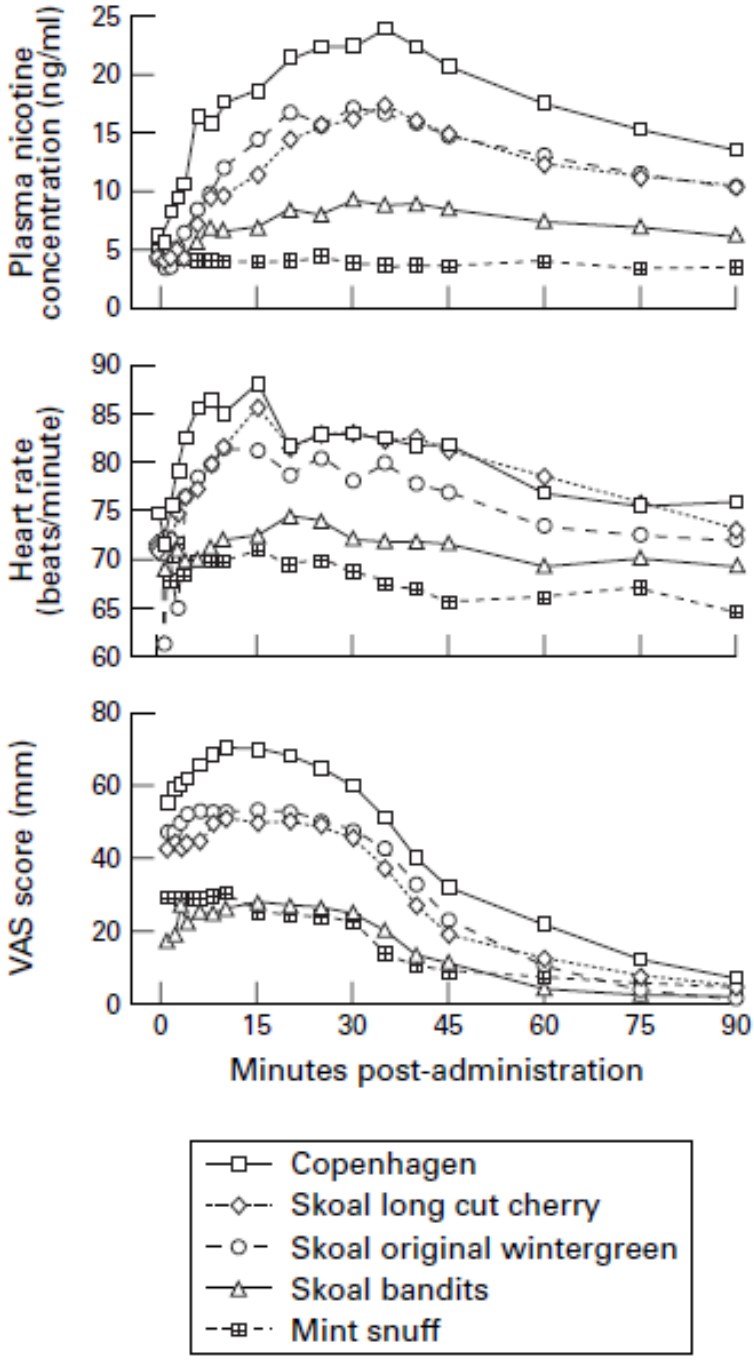
Overall, research indicates that smoking tobacco is the most dependence producing form of nicotine administration given that high levels of nicotine are able to reach the brain in 10 to 20 seconds, which is even faster than intravenous administration (Henningfield & Keenan, 1993; Benowitz, 2009). In fact, Berridge and colleagues (2010) found that arterial blood nicotine levels rapidly rose in their study within four seconds and produced 50% of maximum brain levels within 15 seconds of a single inhalation of cigarette smoke (a “puff”), an effect not possible by transmucosal venous nicotine absorption produced by the use of oral nicotine products whether they are tobacco or medicinal (e.g., snus or nicotine gum). Of course, over the course of puffing on a cigarette, or when other nicotine containing products are used, overall systemic nicotine levels continue to rise, somewhat more gradually, as the product is used (e.g., Rose et al., 2010). Further support for the arterial nicotine delivery of smoked tobacco is the finding that arterial plasma nicotine levels averaged 46.1 ng/ml one minute after smoking a cigarette and this value was much greater than venous levels which averaged 28.2 ng/ml (Henningfield, London & Benowitz, 1990). The figure below illustrates the arterial and venous plasma concentrations for three participants before and after smoking one cigarette (Henningfield & Keenan, 1993)

Figure 13. Time Course of Arterial and Venous Nicotine Concentration for 3 Individual Participants Before and After Smoking One Cigarette.



The reinforcing effects of nicotine are strongly dependent on the speed of delivery to the central nervous system compartment (slower onset, less reinforcing), thus when the onset of effect is delayed for some nicotine products such as smokeless tobacco and NRT, they are less reinforcing (Benowitz, 1990; Fant et al., 1999; West et al., 2000). As shown in Figure 14 below, there was a strong correlation between the rise in plasma nicotine levels and the resulting heart rate and perceived “strength” of the product after use of four different smokeless tobacco products or mint snuff (Fant et al., 1999).

Figure 14. Mean Plasma Nicotine Concentration, Heart Rate, and Visual Analogue Scale (VAS) Score (product "strength") after Administration of Each of 4 Smokeless Tobacco Products or Mint Snuff (from Fant et al., 1999).



Along these lines, the continued use of nicotine replacement products is related to rate of nicotine delivery (faster rate of delivery correlates positively with continued use) suggesting that a product must deliver nicotine at a sufficient rate so as to adequately satiate the smoker and prompt switching (West et al., 2000).

3.6.2 Camel Snus

3.6.2.1 Nicotine Absorption Pharmacokinetic Studies

There are several published studies that have examined pharmacological outcomes that may be relevant to assessing the abuse liability of Camel Snus (Blank & Eissenberg, 2010; Cobb et al., 2010; Hatsukami et al., 2011; Kotlyar et al., 2011; O'Connor et al., 2011; Caraway & Chen, 2013; Li et al., 2013; Burris et al., 2014; Hatsukami et al., 2016a; Krautter et al., 2015; Ogden et al., 2015a, b, c; Round et al., 2015). In addition, four unpublished studies conducted by RJRT also provided relevant information for assessing the abuse liability of Camel Snus: CSD1010, CSD0914, CSD0904, and CSD1101. These published and unpublished studies are described below as a function of key pharmacology outcomes.

As noted previously in Section 2 (Background), it is widely accepted that nicotine is the primary compound in tobacco products that produces reinforcing effects and that underlies the development of physical and psychological dependence. Thus, the most important pharmacokinetic data related to the abuse potential of Camel Snus are the peak plasma concentrations (C_{max}) of nicotine and the speed at which these plasma concentrations are reached (T_{max}) after acute exposure. However, the majority of the published studies on Camel Snus found in this review of the literature, and the unpublished studies conducted by RJRT, have focused on subjective effects, consumer acceptability, and exposure to systemic biomarkers (e.g., TSNAs, PAHs, etc.) rather than key pharmacokinetic outcomes. Nonetheless, results from studies of repeated product use that include biomarker measures such as plasma/serum, urinary, or salivary nicotine, nicotine metabolites (including cotinine), and total nicotine equivalents will be summarized below. In addition, a summary of mouth-level exposure measures from several studies of Camel Snus is provided for a perspective on how much of the product's nicotine is actually extracted during use. Collectively, these pharmacokinetic and tobacco/nicotine exposure measures provide a range of variables that can be used as part of an overall Camel Snus abuse liability assessment.

3.6.2.2 Pharmacokinetics - Absorption

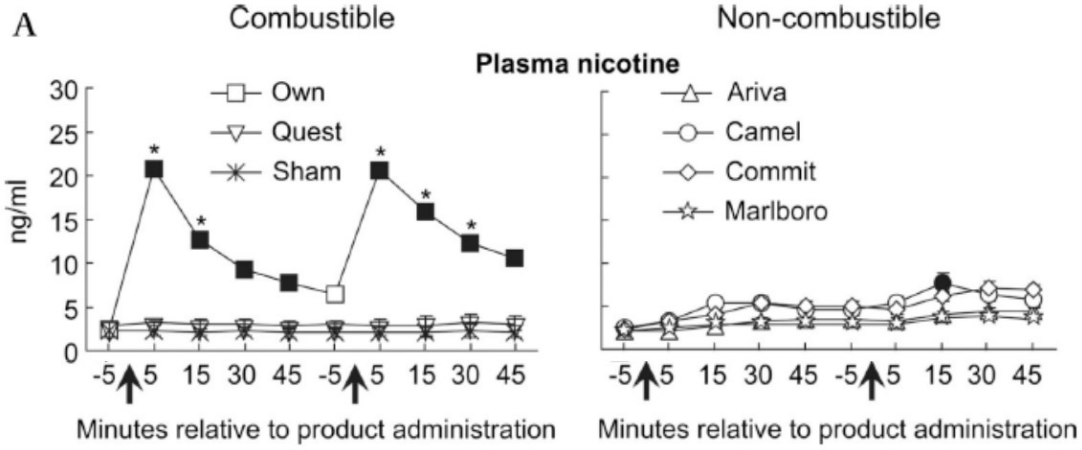
Three studies, one from the literature (Cobb et al., 2010) and two from RJRT (unpublished: CSD0914 and CSD1101), have investigated the absorption (i.e., systemic uptake) pharmacokinetics of nicotine following administration of Camel Snus products, and are summarized below. Subjective effects, physiological effects, and other outcome measures from these studies that are relevant to Camel Snus abuse liability are described elsewhere (Section 3.7, Human Studies).

3.6.2.2.1 Published Literature

Plasma nicotine levels and subjective effects associated with Camel Snus were compared to cigarettes and other products in one published study (Cobb et al., 2010). In this acute, within-subject, laboratory-based study of 28 smokers, study products were administered twice by participants separated by one hour, and blood was drawn before

each product administration, and then at 5, 15, 30, and 45 minutes post-administration for assessment of nicotine levels. Peak increases in plasma nicotine were significantly greater for smoking an own brand cigarette (20.7 ng/ml at 5 minutes post-smoking) compared to Camel Snus use (approximately 5 ng/ml at 15 minutes post-first Camel Snus administration, and 7.6 ng/ml at 15 minutes post-second Camel Snus administration). At the same time point (15 minutes post-second administration) increases in plasma nicotine levels were lower for other smokeless products tested in this study including Marlboro snus (2.9 mg/ml), Ariva tablets (3.4 ng/ml), and 2 mg Commit nicotine lozenge (4.6 ng/ml; see Figure 15 below from publication). Venous nicotine concentrations from Camel Snus are much lower than those reached after smoking. Also, a much sharper and faster rise in nicotine levels and higher C_{max} levels (approximately 25 ng/ml) was observed after a single administration of a relatively high pH and high nicotine traditional moist snuff product (Copenhagen) shown in Figure 14 above. Similar pharmacokinetic results for other traditional smokeless tobacco products have been reported by other investigators, including Benowitz et al. (1988), and underscore the significant impact that smokeless tobacco product formulation has on the release and systemic absorption of nicotine.

Figure 15. Mean Data ±1 SEM for Plasma Nicotine Across Conditions (N=28) from Cobb et al., 2010



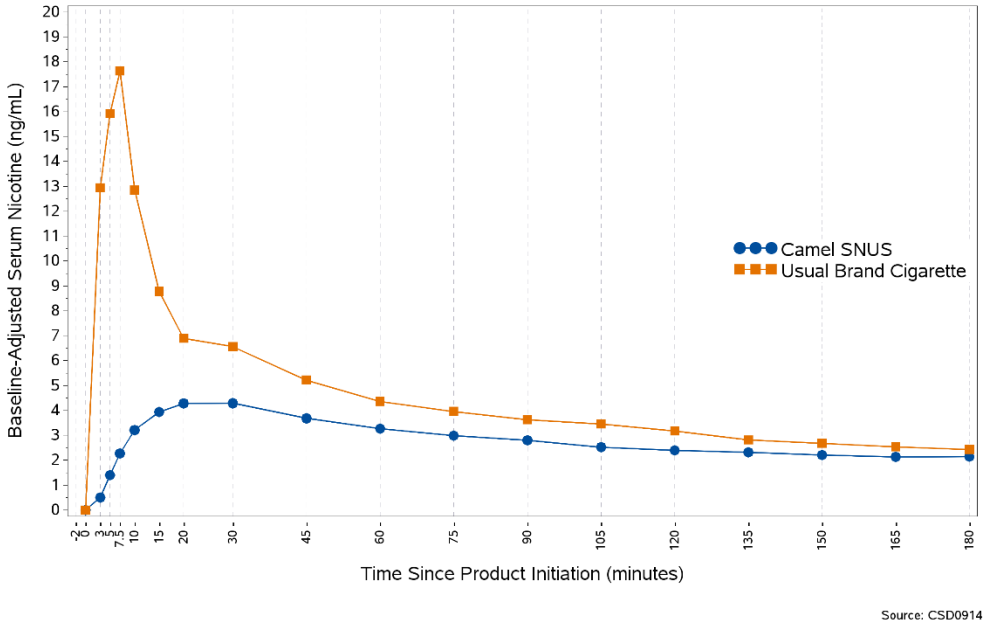
Arrows in Figure 15 above indicate product administration, filled symbols indicate a significant difference relative to baseline, and asterisks (*) indicate a significant difference of OWN product use mean relative to all non-combustible product means at that time point (P<0.05, Tukey's Honestly Significant Difference) (from Cobb et al., 2010).

3.6.2.2.2 Unpublished RJRT Studies

An unpublished study (CSD0914) was conducted by RJRT to evaluate serum nicotine uptake and tobacco abstinence symptoms over a three-hour period following use of Camel Snus (or one of four other smokeless tobacco products; not discussed herein).

Study participants were 15 generally healthy smokers who were instructed not to smoke or use any tobacco product for at least 12 hours before each study visit. At Visit 1, participants smoked their own brand cigarette, and at Visits 2-5 they used one unit of Camel Snus (Mellow or Frost; 600 mg). For the Camel Snus product, participants were asked to place one pouch between either their upper or lower lip and gum and to leave it in place for 15 to 30 minutes. Occasional movement of the pouch was suggested, but not required. Duration of use was measured for all products (see Section 3.7 for more details). Blood was collected and questionnaires were administered just prior to and then at designated times for three hours following the start of product use. The key acute nicotine pharmacokinetic data from this study, adjusted for any residual serum nicotine present at study initiation, are represented in Figure 16 below:

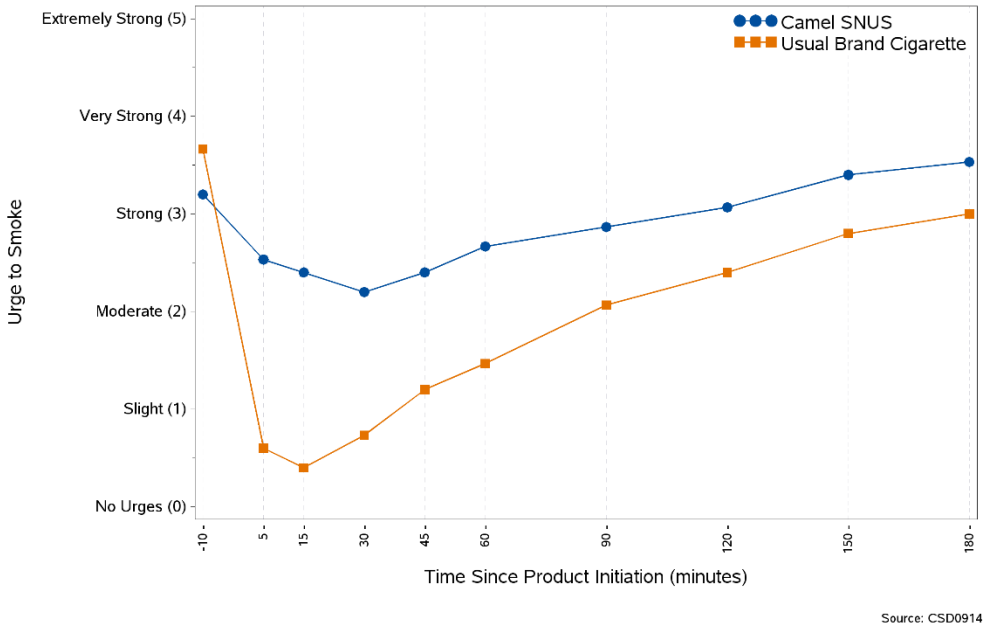
Figure 16. Average Serum Nicotine Value Observed at Each Time Point Following Use of a Single Pouch of Camel Snus or a Single Usual Brand Cigarette (CSD0914)



Serum nicotine uptake measured as the area under the concentration versus-time curve for the 180-minute testing period ($AUC_{0\text{-}180}$) was slightly greater for participants smoking own-brand cigarettes compared to Camel Snus. Although the two products were associated with similar $AUC_{0\text{-}180}$ results (the baseline-adjusted $AUC_{0\text{-}180}$ of Camel Snus is 78% of cigarette), Camel Snus maximum concentration (C_{max}) results were only 25% of own-brand cigarettes (about 5 ng/ml for Camel Snus versus about 20 ng/ml for cigarette). Time to maximum concentration (T_{max}) was approximately 3.4 times shorter for smoking (6.6 minutes) than for Camel Snus (22.7 minutes), consistent with the more rapid uptake of nicotine in the lung versus the oral mucosa. Overall, this study shows that relative to own brand cigarettes, Camel Snus delivers less systemic nicotine and results in a much lower maximum nicotine concentration and longer time to reach

maximum concentration. Questionnaire data collected concurrently over the course of the trial was used to assess the ability of Camel Snus to relieve the participants' urge to smoke, and this was compared to the reductions in urge to smoke provided by a single cigarette of the participants' preferred brand. These findings are presented in Figure 17 below and described in section 3.7 (Human Studies):

Figure 17. Attenuation of Urge to Smoke in Smokers Using a Single Pouch of Camel Snus or Smoking a Single Cigarette (CSD0914)



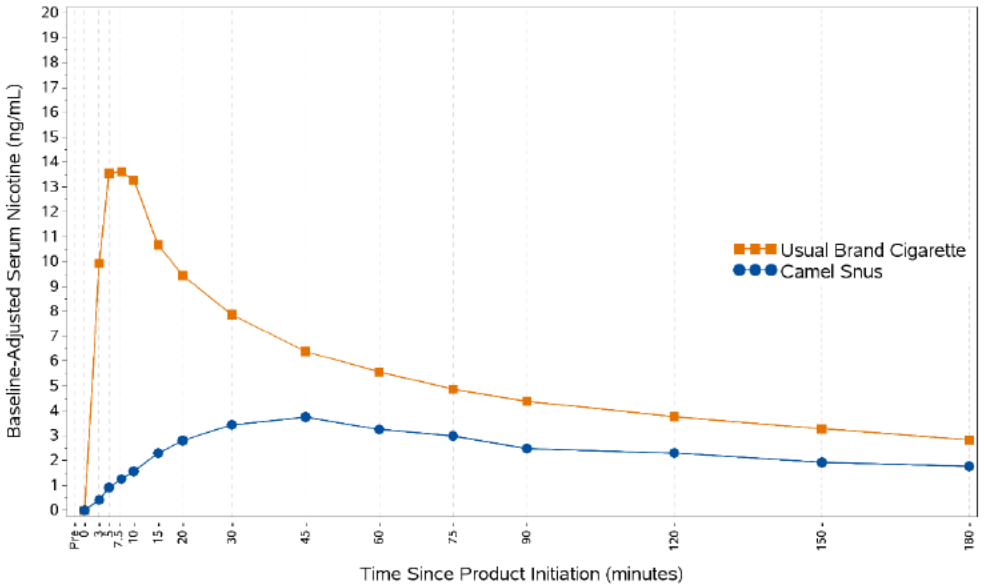
As shown in Figure 17, smoking a usual brand cigarette was more effective in relieving the urge to smoke than was consuming a single pouch of Camel Snus in these smoking participants, but both products produced statistically-significant reductions in smoking urge ($p < 0.05$) within five minutes of initiating their use. Camel Snus provided statistically-significant relief of smoking urges through the 60-minute time point, whereas the single cigarette suppressed smoking urges through the 150-minute time point after product usage began, as shown in Figure 18, below.

Figure 18. Persistence of Statistically-significant Reduction in Urge to Smoke by a Single Pouch of Camel Snus or a Single Cigarette (CSD0914)

Time Point (min)	5	15	30	45	60	90	120	150	180
Usual Brand Cigarette									
Camel Snus									
Figure Key									
	Statistically significant decrease in "Urge to Smoke" from pre-product use rating ($p < 0.05$)								
	No statistically significant decrease in "Urge to Smoke" from pre-product use rating								

Another unpublished study (CSD1101), was a randomized, open-label, crossover study of serum nicotine uptake and tobacco abstinence symptoms in 17 adult smokers. A single unit of own brand cigarettes, Camel Snus (Frost variety, 600 mg),(b) (4) were administered. Outcomes were assessed over a three-hour time period after at least 12-hours of abstinence from tobacco and nicotine. See Figure 19 for acute nicotine pharmacokinetic data from this study (adjusted for residual serum nicotine present at study initiation).

Figure 19. Average Serum Nicotine Value Observed at Each Time Point After Use of a Single Pouch of Camel Snus or a Single Usual Brand Cigarette (CSD1101)

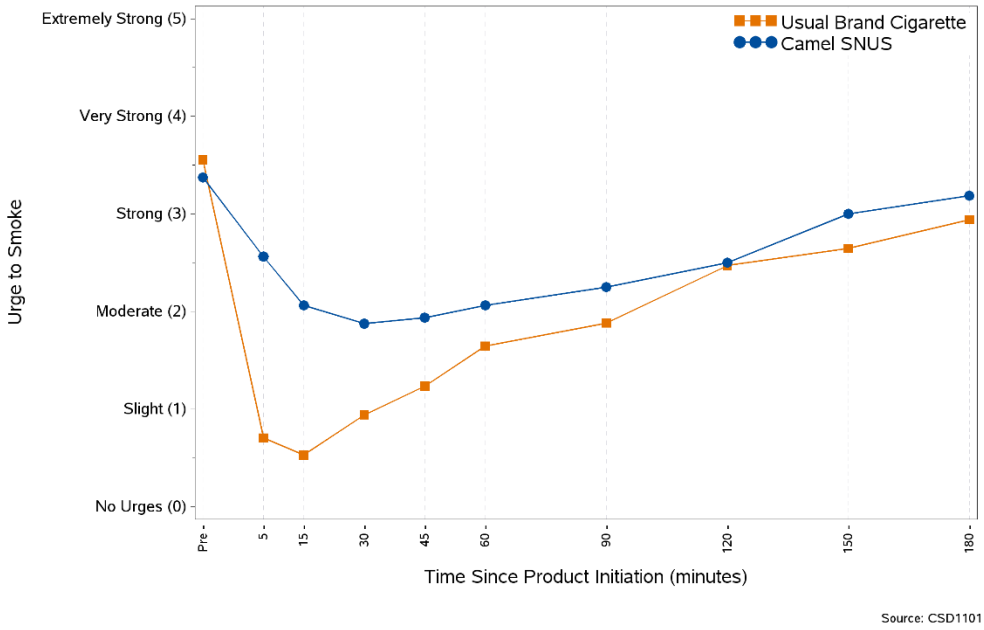


Source: CSD1101

Nicotine uptake variables (AUC and C_{max}) were greatest during smoking and significantly less for Camel Snus. Baseline-adjusted AUC values were 2.3 times greater following usual brand cigarettes (913.1 ng × min/mL) compared with Camel Snus (390.8 ng × min/mL) ($p < 0.05$). The extent of nicotine uptake from Camel Snus relative to usual brand cigarettes (AUC_{ratio}) was 42.6%. Adjustments of C_{max} to account for pre-existing nicotine prior to product administration suggests that the difference across these study products was pronounced, with an approximately four times greater $C_{max(adj)}$ for usual brand cigarettes (14.2 ng/mL) compared with Camel Snus (3.5 ng/mL) ($p < 0.05$). Importantly, the T_{max} was much shorter for the own brand cigarette compared to Camel Snus (9.7 vs 37.4 min, respectively, $p < 0.05$), showing that the speed of nicotine delivery is significantly faster during smoking relative to Camel Snus use. Overall, the results of this study show that use of Camel Snus relative to smoking results in significantly lower systemic nicotine exposure and maximum concentration, and longer time to maximum concentration, and are in accordance with results from study CSD0914.

Questionnaire data collected concurrently over the course of the trial was used to assess the ability of Camel Snus to relieve the participants' urge to smoke, and this was compared to the reductions in urge to smoke provided by a single cigarette of the participants' preferred brand. These findings are presented in Figure 20 below.

Figure 20. Attenuation of Urge to Smoke in Smokers Using a Single Pouch of Camel Snus or Smoking a Single Cigarette (CSD1101)



Smoking one of their usual brand cigarettes was more effective in relieving the urge to smoke than was a single pouch of Camel Snus in these smoking participants, but both

products produced statistically-significant reductions in smoking urge ($p < 0.05$) within five minutes of initiating their use. Camel Snus provided statistically-significant relief of smoking urges through the 120-minute time point, whereas the single cigarette suppressed smoking urges through the 180-minute time point after product usage began, as shown in Figure 21, below.

Figure 21. Persistence of Statistically-significant Reduction in Urge to Smoke by a Single Pouch of Camel Snus or a Single Cigarette (CSD1101)

Time Point (min)	5	15	30	45	60	90	120	150	180
Usual Brand Cigarette									
Camel Snus									
Figure Key									
	Statistically significant decrease in "Urge to Smoke" from pre-product use rating ($p < 0.05$)								
	No statistically significant decrease in "Urge to Smoke" from pre-product use rating								

3.6.2.3 Additional Nicotine, Total Nicotine Equivalents, Cotinine, Mouth Level Exposure Studies

Of less importance than acute nicotine absorption pharmacokinetics to the assessment of abuse potential are more distal measurements of nicotine, total nicotine equivalents, and cotinine levels in plasma/serum, saliva, urine, or saliva over longer periods of time. Such sampling only provides indirect information regarding how reinforcing the product is on its own or relative to a comparator given the lag in time between product use and sampling. However, these outcomes can be important for verifying tobacco use or abstinence, or assessing differences between comparators or over time to compare levels of nicotine exposure relative to a comparator, or to assess changes over time (e.g., change from baseline). As noted below, there can be great variability over time regarding the pharmacokinetics of nicotine following absorption, which is highly variable not only between individuals, but variable based upon the route of nicotine administration and absorption (i.e., inhalation, buccal, transdermal, ingestion, etc.). Specifically, after nicotine is absorbed into systemic circulation, it is rapidly and extensively distributed to body tissues such as brain, muscle, liver, spleen, kidney, and lungs, and is subsequently slowly released into circulation, metabolized, and excreted over time. The plasma half-life of nicotine is only about two hours, however, the terminal elimination half-time as measured by metabolite excretion in urine averages 11 hours due to slow release from tissues (Jacob et al., 1999; Benowitz et al., 2009). Based on this relatively slow elimination from the body, nicotine, cotinine (which has an elimination half-time of about 16 hours), and other metabolites persist for many hours

after tobacco use, and fluctuate based on daily and repeated use patterns. Additionally, nicotine metabolism and excretion is highly variable between individuals, and is dependent on a number of factors such as sex, genetics, race/ethnicity, diet, meals, age, kidney and liver disease, and other medications (Benowitz et al., 2009). In short, nicotine pharmacokinetic outcomes (other than acute absorption levels and rates of absorption, as discussed above) are useful for determining relative tobacco/nicotine exposure levels across time, but are highly variable and less useful for predicting reinforcing effects or abuse liability of tobacco products. Consequently, outcomes of this sort with regards to Camel Snus consumption have been described below, but less extensively compared to nicotine absorption pharmacokinetics.

Nicotine and Total Nicotine Equivalents. Of published studies, one measured nicotine in plasma and total nicotine equivalents (T-NicEq; the sum of nicotine plus multiple metabolites) in urine (Krautter et al., 2015), and three studies measured T-NicEq (Ogden et al., 2015 a, b, c; Round et al., 2015; Hatsukami et al., 2016a). Krautter et al. (2015) conducted a study of smokers who either used Camel Snus while cutting back smoking by 60%, used Camel Snus exclusively, or abstained from all tobacco products for five days, and found that concurrent[1] use was associated with a 46% reduction in plasma nicotine, exclusive Camel Snus use with a 61.9% reduction, and abstinence with a 97.4% reduction. Across groups, mean T-NicEq values at day five were as follows: 15.40 ng/ml (concurrent use), 11.25 ng/ml (Camel Snus), and 0.56 ng/ml (abstinence) (note that significant differences were only observed compared to the baseline and the abstinence group; concurrent use and Camel Snus only did not differ significantly). Similarly, at day five, all groups had statistically significant ($p < 0.05$) reductions in urinary T-NicEq compared to baseline, with a greater, but non-statistically different, reduction observed in the Camel Snus group (47.6%) relative to the concurrent use group (31.8%). A separate study assessed T-NicEq levels at baseline and after four weeks in a randomized study of smokers assigned to use either Camel Snus or 4 mg nicotine gum for 12 weeks, with instructions to completely abstain from smoking (Hatsukami et al., 2016a). However, both groups contained a large number of participants that continued to smoke, and thus were actually concurrent users. For Camel Snus users, at week four there were greater reductions from baseline in mean T-NicEq levels for CO-verified study product-only users (59.5 to 35.6 nmol/ml) compared to concurrent users (66.2 to 55.7 nmol/ml), although statistical results were not reported. Similar results were observed for the NRT group, in which single product users had

[1] Note the terms “concurrent” or “co-occurring” were used in place of the term “dual-use” to describe use of two or more products over a specified time frame (e.g., within day, past month, or past year). As yet, however, there is no consensus on a consistent definition of such “dual use”. For the present purposes, the term refers to use of both cigarettes and smokeless tobacco or of cigarettes and a novel tobacco product, either product being used daily or not daily.” (WHO TobReg, 2015, page 80), as noted elsewhere in this review.

greater T-NicEq reductions (63.6 to 36.0 nmol/ml) compared to concurrent users (65.0 to 51.2 nmol/ml). Ogden et al. (2015 a, b, c) conducted a 24-week study in which smokers were randomized to Camel Snus, tobacco-heating cigarettes, or ultra-low machine yield tobacco-burning cigarettes. Results at 12 and 24 weeks showed that T-NicEq levels for Camel Snus participants were reduced about 9% from baseline, but this was a non-statistically significant change. However, the investigators noted that compliance with the assigned study product was lowest in the Camel Snus group, indicating that the T-NicEq results for Camel Snus participants were more likely representative of concurrent/"dual" (snus and smoking) or poly-tobacco product use rather than complete switching. Lastly, Round et al. (2015) reported on a series of studies conducted to evaluate changes in biomarkers of tobacco exposure and subjective product ratings in smokers switched to concurrent use of cigarettes and Camel Snus, with the goal of reducing cigarettes per day by 75% during the last week. By study end, there was a non-significant, 16% reduction in T-NicEq levels in the Camel Snus concurrent use group relative to baseline.

Additionally, unpublished RJRT studies CSD1010 and CSD0904 also examined similar outcomes. In one randomized study comparing smoking cessation rates with Camel Snus (with or without relative risk information provided) and nicotine lozenges (CSD1010), participants were monitored for up to 12 months. Mean plasma nicotine and cotinine concentrations generally declined progressively for the Camel Snus group with health risk information, as well as for the NRT group. However, for the Camel Snus group without health risk information, after an initial decline, from Month 3 onward mean plasma nicotine increased while mean plasma cotinine remained relatively constant. Continued study product usage in the Camel Snus group was higher than in the NRT group, and may have led to increased nicotine/cotinine concentrations in those groups relative to the NRT users. A separate post-market surveillance study (CSD0904) included confinement to a clinical research unit for approximately 24 hours (Days 1 and 2) and participants completed Day 2 study procedures during a tobacco product abstention period, including collection of urine, blood, buccal cell, and saliva samples for analysis of biomarkers of tobacco exposure and biomarkers of effect. For Camel Snus users, no statistically significant differences in exposure to nicotine were observed versus exclusive cigarette smokers. Measures of nicotine exposure were highest in the groups who used conventional moist snuff, either exclusively or concurrently with cigarettes, compared to the other groups who used tobacco products and to those who used no tobacco products. These data suggest that the exclusive and concurrent users of moist snuff have a greater exposure to nicotine (and its metabolites, as described below) than Camel Snus Users (exclusive and concurrent), exclusive cigarette smokers, and non-smokers.

Cotinine (Urinary). Four published studies examined cotinine levels in urine (Blank et al., 2010; Kotlyar et al., 2011; Burris et al., 2014; Hatsukami et al., 2016a). An additional publication (Hatsukami et al., 2011) indicated that urinary cotinine was

analyzed as part of the study's methodology, but the results were not reported. Blank et al. (2010) conducted a randomized, crossover study in smokers consisting of four, five-day conditions in which they smoked own brand cigarettes, used Camel Snus, used Ariva (dissolvable tobacco), or abstained from all tobacco product use. Results showed that on Day 3, urinary cotinine values for Camel Snus were 58% lower than smoking own brand ($p < 0.05$), and remained lower through Day 5, although not statistically different. Kotlyar et al. (2011) found that in smokers switched to Camel Snus, NRT products (4 mg gum or lozenge), or Taboka (alternative smokeless tobacco product no longer marketed) for four weeks, urinary cotinine levels for all groups were significantly ($p < 0.05$) reduced compared to baseline, with no differences observed between treatments. Burris et al. (2014) conducted a two-week study in three groups of participants: one that continued smoking and two that used snus with cigarettes (i.e., concurrent use) to either "cope" with smoking restrictions or "reduce" use of cigarettes. There were no statistical differences in urinary cotinine between the groups at one or two weeks, but at week two, one of the concurrent use groups (snus to "reduce") had slightly, but not statistically significantly, higher urine cotinine levels compared to cigarette use only. Similar to the reductions noted above for T-NicEq, Hatsukami et al. (2016a) also assessed urine cotinine levels, and found that cotinine was significantly reduced for both the Camel Snus and NRT groups compared to baseline ($p < 0.05$), but with no difference between treatment groups. In addition, Camel Snus was associated with comparable levels of urine cotinine (750 to 1,000 ng/ml) when compared to other alternative tobacco and nicotine products such as Ariva tablets, Taboka snus, and NRT (Blank et al., 2010; Kotlyar et al., 2011; Hatsukami et al., 2016a).

Cotinine (Plasma or Serum). Three published studies examined plasma or serum cotinine levels among Camel Snus users (Krautter et al., 2015; Ogden et al., 2015 a, b, c; Round et al., 2015). Similar to the findings noted above for plasma nicotine and total urinary NicEq, Krautter et al. (2015) also measured plasma cotinine and found that after five days of use, cotinine decreased by 36.2% for concurrent smoking and Camel Snus use, 51.8% for Camel Snus only, and 98.8% for abstinence only. There were no significant differences between concurrent use and Camel Snus use, but significant changes were observed compared to baseline and the abstinence group (these data are similar to those found for plasma nicotine and total urinary NicEq levels in the same study, as noted above). In addition to measuring T-NicEq as described above, Ogden et al. (2015 a, b, c) also measured serum cotinine in their 24-week study of smokers switched to Camel Snus or one of two comparator tobacco products. For Camel Snus, at week 12 there were no significant differences in cotinine levels compared to baseline, but there was a statistically significant increase (about 32%) in cotinine levels at week 24. As mentioned above, these results should be interpreted with caution, because the authors noted a very high percentage of participants in the Camel Snus group that continued to smoke or use other tobacco products during the study period. As noted above, Round et al. (2015) conducted a series of studies to evaluate concurrent use of cigarettes and either Camel Snus or two dissolvable tobacco products, and serum

cotinine levels were reduced at study end relative to baseline by 9.5%, but this was a non-statistically significant change.

In addition, two unpublished studies (CSD1010 and CSD0904) examined cotinine outcomes and they were also described immediately above with regard to nicotine-related outcomes. Overall, one study found that, similar to nicotine levels, mean plasma cotinine concentrations generally declined progressively for the Camel Snus group with health risk information, as well as for the NRT group, while levels for the Camel Snus group without health risk remained relatively constant (CSD1010). Continued study product usage in the Camel Snus groups was higher than in the NRT group, and may have led to increased nicotine/cotinine concentrations in those groups relative to the NRT users. In addition, study CSD904 (method also described immediately above) found that Moist Snuff Users had serum unconjugated cotinine (COT-U) concentrations significantly higher than Cigarette Smokers and Non-Tobacco Users, however, in comparison, COT-U levels in Camel Snus Users were similar.

Mouth-Level Exposure. Much like the use of nicotine metabolite measurements collected after chronic or repeated product use, the use of mouth-level exposure (MLE) measures is informative about relative exposure to nicotine from tobacco products, but is an indirect measure of abuse liability. MLE is an estimation of the exposure to nicotine or other constituents from smoked cigarettes or snus pouches that is obtained by analysis of the portion of the product that remains after use (i.e., the cigarette butt after smoking or the used snus pouch after Camel Snus use). MLE provides another way to characterize the relative amounts of nicotine obtained between comparator products under actual conditions of use. Mouth-level exposure to tar and other constituents from cigarettes (also known as yield-in-use) is measured by analyzing filters from smoked cigarette butts to quantify smoke constituents trapped in the filter, and then correlating those amounts to the amount of smoke passing through the filter using calibration curves derived from machine-smoked cigarettes. Measuring MLE for snus products (also referred to as a snus-after-use [SAU] measurement) involves analyzing used pouches to quantify the remaining constituents, and comparing those values to the quantity of those constituents in unused pouches. MLE (or SAU) is determined by difference. As stated by Caraway and Chen (2013): "*Because expectoration is not typical when using snus, MLE is expected to provide an estimate of maximum potential exposure at the mouth level*." In other words, MLE provides an estimation of the level of nicotine or other constituents (including toxicants such as TSNAs) that have been removed from the product at the mouth level by the user and are available for transmucosal absorption, whereas it does not describe or measure the kinetics involved with the absorption or uptake of those constituents into systemic circulation.

Research has shown that the amount of nicotine extracted by the user and absorbed systemically from NRT gum products is much lower than the nicotine content of the gum (Benowitz, Jacob, & Savanapridi, 1987). The interplay between incomplete nicotine

extraction and slow absorption is likely responsible for the low abuse liability observed for NRT products, as described elsewhere in this report. In a similar fashion, a substantial portion of nicotine may remain in a product such as snus depending on many factors including how long it remains in the mouth, whether it is manipulated by the user (e.g., moved around with the tongue), amount of saliva generated, and so forth.

Three published studies from the literature (Caraway & Chen, 2013; Krautter et al., 2015; Round et al., 2015) and two unpublished studies from RJRT (CSD0914 and CSD0904) that investigated the effects of exclusive and concurrent (or “dual”) Camel Snus use on biomarkers of nicotine and toxicant exposure have included nicotine MLE outcome measures. Note that Ogden et al. (2015 a, b, c) only measured MLE in smokers switched to ultra-low machine yield tobacco-burning cigarettes and thus they did not measure this outcome in Camel Snus users. Relevant details from those studies are summarized below in Table 5. A fourth published study (Li et al., 2013) used an in vitro, model mouth system to investigate nicotine extraction from Camel Snus and other moist snuff products, but is not summarized in Table 5 because it did not involve human use of the product.

Table 5. Summary of Mouth-level Exposure to Nicotine when using Camel Snus

Study Designation or Publication	Study Design	Product Use Condition	Nicotine MLE (mg/pouch)[a]	% Nicotine Removed From Pouch[b]
Caraway and Chen, 2013	Cross-sectional	Camel Snus	2.8 (1.7)	39.2 (23.0)
Krautter et al., 2015	Switching	Camel Snus[c]	2.7 (1.2)	39.7
Krautter et al., 2015	Switching	Camel Snus + Cigarettes[c]	2.7 (1.3)	39.3
Ogden et al., 2015	Switching	Camel Snus + Cigarettes[g]	1.8 (1.1)	32.4 (20.7)
Round et al., 2015	Switching	Camel Snus + Cigarettes	1.6 (1.1)	22.2 (14.7)
CSD0904	Cross-sectional	Camel Snus[d]	1.9 (1.6)	38.5 (30.9)
CSD0904	Cross-sectional	Camel Snus + Cigarettes[d]	1.1 (1.7)	21.3 (33.7)
CSD0904	Cross-sectional	Camel Snus[e]	1.8 (1.6)	35.7 (31.7)
CSD0904	Cross-sectional	Camel Snus + Cigarettes[e]	1.0 (1.5)	20.0 (28.1)
CSD0914	Single Use[f]	Camel Snus	2.3 (1.6)	31.7 (22.8)

[a] Mean (standard deviation); [b] Mean (standard deviation). When standard deviation is not shown, the mean value was calculated from means of mouth-level nicotine and nicotine remaining in used Camel Snus pouches; [c] Day 5 results; [d] Pre-clinic use; [e] In-clinic use; [f] After overnight abstinence; [g] 24-week results

3.6.3 Discussion and Conclusions

In sum, the above findings suggest that on an acute basis, nicotine delivery and venous blood nicotine levels from Camel Snus are substantially lower and slower compared to peak levels from traditional cigarettes. Specifically, on average a single administration of Camel Snus typically produced a C_{max} plasma nicotine boost of about 5 ng/ml, with the T_{max} occurring at about 15-30 minutes after placement of the product in the mouth, whereas after smoking a cigarette these values were approximately 15-20 ng/ml and five minutes. These findings are important for the assessment of abuse liability, because higher peak levels of systemic delivery, and faster attainment of that peak level has been shown to increase the abuse liability of a chemical entity. This supports the conclusion that the abuse liability of Camel Snus is significantly and substantially lower than traditional cigarette smoking. The plasma nicotine boosts and speed of absorption produced by Camel Snus were also lower and slower than has been observed for some oral smokeless tobacco products, particularly the traditional moist snuff products having high pH and high unionized nicotine content such as Copenhagen and Skoal (Fant et al.,1999).

On the other hand, from the perspective of Camel Snus's potential to serve to partially or fully replace nicotine derived by cigarette smoking, the results indicate that Camel Snus somewhat exceeds what is typical of 2 mg oral NRT medications and the FDA approved nicotine inhaler. Specifically, the pharmacokinetics of Camel Snus reveal a profile of more rapid absorption and with higher peak levels than have been reported for nicotine gum or lozenge, or the oral dissolvable tobacco product Ariva. Although of lesser relevance to the assessment of abuse liability, it also appears that exposure to nicotine from repeated, chronic use of Camel Snus is lower than that from chronic smoking or traditional moist snuff usage. Several studies from independent investigators, as well as those from RJRT, reported that measures of nicotine exposure, including serum nicotine, urinary total nicotine equivalents, cotinine (urinary, salivary, and plasma/serum), and MLE are generally lower in exclusive Camel Snus users, or similar to levels for smokers (depending on the measure), but rarely higher. Moist snuff users (exclusive use or concurrently with smoking) tend to have the highest levels of nicotine exposure measures. Interestingly, concurrent use of Camel Snus and cigarettes does not tend to increase these nicotine exposure measures, and in some studies, reduced them (e.g., Krautter et al., 2015; Round et al. 2015; CSD0914). In addition, investigations that included nicotine MLE measures showed that most Camel Snus users, even regular, everyday users, fail to extract large fractions of nicotine from the product with each use, and leave a considerable portion (often more than 60%) of nicotine in used pouches, similar to results found previously with NRT products and with Swedish snus. Whether this reflects nicotine titration to desired levels by users or other non-nicotine factors such as insufficient experience with the product or depleted flavoring after a certain amount of use is not known.

These findings, in combination with the nicotine absorption pharmacokinetics (low and slow), already discussed, are important because they further suggest that Camel Snus

is closer to NRT in these parameters than high unionized nicotine-containing traditional moist snuff, which can provide high nicotine MLE levels per use, and deliver nicotine very rapidly into systemic circulation (e.g., Fant et al., 1999). It should be noted that most of the studies reviewed here involved smokers who were instructed to reduce use of, or switch from their current own brand cigarette to Camel Snus or other test products, and that these were not highly experienced Camel Snus users. It is plausible that experienced Camel Snus users would extract larger amounts of nicotine and thereby produce higher plasma nicotine levels. However, in one unpublished RJRT cross-sectional study (CSD0904) of natural adopters of Camel Snus, MLE values were lower compared to other studies that examined switching behavior. Furthermore, the motivations of the participants may have varied considerably and influenced their nicotine intake. For example, some studies enrolled smokers who were interested in quitting, while others enrolled participants with no intention of quitting. All multi-day, repeat use studies reviewed except one (Krautter et al., 2015) consisted of outpatient testing, in which participants were given their study product supply to consume at home during their normal daily lives with study site visits scheduled at different time points for assessments. The intervention periods studied typically lasted from five days to several weeks (2, 4, 12, or 24), with one RJRT study (CSD1010) following participants for up to 12 months. Although this type of study design may provide a more “real world” set of results, it also makes interpreting the effects of daily, repeated, exclusive Camel Snus use difficult, given the very high likelihood that concurrent use with cigarettes was occurring in many participants, and was documented in several reports. Regardless, the data are encouraging in that very few instances of increased levels of nicotine exposure were reported relative to exclusive smoking, and in most cases the reported levels stayed the same or were reduced. Importantly, although not necessarily related to abuse liability, any net decrease in cigarettes smoked, even without affecting total daily nicotine exposure, would lead to desirable decreases in exposure to smoke-related toxicants, and may be one step closer to eventual smoking cessation.

Collectively, the results from studies reviewed in this section (and further reviewed in Section 3.7) suggest that Camel Snus can deliver sufficient nicotine per pouch used, and per day, to substitute for or replace cigarettes. Systemic, urinary, and mouth-level nicotine exposure measures do not suggest that exclusive Camel Snus use or concurrent use with traditional cigarettes increases nicotine exposure; in fact, in these studies, Camel Snus use often led to lower nicotine exposure levels in persons who used Camel Snus and smoked concurrently. Altogether, these pharmacokinetic parameters are more in line with NRT products (which have been shown to have low abuse liability), than with cigarettes or moist snuff, suggesting that while Camel Snus does have abuse liability, it is not very substantial relative to the most commonly used tobacco products.

3.7 Human Studies of Camel Snus

The focus of this section is on published and unpublished laboratory-based and clinical trial studies that have examined Camel Snus in humans (see Appendix E for an

overview of studies discussed). Outcomes reviewed in this section include: self-administration/usage topography, subjective ratings, subjective and physiological withdrawal, behavioral economics, reducing or stopping smoking, and reducing or stopping smokeless tobacco use. Key Camel Snus studies included for review include: Blank & Eissenberg, 2010; et al., 2010; Hatsukami et al., 2011; Kotlyar et al., 2011; O'Connor et al., 2011; Caraway & Chen, 2013; Burris et al., 2014; O'Connor, June, Bansal-Travers et al., 2014; Rousu et al., 2014; Hatsukami et al., 2016a; Krautter et al., 2015; Ogden et al., 2015 a, b, c; Quisenberry et al., 2015; Round et al., 2015; Carpenter et al., 2016; Meier et al., 2016a). In addition, four unpublished studies conducted by RJRT (CSD0904, CSD0914, CSD1010, and CSD1101) were supplemental to the review of published human studies.

3.7.1 Self-administration and Topography

"Product use" (e.g., amount of snus use and duration of use) was measured across most studies that addressed self-administration/topography of Camel Snus (Blank & Eissenberg, 2010; Hatsukami et al., 2011; Kotlyar et al., 2011; O'Connor et al., 2011; Caraway & Chen, 2013; Burris et al., 2014; Hatsukami et al., 2016a; Krautter et al., 2015; Meier et al., 2016a; Ogden et al., 2015 a, b, c; Round et al., 2015). In addition, most studies included regular smokers, except for one study which examined regular users of Camel Snus that sometimes smoked (Caraway & Chen, 2013).

3.7.1.1 Key Published Studies

Camel Snus pouch use per day ranged from an average of approximately five to eight pouches across several studies (Hatsukami et al., 2011; Kotlyar et al., 2011; O'Connor et al., 2011; Caraway & Chen, 2013; Burris et al., 2014; Krautter et al., 2015; Round et al., 2015). However, some studies reported less snus use when participants were also smoking cigarettes (Caraway & Chen, 2013; Krautter et al., 2015; Round et al., 2015). For example, in one study, natural adopters of Camel Snus (i.e., individuals who self-reported use of Camel Snus for at least three months prior to study participation) used a mean of 5.4 pouches per day when using snus exclusively and an average of 2.8 pouches per day during concurrent use with cigarettes (Caraway & Chen, 2013). In contrast, some studies reported higher daily levels of Camel Snus consumption (e.g., between 10 to 12 pouches per day; Blank & Eissenberg, 2010; Ogden et al., 2015 a, b, c). Differences for this variability in product use are not clear, but regardless, estimates across Camel Snus studies correspond to those examining smokeless tobacco use for which 6 - 10 product uses per day are most commonly reported (Hatsukami and Severson, 1999).

Other studies have compared use of Camel Snus to other nicotine-containing products and found that a similar number of units for each product were consumed daily or weekly (*p*s >0.05; Hatsukami et al., 2011; Kotlyar et al., 2011; Hatsukami et al., 2016a). For example, one randomized controlled trial (N=130) of abstinent smokers found similar average units of product used per day for Camel Snus (6.9 pouches), nicotine gum/lozenge (7.4 pieces) and Taboka (5.8 pouches) (Kotlyar et al., 2011). Similarly, in

a separate study, use of Camel Snus and 4 mg nicotine gum were similar after 6 and 12 weeks of consumption (Hatsukami et al., 2016a; see figure 2A in publication). However, a follow-up analysis on the latter study did find that men self-administered more Camel Snus compared to nicotine gum and vice versa for women suggesting potential gender differences in preference for these products (Allen et al., 2016; see figure 1A in publication).

Only one study of those reviewed examined more detailed self-administration outcomes associated with Camel Snus use by participants (N=53) who were regular Camel Snus users ("natural adopters"; Caraway & Chen, 2013). Overall, the majority of participants reported that they only used one snus pouch at a time (47 participants or 88.7%) with use episodes lasting for 0 to 30 minutes (39 participants or 73.6%). In addition, approximately half of participants reported moving the pouch around in their mouth during use (50.9%) with the other half reporting that they kept the pouch in the same location.

Of note is that two studies included for review examined continued use of product after the end of an intervention period and found that participants were more likely to continue use of Camel Snus compared to Ariva and Marlboro snus in one study ($p < 0.05$) (Hatsukami et al., 2011) and compared to 4 mg nicotine gum in another study ($p < 0.05$) (Hatsukami et al., 2016a). In addition, a third study examined use of Camel Snus provided via free samples to smokers who were not motivated to quit smoking (Meier et al., 2016a). While that study did not examine the exact number of pouches used per day or week, it did find that of the 543 participants, 263, or 48.4%, became persistent users of Camel Snus during the 6-week study (defined as using snus one or more times during the final week in the study and one or more times during any other week in the sampling period). In contrast a smaller portion of participants were either never users (n=100, 18.4%) or experimenters only (n=180; 33.1%).

3.7.1.2 Unpublished RJRT Studies

Three unpublished studies conducted by RJRT examined outcomes related to Camel Snus self-administration (CSD0914, CSD0904, CSD1010). In one acute, laboratory-based study smokers (N=15) used one pouch of Camel Snus during testing (CSD0914). Mean duration of Camel Snus use for this study was 21.1 minutes. However, participants were instructed to keep the pouch in their mouth for 15 to 30 minutes, thus duration of use was impacted by study instructions. In a separate randomized controlled trial of smoking cessation and Camel Snus (N=649) that followed participants up to 12 months, a similar average number of snus pouches used per day was reported when participants used Camel Snus exclusively (5.1 pouches) at week 24-25 and while smoking (5.5 pouches) at the same time point (CSD1010). Similar amounts of product were used during exclusive Camel Snus use relative to concurrent or "dual use" with cigarettes among natural adopters of Camel Snus in study CSD0904.

3.7.2 Subjective Ratings

3.7.2.1 Key Published Studies

In one laboratory-based study of abstinent smokers, Camel Snus increased ratings of "Was the product pleasant?" after use, but ratings on the same measure were not changed by the nicotine lozenge (2 mg) or sham smoking (Cobb et al., 2010), thus the sensitivity of the measure in this study was not clear. In contrast, a randomized controlled trial (N=391) found that ratings of "satisfaction" and "psychological reward" were higher for nicotine gum (4 mg) compared to Camel Snus (Hatsukami et al., 2016a). Similarly, in another study that measured preference for products after sampling, a larger proportion of participants preferred a nicotine lozenge (4 mg; 45%) compared to Camel Snus (14%) (O'Connor et al., 2011). Varied findings across studies have also been reported when comparing the effects of Camel Snus and Ariva dissolvable tobacco tablets. In a laboratory-based study, ratings of pleasantness were significantly greater ($p < 0.05$) for Ariva compared to Camel Snus (Blank & Eissenberg, 2010), whereas a separate randomized controlled trial found that ratings of satisfaction were significantly greater ($p < 0.01$) for Camel Snus compared to Ariva (Hatsukami et al., 2011). Overall, it appears that Camel Snus is associated with subjective ratings such as satisfaction and attractiveness and sometimes such ratings are greater than other alternative nicotine products, but not greater than own brand traditional cigarette use (e.g., Blank & Eissenberg, 2010; Cobb et al., 2010; Burris et al., 2014; Hatsukami et al., 2016a; Krautter et al., 2015).

Ratings of negative subjective effects of smokeless tobacco use, including snus, are generally moderate and similar to those expected with first time use of any nicotine-containing product, e.g. nausea (Burris et al., 2014). However, some smokers not familiar with smokeless tobacco products may find the delivery of free nicotine in the mouth to be unpleasant. For example, in one study a higher percentage of participants believed that Camel Snus contained the most nicotine compared to three other products tested (Marlboro Snus, Stonewall dissolvable tobacco tablets, and 4 mg nicotine lozenges), and also rated Camel Snus as the second least liked product (O'Connor et al., 2011). In another study that involved sampling of smokeless tobacco products and then choosing one to use for two weeks to replace cigarettes, no participant chose the product with the highest nicotine content (General Snus), although equal numbers chose lower nicotine products, including Camel Snus (Hatsukami et al., 2011).

Adverse event reporting was similar between Camel Snus and other nicotine products including nicotine gum (e.g., dizziness, nausea) in clinical trials (Burris et al., 2014; Hatsukami et al., 2016a; Krautter et al., 2015; Ogden et al., 2015 a, b, c). However, excessive salivation and mouth sores were more likely for individuals that used snus in one study, whereas fewer headaches were reported for Camel Snus users compared to nicotine gum users in the same study (Hatsukami et al., 2016a).

3.7.2.2 Unpublished RJRT Studies

None of the unpublished RJRT studies reviewed for this report examined the direct subjective ratings such as satisfaction or pleasure (CSD0904, CSD0914, CSD1010, CSD1101). However, all studies collected data on adverse events of which none were determined to be serious and all were mild in nature (e.g., nausea, throat irritation, headache).

3.7.3 Subjective and Physiological Withdrawal

3.7.3.1 Key Published Studies

Several studies have examined the impact of Camel Snus on the symptoms or signs of nicotine/tobacco withdrawal among regular smokers (e.g., Blank & Eissenberg, 2010; Cobb et al., 2010; Kotlyar et al., 2011; Hatsukami et al., 2011; Burris et al., 2014; Hatsukami et al., 2016a; Krautter et al., 2015). Camel Snus was not as effective at ameliorating subjective ratings of withdrawal compared to smoking in several studies (e.g., Blank & Eissenberg, 2010; Cobb et al., 2010; Kotlyar et al., 2011). However, it did reduce ratings of craving and urge to smoke across time in some studies (Cobb et al., 2010; Krautter et al., 2015; Burris et al., 2014). In addition, some studies found evidence that Camel Snus relieved withdrawal symptoms more effectively than Marlboro snus (Cobb et al., 2010), sham smoking (Cobb et al., 2010), and Ariva tobacco tablets (Cobb et al., 2010; Hatsukami et al., 2011). Comparable craving and withdrawal symptom suppression was reported for Camel Snus and nicotine gum/lozenge or Taboka in three studies (Cobb et al., 2010; Kotlyar et al., 2011; Hatsukami et al., 2016a).

Only one study was identified that examined a physiological sign of tobacco withdrawal among abstinent smokers using Camel Snus (Cobb et al., 2010). This laboratory-based study found that Camel Snus use increased heart rate from 67.8 beats per minute (bpm) to 72.0 bpm 15 minutes after first product administration among abstinent smokers. While this increase was statistically significant ($p < 0.05$), it was much smaller in magnitude compared to the increase in heart rate observed after usual brand cigarette smoking (67.8 bpm to 82.3 bpm minutes after smoking). In contrast, significant increases in heart rate were not seen with use of Marlboro snus, Ariva tobacco tablet, or 2 mg nicotine lozenge in the same study.

Lastly, none of the studies reviewed examined withdrawal among regular users of Camel Snus. Previous research examining smokeless tobacco use, but not Camel Snus specifically, suggests users do experience withdrawal similar to that of smokers and report similar levels of dependence (Holm et al., 1992; Gire & Eissenberg, 2000; European Commission Directorate-General for Health and Consumers, 2008). Further, a review of the literature has determined that withdrawal from smokeless tobacco products is ameliorated by resumption of tobacco use and nicotine administration (Ebbert et al., 2015).

3.7.3.2 Unpublished RJRT Studies

Two unpublished RJRT studies measured subjective withdrawal outcomes across time among smokers who used both a Camel Snus pouch and smoked an own brand cigarette (CSD0914 and CSD1101).

As noted previously in this review (see Pharmacokinetics and Pharmacodynamics section) one study conducted by RJRT (CSD0914) evaluated serum nicotine uptake and tobacco abstinence symptoms over a three-hour period among 15 smokers following use of Camel Snus (0.6 g pouch size) or one of four other smokeless tobacco products (not discussed herein). Participants rated “Urge to smoke” on a scale ranging from 0 “No Urge” to 5 “Extremely Strong” and findings revealed that smoking one usual brand cigarette was more effective in relieving the urge to smoke than was a single pouch of Camel Snus, but both products produced statistically-significant reductions in smoking urge ($p < 0.05$) within five minutes of initiating their use (see Figures 17 and 18). In addition to Urge to Smoke, the same study (CSD0914) examined ratings of other withdrawal-related symptoms and found significant smoking-related reductions in ratings of anxious, irritable, and restless, while Camel Snus did not significantly alter ratings of these symptoms.

A separate study, CSD1101, described previously in this review (see Pharmacokinetics and Pharmacodynamics), also assessed serum nicotine uptake and tobacco abstinence symptoms among 17 smokers after they smoked a usual brand cigarette and after use of Camel Snus (Frost variety, 600 mg), or three other smokeless tobacco test articles (not discussed herein). Similar to study CSD0914, findings revealed that smoking one usual brand cigarette was more effective in relieving the urge to smoke than was a single pouch of Camel Snus, but both products produced statistically-significant reductions in smoking urge ($p < 0.05$) within five minutes of initiating their use.

3.7.4 Behavioral Economics

3.7.4.1 Key Published Studies

Behavioral economic studies allow researchers to quantify the relative reinforcing value of different nicotine/tobacco products, and Camel Snus has been examined in a subset of such studies (e.g., O'Connor et al., 2011; O'Connor et al., 2014; Rouso et al., 2014; Quisenberry et al., 2015). One study examined current smokers (N=56 across two experiments) using an on-line marketplace called the experimental tobacco marketplace (ETM) which allowed smokers to view pictures, information, and prices for several tobacco products: usual brand [traditional] cigarette, Blu disposable electronic cigarette, Camel Snus (Winterchill), Skoal dip (classic flavor), 4 mg nicotine gum, 4 mg nicotine lozenge, or Swisher Sweet cigarillos (Quisenberry et al., 2015). Smokers were given an account balance based on their weekly tobacco purchases and made purchases for products that they then took home for ad-libitum use. Note that the publication included two identical experiments except that the second experiment did not include cigarillos

(i.e., “little cigars”). A week after obtaining their products, smokers returned to report their use of tobacco/nicotine over the previous week and return unused products.

Both studies revealed that as unit price increased the purchasing of traditional cigarettes decreased. In experiment one, when cigarillos were available in the marketplace, only e-cigarettes functioned as a substitute purchase for traditional cigarettes. However, in experiment two, Camel Snus and e-cigarettes functioned as substitutes for traditional cigarettes ($p < 0.05$). These findings suggest that Camel Snus was less appealing compared to usual brand cigarettes and cigarillos, but when the marketplace was narrowed to exclude cigarillos, Camel Snus was more appealing (i.e., able to substitute for cigarettes) compared to smokeless tobacco products such as dip and/or nicotine replacement products.

A separate, web-based study of 1,062 smokers examined behavioral economic outcomes related to a series of web-based purchase tasks and found that Camel Snus, Camel Dissolvable Tobacco, and nicotine lozenges were weak substitutes for cigarettes (O'Connor et al., 2014). A third study of 67 smokers did not include standard behavioral economic outcomes, but did report that after sampling a variety of nicotine-containing products for one week, and then choosing one preferred product to use for an additional week, smokers were willing to pay a median of $3 for a tin of Camel Snus (and Marlboro Snus) compared to $5 for a pack of nicotine lozenges and $2 for dissolvable tobacco tablets (Stonewall) (O'Connor et al., 2011). Thus, participants were willing to pay more for a pack of nicotine lozenges than Camel Snus suggesting greater reinforcing value. Similar findings were reported in a study of 571 smokers who completed an in-person experimental auction bidding task (Rousu et al., 2014). The task required participants to bid on different nicotine products (Camel Snus, Ariva dissolvable tablets, and Nicorette mini-lozenge), as well as cigarettes, and the bidding provided an estimate of the full price participants were willing to pay for products. Overall mean bids were significantly lower ($P<0.05$) for Camel Snus ($1.26) compared to Ariva ($1.56), Nicorette ($2.09), or Marlboro cigarettes ($4.12). These differences in bids suggest that demand for Camel Snus was less than other nicotine products and considerably less than traditional cigarettes. A follow-up analysis of the same day (N=258 smokers) found that participants who were willing to try Camel Snus also bid a higher amount for Camel Snus, while willingness to sample Ariva or nicotine lozenge did not predict bidding/demand for products (Rousu et al., 2015).

Overall, the limited number of studies examining Camel Snus and behavioral economic outcomes, as well as the varied methodologies across studies, makes it difficult to draw definitive conclusions on this aspect of abuse liability assessment. Similar to subjective ratings, some studies found less reinforcing value for Camel Snus compared to other smokeless nicotine products (e.g., NRT, Ariva; O’Connor et al., 2011; Rousu et al., 2014). However, one study did suggest that snus could substitute for cigarettes before other products such as dip or nicotine gum if the availability of products and pricing structure were set in a way that offset what appears to be greater reinforcing value of

smoked tobacco (e.g., traditional cigarettes and cigarillos) (Quisenberry et al., 2015). Importantly, as pointed out by O'Connor et al. (2011 & 2014), smokers' interest in alternatives to cigarettes and how much they are willing to pay for such products are linked to their perceptions of those products based on advertising, as well as available scientific and health risk information (e.g., Hatsukami et al., 2016b).

3.7.4.2 Unpublished RJRT Studies

No unpublished RJRT studies have examined behavioral economic outcomes and Camel Snus.

3.7.5 Reducing or Stopping Smoking

3.7.5.1 Key Published Studies

Several studies were identified that examined the relationship between Camel Snus consumption and reducing smoking or complete cessation (Hatsukami et al., 2011; Kotlyar et al., 2011; O'Connor et al., 2011; Burris et al., 2014; Hatsukami et al., 2016a; Krautter et al., 2015; Ogden et al., 2015 a, b, c; Round et al., 2015; Carpenter et al., 2016). Some of these studies included smokers motivated to stop smoking (e.g., Hatsukami et al., 2011; Kotlyar et al., 2011; Hatsukami et al., 2016a). Some studies reported a relationship between Camel Snus consumption and reductions in cigarettes per day (CPD) (Kotlyar et al., 2011; Burris et al., 2014; Ogden et al., 2015 a, b, c). In one study, 57 smokers unmotivated to quit smoking were randomized to one of three groups: instructions to use Camel Snus to cope with smoking restrictions and a two-week supply of Camel Snus, instructions to use Camel Snus to reduce smoking and a two-week supply of Camel Snus, and a no intervention group (Burris et al., 2014). Significantly greater reductions ($p < 0.001$) in CPD were reported by smokers in both Camel Snus groups compared to the control group (percent change in smoking across groups was as follows: -18.4% coping with smoking restrictions; -37.6% reducing smoking; +4.3% no intervention) (Burris et al., 2014). A separate randomized study (N=163 smokers unmotivated to quit smoking) examined the impact of switching to Camel Snus, tobacco-heating cigarettes, or ultra-low machine yield tobacco-burning cigarettes and usual brand on CPD over 24 weeks (Ogden et al., 2015 a, b, c). Results revealed that those assigned to the Camel Snus group reduced CPD over time (values are for intent-to-treat sample): baseline: 17.2 CPD, 12 weeks: 5.8 CPD, and 24 weeks: 8.3 CPD. In contrast, CPD increased over time for the other groups: tobacco heating group smoked 19.4 CPD at baseline and 23.0 CPD at 24 weeks, and tobacco-burning cigarette group smoked 17.0 CPD at baseline and 27.0 CPD at 24 weeks. Lastly, a third randomized study of smokers (N=130) who were interested in quitting smoking examined CPD after using one of three products across four weeks: Camel Snus, NRT products (4 mg gum or lozenge), or Taboka (Kotlyar et al., 2011). Although mean CPD values were not reported in the text (only depicted in a figure), the proportion of participants who smoked three or more CPD was reported for each group. Proportions of individuals who smoked three or more CPD were statistically similar for Camel Snus

(9.1%) and NRT (13.6%) groups, but proportions for both groups were significantly lower than that for the Taboka group (26.8%; $p < 0.05$).

In contrast, some studies found no reductions in cigarette consumption as a function of Camel Snus use. For example, in one study mean CPD was measured over 14 days during use of Ariva, Camel Snus, Marlboro Snus, and Stonewall among 99 smokers motivated to stop smoking (Hatsukami et al., 2011). During study participation, the mean CPD was significantly higher for the Marlboro Snus group compared to those who chose Stonewall or Camel Snus ($p < 0.05$); no difference from Ariva was noted. However, number of CPD increased over time regardless of product type (see Figure 2 in publication).

A separate study comparing Camel Snus and 4 mg nicotine gum found no significant differences across study products in terms of cigarettes smoked per week (daily cigarette consumption was not reported) and there were similar levels of "dual" product and cigarette use for each intervention (e.g., week 12 "dual" use: 52.9% for Camel Snus and 58.2% for nicotine gum) (Hatsukami et al., 2016a). A follow-up analysis of the same study data reported some differences in continuous abstinence at week 12 between men and women (Allen et al., 2016). That is the authors noted that fewer men in the Camel Snus group (5.6%) completely avoided cigarettes compared to men receiving 4 mg nicotine gum (15%). A similar pattern of results was noted for week 26 and for point prevalence estimates; however, none of these findings were significant at the $p < 0.05$ level. Thus, no significant differences were reported for either men or women on abstinence outcomes in this study. Additionally, a study designed to compare smokers' reactions to numerous nicotine-containing products (Camel Snus, Marlboro Snus, Stonewall dissolvable tablets, and 4 mg nicotine lozenges) found that cigarettes smoked was not predicted by product type during a one week use trial and, regardless of product type, mean CPD decreased significantly from 11.8 to 8.7 ($p < 0.05$) over the duration of the week (O'Connor et al., 2011). Lastly, a recent study examined the impact of a "naturalistic sampling period" of Camel Snus among smokers unmotivated to quit (N=1,236) from across the U.S. (Carpenter et al., 2016). Although the main endpoints were quit attempts and abstinence, the study did find that overall participants reduced the number of CPD by 23% from baseline to a 1-year follow-up ($p < 0.05$), but there was no difference between a Camel Snus group and a no intervention control group.

Note that two additional studies were designed to assess controlled switching to Camel Snus allowing for an assessment of "dual" use (i.e., participants were asked to reduce cigarette consumption by a precise amount, but not asked to completely stop smoking) (Krautter et al., 2015; Round et al., 2015). These studies are best equipped to address the impact of dual use on key biomarkers of exposure rather than smoking behavior, but do offer some insight into the effects of Camel Snus on cigarette consumption. In one study, participants confined to a clinical research unit were asked to reduce CPD to a maximum of 40% of their baseline CPD while consuming as many pouches of Camel

Snus as they wanted, and, as might be expected, this resulted in a statistically significant ($p < 0.05$) reduction in the mean number of CPD smoked at day five of the study (7.62 CPD) compared to the number smoked at baseline (19.24 CPD) (Krautter et al., 2015). Round and colleagues (2015) instructed participants to engage in a stepwise reduction in cigarettes smoking over three weeks (e.g., 25% reduction during week two up to a 75% reduction in week four) while participants used Camel Snus. Mean CPD values at baseline were 22.3 CPD and 9.3 CPD by week four in the Camel Snus group ($p < 0.05$).

Four of the studies reviewed measured clinical outcomes including smoking cessation during and after Camel Snus consumption (Hatsukami et al., 2011; Kotlyar et al., 2011; Hatsukami et al., 2016a; Carpenter et al., 2016). Three of these studies assessed smokers who were interested in quitting smoking and all three also included expired air carbon monoxide as a measure of smoking abstinence (Hatsukami et al., 2011; Kotlyar et al., 2011; Hatsukami et al., 2016a). In contrast, due to study design constraints Carpenter and colleagues (2016) only recruited participants who did not want to quit smoking and also did not include expired air CO as a measure of abstinence (Carpenter et al., 2011).

Two of the studies included NRT products as a comparison group and found equivalent abstinence rates between these products and Camel Snus (Kotlyar et al., 2011; Hatsukami et al., 2016a). One study (N=130) reported that 43.1% of Camel Snus users were continuously abstinent from cigarettes from week one to week four of treatment compared to 40.7% of NRT users and 32.7% of Taboka users ($p > 0.05$) (Kotlyar et al., 2011). However, the study authors noted that the study was not powered to assess the impact of interventions on cessation and thus the data were considered preliminary. In a larger randomized controlled trial (N=391) there was no difference between Camel Snus and nicotine gum on abstinence-related outcomes such as continuous cigarette avoidance (i.e., continuous abstinence from week two to the end of treatment at week 12; 5.6% for Camel Snus and 9.7% for nicotine gum; ($p > 0.05$) or on seven-day cigarette avoidance in an intent-to-treat analysis (21.9% for Camel Snus and 24.6% for nicotine gum; ($p > 0.05$) (Hatsukami et al., 2016a).

A third study (N=135) compared Camel Snus to other noncombustible oral tobacco products (not NRT) and found that although products did not differ in rates of abstinence during the last seven days of treatment, product type did significantly predict point-prevalence abstinence ($p < 0.05$) for the first seven days of the follow-up period with the highest abstinence rate reported for Camel Snus (59.3%) compared to Marlboro Snus (30.4%), Stonewall (29.2%), and Ariva (25.0%) (Hatsukami et al., 2011). The same study also found that participants in the Camel Snus group were significantly less likely to relapse compared to the Ariva group ($p < 0.05$), but not the other groups. One additional study employed a unique study design to examine cessation outcomes as they relate to Camel Snus consumption during a six-week sampling period (Carpenter et al., 2016). That study found that although there were no significant differences on

any abstinence outcomes across the 12 months of follow-up between groups ($p > 0.05$), there were significantly fewer quit attempts for the Camel Snus group compared to the no intervention control ($p > 0.05$).

3.7.5.2 Unpublished RJRT Studies

One RJRT unpublished study addressed abstinence/cessation outcomes after use of Camel Snus (CSD1010). Specifically, this randomized control trial examined smokers (N=216) in three intervention groups: Camel Snus plus information regarding the relative risks of smoking compared to smokeless tobacco products, Camel Snus with no relative risk information, or Nicorette 4 mg nicotine lozenge with no relative risk information. There were no significant differences among groups in terms of continuous smoking abstinence following the quit date ($p > 0.05$). Statistical comparisons across groups examining reductions in CPD were not conducted.

3.7.6 Reducing or Stopping Smokeless Tobacco Use

3.7.6.1 Key Published and Unpublished Studies

No studies were located that examined stopping Camel Snus after regular use or switching to Camel Snus instead of using other smokeless tobacco products. As noted in one study of 56 Camel Snus users, concurrent use of Camel Snus with cigarettes is more common than exclusive Camel Snus use (Caraway and Chen, 2013). That study found that most of the "natural adopters" of Camel Snus (49.1%) were "dual" users of Camel Snus and cigarettes, while a minority used Camel Snus only (13.2%). Also, Camel Snus is still a relatively new product as compared to traditional smokeless tobacco products such as moist snuff and chewing tobacco that dominate the U.S. smokeless tobacco market.

The most commonly used traditional smokeless tobacco products have only been studied by a few investigators exploring outcomes such as dependence and cessation. However, a recent Cochrane Review that systematically examined the effects of behavioral and pharmacologic interventions for the treatment of smokeless tobacco use (including snus) found that some evidence-based interventions designed for stopping smoking (Varenicline, nicotine lozenges, behavioral interventions) helped to promote cessation (Ebbert et al., 2015). Overall, the authors concluded that many of the studies were of low quality and more research was needed.

3.7.7 Additional Considerations

3.7.7.1 Methodological variation across studies

Overall, there was a great deal of variation in study designs across published studies of Camel Snus and these variations should be considered when interpreting results. For example, instructions given to participants regarding the use of snus varied. Some studies gave explicit instructions for product use including use of Camel Snus during study participation (e.g., Kotlyar et al., 2011; Burris et al., 2014; Hatsukami et al., 2016a;

Krautter et al., 2015; Round et al., 2015), while others allowed for ad libitum use (e.g., Blank et al., 2010; Cobb et al., 2010; Caraway and Chen, 2013). In addition, the duration of some studies spanned one to two weeks (Blank & Eissenberg, 2010; Burris et al., 2014), while others included much longer assessment periods (e.g., 12 or 24 weeks; Ogden et al., 2015 a, b, c; Hatsukami et al., 2016a). Lastly, the pouch size (0.4 g, 0.6 g, or 1.0 g) and/or flavor of Camel Snus (e.g., Original, Mellow, Winterchill, Frost, or Spice) varied depending on study design and/or participant preference (see Appendix). More details related to concerns on flavors are included immediately below.

3.7.7.2 Camel Snus flavor and pouch size across studies

The possibility exists that differences in pouch size or flavor could expose users to differing levels of nicotine and thus impact a variety of outcomes reviewed above. Of note is that the Camel Snus product changed in 2008 and thus some studies included for review were impacted by this change due to using either an earlier or later version of the product, or both within the same study (e.g., Cobb et al., 2010; Kotlyar et al., 2011). However, study findings suggest equivalent nicotine delivery across varying products (see Appendix F). For example, smokers switched to concurrent use with 0.4 g Camel Snus in one study extracted a mean of 1.8 mg nicotine per pouch (Ogden et al., 2015) and in a separate study smokers switched to concurrent use of 0.6 g Camel Snus extracted a mean of 1.6 mg per pouch (Round et al., 2015). The table in Appendix F compares urinary biomarkers across RJRT studies and one published study (Hatsukami et al., 2016a) and suggests that outcomes, including nicotine equivalent values, were relatively similar across pouch sizes.

With respect to flavor, data from one of the studies already reviewed (Hatsukami et al., 2016a) was closely examined in a separate publication to determine flavor preference among participants (Meier et al., 2016b). The analyses revealed that flavored Camel Snus, as well as medicinal nicotine products, were more often chosen by smokers. For example, with respect to nicotine gum, only one (0.5%) participant chose the original (unflavored) product and 78 (40.0%) chose mint, 69 (35.4%) fruit and 47 (24.1%) the cinnamon-flavored varieties. For those assigned to Camel Snus, 140 (71.4%) chose Winterchill (mint characterizing flavor), 15 (7.7%) Frost (mint characterizing flavor), 9 (4.6%) Mellow (no characterizing flavor), and 32 (16.3%) Robust (no characterizing flavor). These findings highlight the importance of flavor in the rewarding and reinforcing effects of Camel Snus, and differences in the type of flavored products included in studies could alter behavioral outcomes.

3.7.8 Discussion and Conclusions

In sum, the above review of the literature concerning human studies examining Camel Snus allows for some specific conclusions regarding behavior. Generally Camel Snus was self-administered approximately five to eight times per day across studies and this pattern of use is similar to use of other nicotine-containing products such as nicotine gum and lozenge. Overall, as noted, is the observation that Camel Snus is associated with subjective ratings such as satisfaction and attractiveness and sometimes such

ratings are greater than those for other alternative nicotine products, but not greater than own brand traditional cigarette use (e.g., Blank & Eissenberg, 2010; Cobb et al., 2010; Burris et al., 2014; Hatsukami et al., 2016a; Krautter et al., 2015). These findings align with those regarding relative pharmacokinetics of Camel Snus compared to traditional cigarettes (see Section 3.6, Pharmacokinetics and Pharmacodynamics). However, in some studies Camel Snus was found to be more pleasurable or satisfying compared to other tobacco products (e.g., Ariva, Marlboro Snus, Taboka), but less pleasant or more aversive than other oral nicotine products, such as Ariva and NRT, in other studies (Cobb et al., 2010; Blank & Eissenberg, 2010; O'Connor et al., 2011). With respect to smoking behavior, some studies reported that smokers using Camel Snus were able to reduce or stop smoking at least temporarily and effects were comparable to NRT such as nicotine gum in some studies (Kotlyar et al., 2011; Hatsukami et al., 2016a).

In addition, the above findings suggest that use of Camel Snus is related to reductions in cigarettes smoked per day in some studies and could contribute to or aid in stopping smoking completely. Generally, research to date suggests that many smokers opt to use Camel Snus and/or other noncombustible nicotine products concurrently with smoking rather than completely switching, and reductions in smoking while using Camel Snus are on par with currently available NRTs such as nicotine gum (e.g., Hatsukami et al., 2016a). Of note, a recent systematic review of randomized controlled trials of snus products with smoking cessation endpoints (Rutqvist et al., 2013) determined that two trials of snus products that other than Camel Snus met criteria for inclusion, including one conducted in the U.S. (Fagerström, Rutqvist & Hughes, 2012) and one conducted in Serbia (Joksic et al., 2011). A primary finding across both studies was that smoking cessation rates in the last four weeks of both studies were 12.4% for snus and 6.6% for placebo (RR 1.86, 95% CI 1.09-3.18). Although these studies did not assess Camel Snus, they do provide some support for the proposition that snus can function as a smoking cessation intervention.

Of note, and as mentioned previously in this report (see Section 2, Background), is the consideration that a smoker's perception of Camel Snus or other smokeless products has the potential to influence a smoker's willingness/motivation to try or continue using such products in place of cigarettes (Borland et al., 2012; Lund, 2012; Biener et al., 2014, a, b; Delnevo et al., 2014; Rousu et al., 2014; Hatsukami et al., 2016b; Meier et al. 2016a; Rodu et al., 2016; Wackowski et al., 2016). Results from behavioral economics and product sampling studies reviewed above suggest that smokers find smokeless products such as Camel Snus to be much less desirable relative to continued smoking, and this could be due in part to the advertising or scientific information available to consumers about those products (O'Connor et al., 2011; O'Connor et al., 2014; Quisenberry et al., 2015). For products like Camel Snus to become more attractive substitutes for cigarettes, many factors beyond organoleptic qualities and nicotine delivery kinetics must be considered, including the types of information that are available to potential consumers such as factual information

regarding relative health risks between use of combustible and noncombustible products (Kozlowski and Sweanor, 2016). As noted by O'Connor et al. (2014), "in the absence of health-relevant information smokers may not be really motivated to find alternatives to tobacco products." Despite their importance, such factors are beyond the scope of the present abuse liability assessment of Camel Snus.

In conclusion, it is apparent from the spectrum of human studies reviewed here that Camel Snus is likely modestly reinforcing in smokers, but those reinforcing effects are substantially lower than those provided by smoking cigarettes, more in the range of those provided by NRT and other oral nicotine and tobacco products, and likely influenced by varying qualities of these products that can influence their acceptability (e.g., flavor) and amount of nicotine delivered.

3.8 Epidemiology

This review of the epidemiology of Camel Snus use as it relates to abuse liability includes recent data from Federal Surveys on smokeless tobacco use, including snus. In addition, this review will address surveillance data collected by RJRT regarding Camel Snus use in the U.S (RAI Services Company, 2017). Smokeless tobacco use and associated health effects have been increasingly studied since the 1986 report of an Advisory Committee to the Surgeon General that was focused on smokeless tobacco (USDHHS, 1986, 2010, 2014). Generally speaking, the epidemiology of smokeless tobacco use supports the conclusion that the abuse liability of oral smokeless tobacco products is lower than that of cigarettes, as noted in a review of smokeless tobacco (Henningfield et al., 1997). This conclusion was drawn from observations by Henningfield et al. 1997 that included the following: the common observation of "seasonal" use of smokeless tobacco and much less common "seasonal" smoking among traditional cigarette users, less severe withdrawal following abrupt discontinuation of smokeless tobacco use as compared to cigarette smoking, and pharmacokinetic and pharmacodynamic evidence of slower absorption and slower onset of effects with smokeless tobacco as compared to traditional cigarettes.

In addition, epidemiology research has examined the potential use of smokeless tobacco products for smoking cessation (i.e., as a form of nicotine delivery that can provide cigarette smokers with an alternative to cigarettes and to NRT medications; (e.g., Henningfield & Fagerström, 2001; Foulds et al., 2003; Lund et al., 2010; Ramström & Foulds, 2006; Swedish Match, 2014). For example, the development of nicotine gum was initiated by the observations that Swedish submariners and aviators would use smokeless tobacco products in place of cigarettes when they could not smoke, but would revert to cigarette smoking as their preferred form of tobacco when they could smoke (Fagerström et al., 2008; Elam, 2014a, b). Similar observations were made among U.S. soldiers in situations where smoking was not allowed and/or opportunities to smoke are infrequent or not convenient (e.g., Nelson et al., 2009). These observations of smokeless tobacco and smoking behavior are also consistent with studies that have evaluated the efficacy of oral smokeless tobacco products as

smoking cessation aids (as noted in Section 3.7 of this review). That is, some studies evaluating cessation suggest that although smokeless tobacco does not make smoking cessation easy for most cigarette smoker, it does have the potential to reach people who find NRT medications ineffective or unacceptable when trying to abstain from smoking. That is, despite some findings suggesting smokeless tobacco might not be overall more efficacious than FDA-approved products for smoking cessation it likely reaches some people that NRT does not (Tilashalski, Rodu & Cole, 2005; Ramström & Foulds, 2006; Caldwell et al., 2010; Hatsukami et al., 2011; Kotlyar et al., 2011; Scheffels et al., 2012; Hatsukami et al., 2016a).

3.8.1 Tobacco (not specific to Camel Snus) – Federal Survey Data

The results of several national population surveys sponsored by U.S. Federal agencies support the conclusion that at the population level, the overall risk that any use of smokeless tobacco will lead to daily and/or dependent use is lower than observed for cigarettes. Relevant findings from several of these studies are summarized in Appendix G with each providing percentile data from five federally funded surveys: Monitoring the Future Survey (MTF), the National Youth Tobacco Survey (NYTS), the National Survey on Drug Use and Health (NSDUH), the Current Population Survey Tobacco Use Supplement (CPS-TUS), and the National Health Interview Survey (NHIS).

3.8.1.1 Monitoring the Future (MTF).

The MTF data (Appendix G) are from the 2014 public-use dataset for 8th, 10th, and 12th graders. Note that the 2014 MTF annual report (volume 2) for college students and young adults, a public-use dataset, is not available for the follow-up cohort. Please note that at the time this report was prepared the 2015 data were not available. Below are additional details depending on type of tobacco product.

- **Snus** (past year only) was defined using the survey item: "*During the LAST 12 MONTHS, on how many occasions (if any) have you . . . used snus (a small packet of tobacco that is put in the mouth)?*" Snus was not assessed for any other timeframes relevant to this analysis. It is noted that the definition of snus offered to respondents here includes only pouched, and not loose-packed snus products.
- **Chewing tobacco** – not assessed as a separate item on the MTF survey.
- **Dissolvable tobacco** (past year only) was defined using the survey item: "*During the LAST 12 MONTHS, on how many occasions (if any) have you . . . used dissolvable tobacco products (Ariva, Stonewall, Orbs)?*" Dissolvable tobacco was not assessed for any other timeframes relevant to this analysis.
- **Oral smokeless tobacco** – note that MTF defines smokeless tobacco as any of the following: chewing tobacco, snuff, plug, dipping tobacco, snus, dissolvable tobacco. Additional details of consideration related to this category of products on the MTF:

- MTF does not assess past year use of smokeless tobacco.
- Past month use was defined using the survey item: "*How frequently have you taken smokeless tobacco during the past 30 days?*" Any answer other than 'not at all' was coded as past month use.
- Daily use was defined using the same survey item as past month use; however, MTF methodology defines daily use as "about once a day" or more often in the past 30 days (all other response categories are coded as not daily).

- **Cigarettes**
  - MTF does not assess past year use of cigarettes for 8th, 10th, and 12th graders. Past year use is assessed in the follow-up study (older age cohorts); however, no public-use dataset has been released for the follow-up study, nor was a codebook available at the time these data were collected. The estimates provided in this table for college students and young adults come directly from the 2014 MTF Report, Volume 2 (College Students and Adults 19-55).
  - Past month use was defined using the survey item: "*How frequently have you smoked cigarettes during the past 30 days?*" Any answer other than 'not at all' was coded as past month use.
  - Daily use was defined using the same survey item as past month use; however, MTF methodology defines daily use as one or more cigarettes per day in the past 30 days (all other response categories are coded as not daily).

3.8.1.2 National Youth Tobacco Survey (NYTS).

The NYTS data (Appendix G) include data from the 2014 NYS public-use dataset. Please note that at the time this report was prepared the 2015 data were not available. Below are additional details depending on type of tobacco product.

- **Snus** (past month only) was defined using the survey item: "*In the past 30 days, which of the following products have you used on at least one day: **Snus**, such as Camel or Marlboro?*" Those answering affirmatively were coded as having used within the past month. Snus was not assessed for any other timeframes relevant to this analysis.
- **Chewing tobacco**
  - NYTS does not assess past year chewing tobacco use.

- Past month use was assessed using the survey item: "*During the past 30 days, on how many days did you use chewing tobacco, snuff, or dip*?" Any answer other than "0 days" was coded as past month use.
- Daily use was defined using the same survey item as past month use. Those reporting use on "all 30 days" were coded as daily users; all others were coded as non-daily users.

- **Dissolvable tobacco** (past month only) was defined using the survey item: "*In the past 30 days, which of the following products have you used on at least one day: **Dissolvable tobacco products**, such as Ariva, Stonewall, Camel orbs, Camel sticks, or Camel strips?*" Those answering affirmatively were coded as having used within the past month. Dissolvable tobacco was not assessed for any other timeframes relevant to this analysis.
- **Oral smokeless tobacco** (past month only) – respondents affirming use of at least one of snus, chewing tobacco, or dissolvable tobacco products within the past 30 days were coded as past month users of smokeless tobacco. Oral smokeless tobacco cannot be assessed for any other timeframes relevant to this analysis.
- **Cigarettes**
  - Past year use was assessed via the survey item: "*When was the last time you smoked a cigarette, even one or two puffs?*" Answers of "Earlier today," "Not today but sometime during the past 7 days," "Not during the past 7 days but sometime during the past 30 days," "Not during the past 30 days but sometime during the past 6 months," and "Not during the past 6 months but sometime during the past year" were coded as past year use.
  - Past month use was assessed via the survey item: "*During the past 30 days, on how many days did you smoke cigarettes?*" Any answer other than "0 days" was coded as past month use.
  - Daily use was defined using the same survey item as past month use. Those reporting use on "all 30 days" were coded as daily users; all others were coded as non-daily users.

3.8.1.3 National Survey on Drug Use and Health (NSDUH).

The NSDUH data (Appendix G) are based on the 2013 public-use dataset; the 2014 report is available, but did not include all information needed for this analysis at the time this report was prepared. Below are additional details depending on type of tobacco product.

- **Snus** – Please note that the NSDUH confounds snus use with snuff use in one item, although it is specifically referred to as snuff in the survey. For example, the list of examples offered to respondents taking the survey includes Camel Snus and Marlboro Snus.
    - Respondents who reported using 'snuff' within the past year were coded as past year users ("*How long has it been since you last used snuff?*").
    - Respondents who reported using 'snuff' within the past month were coded as past month users ("*How long has it been since you last used snuff?*").
    - Respondents who reported using 'snuff' within the past month ("*How long has it been since you last used snuff?*") and reported using all 30 of the previous 30 days ("*During the past 30 days…on how many days did you use snuff?*") were coded as daily users.
- **Chewing tobacco**
    - Respondents who reported using chewing tobacco within the past year were coded as past year users ("*How long has it been since you last used chewing tobacco?*").
    - Respondents who reported using chewing tobacco within the past month were coded as past month users ("*How long has it been since you last used chewing tobacco?*").
    - Respondents who reported using chewing tobacco within the past month ("*How long has it been since you last used chewing tobacco?*") and reported using all 30 of the previous 30 days ("*During the past 30 days…on how many days did you use chewing tobacco?*") were coded as daily users.
- **Oral smokeless tobacco**
    - Respondents who reported using either 'snuff' or chewing tobacco in the past year were coded as past year users.
    - Respondents who reported using either 'snuff' or chewing tobacco in the past month were coded as past month users.
    - Respondents who reported using either 'snuff' or chewing tobacco daily in the past month were coded as daily users.
- **Cigarettes**
    - Respondents who reported smoking cigarettes within the past year were coded as past year smokers ("*How long has it been since you last smoked part or all of a cigarette?*").

- Respondents who reported smoking cigarettes within the past month were coded as past month smokers ("*How long has it been since you last smoked part or all of a cigarette?*").
- Respondents who reported smoking cigarettes within the past month ("*How long has it been since you last smoked part or all of a cigarette?*") and reported using all 30 of the previous 30 days ("*During the past 30 days… on how many days did you smoke part or all of a cigarette?*") were coded as daily smokers.

3.8.1.4 Current Population Survey (CPS) Tobacco Use Supplement.

CPS data (presented in Tables 3-8) are from the most recently available CPS-TUS public-use dataset at the time this report was written (i.e., 2010 to 2011). Below are additional details depending on type of tobacco product.

- **Snus** – not assessed as a separate item in CPS-TUS.
- **Chewing tobacco** – not assessed as a separate item in CPS-TUS.
- **Dissolvable tobacco** – not assessed as a separate item in CPS-TUS.
- **Oral smokeless tobacco** – note that CPS-TUS lists the following as examples of smokeless tobacco: moist snuff, dip, spit, "chew tobacco", and snus
  - CPS-TUS does not assess past year use of smokeless tobacco.
  - Past month use was defined using the survey item: "*Do you NOW use smokeless tobacco every day, some days or not at all?*" Responses of "Every day" and "Some days" were coded as past month users.
  - Respondents who reported using smokeless tobacco every day in the past month ("*Do you NOW use smokeless tobacco every day, some days or not at all?*") or reported using all 30 of the previous 30 days ("*On how many of the past 30 days did you use smokeless tobacco?*") among those who classified themselves as some day smokers were coded as daily smokeless tobacco users.
- **Cigarettes**
  - CPS-TUS does not assess past year use of cigarettes.
  - Past month smoking was defined using the survey item: "*Do you now smoke cigarettes every day, some days, or not at all?*" Responses of "Every day" and "Some days" were coded as past month smokers.
  - Respondents who reported smoking every day in the past month ("*Do you now smoke cigarettes every day, some days, or not at all?*") or reported smoking all 30 of the previous 30 days ("*On how many of the past 30 days*

did you smoke cigarettes") among those who classified themselves as some day smokers were coded as daily smokers.

3.8.1.5 National Health Interview Survey (NHIS).

NHIS data (Appendix G) are from 2014, the most recently available NHIS public-use dataset at the time this report was written. Below are additional details depending on type of tobacco product.

- **Snus** – not assessed as a separate item in NHIS.
- **Chewing tobacco** – not assessed as a separate item in NHIS.
- **Dissolvable tobacco** – not assessed as a separate item in NHIS.
- **Oral smokeless tobacco** – note that NHIS lists the following as examples of smokeless tobacco: chewing tobacco, snuff, dip, snus (*snoose*), or dissolvable tobacco. The survey also cautions that smokeless tobacco does not include NRT products, which are considered smoking cessation treatments.
    - NHIS does not assess past year use of smokeless tobacco.
    - Respondents who reported currently using smokeless tobacco every day, some days, or rarely ("*Do you NOW use smokeless tobacco products every day, some days, rarely, or not at all?*") were classified as past month smokeless tobacco users. Those who reported using "Not at all" or who reported never using smokeless tobacco ("*Have you ever used smokeless tobacco products EVEN ONE TIME?*") were classified as non-past month users.
    - Respondents who reported using smokeless tobacco every day in the past month ("*Do you NOW use smokeless tobacco products every day, some days, rarely, or not at all?*") were coded as daily smokeless tobacco users.
- **Cigarettes**
    - NHIS does not assess past year use of cigarettes.
    - Past month smoking was defined using the NHIS-created item SMKSTAT2, which combines two survey items: "*Have you smoked at least 100 cigarettes in your ENTIRE LIFE?*" and "*Do you NOW smoke cigarettes every day, some days or not at all?*" The following SMKSTAT2 answer categories were coded as past month smokers: "Current every day smoker" and "Current some day smoker". Answers of "Former smoker" and "Never smoker" were coded as no past month smoking, while "Smoker, current status unknown" and "Unknown if ever smoked" were coded to missing for the purpose of calculating this prevalence rate.

- Respondents who reported smoking every day in the past month according to the SMKSTAT2 variable (e.g., Current every day smoker) or reported smoking all 30 of the previous 30 days ("*On how many of the PAST 30 DAYS did you smoke a cigarette?*") among those who classified themselves as current someday smokers were coded as daily smokers.

3.8.2 Camel Snus

RAI Services Company's (RAIS) National Tobacco Behavior Monitor (NTBM) is a cross-sectional survey that allows for examination of Camel Snus use patterns from a nationally representative sample of current regular tobacco users (see NTBM Methodological Report 2016, in RAI Services Company, 2017). The NTBM is an online tracking tool that surveys ~2,000-2,750 adults who purchase tobacco products each month and were 18 years of age and older (no age limit on participation, but participants had to be old enough to buy tobacco products). Data collected by the survey includes demographic characteristics, use behavior patterns across tobacco categories, use frequency (number of days used during the past week), and use rate (uses per day on days used during the past week) among others.

NTBM data described below were collected between January 2013 to March 2016 from 95,629 current users of Camel Snus, non-Camel snus and other types of smokeless tobacco (weighted sample consisted of 94,678 respondents). Current users were identified based on self-reported past-30-day (P30D) use, or having used the product type (and brand, where applicable) at least one day during the past 30 days. Additional confirmatory analyses were based on data from RJRT's Consumer Brand Tracker and, in some instances, the NIH and FDA Population Assessment of Tobacco and Health (PATH) Study. Note that for these surveys current users of the different product types were identified based on self-reported past-P7D and P30D use, respectively.

Overall, demographic data for the study sample revealed that P30D users of Camel Snus, as well as the comparator product types, were predominantly between the ages of 25 and 49 years (69.2-75.2%) and male (80.8-85.7%). Regarding race and ethnicity the majority were Caucasian (52.3-65.4%) and 25% or less (16.0-25.3%) were Hispanic.

3.8.2.1 Tobacco Use Patterns Across Products

According to the NTBM, the vast majority of P30D users all products were poly users of other combustible and/or non-combustible products (approximately 93% for Camel Snus, 96% for non-Camel snus, 93% for portioned moist snuff, 92% for loose leaf chew, and 77% for loose moist snuff). A small proportion of current users of Camel Snus were exclusive (solo) users of their product type (7.2%; see Appendix H), as was the case for other product types except for moist snuff users of which slightly more than 20% were exclusive users of a single product. As noted, confirmatory analyses were completed with publicly available data from NIH/FDA's PATH Study were also examined and provide a relatively small sample of P30D Camel Snus users (n=109, weighted) and, of

this sample, 15.5% (n=16) of P30D users of Camel Snus (n=103, weighted) report being exclusive product type users, with the majority (84.5%) being concurrent/poly users of other combustible and/or non-combustible tobacco products. These data, as well as RJRT's brand tracker data, were generally consistent with estimates provided from NTBM indicating the predominant use behavior pattern is concurrent/poly use of other tobacco product types.

3.8.2.2 Tobacco Use Frequency (use in past week)

According to the NTBM, most P30D users of Camel Snus report using one or less days per week (46.2%) or 2-5 days per week (39.2%) with an overall average of 2.4 days per week (see Appendix H). Mean values for use per week were similar compared to other smokeless products with a slightly higher value for loose moist snuff users (mean 3.7 days per week, see Appendix H). Similar rates of weekly use were also reported across the 6 styles of Camel Snus ranging from lowest for the Mint flavor (mean of 2.2 days per week) and highest for the Winterchill flavor (mean 3.0 days per week). Overall, estimates based on data from NTBM indicate a lower mean use frequency (2.4 days/week) for current users of Camel Snus compared to other data sources. That is, Brand Tracker data indicated that mean use per week for P7D users of Came Snus was 3.7 days and PATH data indicated use at 17.0 days per month or slightly more than 4 days per week.

3.8.2.3 Tobacco Use Rate (uses per day on days used in the past week)

According to the NTBM, most P30D users of Camel Snus (57.3%) reported 1-2 uses per day with an overall mean of 3.2 uses per day (see Appendix H). Similar to frequency per week, mean daily use values were similar compared to other smokeless products with a slightly higher value for loose moist snuff users (mean 4.5 uses per day). Similar rates of weekly use were also reported across the 6 styles of Camel Snus ranging from lowest for the Mint flavor (mean of 2.6 uses per day) and highest for the Winterchill flavor (mean 3.9 uses per day). Confirmatory analyses using Brand Tracker data corresponded to these findings such that most P7D users of snus (Camel Snus and non-Camel Snus combined) report an average of snus use 3.4 times per day. Similarly, moist snuff use was elevated compared to snus with a mean of 5.1 uses per day. PATH data analyses also found that P30D users of Camel Snus reported an average of 3.4 uses per day.

3.8.2.4 Concurrent Use of Cigarettes and Camel Snus

NTBM analyses comparing respondents who reported exclusive use of cigarettes and those who used both cigarettes and Camel Snus indicated that mean days smoking per week was lower for concurrent users (4.8 days) compared to smoking cigarettes only (5.9 days; see Appendix H). Confirmatory analyses using Brand Tracker data corresponded to these findings such that mean days smoking per week was lower for concurrent users (6.0 days) compared to smoking cigarettes only (6.6 days).

3.8.3 Discussion and Conclusions

Taken together, Federal Survey data and data collected by RJRT and specific to Camel Snus, indicate that the epidemiology of oral smokeless tobacco use continues to support decades of findings confirming that oral smokeless tobacco can cause and/or sustain nicotine dependence, although the overall prevalence of use in all age categories and risk of graduation from any use to daily and/or dependent use appears lower than that associated with traditional cigarettes. Such data support the viability of oral smokeless tobacco products as potential substitutes for cigarettes among cigarette smokers. These findings also support the conclusion that from an abuse liability perspective, smokeless tobacco products likely carry lower overall abuse liability risk than traditional cigarettes.

The RJRT analyses specific to current users of Camel Snus confirm that use is generally similar to use of other smokeless tobacco products (including loose moist snuff and loose leaf chew tobacco), in terms of demographic characteristics, tobacco use patterns (product use across tobacco categories), use frequency (number of days used during the past week) and use rate (number of uses per day on days used during the past week). Specifically, most users of Camel Snus and other smokeless products also use other combustible and/or non-combustible products (~93%). Further, most users of Camel Snus and other smokeless products do not use daily and use an average of about 3.4 times per day. Lastly, current cigarette users who also use Camel Snus report lower frequency of cigarette use and rate of cigarette use compared to exclusive cigarette users.

Regarding concurrent or co-occurring use, while not directly bearing on the abuse potential assessment of either traditional cigarettes or smokeless tobacco, rates and patterns of concurrent product use within the past 30 days merit comment. Overall, among daily cigarette smokers, concurrent use of smokeless tobacco appeared somewhat more likely to be associated with lower rates of smoking when concurrent use of smokeless tobacco was reported as occurring daily, than simply at least once during the past 30 days, particularly in persons reporting college education (e.g., as shown in Appendix G/Federal Survey Data) There was little apparent overall trend for either higher or lower levels of smoking in association with concurrent use of smokeless tobacco at least once during the past 30 days.

The absence of a strong inverse relationship between smokeless tobacco use and number of cigarettes smoked per day is not surprising given the limitations of the “used at least once in the past 30 days” metric, and the absence of guidance that any potential benefit of smokeless tobacco would be proportional to the extent to which it replaced cigarette smoking. In this regard it is plausible – but not known from the data – that persons in college would have been more likely to have been aware of this relationship and/or more likely to attempt to use smokeless tobacco to reduce smoking.

Regarding “dual use” terminology, this report has adopted the terminology of “concurrent” (or “co-occurring”) use rather than the seemingly in vogue term “dual use”.

In principle, either phrase could be used to describe the phenomenon of co-occurrence as defined by and understood by the metrics used to evaluate patterns of tobacco product use. In practice, however, the term “dual use” has historical meaning and connotation related to the “intent” and health effects of co-occurring product use. For example, in 2002, Henningfield, Rose, and Giovino raised the concern that at least some of the marketing of smokeless tobacco products appeared to encourage the use of smokeless tobacco for the purpose of managing situations where smoking was not allowed. This concern was not unique to smokeless tobacco products. In fact, concerns that some people would use NRT, not to quit smoking but to manage situations where they could not smoke and thus possibly delay smoking cessation were also raised when nicotine gum was being considered for a switch in regulatory status from a prescription to an over-the-counter (OTC) medication in the mid-1990s. In the case of nicotine gum, and later, nicotine patch, these concerns likely contributed to the inclusion of a Drug Facts Label warning against the concurrent use of the NRT product along with cigarette smoking – labeling that persisted for several years beyond the availability of findings that use of NRT by persons who had not quit smoking was more likely to lead to reduced smoking and cessation than to persisting smoking. At least one experimental clinical study has provided data suggesting some similarity between Camel Snus and this aspect of NRT adoption by ongoing smokers. Burris et al. (2014) explored the differential effects of explicit “use snus to cope with smoking restrictions” and “use snus to reduce cigarette smoking” messaging delivered to smokers with no intentions to quit, when those participants were presented with a supply of Camel Snus. Whereas some differences in the use of Camel Snus were seen for these different message themes, both messages significantly increased the participants’ stated intentions to quit smoking and to quit all tobacco use at the end of the study, which the authors characterized as “a clinically significant finding.”

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5 Appendix A: pH, Nicotine, and Free Nicotine in Swedish Match Products

pH, Nicotine, and Free Nicotine Test results for Swedish Snus Products (M195-GLP. Labstat. 2014).

Result	Unit	Statistic	General Original Snus (US) Test Article ID: 1400891	General Original Snus (Sweden) Test Article ID: 1400933	Catch Dry Eucalyptus Mini Snus (Sweden) Test Article ID: 1400934	Granit Snus (Sweden) Test Article ID: 1400935	Skruf Stark Snus (Sweden) Test Article ID: 1400936
pH	NA	Mean	7.84	8.45	7.15	7.93	8.56
		Std. Dev.	0.01	0.01	0.01	0.01	0.03
		N	7	7	7	7	7
		L. Limit (95% C.I.)	7.82	8.43	7.13	7.92	8.53
		U. Limit (95% C.I.)	7.85	8.46	7.16	7.94	8.58
Nicotine	[mg/g smokeless tobacco 'dry weight']	Mean	15.7	16.7	22.2	19.7	25.2
		Std. Dev.	0.3	0.3	0.4	0.5	1.8
		N	7	7	7	7	7
		L. Limit (95% C.I.)	15.4	16.4	21.8	19.3	23.5
		U. Limit (95% C.I.)	16.0	17.0	22.6	20.2	26.9
Free Nicotine	[mg/g smokeless tobacco 'dry weight']	Mean	6.21	12.2	2.62	8.82	19.5
		Std. Dev.	0.12	0.2	0.05	0.22	1.4
		N	7	7	7	7	7
		L. Limit (95% C.I.)	6.10	11.9	2.57	8.62	18.2
		U. Limit (95% C.I.)	6.32	12.4	2.66	9.03	20.8

6 Appendix B: Overview of nicotine content/delivery across products

Route of Nicotine Administration	**C_{max}[a] ng ml^{-1}**	**T_{max}[a,b] min**	**Bioavailability %** [values in brackets calculated using percentages]	**Labeled Content and/or Delivery** (with exception of Camel Snus for which data were provided by RJRT)
Smoking (5 min)				
~2 mg/cigarette[c]	15-30 (venous)	5-8 (venous)	80-90 (of inhaled nicotine) [~1.6-1.8 mg]*	Not Available
	20-60 (arterial)	3-5 (arterial)		
	50 (arterial)	30 (arterial)		
Nasal Spray				
1 mg	5-8 (venous)	11-18 (venous)	60-80 [0.6-0.8 mg]*	1 mg released; .53 mg absorbed (Pfizer, Inc., 2010); 2-12 ng/mL nicotine boost (Pfizer, Inc., 2010)
	10-15 (arterial)	4-6 (arterial)		
Gum (30 min, total dose in gum)				
2 mg	6-9	30	78 [1.56 mg]*	2 mg (GlaxoSmithKline, 2015a)
4 mg	10-17	30	55 [2.2 mg]*	4 mg (GlaxoSmithKline, 2015b)
Inhaler (one 10 mg cartridge, 20 min)				
4 mg released	8.1	30	51-56 [2.04-2.24 mg]*	4 mg released; 2 mg absorbed (Pharmacia and Upjohn Company, 2009); 6 ng/mL nicotine boost (Pharmacia and Upjohn Company, 2009)

Lozenge (20-30 min)				
2 mg	4.4	60	50 [1 mg]*	2 mg (GlaxoSmithKline, 2015)
4 mg	10.8	66	79 [3.16 mg]*	4 mg (GlaxoSmithKline, 2015)
Sublingual Tablet (20-30 min)				
2 mg	3.8	~60	65 [1.3 mg]*	2 mg (Nicofi, 2016)
Transdermal patch (labeled dose)				
15 mg/16 h (Nicotrol)	11-14	6-9 h	75-100 [11.25-15 mg]*	15 mg (Physicians' Desk Reference, 1997)
14 mg/24 h (Nicoderm)	11-16	4-7 h	Not available	14 mg (A-S Medication Solutions, 2015)
21 mg/24 h (Nicoderm)	18-23	3-7 h	68 [14.28 mg]*	21 mg (A-S Medication Solutions, 2015)
21 mg/24 h (Habitrol)	12-21	9-12 h	82 [17.22 mg]*	21 mg (Novartis Consumer Health, Inc, 2010)
Snus				
Camel Snus	~ 3.5 – 5.0	~ 23 - 37	Not available	[9.3-10.2mg/g][d]

Note. Data in the first three columns of the table were adapted from Benowitz, Hukkanen, and Jacob, 2009. The last column ("Labeled Content and/or Delivery") and bottom row (Camel Snus) were added by authors of this submission. [a]C_{max} and T_{max} values represent peripheral venous blood unless otherwise indicated. [b]T_{max} values are measured from the start of the administration. [c]Estimated dose of 2 mg of nicotine per cigarette is higher than the usual 1-1.5 mg per cigarette because nicotine absorption from smoking a cigarette was studied after at least overnight abstinence (Benowitz, Hukkanen, and Jacob, 2009). [d]Value for nicotine content also found in Appendix D in this report.

7 Appendix C: Overview of Camel Snus Styles and Ingredients

Camel Snus Style	Frost	Mellow	Mint	Frost Large	Robust	Winterchill
Pouch Size (g)	*0.6*	*0.6*	*0.6*	*1*	*1*	*1*
Ingredients listed in descending order by weight	Tobacco	Tobacco	Tobacco	Tobacco	Tobacco	Tobacco
	Water	Water	Water	Water	Water	Water
	Sodium Carbonate & Bicarbonate	Sodium Carbonate & Bicarbonate	Sodium Carbonate & Bicarbonate	Sodium Carbonate & Bicarbonate	Sodium Carbonate & Bicarbonate	Sodium Carbonate & Bicarbonate
	Pouch Material	Pouch Material	Pouch Material	Pouch Material	Sodium Chloride	Sodium Chloride
	Propylene Glycol	Propylene Glycol	Propylene Glycol	Propylene Glycol	Pouch Material	Pouch Material
	Natural and Artificial Flavors	Sucralose	Sucralose	Natural and Artificial Flavors	Propylene Glycol	Propylene Glycol
	Sucralose	Sodium Chloride	Natural and Artificial Flavors	Sucralose	Sucralose	Natural and Artificial Flavors
	Sodium Chloride	Natural and Artificial Flavors	Sodium Chloride	Sodium Chloride	Natural and Artificial Flavors	Sucralose

8 Appendix D: Summary of Camel Snus Styles

Summary of Camel Snus Styles Submitted for Consideration for Authorization as MRTPs

Camel Snus Style	Pouch Size (g)	Nicotine (mg/g)*	pH	Unionized Nicotine (mg/g)	Unionized Nicotine (%)
Frost	0.6	10.0	7.7	3.4	34
Mellow	0.6	9.9	7.7	3.1	31
Mint	0.6	9.8	7.7	3.3	33
Frost Large	1.0	10.2	7.7	3.4	34
Winterchill	1.0	9.4	7.7	3.2	34
Robust	1.0	9.3	7.7	3.0	33

*All weights in this table are “wet” weights, that is, as the product is packaged and sold versus “dry” weight, as is often used when reporting in the literature. Values are rounded means.

9 Appendix E: Overview of Human Studies of Camel Snus

Author (Year)/CSD study number, Design, Funding	Participants and Method	Snus and Comparator(s)	Outcomes
Blank and Eissenberg (2010) **Design:** Within-subject laboratory-based study comparing CS, Ariva, OB cigarette, or tobacco abstinence **Sponsor/Affiliation**: NIDA (PHS CA103827)	**Sample** N=21 **Intervention details**: Sessions included 4, 5-day conditions that differed by product used: CS, Ariva, own brand cigarettes, or no tobacco. Pts visited the laboratory for ~1 hr on each of Days 1–5 and also took products home each week.	**Camel Snus details**: Original, Frost, or Spice (chosen by pt). At the time of this study, CS was not available in local retail stores and was obtained at no cost from RJRT. **Comparator(s)**: Ariva mint flavor, OB cigarette, and tobacco abstinence.	**Biomarkers** (e.g., urine cotinine and NNAL) **Product Use** **Subjective ratings including tobacco/nicotine withdrawal** (Hughes-Hatsukami Questionnaire, Tiffany-Drobes Questionnaire of Smoking Urges, and Direct Effects of Nicotine VAS)
Burris et al. (2014) **Design:** RCT comparing brief instructional advice on CS use compared to no use. **Sponsor/Affiliation**: NIH K23DA020482, T32DA007288	**Sample** N=57 **Intervention details:** Brief, instructional ST use among smokers unmotivated to quit. Pts were randomized to a free 2-week supply of CS or a no-supply group. In CS grp, half told to use it to cope with smoking restrictions (Snus to Cope), and half advised to use it to reduce smoking (Snus to Reduce).	**Camel Snus details:** Spice, Frost, or Original. Recommendations were not given regarding how many pouches to use. **Comparator(s):** OB cigarette.	**Biomarkers** (CO, urine cotinine) **Product Use** **Subjective ratings** (e.g., craving to smoke; likeability of Camel Snus) **Adverse events**

Caraway and Chen (2013) **Design:** Prospective study of CS consumers **Sponsor/ Affiliation:** R. J. Reynolds Tobacco Company	**Sample** N=53 **Intervention details:** Pts consumed their usual brand styles ad libitum for 7 days outside of the laboratory in normal life setting.	**Camel Snus details:** 600 mg Original, Spice, and Frost styles. Pt purchased their own usual variety of CS at retail for consumption during the study. **Comparator(s):** N/A	**Biomarkers** (e.g., Nicotine, NNN, NNK). **MLE** **Product Use**
Carpenter et al. (2016) **Design**: RCT comparing CS to no intervention **Sponsor/Affiliation**: NCI/NIH and the National Center for Advancing Translational Science of the NIMH.	**Sample** N=1,236 **Intervention details**: 6 wk sampling period with CS and a 1 year follow up.	**Camel Snus**: CS Winterchill or Robust, 1.0g **Comparator(s)**: no intervention and instructed to smoke/reduce/quit cigarettes as they wished.	**Product Use** **Cessation outcomes** (abstinence at the end of treatment and end of follow-up)
Cobb et al. (2010) **Design**: Latin-square ordered, within-subject laboratory-based study of Ariva, Marlboro Snus, CS, Commit 2 mg nicotine lozenge, OB cigarette, and low nicotine Quest cigarette. **Sponsor/Affiliation**: Funding: Supported by US Public Health Service grants CA103827 and CA120142	**Sample** N=28 **Intervention details**: 2.5 hr sessions that differed by product used. Products were each administered twice per session.	**Camel Snus**: CS Original flavor. RJRT provided product at the start of the study and product was obtained through retail later in study. 14 participants used the 2006 version and 14 used the 2008 version. **Comparator(s)**: Ariva Mint tobacco tablet, Marlboro Snus Mild, Commit Lozenge 2mg, cigarette (actual and sham smoking), Quest cigarette (Step 3)	**Biomarkers** (plasma nicotine, CO) **Subjective ratings** (e.g., direct effects of tobacco, withdrawal)

Hatsukami et al. (2011) **Design:** Multi-site, crossover prospective study comparing five ST products (General Snus, Marlboro Snus, Camel Snus, Stonewall, and Ariva) **Sponsor/Affiliation**: NIH R01-CA135884	**Sample** N=91 **Intervention details**: Two wk sampling phase and a two wk treatment phase. Sampling phase included testing 5 products in a natural environment. At the end of the sampling period, pts chose which product they would use during 2-wk cigarette abstinence phase.	**Camel Snus details**: Frost or Mellow. **Comparator(s)**: General Snus, Marlboro Snus, Stonewall and Ariva.	**Biomarkers** (CO, urine cotinine) **Product use** **Subjective ratings** (e.g., product ratings, withdrawal) **Cessation outcomes** (abstinence at the end of treatment and end of follow-up)
Hatsukami et al. (2016a) **Design**: RCT comparing CS to 4 mg nicotine gum **Sponsor/Affiliation**: NCI R01 CA135884, P30 CA077598, UL1TR000114	**Sample** N=258 **Intervention details**: 12 wks exposure to CS or nicotine gum. Pts instructed to switch completely from smoking. At 26 wks after start of treatment, smoking abstinence and use of any other tobacco/ nicotine products assessed.	**Camel Snus details**: Winterchill or Robust styles. Pts who experienced adverse effects were provided Frost or Mellow. **Comparator(s)**: 4 mg nicotine gum (Nicorette GlaxoSmithKline). Pts who experienced adverse effects were given 2 mg.	**Biomarkers** (e.g., urinary NNAL, cotinine, nicotine) **Product use** **Subjective ratings** (e.g., product ratings, withdrawal) **Cessation outcomes**

Kotlyar et al. (2011) **Design:** RCT comparing CS, 4 mg nicotine gum/lozenge, and Taboka pouched tobacco snuff. **Sponsor/Affiliation**: Funding: P50 DA01333 and K23DA017307	**Sample** N=80 **Intervention details:** Pts smoked normally for 2 wks and then randomized to intervention to be used in place of smoking during a 1 wk sampling period. Then, pts used their product at least 2 hrs/day for 4 wks. Five wks after cessation, pts reduced use until discontinuing all product use.	**Camel Snus details:** Original, Frost, or Spice styles. Most pts used the newer version of CS released in mid-2008. **Comparator(s):** 4mg nicotine gum or lozenge (mint; brand NR); Taboka (mint or regular flavored.	**Biomarkers** (CO, urinary cotinine, total NNAL, total NNN) **Product Use** **Subjective ratings** (withdrawal) **Cessation outcomes**
Krautter et al. 2015 **Design:** RCT comparing CS, Camel Strips, Sticks, Orbs, concurrent use cigarettes and CS, or smoking/tobacco abstinence **Sponsor/Affiliation**: RJRT	**Sample** N=167 **Intervention details:** Pts confined onsite for 7 nights and 6 days. Smoked as usual for 1 day prior to switching to one of 6 conditions for 5 days.	**Camel Snus details:** 600 mg Frost or Mellow. **Comparator(s):** Camel Strips, Sticks, Orbs, cigarettes and snus, or abstinence.	**Biomarkers** (e.g., Nicotine, Cotinine TSNAs, PAHs) **Product Use** **MLE** **Subjective ratings** (withdrawal)
Meier et al. (2016a) **Design**: Prospective study of ad libitum use of CS. **Sponsor/Affiliation**: Funding: NCI, NIDA, NIH, R01 CA154992, K07 CA181351, T32 DA007097, P30 CA138313, UL1 TR000062	**Sample** N=543 **Intervention details**: Pts were given free samples of Camel Snus for use across 6 wks.	**Camel Snus details**: Winterchill or Robust. **Comparator(s)**: None.	**Product Use** **Subjective ratings** (e.g., attitudes, risk perception, product preference).

O'Connor et al. (2011) **Design**: Prospective study of CS, Marlboro snus, Stonewall tablets, and 4 mg Commit nicotine lozenge. **Sponsor/Affiliation**: Funding: NCI via the Roswell Park Cancer Institute Transdisciplinary Tobacco Use Research Center (P50CA114236)	**Sample** N=44 **Intervention details**: Pts were given relative risk information about ST and NRT compared to cigarettes. Pts sampled 4 products and then used all products ad libitum for one wk. Pts then selected one to try for an additional wk.	**Camel Snus details**: Frost **Comparator(s)**: Marlboro Snus, Stonewall dissolvable tobacco tablets, and Commit nicotine lozenge 4mg.	**Biomarkers** (e.g., CO, salivary cotinine). **Product Use** **Subjective ratings** (e.g., ST product liking and willingness to use; willingness to pay for ST and NRT products).
O'Connor et al. 2014 **Design**: Web-based randomized panel comparing willingness to try different ST products. **Sponsor/Affiliation**: Funding: NCI R01CA141609	**Sample** N=492 **Intervention details**: Pts from a U.S.-based internet panel randomized to view ads for three smoking alternatives or non-tobacco products. Pts completed questionnaires about their reactions to messaging	**Camel Snus details**: CS advertisements (no products were consumed by pts) **Comparator(s)**: Camel Dissolvable Tobacco, Commit medicinal nicotine lozenges, Coca-Cola, Vitamin Water, Minute Maid Orange Juice	**Subjective ratings** (willingness to try products) **Behavioral economic outcomes:** (e.g., demand elasticity, peak consumption)
Ogden et al. (2015 a, b, c) (parts 1, 2, and 3) **Design**: Multi-center RCT comparing tobacco-heating cigarettes, CS, or ultra-low machine yield tobacco-burning cigarettes. **Sponsor/Affiliation**: RJRT	**Sample** N= 130 **Intervention details**: Pts randomized to products with a comparison group of never smokers at baseline. Pts' followed for 24 wks.	**Camel Snus details**: 400mg Frost, Spice and Original **Comparator(s)**: Eclipse tobacco-heating cigarette (regular, menthol), tobacco cigarette (Camel non-menthol, Salem menthol)	**Biomarkers** (e.g., nicotine, cotinine) **Product Use** **MLE** **Adverse Events**

Quisenberry et al. (2015) **Design**: Behavioral economic analysis of purchase substitution in an experimental marketplace across a variety of nicotine-containing products **Sponsor/Affiliation**: Funding: International Tobacco Control research programs project P01CA138389 and NIH grant U19CA157345	**Sample** N=22 (first experiment), 34 (second experiment) **Intervention details**: The experimental tobacco marketplace involved pts purchasing nicotine products under different price conditions. Experiment 2 was identical to session 1, but cigarillos were not available for purchase.	**Camel Snus details**: Winterchill **Comparator(s)**: usual brand of cigarettes, Blu disposable electronic cigarettes, classic flavor Skoal dip, white ice mint flavor 4-mg nicotine gum, mint flavored 4-mg nicotine lozenges, and Swisher Sweet cigarillos.	**Behavioral economic outcomes**: cigarette demand as a function of cost; elasticity of cigarette demand when cigarillos were included versus not included. **Product Use**
Round et al., (2015) **Design**: Three prospective studies involving a 3-wk transition from exclusive smoking to reduced smoking and use of Camel Strips, Camel Sticks, or CS. **Sponsor/Affiliation**: RJRT	**Sample** N= 88 **Intervention details**: Pts smoked ad libitum for one week. Pts were instructed to reduce cigarettes per day each week by at least 75% by wk 3 while using Strips, Sticks or CS.	**Camel Snus details**: 600 mg Frost and Mellow **Comparator(s)**: Usual brand cigarettes; Camel Strips and Camel Sticks were examined in separate studies.	**Biomarkers**: (e.g., nicotine, cotinine, TSNAs, PAHs). **Product Use** **MLE** **Subjective ratings** (acceptability of products, sensory properties, etc).

Rousu et al. (2014) **Design**: Behavioral economics study of an experimental auction comparing CS, Ariva, Nicorette Mini Nicotine Lozenge, or Marlboro Cigarettes. **Sponsor/Affiliation**: Funding: NIH grant R01CA141609	**Sample** N = 571 **Intervention details**: Pts were given information (pro-ST, anti-ST, anti-cigarette), offered a free trial of CS, Ariva, or Nicotine lozenge, or experienced no intervention. Pts then completed the experimental auction that included comparators.	**Camel Snus details**: Frost **Comparator(s)**: Ariva, Nicorette Mini Lozenge, Marlboro cigarettes.	**Behavioral economic outcomes** (demand as measured by the auctioning task)
CSD0904 **Design:** Multicenter**, c**ross-sectional post-market surveillance study of natural adopters of different tobacco products **Sponsor/Affiliation**: RJRT	**Sample** N = 317 **Smoking status:** Natural adopters (i.e., pts were using a tobacco product of choice on a regular basis prior to study participation) In addition, non-tobacco users participated as a control grp. **Intervention details:** Seven days of pre-clinic procedures followed by 24 hrs in-patient ad libitum use of product.	**Camel snus details:** 600 mg Frost, Mellow, or Winterchill **Comparator(s):** Moist snuff, traditional cigarettes, concurrent use of cigarettes and moist snuff or CS, and non-tobacco users.	**Biomarkers** (e.g., nicotine, cotinine, TSNAs). **Product use** **MLE** **Subjective ratings** (e.g., quality of life) **Functional capacity** (e.g., spirometry outcomes)

CSD0914 **Design:** Open label, RCT comparing smoke free tobacco products (Camel Orbs, Strips, Sticks, Snus) and traditional cigarettes **Sponsor/Affiliation**: RJRT	**Sample** N =15 **Smoking status**: current smokers **Intervention details**: Pts consumed a single unit of one product at each of five visits after 12-hour nicotine abstinence (session 1 was always own brand cigarette). Pts were given a supply of product to use at home for week prior to next session.	**Camel Snus details:** 600 mg Frost or Mellow **Comparator(s):** Camel Orbs, Strips, and Sticks, as well as own brand traditional cigarette.	**Biomarkers** (e.g., nicotine uptake represented by AUC, C_{max}, T_{max}, etc.) **Product Use** **MLE** **Subjective ratings** (e.g., withdrawal) **Adverse Events**
CSD1010 **Design:** Multicenter, open-label RCT comparing Camel Snus to Nicotine lozenge. **Sponsor/Affiliation**: RJRT	**Sample** N= 216 **Smoking Status:** Current smokers **Intervention details:** Pts provided with supply of assigned test product in their preferred snus variety or lozenge flavor. At Visit 4 (Week 12) pts were no longer provided with test product, but were free to purchase additional products. Pts were monitored for up to 12 mos.	**Camel Snus details:** 600 mg Frost or Mellow **Comparator(s):** Nicorette nicotine lozenge (pt preferred flavor). In addition, there were two Camel Snus groups such that one was informed of the relative risks of smoking versus smokeless tobacco use and the other was not informed of the relative risks.	**Biomarkers** (e.g., blood nicotine and cotinine) **Product use** **Subjective ratings** (e.g., withdrawal) **Cessation outcomes** **Adverse events**

CSD1101 **Design**: RCT open label crossover study comparing traditional cigarette use and Camel Snus consumption **Sponsor/Affiliation**: RJRT	**Sample** N=17 **Smoking status:** Current smokers **Intervention details**: Pts consumed single unit of a product at each of five visits (session 1 was always OB cigarette). Pts given a supply of product to use at home for week prior to next session.	**Camel Snus details**: 600 mg Frost **Comparator(s)**: Primary comparator was traditional cigarette.	**Biomarkers** (e.g., nicotine uptake represented by AUC, T_{max}, etc.) **Subjective ratings** (e.g., withdrawal) **Adverse Events**

Note: *Abbreviations:* B[a]P, benzo[a]pyrene; CO, expired air carbon monoxide; CPD, cigarettes per day; CS, Camel Snus; grp(s), group(s); MNWS, Minnesota Nicotine Withdrawal Scale; mts, minutes; MLE, mouth level exposure; N, sample size; NCI, National Cancer Institute; NIH, National Institutes of Health; NIDA, National Institute on Drug Abuse; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N´-nitrosonornicotine; NR, not reported; NRT, nicotine replacement therapy; OB, own brand; pts, participants; RCT, randomized controlled trial; RJRT, R.J. Reynolds Tobacco Company; SD, standard deviation; ST, smokeless tobacco; VAS, visual analog scale; wk(s), week(s); yr(s), year(s).

10 Appendix F: Urinary Biomarkers and Camel Snus

Urinary nicotine biomarkers by exclusive or dual Camel Snus use across RJRT studies and a published study

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

Note. The terminology "dual use" in the cited reports was changed to "concurrent" when reporting on findings in the present Pinney Associates report. [a] CSD0904: One subject in Camel Snus group and one subject in Dual Use Camel Snus and Cigarettes group used 1.0-g pouch size products. [b] Hatsukami, et al, 2016a: Some participants who experienced adverse effects from use of 1.0-g pouch size products were provided 0.6-g pouch size products. [C] HSD 0702: Intent-to-treat subject group. Similar results were observed for the per-protocol subject group. *Publications associated with these studies are: CSD0901 (Krautter et al., 2015), HSD0702 (Ogden et al., 2015 a,b,c), and CSD905 (Round et al., 2015).

Urinary TSNA biomarkers by exclusive or dual Camel Snus use across RJRT studies and a published study

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

Note. The terminology "dual use" in the cited reports was changed to "concurrent" when reporting on findings in the present Pinney Associates report. [a] CSD0904: One subject in Camel Snus group and one subject in Dual Use Camel Snus and Cigarettes group used 1.0-g pouch size products. [b] Hatsukami, et al, 2016a: Some participants who experienced adverse effects from use of 1.0-g pouch size products were provided 0.6-g pouch size products. [C] HSD 0702: Intent-to-treat subject group. Similar results were observed for the per-protocol subject group. *Publications associated with these studies are: CSD0901 (Krautter et al., 2015), HSD0702 (Ogden et al., 2015 a,b,c), and CSD905 (Round et al., 2015).

11 Appendix G: Federal Survey Data

Use of Smokeless Tobacco Products and Traditional Cigarettes

SURVEY NAME	Oral SLT Past Year	Oral SLT Past Month	Oral SLT Daily Use	Snus Past Year	Snus Past Month	Snus Daily Use	Chewing Tobacco Past Year	Chewing Tobacco Past Month	Chewing Tobacco Daily Use	Cigarette Past Year	Cigarette Past Month		Cigarette Daily Use
MTF 8th grade	—	3.0%	0.5%	2.2%	—	—	—	—	—	—	4.0%		1.4%
MTF 10th grade	—	5.3%	1.8%	4.5%	—	—	—	—	—	—	7.2%		3.2%
MTF 12th grade	—	8.4%	3.4%	5.8%	—	—	—	—	—	—	13.6%		6.7%
MTF college students	—	—	—	5.0%	—	—	—	—	—	22.6%	12.9%		5.2%
MTF young adults (19-28)	—	—	—	4.8%	—	—	—	—	—	27.0%	17.5%		10.7%
NYTS	—	4.4%	—	—	1.3%	—	—	3.8%	1.1%	13.4%	6.3%		1.3%
NSDUH 12-17	4.0%	1.9%	0.4%	3.5%*	1.7%*	0.7%*	2.2%	0.9%	0.1%	10.2%	5.5%		1.1%
NSDUH 18 and older	4.5%	3.4%	1.6%	3.8%*	2.9%*	2.0%*	1.8%	1.1%	0.3%	26.8%	22.8%		13.7%
CPS-TUS	—	1.6%	1.0%	—	—	—	—	—	—	—	16.1%		13.1%
NHIS (18+ only)	—	2.9%	1.5%	—	—	—	—	—	—	—	16.8%		13.2%

No

te. * item includes both snuff and snus; — not assessed by survey; CPS-TUS (Current Population Survey – Tobacco Use Supplement, ages 18+ only). Additionally, dissolvable tobacco use data were limited and only reported for the MTF and NYTS and not included in the table. For the MTF, rates of dissolvable tobacco use were 0.5-1.3% for past year and no rates were reported for month or daily use. For the NYTS, only past month were reported at 0.5%.

Use of Smokeless Tobacco and Traditional Cigarettes Among Males

SURVEY NAME	Oral SLT Past Year	Oral SLT Past Month	Oral SLT Daily Use	Snus Past Year	Snus Past Month	Snus Daily Use	Chewing Tobacco Past Year	Chewing Tobacco Past Month	Chewing Tobacco Daily Use	Cigarette Past Year	Cigarette Past Month	Cigarette Daily Use
MTF												
8th	—	3.8%	0.9%	3.1%	—	—	—	—	—	—	3.5%	1.2%
10th	—	8.9%	3.4%	7.5%	—	—	—	—	—	—	7.7%	3.5%
12th	—	14.3%	6.5%	9.9%	—	—	—	—	—	—	15.2%	7.9%
College	—	—	—	n/a	—	—	—	—	—	n/a	n/a	n/a
Young adults (19-28)	—	—	—	n/a	—	—	—	—	—	n/a	n/a	n/a
NYTS	—	7.0%	—	—	2.0%	—	—	6.4%	2.0%	14.0%	7.2%	1.5%
NSDUH												
12-17	6.6%	3.3%	0.8%	5.8%*	2.9%*	1.2%*	3.8%	1.7%	0.1%	10.4%	5.6%	1.1%
≥18	8.5%	6.6%	3.1%	7.2%*	5.6%*	3.8%*	3.4%	2.1%	0.6%	30.5%	25.8%	14.8%
CPS-TUS	—	3.3%	2.1%	—	—	—	—	—	—	—	18.0%	14.5%
NHIS	—	5.6%	3.0%	—	—	—	—	—	—	—	18.8%	14.4%

Note. * (NSDUH item includes both snuff and snus; see NSDUH section of table notes for additional information); — (not assessed by survey); n/a (estimate not available) CPS-TUS (Current Population Survey – Tobacco Use Supplement, ages 18+ only). Additionally, dissolvable tobacco use data were limited and only reported for the MTF and NYTS and not included in the table. For the MTF, rates of dissolvable tobacco use were 1.1-1.3% for past year and no rates were reported for month or daily use. For the NYTS, only past month were reported at 0.6%.

Use of Smokeless Tobacco and Traditional Cigarettes Among Females

SURVEY NAME	Oral SLT Past Year	Oral SLT Past Month	Oral SLT Daily Use	Snus Past Year	Snus Past Month	Snus Daily Use	Chewing Tobacco Past Year	Chewing Tobacco Past Month	Chewing Tobacco Daily Use	Cigarette Past Year	Cigarette Past Month	Cigarette Daily Use
MTF												
8th	—	2.2%	0.3%	1.4%	—	—	—	—	—	—	4.2%	1.3%
10th	—	1.9%	0.4%	1.7%	—	—	—	—	—	—	6.6%	2.8%
12th	—	2.1%	0.1%	1.5%	—	—	—	—	—	—	11.6%	5.4%
College	—	—	—	n/a	—	—	—	—	—	n/a	n/a	n/a
Young adults (19-28)	—	—	—	n/a	—	—	—	—	—	n/a	n/a	n/a
NYTS	—	1.7%	—	—	0.6%	—	—	1.2%	0.1%	12.6%	5.4%	1.1%
NSDUH												
12-17	1.3%	0.5%	<0.1%	1.1%*	0.4%*	<0.1%*	0.5%	0.1%	<0.1%	10.0%	5.4%	1.0%
≥18	0.7%	0.5%	0.2%	0.6%*	0.3%*	0.2%*	0.3%	0.2%	0.1%	23.4%	20.0%	12.7%
CPS-TUS	—	0.1%	0.1%	—	—	—	—	—	—	—	14.2%	11.7%
NHIS	—	0.4%	0.2%	—	—	—	—	—	—	—	14.8%	12.1%

Note. * (NSDUH item includes both snuff and snus; see NSDUH section of table notes for additional information); — (not assessed by survey); n/a (not available); n/a (estimate not available)
CPS-TUS (Current Population Survey – Tobacco Use Supplement, ages 18+ only). Additionally, dissolvable tobacco use data were limited and only reported for the MTF and NYTS and not included in the table. For the MTF, rates of dissolvable tobacco use were 0.7-1.0% for past year and no rates were reported for month or daily use. For the NYTS, only past month were reported at 0.3%.

Concurrent Use of Smokeless Tobacco and Cigarettes Among Males and Females During the Past 30 Days*

SURVEY NAME	Concurrent Use of Smokeless Tobacco and Cigarettes; Past 30 Days		
	Overall	Male	Female
MTF			
8th	0.5%	0.5%	0.5%
10th	1.1%	1.7%	0.5%
12th	1.5%	2.3%	0.6%
College	—	—	—
Young adults (19-28)	—	—	—
NYTS	2.0%	3.1%	0.8%
NSDUH			
12-17	0.8%	1.4%	0.3%
≥18	1.3%	2.6%	0.2%
CPS-TUS	0.4%	0.8%	<0.1%
NHIS	1.0%	1.8%	0.3%

Note: *****Differences in methodology occur at the past 30-day use level, not the concurrent use level. Some surveys use "now," some use "past month," and some use "past 30 days." Each of those terms was used synonymously when defining past 30-day use. Concurrent use was defined as past 30-day use of cigarettes and past 30-day use of smokeless tobacco for all surveys. Additionally, note that CPS-TUS represents "Current Population Survey – Tobacco Use Supplement, ages 18+ only" and the symbol — represents data not assessed by survey.

Characteristics of Persons Who Have Used Both Smokeless Tobacco and Traditional Cigarettes During the Past 30 Days*

SURVEY NAME	Sex		Age	Race/Ethnicity				Education					
	Male	Female		NH White	NH African American	Hispanic	Other	12-17 Years of Age	<H.S	H.S./ GED	Some College	College	Grad/ Prof
MTF													
8th	52.2%	.8%	—	64.3%	6.0%	9.5%	20.2%	—	—	—	—	—	—
10th	76.8%	23.2%	—	69.2%	8.9%	11.3%	10.6%	—	—	—	—	—	—
12th	53.7%	46.3%	—	70.7%	2.1%	2.2%	25.0%	—	—	—	—	—	—
College	—	—	—		—	—		—	—	—	—	—	—
Young adults (19-28)	—	—	—		—	—			—	—	—	—	—
NYTS	78.9%	21.1%	15.73	63.3%	3.9%	23.1%	9.7%	100%	—	—	—	—	—
NSDUH													
12-17	84.9%	15.1%	15.84	86.3%	0.4%	3.5%	9.8%	100%	—	—	—	—	
≥ 18	93.6%	6.4%	32.38	83.6%	4.8%	8.0%	3.6%	—	19.9%	36.5%	30.5%	56.3%	
CPS-TUS	95.2%	4.8%	33.80	88.4%	2.9%	4.7%	4.0%	—	16.6%	42.8%	21.8%	17.2%	1.6%
NHIS	86.7%	13.3%	37.04	85.7%	5.3%	6.6%	2.4%	—	13.3%	41.4%	17.3%	25.8%	2.2%

Note: Differences in methodology occur at the past 30-day use level, not the concurrent use level. Some surveys use "now" whereas others use "past month" and yet others use "past 30 days". Each of those terms was used synonymously when defining past 30-day use. Concurrent use was defined as past 30-day use of cigarettes and past 30-day use of smokeless tobacco for all surveys. Age values are means. Additionally, note that CPS-TUS represents "Current Population Survey – Tobacco Use Supplement, ages 18+ only" and the symbol — represents data not assessed by survey.).

Cigarettes Per Day (Daily Smokers)

SURVEY NAME	Cigarettes per Day for Daily Smokers				
	Overall (All Daily Smokers)	Daily Smokeless Use, Past Month	Non-Daily Smokeless Use, Past Month	No Past Month Smokeless Use	No Information (Missing) on Past Month Smokeless Use
MTF					
8th	8.65	21.73**	9.02	9.19	8.00
10th	8.17	9.04	4.41	7.36	9.06
12th	7.66	11.56***	9.44	9.55	7.27
College	—	—	—	—	—
Young adults (19-28)	—	—	—	—	—
NYTS	11.30	14.14		9.37	—
NSDUH					
12-17	9.38	10.21	9.01	9.42	—
18 and older	14.94	12.49	15.70	14.93	—
CPS-TUS	15.31	16.72	16.73	15.30	14.58
NHIS	13.55	10.66	15.01	13.54	—

Note: **(Unweighted N=4 leaving uncertainty as to the reliability of these estimates) and *** (Unweighted N=5 leaving uncertainty as to the reliability of these estimates). Additionally, note that CPS-TUS represents "Current Population Survey – Tobacco Use Supplement, ages 18+ only" and the symbol — represents data not assessed by survey.

12 Appendix H: RJRT National Tobacco Behavior Monitor (NTBM)

Tobacco Use Patterns Across Products (NTBM)

Tobacco Product Type†	Camel Snus	Non Camel Snus	Loose Moist Snuff	Portioned Moist Snuff	Loose Leaf Chew
weighted count	*555*	*968*	*2625*	*1322*	*1212*
Use Behavior Category					
solo user (%)[1]	**7.2**	**3.7**	**22.6**	**6.7**	**7.6**
weighted count[2]	*40*	*35*	*594*	*89*	*92*
dual use w/ cigarettes (%)	**8.6**	**4.1**	**6.9**	**3.4**	**1.8**
weighted count	*48*	*40*	*182*	*45*	*22*
dual use w/ combustibles* (%)	**5.0**	**2.9**	**5.7**	**3.9**	**2.5**
weighted count	*28*	*28*	*149*	*52*	*31*
dual/poly use w/ combustibles and non-combustibles (%)	**68.1**	**80.5**	**54.7**	**76.3**	**77.6**
weighted count	*378*	*779*	*1436*	*1008*	*940*
dual/poly use w/ non-combustibles (%)	**11.0**	**8.8**	**10.0**	**9.7**	**10.5**
weighted count	*61*	*86*	*263*	*128*	*128*

Note. Table is identical to that presented in RAI Services Company, 2017. Use of the terminology "dual use" was changed to "concurrent" when reporting on findings in the present Pinney Associates report.
† Respondents reporting use of tobacco product on one or more days during past 30 days; and, Camel Snus, used most often and considered as usual brand. * This includes dual users with cigarettes and/or another combustible product that is typically smoked like cigarettes, such as roll-your-own cigarettes, little cigars, and cigarillos - but who are **not** included within the 'dual use w/ cigarettes' category (only use smokeless product and cigarettes). [1] Bolded values in table represent percentages within categories; some columns may not add to 100% due to rounding/weighting. [2] Italicized values represent weighted counts.

Tobacco Use Frequency (use in past week) among P30D Users (NTBM)

Tobacco Product Type†	Camel Snus	Non Camel Snus	Loose Moist Snuff	Portioned Moist Snuff	Loose Leaf Chew
Weighted count	*555*	*968*	*2625*	*1322*	*1212*
Tobacco Use Frequency (days/week)					
0-1 d/wk (%)[1]	**46.2**	**43.9**	**28.3**	**45.4**	**46.9**
weighted count[2]	*257*	*425*	*743*	*601*	*569*
2-5 d/wk (%)	**39.2**	**44.4**	**37.6**	**39.2**	**41.3**
weighted count	*218*	*430*	*987*	*519*	*500*
6-7 d/wk (%)	**13.9**	**11.7**	**34.1**	**15.3**	**11.8**
weighted count	*77*	*113*	*894*	*203*	*143*
Mean, days/week	**2.4**	**2.4**	**3.7**	**2.5**	**2.4**
95% CI	**(2.3, 2.6)**	**(2.3, 2.6)**	**(3.7, 3.8)**	**(2.4, 2.7)**	**(2.2, 2.5)**

Note. Table is identical to that presented in RAI Services Company, 2017.
† Respondents reporting use of tobacco product on one or more days during past 30 days; and, Camel Snus, used most often and considered as usual brand (and style). [1] Bolded values in table represent percentages within categories (some columns may not add to 100% due to rounding/weighting) and/or means with 95% confidence intervals. [2] Italicized values represent weighted counts.

Tobacco Use Rate (uses per day on days used in the past week) (NTBM)

Tobacco Product Type[†]	Camel Snus	Non Camel Snus	Loose Moist Snuff	Portioned Moist Snuff	Loose Leaf Chew
Weighted count [^]	*425*	*789*	*2284*	*1055*	*944*
Tobacco Use Rate (uses/day)					
1 use/d (%)[1]	**35.2**	**37.2**	**22.2**	**36.7**	**36.7**
weighted count[2]	*150*	*293*	*507*	*387*	*347*
2 uses/d (%)	**22.1**	**21.1**	**18.3**	**19.2**	**22.9**
weighted count	*94*	*166*	*417*	*202*	*216*
3-4 uses/d (%)	**21.1**	**20.8**	**21.3**	**18.7**	**19.5**
weighted count	*90*	*164*	*486*	*198*	*184*
5-6 uses/d (%)	**11.3**	**13.9**	**17.7**	**12.7**	**11.0**
weighted count	*48*	*110*	*404*	*134*	*104*
7+ uses/d (%)	**10.3**	**7.0**	**20.6**	**12.7**	**9.9**
weighted count	*44*	*55*	*470*	*134*	*94*
Mean, uses/day	**3.2**	**2.9**	**4.5**	**3.4**	**3.1**
95% CI	**(2.9, 3.4)**	**(2.8, 3.1)**	**(4.4, 4.7)**	**(3.2, 3.6)**	**(2.9, 3.2)**

Note. Table is identical to that presented in RAI Services Company, 2017.
[†] Respondents reporting use of tobacco product on one or more days during past 30 days; and, Camel Snus, used most often and considered as usual brand. [^] Weighted counts reduced due to non-response on question for product use rate; estimates for percentages within categories and means based on available data (exclude non-responses). [1] Bolded values in table represent percentages within categories (some columns may not add to 100% due to rounding/weighting), and means with 95% confidence intervals. [2] Italicized values represent weighted counts.

Use of Cigarettes and Camel Snus (NTBM)

Tobacco Use Pattern[†]	Cigarettes	Cigarettes with Camel SNUS
Weighted count	*13455*	*433*
Cigarette Use Frequency (d/wk)		
0-1 d/wk (%)[1]	**8.4**	**19.6**
weighted count[2]	*1134*	*85*
2-5 d/wk (%)	**15.1**	**25.3**
weighted count	*2030*	*109*
6-7 d/wk (%)	**76.5**	**55.1**
weighted count	*10292*	*239*
Mean, days/week	**5.9**	**4.8**
95% CI	**(5.9, 5.9)**	**(4.6, 5.0)**

Note. Table is identical to that presented in RAI Services Company, 2017.
[†] Respondents reporting use of tobacco product on one or more days during past 30 days; and, Camel Snus, used most often and considered as usual brand.
[1] Bolded values in table represent percentages within categories (some columns may not add to 100% due to rounding/weighting), and means with 95% confidence intervals. [2] Italicized values represent weighted counts.