6.1.5 Chemistry Studies

6.1.5.1 Rationale for the investigation of tobacco and smoke chemistry in comparative evaluations of different tobacco products

The chemical characterization of tobacco and tobacco smoke has been an active and intensive area of research for many decades. While early work in the field relied exclusively on classical analysis techniques, the advent of modern instrumental analysis techniques rapidly advanced understanding of these two complex chemical mixtures. Currently, more than 5,000 unique chemical constituents have been identified in both tobacco and tobacco smoke (Perfetti and Rodgman 2011). While much is now known about the chemical composition of tobacco and tobacco smoke, there remains uncertainty regarding whether particular components present in tobacco or tobacco smoke are responsible for specific adverse health outcomes. There is, however, broad scientific agreement that several major classes of chemicals present in either tobacco or tobacco smoke are toxic and carcinogenic (USDHHS 2010).

The FDA's MRTPA Draft Guidance (FDA MRTPA Draft Guidance 2012) recommends providing the results of product chemistry testing in an MRTPA. The draft guidance states:

> *"Product analyses regarding the chemistry and engineering of the product may be used to verify and validate the information submitted regarding the formulation of the product. In addition, product analyses will facilitate FDA's understanding of the product, the potential for exposure to harmful or potentially harmful constituents from use of the product, and provide context for evaluating other data submitted in an MRTPA."*

Specifically, FDA recommends that applicants conduct product analyses to determine levels of harmful and potentially harmful constituents (HPHC), including smoke constituents, as appropriate to the product that is the subject of the application. The FDA has identified a full set of 93 HPHCs (FDA 2012c) and currently mandates testing and reporting an abbreviated list of HPHCs (FDA 2012b) in tobacco smoke (18 HPHCs), smokeless tobacco (9 HPHCs) and roll-your-own / cigarette filler (6 HPHCs). The identified HPHCs represent several chemical classes in tobacco and/or mainstream cigarette smoke, including nicotine and related tobacco alkaloids, carbon monoxide, tobacco-specific nitrosamines (TSNAs), polycyclic aromatic hydrocarbons (PAHs), volatile organic compounds (VOCs), carbonyls, aromatic amines, and metals.

The initial criteria for HPHC selection was based on whether the constituent was identified as one or more of the following: a carcinogen, a respiratory toxicant, a cardiovascular toxicant, a reproductive or developmental toxicant, or addictive. FDA selected the constituents on the abbreviated list (Table 6.1.5-1) based on the availability of established analytical methods and a desire to include different chemical classes of tobacco toxicants.

Table 6.1.5-1: Abbreviated list of harmful and potentially harmful constituents

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

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

Chemical analyses provide information about specific characteristics of a tobacco product, *e.g*, HPHC content of tobacco leaf or smoke. However, results of such analyses do not provide insight into actual exposure to HPHCs when a tobacco product is used. Rather, exposure to constituents present in a tobacco product or tobacco smoke is the net result of multiple factors, including the manner of use (*e.g,* smoking vs. placement of tobacco in the mouth), product use behaviors (*e.g,* cigarette puffing behavior or smokeless tobacco time held in mouth), the chemical composition of the product or smoke, and the route of exposure. When smoking cigarettes, the primary sites of exposure are the mouth (during puffing) and the respiratory tract (during and after inhalation). When using a smokeless tobacco product such as Camel Snus, the primary sites of exposure are the mouth and potentially the gastrointestinal tract, with little or no chance of direct lung exposure. Given these significant differences, insight into actual exposure to HPHCs when using either cigarettes or Camel Snus is best accomplished via biomarker measurements. Studies that measure exposure biomarkers provide more accurate assessments of exposure and risk than do product analyses, as biomarkers are the result of product use behavior and not merely the characteristics of the tobacco product itself (Chang *et al.* 2016). Biomarkers capture actual human exposure to tobacco products, or internal dose, in contrast to product analyses which capture external measures of potential exposure. Product analyses can, in some instances, provide information regarding the maximum potential for exposure to a given toxicant that is present in the product.

6.1.5.2 Published chemistry studies of cigarette smoke

The analytical smoking of cigarettes via a machine to determine mainstream smoke yields has been practiced since at least the 1930s (Bradford *et al.* 1936). Prior to the late 1960s, no uniform testing approach existed for the purpose of analytical smoking, leading to different machine smoking regimens (*i.e.,* puffing conditions, butt lengths for termination of smoking, etc.) being practiced around the world. In 1967, a national testing standard was established by the U.S. Federal Trade Commission (FTC) for the determination of tar and nicotine in cigarette smoke. In doing so, the formal testing of cigarettes was mandated and specific directions, including the manner in which cigarettes should be smoked by a machine for analytical testing purposes, were provided (FTC 1967a). The test method became known as the "FTC cigarette test method" and the "Cambridge Filter method."

The FTC described the purpose of the test method in a 1967 News Release announcing the initiation of testing in the FTC laboratory (FTC 1967b). According to the press release, the method was intended to:

- Produce test results "based on a reasonable standardized method"
- Produce test results that are "capable of being presented to the public in a manner that is readily understandable"
- Produce test results "based on a uniform method used by all companies"
- Determine "the amount of tar and nicotine generated when a cigarette is smoked by machine in accordance with the prescribed method"
- Encompass "an amalgam of many choices – some of them arbitrary"

The method was *not* intended to:

- "Precisely duplicate conditions of actual human smoking"
- Gauge "the amount of smoke, or tar and nicotine, which the 'average' smoker will draw from a particular cigarette"
- Measure "the many variations in human smoking habits"

- Determine "the amount of tar and nicotine inhaled by any human smoker"

The stated scope and associated limitations of the test method first announced in 1967, were reiterated by C. Lee Peeler from the FTC's Bureau of Consumer Protection during a 1994 public meeting convened to review the FTC testing method (Peeler 1996):

> "From the outset, the testing was intended to obtain uniform, standardized data about the tar and nicotine yield of mainstream cigarette smoke, ***not*** to replicate actual human smoking. The Commission recognized that individual smoking behavior was just that-too individual to gauge what a hypothetical "average" smoker would get from any particular cigarette: "No two human smokers smoke in the same way. No individual smoker always smokes in the same fashion" (Federal Trade Commission, 1967). The purpose of the testing was "not to determine the amount of 'tar' and nicotine inhaled by any human smoker, but rather to determine the amount of tar and nicotine generated when a cigarette is smoked by machine in accordance with the prescribed method" (Federal Trade Commission, 1967). Indeed, the Cambridge Filter method did not attempt to duplicate an "average" smoker but was "an amalgam of many choices" (Federal Trade Commission, 1967). Because no test could accurately duplicate human smoking, the Commission believed that the most important thing was to make certain the results presented to the public were based on a reasonable, standardized method and could be presented to consumers in an understandable manner."

The FTC test method for determination of tar, nicotine and carbon monoxide was rescinded in 2008 (FTC 2008).

Since the late 1990s, three other test methods that employ analytical smoking machines have been mandated for regulatory reporting purposes within the U.S. (Table 6.1.5-2). A smoking machine regimen referred to as "the Massachusetts smoking regimen" (MDPH regimen) is required as part of nicotine yield reporting for cigarettes in Massachusetts (Massachusetts 1997) and Texas (Texas 1997). More recently, the FDA has issued Draft Guidance recommending that the quantity of each HPHC in cigarette smoke be determined by both non-intense and intense smoking regimens (FDA 2012b). The two smoking regimens are expected to provide the Agency with information about possible different deliveries of HPHCs when a cigarette is smoked. The FDA specified the two smoking regimens as: "By intense smoking regimen we mean Canadian Intense, Health Canada Test Method T-401, and by non-intense smoking regimen we mean ISO 3308:2008 and ISO 5387:2000." Comparison of machine-generated smoke yields with actual mouth-level exposure to tar and nicotine when smoking U.S. cigarettes indicates that the International Organization for Standardization (ISO) and Canadian Intense (HCI) smoking regimens achieve the FDA's stated purpose (Borgerding and Klus 2005). Virtually all mouth-level smoke exposure is less than the amounts produced with the HCI regimen, most smoke exposure is intermediate between the two regimens and some smoke exposure is less than the amount produced with the ISO smoking regimen. As has been recognized since the advent of machine smoking methods, no single set of machine smoking conditions can predict actual human exposure. Smoking machines are operated under fixed conditions, while human smoking behavior is variable. Reviews of machine smoking methods and the relationship to human smoking behavior have been published by a number of authors (Baker 2002; Borgerding and Klus 2005; Dixon and Borgerding 2006; Marian *et al.* 2009).

Table 6.1.5-2: Smoking Regimens used for Regulatory Reporting Purposes in the U.S.

Smoking Regimen Designation:	**FTC Method**	**ISO 4387**	**Massachusetts**	**Canadian Intense**
Introduced in:	United States	International Standard	Massachusetts, Texas	Canada
Stated Purpose:	Cigarette Yield Ratings for Product Comparison	Cigarette Yield Ratings for Product Comparison	Estimate Nicotine Yield for an "Average" Smoker	Estimate "Maximum" Smoke Yields Under Realistic Conditions
Recommended in Current FDA Guidance	No	Yes	No	Yes
Puff Volume (cc)	35	35	45	55
Puff Frequency (s)	60	60	30	30
Puff Duration (s)	2	2	2	2
Vent Blocking (%)	0	0	50	100

Numerous surveys of machine-generated mainstream smoke chemistry have been published in recent years (*e.g,* Chepiga *et al.* 2000; Borgerding *et al.* 2000; Swauger *et al.* 2002; Counts *et al.* 2005; Counts *et al.* 2006; Bodnar *et al.* 2012; Piadé *et al.* 2015; Pazo *et al.* 2016). Studies have been based on one or more of the smoking machine regimens previously discussed. The studies have varied in the number of different U.S. cigarettes tested and in the number of mainstream smoke constituents measured. Examples of the types of studies and information provided include:

- Chepiga *et al.* 2000 summarizes the results of a survey of 29 U.S. cigarette brand styles purchased at retail in 1995. A total of 17 smoke constituents, plus tar, were measured in cigarette smoke generated using the FTC smoking regimen.

- Borgerding *et al.* 2000 is a study submitted to the Commonwealth of Massachusetts in order to establish functional relationships between selected smoke constituents (HPHCs) and tar, nicotine and carbon monoxide yields generated by both the FTC smoking regimen and the Massachusetts smoking regimen. The study was conducted on 26 U.S. cigarette brand styles sampled in 1999 which encompassed a wide range of cigarette design features. A total of 44 smoke constituents plus tar is reported.

- Swauger *et al.* 2002 summarizes the results of three surveys of U.S. cigarette brands which were conducted in 1995, 1998 and 2000. A total of 105 brand styles were analyzed for 19 smoke constituents using the FTC smoking regimen.

- Counts *et al.* 2005 reports results from a cigarette survey of Philip Morris USA and Philip Morris International cigarettes using the ISO, Massachusetts, and HCI smoking regimens. Seven of the brands tested were U.S. cigarettes. Cigarettes were sampled at production facilities from late 2000 to early 2001. Yields are reported for 44 smoke constituents plus tar and pH. Predictive functional relationships were developed between ISO tar yields and constituent yields observed for the three smoking regimens.

- Counts *et al.* 2006 reports on a survey of 26 U.S. cigarette brand styles smoked using the FTC smoking regimen with the goal of developing a *"*market map*"* comparison methodology for application in evaluating new or non-conventional cigarettes. The cigarette brand styles evaluated were sampled in 2002 and represented 30% of the U.S. market. The brand styles sampled were from brand families that represented 83% of the U.S. market. The yields of 42 smoke constituents plus tar are reported.

- Bodnar *et al.* 2012 reports results of a 2009 U.S. market survey that evaluated 95 cigarette brand styles using the HCI smoking regimen. The yields of 19 smoke constituents plus tar are reported.

- Piadé *et al.* 2015 reports on a survey of 568 commercial brand samples (489 unique brand styles) representing 27 different manufacturers. Samples were obtained in 23 countries between 2008 and 2012. The purpose of the study was to examine the transfer of metals and nicotine from tobacco to cigarette smoke using the ISO and HCI smoking regimens.

- Pazo *et al.* 2016 reports results of a sampling of 50 filtered cigarette brands that are analyzed using the ISO and HCI smoking regimens. The cigarette brands studied were from 2011 and represented 76% of U.S. brand families by market share. The yields of 21 volatile organic compounds are reported.

Results from these studies have been generally consistent with respect to the various amounts of HPHCs detected in mainstream smoke. HPHC concentrations in mainstream smoke span several orders of magnitude, including nanogram, microgram and milligram quantities, depending on the compound of interest (Table 6.1.5-3). The specific amounts of individual HPHCs in smoke vary from one cigarette brand style to the next, generally tracking tar and nicotine yields. Greater mainstream smoke yields are observed with more intense smoking regimens (*e.g*, Canadian Intense) than with less intense smoking regimens (*e.g*, ISO). Of note is the fact that while greater absolute HPHC yields are observed with more intense smoking regimens, HPHC yields per milligram of tar or nicotine generally decrease compared to less intense smoking (Dixon and Borgerding 2006).

Table 6.1.5-3: Selected Mainstream Smoke HPHC Yields Determined with Smoking Regimens used for Regulatory Reporting Purposes in the U.S.

Tobacco Product	U.S. Cigarettes	
Smoking Regimen	ISO*	HCI*
Compound	**Per Cigarette**	
Acetaldehyde (µg)	(141, 938)[a] (126, 1143)[b] (129, 601)[d]	(610, 1894)[c] (1098, 2244)[b] (930, 1438)[d]
Arsenic (ng)	(0.6†, 5.1)[a] (BDL, 3.9)[d]	(BQL, 9.7)[d]
B[a]P (ng)	(1.2, 9.5)[a] (1.0, 12)[d]	(9.1, 43)[c] (8.3, 24)[d]
Cadmium (ng)	(4.0, 73)[a] (5.1, 66)[d]	(11, 212)[c] (63, 143)[d]
Crotonaldehyde (µg)	(3.0, 39)[a] (0.9, 18)[b] (3.3, 20)[d]	(35, 75)[c] (29, 53)[b] (37, 58)[d]
Formaldehyde (µg)	(2.4, 61)[a] (4.0, 33)[d]	(55, 269)[c] (29, 66)[d]
Nicotine (mg)	(0.2, 1.0)[a] (0.5, 1.0)[d]	(1.3, 4.9)[c] (1.3, 2.4)[d]
NNK (ng)	(23, 124)[a] (38, 171)[d]	(25, 310)[c] (116, 263)[d]
NNN (ng)	(55, 234)[a] (19, 108)[d]	(34, 516)[c] (249, 392)[d]

Abbreviations: B[a]P = Benzo[a]pyrene; NNN= N'-nitrosonornicotine; NNK= 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, BDL=Below (unreported) Detection Limit, BQL=Below (unreported) Quantitation Limit.
Data sources: [a]Counts *et al.* 2006; [b]Pazo *et al.* 2016; [c]Bodnar *et al.* 2012; [d]Counts *et al.* 2005 (7 U.S. brands only)
* Range of individual product means (minimum, maximum) on a rounded basis.
† Indicates that the value was below the Limit of Quantitation (LOQ). The LOQ is given in the table.

6.1.5.3 Published chemistry studies of Camel Snus

Published studies reporting constituent levels of Camel Snus, as well as those of other novel smokeless products in the U.S. market, began appearing shortly after the introduction of Camel Snus (Hatsukami *et al.* 2007b), reflecting an increased interest in this growing segment of the U.S. tobacco market. Relevant published studies identified by a PubMed and Scopus search of "Camel Snus," and broadened by an examination of post-2005 publications that contained data on constituent levels in smokeless tobacco, are reviewed and summarized in this section of the Application. The studies that were identified provide useful information regarding constituent levels in Camel Snus and provide a basis for comparison to other smokeless tobacco products.

Eighteen studies published between 2007 and 2016 were identified that include chemical analysis results for Camel Snus. Table 6.1.5-4 lists the published studies and briefly summarizes the products tested and the analytes measured in each study. A full listing of individual Camel Snus styles tested is found in Table 6.1.5-5, Table 6.1.5-6 and Table 6.1.5-7.

Table 6.1.5-4: Summary Description of Publications Containing Chemical Analysis Results for Camel Snus

Reference	Title	Products Reported	Analytes Measured
Hatsukami *et al.* 2007b	Changing smokeless tobacco products. New tobacco-delivery systems	12 new smokeless tobacco products (*e.g*, snus), 6 moist snuff, 3 nicotine replacement products	4 TSNAs
Stepanov *et al.* 2008a	New and traditional smokeless tobacco: Comparison of toxicant and carcinogen levels	12 new and 5 traditional smokeless tobacco products	nicotine, 3 minor alkaloids, 4 TSNAs, 6 anions, 8 PAHs, 4 aldehydes, pH
Stepanov *et al.* 2010	Analysis of 23 polycyclic aromatic hydrocarbons in smokeless tobacco by gas chromatography-mass spectrometry	23 moist snuff and 17 snus products	23 PAHs
Hecht *et al.* 2011	Major tobacco companies have technology to reduce carcinogen levels but do not apply it to popular smokeless tobacco products	8 moist snuff and 6 snus products	NNN, NNK
Moldoveanu and Gerardi 2011	Acrylamide analysis in tobacco, alternative tobacco products, and cigarette smoke	6 smokeless tobacco products, 9 cigarettes, assorted tobacco samples	acrylamide
Stepanov *et al.* 2012a	Monitoring tobacco-specific N-nitrosamines and nicotine in novel Marlboro and Camel smokeless tobacco products: Findings from Round 1 of the New Product Watch	8 snus and 10 dissolvable smokeless tobacco products	moisture, pH, total and free nicotine, 4 TSNAs
Stepanov *et al.* 2012b	Increased pouch sizes and resulting changes in the amounts of nicotine and tobacco-specific N-nitrosamines in single pouches of Camel Snus and Marlboro Snus	60 samples of Camel Snus and 87 samples of Marlboro Snus purchased from 2006 to 2010	moisture, pH, total and free nicotine, NNN + NNK

Reference	Title	Products Reported	Analytes Measured
Borgerding *et al.* 2012	The chemical composition of smokeless tobacco: A survey of products sold in the United States in 2006 and 2007	43 U.S., 11 Swedish and 3 reference smokeless tobacco products	nicotine, B[a]P, 4 TSNAs, 5 metals, nitrite, chloride, NDMA
Stepanov *et al.* 2013	Levels of (S)-N'-nitrosonornicotine in U.S. tobacco products	14 moist snuff and 8 snus smokeless tobacco products, 17 cigarette products	moisture, total and (S)-NNN
Lawler *et al.* 2013	Chemical characterization of domestic oral tobacco products: Total nicotine, pH, unprotonated nicotine and tobacco-specific N-nitrosamines	4 plug, 3 loose leaf and 3 twist chewing tobacco products; 5 loose and 4 pouched dry snuff products; 3 snus products; 7 dissolvable tobacco products	moisture, pH, total and free nicotine, 5 TSNAs
Caraway and Chen 2013	Assessment of mouth-level exposure to tobacco constituents in U.S. snus consumers	3 Camel Snus styles	nicotine, 4 TSNAs, B[a]P, 5 metals
Li *et al.* 2013	A novel model mouth system for evaluation of *in vitro* release of nicotine from moist snuff	11 Swedish and 4 U.S. snus, 7 moist snuff, 1 Indian smokeless tobacco product	pH, total and free nicotine
Stepanov *et al.* 2014	Monitoring tobacco-specific N-nitrosamines and nicotine in novel smokeless tobacco products: Findings from Round II of the New Product Watch	12 snus and 11 dissolvable smokeless tobacco products	moisture, pH, total and free nicotine, 4 TSNAs
Hatsukami *et al.* 2015	Evidence supporting product standards for carcinogens in smokeless tobacco products	23 moist snuff and 8 snus products	total and free nicotine, NNN, NNK
McAdam *et al.* 2015a	Analysis of hydrazine in smokeless tobacco products by gas chromatography-mass spectrometry	31 Swedish snus, 43 U.S. smokeless tobacco products (*e.g*, snus, moist and dry snuff, chewing tobacco, pellets)	hydrazine, water
McAdam *et al.* 2015b	The acrylamide content of smokeless tobacco products	31 Swedish snus, 43 U.S. smokeless tobacco (*e.g*, snus, moist and dry snuff, chewing tobacco, pellets)	moisture, pH, reducing sugars, ammonia nitrogen, acrylamide

Reference	Title	Products Reported	Analytes Measured
Cullen *et al.* 2015	Smokeless tobacco products sold in Massachusetts from 2003 to 2012: Trends and variations in brand availability, nicotine contents and design features	99 to 127 smokeless tobacco products per year	total and free nicotine, pH, moisture
Song *et al.* 2016	Chemical and toxicological characteristics of conventional and low-TSNA moist snuff tobacco products	7 U.S. moist snuff, 7 U.S., 3 Swedish and 2 South African snus products	pH, total and free nicotine, B[a]P, 4 TSNAs, 6 metals, formaldehyde, NDMA, nitrate, ammonia, 2 polyols

Abbreviations: TSNA = tobacco-specific nitrosamine, PAH = polycyclic aromatic hydrocarbons, NNN = N'-nitrosonornicotine, NNK = nicotine-derived nitrosamine ketone [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone], B[a]P = benzo[a]pyrene, NDMA = N-nitrosodimethylamine

Twelve of the publications report results for the analysis of tobacco-specific nitrosamines (TSNAs) in Camel Snus. Of these, six also include the analysis of TSNAs in multiple brands of conventional moist snuff. TSNA values for Camel Snus are summarized in Table 6.1.5-5 except for the results from Stepanov *et al.* 2012b, which only reported the sum of NNN+NNK. Values are converted to units of µg/g on an as-is, wet weight basis (as necessary) and are summarized by publication and Camel Snus product style. Factors applied for conversion to µg/g, wet weight basis units are provided in the footnotes to the table. Table 6.1.5-5 includes a comparison of all available published TSNA data with the reported results specific to Camel Snus styles that are the subject of this Application. The overall mean (all Camel Snus styles) and the mean for the Camel Snus styles submitted in this Application are similar for each of the TSNAs reported, in spite of a roughly 3-fold difference between the lowest and highest results reported by multiple laboratories over an eight-year publication time frame.

Table 6.1.5-5: Summary of Studies Reporting Tobacco-Specific Nitrosamines (TSNAs) in Camel Snus (µg/g, as-is)

Camel Snus Style		TSNA			
Variant	Pouch Size (mg)	NNN	NNK	NAT	NAB
Hatsukami *et al.* 2007b					
Original	400	0.79	0.16	0.19	0.008
Spice	400	0.87	0.09	0.20	0.010
Frost	400	0.83	0.16	0.13	0.006
Stepanov *et al.* 2008a[1]					
Original	400	0.791	0.186	0.204	0.008
Spice	400	0.874	0.108	0.210	0.010
Frost	400	0.826	0.184	0.140	0.006

Camel Snus Style		TSNA			
Variant	Pouch Size (mg)	NNN	NNK	NAT	NAB
Borgerding *et al.* 2012[1]					
Frost (2006)	400	0.704	<0.109	0.491	<0.041
Frost (2007)	400	0.684	0.234	0.593	0.051
Original (2006)	400	0.738	<0.109	0.530	<0.041
Original (2007)	400	0.737	0.219	0.656	0.068
Spice (2006)	400	0.725	<0.109	0.494	<0.041
Spice (2007)	400	0.667	0.170	0.559	0.046
Lawler *et al.* 2013					
Frost[5]	400/600[4]	0.425	0.146	0.265	0.028
Spice	400/600[4]	0.369	0.084	0.259	0.028
Original	400/600[4]	0.389	0.140	0.251	0.026
Song *et al.* 2016[2]					
Frost[5]	400/600[4]	0.83	0.27	0.44	0.05
Spice	400/600[4]	0.71	0.17	0.39	0.05
Original	400/600[4]	0.95	0.27	0.45	0.05
Hecht *et al.* 2011[2]					
Frost[5]	600	0.728	0.291	NR	NR
Mellow[5]	600	0.809	0.313	NR	NR
Stepanov *et al.* 2012a[1]					
Mellow[5]	600	0.606	0.285	0.231	0.016
Frost[5]	600	0.634	0.319	0.248	0.018
Robust[5]	1000	0.838	0.390	0.316	0.018
Winterchill[5]	1000	0.605	0.406	0.228	0.014
Caraway and Chen 2013[3]					
Frost[5]	600	0.713	0.238	0.368	0.049
Original	600	0.709	0.230	0.363	0.048
Spice	600	0.654	0.131	0.361	0.047
Stepanov *et al.* 2013					
Mellow[5]	600	1.14	NR	NR	NR
Frost[5]	600	1.04	NR	NR	NR
Robust[5]	1000	1.79	NR	NR	NR
Winterchill[5]	1000	1.20	NR	NR	NR
Stepanov *et al.* 2014[1]					
Robust[5]	1000	1.224	0.485	0.608	0.094
Mellow[5]	600	1.289	0.458	0.606	0.113
Frost[5]	600	1.331	0.468	0.623	0.089
Winterchill[5]	1000	1.215	0.442	0.637	0.088

Camel Snus Style		TSNA			
Variant	Pouch Size (mg)	NNN	NNK	NAT	NAB
Hatsukami *et al.* 2015					
Robust[5]	1000	1.22	0.48	NR	NR
Mellow[5]	600	1.29	0.46	NR	NR
Frost[5]	600	1.32	0.47	NR	NR
Winterchill[5]	1000	1.22	0.44	NR	NR
Mean (All Styles)		0.88	0.26	0.38	0.040
Mean (Selected Styles[5])		1.02	0.37	0.42	0.050

Abbreviations: NNN= N'-nitrosonornicotine; NNK= 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NAT= N'-nitrosoanatabine; NAB = N'-nitrosoanabasine; NR = not reported

[1] Values are reported on a dry weight basis in the cited publication. Reported values are converted to an as-is basis using moisture values reported in the paper.

[2] A 32% moisture value is used to convert values reported in the cited publication from a dry weight basis to an as-is basis.

[3] Values are reported on a per pouch, as-is, basis in the cited publication. A 0.6 g pouch weight is used to convert from µg/pouch to µg/g.

[4] Unable to establish pouch size based on sampling date range stated in paper.

[5] Camel Snus styles submitted in this Application.

Eleven of the publications report results for the nicotine content in Camel Snus and of these, 10 report the calculated amount of unprotonated nicotine based on pH measurements and application of the Henderson-Hasselbalch equation. Nine of the publications report pH results. Reported moisture, pH, and nicotine values are summarized in Table 6.1.5-6. Nicotine values are converted to units of mg/g on an as-is, wet weight basis (as necessary) and are compiled by publication and Camel Snus product style. Factors applied for conversion to mg/g, wet weight basis (wwb) are provided in the footnotes to the table. As with the TSNAs, the overall mean and the mean for the Camel Snus styles submitted in this Application are similar for moisture, pH, nicotine and unprotonated nicotine.

Table 6.1.5-6: A Summary of Studies Reporting Moisture, pH, and Nicotine in Camel Snus (as-is)

Camel Snus Style					
Variant	Pouch Size (mg)	Moisture %	pH	Nicotine (mg/g)	Unprotonated Nicotine (mg/g)
Stepanov *et al.* 2008a[1]					
Original	400	31.2	7.46	19.4	4.19
Spice	400	NR	7.75	17.5	6.30
Frost	400	NR	7.59	16.3	4.40

Camel Snus Style					
Variant	Pouch Size (mg)	Moisture %	pH	Nicotine (mg/g)	Unprotonated Nicotine (mg/g)
Borgerding *et al.* 2012[1]					
Frost (2006)	400	34.1	7.76	13.25	4.70
Frost (2007)	400	32.2	7.72	14.10	4.71
Original (2006)	400	34.3	7.73	13.87	4.70
Original (2007)	400	31.9	7.95	13.49	6.20
Spice (2006)	400	32.8	8.03	13.16	6.66
Spice (2007)	400	32.2	7.81	13.35	5.09
Lawler *et al.* 2013					
Frost[5]	400/600[4]	27.6	7.55	9.99	2.51
Spice	400/600[4]	20.5	7.64	8.97	2.63
Original	400/600[4]	29.5	7.70	11.3	3.68
Song *et al.* 2016[2]					
Frost[5]	400/600[4]	NR	7.76	10.21	3.62
Spice	400/600[4]	NR	7.51	13.78	3.25
Original	400/600[4]	NR	7.53	12.33	3.01
Stepanov *et al.* 2012b[1]					
Multiple	400	31	7.50	13.00	3.20
Multiple[5]	600	31	7.47	11.40	2.60
Multiple[5]	1000	34	7.67	9.40	2.89
Stepanov *et al.* 2012a [1]					
Mellow[5]	600	29.5	7.38	11.80	2.37
Frost[5]	600	29.2	7.43	11.65	2.53
Robust[5]	1000	34.5	7.78	9.12	3.33
Winterchill[5]	1000	33.4	7.68	11.09	3.06
Caraway and Chen 2013[3]					
Frost[5]	600	NR	NR	12.17	NR
Original	600	NR	NR	11.50	NR
Spice	600	NR	NR	10.83	NR
Li *et al.* 2013					
Winterchill[5]	600	NR	7.83	6.52	2.56
Stepanov *et al.* 2014[1]					
Mellow[5]	600	33.2	7.57	9.58	2.56
Frost[5]	600	32.8	7.59	8.96	2.73
Robust[5]	1000	33.5	7.55	8.76	2.27
Winterchill[5]	1000	32.9	7.61	8.90	2.54

Camel Snus Style					
Variant	Pouch Size (mg)	Moisture %	pH	Nicotine (mg/g)	Unprotonated Nicotine (mg/g)
Hatsukami *et al.* 2015					
Robust[5]	1000	NR	NR	8.77	2.27
Mellow[5]	600	NR	NR	9.57	2.55
Frost[5]	600	NR	NR	9.63	2.73
Winterchill[5]	1000	NR	NR	8.91	2.54
Cullen *et al.* 2015					
Multiple 2009-2012[5]	600 & 1000	33.8	7.72	8.75	2.48
Mean (All Styles)		31.6	7.65	11.47	3.46
Mean (Selected Styles[5])		32.1	7.61	9.68	2.65

Abbreviations: NR = not reported
[1] Values are reported on a dry weight basis in the cited publication. Reported values are converted to an as-is basis using moisture values reported in the paper.
[2] A 32% moisture value is used to convert values reported in the cited publication from a dry weight basis to an as-is basis.
[3] Values are reported on a per pouch, as-is, basis in the cited publication. A 0.6 g pouch weight is used to convert from mg/pouch to mg/g.
[4] Unable to establish pouch size based on sampling date range stated in paper.
[5] Camel Snus styles submitted in this application.

An additional set of analytes reported for Camel Snus in multiple papers is summarized in Table 6.1.5-7. Analytes include: benzo[a]pyrene (B[a]P) (5 publications), arsenic, cadmium, chromium, lead and nickel (3 publications) and acrylamide (2 publications).

Table 6.1.5-7: Summary of Studies Reporting B[a]P, Metals and Acrylamide in Camel Snus (ng/g, as-is)

Camel Snus Style								
Variant	Pouch Size (mg)	B[a]P	Arsenic	Cadmium	Chromium	Lead	Nickel	Acrylamide
Stepanov *et al.* 2008a[1]								
Original	400	7.2	NR	NR	NR	NR	NR	NR
Spice	400	ND	NR	NR	NR	NR	NR	NR
Frost	400	ND	NR	NR	NR	NR	NR	NR

Camel Snus Style								
Variant	Pouch Size (mg)	B[a]P	Arsenic	Cadmium	Chromium	Lead	Nickel	Acrylamide
Borgerding *et al.* 2012[1]								
Frost (2006)	400	0.72	124	356	1252	145	1441	NR
Frost (2007)	400	1.29	92	435	984	153	1016	NR
Original (2006)	400	0.79	103	372	1198	181	1369	NR
Original (2007)	400	0.89	< 41	349	823	151	939	NR
Spice (2006)	400	0.87	101	353	985	148	1165	NR
Spice (2007)	400	1.22	73	502	1044	146	1158	NR
Song *et al.* 2016 [2]								
Frost[5]	400/600[4]	0.50	789	544	558	258	877	NR
Spice	400/600[4]	0.51	415	490	904	292	1129	NR
Original	400/600[4]	0.52	762	524	707	313	1020	NR
Stepanov *et al.* 2010[2]								
Original	600	10.3	NR	NR	NR	NR	NR	NR
Spice	600	10.2	NR	NR	NR	NR	NR	NR
Frost[5]	600	10.1	NR	NR	NR	NR	NR	NR
Mellow[5]	600	< 1.1	NR	NR	NR	NR	NR	NR
Caraway and Chen 2013[3]								
Frost[5]	600	0.98	83	331	436	121	643	NR
Original	600	0.88	83	328	430	119	612	NR
Spice	600	1.42	76	326	420	112	572	NR
Moldoveanu and Gerardi 2011								
Frost[5]	600	NR	NR	NR	NR	NR	NR	82.7
Robust[5]	1000	NR	NR	NR	NR	NR	NR	69.9
McAdam *et al.* 2015b								
Mellow[5]	600	NR	NR	NR	NR	NR	NR	68.3
Frost[5]	600	NR	NR	NR	NR	NR	NR	66.3
Mean (All Styles)[6]		2.92	229	409	812	178	995	71.8
Mean (Selected Styles[5])[6]		3.18	436	438	497	189	760	71.8

Abbreviations: NR = not reported

[1] Values are reported on a dry weight basis in the cited publication. Reported values are converted to an as-is basis using moisture values reported in the paper.

[2] A 32% moisture value is used to convert values reported in the cited publication from a dry weight basis to an as-is basis.

[3] Values are reported on a per pouch, as-is, basis in the cited publication. A 0.6 g pouch weight is used to convert from ng/pouch to ng/g.

[4] Unable to establish pouch size based on sampling date range stated in paper.

[5]Camel Snus styles submitted in this application.

[6]Values for the limit of quantitation are included in the mean.

6.1.5.3.1 Summary of Camel Snus chemistry results by individual publication

Hatsukami *et al.* 2007b: A 2007 report by Hatsukami and co-workers addresses *"*changing smokeless tobacco products*"* and summarizes available literature on the toxicity of such products. The report shows that Camel Snus (Original, Spice, Frost) is lower in TSNAs compared with leading conventional smokeless tobacco products of the time (*i.e.*, Copenhagen and Skoal moist snuff). The authors state:

> *"*… in 2006, Camel Snus (marketed by Reynolds American, Inc. (*sic*), Winston-Salem NC) and Taboka Tobaccopak (manufactured by Phillip Morris, Richmond VA) were introduced for test marketing. Camel Snus is manufactured by Swedish Match (*sic*) and adheres to the same manufacturing standards as the other Swedish snus products. Furthermore, retailers store Camel snus in a chilled container, but the product does not have to be refrigerated during use. Camel snus is sold in spice, menthol (*sic*), and original flavors.*"*

Additionally, the authors state:

> *"*… products such as Taboka have relatively low nicotine concentrations (data presented by Phillip Morris at a meeting at the Harvard School of Public Health), whereas Camel Snus is reported to have nicotine amounts that are similar to Camel cigarettes and blood nicotine concentrations potentially similar to levels in cigarette smokers (www.snuscamel.com). This information has not been publicly released by the manufacturers and the products have not been made widely available for analysis.*"*

TSNA values reported for Camel Snus are summarized in Table 6.1.5-5.

Stepanov *et al.* 2008a: Stepanov and co-workers compared constituent levels of new smokeless tobacco products, including Camel Snus, with those of traditional smokeless brands from the U.S. market. Products were purchased in retail stores between August 2006 and August 2007. Taboka Original and Taboka Green were purchased in Indianapolis, Indiana. Four varieties of Marlboro Snus (Rich, Mild, Spice, and Mint) were purchased in Dallas, Texas; while Camel Snus (Original, Spice, and Frost) and Skoal Dry (Regular, Cinnamon, and Menthol) were purchased in Austin, Texas. The authors reported that total TSNAs (the sum of the 4 measured nitrosamines) averaged 1.97 µg/g tobacco for all varieties of Taboka, Marlboro Snus and Camel Snus, which was lower than Swedish Match General snus (3.10 µg/g total TSNAs). Skoal Dry (averaged 4.54 µg/g total TSNAs in 3 varieties tested) had a TSNA content greater than in the other new products (*i.e.*, Taboka, Marlboro Snus and Camel Snus), but lower than that found in traditional Skoal, Copenhagen, and Kodiak. Overall, Taboka, Marlboro Snus, and Camel Snus product styles were reported to contain relatively low amounts of NNN, with the exception of Marlboro Snus Mint (3.28 µg NNN/g tobacco) which contained an amount comparable to traditional U.S. moist snuff products. TSNA values reported for Camel Snus are summarized in Table 6.1.5-5 after conversion from a dry weight basis (dwb) to a wet weight basis (wwb).

Stepanov *et al.* reported that levels of total and unprotonated nicotine in Camel Snus were comparable to those found in conventional smokeless tobacco. The authors state, "Camel Snus, slightly higher in total nicotine and pH than Taboka and Marlboro Snus, contains up to 9 mg unprotonated nicotine per gram dry weight—an amount similar to the most popular traditional brands." In addition, the ratio of minor alkaloids to nicotine in Camel Snus was similar to that observed in traditional smokeless tobacco products. Reported pH, nicotine, and unprotonated nicotine values (wwb) for Camel Snus are shown in Table 6.1.5-6.

Ten-fold lower levels of nitrite were found in the new products (including Camel Snus) and in Swedish Match General snus compared to the traditional moist snuff products. The authors state, "The relatively low levels of nitrite and nitrate in the new smokeless tobacco products probably reflect the manufacturer's effort to reduce toxicity of their products and to limit TSNA formation during tobacco processing." For the products tested, Camel Snus was found to have the highest levels of formate, and more chloride than the other new smokeless tobacco products evaluated.

Trace levels of B[a]P were reported in Marlboro Snus Rich, Mild, and Mint, Camel Snus Original and Skoal Dry Regular and Menthol; averaging 3.12 ng/g tobacco (dwb). B[a]P was detected at higher levels in all traditional smokeless tobacco products tested, averaging 38.2 ng/g (dwb). Reported B[a]P values for Camel Snus (converted to a wwb) are included in Table 6.1.5-7.

The authors emphasize the importance of minimizing the TSNA content of smokeless tobacco products and state:

> "Because of their abundance in some smokeless tobacco products and existing strong evidence supporting their role in causation of oral and pancreatic cancer in smokeless tobacco users, TSNAs have become a reference group of carcinogens in these products, their levels to some extent defining the degree of risk."

Based on the relatively low levels of NNN and NNK found in Camel Snus and other snus products, the authors note that the products likely contain tobaccos processed by "pasteurization," which leads to lower levels of TSNAs. The authors find the observed reduction in carcinogenic TSNA content in Camel Snus and other new smokeless tobaccos "encouraging."

Differences in PAH content are also observed between new smokeless tobacco products such as Camel Snus and traditional smokeless tobacco products. Based on the differences noted, the authors state, "The low levels of PAH in the new smokeless tobacco is a very positive sign (Stepanov *et al.* 2008a, Table 3). Anthracene, BbF, BkF, and BaP are virtually undetectable in these products, while other PAHs are present in trace amounts. However, PAH levels in the most popular brands [of smokeless tobacco] currently used by millions of consumers are in some cases remarkably elevated."

Stepanov *et al.* 2010: In a report by Stepanov and co-workers, a new gas chromatography-mass spectrometry (GC-MS) method was developed to determine 23 polycyclic aromatic hydrocarbons (PAHs) in smokeless tobacco. Both conventional moist snuff products (23 brands) and newer varieties of smokeless tobacco (17 brands referred to as "spit-free") including Camel Snus Original, Spice, Frost and Mellow were analyzed. The list of PAHs determined was extensive and included priority environmental PAH pollutants identified by the U.S. Environmental Protection Agency (EPA), as well as carcinogenic PAHs that, according to the International Agency for Research on Cancer (IARC), are present in cigarette smoke. Moist snuff samples were obtained from retailers in Minneapolis, MN, between July 2007 and July 2009. New spit-free varieties of smokeless tobacco were purchased in retail stores between August 2008 and July 2009.

The total PAH levels (dwb) determined for Camel Snus range from 1,170 to 1,430 ng/g, while the average level found for moist snuff products was 11,600 ng/g. B[a]P levels for Camel Snus range from below the limit of quantitation to 15.2 ng/g (dwb) The average concentration reported for moist snuff products was 56 ng/g (dwb). The authors found generally consistent levels of PAHs for all moist snuff products tested:

> "With the exception of Hawken Long Cut Wintergreen, the levels of individual PAHs were very similar across various brands of conventional moist snuff. Average amounts of detected PAHs in these products ranged from 7.5 ng/g dry weight for DBahA to 4700 ng/g tobacco for PHE."

PAH levels were more variable, but much lower, for the new spit-free products.

> "The levels of PAH in the new spit-free tobacco products were much lower than those in moist snuff (Table 4), total PAHs averaging 1280 (±276) ng/g tobacco. The levels of individual PAH in these products were not as consistent across different brands as in moist snuff: PHE varied from 9.4 ng/g dry weight in Marlboro Snus Peppermint to 79.4 ng/g dry weight in Camel Snus Spice; the FLT content in the same products was 5.6 and 59.7 ng/g dry weight, respectively, and the B[a]P content was below the LOQ and 15.0 ng/g dry weight, respectively (Table 4)."

A single PAH (naphthalene) was found in both types of products at similar levels.

> "The only PAH that was present in both types of smokeless tobacco in comparable amounts was NP: 1730 (±392) ng/g dry weight in moist snuff and 1110 (±207) ng/g dry weight in the spit-free products, accounting for 15 and 87%, respectively, of the average total PAHs in these products."[1]

The authors indicate that their findings demonstrate PAHs are one of the most prevalent groups of carcinogens in moist snuff and that the use of moist snuff can be considered an important source of human exposure to PAHs, along with smoking. They also state, "The low amounts of PAHs in the brand Hawken and in various new spit-free smokeless brands represent direct and strong evidence that their amounts in moist snuff can be also brought to trace

[1] Acronyms within the preceding quotes indicate the following compounds: dibenz[a,h]anthracene (DBahA); phenanthrene (PHE); fluoranthene (FLT); benzo[a]pyrene (B[a]P) and naphthalene (NP).

levels." (Of note is the fact that Hawken is mislabeled as a moist snuff by the authors. Hawken is a loose leaf smokeless tobacco product, rather than a moist snuff tobacco product. Therefore, based on typical tobacco blend and tobacco processing differences between loose leaf and moist snuff tobacco products, it is expected that products like Hawken will have lower amounts of PAHs than moist snuff smokeless tobacco products.)

Hecht *et al.* 2011: Hecht and co-workers analyzed levels of NNN and NNK in samples of Camel Snus (Table 6.1.5-5) as part of a study that compared levels of NNN and NNK in "spit-less" brands (Camel Snus and Marlboro Snus) with market-leading traditional moist snuff brands (Copenhagen, Skoal, Grizzly, and Kodiak). Results obtained showed substantially lower levels of NNN and NNK in "spit-less" snus products (including Camel Snus) compared with traditional moist snuff products, and that the levels of NNN and NNK in Camel Snus were "similar to those found in Swedish snus products."

Moldoveanu and Gerardi 2011: Acrylamide levels were determined in samples of tobacco, tobacco smoke, and several smokeless tobacco products, including Camel Snus. All tobacco values were reported on a ng/g tobacco as-is basis. Based on results from a novel LC-MS-MS method, acrylamide levels in tobacco samples (Moldoveanu and Gerardi 2011,Table IV) ranged from 45.8 ng/g in "mixed stem" tobacco to 119.6 ng/g in tobacco from a commercial cigarette). Acrylamide levels in tobacco from Camel Snus Frost (82.7 ng/g) and Camel Snus Robust (69.9 ng/g) were similar to (86.5 ng/g) or less than (179.9 ng/g) values reported for commercial moist snuff products. The levels found in smokeless tobacco products were generally consistent with levels found in tobacco leaf.

The investigators evaluated smoke from seven commercial cigarettes in the U.S. market, as well as 2R4F and 3R4F reference cigarettes. Smoke samples were collected using several different smoking conditions, including both International Organization for Standardization (ISO) and Health Canada Intense (HCI) regimens for the reference cigarettes. In addition to the ISO and HCI smoking regimens, a smoking regimen consisting of a 60 mL puff volume, 2 s puff duration and 30 s interpuff interval was used for testing of some of the commercial cigarette samples. The cigarettes tested contained 610 to 753 mg of tobacco. Using ISO smoking conditions, acrylamide levels in smoke (ng/cigarette) ranged from 497 ng/cigarette ("Cigarette F") to 2728 ng/cigarette ("Cigarette B"). The intense smoking regimens yielded acrylamide levels 3- to 4-fold higher than ISO smoking conditions. Collectively, the data indicate that acrylamide levels measured in a pouch of Camel Snus are approximately 15-fold lower than acrylamide levels found in the smoke of a single cigarette smoked under ISO conditions, and an additional 3- to 4-fold lower than per cigarette yields when smoked under intense smoking conditions.

Stepanov *et al.* 2012a: Stepanov and colleagues report results for nicotine and TSNA analyses performed on market samples of Camel Snus and Marlboro Snus, as well as other new smokeless products, purchased as part of the "New Product Watch" project, a national program for monitoring oral tobacco products. Products were purchased in 2010 from six separate regions around the country and subsequently analyzed for constituent levels and variability. The products (and number of replicate samples) tested were: Camel Snus Mellow (17), Camel

Snus Frost (17), Camel Snus Robust (1), Camel Snus Winterchill (1), Marlboro Snus Rich (18), Marlboro Snus Mild (18), Marlboro Snus Spearmint (17) and Marlboro Snus Peppermint (18). The sample sizes achieved were sufficient for statistical comparisons in all cases except for Camel Snus Robust and Camel Snus Winterchill. Sample sizes for those two products were too small to be included in the comparisons.

The Marlboro Snus and Camel Snus products differed in pouch size and moisture content, with Camel Snus having larger pouch sizes (600 mg for Camel Snus Mellow and Camel Snus Frost, 1000 mg for Camel Snus Robust and Camel Snus Winterchill, compared with 400 mg for Marlboro Snus) and higher moisture content (29 – 33% moisture for Camel Snus styles versus 14 – 20% moisture for Marlboro Snus products). As reported on a dry weight basis, Camel Snus contained higher levels of TSNAs than Marlboro Snus. However, TSNA levels in both Camel Snus and Marlboro Snus were very low. The authors note that total TSNA levels in Camel Snus in this study were similar to those measured in products purchased in 2006 for their previous study (Stepanov *et al.* 2008a).

All styles of Camel Snus were found to have higher pH, and consequently higher unprotonated nicotine content compared with all flavors of Marlboro Snus. Camel Snus exhibited up to 3-fold variation in calculated unprotonated nicotine by region (driven by small pH differences), but no regional differences in total nicotine. Samples obtained in and near Anchorage, AK produced the lowest levels of unprotonated nicotine, as calculated. Such findings are inconsistent with the fact that all Camel Snus styles contain a common blend of tobaccos and are formulated with an identical buffering system. The authors suggest that smokeless products with higher nicotine content could be more effective at satisfying smokers and completely substituting for cigarettes compared with those containing less nicotine, and postulate that observed differences in nicotine content may explain in part the greater popularity of Camel Snus compared with Marlboro Snus.

Stepanov *et al.* 2012b: A study reported by Stepanov and colleagues examined 60 samples of Camel Snus and 87 samples of Marlboro Snus obtained during 2006 – 2010 to determine whether changes in pouch size were accompanied by changes in TSNA and nicotine content. Constituent levels were consistent among the different product styles tested within a brand family, so results were combined by brand. No differences in moisture content or pH were noted for the three different Camel Snus pouch sizes tested. Total nicotine was lower in the 1000 mg pouch size compared with original 400 mg pouch Camel Snus products when expressed as nicotine per gram wet weight, but the difference was not statistically significant. Likewise, the sum of NNN plus NNK was not different across Camel Snus pouch sizes when expressed on a per gram wet weight basis. On an absolute amount per pouch basis, the largest pouch size (1000 mg) was found to contain the greatest amounts of total nicotine, unprotonated nicotine, and total TSNAs (NNN + NNK).

The authors suggest that even if constituent concentrations remain the same, larger pouch sizes mean higher exposures from a single portion of the product. However, without detailed product use information, it is not possible to, *a priori*, equate larger product sizes with increases in daily exposure to either nicotine or TSNAs. NNN and NNK exposure metrics are best assessed using biomarker measurements. In fact, available biomarker data indicate that exposure to nicotine and TSNAs does not increase when using larger Camel Snus pouch sizes as compared to smaller pouch sizes (Section 2).

Borgerding *et al.* 2012: Borgerding and coworkers published a survey of the chemical composition of smokeless tobacco products sold in the U.S. in 2006 and 2007. The products surveyed included moist, dry and dissolvable snuff, plug and loose leaf chewing tobacco. Camel Snus (Frost, Original, Spice) and other Swedish style snus were included in the moist snuff category. Also included were smokeless tobacco products sampled from the Swedish marketplace and University of Kentucky smokeless tobacco reference products. The survey was intended to provide a temporal point of comparison with future data anticipated from FDA HPHC reporting. Chemical constituents measured in the study were B[a]P and metals (cadmium, lead, arsenic, nickel, chromium) (Table 6.1.5-7); TSNAs (Table 6.1.5-5); and N-nitrosodimethylamine (NDMA), nitrite, chloride, pH and nicotine (Table 6.1.5-6).

TSNA results reported for Camel Snus were much lower than for other U.S. moist snuff and dry snuff products. NNN values observed for Camel Snus for all product styles sampled in 2006 and 2007 ranged from 984 to 1,123 ng/g (dwb), NNK results ranged from below the quantitation limit (~ 170 ng/g dwb) to 345 ng/g, and total TSNAs ranged from 2,041 to 2,468 ng/g. The 23 moist snuff brands averaged 4,058 ng/g NNN, 1,394 ng/g NNK, and 9,786 ng/g total TSNAs. The 5 moist snuff brands from the Swedish market contained similar amounts of TSNAs to Camel Snus and averaged 738 ng/g NNN, 275 ng/g NNK and 1,701 ng/g total TSNAs.

B[a]P results reported for Camel Snus ranged from 1.1 to 1.9 ng/g, similar to the Swedish moist snuff products that averaged of 1.9 ng/g. The average amount of B[a]P found for U.S. moist snuff products was much greater, 61.6 ng/g.

Results reported for arsenic, cadmium and lead were lower for Camel Snus and Swedish moist snuff products compared to U.S. moist snuff products. Nickel and lead levels were similar for all three categories. For all Camel Snus styles, nitrite and NDMA were found to either be below the limit of quantitation (1.89 µg/g and 3.90 ng/g, respectively) or at the detection limit (0.57 µg/g and 1.17 ng/g, respectively). Significant amounts of nitrite (113.5 µg/g average) and NDMA (14.6 ng/g average) were found for U.S. moist snuff brands. The average nitrite and NDMA values reported for Swedish snus brands were 4.6 µg/g and 13.4 ng/g, respectively.

Stepanov *et al.* 2013: Levels of (S)-N'-nitrosonornicotine ((S)-NNN) in a variety of tobacco products, including Camel Snus, were assessed in a study by Stepanov and colleagues. Using chiral gas chromatography, Stepanov *et al.* determined (S)-NNN levels in U.S. moist snuff products (14 brand styles purchased 2010 – 2012), U.S. snus products (4 styles of Camel Snus and 4 styles of Marlboro Snus), and tobacco from U.S. cigarette brands (17 brand styles) purchased in 2010.

Levels of NNN in moist snuff products ranged from 1.21 to 4.25 µg/g of tobacco (wet weight basis), from 0.72 to 1.79 µg/g in snus products, and 0.33 to 4.03 µg/g in cigarette tobacco.

Camel Snus styles (Robust, Mellow, Frost, Winterchill) ranged from 1.04 to 1.79 µg/g. (S)-NNN was the predominant NNN enantiomer in all tested products and averaged 62.9% of total NNN. On average, the amounts of (S)-NNN determined in Camel Snus were lower than either moist snuff products or cigarettes. For some individual moist snuff products, levels of (S)-NNN were similar to Camel Snus.

Lawler *et al.* 2013: CDC researchers investigated the levels of select constituents in a survey of U.S. oral tobacco products, excluding moist snuff, obtained from 2007 – 2009. The authors present data on the three major types of chewing tobacco (plug, loose leaf and twist), on two types of dry snuff (loose and pouched), on snus (including Camel Snus Frost, Spice and Original) and on dissolvable tobacco products. The authors compared their results to previously reported results (Richter *et al.* 2008) from 40 top-selling moist snuff products.

The authors note that the moisture content of the products analyzed in the study (3.87 – 29.5%) was lower than that of previously analyzed moist snuff products (44.5 – 54.5%). They found that chewing tobacco had relatively acidic pH values (4.73 – 5.98) resulting in a small percentage of total nicotine being present in the readily absorbed unprotonated form. Moist snuff, dry snuff, snus, and dissolvable tobacco products generally have more alkaline pH values than chewing tobacco, resulting in higher percentages of unprotonated nicotine. Camel Snus pH values reported were 7.55 to 7.70. Total nicotine concentrations (wet weight basis, wwb) of 3.90 to 40.1 mg/g were observed for all the products tested. Camel Snus total nicotine results were 8.97 to 11.3 mg/g. Camel Snus had the highest level of unprotonated nicotine among the products tested, ranging from 2.51 to 3.69 mg/g. Camel Snus results were comparable to the moist snuff average of 3.8 mg/g found in the Richter *et al.* (2008) study. The moisture, pH, nicotine and unprotonated nicotine values reported are included in Table 6.1.5-6.

For TSNAs (wwb), NNK levels ranged from 49 to 14,600 ng/g and NNN ranged from 74 to 31,300 ng/g for all products tested. Camel Snus results for NNK and NNN were 84 – 146 and 369 – 425 ng/g, respectively (Table 6.1.5-5). The authors summarize observed TSNA values by stating:

> *"*Mean total TSNA levels increased across oral tobacco product categories examined in this study following the trend: dissolvables < snus < dry snuff pouches < loose leaf < twist < plug < dry snuff. Previously reported mean total TSNA levels for moist snuff (Richter *et al.* 2008) are higher than values for plug but lower than dry snuff included in this study.*"*

The authors conclude that the results of their analyses support other reports suggesting newer forms of oral tobacco (*e.g*, snus and dissolvable tobacco products) contain lower TSNA levels than established forms of oral tobacco (*e.g*, dry snuff, twist, loose leaf, and plug products).

Caraway and Chen 2013: As part of a study to assess mouth-level exposure to toxicants, Caraway and Chen published chemical analysis results for Camel Snus samples (Frost, Original, and Spice) before and after use by adult consumers of the product. The baseline constituent levels for the unused products are presented below.

The authors report results for nicotine, TSNAs, B[a]P, arsenic, cadmium, chromium, lead and nickel (Caraway and Chen 2013, Table 2) on a mass/pouch, as-is basis. Using a pouch weight of 0.6 g and a moisture level of 32.3% to convert from a mass per pouch as-is to a mass/g (dwb) basis, mean nicotine for the 3 Camel Snus styles was 17.0 mg/g. For the other analytes tested, mean results (ng/g, dwb) were 1,022 (NNN), 295 (NNK), 537 (NAT), 71 (NAB), 1,924 (total TSNAs), 1.6 (B[a]P), 119 (arsenic), 485 (cadmium), 633(chromium), 173 (lead) and 899 (nickel).

Li *et al.* 2013: Li and colleagues analyzed 23 brands of pouched moist snuff from Sweden, the U.S. and India to determine pouch weight, pH, nicotine content and unprotonated nicotine. The products studied were used to test a novel model mouth system for evaluating the *in vitro* release of nicotine. Camel Snus Winterchill was one of the brands tested. The results (wwb) reported for Camel Snus Winterchill along with the range for all of the products tested (shown in parentheses) are as follows: weight 1.03 (0.36-1.54) g/pouch, pH 7.83 (5.80-10.24), nicotine 6.52 (4.77-16.32) mg/g and unprotonated nicotine: 2.56 (0.09-12.92) mg/g.

Stepanov *et al.* 2014: Stepanov and colleagues report results for nicotine and TSNA analyses performed on market samples of Camel Snus (Robust, Mellow, Frost, Winterchill), Marlboro Snus, Skoal Snus and dissolvable tobacco products. All products were purchased between April and July of 2011. The study sought to obtain representative averages for constituent levels by acquiring a sample of all styles of each brand tested from three different locations within each of six different regions of the U.S. (West, Midwest, Pacific Northwest, Northeast, Mid-Atlantic/Appalachian and South). From the determination of portion weights, the authors reported that Camel Snus Robust and Camel Snus Winterchill have larger pouch sizes than Camel Snus Mellow and Camel Snus Frost ($p<0.0001$). No differences in moisture, TSNAs, total nicotine, pH and unprotonated nicotine were found among the Camel Snus flavor varieties tested. Regional variation was observed for some endpoints. For example, the sum of NNN and NNK was greater in Camel Snus purchased in the Midwest than in any other region. Levels of TSNAs were higher for both Marlboro Snus and Camel Snus (compared to the previous round of testing), with both NNN and NNK contributing to these changes ($p < 0.0001$ for NNN and NNK). For Camel Snus styles, the mean NNN + NNK values reported increased from 1.50 µg/g in Round I to 2.58 µg/g in Round II.

Hatsukami *et al.* 2015: Hatsukami and colleagues report the effects of varying levels of nicotine and TSNAs in smokeless tobacco products, patterns of use, and demographic and tobacco history on extent of exposure to these carcinogens. In the study, the median values (wwb) of total nicotine, free nicotine, NNN and NNK are reported for 31 brand styles from 7 brands of moist snuff and snus. Camel Snus Robust, Mellow, Frost and Winterchill were included in the products tested. Total nicotine reported for Camel Snus (8.77 – 9.63 mg/g) was at the lower end of the range reported for all smokeless tobacco products tested (8.77 – 18.18 mg/g). Free nicotine results reported for Camel Snus (2.27 – 2.73 mg/g) were also within the range observed for other study products (0.57 – 7.58 mg/g). NNN+NNK results reported for Camel Snus (1.66 – 1.79 µg/g) were at the lower end of the range reported for all brands (0.64 – 14.55 µg/g).

McAdam *et al.* 2015a; McAdam *et al.* 2015b: McAdam and co-workers report analytical methodology and test results from a survey of smokeless tobacco products to determine hydrazine (McAdam *et al.* 2015a) and acrylamide (McAdam *et al.* 2015b). All tobacco samples were obtained in 2010 and were chosen to reflect approximately 90% market share of the major smokeless tobacco product categories in the U.S. (43 products) and Sweden (31 products). Camel Snus Mellow and Frost were included in the survey. For all products tested, hydrazine results are below the level of quantitation (26.5 ng/g). For acrylamide, the levels reported for Camel Snus Mellow and Camel Snus Frost were 99.5 and 96.7 ng/g (dwb), respectively. The mean values (ng/g, dwb) reported by product category were: U.S. moist snuff (349), U.S. snus including Camel Snus (432), hard pellets (96), chewing tobacco (205), dry snuff (213), Swedish loose snus (397), and Swedish pouched snus (368). The study also established that acrylamide is not stable on tobacco during storage, with a degradation half-life at 4 – 8 °C estimated at 12.5 days.

Cullen *et al.* 2015: Cullen and co-workers summarize the trends in nicotine content observed for smokeless tobacco products sold in Massachusetts from 2003 to 2012. Values for Camel Snus were reported in aggregate for all styles tested in 2009 – 2012, rather than on an individual style basis. The aggregate values are based on testing for 2 Camel Snus brand styles in 2009, 4 brand styles in 2010 and 2011, and 5 brand styles in 2012. For Camel Snus, the mean (standard deviation) un-ionized nicotine reported was 2.48 (0.23) mg/g, total nicotine was 8.75 (0.29) mg/g, pH was 7.72 (0.015) and moisture content was 33.8% (0.1%). The means for all moist snuff products reported were 3.93 mg/g un-ionized nicotine, 12.00 mg/g total nicotine, 7.59 pH, and 52.4% moisture content. Temporal trend analysis for Camel Snus products showed a significant increasing slope of 0.53 mg/g/y (dwb, p=0.005) for un-ionized nicotine (a result that is inconsistent with other published Camel Snus data, Table 6.1.5-6). Temporal trend slopes for Camel Snus total nicotine, pH and moisture content were not significant, indicating no differences over the 2003 to 2012 time period.

Song *et al.* 2016: Song and co-workers determined a wide range of chemical constituents in 7 conventional and 12 low-TSNA moist snuff tobacco products (Table 6.1.5-8). The low TSNA products tested include 7 products from the U.S., 3 products from Sweden, and 2 products from South Africa. Camel Snus (Frost, Spice, Original) were included in the U.S. products along with 4 Marlboro Snus products. The products were analyzed for pH, nicotine, free nicotine, TSNAs (NNN, NNK, NAB, NAT), metals (arsenic, cadmium, chromium, lead, nickel, selenium), humectants (propylene glycol, glycerol, triethylene glycol), ammonia, B[a]P, formaldehyde, N-nitrosodimethylamine (NDMA), and nitrate. Results are presented on both a dry weight basis and after normalization to the nicotine content.

Nicotine content (dwb) reported for Camel Snus (15.0 – 20.3 mg/g) was slightly lower than the mean reported for conventional moist snuff (24.5 mg/g) as was pH (7.51 – 7.76 vs 7.83) and thus free nicotine (4.4 – 5.3 vs 9.3 mg/g). In comparing mean values found for Camel Snus and conventional moist snuff, B[a]P, NNN, NNK, NAT, NAB, cadmium and nickel were lower for Camel Snus than conventional moist snuff. These endpoints were also lower (all differences statistically significant) when the conventional moist snuff products and low-TSNA products (combined) were compared. Lead, chromium, selenium and NDMA results were similar for Camel Snus and conventional moist snuff. Statistically significant differences were not observed for these endpoints when the conventional and low-TSNA product groups were compared. Arsenic and formaldehyde results are higher for Camel Snus than conventional moist snuff. The observed arsenic difference was statistically significant, but the formaldehyde difference was not, when the conventional moist snuff and low-TSNA product groups were compared.

Table 6.1.5-8: Comparison of the Chemical Constituents (dwb) Measured in Camel Snus, Conventional Moist Snuff and Low-TSNA Snuff (Data from Song *et al.* 2016)

Chemical	Camel Snus Range	Conventional Moist Snuff Mean	Low-TSNA Snuff Products Mean	p-value Conventional vs. Low-TSNA
B[a]P (ng/g)	0.74 – 0.76	77.75	1.47	<0.0001
NNK (μg/g)	0.25 – 0.40	1.55	0.31	<0.0001
NNN (μg/g)	1.04 – 1.39	4.47	1.13	<0.0001
NAT (μg/g)	0.58 – 0.66	4.99	0.71	<0.0001
NAB (μg/g)	0.07 – 0.08	0.33	0.05	<0.0001
Cadmium (μg/g)	0.72 – 0.80	1.28	0.72	<0.0001
Nickel (μg/g)	1.29 – 1.66	3.24	1.75	0.001 – 0.01
Arsenic (μg/g)	0.61 – 1.16	0.27	0.73	0.01 – 0.05
Lead (μg/g)	0.38 – 0.46	0.46	0.65	NS
Chromium (μg/g)	0.82 – 1.33	1.34	2.25	NS
Selenium (μg/g)	0.19 – 0.46	0.27	0.28	NS
NDMA (μg/g)	0.46 – 0.76	0.69	0.21	NS
Formaldehyde (μg/g)	0.61 – 1.16	0.32	0.63	NS

Abbreviations: NS = not significant; B[a]P = Benzo[a]pyrene; NNK= 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN= N'-nitrosonornicotine; NAT= N'-nitrosoanatabine; NAB = N'-nitrosoanabasine; NDMA = N-nitrosodimethylamine

In summary, many of the publications reviewed compare Camel Snus to conventional U.S. moist snuff. When considered collectively, a consistent picture regarding the relative product chemistry profiles for the two types of smokeless tobacco emerges. The principal differences found consistently between Camel Snus and U.S. moist snuff are that Camel Snus contains less tobacco-specific nitrosamines and benzo[a]pyrene than U.S. moist snuff. Additionally, Camel Snus moisture content is lower, the nicotine concentration is similar (but slightly lower), and the tobacco pH is similar to U.S. moist snuff products.

6.1.5.4 Overview of RJRT chemistry studies

RJRT has conducted a number of studies to characterize the chemistry of Camel Snus products in relation to cigarettes and other U.S. smokeless tobacco products. The studies include: (a) market surveys of U.S. cigarettes to determine harmful and potentially harmful constituent

(HPHC) content of smoke (RDM JAB 2016,306), (b) market surveys of U.S. smokeless tobacco products (including Camel Snus) to determine HPHC content (RDM JAB 2016,281), (c) Camel Snus production monitoring to determine HPHC content (RDM JMR 2016,235), (d) a Good Laboratory Practice (GLP) compliant study to determine both HPHC content of Camel Snus and Swedish-made snus, as well as the HPHC content of smoke from leading U.S. cigarettes (LSI 2014 113), and (e) a study to determine the minor alkaloid content of commercial smokeless tobacco (LSI 2016 097).

Table 6.1.5-9: RJRT Chemistry Studies

Reference	Title	Products Tested
RDM JAB 2016,306	Summary of 2014 and 2015 Cigarette Market Surveys	45 commercial U.S. cigarette brand styles in 2014 and 50 commercial U.S. cigarette brand styles in 2015
RDM JAB 2016,281	Summary of 2014 and 2015 Smokeless Market Surveys	43 commercial U.S. smokeless tobacco products (including Camel Snus Frost, Camel Snus Frost Large, Camel Snus Mellow, Camel Snus Mint, Camel Snus Robust, Camel Snus Winterchill) in 2014 and 50 commercial U.S. smokeless tobacco products (including Camel Snus Frost, Camel Snus Frost Large, Camel Snus Mellow, Camel Snus Mint, Camel Snus Robust, Camel Snus Winterchill) in 2015
RDM JMR 2016,235	Analytical Testing of Camel Snus Products	Camel Snus Frost, Camel Snus Frost Large, Camel Snus Mellow, Camel Snus Mint, Camel Snus Robust, Camel Snus Winterchill sampled quarterly
LSI 2014 113	Determination of Smokeless Tobacco HPHC Values for Camel Snus and Other Tobacco Products – M195-GLP	7 commercial U.S. snus brands (including Camel Snus Frost, Camel Snus Frost Large, Camel Snus Mellow, Camel Snus Mint, Camel Snus Robust, Camel Snus Winterchill), 4 commercial Swedish snus brands, and 2 leading US cigarette brands
LSI 2016 097	Characterization of Tobacco-Minor Alkaloids – M273	8 commercial U.S. snus brands (including Camel Snus Frost, Camel Snus Frost Large, Camel Snus Mellow, Camel Snus Mint, Camel Snus Robust, Camel Snus Winterchill), 3 commercial U.S. dry snuff brands, 3 commercial U.S. moist snuff brands, CORESTA Reference Product (CRP1 reference snus)

6.1.5.4.1 Rationale for the selection of cigarette brand styles evaluated in U.S. cigarette market surveys

Since the 1990s, RJRT has conducted several U.S. cigarette market surveys to determine the yields of chemical constituents in mainstream cigarette smoke, including surveys conducted in 1995, 1998, 2000 and 2009 (Chepiga *et al.* 2000; Swauger *et al.* 2002; Bodnar *et al.* 2012). More recently, cigarette market surveys were conducted in 2014 and 2015, contemporaneously with the conduct of smokeless tobacco surveys that included the 6 Camel Snus products that are the subject of this Application. Results from those U.S. cigarette market surveys have been summarized (RDM JAB 2016,306) and form a basis for comparison to Camel Snus chemistry results. The cigarette brand styles selected for the 2014 and 2015 market surveys provided broad representation of the different cigarettes available for purchase in the U.S.

(b) (4)

(b) (4)

[redacted]

6.1.5.4.2 Rationale for the selection of smokeless tobacco brand styles evaluated in U.S. smokeless market surveys

RJRT has conducted a number of market surveys of the chemical constituents in smokeless tobacco, including a study that investigated products purchased in 2006 and 2007 (Borgerding *et al.* 2012). More recently, U.S. smokeless tobacco market surveys were conducted in 2014 and 2015 in the same time period that recent cigarette market surveys were conducted. Results from those studies have been summarized (RDM JAB 2016,281) and form a basis for comparison to recent cigarette chemistry results.

The brand styles selected for the 2014 and 2015 surveys provided broad representation of the different smokeless tobacco products available for purchase in the U.S. Analytes evaluated in these studies consisted of the smokeless tobacco analytes specified in Table 1 of the FDA Draft Guidance for Industry, *"Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act"* issued March 2012 (FDA 2012b) and other analytes of interest.

(b) (4)

[redacted]

(b) (4)

(b) (4)

6.1.5.4.3 2014 and 2015 market surveys of U.S. cigarette mainstream smoke yields

Background: Market surveys to determine the HPHC content of cigarette smoke were conducted in 2014 and 2015. Results from those studies are summarized in the report RDM JAB 2016,306 in support of this Application.

Methodology: U.S. cigarettes were sampled in August 2014 and August 2015 for testing. Quantitative analyses were performed for reportable harmful and potentially harmful constituents (HPHCs) and other selected analytes of interest. All analytical determinations were conducted at R.J. Reynolds Tobacco Company (RJRT) by (b) (4) - (b) (4) Forty-five commercial brand styles were sampled in 2014 and 50 commercial brand styles were sampled in 2015. Cigarette smoke was generated for analysis using the ISO and HCI smoking regimens. Eighteen smoke constituents were measured: including nicotine, acetaldehyde, formaldehyde, crotonaldehyde, acrylamide, arsenic, cadmium, NAB, NAT, NNN, NNK, benzo[a]pyrene, benzo[a]anthracene, benzo[b/j]fluroanthene, benzo[k]fluoranthene, dibenz[a,h]anthracene, indeno[1,2,3-c,d]pyrene and naphthalene.

Results: Combined results of the 2014 and 2015 U.S. cigarette market surveys are tabulated in the summary report in several different ways, including:

- A listing of all data (by individual replicate) measured under ISO smoking conditions grouped by analyte and arranged alphabetically by product name (RDM JAB 2016,306: Appendix A, Table 1).
- A summary of descriptive data (mean, minimum value, maximum value and number of replicates) by year sampled for each cigarette brand style tested under ISO smoking conditions (RDM JAB 2016,306: Appendix A, Table 2).

- The range (minimum and maximum values) of product mean values determined for each analyte tested under ISO smoking conditions in 2014 and 2015 (RDM JAB 2016,306: Appendix A, Table 3). Ranges were determined based upon a single mean value for each of the cigarette brand styles tested. For brand styles tested in both 2014 and 2015, the mean value was based upon the combined data from both years.

- A listing of all the data (by individual replicate) collected under Canadian Intense smoking conditions grouped by analyte and arranged alphabetically by product name (RDM JAB 2016,306: Appendix A, Table 4).

- A summary of descriptive data (mean, minimum value, maximum value and number of replicates) by year sampled for each cigarette brand style tested under Canadian Intense smoking conditions (RDM JAB 2016,306: Appendix A, Table 5).

- The range (minimum and maximum values) of product mean values determined for each analyte tested under Canadian Intense smoking conditions in 2014 and 2015 (RDM JAB 2016,306: Appendix A, Table 6). Ranges were determined based upon a single mean value for each of the cigarette brand styles tested. For brand styles tested in both 2014 and 2015, the mean value was based upon the combined data from both years.

- All 3R4F reference cigarette data (by individual replicate) measured under ISO smoking conditions grouped by analyte (RDM JAB 2016,306: Appendix A, Table 7).

- A summary of descriptive data (mean, minimum value, maximum value and number of replicates) by year sampled for the 3R4F reference cigarette tested under ISO smoking conditions (RDM JAB 2016,306: Appendix A, Table 8).

- All 3R4F reference cigarette data (by individual replicate) measured under Canadian Intense smoking conditions grouped by analyte (RDM JAB 2016,306: Appendix A, Table 9).

- A summary of descriptive data (mean, minimum value, maximum value and number of replicates) by year sampled for the 3R4F reference cigarette tested under Canadian Intense smoking conditions (RDM JAB 2016,306: Appendix A, Table 10).

Mainstream smoke yields determined for U.S. cigarettes with ISO and HCI smoking regimens are summarized in Table 6.1.5-10.

Table 6.1.5-10: Range of Mainstream Smoke Yields Determined in the 2014 and 2015 Cigarette Market Surveys

Tobacco Product	U.S. Cigarettes	U.S. Cigarettes
Smoking Regimen	ISO	HCI
Compound	**Per Cigarette**	
Acetaldehyde (µg)	(81, 892)	(1267, 2381)
Acrylamide (µg)	(0.2, 4.6)	(2.5, 13.9)
Arsenic (ng)	(0.3†, 6.2)	(3.5, 23.2)
B[a]A (ng)	(3.0†, 32.1)	(18.8, 56.4)
B[a]P (ng)	(2.9†, 15.0)	(8.2, 33.0)
B[b/j]FL (ng)	(3.8†, 15.5)	(9.4, 32.7)
B[k]FL (ng)	(1.9†, 3.2)	(3.2†, 7.9)
Cadmium (ng)	(5, 116)	(52, 261)
Crotonaldehyde (µg)	(2†, 21)	(33, 73)
Formaldehyde (µg)	(2†, 47)	(46, 158)
Indeno [c,d]P (ng)	(0.7, 7.5)	(4.6, 15.5)
NAB (ng)	(2, 22)	(3 , 43)
Naphthalene (ng)	(19†, 1758)	(422, 3911)
NAT (ng)	(18, 205)	(38, 428)
Nicotine (mg)	(0.1, 2.1)	(1.4, 4.2)
NNK (ng)	(9, 143)	(29, 290)
NNN (ng)	(11, 175)	(19, 354)

Abbreviations: B[a]A = Benzo[a]anthracene; B[a]P = Benzo[a]pyrene; B[b/j]FL = Benzo[b/j] fluoranthene; B[k]FL = Benzo[k]fluoranthene; Indeno[c,d]P = Indeno[1,2,3-c,d]pyrene; NAB = N'-nitrosoanabasine; NAT= N'-nitrosoanatabine; NNN= N'-nitrosonornicotine; NNK= 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone

Data source: RDM JAB 2016,306

Associated electronic files: Cigar14.xpt; Cigar15.xpt

* Range of individual product means (minimum, maximum)

† Indicates that at least one replicate value was below the Limit of Quantitation (LOQ). For values below the LOQ, the LOQ was used to calculate the mean and the corresponding minimum and maximum values.

6.1.5.4.4 2014 and 2015 market surveys of U.S. smokeless tobacco products

Background: Market surveys to determine the HPHC content of U.S. smokeless tobacco products were conducted in 2014 and 2015. Results from those studies are summarized in RDM JAB 2016,281 submitted in support of this Application.

Methodology: U.S. commercial smokeless tobacco products were sampled in 2014 and 2015 for testing to determine HPHCs. The RJRT and American Snuff Company (ASC) smokeless tobacco products sampled in 2014 were obtained from their respective manufacturing facilities. The other commercial smokeless tobacco products sampled were purchased from retail outlets on

August 2, 2014. All of the commercial smokeless tobacco products sampled in 2015 were purchased from retail outlets on July 9, 2015. Forty-three commercial smokeless tobacco products were sampled in 2014 and 50 commercial smokeless tobacco products were sampled in 2015. Quantitative analyses were performed for reportable HPHCs and other selected analytes of interest. All analytical determinations were conducted at R.J. Reynolds Tobacco Company (RJRT) by (b) (4)

Eighteen chemical constituents were selected for analysis, including nicotine, acrylamide, acetaldehyde, formaldehyde, crotonaldehyde, arsenic, cadmium, NNN, NNK, NAT, NAB, benzo[a]pyrene, benzo[a]anthracene, benzo[b/j]fluoranthene, benzo[k]fluoranthene, dibenz[a,h]anthracene, indeno[1,2,3-c,d]pyrene and naphthalene. In addition, moisture and pH were measured and the free nicotine was calculated based on the measured nicotine content and pH.

Results: Combined results of the 2014 and 2015 U.S. smokeless tobacco market surveys are tabulated in the summary report in several different ways, including:

- A listing of all data (by individual replicate) grouped by analyte and arranged alphabetically by product name (RDM JAB 2016,281: Appendix A, Table 1).
- A summary of descriptive data (mean, minimum value, maximum value and number of replicates) by year sampled for each smokeless tobacco brand style tested (RDM JAB 2016,281: Appendix A, Table 2).
- The range of product means (minimum and maximum) determined for three 0.6 g Camel Snus styles and for other U.S. smokeless tobacco product categories (RDM JAB 2016,281: Appendix A, Table 3).
- The range of product means (minimum and maximum) determined for three 1.0 g Camel Snus styles and for other U.S. smokeless tobacco product categories (RDM JAB 2016,281: Appendix A, Table 4).
- The range of product means (minimum and maximum) determined for all six Camel Snus styles and for other U.S. smokeless tobacco product categories (RDM JAB 2016,281: Appendix A, Table 5).
- A listing of all smokeless reference product data (by individual replicate) grouped by analyte and arranged alphabetically by product name (RDM JAB 2016,281: Appendix A, Table 6).
- A summary of descriptive data (mean, minimum value, maximum value and number of replicates) by year sampled for each smokeless tobacco reference product tested (RDM JAB 2016,281: Appendix A, Table 7).

Comparisons of market survey results for Camel Snus and other U.S. smokeless tobacco products are found in the following series of three tables: Table 6.1.5-11, Table 6.1.5-12 and Table 6.1.5-13. Table 6.1.5-11 compares HPHC results for the three 0.6 gram Camel Snus styles on a per pouch, as-is basis with results from other sub-categories of U.S. smokeless tobacco products (*i.e.*, moist snuff, loose leaf and dry snuff products) expressed per 0.6 g of the products, as-is. Similarly, Table 6.1.5-12 compares HPHC results for the three 1.0 gram Camel Snus styles on a per pouch, as-is basis with results from other sub-categories of U.S. smokeless tobacco products (*i.e.*, moist snuff, loose leaf and dry snuff products) expressed per 1.0 g of the products, as-is. Table 6.1.5-13 compares HPHC results for all six Camel Snus styles with results from other sub-categories of U.S. smokeless tobacco products (*i.e.*, moist snuff, loose leaf and dry snuff products) with results expressed per gram of the products, as-is.

Table 6.1.5-11: Comparison of HPHC Results for Three Camel Snus Styles (0.6 g pouch size) and Other Smokeless Tobacco Products from the U.S. Market (0.6 g basis) – 2014 and 2015 Combined Survey Results

Tobacco Product	Camel Snus (0.6 gram)	Moist Snuff	Loose leaf	Dry snuff
Compound	**Per Pouch (as-is)**	**Per 0.6 gram (as-is)**		
Nicotine (mg)	(5.9, 6.4)*	(4.4, 8.8)	(2.1, 4.9)	(10.4, 18.1)
Moisture (%)	(31.5, 32.3)	(49.2, 56.9)	(23.7, 28.9)	(3.5, 7.2)
pH	(7.6, 7.7)	(6.7, 8.3)	(5.5, 6.1)	(5.7, 6.3)
% Un-ionized nicotine	(30.3, 33.6)	(5.2, 67.1)	(0.3, 1.5)	(0.5, 1.9)
Total free nicotine (mg)	(1.8, 2.1)	(0.3, 4.4)	(0.0, 0.0)	(0.1, 0.3)
Acetaldehyde (ng)	(791, 1545)	(405†, 15567)	(1083, 3926)	(634†, 1785)
Arsenic (ng)	(35, 43)	(27, 112)	(43, 114)	(75, 133)
B[a]P (ng)	(0.6†, 0.7)	(2.3†, 111.7)	(2.0, 3.0)	(16.4, 124.1)
Cadmium (ng)	(235, 249)	(210, 390)	(269, 424)	(639, 910)
Crotonaldehyde (ng)	(351†, 374†)	(282†, 440†)	(394†, 440†)	(406†, 438†)
Formaldehyde (ng)	(639†, 895)	(428†, 2237)	(502†, 540†)	(591, 3952)
NNK (ng)	(194, 261)	(58, 1051)	(110, 520)	(1554, 59620)
NNN (ng)	(652, 856)	(331, 3133)	(510, 1993)	(3561, 28640)

Abbreviations: B[a]P = Benzo[a]pyrene; NNN= N'-nitrosonornicotine; NNK= 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
Data source: RDM JAB 2016,281
Associated electronic files: skless14.xpt; skless15.xpt
* Range of individual product means (minimum, maximum)
† Indicates that at least one replicate value was below the Limit of Quantitation (LOQ). For values below the LOQ, the LOQ was used to calculate the mean and the corresponding minimum and maximum values.

Table 6.1.5-12: Comparison of HPHC Results for Three Camel Snus styles (1.0 g pouch size) and Other Smokeless Tobacco Products from the U.S. Market (1.0 g basis) – 2014 and 2015 Combined Survey Results

Tobacco Product	Camel Snus (1.0 gram)	Moist Snuff	Loose leaf	Dry Snuff
Compound	**Per Pouch (as-is)**	**Per 1.0 gram (as-is)**		
Nicotine (mg)	(10.0, 11.9)	(7.4, 14.7)	(3.5, 8.2)	(17.3, 30.2)
Moisture (%)	(32.4, 32.9)	(49.2, 56.9)	(23.7, 28.9)	(3.5, 7.2)
pH	(7.5, 7.8)	(6.7, 8.3)	(5.5, 6.1)	(5.7, 6.3)
% Un-ionized nicotine	(25.6, 38.0)	(5.2, 67.1)	(0.3, 1.5)	(0.5, 1.9)
Total free nicotine (mg)	(2.6, 4.1)	(0.5, 7.3)	(0.0, 0.1)	(0.1, 0.5)
Acetaldehyde (ng)	(1455, 1832)	(675†, 25945)	(1805, 6543)	(1056†, 2975)
Arsenic (ng)	(67, 72)	(46, 187)	(71, 190)	(125, 222)
B[a]P (ng)	(1.0†, 1.3†)	(3.9†, 186.2)	(3.3, 5.0)	(27.4, 206.8)
Cadmium (ng)	(375, 433)	(350, 650)	(449, 706)	(1065, 1517)
Crotonaldehyde (ng)	(673†, 736†)	(469†, 733†)	(657†, 733†)	(676†, 730†)
Formaldehyde (ng)	(842†, 921†)	(714†, 3728)	(837†, 899†)	(985, 6587)
NNK (ng)	(239, 335)	(97, 1751)	(184, 867)	(2590, 99367)
NNN (ng)	(956, 1368)	(552, 5222)	(851, 3322)	(5935, 47733)

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

Data source: RDM JAB 2016,281

Associated electronic files: skless14.xpt; skless15.xpt

* Range of individual product means (minimum, maximum)

† Indicates that at least one replicate value was below the Limit of Quantitation (LOQ). For values below the LOQ, the LOQ was used to calculate the mean and the corresponding minimum and maximum values.

Table 6.1.5-13: Comparison of HPHC Results for All Camel Snus Styles and Other Smokeless Tobacco Products from the U.S. Market – 2014 and 2015 Survey Results

Tobacco Product	Camel Snus (All Styles)	Moist Snuff	Loose leaf	Dry snuff
Compound	**Per gram (as-is)**			
Nicotine (mg)	(9.8, 11.9)*	(7.4, 14.7)	(3.5, 8.2)	(17.3, 30.2)
Moisture (%)	(31.5, 32.9)	(49.2, 56.9)	(23.7, 28.9)	(3.5, 7.2)
pH	(7.5, 7.8)	(6.7, 8.3)	(5.5, 6.1)	(5.7, 6.3)
% Un-ionized nicotine	(25.6, 38.0)	(5.2, 67.1)	(0.3, 1.5)	(0.5, 1.9)
Total free nicotine (mg)	(2.6, 4.1)	(0.5, 7.3)	(0.0, 0.1)	(0.1 , 0.5)
Acetaldehyde (ng)	(1318, 2575)	(675†, 25945)	(1805, 6543)	(1056†, 2975)
Arsenic (ng)	(59, 72)	(46, 187)	(71, 190)	(125, 222)
B[a]P (ng)	(1.0†, 1.3†)	(3.9†, 186.2)	(3.3, 5.0)	(27.4, 206.8)
Cadmium (ng)	(375, 433)	(350, 650)	(449, 706)	(1065, 1517)
Crotonaldehyde (ng)	(584†, 736†)	(469†, 733†)	(657†, 733†)	(676†, 730†)
Formaldehyde (ng)	(842†, 1491)	(714†, 3728)	(837†, 899†)	(985, 6587)
NNK (ng)	(239, 435)	(97, 1751)	(184, 867)	(2590, 99367)
NNN (ng)	(956, 1427)	(552, 5222)	(851, 3322)	(5935, 47733)

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

Data source: RDM JAB 2016,281

Associated electronic files: skless14.xpt; skless15.xpt

* Range of individual product means (minimum, maximum)

† Indicates that at least one replicate value was below the Limit of Quantitation (LOQ). For values below the LOQ, the LOQ was used to calculate the mean and the corresponding minimum and maximum values.

6.1.5.4.5 Analytical testing of Camel Snus production samples

Background: (b) (4) [redacted]. Results of the testing are summarized in RDM JMR 2016,235 submitted in support of this Application.

Methodology: (b) (4) [redacted]

(b) (4) [redacted]

Results: The results are listed in the summary report (RDM JMR 2016,235) as follows:

- A listing of all data (by individual replicate) arranged alphabetically by product name as well as associated product manufacturing dates and dates of analysis completion (RDM JMR 2016,235: Appendix A, Table 1).

- A summary of descriptive data (mean, minimum value, maximum value and number of replicates) for each Camel Snus brand style (RDM JMR 2016,235: Appendix A, Table 2).

- The range of product means (minimum and maximum) determined for three 0.6 g Camel Snus styles (Frost, Mellow and Mint) (RDM JMR 2016,235: Appendix A, Table 3).

- The range of product means (minimum and maximum) determined for three 1.0 g Camel Snus styles (Frost Large, Robust and Winterchill) (RDM JMR 2016,235: Appendix A, Table 4).

- A listing of all 2013 – 2015 laboratory quality control data, *i.e.*, data from contemporaneous testing of analytical method *"*monitor*"* samples (by individual replicate) for nicotine, anabasine, nornicotine, arsenic, cadmium, benzo[a]pyrene, NNK, NNN, NAB, and NAT (RDM JMR 2016,235: Appendix A, Table 5).

- A summary of descriptive data (mean, minimum value, maximum value and number of replicates) for the quality control samples (RDM JMR 2016,235: Appendix A, Table 6).

- A summary of descriptive data (mean, minimum value and maximum value) per analyte for all six Camel Snus styles (RDM JMR 2016,235: Appendix A, Table 7).

Results from the study provide direct insight into the relative contributions of the analytical methods employed to the overall observed data variability for individual analytes. (b) (4) [redacted].

Figure 6.1.5-1: (b) (4)

(b) (4)

Figure 6.1.5-2: (b) (4) [redacted])

(b) (4) [redacted]

Figure 6.1.5-3: (b) (4)

(b) (4)

Figure 6.1.5-4: (b) (4) [redacted]

(b) (4) [redacted]

6.1.5.4.6 Determination of smokeless tobacco HPHC values for Camel Snus and other tobacco products – Labstat Project M195-GLP

Background: The study was conducted in 2014 and results are summarized in LSI 2014 113. The study had a threefold purpose:

1. To measure Harmful and Potentially Harmful Constituents (HPHC) values for U.S. and Swedish snus products (including Camel Snus Frost, Camel Snus Frost Large, Camel Snus Mellow, Camel Snus Mint, Camel Snus Robust, Camel Snus Winterchill). The HPHC measurements consisted of the smokeless tobacco analytes specified in Table 1 of the FDA Draft Guidance for the industry issued March 2012 (FDA 2012b).

2. To measure the same HPHCs as in item #1 in smoke generated under ISO and HCI smoking regimens for the U.S. leading non-menthol and menthol cigarettes.

3. To conduct statistical comparisons according to a predetermined statistical plan specified in the study protocol.

Methodology: All analyses were conducted by Labstat International ULC, Kitchener, Ontario, Canada according to Good Laboratory Practice (GLP) provisions. The Standards Council of

Canada has recognized Labstat as having the required infrastructure and standard operating procedures (SOPs) in place to enable the completion of GLP compliant studies. The Labstat Study Director stated that "The study was conducted in compliance with the applicable requirements 21 CFR Part 58 (Code of Federal Regulations, Food and Drug Administration) Good Laboratory Practices for Nonclinical Laboratory Studies, as amended on May 21st, 2002, within the context of the study protocol." The Scope of Accreditation (Appendix A) and the Study Protocol (Appendix I) are included in the Final Study Report (LSI 2014 113).

(b) (4)

The cigarettes were smoked with both the ISO and HCI smoking regimens. The following HPHCs were analyzed in cigarette smoke and the smokeless tobacco products: nicotine, B[a]P, formaldehyde, acetaldehyde, crotonaldehyde, NNN, NNK, cadmium and arsenic. The cigarette smoke was also analyzed for total particulate matter (TPM), water, tar and carbon monoxide. Pouch weight, moisture and pH were also determined for the smokeless tobacco products. The smokeless tobacco free nicotine was calculated by the CDC method (CDC 2009b) using the total nicotine and pH results.

Results: Study results are tabulated in the Final Study Report as follows:

- The summary statistics (Mean, Standard Deviation, Number of Replicates, Lower and Upper 95% Confidence Interval) for cigarette test article results expressed on a per cigarette and per mg nicotine basis (LSI 2014 113, Appendix C1).

- The summary statistics for Camel Snus test article results expressed, as appropriate, on a per gram dry weight basis, a per pouch as-is basis, and a per mg nicotine basis. Weight, moisture and pH were reported on an as-is basis only (LSI 2014 113, Appendix C2).

- The summary statistics for other Swedish snus test article results expressed, as appropriate, on a per gram dry weight basis, a per pouch as-is basis, and a per mg nicotine basis. Weight, moisture and pH were reported on an as-is basis only (LSI 2014 113, Appendix C3).

- The data listing for the cigarette test article results (LSI 2014 113, Appendix D1).
- The data listing for the smokeless tobacco test article results (LSI 2014 113, Appendix D2).
- The statistical analysis results comparing each Camel Snus style to other Swedish snus products (LSI 2014 113, Appendix K1). Statistical comparisons are reported for data expressed on per gram dry weight basis, per pouch as-is and a per mg nicotine bases for endpoints including nicotine, free nicotine, B[a]P, formaldehyde, acetaldehyde, NNN, NNK, cadmium and arsenic. A comparison for crotonaldehyde was not possible since the results reported were below the method detection limit.
- The statistical analysis results comparing each Camel Snus style to mainstream smoke yields from market leading cigarettes (LSI 2014 113, Appendix K2). Statistical comparisons are reported for data expressed on a per unit of use basis (per pouch as-is basis for Camel Snus and a per cigarette basis for market leading cigarettes) and on a per mg nicotine basis (both product types) for B[a]P, formaldehyde, acetaldehyde, crotonaldehyde, NNN, NNK, cadmium and arsenic. Nicotine was compared on a per unit of use basis only.

Statistically significant differences were observed for all comparisons of Camel Snus and market leading cigarettes that were performed ($p \leq 0.025$ using a Bonferonni correction for two (ISO and HCI) comparisons). Observed differences were significant regardless of the smoking regimen or basis for comparison. Results for all Camel Snus styles were greater than those of the cigarettes tested for nicotine, NNN, NNK, cadmium and arsenic and less than those of the cigarettes tested for B[a]P, formaldehyde, acetaldehyde, and crotonaldehyde when compared either on a per pouch as-is basis or a per cigarette basis. Results for all Camel Snus styles were less than results for cigarettes for all comparisons on a per mg nicotine basis, except for arsenic, which was greater.

For comparison of results from individual Camel Snus styles and other Swedish snus (LSI 2014 113, Appendix K1), no statistically significant differences ($p \leq 0.05$) were found for any comparison on a per gram dry weight basis, except for NNN and NNK (Camel Snus Winterchill). No statistically significant differences ($p \leq 0.05$) were found for any comparison on a per pouch as-is basis except for NNN (Frost Large, Robust and Winterchill styles) and NNK (Winterchill style). No statistically significant differences ($p \leq 0.05$) were found for any comparison on a per mg nicotine basis except for NNN (all styles), NNK (Frost, Frost Large and Winterchill styles) and cadmium (Frost and Winterchill styles). In all cases, when statistically significant differences were observed, results for Camel Snus styles were greater than results determined for the other Swedish snus products tested.

6.1.5.4.7 Characterization of minor alkaloids in selected smokeless tobacco products – Project M273

Background: The study was conducted in 2016 and results are reported in LSI 2016 097. The purpose of the study was to characterize the minor alkaloid content of all Camel Snus styles and representative styles of other U.S. smokeless tobacco products.

Methodology: All analyses were conducted by Labstat International ULC, Kitchener, Ontario, Canada. Labstat has been accredited by the Standards Council of Canada to International Standard ISO/IEC 17025:2005 *"General requirements for the competence of testing and calibration laboratories."*

U.S. smokeless tobacco products tested included snus, moist snuff and dry snuff. Snus products tested included: Camel Snus Frost, Camel Snus Frost Large, Camel Snus Mellow, Camel Snus Mint, Camel Snus Robust, Camel Snus Winterchill, General White Mint and General Wintergreen. A CORESTA reference product (CRP1 reference snus) was also tested. Moist snuff products tested included: Longhorn Wintergreen, Grizzly Long Cut Wintergreen and Copenhagen Long Cut Wintergreen. Dry snuff products tested included: Navy Sweet, Railroad Mills and W.E. Garrett & Sons.

(b) (4)

[redacted]

The smokeless tobacco samples were analyzed for moisture, nicotine, nornicotine, anabasine, myosmine and anatabine. Three replicates per sample were analyzed.

Results: Study results are summarized in the Test Report prepared by Labstat (LSI 2016 097). With the exception of moisture, all results are reported in units of µg/g (dwb). Individual replicate results, along with average, standard deviation, and 95% confidence limits are reported for all analytes. Student's t-distribution for small sample size was used to calculate the confidence limits.

Reported results, after conversion to an as-is basis, are summarized in Table 6.1.5-14. The standard error was calculated by dividing the standard deviation by the square root of 3.

Comparisons of nornicotine and anabasine results for all Camel Snus styles and other U.S. smokeless tobacco products in the study (three moist snuff, three dry snuff and two snus) are presented graphically in Figure 6.1.5-5 and Figure 6.1.5-6. Camel Snus product nicotine (not shown), nornicotine and anabasine results are within the range of other U.S. smokeless tobacco products.

Table 6.1.5-14: Summary Statistics for the Measured Alkaloid Content per Gram on an as-is Basis

Description	Nicotine* (mg/g)	Nornicotine (µg/g)	Anabasine (µg/g)	Anatabine (µg/g)	Myosmine (µg/g)
Camel Snus Frost	11.5 ± 0.10 (11.0, 11.9)	162 ± 6.7 (133, 191)	53 ± 1.4 (47, 59)	88 ± 1.1 (83, 93)	39 ± 1.7 (31, 46)
Camel Snus Mellow	11.1 ± 0.13 (10.6, 11.7)	141 ± 9.5 (100, 182)	50 ± 0.8 (47, 54)	76 ± 1.4 (71, 82)	37 ± 1.3 (32, 43)
Camel Snus Mint	10.5 ± 0.07 (10.2, 10.8)	141 ± 5.0 (119, 162)	51 ± 1.4 (45, 57)	70 ± 1.0 (66, 75)	38 ± 2.0 (29, 47)
Camel Snus Frost Large	12.6 ± 0.22 (11.6, 13.5)	180 ± 19.7 (95, 265)	58 ± 1.3 (53, 63)	102 ± 2.9 (89, 115)	41 ± 1.9 (33, 49)
Camel Snus Robust	10.8 ± 0.21 (9.9, 11.7)	154 ± 8.6 (117, 191)	52 ± 1.4 (46, 58)	79 ± 0.5 (77, 81)	35 ± 1.5† (26, 44)
Camel Snus Winterchill	10.8 ± 0.02 (10.7, 10.9)	146 ± 2.8 (134, 158)	52 ± 0.5 (50, 54)	81 ± 0.1 (81, 82)	39 ± 0.9 (35, 43)

* Mean ± Standard Error; 95% Confidence Interval for Mean (minimum, maximum); 3 Replicates for each measurement
† One replicate was below the Limit of Quantitation (LOQ). The LOQ was used to calculate the statistical results.

Table 6.1.5-14 (continued): Summary Statistics for the Measured Alkaloid Content per Gram on an as-is Basis

Description	Nicotine* (mg/g)	Nornicotine (µg/g)	Anabasine (µg/g)	Anatabine (µg/g)	Myosmine† (µg/g)
General White Mint Snus	8.0 ± 0.05 (7.7, 8.2)	80 ± 2.0 (72, 89)	25 ± 0.4 (23, 27)	73 ± 0.2 (72, 74)	< 23.8 but ≥ 7.1
General Wintergreen Snus	7.6 ± 0.18 (6.8, 8.3)	86 ± 3.5 (71, 101)	25 ± 0.6 (22, 27)	70 ± 0.8 (67, 73)	< 23.2 but ≥ 7.0
Longhorn Wintergreen Moist Snuff	11.9 ± 0.08 (11.6, 12.3)	121 ± 0.4 (119, 123)	42 ± 0.5 (40, 44)	156 ± 1.4 (150, 162)	< 23.0 but ≥ 6.9
Grizzly Long Cut Wintergreen Moist Snuff	10.4 ± 0.16 (9.8, 11.1)	100 ± 5.6 (76, 124)	44 ± 0.9 (40, 48)	112 ± 2.9 (100, 124)	< 23.4 but ≥ 7.0
Copenhagen Long Cut Moist Snuff	11.7 ± 0.05 (11.5, 12.0)	108 ± 4.3 (90, 127)	40 ± 0.3 (38, 41)	133 ± 0.9 (129, 137)	< 21.7.0 but ≥ 6.5
Navy Dry Snuff	16.2 ± 0.24 (15.2, 17.2)	340 ± 33.1 (197, 482)	64 ± 1.1 (59, 69)	307 ± 8.2 (271, 342)	< 46.2 but ≥ 13.9
Railroad Mills Dry Snuff	22.9 ± 0.11 (22.5, 23.4)	538 ± 38.9 (370, 705)	104 ± 3.1 (90, 117)	494 ± 6.8 (464, 523)	< 45.8 but ≥ 13.8
W.E. Garrett & Sons Dry Snuff	14.1 ± 0.15 (13.4, 14.8)	217 ± 15.2 (151, 282)	53 ± 1.3 (47, 59)	210 ± 2.6 (199, 221)	< 46.9 but ≥ 14.1

* Mean ± Standard Error; 95% Confidence Interval for Mean (minimum, maximum); 3 Replicates for each measurement

† All replicates were below the Limit of Quantitation (50 µg/g) but at or above the Limit of Detection (15 µg/g) on a dry weight basis.

Figure 6.1.5-5: Comparison of Nornicotine (µg/g, as-is) for Camel Snus Styles and Other U.S. Smokeless Tobacco Products Sampled in 2016

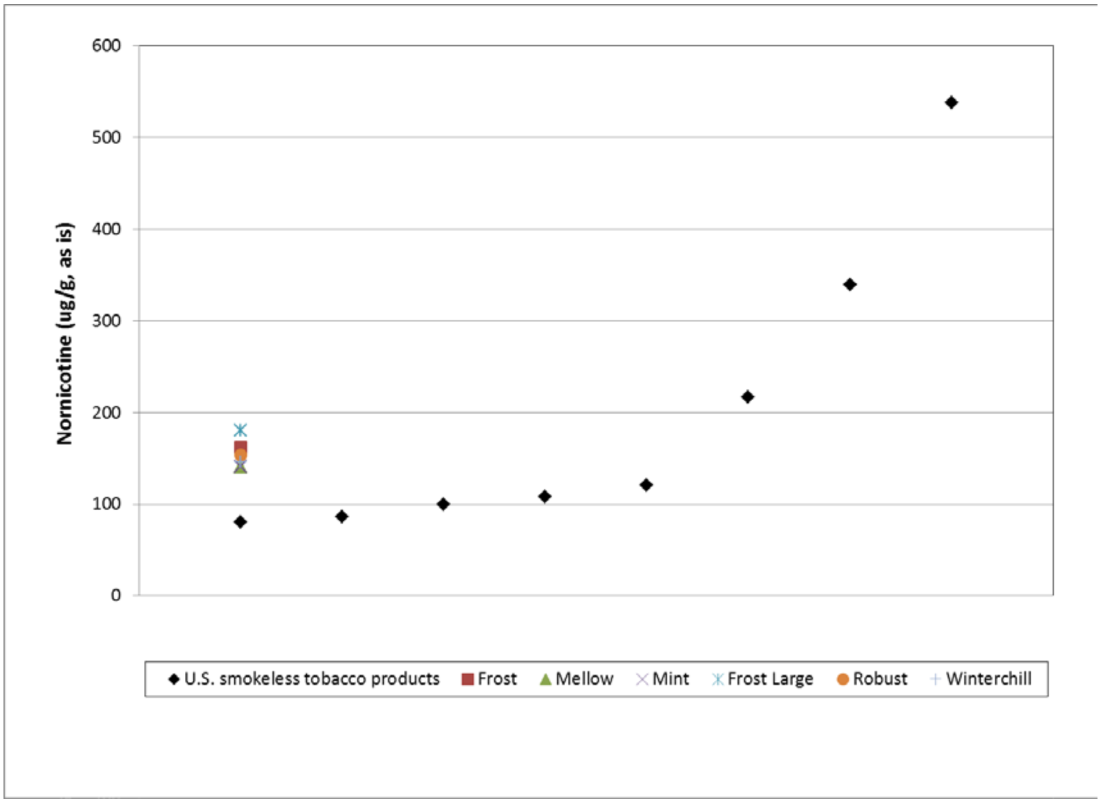
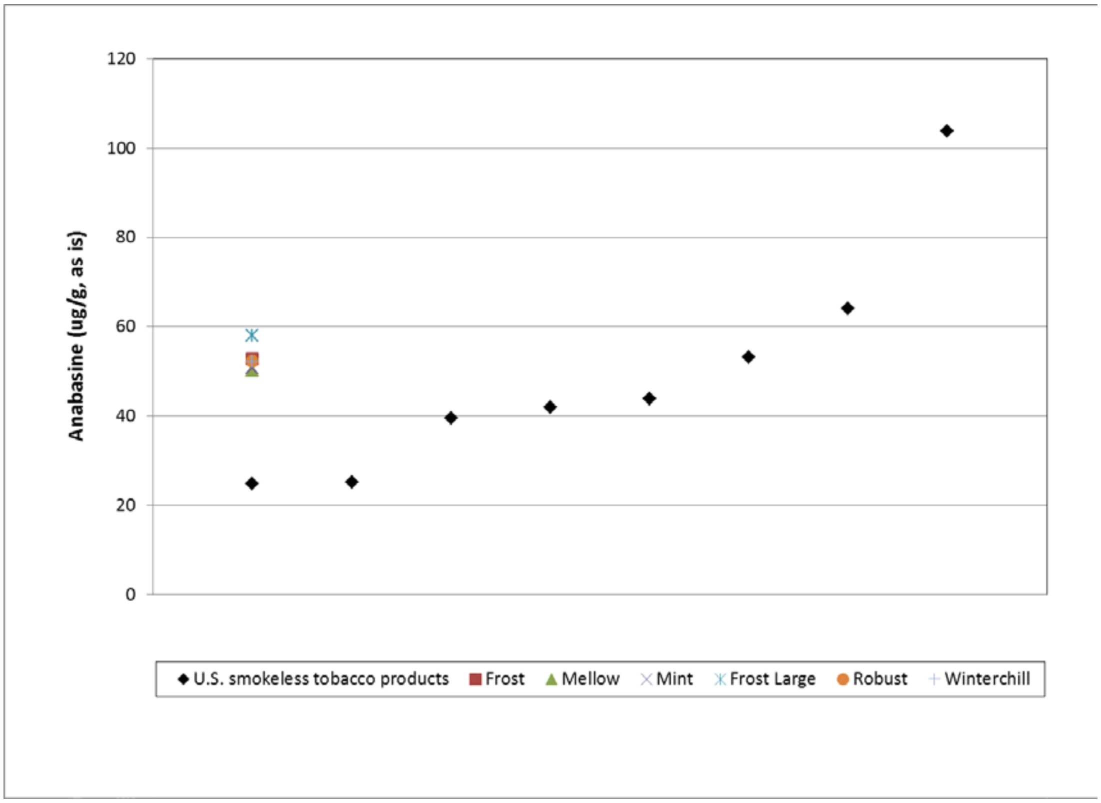


Figure 6.1.5-6: Comparison of Anabasine (µg/g, as-is) for Camel Snus Styles and Other U.S. Smokeless Tobacco Products Sampled in 2016



6.1.5.4.8 Summary of HPHC chemistry results for Camel Snus

Camel Snus HPHC results from the RJRT studies described in this section of the Application have been combined into a data set that serves as the basis for comparing Camel Snus styles to cigarettes and other smokeless tobacco products. Table 6.1.5-15, Table 6.1.5-16 and Table 6.1.5-17 summarize the HPHC results for the 6 Camel Snus styles that are the subject of the Application from three RJRT studies (RDM JAB 2016,281; LS1 2014 113; RDM JMR 2016,235). Descriptive statistics are provided for nicotine (total and calculated free), moisture, pH, acetaldehyde, crotonaldehyde, formaldehyde, arsenic, cadmium, NNK, NNN and B[a]P. Table 6.1.5-15 and Table 6.1.5-16 summarize the overall Mean ± Standard Error, the 95% Confidence Interval for the Mean (minimum, maximum) and the Number of Observations on a per gram (Table 6.1.5-15) and per pouch (Table 6.1.5-16) basis for the 6 Camel Snus styles. Table 6.1.5-17 shows the range of product means determined for all Camel Snus styles on a per gram as-is basis, as well as on a per pouch basis for the 0.6 gram styles, for the 1.0 gram styles, and for all Camel Snus styles. Generally consistent values are observed for all Camel Snus on a per gram basis, especially considering the differences in product sampling methods, product sampling timeframes and analytical laboratory testing methodologies for the 3 studies. As expected, values for the larger 1.0 gram styles are greater than the 0.6 gram styles on a per pouch basis, except for the % un-ionized nicotine, moisture and pH which are not mass (*i.e.*, pouch size) dependent.

Table 6.1.5-15: Summary of Camel Snus Chemistry by Product Style (per gram, as-is)

	Frost*	Mellow	Mint	Frost Large	Robust	Winterchill
Nicotine (mg/g)	10.0 ± 0.15 (9.7, 10.3) N=51	9.9 ± 0.17 (9.6, 10.3) N=51	9.8 ± 0.14 (9.5, 10.1) N=53	10.2 ± 0.16 (9.9, 10.5) N=46	9.3 ± 0.13 (9.0, 9.6) N=44	9.4 ± 0.11 (9.2, 9.7) N=51
Un-ionized (free) Nicotine (%)	34.2 ± 0.82 (32.5, 35.8) N=51	31.2 ± 0.75 (29.7, 32.7) N=49	33.1 ± 0.99 (31.1, 35.1) N=47	33.6 ± 0.94 (31.7, 35.5) N=46	32.7 ± 0.93 (30.9, 34.6) N=40	34.0 ± 0.91 (32.2, 35.8) N=51
Total Free Nicotine (mg/g)	3.4 ± 0.10 (3.2, 3.6) N=51	3.1 ± 0.11 (2.9, 3.3) N=49	3.3 ± 0.12 (3.0, 3.5) N=47	3.4 ± 0.12 (3.2, 3.7) N=46	3.0 ± 0.11 (2.8, 3.3) N=40	3.2 ± 0.10 (3.0, 3.4) N=51
Moisture (%)	33.3 ± 0.13 (33.1, 33.6) N=62	33.5 ± 0.13 (33.2, 33.7) N=61	33.3 ± 0.12 (33.1, 33.6) N=60	33.3 ± 0.13 (33.0, 33.5) N=57	33.7 ± 0.12 (33.5, 34.0) N=52	33.5 ± 0.10 (33.2, 33.7) N=62
pH	7.7 ± 0.02 (7.7, 7.8) N=51	7.7 ± 0.02 (7.6, 7.7) N=50	7.7 ± 0.02 (7.7, 7.8) N=49	7.7 ± 0.02 (7.7, 7.8) N=46	7.7 ± 0.02 (7.7, 7.7) N=42	7.7 ± 0.02 (7.7, 7.8) N=51
Acetaldehyde (ng/g)	1422[†] ± 88.4 (1232, 1611) N=15	1840 ± 146.4 (1527, 2154) N=15	1482[†] ± 112.6 (1241, 1724) N=15	1513[†] ± 101.2 (1295, 1732) N=14	1577[†] ± 106.3 (1347, 1807) N=14	1423[†] ± 123.0 (1159, 1687) N=15
Crotonaldehyde (ng/g)	588[†] ± 41.0 (500, 676) N=15	596[†] ± 43.6 (502, 689) N=15	588[†] ± 40.9 (501, 676) N=15	663[†] ± 48.9 (558, 769) N=14	663[†] ± 49.7 (556, 771) N=14	629[†] ± 48.3 (526, 733) N=15

Abbreviations: B[a]P = Benzo[a]pyrene; NNN= N'-nitrosonornicotine; NNK= 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
Data sources: RDM JAB 2016,281; LS1 2014 113; RDM JMR 2016,235
Associated electronic file: snuschem.xpt
* Mean ± Standard Error; 95% Confidence Interval for Mean (minimum, maximum); N= Number of Observations
† Indicates that at least one replicate value was below the Limit of Quantitation (LOQ). For values below the LOQ, the LOQ was used to calculate the statistical results.

Table 6.1.5-15 (cont.): Summary of Camel Snus Chemistry by Product Style (per gram, as-is)

	Frost*	Mellow	Mint	Frost Large	Robust	Winterchill
Formaldehyde (ng/g)	1340† ± 171.1 (973, 1707) N=15	1275† ± 139.0 (977, 1573) N=15	1136† ± 99.4 (923, 1349) N=15	881† ± 21.8 (833, 928) N=14	917† ± 29.0 (855, 980) N=14	932† ± 59.2 (805, 1059) N=15
Arsenic (ng/g)	79.8 ± 3.69 (72.2, 87.4) N=27	79.0 ± 3.33 (72.1, 85.8) N=27	79.4 ± 3.30 (72.6, 86.2) N=27	79.3 ± 3.48 (72.1, 86.4) N=26	77.5 ± 3.26 (70.8, 84.2) N=25	76.0 ± 2.79 (70.3, 81.8) N=27
Cadmium (ng/g)	401 ± 5.6 (390, 412) N=27	396 ± 5.6 (384, 407) N=27	396 ± 5.7 (385, 408) N=27	418 ± 7.2 (403, 433) N=26	385 ± 7.2 (370, 400) N=25	392 ± 5.6 (381, 404) N=27
NNN (ng/g)	1131 ± 31.3 (1067, 1195) N=29	1083 ± 25.2 (1031, 1135) N=27	1268 ± 60.9 (1143, 1393) N=28	1188 ± 37.1 (1111, 1264) N=26	1007 ± 34.3 (937, 1078) N=25	1104 ± 30.0 (1042, 1166) N=27
NNK (ng/g)	330 ± 21.6 (285, 374) N=29	313 ± 22.8 (266, 360) N=27	360 ± 26.0 (307, 414) N=28	331 ± 22.8 (285, 378) N=26	310 ± 24.0 (260, 359) N=25	349 ± 26.9 (294, 404) N=27
B[a]P (ng/g)	1.0† ± 0.04 (0.9, 1.1) N=27	1.0† ± 0.04 (0.9, 1.1) N=27	1.0† ± 0.04 (0.9, 1.1) N=27	1.2† ± 0.05 (1.1, 1.2) N=27	1.1† ± 0.03 (1.0, 1.1) N=25	1.1† ± 0.03 (1.0, 1.2) N=27

Abbreviations: B[a]P = Benzo[a]pyrene; NNN= N'-nitrosonornicotine; NNK= 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
Data sources: RDM JAB 2016,281; LS1 2014 113; RDM JMR 2016,235
Associated electronic file: snuschem.xpt
* Mean ± Standard Error; 95% Confidence Interval for Mean (minimum, maximum); N= Number of Observations
† Indicates that at least one replicate value was below the Limit of Quantitation (LOQ). For values below the LOQ, the LOQ was used to calculate the statistical results.

Table 6.1.5-16: Summary of Camel Snus Chemistry by Product Style (per pouch, as-is)

	Frost*	Mellow	Mint	Frost Large	Robust	Winterchill
Nicotine (mg)	6.0 ± 0.09 (5.9, 6.2) N=51	6.0 ± 0.10 (5.8, 6.2) N=51	5.9 ± 0.09 (5.7, 6.0) N=53	10.2 ± 0.16 (9.9, 10.5) N=46	9.3 ± 0.13 (9.0, 9.5) N=44	9.4 ± 0.11 (9.2, 9.7) N=51
Un-ionized (free) Nicotine (%)	34.2 ± 0.82 (32.5, 35.8) N=51	31.2 ± 0.75 (29.7, 32.7) N=49	33.1 ± 0.99 (31.1, 35.1) N=47	33.6 ± 0.94 (31.7, 35.5) N=46	32.7 ± 0.93 (30.9, 34.6) N=40	34.0 ± 0.91 (32.2, 35.8) N=51
Total Free Nicotine (mg)	2.1 ± 0.06 (1.9, 2.2) N=51	1.9 ± 0.07 (1.7, 2.0) N=49	2.0 ± 0.07 (1.8, 2.1) N=47	3.4 ± 0.13 (3.2, 3.7) N=46	3.0 ± 0.11 (2.8, 3.3) N=40	3.2 ± 0.10 (3.0, 3.4) N=51
Moisture (%)	33.3 ± 0.13 (33.1, 33.6) N=62	33.5 ± 0.13 (33.2, 33.7) N=61	33.3 ± 0.12 (33.1, 33.6) N=60	33.3 ± 0.13 (33.0, 33.5) N=57	33.7 ± 0.12 (33.5, 34.0) N=52	33.5 ± 0.10 (33.2, 33.7) N=62
pH	7.7 ± 0.02 (7.7, 7.8) N=51	7.7 ± 0.02 (7.6, 7.7) N=50	7.7 ± 0.02 (7.7, 7.8) N=49	7.7 ± 0.02 (7.7, 7.8) N=46	7.7 ± 0.02 (7.7, 7.7) N=42	7.7 ± 0.02 (7.7, 7.8) N=51
Acetaldehyde (ng)	856† ± 53.6 (741, 971) N=15	1106 ± 88.6 (916, 1296) N=15	885† ± 66.9 (742, 1029) N=15	1506† ± 101.0 (1288, 1725) N=14	1576† ± 106.0 (1347, 1805) N=14	1418† ± 120.7 (1159, 1677) N=15
Crotonaldehyde (ng)	353† ± 24.5 (300, 405) N=15	357† ± 26.1 (301, 414) N=15	353† ± 24.7 (300, 406) N=15	663† ± 49.1 (557, 769) N=14	663† ± 49.8 (556, 771) N=14	629† ± 48.5 (525, 733) N=15

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

Data sources: RDM JAB 2016,281; LS1 2014 113; RDM JMR 2016,235

Associated electronic file: snuschem.xpt

* Mean ± Standard Error; 95% Confidence Interval for Mean (minimum, maximum); N= Number of Observations

† Indicates that at least one replicate value was below the Limit of Quantitation (LOQ). For values below the LOQ, the LOQ was used to calculate the statistical results.

Table 6.1.5-16 (cont.): Summary of Camel Snus Chemistry by Product Style (per pouch, as-is)

	Frost*	Mellow	Mint	Frost Large	Robust	Winterchill
Formaldehyde (ng)	806† ± 102.4 (586, 1026) N=15	766† ± 83.5 (587, 945) N=15	679† ± 59.4 (551, 806) N=15	877† ± 23.2 (827, 927) N=14	916† ± 28.6 (855, 978) N=14	929† ± 58.9 (803, 1056) N=15
Arsenic (ng)	48.1 ± 2.35 (43.2, 52.9) N=27	47.4 ± 2.03 (43.3, 51.6) N=27	47.4 ± 1.83 (43.7, 51.2) N=27	78.9 ± 3.25 (72.2, 85.6) N=26	77.4 ± 3.22 (70.8, 84.1) N=25	75.9 ± 2.70 (70.3, 81.4) N=27
Cadmium (ng)	241 ± 3.2 (234, 247) N=27	238 ± 3.3 (231, 244) N=27	237 ± 3.7 (230, 245) N=27	417 ± 7.6 (401, 433) N=26	385 ± 7.3 (370, 400) N=25	392 ± 5.7 (380, 403) N=27
NNN (ng)	680 ± 18.5 (642, 718) N=29	650 ± 15.1 (619, 681) N=27	760 ± 36.9 (684, 835) N=28	1186 ± 37.9 (1108, 1264) N=26	1007 ± 34.3 (936, 1078) N=25	1102 ± 30.1 (1041, 1164) N=27
NNK (ng)	198 ± 12.9 (172, 225) N=29	188 ± 13.7 (160, 216) N=27	216 ± 15.7 (184, 248) N=28	331 ± 22.8 (284, 378) N=26	310 ± 24.0 (260, 359) N=25	348 ± 26.6 (293, 403) N=27
B[a]P (ng)	0.6† ± 0.02 (0.6, 0.7) N=27	0.6† ± 0.02 (0.6, 0.6) N=27	0.6† ± 0.02 (0.5, 0.6) N=27	1.1† ± 0.05 (1.1, 1.2) N=27	1.1† ± 0.03 (1.0, 1.1) N=25	1.1† ± 0.03 (1.0, 1.2) N=27

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

Data sources: RDM JAB 2016,281; LS1 2014 113; RDM JMR 2016,235

Associated electronic file: snuschem.xpt

* Mean ± Standard Error; 95% Confidence Interval for Mean (minimum, maximum); N= Number of Observations

† Indicates that at least one replicate value was below the Limit of Quantitation (LOQ). For values below the LOQ, the LOQ was used to calculate the statistical results.

Table 6.1.5-17: Range of Product Means for Specified Camel Snus Styles, (as-is)

	All Camel Snus Styles, (per gram)	0.6 g Camel Snus Styles, (per pouch)	1.0 g Camel Snus Styles, (per pouch)	All Camel Snus Styles, (per pouch)
Nicotine (mg)	(9.3, 10.2)	(5.9, 6.0)	(9.3, 10.2)	(5.9, 10.2)
Un-ionized (free) Nicotine (%)	(31.2, 34.2)	(31.2, 34.2)	(32.7, 34.0)	(31.2, 34.2)
Total Free Nicotine (mg)	(3.0, 3.4)	(1.9, 2.1)	(3.0, 3.4)	(1.9, 3.4)
Moisture (%)	(33.3, 33.7)	(33.3, 33.5)	(33.3, 33.7)	(33.3, 33.7)
pH	(7.7, 7.7)	(7.7, 7.7)	(7.7, 7.7)	(7.7, 7.7)
Acetaldehyde (ng)	(1422†, 1840)	(856†, 1106)	(1418†, 1576†)	(856†, 1576†)
Crotonaldehyde (ng)	(588†, 663†)	(353†, 357†)	(629†, 663†)	(353†, 663†)
Formaldehyde (ng)	(881†, 1340†)	(679†, 806†)	(877†, 929†)	(679†, 929†)
Arsenic (ng)	(76.0, 79.8)	(47.4, 48.1)	(75.9, 78.9)	(47.4, 78.9)
Cadmium (ng)	(385, 418)	(237, 241)	(385, 417)	(237, 417)
NNN (ng)	(1007, 1268)	(650, 760)	(1007, 1186)	(650, 1186)
NNK (ng)	(310, 360)	(188, 216)	(310, 348)	(188, 348)
B[a]P (ng)	(1.0†, 1.2†)	(0.6†, 0.6†)	(1.1†, 1.1†)	(0.6†, 1.1†)

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

Data sources: RDM JAB 2016,281; LS1 2014 113; RDM JMR 2016,235

Associated electronic file: snuschem.xpt

* (minimum, maximum)

† Indicates that at least one replicate value was below the Limit of Quantitation (LOQ). For values below the LOQ, the LOQ was used to calculate the statistical results.

6.1.5.5 Comparison of Camel Snus HPHC chemistry and corresponding cigarette mainstream smoke yields

The comparison of Camel Snus chemistry with the chemistry of mainstream cigarette smoke presents an "apples and oranges" comparison due to differences in the nature of tobacco and smoke. By definition, there are certain inherent technical limitations and biases that occur when comparing measurements of the two sample matrices. Camel Snus chemistry measurements are based on quantitative analysis of (entire) tobacco samples that involves extraction of an analyte from the tobacco matrix at ambient temperatures. In contrast, mainstream smoke chemistry measurements are based on applying a designated set of smoking conditions that convert a portion of the tobacco present in a cigarette into mainstream smoke. Mainstream smoke is generated from tobacco by numerous complex and overlapping processes that include: burning, pyrolysis, pyrosynthesis, distillation, sublimation and condensation (Borgerding and Klus 2005). During the natural smolder period between the puffs, temperatures of almost 800 °C occur in the center of the burning cone. During a puff, the temperature increases to 910 – 920 °C at the burning zone periphery, about 0.2 to 1.0 mm in front of the paper burn line. The tobacco smoke formed is a complex mixture consisting of more than 5000 compounds (Perfetti and Rodgman 2011). Physically, tobacco smoke is an aerosol consisting of solid/liquid droplets (particulate phase) in a gaseous phase. Thus, cigarette mainstream smoke chemistry is characterized by both relatively large amounts of certain compounds indicative of the burning process, *e.g*, carbon monoxide present in smoke at milligram concentrations, and by thousands of compounds formed from the pyrolysis of tobacco, *e.g*, PAHs present in smoke at nanogram concentrations.

The comparisons of Camel Snus chemistry and cigarette mainstream smoke yields described in this section are limited to reportable HPHCs that are common to both product types (Table 6.1.5-1). Therefore key chemistry differences that are driven by something unique to cigarettes, *e.g*, the presence of carbon monoxide in smoke, are not captured in the comparisons. Such differences, however, are evident in biomarker of exposure data that compare Camel Snus and cigarettes, *e.g*, COHb and urine mutagenicity.

Table 6.1.5-18, Table 6.1.5-19, Table 6.1.5-20 and Table 6.1.5-21 summarize HPHC results for Camel Snus and U.S. cigarettes from four RJRT studies (RDM JAB 2016,281; RDM JAB 2016,306; LSI 2014 113; RDM JMR 2016,235). The tables include results for acetaldehyde, arsenic, B[a]P, cadmium, crotonaldehyde, formaldehyde, nicotine, NNK and NNN. Cigarette mainstream smoke results are tabulated on a per cigarette basis for both ISO and HCI smoking regimens. Table 6.1.5-18 includes all styles of Camel Snus, with snus results expressed on a per gram, as-is basis. Table 6.1.5-19 includes the HPHC ranges for all Camel Snus styles expressed on a per pouch basis. Table 6.1.5-20 and Table 6.1.5-21 tabulate the HPHC ranges for 0.6 g and 1.0 g Camel Snus styles, respectively, on a per pouch basis for comparison with the cigarette smoke results.

Comparison of Camel Snus results with cigarette mainstream smoke yield results for the 9 HPHCs tested reveals that HPHC results are greater for Camel Snus styles in some instances and for cigarette smoke yields in other instances. A defining characteristic that drives which product type is greater is the source of the HPHC, *i.e.*, whether the HPHC is present in tobacco or primarily formed during smoking via mainstream smoke formation processes. For the HPHCs primarily present in tobacco, the levels are greater in Camel Snus since only a portion of what is present in cigarette tobacco is transferred into smoke. Nicotine, TSNAs and metals fall into this category. For such a compound to be present in mainstream cigarette smoke, it must be volatilized from tobacco during active puffing, condense into smoke and survive filtration by both the tobacco column and filter. It has been demonstrated that only 30%, or less, of compounds present in tobacco are transferred to mainstream cigarette smoke using the HCI smoking regimen (Piadé *et al.* 2015). Therefore, unless a given constituent level in cigarette tobacco is approximately three-fold greater than in a smokeless tobacco product, the amount in cigarette smoke is expected to be lower using current machine testing regimens.

Conversely, HPHCs that are formed primarily by pyrolysis or combustion of tobacco are expected to be present at higher levels in cigarette smoke than in smokeless tobacco. This is shown clearly for acetaldehyde, crotonaldehyde, formaldehyde and B[a]P in Table 6.1.5-18, Table 6.1.5-19, Table 6.1.5-20 and Table 6.1.5-21. The concept is also evident in the study by Moldoveanu and Gerardi (Moldoveanu and Gerardi 2011) concerning acrylamide levels in tobacco, tobacco smoke and smokeless tobacco. Acrylamide is formed by the Maillard reaction of asparagine and carbohydrates that is typical when cooking carbohydrate foods. The temperature necessary for the reaction to occur is much lower than the combustion temperature of tobacco and could possibly occur during the heat treatment of smokeless tobacco during processing. Moldoveanu and Gerardi report that in cigarette tobacco, acrylamide levels range from 50 to 120 ng/g whereas Camel Snus values are 82.7 (Camel Snus Frost) and 69.9 ng/g (Camel Snus Robust). Yields in cigarette smoke using the less intense ISO smoking regime are 497 to 2728 ng/cigarette. Considering the weight of tobacco in the cigarettes, the smoke yield is 15 to 80 times the mass initially in the cigarette tobacco filler.

In summary, distinct differences in HPHC results are observed between Camel Snus styles and cigarettes, with some HPHCs greater than, and others less than that of cigarettes. The significance of the observed differences depends upon their context. Chemical analyses provide information about specific characteristics of a tobacco product. However, results of such analyses do not provide insight into actual exposure to HPHCs when a tobacco product is used. Rather, exposure to constituents present in a tobacco product or tobacco smoke is the result of multiple factors, including the manner of use (*e.g,* smoking vs. placement of tobacco in the mouth), individual product use behaviors (*e.g,* cigarette puffing behavior or smokeless tobacco time held in mouth), the chemical composition of the product or smoke, and the route of exposure. Studies that measure exposure biomarkers provide more accurate assessments of exposure and risk than do product analyses, as biomarkers are the result of product use behavior and not merely the characteristics of the tobacco product itself (Chang *et al.* 2016).

It has been observed that *"*people do not smoke like a machine.*"* Similarly, people do not use smokeless tobacco according to the parameters of an analytical test method. For example, while chemical analysis of smokeless tobacco is intended to be quantitative and to thoroughly extract all of the mass of a given constituent from tobacco, constituent extraction during actual product use by a consumer is typically less. This is clearly shown in the mouth-level exposure studies included in this Application that entail analysis of Camel Snus before and after use by human subjects. Thus, the degree of extraction and retention of a tobacco constituent by the consumer cannot be inferred from chemical analysis alone. However, product analyses can, in some instances, provide information regarding the maximum potential for exposure to a given toxicant that is present in a tobacco product.

Table 6.1.5-18: Comparison of HPHC Ranges for Camel Snus (per gram) and U.S. Cigarettes

Tobacco Product	Camel Snus (All Styles)	U.S. Cigarettes	U.S. Cigarettes
Smoking Regimen		ISO	HCI
Compound	**Per gram (as-is)**	**Per Cigarette**	
Acetaldehyde (μg)	(1.4†, 1.8)*	(81, 892)	(1267, 2381)
Arsenic (ng)	(76.0, 79.8)	(0.3†, 6.2)	(3.5, 23.2)
B[a]P (ng)	(1.0†, 1.2†)	(2.9†, 15.0)	(8.2, 33.0)
Cadmium (ng)	(385, 418)	(5, 116)	(52, 261)
Crotonaldehyde (μg)	(0.6†, 0.7†)	(2†, 21)	(33, 73)
Formaldehyde (μg)	(0.9†, 1.3†)	(2†, 47)	(46, 158)
Nicotine (mg)	(9.3, 10.2)	(0.1, 2.1)	(1.4, 4.2)
NNK (ng)	(310, 360)	(9, 143)	(29, 290)
NNN (ng)	(1007, 1268)	(11, 175)	(19, 354)

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

Data sources: RDM JAB 2016,281; RDM JAB 2016,306; LSI 2014 113; RDM JMR 2016,235

* Range of individual product means (minimum, maximum)

† Indicates that at least one replicate value was below the Limit of Quantitation (LOQ). For values below the LOQ, the LOQ was used to calculate the mean and the corresponding minimum and maximum values.

Table 6.1.5-19: Comparison of HPHC Ranges for Camel Snus (per pouch) and U.S. Cigarettes

Tobacco Product	Camel Snus (All Styles)	Cigarettes	Cigarettes
Smoking Regimen		ISO	HCI
Compound	**Per Pouch (as-is)**	**Per Cigarette**	
Acetaldehyde (µg)	(0.9†, 1.6†)*	(81, 892)	(1267, 2381)
Arsenic (ng)	(47.4, 78.9)	(0.3†, 6.2)	(3.5, 23.2)
B[a]P (ng)	(0.6†, 1.1†)	(2.9†, 15.0)	(8.2, 33.0)
Cadmium (ng)	(237, 417)	(5, 116)	(52, 261)
Crotonaldehyde (µg)	(0.4†, 0.7†)	(2†, 21)	(33, 73)
Formaldehyde (µg)	(0.7†, 0.9†)	(2†, 47)	(46, 158)
Nicotine (mg)	(5.9, 10.2)	(0.1, 2.1)	(1.4, 4.2)
NNK (ng)	(188, 348)	(9, 143)	(29, 290)
NNN (ng)	(650, 1186)	(11, 175)	(19, 354)

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

Data sources: RDM JAB 2016,281; RDM JAB 2016,306; LSI 2014 113; RDM JMR 2016,235

* Range of individual product means (minimum, maximum)

† Indicates that at least one replicate value was below the Limit of Quantitation (LOQ). For values below the LOQ, the LOQ was used to calculate the mean and the corresponding minimum and maximum values.

Table 6.1.5-20: Comparison of HPHC Ranges for Camel Snus (0.6 g Styles) and U.S. Cigarettes

Tobacco Product	Camel Snus (0.6 g Styles)	Cigarettes	Cigarettes
Smoking Regimen		ISO	HCI
Compound	**Per Pouch (as-is)**	**Per Cigarette**	
Acetaldehyde (µg)	(0.9†, 1.1)	(81, 892)	(1267, 2381)
Arsenic (ng)	(47.4, 48.1)	(0.3†, 6.2)	(3.5, 23.2)
B[a]P (ng)	(0.6†, 0.6†)	(2.9†, 15.0)	(8.2, 33.0)
Cadmium (ng)	(237, 241)	(5, 116)	(52,261)
Crotonaldehyde (µg)	(0.4†, 0.4†)	(2†, 21)	(33, 73)
Formaldehyde (µg)	(0.7†, 0.8†)	(2†, 47)	(46, 158)
Nicotine (mg)	(5.9, 6.0)	(0.1, 2.1)	(1.4, 4.2)
NNK (ng)	(188, 216)	(9, 143)	(29, 290)
NNN (ng)	(650, 760)	(11, 175)	(19, 354)

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

Data sources: RDM JAB 2016,281; RDM JAB 2016,306; LSI 2014 113; RDM JMR 2016,235

* Range of individual product means (minimum, maximum)

† Indicates that at least one replicate value was below the Limit of Quantitation (LOQ). For values below the LOQ, the LOQ was used to calculate the mean and the corresponding minimum and maximum values.

Table 6.1.5-21: Comparison of HPHC Ranges for Camel Snus (1.0 g Styles) and U.S. Cigarettes

Tobacco Product	Camel Snus (1.0 gram)	Cigarettes	Cigarettes
Smoking Regimen		ISO	HCI
Compound	**Per Pouch (as-is)**	**Per Cigarette**	
Acetaldehyde (µg)	(1.4†, 1.6†)*	(81, 892)	(1267, 2381)
Arsenic (ng)	(75.9, 78.9)	(0.3†, 6.2)	(3.5, 23.2)
B[a]P (ng)	(1.1†, 1.1†)	(2.9†, 15.0)	(8.2, 33.0)
Cadmium (ng)	(385, 417)	(5, 116)	(52, 261)
Crotonaldehyde (µg)	(0.6†, 0.7†)	(2†, 21)	(33, 73)
Formaldehyde (µg)	(0.9†, 0.9†)	(2†, 47)	(46, 158)
Nicotine (mg)	(9.3, 10.2)	(0.1, 2.1)	(1.4, 4.2)
NNK (ng)	(310, 348)	(9, 143)	(29, 290)
NNN (ng)	(1007, 1186)	(11, 175)	(19, 354)

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

Data sources: RDM JAB 2016,281; RDM JAB 2016,306; LSI 2014 113; RDM JMR 2016,235

* Range of individual product means (minimum, maximum)

† Indicates that at least one replicate value was below the Limit of Quantitation (LOQ). For values below the LOQ, the LOQ was used to calculate the mean and the corresponding minimum and maximum values.

6.1.5.6 Comparison of Camel Snus and other U.S. smokeless tobacco chemistry

Table 6.1.5-22, Table 6.1.5-23, and Table 6.1.5-24 summarize Camel Snus and other U.S. smokeless tobacco (loose leaf chewing tobacco, moist snuff and dry snuff) HPHC results from three RJRT studies (RDM JAB 2016,281; LSI 2014 113; RDM JMR 2016,235). The tables include results for nicotine (total and calculated free), moisture, pH, acetaldehyde, arsenic, B[a]P, cadmium, crotonaldehyde, formaldehyde, NNK and NNN. Table 6.1.5-22 combines all styles of Camel Snus and provides a comparison to results for other smokeless tobacco by sub-category on a per gram (as-is) basis. Table 6.1.5-23 combines the 0.6 g pouch size styles of Camel Snus and shows results along with the other smokeless tobacco by sub-category on a per 0.6 gram (as-is) basis. Table 6.1.5-24 combines the 1.0 g pouch size styles of Camel Snus and shows results for other smokeless tobacco by sub-category on a per 1.0 gram (as-is) basis.

Table 6.1.5-22: Comparison of HPHC Ranges for Camel Snus and Other Smokeless Tobacco Products from the U.S. Market

Tobacco Product	Camel Snus (All Styles)	Moist Snuff	Loose leaf	Dry snuff
Compound	**Per gram (as-is)**			
Nicotine (mg)	(9.3, 10.2)*	(7.4, 14.7)	(3.5, 8.2)	(17.3, 30.2)
Moisture (%)	(33.3, 33.7)	(49.2, 56.9)	(23.7, 28.9)	(3.5, 7.2)
pH	(7.7, 7.7)	(6.7, 8.3)	(5.5, 6.1)	(5.7, 6.3)
% Un-ionized nicotine	(31.2, 34.2)	(5.2, 67.1)	(0.3, 1.5)	(0.5, 1.9)
Total free nicotine (mg)	(3.0, 3.4)	(0.5, 7.3)	(0.0, 0.1)	(0.1 , 0.5)
Acetaldehyde (ng)	(1422†, 1840)	(675†, 25945)	(1805, 6543)	(1056†, 2975)
Arsenic (ng)	(76.0, 79.8)	(46, 187)	(71, 190)	(125, 222)
B[a]P (ng)	(1.0†, 1.2†)	(3.9†, 186.2)	(3.3, 5.0)	(27.4, 206.8)
Cadmium (ng)	(385, 418)	(350, 650)	(449, 706)	(1065, 1517)
Crotonaldehyde (ng)	(588†, 663†)	(469†, 733†)	(657†, 733†)	(676†, 730†)
Formaldehyde (ng)	(881†, 1340†)	(714†, 3728)	(837†, 899†)	(985, 6587)
NNK (ng)	(310, 360)	(97, 1751)	(184, 867)	(2590, 99367)
NNN (ng)	(1007, 1268)	(552, 5222)	(851, 3322)	(5935, 47733)

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

Data sources: RDM JAB 2016,281; LSI 2014 113; RDM JMR 2016,235

* Range of individual product means (minimum, maximum)

† Indicates that at least one replicate value was below the Limit of Quantitation (LOQ). For values below the LOQ, the LOQ was used to calculate the mean and the corresponding minimum and maximum values.

Table 6.1.5-23: Comparison of HPHC Ranges for Camel Snus (0.6 g pouch size) and Other Smokeless Tobacco Products from the U.S. Market (0.6 g basis)

Tobacco Product	Camel Snus (0.6 gram)	Moist Snuff	Loose leaf	Dry snuff
Compound	**Per Pouch (as-is)**	**Per 0.6 gram (as-is)**		
Nicotine (mg)	(5.9, 6.0)*	(4.4, 8.8)	(2.1, 4.9)	(10.4, 18.1)
Moisture (%)	(33.3, 33.5)	(49.2, 56.9)	(23.7, 28.9)	(3.5, 7.2)
pH	(7.7, 7.7)	(6.7, 8.3)	(5.5, 6.1)	(5.7, 6.3)
% Un-ionized nicotine	(31.2, 34.2)	(5.2, 67.1)	(0.3, 1.5)	(0.5, 1.9)
Total free nicotine (mg)	(1.9, 2.1)	(0.3, 4.4)	(0.0, 0.0)	(0.1, 0.3)
Acetaldehyde (ng)	(856†, 1106)	(405†, 15567)	(1083, 3926)	(634†, 1785)
Arsenic (ng)	(47.4, 48.1)	(27, 112)	(43, 114)	(75, 133)
B[a]P (ng)	(0.6†, 0.6†)	(2.3†, 111.7)	(2.0, 3.0)	(16.4, 124.1)
Cadmium (ng)	(237, 241)	(210, 390)	(269, 424)	(639, 910)
Crotonaldehyde (ng)	(353†, 357†)	(282†, 440†)	(394†, 440†)	(406†, 438†)
Formaldehyde (ng)	(679†, 806†)	(428†, 2237)	(502†, 540†)	(591, 3952)
NNK (ng)	(188, 216)	(58, 1051)	(110, 520)	(1554, 59620)
NNN (ng)	(650, 760)	(331, 3133)	(510, 1993)	(3561, 28640)

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

Data sources: RDM JAB 2016,281; LSI 2014 113; RDM JMR 2016,235

* Range of individual product means (minimum, maximum)

† Indicates that at least one replicate value was below the Limit of Quantitation (LOQ). For values below the LOQ, the LOQ was used to calculate the mean and the corresponding minimum and maximum values.

Table 6.1.5-24: Comparison of HPHC Ranges for Camel Snus (1.0 g pouch size) and Other Smokeless Tobacco Products from the U.S. Market (1.0 g basis)

Tobacco Product	Camel Snus (1.0 gram)	Moist Snuff	Loose leaf	Dry Snuff
Compound	**Per Pouch (as-is)**	**Per 1.0 gram (as-is)**		
Nicotine (mg)	(9.3, 10.2)	(7.4, 14.7)	(3.5, 8.2)	(17.3, 30.2)
Moisture (%)	(33.3, 33.7)	(49.2, 56.9)	(23.7, 28.9)	(3.5, 7.2)
pH	(7.7, 7.7)	(6.7, 8.3)	(5.5, 6.1)	(5.7, 6.3)
% Un-ionized nicotine	(32.7, 34.0)	(5.2, 67.1)	(0.3, 1.5)	(0.5, 1.9)
Total free nicotine (mg)	(3.0, 3.4)	(0.5, 7.3)	(0.0, 0.1)	(0.1, 0.5)
Acetaldehyde (ng)	(1418†, 1576†)	(675†, 25945)	(1805, 6543)	(1056†, 2975)
Arsenic (ng)	(75.9, 78.9)	(46, 187)	(71, 190)	(125, 222)
B[a]P (ng)	(1.1†, 1.1†)	(3.9†, 186.2)	(3.3, 5.0)	(27.4, 206.8)
Cadmium (ng)	(385, 417)	(350, 650)	(449, 706)	(1065, 1517)
Crotonaldehyde (ng)	(629†, 663†)	(469†, 733†)	(657†, 733†)	(676†, 730†)
Formaldehyde (ng)	(877†, 929†)	(714†, 3728)	(837†, 899†)	(985, 6587)
NNK (ng)	(310, 348)	(97, 1751)	(184, 867)	(2590, 99367)
NNN (ng)	(1007, 1186)	(552, 5222)	(851, 3322)	(5935, 47733)

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

Data sources: RDM JAB 2016,281; LSI 2014 113; RDM JMR 2016,235

* Range of individual product means (minimum, maximum)

† Indicates that at least one replicate value was below the Limit of Quantitation (LOQ). For values below the LOQ, the LOQ was used to calculate the mean and the corresponding minimum and maximum values

Camel Snus HPHC results are lower than those of many other smokeless tobacco products sold in the United States. Table 6.1.5-25 is a product chemistry comparison of Camel Snus to 67 U.S. smokeless tobacco products sampled in 2014 and 2015 (RDM JAB 2016,281). The table shows the percentage of the smokeless tobacco products with HPHC levels greater than each of the 6 Camel Snus styles on a per gram, as-is basis. For 9 of the 13 endpoints measured, Camel Snus values are lower than the majority of the other smokeless brands tested. Camel Snus is lower than 97% of the other brands in B[a]P content and is lower than over 90% of the other brands in crotonaldehyde and arsenic content. From 87 to 96% of the other brands have higher cadmium content than Camel Snus. Nicotine, moisture and NNN content are lower in Camel Snus than 60 – 85% of the other smokeless tobacco styles, while 49 – 61% of the other smokeless tobacco styles are greater than Camel Snus for NNK and acetaldehyde. About 1/2 to 1/3 of the other smokeless brands have higher pH, un-ionized nicotine and formaldehyde values than the Camel Snus brands.

Table 6.1.5-25: Product Chemistry Comparison: Percentage of U.S. Smokeless Tobacco Products* Greater than Camel Snus (per gram, as-is)

	Frost*	Mellow	Mint	Frost Large	Robust	Winterchill
Nicotine (mg/g)	81	81	82	79	85	85
Un-ionized (free) Nicotine (%)	34	34	34	34	34	34
Total Free Nicotine (mg/g)	43	48	45	43	51	45
Moisture (%)	76	76	76	76	76	76
pH	34	34	34	34	34	34
Acetaldehyde (ng/g)	61	54	60	58	58	61
Crotonaldehyde (ng/g)	93	93	93	90	90	93
Formaldehyde (ng/g)	30	30	31	79	45	40
Arsenic (ng/g)	94	94	94	94	94	94
Cadmium (ng/g)	87	88	88	87	96	91
NNN (ng/g)	76	79	60	69	87	78
NNK (ng/g)	58	63	49	58	66	51
B[a]P (ng/g)	97	97	97	97	97	97

*Percentages are calculated in comparison to results for the 67 U.S. smokeless tobacco products sampled in 2014 and 2015 (results reported in RDM JAB 2016,281). Of the 67, 43 were unique products as some products were analyzed in both years. Camel Snus data are summarized in Table 6.1.5-18.

Table 6.1.5-26 summarizes and compares HPHC results for Camel Snus styles to those of other styles of U.S. smokeless tobacco on a product sub-category basis (*i.e.*, moist snuff, dry snuff and loose leaf product categories) based on the numerical ranges shown in Table 6.1.5-22 (all values expressed on a per gram, as-is basis). In general, Camel Snus chemistry is most similar to moist snuff and least similar to dry snuff among the spectrum of types of U.S. smokeless tobacco. However, as shown in Table 6.1.5-25, for 9 of the 13 chemical constituents and measures, Camel Snus values are lower than those of the majority of the other U.S. smokeless tobacco brands.

Moist Snuff comparison: The range of moist snuff results determined brackets the range of results for Camel Snus for all analytes except moisture and B[a]P. This means that some brands of moist snuff have analyte levels below the range of means for Camel Snus and some brands have higher analyte levels (a relationship designated "Equal to Camel Snus" in Table 6.1.5-26). Moisture and B[a]P results for moist snuff are greater than Camel Snus with no overlap of the range of means found for either analyte (a relationship designated "Greater than Camel Snus" in Table 6.1.5-26). Camel Snus moisture is consistently lower than moist snuff for by about 20% (absolute moisture units). Moist snuff B[a]P results range from 3 times to over 150 times greater than the levels found in Camel Snus styles. In general, Camel Snus HPHC chemistry profiles are more similar to moist snuff than to the other two types of U.S. smokeless tobacco.

(b) (4)

[redacted]

Dry Snuff comparison: Dry snuff results are greater than those of Camel Snus styles for 7 of the HPHCs (nicotine, arsenic, B[a]P, cadmium, crotonaldehyde, NNK and NNN) with no overlap in ranges. The greatest differences observed are for B[a]P (27 – 170 X), NNK (8 – 276 X), and NNN (6 – 38 X) based on the minimum and maximum values for the ranges in Table 6.1.5-22. It is difficult to make a definitive assessment for crotonaldehyde since the upper and lower limits of the range contain values below the LOQ for both types of products. Dry snuff results are lower than those of Camel Snus styles for moisture, pH and free nicotine, with no overlap in the range of mean values. Dry snuff values for formaldehyde tend to be greater than those found for Camel Snus but there is an overlap in the range of values determined. The upper and lower limits of the range for Camel Snus contain formaldehyde values below the LOQ, but this is not the case for dry snuff. Dry snuff acetaldehyde values bracket the Camel Snus results. In general, differences between the HPHC chemistry profiles of Camel Snus and dry snuff products are greater than for comparisons of Camel Snus to moist snuff or loose leaf tobacco products.

Table 6.1.5-26: Summary Comparison of the Range of Means from RJRT Studies for Camel Snus and Other U.S. Smokeless Tobacco

	Relationship of Other Smokeless Tobacco Products to Camel Snus Styles				
Analyte	**Greater than Camel Snus**[1]	**Greater than or Equal to Camel Snus**[2]	**Equal to Camel Snus**[3]	**Less than or Equal to Camel Snus**[4]	**Less than Camel Snus**[5]
Nicotine	Dry Snuff		Moist Snuff		(b) (4)
Moisture	Moist Snuff				(b) (4) Dry Snuff
pH			Moist Snuff		(b) (4) Dry Snuff
% un-ionized nicotine			Moist Snuff		(b) (4) Dry Snuff
Free nicotine			Moist Snuff		(b) (4) Dry Snuff
Acetaldehyde		(b) (4)	Moist Snuff Dry Snuff		
Arsenic	Dry Snuff		Moist Snuff (b) (4)		
B[a]P	Moist Snuff (b) (4) Dry Snuff				
Cadmium	Loose Leaf Dry Snuff		Moist Snuff		
Crotonaldehyde	Dry Snuff	(b) (4)	Moist Snuff		
Formaldehyde		Dry Snuff	Moist Snuff	(b) (4)	
NNK	Dry Snuff		Moist Snuff (b) (4)		
NNN	Dry Snuff		Moist Snuff (b) (4)		

[1]Lower limit of product range > upper limit of Camel Snus range. No overlap in ranges.
[2]Lower limit of product range > lower limit of Camel Snus range; Upper limit of product range > upper limit of Camel Snus range. Partial overlap in ranges.
[3]Lower limit of product range < lower limit of Camel Snus range; Upper limit of product range > upper limit of Camel Snus range. Product range completely contains Camel Snus range.
[4]Upper limit of product range > lower limit of Camel Snus range > lower limit of product range; Upper limit of product range < upper limit of Camel Snus range. Partial overlap in ranges.
[5]Upper limit of product range < lower limit of Camel snus range. No overlap in ranges.

6.1.5.7 Comparison of Camel Snus chemistry to other current Swedish snus products

Camel Snus HPHC chemistry is generally consistent with other Swedish snus manufactured in Sweden. In the RJRT study M195-GLP (LSI 2014 113), 5 Swedish snus brand styles manufactured in Sweden (4 from Sweden and 1 sold in the U.S.) are compared to the 6 Camel Snus styles that are the subject of this Application on a per pouch basis, as well as a dry weight and per mg nicotine bases. Nicotine, free nicotine, B[a]P, formaldehyde, acetaldehyde, NNN, NNK, cadmium and arsenic results are compared in the study. All crotonaldehyde results were below detection limits, so product comparisons were not possible. On a per pouch as-is basis, there are no statistically significant differences ($p \leq 0.05$) found for any HPHC comparisons of Camel Snus Frost, Camel Snus Mellow or Camel Snus Mint and other Swedish snus styles for the different analytes tested. For the larger pouch size Camel Snus styles (Frost Large, Robust and Winterchill), no statistically significant differences are found compared to the Swedish styles except for NNN (Frost Large, Robust and Winterchill) and NNK (Winterchill only).

6.1.5.8 Comparison of Camel Snus chemistry reported in the scientific literature to results from RJRT studies

Camel Snus chemistry results reported in the peer-reviewed literature agree well with results found in RJRT studies. For analytes summarized in Table 6.1.5-5 and Table 6.1.5-6 there are a large number of reported values: nicotine (19), unprotonated nicotine (18), NNN (21), NNK (17), pH (14) and moisture (12). For NNN, the literature values for the selected styles that are the subject of this Application range from 425 to 1790 ng/g with a mean value of 1013 ng/g. For RJRT studies, mean values for NNN range from 1007 to 1268 ng/g (Table 6.1.5-17). For NNK, the literature range for selected styles is 146 to 485 ng/g with a mean of 370 ng/g. The mean NNK values for the 6 Camel Snus styles in RJRT studies range from 310 to 360 ng/g (Table 6.1.5-17). The mean literature value for moisture is 32.1% while the range for the 6 styles in RJRT studies is 33.3 to 33.7% (Table 6.1.5-17). For the 2014 and 2015 market surveys conducted by RJRT (RDM JAB 2016,281), the mean moisture value for all styles is 32.3%. For pH, the mean literature value for selected styles is 7.6 and the RJRT mean pH value is 7.7. The mean nicotine value (selected styles) from the literature is 9.68 mg/g while the mean values for the 6 styles in RJRT studies bracket this with a range of 9.3 to 10.2 mg/g. The mean literature free (un-ionized) nicotine value (selected styles) of 2.6 mg/g is also similar to, but slightly less than, the range found for RJRT studies of 3.0 to 3.4 mg/g.

While similar, the literature values shown in Table 6.1.5-7 do not agree to the same extent with RJRT study results (Table 6.1.5-17) as found for the analytes in Table 6.1.5-5 and Table 6.1.5-6. The greater differences observed may be due to the limited number of reported values as well as potential differences in analytical methods, sample preparation techniques and laboratory equipment for the different studies. For example, only 4 values for B[a]P are reported for selected Camel Snus styles in the literature which range from 0.5 to 10.1 ng/g, with a mean value of 3.18 ng/g. RJRT studies found 1.0 to 1.2 ng/g. The literature mean cadmium content of 438 ng/g is similar to the range of 385 to 418 ng/g found in RJRT studies. The mean literature acrylamide content of 71.8 ng/g is similar to the mean value of 79.1 ng/g for the 2014 and 2015 market survey values (RDM JAB 2016,281) for the 6 Camel Snus styles as well. The largest difference between results reported in the literature and in RJRT studies is for arsenic content. Two values of 83 and 789 ng/g are reported for selected styles in the literature, with a mean of 436 ng/g. The range of means for RJRT studies is 76.0 to 79.8 ng/g.

In summary, there is good overall agreement between the HPHC chemistry values reported in peer-reviewed literature and in RJRT studies. Differences that are observed may be due in whole or in part to differences in analytical methodology employed for conducting quantitative chemical analysis in different laboratories.