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CONFIDENTIAL, NOT FOR PUBLIC DISCLOSURE

December 20, 2018

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Deirdre Kittner, Ph.D., MPH
Deputy Director, Division of Population Health Science
Office of Science
Food and Drug Administration
Center for Tobacco Products
Document Control Center (DCC)
Building 71, Room G335
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: PARTIAL RESPONSE (DEFICIENCY 24) to AUGUST 10, 2018 ADVICE/INFORMATION REQUEST for PM0000427-PM0000432 and MR0000068-MR0000073

Dear Drs. Rosenfeldt and Kittner:

RAI Services Company ("RAIS")[1] hereby submits the following, on behalf of R.J. Reynolds Tobacco Company ("RJRT"), in response to the United States Food and Drug Administration's ("FDA") Center for Tobacco Products ("CTP") August 10, 2018, ADVICE/INFORMATION REQUEST letter regarding RAIS's submission of Premarket Tobacco Applications ("PMTAs") and Applications Seeking a Modified Risk Tobacco Product Order ("MRTP Applications"), submitted under Section 910(b) and Section 911(d) of the Food, Drug, and Cosmetic Act ("FDCA"), respectively, on March 30, 2017 for the following tobacco products:

- PM0000427/MR0000072, Camel Snus Robust
- PM0000428/MR0000070, Camel Snus Mellow

[1] RAI Services Company ("RAIS") bears primary responsibility for regulatory compliance for Reynolds American Inc.'s operating companies, including R.J. Reynolds Tobacco Company ("RJRT"), American Snuff Co., LLC ("ASC"), Santa Fe Natural Tobacco Company, Inc. ("SFNTC"), and R.J. Reynolds Vapor Company ("RJRV"). References to RAIS in this letter refer to itself and RJRT where applicable.

- PM0000429/MR0000069, Camel Snus Frost Large
- PM0000430/MR0000071, Camel Snus Mint
- PM0000431/MR0000073, Camel Snus Winterchill
- PM0000432/MR0000068, Camel Snus Frost

This response refers to Deficiency Twenty-Four (24) in the aforementioned ADVICE/INFORMATION REQUEST. Deficiencies not addressed in this submission will be covered in separate responses. In this response, we have repeated CTP's requests, verbatim and in bold italics, followed by RAIS's response.

Please note that the enclosed response may contain confidential commercial and non-public trade secret information belonging to RAIS, RJRT, or RJRT's vendors. All such confidential and trade secret information is exempt from public disclosure under § 301(j) and § 906(c) of the FDCA, 5 U.S.C. § 552(b)(4), 18 U.S.C. § 1905, and 21 C.F.R. § 20.61 and any similar or related laws and regulations. RAIS and RJRT respectfully request that FDA maintain the confidentiality of this information.

Should you have any questions or require any additional information, please contact me at your earliest convenience.

P.P

Respectfully submitted,

Michael W. Ogden, Ph.D.
Senior Vice President
Scientific & Regulatory Affairs
RAI Services Company

FDA-Listed Deficiencies and RAIS Response

24. Your MRTPAs/PMTAs provide data from eight clinical studies of Camel Snus products (HSD0702_QOL, CSD0804_SMA, CSD0901_SSSO, CSD_0904_PMS, CSD0905_SL, CSD_0914_SUL, CSD1010_SS, CSD1101_STM) that assessed pharmacokinetics (PK), biomarkers, likelihood of use, and actual use for evaluation and review. The applications seek authorization for six CamelSNUS products: three 600 mg pouch flavors (Frost, Mellow, and Mint) and three 1000 mg pouch flavors (Frost, Robust, and Winterchill). However, the submitted studies do not include data for each of these six Camel Snus products. For example, no PK data from Mint (600 mg pouch flavor) or the three 1000 mg pouch Camel Snus products were provided. Additionally, data pertaining to biomarkers of exposure, biomarkers of harm, actual consumption and use behavior, rates of complete switching from smoking cigarettes over time, and questionnaires that assess dependence, withdrawal, and other subjective effects (e.g., FTND, MPSS, QSU) were not assessed in the 600 mg pouch Mint flavor product or any of the three 1000 mg pouch products. Provide bridging data or a scientific rationale for how the data from Camel Snus products in the clinical studies are applicable to the specific products in your applications. If you choose to provide a scientific rationale, ensure that it explains how data from products with different pouch sizes or flavors are applicable to the products in your applications. If applicable data for the six products exists in the applications, indicate the location of this data. Data relevant to each of the six Camel Snus products in your applications is important for a behavioral and clinical pharmacology assessment for each individual product.

RAIS RESPONSE TO DEFICIENCY 24

RAIS understands FDA's request to be for either bridging data or a scientific rationale for how the data from the specific Camel Snus products tested in the clinical studies provided in the MRTPAs/PMTAs are applicable to all six Camel Snus products that are the subject of the MRTPAs/PMTAs. RAIS offers below both bridging data and a scientific rationale. The bridging data provided demonstrate that all six styles of Camel Snus share common physical and compositional characteristics, comparable levels of HPHCs on a per-gram basis, consistent low biological activity, common usage patterns and a singular position in the tobacco and nicotine product risk continuum. The scientific rationale provided for the suitability and utility of the data from the clinical studies that were included in the applications to inform all six Camel Snus styles (five flavor varieties and two pouch sizes) is based on the consistency of the bridging data across all Camel Snus styles, together with observations from available data that biomarker and other responses are consistent for users of Camel Snus styles (1) that contain either a "mint" or "non-mint" flavor, two general types of flavors that represent the flavor range of Camel Snus varieties, and (2) that represent both Camel Snus pouch sizes (0.6 g and 1.0 g) (*see* Section 2.9.1.2.9 of the Camel Snus MRTPAs/PMTAs).

I. BRIDGING DATA

A. Product Characteristics

All six Camel Snus styles share common physical and compositional characteristics

As discussed in Section 3.1 of the Camel Snus MRTPAs/PMTAs, all six Camel Snus products are portioned, pouched smokeless products within the snus sub-category. All six Camel Snus products use a common blend of tobaccos and manufacturing process (b) (4)

(b) (4)

Relative to snus products sold in Sweden and other markets, all six Camel Snus products are manufactured using a process consistent with snus. Camel Snus differs from its Swedish origins only in its taste profile, which was formulated using flavors and humectants consistent with the taste preferences of American smokers. Flavorings were adapted to the American palate using ingredients commonly used in existing smokeless tobacco products and those commonly used in foods. RJRT also developed two different Camel Snus pouch sizes (0.6 g and 1.0 g) to appeal to different consumer preferences. Some Camel Snus users prefer larger pouches and some prefer smaller pouches.

The primary differences between snus, including the six Camel Snus styles, and the various types of moist snuff tobacco products prevalent in the United States today are the tobacco types used and the manufacturing processes employed with those tobaccos. The tobaccos used in all six Camel Snus styles contain lower levels of toxicants than the tobaccos used in most other smokeless tobacco products, and the special heat-treatment steps employed in snus manufacturing further minimize the quantities of those constituents in the final product. It is generally accepted that heat treatment, along with selection of tobaccos, limits the levels of some harmful and potentially harmful constituents ("HPHCs"). Tobacco-specific nitrosamines (TSNAs) are formed from tobacco alkaloids during tobacco curing, fermentation, and aging. Using heat treatment inhibits microbial growth and thereby minimizes further development of TSNAs in finished smokeless tobacco products.

Table 1 below (excerpted from Table 3.1-3 in Section 3.1.5 of the MRTPAs/PMTAs) presents final product design features for the six Camel Snus varieties. RAIS notes that these features are consistent across all six styles of Camel Snus, the only differences stemming from the increase in tobacco with the 1.0 g pouch size. While these design differences, specifically tobacco weight, do proportionally affect HPHC content on a unit of use basis (*see* Section I.B. CHEMISTRY), they do not manifest differences in biomarkers of exposure (*see* Section II. SCIENTIFIC RATIONALE) and, thus,

bridging across the six styles of Camel Snus from a product design perspective is appropriate.

Table 1. Final Camel Snus Pouch Design Features

Specification (unit) (Lower Limit / Upper Limit)	Camel Snus Frost	Camel Snus Mint	Camel Snus Mellow	Camel Snus Frost Large	Camel Snus Winterchill	Camel Snus Robust
(b) (4)						

B. Chemistry

All six of the subject Camel Snus styles contain comparable levels of HPHCs on a per-gram basis

As summarized in Sections 2.9.5 and 6.1.5.6 of the Camel Snus MRTPAs/PMTAs, three RJRT studies conducted chemical analyses of HPHC content in each of the six Camel Snus styles (i.e., RDM JAB 2016, 281; LSI 2014 113; RDM JMR 2016, 235). Summary HPHC data and descriptive statistics for each of the six Camel Snus products is provided in Section 6 of the MRTPAs/PMTAs (*see* Table 6.1.5-15 and Table 6.1.5-16 for a summary of Camel Snus chemistry by product style) and a few these constituents are presented graphically below. Using nicotine and total free nicotine (a function of nicotine content and product pH) as an example, it is evident that the equivalency of design features and use of a common blend of low-toxicant tobaccos across all six styles of Camel Snus drives consistency in HPHC content on a per-gram basis (Figure 1). This fact is further evident with NNN and NNK (Figure 2) and the remaining smokeless tobacco HPHCs measured in RJRT's chemistry studies (*see* Section 6.1.5.6 of the Camel Snus MRTPAs/PMTAs).

In sum, absolute HPHC content is consistent across all styles of Camel Snus of a given pouch size. Importantly, these differences, which are driven by tobacco inclusion, do not manifest differences in biomarkers of exposure (*see* Section II. SCIENTIFIC RATIONALE) and, thus, bridging across the six

styles of Camel Snus from a product chemistry perspective is appropriate.

Figure 1. HPHC Content is Comparable Across All Camel Snus Styles on a Per-Gram Basis – Nicotine and Total Free Nicotine

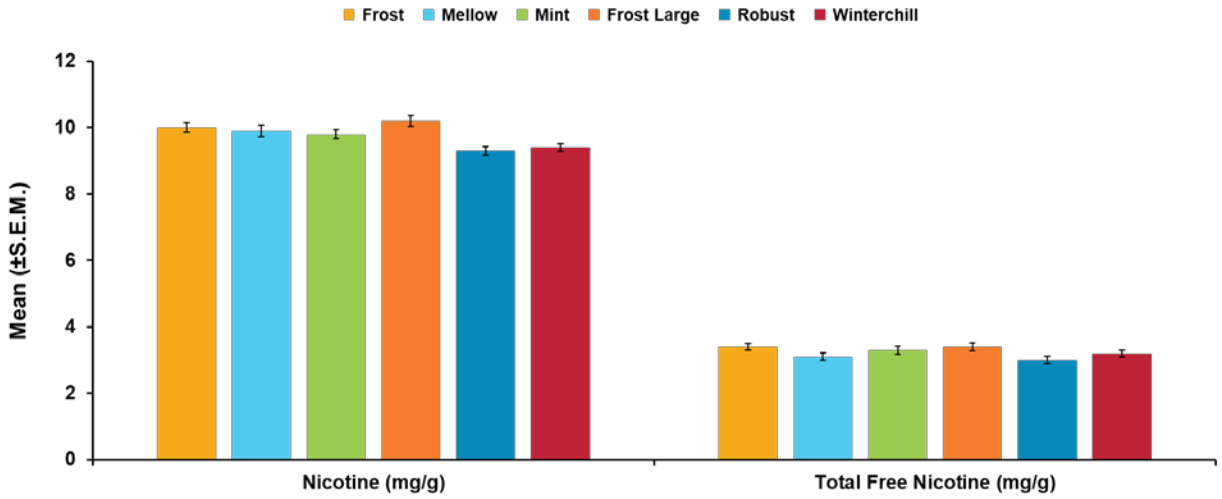
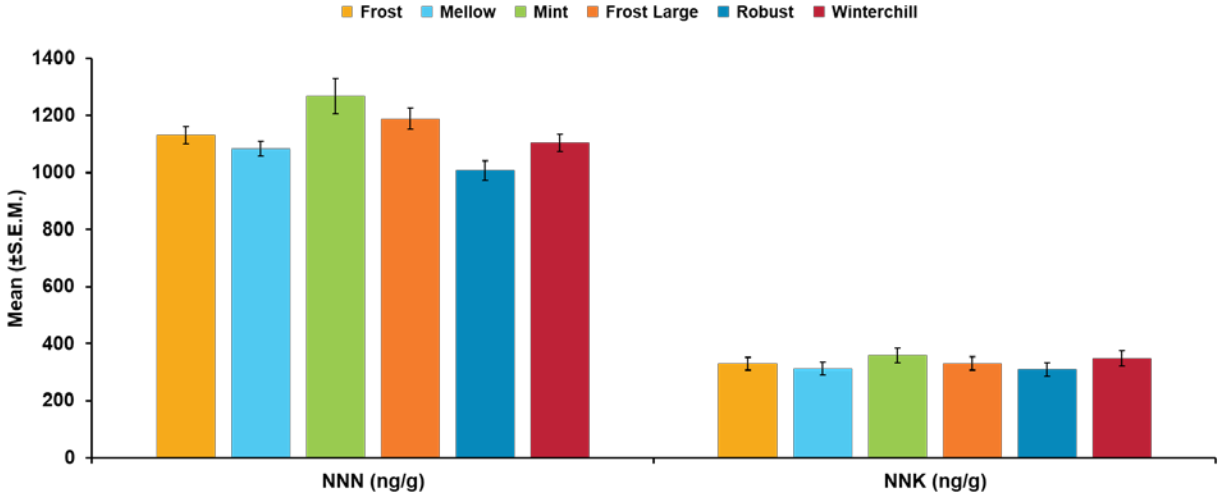


Figure 2. HPHC Content is Comparable Across All Camel Snus Styles on a Per-Gram Basis – TSNAs



C. Non-Clinical Studies

In vitro genotoxicity and cytotoxicity studies demonstrate that all six Camel Snus varieties exhibit no mutagenicity and consistently low cytotoxicity

Extracts of all six Camel Snus products were included in the in vitro mutagenicity and cytotoxicity assays conducted in accordance with Good Laboratory Practices. These studies included the Ames mutagenicity assay (study M194A-GLP) and the Neutral Red Uptake cytotoxicity assay (study M194B-GLP) both of which are found in Section 7_2_INVITRO and discussed in Sections 2.9.3.2 and 6.1.3 of the MRPTAs/PMTAs. No biological response was observed above spontaneous revertant levels or baseline values for any of the six products in the Ames assay, regardless of pouch size or flavor variety. This complete lack of statistically-significant or biologically-relevant differences among the six Camel Snus flavor and size varieties in the Ames bacterial mutagenicity assay contrasted to a highly significant degree with the robust mutagenic activity of the TPM from the two leading brands of U.S. cigarettes. Further, comparisons among the six subject Camel Snus products, normalized by nicotine content, demonstrated no differences in mammalian cell cytotoxicity in the Neutral Red Uptake assay. These findings are direct measures of cytotoxic effects consequent to HPHC permeation through the mammalian cell membrane, and demonstrate no differences among Camel Snus products, regardless of pouch size or flavor variety, with respect to cytotoxicity. As there is no evidence that flavors, other added ingredients, or pouch size have any measurable effects on cytotoxicity, these results provide additional support for the bridging of clinical data across the six Camel Snus products.

D. Product Use

All Camel Snus styles exhibit common usage patterns

All six styles of Camel Snus are used in a consistent manner. The pouches are intended to be placed in the mouth, under the lip, and used as is. Typically, there is no expectoration (spitting) during use. Camel Snus pouches are used for a length of time determined by the user. For all styles, Camel Snus flavor typically lasts approximately 30 minutes. Camel Snus is not consumed in its entirety; rather, the Camel Snus pouch is removed from the user's mouth after use and then disposed of. As such, Camel Snus users are exposed to only a fraction of any harmful or potentially harmful constituents (HPHCs) present in the low-toxicant tobacco blend.

As summarized in Section 3.5 of the MRTPAs/PMTAs, Camel Snus product use patterns are generally consistent with that of other smokeless tobacco products sold in the U.S. and are consistent for all styles of Camel Snus (*see* Table 3.5.2-2, Table 3.5.2-4, and Table 3.5.2-6). While individual Camel Snus users may have a flavor preference, product use patterns (e.g., days used per week and uses per day) are consistent for all styles of Camel Snus (*see* Table 3.5.2-5 and Table 3.5.2-3, respectively).

As discussed below in Section II. SCIENTIFIC RATIONALE, use of Camel Snus results in exposure to only a fraction of HPHCs and nicotine present initially in the product. In addition, biomarker data demonstrate consistent exposure patterns to nicotine and HPHCs for Camel Snus varieties

containing different flavor types (mint vs. non-mint) and consisting of both pouch sizes. Observed exposure patterns are not only consistent for the different Camel Snus styles studied, but also significantly different from that of cigarettes regardless of flavor or pouch size. As such, all six styles of Camel Snus occupy the same position on the tobacco and nicotine product risk continuum, a position like other smokeless tobacco products that is well below that of combusted tobacco products such as cigarettes and somewhat greater than that of nicotine replacement therapy (NRT) products (*see* Section I.E. Tobacco Product Risk Continuum below and Section 2.5.6 of the MRTPAs/PMTAs).

E. Tobacco Product Risk Continuum

All Camel Snus styles fall in a singular position in the tobacco and nicotine product risk continuum

As discussed in Section 2.5.6 of the Camel Snus MRTPAs/PMTAs, there is a scientific consensus for the tobacco product risk continuum. Public-health researchers have described this differentiation in risk through a construct called a "continuum of risk," with combustible tobacco products on one end and smokeless tobacco and nicotine products on the other.[2]

In this continuum, cigarette smoking is identified as the most risky behavior as consumers are exposed by inhalation to products of incomplete combustion from the burning of cigarettes, as well as other substances in cigarettes that transfer from tobacco to smoke. Because smokeless products do not undergo combustion during use, users of smokeless tobacco products are not exposed to tar, carbon monoxide, or other products of incomplete combustion. In addition, smokeless tobacco users are exposed to much lower quantities of combustion-related products, i.e., to whatever combustion-related products, if any, remain from the curing of the tobacco in smokeless tobacco products or from natural environmental sources (as with food). These differences in exposure, as well as differences in routes of exposure (inhalation vs. oral absorption), result in significantly lower risk profiles for smokeless tobacco users as compared with cigarette smokers, as demonstrated in many epidemiological studies (*see* Section 2.8 and Section 2.9 of the Camel Snus MRTPAs/PMTAs).

Epidemiological studies in both the U.S. and Sweden examine the health effects associated with many different brands and styles of smokeless tobacco (e.g., Henley et al. 2005[3]; Luo et al. 2007[4]). These data demonstrate that smokeless tobacco use presents significantly reduced risk for lung cancer, oral cancer, respiratory disease, and heart disease relative to cigarette smoking (*see* Section 2 and Section 6 of the Camel Snus MRTPAs/PMTAs).

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[2] Zeller M, Hatsukami D. The strategic dialogue on tobacco harm reduction: a vision and blueprint for action in the US. Tob Control. 2009. 18: 324-332.

[3] Henley SJ, Thun MJ, Connell C, Calle EE. Two large prospective studies of mortality among men who use snuff or chewing tobacco (United States). Cancer Causes & Control. 2005 May 1;16(4):347-58.

[4] Luo J, Ye W, Zendehdel K, Adami J, Adami HO, Boffetta P, Nyrén O. Oral use of Swedish moist snuff (snus) and risk for cancer of the mouth, lung, and pancreas in male construction workers: a retrospective cohort study. The Lancet. 2007 Jun 16;369(9578):2015-20.

Compared with the smokeless tobacco products that were used by the participants in the U.S. and Swedish epidemiology studies, each of the six styles of Camel Snus have lower levels of HPHCs (s*ee* Section 2.8.2.3, Section 2.8.3.3, and Section 2.8.3.4 of the Camel Snus MRTPAs/PMTAs). In addition, each of the six styles of Camel Snus is used as or less frequently, and in smaller quantities than the products that were used by participants in the epidemiology studies (*see* Section 2.8.2.5, Section 2.8.3.5, and Section 3.5.2 of the Camel Snus MRTPAs/PMTAs).

Taken together and for the reasons outlined above (i.e., common physical and compositional characteristics, comparable levels of HPHCs on a per-gram basis, consistent low biological activity and common usage patterns), all Camel Snus styles that pose less harm to the individual fall together in a singular position on one end of the continuum of risk, and the products that pose the highest risk, conventional cigarettes, fall on the other end.

II. SCIENTIFIC RATIONALE

A. Clinical study endpoints can be applied to all Camel Snus products

The above sections demonstrated that the physical and compositional characteristics, HPHC levels, in vitro mutagenicity and cytotoxicity responses, and product usage patterns are consistent across the six Camel Snus variants. These results provide a basis for bridging the clinical study data to the products for which no or limited clinical study data exist. To provide further scientific rationale for bridging, the clinical data including biomarker data and mouth-level exposure data were compared across the Camel Snus products for which data exist and demonstrate that constituent exposures are consistent, regardless of pouch size or flavor variety. Specific comparisons are provided below in more detail.

B. Human exposure to tobacco constituents is comparable across flavor variants

i. Biomarkers of Tobacco Exposure

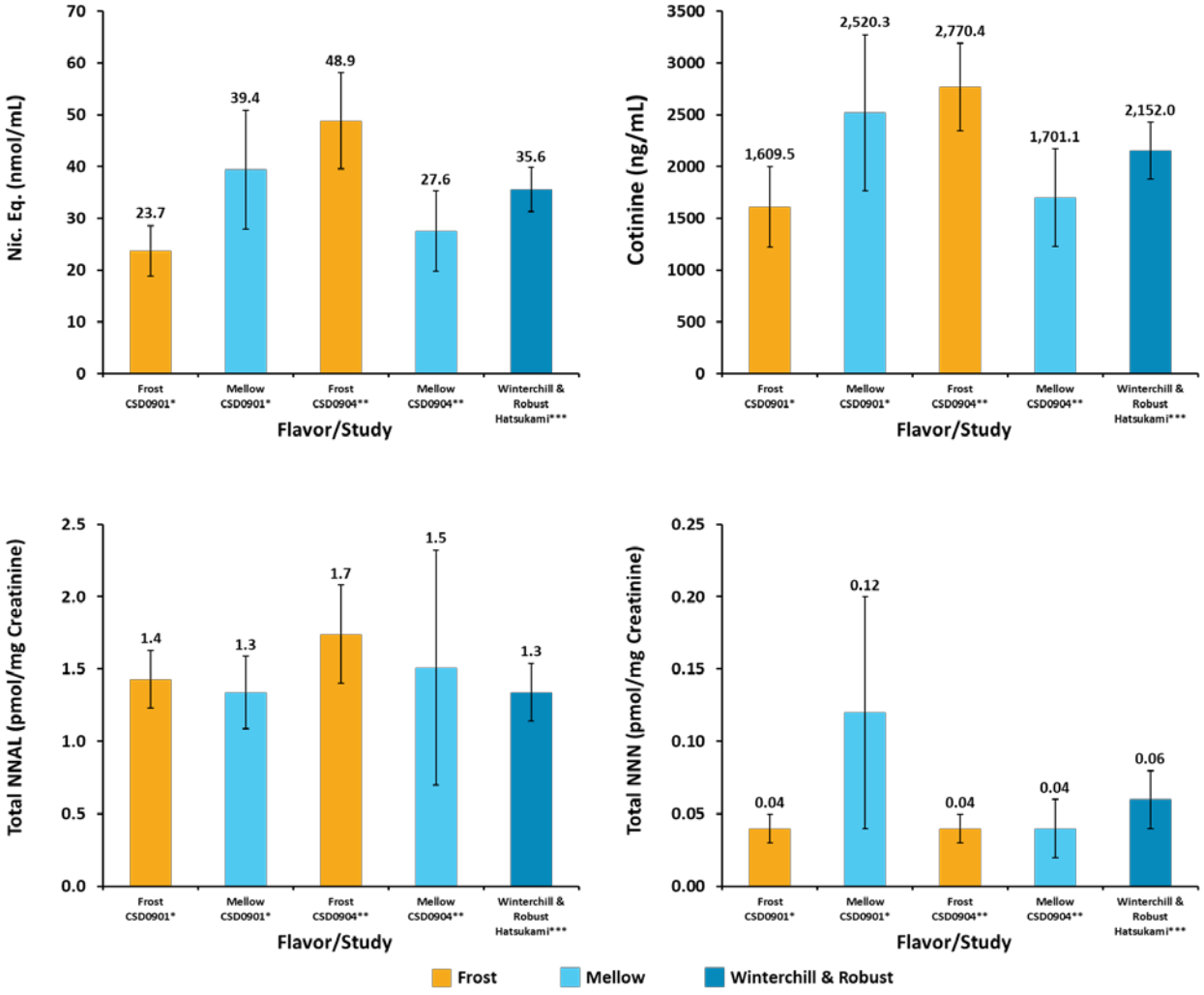
A comparison of the available biomarker data that examined exposure to tobacco constituents shows comparable constituent exposures from use of different flavor varieties, and contrasts to exposures from cigarette smoking.

Biomarker results of three studies (2 RJRT-sponsored, 1 non-RJRT) that included four Camel Snus products were broken out by flavor where possible. CSD0901 and CSD0904 included participants who used Camel Snus Frost and Camel Snus Mellow, one “mint” and one “non-mint” style, respectively, that together represent the flavor range of Camel Snus varieties. (CSD0904 also included one participant who used Camel Snus Winterchill.) Hatsukami et al., 2016 included participants who used Camel Snus Winterchill and Camel Snus Robust. (For study data and discussion, *see* Section 7_4_CLIN and Sections 2 and 6.1.2 of the Camel Snus MRTPAs/PMTAs, respectively.) The data from CSD0901 and CSD0904 were summarized by flavor; whereas, for Hatsukami et al., 2016, the data according to flavor were not available to RAIS. The units of the

results in CSD0901 and CSD0904 were converted to the units used in Hatsukami et al., 2016 to permit direct comparison. The biomarker data included in Hatsukami et al., 2016 were limited to nicotine, cotinine (a biomarker of nicotine), NNN, and NNAL (a biomarker of NNK). Results are shown in Figure 3.

Nicotine exposure is consistent across flavors as shown by means and standard errors for urinary nicotine and cotinine in the graphs below. Comparable results were also observed across flavors for NNK and NNN exposure as measured by urinary total NNAL and total NNN, respectively. The results show that the variation within flavor across studies was greater than the variation between flavors in the same study, which provides scientific rationale for the application of exposure biomarker data to flavors for which such data do not exist. (*See* RAIS RESPONSE TO DEFICIENCY 13a.ii. for biomarker results by Camel Snus style for all applicable RJRT-sponsored studies.)

Figure 3. Use of Different Camel Snus Flavor Varieties Results in Consistent Exposure to Nicotine and TSNAs



* 1-week switch; ** Natural adopters (>24 weeks); *** 4-week switch (Hatsukami, 2016).
Blocks, mean; bars, standard error.

The biomarkers of exposure to HPHCs were also compared to exposure from cigarette smoking, by Camel Snus flavor based on data from CSD0901 and CSD0904. A graphical summary of these analyses for CSD0901 is shown in Figure 4 - Figure 6 to illustrate this point; however, comparable results were observed for CSD0904 (*see* RAIS RESPONSE TO DEFICIENCY 13a.ii.). These results show that the exposures to HPHCs (as designated on FDA's Established list of HPHCs[5]) from Camel Snus use of either Frost or Mellow variants are consistent, and the exposure to all HPHCs that are

[5] Food and Drug Administration. Harmful and potentially harmful constituents in tobacco products and tobacco smoke; Established list. 2012. Docket No. FDA-2012-N-0143. https://www.federalregister.gov/documents/2012/04/03/2012-7727/harmful-and-potentially-harmful-constituents-in-tobacco-products-and-tobacco-smoke-established-list

products of combustion are different by a large and statistically significant magnitude compared to smoking, used as the baseline. Biomarker levels from smoking for each HPHC are represented by the red line as 0% difference from smoking. This is true for HPHCs designated as carcinogens, respiratory toxicants, and cardiovascular toxicants (*see* RAIS RESPONSE TO DEFICIENCY 13a.i., Table 2, for a list of constituents and associated disease relevance). The biomarker results taken in totality demonstrate that Camel Snus users of either Frost or Mellow are exposed to comparable levels of HPHCs designated as carcinogens, respiratory toxicants, and cardiovascular toxicants and that their exposure similarly contrasts to the generally higher exposure to these constituents from cigarette smoking.

Figure 4. Use of Either Camel Snus Frost or Mellow Results in Consistent Decreases in Exposure to Carcinogens from Smoking

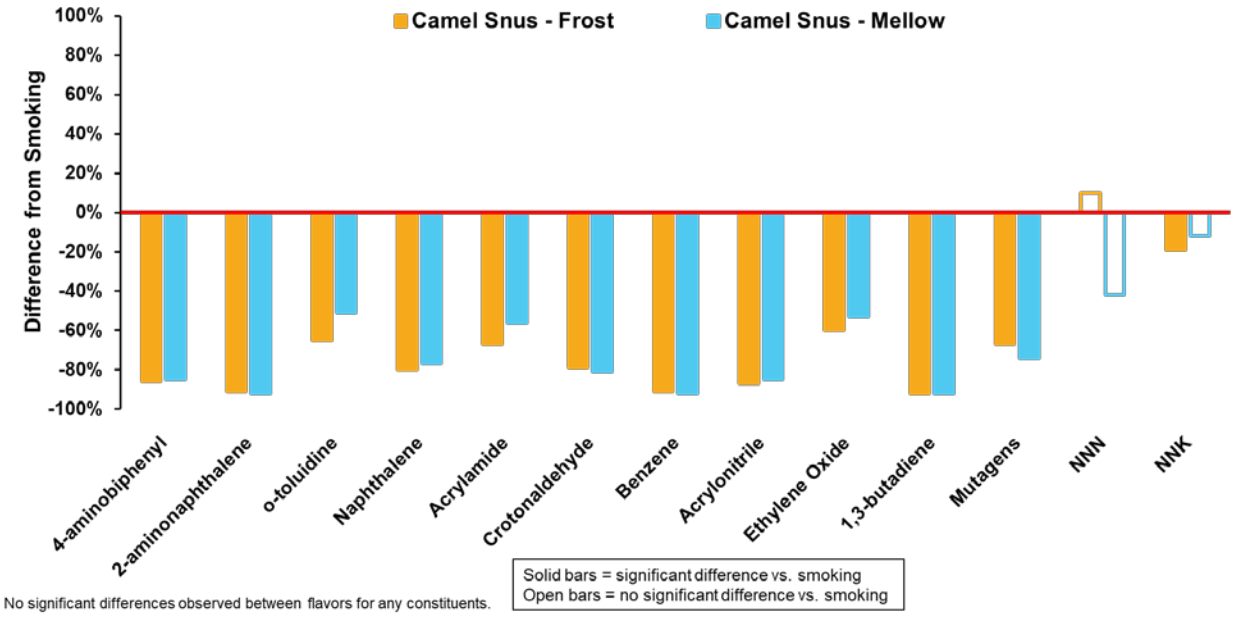
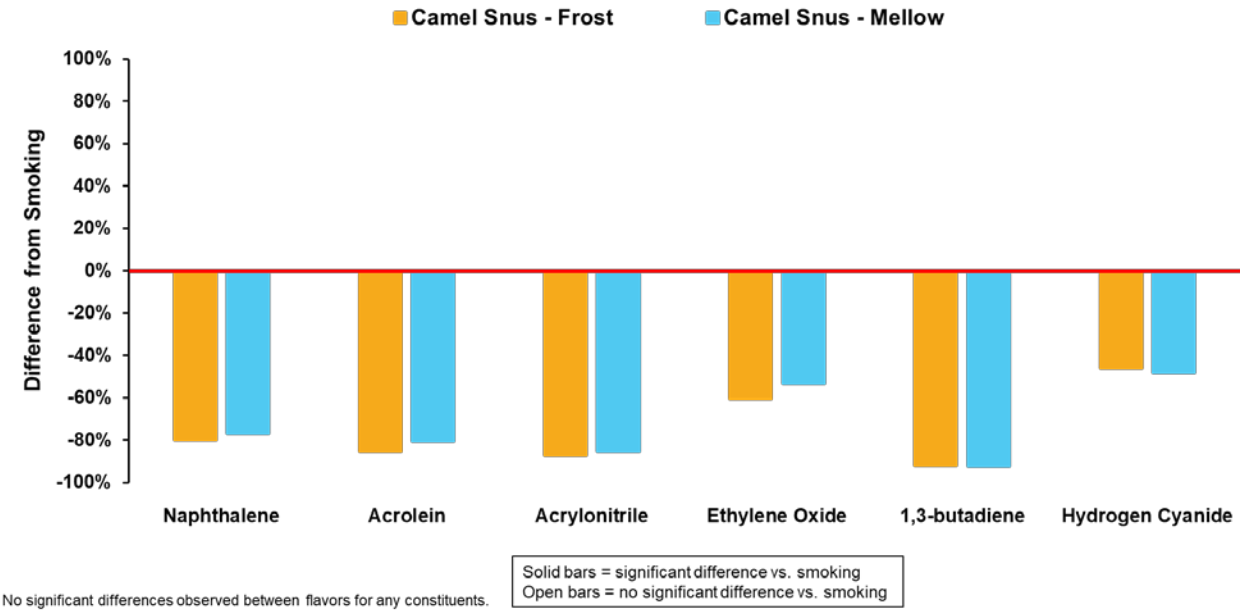
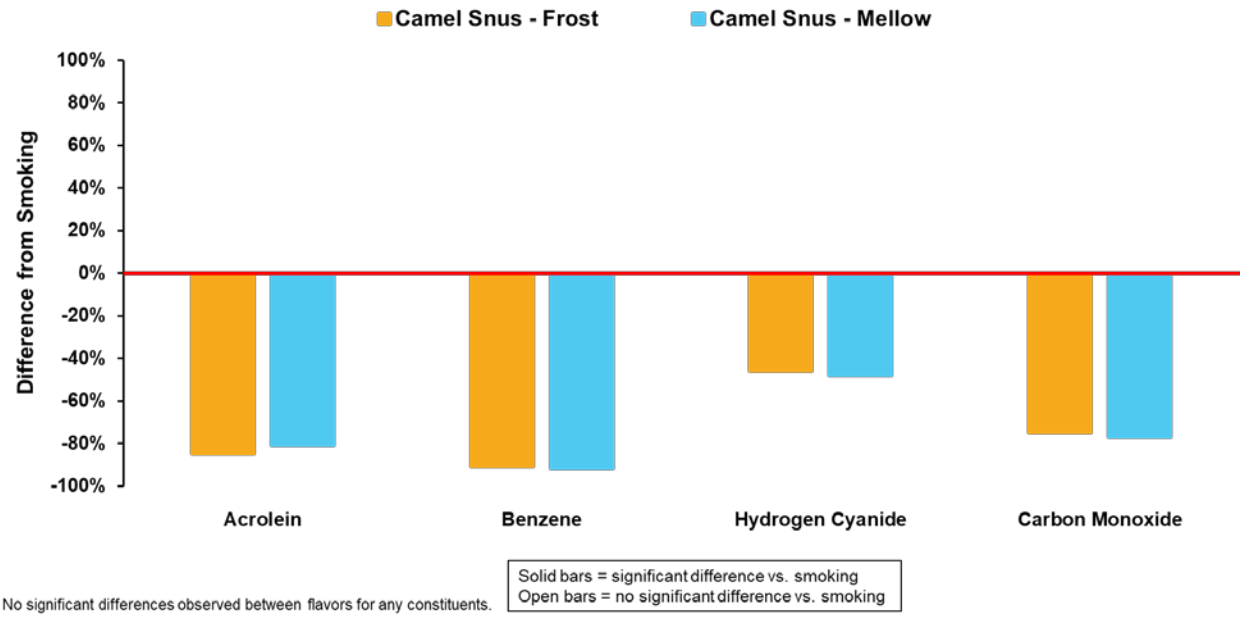


Figure 5. Use of Camel Snus Frost or Mellow Results in Consistent Decreases in Exposure to Respiratory Toxicants from Smoking



No significant differences observed between flavors for any constituents.

Figure 6. Use of Camel Snus Frost or Mellow Results in Consistent Decreases in Exposure to Cardiovascular Toxicants from Smoking



No significant differences observed between flavors for any constituents.

ii. Mouth-level exposure

An examination of the mouth-level exposure from use of Camel Snus demonstrates that only a fraction of the constituents present in a snus pouch are extracted during use and that comparable amounts of constituents are extracted with use of different flavor variants (*see* Section 2.9.1.2.8 of the Camel Snus MRTPAs/PMTAs). Four clinical studies measured the constituent levels extracted from use of Camel Snus Frost and Mellow: CSD0804 (Frost only), CSD0901, CSD0904, and CSD0905. The percentages of nicotine, NNN, and NNK extracted from the different products are shown in Figure 7 and Figure 8. As stated in Section I.A. Product Characteristics above, the same mass of the same tobacco blend is included in both products, so the same percentage extraction indicates the same amount of constituent is removed from the pouch during use. The results in Figure 7 and Figure 8 show the percent extractions of nicotine, NNN and NNK are comparable for both flavor variants.

These results, together with the consistent product use amounts for each flavor discussed above in Section I.D. Product Use and presented in Section 3.5 of the MRTPAs/PMTAs, are consistent with the comparable biomarker results shown for the different flavors.

Figure 7. Percent Extraction of Nicotine from Use of Camel Snus Frost and Mellow

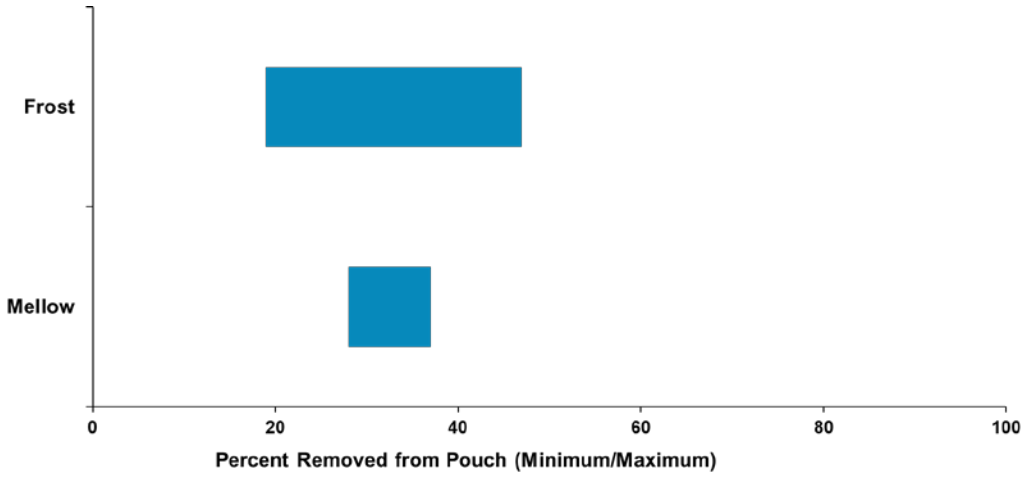
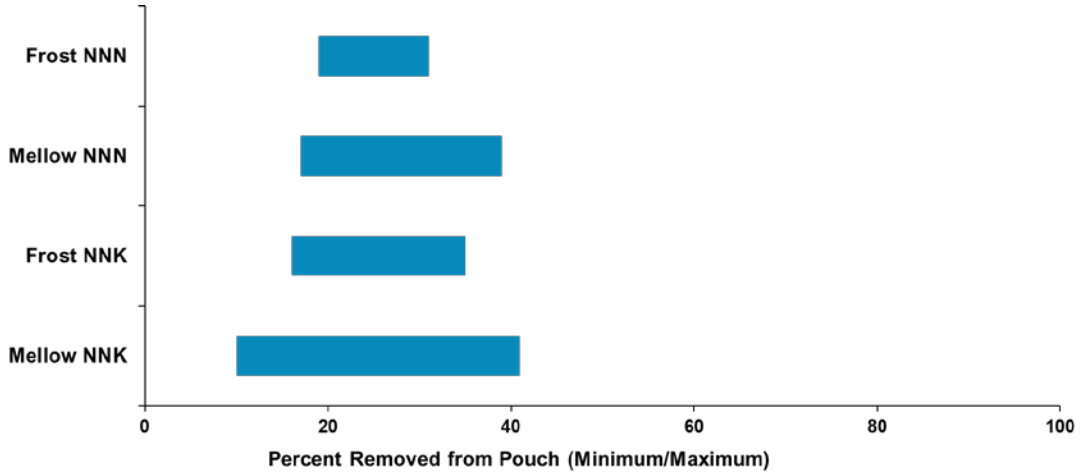


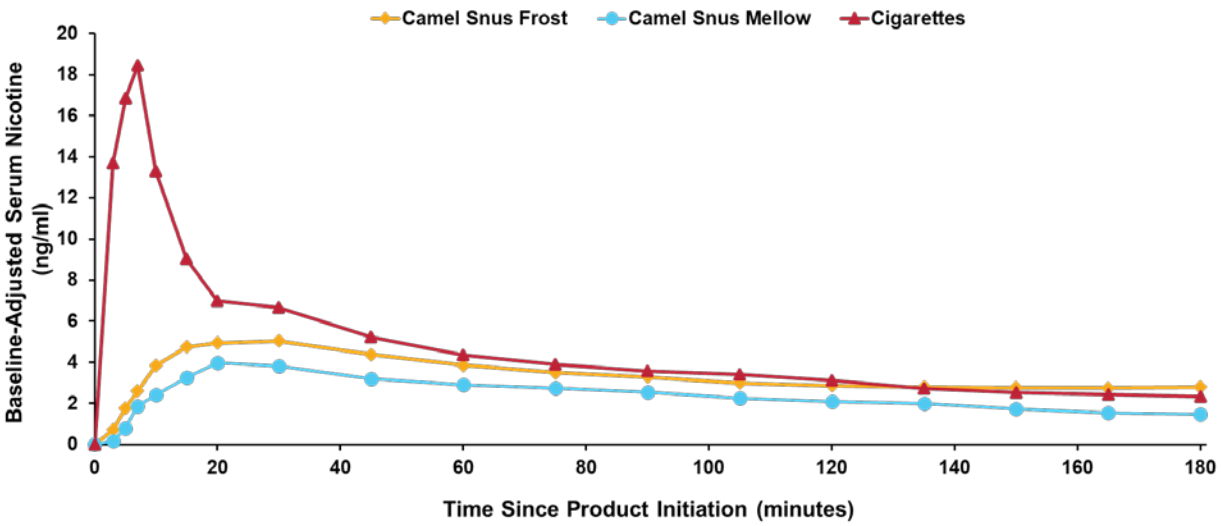
Figure 8. Percent Extraction of TSNAs from Use of Camel Snus Frost and Mellow



iii. Nicotine pharmacokinetics

A comparison of the available serum nicotine data used to determine nicotine pharmacokinetic parameters in study CSD0914 for participants who used either Camel Snus Frost or Camel Snus Mellow shows no difference in nicotine pharmacokinetics from use of different flavor varieties (*see* Section 6.1.2.3.2.3 of the Camel Snus MRTPAs/PMTAs). In agreement, the urinary nicotine biomarker data measured in CSD0901, CSD0904, and Hatsukami, et al. 2016 show that daily nicotine exposure does not differ among different flavors or pouch sizes. Nicotine concentration-versus-time curves from use of Camel Snus Frost and Mellow are shown in Figure 9. The curves for the two Camel Snus products are comparable to each other and indicate slower and lower nicotine uptake that contrasts to the quicker, higher nicotine uptake from smoking a cigarette. Together, the results demonstrate the consistency of the two Camel Snus products with each other and the difference from combustible cigarettes.

Figure 9. CSD0914 – Serum Nicotine by Camel Snus Style and Usual Brand Cigarette



Whereas users may subjectively choose one flavor or size variety over another, flavor preference has been shown to contribute to product liking and attractiveness, but not to the pharmacologic abuse liability of these or other nicotine-delivering products, including flavored NRT gums and lozenges (*see* Henningfield et al. 2017 in Section 6 of the MRTPAs/PMTAs and references therein).

Summary of clinical study data across flavors

Taken together, the totality of the biomarker data and nicotine pharmacokinetic data summarized by flavor and compared to smokers, and the mouth-level exposure data summarized by flavor, demonstrate the consistencies among these endpoints across mint and non-mint flavor variants (two general types of flavors that represent the flavor range of Camel Snus varieties). These data provide scientific rationale to justify the application of the full set of biomarkers of exposure data and nicotine pharmacokinetic data, in addition to the other clinical study endpoints not discussed, for Camel Snus Frost and Mellow to the other four Camel Snus products (i.e., Mint, Frost Large, Winterchill, and Robust) for which a full set of data does not exist. In addition, the foundational physical and compositional characteristics, HPHC levels, in vitro mutagenicity and cytotoxicity responses, and product usage patterns for all six Camel Snus styles highlight the consistencies across flavor varieties (*see* Section I. BRIDGING DATA) and further support the bridging of clinical study data across flavors. Additional rationale is detailed below to further justify the application of the clinical data with use of the 0.6 g pouches to the 1.0 g pouches.

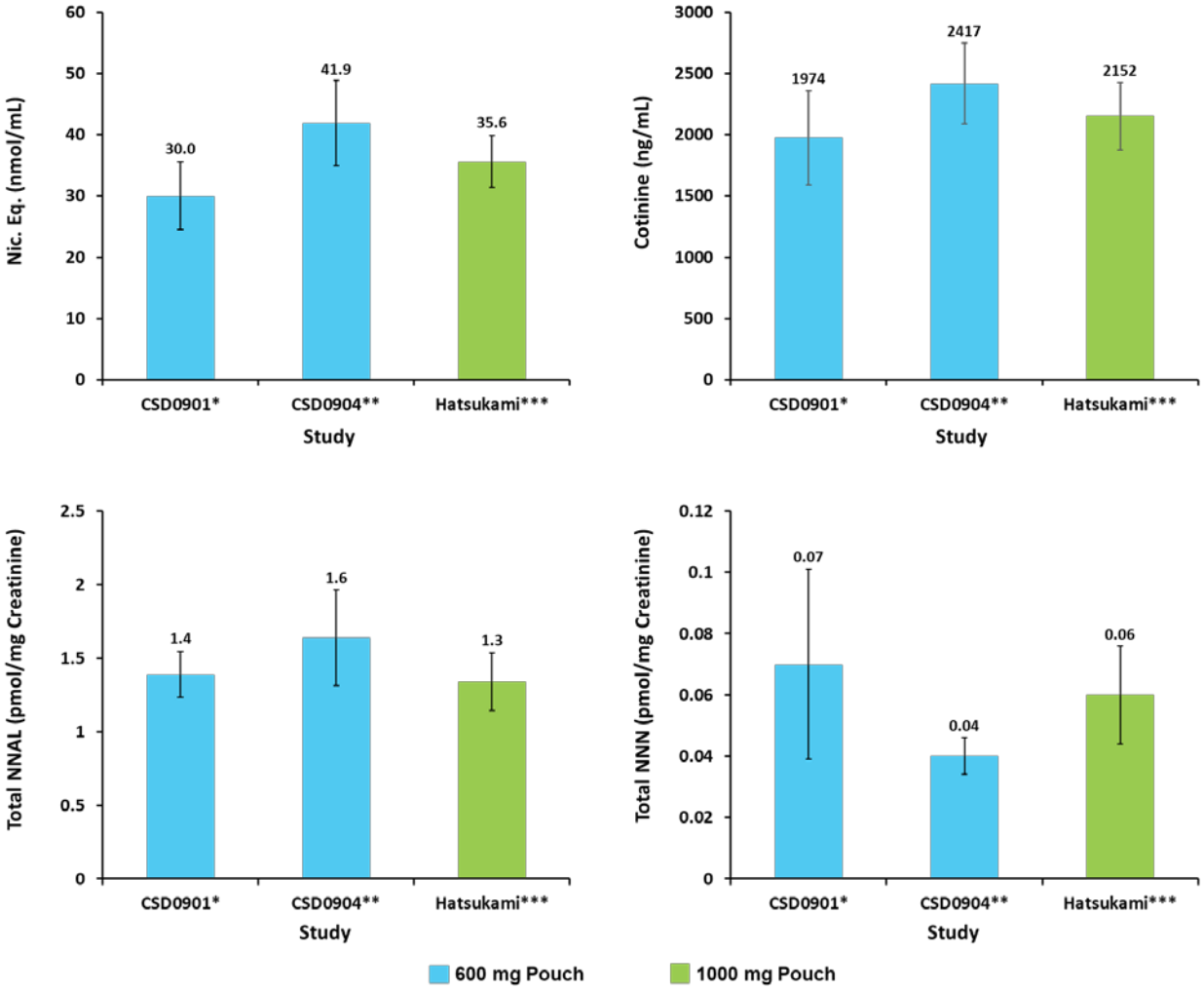
C. Human exposure to tobacco constituents is consistent across pouch sizes

i. Biomarkers of tobacco exposure

A comparison of the available biomarker data that examined exposure to tobacco constituents in studies of participants who used either 1.0 g pouches or 0.6 g pouches shows comparable constituent exposure from use of different pouch sizes. Data and rationale to demonstrate that exposure to nicotine, NNN and NNK are consistent from use of 1.0 g and 0.6 g pouch sizes can be found in Section 2.9.1.2.9 of the Camel Snus MRTPAs/PMTAs. Specifically, the results of three clinical studies were compared: CSD0901, CSD0904, and Hatsukami et al., 2016. CSD0901 and CSD0904 included use of the 0.6 g pouch size (Frost and Mellow), and Hatsukami et al., 2016 included use of the 1.0 g pouch size (Robust and Winterchill). The units of the results in CSD0901 and CSD0904 were converted to the units used in Hatsukami et al., 2016 to permit direct comparison. The biomarker data included in Hatsukami et al., 2016 was limited to nicotine, cotinine (a biomarker of nicotine), NNN and NNAL (a biomarker of NNK).

As seen in Figure 10, comparable urinary nicotine and TSNA biomarker levels were observed with use of both Camel Snus pouch sizes. These results demonstrate that pouch size does not affect exposure to HPHCs, and provide scientific rationale for the applicability of the extensive biomarker data collected with the use of Camel Snus 0.6 g styles to all 1.0 g styles.

Figure 10. Use of Different Camel Snus Pouch Sizes Results in Comparable Exposure to Nicotine and TSNAs



* 1-week switch; ** Natural adopters (>24 weeks); *** 4-week switch (Hatsukami, 2016)
Blocks, mean; bars, standard error.

ii. Nicotine pharmacokinetics

Nicotine pharmacokinetics following use of one Camel Snus pouch was not examined for the 1.0 g products; however, the available nicotine pharmacokinetic data comparisons by flavor (*see* Section II.B.iii. Nicotine pharmacokinetics) together with the urinary nicotine biomarker data consistencies with use across pouch sizes presented above (*see* Section II.C.i. Biomarkers of tobacco exposure) and the comparable product use data across pouch sizes presented in Section 3.5 of the MRTPAs/PMTAs suggest that the nicotine pharmacokinetic data for Camel Snus Frost and Mellow can be bridged to the 1.0 g pouch size products. Because the product use per day of the 1.0 g

pouches is comparable to the 0.6 g pouches (*see* Section I.D. Product Use) and the urinary biomarkers of nicotine are also consistent, this suggests that the nicotine exposure resulting from a single use of a 1.0 g pouch or a 0.6 g pouch of Camel Snus is also consistent. This scientific rationale justifies the application of the nicotine pharmacokinetic data from a single use of a 0.6 g pouch to a 1.0 g pouch (*see* Henningfield et al. 2017 in Section 6 of the MRTPAs/PMTAs).

Summary of Clinical Study Data Across Pouch Size

Taken together, the totality of the biomarker data and the urinary nicotine data applied to both the product use data and the nicotine pharmacokinetic data by flavor discussed above, demonstrate the consistencies among these endpoints across pouch sizes. These data provide scientific rationale to justify the application of the full set of biomarkers of exposure data and nicotine pharmacokinetic data, in addition to the other clinical study endpoints not discussed, for the Camel Snus 0.6 g styles to the three 1.0 g Camel Snus styles. In addition, the foundational physical and compositional characteristics, HPHC levels, in vitro mutagenicity and cytotoxicity responses, and product usage patterns discussed above further supports the bridging of data across pouch sizes.

D. Camel Snus styles are comparable to each other and different than other marketed tobacco products

The above sections provide bridging data and scientific rationale to justify the application of available clinical study data for Camel Snus Frost, Mellow, Winterchill and Robust to the other two styles (Mint and Frost Large) for which clinical study data do not exist. The justification above provides a comparison of Camel Snus data from one style to another, which shows consistency across all six styles, including consistency across all flavor variants and pouch sizes. Additionally, justification for the application of available clinical study data across all styles is evident when comparing Camel Snus to other currently marketed smokeless and combustible tobacco products as summarized below.

i. HPHC levels in Camel Snus are comparable or lower than U.S. smokeless tobacco products

As discussed in Section 2.9.5.5 and 6.1.5.6 of the MRTPAs/PMTAs, Camel Snus contains comparable or lower levels of HPHCs relative to other smokeless tobacco products sold in the United States. Figure 11 - Figure 14 below show the amounts of several HPHCs by smokeless tobacco product sub-category. In every example, the constituent amounts in all six Camel Snus products, grouped together, are either at the mid-range or at the low end of the range of the moist snuff products, which make up a significant portion of the market of smokeless tobacco products and are used in the most similar manner to Camel Snus. Further discussion on a comparison of the HPHC data for the Camel Snus products that are subject of the MRTPAs/PMTAs to commercially marketed U.S. moist snuff products is provided in RAIS RESPONSE TO DEFICIECNY

30b.

Figure 11. Nicotine levels in Camel Snus compared to other U.S. smokeless tobacco products

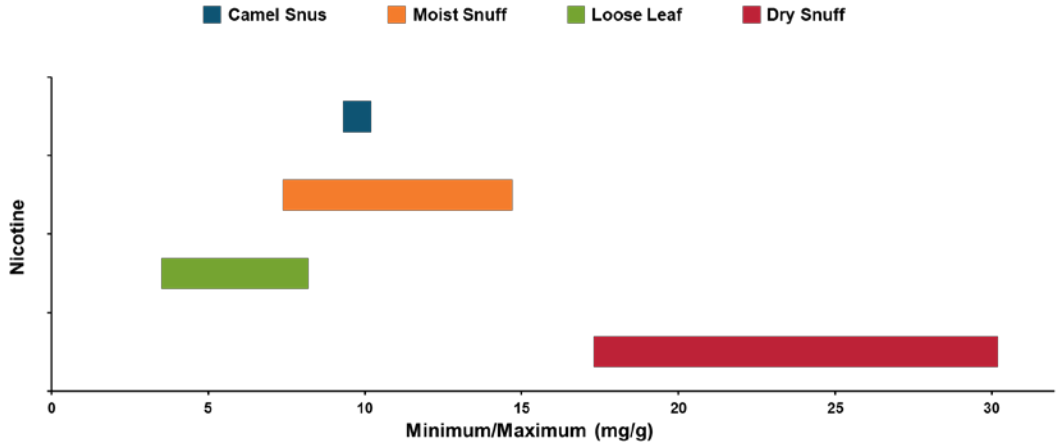
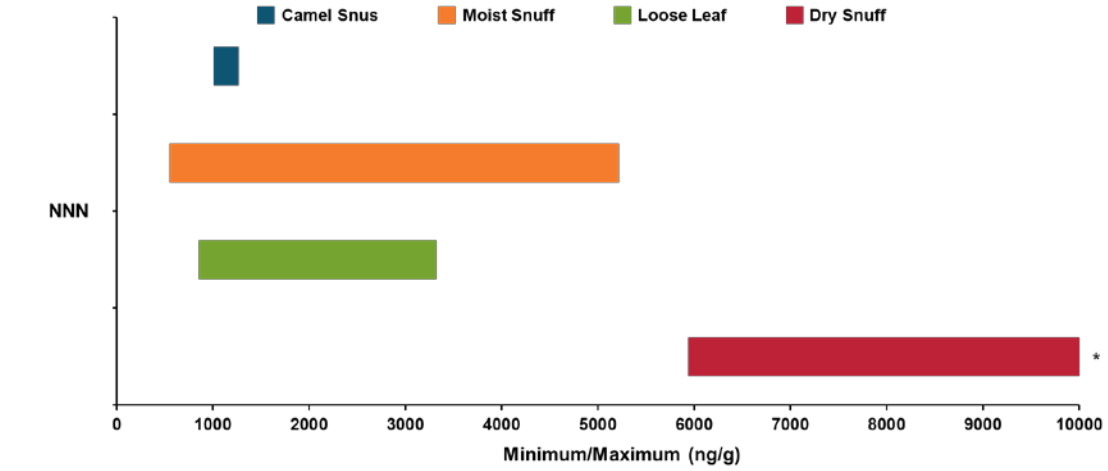
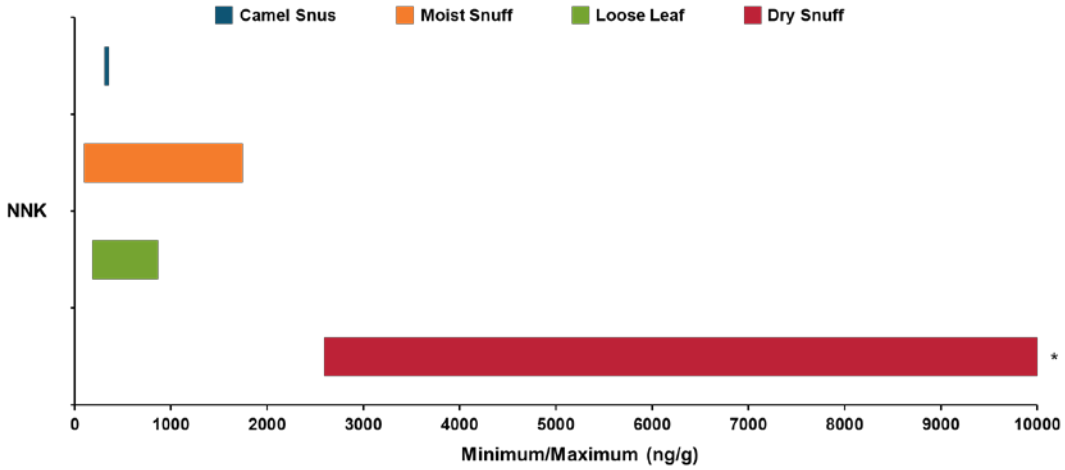


Figure 12. NNN levels in Camel Snus compared to other U.S. smokeless tobacco products



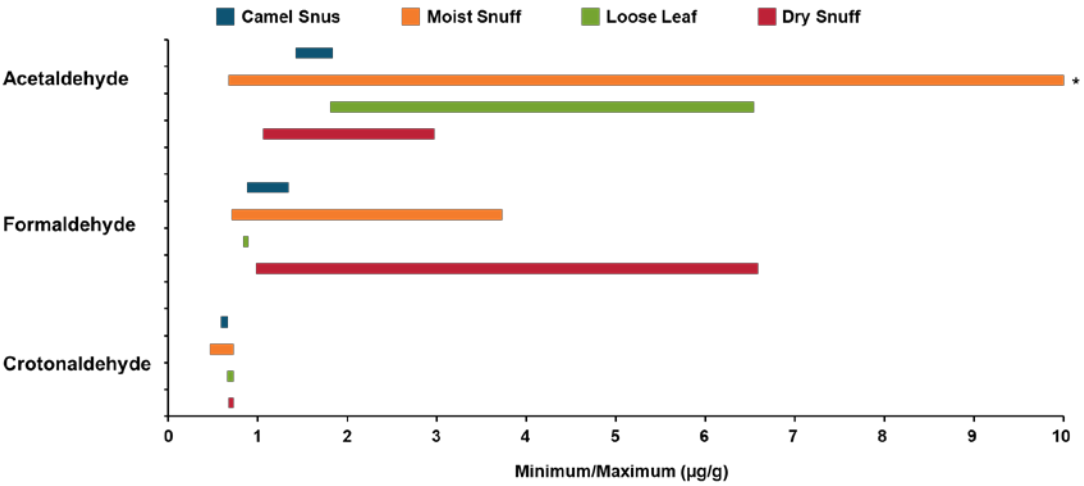
*Value >10,000 ng/g

Figure 13. NNK levels in Camel Snus compared to other U.S. smokeless tobacco products



*Value >10,000 ng/g

Figure 14. Carbonyl levels in Camel Snus compared to other U.S. smokeless tobacco products



*Value >10 µg/g

ii. Biomarkers of exposure from Camel Snus use are less than or similar to U.S. moist snuff use and less than smoking

One biomarker study, CSD0904, included groups of exclusive Camel Snus users, exclusive moist snuff users, and exclusive cigarette smokers. Biomarkers of exposure to HPHCs designated as carcinogens, respiratory toxicants, and cardiovascular toxicants were compared across groups. Figure 15 – Figure 17 show biomarkers by HPHC category from use of Camel Snus and moist snuff, side by side, in comparison to exposures from cigarette smoking, used as the baseline. Biomarker levels from smoking for each HPHC are represented by the red line as 0% difference from smoking.

Figure 15. Differences in exposure to carcinogens from smoking for Camel Snus and moist snuff

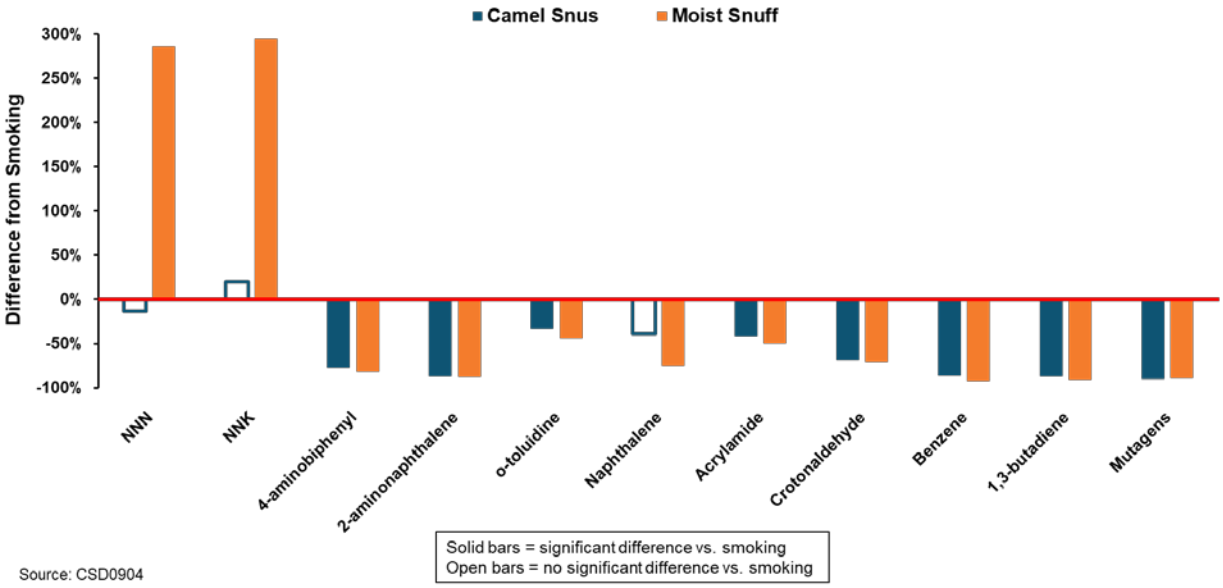


Figure 16. Differences in exposure to respiratory toxicants from smoking for Camel Snus and moist snuff

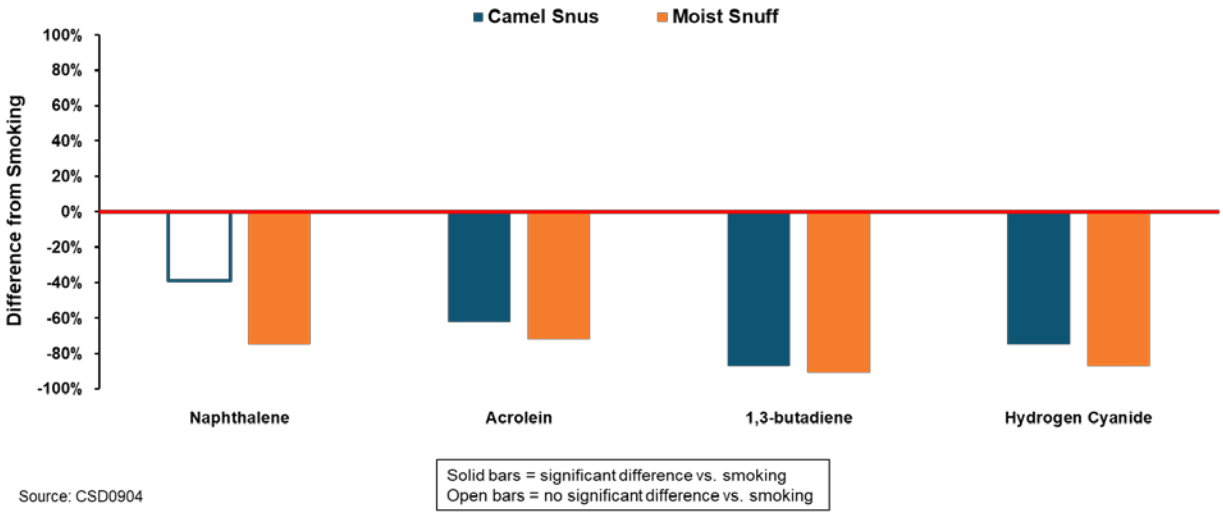
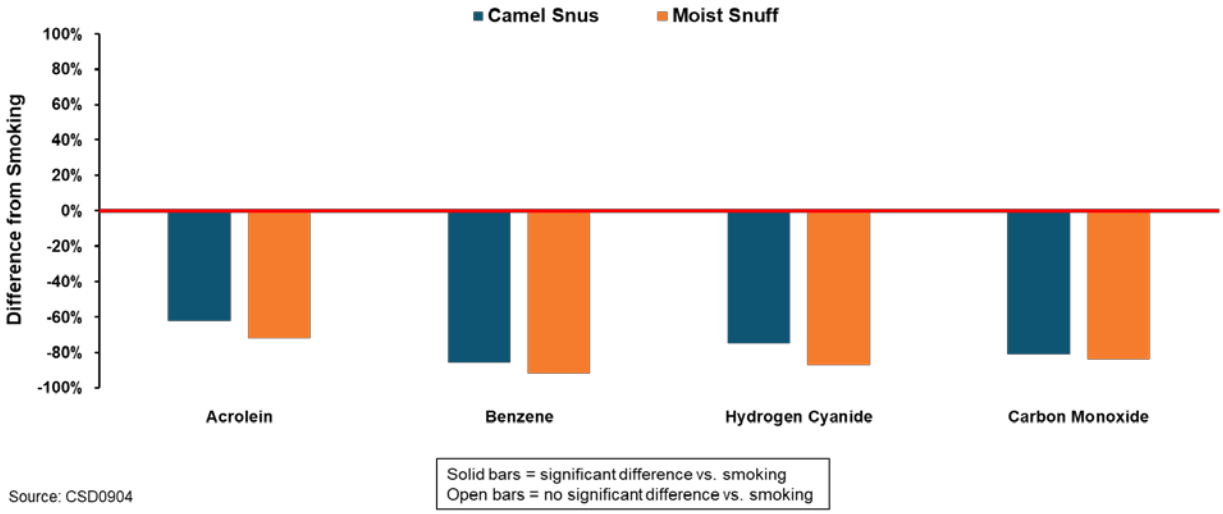
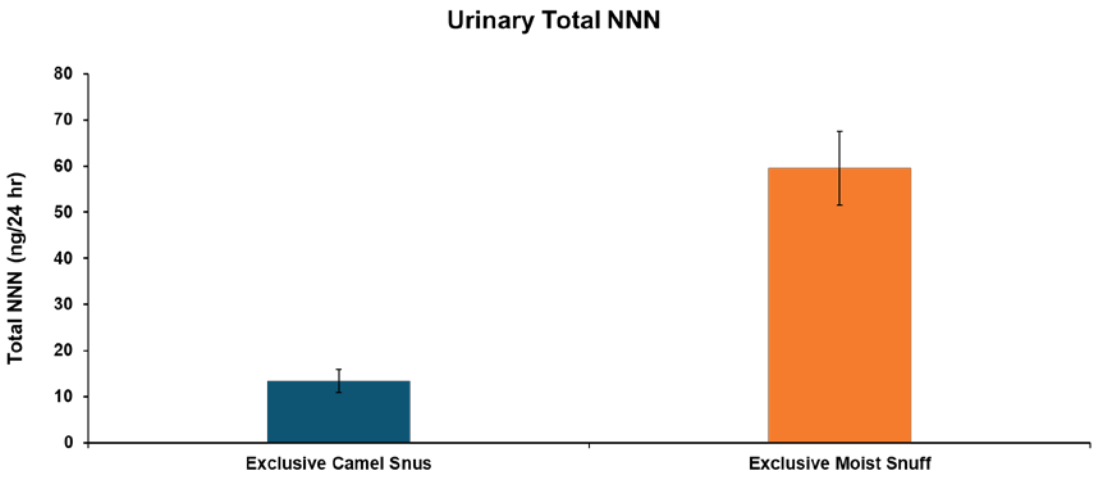


Figure 17. Differences in exposure to cardiovascular toxicants from smoking for Camel Snus and moist snuff



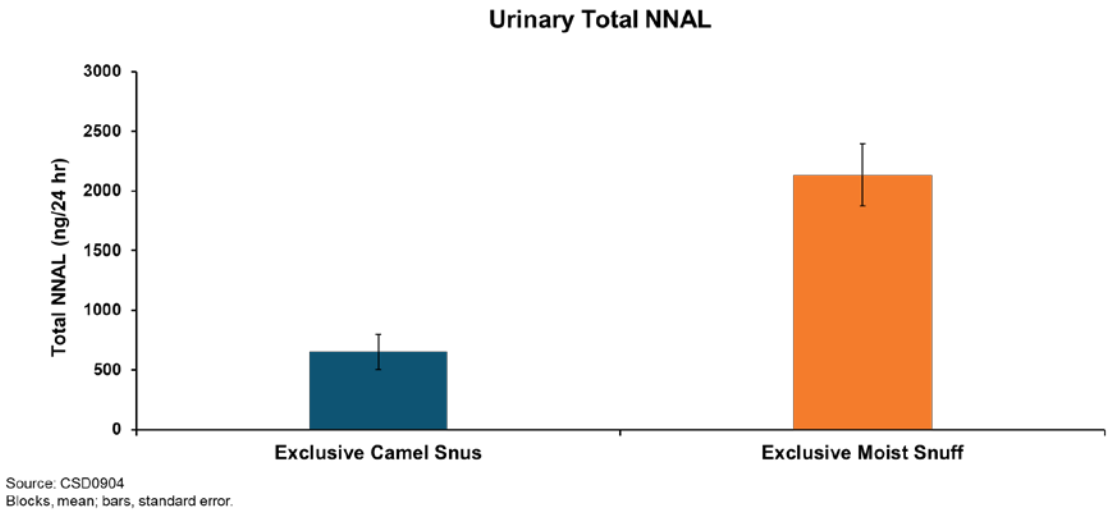
Differences in exposure to HPHCs from use of Camel Snus compared to smoking were generally the same as the differences in exposure from use of U.S. moist snuff compared to smoking, with two notable exceptions. Exposure to NNN and NNK from moist snuff use showed a nearly 300% increase compared to smoking, while exposure to NNN and NNK from Camel Snus use was not statistically significantly different than smoking (*see* RAIS RESPONSE TO DEFICIECNY 30c for further discussion regarding the results of the CSD0904 study). The mass/24 hr urine results for these biomarkers from Camel Snus use and moist snuff use are shown in Figure 18 and Figure 19 and show an approximately 600% and 400% increase in exposure to NNN and NNK, respectively, from moist snuff use compared to Camel Snus use. As discussed above, exposures to NNN and NNK are consistent among 0.6 g and 1.0 g Camel Snus products and, therefore, contrast with the increased exposure to these constituents from moist snuff use. This further strengthens the rationale for the application of biomarker endpoints from use of Camel Snus Frost and Mellow to all other styles of Camel Snus.

Figure 18. Urinary Total NNN mass/24 hours from ad libitum Camel Snus use and ad libitum moist snuff use



Source: CSD0904
Blocks, mean; bars, standard error.

Figure 19. Urinary Total NNAL mass/24 hours from ad libitum Camel Snus use and ad libitum moist snuff use



Exposure to HPHCs from use of either Camel Snus or moist snuff, with the exception of TSNAs in the case of moist snuff, were generally consistent and statistically significantly decreased as compared to exposures from smoking. Generally, cigarette smoking results in the greatest exposure to HPHCs, for products of combustion in particular. Further, the exposure to these constituents with Camel Snus use is generally similar to the exposure observed from no tobacco use (*see* Table 6.1.2-32 in Section 6 the MRTPAs/PMTAs).

The totality of these biomarker data demonstrate that as a sub-category of smokeless tobacco, use of Camel Snus results in the same or lower exposure to HPHCs designated as carcinogens, respiratory toxicants, and cardiovascular toxicants than U.S. moist snuff products. In addition, exposure to HPHCs from use of either Camel Snus or U.S. moist snuff generally results in statistically significant decreases in HPHC exposure relative to smoking, with the exception of exposure to TSNAs which is much greater from moist snuff use than from either Camel Snus use or smoking. These differences between tobacco product categories and sub-categories demonstrate that the data across Camel Snus products are consistent with each other and differ from products of other categories (i.e., cigarettes) and sub-categories (i.e., moist snuff). This provides additional rationale to justify the application of the full set of clinical study data from use of Camel Snus Frost and Mellow to the other four Camel Snus styles for which full clinical study data do not exist.

Conclusion

In summary, the bridging data provided above demonstrate that all six styles of Camel Snus share common physical and compositional characteristics, comparable levels of HPHCs on a per-gram basis, consistent low biological activity, common usage patterns, and a singular position on the tobacco and nicotine product risk continuum. The scientific rationale provided by examination of

the clinical biomarker and mouth-level exposure data by flavor and pouch size demonstrate the consistency in exposures from use of “mint” and “non-mint” products and from use of 0.6 g and 1.0 g products. Further, the examination of Camel Snus clinical data as a composite compared across other tobacco product types, demonstrate that data collected from Camel Snus use are consistent across styles and differs from other tobacco products such as cigarettes and moist snuff. Together the bridging data and the scientific rationale justify the application of the full set of clinical data from use of Camel Snus Frost and Mellow to the other four Camel Snus styles for which full sets of clinical study data do not exist.