**Docket number: FDA-2017-N-4678-0001**

# Reynolds' own data do not support their claim that because exclusive users of Camel Snus experience lower levels of exposure to some toxicants, they will reduce their risk of harm from lung cancer, oral cancer, respiratory disease, and heart disease

Gideon St. Helen, PhD, Benjamin Chaffee, DDS, PhD, Lauren Lempert JD, MPH,
Stanton Glantz, PhD
UCSF TCORS
August 23, 2018

RJ Reynolds Tobacco Company (Reynolds) seeks risk modification orders under the Family Smoking Prevention and Tobacco Control Act (TCA) Section 911(g)(1) for six Camel Snus products (Camel Snus Frost, Camel Snus Frost Large, Camel Snus Mellow, Camel Snus Mint, Camel Snus Robust, and Camel Snus Winterchill). In its modified risk tobacco product application (MRTP), Reynolds seeks to demonstrate that the results of its own studies on the six Camel Snus products, combined with the body of U.S. smokeless tobacco epidemiology studies, human clinical studies, preclinical toxicology studies, and chemistry studies, provide sufficient scientific basis to conclude that, for individuals who are current cigarette smokers, switching completely from smoking cigarettes to Camel Snus can significantly or greatly reduce those individual's risk for lung cancer, oral cancer, respiratory disease, and heart disease. Additionally, Reynolds seeks to demonstrate that an MRTP order will benefit the population as a whole, taking into account both users and current non-users of tobacco products.

At the core of Reynolds' reduced risk claim is the argument that smokers who switch completely to Camel Snus reduce their health risks for two principal reasons: (1) Camel Snus toxicant content is comparable to, or less than, the historical U.S. and Swedish smokeless tobacco products on which epidemiological studies are based, and (2) Camel Snus usage patterns suggest lower levels of toxicant exposure compared to the historical patterns reflected in U.S. and Swedish epidemiology. (Executive Summary, pp. 78-79) In other words, Reynolds appears to argue that because exclusive users of Camel Snus experience lower levels of exposure to some toxicants, these exclusive users of Camel Snus will have reduced risk of harm from lung cancer, oral cancer, respiratory disease, and heart disease. In this comment, we focus on the sufficiency of the evidence Reynolds submitted in its chemistry studies to support this claim. We show that Reynolds' own studies show that, rather than reducing levels of exposure, users of Camel Snus are in fact exposed to greater levels of some dangerous toxicants, including NNN, NNK, cadmium, and arsenic. Moreover, Reynolds' argument is based on the premise that users will "switch completely" from cigarette smoking to Camel Snus. However, studies have shown that most users of smokeless tobacco products are dual users. Therefore, most users of Camel Snus will likely also be smoking cigarettes concurrently, which would actually increase their exposure to these dangerous toxicants and would thereby increase their risk of several tobacco-related diseases.

TCA Section 911(g)(1) requires Reynolds to demonstrate that Camel Snus, "*as it is actually used by consumers"*, will (A) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and (B) benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products." (Emphasis added.) It is essential that Reynolds meet all parts of this statutory

mandate, and the studies Reynolds relies on must be based on how the product is *actually used by consumers.* Therefore, as a preliminary matter, Reynolds' scientific studies must acknowledge that most users of smokeless tobacco products (including Snus) are dual users, and FDA must address whether Reynolds has demonstrated that Camel Snus users will completely switch from smoking cigarettes to using Camel Snus. Studies conducted or financed by Reynolds and cited in its MRTP application show that dual or poly-use with cigarettes or other tobacco products is the predominant use pattern among snus users (CSD0804: 13% exclusive snus use; 87% dual or poly use; National Tobacco Behavior Monitor: 7% exclusive snus use; 93% dual or poly use; Brand Tracker Survey: 3.5% exclusive use; 96.5% dual or poly use). Published studies conducted independent of the tobacco industry also show dual and poly use to be the dominant snus use pattern.[1] If Reynolds failed to demonstrate that snus users will switch completely with sufficient scientific evidence, then Reynolds' studies must consider the increased toxicant exposure and concomitant increased health risks that would affect individuals who smoke cigarettes concurrently while using Camel Snus.

**Reynolds downplays their own findings of higher nitrosamine and heavy metal levels in Camel snus compared to tobacco smoke**

Reynolds' own data, as summarized in the Executive Summary of their MRTP application, show that Camel Snus does not meet the legal standard for making a reduced risk claim, and should not be marketed as a modified risk tobacco product. On page 187 of the Executive Summary, Reynolds makes the statement that "cigarette smoke is far more chemically complex than smokeless tobacco and contains many more FDA-designated and reportable HPHCs" (HPHCs, harmful and potentially harmful constituents). This is true, since tobacco smoke contains thousands of chemical products of pyrolysis and combustion reactions that are absent or, if present, are at lower levels in smokeless tobacco products. More important, Reynolds states on page 189 of the Executive Summary that "Camel Snus contains lower levels of some HPHCs and ***greater amounts of others*** relative to tobacco smoke." This admission by Reynolds is significant and is critical to the assessment of whether Camel Snus is a reduced harm product. As will be discussed below, tobacco-specific nitrosamine (TSNA) levels are higher in smokeless tobacco than tobacco smoke and systemic exposure to TSNAs from smokeless tobacco use can exceed that of cigarette smokers.[2] One such TSNA, NNK, a potent pulmonary carcinogen, can induce lung tumors in rodents, ***independent of route of administration***,[3] suggesting that reduced risk claims, including lung cancer, for Camel Snus are questionable and FDA should not approve these claims.

---

[1] Lee YO, Hebert CJ, Nonnemaker JM, Kim AE. Multiple tobacco product use among adults in the United States: cigarettes, cigars, electronic cigarettes, hookah, smokeless tobacco, and snus. Prev Med. 2014 May;62:14-9.
Biener L, Roman AM, Mc Inerney SA, Bolcic-Jankovic D, Hatsukami DK, Loukas A, O'Connor RJ, Romito L. Snus use and rejection in the USA. Tob Control. 2016 Jul;25(4):386-92.

[2]Benowitz NL, Renner C, Lanier A, Tyndale RF, Hatsukami DK, Lindgren BR, Stepanov I, Watson CH, Sosnoff C, Jacob P. Exposure to nicotine and carcinogens among South Western Alaskan Native cigarette smokers and smokeless tobacco user. Cancer Epidemiology and Prevention Biomarkers. 2012:cebp. 1178.2011.
IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Smokeless tobacco and some tobacco-specific N-nitrosamines. IARC Monogr Eval Carcinog Risks Hum 2007;89:1–592.

[3] Hecht, Stephen S., and Dietrich Hoffmann. "Tobacco-specific nitrosamines, an important group of carcinogens in tobacco and tobacco smoke." Carcinogenesis 9.6 (1988): 875-884.
Rivenson, Abraham, et al. "Induction of lung and exocrine pancreas tumors in F344 rats by tobacco-specific and Areca-derived N-nitrosamines." Cancer Research 48.23 (1988): 6912-6917.

The constituents that Reynolds have identified at higher levels in Camel Snus compared to tobacco smoke are tobacco-specific nitrosamines, such as NNN and NNK, the heavy metals, arsenic and cadmium, and nicotine (Table 2.9.5-3, Executive Summary p. 190). NNN and NNK are human carcinogens linked to esophageal cancer[4] and lung cancer[5], respectively. Heavy metals, such as cadmium and arsenic, contribute to cancer and cardiopulmonary disease, with greater contribution to cancer and non-cancer risk than tobacco-specific nitrosamines.[6] Higher levels of NNK, NNN, and heavy metals in Camel Snus compared to tobacco smoke contradicts the idea that Camel Snus is a reduced risk product, and may in fact present similar or higher risks for diseases related to these four constituents relative to tobacco smoke. Reynolds argues that "product chemistry data are not a measure of actual toxicant exposure when consumers use a tobacco product." (Exec. Summary p. 190) Rather, "Camel Snus users are exposed to only a fraction of the TSNAs and nicotine present in Camel Snus under actual conditions of use." (Exec. Summary p. 191) While we agree that users of tobacco products are exposed to a fraction of the constituents in that product (this is true for all products and constituents – smokers typically breath in 1 mg of nicotine from a cigarette stick containing 10-14 mg of nicotine[7]), we strongly disagree with Reynolds downplaying the importance of product chemistry to systemic exposure and health risks. Systemic exposure to tobacco toxicants is a function of the chemistry of the products, constituent delivery and bioavailability, and user characteristics (use patterns). In assessing potential health risks of tobacco products, the importance of these individual factors should not be minimized. Users of smokeless tobacco products in the U.S. have higher intake of NNK precisely because the NNK levels are typically higher in smokeless tobacco products in the U.S. than in cigarette smoke, as Reynolds' own data support. Of further concern, under "actual conditions of use," most Camel Snus users will likely continue to smoke cigarettes, rather than "switch completely" to Camel Snus.[8] Even if they reduce their cigarette consumption, they will still be exposed to substantial amounts of both smokeless tobacco toxicants and smoke toxicants.

Reynolds claims on page 191 of the Executive Summary that Camel Snus has comparable or lower levels of HPHCs relative to other smokeless tobacco products sold in the U.S. That statement is not accurate. An independent study showed that Camel Snus products had ***higher NNN and NNK*** normalized by dry weight than Marlboro Snus products.[9] The NNN in Camel Snus ranged from 0.86-1.28 ug/g compared to a range of 0.42-0.47 ug/g in Marlboro Snus. Similarly, the NNK in Camel Snus ranged from 0.40-0.61 ug/g compared to 0.13-0.16 ug/g in Marlboro Snus. Further, Camel Snus contains higher levels of tobacco-specific nitrosamines

---

[4] Yuan, Jian-Min, et al. "Urinary levels of the tobacco-specific carcinogen N′-nitrosonornicotine and its glucuronide are strongly associated with esophageal cancer risk in smokers." Carcinogenesis 32.9 (2011): 1366-1371.

[5] Hecht, Stephen S. "Tobacco smoke carcinogens and lung cancer." JNCI: Journal of the National Cancer Institute 91.14 (1999): 1194-1210.

[6] Fowles J, Dybing E. Application of toxicological risk assessment principles to the chemical constituents of cigarette smoke. Tob Control 2003;12(4):424-430.

[7] Hukkanen J, Jacob III P, Benowitz NL. Metabolism and disposition kinetics of nicotine. Pharmacological Reviews. 2005;57(1):79-115.

[8] Tomar, Scott L., Hillel R. Alpert, and Greg N. Connolly. "Patterns of dual use of cigarettes and smokeless tobacco among US males: findings from national surveys." Tobacco Control (2009): tc-2009.
Rath, Jessica M., et al. "Patterns of tobacco use and dual use in US young adults: the missing link between youth prevention and adult cessation." Journal of environmental and public health 2012 (2012).

[9] Stepanov, Irina, et al. "Monitoring tobacco-specific N-nitrosamines and nicotine in novel Marlboro and Camel smokeless tobacco products: findings from Round 1 of the New Product Watch." Nicotine & Tobacco Research 14.3 (2011): 274-281.

compared to Swedish Snus.[10] Also, an internal 2007 document from Reynolds reported higher cadmium and chromium in Camel Snus compared to Swedish Snus.[11]

***In summary, Reynolds' own data show that Camel Snus has higher levels of nitrosamines and heavy metals compared to tobacco smoke and FDA should not overlook these results. Further, contrary to Reynolds' statement, Camel Snus has considerably higher levels of NNN and NNK compared to at least one other major US brand of Snus as well as Swedish Snus.***

Reynolds conducted human studies of exclusive Camel Snus use, dual use, and switching to examine systemic exposure to various HPHCs using biomarkers. Reynolds reported that Camel Snus results in "lower exposure to combustion-related compounds in exclusive users." Biomarkers of polycyclic aromatic hydrocarbons (PAHs), phenanthrene and fluorene, were lower following exclusive Camel Snus use compared to smoking while biomarkers of other PAHs, pyrene and naphthalene, were comparable to smoking. To explain the comparable levels of pyrene and naphthalene between Camel Snus and tobacco smoking, Reynolds argues that these two PAHs are not specific to tobacco and can be affected by environmental exposures and genetics. Reynolds used one of our studies to support this explanation,[12] but our findings do not support this conclusion. While in general, PAHs are not specific to tobacco, we found that metabolites of fluorene and naphthalene (lighter molecular weight PAHs) are more specific to tobacco smoke and pyrene and phenanthrene are less specific. Our study suggested that while naphthalene can be produced from other sources, biomarkers of naphthalene were highly selective of tobacco smoke. Biomarkers of naphthalene measured after smoking likely originate from smoking. For this reason, the comparable levels of biomarkers of naphthalene during Camel Snus use and smoking that Reynolds reported indicate that Camel Snus may be a source of naphthalene. While we agree that there are other contributing sources of PAHs, ***it is likely that PAHs are present in Camel Snus as contaminants,[13] derived during the flue curing of tobacco. This is particularly relevant to heavier, less volatile PAHs, which are likely to be more carcinogenic.***

Regarding tobacco-specific nitrosamines (TSNA), Reynolds states that "Camel Snus use results in either similar or reduced exposure to toxicants present in tobacco when compared to exclusive cigarette smoking" (Executive Summary, p 138). Importantly, Reynolds states that their own sponsored study found "urinary levels of NNN, NAT, NAB and NNAL to be similar between exclusive Camel Snus users and cigarette smokers." To explain why Camel Snus use resulted in comparable PAH and TSNA biomarker levels to smoking, Reynolds argued that smoking decreased during confinement while Camel Snus use was consistent. "Opportunities to smoke while in-clinic were limited by study procedures and requirements to smoke inside a designated area. As such, these levels reflect less exposure from cigarettes than would be expected when smoking ad libitum outside the clinic…. Camel Snus users used consistent

[10] Stepanov, Irina, et al. "Tobacco-specific nitrosamines in new tobacco products." Nicotine & Tobacco Research 8.2 (2006): 309-313.

[11] https://www.industrydocumentslibrary.ucsf.edu/tobacco/docs/#id=zpcn0191

[12] St.Helen G, Goniewicz ML, Dempsey D, et al. Exposure and kinetics of polycyclic aromatic hydrocarbons (PAHs) in cigarette smokers. Chem Res Toxicol 2012;25(4):952-964

[13] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Smokeless tobacco and some tobacco-specific N-nitrosamines. IARC Monogr Eval Carcinog Risks Hum 2007;89:1–592.

amounts of product both before and during clinical confinement. Therefore, these results likely under-represent differences in exposure between the two groups." (Executive Summary, p 138)

This argument by Reynolds should not be allowed to stand. Reynolds' own data show that levels of TSNAs in Camel Snus were higher than in cigarette smoke (Table 2.9.5-3, Executive Summary p. 190). Therefore, human studies showing similar TSNA biomarker levels from use of Camel Snus compared to smoking are not surprising and are consistent with independent studies showing similar levels of NNK biomarkers in smokers and smokeless tobacco users.[14] Further, cigarette smokers are known to titrate their desired nicotine dose by changing their smoking behavior and maintain a constant daily nicotine intake.[15] If participants reduced their cigarette consumption during the study, it is unlikely that biomarker levels would decrease significantly unless the reduction in consumption was dramatic. Reynolds gave no evidence of a dramatic decrease in number of cigarettes smoked by participants in the study.

On page 138 of the Executive Summary, Reynolds claims that the "TSNA biomarker results … demonstrate that exclusive Camel Snus users exhibit reduced or similar levels of these compounds when compared with cigarette smokers." It must be emphasized that similar levels of TSNAs from smokeless tobacco use compared to cigarette smoke in no way indicates that Camel Snus is a reduced risk product. Moreover, in addition to demonstrating that Camel Snus products will benefit the health of the population as a whole, TCA section 911(g)(1) requires Reynolds to demonstrate that the product, as it is actually used by consumers, will "***significantly reduce harm*** and the risk of tobacco-related disease to individual tobacco users." FDA's 2012 Guidance for Industry on Modified Risk Tobacco Product Applications (pp. 17-18) says, "An MRTPA must provide scientific evidence regarding the effect of the product on the health of individuals so that FDA can determine whether the MRTP does, in fact, modify risk as claimed by the applicant… In the case of an application for a risk modification order, the MRTPA must provide scientific evidence to demonstrate that the product significantly reduces harm and the risk of tobacco-related disease to individual users." Even if Reynolds showed that Camel Snus users are exposed to lower levels of some toxicants found in cigarette smoke, which is turn resulted in a *somewhat lower* overall risk compared with cigarettes, FDA must not issue a MRTP order unless Reynolds demonstrated that, as actually used by consumers, Camel Snus will result in a *significant reduction* in harm and the risk of tobacco-related disease.

On page 158 of the Executive Summary, Reynolds states, "Because Camel Snus is consumed orally, exclusive use of Camel Snus eliminates the direct exposure of lung tissues to toxicants, thereby mitigating some of the potentially harmful effects of those compounds experienced by cigarette smokers." This statement is troubling. As said before, NNK, the lung carcinogen, can induce lung tumors in rodents ***independent of route of administration***.[16] It is also notable that one of Reynolds' three advertising executions claims that Camel Snus reduces

---

[14] Hecht, Stephen S., et al. "Similar exposure to a tobacco-specific carcinogen in smokeless tobacco users and cigarette smokers." Cancer Epidemiology and Prevention Biomarkers 16.8 (2007): 1567-1572.

[15] Ashton, Heather, R. Stepney, and J. W. Thompson. "Self-titration by cigarette smokers." Br Med J 2.6186 (1979): 357-360.

Herning, Ronald I., et al. "How a cigarette is smoked determines blood nicotine levels." Clinical Pharmacology & Therapeutics 33.1 (1983): 84-90.

[16] Hecht, Stephen S., and Dietrich Hoffmann. "Tobacco-specific nitrosamines, an important group of carcinogens in tobacco and tobacco smoke." Carcinogenesis 9.6 (1988): 875-884.

Rivenson, Abraham, et al. "Induction of lung and exocrine pancreas tumors in F344 rats by tobacco-specific and Areca-derived N-nitrosamines." Cancer Research 48.23 (1988): 6912-6917.

the risk of lung cancer and respiratory disease, but not the risk of oral cancer or heart disease. This suggests that Reynolds is aware that it did not present sufficient scientific evidence to support its claim that Camel Snus reduces the risk of oral cancer or heart disease. In the event that FDA issues a MRTP order based on any of the three advertising executions, FDA should consider requiring additional disclosures on Camel Snus labels pursuant to TCA section 911(h)(3)(A) and in their marketing claims that use of Camel Snus can increase the risk of certain tobacco-related diseases, including pancreatic cancer, X, Y, and Z. Additionally, pursuant to TCA section 911(h)(3)(B), FDA should consider requiring Reynolds to disclose on Camel Snus labels that any reduced risk is conditioned on using Camel Snus exclusively and not at the same time as other tobacco products.

***In summary, based on findings of comparable levels of biomarkers of some PAHs and TSNAs from Camel Snus use relative to smoking, Reynolds' own data do not support their claim that because exclusive users of Camel Snus experience lower levels of exposure to some toxicants, these exclusive users of Camel Snus will reduce their risk of harm from lung cancer, oral cancer, respiratory disease, and heart disease. Additionally, Reynolds' cited studies fail to recognize that smokeless tobacco products like Camel Snus are rarely used exclusively; rather, smokeless tobacco products are typically used concurrently with cigarettes and/or other tobacco products.***