



Chemical Composition of Spitless Tobacco and Nicotine Pouch Products Commercially Available in Northern European and North American Markets: A Targeted Review of Manufacturing Processes and Harmonized Secondary Analysis Evaluating Impact on Dental Health

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Chemical Composition of Spitless Tobacco and Nicotine Pouch Products Commercially Available
in Northern European and North American Markets: A Targeted Review of Manufacturing
Processes and Harmonized Secondary Analysis Evaluating Impact on Dental Health

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Abstract

Sales of moist snuff, snus, and nicotine pouch products (NPPs) have grown despite declining use of traditional tobacco products. We compare the differences in manufacturing processes and chemical composition of these products across North America and Northern Europe by performing a targeted review and harmonized secondary analysis of published datasets (2008–2025), evaluating implications for dental health. Reported values were unit-standardized; tobacco-leaf products were converted to dry-weight basis (DWB) where possible. Free nicotine (%) came from source data or was derived via the Henderson-Hasselbalch approximation (pK_a 8.02). Conventional moist snuff exhibited the highest and most variable TSNAs, while snus generally showed lower TSNAs but substantial free-nicotine fractions at higher pH. NPPs were heterogeneous: most datasets reported basic pH and high free-nicotine percentages, and although TSNAs were frequently below detection limits, several products exceeded detection limits. Even where TSNAs and HPHCs are reduced (snus, NPPs), detectable toxicants remain. Prolonged use is linked to localized oral injury and periodontal risk; evidence for long-term outcomes is limited for NPPs. These findings underscore the need for greater regulation and education around the potential harms of all smokeless tobacco and nicotine products, including those positioned as harm-reduction alternatives. For dental practice, these findings support routine screening for mucosal changes and periodontal risk in users of moist snuff, snus, and nicotine pouches, with counseling on pH-driven free-nicotine exposure.

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Chapter I.

Introduction

Worldwide, the use of tobacco products has been slowly declining over the past decade; the World Health Organization (WHO) estimates that there will be 1.27 billion global users of tobacco in 2025, down from the last reported statistic of 1.30 billion global users in 2015 (World Health Organization, 2021). As traditional tobacco use continues to decline, alternative tobacco and nicotine products have grown in popularity, particularly in underage and youth populations (Owusu *et al.*, 2019). This trend has been concerning to public health officials and healthcare practitioners alike.

Of the many classes of alternative tobacco products available to the public, much research has been done documenting the prevalence of vaping among youth populations as well as characterizing the detrimental effects to health with prolonged use, yet there has not been as much activity examining the prolonged habitual use of pre-portioned orally administered smokeless spitless tobacco and nicotine products, including traditional moist snuff tobacco, snus and novel nicotine pouch products only recently introduced to the market. Snus is an oral smokeless tobacco product consisting of finely ground moist tobacco that is typically packaged in ready-to-use pouches resembling small tea bags which are placed in the gingival fold behind the upper lip without chewing (Foulds *et al.*, 2003; Lawler *et al.*, 2020). Unlike traditional chewing tobacco, snus does not require frequent spitting; as a result, snus is often marketed as a discreet smokeless tobacco product (Delnevo *et al.*, 2014). Recently, a new product category has emerged to compete with pre-portioned snus pouches which has quickly surged in popularity among

American adolescents and young adults (Liu & Halpern-Felsher, 2024); large tobacco companies have started producing flavored nicotine pouches, similar in form factor to pre-portioned pouches of snus but marketed to consumers as a tobacco-free alternative to snus and other commonly consumed tobacco products (Robichaud *et al.*, 2020).

Within the academic community, there has been some debate on the efficacy of Swedish snus as a harm-reduction measure, with multiple reports claiming the long-term use of snus is not a significant risk factor for developing oral cancers, but these studies have primarily focused on Swedish populations (Araghi *et al.*, 2021; Luo *et al.*, 2007; Roosaar *et al.*, 2006; Zatterstrom *et al.*, 2004). One of the major problems with these studies is the inherent bias towards Swedish and European populations, and as such evidence is limited for North American populations and published data are sparse for novel tobacco-derived nicotine (TDN) and synthetic nicotine (SyN) products. Due to this, it is still unclear whether long-term use of pre-portioned snus and similar nicotine pouch products commonly found in the United States will contribute to an increased risk of oropharyngeal disease and other tobacco-related comorbidities.

The aim of this study is to investigate the differences in manufacturing of moist snuff, snus, as well as novel TDN and SyN pouch products popularly consumed in North America and Northern Europe by performing a harmonized secondary analysis of published chemical composition datasets, critically review a selection of published case studies, meta-analyses and epidemiological studies examining the effects of prolonged habitual use of these tobacco/nicotine pouch products on the oral cavity and pharynx, and ultimately evaluate the potential for these products to be used as a harm-reduction measure in the fight against tobacco-related comorbidities.

Finally, this research is important because it will help better characterize the differences between pre-portioned snus, TDN and SyN pouch products sold across North American and Northern European geographies, as well as how these chemical differences could contribute to the risk of developing diseases of the oral cavity and other related tobacco-related comorbidities in North American and European consumers. This is especially important considering that use of pre-portioned snus and novel nicotine pouch products has been growing in popularity, possibly due to perceptions of reduced harm, particularly in underage and youth populations across America (Liu & Halpern-Felsher, 2024; Lund & Scheffels, 2014; Owusu *et al.*, 2019). This research clarifies the differences between these product categories and could help better educate and further reduce harm to youth and adults around the world.

Definition of Terms

“B[a]P”: Benzo[a]pyrene, a member of the polycyclic aromatic hydrocarbon (PAH) group of compounds

“Chewing Tobacco”: Traditional chewing tobacco, also known as “dip tobacco”; this smokeless tobacco product is chewed to extract the juices which build up and cause frequent spitting

“Dry Snuff”: Smokeless tobacco product consisting of finely powdered tobacco that may also include aromatic adulterants; typically refers to a class of smokeless tobacco products intended for nasal inhalation

“Free Nicotine”: Unprotonated/unionized nicotine, the form of nicotine that is bioavailable

“HPHCs”: Constituents the U.S. FDA Center for Tobacco Products designates as Harmful and Potentially Harmful Constituents in tobacco products and tobacco smoke

“IARC Group 1 Carcinogen”: Agents classified by the World Health Organization’s International Agency for Research on Cancer as carcinogenic to humans; there are 133 agents classified as IARC Group 1 Carcinogens as of March 2025

“Lotus Project”: A strategic plan to develop a low-nicotine starter smokeless tobacco product in a teabag-like pouch to target new users with the explicit intention of having them eventually graduate to stronger traditional moist snuff products with higher doses of nicotine

“Moist Snuff”: Smokeless tobacco product consisting of finely ground or shredded tobacco; typically refers to a class of smokeless tobacco products intended for oral use

“NAA”: N’-nitrosamino acids, part of a class of compounds called N’-nitrosamines that are considered potentially cancer causing chemicals by the FDA

“NAB”: N’-nitrosoanabasine, a known carcinogenic TSNA

“NAT”: N’-nitrosoanatabine, a known carcinogenic TSNA

“NDELA”: N’-nitrosodiethanolamine, a known TSNA

“NDMA”: N’-nitrosodimethylamine, a known TSNA

“Nicotine Degradants”: A variety of compounds produced by the oxidation and/or photolysis of nicotine when exposed to light or air

“Nicotine Pouch”: Tobacco-free orally administered nicotine products sold as pre-portioned pouches; can be produced from tobacco-derived nicotine or chemically synthesized nicotine

“NMOR”: N’-nitrosomorpholine, a known TSNA

“NNK”: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, a commonly studied TSNA that has been classified as an IARC Group 1 carcinogen by the WHO and is designated a Harmful or Potentially Harmful Constituent (HPHC) of smokeless tobacco products by the U.S. FDA Center for Tobacco Products

“NNN”: N’-nitrosornicotine, a commonly studied TSNA that has been classified as an IARC Group 1 carcinogen by the WHO and is designated a Harmful or Potentially Harmful Constituent (HPHC) of smokeless tobacco products by the U.S. FDA Center for Tobacco Products

“NPIP”: N’-nitrosopiperidine, a known TSNA

“NPP”: Nicotine Pouch Products

“NPYR”: N’-nitrosopyrrolidine, a known TSNA

“NSAR”: N’-nitrososarcosine, a known TSNA

“MNBA”: 4-(methylnitrosamino)butyric acid, a commonly studied N-nitrosamino acid

“MNPA”: 3-(methylnitrosamino)propionic acid, a commonly studied N-nitrosamino acid

“PAH”: Polycyclic aromatic hydrocarbons

“Snuff”: General term for classes of smokeless tobacco consisting of finely ground or shredded tobacco with varying moisture content; can refer to nasal powdered tobacco with aromatic additives, as well as orally administered smokeless products

“Snuff dipping”: Placement of moist snuff between the cheek and gum (often behind the upper lip)

“Snus”: A traditionally Swedish heat-treated moist snuff tobacco product intended for oral use

“Snus-induced lesions (SIL)”: Characteristic mucosal lesions at the application site in habitual snus users

“Smokeless tobacco”: A class of tobacco products consumed without requiring the combustion of plant material; typically refers to chewing tobaccos, dry and moist snuff/snus, as well as other regional and ethnic variants of orally or nasally administered tobacco products

“SyN”: Synthetic nicotine

“TDN”: Tobacco-derived nicotine

“Tobacco Minor Alkaloids”: A variety of compounds formed endogenously within tobacco that may also contribute to addiction by mimicking or enhancing the effects of nicotine (ex. myosmine, nornicotine)

“TSNA”: Tobacco-specific N-nitrosamines

History of Smokeless Tobacco Products

Tobacco is thought to have been cultivated and consumed by humans for the past 5,000 years on the North and South American continents; the discovery of tobacco seeds at archaeological excavations in Mexico and Peru serves as evidence of human tobacco consumption as early as 3500 BCE (Voges, 1984). Tobacco was then rediscovered by European explorers in 1492 that observed Native Americans using it for medicinal purposes, and by the late 16th century had been adopted by European physicians claiming it as a miracle plant and panacea for a wide variety of ailments (Stewart, 1967). Around the 17th century, controversy arose over tobacco’s use as medicine with some physicians

warning of its harmful and addictive effects but tobacco continued to be used widely medicinally throughout the American colonies and early United States up until the 19th century when the active chemical nicotine had been isolated; by the mid-19th century, tobacco had largely fallen out of favor as a medicine, but widespread recreational consumption continued nonetheless (Stewart, 1967).

As the tobacco trade exploded globally in the 16th century, the Dutch started promoting the use of powdered tobacco which they called “snuff”, and by the 17th century, snuff had become an expensive commodity; the habit of taking snuff had become a fashionable status symbol among the wealthy, and ornate, intricately designed snuffboxes made of gold and silver became status symbols among the elite, often even being presented as gifts to diplomatic officials to maintain good relations (Christen *et al.*, 1982; Thompson, 1870). It was around this time that snuff was introduced to Sweden, where its popularity continued to rise among aristocrats until the 18th century when the practice spread to the general Swedish population as well (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2007). Snuff continued to soar in popularity around the world and remained the predominant form of tobacco use until the 19th century, far exceeding the amount used for smoking or chewing (Sapundzhiev & Werner, 2003). By the 1800s in Europe, there were three main types of snuff – Scotch snuff, which was dry, strong, unflavored and finely ground, Maccaboy snuff, which was heavily scented, and Rapee snuff, also known as Swedish snuff, which was grated more coarsely (Heimann, 1960).

Around the same time, as a newly independent nation, Americans started forging a distinct cultural identity by rejecting European cultural practices en masse, and as a

result, the perceived formality around snuff boxes and association of nasal snuff usage with British colonial tyranny greatly impeded any significant growth in popularity (Christen & Glover, 1987; Heimann, 1960; Thompson, 1870). By the 1870s, whatever popularity nasal snuff retained had largely faded; according to Thompson (1870), “[nasal snuff] has had its ‘high day,’ and is now practised [sic] only by a few commercial travellers [sic], bank managers, foremen at public works, and old women. There may be exceptions, but the habit is not a fashionable one” (p. 40). Though nasal snuff use all but died out in America, oral snuff use quickly rose in popularity to take its place; by the late 1800s, snuff dipping was so common that as many as 95% of Southern, poor, white women regularly used some form of moist snuff orally (Christen & Glover, 1987).

By the late 19th century, tobacco consumption was widespread across Europe and the Americas, and chewing tobacco quickly became popular with farmers, miners and sailors who could not smoke due to the significant risk of fire associated with their profession (Thompson, 1870). Interestingly, chewing tobacco was the only uniquely American tobacco custom that was not an imitation of another popular European route of administration; it would seem that for the American explorers pushing on westward across vast, windy plains in the spirit of manifest destiny, chewing tobacco was simply more convenient than smoking (Christen & Glover, 1987; Heimann, 1960). Chewing tobacco continued to grow in popularity, reaching a peak in 1890 with nearly three pounds chewed that year for every man, woman and child in America (Heimann, 1960). As chewing tobacco grew in popularity, public outcry against the unsanitary spitting practices associated with the habit grew as well, eventually culminating in the enactment

of anti-spitting laws which ultimately resulted in a rapid decline in the popularity of the practice (Christen & Glover, 1987).

By the beginning of the 20th century, snuff was predominantly used orally in Sweden and was dominating total tobacco sales by the late 1920s, where Swedish men consumed about 7,000 tons of moist snuff (Nordgren & Ramström, 1990). Originally invented in the early 1800s, Swedish snus is differentiated from other orally administered moist snuff tobacco products due to a specific heat treatment process during manufacturing (Rutqvist *et al.*, 2011). Snus is traditionally consumed by forming a portion into a ‘pinch’ and placing it between the anterior part of the upper lip and the gum; this is far from the salivary glands, which prevents the excessive formation of saliva and as a result, prevents the need for frequent spitting as seen with similar smokeless tobacco products which had frustrated the American public shortly prior (Christen & Glover, 1987; Nordgren & Ramström, 1990; Rutqvist *et al.*, 2011).

Rising Popularity of Snus and Moist Snuff

Over the following few decades, snus use steadily decreased and by the early 1960s, it seemed that snus use would fade from popularity the way nasal snuff had almost a century before. According to Nordgren & Ramström (1990), “the typical [snus] dipper was an old, poorly educated, not very sophisticated man from a rural area” while “less than 10% of boys and young men used [snus]”. At the time, the Swedish Tobacco Company (now Swedish Match AB) enjoyed almost complete dominance over the Swedish snus market, and even in the late 1960s, snus was still only produced in a single factory using similar recipes and production techniques as the 1800s (Nordgren & Ramström, 1990; Rutqvist *et al.*, 2011). Faced with decreasing sales, the Swedish

Tobacco Company embarked on a large-scale billboard advertising campaign for the first time in its history to make snus more popular in wider consumer groups and increase total sales (Nordgren & Ramström, 1990). This proved to be highly successful, with snus sales dramatically changing course – consumption had doubled from 1968 to 1969 – and by 1973, the first portion-packed snus was introduced in Sweden (Nordgren & Ramström, 1990; Swedish Match AB, 2013). Snus sales continued to steadily increase in Sweden until peaking around the mid-2000s (Rutqvist *et al.*, 2011).

Meanwhile, in the United States, despite public outcry and subsequent legal measures to discourage spitting in public, chewing tobacco remained the most popular form of tobacco product used at the start of the 20th century, but by the early 1960s, consumption had shrunk to almost a quarter of that seen at the turn of the century (Connolly *et al.*, 1986). Just as it seemed that cigarettes had all but killed the demand for smokeless tobacco products, a great resurgence was observed in the early 1970s, with a particularly significant upswing in the use of moist snuff resulting in a staggering 55% increase in sales from 1978 to 1984 (Christen *et al.*, 1982; Connolly *et al.*, 1986). Coincidentally, a joint venture between U.S. Tobacco Company (now U.S. Smokeless Tobacco Company) and Swedish Tobacco Company had formed in 1972; this joint venture, called United Scandia International, was responsible for the Lotus Project, a strategic plan to develop a low-nicotine starter smokeless tobacco product in a teabag-like pouch and target “new users, mainly cigarette smokers, age group 15-35”, with the explicit goal of graduating new users to stronger products with higher doses of nicotine (Connecticut’s Official State Website, n.d.; Connolly, 1995; New Jersey Department of the Treasury Division of Revenue & Enterprise Services, n.d.). The next year in 1973, the

U.S. Tobacco Company tested the market with a pouched product called the “Good Luck Sak-Pak” and quickly realized the novel product category’s potential to expand the smokeless tobacco market due to the unexpectedly high recruitment rate for never-smokers when compared to loose snuff (Hendlin *et al.*, 2017). By 1983, the pre-portioned pouch had become so successful as a product category that the U.S. Tobacco Company reintroduced the pre-portioned pouch product concept with Skoal Bandits, finally manifesting the vision of the Lotus Project originally developed by United Scandia International a decade prior (Connolly, 1995). Ultimately, the project can be considered a success; at the time, Skoal was already the second most recognizable American tobacco brand, and by launching a new nationwide marketing campaign that included advertisements and free samples, the rate of smokeless tobacco use among young adult males nearly quadrupled – from 2.2% to 8.4% – between 1970 and 1991 (Hendlin *et al.*, 2017).

Since the mid-1980s, the popularity of loose-leaf and plug/twist chewing tobaccos have steadily continued to fall in the United States, with a staggering 82% drop in total pounds of loose-leaf chewing tobacco sold in 2002 compared to 1986, and an even more massive 97% drop was observed in the total pounds of plug/twist chewing tobacco sold during the same period (Federal Trade Commission, 2023). Sales of dry snuff followed a similar trend with total pounds sold dropping by 94% from 1986 to 2022 (Federal Trade Commission, 2023). In contrast, during the same period, sales of moist snuff tripled from ~36 million pounds sold in 1986 to a peak of ~109 million pounds sold in 2020, while sales of snus showed nearly exponential 10X growth from ~170,000 pounds sold in 2008 to ~1.6 million pounds in 2022 (Federal Trade Commission, 2023).

Background of the Problem

Today, despite smokeless tobacco products themselves being classified as Group 1 carcinogens by the WHO's International Agency for Research on Cancer (IARC), smokeless tobacco products are still used worldwide; the global market size was valued at \$21.4 billion in 2024 and is projected to reach \$30.5 billion in 2033 (Research and Markets, 2025). During the period between 2012–2015, total healthcare expenditure due to smokeless tobacco use among U.S. adults was estimated to cost \$3.4 billion (in 2014 dollars), and with demand and usage of smokeless tobacco forecasted to continue growth worldwide, the ballooning costs to support public health will only continue to increase (Wang *et al.*, 2018). With multiple categories of products including loose-leaf chewing tobacco, plug/twist chewing tobacco, dry snuff, moist snuff and snus, the manufacturing processes, composition, and popularity of these products varies significantly across geographies. Though the use of traditional chewing tobaccos have been steadily declining over the past four decades, the relatively newer product categories of moist snuff and snus have continued to soar in popularity. In addition, large tobacco companies have recently introduced the novel product categories of “tobacco-free” orally administered pre-portioned spitless TDN and SyN pouch products, which have since surged in popularity among American adolescents and young adults (Liu & Halpern-Felsher, 2024; Robichaud *et al.*, 2020); these flavored nicotine pouch products are similar in form factor to pre-portioned snus and are increasingly being marketed to consumers as a tobacco-free alternative to snus and other commonly consumed tobacco products (Liu & Halpern-Felsher, 2024; Robichaud *et al.*, 2020).

A number of toxicants and carcinogens are present in smokeless tobacco products, but tobacco-specific N-nitrosamines (TSNAs) are of particular concern because these compounds are among the most abundant and potent carcinogens found in tobacco products (Stepanov *et al.*, 2012; Lawler *et al.*, 2020). Though N'-nitrosonornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), N'-nitrosoanatabine (NAT), and N'-nitrosoanabasine (NAB) are all commonly studied TSNAs, only NNN and NNK have been classified as IARC Group 1 carcinogens to humans by the WHO (Edwards *et al.*, 2017; Stepanov *et al.*, 2012). In 2012, the U.S. Food & Drug Administration (FDA) mandated the reporting of levels of nine Harmful and Potentially Harmful Constituents (HPHCs) for smokeless tobacco products: acetaldehyde, arsenic, benzo[*a*]pyrene, cadmium, crotonaldehyde, formaldehyde, nicotine (total and free), NNK and NNN (FDA Center for Tobacco Products, 2020).

Furthermore, compounds commonly referred to as nicotine degradants such as anabasine, anatabine, cotinine, nicotine-N-oxide, β -nicotyrine, nornicotine and myosmine are required to be monitored by the U.S. Pharmacopeia monograph for TDN and synthetically produced nicotine; of these, the tobacco minor alkaloids myosmine and nornicotine are both known to be common intermediates in the chemical synthesis of nicotine and therefore are likely to be present in SyN as impurities (Alalwan *et al.*, 2024; Cheetham *et al.*, 2022). Nornicotine should be considered a carcinogen precursor as nitrosation of nornicotine results in the production NNN, and this reaction has been shown to occur endogenously in human saliva without the deliberate addition of any other substance (Knezevich *et al.*, 2013).

Microbial presence is also thought to be able to contribute to TSNA formation through the production of nitrite which is required for the nitrosation reaction of endogenous pyridine alkaloids like nicotine and nornicotine to produce TSNA (Edwards *et al.*, 2017; Foulds *et al.*, 2003; Lawler *et al.*, 2020). Prior studies have suggested that the differences in manufacturing processes, storage and distribution of these spitless tobacco products across the North American and Northern European geographies affect the product's final chemical composition, with a notable increase in the concentrations of TSNA and other known and suspected carcinogens and irritants within pre-portioned snus products labeled for sale in the United States when compared to Northern Europe (Djordjevic *et al.*, 1993; Foulds *et al.*, 2003; Lawler *et al.*, 2020; Stepanov *et al.*, 2012). In addition, detectable levels of TSNA have been found in many of the recently introduced TDN and SyN pouch products, casting doubt on the idea that SyN pouch products are a safer alternative to snus and TDN pouch products, a claim commonly made by tobacco companies (Alalwan *et al.*, 2024; Mallock *et al.*, 2024).

There have been multiple pooled cohort studies from Swedish populations claiming that the long-term use of snus is not a significant risk factor for developing oral cancers (Araghi *et al.*, 2021; Luo *et al.*, 2007; Roosaar *et al.*, 2006). Additional studies on European demographics have suggested that there are no clear associations between snus usage and other tobacco-related comorbidities for never-smokers, while other studies have suggested increased risk for pancreatic cancer in never-smokers (Lee, 2011; Luo *et al.*, 2007). As a result, snus has gained increasing interest as a potential smoking cessation aid in these and other retrospective cohort studies on Swedish populations including evaluation via a randomized, double-blind, placebo-controlled clinical trial in a

Serbian population suggesting that participants in the snus group were more likely to quit smoking completely (Foulds *et al.*, 2003; Gilljam & Galanti, 2003; Joksic *et al.*, 2011; Rodu *et al.*, 2002; Sohlberg & Wennberg, 2020). Though there have been multiple reports of lack of association of snus use with oral cancer and potential for use as a smoking cessation aid, snus use is still known to cause damage to the oral cavity (Frithiof *et al.*, 1983; Kopperud *et al.*, 2023; Roosaar *et al.*, 2006; Zatterstrom *et al.*, 2004).

Moreover, it has been suggested that novel nicotine pouch products have lower abuse liabilities as they have been shown to deliver nicotine more slowly and in lower quantities than traditional tobacco products such as cigarettes (Henningfield & Keenan, 1993; Jackson *et al.*, 2023). However, the validity of this claim is still actively debated as users have also reported that the slower and less potent delivery of nicotine makes these products significantly less satisfying and rewarding, ultimately helping relieve cigarette craving symptoms but not as much as cigarettes themselves (Rensch *et al.*, 2021). Furthermore, due to the recent introduction of nicotine pouch products as a new product category competing with more traditional pre-portioned snus, there is a notable lack of data on the dental health effects of long-term and prolonged habitual use of these products, but due to the similarities in method of administration, it is likely that localized gingival recession will develop as documented in habitual users of traditional pre-portioned snus (Jackson *et al.*, 2023).

Question and Hypothesis

The aim of this study is to investigate the differences in manufacturing and chemical composition of moist snuff, snus, as well as novel TDN and SyN pouch products popularly consumed in North America and Northern Europe and evaluate the

impact to dental health and potential for these products to be used as a harm-reduction measure to combat the prevalence of tobacco-related comorbidities. We hypothesize that all loose and pre-portioned tobacco-leaf and nicotine pouch products marketed in North America and Northern Europe contain detectable concentrations of known and suspected carcinogens, toxicants or irritants with brand-level variation due to manufacturing, storage and distribution. As a result, we should expect that prolonged pre-portioned spitless tobacco and similar nicotine pouch product usage will be associated with risk of developing dental, gingival or oropharyngeal disease for American and European consumers. We would reject our hypothesis only if no analytes were detectable across products; this could be due to lack of research examining the chemical composition of the most novel TDN and SyN pouch products only recently introduced and marketed to consumers. Moreover, due to the recent introduction of these new product categories, our ability to evaluate the long-term dental, gingival and oropharyngeal effects of prolonged habitual use of orally administered spitless nicotine products will be severely limited.

Implications of Research

Our justification for critically evaluating selected case studies, meta-analyses and epidemiological studies examining both pre-portioned tobacco leaf snus as well as similar pre-portioned spitless nicotine pouch products is due to the almost identical form factor and oral method of administration for these product categories. In addition, these products directly compete with each other, often intentionally obscuring the differences between these product categories while being marketed to the same target consumer demographics. By investigating composition differences, examining oral/dental health outcomes, and evaluating harm-reduction claims, we will help better characterize the

differences between these products and help develop a better understanding of the potential impact to youth, adolescent and adult populations as these product categories continue to rapidly grow in popularity across North America and Northern Europe.

Chapter II.

Materials and Methods

We performed a targeted literature review and harmonized secondary analysis of published datasets characterizing the chemical composition of moist snuff, snus, and nicotine pouch products marketed and commercially available in the United States and Northern Europe between 2000–2025, evaluating findings in the context of oral and dental health. Sources were identified through Harvard HOLLIS searches and linked databases and included peer-reviewed journal articles, literary reviews, case reports, secondary references and publicly available datasets. Chemical composition studies were eligible for inclusion if they analyzed products from the specified markets and reported at least one of the following analytes: pH, NNN, NNK, B[a]P, total nicotine, or free nicotine. Epidemiologic studies were eligible if they were human cohort, case-control, or case-report designs with study location specified within North American or Northern European populations, assessed exposure to moist snuff, snus, or nicotine pouches, and reported dental, gingival or oropharyngeal outcomes. This study only involved secondary analysis of published data; since no primary research was conducted on live humans, animals or any other biospecimens, IRB review was not required.

Data Harmonization

Across all studies, we harmonized reported measures of analytes of interest based on product category. Significant variation in study methodologies was observed, with

some studies reporting results on a wet-weight basis (WWB), while others reported results on a dry-weight basis (DWB). We observed that all included studies reporting on the chemical composition of moist snuff and snus products that originally reported results in WWB provided the associated % Moisture values required for conversion to DWB, but not all studies that originally reported in DWB provided the required % Moisture values to harmonize to WWB. As a result, we chose to harmonize reported results for the moist snuff and snus product categories to DWB to maximize comparability and enable accurate trending for the tobacco-leaf products that had been repeatedly independently analyzed. The exact equation used to convert originally reported WWB values to DWB is shown below, where $Analyte_{DWB}$ represents the dry-weight basis concentration, $Analyte_{WWB}$ represents the wet-weight basis concentration, and % Moisture represents the WWB moisture mass-percent value:

$$Analyte_{DWB} = \frac{Analyte_{WWB}}{1 - \left(\frac{\% Moisture}{100}\right)}$$

For NPPs, all included studies originally reported results in WWB, but associated % Moisture values were not always available, preventing conversion to DWB. Therefore, to avoid speculative conversions and drawing false conclusions, results are reported in WWB values as originally published.

Due to the variation in experimental methodologies employed by source studies, unit harmonization calculations were performed when necessary to enable accurate comparison and trending within product categories; specifically, NNN and NNK values originally reported in $\mu\text{g/g}$ were harmonized to ng/g , while Total Nicotine values originally reported as %wt were harmonized to mg/g . All included source studies that originally reported B[a]P, Free Nicotine, and % Free Nicotine values consistently

reported B[a]P in ng/g, Free Nicotine in mg/g and % Free Nicotine as a unitless ratio of Free Nicotine content out of the Total Nicotine content expressed as a percentage; as a result, unit harmonization was not required and was not performed for these analytes.

When % Free Nicotine or Free Nicotine values were not originally provided, derivation calculations were performed when possible; the order of precedence chosen for reported % Free Nicotine and Free Nicotine values in this study are described as follows and are listed in order of decreasing priority:

1. Use reported values as-is if originally provided by source studies.
2. Calculate % Free Nicotine from the ratio of originally provided Free Nicotine to Total Nicotine values.
3. Estimate % Free Nicotine via the Henderson-Hasselbalch approximation with provided pH values, then calculate the Free Nicotine values from the originally reported Total Nicotine values.

The minimum requirements to calculate derived values and the exact equations used are described in detail below.

When Free Nicotine and Total Nicotine values were originally provided, % Free Nicotine concentrations were derived using the fractional-percent equation shown below:

$$\% \text{ Free Nicotine} = \frac{\text{Free Nicotine (mg/g)}}{\text{Total Nicotine (mg/g)}} \times 100\%$$

Alternatively, when Free Nicotine values were not available but both pH and Total Nicotine values were originally provided, estimated % Free Nicotine values were derived using the Henderson-Hasselbalch approximation with a pK_a of 8.02 for the nicotine free-base fraction chosen for derivation calculations (25 °C; CRC Handbook of Chemistry and

Physics, 71st ed.). Using a pK_a of 7.90 resulted in $\leq 6.9\%$ change in calculated values and did not affect study conclusions; a summary of the sensitivity analysis performed is included in Appendix 1, Table 19. The equation used to calculate derived values is shown below:

$$\% \text{ Free Nicotine} = \frac{1}{1 + 10^{pK_a - pH}} \times 100\%$$

Free Nicotine values were then calculated using the Henderson-Hasselbalch-derived % Free Nicotine values by rearranging the fractional-percent equation previously described to solve for Free Nicotine, as shown below:

$$\text{Free Nicotine (mg/g)} = \frac{\% \text{ Free Nicotine} \times \text{Total Nicotine (mg/g)}}{100\%}$$

All originally provided pH values were reported and used in derivation calculations as-is; no basis or unit harmonization calculations were required or performed. Generalized terminology to describe pH was used in Chapter III: Results solely to aid in readability; the descriptors used are not clinical thresholds but are mapped to the following numeric ranges: moderately acidic 5.5–6.2; slightly acidic 6.3–6.8; near neutral 6.9–7.1; slightly basic 7.2–7.8; moderately basic 7.9–8.6; strongly basic >8.6 .

As for rounding and decimal precision, analyte-specific precision rules are described as follows: pH to 0.01, nicotine to 0.1 mg/g, NNN, NNK and B[a]P to 1 ng/g, otherwise rounding to the coarsest source precision reported. Since source studies originally reported analyte concentrations to between two and four significant figures or to one or two fixed decimal places, we carried reported precision throughout all derivation and harmonization calculations, treating each reported value as the midpoint ± 0.5 of its least significant digit. All conversions used full floating-point precision; results

were rounded for display per analyte-specific rounding rules or, when mixed, to the coarsest precision in the contributing data. Values reported as ND, <LOD, <LOQ, or BQL were treated as missing and were excluded from analysis prior to data harmonization and were not imputed. Summary statistics (min/max/median/mean) were calculated from unrounded numbers and rounded for display using the same analyte precision rules previously described. Rounding was constrained to the coarsest precision presented in source data to avoid overstating resolution and implying false precision.

All harmonization and derivation calculations were performed in Microsoft Excel for Mac (v16.97) using a versioned template with embedded cell formulas; the workbook is available upon request. Studies with notable exceptions that required deviation from the data harmonization methods previously mentioned are described below, and a summary of study-specific harmonization and derivation actions are included in Appendix 1, Table 20.

Due to inconsistencies observed in the original NNN standard deviation (SD) values reported by Richter *et al.* (2008), our data harmonization methods deviated from the general methods previously described. Specifically, a mix of whole number and single digit decimal places corresponding to three or four significant figures was observed: e.g., ‘149.2’, ‘642’, ‘16049’, etc. As a result, NNN SD values were harmonized to four significant figures to preserve the authors’ full measurement resolution while enforcing a consistent numeric rule across the dataset. A sensitivity analysis testing the impact of adopting a three-significant figure rule changed individual SDs by $\leq 0.31\%$ and did not affect conclusions; a summary of the sensitivity analysis is included in Appendix 1, Table 21.

For the McAdam *et al.* (2013, 2019) dataset, Total Nicotine values were originally reported as WWB in McAdam *et al.* (2019), while the associated % Moisture values for the same exact product sample set were published in McAdam *et al.* (2013). As a result, the provided % Moisture values from McAdam *et al.* (2013) were applied to the paired Total Nicotine WWB values reported in McAdam *et al.* (2019) to obtain harmonized DWB values using the conversion calculation previously described. All other analytes reported in McAdam *et al.* (2013) were already expressed in DWB and no further harmonization calculations were required.

For the Lawler *et al.* (2020) dataset, since analyte mean values were reported in WWB as least-squares means (LS-means) by region/form-factor/strength rather than as per-product values, stratum-specific least-squares means (LS-means) were converted from WWB to DWB using associated reported % Moisture least-squares mean (LS-mean) values for each grouping. Additionally, due to the significant imbalance in sample size across strata, mean values were harmonized and summarized as singular DWB values in the originally reported groupings, with full detailed results included in Appendix 2.

Research Limitations

Since this study is a secondary analysis of published datasets with no underlying data collected or produced, the constraints present within included source studies are also inherited by this study. For example, significant variation was observed across source studies and reported product categories, basis of reported values (WWB vs. DWB), and analytical methods performed; as a result, harmonization calculations were able to reduce but not eliminate residual differences between studies. A second limitation encountered

was for the NPP product category specifically; since % Moisture values were not always available, values remained in WWB as originally reported, limiting cross-category comparability. Another limitation was that some studies aggregated experimentally determined chemical composition results by source region/form factor/product strength strata rather than per-product values, reporting aggregate stratum-specific least-squares means (LS-means) which greatly inhibited product-level inferences. Additionally, multiple source studies originally reported non-detect (ND), below limit of detection (<LOD), below limit of quantification (<LOQ/BQL) values; these values were excluded instead of imputed, resulting in left-censoring that could introduce bias upward. Finally, due to the recent introduction of the NPP product category, the available evidence base is severely lacking with long-term health effects and accurate, generalizable market-representative composition has yet to be comprehensively characterized. As a result, not enough data was available to meaningfully trend analytes of interest, limiting our ability to analyze and draw generalizable conclusions about NPP composition.

Conflict of Interest Statement

I am currently employed as a life sciences software solutions senior analyst at the consulting firm Accenture. My work at Accenture only involves the implementation, upgrading, and troubleshooting specialized laboratory software for client organizations in the biopharmaceutical industry. I have never had any direct or indirect contact or connection with any of Accenture's clients that operate in the tobacco, alternative nicotine products, or tobacco-cessation industries. Additionally, neither my employer nor my colleagues has influenced the subject of this study. As such, I have no conflicting or competing interests that could influence the design or outcome of this study.

Chapter III.

Results

This chapter is divided into three sections, each reporting on the manufacturing process and harmonized chemical composition of a distinct category of smokeless tobacco product; the first section focuses on moist snuff, the second on snus and the third on nicotine pouch products.

Manufacturing & Chemical Composition of Moist Snuff

American moist snuff products are produced by fermenting blends high in fire-cured tobacco, which are then processed into fine particles and sold loose, or as small pre-portioned cellulose pouches, with the final product containing as much as 50% moisture (Foulds *et al.*, 2003; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2007; Philip Morris International, n.d.). Total nicotine is controlled through the selection and blending of tobacco leaf, while the levels of free nicotine are controlled by adjusting the pH through fermentation, by adding alkaline buffering agents such as sodium carbonate and ammonium carbonate, or by altering moisture content (Connolly, 1995). Free nicotine is formed as the pH increases and is rapidly absorbed across the mucosal membranes (Connolly, 1995).

Moist snuff is known to contain a number of toxicants and carcinogens, but TSNA's are of particular concern because these compounds are among the most abundant and potent carcinogens found in tobacco products (Stepanov *et al.*, 2012; Lawler *et al.*,

2020). This group of compounds includes several nitrosated derivatives of endogenous pyridine alkaloids such as nicotine and nornicotine (Edwards *et al.*, 2017). TSNA's are naturally found in green, mature tobacco leaves but can increase during the curing, storage, fermentation, and processing of tobacco leaves (Bhide *et al.*, 1987; Staaf *et al.*, 2005). During curing, aging, and fermentation, nitrate-reducing microorganisms convert nitrate to nitrite, which interacts with tobacco alkaloids under low pH conditions, resulting in the formation of potent TSNA's including NNN and NNK (Brunnemann *et al.*, 1996); as a result, various strategies have been proposed to lower TSNA levels such as sanitizing fermentation equipment and using non-nitrate reducing bacteria or agents like green tea extract or ascorbic acid to neutralize nitrite (Tyx *et al.*, 2022).

Moist snuff products are not typically refrigerated; rather, they are stored and sold at room temperature (Foulds *et al.*, 2003). Djordjevic *et al.* (1993) demonstrated that storage conditions significantly impact the levels of TSNA's and N-nitrosamino acids (NAAs) in commercial moist snuff. When stored in cold storage at 4°C over a 32 week period, they observed no significant increase in these compounds; in contrast, at room temperature, levels of nitrite, individual TSNA's, and NAA started to rise after 4 weeks of storage. By 24 weeks, levels of NNN and 3-(methylnitrosamino)propionic acid (MNPA) had nearly tripled, levels of NNK increased 4.4 times higher and 4-(methylnitrosamino)butyric acid (MNBA) levels increased 6.3-fold (Djordjevic *et al.*, 1993). Moreover, when moist snuff was stored in an incubator set at 37°C with 85% relative humidity and constant airflow, increases were noted across moisture, pH, nitrite, TSNA's, and NAAs throughout the storage duration, while nicotine levels remained relatively unchanged. By the 8 week mark, individual TSNA concentrations increased

significantly – up to 4.7-fold for NNK, with NNN and NAT rising 2.5 fold (Djordjevic *et al.*, 1993). The largest increases at both ambient and elevated temperatures were observed for NNK, an IARC Group 1 carcinogen and FDA-listed HPHC for smokeless tobacco (Djordjevic *et al.*, 1993; FDA Center for Tobacco Products, 2020; IARC, 2025).

Richter *et al.* (2008) analyzed 40 of the most popular moist snuff products of 2004 which collectively comprised over 97% of market share in the United States that year. One product, “Oregon Mint Snuff”, did not contain detectable levels of TSNA or nicotine and was excluded from further analysis. TSNA and nicotine concentrations were originally reported on a wet-weight basis and varied dramatically across brands, product lines and flavor profiles. Data were harmonized as described in Chapter II: Materials & Methods, Data Harmonization. Significant variation was observed in pH, with products ranging from moderately acidic with a minimum pH of 5.54 to strongly basic with a maximum pH of 8.62 and slightly basic mean pH of 7.55. Notably, among the 39 brands with detectable concentrations of TSNA and nicotine, NNN content varied from 4,412 ng/g to a notably high 91,122 ng/g with a mean of 14,479 ng/g, while levels of NNK ranged from 666 ng/g to 21,306 ng/g with a mean of 3,827 ng/g. Free nicotine ranged from 0.01 mg/g to 16.69 mg/g with a mean of 8.06 mg/g; expressed as a percentage of total nicotine, free nicotine concentrations ranged from 0.3% and 79.9% with a mean of 32.6%. Interestingly, the brand with the highest concentration of NNN was found to contain three times more total TSNA than the next highest brand but did not contain significantly greater levels of free nicotine; in contrast, the brand with the highest concentration of free nicotine was found to have lower than average concentrations of NNN (Richter *et al.*, 2008).

Table 1. Moist Snuff Summary – Richter *et al.* (2008).

Analyte	pH	NNN (ng/g)	NNK (ng/g)	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine (%)
Min	5.54	4412	666	6.09	0.01	0.3
Max	8.62	91122	21306	37.36	16.69	79.9
Analyte	pH	NNN (ng/g)	NNK (ng/g)	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine (%)
Median	7.72	10935	2683	27.02	9.48	34.2
Mean	7.55	14479	3827	24.76	8.06	32.6

Summary of key analytes for moist snuff products analyzed by Richter et al. (2008); complete harmonized result dataset included in Appendix 2.

Song *et al.* (2016) analyzed the chemical compositions of 7 popular conventional moist snuff products purchased from retail outlets in the United States between 2007 and 2009. Levels of 19 chemical constituents including 4 TSNAs, 6 metals, 3 humectants, and 5 other HPHCs and toxicants were reported on a dry-weight basis. Data were harmonized as described in Chapter II: Materials & Methods, Data Harmonization. All products tested were slightly to moderately basic, with pH varying between 7.50 and 8.44 with a moderately basic mean of 7.83. NNN content varied from 2,930 ng/g to 5,820 ng/g with a mean of 4,470 ng/g while concentrations of NNK ranged from 960 ng/g to 3,040 ng/g with a mean of 1,550 ng/g. B[a]P levels varied significantly, with a minimum detected concentration of 32.71 ng/g, a maximum of 106.73 ng/g, and mean of 77.75 ng/g. Free nicotine content ranged from 6.362 mg/g to 12.928 mg/g with a mean of 9.273 mg/g; expressed as a percentage of total nicotine, free nicotine concentrations ranged from 23.19% and 72.47%, with a mean of 39.98% (Song *et al.*, 2016).

Table 2. Moist Snuff Summary – Song *et al.* (2016).

Analyte	pH	NNN (ng/g)	NNK (ng/g)	B[a]P (ng/g)	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine (%)
Min	7.50	2930	960	32.71	17.84	6.362	23.19
Max	8.44	5820	3040	106.73	27.43	12.928	72.45
Median	7.66	4760	1540	81.60	25.76	8.153	30.39
Mean	7.83	4470	1550	77.75	24.48	9.273	39.98

Summary of key analytes for moist snuff products analyzed by Song et al. (2016); complete harmonized result dataset included in Appendix 2.

McAdam *et al.* (2013, 2019) analyzed the PAH and nicotine content within a variety of smokeless tobacco products obtained from the United States and Sweden in 2008–2009. Results from the same product sample set was reported in both studies. All 16 moist snuff brands analyzed were from the United States. HPHC content was originally reported on a dry-weight basis, while nicotine concentrations were originally reported on a wet-weight basis (McAdam *et al.*, 2013, 2019). Data were harmonized as described in Chapter II: Materials & Methods, Data Harmonization. All products tested were near-neutral to moderately basic, with pH varying from 7.0 to 8.4 with a moderately basic mean of 7.9 (McAdam *et al.*, 2019). Concentrations of B[a]P varied from a minimum of 35.80 ng/g to a maximum of 167.00 ng/g with a mean of 87.44 ng/g (McAdam *et al.*, 2013). Total nicotine content ranged between 18.9 mg/g and 35.2 mg/g with a mean of 26.7 mg/g. Calculated free nicotine content ranged between 2.1 mg/g and 19 mg/g with a mean of 12 mg/g; expressed as a percentage of total nicotine, free nicotine concentrations were calculated to vary between 8.7% and 70.6%, with a mean of 44.1% (McAdam *et al.*, 2019).

Table 3. Moist Snuff Summary – McAdam *et al.* (2013, 2019).

Analyte	pH	B[a]P (ng/g)	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine (%)
Min	7.0	35.80	18.9	2.1	8.7
Max	8.4	167.00	35.2	19	70.6
Median	8.0	81.10	27.3	13	48.8
Mean	7.9	87.44	26.7	12	44.1

Summary of key analytes for moist snuff products analyzed by McAdam et al. (2013, 2019); complete harmonized result dataset included in Appendix 2.

Stepanov *et al.* (2013) focused on characterizing the enantiomeric composition of NNN on a wet-weight basis in 14 conventional moist snuff products obtained from retailers in the United States between 2010–2012; data were harmonized as described in Chapter II: Materials & Methods, Data Harmonization. Overall levels of NNN varied from a minimum of 2,750 ng/g to a maximum of 8,910 ng/g with a mean of 4,880 ng/g; expressed as a percentage of total NNN content, concentrations of (S)-NNN were found to range from 50.2% to 65.5% with a mean of 57.0%. Notably, the (S)-NNN enantiomer with higher tumorigenicity was found to be the predominant enantiomer present in all 14 conventional moist snuff products analyzed.

Table 4. Moist Snuff Summary – Stepanov *et al.* (2013).

Analyte	NNN (ng/g)	(S)-NNN (ng/g)	(S)-NNN (%)
Min	2750	1610	50.2
Max	8910	5240	65.5
Median	4280	2470	57.2
Mean	4880	2800	57.0

Summary of key analytes for moist snuff products analyzed by Stepanov et al. (2013); complete harmonized result dataset included in Appendix 2.

Tyx *et al.* (2022) investigated the relationship between microbiotas in moist snuff products and chemical constituents for 37 moist snuff products obtained from a vendor in the United States in 2016. Results were originally reported on a wet-weight basis. Data were harmonized as described in Chapter II: Materials & Methods, Data Harmonization. Reported pH values varied between a near-neutral to slightly acidic 6.89 and a moderately basic 8.20 with a slightly basic mean of 7.61. NNN content was found ranging from 2,620 ng/g to 7,780 ng/g with a mean of 4,010 ng/g. Concentrations of NNK ranged from 662 ng/g to 4,150 ng/g with a mean of 1,290 ng/g. Concentration of free nicotine was found to vary between 1.92 mg/g to 16.21 mg/g with a mean of 8.59 mg/g; expressed as a percentage of total nicotine, free nicotine levels ranged from 6.9% to 60.2% with a mean of 29.8% (Tyx *et al.*, 2022).

Table 5. Moist Snuff Summary – Tyx *et al.* (2022).

Analyte	pH	NNN (ng/g)	NNK (ng/g)	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine (%)
Min	6.89	2620	662	24.1	1.92	6.9
Max	8.20	7780	4150	35.3	16.21	60.2
Median	7.62	3460	1140	28.7	8.41	28.5
Mean	7.61	4010	1290	29.0	8.59	29.8

Summary of key analytes for moist snuff products analyzed by Tyx et al. (2022); complete harmonized result dataset included in Appendix 2.

Back *et al.* (2023) analyzed the chemical composition of two moist snuff products, one loose and the other pouched, obtained from the United States; the date range the products were obtained was not mentioned. Levels of 43 chemical constituents including the 9 HPHCs identified as relevant for smokeless tobacco products by the FDA were originally reported on a wet-weight basis. Data were harmonized as described in

Chapter II: Materials & Methods, Data Harmonization. Both products analyzed were slightly to moderately basic with pHs of 7.7 and 7.9 for the loose and pouched products respectively. NNN content was 7,720 ng/g and 5,270 ng/g, while concentrations of NNK were 4,830 ng/g and 1,920 ng/g for the loose and pouched products respectively; notably, 27 of the 43 compounds were quantifiable in the loose products and 26 of 43 in the pouched products (Back *et al.*, 2023). Concentrations of B[a]P were 240 ng/g and 154 ng/g in the loose and pouched products respectively (Back *et al.*, 2023). Total nicotine content was observed at 21.21 mg/g and 17.65 mg/g, while free nicotine content was 6.87 mg/g and 7.60 mg/g for the loose and pouched products respectively. Expressed as a percentage of total nicotine, free nicotine concentrations were calculated to be 32.37% and 43.14% for the loose and pouched products respectively (Back *et al.*, 2023).

Table 6. Moist Snuff Summary – Back *et al.* (2023).

Analyte	pH	NNN (ng/g)	NNK (ng/g)	B[a]P (ng/g)	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine (%)
Loose	7.7	7720	4830	240	21.21	6.87	32.37
Pouched	7.9	5270	1920	154	17.65	7.60	43.14

Summary of key analytes for moist snuff products analyzed by Back et al. (2023); complete harmonized result dataset included in Appendix 2.

Manufacturing & Chemical Composition of Snus

Whereas moist snuff is unpasteurized and is produced from fermented fire-cured tobacco, snus consists of finely ground air- or sun-cured tobacco, salt, humidifying agents, chemical buffering agents and food-grade flavorings (Foulds *et al.*, 2003; Lawler *et al.*, 2020; Lee, 2011). By tradition, Swedish snus production has included heat

treatment with steam, and it has been suggested that the heating process kills microorganisms to prevent further nitrite formation (Foulds *et al.*, 2003; Lawler *et al.*, 2020). The product is then packaged and refrigerated during storage by manufacturers as well as retailers (Foulds *et al.*, 2003).

Similar to conventional moist snuff, the chemical composition of snus has been well characterized with multiple studies analyzing the levels of TSNAs and HPHCs detected in popular brands and product lines at different timepoints over the past two decades (Azzopardi *et al.* 2021; Back *et al.* 2023; Lawler *et al.*, 2020; McAdam *et al.*, 2013, 2019; Song *et al.*, 2016; Stepanov *et al.*, 2012, 2013, 2014).

Song *et al.* (2016) analyzed the chemical composition of 7 popular American snus products and 3 Swedish snus products purchased from retail outlets in the United States and Sweden between 2007 and 2009. Levels of 19 chemical constituents including 4 TSNAs, 6 metals, 3 humectants, and 5 other HPHCs and toxicants were reported on a dry-weight basis. Data were harmonized as described in Chapter II: Materials & Methods, Data Harmonization; sample sizes were too small to meaningfully identify any significant differences in analyte content or concentration between the American and Swedish brands analyzed. For all products tested, pH ranged from a slightly acidic 6.53 to a moderately basic 8.03 with a slightly basic mean pH of 7.37. NNN content ranged from 770 ng/g to 2,430 ng/g with a mean of 1,140 ng/g, while concentrations of NNK ranged from 200 ng/g to 460 ng/g with a mean of 306 ng/g. B[a]P levels varied from 0.55 ng/g to 3.13 ng/g with a mean of 1.07 ng/g. Free nicotine content ranged from 0.492 mg/g to 14.743 mg/g with a mean of 4.934 mg/g; expressed as a percentage of total nicotine,

free nicotine concentrations were calculated to range between 3.13% and 50.58%, with a mean of 25.11%.

Table 7. Snus Summary – Song *et al.* (2016).

Analyte	pH	NNN (ng/g)	NNK (ng/g)	B[a]P (ng/g)	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine (%)
Min	6.53	770	200	0.55	15.01	0.492	3.13
Max	8.03	2430	460	3.13	31.67	14.743	50.58
Median	7.52	955	290	0.75	16.16	4.609	24.03
Mean	7.37	1140	306	1.07	18.14	4.934	25.11

Summary of key analytes for snus products analyzed by Song et al. (2016); complete harmonized result dataset included in Appendix 3.

McAdam *et al.* (2013, 2019) examined a variety of smokeless tobacco products obtained from the United States and Sweden in 2008–2009. All 10 loose snus brands and 22 pre-portioned snus brands analyzed were from Sweden. HPHC content was originally reported on a dry-weight basis, while nicotine concentrations were originally reported on a wet-weight basis (McAdam *et al.*, 2013, 2019). Data were harmonized as described in Chapter II: Materials & Methods, Data Harmonization. For the products examined, pH ranged from a slightly basic 7.5 to a strongly basic 8.8 with a moderately basic mean of 8.5 (McAdam *et al.*, 2019). Concentrations of B[a]P varied from a minimum of 1.88 ng/g to a maximum of 5.23 ng/g with a mean of 2.93 ng/g (McAdam *et al.*, 2013). Total nicotine content ranged between 15.6 mg/g and 23.1 mg/g with a mean of 18.2 mg/g. Calculated free nicotine content ranged between 4.5 mg/g and 19 mg/g with a mean of 13 mg/g; expressed as a percentage of total nicotine, free nicotine concentrations were

calculated ranging between 23.2% and 85.8%, with a mean of 72.6% (McAdam *et al.*, 2019).

Table 8. Snus Summary – McAdam *et al.* (2013, 2019).

Analyte	pH	B[a]P (ng/g)	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine (%)
Min	7.5	1.88	15.6	4.5	23.2
Max	8.8	5.23	23.1	19	85.8
Median	8.7	2.69	17.3	14	82.7
Mean	8.5	2.93	18.2	13	72.6

Summary of key analytes for snus products analyzed by McAdam et al. (2013, 2019); complete harmonized result dataset included in Appendix 3.

Stepanov *et al.* (2012, 2013, 2014) conducted coordinated analyses of Marlboro and Camel snus product lines as part of the New Product Watch Project; data were harmonized as described in Chapter II: Materials & Methods, Data Harmonization. Stepanov *et al.* (2012) analyzed the composition of 8 American snus product lines obtained between July and September of 2010 as part of Round I of the New Product Watch Project; results were originally reported on a dry-weight basis. Variation in pH was strongly correlated to manufacturer, with all four Marlboro Snus products found to be slightly acidic and all four Camel Snus products slightly basic; among the products tested, pH was observed to range from a slightly acidic 6.68 to a slightly basic 7.68 with a near-neutral to slightly basic mean of 7.16 (Stepanov *et al.*, 2012). NNN content varied from 420 ng/g to 1,280 ng/g with a mean of 711 ng/g, while levels of NNK varied from 132 ng/g to 609 ng/g with a mean of 335 ng/g (Stepanov *et al.*, 2012). Total nicotine content was observed ranging from 13.93 mg/g to 24.84 mg/g, while free nicotine content was observed ranging from 0.84 mg/g to 5.09 mg/g with a mean of 2.61 mg/g. Expressed

as a percentage of total nicotine, concentration of free nicotine ranged from 4.5% to 36.5% with a mean of 16.3% (Stepanov *et al.*, 2012). A separate analysis was conducted with new product samples obtained between April and July of 2011 as part of Round II of the New Product Watch Project, with results also reported on a dry-weight basis.

Variation in pH was still strongly correlated to manufacturer, with the Marlboro Snus products being slightly acidic while the Camel Snus products were slightly basic; in this analysis, pH was observed to range from 6.65 to 7.61 with a mean of 7.16 (Stepanov *et al.*, 2014). Interestingly, TSNA content was found to have roughly doubled in the new product sample set compared to the levels seen in Round I of the New Product Watch Project; NNN concentrations were found to range between 668 ng/g and 1,980 ng/g with a mean of 1,310 ng/g, while levels of NNK varied from 185 ng/g to 730 ng/g with a mean of 459 ng/g (Stepanov *et al.*, 2014). Total nicotine content was more consistent, ranging from 13.18 mg/g to 22.56 mg/g, while free nicotine content was observed ranging from 0.83 mg/g to 4.06 mg/g with a mean of 2.41 mg/g. Expressed as a percentage of total nicotine, concentration of free nicotine ranged from 4.7% to 28.3% with a mean of 16.4% (Stepanov *et al.*, 2014). Stepanov *et al.* (2013) re-analyzed the product lines on a wet-weight basis with a specific focus on characterizing the enantiomeric composition of NNN. Due to the differences in sample lots and reporting methodologies between the 2013 and 2014 papers, discrepancies in NNN concentration are expected. Nevertheless, the concentration ranges were found to overlap after harmonization, as shown in Appendix 3. Similar to the conventional moist snuff brands examined, the more tumorigenic (S)-NNN enantiomer was found to be the predominant enantiomer present in all 8 American snus products analyzed as well (Stepanov *et al.*, 2013). Interestingly, the

percent contribution of the (S)-NNN to total NNN in the snus products analyzed was significantly higher than that of the moist snuff products tested (Stepanov *et al.*, 2013).

Table 9. Snus Summary – Stepanov *et al.* (2012).

Analyte	pH	NNN (ng/g)	NNK (ng/g)	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine (%)
Min	6.68	420	132	13.93	0.84	4.5
Max	7.78	1280	609	24.84	5.09	36.5
Median	7.10	665	284	17.78	2.30	12.7
Mean	7.16	711	335	17.97	2.61	16.3

Summary of key analytes for snus products analyzed by Stepanov et al. (2012); complete harmonized result dataset included in Appendix 3.

Table 10. Snus Summary – Stepanov *et al.* (2014).

Analyte	pH	NNN (ng/g)	NNK (ng/g)	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine (%)
Min	6.65	688	185	13.18	0.83	4.7
Max	7.61	1980	730	22.56	4.06	28.3
Median	7.18	1300	464	16.05	2.33	16.0
Mean	7.16	1310	459	16.47	2.41	16.4

Summary of key analytes for snus products analyzed by Stepanov et al. (2014); complete harmonized result dataset included in Appendix 3.

Lawler *et al.* (2020) analyzed 56 Northern European and 8 American snus products purchased from 2013–2014, reporting least-squares means (LS-means) by region, form factor, and strength on a wet-weight basis. Data were harmonized as described in Chapter II: Materials & Methods, Data Harmonization; LS-means were converted to DWB values using strata-specific moisture LS-means, reporting harmonized result values in the same region/form-factor/strength groupings the source study

originally reported results in. Of the Northern European brands examined, 7 were loose snus products and 49 were pre-portioned snus products, while the American brands included in the study were all pre-portioned snus products. The LS-means of analytes of interest for the U.S. Standard Portion stratum are as follows: mean pH was 6.62, mean NNN concentration was 1,520 ng/g, mean NNK concentration was 464 ng/g. Mean total nicotine was 15.6 mg/g, while mean free nicotine was 1.5 mg/g; expressed as a percentage of total nicotine, mean free nicotine concentration was 11.1%. The LS-means of analytes of interest for the Northern European Standard Portion stratum are as follows: mean pH was 8.08, mean NNN concentration was 1,130 ng/g, mean NNK concentration was 316 ng/g. Mean total nicotine was 21.0 mg/g, while mean free nicotine was 10.3 mg/g; expressed as a percentage of total nicotine, mean free nicotine concentration was 49.8%. The LS-means of analytes of interest for the Northern European Standard Loose stratum are as follows: mean pH was 7.53, mean NNN concentration was 963 ng/g, mean NNK concentration was 226 ng/g. Mean total nicotine was 23.9 mg/g, while mean free nicotine was 6.1 mg/g; expressed as a percentage of total nicotine, mean free nicotine concentration was 27.5%. The LS-means of analytes of interest for the Northern European Strong Portion stratum are as follows: mean pH was 8.18, mean NNN concentration was 1,310 ng/g, mean NNK concentration was 569 ng/g. Mean total nicotine was 30.3 mg/g, while mean free nicotine was 18.0 mg/g; expressed as a percentage of total nicotine, mean free nicotine concentration was 60.1%. On average, the American products were found to be more acidic and contained lower free nicotine than the Northern European products, but these observations should be interpreted with

caution given the significant sample size imbalance between regions and the confounding of region with form factor.

Table 11. Snus Summary – Lawler *et al.* (2020).

Aggregated Product Strata LS-Means	pH	NNN (ng/g)	NNK (ng/g)	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine (%)
U.S. Standard Portion	6.62	1520	464	15.6	1.5	11.1
Northern European Standard Portion	8.08	1130	316	21.0	10.3	49.8
Northern European Standard Loose	7.53	963	226	23.9	6.1	27.5
Northern European Strong Portion	8.18	1310	569	30.3	18.0	60.1

Summary of key analytes for snus products analyzed by Lawler et al. (2020); complete harmonized result dataset (Mean ± SD, Min-Max) included in Appendix 3. Sample sizes by group: U.S. Standard Portion (n=8), Northern European Standard Portion (n=33), Northern European Standard Loose (n=6), Northern European Strong Portion (n=16).

Azzopardi *et al.* (2021) analyzed the chemical composition of 3 snus product samples commercially available in Scandinavian markets between 2018–2020. Each of the three snus product samples was analyzed in duplicate, and levels of 26 chemical constituents including moisture, nicotine, 4 TSNAs, 5 metals, and 15 other HPHCs and toxicants were reported on a wet-weight basis. Reported data were harmonized as described in Chapter II: Materials & Methods, Data Harmonization. All three products analyzed were moderately to strongly basic with a minimum pH of 7.8, a maximum pH of 8.7, and a moderately basic mean pH of 8.4 (Azzopardi *et al.*, 2021). Concentrations of NNN ranged from 858 ng/g to 1,210 ng/g with a mean of 1,080 ng/g, while concentrations of NNK ranged from 169 ng/g to 382 ng/g with a mean of 247 ng/g.

Calculated total nicotine content ranged from 22.9 mg/g to 33.7 mg/g with a mean of 28.4 mg/g, while free nicotine content ranged from 12.7 mg/g to 23.5 mg/g. Expressed as a percentage of total nicotine, concentration of free nicotine was calculated to range from 37.6% to 82.7% with a mean of 67.7%. Notably, quantifiable levels of cadmium, chromium, nickel, arsenic, lead, and acetaldehyde were also observed in all products tested (Azzopardi *et al.*, 2021). However, these findings should be interpreted with caution due to the extremely small and exclusively Scandinavian sample set.

Table 12. Snus Summary – Azzopardi *et al.* (2021).

Analyte	pH	NNN (ng/g)	NNK (ng/g)	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine (%)
Min	7.8	858	169	22.9	12.7	37.6
Max	8.7	1210	382	33.7	23.5	82.7
Median	8.7	1170	191	28.5	19.0	82.7
Mean	8.4	1080	247	28.4	18.4	67.7

Summary of key analytes for snus products analyzed by Azzopardi et al. (2021); complete harmonized result dataset included in Appendix 3.

Back *et al.* (2023) analyzed the chemical composition of a single snus product sample obtained from Sweden and measured in triplicate; the date range the product was obtained was not mentioned. Levels of 43 chemical constituents including the 9 HPHCs identified as relevant for smokeless tobacco products by the FDA were reported on a wet-weight basis; data was harmonized as described in Chapter II: Materials & Methods, Data Harmonization. The product analyzed was strongly basic with a pH of 8.9. NNN content was found to be 898 ng/g, while the concentration of NNK was 388 ng/g. Concentration of total nicotine was 16.59 mg/g, while free nicotine content was observed to be 14.51

mg/g. Expressed as a percentage of total nicotine, the concentration of free nicotine was calculated to be 88.35%. Additionally, 19 of all 43 compounds tested for were observed in quantifiable levels including 5 nitrosamines, 6 heavy metals, acetaldehyde, ammonia, anabasine, formaldehyde, nor nicotine, ochratoxin A, and polonium-210 (Back *et al.*, 2023). Since only 1 product sample from a single manufacturer was tested, these results serve merely as a product-specific snapshot in time and cannot be considered a valid representation of the broader snus market. Corresponding

Table 13. Snus Summary – Back *et al.* (2023).

Analyte	pH	NNN (ng/g)	NNK (ng/g)	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine (%)
Results	8.9	898	388	16.59	14.51	88.35

Summary of key analytes for snus products analyzed by Back et al. (2023); harmonized results included in Appendix 3.

Manufacturing & Chemical Composition of NPPs

Nicotine pouch products are a novel category of products marketed as a convenient, discreet, tasty, and tobacco-free way to use nicotine by large tobacco companies (Ye & Rahman, 2023). Though nearly identical in form and method of administration as snus, nicotine pouch products differ in composition by using a permeable pouch with a non-tobacco substrate to which nicotine and flavors are added (Azzopardi *et al.*, 2022). The outer pouch material can be comprised of cellulose compounds woven together or other viscose fibers bound together by chemical, heat or solvent treatment, which serves as the container for the nicotine-containing substrate (Azzopardi *et al.*, 2022; Philip Morris International, 2025). The non-tobacco substrate filler is mainly composed of water and microcrystalline cellulose which absorbs

pharmaceutical grade nicotine and comprises up to 80–90% of the product, while gum and hydrophilic solvents to stabilize humidity levels account for the remainder of the binding agents (Azzopardi *et al.*, 2022; Philip Morris International, 2025). Other essential components include food-grade ingredients such as pH buffers, filling agents, salt, taste additives, flavorings and sweeteners (Azzopardi *et al.*, 2022; Philip Morris International, 2025). Sodium carbonate and bicarbonate are commonly used to regulate the pH, which is critical to determining the rate of release of nicotine; if the pH is too neutral, the nicotine will not transfer across the oral mucosa, while anything above pH 9.1 becomes too basic, causing irritation to the oral mucosa (Philip Morris International, 2025).

The tobacco-free nicotine used in nicotine pouch products can be either extracted from tobacco or synthesized; this distinction has had critical regulatory implications as products containing TDN were always regulated by the FDA Center for Tobacco Products, but products containing SyN originally were not under the domain of any regulatory authority (Cheetham *et al.*, 2022). On April 14, 2022, federal law clarified FDA authority to regulate products containing nicotine from any source, including SyN (FDA Center for Tobacco Products, 2024). Whereas TDN is typically ~99.3% (S)-nicotine, SyN can range from racemic (50/50 R/S) to ~99% (S)-nicotine, depending on synthesis and purification (Cheetham *et al.*, 2022).

Azzopardi *et al.* (2021) analyzed the chemical composition of 4 nicotine pouch product samples from a single manufacturer that were commercially available in Scandinavian markets between 2018–2020. All 4 samples were measured in triplicate, reporting on levels of 26 chemical constituents including moisture, nicotine, 4 TSNAs, 5 metals, as well as 15 other HPHCs and toxicants on a wet-weight basis; data was

harmonized as described in Chapter II: Materials & Methods, Data Harmonization. All four products analyzed were moderately to strongly basic with a minimum pH of 8.5, a maximum pH of 8.7, and a moderately-to-strongly basic mean pH of 8.6 (Azzopardi *et al.*, 2021). Total nicotine content was calculated to range from 5.80 mg/g to 17.0 mg/g with a mean of 11.4 mg/g, while free nicotine concentrations were calculated to vary between 4.80 mg/g and 13.5 mg/g with a mean of 9.02 mg/g. Expressed as a percentage of total nicotine, free nicotine content ranged from 75.1% to 82.7% with a mean of 79.1% (Azzopardi *et al.*, 2021). However, these findings should be interpreted with caution as the extremely small sample size of only four product samples from the same manufacturer greatly limits generalizability.

Table 14. Nicotine Pouch Summary – Azzopardi *et al.* (2021).

Analyte	pH	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine (%)
Min	8.5	5.80	4.80	75.1
Max	8.7	17.0	13.5	82.7
Median	8.6	11.5	8.90	79.2
Mean	8.6	11.4	9.02	79.1

Summary of key analytes for nicotine pouch products analyzed by Azzopardi et al. (2021); complete harmonized result dataset included in Appendix 4.

Stanfill *et al.* (2021) analyzed the chemical composition of 37 nicotine pouch products from 6 manufacturers obtained from the United States in 2019, reporting results on a wet-weight basis; data were harmonized as described in Chapter II: Materials & Methods, Data Harmonization. Though most products examined were slightly to moderately basic, pH was observed ranging from a near neutral 6.94 to a strongly basic 10.1 with the overall mean being moderately basic at 8.28 across all 37 products (Stanfill

et al., 2021). Total nicotine content was observed ranging from 3.42 mg/g to 18.4 mg/g with a mean of 10.1 mg/g, while free nicotine content varied significantly from a minimum of 0.364 mg/g to a maximum of 17.9 mg/g. Expressed as a percentage of total nicotine, free nicotine concentrations ranged from 7.68% to 99.2% with a mean of 57.2% (Stanfill *et al.*, 2021).

Table 15. Nicotine Pouch Summary – Stanfill *et al.* (2021).

Analyte	pH	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine (%)
Min	6.94	3.42	0.364	7.68
Max	10.1	18.4	17.9	99.2
Median	8.12	8.36	5.05	55.7
Mean	8.28	10.1	6.09	57.2

Summary of key analytes for nicotine pouch products analyzed by Stanfill et al. (2021); complete harmonized result dataset included in Appendix 4.

Mallock *et al.* (2024) analyzed the chemical composition of 46 anonymized pouch products from 20 producers obtained from Germany in 2021, reporting results on a wet-weight basis. Data were harmonized as described in Chapter II: Materials & Methods, Data Harmonization. Two of the products examined did not contain detectable levels of nicotine and were excluded from further analysis. Additionally, most of the products examined had NNN and NNK concentrations that were ND/BQL; as a result, these values were excluded from further analysis rather than imputed. The pH of the remaining 44 products varied significantly from a moderately acidic 5.5 to a strongly basic 10.5 with a strongly basic mean pH of 8.9. Total nicotine content ranged from a minimum of 4.48 mg/g to a maximum of 75.5 mg/g with a mean of 20.8 mg/g, while free nicotine content varied between 0.0181 mg/g and 65.4 mg/g with a mean of 17.7 mg/g. Expressed as a

percentage of total nicotine, concentration of free nicotine was found to range from 0.3% to 100% with a mean of 79% (Mallock *et al.*, 2024). Only 15 out of the 44 products analyzed contained detectable levels of NNN, resulting in a detection frequency of 34.1%, while only 3 out of the 44 products analyzed contained detectable levels of NNK, corresponding to a detection frequency of 6.8%. Of the products tested with detectable levels of NNN, concentrations ranged from a minimum of 0.7 ng/g to a maximum of 26 ng/g, with a mean of 5.2 ng/g, and a median of 2.5 ng/g. In contrast, of the products tested with detectable levels of NNK, concentrations ranged from a minimum of 0.7 ng/g to a maximum of 14 ng/g with a mean of 5.6 ng/g and a median of 1.6 ng/g. Due to the low, and extremely low detection frequencies for NNN and NNK respectively, the median values evaluated alongside the mean values provide a more complete picture of the concentration distribution, especially for right-skewed, sparsely detected analytes.

Table 16. Nicotine Pouch Summary – Mallock *et al.* (2024).

Analyte	pH	NNN (ng/g)	NNK (ng/g)	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine (%)
Min	5.5	0.7	0.7	4.48	0.0181	0.30
Max	10.5	26	14	75.5	65.4	100
Median	8.8	2.5	1.6	14.8	12.3	86
Mean	8.9	5.9	5.6	20.8	17.7	79

Summary of key analytes for nicotine pouch products analyzed by Mallock et al. (2024); complete harmonized result dataset included in Appendix 4.

Table 17. Nicotine Pouch TSNA Summary Results – Mallock *et al.* (2024).

Analyte	NNN ^a (ng/g)	NNK ^a (ng/g)
n (total)	44	44
n (detects)	15	3
Detection %	34.1%	6.8%

Analyte	NNN ^a (ng/g)	NNK ^a (ng/g)
Min (detects)	0.7	0.7
Max (detects)	26	14
Median (detects)	2.5	1.6
Mean (detects)	5.2	5.6

Summary results for detected TSNA concentrations in nicotine pouch products analyzed by Mallock et al. (2024); all products analyzed were obtained in 2021.

^a Results originally reported in ng/pouch and converted to ng/g. Values on WWB; ND/BQL excluded.

Back *et al.* (2023) analyzed the chemical composition of 2 nicotine pouch products, one dry and one moist, produced from the same manufacturer and obtained Sweden; the date range the products were obtained was not mentioned. Levels of 43 chemical constituents including the 9 HPHCs identified as relevant for smokeless tobacco products by the FDA were measured in triplicate and reported on a wet-weight basis; data were harmonized as described in Chapter II: Materials & Methods, Data Harmonization. Both products analyzed were moderately basic with a pH of 8.3. Total nicotine content was observed at 7.63 mg/g and 12.00 mg/g, while free nicotine concentrations were found to be 4.87 mg/g and 7.87 mg/g for the dry and moist products respectively. Expressed as a percentage of total nicotine, free nicotine concentration was 65.58% for both products tested. Of the compounds analyzed, 38 were below quantification levels; notably, levels of formaldehyde, chromium and ammonia were quantifiable, while quantifiable levels of nickel were only observed in the dry product (Back *et al.*, 2023). With the entire sample set consisting of only two products from a single manufacturer, these findings are purely descriptive and not generalizable to the broader NPP market.

Table 18. Nicotine Pouch Summary – Back *et al.* (2023).

Analyte	pH	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine (%)
Dry	8.3	7.63	4.87	65.58
Moist	8.3	12.00	7.87	65.58

Summary of key analytes for NPPs analyzed by Back et al. (2023); complete harmonized result dataset included in Appendix 4.

Chapter IV.

Discussion

Chemical Composition of Moist Snuff and Impact on Dental Health

Moist snuff was the predominant form of smokeless tobacco in the United States in 2020 comprising about 86.3% of the smokeless tobacco market by weight that year (Federal Trade Commission, 2023); that year, the brands Copenhagen, Grizzly, and Skoal were the top three most popular brands by dollar share in the United States accounting for a combined 75% of all smokeless tobacco product sales that year (Convenience Store News, 2020). In response to the growing interest in smokeless tobacco products and concern about TSNA formation, the tobacco industry started implementing new manufacturing practices aimed at targeting the formation of TSNAs during fermentation and product storage; by 2005, protocols were introduced to sanitize fermentation vessels prior to use and inoculated with starter culture that did not contain detectable levels of nitrate reducing bacteria (Fisher *et al.*, 2012). In the years following the implementation of these sanitation and bacteria control practices, TSNA levels in select moist snuff products at the end of their shelf life were found to remain consistent with the levels observed in pre-fermented cured tobacco leaf and post-fermentation levels (Fisher *et al.*, 2012).

Since then, the chemical composition of conventional moist snuff has been extensively characterized, with multiple studies quantifying and publishing levels of TSNAs and HPHCs detected in popular brands and product lines at different timepoints

over the past two decades (Back *et al.*, 2023; McAdam *et al.*, 2013, 2019; Richter *et al.*, 2008; Song *et al.*, 2016; Stepanov *et al.*, 2013; Tyx *et al.*, 2022). Chronologically, Richter *et al.* (2008) analyzed the chemical composition of 40 of the most popular moist snuff products in the United States in 2004, Song *et al.* (2016) analyzed the chemical composition of 7 popular moist snuff products in the United States between 2007 and 2009, McAdam *et al.* (2013, 2019) performed two separate analyses examining different chemical constituents of 16 popular moist snuff products in the United States between 2008 and 2009, Stepanov *et al.* (2013) analyzed the chemical composition of 14 commonly available moist snuff products in the United States between 2010 and 2012, Tyx *et al.* (2022) analyzed the chemical composition of 37 commonly available moist snuff products in the United States in 2016, and Back *et al.* (2023) analyzed the chemical composition of 2 specifically sourced moist snuff products, one loose and the other pouched, within three weeks of obtaining the products, but the date range the product samples were obtained was not mentioned.

Of the studies reviewed, McAdam *et al.* (2013, 2019) and Back *et al.* (2023) were funded by the tobacco industry. Notably, both studies by McAdam *et al.* published separate chemical analyses on the same set of moist snuff product samples obtained from the United States and Sweden in 2008–2009, while Back *et al.* selected an extremely small sample size of 2 products tested, one for a loose moist snuff product, and the other for a pouched moist snuff product. In contrast, though Song *et al.* (2016) contributing author Peter Shields serves as an expert witness in tobacco company litigation on behalf of plaintiffs, the authors have not declared any conflicts of interest, and the robustness of the study design is clearly evident. In addition, Tyx *et al.* (2022) contributing author Lisa

Keong was provided support in the form of a salary from Battelle Analytical Services, though the authors have stated this did not influence the study design, data collection and analysis, decision to publish, or preparation of the manuscript. In contrast, the authors have reaffirmed that the commercial affiliation of one author does not alter their adherence to PLOS ONE journal policies, which is supported by the robust study design.

Harmonized time series for selected products that had been repeatedly independently analyzed for NNN and NNK (DWB) are shown in Figures 1–2; points reflect study-level summaries after unit/basis harmonization, with ND/<LOD/<LOQ/BQL values excluded, and year set to the midpoint for studies reporting a time range for product acquisition.

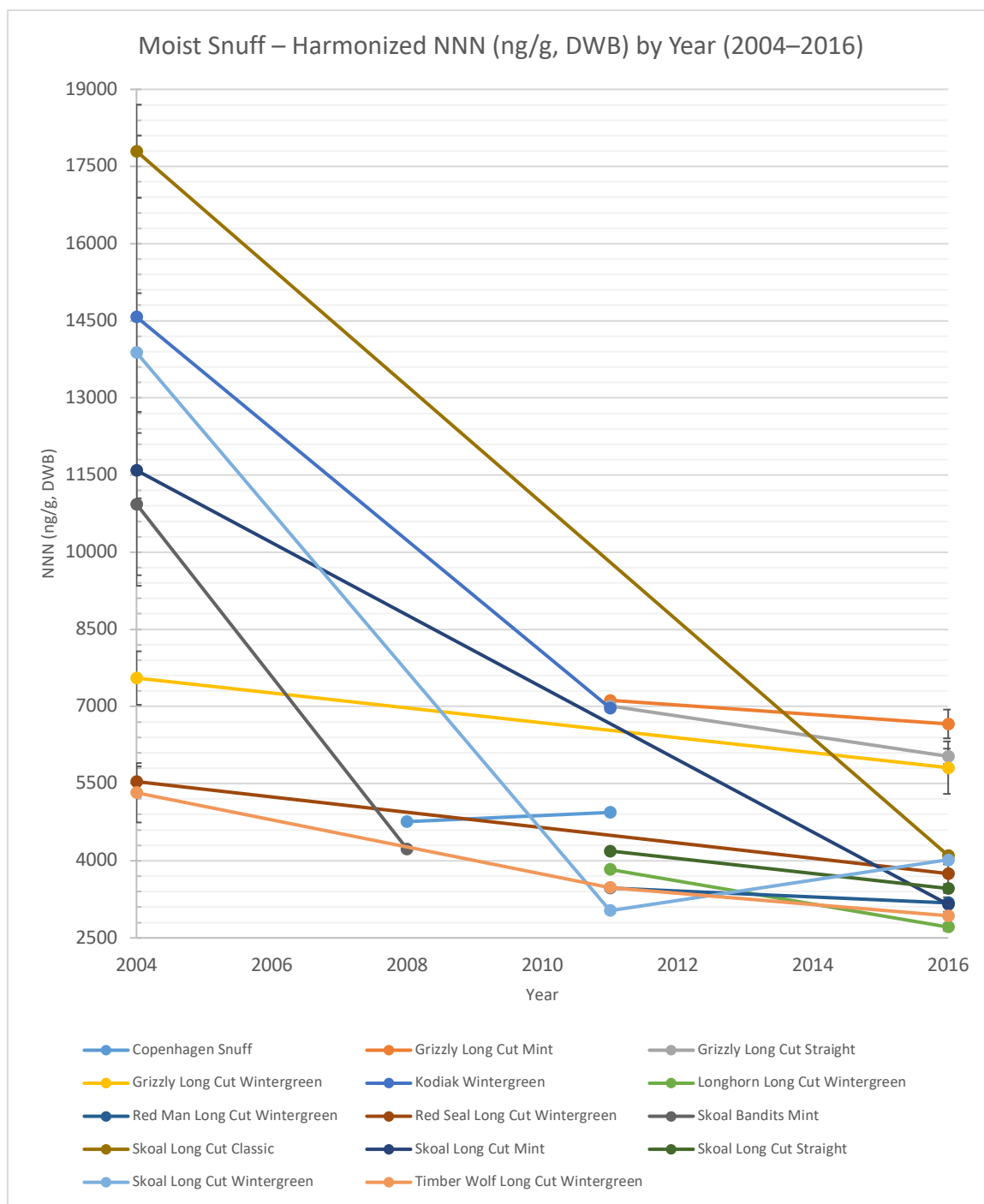


Figure 1. Moist Snuff – Harmonized NNN (ng/g, DWB) by Year (2004–2016).

Points summarize study-level means after unit/basis harmonization to DWB; ND/<LOD/<LOQ/BQL excluded. When studies reported acquisition windows, the year reflects the midpoint; error bars depict SD when available. Per-product results and precision rules are included in Appendix 2.

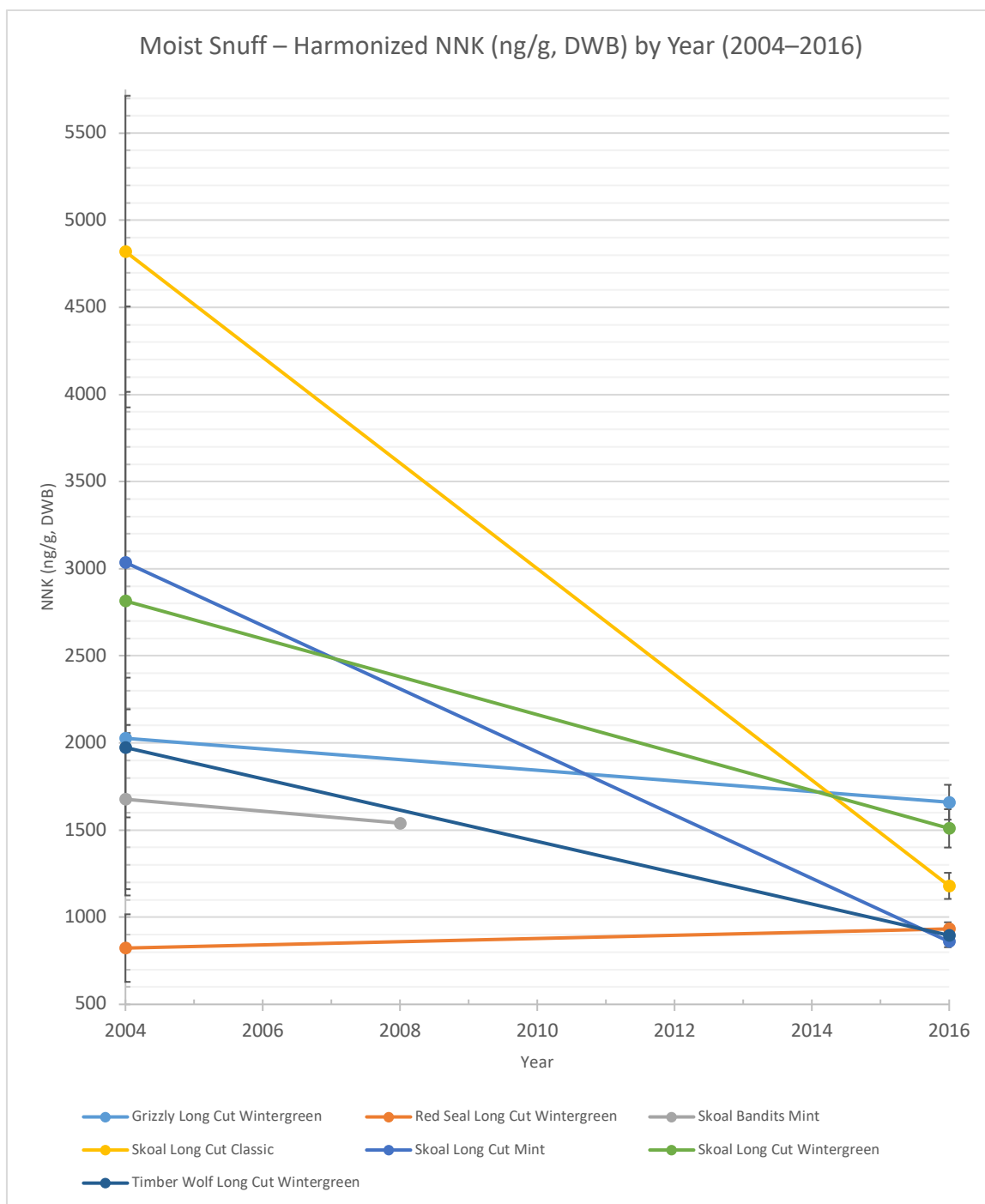


Figure 2. Moist Snuff – Harmonized NNK (ng/g, DWB) by Year (2004–2016).

Points summarize study-level means after unit/basis harmonization to DWB; ND/<LOD/<LOQ/BQL excluded. When studies reported acquisition windows, the year reflects the midpoint; error bars depict SD when available. Per-product results and precision rules are included in Appendix 2.

Consistent with the manufacturing process changes implemented ~2005 and subsequent regulatory focus on HPHCs, the harmonized time series in Figures 1–2 show a downward shift in TSNA levels (NNN and NNK) over 2004–2016 across independently repeatedly sampled American moist snuff brands. Although study designs and reporting conventions vary, the directionality of decline is robust to the harmonization rules applied (unit/basis conversion to DWB; exclusion of ND/<LOD/<LOQ/BQL), and the largest step-down is apparent in products sampled after ~2005, chronologically aligning with industry sanitation/bacteria-control protocols and, later, the FDA’s 2012 HPHC reporting requirements. From a public-health perspective, lower TSNA content reduces cumulative exposure among users; however, quantifiable TSNAs persist even in more recent products, underscoring that risk is reduced but not eliminated and that ongoing surveillance and further reductions remain warranted.

Over time, moist snuff products appear to have trended towards more basic formulations; this is likely due to the increased concentration of free nicotine formed as the pH increases, increasing bioavailability as the unionized nicotine which is then rapidly absorbed across the mucosal membranes of the oral cavity, ultimately resulting in more effective delivery of nicotine directly to the bloodstream. Overall TSNA levels appear to have decreased over time, with a significant decrease observed in products sampled after 2005, supporting the argument that the protocols introduced by the tobacco industry to sanitize fermentation vessels prior to use and inoculate batches with starter culture that did not contain detectable levels of nitrate reducing bacteria was effective. The increased focus on HPHCs also aligns with the timeline of the FDA mandating the reporting of levels of HPHCs in smokeless tobacco products in 2012. Although TSNA

and HPHC levels have decreased over the past two decades, it is still of great concern that product samples obtained as recently as 2016 all still contained quantifiable levels of TSNAs, heavy metals, and other HPHCs, supporting the IARC's initial decision to classify smokeless tobacco products as Group 1 carcinogens that cause cancers of the oral cavity, esophagus and pancreas which was then reaffirmed during subsequent reviews in 2007 and 2012.

Chemical Composition of Snus and Impact on Dental Health

Snus has rapidly grown in popularity in the United States with nearly exponential 10X growth from ~170,000 pounds sold in 2008 to ~1.6 million pounds in 2022 (Federal Trade Commission, 2023). With the increasing body of evidence suggesting that the manufacturing process of producing moist snuff from fermented fire-cured tobacco is correlated with higher TSNA content, snus is differentiated by being produced with air- or sun-cured tobacco which is pasteurized prior to packaging, and as a result, has been marketed by tobacco companies as a “low-TSNA” alternative to moist snuff (Rutqvist *et al.*, 2011; Song *et al.*, 2016). Though snus is a traditional Swedish smokeless tobacco product with usage dating back to the early 1800s, the modern pouched form factor was introduced in the early 1970s in Sweden and the United States (Hendlin *et al.*, 2017; Swedish Match AB, 2013). Though the pouched form factor was originally introduced to the American market almost half a century ago, popularity only began to surge in the mid-2000s, with the U.S. Federal Trade Commission introducing a distinct category for the reporting of snus sales in 2008 and has continued to increase in popularity since then.

Due to the rising popularity of snus and increasing regulatory scrutiny of smokeless tobacco products, the chemical composition of snus has been well

characterized, with multiple studies quantifying and publishing levels of TSNAs and HPHCs detected in popular brands and product lines at different timepoints over the past two decades (Azzopardi *et al.*, 2021; Back *et al.*, 2023; Lawler *et al.*, 2020; McAdam *et al.*, 2013, 2019; Song *et al.*, 2016; Stepanov *et al.*, 2012, 2013). When examining the analyses of snus samples chronologically, Song *et al.* (2016) analyzed the chemical composition of 7 popular American snus products and 3 Swedish snus products obtained between 2007 and 2009, McAdam *et al.* (2013, 2019) performed two separate analyses examining different chemical constituents of 10 Swedish loose snus brands and 22 Swedish pre-portioned snus brands obtained between 2008 and 2009, Stepanov *et al.* (2012, 2013) performed two separate analyses examining different chemical constituents of 8 American snus product lines obtained between July and September of 2010, Lawler *et al.* (2020) analyzed 56 Northern European and 8 American snus products purchased between 2013 and 2014, Azzopardi *et al.* (2021) analyzed 3 Scandinavian snus products obtained between 2018 and 2020, and Back *et al.* (2023) analyzed the chemical composition of 1 specifically sourced Swedish snus product within three weeks of obtaining the product, but the date range the product samples were obtained was not mentioned.

Of the studies reviewed, McAdam *et al.* (2013, 2019), Azzopardi *et al.* (2021) and Back *et al.* (2023) were funded by the tobacco industry. Notably, both studies by McAdam *et al.* published separate chemical analyses on the same set of Swedish snus product samples obtained in 2008–2009, while Azzopardi *et al.* and Back *et al.* selected extremely small sample sizes of 3 Scandinavian snus products tested and 1 Swedish snus product tested respectively. Despite Peter Shields serving as an expert witness for

plaintiffs in tobacco litigation, Song *et al.* (2016) declared no conflicts of interest, and the study design remains robust.

Figures 3–4 plot DWB-harmonized NNN and NNK for snus over 2008–2011 from studies that reported per-product DWB values or data convertible to DWB. Stratum-level DWB LS-means (e.g., Lawler *et al.*, 2020) and very small DWB sample sets (e.g., Azzopardi *et al.*, 2021; Back *et al.*, 2023) were not trended due to a lack of comparable data.

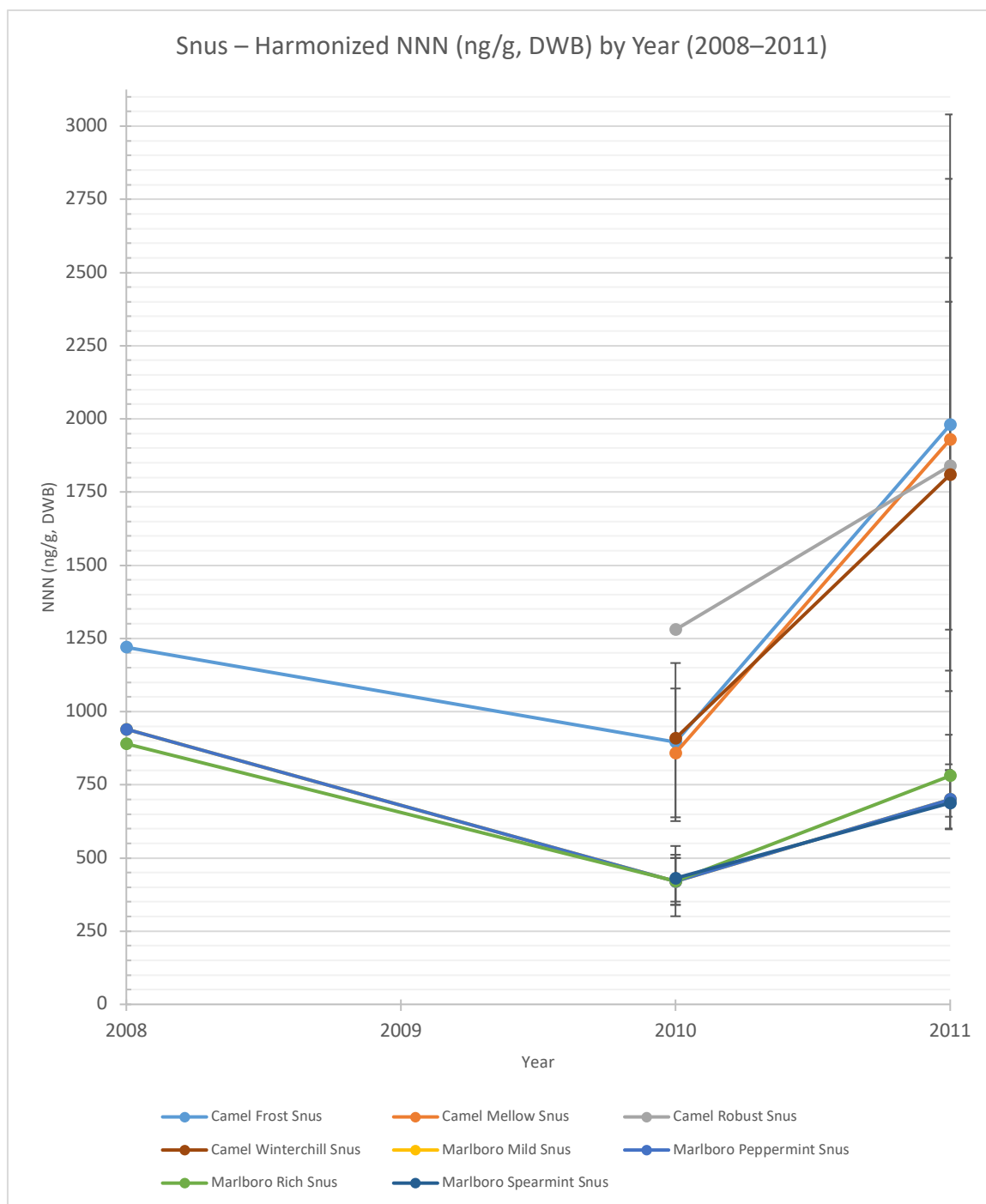


Figure 3. Snus – Harmonized NNN (ng/g, DWB) by Year (2008–2011).

Points summarize study-level means after unit/basis harmonization to DWB; ND/<LOD/<LOQ/BQL excluded. When studies reported acquisition windows, the year reflects the midpoint; error bars depict SD when available. Per-product results and precision rules are included in Appendix 3.

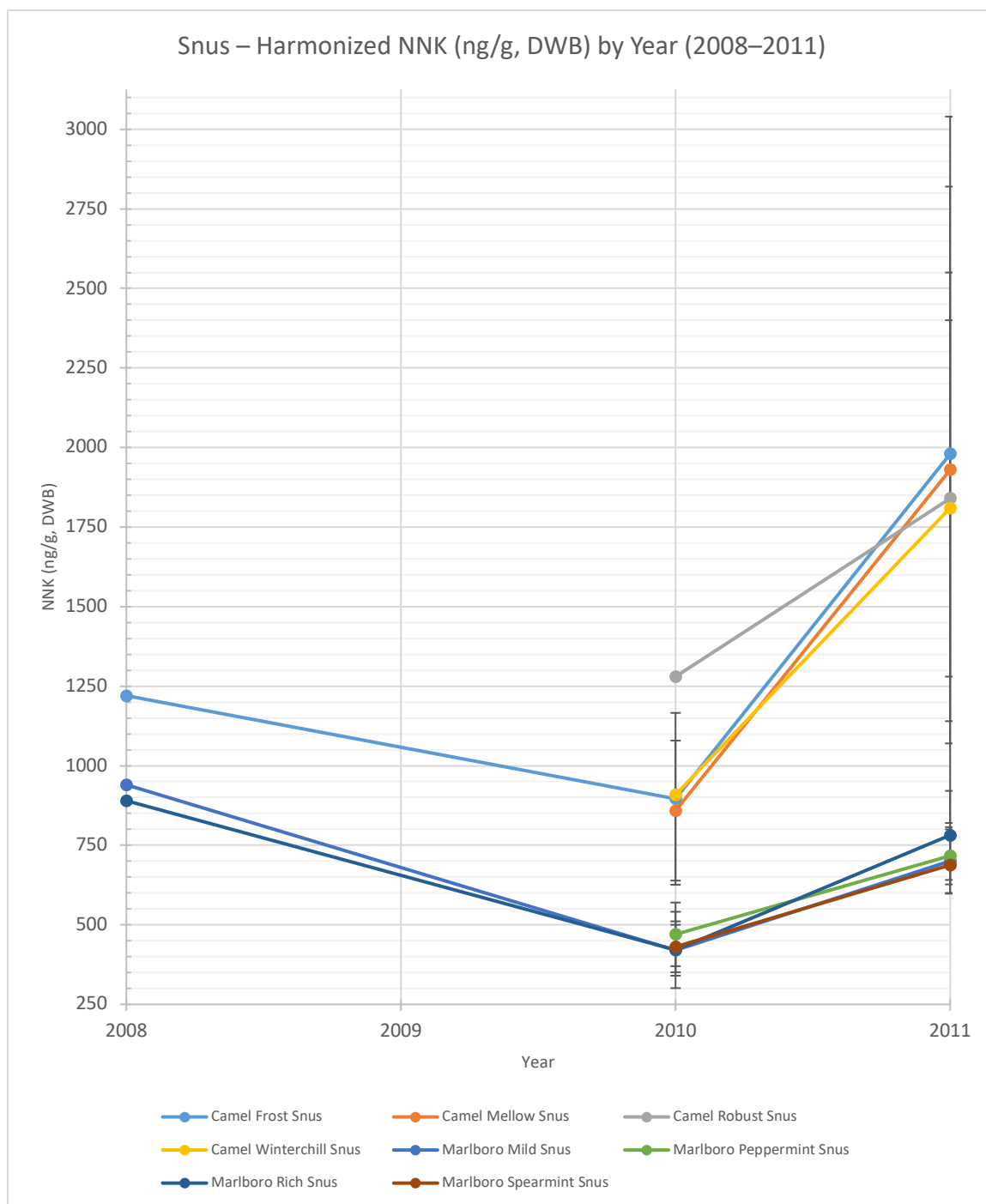


Figure 4. Snus – Harmonized NNK (ng/g, DWB) by Year (2008–2011).

Points summarize study-level means after unit/basis harmonization to DWB; ND/<LOD/<LOQ/BQL excluded. When studies reported acquisition windows, the year reflects the midpoint; error bars depict SD when available. Per-product results and precision rules are included in Appendix 3.

Though not as significant as observed with moist snuff, overall TSNA levels in snus products also appear to have decreased over time; while levels of TSNA, HPHCs and other toxic chemicals in snus products have consistently been found to be lower than similar moist snuff alternatives, the consistent observation of quantifiable levels of TSNA, heavy metals, and other HPHCs in samples of snus products obtained as recently as 2018–2020 should still be of concern to consumers, public health officials and healthcare practitioners alike. Within the narrower 2008–2011 window for which comparable per-product DWB data are available, Figures 3–4 indicate a modest downward shift in NNN and NNK among repeatedly sampled snus products. This trend observed is consistent with process controls used in snus manufacturing and with broader regulatory attention to HPHCs, but the short time span, study heterogeneity, and the fact that aggregated least-squares means (LS-means) (e.g., Lawler *et al.*, 2020) were not trended argue for cautious interpretation and continued monitoring. As expected with repeated application of carcinogens, toxins, and irritants on sensitive mucosal epithelia, chronic usage of snus results in damage to the oral cavity; habitual users tend to develop characteristic SILs at the site of administration of the product, but symptoms can include moderate to severe epithelial dysplasia as well as the possibility of irreversible gingival retraction (Frithiof *et al.*, 1983; Kopperud *et al.*, 2023; Roosaar *et al.*, 2006; Zatterstrom *et al.*, 2004).

Chemical Composition of NPPs and Impact on Dental Health

Large tobacco companies have recently introduced the novel product categories of orally administered pre-portioned spitless TDN and SyN pouch products, which have since quickly surged in popularity among American adolescents and young adults (Liu &

Halpern-Felsher, 2024; Robichaud *et al.*, 2020). Just as snus was originally marketed as a “low-TSNA” alternative to moist snuff in the mid-2000s, these novel flavored nicotine pouch products are increasingly being marketed to consumers as a “tobacco-free” or “zero exposure to tobacco-specific nitrosamines (TSNAs)” alternative to snus and other commonly consumed tobacco products (Alalwan *et al.*, 2024; Liu & Halpern-Felsher, 2024; Robichaud *et al.*, 2020). Introduced to the American market in 2016, nicotine pouch products grew five-fold in popularity in the 2-year period between Q4 2019 and Q1 2022, where overall sales increased from 126.06 million units from August – December 2019 to 808.14 million units sold from January – March 2022 (Majmundar *et al.*, 2022; Zamarripa *et al.*, 2025). Compared to the massive rise in popularity of snus with pounds sold increasing almost by a factor of 10X over the 14-year period between 2008 and 2022, the rapid adoption of nicotine pouch products by the American public is of great concern to public health officials and healthcare practitioners alike.

Due to the recent introduction of the oral nicotine pouch product category to the market, the chemical composition of nicotine pouch products has not been extensively studied with only a few studies quantifying and publishing levels of TSNAs, HPHCs and other suspected toxins and irritants observed in popular brands over the past few years (Azzopardi *et al.*, 2021; Back *et al.*, 2023; Mallock *et al.*, 2024; Stanfill *et al.*, 2021). When examining the analyses of nicotine pouch product samples chronologically, Azzopardi *et al.* (2021) analyzed the chemical composition of 4 nicotine pouch products from a single manufacturer obtained from Scandinavian markets between 2018 and 2020, Stanfill *et al.* (2021) analyzed 37 nicotine pouch products purchased in the United States in 2019, Mallock *et al.* (2024) analyzed the chemical composition of 46 nicotine pouch

products from 20 manufacturers obtained from Germany in 2021, and Back *et al.* (2023) analyzed the chemical composition of 2 specifically sourced nicotine pouch products from one manufacturer within three weeks of obtaining the products from Sweden, but the date range the product samples were obtained was not mentioned.

Of the studies reviewed, Azzopardi *et al.* (2021) and Back *et al.* (2023) were funded by the tobacco industry. Notably, both the studies by Azzopardi *et al.* and Back *et al.* each selected and tested an extremely small sample sizes of 4 nicotine pouch products available in Scandinavian markets and 2 nicotine pouch products obtained from Sweden respectively.

Trend plots were not generated for NPPs because TSNAs were frequently non-detect and reporting bases varied (e.g., ng/pouch vs. ng/g); see Tables 16–18 for cross-sectional summaries.

Despite claims of being a “zero exposure to tobacco-specific nitrosamines (TSNAs)” alternative to snus, recent industry-sponsored and non-industry studies have refuted this claim with empirical evidence; Azzopardi *et al.* (2021) observed the presence of TSNAs below quantification levels in the 4 Scandinavian nicotine pouch products tested between 2018 and 2020, while Mallock *et al.* (2024) demonstrated that 26 of the 46 nicotine pouch products obtained from Germany in 2021 had TSNAs levels above the detection limit. Moreover, the repeated detection of TSNAs, HPHCs, heavy metals, toxicants, and other irritants in European nicotine pouch products should be of great concern to the general public, while the notable lack of chemical composition data from American nicotine pouch products further adds to the well-justified concern over the long-term health effects of this novel category of smokeless tobacco products. Finally,

due to the recent introduction of nicotine pouch products as a novel product category competing with more traditional pre-portioned snus, there is a notable lack of data on the dental health effects of long-term and prolonged habitual use of these products, but due to the similarities in method of administration, it is likely that localized gingival recession will develop as documented in habitual users of traditional pre-portioned snus, while severe long-term use could result in symptoms ranging in severity from localized inflammation, dysbiosis, alveolar bone loss and dysregulation of microRNAs which have been shown to impact the pathogenesis of periodontal disease (Jackson *et al.*, 2023; Ye and Rahman, 2023).

Evaluation of Snus and NPPs as Harm Reduction Measures

Compared to traditional loose and pouched moist snuff products, snus and nicotine pouch products do appear to contain lower concentrations of TSNAs, HPHCs, heavy metals, toxicants and irritants; however, despite lower concentrations, detectable levels of these known carcinogens and toxic chemicals have still consistently been observed in both categories of newer smokeless tobacco products. Prior to the introduction of the novel nicotine pouch product category, multiple studies have attempted to distance snus usage from the development of tobacco-related comorbidities commonly observed; there have been multiple pooled cohort studies from Swedish populations claiming that the long-term use of snus is not a significant risk factor for developing oral cancers, while additional studies on European demographics have suggested that there is no clear association between snus usage and other tobacco-related comorbidities for never-smokers, while other studies have suggested increased risk for pancreatic cancer in never-smokers (Araghi *et al.*, 2021; Lee, 2011; Luo *et al.*, 2007;

Roosaar *et al.*, 2006). As a result, snus even gained interest as a potential smoking cessation aid in these and other retrospective cohort studies on Swedish populations including evaluation via a randomized, double-blind, placebo-controlled clinical trial in Serbian populations suggesting that participants in the snus group were more likely to quit smoking completely (Foulds *et al.*, 2003; Gilljam & Galanti, 2003; Joksic *et al.*, 2011; Rodu *et al.*, 2002; Sohlberg & Wennberg, 2020).

However, most of these studies have included data from the Swedish construction worker cohort study, where from 1969 through 1992 all Swedish construction workers were offered preventative health check-ups and data was compiled centrally, including each participant's National Identification Number, a personal identifier included each participant's date of birth. Multiple retroactive meta-analyses of this original dataset have been conducted, including from those with conflicts of interest with the tobacco industry, selecting for and exploring various confounding factors including but not limited to: sex, age, BMI, concurrent cigarette and snus use, ex-cigarette usage but continued snus use, other tobacco-related comorbidities as justifiable exclusion criteria (Lee, 2011; Lee & Hamling, 2009; Luo *et al.*, 2007; Nyrén *et al.*, 1996; Wilson *et al.*, 2016). Overall, the lack of feasibility of conducting more long-term epidemiological studies coupled with the repeated publications of meta-analyses intentionally excluding large swaths of the original sample set has ultimately served to obfuscate any clear links between long-term snus use and commonly observed tobacco-related comorbidities. Still, public health officials and health practitioners alike can be comforted by the fact that smokeless tobacco products themselves, including snus products, have been classified as Group 1 carcinogens by the WHO's IARC.

Though snus has been classified as a smokeless tobacco product, nicotine pouch products do not fall under the WHO's IARC classification of smokeless tobacco products; despite this, the FDA still considers nicotine pouch products as tobacco products and regulates their production and sale within the United States. Furthermore, while it has been suggested that novel nicotine pouch products have lower abuse liabilities as they have been shown to deliver nicotine more slowly and in lower quantities than traditional tobacco products such as cigarettes, the validity of this claim is still actively debated as users have also reported that the slower and less potent delivery of nicotine makes these products significantly less satisfying and rewarding, ultimately helping relieve cigarette craving symptoms but not as much as cigarettes themselves (Henningfield & Keenan, 1993; Jackson *et al.*, 2023; Rensch *et al.*, 2021). Despite the possible potential for lower abuse liabilities, nicotine pouch products are fundamentally different from oral nicotine replacement therapies such as nicotine gum; according to Philip Morris International in the article All about: Snus, snuff, and nicotine pouches (n.d.):

“While nicotine gum is widely recognized as a cessation aid, nicotine pouches are not, and should be used by adult smokers who would otherwise continue smoking cigarettes.”

Conclusion

Across two decades of sampling, detectable toxicants persist in all spitless tobacco categories examined. Conventional moist snuff continues to exhibit the highest and most variable TSNA (NNN, NNK), despite post-2005 manufacturing changes that appear to have reduced levels relative to early 2000s products. Snus typically presents lower TSNA than moist snuff but often at higher pH, yielding substantial free-nicotine

fractions. Modern nicotine pouch products (NPPs) are chemically heterogeneous; most products are basic with high free-nicotine percentages, and while TSNA's are frequently non-detect, multiple datasets report detectable NNN/NNK in a subset of products. Together, these patterns support a risk continuum rather than a risk-free category. Repeated application of basic, nicotine-containing pouches at the gingival margin plausibly promotes localized mucosal injury, gingival recession, and periodontal risk, consistent with findings in long-term snus users; due to the recent introduction of NPPs, long-term oral-health outcomes have yet to be characterized. Lower TSNA's in snus and some NPPs may reduce, but not eliminate, carcinogen exposure compared with conventional moist snuff, but quantifiable toxicants and irritants still remain across categories. Overall, this research reinforces the need for more research examining the long-term use of NPPs to better characterize the impact on dental health and highlights the efficacy and need for more regulation to make products safer, as well as education for consumers and the general public to increase awareness of the potential harms of all smokeless tobacco and nicotine pouch products, including those positioned as harm-reduction alternatives. Clinically, a brief chairside assessment of pouch use, site-specific mucosal inspection, and basic pH/nicotine education are pragmatic steps to mitigate localized oral harm while broader surveillance and regulation evolve.

Appendix 1.

Sensitivity Analyses & Detailed Harmonization Methods

This Appendix documents sensitivity analyses and study-specific harmonization steps referenced in Chapter II: Materials & Methods, Data Harmonization. Table 19 quantifies the impact of pK_a choice on derived % free nicotine across the observed pH range. Tables 20–21 summarize per-study harmonization/derivation actions and the sensitivity of Richter *et al.* (2008) NNN SD values to number of significant figures.

Table 19. Sensitivity Analysis of pK_a Assumptions on Derived % Free Nicotine.

pH	Derived Free Nicotine (%) $pK_a = 8.02$	Derived Free Nicotine (%) $pK_a = 7.90$	Δ (%)
5.5	0.3	0.4	0.1
6.5	2.9	3.8	0.9
7	8.7	11.2	2.5
7.5	23.2	28.5	5.3
8	48.8	55.7	6.9
8.5	75.1	79.9	4.8
9.5	96.8	97.5	0.7
10.5	99.7	99.7	0

Across the pH range of products in this review (5.5–10.5), using a pK_a of 7.90 instead of 8.02 for the Henderson-Hasselbalch approximation-derived % Free Nicotine values results in a shift of $\leq 6.9\%$, with the largest differences near pH 8.0; qualitative comparisons remain unchanged, and conclusions are not affected.

Table 20. Study-Specific Harmonization and Derivation Actions Performed.

Study & Product Category	Harmonization	Derivation	Notable Exceptions
Richter <i>et al.</i> (2008) Moist Snuff	WWB $\Rightarrow$ DWB	—	NNN SDs standardized to 4 sig figs
Song <i>et al.</i> (2016) Moist Snuff	$\mu\text{g/g} \Rightarrow \text{ng/g}$	$\%F_N = (F_N \div T_N) \times 100\%$	—
McAdam <i>et al.</i> (2013, 2019) Moist Snuff	2019 T_N WWB $\Rightarrow$ DWB using 2013 $\%M$	HH $\Rightarrow \%F_N$ $F_N = T_N \times (\%F_N \div 100\%)$	Cross-paper batch pairing for moisture $\Rightarrow$ nicotine.
Stepanov <i>et al.</i> (2013) Moist Snuff	WWB $\Rightarrow$ DWB $\mu\text{g/g} \Rightarrow \text{ng/g}$	—	Focus on (S)-NNN
Tyx <i>et al.</i> (2022) Moist Snuff	WWB $\Rightarrow$ DWB	—	—
Back <i>et al.</i> (2023) Moist Snuff	WWB $\Rightarrow$ DWB $\mu\text{g/g} \Rightarrow \text{ng/g}$	$\%F_N = (F_N \div T_N) \times 100\%$	—
Song <i>et al.</i> (2016) Snus	$\mu\text{g/g} \Rightarrow \text{ng/g}$	$\%F_N = (F_N \div T_N) \times 100\%$	—
McAdam <i>et al.</i> (2013, 2019) Snus	2019 T_N WWB $\Rightarrow$ DWB using 2013 $\%M$	HH $\Rightarrow \%F_N$ $F_N = T_N \times (\%F_N \div 100\%)$	Cross-paper batch pairing for moisture $\Rightarrow$ nicotine.
Stepanov <i>et al.</i> (2012) Snus	$\mu\text{g/g} \Rightarrow \text{ng/g}$	—	—
Stepanov <i>et al.</i> (2014) Snus	$\mu\text{g/g} \Rightarrow \text{ng/g}$	—	—
Lawler <i>et al.</i> (2020) Snus	WWB LS-means $\Rightarrow$ DWB using stratum-specific LS-mean $\%M$	HH $\Rightarrow \%F_N$ (stratum-specific) $F_N = T_N \times (\%F_N \div 100\%)$ (stratum-specific)	Reported as aggregated region $\times$ form-factor $\times$ strength strata

Study & Product Category	Harmonization	Derivation	Notable Exceptions
Azzopardi <i>et al.</i> (2021) Snus	WWB $\Rightarrow$ DWB %wt $\Rightarrow$ mg/g	HH $\Rightarrow$ %F _N $F_N = T_N \times (\%F_N \div 100\%)$	B[a]P <LOQ treated as missing
Back <i>et al.</i> (2023) Snus	WWB $\Rightarrow$ DWB $\mu\text{g/g} \Rightarrow \text{ng/g}$	%F _N = $(F_N \div T_N) \times 100\%$	B[a]P <LOQ treated as missing
Azzopardi <i>et al.</i> (2021) Nicotine Pouch	%wt $\Rightarrow$ mg/g	HH $\Rightarrow$ %F _N $F_N = T_N \times (\%F_N \div 100\%)$	NNN, NNK, B[a]P <LOQ treated as missing
Stanfill <i>et al.</i> (2021) Nicotine Pouch	—	%F _N = $(F_N \div T_N) \times 100\%$	—
Mallock <i>et al.</i> (2024) Nicotine Pouch	ng/pouch $\Rightarrow$ ng/g	$F_N = T_N \times (\%F_N \div 100\%)$	Product names anonymized NNN, NNK ND/BQL treated as missing
Back <i>et al.</i> (2023) Nicotine Pouch	—	%F _N = $(F_N \div T_N) \times 100\%$	Extremely low detection frequency for TSNA NNN, NNK, B[a]P <LOQ treated as missing

Summary of harmonization and derivation calculations performed by study; referenced terms are defined as follows: WWB: wet-weight basis; DWB: dry-weight basis; %F_N: % Free nicotine out of total nicotine; T_N: Total nicotine (mg/g); F_N: Free nicotine (mg/g); HH: Henderson-Hasselbalch approximation; %M: wet-weight basis moisture mass-percent value .

Table 21. Sensitivity Analysis of Harmonized NNN SD Values by Richter *et al.* (2008) to Number of Significant Figures.

Originally Reported SD Value	4-sf (used)	3-sf (test)	Absolute Δ	Relative Δ
149.2	149.2	149	0.2	0.13%
642	642	642	0	0.00%
16,049	16,050	16,000	50	0.31%

Impact of using 3 vs. 4 significant figures on harmonized NNN SD values originally reported by Richter et al. (2008); absolute and relative differences are $\leq 0.31\%$.

Appendix 2.

Harmonized Detailed Results – Moist Snuff Products

Values are means $\pm$ SD; units are mg/g for nicotine and ng/g for TSNA/B[a]P; pH matches the level of precision originally reported. All moist snuff values are on a dry-weight basis (DWB) after unit/basis harmonization; ND/<LOD/<LOQ/BQL entries are displayed as text and excluded from summary statistics. Rounding follows the rules defined in Chapter II: Materials & Methods, Data Harmonization.

Table 22. Moist Snuff Detailed Results – Richter *et al.* (2008).

Product Name	pH (mean $\pm$ SD)	NNN (mean ng/g $\pm$ SD)	NNK (mean ng/g $\pm$ SD)	Total Nicotine (mean mg/g $\pm$ SD)	Free Nicotine (mg/g)	Free Nicotine (%)
W.B. Cut Regular	5.71 $\pm$ 0.01	6245 $\pm$ 299.8	666 $\pm$ 92.6	37.36 $\pm$ 0.22	0.18	0.5
Red Seal Fine Cut	7.55 $\pm$	5565 $\pm$	1248 $\pm$	30.39 $\pm$	7.69	25.3
Wintergreen	0.00	465.3	70.9	0.22		
Timber Wolf Long	7.62 $\pm$	5322 $\pm$	1974 $\pm$	30.66 $\pm$	8.77	28.7
Cut Wintergreen	0.02	577.4	401	0.28		
Timber Wolf Fine	7.41 $\pm$	19189 $\pm$	4592 $\pm$	27.93 $\pm$	5.52	19.8
Cut Regular	0.01	3157	1290	0.17		
Timber Wolf	7.41 $\pm$	6254 $\pm$	1998 $\pm$	30.17 $\pm$	10.57	34.9
Straight Regular	0.01	2451	390	0.31		
Skoal Long Cut	7.52 $\pm$	16409 $\pm$	3740 $\pm$	29.16 $\pm$	6.99	24.0
Berry Blend	0.02	3390	1290	0.15		
Skoal Straight Cut	7.52 $\pm$	19439 $\pm$	7386 $\pm$	29.15 $\pm$	9.76	33.9
Regular	0.02	2806	2070	0.29		
Skoal Key	7.90 $\pm$	91122 $\pm$	21306	28.24 $\pm$	12.16	43.1
	0.01	34370	$\pm$ 841	0.22		
Grizzly Fine Cut	7.81 $\pm$	18810 $\pm$	3662 $\pm$	28.51 $\pm$	10.89	38.1
Regular	0.00	1902	323	0.20		
Skoal Fine Cut	7.66 $\pm$	18015 $\pm$	4358 $\pm$	28.18 $\pm$	8.56	30.9
Wintergreen	0.01	3788	1230	0.38		

Product Name	pH (mean ± SD)	NNN (mean ng/g ± SD)	NNK (mean ng/g ± SD)	Total Nicotine (mean mg/g ± SD)	Free Nicotine (mg/g)	Free Nicotine (%)
Red Seal Fine Cut	8.00 ±	30810 ±	8486 ±	28.64 ±	13.94	49.7
Regular	0.02	9794	1990	0.38		
Copenhagen Long	7.91 ±	4760 ±	1968 ±	28.06 ±	12.25	44.0
Cut Regular	0.01	1247	1900	0.19		
Timber Wolf Fine	7.22 ±	6089 ±	2248 ±	27.50 ±	3.73	13.7
Cut Wintergreen	0.01	1038	82.5	1.10		
Red Seal Long Cut	7.67 ±	5539 ±	823 ±	27.95 ±	8.69	31.0
Wintergreen	0.01	296.5	194	0.43		
Copenhagen	7.73 ±	8411 ±	2025 ±	27.30 ±	9.20	34.2
Regular	0.01	637.4	460	0.61		
Skoal Long Cut	7.77 ±	30045 ±	7340 ±	27.47 ±	9.83	36.0
Regular	0.00	1354	113	0.44		
Timber Wolf Cool	7.84 ±	5607 ±	1432 ±	28.00 ±	11.05	39.5
Wintergreen	0.00	1986	877	0.38		
Skoal Long Cut	7.75 ±	13882 ±	2815 ±	27.33 ±	9.48	35.5
Wintergreen	0.01	1154	1690	0.65		
Skoal Long Cut	7.83 ±	17796 ±	4820 ±	27.61 ±	10.85	39.3
Classic	0.02	906.8	894	0.52		
Skoal Long Cut	7.49 ±	13158 ±	3331 ±	26.67 ±	6.10	23.4
Cherry	0.02	2887	2020	0.48		
Renegades	6.70 ±	5640 ±	1619 ±	26.40 ±	1.19	4.5
Wintergreen	0.01	526.2	186	0.38		
Copenhagen Black	7.82 ±	9664 ±	4965 ±	27.02 ±	10.50	38.9
Bourbon	0.01	1027	4760	0.16		
Redwood Regular	7.44 ±	16565 ±	4828 ±	25.46 ±	5.33	21.0
	0.01	2823	578	0.30		
Skoal Long Cut	7.85 ±	11592 ±	3036 ±	25.27 ±	10.19	40.3
Mint	0.01	2245	979	0.27		
Silver Creek Fine	7.08 ±	12544 ±	6171 ±	25.23 ±	2.62	10.3
Cut Wintergreen	0.00	514.7	254	0.64		
Rooster Long Cut	7.85 ±	11559 ±	2395 ±	25.13 ±	10.11	40.3
Icy Mint	0.01	1280	2030	0.31		
Rooster Long Cut	7.86 ±	24354 ±	6002 ±	24.31 ±	9.87	40.6
Bold Wintergreen	0.01	1265	315	0.16		
Silver Creek Long	6.64 ±	21379 ±	8765 ±	20.81 ±	0.83	4.0
Cut Straight	0.01	2564	1130	0.29		
Regular						
Silver Creek Long	7.08 ±	5510 ±	1911 ±	20.67 ±	2.11	10.2
Cut Wintergreen	0.01	508.5	67.5	0.31		
Kodiak Straight Cut	8.29 ±	9403 ±	2410 ±	20.69 ±	13.42	65.1
Regular	0.01	1728	1180	0.20		

Product Name	pH (mean ± SD)	NNN (mean ng/g ± SD)	NNK (mean ng/g ± SD)	Total Nicotine (mean mg/g ± SD)	Free Nicotine (mg/g)	Free Nicotine (%)
Kodiak Ice Long Cut Regular	8.62 ± 0.06	9722 ± 387.3	2635 ± 207	20.94 ± 0.18	16.69	79.9
Kodiak Wintergreen	8.49 ± 0.02	14575 ± 3526	3672 ± 1060	20.13 ± 0.22	15.03	75.6
Grizzly Long Cut Wintergreen	8.42 ± 0.03	7553 ± 520.0	2027 ± 76.8	19.54 ± 0.17	13.95	71.5
Cougar Long Cut Natural	8.16 ± 0.03	8594 ± 798.1	2683 ± 438	19.45 ± 0.13	11.21	58.0
Cougar Long Cut Wintergreen	7.44 ± 0.02	19565 ± 2266	3473 ± 135	18.24 ± 0.34	3.83	20.8
Cougar Regular	8.07 ± 0.01	9907 ± 339.0	2284 ± 89.5	18.39 ± 0.23	9.72	52.9
Skoal Bandits Mint	6.72 ± 0.00	10935 ± 1383	1677 ± 516	13.77 ± 0.25	0.67	4.8
Skoal Bandits Wintergreen	6.84 ± 0.00	8754 ± 215.6	1444 ± 389	11.98 ± 0.19	0.75	6.3
Hawken Rough Wintergreen	5.54 ± 0.01	4412 ± 262.0	1043 ± 332	6.09 ± 0.03	0.01	0.3
Min	5.54	4412	666	6.09	0.01	0.3
Max	8.62	91122	21306	37.36	16.69	79.9
Median	7.72	10935	2683	27.02	9.48	34.2
Mean	7.55	14479	3827	24.76	8.06	32.6

Harmonized results for parameters of interest of moist snuff products analyzed by Richter et al. (2008); all products analyzed were obtained in 2004. Results originally reported in WWB; DWB values displayed were calculated using reported Moisture % values as described in Chapter II: Materials & Methods, Data Harmonization.

Table 23. Moist Snuff Detailed Results – Song et al. (2016).

Product Name	pH	NNN ^a (ng/g)	NNK ^a (ng/g)	B[a]P (ng/g)	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine ^b (%)
Husky Long Cut Straight	7.50	4860	1630	62.42	27.43	6.362	23.19
Grizzly Fine Cut Wintergreen	8.44	5820	3040	101.27	17.84	12.928	72.45
Timber Wolf Fine Cut Natural	7.66	5030	1040	106.73	26.83	8.153	30.39

Product Name	pH	NNN ^a (ng/g)	NNK ^a (ng/g)	B[a]P (ng/g)	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine ^b (%)
Copenhagen Mid-Cut Black Bourbon Flavoured	7.58	2930	980	75.25	25.76	6.862	26.64
Copenhagen Pouches	8.13	3670	960	84.27	22.20	12.497	56.30
Copenhagen Snuff	7.64	4760	1630	81.60	26.31	7.740	29.42
Skoal Bandits Mint	7.87	4230	1540	32.71	25.02	10.371	41.45
Min	7.50	2930	960	32.71	17.84	6.362	23.19
Max	8.44	5820	3040	106.73	27.43	12.928	72.45
Median	7.66	4760	1540	81.60	25.76	8.153	30.39
Mean	7.83	4470	1550	77.75	24.48	9.273	39.98

Summary of key analytes for moist snuff products analyzed by Song et al. (2016); all products analyzed were obtained between 2007–2009. All results originally reported in DWB.

^a Results originally reported in µg/g.

^b Free Nicotine (%) calculated from reported Free Nicotine (mg/g) and Total Nicotine (mg/g) content as described in Chapter II: Materials & Methods, Data Harmonization.

Table 24. Moist Snuff Detailed Results – McAdam et al. (2013, 2019).

Product Name	pH (mean ± SD)	B[a]P ^a (mean ng/g ± SD)	Total Nicotine ^b (mg/g)	Free Nicotine ^c (mg/g)	Free Nicotine ^d (%)
Copenhagen Long Cut	8.1 ± 0.03	74.00 ± 2.80	23.3	13	54.6 ± 1.7
Copenhagen Long Cut Straight	8.2 ± 0.01	92.00 ± 3.90	18.9	11	60.2 ± 0.6
Grizzly Long Cut Natural	8.1 ± 0.02	100.00 ± 1.00	35.2	19	54.6 ± 1.1
Husky Fine Cut Natural	8.0 ± 0.01	68.80 ± 2.90	28.4	14	48.8 ± 0.6
Husky Long Cut Straight	8.1 ± 0.01	35.80 ± 2.80	26.5	14	54.6 ± 0.6
Husky Wintergreen	7.5 ± 0.03	62.40 ± 3.70	28.6	6.6	23.2 ± 1.2
Kayak Long Cut Straight	7.1 ± 0.02	86.30 ± 1.00	23.9	2.6	10.7 ± 0.4

Product Name	pH (mean ± SD)	B[a]P ^a (mean ng/g ± SD)	Total Nicotine ^b (mg/g)	Free Nicotine ^c (mg/g)	Free Nicotine ^d (%)
Kodiak Long Cut Straight	8.2 ± 0.02	150.00 ± 3.00	24.3	15	60.2 ± 1.1
Kodiak Wintergreen	8.4 ± 0.01	167.00 ± 7.00	22.6	16	70.6 ± 0.5
Silver Creek	7.0 ± 0.03	97.20 ± 3.80	23.7	2.1	8.7 ± 0.5
Skoal Straight	7.8 ± 0.01	61.00 ± 8.60	30.2	11	37.6 ± 0.5
Timber Wolf Fine Cut Natural	8.0 ± 0.00	85.70 ± 2.20	26.2	13	48.8 ± 0.0
Timber Wolf Long Cut Straight	8.0 ± 0.01	91.30 ± 2.00	30.0	15	48.8 ± 0.6
Marlboro Original Long Cut	7.9 ± 0.01	76.30 ± 3.70	28.2	12	43.1 ± 0.6
Red Seal Fine Cut Natural	7.8 ± 0.00	74.70 ± 2.10	29.2	11	37.6 ± 0.0
Red Seal Long Cut Natural	7.9 ± 0.02	76.50 ± 1.10	28.1	12	43.1 ± 1.1
Min	7.0	35.80	18.9	2.1	8.7
Max	8.4	167.00	35.2	19	70.6
Median	8.0	81.10	27.3	13	48.8
Mean	7.9	87.44	26.7	12	44.1

Summary of key analytes for moist snuff products analyzed by McAdam et al. (2013, 2019); products analyzed were obtained between 2008–2009.

^a Results originally reported in DWB.

^b Results originally reported in WWB; DWB values displayed were calculated using reported Moisture % values as described in Chapter II: Materials & Methods, Data Harmonization.

^c Free Nicotine (mg/g) calculated from reported Total Nicotine (mg/g) and calculated Free Nicotine (%) values as described in Chapter II: Materials & Methods, Data Harmonization.

^d Free Nicotine (%) estimated via the Henderson-Hasselbalch approximation ($pK_a = 8.02$ at 25°C) as described in Chapter II: Materials & Methods, Data Harmonization.

Table 25. Moist Snuff Detailed Results – Stepanov et al. (2013).

Product Name	NNN ^a (ng/g)	(S)-NNN ^a (ng/g)	(S)-NNN (%)
Timber Wolf Long Cut Wintergreen	3480	1740	50.2
Skoal Long Cut Wintergreen	3030	1710	56.1

Product Name	NNN ^a (ng/g)	(S)-NNN ^a (ng/g)	(S)-NNN (%)
Longhorn Long Cut Wintergreen	3830	2020	52.6
Red Man Long Cut Wintergreen	3470	1810	52.1
Kodiak Wintergreen	6970	4070	58.5
Copenhagen Snuff	4940	3230	65.5
Copenhagen Long Cut	4860	2760	56.8
Skoal Long Cut Straight	4190	2370	56.8
Skoal Bandits Wintergreen	4370	2570	58.6
Pouches			
Grizzly Snuff	8910	5240	59.0
Red Seal Fine Cut Natural	3370	1930	57.5
Husky Natural	2750	1610	58.4
Grizzly Long Cut Straight	7010	3950	56.4
Grizzly Long Cut Mint	7120	4220	59.3
Min	2750	1610	50.2
Max	8910	5240	65.5
Median	4280	2470	57.2
Mean	4880	2800	57.0

Summary of key analytes for moist snuff products analyzed by Stepanov et al. (2013); all products analyzed were obtained between 2010–2012. Results originally reported in WWB; DWB values displayed were calculated using reported Moisture % values as described in Chapter II: Materials & Methods, Data Harmonization.

^a Results originally reported in µg/g.

Table 26. Moist Snuff Detailed Results – Tyx et al. (2022).

Product Name	pH	NNN (mean ng/g ± SD)	NNK (mean ng/g ± SD)	Total Nicotine (mean mg/g ± SD)	Free Nicotine (mg/g)	Free Nicotine (%)
Copenhagen Long Cut Straight A	7.84	3410 ± 170	1240 ± 35	29.7 ± 0.2	11.82	39.8
Copenhagen Long Cut Natural	7.71	2980 ± 140	778 ± 14	27.8 ± 0.2	9.13	32.9
Copenhagen Long Cut Straight B	7.26	3500 ± 190	1330 ± 150	28.7 ± 0.2	4.26	14.8
Copenhagen Long Cut Wintergreen	7.74	2840 ± 69	815 ± 55	26.6 ± 0.5	9.15	34.4
Grizzly Long Cut Mint	7.85	6660 ± 280	1950 ± 100	32.1 ± 0.7	12.95	40.3

Product Name	pH	NNN (mean ng/g $\pm$ SD)	NNK (mean ng/g $\pm$ SD)	Total Nicotine (mean mg/g $\pm$ SD)	Free Nicotine (mg/g)	Free Nicotine (%)
Grizzly Long Cut Natural Extra	7.49	7780 $\pm$ 300	1630 $\pm$ 61	35.3 $\pm$ 1.1	8.05	22.8
Grizzly Long Cut Natural Premium	7.54	5850 $\pm$ 110	1400 $\pm$ 48	34.7 $\pm$ 0.8	8.63	24.9
Grizzly Long Cut Straight	7.85	6030 $\pm$ 150	2700 $\pm$ 87	32.0 $\pm$ 0.4	12.92	40.3
Grizzly Long Cut Wintergreen	8.20	5810 $\pm$ 510	1660 $\pm$ 100	26.9 $\pm$ 0.2	16.21	60.2
Husky Fine Cut Natural	7.54	3220 $\pm$ 34	814 $\pm$ 48	30.2 $\pm$ 0.0	7.51	24.9
Husky Long Cut Wintergreen	7.47	2830 $\pm$ 90	864 $\pm$ 59	30.3 $\pm$ 0.0	6.67	22.0
Kayak Long Cut Straight	6.89	7090 $\pm$ 510	2440 $\pm$ 64	28.0 $\pm$ 0.6	1.92	6.9
Kayak Long Cut Wintergreen	7.81	6220 $\pm$ 710	4150 $\pm$ 43	27.5 $\pm$ 0.2	10.49	38.1
Kodiak Long Cut Straight	7.22	4430 $\pm$ 390	1140 $\pm$ 24	24.7 $\pm$ 0.6	3.38	13.7
Kodiak Long Cut Wintergreen	8.09	5880 $\pm$ 530	2370 $\pm$ 150	24.1 $\pm$ 0.2	13.01	54.0
Longhorn Long Cut Mint	7.87	2790 $\pm$ 86	888 $\pm$ 20	30.2 $\pm$ 0.2	12.53	41.5
Longhorn Long Cut Natural	7.82	2620 $\pm$ 210	887 $\pm$ 16	26.4 $\pm$ 0.4	10.19	38.7
Longhorn Long Cut Straight	7.94	3650 $\pm$ 210	1150 $\pm$ 57	31.1 $\pm$ 0.2	14.11	45.4
Longhorn Long Cut Wintergreen	7.93	2710 $\pm$ 67	820 $\pm$ 67	28.7 $\pm$ 0.4	12.84	44.8
Red Man Long Cut Straight	7.64	2840 $\pm$ 140	745 $\pm$ 20	28.6 $\pm$ 0.4	8.41	29.4
Red Man Long Cut Wintergreen	7.90	3180 $\pm$ 58	771 $\pm$ 33	28.9 $\pm$ 0.2	12.47	43.1
Red Seal Long Cut Mint	7.43	2980 $\pm$ 73	831 $\pm$ 34	28.9 $\pm$ 0.5	5.92	20.4
Red Seal Long Cut Natural	7.33	3600 $\pm$ 130	724 $\pm$ 4.7	31.9 $\pm$ 0.7	5.42	17.0
Red Seal Long Cut Straight	7.71	5320 $\pm$ 150	1990 $\pm$ 46	28.0 $\pm$ 0.5	9.20	32.9
Red Seal Long Cut Wintergreen	7.34	3750 $\pm$ 250	933 $\pm$ 38	31.9 $\pm$ 0.4	5.51	17.3

Product Name	pH	NNN (mean ng/g $\pm$ SD)	NNK (mean ng/g $\pm$ SD)	Total Nicotine (mean mg/g $\pm$ SD)	Free Nicotine (mg/g)	Free Nicotine (%)
Skoal Long Cut Classic	7.62	4100 $\pm$ 57	1180 $\pm$ 75	31.8 $\pm$ 0.4	9.06	28.5
Skoal Long Cut Mint	7.30	3150 $\pm$ 140	860 $\pm$ 32	28.7 $\pm$ 0.2	4.60	16.0
Skoal Long Cut Straight	7.45	3460 $\pm$ 87	1310 $\pm$ 62	29.7 $\pm$ 0.2	6.32	21.2
Skoal Long Cut Wintergreen	7.56	4020 $\pm$ 91	1510 $\pm$ 110	29.8 $\pm$ 0.2	7.66	25.7
Skoal Xtra Long Cut Crisp	7.19	3200 $\pm$ 150	1470 $\pm$ 68	30.5 $\pm$ 2.0	3.93	12.9
Skoal Xtra Long Cut Wintergreen	7.49	3850 $\pm$ 79	1370 $\pm$ 59	27.8 $\pm$ 0.2	6.33	22.8
Stokers Long Cut Natural	8.07	3400 $\pm$ 100	662 $\pm$ 44	25.6 $\pm$ 0.4	13.52	52.9
Stokers Long Cut Straight	7.92	2990 $\pm$ 120	714 $\pm$ 21	28.2 $\pm$ 4.1	12.47	44.3
Stokers Long Cut Wintergreen	7.46	3050 $\pm$ 93	743 $\pm$ 41	25.1 $\pm$ 0.4	5.41	21.6
Timber Wolf Long Cut Natural	7.09	2870 $\pm$ 210	924 $\pm$ 76	26.2 $\pm$ 0.4	2.77	10.5
Timber Wolf Long Cut Straight	7.33	3460 $\pm$ 240	1170 $\pm$ 24	28.4 $\pm$ 0.6	4.81	17.0
Timber Wolf Long Cut Wintergreen	7.65	2930 $\pm$ 260	896 $\pm$ 46	27.5 $\pm$ 0.4	8.24	29.9
Min	6.89	2620	662	24.1	1.92	6.9
Max	8.20	7780	4150	35.3	16.21	60.2
Median	7.62	3460	1140	28.7	8.41	28.5
Mean	7.61	4010	1290	29.0	8.59	29.8

Summary of key analytes for moist snuff products analyzed by Tyx et al. (2022); all products analyzed were obtained in 2016. Results originally reported in WWB; DWB values displayed were calculated using reported Moisture % values as described in Chapter II: Materials & Methods, Data Harmonization.

Table 27. Moist Snuff Detailed Results – Back *et al.* (2023).

Product Name	pH	NNN ^a (mean ng/g ± SD)	NNK ^a (ng/g)	B[a]P (ng/g)	Total Nicotine (mean mg/g ± SD)	Free Nicotine (mg/g)	Free Nicotine ^b (%)
CORESTA	7.7	7720 ±	4830 ±	240 ±	21.21 ±	6.87 ±	32.37 ±
CRP2.1 Moist Snuff Reference		130	110	13	0.13	0.04	0.28
Grizzly	7.9	5270 ±	1920 ±	154 ±	17.65 ±	7.60 ±	43.14 ±
Wintergreen Pouches		130	21	6	0.25	0.10	0.85
Min	7.7	5270	1920	154	17.65	6.87	32.37
Max	7.9	7720	4830	240	21.21	7.60	43.14
Median	7.8	6500	3380	197	19.43	7.24	37.76
Mean	7.8	6500	3380	197	19.43	7.24	37.76

Summary of key analytes for moist snuff products analyzed by Back et al. (2023); authors did not state when the products were obtained. Results originally reported in WWB; DWB values displayed were calculated using reported Moisture % values as described in Chapter II: Materials & Methods, Data Harmonization.

^a Results originally reported in µg/g.

^b Free Nicotine (%) calculated from reported Free Nicotine (mg/g) and Total Nicotine (mg/g) content as described in Chapter II: Materials & Methods, Data Harmonization.

Appendix 3.

Harmonized Detailed Results – Snus Products

Values are means $\pm$ SD; units are mg/g for nicotine and ng/g for TSNA/B[a]P; pH matches the level of precision originally reported. All snus values are on a dry-weight basis (DWB) after unit/basis harmonization; ND/<LOD/<LOQ/BQL entries are displayed as text and excluded from summary statistics. For Lawler et al. (2020), we present basis-harmonized stratum-level LS-means in the region/form-factor/strength groupings originally reported. Rounding follows the rules defined in Chapter II: Materials & Methods, Data Harmonization.

Table 28. Snus Detailed Results – Song *et al.* (2016).

Product Name	pH	NNN ^a (ng/g)	NNK ^a (ng/g)	B[a]P (ng/g)	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine ^b (%)
Camel Frost Snus	7.76	1220	400	0.74	15.01	5.325	35.46
Camel Spice Snus	7.51	1040	250	0.75	20.26	4.784	23.61
Camel Original Snus	7.53	1390	400	0.76	18.13	4.433	24.45
Marlboro Mild Snus	6.53	940	210	0.55	15.70	0.492	3.13
Marlboro Mint Snus	6.74	950	200	0.55	15.10	0.753	4.99
Marlboro Rich Snus	6.79	890	300	0.56	16.10	0.896	5.56
Marlboro Spice Snus	6.84	960	280	0.56	15.93	0.987	6.20
Ettan Loose	8.03	780	310	1.79	17.25	8.724	50.58

Product Name	pH	NNN ^a (ng/g)	NNK ^a (ng/g)	B[a]P (ng/g)	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine ^b (%)
General	8.03	770	250	1.35	16.22	8.203	50.58
Mini Portion							
Skruf	7.96	2430	460	3.13	31.67	14.743	46.55
Stark Portion							
Min	6.53	770	200	0.55	15.01	0.492	3.13
Max	8.03	2430	460	3.13	31.67	14.743	50.58
Median	7.52	955	290	0.75	16.16	4.609	24.03
Mean	7.37	1140	306	1.07	18.14	4.934	25.11

Summary of key analytes for snus products analyzed by Song et al. (2016); all products analyzed were obtained between 2007–2009. All results originally reported in DWB.

^a Results originally reported in µg/g.

^b Free Nicotine (%) calculated from reported Free Nicotine (mg/g) and Total Nicotine (mg/g) content as described in Chapter II: Materials & Methods, Data Harmonization.

Table 29. Snus Detailed Results – McAdam *et al.* (2013, 2019).

Product Name	pH (mean ± SD)	B[a]P ^a (mean ng/g ± SD)	Total Nicotine ^b (mg/g)	Free Nicotine ^c (mg/g)	Free Nicotine ^d (%)
General Loose	8.7 ± 0.00	1.88 ± 0.11	16.5 ± 0.326	14	82.7 ± 0.0
Ettan Loose	8.8 ± 0.00	2.56 ± 0.38	17.3 ± 0	15	85.8 ± 0.0
Grovsnus Loose	8.7 ± 0.00	2.65 ± 0.27	17.3 ± 0	14	82.7 ± 0.0
Goteborgs Rape Loose	8.4 ± 0.01	3.28 ± 0.39	15.6 ± 0.330	11	70.6 ± 0.5
Kronan Loose	8.8 ± 0.01	2.53 ± 0.22	17.9 ± 0.164	15	85.8 ± 0.3
Granit Loose	8.5 ± 0.01	2.42 ± 0.13	16.6 ± 0.306	12	75.1 ± 0.4
LD Loose	8.7 ± 0.00	5.23 ± 0.46	16.0 ± 0.158	13	82.7 ± 0.0
Skruf Strong Loose	8.1 ± 0.02	2.81 ± 0.48	23.1 ± 0.327	13	54.6 ± 1.1
T. Montecristo Habanos Loose	7.5 ± 0.07	2.73 ± 0.27	19.5 ± 0.153	4.5	23.2 ± 2.9

Product Name	pH (mean $\pm$ SD)	B[a]P ^a (mean ng/g $\pm$ SD)	Total Nicotine ^b (mg/g)	Free Nicotine ^c (mg/g)	Free Nicotine ^d (%)
Knox Loose	8.7 $\pm$ 0.02	3.22 $\pm$ 0.40	22.6 $\pm$ 0	19	82.7 $\pm$ 0.7
General White Portion	8.8 $\pm$ 0.03	2.49 $\pm$ 0.35	17.4 $\pm$ 0.156	15	85.8 $\pm$ 0.8
General Mini Portion	8.3 $\pm$ 0.02	2.90 $\pm$ 0.26	16.3 $\pm$ 0.586	11	65.6 $\pm$ 1.0
General Portion	8.5 $\pm$ 0.01	2.33 $\pm$ 0.25	17.7 $\pm$ 0.310	13	75.1 $\pm$ 0.4
Ettan Portion	8.5 $\pm$ 0.01	1.58 $\pm$ 0.26	17.0 $\pm$ 0.294	13	75.1 $\pm$ 0.4
Grovsnus Portion	8.6 $\pm$ 0.01	2.17 $\pm$ 0.33	17.0 $\pm$ 0.582	13	79.2 $\pm$ 0.4
Grovsnus White Portion	8.6 $\pm$ 0.01	2.09 $\pm$ 0.13	18.5 $\pm$ 0	15	79.2 $\pm$ 0.4
Goteborgs Rape White Portion	8.5 $\pm$ 0.01	2.07 $\pm$ 0.26	18.3 $\pm$ 0	14	75.1 $\pm$ 0.4
Kronan Portion	8.2 $\pm$ 0.02	1.84 $\pm$ 0.13	17.8 $\pm$ 0.286	11	60.2 $\pm$ 1.1
Catch Licorice Mini Portion	8.5 $\pm$ 0.00	2.02 $\pm$ 0.17	16.5 $\pm$ 0.293	12	75.1 $\pm$ 0.0
Catch White Licorice Portion	8.6 $\pm$ 0.00	2.04 $\pm$ 0.31	18.1 $\pm$ 0	14	79.2 $\pm$ 0.0
Catch Dry White Eucalyptus Mini Portion	7.5 $\pm$ 0.02	1.99 $\pm$ 0.40	22.9 $\pm$ 0.0945	5.3	23.2 $\pm$ 0.8
Catch Dry White Licorice Mini Portion	7.6 $\pm$ 0.05	1.90 $\pm$ 0.18	23.4 $\pm$ 0.483	6.4	27.5 $\pm$ 2.3
Granit White Portion	8.3 $\pm$ 0.01	2.46 $\pm$ 0.40	17.1 $\pm$ 0.633	11	65.6 $\pm$ 0.5
Granit Portion	8.6 $\pm$ 0.01	2.13 $\pm$ 0.23	16.3 $\pm$ 0.151	13	79.2 $\pm$ 0.4
Tre Ankare White Portion	8.7 $\pm$ 0.00	1.89 $\pm$ 0.36	17.5 $\pm$ 0.318	14	82.7 $\pm$ 0.0
LD Original Portion	8.7 $\pm$ 0.02	5.11 $\pm$ 0.17	13.7 $\pm$ 0.145	11	82.7 $\pm$ 0.7
Level Portion	8.5 $\pm$ 0.01	4.05 $\pm$ 0.73	13.3 $\pm$ 0.420	10	75.1 $\pm$ 0.4
Skruf Strong Portion	8.8 $\pm$ 0.01	2.69 $\pm$ 0.08	22.4 $\pm$ 0	19	85.8 $\pm$ 0.3
Knox Portion	8.0 $\pm$ 0.01	3.36 $\pm$ 0.48	20.8 $\pm$ 0.275	10	48.8 $\pm$ 0.6
Wise Citrus & Menthol Portion	9.5 $\pm$ 0.04	3.56 $\pm$ 0.41	26.2 $\pm$ 3.97	25	96.8 $\pm$ 0.3

Product Name	pH (mean $\pm$ SD)	B[a]P ^a (mean ng/g $\pm$ SD)	Total Nicotine ^b (mg/g)	Free Nicotine ^c (mg/g)	Free Nicotine ^d (%)
T. Romeo y Julieta Portion	8.3 $\pm$ 0.00	2.48 $\pm$ 0.24	23.8 $\pm$ 0	16	65.6 $\pm$ 0.0
1847 Original Portion	8.6 $\pm$ 0.00	2.46 $\pm$ 0.39	15.4 $\pm$ 0	12	79.2 $\pm$ 0.0
Min	7.5	1.88	15.6	4.5	23.2
Max	8.8	5.23	23.1	19	85.8
Median	8.7	2.69	17.3	14	82.7
Mean	8.5	2.93	18.2	13	72.6

Summary of key analytes for snus products analyzed by McAdam et al. (2013, 2019); products analyzed were obtained between 2008–2009.

^a Results originally reported in DWB.

^b Results originally reported in WWB; DWB values displayed were calculated using reported Moisture % values as described in Chapter II: Materials & Methods, Data Harmonization.

^c Free Nicotine (mg/g) calculated from reported Total Nicotine(mg/g) and calculated Free Nicotine (%) values as described in Chapter II: Materials & Methods, Data Harmonization.

^d Free Nicotine (%) estimated via the Henderson-Hasselbalch approximation ($pK_a = 8.02$ at 25°C) as described in Chapter II: Materials & Methods, Data Harmonization.

Table 30. Snus Detailed Results – Stepanov et al. (2012).

Product Name	pH (mean $\pm$ SD)	NNN ^a (mean ng/g $\pm$ SD)	NNK ^a (mean ng/g $\pm$ SD)	Total Nicotine (mean mg/g $\pm$ SD)	Free Nicotine (mean mg/g $\pm$ SD)	Free Nicotine (mean % $\pm$ SD)
Marlboro Rich Snus	6.72 $\pm$ 0.14	421 $\pm$ 120	132 $\pm$ 30.0	24.84 $\pm$ 2.30	1.23 $\pm$ 0.38	4.9 $\pm$ 1.6
Marlboro Mild Snus	6.68 $\pm$ 0.10	420 $\pm$ 80.0	160 $\pm$ 30.0	18.93 $\pm$ 1.89	0.84 $\pm$ 0.21	4.5 $\pm$ 1.1
Marlboro Spearmint Snus	6.79 $\pm$ 0.07	431 $\pm$ 80.0	164 $\pm$ 30.0	18.82 $\pm$ 1.69	1.05 $\pm$ 0.16	5.6 $\pm$ 1.9
Marlboro Peppermint Snus	6.81 $\pm$ 0.09	470 $\pm$ 100	162 $\pm$ 20.0	19.38 $\pm$ 2.10	1.13 $\pm$ 0.81	5.8 $\pm$ 1.2
Camel Robust Snus	7.78	1280	595	13.93	5.09	36.5
Camel Mellow Snus	7.38 $\pm$ 0.19	859 $\pm$ 220	404 $\pm$ 150	16.74 $\pm$ 2.56	3.36 $\pm$ 1.32	19.6 $\pm$ 6.2
Camel Frost Snus	7.43 $\pm$ 0.23	896 $\pm$ 270	450 $\pm$ 120	16.46 $\pm$ 1.87	3.58 $\pm$ 1.32	21.8 $\pm$ 7.8

Product Name	pH (mean ± SD)	NNN ^a (mean ng/g ± SD)	NNK ^a (mean ng/g ± SD)	Total Nicotine (mean mg/g ± SD)	Free Nicotine (mean mg/g ± SD)	Free Nicotine (mean % ± SD)
Camel Winterchill Snus	7.68	909	609	14.65	4.59	31.4
Min	6.68	420	132	13.93	0.84	4.5
Max	7.78	1280	609	24.84	5.09	36.5
Median	7.10	665	284	17.78	2.30	12.7
Mean	7.16	711	335	17.97	2.61	16.3

Summary of key analytes for snus products analyzed by Stepanov et al. (2012); products analyzed were obtained from July–September 2010. All results originally reported in DWB.

^a Results originally reported in µg/g.

Table 31. Snus Detailed Results – Stepanov et al. (2013).

Product Name	NNN ^a (ng/g)	(S)-NNN ^a (ng/g)	(S)-NNN (%)
Marlboro Rich Snus	885	577	65.2
Marlboro Mild Snus	988	658	67.6
Marlboro Spearmint Snus	907	578	63.8
Marlboro Peppermint Snus	970	628	64.6
Camel Robust Snus	2700	1800	66.6
Camel Mellow Snus	1700	1090	63.9
Camel Frost Snus	1570	1040	66.4
Camel Winterchill Snus	1790	1320	73.5
Min	885	577	63.8
Max	2700	1800	73.5
Median	1280	849	65.8
Mean	1440	961	66.5

Summary of key analytes for snus products analyzed by Stepanov et al. (2013); all products analyzed were obtained from 2010–2012. Results originally reported in WWB; DWB values displayed were calculated using reported Moisture % values as described in Chapter II: Materials & Methods, Data Harmonization.

^a Results originally reported in µg/g.

Table 32. Snus Detailed Results – Stepanov *et al.* (2014).

Product Name	pH (mean $\pm$ SD)	NNN ^a (mean ng/g $\pm$ SD)	NNK ^a (mean ng/g $\pm$ SD)	Total Nicotine (mean mg/g $\pm$ SD)	Free Nicotine (mean mg/g $\pm$ SD)	Free Nicotine (mean % $\pm$ SD)
Marlboro Rich Snus	6.72 $\pm$ 0.14	781 $\pm$ 140	185 $\pm$ 30.0	22.56 $\pm$ 2.53	1.23 $\pm$ 0.71	5.6 $\pm$ 3.5
Marlboro Mild Snus	6.68 $\pm$ 0.10	700 $\pm$ 100	220 $\pm$ 30.0	17.76 $\pm$ 1.88	0.83 $\pm$ 0.49	4.7 $\pm$ 3.0
Marlboro Spearmint Snus	6.79 $\pm$ 0.07	688 $\pm$ 90.0	242 $\pm$ 40.0	17.95 $\pm$ 1.49	1.10 $\pm$ 0.48	6.1 $\pm$ 2.7
Marlboro Peppermint Snus	6.81 $\pm$ 0.09	717 $\pm$ 90.0	220 $\pm$ 30.0	18.38 $\pm$ 1.99	1.05 $\pm$ 0.49	5.8 $\pm$ 3.0
Camel Robust Snus	7.78	1840 $\pm$ 560	730 $\pm$ 200	13.18 $\pm$ 1.34	3.42 $\pm$ 1.06	25.9 $\pm$ 7.2
Camel Mellow Snus	7.38 $\pm$ 0.19	1930 $\pm$ 1110	685 $\pm$ 190	14.34 $\pm$ 1.80	3.83 $\pm$ 1.00	26.6 $\pm$ 6.1
Camel Frost Snus	7.43 $\pm$ 0.23	1980 $\pm$ 840	696 $\pm$ 160	14.34 $\pm$ 1.45	4.06 $\pm$ 1.34	28.0 $\pm$ 7.6
Camel Winterchill Snus	7.68	1810 $\pm$ 740	695 $\pm$ 140	13.27 $\pm$ 1.28	3.78 $\pm$ 0.87	28.3 $\pm$ 5.6
Min	6.65	688	185	13.18	0.83	4.7
Max	7.61	1980	730	22.56	4.06	28.3
Median	7.18	1300	464	16.05	2.33	16.0
Mean	7.16	1310	459	16.47	2.41	16.4

Summary of key analytes for snus products analyzed by Stepanov et al. (2014); all products analyzed were obtained from April–July 2011.

^a Results originally reported in $\mu\text{g/g}$.

Table 33. Snus Detailed Results – Lawler *et al.* (2020).

Aggregated Product Strata		pH	NNN (ng/g)	NNK (ng/g)	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine (%)
U.S. Standard Portion (n = 8)	Mean $\pm$ SD	6.62 $\pm$ 1.04	1520 $\pm$ 712	464 $\pm$ 284	15.6 $\pm$ 6.39	1.45 $\pm$ 6.38	11.1 $\pm$ 36.2
	Min	5.87	725	210	11.6	0.12	0.708
	Max	7.66	2310	827	19.7	4.12	30.6

Aggregated Product Strata		pH	NNN (ng/g)	NNK (ng/g)	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine (%)
Northern European Standard Portion (n = 33)	Mean	8.08 ±	1130 ±	316 ±	21.0 ±	10.3 ±	49.8 ±
	± SD	1.33	1120	441	10.3	10.4	45.7
	Min	6.94	459	92.7	13.3	1.83	7.68
	Max	9.1	1900	788	30	23.2	92.3
Northern European Standard Loose (n = 6)	Mean	7.53 ±	963 ±	226 ±	23.9 ±	6.10 ±	27.5 ±
	± SD	0.65	678	287	7.12	6.25	24.5
	Min	7.19	400	93.6	14.1	3.69	12.8
	Max	8.18	1710	357	42.7	11.6	58.8
Northern European Strong Portion (n = 16)	Mean	8.18 ±	1310 ±	569 ±	30.3 ±	18.0 ±	60.1 ±
	± SD	0.98	866	358	8.99	8.32	35.0
	Min	7.88	90.5	76.6	19.9	10.8	42
	Max	8.65	3530	1270	37.7	28.7	81

Summary of key analytes for snus products analyzed by Lawler et al. (2020); all products analyzed were obtained from 2013–2014. Results originally reported in WWB; DWB values displayed were calculated using reported strata-specific Moisture % LS-mean values as described in Chapter II: Materials & Methods, Data Harmonization. Harmonized DWB LS-means are reported by region/form-factor/strength.

Table 34. Snus Detailed Results – Azzopardi et al. (2021).

Product Name	pH	NNN (ng/g)	NNK (ng/g)	Total Nicotine ^a (mg/g)	Free Nicotine ^b (mg/g)	Free Nicotine ^c (%)
Granit Ice Blue White	8.7	1170	382	22.9	19.0	82.7
Skruf Slim Fresh	7.8	858	191	33.7	12.7	37.6
XStrong Mint						
G3 Slim White	8.7	1210	169	28.5	23.5	82.7
XStrong Blue						
Mint						
Min	7.8	858	169	22.9	12.7	37.6
Max	8.7	1210	382	33.7	23.5	82.7
Median	8.7	1170	191	28.5	19.0	82.7
Mean	8.4	1080	247	28.4	18.4	67.7

Summary of key analytes for snus products analyzed by Azzopardi et al. (2021); all products analyzed were obtained from 2018–2020. Results originally reported in WWB; DWB values displayed were calculated using reported Moisture % values as described in Chapter II: Materials & Methods, Data Harmonization. B[a]P values < LOQ treated as missing.

^a Results originally reported as %wt.

^b Free Nicotine (mg/g) calculated from reported Total Nicotine (mg/g) and calculated Free Nicotine (%) values as described in Chapter II: Materials & Methods, Data Harmonization.

^c Free Nicotine (%) estimated via the Henderson-Hasselbalch approximation ($pK_a = 8.02$ at 25°C) as described in Chapter II: Materials & Methods, Data Harmonization.

Table 35. Snus Detailed Results – Back et al. (2023).

Product Name	pH	NNN ^a (mean ng/g ± SD)	NNK ^a (mean ng/g ± SD)	Total Nicotine (mean mg/g ± SD)	Free Nicotine (mean mg/g ± SD)	Free Nicotine ^b (mean % ± SD)
General Original Large Portion	8.9	898 ± 20	388 ± 20	16.59 ± 0.78	14.51 ± 0.57	88.35 ± 5.35

Summary of key analytes for a snus product analyzed by Back et al. (2023); one Swedish product measured in triplicate, product acquisition date not stated. Results originally reported in WWB; DWB values displayed were calculated using reported Moisture % values as described in Chapter II: Materials & Methods, Data Harmonization.

^a Results originally reported in µg/g.

^b Free Nicotine (%) calculated from reported Free Nicotine (mg/g) and Total Nicotine (mg/g) content as described in Chapter II: Materials & Methods, Data Harmonization.

Appendix 4.

Harmonized Detailed Results – Nicotine Pouch Products

Values are means $\pm$ SD; units are mg/g for nicotine and ng/g for TSNA; pH matches the level of precision originally reported. All nicotine pouch product values remain on a wet-weight basis (WWB) as moisture was not consistently reported. Where sources reported mean (SE) (e.g., Stanfill *et al.* 2021), we retain that format. ND/<LOD/<LOQ/BQL entries are displayed as text and excluded from summary statistics. Rounding follows the rules defined in Chapter II: Materials & Methods, Data Harmonization.

Table 36. Nicotine Pouch Detailed Results – Azzopardi *et al.* (2021).

Product Name	pH	Total Nicotine ^a (mg/g)	Free Nicotine ^b (mg/g)	Free Nicotine ^c (%)
LYFT Freeze	8.6	17.0	13.5	79.2
LYFT Lime Strong	8.6	14.0	11.1	79.2
LYFT Berry Frost	8.7	5.80	4.80	82.7
LYFT Mint	8.5	8.90	6.69	75.1
Min	8.5	5.80	4.80	75.1
Max	8.7	17.0	13.5	82.7
Median	8.6	11.5	8.90	79.2
Mean	8.6	11.4	9.02	79.1

Summary of key analytes for nicotine products analyzed by Azzopardi et al. (2021); four products obtained from Scandinavia between 2018–2020 were analyzed. Results originally reported in WWB; no basis conversion was performed as described in Chapter II: Materials & Methods, Data Harmonization.

^a Results originally reported as %wt.

^b Free Nicotine (mg/g) calculated from reported Total Nicotine (mg/g) and calculated Free Nicotine (%) values as described in Chapter II: Materials & Methods, Data Harmonization.

^c Free Nicotine (%) estimated via the Henderson-Hasselbalch approximation ($pK_a = 8.02$ at 25°C) as described in Chapter II: Materials & Methods, Data Harmonization.

Table 37. Nicotine Pouch Detailed Results – Stanfill *et al.* (2021).

Product Name	pH, mean (SE)	Total Nicotine (mean mg/g ± SD)	Free Nicotine (mean mg/g ± SD)	Free Nicotine ^a (mean % ± SD)
Velo Citrus 2mg	7.32 (0.02)	8.92 ± 2.4	1.48 ± 0.40	16.6 ± 1.1
Velo Mint 2mg	7.19 (0.07)	8.02 ± 2.9	1.03 ± 0.38	12.9 ± 3.1
Velo Citrus 4mg	7.45 (0.04)	7.44 ± 3.5	1.58 ± 0.74	21.2 ± 2.7
Velo Mint 4mg	7.33 (0.04)	8.21 ± 3.2	1.39 ± 0.54	17.0 ± 2.2
Rogue Wintergreen 3mg	8.05 (0.02)	3.42 ± 0.10	1.77 ± 0.052	51.7 ± 2.0
Rogue Peppermint 3mg	8.42 (0.02)	3.43 ± 0.10	2.45 ± 0.069	71.5 ± 1.6
Rogue Honey Lemon 3mg	6.94 (0.06)	4.74 ± 0.052	0.364 ± 0.0035	7.68 ± 1.7
Rogue Mango 3mg	7.59 (0.01)	4.44 ± 0.43	1.20 ± 0.12	27.1 ± 0.79
Rogue Wintergreen 6mg	8.34 (0.02)	6.06 ± 0.47	4.10 ± 0.31	67.6 ± 1.7
Rogue Peppermint 6mg	8.12 (0.13)	8.28 ± 0.36	4.62 ± 0.21	55.7 ± 13
Rogue Honey Lemon 6mg	7.42 (0.03)	10.0 ± 0	2.01 ± 0.017	20.1 ± 1.9
Rogue Mango 6mg	7.96 (0.04)	8.97 ± 0.14	4.18 ± 0.069	46.6 ± 4.0
ZYN Cool Mint 3mg	8.29 (0.07)	8.32 ± 0.17	5.41 ± 0.12	65.1 ± 6.3
ZYN Peppermint 3mg	8.52 (0.18)	7.97 ± 0.50	6.05 ± 0.38	76.0 ± 13
ZYN Coffee 3mg	8.95 (0.04)	7.57 ± 0.36	6.77 ± 0.33	89.5 ± 1.5
ZYN Cinnamon 3mg	8.88 (0.07)	8.36 ± 0.38	7.35 ± 0.35	87.9 ± 3.0
ZYN Wintergreen 3mg	8.03 (0.01)	8.23 ± 0.28	4.16 ± 0.14	50.6 ± 1.0
ZYN Spearmint 3mg	8.84 (0.10)	7.36 ± 0.87	6.39 ± 0.76	86.9 ± 4.6
ZYN Peppermint 6mg	8.04 (0.11)	15.5 ± 0.35	7.91 ± 0.21	51.2 ± 11
ZYN Coffee 6mg	8.45 (0.18)	17.6 ± 0.17	12.8 ± 0.17	72.9 ± 14
ZYN Cinnamon 6mg	8.42 (0.12)	17.7 ± 0.17	12.7 ± 0	71.5 ± 9.7
ZYN Wintergreen 6mg	8.12 (0.04)	17.0 ± 0.69	9.45 ± 0.36	55.7 ± 3.9
ZYN Spearmint 6mg	9.19 (0.04)	13.9 ± 1.2	13.0 ± 1.2	93.7 ± 0.95
ON! Licorice 3mg	9.36 (0.03)	5.91 ± 0.017	5.65 ± 0.017	95.6 ± 0.50
ON! Citrus 3mg	9.39 (0.02)	8.13 ± 1.2	7.80 ± 1.2	95.9 ± 0.31
ON! Mint 3mg	9.39 (0.03)	7.42 ± 0.33	7.12 ± 0.31	95.9 ± 0.47
ON! Licorice 6mg	9.66 (0.03)	13.5 ± 1.9	13.2 ± 1.9	97.8 ± 0.26
ON! Citrus 6mg	9.56 (0.05)	17.5 ± 1.0	17.0 ± 1.0	97.2 ± 0.54
ON! Mint 6mg	9.52 (0.07)	18.4 ± 2.6	17.9 ± 2.4	96.9 ± 0.83
White Fox	10.1 (0.03)	13.7 ± 0.17	13.6 ± 0.17	99.2 ± 0.098
LYFT Mint	7.71 (0.09)	8.24 ± 1.0	2.71 ± 0.33	32.9 ± 7.9
LYFT Lime	7.54 (0.07)	9.15 ± 0.62	2.27 ± 0.16	24.9 ± 5.2
LYFT Melon	7.71 (0.13)	9.21 ± 1.2	3.03 ± 0.38	32.9 ± 11

Product Name	pH, mean (SE)	Total Nicotine (mean mg/g ± SD)	Free Nicotine (mean mg/g ± SD)	Free Nicotine ^a (mean % ± SD)
LYFT Blueberry	6.96 (0.04)	10.4 ± 0.17	0.833 ± 0.016	8.01 ± 1.2
LYFT Liquorice	7.85 (0.02)	12.5 ± 0.69	5.05 ± 0.28	40.3 ± 1.9
LYFT Lime Strong	7.77 (0.06)	13.2 ± 1.0	4.75 ± 0.35	36.0 ± 5.5
LYFT Ice Cool strong	7.93 (0.01)	13.6 ± 0.35	6.10 ± 0.12	44.8 ± 0.99
Min	6.94	3.42	0.364	7.68
Max	10.1	18.4	17.9	99.2
Median	8.12	8.36	5.05	55.7
Mean	8.28	10.1	6.09	57.2

Summary of key analytes for nicotine pouch products analyzed by Stanfill et al. (2021); 37 U.S. products were obtained in 2019 and analyzed. SE = standard error of mean; values and SEs as originally reported. pH presented to 0.01 to match study precision. Results originally reported in WWB; no basis conversion was performed as described in Chapter II: Materials & Methods, Data Harmonization.

^a Free Nicotine (%) calculated from reported Free Nicotine (mg/g) and Total Nicotine (mg/g) content as described in Chapter II: Materials & Methods, Data Harmonization.

Table 38. Nicotine Pouch Detailed Results – Mallock *et al.* (2024).

Product Name	pH	NNN (ng/g)	NNK (ng/g)	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine ^a (%)
Product 3: Nicotine Strength Score 1 of 4	8.0	–	–	4.48	2.20	49
Product 4: Nicotine Strength Score 1 of 4, "Easy" Product Line Descriptor	8.8	–	–	8.18	7.03	86
Product 5: Nicotine Strength Score 1 of 4, "Easy" Product Line Descriptor	8.8	1.3	–	5.11	4.39	86
Product 6: Nicotine Strength Score 3 of 4	8.4	–	14	10.3	7.31	71
Product 7: Nicotine Strength Score 2 of 4	8.7	–	1.6	6.90	5.73	83

Product Name	pH	NNN (ng/g)	NNK (ng/g)	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine ^a (%)
Product 8: Nicotine Strength Score 2 of 4, 6mg/pouch	8.9	2.1	—	9.30	8.28	89
Product 9: Nicotine Strength Score 2 of 4	7.6	—	—	9.46	2.65	28
Product 10: Nicotine Strength Score 2 of 4, 6mg/pouch	8.8	—	—	9.28	7.98	86
Product 11: Nicotine Strength Score 3 of 5, "Medium" Product Line Descriptor	5.5	—	—	6.02	0.0181	0.30
Product 12: Nicotine Strength Score 3 of 4, "Strong" Product Line Descriptor	8.7	—	—	9.22	7.65	83
Product 13: Nicotine Strength Score 2 of 4, "Medium" Product Line Descriptor, 6mg/pouch	9.0	4.4	—	8.15	7.42	91
Product 14: Nicotine Strength Score 5 of 5, "Extra Strong" Product Line Descriptor, 20mg	8.3	—	—	18.7	12.3	66
Product 15: Nicotine Strength Score 4 of 5, 8mg/pouch	8.7	—	—	11.7	9.71	83
Product 16: Nicotine Strength Score 3 of 4, "Strong" Product Line Descriptor, 10mg/pouch	9.8	—	—	12.6	12.3	98
Product 17: Nicotine Strength Score 5 of 5, "Extra Strong" Product Line Descriptor, 20mg	9.1	—	—	17.8	16.4	92

Product Name	pH	NNN (ng/g)	NNK (ng/g)	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine ^a (%)
Product 18: Nicotine Strength Score 5 of 5, "Extra Strong" Product Line Descriptor	7.7	—	—	16.5	5.45	33
Product 19: Nicotine Strength Score 2 of 4, 6mg/pouch	8.0	0.7	—	10.6	5.19	49
Product 20: Nicotine Strength Score 1 of 5	9.0	2.0	—	15.9	14.5	91
Product 21: Nicotine Strength Score 3 of 4	8.7	1.6	—	10.7	8.88	83
Product 22: Nicotine Strength Score 4 of 5, "Strong" Product Line Descriptor	8.5	—	—	18.7	14.2	76
Product 23: Nicotine Strength Score 3 of 4, "Strong" Product Line Descriptor	8.8	—	—	12.9	11.1	86
Product 24	10.3	—	—	14.1	14.0	99
Product 25	9.8	—	—	13.2	12.9	98
Product 26: Nicotine Strength Score 4 of 4, "X-Strong" Product Line Descriptor	8.2	7.7	—	21.7	13.2	61
Product 27: Nicotine Strength Score 3 of 4, "Strong" Product Line Descriptor, 10mg/pouch	9.2	12	—	16.1	15.1	94
Product 28: Nicotine Strength Score 4 of 4	8.0	1.3	—	15.3	7.50	49
Product 29: Nicotine Strength Score 4 of 4, "X-Strong" Product Line Descriptor	8.2	—	—	16.6	10.1	61
Product 30: 16mg/g	9.5	—	—	14.3	13.9	97

Product Name	pH	NNN (ng/g)	NNK (ng/g)	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine ^a (%)
Product 31: "Extra Strong" Product Line Descriptor	9.9	—	—	17.1	16.9	99
Product 32: Nicotine Strength Score 5 of 6, "Ultra" Product Line Descriptor	8.2	4.6	—	14.0	8.54	61
Product 33: "Power" Product Line Descriptor, 20mg/pouch	10.2	—	—	14.1	14.0	99
Product 34: Nicotine Strength Score 5 of 6, "Ultra" Product Line Descriptor	9.0	1.0	—	14.1	12.8	91
Product 35	10.2	—	—	17.6	17.4	99
Product 36: Nicotine Strength Score 4 of 4, "Extreme Strong" Product Line Descriptor	8.1	—	—	24.3	13.4	55
Product 37	8.0	—	0.7	23.1	11.3	49
Product 38: "Danger Strong" Product Line Descriptor	9.9	—	—	25.8	25.5	99
Product 39: Nicotine Strength 6 of 6, "Max" Product Line Descriptor	8.4	5.6	—	16.3	11.6	71
Product 40: "Extreme" Product Line Descriptor	10.0	4.1	—	44.7	44.3	99
Product 41: "Hard" Product Line Descriptor	8.7	—	—	75.5	62.7	83
Product 42: "Hard" Product Line Descriptor	9.9	2.5	—	66.1	65.4	99
Product 43: 25mg	9.7	—	—	46.9	46.0	98
Product 44: "Hard" Product Line Descriptor	9.7	26	—	63.8	62.5	98

Product Name	pH	NNN (ng/g)	NNK (ng/g)	Total Nicotine (mg/g)	Free Nicotine (mg/g)	Free Nicotine ^a (%)
Product 45: "Brutal" Product Line Descriptor, 50mg/pouch	10.1	–	–	64.8	64.2	99
Product 46: "Brutal" Product Line Descriptor, 50mg/pouch	10.5	–	–	44.7	44.7	100
Min	5.5	0.7	0.7	4.48	0.0181	0.30
Max	10.5	26	14	75.5	65.4	100
Median	8.8	2.5	1.6	14.8	12.3	86
Mean	8.9	5.9	5.6	20.8	17.7	79

Summary of key analytes for nicotine pouch products analyzed by Mallock et al. (2024); 44 anonymized German products were obtained in 2021 and analyzed. Results originally reported in WWB; no basis conversion was performed. ND/BQL values were excluded prior to analysis as described in Chapter II: Materials & Methods, Data Harmonization.

^a Free Nicotine (%) calculated from reported Free Nicotine (mg/g) and Total Nicotine (mg/g) content as described in Chapter II: Materials & Methods, Data Harmonization.

Table 39. Nicotine Pouch Detailed Results – Back et al. (2023).

Product Name	pH	Total Nicotine (mean mg/g ± SD)	Free Nicotine (mean mg/g ± SD)	Free Nicotine ^a (mean % ± SD)
ZYN (Dry)	8.3	7.63 ± 0.21	4.87 ± 0.36	65.58 ± 5.03
ZYN (Moist)	8.3	12.00 ± 0.00	7.87 ± 0.00	65.58 ± 0.00
Min	8.3	7.63	4.87	65.58
Max	8.3	12.00	7.87	65.58
Mean	8.3	9.82	6.37	65.58

Summary of key analytes for nicotine pouch products analyzed by Back et al. (2023); two products from one Swedish manufacturer were analyzed, product acquisition date not mentioned. Results originally reported in WWB; no basis conversion was performed as described in Chapter II: Materials & Methods, Data Harmonization.

^a Free Nicotine (%) calculated from reported Free Nicotine (mg/g) and Total Nicotine (mg/g) content as described in Chapter II: Materials & Methods, Data Harmonization.

References

- Alalwan, M. A., Mays, D., Berman, M. L., El-Hellani, A., Keller-Hamilton, B. L., Brinkman, M. C., Wagener, T. L., & Tackett, A. P. (2024). Oral nicotine pouch manufacturer's reduced exposure claims require evidence and regulatory oversight. *Tobacco Control*. <https://doi.org/10.1136/tc-2024-058610>
- Araghi, M., Galanti, M. R., Lundberg, M., Liu, Z., Ye, W., Lager, A., Engström, G., Alfredsson, L., Knutsson, A., Norberg, M., Wennberg, P., Lagerros, Y. T., Bellocco, R., Pedersen, N. L., Östergren, P.-O., & Magnusson, C. (2021). No association between moist oral snuff (snus) use and oral cancer: Pooled analysis of nine prospective observational studies. *Scandinavian Journal of Public Health*, 49(8), 833–840. <https://doi.org/10.1177/1403494820919572>
- Azzopardi, D., Liu, C., & Murphy, J. (2021). Chemical characterization of tobacco-free “modern” oral nicotine pouches and their position on the toxicant and risk continuums. *Drug and Chemical Toxicology*, 45(5), 2246–2254. <https://doi.org/10.1080/01480545.2021.1925691>
- Back, S., Masser, A. E., Rutqvist, L. E., & Lindholm, J. (2023). Harmful and potentially harmful constituents (HPHCs) in two novel nicotine pouch products in comparison with regular smokeless tobacco products and pharmaceutical nicotine replacement therapy products (NRTs). *BMC Chemistry*, 17(1), 9. <https://doi.org/10.1186/s13065-023-00918-1>
- Bhide, S. V., Nair, J., Maru, G. B., Nair, U. J., Rao, B. V. K., Chakraborty, M. K., & Brunnemann, K. D. (1987). Tobacco-specific N-nitrosamines [TSNA] in green mature and processed tobacco leaves from India. *Beiträge Zur Tabakforschung International*, 14(1), 29–32. <https://doi.org/10.2478/cttr-2013-0581>
- Brunnemann, K. D., Prokopczyk, B., Djordjevic, M. V., & Hoffmann, D. (1996). Formation and analysis of tobacco-specific N-nitrosamines. *Critical Reviews in Toxicology*, 26(2), 121–137. <https://doi.org/10.3109/10408449609017926>
- Cheetham, A. G., Plunkett, S., Campbell, P., Hilldrup, J., Coffa, B. G., Gilliland, S., & Eckard, S. (2022). Analysis and differentiation of tobacco-derived and synthetic nicotine products: Addressing an urgent regulatory issue. *PLoS One*, 17(4), e0267049. <https://doi.org/10.1371/journal.pone.0267049>
- Christen, A. G., & Glover, E. D. (1987). History of Smokeless Tobacco Use in the United States. *Health Education (Washington, D.C. 1975)*, 18(3), 6–13. <https://doi.org/10.1080/00970050.1987.10614497>

- Christen, A. G., Swanson, B. Z., Glover, E. D., & Henderson, A. H. (1982). Smokeless Tobacco: The Folklore and Social History of Snuffing, Sneezing, Dipping, and Chewing. *The Journal of the American Dental Association* (1939), 105(5), 821–829. <https://doi.org/10.14219/jada.archive.1982.0453>
- Connecticut's Official State Website. (n.d.). Online Business Search. Retrieved March 29, 2025, from <https://service.ct.gov/business/s/onlinebusinesssearch?businessNameEn=HEPBxaDWCgQ%2BqTIXYQn8%2B4b4NvWuXhjU38kkfoW7J09Jpzq8qbYzfX8UzI0M%2FVHo>
- Connolly, G. N., Winn, D. M., Hecht, S. S., Henningfield, J. E., Walker, B., & Hoffmann, D. (1986). The Reemergence of Smokeless Tobacco. *The New England Journal of Medicine*, 314(16), 1020–1027. <https://doi.org/10.1056/NEJM198604173141605>
- Connolly, G. N. (1995). The marketing of nicotine addiction by one oral snuff manufacturer. *Tobacco Control*, 4(1), 73–79. <https://doi.org/10.1136/tc.4.1.73>
- Convenience Store News. (2020). Dollar share of smokeless tobacco sales in the United States in 2020, by brand* [Graph]. Statista. <https://www-statista-com.ezp-prod1.hul.harvard.edu/statistics/1096963/smokeless-tobacco-market-share-us-by-region/>
- Delnevo, C. D., Wackowski, O. A., Giovenco, D. P., Manderski, M. T. B., Hrywna, M., & Ling, P. M. (2014). Examining market trends in the United States smokeless tobacco use: 2005–2011. *Tobacco Control*, 23(2), 107–112. <https://doi.org/10.1136/tobaccocontrol-2012-050739>
- Djordjevic, M. V., Fan, Jingrun., Bush, L. P., Brunnemann, K. D., & Hoffmann, Dietrich. (1993). Effects of storage conditions on levels of tobacco-specific N-nitrosamines and N-nitrosamino acids in U.S. moist snuff. *Journal of Agricultural and Food Chemistry*, 41(10), 1790–1794. <https://doi.org/10.1021/jf00034a051>
- Edwards, S. H., Rossiter, L. M., Taylor, K. M., Holman, M. R., Zhang, L., Ding, Y. S., & Watson, C. H. (2017). Tobacco-Specific Nitrosamines in the Tobacco and Mainstream Smoke of U.S. Commercial Cigarettes. *Chemical Research in Toxicology*, 30(2), 540–551. <https://doi.org/10.1021/acs.chemrestox.6b00268>
- FDA Center for Tobacco Products. (2020, July 28). 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. FDA. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reporting-harmful-and-potentially-harmful-constituents-tobacco-products-and-tobacco-smoke-under>
- FDA Center for Tobacco Products. (2024, February 6). Regulation and Enforcement of Non-Tobacco Nicotine (NTN) Products. FDA; FDA.

<https://www.fda.gov/tobacco-products/products-ingredients-components/regulation-and-enforcement-non-tobacco-nicotine-ntn-products>

Federal Trade Commission. (2023). Smokeless Tobacco Report for 2022 (Smokeless Tobacco Report, pp. 28–34). Federal Trade Commission.

https://www.ftc.gov/system/files/ftc_gov/pdf/2022-Smokeless-Tobacco-Report.pdf

Fisher, M. T., Bennett, C. B., Hayes, A., Kargalioglu, Y., Knox, B. L., Xu, D., Muhammad-Kah, R., & Gaworski, C. L. (2012). Sources of and technical approaches for the abatement of tobacco specific nitrosamine formation in moist smokeless tobacco products. *Food and Chemical Toxicology*, 50(3–4), 942–948. <https://doi.org/10.1016/j.fct.2011.11.035>

Foulds, J., Ramstrom, L., Burke, M., & Fagerström, K. (2003). Effect of smokeless tobacco (snus) on smoking and public health in Sweden. *Tobacco Control*, 12(4), 349–359. <https://doi.org/10.1136/tc.12.4.349>

Frithiof, L., Anneroth, G., Lasso, U., & Sederholm, C. (1983). The snuff-induced lesion. A clinical and morphological study of a Swedish material. *Acta Odontologica Scandinavica*, 41(1), 53–64. <https://doi.org/10.3109/00016358309162303>

Gilljam, H., & Galanti, M. R. (2003). Role of snus (oral moist snuff) in smoking cessation and smoking reduction in Sweden. *Addiction*, 98(9), 1183–1189. <https://doi.org/10.1046/j.1360-0443.2003.00379.x>

Heimann, R.K. (1960) *Tobacco and Americans*, New York, McGraw-Hill, pp. 65, 118, 236.

Hendlin, Y. H., Veffler, J. R., Lewis, M. J., Ling, P. M. (2017). Beyond the brotherhood: Skoal Bandits' role in the evolution of marketing moist smokeless tobacco pouches. *Tobacco Induced Diseases*, 15(December), 46. <https://doi.org/10.1186/s12971-017-0150-y>

Henningfield, J. E., & Keenan, R. M. (1993). Nicotine delivery kinetics and abuse liability. *Journal of Consulting and Clinical Psychology*, 61(5), 743–750. <https://doi.org/10.1037/0022-006X.61.5.743>

IARC. (2025). Agents Classified by the IARC Monographs, Volumes 1-138. https://monographs.iarc.who.int/wp-content/uploads/2019/07/Classifications_by_cancer_site.pdf

IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (Ed.). (2007). *Smokeless Tobacco and Some Tobacco-specific N-Nitrosamines* (Vol. 89). World Health Organization, International Agency for Research on Cancer ; distributed by WHO Press. <https://www.ncbi.nlm.nih.gov/books/NBK326503/>

- Jackson, J. M., Weke, A., & Holliday, R. (2023). Nicotine pouches: A review for the dental team. *British Dental Journal*, 235(8), 643–646. <https://doi.org/10.1038/s41415-023-6383-7>
- Joksic, G., Spasojevic-Tisma, V., Antic, R., Nilsson, R., & Rutqvist, L. E. (2011). Randomized, placebo-controlled, double-blind trial of Swedish snus for smoking reduction and cessation. *Harm Reduction Journal*, 8, 25. <https://doi.org/10.1186/1477-7517-8-25>
- Knezevich, A., Muzic, J., Hatsukami, D. K., Hecht, S. S., & Stepanov, I. (2013). Nor nicotine Nitrosation in Saliva and Its Relation to Endogenous Synthesis of N'-Nitrosanor nicotine in Humans. *Nicotine & Tobacco Research*, 15(2), 591–595. <https://doi.org/10.1093/ntr/nts172>
- Kopperud, S. E., Ansteinsson, V., Mdala, I., Becher, R., & Valen, H. (2023). Oral lesions associated with daily use of snus, a moist smokeless tobacco product. A cross-sectional study among Norwegian adolescents. *Acta Odontologica Scandinavica*, 81(6), 473–478. <https://doi.org/10.1080/00016357.2023.2178502>
- Lawler, T. S., Stanfill, S. B., Zhang, L., Ashley, D. L., & Watson, C. H. (2013). Chemical characterization of domestic oral tobacco products: Total nicotine, pH, unprotonated nicotine and tobacco-specific N-nitrosamines. *Food and Chemical Toxicology*, 57, 380–386. <https://doi.org/10.1016/j.fct.2013.03.011>
- Lawler, T. S., Stanfill, S. B., Tran, H. T., Lee, G. E., Chen, P. X., Kimbrell, J. B., Lisko, J. G., Fernandez, C., Caudill, S. P., deCastro, B. R., & Watson, C. H. (2020). Chemical analysis of snus products from the United States and northern Europe. *PLOS ONE*, 15(1), e0227837. <https://doi.org/10.1371/journal.pone.0227837>
- Lee, P. N. (2011). Summary of the epidemiological evidence relating snus to health. *Regulatory Toxicology and Pharmacology*, 59(2), 197–214. <https://doi.org/10.1016/j.yrtph.2010.12.002>
- Lee, P. N., & Hamling, J. (2009). Systematic review of the relation between smokeless tobacco and cancer in Europe and North America. *BMC Medicine*, 7, 36. <https://doi.org/10.1186/1741-7015-7-36>
- Lide, D. R. (Ed.). (1990). *CRC Handbook of Chemistry and Physics* (71st ed.). CRC Press.
- Liu, J., & Halpern-Felsher, B. (2024). Popularity of Zyn and other nicotine pouch brands among U.S. adolescents, young adults, and adults in 2021. *Preventive Medicine*, 185, 108068-. <https://doi.org/10.1016/j.ypmed.2024.108068>
- Lund, I., & Scheffels, J. (2014). Perceptions of relative risk of disease and addiction from cigarettes and snus: Psychology of Addictive Behaviors. *Psychology of Addictive Behaviors*, 28(2), 367–375. <https://doi.org/10.1037/a0032657>

- Luo, J., Ye, W., Zendehdel, K., Adami, J., Adami, H.-O., Boffetta, P., & Nyrén, O. (2007). 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. *Lancet* (London, England), 369(9578), 2015–2020. [https://doi.org/10.1016/S0140-6736\(07\)60678-3](https://doi.org/10.1016/S0140-6736(07)60678-3)
- Majmundar, A., Okitondo, C., Xue, A., Asare, S., Bandi, P., & Nargis, N. (2022). Nicotine Pouch Sales Trends in the US by Volume and Nicotine Concentration Levels From 2019 to 2022. *JAMA Network Open*, 5(11), e2242235. <https://doi.org/10.1001/jamanetworkopen.2022.42235>
- Mallock, N., Schulz, T., Malke, S., Dreijack, N., Laux, P., & Luch, A. (2024). Levels of nicotine and tobacco-specific nitrosamines in oral nicotine pouches. *Tobacco Control*, 33(2), 193–199. <https://doi.org/10.1136/tc-2022-057280>
- McAdam, K. G., Faizi, A., Kimpton, H., Porter, A., & Rodu, B. (2013). Polycyclic aromatic hydrocarbons in US and Swedish smokeless tobacco products. *Chemistry Central Journal*, 7(1), 151. <https://doi.org/10.1186/1752-153X-7-151>
- McAdam, K. G., Kimpton, H., Faizi, A., Porter, A., & Rodu, B. (2019). The composition of contemporary American and Swedish smokeless tobacco products. *BMC Chemistry*, 13(1), 31. <https://doi.org/10.1186/s13065-019-0548-0>
- New Jersey Department of the Treasury Division of Revenue & Enterprise Services. (n.d.). Business Name Search. Retrieved March 29, 2025, from <https://www.njportal.com/DOR/BusinessNameSearch/Search/BusinessName>
- Nordgren, P., & Ramström, L. (1990). Moist snuff in Sweden—Tradition and evolution. *British Journal of Addiction*, 85(9), 1107–1112. <https://doi.org/10.1111/j.1360-0443.1990.tb03435.x>
- Nyrén, O., Bergström, R., Nyström, L., Engholm, G., Ekbom, A., Adami, H.-O., Knutsson, A., & Stjernberg, N. (1996). Smoking and Colorectal Cancer: A 20-Year Follow-up Study of Swedish Construction Workers. *JNCI: Journal of the National Cancer Institute*, 88(18), 1302–1307. <https://doi.org/10.1093/jnci/88.18.1302>
- Owusu, D., Mamudu, H. M., Collins, C., Robertson, C., Wang, L., Rafie, B., & Littleton, M. A. (2019). The Usage and Associated Factors of Alternative Tobacco Products among School-going Youth in Central Appalachia. *Journal of Health Care for the Poor and Underserved*, 30(1), 249–264.
- Philip Morris International. (n.d.). All about: Snus, snuff, and nicotine pouches. All about: Snus, Snuff, and Nicotine Pouches. Retrieved April 13, 2025, from <https://www.pmi.com/our-science/www.pmi.com/our-science/snus-snuff-nicotine-pouches-explained>

- Philip Morris International. (2025). Nicotine Pouches | Oral Products—PMI Science. Wwww.Pmiscience.Com. <https://www.pmiscience.com/en/products/oral-nicotine-pouches/>
- Rensch, J., Liu, J., Wang, J., Vansickel, A., Edmiston, J., & Sarkar, M. (2021). Nicotine pharmacokinetics and subjective response among adult smokers using different flavors of on!® nicotine pouches compared to combustible cigarettes. *Psychopharmacology*, 238(11), 3325–3334. <https://doi.org/10.1007/s00213-021-05948-y>
- Research and Markets. (2025, January 27). Smokeless Tobacco Market Share, Trends and Forecast Report. <https://www.globenewswire.com/news-release/2025/01/27/3015492/28124/en/Smokeless-Tobacco-Market-Share-Trends-and-Forecast-Report-2025-2033-with-Altria-Group-British-American-Tobacco-DS-Group-Imperial-Brands-Japan-Tobacco-Mac-Baren-Tobacco-Swedish-Mate.html>
- Richter, P., Hodge, K., Stanfill, S., Zhang, L., & Watson, C. (2008). Surveillance of moist snuff: Total nicotine, moisture, pH, un-ionized nicotine, and tobacco-specific nitrosamines. *Nicotine & Tobacco Research*, 10(11), 1645–1652. <https://doi.org/10.1080/14622200802412937>
- Robichaud, M. O., Seidenberg, A. B., & Byron, M. J. (2020). Tobacco companies introduce ‘tobacco-free’ nicotine pouches. *Tobacco Control*, 29(e1), e145–e146. <https://doi.org/10.1136/tobaccocontrol-2019-055321>
- Rodu, B., Stegmayr, B., Nasic, S., & Asplund, K. (2002). Impact of smokeless tobacco use on smoking in northern Sweden. *Journal of Internal Medicine*, 252(5), 398–404. <https://doi.org/10.1046/j.1365-2796.2002.01057.x>
- Roosaar, A., Johansson, A. L. V., Sandborgh-Englund, G., Nyrén, O., & Axéll, T. (2006). A long-term follow-up study on the natural course of snus-induced lesions among Swedish snus users. *International Journal of Cancer*, 119(2), 392–397. <https://doi.org/10.1002/ijc.21841>
- Rutqvist, L. E., Curvall, M., Hassler, T., Ringberger, T., & Wahlberg, I. (2011). Swedish snus and the GothiaTek® standard. *Harm Reduction Journal*, 8(1), 11. <https://doi.org/10.1186/1477-7517-8-11>
- Sapundzhiev, N., & Werner, J. A. (2003). Nasal snuff: historical review and health related aspects. *The Journal of Laryngology & Otology*, 117(9), 686–691. doi:10.1258/002221503322334486
- Sohlberg, T., & Wennberg, P. (2020). Snus cessation patterns—A long-term follow-up of snus users in Sweden. *Harm Reduction Journal*, 17, 1–9. <https://doi.org/10.1186/s12954-020-00405-z>

- Song, M.-A., Marian, C., Brasky, T. M., Reisinger, S., Djordjevic, M., & Shields, P. G. (2016). Chemical and toxicological characteristics of conventional and low-TSNA moist snuff tobacco products. *Toxicology Letters*, 245, 68–77. <https://doi.org/10.1016/j.toxlet.2016.01.012>
- Staaf, M., Back, S., Wiernik, A., Wahlberg, I., Long, R. C., & Young, J. H. (2005). Formation of Tobacco-Specific Nitrosamines (TSNA) During Air-Curing: Conditions and Control. *Contributions to Tobacco & Nicotine Research*, 21(6), 321–330. <https://doi.org/10.2478/cttr-2013-0798>
- Stanfill, S., Tran, H., Tyx, R., Fernandez, C., Zhu, W., Marynak, K., King, B., Valentín-Blasini, L., Blount, B. C., & Watson, C. (2021). Characterization of Total and Unprotonated (Free) Nicotine Content of Nicotine Pouch Products. *Nicotine & Tobacco Research*, 23(9), 1590–1596. <https://doi.org/10.1093/ntr/ntab030>
- Stepanov, I., Biener, L., Knezevich, A., Nyman, A. L., Bliss, R., Jensen, J., Hecht, S. S., & Hatsukami, D. K. (2012). 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), 274–281. <https://doi.org/10.1093/ntr/ntr209>
- Stepanov, I., Yershova, K., Carmella, S., Upadhyaya, P., & Hecht, S. S. (2013). Levels of (S)-N'-Nitrosonornicotine in U.S. Tobacco Products. *Nicotine & Tobacco Research*, 15(7), 1305–1310. <https://doi.org/10.1093/ntr/nts249>
- Stepanov, I., Biener, L., Yershova, K., Nyman, A. L., Bliss, R., Parascandola, M., & Hatsukami, D. K. (2014). Monitoring Tobacco-Specific N-Nitrosamines and Nicotine in Novel Smokeless Tobacco Products: Findings From Round II of the New Product Watch. *Nicotine & Tobacco Research*, 16(8), 1070–1078. <https://doi.org/10.1093/ntr/ntu026>
- Stewart, G. G. (1967). A HISTORY OF THE MEDICINAL USE OF TOBACCO 1492–1860. *Medical History*, 11(3), 228–268. <https://doi.org/10.1017/S0025727300012333>
- Swedish Match AB. (2013, October 17). Swedish Match—Svenska Tobaks AB. Company History: Svenska Tobaks AB. <https://www.swedishmatch.com/Our-company/Company-history/Svenska-Tobaks-AB/>
- Thompson, J. (1870). Three fashionable luxuries : namely, smoking, chewing, and snuffing, or, Facts about tobacco, including its history, nature, and effects. Published by the author.
- Tyx, R. E., Rivera, A. J., Satten, G. A., Keong, L. M., Kuklenyik, P., Lee, G. E., Lawler, T. S., Kimbrell, J. B., Stanfill, S. B., Valentin-Blasini, L., & Watson, C. H. (2022). Associations between microbial communities and key chemical constituents in U.S. domestic moist snuff. *PLOS ONE*, 17(5), e0267104. <https://doi.org/10.1371/journal.pone.0267104>

- Voges E. The pleasures of tobacco — How it all began and the whole story. *Tob. J. int.* 1984;1:80–82.
- Wang, Y., Sung, H.-Y., Lightwood, J., Chaffee, B. W., Yao, T., & Max, W. (2018). Health Care Utilization and Expenditures Attributable to Smokeless Tobacco Use Among US Adults. *Nicotine & Tobacco Research*, 20(11), 1359–1368. <https://doi.org/10.1093/ntr/ntx196>
- Wilson, K. M., Markt, S. C., Fang, F., Nordenvall, C., Rider, J. R., Ye, W., Adami, H.-O., Stattin, P., Nyrén, O., & Mucci, L. A. (2016). Snus use, smoking and survival among prostate cancer patients. *International Journal of Cancer*, 139(12), 2753–2759. <https://doi.org/10.1002/ijc.30411>
- World Health Organization. (2021, November 16). Tobacco use falling: WHO urges countries to invest in helping more people to quit tobacco. World Health Organization. <https://www.who.int/news/item/16-11-2021-tobacco-use-falling-who-urges-countries-to-invest-in-helping-more-people-to-quit-tobacco>
- Ye, D., & Rahman, I. (2023). Emerging Oral Nicotine Products and Periodontal Diseases. *International Journal of Dentistry*, 2023, 1–7. <https://doi.org/10.1155/2023/9437475>
- Zamarripa, C. A., Dowd, A. N., Elder, H. J., Czaplicki, L., Tfayli, D., Rastogi, K., Thrul, J., Strickland, J. C., Moran, M. B., & Spindle, T. R. (2025). A comprehensive review on oral nicotine pouches: Available scientific evidence and future research needs. *Experimental and Clinical Psychopharmacology*, 33(2), 123–132. <https://doi.org/10.1037/pha0000755>
- Zatterstrom, U., Svensson, M., Sand, L., Nordgren, H., & Hirsch, J. (2004). Oral cancer after using Swedish snus (smokeless tobacco) for 70 years – a case report. *Oral Diseases*, 10(1), 50–53. <https://doi.org/10.1111/j.1601-0825.2004.00959.x>