Changing Smokeless Tobacco Products

New Tobacco-Delivery Systems

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Abstract: Smokeless or noncombusted oral tobacco use as a substitute for cigarette smoking has been gaining greater interest and attention by the public health community and the tobacco industry. In order for the product to appeal to smokers, tobacco companies have been manufacturing new noncombusted oral tobacco (i.e., moist snuff) that is lower in moisture content and nitrosamine levels, packaged in small sachets and "spitless." While the primary motives of the major tobacco companies are to maintain or increase tobacco use, some members of the public health community perceive the use of noncombusted oral tobacco products as a harm reduction tool. Because cigarette smoking is associated with greater toxicant exposure compared to noncombusted oral tobacco, reduced mortality and morbidity are hypothesized to ensue, if cigarette smokers switched completely to these products. However, variability exists in levels of nicotine and toxicants and potential health consequences from use within and across countries. Therefore, promulgating noncombusted oral tobacco products as a safer alternative to smoking or as a substitute for smoking may engender more rather than less harm. To date, limited research is available on the effects of marketing noncombusted oral tobacco products to smokers, to support the use of these products as a harm reduction tool, and to determine the effects of varying levels of tobacco toxicants including nicotine on health. The need exists for manufacturing standards to lower toxicant levels of all noncombusted oral tobacco products, for the formulation of appropriate tobacco-product regulations and for the development of a strategic plan by the public health community to address this controversial topic.
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Introduction

Marketing strategies and types of available smokeless tobacco products have been evolving in the United States. Products are being manufactured to appeal to cigarette smokers (e.g., spitless, in small tea-like packets, different flavorings) and promoted to be used in situations where they cannot smoke or as a substitute or alternative to smoking. The U.S. Smokeless Tobacco Company (USSTC; Greenwich CT) filed a request for an Advisory Opinion with the Federal Trade Commission (FTC) seeking guidance "regarding the acceptability of communicating in advertising that smokeless tobacco products are considered to be a significantly reduced risk alternative as compared to cigarette smoking" (letter submitted in February 2002, withdrawn August 2002, additional information submitted in May 2003). The availability and marketing of these products address two primary concerns faced by cigarette smokers: increasing bans on smoking and health risks associated with smoking. For tobacco companies, these products may serve to maintain tobacco use among existing smokers and to recruit new tobacco users.

In the public health community, smokeless tobacco use as a complete substitute for cigarette smoking or as a method of cessation is gaining support, but remains hotly debated. Tobacco harm-reduction approaches, such as the use of smokeless tobacco among smokers unwilling or unable to quit, have been considered as a feasible alternative that can potentially reduce tobacco-related morbidity and mortality, even with continued use of products that contain tobacco constituents.[1] A thoughtful, unbiased examination of the feasibility of methods to reduce tobacco-related harms that do not preempt other tobacco-control measures such as prevention and cessation is urgently needed. Currently, cigarette smoking is the leading cause of death in the U.S., accounting for approximately one in six deaths (438,000 each year) and 5.5 million years of potential life lost. In 2005, approximately one fifth (45.1 million) of the U.S. adult population were smokers.[2] Although an estimated 70% of smokers (33.2 million) would like

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to quit, successful long-term abstinence remains low (2.5% or 1.2 million smokers per year).[3,4] Worldwide, approximately 1.3 billion people smoke and about 4.9 million die from tobacco-related illnesses each year. If present consumption patterns continue, an estimated 10 million people will die each year from tobacco-related disease by the year 2020.[5,6]

Excepting nicotine pharmaceuticals, of the various currently available potential reduced exposure products (PREPs) that may result in actual harm reduction, smokeless tobacco products have the greatest potential to reduce risk for disease if smokers completely switch from cigarettes to these products. For example, the relative risk for disease with "low-nitrosamine" smokeless tobacco is considered to be at least 90% less than cigarette smoking.[7] In a report by the Tobacco Advisory Group of the Royal College of Physicians,[8] smokeless tobacco use is considered 10–1000 times less hazardous than cigarette smoking, depending on the product. Unlike cigarette smoking, smokeless tobacco use has not been linked to many of the smoking-related cancers[9,10] or to pulmonary disease.[11] Epidemiologic data from Sweden have been used to support the hypothesis that switching from cigarettes to smokeless tobacco products can significantly reduce tobacco-related morbidity and mortality among tobacco consumers. A reduction in lung cancer in Sweden has been observed in men. This reduction has been attributed by some investigators to the increased use of "snus" (i.e., Swedish snuff) and a corresponding reduction in cigarette smoking.[12,13] The decline in smoking has not been as dramatic in women, potentially due to the limited uptake of snus among women. Other researchers have debated this interpretation based on the observation that the prevalence of smokeless tobacco use is "not consistently associated with a reduction in smoking initiation or prevalence."[14] Many public health scientists and advocates are concerned that the Swedish experience would not be replicated elsewhere. However, if a significant number of current smokers who would not have otherwise quit switched completely to "low-nitrosamine" oral tobacco products, then a significant reduction in prevalence of tobacco-related disease is likely to occur.[7]

The aims of this article are to describe the extant literature on newer smokeless tobacco products directed at smokers, the currently existing literature on the toxicity of these products, including nicotine addiction, and future directions for research.

Types of Smokeless Tobacco Products

Several types of smokeless tobacco products are available which can be administered orally or nasally. Moist snuff is finely ground or shredded tobacco sold either loose or in packets (i.e., sachets) and used orally. A user places a pinch or dip between the cheek and gum. Dry snuff is fine powdered tobacco and can be used either orally or nasally. Chewing tobacco comes as twist, plug, or loose leaf. The user places a "wad" of this product inside the cheek. Moist snuff and chewing tobacco may require spitting and therefore has been referred to as "spit tobacco." Other smokeless tobacco products are tobacco mixed with other substances. Alaskan natives, for example, mix tobacco leaves with ash from a woody fungus that grows on the bark of birch trees (i.e., punk ash). This product is frequently referred to as Iq-mik.[15] In India, Southeast Asia, or the United Kingdom, tobacco is mixed with areca nut, lime, flavorings, or spices and is either manufactured or handmade (e.g., betel quid in India). Newer products being marketed primarily to cigarette smokers are sold as pouched, "spitless" moist snuff or compressed tobacco lozenges. Swedish Match (Stockholm, Sweden) introduced a Swedish snus, Exalt, to the U.S., but this product is no longer sold in this country. The processing of Swedish snus involves heat treatment or pasteurization rather than fermentation. This leads to lower levels of tobacco-specific nitrosamines (TSNAs) than in some American products. Furthermore, Swedish Match has introduced voluntary standards, called GothiaTek® (www.gothiatek.com) that set limits for oral tobacco constituents, and specify standards for manufacturing and for the provision of consumer information. Because snus is included in the Swedish Food Act, only additives and flavorants that are permitted in foods are allowed in snus. In addition, Swedish Match reports that the nontobacco-specific compounds have established limits that are comparable to food products. The manufacturers recommend that retailers refrigerate the products to keep them "fresh" (e.g., prevent further nitrosamine formation) and to meet the "best-before" criteria.

The U.S. Smokeless Tobacco Company (USSTC) introduced Revel in 2001. This product is marketed as a "unique, discreet option for adult smokers seeking an alternative that allows them to enjoy real tobacco satisfaction without lighting up." Revel was developed "for smokers living in a no-smoking world" and is described as "not like nicotine gum or tobacco-cessation product." The products are 100% American tobacco and available in mint, wintergreen, and cinnamon. In 2006, USSTC manufactured and now is test-marketing Skoal Dry, which is likely to replace Revel. This product uses a bigger pouch than Revel and comes in regular and mint flavors. The method of curing and processing of these products is publicly unknown. Also, in 2006, Camel Snus (marketed by Reynolds American, Inc., Winston-Salem NC) and Taboka Tobaccopak (manufactured by Phillip Morris, Richmond VA) were introduced for test marketing. Camel Snus is manufactured by Swedish Match and adheres to the same manufacturing standards as the other Swedish snus products. Furthermore, retailers store Camel snus in a chilled container, but the product does not have to be

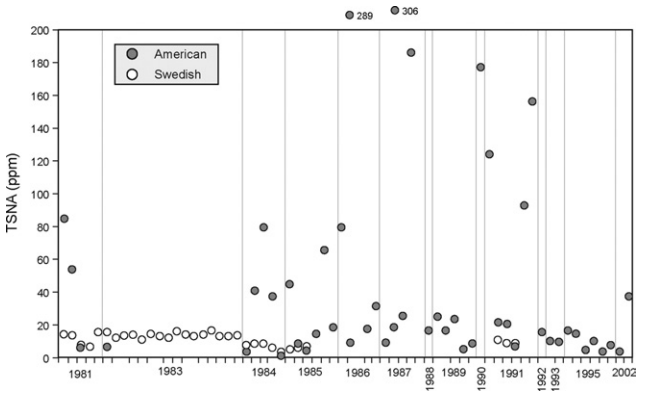

Figure 1. Historic levels of tobacco-specific nitrosamines in noncombusted oral tobacco products.[25]
ppm, parts per million; TSNA, tobacco-specific nitrosamine.

refrigerated during use. Camel snus is sold in spice, menthol, and original flavors. Taboka, similar to Swedish snus, contains pasteurized tobacco. However, compared to Swedish snus, this product is lower in moisture content, includes a flavor-strip technology, has a reduced salt content, and does not require refrigeration. It comes in original (Taboka) or mint (Taboka Green) flavors. Recently, Phillip Morris announced that it was test-marketing Marlboro snus.[16]

In 2001 and 2003, Star Scientific (Chester VA) introduced two smokeless tobacco potentially-reduced-exposure products, Ariva and Stonewall. Ariva was also designed to be used by smokers in situations where they cannot smoke, while Stonewall was designed as an alternative to moist snuff.[17] Both products have been through the process of "Star-curing," an innovative method of curing tobacco which may nearly eliminate the TSNAs, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N′-nitrosonornicotine (NNN), from the tobacco. Star-curing is a patented two-step process that does not involve chemicals, solvents, or other additives. The leaf is dried in a barn for approximately 24–36 hours at about 100–110°F, until it turns yellow. It is then pressed to remove moisture and microwaved until moisture is reduced by an additional 10%.[18] According to research by Star Scientific and independent sources, the StarCured process preserves the normal nicotine and monoamine oxidase (MAO) inhibitor content, while reducing TSNAs to "almost undetectable levels."[19,20]

The newer smokeless tobacco products make the term "spit tobacco" seem antiquated. Furthermore, because newer cigarette-like devices that are being developed have been shown to emit minimal secondhand smoke,[21] the term smokeless tobacco appears to lack specificity. In this paper, these products are predominantly referred to as "noncombusted oral tobacco products," which seems to be a more specific and descriptive terminology for the current "smokeless tobacco" products.

Toxicants of Noncombusted Oral Tobacco Products

Although oral tobacco products lack the toxicants associated with combustion, they include 28 known carcinogens.[22] Some of these carcinogens are TSNAs. The TSNAs that have been most strongly linked to cancer are NNK and NNN. These TSNAs are formed during curing, processing, and aging of tobacco and are present in both burned and unburned tobacco. According to the International Agency for Research on Cancer (IARC), these TSNAs are considered Group 1 carcinogens. They cause tumors of the oral cavity, esophagus, pancreas, and lung in laboratory animals.[23,24] The TSNAs in some noncombusted oral tobacco products manufactured in Sweden and the U.S. have decreased over time. Products in Sweden are now typically below 10 ppm and products in the U.S. are typically below 20 ppm (Figure 1).[25] Several studies have examined amounts of TSNAs in oral tobacco products in various countries.[26–30] Figure 2 shows a compilation of a few of the recent studies that have measured NNN and NNK in the U.S.,[28] Sweden,[30] and India[29] and illustrates three primary points. First, there is a wide variability in carcinogen levels among oral tobacco forms found in the U.S., Sweden, and India. The highest levels reported are found in a product made in Sudan called toombak, which is a mixture of tobacco and sodium bicarbonate (amounts not shown in Figure 2). The levels of TSNAs in this type of product are in the thousands of micrograms per gram dry weight.[26] Second, there are significant differences in TSNAs among the various U.S. brands despite the general decrease in overall levels of carcinogens (Figure 1). These differences occur even within the same U.S. brand bought in different locations[31,32] (e.g., Copenhagen had NNK values varying from 1.45 to 3.20

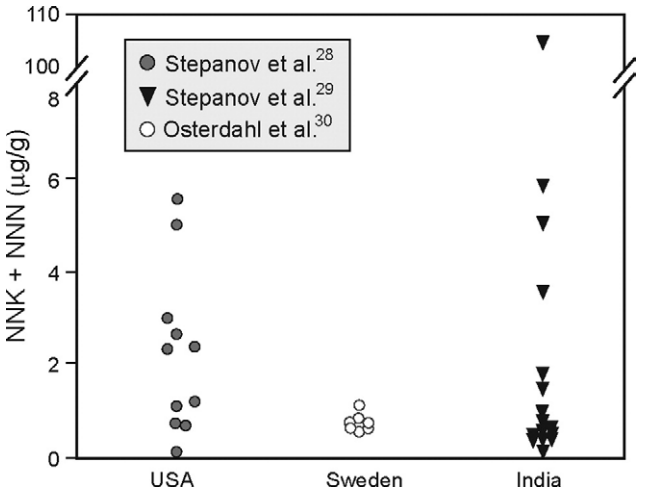

Figure 2. NNK and NNN levels in noncombusted oral tobacco products across and within countries.
NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, nitrosonornicotine.

Table 1. Tobacco-specific nitrosamine levels[28]

Tobacco products	Tobacco-specific nitrosamine level (μg/g product wet weight)				
	NNN	NNK	NAT	NAB	Total
New tobacco products					
Hard snuff					
Ariva	0.019	0.037	0.12	0.008	0.19[a]
Stonewall	0.056	0.043	0.17	0.007	0.28[b]
Swedish snus					
General	0.98	0.18	0.79	0.06	2.0[c]
Spit-free tobacco packets					
Exalt					
Purchased in Sweden	2.3	0.27	0.98	0.13	3.7[d]
Purchased in the U.S.	2.1	0.24	0.68	0.05	3.1[b]
Revel					
Mint flavor	0.62	0.033	0.32	0.018	0.99[b]
Wintergreen flavor	0.64	0.032	0.31	0.017	1.0[b]
Camel Snus					
Original	0.79	0.16	0.19	0.008	1.15[b]
Spice	0.87	0.09	0.20	0.010	1.17[b]
Frost	0.83	0.16	0.13	0.006	1.12[b]
Taboka					
Taboka	0.91	0.06	0.30	nd	1.27[b]
Taboka Green	0.82	0.07	0.24	0.002	1.13[b]
Nicotine replacement therapy products					
NicoDerm CQ (patch, 24-mg nicotine)[e]	nd	0.008	nd	nd	0.008[b]
Nicorette (gum, 4-mg nicotine)[e]	0.002	nd	nd	nd	0.002[b]
Commit (lozenge, 2-mg nicotine)[e]	nd	nd	nd	nd	nd[b]
Conventional smokeless tobacco products					
Copenhagen					
Snuff	2.2	0.75	1.8	0.12	4.8[b]
Long cut	3.9	1.6	1.9	0.13	7.5[b]
Skoal					
Long cut straight	4.5	0.47	4.1	0.22	9.2[b]
Bandits	0.9	0.17	0.24	0.014	1.3[b]
Kodiak					
Ice	2.0	0.29	0.72	0.063	3.1[b]
Wintergreen	2.2	0.41	1.8	0.15	4.5[b]

[a]Mean of five analyses, each performed in duplicate.
[b]Single analysis performed in duplicate.
[c]Mean of two analyses, each performed in duplicate.
[d]Mean of three analyses, each performed in duplicate.
[e]Values are expressed per piece.
NNN, *N*′-nitrosonornicotine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NAT, N-nitrosoanatabine; NAB, N-nitrosoanabasine; nd, not detected.

μg/g dry weight with a coefficient of variation of 32.9%[32]) and can vary depending on length of time on the shelves.[33] Products manufactured in Sweden and sold in the U.S. also show some variability and higher levels of TSNAs than the snus products sold in Sweden.[28] The differences in TSNAs among oral tobacco products used in India are more dramatic with values ranging from 1.2 to 128 μg/g product wet weight. Third, products in Sweden tend to have uniformly lower nitrosamine levels than American products, which is, in part, due to the GothiaTek® standards developed and adhered to by the manufacturers of Swedish snus.

Table 1 shows data on the newer oral tobacco products[28] introduced in the U.S. This table clearly demonstrates that the levels of total TSNAs are highest in the conventional and most popular oral tobacco products sold in the U.S (i.e., Copenhagen and Skoal),[34] with TSNAs ranging from 4.8 to 9.2 μg/g product wet weight. The Swedish products such as General Snus and Exalt are somewhat lower in TSNAs with values ranging from 2.0 to 3.7 μg/g product wet weight. The lowest levels of TSNAs are observed in oral tobacco products manufactured by Star Scientific, tobacco lozenges such as Ariva and Stonewall, 0.19 and 0.26 μg/g product wet weight, respectively. The medicinal nicotine products tended to have extremely low or nondetectable levels of nitrosamines.

A critical question is how the levels of nitrosamines in tobacco products translate into the uptake of carcinogens in humans. Figure 3 shows the results from a compilation of studies that had been conducted. The concentrations of metabolites of NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-butanol [NNAL]

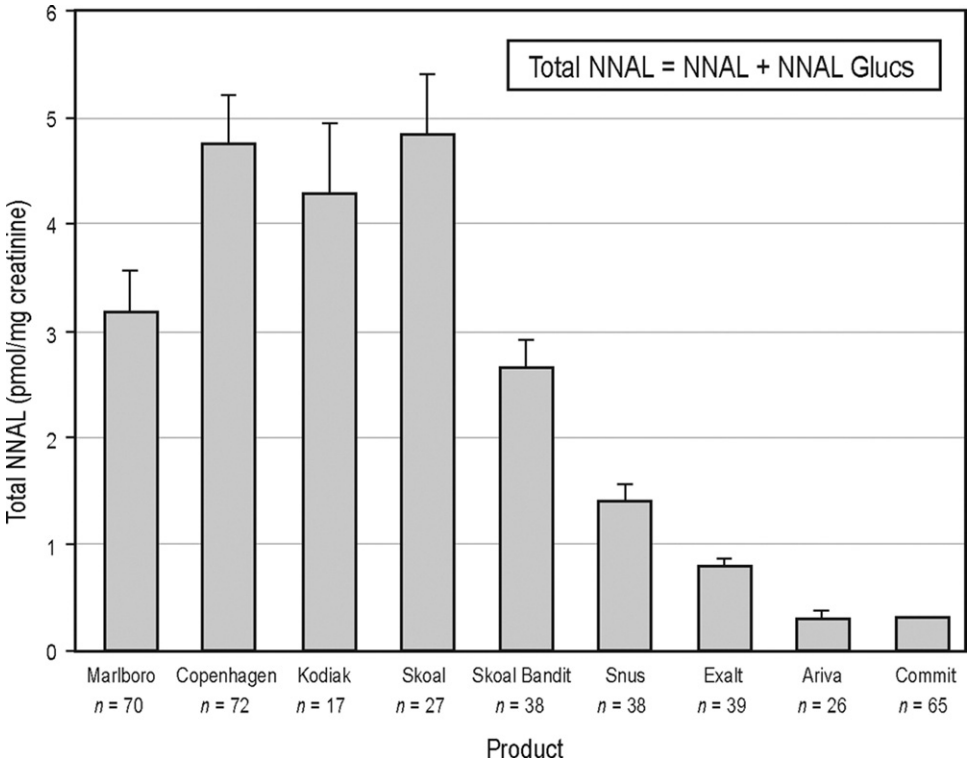

Figure 3. Total NNAL concentrations in urine: users of different brands of noncombusted oral tobacco products, medicinal nicotine (Commit), and Marlboro cigarettes.
NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-butanol.

and its glucuronides [NNAL-Glucs] or total NNAL, which serves as a biomarker for exposure to carcinogens, were examined across different brands of noncombusted oral tobacco products and compared to Commit (GlaxoSmithKline, Pittsburgh PA), a medicinal nicotine that is FDA-approved for smoking cessation. These data represent analyses of the information collected from separate studies[35–39] and some of the studies involved subjects who were noncombusted oral tobacco users while others involved cigarette smokers who switched to noncombusted oral tobacco products. In spite of these limitations, the concentrations of total NNAL parallel the NNK levels in these products. This figure also illustrates the diversity of toxicant uptake across products and that some of the more conventional oral tobacco products result in higher total NNAL levels than smokers of Marlboro cigarettes, providing a cautionary note that switching to noncombusted oral tobacco products does not necessary result in reduced toxicant exposure.

Unfortunately, the majority of existing studies have examined the human uptake of only a few of the carcinogens in these products.[36,37,39–44] Table 2 lists other carcinogens that have been found in noncombusted oral tobacco products. To obtain an accurate picture of the potential harm associated with these products, a more comprehensive assessment of the levels and uptake of toxicants in these products is necessary. Additionally, it is notable that these data are over 20 years old and require updating.

Reduction of Toxicant Exposure in Noncombusted Oral Tobacco Users and Cigarette Smokers

The variability of toxicants in noncombusted oral tobacco products begs the question of whether users of high nitrosamine cigarettes or "traditional" smokeless tobacco products can reduce their level of toxicant uptake through product substitution. Unfortunately, few studies have addressed this question. The studies conducted to determine the effects of switching smoke-

Table 2. Other carcinogens in processed tobacco[45,46]

Carcinogen	Amount (per gram)
Benzo[*a*]pyrene	0.1–90 ng
Formaldehyde	1.6–7.4 μg
Acetaldehyde	1.4–7.4 μg
Crotonaldehyde	0.2–2.4 μg
1,1-Dimethylhydrazine	60–147 ng
Ethyl carbamate	310–375 ng
Hydrazine	14–51 ng
Arsenic	500–900 ng
Nickel	2–6 μg
Chromium	1–2 μg
Cadmium	1.3–1.6 μg
Lead	8–10 μg
Polonium-210	0.2–1.2 pCi

less tobacco users to a lower nitrosamine noncombusted oral tobacco product demonstrate that a significant reduction in toxicants can occur.[35,36,39] In one study, Copenhagen and Kodiak users were randomly assigned to General Snus, a Swedish product with about 60 to 75% lower NNK than the leading U.S. smokeless tobacco brands, or to nicotine patch for a period of 4 weeks. The results showed a significant reduction in concentrations of total NNAL when subjects switched from their usual brand to General Snus (about 50% reduction compared to baseline), but a significantly greater reduction with the nicotine patch (about 90% reduction compared to baseline[35]). In another study, Copehagen or Skoal Original users were switched to Skoal Bandits, which is lower in TSNAs.[36] Again, a significant reduction in total NNAL was observed, with concentrations that were similar to those observed with General Snus. General Snus is higher in nicotine content than Skoal Bandits and surprisingly, very little increased use of Skoal Bandits was observed even with this low nicotine content. Both these studies would indicate that smokeless tobacco users can significantly reduce their toxicant exposures by switching to a product with lower TSNAs.

Similarly, few studies have addressed whether or not cigarette smokers can reduce their toxicant exposure if they switched to the noncombusted oral tobacco products. Two pilot studies were conducted using a within-subject crossover design in which subjects were assigned, in randomized order, to medicinal nicotine lozenge for 2 weeks and an oral tobacco product for 2 weeks.[39] The oral tobacco product in the first study was Exalt, a Swedish Match snus product in a sachet. In the second study, the oral product was Ariva, a tobacco lozenge. The results from the first study showed that both Exalt and the nicotine lozenge resulted in a significant reduction in total NNAL concentrations; however, the nicotine lozenge led to a significantly greater reduction in total NNAL concentrations. In the second study, significant reductions in total NNAL concentrations were observed for both the nicotine lozenge and Ariva and the levels of reduction were similar. The main point of these studies is that smokers can dramatically reduce their exposure to a tobacco-specific carcinogen when they switch to lower nitrosamine oral tobacco products. Whether or not this reduction would reduce the risk for adverse health outcomes is unknown.

Health Effects from Noncombusted Oral Tobacco Products

In the U.S. in 2005, 7.7 million (3.2%) of Americans aged 12 or older were current (past month) noncombusted oral tobacco users.[47] Noncombusted oral tobacco use in the U.S. is higher among whites, men, American Indians/Alaska natives, people living in southern or north central states, and among people who are employed in blue-collar occupations, service/laborer jobs, or are unemployed.[48] In India, it is estimated that 22% of men use noncombusted oral tobacco exclusively, and 8% use noncombusted oral tobacco and smoke concomitantly.[49] Approximately 23% of Swedish men report use of noncombusted oral tobacco (i.e., snus).[13] In Sudan, about 40% of men and 10% of women use noncombusted oral tobacco (i.e., toombak).[50]

Although the overall exposure to toxicants with noncombusted oral tobacco is significantly lower than with cigarettes, oral tobacco is addictive and not safe. The controversy centers on whether these products should be promoted as safer than cigarettes with the risk of the unintended consequence of misleading consumers into assuming they are safe.

As summarized by Critchley et al.,[51] extant literature on the adverse effects of noncombusted oral tobacco is comprised of many studies with insufficient power to estimate precise risks, methodologic limitations, and inconsistency of findings, as well as by a paucity of studies on noncancer health effects. However, these studies provide the only means of assessing potential risks associated with use of these products. No data are available on the health effects of the newer "low-nitrosamine" noncombusted oral tobacco products aimed toward cigarette smokers. But, parallel to observations made with toxicant-concentration levels, the available literature suggests that adverse health consequences may vary by product type which is strongly associated with geography and the country of product origin.[13,51] For example, some of the noncombusted oral tobacco products used in India have high concentration of TSNAs compared to products from other countries (i.e., Sweden and U.S.), and India also has the highest estimated deaths from oral cancer.[27,51] In the U.S. where moist snuff widely used, the estimated number of deaths from oral cancer may be higher than in Sweden where snus is used.[51] To date, published studies predominantly relate to oral tobacco product use in the U.S., Sweden, and India.[13,51,52]

The link between oral tobacco use and adverse cardiovascular outcomes has been controversial.[51] A recent large, multinational case-control study observed an association between nonfatal acute myocardial infarction (AMI) and chewing tobacco use.[53] However, the small number of snuff users precluded the ability to draw conclusions about the effects of this form of tobacco on AMI risk. In the U.S., data from the Cancer Prevention Study-I (CPS-I) and CPS-II suggest that current chewing tobacco and snuff use is associated with an increased risk of death from coronary heart disease and cerebrovascular disease.[54] In Sweden, an early case–control study observed a higher risk of death from all cardiovascular conditions among snus users.[55] However, four Swedish population-based case–control

studies observed no association between moist snuff and the incidence of myocardial infarction[56–58] or stroke.[59]

The relationship between oral tobacco use and the development of risk factors for cardiovascular disease (i.e., metabolic syndrome and diabetes) is also conflicting. High consumption of Swedish snus has been associated with the development of metabolic syndrome (i.e., obesity, impaired glucose regulation, dyslipidemia, and hypertension).[60] An association between snus use and diabetes has been observed in one study[61] but not in another.[62] In the U.S., data from the CPS-I and CPS-II suggest no relationship between smokeless tobacco use and diabetes.[54]

Data from the U.S., Sweden, and India suggest an association between oral tobacco use and adverse health consequences for pregnant mothers and their fetuses. Oral tobacco (i.e., snuff) use in Sweden has been associated with lower birthweight, increased preterm delivery, and increased rate of pre-eclampsia.[63] Among Alaska natives who use Iq'mik, oral tobacco use is associated with neurobehavioral changes in newborns.[64] In India, the use of oral tobacco is associated with an increased risk for preterm delivery, low birthweight, and stillbirth.[65,66] Oral tobacco use in India has also been associated with a general decrease in reproductive health.[67]

Available data suggest a strong association between oral tobacco use and extra-oral cancer in India with several reports of an association from the U.S. and Sweden. In India, oral tobacco use has been associated with esophageal cancer.[68] In the U.S., data from CPS-I suggested an association between current smokeless tobacco use and death from cancer of the digestive system, and data from CPS-II observed a similar association for all cancer.[54] An association between oral tobacco use and kidney and pancreatic cancer was suggested by two U.S. case-control studies.[69,70] Two Swedish studies found no association between snus use and gastric or esophageal cancer[71,72] but one observed an association with pancreatic cancer.[73]

A systematic review of the literature concluded that available data strongly and consistently support an association between oral cancer and oral tobacco use in India, which leads to approximately 10,000 deaths annually.[51] Data from the U.S. suggest an association between oral cancer and oral tobacco use.[74,75] However, the U.S. data have been limited by small sample sizes and inadequate power to detect significant risks. Swedish studies have not shown an increased risk for oropharyngeal cancers among current oral tobacco users.[76,77] Importantly, the IARC Monographs Working Group has reviewed the available evidence and has concluded that "there is sufficient evidence that smokeless tobacco causes oral cancer and pancreatic cancer in humans" and that smokeless tobacco is "carcinogenic to humans."[78]

No literature is available to elucidate if cigarette smokers or users of high-nitrosamine tobacco products who switch to low-nitrosamine products can reduce significantly their risk for disease.

Addiction Potential of Products

The addiction potential of a drug is also considered a tobacco-related harm. The addiction potential of a tobacco product depends on the amount of nicotine that is absorbed and the speed of nicotine delivery; the greater the magnitude of nicotine absorption and the faster the rate of absorption, the more addictive the product. The amount and speed of systemic absorption of nicotine are dependent on the product pH, nicotine content, and route of administration, with cigarette smoking resulting in the fastest rate of delivery. pH levels determine the amount of free nicotine. Higher pH levels (i.e., more alkalinity) create more free nicotine available for absorption in the bloodstream. Free or non-ionized nicotine is more readily absorbed

Table 3. Nicotine content in noncombusted oral tobacco products

Dose	Product	pH	Nicotine content (mg/g)	Free nicotine (mg/g)
Low	**Hawken**[31,82,84]			
	Wintergreen	5.2–5.7	3.2–4.3	**0.01–0.02**
	Skoal Bandits[31,84]			
	Straight	5.2–5.4	7.9–10.1	**0.02–0.03**
	Skoal Bandits[31,82,83]			
	Wintergreen	6.9–7.1	7.1–8.5	**0.5–1.0**
Medium	**Skoal Long Cut**			
	Straight[82,83]	7.5–7.6	10.3–12.9	**2.4–3.7**
	Wintergreen[31,83]	7.4–7.8	10.5–11.0	**2.0–4.1**
	Cherry[83]	7.5	11.4	**2.6**
	Skoal Original[83]			
	Wintergreen	7.6	10.4	**2.9**
High	**Kodiak**[31,82,84]			
	Wintergreen	8.2–8.4	8.6–10.9	**5.8–6.5**
	Copenhagen[31,82–84]	7.6–8.6	11.1–12.7	**3.1–9.4**

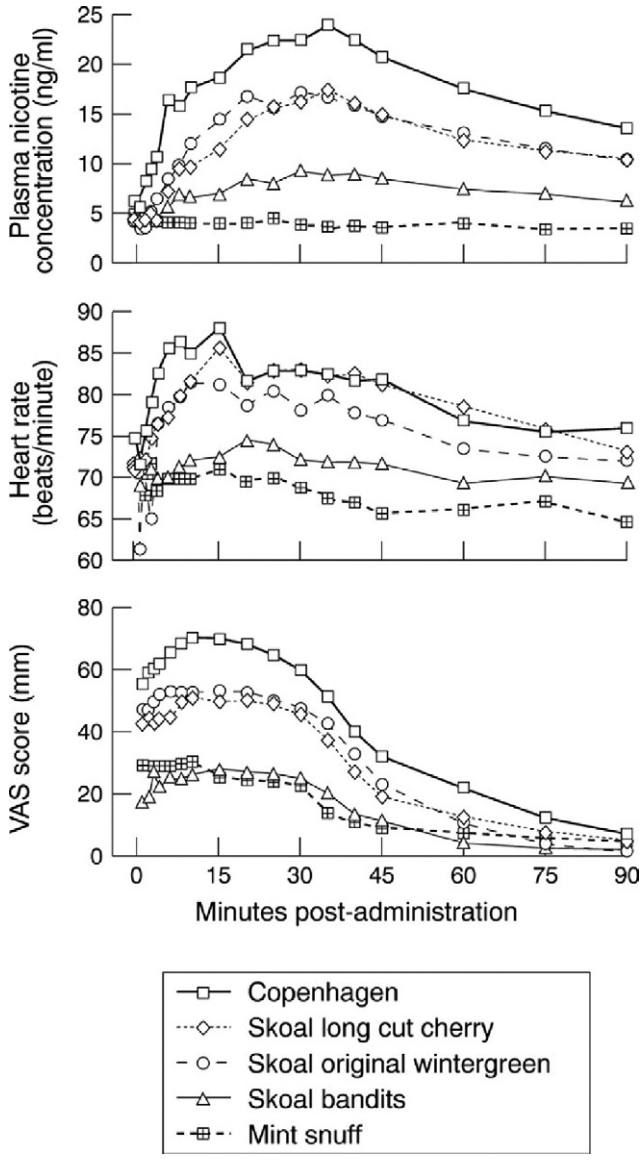

Figure 4. Mean plasma nicotine concentration, heart rate, and visual analog scale (VAS) score (product "strength") after administration of each of four oral tobacco products or mint snuff.[85]

through cell membranes than ionized nicotine. Oral tobacco products vary widely in pH and nicotine levels.[26,31,33,79–82] Table 3 shows the amount of free nicotine in different oral tobacco products. The products with the highest free-nicotine levels are the most popular conventional brands (e.g., Copenhagen and Kodiak) used in the U.S., whereas products low in free-nicotine levels have lower use prevalence.[47] The free-nicotine content of the oral tobacco products parallels the plasma nicotine concentrations, as seen in Figure 4. Furthermore, the plasma-nicotine concentrations determine the perceived strength of the dip and the physiologic response.[85]

To date few studies have examined the free-nicotine content of the newer oral tobacco products. Table 4 presents the nicotine content in some of these products.[86] In a recent study that examines the pharmacokinetics of the newer oral tobacco products,[87] products such as Ariva and Revel result in very low nicotine concentrations, whereas product such as Stonewall had concentrations that were comparable to 4-mg medicinal nicotine lozenges. Copenhagen showed the most rapid absorption and highest concentration of nicotine. The peak nicotine concentration is similar to concentrations observed for cigarettes.[88] Products such as Taboka have relatively low nicotine concentrations (data presented by Phillip Morris at a meeting at the Harvard School of Public Health), whereas Camel Snus is reported to have nicotine amounts that are similar to Camel cigarettes and blood nicotine concentrations potentially similar to levels in cigarette smokers (www.snuscamel.com). This information has not been publicly released by the manufacturers and the products have not been made widely available for analysis.

The pattern of use for low- and high-nicotine products requires research. The low-nicotine products have the advantage of being lower in addictive potential, but may not be readily used by oral tobacco users or may not provide a good substitute for cigarette smoking, potentially leading to dual use of the cigarettes and noncombusted oral tobacco products. The high-nicotine, low-nitrosamine products have potential for abuse and to sustain addiction, but may provide a better substitute for more toxic tobacco products such as cigarettes.

Summary

In summary, noncombusted oral tobacco products are changing. These products are now being targeted to cigarette smokers for use in situations where a smoker cannot smoke or as an alternative to smoking. They are manufactured to appeal to smokers. Although these products contain lower levels of total carcinogens compared to cigarettes or the most popular conventional brands of oral tobacco products sold in the U.S. or in the world, some of these products still contain considerable amounts of carcinogenic nitrosamines which are far higher than those permitted in food.[89] To date, medicinal nicotine products have the lowest toxicant concentrations. The amounts of free nicotine in these noncombusted oral tobacco products vary widely as well. Some of these newer products contain significant amounts of nicotine, whereas other products contain

Table 4. Nicotine content of newer noncombusted oral tobacco products marketed as alternatives to cigarette smoking[82]

Product	pH	Nicotine (mg/g)
Stonewall	7.7	1.5
Revel	7.2	1.1
Ariva	7.4	0.6

low levels of nicotine. The consequent pattern and persistence of use may depend on the nicotine content of the product but there are no data to determine this relationship.

Future Directions and Research

One of the conclusions in the Institute of Medicine (IOM) report, Clearing the Smoke,[1] was the following: "Regulation of all tobacco products, including conventional ones as recommended by the IOM,[90] as well as all other PREPs is a necessary precondition for assuring a scientific basis for judging the effects of using PREPs and for assuring that the health of the public is protected." The necessity for regulation of tobacco products is supported by: (1) the data showing tremendous variability in levels of toxicants in these products, (2) the capability of producers to reduce toxicant levels in tobacco products and to control degree of potential product addiction, and (3) the need for independent scientific evaluation of these products. Renewed efforts to discuss and implement the regulation of tobacco products is critical to**:** (1) significantly improve the public health of this nation, (2) ensure that any deceptive practices of the tobacco industry are caught, (3) not have to rely on litigation as the only method to set limits on these deceptive practices, and (4) ensure that consumers are provided accurate information. The research that is necessary to understand the public health impact of these products is extensive[91,92] and includes preclinical and clinical research, consumer testing, and post-marketing surveillance.

Preclinical Research

Examine and identify the toxic constituents of the products and determine factors that may alter the levels of these toxicants including nicotine (e.g., shelf time, heat); and undertake in vitro and in vivo studies determining the toxicity of these products on cells and animals.

Clinical Research

Conduct human clinical trials that: (1) determine factors associated with palatability and maintenance of use of these products; (2) examine the uptake of toxicants using biomarkers for exposure and toxicity associated with different disease states[93]; (3) examine the natural pattern of use of these products as a cessation tool, as a substitute for smoking in situations where smoking is prohibited or people cannot smoke, or as a method to reduce smoking and determine the toxicant exposure associated with these patterns of use; and (4) conduct clinical trials with noncombusted oral tobacco products as a cessation tool compared to existing pharmacologic therapies in an effort to improve existing cessation medications if noncombusted oral tobacco products prove to be more efficacious. For example, development and approval of medications that have more rapid absorption of nicotine, higher levels of nicotine and greater palatability may be critical to compete against more toxic noncombusted oral tobacco products.

Consumer Testing

Conduct consumer testing of these products to: (1) examine how the labeling, messages, promotion, marketing and placement of these products affect consumer perception of these products; (2) determine how consumer feelings, beliefs, attitudes, and knowledge affects uptake or manner of use of these products; and (3) determine methods for labeling, messaging, promotion, marketing and placement of products that would reduce public health harm associated with the use of these products.

Post-Marketing Surveillance

Conduct post-marketing surveillance of these products to determine: (1) who is using them; (2) how they are being used; (3) toxicant exposure; (4) potential health harms associated with their use; (5) whether they serve as a gateway or substitute for cigarette smoking; and (6) the extent to which their introduction and marketing increases uptake, maintenance or relapse to tobacco products.

As a final word, the potential to do harm or to benefit the public health by the introduction of these products is tremendous. To circumvent public health harm, an infrastructure and funding that allow comprehensive and collaborative research efforts are necessary. To date, examination of the toxicity and impact of these products is occurring on an international level and U.S. efforts should coincide with these efforts. For example, WHO has convened a Study Group on Tobacco Regulation to produce documents that describe principles and provide guidelines for implementing articles of the WHO Framework Convention on Tobacco Control that are associated with tobacco product testing (Articles 9 and 10). One of the documents, "Guiding Principles for the Development of Tobacco Product Research and Testing Capacity and Proposed Protocols for the Initiation of Tobacco Product Testing"[94] provides guidelines for the testing and assessment and for the regulation of contents and emissions from tobacco products. A long-term vision and direction for tobacco control as well as coordinated and complimentary activities amongst organizations, tobacco-control advocates, policy makers, and researchers are critical at this juncture in tobacco control.

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