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# Chemical characterization of tobacco-free "modern" oral nicotine pouches and their position on the toxicant and risk continuums

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**ABSTRACT**

As compared with cigarette smoking, use of Swedish snus is associated with significantly fewer health risks. Nicotine pouches (NPs), a new form of oral nicotine product, are smokeless and tobacco-free, comprising a nicotine-containing cellulose matrix inside a fiber pouch. NPs are similar in appearance/use to snus, but without tobacco, have the potential to further reduce tobacco-related harm. This study aimed to evaluate toxicant levels of NPs to estimate their position on the tobacco/nicotine product continuums of toxicant delivery and risk. NPs, snus and nicotine replacement therapy products (NRTs) were analyzed for 24–26 compounds applicable to oral tobacco, and their levels were compared. Twenty of these compounds were further used to compare the toxicant profile of NPs, as well as estimated daily toxicant exposure from NP use, with that of tobacco/nicotine products spanning the risk continuum. Of the compounds measured, 22 (NPs), 22 (lozenge NRT), 20 (gum NRT), and 11 (snus) were not quantifiable. Compared with snus, NPs had lower levels of 10 HPHCs and comparable/undetectable levels of a further 13. Across the product categories, NPs and NRTs had the lowest toxicant profiles and estimations of relative toxicant exposure. Based on the present chemical analysis and estimated exposure, use of NPs appears likely to expose users to lower levels of toxic compounds than Swedish snus, which is recognized to offer reduced levels of harm than associated with tobacco smoking. We conclude that NPs should be placed close to NRTs on the tobacco/nicotine product toxicant delivery continuum, although further studies will be needed to confirm this.

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## Introduction

The health risks of cigarette smoking are well established, but most smoking-related diseases are not directly caused by the addictive compound nicotine, which is considered by regulatory and healthcare bodies to be relatively harmless at the levels present in tobacco (RCP 2016; PHE 2019), but by the toxic chemicals in the inhaled smoke of combusted tobacco (US Department of Health and Human Services (DHHS) 2014). As a result, the concept of tobacco harm reduction through the use of alternative tobacco and/or nicotine products with fewer health risks relative to cigarette smoking was proposed in 2001 by the US Institute of Medicine, who called for the development and study of tobacco and nicotine products with fewer relative risks (Stratton *et al*. 2001).

Since then, several studies have explored the 'Swedish experience' (Swedish Match 2020) as a potential factor in tobacco harm reduction (e.g., Gartner *et al*. 2007, Clarke *et al*. 2019). In Sweden, overall tobacco product use is similar to that in other European countries (Clarke *et al*. 2019), but the incidence of smoking-related mortality is among the lowest in Europe (Ferlay *et al*. 2013, Swedish Match 2020). This is because the majority of Swedish tobacco consumers use 'snus', a moist oral smokeless tobacco product (STP), rather than cigarettes (EC 2017, Clarke *et al*. 2019, WHO 2019). In 2017, the population incidence of daily cigarette smoking was reported as approximately 5% in Sweden versus a European average of 25%; in contrast, daily snus use in Sweden was 20% (EC 2017, Clarke *et al*. 2019). The 'Swedish experience' is supported by numerous epidemiological and prevalence studies (reviewed in Lee 2011, Clarke *et al*. 2019, Ramboll 2019).

Swedish snus is a ground or cut moist tobacco product, produced either in loose tobacco form or contained in a pouch, and is placed under the upper lip against the gum, where the released nicotine is absorbed through the oral mucosa. The range of systemic exposure to nicotine from snus is similar to that from tobacco smoking, although nicotine is absorbed more rapidly from cigarette smoke than from snus (Digard *et al*. 2013a). The reduced health risks from Swedish snus are mainly due to the lack of direct lung exposure to toxicants during snus use, as well as the absence of tobacco combustion, which results in lower levels of many cigarette smoke toxicants. Swedish snus is also regulated

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under the Swedish Food Act, which stipulates upper limits on certain toxicants (Swedish Food Agency 2016). Furthermore, Swedish snus contains air-cured tobacco that is pasteurized during product manufacture (Lawler *et al*. 2020), an important processing step that serves to constrain tobacco-specific nitrosamine (TSNA) levels (Lawler *et al*. 2020; Song *et al*. 2016). The levels of many toxicants are lower in Swedish snus products than in other STP styles (McAdam *et al*. 2013, 2015, 2018, 2019).

Based on the concept of harm reduction, McNeill and Munafò (2013) introduced the idea of a risk continuum of tobacco and nicotine products from cigarettes to nicotine replacement therapies (NRTs) that deliver nicotine dermally, orally or by inhalation. NRTs, considered to be the least risky of all nicotine products in this context, are regulated as medicinal nicotine products, which are designed to be used for short periods of time to help quit cigarette smoking. However, the relatively slow and low uptake of nicotine from NRTs in comparison to cigarettes (Schneider *et al*. 2001, Le Houezec 2003) may limit the potential of these products to satisfy a smoker's craving for nicotine and may cause smokers who have quit to relapse. In addition, the long-term health effects of NRTs have not been extensively evaluated (Lee and Fariss 2017), although, as discussed above, exposure to medicinal nicotine at levels found in consumer products is generally considered to be a low risk activity (RCP 2007).

The tobacco industry has been developing alternative, potentially 'reduced risk' oral products for nicotine delivery that may be less harmful to health as compared with traditional STPs. Similar in concept to snus but containing no tobacco, nicotine pouch (NP) products (e.g., Zyn from Swedish Match, On! from Altria, Velo from RJ Reynolds Vapor, and Lyft or Velo from British American Tobacco [BAT]) have been commercially available in some countries since the mid-2010s. These smokeless, oral, tobacco-free products come in pouches that are placed between the gum and lip and deliver nicotine through the oral mucosa in the same way as snus. Gradual dissolution releases flavorings, generating a taste sensation, and nicotine, which is absorbed via the mucous membranes in the mouth before entering the bloodstream. Release of nicotine will be dependent on the usage pattern of individual consumers, but is expected to be comparable to that of traditional snus.

The aim of the present study was to take a first step in establishing the position of NPs on the nicotine product risk continuum, by conducting a detailed chemical analysis of NPs, lozenge and gum NRTs, and Swedish-style snus. We focused on the toxicants most frequently used to characterize STPs: namely, the FDA smokeless tobacco reporting list (FDA 2012) and GothiaTek® standard compounds (Swedish Match 2016). Market surveys conducted in Sweden from 2018 to 2020 were also used to evaluate daily consumption of NPs and snus, and thereby estimate daily exposure to toxicants from these products; for comparison, daily exposure from NRTs was estimated based on recommended pharmaceutical dosages. We discuss our findings in relation to literature values for combustible cigarette smoke, tobacco heating product (THP) and e-cigarette aerosols, allowing us to estimate the relative position of NPs on the wider toxicant delivery and risk continuums.

## Materials and methods

### *Nicotine pouch products*

Nicotine pouches are oral, smokeless, tobacco-free pouches that, similar to snus, are placed between the gum and lip and deliver in nicotine through the oral mucosa. The products manufactured by BAT are composed of a permeable pouch material and a non-tobacco substrate to which nicotine and flavors are added. The outer pouch material is composed of viscose fibers bound together by chemical, heat or solvent treatment, and the non-tobacco substrate is mainly composed of water and microcrystalline cellulose, which together constitute approximately 80–90% of the NP. Other food-grade standard ingredients are contained within this matrix including a pH buffer, a filling agent, salt, taste additives and flavorings, sweeteners, and pharmaceutical grade nicotine.

Visually, the product does not differ from pouched snus, except that it is white rather than brown due to the absence of tobacco (although some pouch flavors may have a slight colored tint). The pouches are typically sold in multiples in small plastic containers (Figure 1).

Apart from the absence of tobacco, NPs are compositionally similar to Swedish snus, which (in addition to heat-treated or 'pasteurised' tobacco) typically contains sodium chloride, water, humidifying agents, buffering agents (sodium carbonate), and various food-grade flavorings. Like snus, NPs are manufactured in various flavor variants (e.g., peppermint, spearmint, licorice, citrus, berry), which are similar or equivalent flavor styles to those applied to traditional snus products. All ingredients used in BAT's NPs comply with regulatory food standards (EU 2009) and are generally recognized as safe (GRAS) (FDA 2019). In short, all flavor ingredients meet a minimum of one of the following standards: GRAS; authorized for use in food by the FDA; authorized for use in food by the European Union; considered GRAS by the Flavor and Extract Manufacturers Association; included in the International Organization of the Flavor Industry Global Reference List of flavoring materials that are considered to be safe for their intended use by one or more internationally recognized assessment bodies. In addition, the use levels of the flavor ingredients are toxicologically assessed to minimize risks to the consumer. The nicotine in BAT's NPs is pharmaceutical grade (USP, n.d.), and is a natural product derived from tobacco. Nicotine strength of NPs varies between products but is slightly lower on average than that of traditional snus. Similar to snus (Lawler *et al*. 2020), nicotine strength of NPs is lower in US brands than in Swedish brands.

### *Comparison of oral nicotine product toxicant profiles: NPs, snus and NRTs*

Four variants of BAT NPs (Lyft Freeze, Lyft Lime Strong, Lyft Berry Frost and Lyft Mint) with similar flavorings to a number

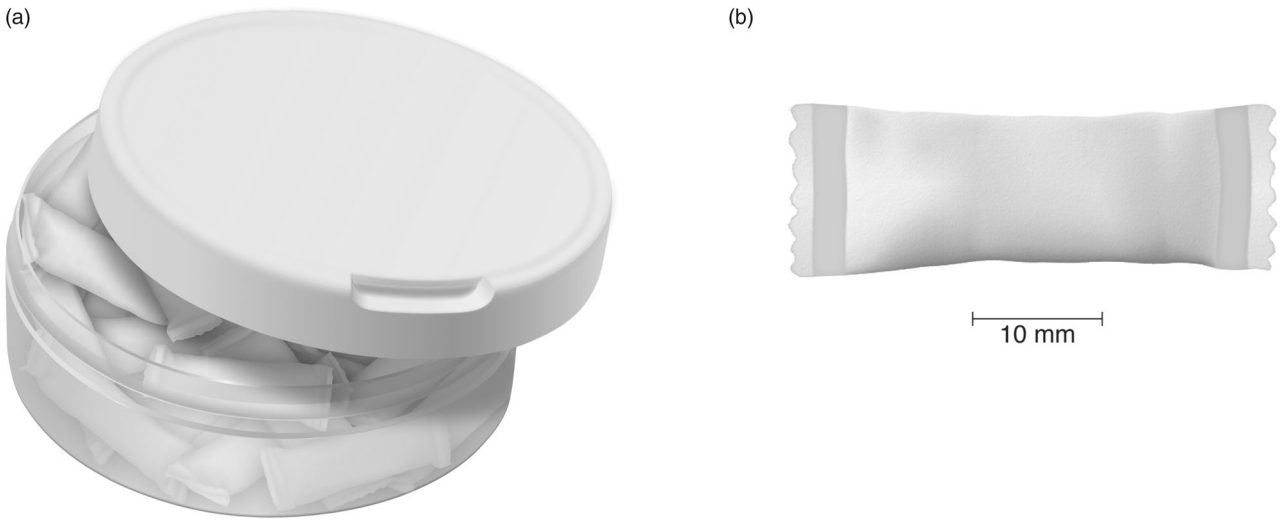


Figure 1. An artist's illustration of a typical nicotine pouch. (a) As sold in container with lid. (b) Individual pouch.

of existing snus products were analyzed along with a BAT snus product (Granit Ice Blue White), two leading non-BAT snus products (Skruf Slim Fresh XStrong Mint and G3 Slim White XStrong Blue Mint) that currently are or were available in some Scandinavian markets, and two well-known commercially available NRTs in lozenge (Nicorette 4 mg) and gum (Nicorette 4 mg) format. Products were analyzed for 26 compounds applicable to oral tobacco products, including known harmful and potentially harmful constituents (HPHCs) from the FDA smokeless tobacco reporting list, and the GothiaTek® Standard list of toxicants (other than agrochemicals because the NPs are synthetic products rather than agriculturally sourced). Also included were cigarette smoke toxicants (nine smoke constituents prioritized by the WHO's Tobacco Product Regulation Group, 'TobReg9', with the exception of carbon monoxide) not already included in the FDA smokeless tobacco and GothiaTek® lists of toxicants. Analyses were conducted at an independent contract laboratory (Eurofins, Lidkoping, Sweden, accredited to EN ISO/IEC 17025:2017, DAKKS D-PL-14602–01-00, ISO/IEC 17025:2017 SWEDAC ackred. nr. 1977, ISO/IEC 17025:2017 SWEDAC ackred. nr. 1125) using in-house and standardized analytical methods. The analytical methods used to quantify the 26 compounds in lozenge and gum NRTs, NPs and snus are summarized in Table 1, and further details can be requested from the Analytical Laboratory. Three replicate analyses were conducted for NPs and NRTs, two were conducted for snus products.

### Market research data

Market surveys on tobacco and nicotine product use, including snus and NPs, were conducted on a quarterly basis in Sweden between 2018 and 2020 through an international market research agency (Kantar, London). Approximately 1,300 participants from an actively managed panel aged 18–64 years completed each survey. Participants were recruited by opt-in email, co-registration, e-newsletter campaigns, affiliate networks and social media.

### Estimates of toxicant intake

To determine the relevance of the toxicant profiles to relative health risks, we estimated toxicant intake by calculating Daily Exposure to Toxicants ($D_{ET}$, in units of mass) for each product. $D_{ET}$ was estimated from the toxicant content of the product ($T_{C,}$ mass units) and the oral product exposure factor ($E_{fO}$), which combines estimates of the fraction of toxicants extracted during individual product use with daily consumption, as follows:

$$D_{ET} = (T_C * E_{fO}) \quad (1)$$

where $E_{fO} = (f_{EU} * ADM)$; ADM is the average daily mass of products consumed by a user and is calculated from the numbers of products consumed per day and product mass per portion; and $f_{EU}$ is the extraction efficiency (a dimensionless value between 0 and 1), indicating the extent to which compounds are extracted from the product minus losses through events such as expectoration. For the oral products investigated in the present study, little or no expectoration is observed; therefore, losses during use are expected to be near zero.

## Results

### Toxicant contents of oral nicotine products

Quantitative data on the HPHC contents of two types of NRT, four NP variants and three snus products are summarized in Table 2. Data are presented as either μg/g or ng/g, because the portion sizes were in the gram range for all products. For nicotine and moisture, data are present as percentages. Table 2 shows that 4 of the 26 measured compounds were present at quantifiable levels in the NPs. In addition to moisture and nicotine content, extremely low levels of chromium and formaldehyde were detected in some, but not all, samples at approximately the limits of quantification. For the lozenge NRT, in addition to nicotine (which was present but not measured), 3 of the 25 measured compounds were quantified: moisture, nickel and chromium (in only one of the three replicates). Similarly, for the gum NRT, 5 of the 25 measured

Table 1. Harmful and potentially harmful constituents analyzed and summary of analytical methods used for NPs, snus and NRTs.

| Analyte | Method code | Brief description |
|---|---|---|
| Nicotine | Health Canada method: T-301[a] | Nicotine was extracted from the products with alkaline methanol under ultrasonication. The liquid extract was then filtered and diluted prior to quantification by LC-MS. Quantification was performed against a 5-point standard curve and by using deuterated nicotine as internal standard. |
| Metals: Cadmium, chromium, nickel, arsenic, lead | EN ISO 17294-2:2016/EN 13805:2014 | The products were digested in microwave oven with a mix of nitric acid, hydrochloric acid and hydrochloric peroxide, followed by detection and quantification of metals by ICP-MS. |
| Mercury | EN 16277:2012 | Mercury was extracted by digestion, according to Annex D of EN16277:2012, with a mix of nitric acid, hydrochloric acid, hydrochloric peroxide. Detection and quantification were by CV-AFS. |
| TSNAs: NAB, NAT, NNK, NNN | In-house LW0A0 | TSNAs were extracted from the products with ethylacetate in presence of d-labelled specific internal standards, followed by detection and quantification by HPLC-MS/MS. |
| Benzo(a)pyrene | In-house LW0R7 | Benzo(a)pyrene extraction was performed with methanol, in presence of a d-labelled specific internal standard, followed by detection and quantification by HPLC-FLD. |
| NDMA | In-house LP061 | NDMA was extracted with ethylacetate in presence of specific internal standard, followed by detection and quantification with HPLC-MS/MS. |
| Nitrite | In-house LW09I | Nitrite was extracted in water, derivatised with sulfanilamide and n-acetylethylendiaminehydrochloride and analyzed as a red complex at 540 nm. |
| Carbonyls: Formaldehyde, acetaldehyde, crotonaldehyde, acrolein | CORESTA CRM-86 | Carbonyls were analyzed according to CORESTA CRM-86. Extraction and derivatisation occured in a two-phase system consisting of aqueous buffer and isohexane, using DNPH as the derivatising agent in the presence of specific internal standards, followed by detection and quantification on UPLC-MS/MS. |
| Aflatoxins: B1, B2, G1, G2 | EN 14123 (mod) | Aflatoxins were extracted and transferred to a phosphate buffer saline and cleaned with monoclonal antibody affinity column. After elution from the column the aflatoxins were post-derivatised followed by detection and quantification on HPLC-FLD. |
| Ochratoxin A | NMKL 143 | Ochratoxin was extracted with a mix of acetonitrile and water, followed by a concentration step on a preparative column based on monoclonal antibody technology. The eluate is subsequently analyzed by LC-FLD. |
| 1,3-Butadiene and benzene | In-house HS-GC-MS | 1,3-Butadiene and benzene were analyzed using headspace GC-MS. |

[a]Deviations to method T-301 include determination with LC-MS instead of GC-MS and addition of the internal standard during final dilution.

Abbreviations: CORESTA: Cooperation Center for Scientific Research Relative to Tobacco; CRM: CORESTA recommended method; CV-AFS: cold vapor atomic fluorescence spectroscopy; DNPH: 2,4-Dinitrophenylhydrazine; FDA: US Food and Drug Administration; GC-MS: gas chromatography–mass spectrometry; HPLC-FLD: high-performance liquid chromatography with fluorescence detection; HPLC-MS/MS: HPLC with mass spectrometry; HS-GC-MS: Headspace GC-MS; ICP-MS: inductively coupled plasma MS; LC-FLD: liquid chromatography with fluorescence detection; NAB: N-nitrosoanabasine; NAT: N-nitrosoanatabine; NDMA: N-Nitrosodimethylamine; NNK: 4-(methylnitrosamino)-1–(3-pyridyl)-1-butanone; NNN: *N*-nitrosonornicotine; TSNA: tobacco-specific nitrosamines; UPLC-MS/MS: ultraperformance liquid chromatography–tandem MS.

compounds were present at quantifiable levels (in addition to unmeasured nicotine): moisture and low levels of cadmium, chromium, nickel and lead. In the snus samples, by contrast, in addition to moisture and nicotine, 11 toxicants were present at quantifiable levels, namely cadmium, chromium, nickel, arsenic, lead, NNN, NNK, NDMA, formaldehyde, acetaldehyde and ochratoxin A. The concentrations of these quantified toxicants were present in snus at substantially higher levels than those in NPs or NRTs. Although NAB and NAT were not measured, it is likely these TSNAs would also be present in the snus samples tested in this study.

In comparison to snus, the NPs contained lower levels of the metals arsenic, cadmium, chromium, Ni, and lead, the nitrosamines NDMA, NNK and NNN, acetaldehyde, and ochratoxin. Formaldehyde content was largely comparable between the two product types, but none of the measured HPHCs were higher in NPs than in snus.

Regarding the NRTs, higher levels were detected in the gum NRT than in the lozenge NRT or NP for cadmium, chromium, nickel and lead, and nickel levels were higher in the lozenge NRT than in the NP. In contrast, the formaldehyde content of the NPs was higher than that in both NRT products. Collectively, these findings suggest that NPs have the potential for a lower toxicant profile as compared with Swedish snus, and a comparable profile to those of NRT products.

### *Consumer use data for NPs and snus*

Quarterly market surveys were conducted by BAT in Sweden through the Kantar market research agency throughout 2018 and 2020. The data suggest that the average daily consumption (ADC) of NPs is lower than that of snus (Table 3). The mean NP ADC was 8.6 (range 7.7–10.4) pouches/day among solus NP users (sample size 20–238) versus 12.0 (range 11.6–12.4) pouches/day among solus traditional snus users (sample size 1092–1345).

## Discussion

### *Toxicant contents of oral nicotine products*

The present study evaluated the toxicant levels of NPs in relation to other oral nicotine products to estimate the

Table 2. Toxicant content of NPs, snus and NRTs.

| | | Snus | | | | | Nicotine Pouch | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Analyte | Units | Granit Ice Blue White | Skruf Slim Fresh XStrong Mint | G3 Slim White XStrong Blue Mint | NRT lozenge Nicorette peppermint 4 mg | NRT gum Nicorette peppermint 4 mg | Lyft Freeze | Lyft Lime Strong | Lyft Berry Frost | Lyft Mint |
| Product mass | g | 0.7 | 0.7 | 0.7 | 0.623 | 1.265 | 0.7 | 0.7 | 0.7 | 0.7 |
| Replicates | | 2 | 2 | 2 | 3[a] | 3[a] | 3[a] | 3[a] | 3[a] | 3[a] |
| pH | | 8.7 | 7.8 | 8.7 | 8.0 | 10.6 | 8.6 | 8.6 | 8.7 | 8.5 |
| Moisture | % | 47.7 | 34.7 | 47.3 | 1.1 | 3.3 | 49.5 | 43.9 | 50.4 | 48.2 |
| Nicotine | % | 1.2 | 2.2 | 1.5 | n/a | n/a | 1.7 | 1.4 | 0.58 | 0.89 |
| Formaldehyde | µg/g | 1.5 | 1.2 | <1.0 | <1.0 | <1.0 | <1.0 | <1.0–1.0[b] | 1.13 | 1.10 |
| Acetaldehyde | µg/g | 7.1 | 9.2 | 8.4 | <1.0 | <1.0 | <1.0 | <1.0 | <1.0 | <1.0 |
| Acrolein | µg/g | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 |
| Crotonaldehyde | µg/g | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 |
| NAB | ng/g | n/a | n/a | n/a | <10 | <10 | <10 | <10 | <10 | <10 |
| NAT | ng/g | n/a | n/a | n/a | <10 | <10 | <10 | <10 | <10 | <10 |
| NNN | ng/g | 610 | 560 | 640 | <10 | <10 | <10 | <10 | <10 | <10 |
| NNK | ng/g | 200 | 125 | 89 | <10 | <10 | <10 | <10 | <10 | <10 |
| NDMA | ng/g | <0.2 | 0.23 | 0.37 | <0.2 | <0.2 | <0.2 | <0.2 | <0.2 | <0.2 |
| Benzo(a)pyrene | ng/g | <1.0 | <1.0 | <1.0 | <1.0 | <1.0 | <1.0 | <1.0 | <1.0 | <1.0 |
| 1,3-Butadiene | ng/g | <20 | <20 | <20 | <20 | <20 | <20 | <20 | <20 | <20 |
| Benzene | ng/g | <5.0 | <5.0 | <5.0 | <5.0 | <5.0 | <5.0 | <5.0 | <5.0 | <5.0 |
| Cadmium | ng/g | 285 | 460 | 245 | <10 | 29 | <10 | <10 | <10 | <10 |
| Chromium | ng/g | 1550 | 1700 | 815 | <50–52[c] | 743 | <50–70[c] | <50 | <50–80[c] | <50-51[c] |
| Mercury | ng/g | <20 | <20 | <20 | <20 | <20 | <20 | <20 | <20 | <20 |
| Nickel | ng/g | 1400 | 2000 | 885 | 80 | 223 | <50 | <50 | <50 | <50 |
| Arsenic | ng/g | 92 | 130 | 94 | <50 | <50 | <50 | <50 | <50 | <50 |
| Lead | ng/g | 210 | 340 | 190 | <20 | 55 | <20 | <20 | <20 | <20 |
| Nitrite | µg/g | <1.0 | <1.0 | <1.0 | <1.0 | <1.0 | <1.0 | <1.0 | <1.0 | <1.0 |
| Aflatoxin B1 | ng/g | <1.0 | <1.0 | <1.0 | <0.1 | <1.0 | <1.0 | <1.0 | <1.0 | <1.0 |
| Aflatoxin B2 | ng/g | <1.0 | <1.0 | <1.0 | <0.1 | <1.0 | <1.0 | <1.0 | <1.0 | <1.0 |
| Aflatoxin G1 | ng/g | <1.0 | <1.0 | <1.0 | <0.1 | <1.0 | <1.0 | <1.0 | <1.0 | <1.0 |
| Aflatoxin G2 | ng/g | <1.0 | <1.0 | <1.0 | <0.1 | <1.0 | <1.0 | <1.0 | <1.0 | <1.0 |
| Ochratoxin A | ng/g | <0.5 | 1.6 | 1.1 | <0.5 | <0.5 | <0.5 | <0.5 | <0.5 | <0.5 |

[a]Aflatoxins were measured with two replicates; [b]two replicates were ≥ LOQ, [c]one replicate was ≥ LOQ.

Abbreviations: n/a: not analyzed; NAB: *N*-nitrosoanabasine; NAT: *N*-nitrosoanatabine; NDMA: N-Nitrosodimethylamine; NNK: 4-(methylnitrosamino)-1–(3-pyridyl)-1-butanone; NNN: *N*-nitrosonornicotine; NRT: nicotine replacement therapy.

Table 3. Average daily consumption of traditional Swedish snus and NPs.

| | Traditional snus | | Nicotine pouches | |
|---|---|---|---|---|
| Survey | ADC (pouches/day) | Sample size (*n*) | ADC (pouches/day) | Sample size (*n*) |
| Q1 2018 | 12.2 | 1345 | 8.7 | 39 |
| Q2 2018 | 12.1 | 1261 | 8.2 | 20 |
| Q3 2018 | 11.6 | 1242 | 9.0 | 36 |
| Q4 2018 | 11.6 | 1244 | 8.4 | 43 |
| Q1 2019 | 11.7 | 1202 | 8.8 | 35 |
| Q2 2019 | 11.8 | 1197 | 7.7 | 62 |
| Q3 2019 | 12.1 | 1194 | 10.4 | 68 |
| Q4 2019 | 11.9 | 1192 | 8.4 | 99 |
| Q1 2020 | 11.7 | 1102 | 7.8 | 190 |
| Q2 2020 | 12.3 | 1104 | 8.0 | 196 |
| Q3 2020 | 12.4 | 1092 | 9.5 | 228 |
| Q4 2020 | 12.3 | 1123 | 8.6 | 238 |
| **Mean** | **12.0** | **1192** | **8.6** | **105** |

Abbreviations: ADC: average daily consumption.

position of these relatively new nicotine products on the toxicant delivery and risk continuums of tobacco and nicotine products. Owing to their similarity to snus in terms of both composition and physical usage, targeted analyses were used to measure both toxicants relevant to oral tobacco products and toxicants from the WHO TobReg9 priority list, which was established to address key HPHCs in cigarette smoke (Burns *et al*. 2008), but has been used for comparative assessments of other tobacco and nicotine products (e.g., Margham *et al*. 2016).

Among the four NP variants tested, levels of 22 of the 26 compounds were too low to quantify, as compared with 22 of 25 for the lozenge NRT, 20 of 25 for the gum NRT, and 11 of 24 compounds for the snus. Notably, the two toxicants detected in the NPs (chromium and formaldehyde) were present at extremely low levels, close to the quantification limits. Formaldehyde, a mammalian metabolite (Restani and Galli 1991), is present in fruits, vegetables, dairy products, meat, fish and shellfish at levels of 1–100 mg/kg, with an average adult consuming between 1.5 and 14 mg/day (WHO, 2001). Based on the highest mean formaldehyde level of 1.1 mg/kg detected in Lyft Berry Frost, a pouch weight of 0.7 g, and ADC of 8.6 pouches per day, NPs would increase daily formaldehyde exposure by approximately 0.004 mg/day (assuming 58% extraction). Thus, the extremely low levels of formaldehyde in NPs are unlikely to represent a toxicological concern. Chromium, an IARC Group 1 carcinogen in its +6 oxidation state but a Group 3 compound in its +3 state, is also present in fruits, vegetables, grain products and meat; for example, a half-cup serving of broccoli contains approximately 11 µg of chromium (US National Institutes of Health (NIH) 2020), corresponding to approximately 40 times the amount of chromium that a NP user may be exposed to daily (i.e., 0.28 µg/day, assuming 8.6 pouches per day and using the worst-case single measurement of 0.08 mg/kg in Lyft Berry Frost).

The presence of toxicants in NRTs has been reported previously by Stepanov *et al*. (2006) and Nessa *et al*. (2016), who measured trace levels of some TSNAs in gum and patch NRTs, and lead, cadmium and nickel in gum NRT respectively. The levels of these metals in the gum NRT (Nessa *et al*. 2016) were comparable to those found in the gum NRT in this study except for lead, which was approximately 10-fold lower in this study [824 ng/gum vs 55 ng/g (70 ng/gum)].

In addition to the greater number of toxicants detected in snus, the levels of those that were quantified were higher in snus than in NPs, apart from nicotine and formaldehyde. Overall, the toxicant analysis suggests that NPs have the potential for a lower toxicant profile relative to that of Swedish snus, and comparability with those of NRT products, consistent with the tobacco-free composition of both NPs and NRTs.

To evaluate the toxicant contents of NPs in comparison to other tobacco and nicotine products on the risk continuum, we also reviewed the emissions of 20 of the HPHCs for which data were available for conventional cigarettes, THPs and e-cigarettes (Supplementary Methods and Table S1). Notably, cigarette smoke contained quantifiable levels of 18 of the 20 measured compounds, THP aerosol contained 12 compounds at quantifiable levels, while e-cigarette vapor contained 7 compounds at quantifiable levels. By contrast, NPs had quantifiable levels of only 3 of these 20 HPHCs. Thus, the toxicant content of NPs is considerably lower than that of inhalation tobacco product emissions, consistent with placement of NPs near the lowest exposure end of the toxicant delivery continuum.

## *Estimated daily exposure to toxicants resulting from use of oral tobacco products*

On its own, the toxicant contents of products is insufficient to establish potential health risks to a user; the frequency of product use and the extent of toxicant extraction from the product will also affect toxicant exposure during use. We therefore estimated likely exposure to toxicants ($D_{ET}$, in units of mass) for the different products based on extraction efficiency ($f_{EU}$) and ADC.

First, we derived $f_{EU}$ values based on published data for extraction of nicotine as a bridging compound. However, for compounds that show significantly less extraction than nicotine such as metals (Cuello-Nuñez *et al*. 2018), these estimations should be viewed as conservative. Using reported nicotine extraction of 44–72% for gum NRT (Benowitz *et al*. 1987, Lunell and Lunell 2005a, Lunell and Curvall 2011, Digard *et al*. 2013a, Hansson *et al*. 2019), 30–39% for snus (Lunell and Lunell 2005a, Caraway and Chen 2013, Digard *et al*. 2013a, b, Lunell *et al*. 2020), and 56% and 59% for NPs (Lunell *et al*. 2020), we calculated average $f_{EU}$ values of 0.62, 0.33 and 0.58 for gum, snus and NPs, respectively; in addition, we assumed $f_{EU} = 1$ for the lozenge NRT, which dissolves completely in the user's mouth. These $f_{EU}$ values were assigned to the extraction of all toxicants except for metals from snus, which have been established as having extraction efficiencies of 10% or less (Lunell and Lunell 2005b, Caraway and Chen 2013); we therefore used $f_{EU} = 0.1$ for cadmium, nickel and mercury, and conservative estimates of $f_{EU} = 0.05$ for arsenic, chromium and lead (Supplementary Table 2).

Next, ADC values from the market surveys (NP, 8.6 pouches/day; snus, 12.0 pouches/day) or published data (NRT lozenge/gum, 8–12 pieces/day [EMC 2020, HPRA 2020]) were

multiplied by average product weight (NP/snus, 0.7 g/pouch; NRT lozenge, 0.623 g; NRT gum, 1.265 g) to determine an average daily mass (ADM) consumption values of 6.02 g, 8.40 g, 6.23 g and 12.65 for NPs, snus, lozenge and gum, respectively (Supplementary Table S2). Lastly, the $f_{EU}$ and ADM values were coupled with our toxicant content data (Table 2) to estimate $D_{ET}$ in accordance with Equation (1) in Materials and Methods. Where the toxicant content for any product was too low to be quantified (Table 2), $D_{ET}$ could not be estimated with confidence and was therefore reported as NQ (not quantified).

The data show that, as compared with snus, use of NPs would have lower estimated daily exposure to acetaldehyde (19.7–25.5 μg/day vs NQ), NNN (1.5–1.8 μg/day vs NQ), NNK (0.2–0.6 μg/day vs NQ), NDMA (NQ–1.0 ng/day vs NQ), cadmium (∼0.2–0.4 μg/day vs NQ), chromium (0.34–0.71 vs <0.18–0.28 μg/day), nickel (0.7–1.6 μg/day vs NQ), arsenic (38.6–54.6 ng/day vs NQ) and lead (79.8–143 ng/day vs NQ) (Supplementary Table S3). Estimated exposure to formaldehyde was comparable between snus and NPs at ∼3–4 μg/day, but none of the estimated exposures were higher from NPs. As compared with NRTs, use of NPs would show higher estimated exposure to formaldehyde (NQ vs <3.5–4.0 μg/day), but lower estimated exposure to cadmium (gum 0.2 μg/day vs NQ), chromium (<0.31–5.83 vs <0.18–0.28 μg/day), nickel (0.5–1.7 μg/day vs NQ) and lead (gum 0.4 μg/day vs NQ). Based on these estimates, use of both NPs and NRTs may offer lower toxicant exposure as compared with snus.

We also estimated $D_{ET}$ for cigarettes, THPs and vapor products based on available data for 18 toxicants (Supplementary Methods and Table S3). The data indicate that, as compared with conventional smoking, use of NPs would result in lower daily exposure to 16 of the 18 toxicants, while use of snus would result in lower exposure to 10 of the 18 toxicants (Supplementary Table S3). Thus, on the basis of both the measured toxicant contents and daily exposure estimates, NPs are likely to fall between snus and NRTs on the toxicant delivery continuum, with substantially less toxicant exposure relative to cigarettes, THPs, snus and even vapor products. Recent toxicological *in vitro* testing supports this notion, demonstrating reductions in biological activity for NPs as compared with both snus and a combustible cigarette (Bishop *et al.* 2020).

Although our data suggest that NPs may occupy a similar position to NRTs near the lowest exposure end of the toxicant delivery continuum, we note that a substantial reduction in toxicants in itself is not sufficient to determine fully a reduced risk to health and does not imply that exposure to a toxicant at the same level from different product categories will have the same disease-induction mechanism or consequences. Further research on consumption, toxicant transfers and clinical data will be required to provide more robust insight into the potential health risks associated with NP use.

### *Relative positioning of NPs on the risk continuum*

In a Delphi-based study, global health experts previously evaluated the position of tobacco and nicotine products on the risk continuum in terms of maximum relative harm (MRH), placing snus at 5%, e-cigarettes at 4% and NRTs at ∼2% relative to cigarettes (Nutt *et al.* 2014). Based on the toxicant findings and ADC reported in the present study, NPs would be expected to have an MRH close to that of NRTs. However, the long-term health risks of many of these products (i.e., e-cigarettes, NRTs, NPs) are not fully characterized and further research might influence their exact position on the risk continuum; in addition, it should be noted that NRTs are not currently intended for long-term use.

It is not only direct health risks that should be considered, but also the impact of the product on other factors such as air quality, initiation and cessation (Proctor *et al.* 2017). Because they are colorless and do not smell of tobacco, NPs may have other user benefits including personal hygiene, presenting a more acceptable choice for those smokers who have historically rejected snus. In addition, NPs do not emit an aerosol during usage, and thus have zero impact on air quality. Lastly, dependence on conventional cigarettes and snus has been shown to be similar, and higher than that on NRTs (Fagerstrom 2018), which will make it harder to quit smoking than to stop using NRTs. In future studies, it will be important to determine the uptake of NPs by non-nicotine users, as well as user dependence on these products.

While regulatory and healthcare bodies agree that, at the level of exposure from tobacco products, nicotine is comparatively harmless (RCP 2016, Gottlieb 2017, PHE 2019), it is toxic in high doses (Schep *et al.* 2009) and there is a case for regulation to limit the strength of nicotine in NPs. Oral products with extremely high nicotine strengths have entered some markets, leading to concerns about nicotine poisoning and resulting in a ban of the NP category in some cases (Kondratieva 2020). To overcome potential issues of nicotine poisoning/overdose, sensible science-based regulation should be implemented, for example, nicotine ceilings. In the absence of bespoke regulation, product standards will be necessary to ensure regulator confidence in the NP category. Studies are underway to bridge the science/research gaps and address the lack of data on NPs, particularly on product use behavior and nicotine pharmacokinetics.

## Conclusion

In summary, NPs may provide a lower toxicant-exposure source of nicotine for current smokers who seek a substitute to cigarettes, in particular for those who find NRTs ineffective. Based on their similarity to snus in physical usage, but due to the absence of tobacco, lower toxicant profile and reduced ADC, NPs may also offer fewer health risks than snus when smokers switch to using them exclusively. NP toxicant contents, and estimates of exposure in comparison to other products suggest that NPs may be positioned between Swedish snus and NRTs on the tobacco and nicotine toxicant continuum. However, more definitive use behavior data, and ultimately clinical data are required to confirm the potential of NPs to be reduced exposure and risk nicotine products.

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## Author contributions

DA managed the NRT testing, analyzed the data and prepared the manuscript. CL reviewed the manuscript and provided expert guidance. JM reviewed the manuscript, provided expert guidance and conceived the idea of the study. All authors read and approved the final manuscript.

## Disclosure statement

All authors are employees of BAT, a company that manufactures tobacco and nicotine products.

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## Data availability statement

All data and materials are available upon request.

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