Review of: "Nicotine Pouch Sales Trends in the US by Volume and Nicotine Concentration Levels From 2019 to 2022"

Mohamadi Sarkar[1], Maria Gogova[1]

1 Altria

Potential competing interests: Authors are employees of Altria Client Services LLC.

Sarkar M and Gogova M.

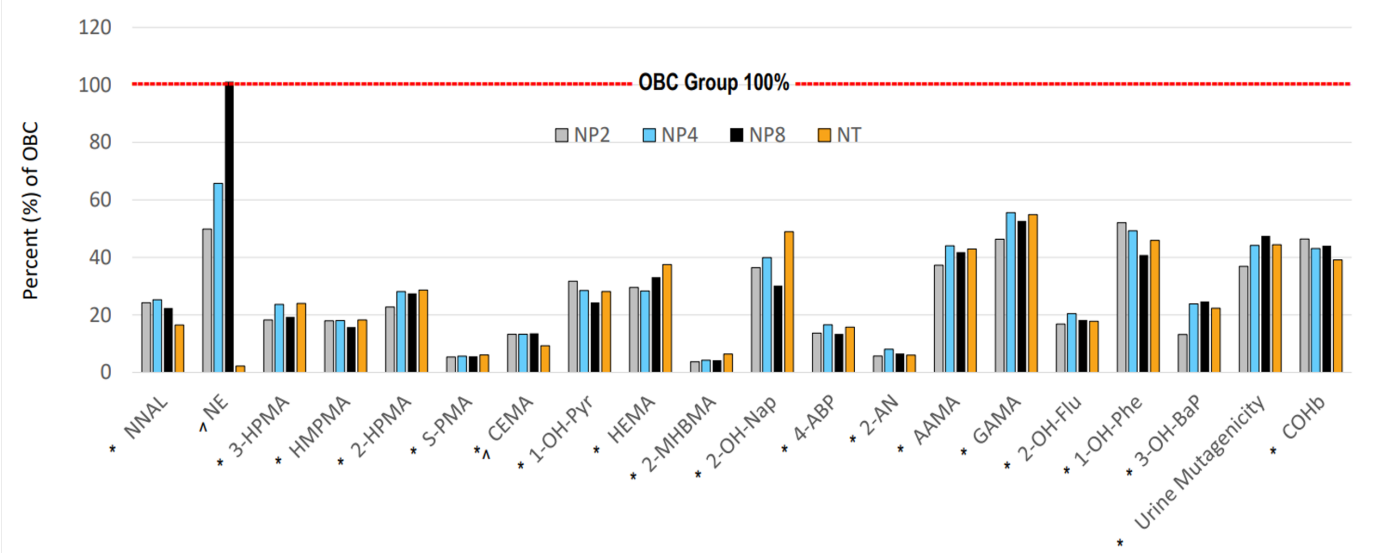
Center for Research and Technology, Altria Client Services LLC., Richmond VA.

We read the publication by Majmundar et al[1] with great interest. We are encouraged by the authors findings because the trajectory of nicotine pouch sales indicates that adult tobacco consumers might be increasingly trying and switching from harmful tobacco products like cigarettes. This is very promising because we believe that oral nicotine pouches (NP), including on!® (*on!*NPs[a]) that we market, are a reduced harm option for adults who smoke but cannot or will not quit cigarettes. In fact, our market data show a 72% increase in shipment volume for *on!*NPs through the third quarter of 2022, and our retail point-of-purchase data consistently demonstrate that the vast majority of *on!*NP adopters were adult smokers or dippers. The authors' conclusions regarding potential use by nonusers, including youth, and potential abuse liability, while legitimate issues, are misplaced. Undoubtedly, the potential risks of youth and adult nonusers starting the use of NPs is important, however this should be weighed against the switching potential among adults who smoke. The totality of our evidence indicates a net benefit to the population, because higher proportion of adults, who are not intending to quit smoking, switch from cigarettes to *on!*NPs relative to the low likelihood of use among youth and adult nonusers. This is notable progress towards harm reduction.

We have submitted a Premarket Tobacco Product Application (PMTA) to FDA for authorization to continue to market the *on!*NPs. In our application we included several lines of scientific evidence to demonstrate that these products are appropriate for the protection of public health. We present here some scientific evidence specific for *on!*NPs that help illustrate the harm reduction potential of these products and address some of the concerns raised in the publication.

Switching completely to *on!*NPs substantially reduces exposure to harmful and potentially harmful constituents

Figure 1 – Percent reduction in biomarkers of exposure among adult smokers switching to *on!*NPs compared to cigarette smoking and smoking abstinence



NP#= *on!*NPs, numbers reflect 2mg, 4mg and 8mg nicotine levels; NT=No tobacco use; OBC=Own Brand Cigarette; * NP groups compared to the Cigarette group – all BOEs (except NE) were statistically significantly different between the *on!*NP groups and the continued smoking group (p-values were < 0.0003); ^ *on!*NP groups compared to the No Tobacco group – only the NE and CEMA were statistically significantly different. Adult smokers were randomized into switching to either the 2 mg (NP2=28), 4 mg (NP4=30) or 8 mg *on!*NPs (NP8=30) or allowed to continue smoking (0BC group=29) or into a group that stopped all tobacco use (NT=29).

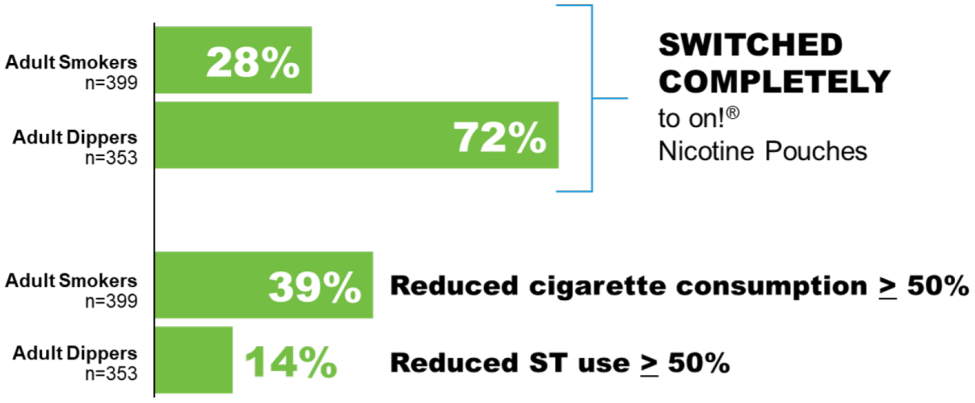
1-OH-Pyr = 1-hydroxypyrene; 1-OH-Phe = 1-OH-phenanthrene; 2-AN = 2-aminonaphthalene; 2-HPMA = 2hydroxypropyl-mercapturic acid; 2MHBMA = 2-hydroxybutenyl-mercapturic acid; 2-OH-Nap = 2-Naphthol; 2-OH-Flu = 2-OH-fluorene; 3-OH-BaP = 3-hydroxybenzo(a)pyrene; 3-HPMA = 3hydroxypropylmercapturic acid; HMPMA = 3-hydroxy-1-methylpropylmercapturic acid; 4-ABP = 4-aminobiphenyl; AAMA = N-acetyl-S-(2-carbamoylethyl)-l-cysteine; CEMA = 2cyanoethylmercapturic acid; COHb = carboxyhemoglobin; Cr = creatinine; CS = continued smoking; GAMA = N-acetyl-S-(2-carbamoyl-2-hydroxyethyl)-l-cysteine; HEMA = 2hydroxyethyl mercapturic acid; NE = nicotine equivalents; NNAL = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; SPMA = S-phenyl mercapturic acid.

Because the *on!*NPs only contain tobacco-derived nicotine and non-tobacco ingredients and not cut, ground, powdered or leaf tobacco, most HPHCs are either absent or substantially reduced [2]. And, our randomized controlled clinical study [3] confirms that biomarkers for most HPHCs are substantially reduced relative to continued smoking and exposure reductions are comparable to tobacco abstinence (Figure 1). These biomarkers are indicators of exposure to HPHCs that are classified by the FDA as carcinogens, respiratory toxicants, cardiovascular toxicants, reproductive or developmental toxicants, or as addictive constituents [4]. Therefore, substantial reductions in biomarkers (except nicotine) indicate the harm reduction opportunity for those adults who switch from cigarettes to *on!*NPs. Such reductions depend on switching behavior.

Many adults using *on!*NPs reduced their tobacco consumption or switched completely

Importantly, we observe considerable switching behavior in a six-week actual use study (AUS) with*ad libitum* use of NPs [5]. When offered free open access to the portfolio of NPs, adults who use tobacco products (without intentions to quit them), either reduced their tobacco consumption or switched completely (Figure 2).

Figure 2 – Proportion of adults who smoke or adults who dip that either reduced their cigarette or smokeless tobacco (ST) product consumption by at least 50%.



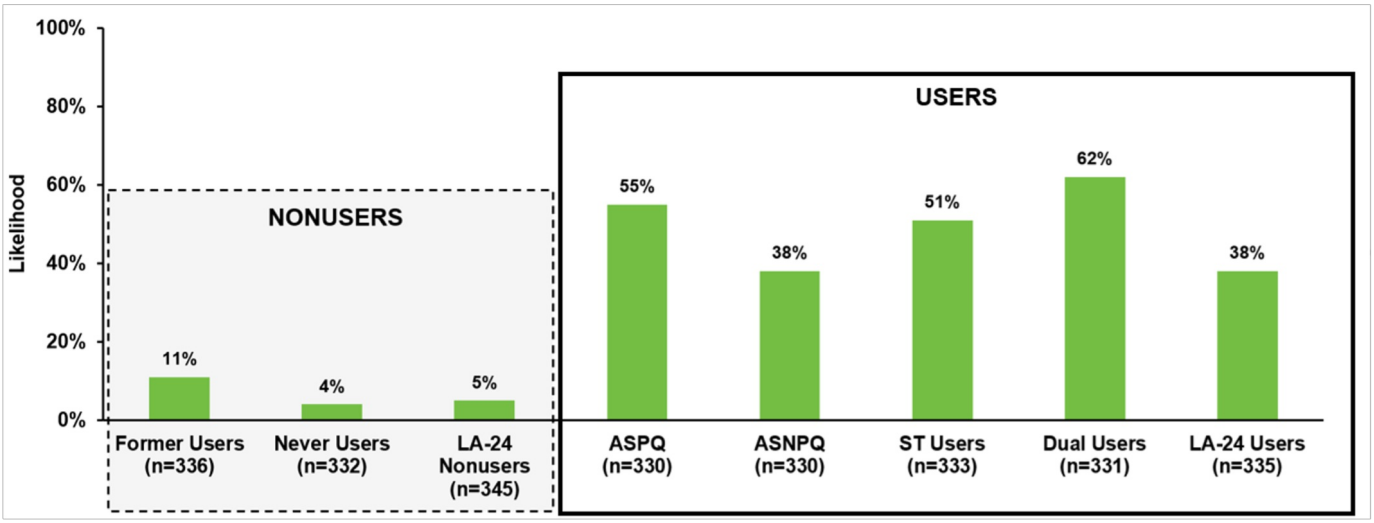
Results shown are proportion of study participants from adults who were either current cigarette smokers, users of smokeless tobacco (ST) products (dippers) or use both product (n = 1,147 complete). The study participants were not planning to quit tobacco use in the next 30 days and had interest in trying and after a brief trial period were interested in using them for the duration of the study. There were offered free choice of a portfolio of TPs (seven flavors at five nicotine levels) to use at-home, ad-libitum, for 6-weeks.

The range of nicotine levels in *on!*NPs offer adults who smoke options to choose the nicotine level they need to switch from combustible cigarettes

Providing adults who smoke with products that deliver nicotine in a less harmful manner is critical to achieving harm reduction for smokers. As cited by Koh and Fiore [6], this principle dates back to at least 1976, when Dr Michael Russell observed that “people smoke for the nicotine but die from the tar.” The portfolio of *on!*NPs contain a range of nicotine levels (1.5 mg, 2 mg, 3.5 mg, 4 mg and 8 mg), inclusive of levels that are lower than and comparable to snus and moist snuff [2]. While the *on!*NPs contain nicotine, which is addictive[b], the availability of a range of nicotine levels that can satisfy adults who smoke is essential to support switching from cigarettes to *on!*NPs.

The likelihood of *on!*NP use among nonusers is low

Figure 3 – Proportion of nonusers and tobacco products users indicating likelihood to use *on!*NPs.



Results shown in the chart are from n=5037 adult users and nonusers of tobacco products. Likelihood to use the *on!*NPs was based on an intention composite score >3.5 and a "Yes" answer to purchase intent question. The responses were obtained after showing promotional materials for *on!*NPs that a tobacco nonuser might encounter (e.g., images of packaging); ASNPQ=adult smokers planning to quit; ASNPQ=adult smokers not planning to quit; ST=smokeless tobacco; DU=dual user of cigarettes and smokeless tobacco; LA=Legal age to purchase tobacco.

The concern raised by the authors about the potential for experimentation or dependence potential among nicotine-naïve individuals are not supported by the current evidence. To the contrary, in a study conducted among nearly 5,000 users and nonusers of tobacco products [7], we observe low likelihood of use of*on!*NPs among nonusers (Figure 3). The likelihood of use among nonusers was substantially lower than users of tobacco product. Conversely, the higher likelihood of use demonstrated among users is further established from the switching behavior observed in the AUS (Figure 2).

The likelihood of youth use of *on!*NPs is low

The authors also state that *"[n]icotine pouch promotions highlight youth-appealing flavors*." We agree that no youth should use any tobacco product. Encouragingly, the National Youth Tobacco Survey[c] indicates low prevalence of use of nicotine pouches, flavored or otherwise. The prevalence of current use of nicotine pouches was 0.8% in 2021 and 1.1% in 2022, among middle and high school students. Overall, these observations demonstrate that despite the availability of flavor options, youth use of nicotine pouches is extremely low.

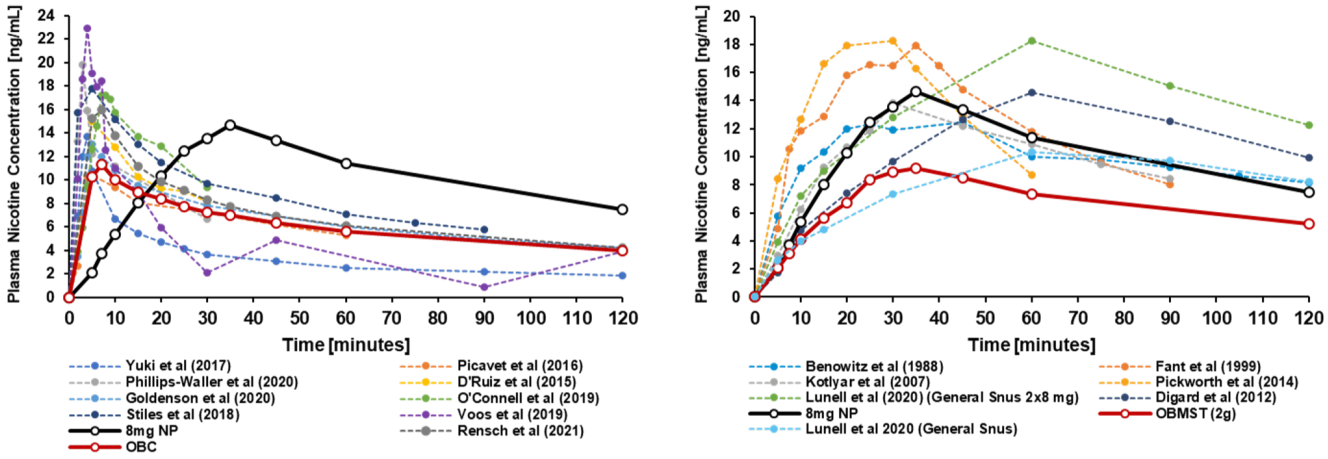
Indeed, the balance between the risk of youth uptake and benefit of adult switching from cigarettes must be carefully weighed [8]. The current evidence suggests, however, that youth use of nicotine pouches is low; while an analysis of the AUS data indicates that flavors are a significant factor in switching to *on!*NPs from cigarettes for adults who smoke [9]. In our AUS we have observed that at the end of 6-weeks, ~50% of adults who smoke stated flavors as one of the main reasons to purchase the *on!*NPs in the future. Therefore, based on the currently available evidence, the benefit of

accelerating switching from cigarettes among adults who smoke appears to outweigh the potential risk of youth uptake of nicotine pouches.

The abuse liability of *on!*NPs is not higher than cigarettes

We also find the authors concerns regarding abuse liability to be unwarranted. The authors make a speculative statement, that "*Increasing sales of products with the highest (8 mg) nicotine concentration level raise concerns about abuse liability among individuals who use nicotine*" without providing any supporting data. In fact, as shown in Figure 2 of the manuscript [1], the increase in sale of the 8 mg*on!*NP is comparable to the 4 mg product. The authors do not provide their rationale of focusing only on the 8 mg product.

Figure 4 – Plasma Nicotine Values Over Time During Use of the 8mg *on!*NP and Representative Published data



Plasma nicotine values over time during use of the 8 mg NP and representative published data for a cigarettes and b smokeless tobacco products. The plasma pharmacokinetic profiles from the published literature (dotted lines) are replotted from estimated values based on figures in the publications. For consistency, all data has been baseline adjusted. Results from our study (solid lines) are presented; only the 8 mg NP nicotine PK profile is presented because the 8 mg NP exhibited the highest nicotine PK relative to the lower nicotine level NPs. NP, nicotine pouch; OBC, own brand cigarette; OBMST, own brand moist smokeless tobacco. The specific citations can be found in Rensch *et al* (10).

Nonetheless, this stated concern regarding abuse liability is not supported by the results of our randomized clinical study, in which we assessed the nicotine pharmacokinetic profile of the NPs and subjective responses among adults who smoke cigarettes and use ST products [10]. As reported in this peer-reviewed publication, we have demonstrated that these products, are not reasonably likely to increase nicotine dependence and addiction relative to cigarette and ST products already available in the market. Specifically, the evidence indicates that the 8 mg products do not have higher abuse liability than cigarettes or ST products (Figure 4). The maximum nicotine plasma levels during use of the 8 mg product were within the range typically reported for cigarettes and ST products in the published literature. Additionally, abuse

liability-related positive subjective ratings for the 8 mg product were lower [10]. Importantly, abuse liability should be viewed in the context of its role in reducing smoking-related harm. Some degree of abuse liability has been proposed to support overall population tobacco harm reduction [11][12]. A smoke-free product with low abuse liability likely will not be adopted or used extensively and may not encourage existing smokers to switch from cigarettes [13].

Accurate communication regarding the risk differential between cigarettes and *on!* NPs is urgently needed for adults who smoke to make an informed switching decision

Lastly, the authors conclude that *"[h]ealth campaigns warning of potential adverse health outcomes of nicotine pouches are needed."* Indeed, these products contain nicotine, which is addictive. When switching to NPs, adults who smoke are not likely to experience any additional adverse health outcomes beyond that from nicotine. On the contrary, they stand to benefit by reducing their risks of smoking-related diseases. The *on!* NPs are intended for oral use; thus, they do not lead to pulmonary exposure. Adults who smoke cigarettes will reduce exposure to most HPHCs, including carcinogens, respiratory and cardiovascular toxicants when switching to *on!* NPs. Given these facts, we believe that more than a campaign warning of potential adverse health outcomes, a campaign providing accurate information to adults who smoke is urgently needed. Adult smokers must be informed that, while quitting smoking is the best way to reduce their health risks, if they cannot or will not quit, their risks of smoking-related diseases will be reduced by switching to nicotine pouches. Overall, we conclude that *on!* NPs offer a unique harm reduction opportunity for adults who smoke and increased sales of nicotine pouches, specifically of *on!* NPs, should be considered a positive step in the direction of harm reduction.

Footnotes

[a] on!® is a registered trademark of Helix Innovations, LLC and will be written as*on!* throughout this response, to differentiate from the nicotine pouch category. Since we only have the scientific evidence specific to *on!* we can only address the authors comments related to *on!* but not for the entire nicotine pouch category.

[b] Potential adult tobacco users are accordingly warned by the following statement, as required by law (21 CFR § 1143.5), which occupies 30% of the front label of the can – "WARNING: This product contains nicotine. Nicotine is an addictive chemical."

[c] Source: https://www.cdc.gov/tobacco/data_statistics/surveys/NYTS/. The first year that NYTS included a section regarding awareness and use of nicotine pouches was 2021. The questionnaire included a list of product brands to describe the category ("[…] "nicotine pouches" such as Zyn, on!, or Velo. The survey did not assess brand-level awareness or use of nicotine pouches.

References

1. [a, b]*Anuja Majmundar, Christian Okitondo, Ashley Xue, Samuel Asare, et al. (2022).Nicotine Pouch Sales Trends in the US by Volume and Nicotine Concentration Levels From 2019 to 2022. JAMA Netw Open, vol. 5 (11), e2242235. doi:10.1001/jamanetworkopen.2022.42235.*
2. [a, b]*Wagner KAD et al. (2022). A Comparison of HPHCs in on!® Nicotine Pouches to HPHCs in Cigarettes and Swedish Snus. Paper presented at: 75th Tobacco Science Research Conference, New Orleans, LA, Sept. 11-14, 2022.*
3. [^]*Rensch J EJ et al. (2022). A Randomized, Controlled, Open-label, In-clinic Study Evaluating Changes in Biomarkers of Exposure in Adult Smokers Who Switch to on!® Nicotine Pouches for Seven Days. Clinical Pharmacology in Drug Development. (Special Issue: 2022 Annual Meeting American College of Clinical Pharmacology).*
4. [^]*FDA. Guidance for Industry. 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, Draft Guidance. In: Services. USDoHaH, ed2012.*
5. [^]*Becker EM et al. (2021). Impact of using an oral tobacco derived nicotine pouch product on cigarette consumption among adult smokers under near real-world conditions over six-weeks. Paper presented at: 27th Annual Meeting of the Society for Research on Nicotine and Tobacco. Feb. 24-27, 2021.*
6. [^]*Howard K. Koh, Michael C. Fiore. (2022). The Tobacco Industry and Harm Reduction. JAMA, vol. 328 (20), 2009. doi:10.1001/jama.2022.20679.*
7. [^]*Leighty J MS et al. Evaluation of Tobacco Nonusers' Intentions Toward an Oral Tobacco-derived Nicotine Pouch Product as the Result of Viewing Promotional Materials. Paper presented at: Society of Nicotine and Tobacco Research 26th Annual Meeting, New Orleans March 11-14, 20202020.*
8. [^]*David J. K. Balfour, Neal L. Benowitz, Suzanne M. Colby, Dorothy K. Hatsukami, et al. (2021)Balancing Consideration of the Risks and Benefits of E-Cigarettes. Am J Public Health, vol. 111 (9), 1661-1672. doi:10.2105/ajph.2021.306416.*
9. [^]*McCaffrey SL et al. Examination of association between flavors and nicotine strengths of an oral tobacco-derived nicotine pouch product and cigarettes per day over six weeks of ad libitum use. Paper presented at: Soceity for Research on Nicotine and Tobacco, 27th Annual Meeting, Feb. 24-27, 20212021.*
10. [a, b]*Jianmin Liu, Jesse Rensch, Jingzhu Wang, Xiaohong Jin, et al. (2022).Nicotine pharmacokinetics and subjective responses after using nicotine pouches with different nicotine levels compared to combustible cigarettes and moist smokeless tobacco in adult tobacco users. Psychopharmacology, vol. 239 (9), 2863-2873. doi:10.1007/s00213-022-06172-y.*
11. [^]*David B. Abrams, Allison M. Glasser, Jennifer L. Pearson, Andrea C. Villanti, et al. (2018).Harm Minimization and Tobacco Control: Reframing Societal Views of Nicotine Use to Rapidly Save Lives. Annu. Rev. Public Health, vol. 39 (1), 193-213. doi:10.1146/annurev-publhealth-040617-013849.*
12. [^]*David B. Abrams, Allison M. Glasser, Andrea C. Villanti, Jennifer L. Pearson, et al. (2018).Managing nicotine without smoke to save lives now: Evidence for harm minimization. Preventive Medicine, vol. 117 , 88-97. doi:10.1016/j.ypmed.2018.06.010.*
13. [^]*Institute_of_Medicine_(IOM). (2012). Scientific Standards for Studies on Modified Risk Tobacco Products.*