Characterization of on!® Nicotine Pouches – Part 1: HPHCs

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ABSTRACT

on!® is an oral tobacco-derived nicotine pouch product that does not contain cut, ground, powdered or leaf tobacco. In order to issue market authorization, FDA must determine whether the on!® nicotine pouches are appropriate for the protection of public health (APPH). We characterize the levels of harmful and potentially harmful constituents (HPHCs) for the portfolio of on!® nicotine pouches to inform the determination of APPH.

FDA has not issued specific guidance for reporting HPHCs for oral tobacco-derived nicotine products, such as on!® nicotine pouches. Absent specific guidance from FDA, we measured the abbreviated list of HPHCs in on!® nicotine pouches according to the guidance for smokeless tobacco products, recognizing that these products do not meet the statutory definition of a smokeless tobacco product.[1] The HPHCs evaluated included nicotine, NNN, NNK, B[a]P, acetaldehyde, formaldehyde, crotonaldehyde, cadmium and arsenic. The objective of this work was to determine HPHCs in on!® nicotine pouches and compare those results to commercially available tobacco products such as cigarettes, smokeless tobacco including snus, and an oral nicotine replacement therapy (NRT) product. Except for nicotine, we observe either no detectable levels or significant reductions in HPHCs when compared to traditional combustible and smokeless tobacco products, including snus, and comparable results relative to the NRT.

STUDY OVERVIEW

- on!® is an oral tobacco-derived nicotine pouch product that does not contain cut, ground, powdered or leaf tobacco.
- We quantified the levels of abbreviated HPHCs for three manufacturing lots of on!® Mint nicotine pouches produced in 5 nicotine strengths.
- We compared the HPHC levels found in on!® Mint nicotine pouches to cigarettes, General® Snus and Nicorette® Fresh Mint™ Gum.

METHODS

on!® nicotine pouches were analyzed using methods that were fully validated and included on the laboratory's ISO 17025 scope of accreditation at the time of the testing.

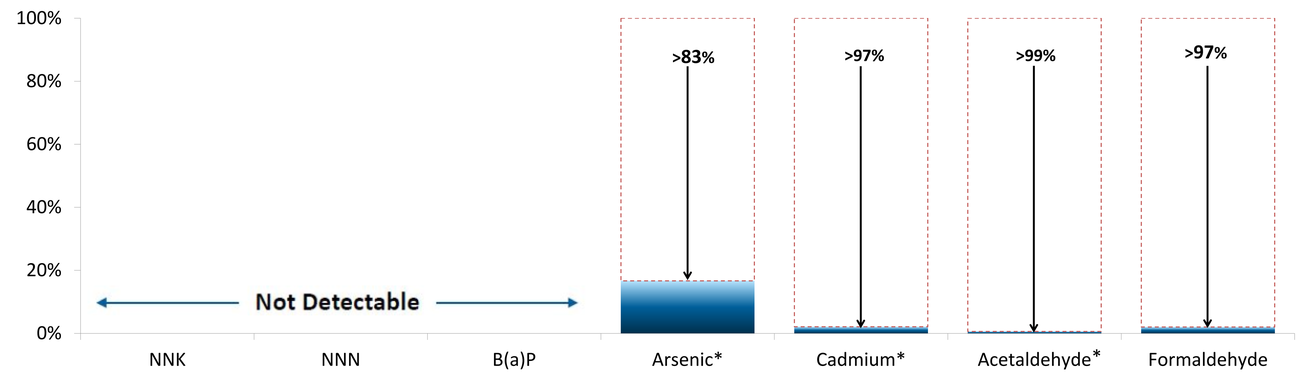
- Nicotine and pH: on!® nicotine pouches were analyzed in accordance with the Centers for Disease Control and Prevention's *Protocol for Analysis of Nicotine, Total Moisture and pH in Smokeless Tobacco Products*, as published in the Federal Register Vol. 64, No. 55 March 23, 1999 (and as amended in Vol. 74, No. 4, January 7, 2009).
- NNN & NNK: on!® nicotine pouches were analyzed in accordance with ISO 21766:2018, *Tobacco and Tobacco Products - Determination of Tobacco-specific Nitrosamines in Tobacco Products - Method using LC-MS/MS.*
- Benzo[a]pyrene: on!® nicotine pouches were analyzed in accordance with CORESTA Recommended Method No. 82 - *Determination of Benzo[a]pyrene in Tobacco Products by GC-MS.*
- Acetaldehyde, Crotonaldehyde, & Formaldehyde: on!® nicotine pouches were analyzed in basic accordance with CORESTA Recommended Method No. 86 - *Determination of Select Carbonyls in Tobacco and Tobacco Products by UHPLC-MS/MS.*
- Arsenic and Cadmium: *on!®* nicotine pouches were analyzed by digesting intact pouches in a closed vessel microwave digestion system using nitric acid. The digestate was analyzed by inductively-coupled plasma mass spectrometry (ICP-MS) equipped with a collision cell.

HPHC RESULTS FOR on!® MINT NICOTINE POUCHES (PER PORTION BASIS)[1]

HPHC[1]	Units	Reporting Limit	1.5 mg Nicotine	2 mg Nicotine	3.5 mg Nicotine	4 mg Nicotine	8 mg Nicotine
Nicotine (total)	mg/pouch	0.75	1.54 (0.09)	2.04 (0.18)	3.57 (0.25)	4.16 (0.27)	8.32 (0.34)
pH	NA	NA	8.42 (0.34)	8.81 (0.19)	8.20 (0.27)	8.75 (0.18)	8.26 (0.23)
Nicotine (free) ‡	mg/pouch	NA	1.06 (0.21)	1.74 (0.15)	2.16 (0.59)	3.49 (0.14)	5.23 (0.60)
NNN	ng/pouch	40	ND	ND	ND	ND	ND
NNK	ng/pouch	40	ND	ND	ND	ND	ND
B[a]P	ng/pouch	0.13	ND	ND	ND	ND	ND
Acetaldehyde	µg/pouch	0.05	0.063 (0.029)	BLOQ	BLOQ	BLOQ	BLOQ
Formaldehyde	µg/pouch	0.05	0.111 (0.018)	0.109 (0.015)	0.115 (0.016)	0.109 (0.020)	0.100 (0.009)
Crotonaldehyde	µg/pouch	0.025	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ
Cadmium	ng/pouch	5	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ
Arsenic	ng/pouch	5	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ

The HPHC results represent the average of three manufacturing lots where the numbers in parenthesis represent standard deviation of the 21 replicates.
ND = Not detected; BLOQ = Below limit of quantitation
‡ = Free nicotine is estimated using the Henderson-Hasselbalch equation, subject to limitations described in Lauterbach, et al., 2011.[4]

PERCENT REDUCTION IN HPHC LEVELS OF on!® 4 MG MINT COMPARED TO GENERAL® SNUS IN MARKET[2]



*Arsenic, Cadmium and Acetaldehyde were below the limit of quantification (BLOQ) in on!® products. The limits of quantification (LOQ) were used to estimate the percent reduction. Results show HPHC reductions in our 4 mg Mint on!® nicotine pouches and may vary for other SKUs. HPHC levels are compared on per unit of use basis.

PRODUCT COMPARISONS (PER PORTION BASIS)

HPHC[1]	Mass per Unit of Use	on!® Mint Nicotine Pouches Maximum Levels‡	General® Snus[2]	Cigarettes[3]	Nicorette® Fresh Mint™ Gum 2 mg
Nicotine (total)	mg	8.32	7.22	2.59	2.02
Nicotine (free)	mg	5.23	5.17	NC	2.00
NNN	ng	ND	0.303	145	ND
NNK	ng	ND	0.098	284	ND
B[a]P	ng	ND	0.265	20.5	ND
Acetaldehyde	µg	0.063	9.41	1690	BLOQ
Formaldehyde	µg	0.115	6.60	59.2	ND
Crotonaldehyde	µg	BLOQ	BLOQ	91.2	BLOQ
Cadmium	ng	BLOQ	240	114	50.7
Arsenic	ng	BLOQ	30.0	11.3	47.3

ND = Not detected
BLOQ = Below limit of quantitation
NC = Not calculated because pH was not measured
‡ = Data represent the maximum values for on!® Mint for the five nicotine strengths over three manufacturing lots.

STRENGTHS & LIMITATIONS

- In the absence of an established list of HPHCs for novel, oral tobacco-derived nicotine products, we tested the products for the abbreviated list of HPHCs for smokeless tobacco products from the 2012 Draft Guidance.[1]
- This study included the analysis of three manufacturing lots.
- All data were generated with validated methods that were included on the laboratory's scope of ISO 17025 accreditation.

CONCLUSIONS

- We quantified the levels of HPHCs in on!® nicotine pouches and provided a comparison to other tobacco products as required under section 910(b)(1)(A) of the FD&C Act.
- Chemical analyses of on!® nicotine pouches showed low or nondetectable levels of HPHCs. Nicotine, acetaldehyde and formaldehyde were the only HPHCs with quantifiable levels. All other HPHCs were either not detected or BLOQ.
  - Compared with cigarettes, on!® nicotine pouches have significantly lower levels of all HPHCs.
  - Compared with General® Snus, on!® nicotine pouches have significantly lower levels of all HPHCs.
  - Compared with Nicorette® Gum, on!® nicotine pouches have significantly lower levels of arsenic and cadmium. Acetaldehyde and formaldehyde are reportable in on!®, but not in Nicorette® Gum.
- A toxicological risk assessment was conducted on the two quantifiable HPHCs, acetaldehyde and formaldehyde, with an estimated daily exposure of 20 pouches/day (1 pack/day) and 100% bioavailability. Using established regulatory values developed by the Texas Commission on Environmental Quality (TCEQ), US EPA IRIS, and California EPA (CalEPA), it was determined that potential exposure to both acetaldehyde and formaldehyde were well below established regulatory values and would not introduce a non-cancer risk. Only formaldehyde was evaluated for potential cancer because there is no established oral cancer slope factor for acetaldehyde. The excess lifetime cancer risk for oral exposure to formaldehyde was estimated to be approximately 10^{-6}. Taken together, neither HPHC is introducing a significant non-cancer or cancer risk.

REFERENCES

1. 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 Cosmetics Act (3/2012).
2. General® snus HPHC data source: FDA reviewer notes - Chemistry Review of Pre-market Tobacco Applications (PMTAs) Submitted by Swedish Match North America for Snus Smokeless Tobacco Product, 10/30/2015 (obtained by Freedom of Information Act request).
3. Oldham MJ, et al. (2014) Insights from Analysis for Harmful and Potentially Harmful Constituents (HPHCs) in Tobacco Products. Regul Toxicol Pharmacol 70:138-148. (Appendix Table 2).
4. Lauterbach JH, et al. (2011) Free-base Nicotine in Tobacco Products. Part II. Determination of Free-base Nicotine in the Aqueous Extracts of Smokeless Tobacco Products and the Relevance of these Findings to Product Design Parameters. Regul Toxicol Pharmacol 59:8-18.