

A Comparison of HPHCs in on!® Nicotine Pouches to HPHCs in Cigarettes and Swedish Snus

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75TH TSRC, Poster #14
September 11 – 14, 2022

Abstract

on!® nicotine pouches (on!® NP) are oral tobacco-derived nicotine products intended for adult tobacco consumers aged 21 years or older. These products are smoke-free and do not contain cut, ground, powdered or leaf tobacco. A modified risk tobacco product application (MRTPA) must, in part, provide scientific evidence that marketing the product would reduce the harm or risk of tobacco-related diseases in order for the Food and Drug Administration (FDA) to issue an order under section 911(g) of the FD&C Act. One aspect of this scientific evidence is demonstrating that substantial reductions in exposure to harmful and potentially harmful constituents (HPHCs) occur when using the candidate product compared to other tobacco products.

We characterized the on!® portfolio of products for constituents from the FDA abbreviated list of HPHCs in cigarette smoke, smokeless tobacco, and the Swedish GOTHIA TEK® standard and compared these results to cigarette smoke and Swedish snus, respectively. We demonstrated an absence of a majority of the 35 smoke HPHCs and GOTHIA TEK® constituents that were tested in on!® NP. Only five of the 35 constituents (4-aminobiphenyl, acetaldehyde, formaldehyde, chromium, nickel) were above the limits of quantitation (LOQ) in any of the 35 on!® NP products tested. HPHC reductions for the five detectable HPHCs in on!® NP were >98% when compared to 1R6F non-intense smoke and 55-97% when compared to four General® snus products previously determined by the FDA to be MRTPs. These results establish a significant HPHC exposure reduction potential for on!® NP when compared to other tobacco products. Additionally, a toxicological risk assessment conducted on the five quantifiable HPHCs with an estimated daily exposure of 20 on!® NP/day (one pack/day) and 100% bioavailability demonstrated that the maximum HPHC concentrations on!® NP were below levels of toxicological concern.

Introduction

- We demonstrate that the 35 on!® NP products tested have substantially reduced HPHC levels compared to cigarettes and four General® snus products FDA previously determined to be modified risk tobacco products¹
 - The General® snus products included General Portion Original Large, General Mint Portion White Large, General Portion White Large, General Wintergreen Portion White Large
- To demonstrate the reduced risk potential of on!® NP compared to cigarettes, we compared the HPHCs measured in on!® NP to literature values from FDA's abbreviated list of HPHCs in cigarette smoke.^{2,3} We also included three additional smoke constituents (3-aminobiphenyl, o-toluidine and styrene).
- To further demonstrate the reduced risk potential of on!® NP, we compared the constituents from the GOTHIA TEK® list to four General® snus products authorized as MRTPs^{1,4}

HPHC Results

- All testing was conducted at ISO 17025 accredited laboratories and all methods were validated for the matrices.
 - One lot of the 35 on!® NP products were tested for the cigarette smoke and smokeless tobacco HPHCs at Enthalpy Analytical, LLC (Henrico, VA). Three additional lots of the 35 on!® NP products were tested for the smokeless tobacco HPHCs by Altria Client Services LLC. The highest HPHC results determined in the four lots are presented herein.
 - One lot of the 35 on!® NP products and the four General® snus products were tested for the GOTHIA TEK® constituents at Eurofins Food & Feed Testing Sweden AB (Lidköping, Sweden)
- Smoke related HPHCs:
 - All smoke related HPHCs evaluated were below the limit of quantitation (BLOQ) in on!® NP except 4-aminobiphenyl. The 1R6F non-intense smoke yield for 4-aminobiphenyl is 40 times greater than the maximum amount of 4-aminobiphenyl determined in on!® NP. This represents a >98% reduction of 4-aminobiphenyl in on!® NP compared to cigarette smoke.
- GOTIA TEK® constituents:
 - All GOTHIA TEK® list constituents were BLOQ in the candidate products, except formaldehyde, acetaldehyde, chromium and nickel. The mean levels of these HPHCs are 7-33 times higher in the General® snus products than the maximum levels determined in the 35 varieties of on!® NP
 - Arsenic, cadmium, lead, NAB, NAT, NNK, NNN, and ochratoxin A were reportable in the General® snus products, but were BLOQ in all 35 varieties of on!® NP

Toxicological Risk Assessment

- For the majority of HPHCs, except for nicotine, the levels were below the limit of quantification (BLOQ) and represent substantial reductions relative to cigarette smoke and four General® snus products that the FDA previously determined to be modified risk tobacco products¹
 - Five (5) HPHCs (4-aminobiphenyl, formaldehyde, acetaldehyde, chromium, and nickel) were identified above the LOQ in on!® NP
- A toxicological risk assessment was conducted on the five quantifiable HPHCs with an estimated daily exposure of 20 pouches/day (one 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:
 - Oral exposure to acetaldehyde, chromium, formaldehyde, and nickel were well below established regulatory values and would not introduce a non-cancer risk
 - Oral exposure to 4-aminobiphenyl, chromium, and formaldehyde was estimated to have an excess lifetime cancer risk in the 10⁻⁶ range (1 in 1,000,000) or lower

Conclusion

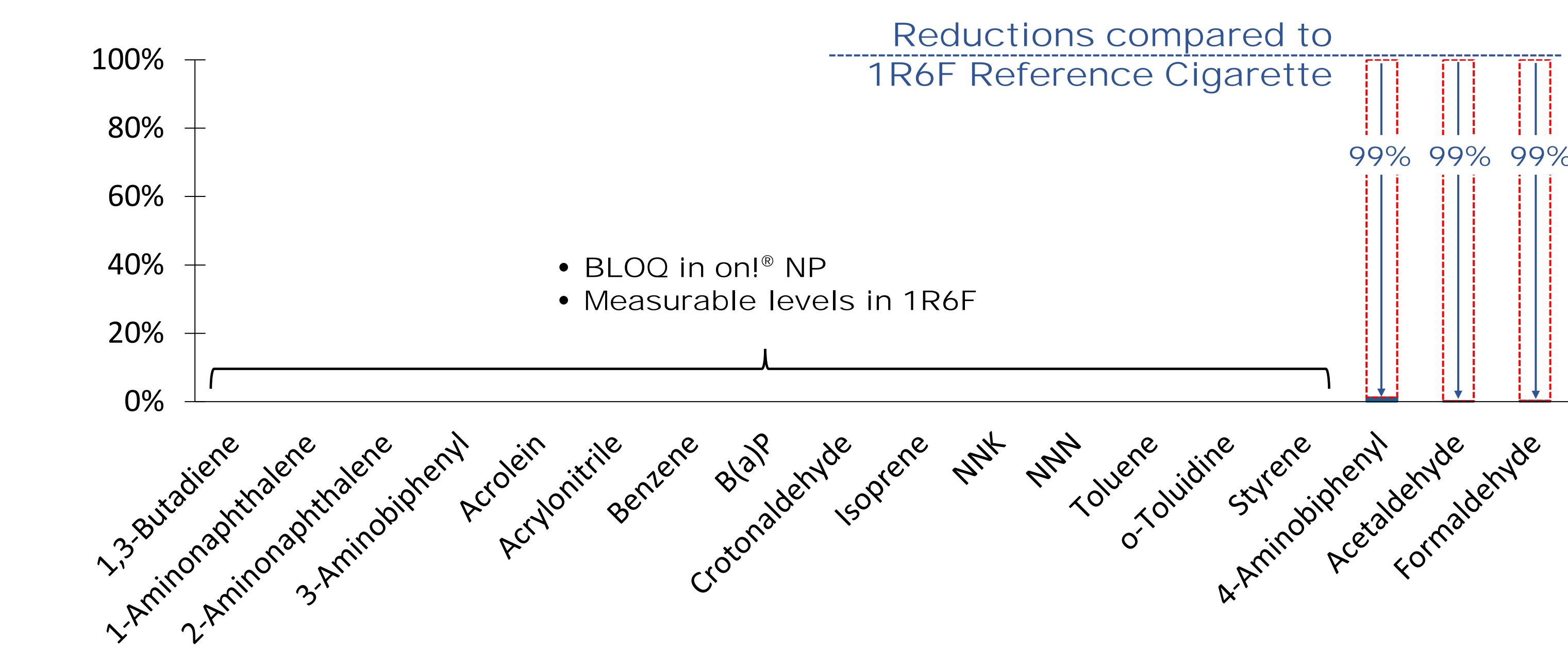
- Substantially lower levels of smoke related HPHCs in on!® NP compared to cigarette smoke suggest that adult smokers switching completely from cigarettes to on!® NP will reduce their exposure to these constituents. Sustained reductions in exposure would likely lead to reductions in smoking-related diseases.
- The HPHC data consistently demonstrates that the candidate products have substantially lower levels of HPHCs compared to four General® snus products that the FDA previously determined to be modified risk tobacco products.¹

References

- Modified Risk Granted Orders – Risk Modification. FDA Center for Tobacco Products. MR0000020 -MR0000022, MR0000024-MR0000025, MR0000027-MR0000029 (October 22, 2019), available at <https://www.fda.gov/media/131922/download>.
- FDA Draft Guidance 2012: 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; 77 Fed. Reg. 20034 (April 3, 2012).
- Guy Jaccard, Donatien Tatin Djoko, Alexandra Korneliou, Regina Stabbert, Maxim Belushkin, Marco Esposito; "Mainstream smoke constituents and in vitro toxicity comparative analysis of 3R4F and 1R6F reference cigarettes", Toxicology Reports, Volume 6, 2019, Pages 222-231.
- GOTHIA TEK® limits for undesired components – Swedish Match: <https://www.swedishmatch.com/Snus-and-health/GOTHIA TEK/GOTHIA TEK-standard/>

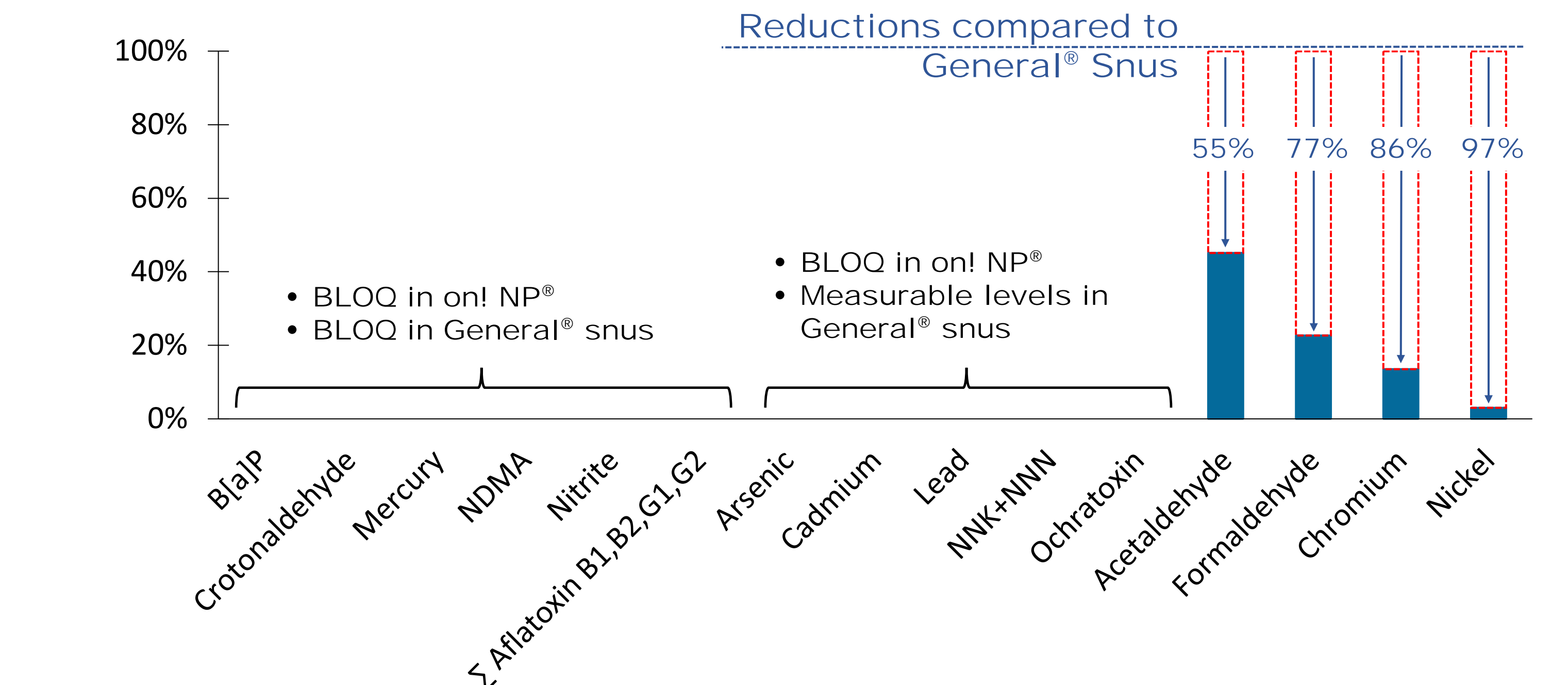
We demonstrate a substantial HPHC exposure reduction potential for on!® nicotine pouches when compared to cigarette smoke and Swedish snus

Figure 1: Percent Reduction in Cigarette Smoke HPHCs — Maximum Levels in on!® Nicotine Pouches Compared to 1R6F Intense Mainstream Smoke ^{1,2}



- HPHC = Harmful and Potentially Harmful Constituents. Constituents described in the abbreviated list of HPHCs in smoke from the 2012 Draft Guidance, 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 (FDCA). Nicotine not shown. Ammonia and carbon monoxide were not tested. 3-Aminobiphenyl, o-toluidine, and styrene are additional smoke analytes not included on the FDA Abbreviated list of HPHCs.
- Data Source: Intense smoke yields from Guy Jaccard, et al, "Mainstream smoke constituents and in vitro toxicity comparative analysis of 3R4F and 1R6F reference cigarettes", Toxicology Reports, Volume 6, 2019, Pages 222-231.

Figure 2: Percent Reduction in GOTHIA TEK® Constituents — Maximum Levels in on!® Nicotine Pouches Compared to Mean Levels in General® Snus ^{1,2}



- GOTHIA TEK® limits for undesired components – Swedish Match: <https://www.swedishmatch.com/Snus-and-health/GOTHIA TEK/GOTHIA TEK-standard/>
- Data source: Mean HPHC level determined in the four MRTP authorized General® snus products tested for this study. The four General® snus products include General Portion Original Large, General Mint Portion White Large, General Portion White Large, General Wintergreen Portion White Large.

Table 1: Cigarette Smoke HPHC Levels in on!® Nicotine Pouches Compared to 1R6F Non-Intense (ISO 3308) and Intense Mainstream Smoke (ISO 20778) ^{1,2,3}

Constituent ¹	on!® nicotine pouches ² Max (Min-Max) level of 35 flavor and nicotine level combinations (unit/portion)	1R6F Non-Intense Mainstream Cigarette Smoke ¹ (unit/cigarette)	1R6F Intense Mainstream Cigarette Smoke ¹ (unit/cigarette)
1,3-Butadiene (µg)	BLOQ (<1.26)	39.3	102
1-Aminonaphthalene (ng)	BLOQ (<0.025)	13.8	26.7
2-Aminonaphthalene (ng)	BLOQ (<0.012)	10.7	16.2
3-Aminobiphenyl (ng)	BLOQ (<0.038)	2.33	4.49
Acrolein (µg)	BLOQ (<0.025)	51.8	173
Acrylonitrile (µg)	BLOQ (<0.25)	5.23	19.2
Benzene (µg)	BLOQ (<0.63)	33.7	82.3
Benzo(a)pyrene (ng)	BLOQ (<0.26)	6.94	13.8
Crotonaldehyde (µg)	BLOQ (<0.013)	10	55
Isoprene (µg)	BLOQ (<0.24)	286	752
NNK (ng)	BLOQ (2.6)	84.5	192
NNN (ng)	BLOQ (2.6)	100	230
Toluene (µg)	BLOQ (<0.25)	47.2	132
o-Toluidine (ng)	BLOQ (<0.030)	59.4	109
Styrene (µg)	BLOQ (<2.01)	4.97	20.4
4-Aminobiphenyl (ng)	0.0362 (0.0173 - 0.0362)	1.48	3.13
Acetaldehyde (µg)	2.84 (<0.05 - 2.84)	532	1601
Formaldehyde (µg)	0.249 (0.073 - 0.249)	33.5	104

- HPHC = Harmful and Potentially Harmful Constituents. Constituents described in the FDA abbreviated list of HPHCs in smoke from the 2012 Draft Guidance, 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 (FDCA). Nicotine not shown. Ammonia and carbon monoxide were not tested. 3-Aminobiphenyl, o-toluidine, and styrene are additional smoke analytes not included on the FDA Abbreviated list of HPHCs.
- Values are the maximum and range (min – max) among the 35 the flavor and nicotine level combinations of on!® NP on a wet weight basis. BLOQ = below the limit of quantitation; A value next to "<" sign indicates the limit of quantitation (LOQ).
- Data Source: Intense smoke yields from Guy Jaccard, et al, "Mainstream smoke constituents and in vitro toxicity comparative analysis of 3R4F and 1R6F reference cigarettes", Toxicology Reports, Volume 6, 2019, Pages 222-231.

Table 2: GOTHIA TEK® list constituents Levels in on!® Nicotine Pouches Compared to Mean Levels in General® Snus ^{1,2}

Constituent ¹ (unit/consumable)	on!® nicotine pouches ² Max level (Min-Max) of 35 flavor and nicotine level combinations (unit/portion)	General® Snus ³ Mean (Min-Max) (unit/portion)
B[a]P (ng)	BLOQ (<0.26)	BLOQ (<0.99)
Crotonaldehyde (µg)	BLOQ (<0.013)	BLOQ (<0.049)
Mercury (µg)	BLOQ (<0.0063)	BLOQ (<0.020)
NDMA (ng)	BLOQ (<0.053)	BLOQ (<0.20)
Nitrite (µg)	BLOQ (<0.26)	BLOQ (<0.99)
Σ Aflatoxin B1, B2, G1, G2 (ng)	BLOQ (<1.1)	BLOQ (<3.9)
Arsenic (µg)	BLOQ (<0.013)	0.060 (0.060 - 0.060)
Cadmium (µg)	BLOQ (<0.0026)	0.26 (0.25 - 0.27)
Lead (µg)	BLOQ (<0.0063)	0.14 (0.10 - 0.25)
NNK+NNN (ng)	BLOQ (<5.3)	400 (360 - 470)
Ochratoxin (ng)	BLOQ (<0.13)	0.66 (0.54 - 0.78)
Acetaldehyde (µg)	2.84 (<0.05 - 2.84)	6.3 (5.2 - 8.1)
Formaldehyde (µg)	0.249 (0.073 - 0.249)	1.1 (0.96 - 1.1)
Chromium (µg)	0.046 (0.014 - 0.046)	0.34 (0.29 - 0.44)
Nickel (µg)	0.026 (0.013 - 0.026)	0.86 (0.70 - 1.2)
Nicotine (mg)	8.5 (1.5 - 8.5)	6.8 (6.4 - 7.2)
Free Nicotine (mg)	5.4 (1.1 - 5.4)	4.9 (4.4 - 5.2)
pH	8.8 (8.0 - 8.8)	8.4 (8.3 - 8.7)

- GOTHIA TEK® limits for undesired components – Swedish Match: <https://www.swedishmatch.com/Snus-and-health/GOTHIA TEK/GOTHIA TEK-standard/>
- Values are maximum and range (min – max) among the 35 the flavor and nicotine level combinations of on!® NP on a wet weight basis. BLOQ = below the limit of quantitation; A value next to "<" sign indicates the limit of quantitation (LOQ).
- Data Source: Mean HPHC level determined in the four MRTP authorized General® snus products tested for this study on a wet weight basis. The four General® snus products include General Portion Original Large, General Mint Portion White Large, General Portion White Large, General Wintergreen Portion White Large.



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