

ABSTRACT

FDA guidance is intended to assist in submitting PMTAs under section 910 of the FD&C Act, including reporting of HPHCs in tobacco and nicotine products and tobacco smoke under section 904(a)(3) of the FD&C Act.

The Nic Nac lozenges contain synthetic nicotine blended with xylitol, binders, and flavors. They do not contain cut, ground, powdered, or leaf tobacco and are made by blending all of the ingredients and compressing into a lozenge, using a tablet press. The use of these lozenge products is similar to a typical oral NRT lozenges such as Nicorette. Complete list of HPHC analytes (nicotine, carbonyls, TSNA, metals and PAH) were analyzed for the highest nicotine strength (6mg) and partial HPHC analytes (nicotine and carbonyls) were tested at lower nicotine strength (3mg). These constituents originate from controlled trace impurities in raw materials and packaging and do not vary with nicotine content. Because the highest strength contains the same ingredients with the most conservative exposure scenario and demonstrated uniformly non-detected or extremely low levels, the 6mg product serves as an appropriate worst-case variant for these HPHCs.

HPHC results were evaluated both on a per-lozenge and on daily-consumption survey basis. Among tested HPHCs, acetaldehyde, crotonaldehyde, NNK, NNN, arsenic, cadmium and benzo[a]pyrene were not detected or were below quantitation limits for 6mg products. Only formaldehyde was detected in tested HPHC and it was present low levels in all products. Estimated daily formaldehyde exposure from the Nic Nac lozenges was calculated using the measured daily product-consumption rate and compared with established health-based oral exposure benchmarks, including the Permissible Daily Exposure approach under ICH M7(R2), the ATSDR Minimal Risk Level, and the ECHA Derived No-Effect Level, as applicable. Comparatively, the estimated daily formaldehyde exposure from the Nic Nac lozenges was several orders of magnitude below the applicable oral health-based exposure benchmarks.

Overall, the HPHC testing results indicate that the Nic Nac oral nicotine lozenges contain no detectable or quantifiable levels of the tested TSNA, selected metals, benzo[a]pyrene, acetaldehyde, or crotonaldehyde, and only low levels of formaldehyde. Accordingly, formaldehyde at the measured concentrations is not expected to present a toxicological concern under the evaluated conditions of use and support the conclusion that HPHC-related exposures from these products are low.

STUDY DESIGN AND METHODS

The tests were conducted at Labstat International Inc., Kitchener, Ontario, Canada.

Nic Nac Lozenge Products

Nic Nac Lozenge Product Description	Target Nicotine Level (mg/lozenge)
Nic Nac Grapefruit	3.0 and 6.0
Nic Nac Cool	3.0 and 6.0
Nic Nac Wintergreen	3.0 and 6.0
Nic Nac Tangerine	3.0 and 6.0
Nic Nac Peppermint	3.0 and 6.0
Nic Nac Lemon	3.0 and 6.0
Nic Nac Spearmint	3.0 and 6.0
Nic Nac Classic	3.0 and 6.0
Nic Nac Blood Orange	3.0 and 6.0



HPHC Analyses

Analysis Panel		Analytes	Replicates
Nicotine		Nicotine	7
Carbonyls		Acetaldehyde; Crotonaldehyde; Formaldehyde	7
PAH		Benzo(a)pyrene (B(a)P)	5
TSNAs		4-[methyl(nitroso)amino]-1-(3-pyridinyl)-1-Butanone (NNK); N-nitrosomonicotine (NNN)	5
Metals		Arsenic; Cadmium	5

Method Specific LOD and LOQ For HPHC Constituents

Analyte	Unit of Measure	LOD	LOQ
Nicotine	mg/lozenge	0.038	0.125
Acetaldehyde	µg/lozenge	0.015	0.051
Crotonaldehyde	µg/lozenge	0.018	0.06
Formaldehyde	µg/lozenge	0.022	0.073
Arsenic	ng/lozenge	3.51	11.7
Cadmium	ng/lozenge	4.12	13.7
B(a)P	ng/lozenge	0.017	0.055
NNK	ng/lozenge	1.13	3.76
NNN	ng/lozenge	0.739	2.46

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RESULTS

HPHC Analysis Of Nic Nac Oral Nicotine Lozenges																																					
HPHC Constituents	Unit	Nic Nac Grapefruit				Nic Nac Cool				Nic Nac Wintergreen				Nic Nac Tangerine				Nic Nac Peppermint				Nic Nac Lemon				Nic Nac Spearmint				Nic Nac Classic				Nic Nac Blood Orange			
		3 mg		6 mg		3 mg		6 mg		3 mg		6 mg		3 mg		6 mg		3 mg		6 mg		3 mg		6 mg		3 mg		6 mg		3 mg		6 mg					
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD				
Nicotine	mg/lozenge	3.49	0.17	6.56	0.16	3.47	0.03	6.47	0.34	3.56	0.07	6.38	0.06	3.56	0.05	6.48	0.24	3.79	0.21	6.92	0.3	3.53	0.24	6.55	0.4	3.49	0.12	6.57	0.47	3.4	0.21	6.99	0.07	3.74	0.13	6.06	0.18
Acetaldehyde	µg/lozenge	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL
Crotonaldehyde	µg/lozenge	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL
Formaldehyde	µg/lozenge	0.409	0.04	0.446	0.083	0.372	0.035	0.338	0.008	0.299	0.025	0.317	0.026	0.408	0.038	0.437	0.008	0.327	0.019	0.364	0.027	0.502	0.021	0.613	0.013	0.325	0.02	0.504	0.014	0.286	0.031	0.401	0.026	0.36	0.024	0.397	0.019
Arsenic	ng/lozenge	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL
Cadmium	ng/lozenge	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL
B(a)P	ng/lozenge	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL
NNK	ng/lozenge	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL
NNN	ng/lozenge	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL	NT	NT	BDL	BDL
BDL, Below detection limit; NT, Not Tested																																					

BDL, Below detection limit; NT, Not Tested

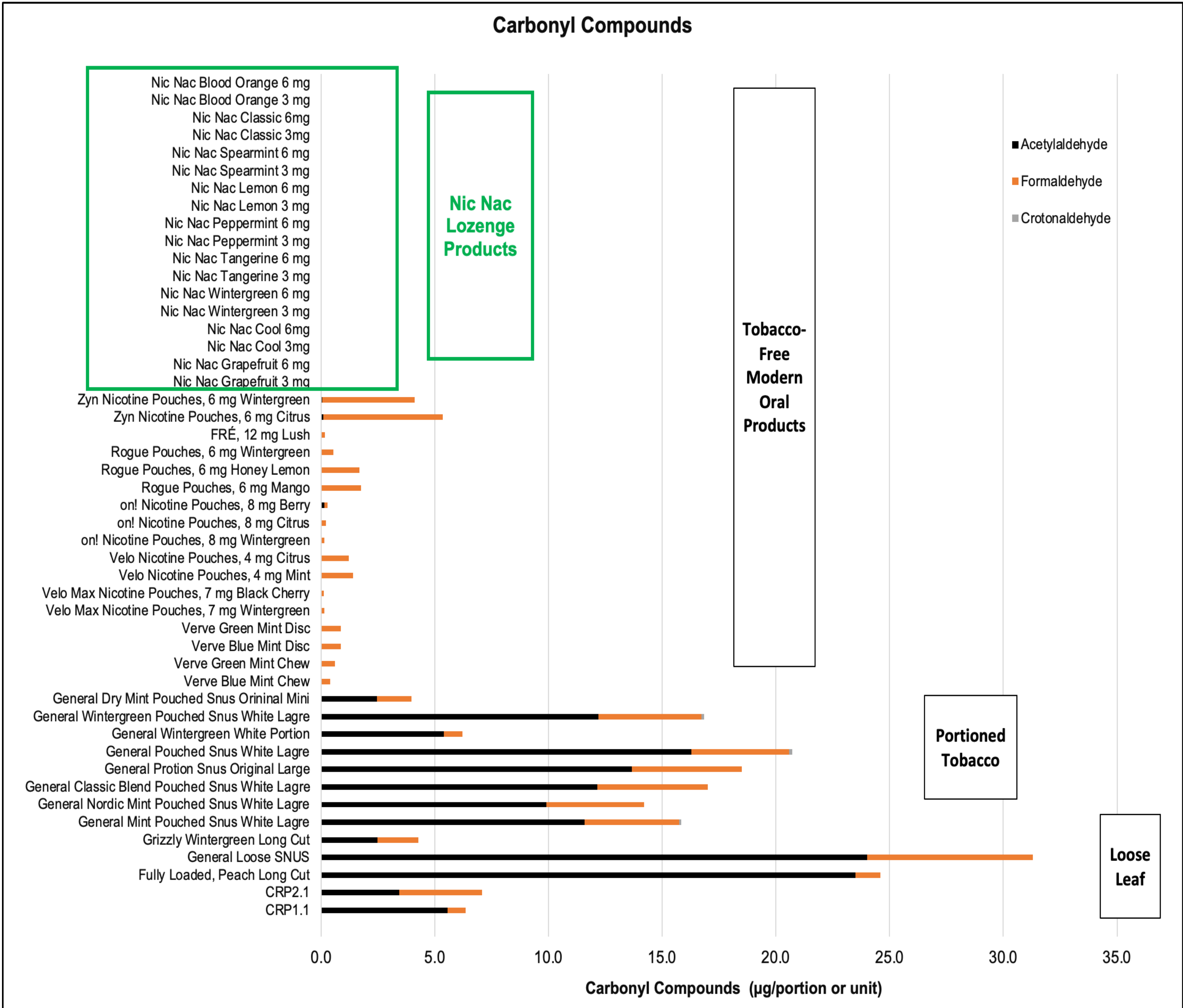
Comparative Calculated Daily Formaldehyde Exposure And Health-based Oral Exposure Benchmarks

To estimate daily formaldehyde exposure from the Nic Nac lozenges to consumers, the formaldehyde per lozenge values were normalized with the average 7 lozenge/day consumption as determined by the Nic Nac Product Use Survey study and compared with the available health-based oral exposure benchmarks for formaldehyde on per day exposure basis

Nic Nac Lozenge Products	Nicotine Strength (mg/lozenge)	Formaldehyde				
		per Lozenge	Calculated Daily Exposure*	Fold Below Health-Based Oral Exposure Benchmarks		
		µg	µg/day	ICH	ATSDR	US EPA
Nic Nac Grapefruit	3.0	0.409	2.863	3493	4890	4890
	6.0	0.446	3.122	3203	4484	4484
Nic Nac Cool	3.0	0.372	2.604	3840	5376	5376
	6.0	0.338	2.366	4227	5917	5917
Nic Nac Wintergreen	3.0	0.299	2.093	4778	6689	6689
	6.0	0.317	2.219	4507	6309	6309
Nic Nac Tangerine	3.0	0.408	2.856	3501	4902	4902
	6.0	0.437	3.059	3269	4577	4577
Nic Nac Peppermint	3.0	0.327	2.289	4369	6116	6116
	6.0	0.364	2.548	3925	5495	5495
Nic Nac Lemon	3.0	0.502	3.514	2846	3984	3984
	6.0	0.613	4.291	2330	3263	3263
Nic Nac Spearmint	3.0	0.325	2.275	4396	6154	6154
	6.0	0.504	3.528	2834	3968	3968
Nic Nac Classic	3.0	0.286	2.002	4995	6993	6993
	6.0	0.401	2.807	3563	4988	4988
Nic Nac Blood Orange	3.0	0.360	2.52	3968	5556	5556
	6.0	0.397	2.779	3598	5038	5038
ICH M7(R2)-AI or PDE (Oral)				10000 µg/day		
ATSDR - MRL (Oral)**				14000 µg/day		
US EPA (Oral)**				14000 µg/day		

*Calculated daily exposure based on 7 Nic Nac nicotine lozenge/day consumption (internal Survey study); ** Based on 70 kg. human body weight

Comparative Carbonyl Compounds In Nic Nac Lozenge Products With Market Comparators



CONCLUSIONS

The HPHC analysis of the Nic Nac oral nicotine lozenge products demonstrated the following:

- The carbonyl compounds (acetaldehyde and crotonaldehyde), metals (cadmium, arsenic), nitrosamine compounds (NNK and NNN) and B(a)P were either not detected or below limits of quantitation.
- Low levels of formaldehyde detected for the Nic Nac lozenge products were significantly below the applicable oral health-based exposure benchmarks by ICH-Acceptable Intake, ASTDR-Minimum Risk Levels (MRL) and US EPA presenting minimal risk to the consumers.
- Carbonyl levels in Nic Nac products were similar to or lower than levels reported for marketed modern oral nicotine products and conventional tobacco-based oral products, respectively.
- Overall, the HPHC profile of Nic Nac oral nicotine lozenges was characterized by non-detectable or non-quantifiable levels of the tested TSNA, selected metals, B(a)P, acetaldehyde, and crotonaldehyde, with low levels of formaldehyde detected. Estimated formaldehyde exposures were several orders of magnitude below applicable health-based oral exposure benchmarks. These results support a low HPHC-related toxicological concern for Nic Nac under the evaluated conditions of use. These findings reduce uncertainty regarding product-related chemical exposures and contribute to the individual health-risk component of the overall weight of evidence relevant to an APPH determination.

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