Published in final edited form as:
Cancer Epidemiol Biomarkers Prev. 2017 October ; 26(10): 1525–1530. doi:
10.1158/1055-9965.EPI-17-0338.

Tobacco product use patterns, nicotine and tobacco-specific nitrosamine exposure: NHANES 1999–2012

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Abstract

Background—Few studies have examined differences in product consumption patterns and nicotine and tobacco-specific nitrosamines (TSNAs) exposure between single versus dual and poly-tobacco users. We applied the Tobacco Product Use Patterns (T-PUPs) model to fill this gap in the literature.

Methods—Data from adults (aged >18 years) who used any tobacco products during the five days prior to participating in the 1999–2012 National Health and Nutrition Examination Survey (NHANES) were analyzed. Participants were classified into seven T-PUPs: (1) cigarettes only, (2) non-cigarette combustibles only, (3) non-combustibles only, (4) dual non-cigarette combustibles and non-combustibles, (5) dual cigarettes and non-combustibles, (6) dual cigarettes and non-cigarette combustibles, and (7) poly-tobacco use. Weighted regression models were used to compare product consumption, serum cotinine, and urinary total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (i.e., NNAL) levels between single, dual, and poly-tobacco T-PUPs.

Results—Dual and poly-tobacco T-PUPs were associated with lower product consumption compared to single product T-PUPs only in some cases (e.g., dual cigarette and non-combustible users smoked cigarettes on 0.6 fewer days in the past five days compared to cigarette-only users; $p<0.05$). Dual and poly-tobacco T-PUPs had either non-distinguishable or higher levels of serum cotinine and urinary total NNAL than corresponding single product T-PUPs.

Conclusion—Product consumption, and nicotine and TSNAs exposure of dual and poly-tobacco product category users somewhat differ from those of single product category users as defined by the T-TUPs model.

Impact—Higher levels of cotinine and NNAL among dual- and poly-tobacco T-TUPs users compared to the single product T-TUPs users may indicate health concerns.

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Keywords

dual use; polytobacco use; biomarkers; surveillance; adult

INTRODUCTION

The prevalence of current cigarette smoking among adults in the U.S. has declined in recent years from 23.9% in 2005 to 16.7% in 2015. (1) Meanwhile, dual- and poly-tobacco use has become a public health concern given an increasing popularity of non-cigarette tobacco products (e.g., cigars, hookah, electronic nicotine delivery systems). Multiple tobacco product use is also prevalent among adult tobacco users. For example, among U.S. adult tobacco users in 2010, 8.6% of cigarette smokers, 50.3% of cigar users, 54.8% of chewing tobacco users, and 42.5% of snuff users reported using at least one additional tobacco product every day or some days. (2)

Two limitations characterize current literature on dual- and poly-tobacco use. First, researchers have defined dual and/or poly-tobacco use as consumption of any two or more tobacco products. (2, 3) This definition neglects the relative difference in health risks associated with nicotine delivery mechanisms that fall on a risk continuum with non-combustible products being the relatively less harmful and cigarettes being the most harmful tobacco products. Non-cigarette combustible generally are also less harmful than cigarette largely due to the lower frequency of product use compared to cigarettes. (4) To overcome this limitation, we developed the Tobacco Product Use Patterns (T-PUPs) Model to classify tobacco product use, incorporating the risk continuum framework of tobacco product categories (cigarettes; non-cigarette combustibles, e.g., cigars, pipes, hookah; non-combustibles, e.g., chewing tobacco, snuff) and the number of product categories used (one, two, or three). This results in seven mutually exclusive categories: cigarettes only, non-cigarette combustibles only, non-combustibles only, dual non-cigarette combustibles and non-combustibles (i.e., using at least one non-cigarette combustible and at least one non-combustible), dual cigarettes and non-combustibles (i.e., using cigarettes and at least one non-combustible), dual cigarettes and non-cigarette combustibles (i.e., using cigarettes and at least one non-cigarette combustible), and poly-tobacco use (i.e., using cigarettes and at least one non-cigarette combustible and one non-combustible). We applied this model to youth tobacco users participated in the National Youth Tobacco Survey (5) and discerned differences between T-TUPs in demographic characteristics smoking-related beliefs, and exposure to tobacco advertising. To date, this model has not been applied to U.S. adult tobacco users.

Second, the literature is lacking documentation on intensity of product consumption among dual- and poly-tobacco users compared to single-product category users, as well as likely differences in exposure to key biomarkers of nicotine dependence and cancer risks such as cotinine and tobacco-specific nitrosamines. To overcome these limitations in the literature, we applied the T-TUPs model to a national representative sample of U.S. adult tobacco users who participated in the National Health and Nutrition Examination Survey (NHANES). We then examined how levels of exposure to nicotine and tobacco-specific nitrosamines among dual and poly-tobacco product category users differ from those of single tobacco product category users.

MATERIALS AND METHODS

Study population

NHANES is a nationally representative sample of non-institutionalized civilian U.S. population obtained through a complex multistage sampling design. The National Center for Health Statistics has conducted the study annually since 1999. Participants completed home interviews about their health. They completed an additional survey at a Mobile Examination Center (MEC) where they provided information on recent tobacco use and received a medical examination during which biospecimens (e.g., blood and urine) were collected. Additional information on NHANES is available online. (6) We pooled NHANES data collected between 1999 and 2012 to maximize the sample size for each T-PUP. The National Institutes of Health Office of Human Subjects Research Protections determined the analysis to be exempted from Institutional Review Board review. This was a secondary data analysis on de-identified data and therefore exempted from obtaining informed written consent from the participants.

Tobacco product use categorization

We classified participants into seven mutually exclusive categories based on the T-PUPs model. (5) While preserving the relative placement of tobacco products along a risk continuum, the T-PUPs model is parsimonious in classifying users of any number of tobacco products based on products nicotine delivery mechanisms. These characteristics make the T-PUPs an appropriate model for population-level surveillance. Tobacco use was determined based on number of days on which participants used cigarettes, pipes, cigars, chewing tobacco, and snuff in the past five days (i.e., “During the past five days (including today), on how many days did you [smoke cigarettes/smoke cigars/smoke pipes/use chewing tobacco/use snuff]?”). Intensity of consumption was assessed for cigarettes, cigars, and pipes using the question “During the past five days (including today), on the days you smoked [cigarettes/cigars/pipes], how many [cigarettes/cigars/pipes] did you smoke each day?” We classified participants who reported using cigarettes exclusively in the past five days as cigarette-only users. Similarly, we classified participants who reported using exclusively cigars and/or pipe as non-cigarette combustible-only users, and those who reported using exclusively chewing tobacco and/or snuff as non-combustibles-only users. Participants who reported using products from any two combinations of product categories (i.e., cigarettes, non-cigarette combustibles, non-combustibles) were classified as dual-category users: dual non-cigarette combustible and non-combustible users, dual cigarette and non-combustible users, and dual cigarette and non-cigarette combustible users. Finally, participants who reported using products from all three product categories were classified as poly-tobacco users.

Biomarkers of exposure

Data on serum cotinine were available for the 1999–2012 survey years while data on urinary total NNAL was available for 2007–2012. Cotinine is a primary metabolite of nicotine, and is highly sensitive and specific to tobacco use. (7) Serum cotinine has a relatively longer half-life than other biomarkers (e.g., carbon monoxide) of 16 hours in the general population on average, and therefore is also a recommended biomarker to assess nicotine intake over time and severity of nicotine dependence. (7) An isotope dilution-high-performance liquid chromatography/atmospheric pressure chemical ionization-tandem mass spectrometry process was used to measure serum cotinine. Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (i.e., NNAL), a tobacco-specific nitrosamine and a known lung carcinogen, has an estimated half-life between 10–18 days. (8) A liquid chromatography linked to tandem mass spectrometry approach was used to measure urinary total NNAL. Urinary total NNAL readings were divided by urinary creatinine levels and then log transformed to normalize the data. A detailed description of laboratory methods employed to ascertain levels of serum cotinine and urinary NNAL in NHANES are published. (9)

Covariates

Information on gender, age, race/ethnicity, and education attainment was collected. We categorized participants into five racial/ethnic groups: Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other race (including multi-race). We created three categories for education attainment: less than high school graduate, high school graduate or graduate education diploma, and more than high school graduate.

Statistical analysis

We limited our analyses to tobacco users aged 18 years or above since those participants have legal access to tobacco products. The total sample size for our analysis was 9158 of which 9157 participants had serum cotinine measurements and 3864 had urinary total NNAL measurements. We conducted bivariate analysis to examine correlates of T-PUPs. We used general linear models to compare consumption of single tobacco products based on number of days and quantity used on the day used across T-PUPs that include the use of such product. For example, number of days smoking cigarettes and number of cigarettes smoked on the day smoked during the past five days were assessed across cigarette-only, dual cigarette and non-cigarette combustible, dual cigarette and noncombustible, and poly-tobacco users. In these analyses, users of the single-category T-PUPs (i.e., cigarette only, non-cigarette combustible only, and non-combustible only) were set as references. Lastly, we used general linear models to compare levels of serum cotinine and urinary total NNAL between dual- and poly-tobacco T-PUPs (i.e., dual non-cigarette combustibles and non-combustibles, dual cigarettes and non-combustibles, dual cigarettes and non-cigarette combustibles, and poly-tobacco) and their respective single-category non-cigarette T-PUP (i.e., cigarettes only, non-cigarette combustibles only, and non-combustibles only). For example, we used non-cigarette combustible users as a reference category when examining cotinine and NNAL levels among dual non-cigarette combustible and noncombustible, dual cigarette and non-cigarette combustible, and poly-tobacco users. Similarly, we used non-combustible users as a reference for dual non-cigarette combustible and noncombustible, dual cigarette and non-cigarette combustible, and poly-tobacco users. General linear models were conducted using PROC SURVEYREG adjusted for age, gender, race/ethnicity, and education. While body mass index (BMI) was included as a covariate in previous reports, (9, 10) we found that adjusting for BMI did not substantially change our findings. We therefore did not control for BMI for model parsimony. Significance threshold was set to 0.05. We used SAS® version 9.4 (SAS Institute: Cary, NC) to conduct the analyses. All analyses were weighted to account for sampling design and representativeness of population using the MEC weights, masked variance pseudo-primary sampling unit (PSU), and masked variance pseudo-stratum.

RESULTS

Overall and T-PUP-specific weighted sample characteristics appear in Table 1. The most common T-PUP was cigarettes only (82.7%), followed by non-combustibles only (7.4%), non-cigarette combustibles only (6.8%), dual cigarettes and non-combustibles (1.4%), dual cigarettes and non-cigarette combustibles (1.4%), dual non-cigarette combustibles and non-combustibles (0.2%), and poly-tobacco (0.1%). Demographic characteristics differed by T-PUPs. For example, men comprised 53.9% of cigarette-only users and >86% of all remaining T-PUPs ($p < 0.0001$). Tobacco users aged 18–25 years comprised >32% of all dual- and poly-tobacco T-PUPs, and <19% of cigarette only, non-cigarette combustible only, and non-combustible only users ($p < 0.0001$). Non-cigarette combustible and dual cigarette and non-cigarette combustible users had the highest proportion of non-Hispanic Black (>20%) whereas dual cigarette and non-combustible users had the highest proportion of non-Hispanic White (91.7%). Finally, non-cigarette combustible users had the highest proportion of attaining high school education or above (57.7%) than users of other T-PUPs ($p < 0.0001$).

Data on tobacco product consumption by T-PUPs appear in Table 2. Compared to cigarette-only users, dual cigarette and non-combustible users smoked cigarettes on 0.6 fewer days and 3.3 fewer cigarettes on the day smoked in the past five days ($p < 0.05$). However, days smoked in the past five days and cigarettes smoked on the day smoked did not differ between cigarette-only, dual cigarette and non-cigarette combustible, and poly-tobacco users. Compared to non-cigarette combustible only users, dual non-cigarette combustible and non-combustible users smoked 3.6 more cigars on the day they smoked cigars whereas poly-tobacco users smoked 0.7 fewer cigars on the day they smoked cigars ($p < 0.01$). Finally, compared to noncombustible-only users, dual non-cigarette combustible and noncombustible, dual cigarettes and noncombustible, and poly-tobacco users consumed chewing tobacco and snuff on fewer days during the past five days ($p < 0.01$).

Mean serum cotinine and urinary total NNAL levels by T-PUPs appear in Table 3. Compared to cigarette-only users, adjusted mean serum cotinine level among dual cigarette and noncombustible users was 62.2 ng/mL higher ($p < 0.05$). Compared to non-cigarette combustible only users, dual cigarette and non-cigarette combustible users, and dual non-cigarette combustible and non-combustible users had higher adjusted mean levels of serum cotinine (93.1 ng/mL and 60.3 ng/mL higher, respectively; $p < 0.05$). Compared to non-combustible only users, adjusted mean serum cotinine level among dual cigarette and non-combustible users was 45.2 ng/mL higher ($p < 0.05$). Regarding urinary total NNAL, data from dual non-cigarette combustible and non-combustible users (n=8) and poly-tobacco users (n=7) were not presented due to small number of participants in these T-PUPs. Compared to cigarette-only users, dual cigarette and non-cigarette combustible users, and dual cigarette and noncombustible users had higher adjusted mean levels of urinary total NNAL (54.4 ng/mL and 259.6 ng/mL higher, respectively). Compared to non-cigarette combustible only users, dual cigarette and non-cigarette combustible users, and dual non-cigarette combustible and noncombustible users had higher adjusted mean levels of urinary total NNAL (161.1 ng/mL and 199.5 ng/mL higher, respectively).

DISCUSSION

This study is one of the first to compare tobacco product consumption and exposure to nicotine and tobacco-specific nitrosamines of dual product category users and poly-tobacco product category users against single product category users, while including different types of tobacco products, including pipe, cigars, and smokeless tobacco that have not been simultaneously studied previously. We found that dual- and poly-tobacco product category use does not necessarily translate to lower consumption of individual products. On one hand, for example, compared to cigarette-only users, dual cigarette and non-combustible users reported smoking fewer days and fewer cigarettes; similarly, compared to non-combustible only users, dual non-cigarette combustible and non-combustible users, dual cigarette and non-combustible users, and poly-tobacco users reported using non-combustibles on fewer days. On the other hand, for example, compared to cigarette-only users, dual cigarette and non-cigarette combustible users and poly-tobacco users showed no difference in cigarette consumption, in agreement with a previous study showing that cigarette consumption did not differ by smokeless tobacco use consumption among men. (11) These findings suggest that some dual- and poly-tobacco product category users may have higher exposure to harmful and potentially harmful constituents of tobacco products, e.g., acetaldehyde, arsenic, and cadmium. Additionally, the lower consumption of non-combustible tobacco products associated with dual and poly-tobacco users than non-combustible only users may not yield net health benefits, since this could be offset by addition of cigarettes and non-cigarette combustible products that are probably more detrimental to health.

We found that dual- and poly-tobacco T-TUPs users had either equal or higher levels of serum cotinine and urinary total NNAL than single-product category T-PUPs users. These findings are supported by previous studies that reported higher levels of serum cotinine and urinary NNAL among dual cigarette and smokeless tobacco users compared to exclusive cigarette users. (10–12) This could be due to the route of administration for non-combustible products that provides longer absorption time, or due to higher levels of nicotine and tobacco-specific nitrosamines in non-combustible products included in the analysis. (13, 14) Our findings provide partial support to the argument that individuals with higher nicotine dependency may use tobacco products from multiple product categories to obtain nicotine from additional sources, perhaps especially when the environment does not allow the use of a specific product category (e.g., combustible users adding non-combustibles to circumvent smoke-free policies). However, finding on poly-tobacco T-PUP users showing statistically non-distinguishable level of serum cotinine from those of single-category T-PUPs users may suggest that tobacco dependence is not the only explanation for dual- and poly-tobacco product category use. Future studies need to further examine the role of nicotine dependency in dual- and poly-tobacco use patterns.

Our analyses have several limitations. First, NHANES did not have data on all tobacco products. While electronic cigarettes, hookah, and snus became increasingly popular after 2010, (15, 16), we were unable to include these products in our analysis. Future studies need to include these tobacco products to confirm our findings. Second, individuals who did not use any tobacco products in the past five days were excluded from the analysis, and therefore our findings may not be generalizable to intermittent tobacco users. Third, we did not analyze exposure to all known harmful and potentially harmful constituents of tobacco products. While our analysis on serum cotinine and urinary total NNAL may provide some indications on potential health risks associated with each T-PUP, to fully examine health risks associated with each T-PUP, we need to assess exposure to other tobacco product constituents that have known health risks and to directly examine disease risks using carefully conducted epidemiologic studies. The Population Assessment on Tobacco and Health (PATH) Study includes a comprehensive list of biomarkers for tobacco product constituents, which can be used to validate our findings, and to perform a holistic comparison of health risks across T-PUPs. Fourth, prevalence of dual- and poly-tobacco T-PUPs was quite low in our current sample, which limited the statistical power to detect differences between T-PUPs and our ability to rank order all seven T-PUPs based on cotinine and NNAL levels. Studies with larger samples, especially those that purposefully sample dual- and poly-tobacco users and collect a broad range of biomarker data, are essential to understand tobacco consumption and health risks associated with all T-PUPs categories. Fifth, the cross-sectional nature of NHANES limited our ability to examine how changes from one T-PUP to another influence tobacco consumption, serum cotinine levels, and urinary NNAL levels. Finally, measures on smokeless tobacco consumption beyond the number of days used, as well as specific smokeless tobacco product use given the variability in constituent yields across these products, (13) are needed to better quantify the intensity of smokeless tobacco use to enable more detail comparisons on non-combustible products consumption across T-PUPs.

In conclusion, tobacco product consumption, and nicotine and tobacco-specific nitrosamine exposure of dual and poly-tobacco product category users somewhat differ from those of single product category users as defined by the T-TUPs model. With an increasing availability of various tobacco products and prevalence of dual- and poly-tobacco use, research is needed to examine variations in tobacco product consumption and associated health risks with a comprehensive set of biomarkers that capture the physiological underpinnings of tobacco product use patterns.

Acknowledgments

Financial Support: Drs. Choi, Sabado, and El-Toukhy's effort was supported by the Division of Intramural Research, National Institute on Minority Health and Health Disparities. Drs. Vogtmann and Freedman's effort was supported by the Intramural Research Program of the National Cancer Institute. Dr. Hatsukami's effort was supported by a research grant funded by the National Cancer Institute (Grant #: U19CA157345; PI: Hatsukami).

Abbreviations list

BMI	Body Mass Index
CIG	Cigarettes

HPHCs	Harmful and potentially harmful constituents
MEC	Mobile Examination Center
NCC	Non-cigarette combustibles
NC	Non-combustibles
NHANES	National Health and Nutrition Examination Survey
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
PATH	Population Assessment on Tobacco and Health
POLY	Poly-tobacco
PSU	Pseudo-primary sampling unit
TSNA	Tobacco-specific nitrosamines
T-PUP	Tobacco product use patterns

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Table 1

Weighted overall demographic characteristics and by tobacco product use pattern category among adult tobacco users, NHANES 1999–2012.

	Overall		CIG		NCC		NC		NCC&NC		CIG&NC		CIG&NCC		POLY		P value
	n	Wt %	n	Wt %	n	Wt %	n	Wt %	n	Wt %	n	Wt %	n	W%	n	W%	
Overall	9158	100	7677	82.7	635	6.8	536	7.4	20	0.2	100	1.4	174	1.4	15	0.1	
Gender																	
Male	5652	60.4	4345	53.9	542	86.6	481	94.9	20	100.0	100	100.0	149	88.2	15	100.0	< 0.0001
Female	3506	39.6	3332	46.1	93	13.4	55	5.1	0	0	0	0	25	11.8	0	0	
Age																	
18–25	2016	19.0	1586	18.4	181	18.9	67	13.5	7	32.4	51	49.0	110	48.7	13	90.9	< 0.0001
26–35	1680	21.0	1441	21.4	100	15.9	95	22.1	1	11.1	22	25.8	19	12.7	2	0.9	
36–50	2620	33.6	2284	34.1	139	29.4	155	37.2	4	30.7	15	17.8	23	24.6	0	0	
51–64	1808	19.4	1569	19.6	116	24.6	95	16.7	4	15.0	9	6.7	15	11.2	0	0	
65+	1034	7.0	797	6.4	99	11.2	124	10.4	4	10.7	3	0.6	7	2.8	0	0	
Race/ethnicity																	
Mex-Am	1372	6.2	1279	7.0	40	2.6	31	2.4	2	2.2	6	2.3	13	2.0	1	1.2	< 0.0001
Hispanic	515	4.5	468	5.0	29	4.2	6	0.7	0	0	2	2.0	10	5.1	0	0	
NH White	4587	71.7	3710	70.1	298	69.8	404	88.8	13	90.9	84	91.7	65	63.1	13	95.7	
NH Black	2253	12.4	1839	12.4	250	20.2	79	5.3	4	5.2	4	1.0	76	23.8	0	0	
Other/Mix	431	5.0	381	5.4	18	3.2	16	2.8	1	1.6	4	3.0	10	5.9	1	3.1	
Education																	
<HS	3180	26.0	2774	27.6	129	13.6	170	20.6	8	23.8	25	16.9	69	32.2	5	24.1	< 0.0001
HS/GED	2642	31.3	2196	31.1	187	28.8	165	34.9	6	46.3	38	38.6	41	26.4	9	68.9	
>HS	3262	42.7	2661	41.4	310	57.7	197	44.5	6	29.8	33	44.5	54	41.4	1	7.0	

Note: CIG=cigarettes only; NCC=non-cigarette combustibles only; NC=non-combustibles only; NCC&NC=dual non-cigarette combustibles and non-combustible; CIG&NC=dual cigarettes and non-combustibles; CIG&NCC=dual cigarettes and non-cigarette combustibles; POLY=poly-tobacco. Mex-Am=Mexican American; NH=non-Hispanic. HS=high school. Unweighted n and weight percentages are presented. P values are from chi-square tests.

Table 2

Tobacco product use behaviors by tobacco product use pattern category among tobacco users, NHANES 1999–2012.

	CIG		NCC		NC		NCC&NC		CIG&NC		CIG&NCC		POLY	
	mean	95% CI	mean	95% CI	mean	95% CI	mean	95% CI	mean	95% CI	mean	95% CI	mean	95% CI
# of days a product used in past 5 days														
Cigarette	4.4	4.4–4.4							3.9*	3.6–4.3	4.3	4.0–5.6	3.7	2.7–4.6
Pipe			3.5	3.0–3.9			3.1	1.4–4.8			2.0	1.6–2.4	2.3	1.5–3.0
Cigar			2.7	2.5–2.8			3.0	2.6–3.4			2.5	2.2–2.7	2.2	1.6–2.8
Chew					4.2	4.0–4.4	3.0**	2.1–3.8	3.3**	2.8–3.8			2.3**	1.0–3.6
Snuff					4.3	4.0–4.5	2.5**	0 5.2	3.2**	2.3–4.1			2.1**	0.2–3.9
# of times product used on the day a product was use in past 5 days														
Cigarette	13.9	13.5–14.5							10.6*	7.9–13.0	15.5	9.8–21.3	11.2	5.3–17.0
Pipe			5.2	2.6–7.8			4.4	1.6–7.3			1.6	1.1–2.1	1.8	1.5–2.2
Cigar			2.6	2.3–2.8			6.2*	3.3–9.1			2.3	2.1–2.5	1.9**	1.6–2.2

Note: CIG=cigarettes only; NCC=non-cigarette combustibles only; NC=non-combustibles only; NCC&NC=dual non-cigarette combustibles and non-combustible; CIG&NC=dual cigarettes and non-combustibles; CIG&NCC=dual cigarettes and non-cigarette combustibles; POLY=poly-tobacco. Unadjusted means and confidence intervals (CI) are presented. Estimates are adjusted for age, gender, race/ethnicity, and education. Tobacco product use in dual and poly-tobacco use T-PUPs were compared to corresponding single product category T-PUPs (e.g., CIG&NC, CIG&NCC, and POLY were compared to CIG).

* $p < 0.05$.

** $p < 0.01$.

Table 3

Serum cotinine and urinary total NNAL by tobacco product use pattern categories among tobacco users, NHANES 1999–2012

	CIG	NCC	NC	NCC&NC	CIG&NC	CIG&NCC	POLY
Cotinine (ng/mL)							
N	7277	602	521	18	98	169	13
Means							
Arithmetic (95% CI)	204.8 (199.2–210.1)	86.1 (99.3–99.3)	322.0 (289.3–354.6)	266.1 (120.4–411.8)	229.8 (199.3–260.3)	192.3 (169.0–215.6)	136.5 (50.0–222.9)
Geometric							
Unadjusted (95% CI)	125.5 (118.6–132.8)	14.5 (10.9–19.3)	174.6 (141.7–215.1)	110.1 (39.9–303.9)	182.2 (146.8–226.1)	129.0 (105.1–158.5)	44.0 (10.01–193.0)
Adjusted (95% CI)	94.0 (87.6–100.7)	9.7 (7.4–12.7)	111.0 (89.2–138.2)	70.0 (31.1–157.7)[b]	156.2 (125.2–194.8)[ac]	102.8 (83.4–126.6)[b]	38.6 (8.9–167.4)
NNAL							
N	3238	270	228	8	46	67	7
Arithmetic (ng/mL) (95% CI)	0.37 (0.3–0.4)	0.2 (0.2–0.3)	1.7 (1.3–2.2)	--	0.87 (0.6–1.1)	0.52 (0.4–0.7)	--
Arithmetic (pg/mL) (95% CI)	368.8 (332-7–405.1)	204.4 (131.6–277.1)	1321.8 (1029.7–1613.9)	--	575.2 (370.3–780.0)	304.5 (222.4–386.5)	--
Geometric (pg/mL)							
Unadjusted (95% CI)	195.7 (173.9–220.2)	43.9 (29.6–60.1)	538.2 (417.1–694.4)	--	348.5 (204.1–595.0)	196.1 (138.9–277.0)	--
Adjusted (95% CI)	143.3 (132.0–155.6)	36.6 (25.5–52.7)	397.6 (302.8–522.3)	--	402.3 (260.2–621.9)[a]	197.7 (155.5–251.4)[ab]	--

Note: CIG=cigarettes only; NCC=non-cigarette combustibles only; NC=non-combustibles only; NCC&NC=dual non-cigarette combustibles and non-combustible; CIG&NC=dual cigarettes and non-combustibles; CIG&NCC=dual cigarettes and non-cigarette combustibles; POLY=poly-tobacco. NNAL= total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol. Adjusted estimates are adjusted for age, gender, race/ethnicity, and education. Tobacco product use in dual and poly-tobacco use T-PUPs were compared to corresponding single product category T-PUPs (e.g., CIG&NC, CIG&NCC, and POLY were compared to CIG). Urinary total NNAL estimates were adjusted for urinary creatinine.

[a], $p < 0.05$, reference=CIG;

[b] $p < 0.05$, reference=NCC;

[c] $p < 0.05$, reference=NC.