



Published in final edited form as:

*Chem Res Toxicol.* 2021 March 15; 34(3): 704–712. doi:10.1021/acs.chemrestox.0c00215.

## Volatile Organic Compounds in Mainstream Smoke of Sixty Domestic Little Cigar Products

**An T. Vu,**

Office of Science, Center for Tobacco Products, U.S. Food and Drug Administration, Calverton, Maryland 20705, United States

**Matthew D. Hassink,**

Office of Science, Center for Tobacco Products, U.S. Food and Drug Administration, Calverton, Maryland 20705, United States

**Kenneth M. Taylor,**

Office of Science, Center for Tobacco Products, U.S. Food and Drug Administration, Calverton, Maryland 20705, United States

**Megan McGuigan,**

Tobacco and Volatiles Branch, Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia 30341, United States

**Ashley Blasiole,**

Tobacco and Volatiles Branch, Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia 30341, United States

**Liza Valentin-Blasini,**

Tobacco and Volatiles Branch, Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia 30341, United States

**Katrice Williams,**

Battelle Memorial Institute, Atlanta, Georgia 30329, United States

**Clifford H. Watson**

Tobacco and Volatiles Branch, Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia 30341, United States

### Abstract

The mainstream smoke yields of five volatile organic compounds (VOCs) were determined from 60 commercial U.S. little cigar products under ISO 3308 and Canadian Intense (CI) smoking regimens on linear smoking machines using a gas sampling bag collection. The five VOCs,

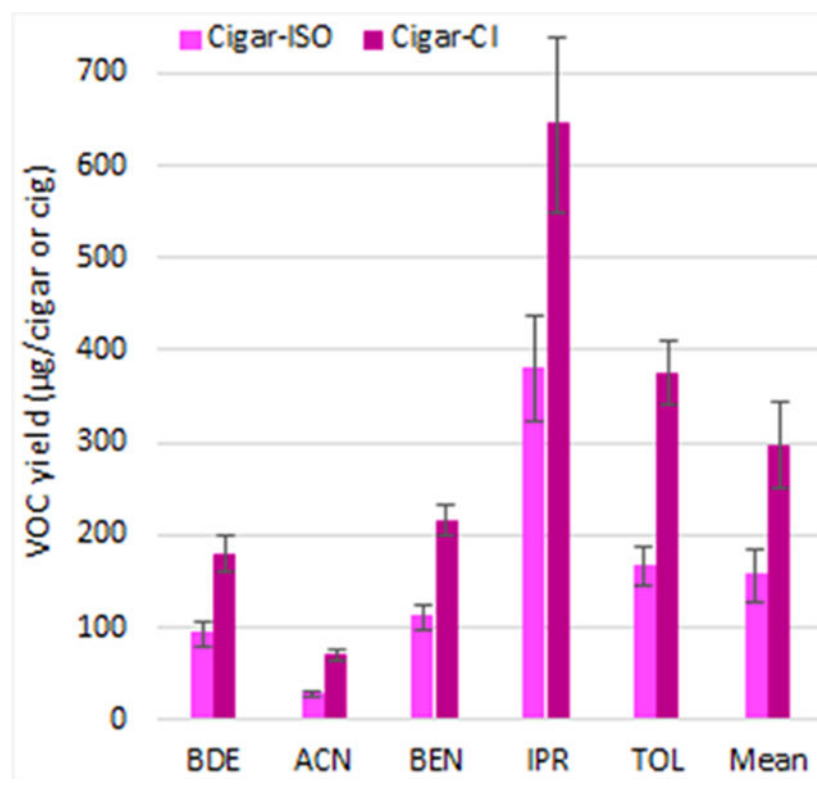
---

**Corresponding Author Kenneth M. Taylor** – Phone: 240-402-4192; Kenneth.Taylor@fda.hhs.gov; Fax: 301-890-5772.

The authors declare no competing financial interest.

1,3-butadiene, acrylonitrile, benzene, isoprene, and toluene were analyzed using an automated GC/MS analytical method validated for measuring various VOCs in mainstream smoke. The VOCs range in amounts from micrograms to milligrams per little cigar. VOC deliveries vary considerably among the little cigar products under the ISO smoking regimen primarily due to varying filter ventilation. Under the CI smoking regimen where filter ventilation is blocked, the delivery range narrows, although individual and total VOC yields are approximately 2 fold higher than those under the ISO smoking regimen. Correlation analysis reveals strong associations between acrylonitrile and 1,3-butadiene or toluene under the ISO smoking regimen. Compared to cigarettes, little cigars delivered substantially higher VOC mainstream smoke yields under both ISO and CI smoking regimens. Moreover, little cigar smoke also contains higher VOCs than cigarette smoke when adjusted for mass of tobacco.

## Graphical Abstract



## INTRODUCTION

While cigarette consumption has been on a steady decline in recent decades, cigar consumption has increased dramatically since the 1990s.<sup>1</sup> This is due largely to the less stringent regulations particularly on cigar advertising and promotional activities, and the relatively lower cost of cigars as a result of tax rate disparities between cigars and cigarettes.<sup>2</sup> Additionally, some smokers misperceive cigar smoking as being less harmful than cigarette smoking.<sup>3,4</sup> Moreover, unlike cigarettes, cigars are often marketed in a wide variety of flavors making them more appealing, particularly to adolescents and young adults.<sup>5</sup> Because tobacco smoke from both cigarettes and cigars is formed from incomplete

combustion of tobacco, cigar smoke has been shown to contain the same or higher concentration of toxic and carcinogenic chemicals than cigarette smoke.<sup>6</sup> Cigar smoking is known to cause adverse health effects such as cancers of the lung, larynx, oral cavity, and esophagus.<sup>6,7</sup> Regular cigar smokers who consume several cigars per day have an increased risk of coronary heart disease (CHD) and chronic obstructive pulmonary disease (COPD).<sup>6,7</sup>

The U.S. Department of the Treasury defines a cigar as a roll of tobacco wrapped in leaf tobacco or in a substance that contains tobacco.<sup>8</sup> Cigars are typically divided into four main categories according to their dimensions and manufacturing processes: little cigars, small cigars (or cigarillos), regular cigars, and premium cigars.<sup>5</sup> Little cigars have many product dimensions similar to cigarettes such as shape, size (70–100 mm in length), filters (cellulose acetate), and packaging (20/package).<sup>9</sup> However, their tobacco can differ from that used in cigarette tobacco filler. Little cigars contain air-cured and fermented tobaccos, and are wrapped either in reconstituted tobacco or in cigarette paper that contains tobacco and/or tobacco extract.<sup>6</sup> In contrast, American blended cigarettes typically contain a blend of mainly flue-cured tobacco together with burley, oriental, and reconstituted tobaccos, and are wrapped in cigarette paper.<sup>10</sup> Little cigars are often longer and can contain more tobacco mass than cigarettes on a per stick basis.<sup>11</sup> Cigarette smoke is fairly well-characterized, but limited information exists on mainstream and sidestream smoke constituents of little cigars. Previous studies indicated that mainstream smoke yields of little cigars differ from those of cigarettes.<sup>9,11,12</sup> In particular, little cigar smoke tends to contain higher level of free-base nicotine than cigarettes.<sup>13</sup> Additionally, certain little cigar products delivered higher yields of carbon monoxide<sup>14</sup> and carcinogens such as tobacco-specific nitrosamines (TSNAs) and benzo(a)pyrene than cigarettes.<sup>11</sup> Moreover, some smokers inhale little cigar smoke similar to inhaling cigarette smoke.<sup>7</sup> In May 2016, the Federal Food and Drug Administration issued a rule extending its authority to regulate all tobacco products including cigars.<sup>15</sup> Given the public health and regulatory importance of cigars, our current research effort focuses on increasing the available data on cigar products and their toxicant delivery. Toward this end, we investigated the mainstream smoke yields of five volatile organic compounds (VOCs) from 60 commercial U.S. little cigar products under both nonintense and intense machine smoking regimens. These five VOCs include 1,3-butadiene, acrylonitrile, benzene, isoprene, and toluene. Based on findings of the International Agency for Research on Cancer, the U.S. Environmental Protection Agency, the National Toxicology Program, the National Institute for Occupational Safety and Health, or the Agency for Toxic Substances and Disease Registry, the FDA identified 1,3-butadiene, acrylonitrile, benzene, and isoprene as carcinogens, and 1,3-butadiene, acrylonitrile, benzene, and toluene as respiratory or cardiovascular toxicants and/or developmental toxicants in its published list of 93 harmful and potentially harmful constituents (HPHCs) in tobacco products and tobacco smoke in the *Federal Register*.<sup>16</sup> The FDA also recommends cigarette manufacturers to test and report the quantities of these five HPHCs (and others) in cigarette smoke.<sup>17</sup> Additionally, to gain qualitative insight into their relative toxicities, we also compared the measured mainstream smoke VOC levels of the 60 little cigar products to those of the 50 popular commercial U.S. cigarette products studied previously.<sup>18,19</sup>

## MATERIALS AND METHODS

### Little Cigar Samples.

The little cigar products selected for this study consist of 60 U.S. little cigar products chosen to represent the majority of the U.S. little cigar market share based on Neilson's 2012 and 2013 sales data which includes many high market share products as well as some select low market share products. The 60 little cigar products consist of 40 brands with various sub-brands, lengths (70–100 mm), tobacco weight (0.7–1.3 g) and package types (hard pack or soft pack). They contain various flavor descriptors including light, mild, classic, natural, regular, menthol, and full flavor, as well as characterizing flavors that were banned in U.S. cigarettes such as caramel, cherry, coffee, grape, and peach. Most (57) little cigar products contain a cellulose acetate filter. The three shortest little cigar products that are 70 mm in length do not contain a filter. All little cigar products were purchased between July 2016 and May 2017 from retail outlets in the greater metropolitan Atlanta area in Georgia, U.S. The little cigar packs were assigned unique identification numbers, and logged into a database. Samples were stored at  $-80\text{ }^{\circ}\text{C}$  in their original packaging until needed. A 3R4F reference cigarette (University of Kentucky, Lexington, KY) was included with each smoking machine run for quality control (QC). Seven little cigars of each brand variety were smoked and individual VOC analyte levels were measured simultaneously for each cigar.

### Reagents and Materials.

Mainstream smoke VOC levels analyzed in this study included 1,3-butadiene, acrylonitrile, benzene, isoprene, and toluene. Custom VOC calibration and deuterated internal standard mixtures were purchased from O2Si Smart Solutions (Charleston, SC). The formulation of the VOC calibration mixture is 500 mg/L 1,3-butadiene, 100 mg/L acrylonitrile, 500 mg/L benzene, 5000 mg/L isoprene, and 500 mg/L toluene. The formulation of the deuterated VOC internal standard mixture is 500 mg/L 1,3-butadiene-d6, 200 mg/L acrylonitrile-d3, 500 mg/L benzene-d6, 500 mg/L furan-d4, and 500 mg/L toluene-d8. All dilutions were prepared in methanol. Methanol (P&T grade) was purchased from Fisher Scientific (Suwanee, GA). Tedlar sampling bags (1 L) were purchased from NewStar Environmental (Roswell, GA) and were fitted with butyl rubber O-rings.

### Sample Preparation and Analysis Procedure.

Little cigars were conditioned at  $22\text{ }^{\circ}\text{C}$  and 60% relative humidity for at least 48 h prior to smoking according to ISO 3402:1999. Prior to use, each port of the smoking machine was flushed with 85 blank puffs to remove any remaining VOCs in the lines from previous smoke runs. Background levels were assessed from a blank port of the smoking machine with each sample run and were below VOC limits of detection (LOD). LODs were as follows: 1,3-butadiene ( $0.732\text{ }\mu\text{g/cig}$ ), acrylonitrile ( $0.152\text{ }\mu\text{g/cig}$ ), benzene ( $0.431\text{ }\mu\text{g/cig}$ ), isoprene ( $5.43\text{ }\mu\text{g/cig}$ ), and toluene ( $0.478\text{ }\mu\text{g/cig}$ ). Internal standard ( $20\text{ }\mu\text{L}$ ) was added to each Tedlar bag via gastight syringe, and the Tedlar bags were connected and opened. Little cigars were then smoked according to ISO 3308 and CI protocols using equipment and procedures reported previously.<sup>20</sup> After smoking, methanol (5 mL) was injected into the Tedlar bags through the syringe port. The bags were then placed onto an orbital shaker for 15 min at 130 rpm. After shaking, an aliquot of the methanol extract was removed and

placed into an autosampler vial for GC/MS analysis. VOCs were quantitatively analyzed using a 7890A/5975C GC/MS (Agilent Technologies, Palo Alto, CA) with a Dual Rail Autosampler (Leap, Carrboro, NC). Chromatographic separation was achieved with an Agilent DB-VRX capillary column (40 m × 0.18 mm × 1 μm). The GC inlet temperature was maintained at 220 °C with a 50:1 split ratio. A 1 μL liquid sample injection was made into a constant flow of helium carrier gas at 1 mL/min. The GC oven was initially held at 35 °C for 5 min, then ramped to 215 °C at 10 °C/min. Mass spectrometry was performed using electron ionization in selective ion monitoring (SIM) mode with the source heated to 230 °C. Ions monitored were as follows (quantitation, confirmation, internal standard): 1,3-butadiene (*m/z* 54, 53, 60); acrylonitrile (52, 53, 56); benzene (78, 77, 84); Isoprene (67, 68, 72); toluene (91, 92, 100). The data was processed using the instruments quantitation software (MassHunter). Calibration curves were constructed as the response ratio vs the calibration standard amount using a linear regression with 1/x weighting. Calibration curve R<sup>2</sup> was 0.990. Method accuracy was assessed by evaluating the accuracies of spikes at the low, middle, and high range of the calibration curve for each analyte. Accuracies ranged from 91.2 to 108%. Unknown samples were quantitated against the calibration curve with final results reported as μg/cigar.

### Statistical Analysis.

Pearson product-moment correlation coefficients (*r*) were calculated using Microsoft Excel 2013 software with the correlation data analysis function. *P*-values, which measure statistical significance of correlation, were calculated using Microsoft Excel 2013 software with the regression data analysis function. Correlations are considered statistically significant when *p*-values are less than 0.05.

## RESULTS AND DISCUSSION

### VOC Yields in 3R4F Reference Cigarette.

At the time this study was conducted, there were no cigar reference products that were widely accepted by the scientific community. However, since little cigars have similar product dimensions to cigarettes, and some smokers inhale little cigar smoke similar to inhaling cigarette smoke, machine cigarettes smoking parameters have been employed for smoke analyses of little cigars.<sup>4</sup> Thus, for data quality control, we measured the levels of the five VOCs in mainstream smoke of 3R4F reference cigarette using both ISO (nonintense) and CI smoking regimens. Results are provided in Table 1 and depicted in Figure 1. 3R4F VOC values are an average of 73 experiments with the ISO smoking regimen and 67 experiments under the CI smoking regimen. As shown in Figure 1, compared to the 3R4F mainstream smoke VOC data reported in 2014<sup>20</sup> the levels of 1,3-butadiene, acrylonitrile, benzene, and toluene are comparable for both smoking regimens.

Figure 2 shows the relative standard deviation (RSD) of 3R4F VOC yields which range from 12.6% to 21.1% using the ISO smoking regimen and from 6.7% to 20.5% using the CI smoking regimen. As shown, other than 1,3-butadiene yield, the ISO smoking regimen has substantial higher VOC yield variability than the CI smoking regimen as indicated by their

RSD values. Similar higher VOC yield variability associated with ISO smoking compared to CI smoking was also observed in 3R4F mainstream smoke VOC data reported in 2014.<sup>20</sup>

### VOC Yields in U.S. Little Cigars.

The mainstream smoke yields for the five VOCs, 1,3-butadiene, acrylonitrile, benzene, isoprene, and toluene, in 60 commercial U.S. little cigar products measured using both ISO and CI smoking regimens are provided in Table 1. Little cigar brands are sorted by total ISO VOC smoke yield. As shown, the five VOCs were detected in all 60 little cigar products at levels ranging from 12  $\mu\text{g}$  to 1.4 mg. As expected, all individual CI VOC yields are higher than individual ISO VOC yields, with an average increase of approximately 2.2 fold.

Total VOC yield of the little cigar products were calculated by summation of individual amounts of the five VOC yields. Figure 3 depicts total mainstream smoke VOC yields of the 60 little cigar products measured with both ISO and CI smoking regimens. As shown, total VOC yields with the ISO smoking regimen vary considerably among the commercial little cigar products ranging from 0.39 mg to 1.25 mg per cigar. Thus, the ISO VOC yield difference between the highest and lowest VOC delivery little cigars is 3.2 fold. For the CI smoking regimen, total VOC yields, which range from 1.0 to 2.8 mg per cigar, are greater than total ISO VOC yields with an average increase of approximately 2 fold over ISO smoking. However, CI VOC relative yield difference between the highest and lowest VOC delivery little cigars is smaller at 2.2 fold. The wide filter ventilation range among the little cigar products (0.13–54%) contributes to the wide range of VOC deliveries for the ISO smoking regimen. Indeed, Santa Fe SP Menthol and Santa Fe SP Mild with high filter ventilation (42.1% and 53.9%, respectively) generated the lowest total ISO VOC yields (Table 1). In contrast, VOC delivery range narrows for the CI smoking regimen where filter ventilation is blocked. Notably, Panter Desert Tin Coffee and Cafe Creme Original Tin, both of which contain a substantial tobacco mass (1.03–1.04 g/cigar) and lack a filter, generated the highest total VOC yields for both ISO and CI smoking regimens. However, product flavor profile based on package labeling and/or package type do not appear to affect VOC yields (Table 1).

We also examined correlations among the little cigar VOC yields. Pearson correlation coefficients ( $r$ ) and  $p$ -values were calculated using Microsoft Excel 2013 software and are provided in Table 2. For the ISO smoking regimen, all correlations among the five VOCs and total VOC show high statistical significance with  $p$ -values below 0.01. Most correlations between the five VOCs and total VOC range from moderate ( $r > 0.46$ ) to strong linear relationships ( $r > 0.94$ ). Strong associations exist between acrylonitrile and 1,3-butadiene or toluene, and between total VOC and 1,3-butadiene or isoprene ( $r = 0.9$ ). Correlation between benzene and isoprene is weak with an  $r$  value of 0.36. For the CI smoking regimen, correlations among all VOC yields are considerably weaker than under the ISO regimen with several  $r$  values below 0.5 (Table 2). Some associations are statistically insignificant with  $p$ -values higher than 0.05. Notably, no correlation exists between isoprene and benzene or toluene under the CI smoking regimen.

Figure 4 depicts the average individual VOC yields of the 60 little cigar products measured using both ISO and CI smoking regimens. As shown, similar to total VOC yields, yields of



all individual VOCs are higher with CI smoking than ISO smoking. The order of decreasing VOC smoke yield is isoprene > toluene > benzene > 1,3-butadiene > acrylonitrile under both smoking regimens. Compared to the average individual VOC yields of 50 popular commercial U.S. cigarette products reported in 2014,<sup>20</sup> VOC yields of little cigars are substantially higher (80–300%) than those of cigarettes measured under both ISO and CI smoking regimens (Figure 4). The higher VOC yields of little cigars are in part attributable to their substantially higher average tobacco filler mass of 1085 mg/cigar, which is 416 mg more than the average cigarette tobacco filler mass of 669 mg/cigarette. Little cigars are also longer which allows them to hold more tobacco filler mass than cigarettes.<sup>11</sup> The average length of the 60 little cigars is 97 mm, whereas the average length of the 50 cigarettes is 90.2 mm. Similar to little cigars, yields of cigarette individual VOCs are also higher with CI smoking than ISO smoking (Figure 4). Since little cigars contain higher tobacco filler mass than cigarettes, VOC yields are normalized per gram of filler tobacco (Table 1). As shown in Figure 5, little cigar smoke also contains considerably more 1,3-butadiene, acrylonitrile, benzene, and toluene per gram of tobacco burned than cigarette smoke<sup>20</sup> under both ISO and CI smoking regimens. However, the adjusted VOC yield increase for little cigar smoke narrows (12–150%) compared to the unadjusted VOC yield increase (80–300%).

We also compared VOC yield variability between little cigar and cigarette products. As shown in Figure 6, under the ISO smoking regimen, little cigars exhibit lower VOC yield variability than cigarettes.<sup>20</sup> This is in part attributable to the wider filter ventilation range of cigarettes (range: 0.1–67%, average: 30.3%)<sup>21</sup> compared to that of little cigars (range: 0.13–54%, average: 11.0%). Conversely, little cigars exhibit comparable VOC yield variability to that of cigarettes when filter ventilation is blocked under the CI smoking regimen (Figure 6). In particular, CI smoke yield variabilities of acrylonitrile, benzene, and toluene are equivalent between little cigars and cigarettes.

In summary, this study provides measurements of five mainstream smoke VOC yields generated from 60 popular U.S. little cigar products for both the ISO (nonintense) and CI machine smoking regimens. The study is limited to little cigar products purchased in the Atlanta, Georgia area between July 2016 and May 2017 that represent the majority but not total U.S. little cigar market. The study identifies considerable differences in mainstream smoke VOC levels among different little cigar brands. Highest VOC levels were found in Panther Desert Tin Coffee and Cafe Creme Original Tin, both of which lack a filter. Similar to cigarettes, all individual and total VOC yields in little cigars are higher with CI smoking than ISO smoking. However, little cigars delivered substantially higher VOC smoke yields than cigarettes under both ISO and CI smoking regimens. Moreover, little cigar smoke also contains considerably higher VOCs than cigarette smoke when smoke yields are adjusted for mass of filler tobacco. Correlation analysis reveals strong associations between acrylonitrile and 1,3-butadiene or toluene under the ISO smoking regimen. Correlations among individual VOC yields are considerably weaker under the CI smoking regimen.

## Acknowledgments

### Funding

This research was funded by the U.S. Food and Drug Administration, Center for Tobacco Products.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Food and Drug Administration or the Centers for Disease Control and Prevention. The use of brand names in this manuscript does not constitute an endorsement by either the FDA or CDC.

## ABBREVIATIONS

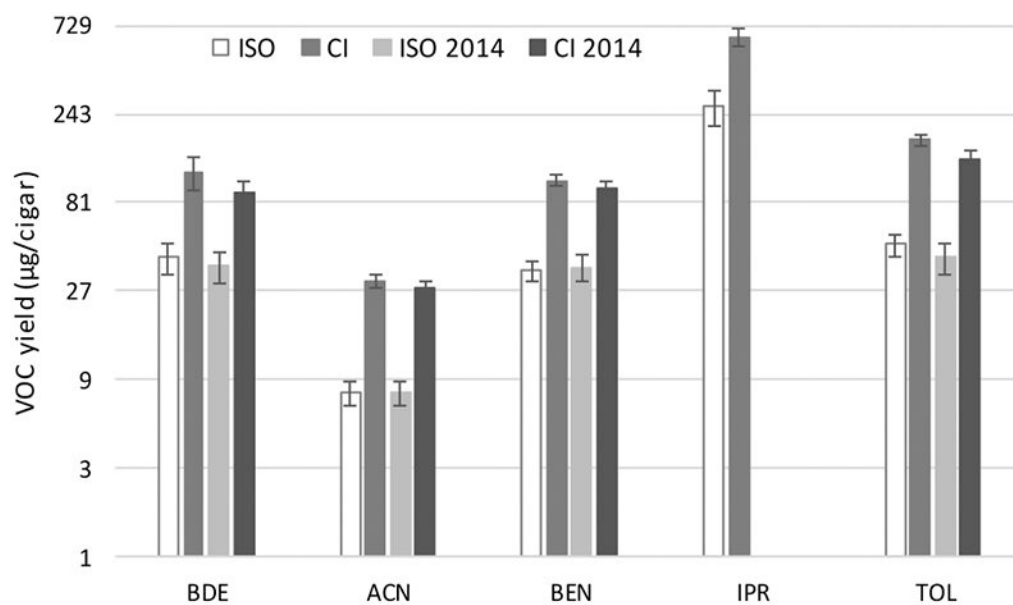
<b>ACN</b>	acrylonitrile
<b>BDE</b>	1,3-butadiene
<b>BEN</b>	benzene
<b>CI</b>	Canadian Intense
<b>IPR</b>	isoprene
<b>ISO</b>	International Organization of Standardization
<b>TOL</b>	toluene
<b>VOC</b>	volatile organic compound

## REFERENCES

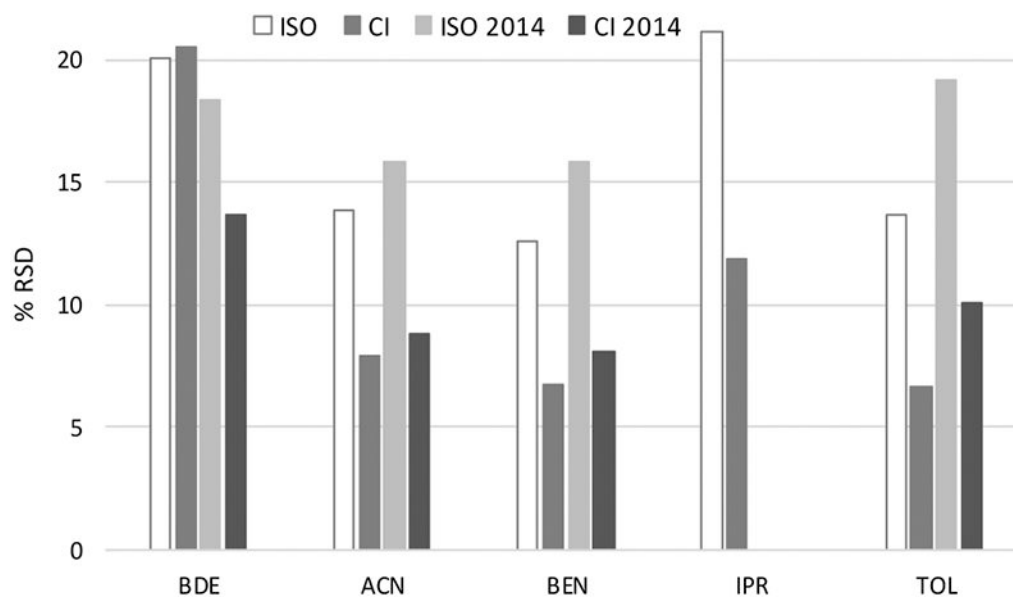
- (1). Centers for Disease Control and Prevention (2012) Consumption of Cigarettes and Combustible Tobacco—United States, 2000–2011. *MMWR Morb Mortal Wkly Rep* 61, 565–569. [PubMed: 22854624]
- (2). Government Accountability Office (April 2012). Tobacco Taxes: Large Disparities in Rates for Smoking Products Trigger Significant Market Shifts to Avoid Higher Taxes. [GAO-12-475]. <https://www.gao.gov/assets/gao-12-475.pdf> (accessed February 2020).
- (3). Malone RE, Yerger V, and Pearson C (2001) Cigar risk perceptions in focus groups of urban African American youth. *J. Subst. Abuse* 13 (4), 549–561. [PubMed: 11775082]
- (4). Smith SY, Curbow B, and Stillman FA (2007) Harm perception of nicotine products in college freshmen. *Nicotine Tob. Res* 9 (9), 977–982. [PubMed: 17763115]
- (5). Delnevo CD, et al. (2015) Preference for flavoured cigar brands among youth, young adults and adults in the USA. *Tobacco Control* 24 (4), 389–394. [PubMed: 24721967]
- (6). U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute (NCI). Cigars: Health Effects and Trends. Smoking and Tobacco Control, Monograph No. 9, Bethesda, MD. 1998, [https://cancercontrol.cancer.gov/brp/tcrb/monographs/9/m9\\_complete.pdf](https://cancercontrol.cancer.gov/brp/tcrb/monographs/9/m9_complete.pdf) (accessed February 2020).
- (7). Baker F, et al. (2000) Health Risks Associated with Cigar Smoking. *J. Am. Med. Assoc.* 284 (6), 735–740.
- (8). 26 U.S. Code §5702(a).
- (9). Delnevo CD, and Hrywna M (2007) A whole’ nother smoke” or a cigarette in disguise: How RJ Reynolds reframed the image of little cigars. *Am. J. Public Health* 97 (8), 1368–1375. [PubMed: 17600253]
- (10). Roemer E, Schramke H, Weiler H, Buettner A, Kausche S, Weber S, Berges A, Stueber M, Muench M, Trelles-Sticken E, Pype J, Kohlgrueber K, Voelkel H, and Wittke S (2012) Mainstream smoke chemistry and in vitro and in vivo toxicity of the reference cigarettes 3R4F and 2R4F. *Contrib. Tob. Res* 25, 316–335.
- (11). Hamad SH, Johnson NM, Tefft ME, Brinkman MC, Gordon SM, Clark PI, and Buehler SS (2017) Little Cigars vs 3R4F Cigarette: Physical Properties and HPHC Yields. *Tob. Regul Sci* 3 (4), 459–478. [PubMed: 29911130]
- (12). Klupinski TP, Strozier ED, Friedenber DA, et al. (2016) Identification of new and distinctive exposures from little cigars. *Chem. Res. Toxicol* 29 (2), 162–168. [PubMed: 26605856]



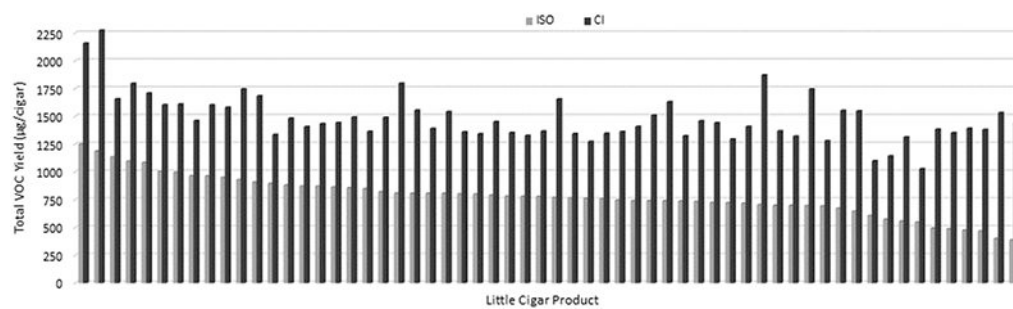
- (13). Pankow JF (2001) A consideration of the role of gas/particle partitioning in the deposition of nicotine and other tobacco smoke compounds in the respiratory tract. *Chem. Res. Toxicol* 14 (11), 1465–1481. [PubMed: 11712903]
- (14). Pickworth WB, Rosenberry ZR, and Koszowski B (2017) Toxicant exposure from little cigar smoking: further support for product regulation. *Tob. Control* 26, 269–276. [PubMed: 27122063]
- (15). Food and Drug Administration (2016) Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Restrictions on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products. *Fed. Regist* 81 (90), 28973–29106. [PubMed: 27192730]
- (16). Food and Drug Administration (2012) Harmful and potentially harmful constituents in tobacco products and tobacco smoke; Established list. *Fed. Regist* 77 (64), 20034–20037.
- (17). Food and Drug Administration (2012). Draft 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. <https://www.fda.gov/media/83375/download> (accessed February 2020).
- (18). Vu AT, Taylor KM, Holman MR, et al. (2015) Polycyclic aromatic hydrocarbons in the mainstream smoke of popular U.S. cigarettes. *Chem. Res. Toxicol* 28 (8), 1616–1626. [PubMed: 26158771]
- (19). Pazo DY, Moliere F, Sampson MM, et al. (2016) Mainstream Smoke Levels of Volatile Organic Compounds in 50 US Domestic Cigarette Brands Smoked with the ISO and Canadian Intense Protocols. *Nicotine Tob. Res* 18 (9), 1886–1894. [PubMed: 27113015]
- (20). Sampson MM, Chambers DM, Pazo DY, et al. (2014) Simultaneous Analysis of 22 Volatile Organic Compounds in Cigarette Smoke Using Gas Sampling Bags for High-Throughput Solid-Phase Microextraction. *Anal. Chem* 86, 7088–7095. [PubMed: 24933649]
- (21). Agnew-Heard KA, Lancaster VA, Bravo R, Watson C, Walters MJ, and Holman MR (2016) Multivariate Statistical Analysis of Cigarette Design Feature Influence on ISO TNCO Yields. *Chem. Res. Toxicol* 29 (6), 1051–1063. [PubMed: 27222918]



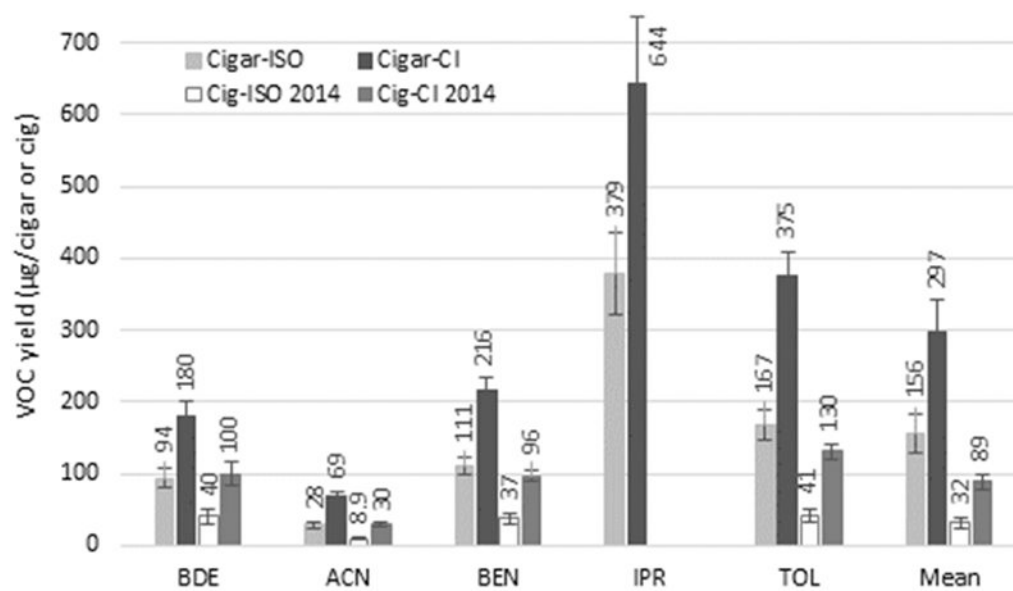
**Figure 1.** VOC Levels in 3R4F cigarette. Y-axis depicts VOC yield on a log-10 scale. VOC abbreviations: BDE, 1,3-butadiene; ACN, acrylonitrile; BEN, benzene; IPR, isoprene; TOL, toluene.



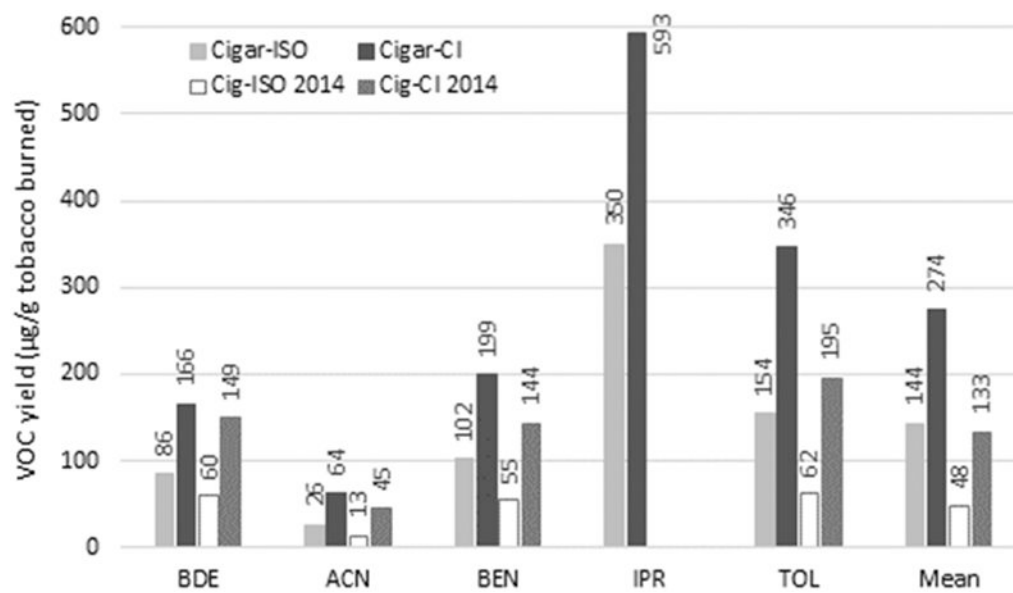
**Figure 2.**  
Relative standard deviation of 3R4F VOC yields.



**Figure 3.** Total VOC yields. Little cigar product list and order are shown in Table 1.

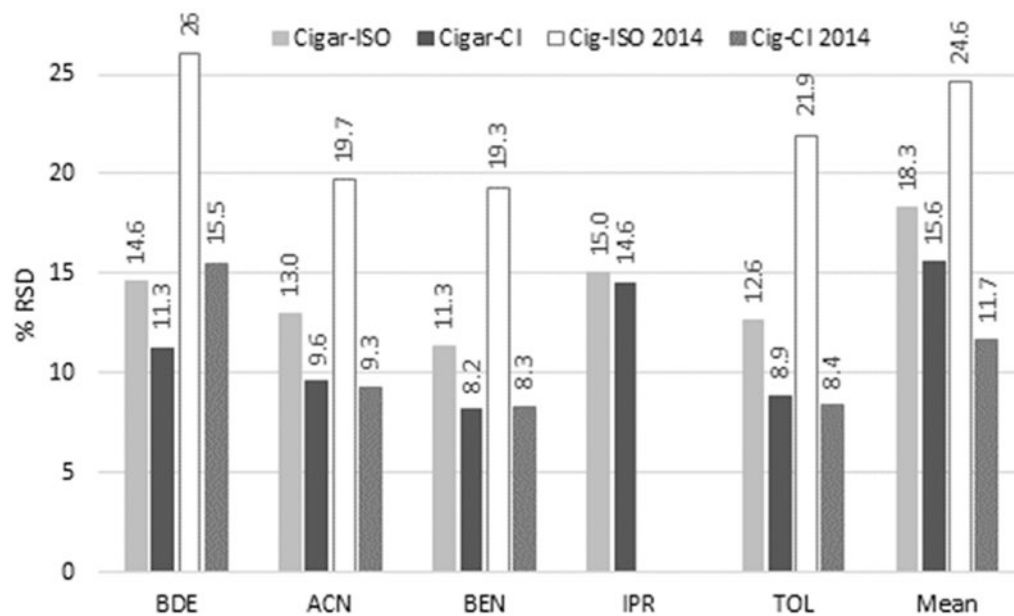


**Figure 4.** Comparison of average individual VOC yields between little cigar and cigarette products.



**Figure 5.**  
VOC yields adjusted for mass of filler tobacco.





**Figure 6.**  
Comparison of VOC yield variability between little cigar and cigarette products.

**Table 1.** VOC Levels in Mainstream Smoke of 60 Commercial U.S. Little Cigar Products Measured Under ISO and CI Smoking Regimens

little cigar product <sup>a</sup>	VOC <sup>b</sup> (mean ± SD, μg/cigar)													
	ISO					CI								
	BDE	ACN	BEN	IPR	TOL	total VOC <sup>c</sup>	total VOC normalized to tobacco <sup>d</sup>	BDE	ACN	BEN	IPR	TOL	total VOC <sup>c</sup>	total VOC normalized to tobacco <sup>d</sup>
Panther Desert Tin Coffee	157 ± 23	43 ± 4.0	130 ± 14	698 ± 60	221 ± 18	1250 ± 69	1210	243 ± 27	87 ± 8.1	211 ± 22	1240 ± 154	377 ± 42	2158 ± 163	2090
Cafe Creme Original Tin	129 ± 22	41 ± 5.7	107 ± 7.9	714 ± 94	195 ± 32	1186 ± 102	1143	242 ± 28	90 ± 11	203 ± 25	1373 ± 392	367 ± 42	2276 ± 397	2192
American Made 100s SP Full Flavor	133 ± 10	40 ± 4.7	197 ± 11	542 ± 66	222 ± 17	1134 ± 70	1057	199 ± 25	71 ± 5.1	306 ± 34	675 ± 92	407 ± 37	1657 ± 108	1545
Action Red 100s Box Full Flavor	127 ± 13	49 ± 4.2	140 ± 14	520 ± 81	259 ± 28	1096 ± 88	868	213 ± 22	95 ± 6.5	232 ± 14	762 ± 105	494 ± 35	1795 ± 114	1423
Double Diamond 100s Box Grape	136 ± 17	49 ± 4.5	148 ± 8.4	502 ± 55	250 ± 10	1084 ± 59	840	223 ± 19	96 ± 7.1	244 ± 12	685 ± 104	460 ± 20	1709 ± 109	1323
Beach Palm Filter 100s Box Full Flavor	134 ± 12	44 ± 3.1	153 ± 5.4	417 ± 66	256 ± 8.9	1003 ± 68	740	224 ± 13	90 ± 6.1	256 ± 9.1	563 ± 78	470 ± 20	1604 ± 82	1183
Dark Horse 100s Box Regular	130 ± 13	42 ± 4.4	149 ± 14	442 ± 41	232 ± 26	996 ± 52	740	202 ± 16	82 ± 4.5	241 ± 14	663 ± 98	421 ± 40	1610 ± 108	1196
Swisher Sweets SP Regular	113 ± 6.5	37 ± 1.8	116 ± 8.8	513 ± 68	184 ± 14	963 ± 71	1027	183 ± 18	77 ± 8.2	194 ± 15	655 ± 61	351 ± 24	1460 ± 70	1557
Buffalo 100s Box Full Flavor	128 ± 8.1	41 ± 3.6	142 ± 5.2	404 ± 27	247 ± 19	963 ± 35	741	212 ± 21	85 ± 6.3	229 ± 13	623 ± 49	453 ± 26	1603 ± 61	1233
Double Diamond 100s Box Mild	126 ± 12	40 ± 3.0	137 ± 5.8	421 ± 23	224 ± 14	949 ± 31	704	206 ± 24	81 ± 5.6	223 ± 10	652 ± 71	419 ± 18	1581 ± 78	1173
Talon Regular SP	90 ± 12	22 ± 2.4	87 ± 7.6	594 ± 95	136 ± 13	930 ± 97	987	176 ± 17	58 ± 5.4	171 ± 8.3	1029 ± 129	312 ± 16	1746 ± 132	1855
Talon 100s SP Menthol	115 ± 12	27 ± 2.2	105 ± 10	497 ± 61	162 ± 8.1	907 ± 64	999	210 ± 31	65 ± 6.2	199 ± 9.0	851 ± 67	359 ± 18	1684 ± 77	1853
Gold Rush Original Red Box	117 ± 8.0	44 ± 4.7	140 ± 8.0	371 ± 43	224 ± 15	895 ± 48	784	183 ± 26	78 ± 6.6	222 ± 14	445 ± 62	408 ± 27	1336 ± 74	1170

little cigar product <sup>a</sup>	VOC <sup>b</sup> (mean ± SD, µg/cigar)													
	ISO					CI								
	BDE	ACN	BEN	IPR	TOL	total VOC VOC <sup>c</sup>	total VOC normalized to tobacco <sup>d</sup>	BDE	ACN	BEN	IPR	TOL	total VOC VOC <sup>c</sup>	total VOC normalized to tobacco <sup>d</sup>
Bella Filter 100s Box Full Flavor	98 ± 6.2	34 ± 4.1	127 ± 6.7	398 ± 80	223 ± 16	880 ± 82	761	170 ± 15	76 ± 7.6	218 ± 12	572 ± 76	446 ± 27	1483 ± 84	1283
Hat's Off 100s Box Full Flavor	103 ± 12	37 ± 3.6	127 ± 7.0	408 ± 52	197 ± 27	871 ± 60	673	183 ± 28	75 ± 8.5	214 ± 15	549 ± 33	386 ± 30	1407 ± 56	1087
Westfort 100s Box Light	86 ± 11	28 ± 2.7	97 ± 7.8	496 ± 69	163 ± 14	871 ± 72	857	144 ± 6.8	60 ± 3.0	172 ± 7.8	720 ± 79	339 ± 20	1434 ± 82	1411
Swisher Sweets SP Caramel	102 ± 19	37 ± 5.4	114 ± 11	438 ± 58	171 ± 24	862 ± 67	938	170 ± 15	72 ± 6.7	187 ± 18	675 ± 133	339 ± 29	1443 ± 138	1569
Cheyenne 100s Box Full Flavor	104 ± 12	29 ± 1.3	161 ± 14	375 ± 47	187 ± 13	856 ± 52	831	177 ± 24	64 ± 7.2	268 ± 28	588 ± 51	395 ± 27	1493 ± 69	1449
Swisher Sweets SP Peach	100 ± 13	30 ± 3.2	106 ± 9.3	455 ± 48	158 ± 16	848 ± 54	934	171 ± 15	68 ± 5.1	190 ± 15	604 ± 85	330 ± 32	1364 ± 93	1502
Golden Harvest Filter Box Full Flavor	102 ± 17	26 ± 3.5	137 ± 13	393 ± 70	163 ± 18	820 ± 75	752	184 ± 23	62 ± 4.5	256 ± 13	625 ± 86	362 ± 16	1490 ± 92	1366
Captain Black SP Sweet	88 ± 6.9	21 ± 1.8	81 ± 4.3	498 ± 88	122 ± 4.8	810 ± 89	922	186 ± 29	68 ± 8.5	191 ± 27	1047 ± 85	306 ± 28	1798 ± 98	2046
Phillies Filter 100s SP Menthol	77 ± 11	22 ± 3.3	86 ± 9.5	465 ± 59	157 ± 14	807 ± 63	737	159 ± 30	62 ± 8.9	181 ± 16	794 ± 104	359 ± 41	1555 ± 117	1420
Supreme Blend 100s Box Full Flavor	100 ± 13	27 ± 2.4	140 ± 10	371 ± 57	168 ± 11	806 ± 61	779	184 ± 24	64 ± 10	252 ± 25	547 ± 85	344 ± 34	1391 ± 98	1343
Cafe Creme Blue Tin	93 ± 15	26 ± 3.8	84 ± 16	464 ± 82	138 ± 25	805 ± 88	986	200 ± 37	59 ± 6.7	164 ± 30	832 ± 98	286 ± 46	1541 ± 118	1886
Dean's Filter 100s SP Full Flavor	101 ± 11	26 ± 3.1	141 ± 14	360 ± 62	173 ± 13	801 ± 66	770	174 ± 18	58 ± 5.6	247 ± 21	524 ± 56	357 ± 32	1359 ± 70	1306
Swisher Sweets SP Cherry	101 ± 11	32 ± 5.7	105 ± 10	394 ± 56	168 ± 21	800 ± 62	872	166 ± 16	68 ± 6.8	182 ± 19	608 ± 71	318 ± 31	1342 ± 82	1462
Cheyenne 100s HP Menthol	91 ± 12	24 ± 4.5	132 ± 22	391 ± 68	152 ± 26	790 ± 77	764	172 ± 13	62 ± 3.7	265 ± 14	588 ± 57	364 ± 22	1451 ± 64	1404
Red Buck 100s SP Regular	101 ± 11	28 ± 2.1	140 ± 6.0	351 ± 50	162 ± 12	782 ± 53	748	184 ± 18	63 ± 7.3	250 ± 15	523 ± 107	333 ± 21	1354 ± 112	1295

little cigar product <sup>a</sup>	VOC <sup>b</sup> (mean ± SD, μg/cigar)												
	ISO						CI						
	BDE	ACN	BEN	IPR	TOL	total VOC normalized to tobacco <sup>d</sup>	BDE	ACN	BEN	IPR	TOL	total VOC normalized to tobacco <sup>d</sup>	
Smoker's Choice Original Red SP	113 ± 50	31 ± 8.9	117 ± 36	341 ± 104	178 ± 48	779 ± 131	174 ± 23	72 ± 3.0	210 ± 12	486 ± 61	385 ± 16	1327 ± 68	1164
Action Gold 100s Box Light	102 ± 8.7	34 ± 3.8	117 ± 14	332 ± 37	193 ± 12	778 ± 42	186 ± 24	73 ± 7.5	208 ± 19	511 ± 88	388 ± 37	1366 ± 101	999
King Edwards SP Regular	93 ± 8.3	28 ± 3.0	102 ± 14	373 ± 70	174 ± 15	769 ± 73	192 ± 15	81 ± 6.7	240 ± 11	680 ± 48	463 ± 30	1655 ± 60	1330
Cheyenne 100s HP Cherry	97 ± 8.8	25 ± 2.7	144 ± 15	317 ± 51	181 ± 20	765 ± 58	161 ± 9.8	55 ± 7.8	259 ± 27	489 ± 94	380 ± 35	1344 ± 104	1356
Golden Harvest Blue Box Light	93 ± 3.0	32 ± 2.5	109 ± 7.8	346 ± 23	182 ± 17	762 ± 30	163 ± 16	70 ± 2.7	196 ± 13	464 ± 71	380 ± 25	1273 ± 78	1094
Derringer 100s HP Full Flavor	90 ± 9.4	24 ± 1.6	130 ± 8.7	355 ± 47	156 ± 11	756 ± 50	166 ± 15	58 ± 4.2	242 ± 18	543 ± 68	338 ± 21	1347 ± 75	1465
Remington Filter 100s HP Regular	99 ± 6.3	26 ± 1.6	135 ± 6.8	331 ± 23	155 ± 11	745 ± 27	194 ± 22	61 ± 3.7	233 ± 13	547 ± 82	327 ± 28	1362 ± 90	1262
Sandia 100s Box Full Flavor	95 ± 12	28 ± 2.0	105 ± 6.0	334 ± 44	178 ± 8.8	740 ± 47	176 ± 19	63 ± 4.1	197 ± 7.5	591 ± 37	380 ± 19	1408 ± 47	1062
Captain Black 100s SP	91 ± 18	20 ± 2.1	79 ± 4.7	432 ± 52	118 ± 6.0	740 ± 55	182 ± 12	61 ± 4.7	168 ± 13	813 ± 75	285 ± 14	1509 ± 79	1836
Vaquero 100s Box Natural	84 ± 9.6	28 ± 3.3	105 ± 14	318 ± 29	204 ± 26	740 ± 43	202 ± 7.8	83 ± 3.4	242 ± 5.4	616 ± 83	489 ± 17	1631 ± 86	1415
Smoker's Choice SP Menthol	91 ± 11	30 ± 5.2	113 ± 18	321 ± 46	181 ± 29	737 ± 59	164 ± 4.7	67 ± 4.8	208 ± 12	483 ± 57	402 ± 18	1324 ± 61	1099
Westfort 100s HP Grape	82 ± 12	23 ± 2.0	95 ± 3.3	390 ± 33	143 ± 13	733 ± 37	176 ± 21	60 ± 5.4	190 ± 13	675 ± 75	358 ± 28	1459 ± 84	1349
Racer 100s Box Full Flavor	92 ± 18	26 ± 2.1	95 ± 5.9	345 ± 60	165 ± 19	722 ± 65	167 ± 13	71 ± 4.3	193 ± 4.6	623 ± 52	387 ± 16	1442 ± 57	1324
Sparrow Original Blend SP	92 ± 6.8	31 ± 5.5	104 ± 13	310 ± 28	184 ± 25	721 ± 41	155 ± 20	73 ± 8.3	197 ± 15	482 ± 38	387 ± 28	1295 ± 54	1171
Richwood 100s Box Original	82 ± 13	21 ± 2.2	119 ± 11	363 ± 39	132 ± 15	717 ± 45	160 ± 8.0	60 ± 3.0	251 ± 18	599 ± 82	338 ± 22	1408 ± 88	1397
Phillies 100s SP Sweet	74 ± 7.5	23 ± 3.1	80 ± 8.6	376 ± 28	151 ± 17	705 ± 35	186 ± 23	76 ± 6.5	213 ± 15	950 ± 91	446 ± 48	1871 ± 106	1694

little cigar product <sup>a</sup>	VOC <sup>b</sup> (mean ± SD, μg/cigar)												
	ISO						CI						
	BDE	ACN	BEN	IPR	TOL	total VOC normalized to tobacco <sup>d</sup>	BDE	ACN	BEN	IPR	TOL	total VOC normalized to tobacco <sup>d</sup>	
Stampede Regular 100s Box	85 ± 10	21 ± 2.3	114 ± 10	346 ± 50	132 ± 12	698 ± 53	161 ± 8.0	55 ± 4.5	234 ± 11	595 ± 79	324 ± 26	1369 ± 85	1484
Double Diamond 100s Box Full Flavor	80 ± 13	26 ± 3.5	107 ± 20	302 ± 50	182 ± 33	697 ± 64	161 ± 20	64 ± 6.0	197 ± 9.2	512 ± 26	387 ± 44	1321 ± 56	982
Hav-A-Tampa 100s SP Sweet	72 ± 28	21 ± 8.4	86 ± 30	361 ± 65	156 ± 66	695 ± 101	184 ± 50	66 ± 19	196 ± 49	909 ± 124	390 ± 125	1745 ± 191	2057
Wrangler Filter 100s Box Full Flavor	86 ± 9.6	31 ± 2.4	98 ± 14	292 ± 61	185 ± 28	692 ± 70	143 ± 14	68 ± 6.3	186 ± 15	494 ± 78	390 ± 37	1280 ± 89	1081
305's 100s Box Full Flavor	66 ± 5.9	16 ± 1.6	67 ± 4.1	425 ± 96	100 ± 5.3	673 ± 97	168 ± 12	52 ± 4.7	164 ± 9.2	864 ± 59	304 ± 20	1553 ± 64	1507
Santa Fe SP Grape	77 ± 4.5	26 ± 2.4	101 ± 7.3	257 ± 22	183 ± 18	645 ± 29	192 ± 13	83 ± 4.4	240 ± 11	565 ± 28	468 ± 28	1548 ± 43	1349
Cherokee Box Full Flavor	80 ± 10	19 ± 3.3	92 ± 13	281 ± 39	134 ± 23	606 ± 48	144 ± 15	53 ± 7.8	171 ± 18	441 ± 64	290 ± 36	1099 ± 77	1349
Seneca Box Full Flavor	71 ± 7.2	24 ± 1.8	91 ± 6.8	223 ± 39	162 ± 12	572 ± 42	143 ± 12	64 ± 3.5	181 ± 10	382 ± 59	375 ± 28	1144 ± 67	1001
Cheyenne 100s HP Classic	65 ± 4.4	17 ± 2.4	95 ± 5.6	271 ± 40	109 ± 10	556 ± 42	176 ± 20	60 ± 5.0	237 ± 15	514 ± 69	327 ± 23	1314 ± 77	1256
Prime Time Box Sweet	62 ± 8.4	21 ± 2.0	67 ± 5.4	284 ± 37	113 ± 7.0	546 ± 39	121 ± 13	53 ± 3.9	128 ± 8.8	485 ± 44	241 ± 17	1028 ± 50	1341
Clipper 100s Box Full Flavor	60 ± 7.1	15 ± 2.3	89 ± 12	232 ± 50	96 ± 12	493 ± 53	165 ± 18	58 ± 5.4	240 ± 18	573 ± 77	348 ± 22	1383 ± 84	1251
Smoker's Best Filter 100s Box Full Flavor	58 ± 8.3	12 ± 1.8	86 ± 14	241 ± 65	89 ± 13	487 ± 68	158 ± 10	62 ± 4.2	240 ± 30	551 ± 81	341 ± 35	1353 ± 94	1243
Santa Fe 100s SP Original	61 ± 17	18 ± 5.2	71 ± 19	200 ± 53	125 ± 37	475 ± 70	178 ± 11	75 ± 4.4	212 ± 15	503 ± 35	423 ± 39	1391 ± 56	1174
Stampede Filter 100s Box Mild	52 ± 6.6	14 ± 0.7	85 ± 7.8	225 ± 20	91 ± 7.7	468 ± 23	171 ± 16	57 ± 3.8	255 ± 14	564 ± 62	333 ± 22	1381 ± 69	1362
Santa Fe SP Mild	48 ± 16	15 ± 5.1	62 ± 19	174 ± 59	102 ± 30	400 ± 71	188 ± 16	81 ± 10	234 ± 21	557 ± 110	473 ± 50	1533 ± 125	1239

little cigar product <sup>a</sup>	VOC <sup>b</sup> (mean ± SD, µg/cigar)													
	ISO							CI						
	BDE	ACN	BEN	IPR	TOL	total VOC normalized to tobacco <sup>d</sup>	BDE	ACN	BEN	IPR	TOL	total VOC <sup>c</sup>	total VOC normalized to tobacco <sup>d</sup>	
Santa Fe SP Menthol	46 ± 3.5	13 ± 1.6	56 ± 7.6	176 ± 17	95 ± 13	386 ± 23	334	176 ± 23	77 ± 3.5	216 ± 10	562 ± 56	416 ± 16	1447 ± 64	1250
Mean	94 ± 14	28 ± 3.6	111 ± 13	379 ± 57	167 ± 21	779 ± 29	730	180 ± 20	69 ± 6.6	216 ± 18	644 ± 94	375 ± 33	1484 ± 46	1393
3R4F <sup>e</sup>	41 ± 8.2	7.7 ± 1.1	35 ± 4.4	268 ± 57	48 ± 6.6	399 ± 58	515	118 ± 24	31 ± 2.4	106 ± 7.2	633 ± 75	176 ± 12	1064 ± 80	1373

<sup>a</sup>Little cigars are sorted by total ISO VOC smoke yield. Little cigar description abbreviations: HP, hard pack; SP, soft pack; 100s, 100 mm cigar length.

<sup>b</sup>VOC abbreviations: BDE, 1,3-butadiene; ACN, acrylonitrile; BEN, benzene; IPR, isoprene; TOL, toluene. Individual VOC quantities were determined from 7 experiments.

<sup>c</sup>Sum of quantities of the five individual VOCs.

<sup>d</sup>Total VOC values are normalized per gram of tobacco.

<sup>e</sup>VOC values for 3R4F are average of 73 experiments under the ISO smoking regimen and 67 experiments under the CI smoking regimen.



Table 2.

Pearson Coefficients and *P*-Values for Correlations Between VOC Levels<sup>a</sup>

	ISO					CI				
	BDE	ACN	BEN	IPR	TOL	BDE	ACN	BEN	IPR	TOL
ACN	0.902 (<0.001)					0.714 (<0.001)				
BEN	0.777 (<0.001)	0.698 (<0.001)				0.357 (0.005)	0.230 (0.077)			
IPR	0.731 (<0.001)	0.593 (<0.001)	0.358 (0.005)			0.561 (<0.001)	0.231 (0.076)	-0.215 (0.099)		
TOL	0.845 (<0.001)	0.935 (<0.001)	0.746 (<0.001)	0.456 (<0.001)		0.466 (<0.001)	0.793 (<0.001)	0.464 (<0.001)	-0.086 (0.515)	
total VOCa	0.938 (<0.001)	0.855 (<0.001)	0.683 (<0.001)	0.896 (<0.001)	0.784 (<0.001)	0.807 (<0.001)	0.566 (<0.001)	0.132 (0.314)	0.891 (<0.001)	0.341 (0.008)

<sup>a</sup> *P*-values are in parentheses.