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Mainstream Smoke Levels of Volatile Organic Compounds in 50 US Domestic Cigarette Brands Smoked with the ISO and Canadian Intense Protocols

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Abstract

Introduction—A significant portion of the increased risk of cancer and respiratory disease from exposure to cigarette smoke is attributed to volatile organic compounds (VOCs). In this study, 21 VOCs were quantified in mainstream cigarette smoke from 50 U.S. domestic brand varieties that included high market share brands and two Kentucky research cigarettes (3R4F and 1R5F).

Methods—Mainstream smoke was generated under ISO 3308 and Canadian Intense (CI) smoking protocols with linear smoking machines with a gas sampling bag collection followed by SPME/GC/MS analysis.

Results—For both protocols, mainstream smoke VOC amounts among the different brand varieties were strongly correlated between the majority of the analytes. Overall, Pearson correlation (r) ranged from 0.68 to 0.99 for ISO and 0.36 to 0.95 for CI. However, monoaromatic compounds were found to increase disproportionately compared to unsaturated, nitro, and carbonyl compounds under the CI smoking protocol where filter ventilation is blocked.

Conclusions—Overall, machine generated “vapor phase” amounts (μg/cigarette) are primarily attributed to smoking protocol (e.g., blocking of vent holes, puff volume, and puff duration) and filter ventilation. A possible cause for the disproportionate increase in monoaromatic compounds could be increased pyrolysis under low oxygen conditions associated with the CI protocol.

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DECLARATION OF INTERESTS

None to declare.

INTRODUCTION

Large amounts of toxic volatile organic compounds (VOCs) are produced during the burning of cigarettes from incomplete combustion of tobacco.[1,2] The VOCs found in this cigarette smoke have been attributed to diseases of the respiratory (e.g., benzene, toluene, styrene)[3] and cardiovascular system (e.g., benzene, toluene, xylenes, ethylbenzene, styrene),[4] and have been identified as neurological and developmental toxicants (e.g., toluene).[5] For some of these VOCs (i.e., toluene and benzene), cigarette smoke is the primary source of non-occupational exposure in the U.S. population.[6] Therefore, quantifying a smoker's exposure to these VOCs is important for evaluating the impact of mainstream cigarette smoke toxicants on public health. Although the literature on cigarette design, pyrolysis and combustion chemistry, and smoking behavior is sizable; there are limited data on VOC deliveries for commercial cigarettes using multiple smoking machine protocols with which to estimate exposure ranges among smokers.

In 2009, a comprehensive domestic-brand market survey of mainstream smoke was performed by Bodnar et al. This survey involved measuring 6 VOC levels for 61 brand varieties using the Canadian Intense protocol.[7] Other survey-style studies that preceded this survey were less comprehensive using fewer cigarette brand varieties, but included more VOCs.[8,9] At the time these studies were performed, only five VOCs were recommended for regulatory action by the World Health Organization (WHO).[10] In 2012, the Food and Drug Administration (FDA) published a list of 93 harmful and potentially harmful constituents (HPHCs), including 33 VOCs (boiling point < 250°C and excluding volatile amines) in mainstream cigarette smoke. In the same year, the FDA issued a draft guidance under section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act for the tobacco industry to report levels for 20 of the 93 HPHCs, 9 of which were VOCs in tobacco smoke.[11] Therefore, reporting these VOCs under section 904(a)(3) is best achieved using a comprehensive method suitable for simultaneous quantification of VOCs that have a broad range of reactivities and volatilities. In addition, when conducting a comprehensive market study involving many brand varieties and more than one smoking machine protocol, achieving high throughput is important.

A commonly used mainstream smoking protocol is the ISO protocol (3308:2012). Reporting VOCs generated with the ISO protocol is important because there are many historical data available for comparison and it is the only internationally standardized protocol for smoke generation.[12] Because an individual's smoking topography can vary greatly,[13] smoke emissions using the ISO protocol can underestimate VOC levels experienced by smokers; for example, those who obstruct the filter ventilation holes with their fingers or lips will inhale higher levels of VOCs than measured under ISO smoking machine protocols.[14] The Canadian Intense (CI) smoking machine protocol was developed to better characterize more intense smoking behavior by increasing puff volume, shortening interpuff interval (IPI), and blocking ventilation holes compared to the ISO protocol.[15]

In this study, we characterize mainstream smoke in 50 U.S. domestic filtered cigarette brand varieties smoked with the ISO and CI protocols on linear smoking machines using an analytical method capable of measuring 21 VOCs (of which 13 are listed by the FDA as

HPHCs). Thirty-two of the brand varieties selected are from the five top-selling manufacturers in 2011 and the remaining 18 are lower volume selling brands or had unique characteristics (e.g., tobacco blend or filter type). By including brands that encompass the majority of the cigarette market, this data will provide useful insight when interpreting exposure levels for U.S. smokers.

EXPERIMENTAL

Cigarette Samples

The 50 filtered cigarette brand varieties selected were from manufacturers [Philip Morris, Reynolds, Lorillard, Commonwealth, and Santa Fe a division of Reynolds American Inc.] that supplied 89% of the market share as deduced from the year-end 2011 Maxwell report.[16] Following procurement, cigarettes were handled and stored in a similar manner as described elsewhere.[17] Thirty-two of the 50 brand varieties represent 76% of the brand family market share.[16] The brand families of these 32 brand varieties were as follows: 13 Marlboro, 4 Basic, 4 Winston, 3 Newport, 2 Camel, 2 Doral, 2 Kool, 1 Maverick, and 1 Pall Mall. The remaining 18 brand varieties were lower volume selling brands and selected in order to get a broad representation of tobacco brands or had unique characteristics (e.g., filter design, tobacco formulation, percent filter ventilation). These tobacco products included: 4 Salem, 2 Benson & Hedges, 1 Natural American Spirit, 1 Capri, 1 Carlton, 1 Kent, 1 Merit, 1 Misty, 1 Now, 1 Parliament, 1 True, 1 USA Gold, 1 Vantage, 1 Virginia Slims. Overall, cigarette brand varieties consisted of 3 slim, 26 king, and 21 100-sized cigarettes and packaging consisted of 13 box and 37 soft packs. All products were purchased in the metropolitan Atlanta area in November 2011. Two research cigarettes, 3R4F and 1R5F (University of Kentucky, Lexington, KY), were included in each smoking machine run as quality control samples. Seven cigarettes of each brand variety were smoked and individual analyte levels were measured simultaneously for each cigarette.

Reagents and Materials

VOCs quantified in this study included six unsaturated and nitro compounds (acrylonitrile, furan, 1,3-butadiene, 2,5-dimethylfuran, vinyl chloride, and nitrobenzene), seven carbonyls (acetaldehyde, butanal, crotonaldehyde, 2-butanone, 2-pentanone, 3-pentanone, and vinyl acetate), and eight monoaromatic hydrocarbons (benzene, toluene, ethylbenzene, *m*/*p*-xylene (unresolved), *o*-xylene, styrene, and 3-ethyltoluene). VOC intermediate standard solutions were purchased from O2Si Smart Solutions (Charleston, SC). Concentrations of the prepared intermediate standards and final standards were the same as described by Sampson et al.[18] Third party standards purchased from Supelco (Bellefonte, PA) were checked against the primary standards and agreed within 0.5–20%. Isotopically labeled analogs were used for all VOCs and were purchased from Sigma-Aldrich (Saint Louis, MO), C/D/N Isotopes, Inc. (Pointe-Claire, Quebec, Canada), and Cambridge Isotope Laboratories, Inc. (Tewksbury, MA) as neat liquids in flame-sealed ampules with ≥98% isotopic purity and ≥97% chemical purity, except [$^{2}H_{6}$] crotonaldehyde (95% chemical purity). Gas sampling bags (1-L) were purchased from Newstar Environmental (Roswell, GA) and were fitted with butyl rubber O-rings, which are less permeable than standard silicone rubber O-rings.[18,19] Cambridge filter pads were obtained from Whatman (Buckinghamshire, UK) and following sample collection were placed in 20-mL headspace vials from MicroLiter Analytical Supplies (Suwanee, GA) for analysis. Pre-cleaned PTFE-backed crimp caps were purchased from The Lab Depot (Dawsonville, GA).

Cigarette Preparation and Analysis Procedure

Cigarettes were conditioned using ISO 3402:1999 and smoked according to ISO 3308 and CI protocols using equipment and procedures reported previously.[18] Resulting vapor phase and particulate phase samples were analyzed using the headspace SPME/GC/MS method reported previously where analytical figures of merit including precision, accuracy, and analyte-specific biases are characterized and discussed.[18] Note that in cigarette testing using commercial smoking machines, the gas phase portion of the mainstream smoke is commonly referred to as the “vapor phase” and the particulate trapped on the Cambridge filter pads as “particulate phase”. This Cambridge filter pad approach differs from gas and particulate phase partitioning studies by Pankow et al.[20] where the quantification of VOCs and particulates were determined using a different trapping technique. In our work we used 3 clearing puffs (puffs taken after smoking was completed) to help “sweep” the VOC residue from the particulate phase into the volatile gas-sampling bag. Three clearing puffs was an optimal trade-off with respect to moving VOC residue to the gas sampling bag versus collecting excessive sample volumes. The clearing puffs were sufficient to remove residual VOC levels on the particulate phase near or below our limit of quantitation for most of the VOCs with the exception of o-xylene, styrene and 3-ethyltoluene. Particulate phase residue levels for o-xylene, styrene and 3-ethyltoluene were highest for the ISO protocol and cigarettes with the lowest filter ventilation, which ranged from 0.67 to 15.7% for o-xylene, 2.2 to 27.1% for styrene and 7.9 to 57.8% for 3-ethyltoluene. For this reason, particulate phase VOCs quantities for o-xylene, styrene, and 3-ethyltoluene were added to the vapor phase amounts.

The VOCs were measured simultaneously; however, when an individual VOC failed quality control requirements, results from either an additional analysis of the same cigarette brand variety were used to replace the failed run (preferred approach) or results from two cigarettes with similar puff number were combined, which occurred with less than 1% of the total results.

ISO protocol smoke collection runs consisted of a maximum of 14 cigarette samples (including two pairs of 3R4F and 1R5F cigarette QCs) and a smoking run sample blank filling up to 15 ports of the automated linear 16-port ASM 500 smoking machine (Cerulean, Milton Keynes UK). Due to mechanical constraints of the ASM500, the CI protocol smoking machine runs were split into two runs where the first run consisted of eight cigarettes (including one 3R4F and one 1R5F QC) smoked on ports 1 through 8 and the second run consisted of up to six cigarettes (including one 3R4F and one 1R5F QC) smoked on ports 9 through 15. CI protocol smoke runs contained one smoking run sample blank with the first group of cigarettes. Cigarettes and the smoking run sample blank were rotated onto a different port for each replicate run to account for puff-engine variability.

The amount of filter ventilation for the different cigarette brand varieties was determined using a C^2 Hopper (Cerulean, Milton Keynes UK) instrument. Median filter ventilation levels of cigarettes for each brand variety were determined from measurements of seven unconditioned cigarettes from each pack.

Statistical Analysis and Calculations

Descriptive statistical analyses were performed using JMP (Version 8.0, SAS, Cary, NC). Pearson correlation and Spearman coefficients, r, were estimated using the pairwise method.

The CI/ISO protocol ratio is the ratio of total mainstream smoke volumes between the two protocols, which is determined by the median puff number and adjusted by factoring in smoke dilution from filter ventilation. For example, for calculated mainstream smoke volume difference for the Carlton 100s between the two protocols, the product of the puff number (8.5) and puff volume (55 mL) from the CI protocol analysis was divided by the puff number (9.2) and puff volume (35 mL) from the ISO protocol. This quantity was then multiplied by the ratio of the fraction of mainstream smoke sampled between the two protocols due to filter ventilation, which equaled 1 - 0 for the CI and 1 - 0.823 for the ISO protocol. The resulting equation defined as the CI/ISO protocol ratio is $[(8.5 \text{ CI puffs} \times 55 \text{ mL})/(9.2 \text{ ISO puffs} \times 35 \text{ mL})] \times [(1-0)/(1 - 0.823)]$.

RESULTS

The median (interquartile range) vapor phase VOC amounts (µg/cigarette) 50 commercial cigarette brand varieties and for the research cigarettes, as measured using the ISO and CI smoking machine protocols, are arranged into three groups according to compound class based on functional group that include six unsaturated and nitro compounds (Supplemental Table I), eight carbonyls (Supplemental Table II), and eight monoaromatic hydrocarbons (Supplemental Table III). Cigarette brand varieties in these tables are ranked by increasing percent filter ventilation. The distribution of filter ventilation for this group of cigarettes ranged from 0.1 to 82.3%. Analyte deliveries for the ISO protocol were between 0.05 and 98 µg/cigarette, while deliveries for the CI protocol were between 0.69 and 308 µg/cigarette with the exception of acetaldehyde and vinyl chloride. Acetaldehyde was present at the highest amounts among all 50 cigarette brand varieties with a range of 123–1115 µg/cigarette for the ISO protocol and 1183–2170 µg/cigarette for the CI protocol. Vinyl chloride, the compound present in the lowest amount, ranged from <0.005 to 0.045 µg/cigarette for the ISO protocol and 0.051 to 0.096 µg/cigarette for the CI protocol.

The Natural American Spirit cigarettes, a cigarette brand variety with a high proportion of flue-cured or bright leaf tobacco compared to the other brand varieties, exhibited higher median puff numbers of 11.4 using the ISO protocol and 16.4 using the CI protocol. With the Natural American Spirit cigarettes excluded, puff numbers using the ISO protocol range from 6.0 to 11.4 with a median of 8.0 and using the CI protocol from 7.3 to 12.1 with a median of 9.2. The distributions of number of lit puffs among the different brand varieties were normally distributed using either the ISO protocol ($p = 0.07$) or CI protocol ($p = 0.02$), excluding the Natural American Spirit cigarettes.

Relative VOC levels generated from the different cigarettes between the two protocols are compared by taking the ratio of median VOCs levels by CI to ISO (Table I). The selected results in Table I include a comparison of cigarettes with filter ventilation from 0 to 20% and at 30%, 40%, 50%, and above 65%. All 50 brand varieties were not included in Table I because of space limitations, but can be calculated from data in supplemental Tables I–III. Summary statistics for the different cigarette brand varieties were compared with calculated amount differences expected based on differences in total volume of smoke generated by the smoking protocols, the CI/ISO protocol ratio. The CI/ISO protocol ratio is determined by the median puff number and adjusted by factoring in smoke dilution estimated from filter ventilation as described in the experimental.

Pearson correlation results and scatter plots among the 50 brand varieties comparing the ISO and CI protocols are separated by compound class in Figs. 1–3. For the correlation results, the Natural American Spirit cigarettes were excluded; however, they are plotted in the scatter plots and are represented with the open circles. In the scatter plots, the data points corresponding to the ISO protocol are colored in black and the CI protocol are grey.

Correlation results between VOCs using the ISO protocol for the different brand varieties ranged from 0.65 to 0.99, and for the CI protocol from 0.35 to 0.96. Nearly all sample results by analyte fell within a normal distribution and Spearman correlation analyses yielded similar correlation strengths. The Natural American Spirit cigarette tended to fall outside the normal distribution of these brand varieties.

Correlations between the unsaturated and nitro compounds have strengths ranging from 0.68 to 0.87 for ISO (black) and 0.36 to 0.72 for CI (grey) protocols (Fig. 1). The carbonyl compound class has correlation coefficients ranging from 0.59 to 0.99 for ISO (black) and 0.35 to 0.94 for CI (grey) protocols (Fig. 2). Correlations between the different monoaromatic hydrocarbons are the strongest with correlations ranging from 0.88 to 0.99 for the ISO (black) and 0.83 to 0.96 for the CI (grey) protocols (Fig. 3).

In addition, most VOCs trended well between protocols with the exception of styrene. A comparison of scatter plots across compound classes demonstrating this offset are shown in Supplemental Figure 1 for styrene vs. 2,3-butandione, butanal, acrylonitrile, and 2,5-dimethylfuran for VOC levels in mainstream smoke obtained by ISO (black) and CI (grey) protocols. The Natural American Spirit cigarettes are represented with open circles.

DISCUSSION

Because there are number of cigarette design variables that influence the amount of VOCs produced by smoking a cigarette, we narrowed the scope of this paper to filter ventilation and puff number, which we and others have determined to be dominant cigarette design variables[21,22] encompassing the influence of other cigarette design variables such as tobacco weight, rod length, and paper porosity. Substantially higher VOC deliveries from the CI protocol compared to ISO (Supplemental Tables I–III) primarily result from differences in filter ventilation after adjusting for total puff volume. This relationship can be characterized by comparing the relative magnitude of VOCs from cigarettes with different degrees of ventilation smoked under both protocols. For the CI protocol (55-ml puff/30s), the amount of total mainstream smoke volume per cigarette was 3.14 times more than the amount of mainstream smoke volume per cigarette generated by the ISO protocol (35-ml puff/60s). The influence of mainstream smoke volume on measured VOC levels can be evaluated on cigarettes with no filter ventilation because they are not affected by ventilation hole blocking specified with the CI protocol. Best suited for this comparison are the Newport Green king hard and soft pack cigarettes, which have no ventilation holes and the lowest measured filter ventilation of 0.1%. With the CI protocol, more total volume per cigarette was collected by a factor of 2.1 for the hard pack and 2.0 for the soft pack than with the ISO protocol based on median puff number (where median puff number for the hard pack using ISO was 6.0 and 8.1 for CI, and for the soft pack median puff number using ISO was 7.3 and 9.2 for CI). As summarized in Table I, the corresponding VOC amounts (μg/cigarette) measured between the two protocols differ by a median factor of 2.4 and 2.3, respectively. The similarity between CI/ISO protocol ratios of 2.1 for the hard pack and 2.0 for the soft pack (Table I) with ratios between measured analyte amounts (i.e., median value of 2.4[Table I]) suggests that higher analyte levels for these brand varieties are mainly driven by differences in volume of mainstream smoke.

In general, the VOC levels measured between smoking protocols is maintained for cigarettes with filter ventilation of <20%, where the CI/ISO protocol ratios range from 1.9 to 2.5 (Table I). These analyte amount ratios, which ranged from 1.7 to 5.8, correspond closely to ratios between the two protocols. Those analytes that have the highest ratios between protocols are m/p-xylene (2.7–4.1), ethylbenzene (3.2–4.4), o-xylene (3.3–4.7), styrene (3.5–5.3), and 3-ethyltoluene (2.6–5.8). Relative levels of these compounds increase gradually with filter ventilation up to approximately 40%, at which point the increase in these VOCs is much steeper. Higher ratios for these lower volatility VOCs (e.g., higher boiling point and polarity) may be the result of more incomplete combustion due to higher flow rate through the tobacco rod when puffing.

The brand variety with the largest difference in analyte levels between the two protocols (i.e., CI/ISO) is the Carlton 100s hard pack, the cigarette with the highest measured filter ventilation (82.3%) among the brand varieties in this study. For the Carlton 100s hard pack, analyte levels differed by factors of 11.5 to 76.2 (median of 18.6 among all analytes) between protocols (CI/ISO), with furan being the lowest factor in this range and styrene (an IARC group 2B carcinogen) the highest. The brand variety with the second highest measured filter ventilation (66.6%) was the True Silver king soft pack. Analyte levels between the smoking protocols for the True Silver ranged from factors of 4.7 to 20.8 (median of 6.9 among all analytes) with furan among the lowest, yielding a factor of 5.0, and styrene the highest, yielding a factor of 20.8. The factor of 4.7 corresponds to 1,3-butadiene (Table I). These relative VOC levels measured between the protocols are greater than those that result solely from filter ventilation and total puff volume, which total a factor of 13.6 for the Carlton 100s and 5.4 for the True Silver. The True Silver CI/ISO protocol ratio was closer to this calculated value for many of the analytes, but monoaromatic VOCs disproportionately greater as previously seen with lower ventilated cigarettes.

However, within a protocol the difference in analyte levels between the Carlton 100s and True Silver are more in agreement with attenuation resulting from puff volume and filter ventilation. For example, analyte level differences using the ISO protocol are on average three times lower for the Carlton 100s than the True Silver. This difference can be mostly attributed to the higher attenuation from filter ventilation between the two cigarettes, which differs by a factor of 1.9 (1-0.666 for True Silver/1-0.823for Carlton 100s) and reduces to a factor of 1.7 upon taking into account the number of puffs (8.3 for True Silver vs. 9.2 for Carlton 100s). Other noteworthy design differences between these two highly ventilated cigarettes include the amount of the tobacco (collinear with puff number), rod length, and filter. The average tobacco weight (645.5 mg for the True Silver and 584.7 mg for the Carlton 100s) and median puff number for the True Silver were both 1.1 times that for the Carlton 100s. Also, the True Silver king cigarettes have an 83 mm rod and 15 mm long filter (designed with a 10 mm plastic filter recess placing the vent holes 13 mm from the tobacco rod) compared to the Carlton 100s that have a 97 mm rod and 30 mm long filter with vent holes 18 mm from the tobacco rod. The design of the Carlton 100s likely maintains a higher flow rate through the vent holes compared to the True Silver because the cigarette rod shortens during smoking, effectively reducing the quantity of VOCs drawn into the collection bag.

This data show that smoking machine protocol and filter ventilation are principle parameters that influence VOC yield among the 50 cigarette brand varieties. Although VOC levels between the two protocols are lower in more highly ventilated cigarettes, relative VOC levels between the two protocols increase gradually for most analytes up to a filter ventilation of 50%, at which point VOCs increase steeply as filter ventilation approached 80%. This trend is most pronounced for the monoaromatic compounds, particularly styrene. Large amount variations of toxic VOCs, such as styrene, among highly ventilated cigarettes underscore the importance of different protocols to bracket the broad range of mainstream smoke levels.

Although vapor phase VOC amounts vary among cigarette brand varieties, VOCs are moderately to very highly correlated between analytes with r ranging from 0.65 to 0.99 using the ISO protocol. These moderate to high correlation coefficients are likely driven by similarity in pyrolysis pathways of the various VOCs regardless of smoking protocol or attenuation by filter ventilation. VOCs yielding r of 0.99 are o-xylene vs. ethylbenzene (Fig. 3), o-xylene vs. m/p-xylene (Fig. 3), 2-pentanone vs.3-pentenone (Fig. 2), and 2-pentenone vs.2-butanone (Fig. 2). Using the CI protocol, which removes the influence of filter ventilation, VOCs are slightly to very highly correlated with r ranging from 0.36 to 0.95. The weakest correlations for both protocols include 1,3-butadiene (r ranging from 0.73–0.87 for ISO and 0.36–0.54 for CI), and vinyl chloride (r ranging from 0.68–0.79 for ISO and 0.46–0.59 for CI). The lower degree of linearity for 1,3-butadiene and vinyl chloride can be attributed to their high reactivity. In addition, vinyl chloride (shown to be associated with the inorganic chloride content of the tobacco)[23] is near the limit of quantitation (LOQ) of 0.005 µg/cigarette, where under the ISO protocol, median level is 0.027 µg/cigarette.

Between analyte pairs, most linear trends are conserved for the combined ISO and CI protocol scatter plots (Figs. 1–3). Independent regression slopes of the trends between analytes under both smoking protocols (not shown) are within 25% of each other for more than 14 of the 21 analytes. Those analytes that trend the least closely between protocols involve combinations of the monoaromatic compounds with other compound groups as shown in Supplemental Fig. 1. Similar trend behavior among smoking protocols (ISO, Massachusetts Department of Public Health, and CI) was noted by Counts et al. in their study of tar and VOC levels.[22]

The scatter plots (Figs.1–3) for nitromethane reveal the difference between the Natural American Spirit cigarettes and the rest of the brands in this study. The Natural American Spirit cigarettes, represented with circles on the scatter plots, have lower nitromethane levels (Fig. 1), yet tended to have among the highest levels of the other VOCs for both protocols. We attribute these relatively higher VOC levels to differences in tobacco blend. The Natural American Spirit cigarettes consist of a higher proportion of flue-cured (bright leaf) tobacco (approx.90%) and lower percentage of air-cured (burley) tobacco (< 10%). In comparison the 3R4F research cigarette contains approximately 35% flue-cured tobacco and 22% burley tobacco.[24] Flue-cured tobacco has a lower amount of nitrate (typically below 1%) than air-cured (from 1.1–5.0%).[25,26] A consequence of higher tobacco nitrate amount is increased production of nitromethane.[26,27] Thus, the relatively lower nitromethane levels measured in the mainstream smoke of the Natural American Spirit cigarettes are consistent with its lower tobacco nitrate content compared to other commercial blended tobacco cigarettes. Furthermore, it has been reported that monoaromatic VOC levels are higher in mainstream smoke produced from flue-cured tobacco than from burley tobacco, presumably because of higher nitrate levels that improve combustion in the burley tobacco and because of competitive reactions of pyrolytic radicals with nitrate that inhibit the formation of aromatic hydrocarbons.[27,28] Monoaromatic VOCs in the mainstream smoke of Natural American Spirit cigarettes were among the highest of all brand varieties for both protocols.

As depicted in Supplemental Fig. 1, the monoaromatic VOCs, especially styrene, 3-ethyltoluene, xylenes, and ethylbenzene, were present at proportionally higher amounts than the other compound classes under the CI smoking protocol. Proportionally higher levels for these monoaromatic VOCs were also noted above for the more ventilated cigarettes, especially for styrene, which is found to be 74 times higher under the CI smoking protocol. These results further show that the relative production of certain VOCs, especially the monoaromatic compounds can be influenced by parameters that are defined by smoking topography (e.g., blocking of vent holes, puff volume, and puff duration).

CONCLUSION

This work characterizes 21 harmful VOCs (13 listed as HPHCs by the FDA) in mainstream cigarette smoke from 50 U.S. domestic cigarette brand varieties and two research cigarettes through the use of a high throughput multianalyte analysis approach. Although machine and human smoking are quite different, this study design also employed two smoking protocols so as to capture the range of constituent levels that a smoker might inhale.

Furthermore, this work reveals the interrelations of VOC levels with respect to both smoking conditions and select cigarette design parameters. Amounts per cigarette for most VOCs were moderately to strongly correlated and correlations were highly influenced by cigarette design parameters that affect total puff volume and by cigarette filter ventilation where VOC levels increase with total puff volume and decrease filter ventilation. We observed that the increase in monoaromatic compounds under CI smoking parameters were not as proportionate with the decreased filter ventilation as the unsaturated, nitro, and carbonyl compounds. As a result, the monoaromatic signatures between the two smoking protocols are distinctly different, independent of cigarette brand variety. We believe this difference permits comparison of relative smoking machine amounts with those pharmacokinetically delivered that can be quantified through biomonitoring, which will improve exposure assessment. This comparison of different brand varieties smoked under different protocols demonstrates the importance of cigarette design factors and smoking topography (e.g., vent blocking) on VOC yields in mainstream tobacco smoke.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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IMPLICATIONS

This is the most comprehensive assessment of volatile organic compounds (VOCs) in cigarette smoke to date, encompassing 21 toxic VOCs, 50 different cigarette brand varieties, and two different machine smoking protocols (ISO and Canadian Intense). For most analytes relative proportions remain consistent among U.S. cigarette brand varieties regardless of smoking protocol, however the Canadian Intense smoking protocol did cause up to a factor of 6 increase in the proportion of monoaromatic compounds. This study serves as a basis to assess VOC exposure as cigarette smoke is a principle source of overall population-level VOC exposure in the United States.

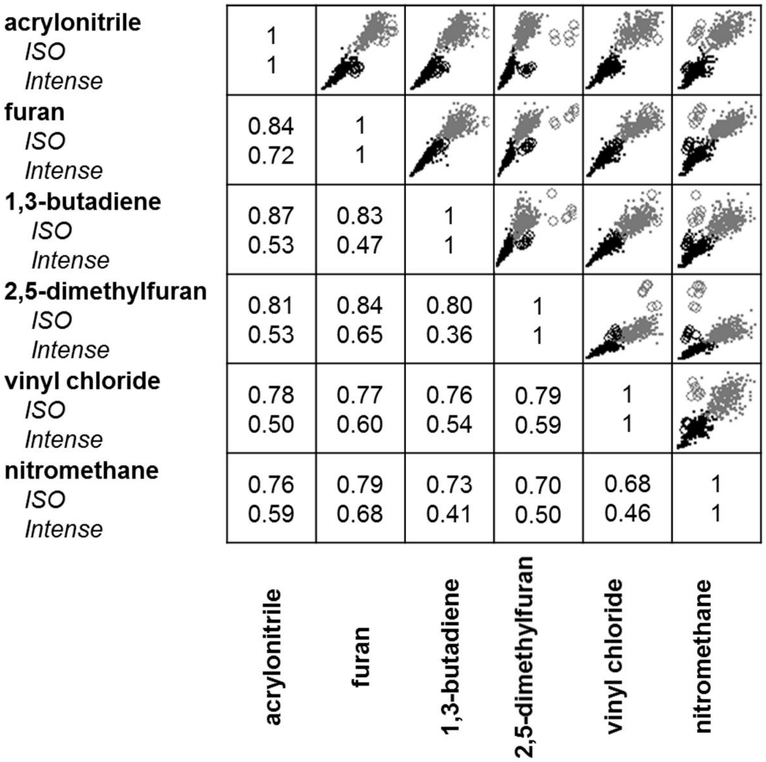

Figure 1.

Pearson correlation and scatter plots of mainstream smoke VOC levels for unsaturated and nitro compounds collected using the ISO (black) and Canadian Intense (grey) protocols. Pearson results encompass 49 brand varieties with the Natural American Spirit cigarettes excluded. Natural American Spirit cigarettes are included in the scatter plots represented with the open circles

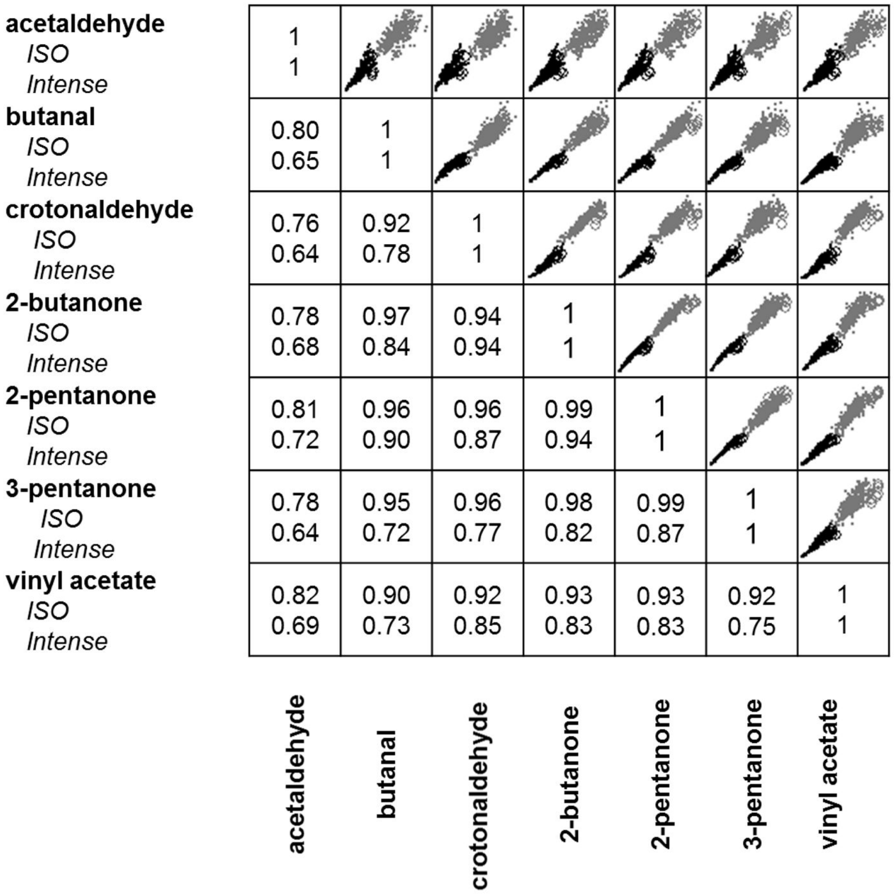

Figure 2.

Pearson correlation and scatter plots of smoke VOC levels for carbonyl compounds collected using the ISO (black) and Canadian Intense (grey) smoking protocols. Pearson results encompass 49 brand varieties with the Natural American Spirit cigarettes excluded. Natural American Spirit cigarettes are included in the scatter plots represented with the open circles

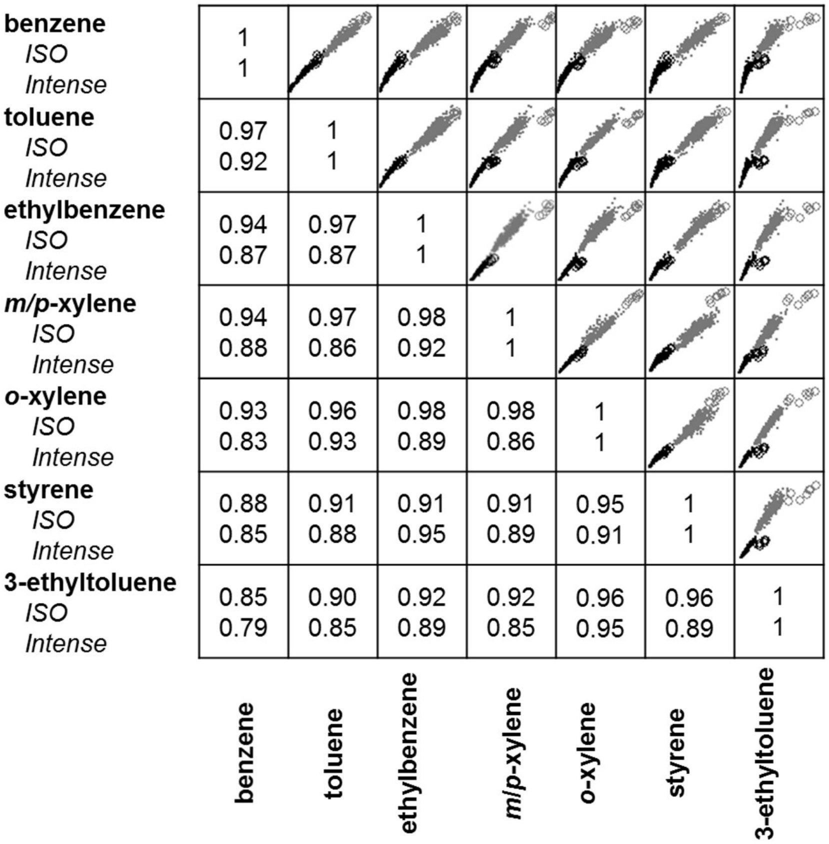

Figure 3.

Pearson correlation and scatter plots of smoke VOC levels for the monoaromatic compounds collected using the ISO (black) and Canadian Intense (grey) smoking protocols. Pearson results encompass 49 brand varieties with the Natural American Spirit cigarettes excluded. Natural American Spirit cigarettes are included in the scatter plots represented with the open circles

Table I

Comparison of protocol ratio (Canadian Intense/ISO protocol ratio) of median VOC levels among different cigarettes. Summary statistics of these ratios are compared with calculated ratios expected based on differences in the smoking protocols that have been adjusted for dilution by filter ventilation

	Newport green king box menthol	**Newport green king soft menthol**	**Marlboro red king box**	**Marlboro red 100s box**	**Salem green king box menthol**	**Marlboro red 100s soft**	**Marlboro red king soft**	**Marlboro green king box menthol**	**Winston red king box**	**USA gold 100s soft**	**Winston red 100s box**	**Kool green king box menthol**	**3R4F**	**Marlboro gold 100s box**	**Kent golden king soft**	**Salem silver 100s box menthol**	**True silver king soft**	**1R5F**	**Carlton 100s box**
Nitro and Unsaturated																			
nitromethane	1.6	1.6	2.4	2.5	2.0	2.5	2.6	3.4	2.3	2.1	3.0	2.7	3.1	2.8	2.3	5.2	5.3	9.1	17.3
1,3-butadiene	2.0	2.0	1.9	2.5	1.9	2.2	2.3	2.3	1.9	2.7	2.0	2.3	2.6	2.2	2.4	2.9	4.7	7.1	12.4
furan	1.9	1.7	1.9	2.4	2.0	2.0	2.1	2.0	1.8	2.5	2.3	2.4	2.5	2.1	2.6	3.3	5.0	6.2	11.5
2,5-dimethylfuran	2.3	2.2	2.2	2.5	2.0	2.6	2.7	2.5	2.1	2.6	2.3	2.3	2.8	2.7	3.0	3.3	5.2	6.4	13.3
vinyl chloride	2.2	1.9	2.3	2.2	2.1	2.4	2.4	2.6	1.9	2.6	2.6	2.5	2.7	2.5	2.6	4.2	6.4	7.1	15.5
acrylonitrile	2.8	2.6	2.4	2.7	2.4	2.8	2.9	3.0	2.5	2.9	2.5	2.7	3.8	2.9	3.5	5.1	9.0	15.3	32.4
Carbonyl																			
vinyl acetate	2.2	2.2	2.3	2.3	2.2	2.6	2.4	2.5	2.1	2.6	2.3	2.4	2.7	2.6	2.3	3.5	5.4	6.9	13.6
acetaldhyde	1.9	1.7	2.0	2.0	2.6	2.2	2.2	3.0	2.3	3.0	3.0	2.8	2.8	2.9	2.8	3.4	6.0	6.8	14.2
butanal	2.3	2.3	2.6	2.7	2.5	3.0	2.9	2.7	2.6	2.7	2.5	3.0	3.2	2.4	2.9	3.6	5.5	9.6	14.6
2-butanone	2.1	2.2	2.5	2.4	2.3	2.9	3.0	2.6	2.4	2.9	2.5	2.8	3.1	2.6	3.1	3.4	6.3	8.9	15.5
methylvinylketone	2.5	2.5	2.6	2.8	3.0	3.3	3.0	3.3	2.8	2.9	3.2	3.1	3.5	4.1	2.9	3.6	6.9	11.3	18.6
2-pentanone	2.5	2.3	2.6	2.7	2.4	2.9	3.1	2.9	2.4	3.0	2.5	2.9	3.5	3.0	3.3	4.2	7.6	11.8	22.5
3-pentanone	2.4	2.4	2.7	2.6	2.1	3.3	3.2	2.7	2.4	2.7	2.3	2.8	3.6	3.3	3.4	5.0	9.4	12.1	28.7
crotonaldehyde	2.3	2.5	2.8	2.9	2.8	3.4	3.1	3.0	2.9	3.6	3.0	3.5	4.6	3.7	4.0	7.5	11.3	19.5	41.8
Monoaromatic																			
benzene	2.1	2.0	2.1	2.6	2.3	2.4	2.3	2.3	2.1	2.6	2.4	2.6	2.8	2.6	2.5	3.4	5.4	6.9	14.6
toluene	2.6	2.5	2.6	3.2	2.5	2.8	3.0	2.9	2.4	3.1	2.7	2.9	3.6	3.1	3.3	3.5	7.3	11.9	20.6
m/p-xylene	3.0	3.1	3.5	3.9	3.1	4.1	4.1	3.5	2.7	4.1	3.4	3.9	5.0	4.1	4.2	5.1	11.7	14.1	27.2
o-xylene	3.6	3.5	3.7	4.7	3.3	4.3	4.5	4.1	3.3	4.7	3.9	4.4	5.6	5.1	5.4	5.1	11.2	16.2	29.9
ethylbenzene	3.2	3.2	3.4	3.9	3.4	3.9	3.8	3.9	3.3	4.4	3.6	4.2	5.2	4.3	4.6	5.5	13.7	17.9	35.5
3-ethyltoluene	4.1	3.9	3.8	5.8	3.3	4.8	4.7	4.5	2.6	5.3	4.1	4.9	6.9	6.1	6.0	6.8	13.9	20.7	51.4
styrene	4.4	4.2	4.1	5.2	3.5	5.1	4.9	5.0	3.7	5.3	4.2	4.9	7.6	6.4	6.3	9.6	20.8	26.0	76.2

	Newport green king box menthol	Newport green king soft menthol	Marlboro red king box	Marlboro red 100s box	Salem green king box menthol	Marlboro red 100s soft	Marlboro red king soft	Marlboro green king box menthol	Winston red king box	USA gold 100s soft	Winston red 100s box	Kool green king box menthol	3R4F	Marlboro gold 100s box	Kent golden king soft	Salem silver 100s box menthol	True silver king soft	1R5F	Carlton 100s box
Median	2.4	2.3	2.6	2.7	2.4	2.9	3.0	2.9	2.4	2.9	2.6	2.9	3.5	2.9	3.0	4.2	6.9	10.8	18.6
Minimum	1.9	1.7	1.9	2.0	1.9	2.0	2.1	2.0	1.8	2.5	2.0	2.3	2.5	2.1	2.3	2.9	4.7	6.2	11.5
Maximum	4.4	4.2	4.1	5.8	3.5	5.1	4.9	5.0	3.7	5.3	4.2	4.9	7.6	6.4	6.3	9.6	20.8	26.0	76.2
CI/ISO ratio of total volumes that have been adjusted for dilution by filter ventilation	2.1	2.0	2.2	2.2	1.9	2.5	2.3	2.4	2.1	2.3	2.2	2.2	2.8	2.5	3.1	3.3	5.4	6.9	13.6
% tip ventilation	0.1	0.1	8.9	12.8	13.1	14.0	14.6	15.2	17.2	18.9	19.1	20.0	29.0	30.1	41.3	50.1	66.6	69.0	82.3

Table II

Summary of range of Pearson correlation results, *r*, between analytes for the 50 brand varieties. Minimum and maximum coefficients are for the dependent analyte paired with all the other analytes. For example, the maximum *r* of 0.99 for 2-pentanone using ISO occurs when paired with 3-pentenone (Figure 2) and the minimum *r* of 0.77 occurs with vinyl chloride (data not shown).

Dependent Variable	ISO			Canadian Intense		
	Minimum *r*	**Maximum *r***	**Range**	**Minimum *r***	**Maximum *r***	**Range**
2-pentanone	0.77	0.99	0.22	0.49	0.94	0.44
3-pentanone	0.76	0.99	0.22	0.39	0.87	0.48
ethylbenzene	0.73	0.99	0.26	0.55	0.94	0.39
2-butanone	0.77	0.99	0.22	0.55	0.94	0.39
o-Xylene	0.71	0.99	0.27	0.51	0.96	0.45
m/*p*-xylene	0.65	0.99	0.33	0.46	0.92	0.45
3-ethyltoluene	0.71	0.98	0.27	0.53	0.96	0.43
butanal	0.73	0.97	0.23	0.35	0.90	0.55
benzene	0.72	0.97	0.26	0.53	0.92	0.39
Toluene	0.75	0.97	0.23	0.48	0.93	0.46
crotonaldehyde	0.76	0.96	0.20	0.56	0.94	0.38
styrene	0.74	0.96	0.23	0.40	0.94	0.53
acrylonitrile	0.76	0.94	0.18	0.50	0.85	0.35
vinyl acetate	0.78	0.94	0.17	0.53	0.85	0.32
furan	0.66	0.92	0.26	0.47	0.87	0.41
1,3-butadiene	0.72	0.89	0.18	0.36	0.58	0.23
2,5-dimethyl furan	0.68	0.88	0.20	0.36	0.72	0.36
methyl vinyl ketone	0.59	0.85	0.25	0.35	0.76	0.41
vinyl chloride	0.68	0.83	0.16	0.37	0.67	0.30
acetaldehyde	0.59	0.82	0.23	0.37	0.73	0.36
nitromethane	0.59	0.81	0.22	0.37	0.73	0.36