HHS Public Access

Author manuscript

Tob Regul Sci. Author manuscript; available in PMC 2018 December 01.

Published in final edited form as:

Tob Regul Sci. 2017 December 1; 3(1): 81–94.

Chemical Characterization of Mainstream Smoke from SPECTRUM Variable Nicotine Research Cigarettes

Yan S. Ding, PhD,
Team Lead, Tobacco and Volatiles Branch, US Centers for Disease Control and Prevention, Atlanta, GA

Patricia Richter, PhD,
Deputy Branch Chief, Tobacco and Volatiles Branch, US Centers for Disease Control and Prevention, Atlanta, GA

Bryan Hearn, PhD,
Chemist, Tobacco and Volatiles Branch, US Centers for Disease Control and Prevention, Atlanta, GA

Liqin Zhang, MS,
Chemist, Tobacco and Volatiles Branch, US Centers for Disease Control and Prevention, Atlanta, GA

Roberto Bravo, PhD,
Team Lead, Tobacco and Volatiles Branch, US Centers for Disease Control and Prevention, Atlanta, GA

Xizheng Yan, BS,
Chemist, Tobacco and Volatiles Branch, US Centers for Disease Control and Prevention, Atlanta, GA

Jose J. Perez, BS,
Chemist, Tobacco and Volatiles Branch, US Centers for Disease Control and Prevention, Atlanta, GA

Michele Chan, BS,
Chemist, Oak Ridge Institute for Science and Education, Oak Ridge, TN

Jared Hughes, BS,
Chemist, Oak Ridge Institute for Science and Education, Oak Ridge, TN

Patrick Chen, BS,
Chemist, Oak Ridge Institute for Science and Education, Oak Ridge, TN

Wayne Chen, BS,
Chemist, Oak Ridge Institute for Science and Education, Oak Ridge, TN

Correspondence Dr Ding; yding@cdc.gov.

Conflict of Interest Disclosure Statement

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. The authors declare no conflict of interest.

Joshua Wong, BS,
Chemist, Oak Ridge Institute for Science and Education, Oak Ridge, TN

Sydney Holmberg, BS,
Chemist, Oak Ridge Institute for Science and Education, Oak Ridge, TN

Shakia Smith, BS,
Chemist, Oak Ridge Institute for Science and Education, Oak Ridge, TN

Morgan Larango, BS,
Chemist, Oak Ridge Institute for Science and Education, Oak Ridge, TN

Liza Valentín-Blasini, PhD, and
Lab Chief, Tobacco and Volatiles Branch, US Centers for Disease Control and Prevention, Atlanta, GA

Clifford H. Watson, PhD
Lab Director, Tobacco and Volatiles Branch, US Centers for Disease Control and Prevention, Atlanta, GA

Abstract

Objective—Our objective was to characterize mainstream smoke constituent deliveries from SPECTRUM variable nicotine research cigarettes under 2 machine smoking regimens. SPECTRUM cigarettes are manufactured by the 22nd Century company for the National Institute on Drug Abuse, National Institutes of Health to contain varying (including reduced) levels of nicotine.

Methods—Mainstream smoke constituent deliveries of “tar,” nicotine, carbon monoxide, tobacco-specific nitrosamines (N’-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)), benzo[a]pyrene, aromatic amines, and carbonyls were analyzed in 23 varieties of SPECTRUM cigarettes using ISO 17025 accredited methods.

Results—Data are presented as means and standard deviations of 5 replicates for all analytes.

Conclusions—Under the ISO smoking regimen, mean levels of many smoke emissions for SPECTRUM varieties were comparable to the 3R4F research cigarette. Calculated SPECTRUM elasticity ranged from 1.6 to 4.0. Accordingly, under intense machine smoking conditions differences in emissions of SPECTRUM cigarettes were apparent. In addition, NNN increased with smoke nicotine while the same rate of change was not seen for NNK. It is important to monitor levels of chemicals of public health concern and regulatory interest as technologies emerge to reduce levels of nicotine or other targeted chemicals in tobacco products.

Keywords

cigarette mainstream smoke; nicotine; tar; TSNA; BaP; aromatic amines; carbonyls

Tobacco use remains the single largest preventable cause of death and disease in the United States[1] (US) and nicotine is one of the major constituents in tobacco that causes addiction.[2] In addition to nicotine, a smoker is exposed to thousands of chemicals with each cigarette smoked.[3] Despite progress in reducing the prevalence of smoking among adults in the US,[4]

cigarette smoking still results in approximately 480,000 premature deaths and more than $300 billion in direct healthcare expenditures and productivity losses each year.[1] Reduced nicotine cigarettes have been proposed as a method to change smoking behavior and may aid the smoker's interest in quitting.[2,5–6]

The 22nd Century SPECTRUM cigarettes were manufactured under subcontract to the National Institute on Drug Abuse with reduced-nicotine filler achieved through genetic engineering and plant breeding.[7–8] Other available experimental cigarettes (Kentucky Research Cigarettes, CORESTA Monitor) are for analytical chemistry research and are labeled as "not for human consumption."[9–10] These cigarettes are used to monitor the accuracy and stability of emissions generated using machine smoking. 3R4F also functions as a well-characterized comparator as it contains a tobacco blend that is representative of many domestic cigarettes sold in the US.[9–10] In contrast, the SPECTRUM research cigarettes were developed for research studies that require people to smoke cigarettes that deliver varying doses of nicotine.[11] Studies show that smokers can modify their smoking behavior when smoking cigarettes that reduce smoke nicotine through filter ventilation; however, this compensatory behavior does not occur with cigarettes made with extremely reduced nicotine content (0.05 mg) in the filler, so exposure to smoke toxicants does not increase.[6,12–13]

The physical properties, nicotine content, and levels of chemicals in SPECTRUM tobacco filler have recently been reported.[14–15] Hatsukami et al[11] reported on the acceptability and dose-response pharmacological effects of SPECTRUM cigarettes used by adult smokers. In addition, in several published studies, SPECTRUM cigarettes have been used to investigate the role of nicotine toxicity in blood brain barrier endothelial cells[16–17] and to study nicotine dose assignment in a clinical study of depression.[18] As use of SPECTRUM cigarettes as a research tool grows, additional information on the physical and chemical properties of the cigarettes will inform researchers and encourage research in areas such as interactions among nicotine and other smoke constituents, smoking behavior, compensation, and exposure to harmful and potentially harmful constituents in tobacco smoke. Whereas tar and nicotine levels are provided by the manufacturer for SPECTRUM cigarettes, levels of other important constituents have not been previously available. The previous study[14] and the findings reported herein provide researchers with comprehensive characterization of the physical properties and the chemical composition of the tobacco filler and mainstream tobacco smoke to aid in the design and interpretation of clinical studies or studies of adult smokers using reduced nicotine cigarettes.

In this study we contribute to the characterization of SPECTRUM research cigarettes by examining mainstream smoke deliveries of select constituents (tar, nicotine, carbon monoxide, tobacco-specific nitrosamines, benzo[a]pyrene, aromatic amines, and carbonyls), on the US Food and Drug Administration (FDA) list of harmful or potentially harmful chemicals. Information on mainstream smoke deliveries from SPECTRUM cigarettes, as well as confirmation of nicotine availability in mainstream smoke, will provide evidence for studies of smoking behavior and addiction. These findings and research based on these findings also could aid policymakers and regulatory agencies when considering the impact

of reduced nicotine cigarettes on the complex relationships among nicotine levels, addiction, smoking behavior, and potential exposures.

METHODS

SPECTRUM Cigarette Samples

Twenty-three varieties of SPECTRUM research cigarettes (Table 1) were obtained from the National Institute on Drug Abuse (NIDA, Bethesda, MD, USA) in 2014 and stored in their original packaging at −70°C upon receipt. Results are reported on an “as received” basis unless otherwise noted.

Quantitative Analytical Measurements

All quantitative methods were performed under a strict quality assurance/quality control (QA/QC) protocol. Each analytical method below has been fully validated and has sufficient dynamic range for all samples. All reported data fell between the lowest and highest calibration curve points for their respective analytical method. Any measured value lower than the lowest calibration point was reported as a non-detect. All run QCs were checked using a modified Westgard protocol.[19] Any data failing QC were excluded and the measurements were repeated.

Machine-smoke Regimens

Cigarettes were placed in a plastic bin and conditioned at 22 °C and 60% relative humidity for at least 48 hours prior to machine smoking according to ISO 3402.[20] Cambridge filter pads (CFPs) were also conditioned unless stated otherwise (eg, carbonyl analysis). Cigarettes were smoked under 2 different regimens, the International Organization for Standardization (ISO) method[21] (35 mL puff volume, 60 sec puff interval, 2 sec puff duration, and filter-tip vents open) and the Canada Intense (CI) method[22] (55 mL puff volume, 30 sec puff interval, 2 sec puff duration, and filter tip vents 100% blocked). Cigarettes were smoked to the marked length of the filter overwrap (tipping) plus 3 mm. Two types of 20-port linear machines were used (Cerulean SM450, Milton Keynes, UK and Borgwaldt LX-20, Richmond, VA, USA). Each variety was tested with 5 replicate measures per smoking regimen. Sample replicates were smoked on the same smoking machine if possible.

Tar, Nicotine, and Carbon Monoxide (TNCO)

The standard procedures previously described[23] for ISO and CI TNCO determinations were used with a few modifications. Briefly, the gas and particulate phases of the mainstream cigarette smoke from 5 (ISO) or 3 (CI) cigarettes per sample replicate were collected in vapor phase collection bags and on CFPs, respectively. The percentage by volume of CO (% CO) was determined from the vapor phase collection bags using a non-dispersive infrared (IR) analyzer. The total particulate matter (TPM) was determined gravimetrically by calculating the weight difference of the CFP before and after smoking divided by the number of cigarettes smoked per pad. The TPM was then extracted with 20 mL of extraction solution (isopropyl alcohol containing approximately 0.1 mg/mL anethole and 1 mg/mL methanol internal standards) by gently shaking at 160 rpm for 30 min. A blank, conditioned

CFP was extracted concurrently with smoke samples for background water subtraction. The extract was then analyzed for nicotine and water by gas chromatography-flame ionization detection (GC-FID) and GC-thermal conductivity detection (GC-TCD), respectively. Calibration curves were constructed with 10 different analyte concentrations – ranging from 0.004 to 1.0 mg/mL for nicotine and 0 to 5.0 mg/mL for water – plotted against the area ratios of analyte-to-internal standard. The determined water content of the blank CFP was then subtracted from all sample water concentrations. The reported "tar" content was derived by subtraction of the determined water and nicotine contents from the TPM content.

Tobacco-specific Nitrosamines (TSNAs)

The smoke sample preparation was based on a published method[24] with one minor modification (no ascorbic acid pretreatment needed for CFPs prior to smoking). One cigarette sample was smoked per CFP (both ISO and CI regimens). Mainstream smoke TPM was collected on CFPs. After smoking, each CFP was spiked with isotopically-labeled TSNA solutions followed by solvent extraction using ammonium acetate solution. An aliquot was injected into an Agilent Technologies (Wilmington, DE, USA) high-performance liquid chromatograph coupled with an API 5500 triple quadrupole mass tandem spectrometer (HPLC-MS/MS) (Applied Biosystems, Foster City, California) to analyze TSNAs (NNN (N-nitrosonornicotine), and NNK (4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone)). The HPLC column selection and mass spectrometry (MS) parameters were previously described.[25]

Benzo[a]pyrene (BaP)

Benzo[a]pyrene (BaP) analysis was based on a previously published method for the detection of polycyclic aromatic hydrocarbons (PAHs) in mainstream smoke.[26] Three cigarettes were smoked per CFP for the ISO regimen and one cigarette was smoked per CFP for the CI regimen. Mainstream cigarette smoke TPM was collected on CFPs. The PAHs were extracted from TPM captured on the CFP along with an internal standard spiked on the CFP. After purification by solid-phase extraction, BaP was analyzed by gas chromatography coupled with mass spectrometry (GC/MS) (Agilent Technologies, Wilmington, DE, USA).

Aromatic Amines

Three cigarettes were smoked per CFP for the ISO regimen and one cigarette was smoked per CFP for the CI regimen. Mainstream cigarette smoke TPM was collected on CFPs. After smoking, CFPs were placed into 15 mL vials, spiked with deuterium-labeled internal standards, and extracted with toluene by shaking for 30 minutes at 160 rpm on an orbital shaker. A 200 μL portion was aliquoted into a 2 mL gas chromatography vial with a 300 μL insert and derivatized with heptafluorobutyric anhydride. Aromatic amines were analyzed by gas chromatography coupled with tandem mass spectrometry (GC-MS/MS) (Agilent Technologies, Wilmington, DE, USA) operating under the negative chemical ionization mode using multiple reaction monitoring. Quantitation was done in the instrument's standard software (Mass Hunter, Agilent Technologies, Wilmington, DE, USA) by isotopic dilution mass spectrometry, dividing the analyte peak area by the internal standard peak area, both for the calibration curves and the samples. Ten aromatic amines, o-, m-, and p-

toluidine, 2,6-dimethylanaline, o-anisidine, 1- and 2-aminonaphthalene, and 2-, 3-, and 4-aminobiphenyl are reported here.

Carbonyls

Carbonyls analysis was based on a published method on the derivatization and quantification of 7 carbonyls in cigarette mainstream smoke.[27] One cigarette was smoked per CFP (for both ISO and CI regimens). Prior to smoking, CFPs were pretreated with the derivatization agent 2,4-dinitrophenylhydrazine (DNPH). Mainstream carbonyls generated under either the ISO or CI regimen were derivatized and collected on the DNPH-pretreated CFPs. After smoking, internal standard solution was spiked onto each CFP and the CFP was extracted with acetonitrile containing 2% pyridine. The extract was diluted with 50% ammonium acetate and acetonitrile solution and an aliquot was injected into an ultra-high pressure liquid chromatography coupled with a triple quadruple tandem mass spectrometer (UPLC-MS/MS) (Agilent Technologies, Wilmington, DE, USA, and Applied Biosystems, Foster City, CA, USA). Seven carbonyls, formaldehyde, acetaldehyde, acrolein, acetone, propionaldehyde, crotonaldehyde, and methyl ethyl ketone are reported here.

RESULTS

Tar, Nicotine, and Carbon Monoxide (TNCO)

Table 2 lists mainstream smoke deliveries of “tar,” nicotine, and CO from 23 varieties of SPECTRUM cigarettes. The manufacturer determined target “tar” and nicotine values (ISO smoking regimen only) provided by the National Institute on Drug Abuse are included with the analytical test results (Table 1). The measured “tar” and nicotine deliveries showed consistent agreement with the NIDA-specified yields (Table 1) for all varieties tested under ISO smoking regimen. Under the CI smoking regimen, there was a 2.2 to 7.6 fold increase in “tar,” a 1.6 to 3.9 fold increase in nicotine, and a 1.9 to 6.7 fold increase in CO levels relative to levels in mainstream smoke generated with the ISO smoking regimen. When machine smoked under intense conditions the “tar” levels among the 23 SPECTRUM varieties increased overall but the range of values decreased approximately 3-fold (tar: 21.7 ± 2.3 mg/cig to 38.5 ± 3.8 mg/cig for CI) compared to ISO smoking conditions (tar: 3.2 ± 0.2 mg/cig to 15.9 ± 0.7 mg/cig for ISO). Similarly, the range of CO under intense conditions had a 1.3 fold range (27.1 ± 4.0 mg/cig to 35.3 ± 4.3 mg/cig for CI) versus a 3.3 fold range (4.9 ± 0.2 mg/cig to 16.1 ± 0.9 mg/cig for ISO) under ISO conditions. In contrast, the range of nicotine levels was large across both CI (0.04 ± 0.00 mg/cig to 3.3 ± 0.18 mg/cig) and ISO (0.01 ± 0.00 mg/cig to 1.68 ± 0.1 mg/cig) smoking machine conditions. Under CI smoking conditions, 12 of the 23 SPECTRUM varieties delivered mean nicotine levels of less than 0.5 mg per cigarette; 6 of which delivered less than 0.1 mg nicotine per cigarette. NRC600, NRC601, and NRC602 yielded CI nicotine deliveries at or near 3R4F nicotine deliveries; whereas average mainstream smoke nicotine deliveries of 2 SPECTRUM cigarettes (NRC700 and NRC701) were greater than the average smoke nicotine deliveries of the 3R4F research cigarette.

Cigarette “elasticity,” defined here as the ratio of nicotine levels generated under CI conditions and nicotine levels generated under ISO conditions was grouped by visual

inspection of cigarettes by percent filter ventilation[14] were: 1.8 (range 1.6 to 2.0) for 8 SPECTRUM varieties with less than 20% filter ventilation (range 14 to 18%); 2.0 (range 1.8 to 2.3) for 13 varieties with filter ventilation between 23 and 32%; and, 4.0 for 2 varieties with filter ventilation above 60%.

Tobacco-specific Nitrosamines (TSNAs)

Table 3 lists mainstream smoke deliveries of NNN and NNK from 23 varieties of SPECTRUM cigarettes. The NNN levels ranged from 26.6 ± 1.2 to 185.4 ± 28.8 ng/cig (ISO) and 115.5 ± 16.0 to 342.9 ± 42.4 ng/cig (CI), respectively. Levels of NNK ranged from 7.9 ± 0.6 to 84.5 ± 5.0 ng/cig (ISO) and 31.9 ± 3.9 to 144 ± 28.7 ng/cig (CI), respectively. Data from research cigarette 3R4F are listed in the same table for comparison. NNK levels from the 3R4F cigarette (96.2 ± 11.4 ng/cig, ISO; 251.8 ± 33.3 ng/cig, CI) were at the upper range of NNK levels measured for the 23 SPECTRUM varieties when cigarettes were machine smoked under ISO conditions but exceeded the range of NNK levels measured for the 23 SPECTRUM varieties under CI conditions. Whereas, NNN levels from 3R4F cigarette (108.9 ± 8.7 ng/cig, ISO; 266.7 ± 27.2 ng/cig, CI) were within the range of NNN levels measured for the 23 SPECTRUM varieties under these smoking regimens. Figure 1 presents mainstream smoke NNN and NNK levels for SPECTRUM cigarettes and the 3R4F cigarette versus mainstream smoke nicotine when generated under ISO or CI conditions.

Benzo[a]pyrene (BaP)

Table 3 also lists mainstream smoke BaP deliveries from 23 varieties of SPECTRUM cigarettes. Under ISO smoking regimen, mean BaP levels range from 2.0 ± 0.2 to 8.7 ± 1.7 ng/cig among the 23 varieties, comparable to that of the 3R4F (6.9 ± 0.8 ng/cig). Under the CI smoking regimen, BaP levels in 3R4F research cigarettes (17.8 ± 2.5 ng/cig) were comparable to the upper range of levels measured in SPECTRUM cigarettes (14.7 ± 1.3 ng/cig).

Aromatic Amines

Table 4 lists mainstream smoke deliveries from 23 varieties of SPECTRUM cigarettes for 10 aromatic amines including 3 sets of isomers (o-, m-, and p-toluidine, 1-, and 2-aminonaphthalene, and 2-, 3-, and 4-aminobiphenyl). Under the ISO smoking regimen, mean levels of all 10 aromatic amines from 23 SPECTRUM varieties were comparable to those from research cigarette 3R4F. However, under the CI smoking regimen mean levels of 2-aminobiphenyl, o-toluidine, m-toluidine, p-toluidine, and 2,6-dimethylaniline for the 3R4F were below the range of mean levels for the SPECTRUM cigarette varieties.

Carbonyls

Table 5 lists mainstream smoke carbonyl deliveries from 23 varieties of SPECTRUM cigarettes. Levels of formaldehyde from 10 SPECTRUM varieties were below ambient air levels (labeled as non-detected) when machine smoked with the ISO smoking regimen. Among the carbonyl compounds at levels above the limits of detection, acrolein had the widest range (7-fold) in mainstream smoke levels from the SPECTRUM cigarettes when

machine smoked under ISO conditions (8.6 ± 1.9 to 62.7 ± 4.6 μg/cig). All carbonyl compounds were above ambient air level when machine smoked under CI conditions and formaldehyde had the widest range (13-fold) (3.4 ± 2.2 to 45.6 ± 12.4 μg/cig). Other carbonyl compounds had a narrower range between minimum and maximum mean levels when measured in SPECTRUM cigarettes machine smoked under CI conditions.

Levels of all carbonyls in the mainstream smoke of the 3R4F research cigarette fell within the range measured across the 23 SPECTRUM varieties under ISO smoking machine regimens. Levels of formaldehyde and acrolein in the mainstream smoke of 3R4F smoked under CI conditions were above the range of SPECTRUM levels.

Discussion

Due to the unique processes used in the manufacture of cigarettes with very low nicotine levels, there can be questions about the impact of the design and features of SPECTRUM cigarettes on levels of smoke constituents other than nicotine. For comparison purposes we provide data for a commonly used reference cigarette, the Kentucky Research cigarette. This research cigarette, although not intended for human consumption, contains a mixture of bright, burley, oriental, and reconstituted tobaccos “typical” of a medium-delivery, American-blended cigarette and is designed to be representative of many domestic cigarettes sold in the US.[9] The data provided in this study for all varieties of SPECTRUM cigarettes and comparisons with a research cigarette representative of medium-delivery blended cigarettes will allow researchers to compare levels of smoke constituents in the mainstream smoke of SPECTRUM cigarettes with commercial cigarettes or other experimental cigarettes.

Good agreement was observed between the provided TNCO characterization data and our laboratory measurements under ISO smoking conditions. Under ISO conditions all but 6 varieties of SPECTRUM cigarettes delivered lower nicotine levels than the 3R4F. Oftentimes, nicotine deliveries increase significantly from ISO to CI smoking conditions. This is because of the more intensive CI smoking regimen, in which, larger puffs are taken at increased frequency with filter ventilation holes blocked to emulate the potential upper smoke delivery a smoker could possibly achieve under more intense patterns of smoking behavior. Under CI smoking conditions there were 12 varieties that delivered mean levels of less than 0.5 mg nicotine/cigarette and 6 of those were below 0.1 mg nicotine/cigarette. Of note, even under the CI smoking conditions, mainstream nicotine levels of all but 2 SPECTRUM cigarettes (NRC700, and NRC701) were below nicotine levels of the 3R4F research cigarette. Studies involving the smoking of SPECTRUM cigarettes by people may benefit from their ability to maintain reduced-nicotine deliveries under typical human smoking behaviors, and to deliver a broad range of mainstream smoke nicotine levels identical to commercially-available cigarette brands.

Reduced nicotine cigarettes, like Spectrum Cigarettes, are currently being used in studies to evaluate the impact of reduced nicotine cigarette on addiction. Change in a smokers’ use behavior, such as by taking larger or more frequent puffs to obtain their desired amount of nicotine from a cigarette, is known as compensation.[13,28] Cigarettes are manufactured to allow smoker compensation through a range of design features including filter ventilation,

paper porosity, and tobacco packing density (Brown & Williamson Bates 575251646/9).[29] Collectively these design features contribute to a cigarette's "elasticity," a term that indicates the amount of smoke a smoker can take out of a cigarette (British American Tobacco. Bates 620825233/41).[30] There are multiple ways to calculate elasticity for a cigarette (eg, Chaiton et al 2005; Brown & Williamson Bates 575251646/9; Phillip Morris 2005 Bates 3039732438–3039732444)[29,31–32] but all incorporate puff volume because smoke emissions from the tobacco rod and filter retention and filter ventilation depend on puff volume (Brown & Williamson 1992 Bates 575251611/43).[33] Our calculated elasticity values demonstrate that there can be a range of elasticities across the 23 SPECTRUM varieties. This has also been shown in industry documents for commercial cigarette brand families (eg, Phillip Morris 2005 Bates 3039732438–3039732444).[32] The limits in how much nicotine can be taken from a cigarette is an important consideration when designing studies that use reduced nicotine cigarettes and when interpreting the use behavior and the toxicant exposures of the study participants. Some longer-term (3- to 6-week) studies[6,12] have shown that smokers do not experience higher exposures to smoke constituents when provided with very low nicotine content cigarettes. It has been suggested that compensatory behavior does not occur with extremely reduced nicotine cigarettes[6,12–13] However, to the extent that smokers are able to compensate, they will be at risk of increased exposure to harmful constituents.

Levels of mainstream smoke constituents from the SPECTRUM cigarettes were similar to or lower than the 3R4F (eg, NNK, formaldehyde, and acrolein under CI conditions) and some were elevated (eg, aromatic amines under CI conditions) relative to the 3R4F. Whether such differences in deliveries of specific constituents would impact the associated health burden of smoking a SPECTRUM cigarette is not known. Visual examination of levels of carcinogenic NNN and NNK versus nicotine under different smoking conditions suggests that whereas NNN generally increases with smoke nicotine, the same rate of change is not seen among the SPECTRUM varieties for NNK (Figure 1). This is possibly due to tobacco blend differences in the 23 varieties of SPECTRUM cigarettes and uncoupling of normal nitrosamine formation pathways as nicotine is a major precursor for NNK while nornicotine is a major precursor for NNN.[34] We have reported previously that nicotine levels in SPECTRUM tobacco ranged from very low to within the range reported for commercial products (0.28 – 25.0 mg/g) whereas other alkaloids, including nornicotine (14.8 – 28.7 μg/g), were not reduced compared to levels reported in commercial products.[14]

Given the chemical complexity of cigarette smoke, typically only select constituents are monitored to see which, if any, chemical changes occur as products are modified to delivery less nicotine. Future work on SPECTRUM cigarettes, or other low nicotine cigarettes, could focus on examining a wider array of chemical constituents or investigate possible toxicological implications of cigarettes modified to deliver reduced levels of nicotine.

IMPLICATIONS FOR TOBACCO REGULATION

Machine-generated cigarette smoke emissions do not provide true estimates of human exposure.[35] However, information on levels of harmful and potentially harmful constituents in the mainstream smoke of all 23 varieties of SPECTRUM cigarettes provides researchers

and regulators with key information on potential exposures to users of reduced nicotine cigarettes. In addition, information on levels of toxicants and carcinogens may assist in the design of studies of the toxicity of SPECTRUM cigarettes, a research tool intended for investigating exposure and behavioral effects of different nicotine levels in cigarettes.

Acknowledgments

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the US Department of Health and Human Services, or the US Centers for Disease Control and Prevention. Use of trade names and commercial sources is for identification only and does not imply endorsement by the US Department of Health and Human Services, or the US Centers for Disease Control and Prevention.

References

1. US Department of Health and Human Services (USDHHS). Surgeon General's Report: The Health Consequences of Smoking—50 Years of Progress. Rockville, MD: USDHHS, Publc Health Service, Office of the Surgeon General; 2014. p. 944
2. US Department of Health and Human Services (USDHHS). A Report of the Surgeon General. Rockville, MD: USDHHS, Public Health Service, US Centers for Disease Control, Office on Smoking and Health; 1988. The Health Consequences of Smoking. Nicotine Addiction; p. 643
3. Rodgman, A., Perfetti, T. The Chemical Components of Tobacco and Tobacco Smoke. 2nd. Boca Raton, FL: CRC Press; 2013. p. 2332
4. Jamal A, Homa D, O'Connor E, et al. Current cigarette smoking among adults – United States, 2005–2014. MMWR Morb Mortal Wkly Rep. 2015; 64(44):1233–1240. [PubMed: 26562061]
5. Walker N, Bullen C, McRobbie H. Reduced-nicotine content cigarettes: is there potential to aid smoking cessation? Nicotine Tob Res. 2009; 11(11):1274–1279. [PubMed: 19793786]
6. Hatsukami DK, Kotlyar M, Hertsgaard LA, et al. Reduced nicotine content cigarettes: effects on toxicant exposure, dependence and cessation. Addiction. 2010; 105(2):343–355. [PubMed: 20078491]
7. 22nd Century Group Inc. SPECTRUM Government Research Cigarettes. Available at: http://www.xxiicentury.com/spectrum/. Accessed September 6, 2016
8. National Institute on Drug Abuse, Nicotine Research Cigarettes Drug Supply Program. Available at: http://www.drugabuse.gov/nicotine-research-cigarette-drug-supply-program. Accessed September 7, 2016
9. University of Kentucky. Center for Tobacco Reference Products. Available at https://ctrp.uky.edu/. Accessed September 7, 2016
10. Cooperation Centre for Scientific Research Relative to Tobacco. CORESTA Monitors. Available at https://www.coresta.org/coresta-monitors. Accessed September 7, 2016
11. Hatsukami DK, Heishman SJ, Vogel RI, et al. Dose–response effects of Spectrum research cigarettes. Nicotine Tob Res. 2013; 15(6):1113–1121. [PubMed: 23178320]
12. Ding YS, Ward J, Hammond D, Watson CH. Mouth-level intake of benzo[a]pyrene from reduced nicotine cigarettes. Int J Environ Res Public Health. 2014; 11(11):11898–11914. [PubMed: 25411724]
13. Benowitz NL, Jacob P, Herrera B. Nicotine intake and dose response when smoking reduced-nicotine content cigarettes. Clin Pharmacol Ther. 2006; 80(6):703–714. [PubMed: 17178270]
14. Richter P, Steven PR, Bravo R, et al. Characterization of SPECTRUM variable nicotine research cigarettes. Tob Regul Sci. 2016; 2(2):94–105. [PubMed: 26779559]
15. Pappas RS, Gray N, Gonzalez-Jimenez N, et al. Triple quad-ICP-MS measurement of toxic metals in mainstream cigarette smoke from Spectrum research cigarettes. J Anal Toxicol. 2016; 40(1):43–48. [PubMed: 26359486]
16. Naik P, Fofaria N, Prasad S, et al. Oxidative and pro-inflammatory impact of regular and denicotinized cigarettes on blood brain barrier endothelial cells: is smoking reduced or nicotine-free products really safe? BMC Neurosci. 2014; 15(1):1–14. [PubMed: 24380503]

17. Naik P, Sajja RK, Prasad S, Cucullo L. Effect of full flavor and denicotinized cigarettes exposure on the brain microvascular endothelium: a microarray-based gene expression study using a human immortalized BBB endothelial cell line. BMC Neurosci. 2015; 16(1):1–14. [PubMed: 25655275]
18. Pacek LR, Vandrey R, Tidey JW, et al. The impact of nicotine dose assignment on affect and depression during extended exposure to experimental Spectrum cigarettes: findings from CENIC Project 1 Study 1. Drug Alcohol Depend. 2015; 156:e168–e169.
19. Caudill SP, Schleicher RL, Pirkle JL. Multi-rule quality control for the age-related eye disease study. Stat Med. 2008; 27(20):4094–4106. [PubMed: 18344178]
20. International Organization for Standardization (ISO) 3402:1999 Tobacco and tobacco products – atmosphere for conditioning and testing. Available at: http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=28324. Accessed September 7, 2016
21. International Organization for Standardization (ISO) 3308: Routine analytical cigarette-smoking machine – definitions and standard conditions. Available at http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=60404. Accessed September 7, 2016
22. World Health Organization. WHO TobLabNet, Standard Operating Procedure for Intense Smoking of Cigarettes. Available at: http://apps.who.int/iris/bitstream/10665/75261/1/9789241503891_eng.pdf. Accessed September 7, 2016
23. Calafat AM, Polzin GM, Saylor J, et al. Determination of tar, nicotine, and carbon monoxide yields in the mainstream smoke of selected international cigarettes. Tob Control. 2004; 13(1):45–51. [PubMed: 14985595]
24. Ding YS, Zhang L, Jain RB, et al. Levels of tobacco-specific nitrosamines and polycyclic aromatic hydrocarbons in mainstream smoke from different tobacco varieties. Cancer Epidemiol Biomarkers Prev. 2008; 17(12):3366–3371. [PubMed: 19064552]
25. Wu W, Ashley DL, Watson CH. Simultaneous determination of five tobacco-specific nitrosamines in mainstream cigarette smoke by isotope dilution liquid chromatography/electrospray ionization tandem mass spectrometry. Anal Chem. 2003; 75(18):4827–4832. [PubMed: 14674460]
26. Ding YS, Yan XJ, Jain RB, et al. Determination of 14 polycyclic aromatic hydrocarbons in mainstream smoke from U.S. brand and non-U.S. brand cigarettes. Environ Sci Technol. 2006; 40(4):1133–1138. [PubMed: 16572766]
27. Ding YS, Yan X, Wong J, et al. In-situ derivatization and quantification of seven carbonyls in cigarette mainstream smoke. Chem Res Toxicol. 2016; 29(1):125–131. [PubMed: 26700249]
28. Hatsukami DK, Le CT, Zhang Y, et al. Toxicant exposure in cigarette reducers versus light smokers. Cancer Epidemiol Biomarkers Prev. 2006; 15(12):2355–2358. [PubMed: 17164356]
29. Brown & Williamson, Elasticity. Truth Tobacco Industry Documents. 1992. p. 575251646-575251649.Available at: https://industrydocuments.library.ucsf.edu/tobacco/docs/#id=lkxk0037Accessed September 7, 2016
30. Brown & Williamson. Smoke Assessment and Properties of Cigarettes and Smoke; Truth Tobacco Industry Documents. 1996. p. 620825233-620825241.Available at https://industrydocuments.library.ucsf.edu/tobacco/docs/#id=ftgv0132Accessed September 7, 2016
31. Chaiton MO, Collinshaw NE, Callard AJ. Smoker preference for “elastic cigarettes” in the Canadian cigarette market. Chronic Dis Can. 2005; 26(1):20–24. [PubMed: 16117842]
32. Philip Morris. Reducing Smoking Elasticity; Truth Tobacco Industry Documents. 2005. p. 3039732438-3039732444.Available at https://industry-documents.library.ucsf.edu/tobacco/docs/#id=rfpv0219Accessed September 7, 2016
33. Brown & Williamson. Elasticity of Cigarettes; Truth Tobacco Industry Documents. 1992. p. 575251611-575251643.Available at https://industry-documents.library.ucsf.edu/tobacco/docs/#id=zpfl0138Accessed September 7, 2016
34. Carmella SG, Mcintee EJ, Chen M, Hecht SS. Enantiomeric composition of N’-nitrosonornicotine and N’-nitrosoanatabine in tobacco. Carcinogenesis. 2000; 21(4):839–843. [PubMed: 10753225]
35. Burns DM, Dybing E, Gray N, et al. Mandated lowering of toxicants in cigarette smoke: a description of the World Health Organization TobReg proposal. Tob Control. 2008; 17(2):132–141. [PubMed: 18375736]

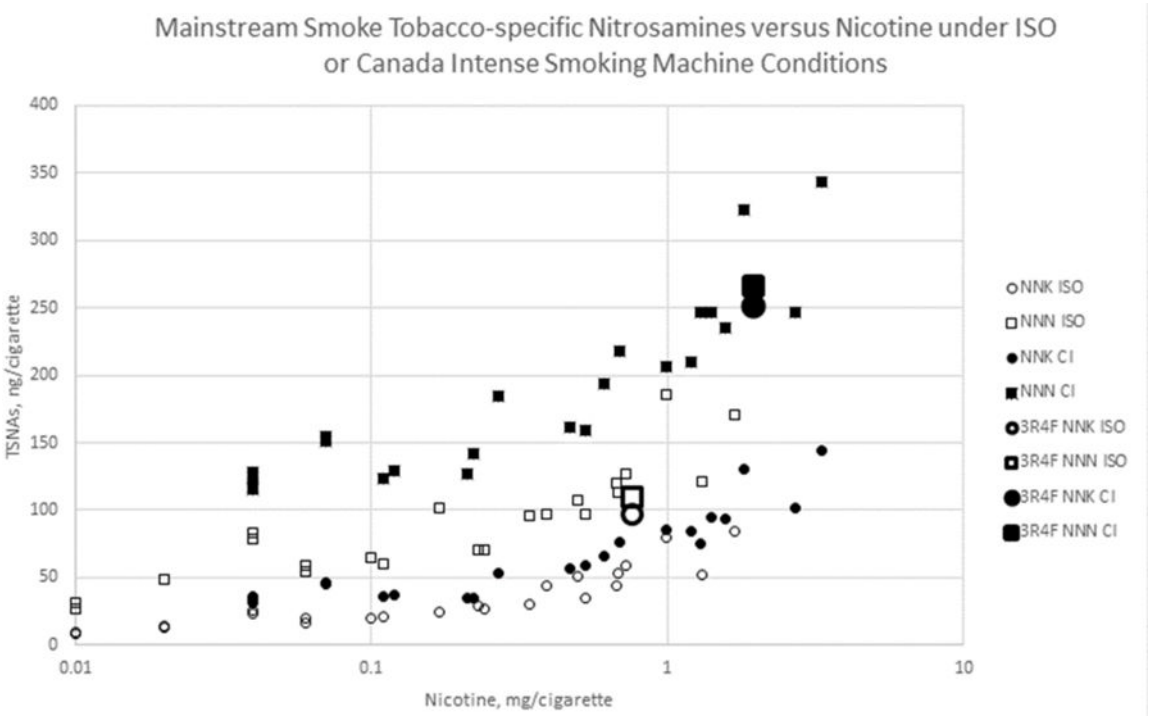

Figure 1.
Relation of Mainstream Smoke TSNA and Nicotine Levels on a Log Scale

Table 1

Description of 23 Varieties of SPECTRUM Cigarettes

Product Code	Type	Specifications (mg/cig)	
		Tar	Nicotine
NRC100	Reduced Nicotine-High Ventilation	3 ± 1.5	0.02 ± 0.01
NRC101	Reduced Nicotine-High Ventilation Menthol	3 ± 1.5	0.02 ± 0.01
NRC102	Reduced Nicotine	9 ± 1.5	0.03 ± 0.01
NRC103	Reduced Nicotine-Menthol	9 ± 1.5	0.03 ± 0.01
NRC104	Reduced Nicotine-High Tar	13 ± 2	0.04 ± 0.02
NRC105	Reduced Nicotine-High Tar-Menthol	13 ± 2	0.04 ± 0.02
NRC200	Reduced Nicotine	9 ± 1.5	0.07 ± 0.02
NRC201	Reduced Nicotine-Menthol	9 ± 1.5	0.07 ± 0.02
NRC300	Reduced Nicotine	9 ± 1.5	0.12 ± 0.03
NRC301	Reduced Nicotine-Menthol	9 ± 1.5	0.12 ± 0.03
NRC302	Reduced Nicotine-High Tar-Menthol	13 ± 2	0.16 ± 0.03
NRC400	Reduced Nicotine	9 ± 1.5	0.26 ± 0.06
NRC401	Reduced Nicotine-Menthol	9 ± 1.5	0.26 ± 0.06
NRC402	Reduced Nicotine-High Tar	13 ± 2	0.33 ± 0.06
NRC404	Reduced Nicotine-High Tar	13 ± 2	0.6 ± 0.12
NRC405	Reduced Nicotine-High Tar-Menthol	13 ± 2	0.4 ± 0.08
NRC500	Reduced Nicotine-High Tar	13 ± 2	0.7 ± 0.15
NRC501	Reduced Nicotine-High Tar-Menthol	9 ± 1.5	0.6 ± 0.12
NRC600	Conventional Nicotine	10.5 ± 1.5	0.8 ± 0.15
NRC601	Conventional Nicotine-Menthol	10.5 ± 1.5	0.8 ± 0.15
NRC602	Conventional Nicotine-High Tar-Menthol	16 ± 2	1.1 ± 0.2
NRC700	Low Tar/Nicotine Ratio-High Tar	16 ± 2	1.6 ± 0.3
NRC701	Low Tar/Nicotine Ratio-Menthol	12 ± 2	1.2 ± 0.2

Note.

Provided by the National Institute on Drug Abuse (NIDA) upon purchase of SPECTRUM cigarette samples. Mean ± standard deviation.

Table 2

Mainstream Smoke Deliveries of Tar, Nicotine, and CO from SPECTRUM Cigarettes (N = 5)

Product Code	Tar (mg/cig)		Nicotine (mg/cig)		CO (mg/cig)	
	ISO[a]	CI[b]	ISO[a]	CI[b]	ISO[a]	CI[b]
NRC100	3.2 ± 0.2	22.9 ± 1.7	0.01 ± 0.00	0.04 ± 0.00	5.1 ± 0.5	32.0 ± 1.5
NRC101	3.3 ± 0.2	25.2 ± 1.6	0.01 ± 0.00	0.04 ± 0.00	4.9 ± 0.2	32.9 ± 2.1
NRC102	6.9 ± 0.6	21.9 ± 1.5	0.02 ± 0.00	0.04 ± 0.00	11.1 ± 0.8	28.8 ± 1.2
NRC103	7.2 ± 0.9	21.7 ± 2.3	0.02 ± 0.00	0.04 ± 0.01	11.7 ± 1.8	27.1 ± 4.0
NRC104	12.2 ± 0.6	30.0 ± 2.7	0.04 ± 0.00	0.07 ± 0.01	14.4 ± 0.5	29.6 ± 2.4
NRC105	12.8 ± 0.8	34.8 ± 4.6	0.04 ± 0.01	0.07 ± 0.01	14.8 ± 1.0	32.3 ± 3.8
NRC200	7.0 ± 0.6	23.4 ± 3.1	0.06 ± 0.00	0.12 ± 0.01	11.9 ± 1.1	30.0 ± 1.3
NRC201	7.4 ± 0.5	24.0 ± 2.0	0.06 ± 0.00	0.11 ± 0.01	12.6 ± 0.8	30.0 ± 1.0
NRC300	7.4 ± 0.4	25.0 ± 3.0	0.11 ± 0.01	0.22 ± 0.02	12.3 ± 0.9	31.5 ± 3.4
NRC301	7.4 ± 0.5	24.7 ± 1.9	0.10 ± 0.01	0.21 ± 0.01	12.3 ± 0.7	30.9 ± 2.6
NRC302	13.3 ± 0.6	28.6 ± 1.7	0.17 ± 0.02	0.27 ± 0.02	15.1 ± 0.7	29.0 ± 2.4
NRC400	8.3 ± 0.4	24.2 ± 3.0	0.23 ± 0.01	0.47 ± 0.08	13.4 ± 0.7	30.3 ± 3.0
NRC401	8.4 ± 0.3	28.2 ± 3.4	0.24 ± 0.02	0.53 ± 0.07	14.3 ± 0.7	33.5 ± 2.0
NRC402	11.2 ± 0.9	29.3 ± 1.2	0.34 ± 0.04	0.61 ± 0.05	15.0 ± 1.0	31.6 ± 1.0
NRC404	13.7 ± 1.1	37.3 ± 4.5	0.50 ± 0.04	0.99 ± 0.13	15.1 ± 1.1	32.3 ± 2.6
NRC405	14.2 ± 1.8	36.0 ± 3.6	0.39 ± 0.03	0.69 ± 0.05	15.8 ± 1.6	30.7 ± 3.4
NRC500	12.0 ± 0.5	31.5 ± 2.2	0.67 ± 0.02	1.30 ± 0.12	14.6 ± 0.9	30.2 ± 3.5
NRC501	9.8 ± 0.7	32.3 ± 7.3	0.53 ± 0.05	1.20 ± 0.30	14.9 ± 0.4	35.3 ± 4.3
NRC600	9.7 ± 0.3	29.3 ± 2.1	0.72 ± 0.06	1.56 ± 0.29	14.0 ± 0.7	31.8 ± 1.7
NRC601	9.5 ± 0.6	26.7 ± 8.0	0.68 ± 0.06	1.40 ± 0.34	13.8 ± 0.6	29.1 ± 4.9
NRC602	15.9 ± 0.7	38.5 ± 3.8	0.99 ± 0.07	1.82 ± 0.14	15.9 ± 0.3	31.0 ± 3.4
NRC700	15.6 ± 1.0	37.4 ± 0.9	1.68 ± 0.10	3.30 ± 0.18	16.1 ± 0.9	31.2 ± 2.5
NRC701	12.0 ± 0.8	32.0 ± 1.6	1.31 ± 0.05	2.69 ± 0.21	15.6 ± 0.8	31.3 ± 0.6
3R4F	8.5 ± 0.7	26.6 ± 3.4	0.77 ± 0.10	1.96 ± 0.36	10.8 ± 1.0	30.5 ± 2.5

Note.

[a] = ISO (35 mL puff volume, 60 sec puff interval, 2 sec puff duration, and filter-tip vent open).

[b] = CI (55 mL puff volume, 30 sec puff interval, 2 sec puff duration, and 100% vent block). Mean ± standard deviation.

Table 3

Mainstream Smoke Deliveries of NNN, NNK and Benzo[a]pyrene (BaP) from SPECTRUM Cigarettes (N = 5)

Product Code	NNKc (ng/cig)		NNNd (ng/cig)		BaP (ng/cig)	
	ISO[a]	CI[b]	ISO[a]	CI[b]	ISO[a]	CI[b]
NRC100	9.4 ± 1.3	34.2 ± 5.6	31.2 ± 3.4	128.3 ± 13.8	2.1 ± 0.2	9.6 ± 0.8
NRC101	7.9 ± 0.6	35.9 ± 3.5	26.6 ± 1.2	124.5 ± 11.0	2.0 ± 0.2	10.0 ± 1.2
NRC102	14.5 ± 2.7	31.9 ± 3.9	49.1 ± 5.7	115.5 ± 16.0	3.3 ± 0.3	8.8 ± 0.4
NRC103	13.4 ± 2.2	34.0 ± 5.4	48.4 ± 5.1	117.6 ± 6.7	3.5 ± 0.5	9.4 ± 0.7
NRC104	25.5 ± 4.5	46.2 ± 7.1	83.2 ± 9.3	150.9 ± 30.0	6.0 ± 0.4	13.8 ± 1.4
NRC105	23.3 ± 2.7	45.0 ± 2.3	78.7 ± 12.3	155.0 ± 11.3	6.1 ± 0.6	13.7 ± 0.9
NRC200	19.6 ± 3.2	37.5 ± 7.2	58.5 ± 8.7	129.2 ± 25.3	3.3 ± 0.2	9.3 ± 0.5
NRC201	17.0 ± 2.8	35.7 ± 3.8	54.3 ± 6.9	123.2 ± 4.9	3.4 ± 0.3	9.0 ± 1.0
NRC300	20.7 ± 3.8	35.1 ± 5.6	60.5 ± 3.3	142.4 ± 5.9	3.5 ± 0.4	9.2 ± 0.5
NRC301	19.5 ± 3.5	34.7 ± 6.6	64.4 ± 3.7	126.5 ± 12.9	3.4 ± 1.0	6.3 ± 0.7
NRC302	24.3 ± 2.1	53.6 ± 2.7	102.0 ± 16.2	184.4 ± 19.0	5.8 ± 0.8	10.8 ± 0.9
NRC400	29.5 ± 2.5	56.6 ± 11.5	70.6 ± 4.2	160.9 ± 36.8	3.9 ± 0.7	7.9 ± 1.2
NRC401	26.9 ± 5.0	59.2 ± 4.6	70.5 ± 8.0	159.0 ± 9.7	3.7 ± 0.7	8.4 ± 1.2
NRC402	30.8 ± 4.4	66.4 ± 14.7	96.3 ± 13.7	194.0 ± 38.6	5.9 ± 0.9	10.5 ± 0.8
NRC404	51.0 ± 4.7	85.0 ± 8.4	107.7 ± 17.7	206.0 ± 27.7	7.3 ± 0.3	12.9 ± 1.5
NRC405	44.5 ± 2.7	75.8 ± 12.1	97.1 ± 9.4	217.6 ± 20.3	7.0 ± 0.6	10.5 ± 0.5
NRC500	43.7 ± 4.6	75.2 ± 14.5	119.8 ± 17.1	247.1 ± 9.3	6.4 ± 1.1	11.5 ± 0.3
NRC501	34.7 ± 6.3	84.1 ± 12.5	97.4 ± 14.4	209.6 ± 14.2	4.4 ± 0.9	8.3 ± 0.9
NRC600	59.5 ± 11.7	93.9 ± 14.4	126.5 ± 18.8	234.7 ± 8.9	5.1 ± 0.9	8.5 ± 0.9
NRC601	53.5 ± 8.4	94.6 ± 17.1	113.6 ± 10.5	246.9 ± 45.0	4.7 ± 0.7	8.3 ± 1.2
NRC602	79.7 ± 14.3	130.6 ± 20.0	185.4 ± 28.8	322.4 ± 12.2	7.0 ± 0.9	12.0 ± 1.0
NRC700	84.5 ± 5.0	144.0 ± 28.7	171.1 ± 9.4	342.9 ± 42.4	8.7 ± 1.7	14.7 ± 1.3
NRC701	52.6 ± 3.1	102.1 ± 9.1	120.9 ± 13.4	247.0 ± 25.2	6.5 ± 1.2	10.9 ± 1.1
3R4F	96.2 ± 11.4	251.8 ± 33.3	108.9 ± 8.7	266.7 ± 27.2	6.9 ± 0.8	17.8 ± 2.5

Note.

[a] = ISO (35 mL puff volume, 60 sec puff interval, 2 sec puff duration, and filter-tip vent open).

[b] = CI (55 mL puff volume, 30 sec puff interval, 2 sec puff duration, and 100% vent block).

[c] = NNK, 4-(Methylnitrosamino)-1-(3-pyridy1)-1-butanone. d NNN, N-nitrosonornicotine. Mean ± standard deviation.

Table 4

Mainstream Smoke Deliveries of Aromatic Amines from SPECTRUM Cigarettes (N = 5)

Product Code	o-Toluidine(ng/cig)		m-Toluidine(ng/cig)		p-Toluidine(ng/cig)		2,6-Dimethylaniline(ng/cig)		o-Anisidine (ng/cig)	
	ISO[a]	CI[b]	ISO[a]	CI[b]	ISO[a]	CI[b]	ISO[a]	CI[b]	ISO[a]	CI[b]
NRC100	21.2 ± 9.7	127.3 ± 14.8	23.4 ± 9.8	136.3 ± 4.6	25.5 ± 16.2	99.8 ± 6.1	7.5 ± 2.9	34.4 ± 2.4	0.7 ± 0.1	2.7 ± 0.3
NRC101	21.7 ± 2.2	131.7 ± 14.5	24.9 ± 2.6	138.3 ± 6.6	23.4 ± 1.4	101.1 ± 10.8	7.1 ± 0.8	36.0 ± 2.8	0.7 ± 0.3	3.0± 0.2
NRC102	51.5 ± 7.8	134.8 ± 18.9	50.1 ± 8.2	134.9 ± 4.1	45.8 ± 10.5	99.8 ± 7.2	15.3 ± 1.6	36.1 ± 1.5	1.2 ± 0.7	2.7 ± 0.3
NRC103	53.5 ± 7.4	154.6 ± 19.8	52.5 ± 6.5	153.9 ± 10.7	45.2 ± 5.1	114.2 ± 12.4	16.4 ± 1.9	42.4 ± 3.1	1.0 ± 0.1	3.4 ± 0.2
NRC104	96.3 ± 9.5	202.5 ± 19.2	99.9 ± 9.3	227.2 ± 10.6	75.2 ± 14.6	165.2 ± 10.9	29.7 ± 1.7	54.7 ± 2.6	2.1 ± 0.1	5.2 ± 0.2
NRC105	85.7 ± 11.4	189.5 ± 25.5	89.9 ± 11.5	210.9 ± 14.8	66.1 ± 4.9	153.8 ± 13.7	26.8 ± 4.1	50.1 ± 5.3	1.7 ± 0.2	4.4 ± 0.7
NRC200	57.0 ± 8.0	146.3 ± 10.6	59.3 ± 7.3	153.8 ± 9.1	51.1 ± 5.8	114.8 ± 12.0	17.1 ± 2.1	40.2 ± 2.0	1.0 ± 0.1	3.3 ± 0.3
NRC201	56.7 ± 6.3	132.4 ± 23.5	57.7 ± 5.2	139.5 ± 15.3	49.5 ± 3.3	104.3 ± 8.4	17.2 ± 2.1	36.4 ± 4.3	1.0 ± 0.1	2.8 ± 0.5
NRC300	57.6 ± 5.0	140.8 ± 9.6	57.4 ± 3.9	143.9 ± 11.5	49.2 ± 4.0	106 ± 16.4	17.5 ± 1.4	38.3 ± 3.1	1.0 ± 0.1	3.3 ± 0.4
NRC301	48.6 ± 3.0	119.3 ± 13.1	48.4 ± 2.9	127.3 ± 11.2	42.1 ± 5.5	104.2 ± 10.1	18.5 ± 1.8	40.2 ± 5.6	1.0 ± 0.3	1.7 ± 1.1
NRC302	80.0 ± 4.4	183.4 ± 7.2	82.4 ± 5.8	210.1 ± 9.9	59.5 ± 6.2	169.2 ± 8.2	29.4 ± 3.2	60.5 ± 2.9	1.8 ± 0.3	4.1 ± 0.9
NRC400	58.8 ± 5.3	133.6 ± 8.3	57.4 ± 4.8	149.3 ± 8.3	50.7 ± 8.2	124.0 ± 7.0	21.4 ± 3.1	45.7 ± 3.6	1.3 ± 0.3	3.1 ± 0.9
NRC401	54.5 ± 1.8	136.2 ± 15.2	54.5 ± 2.6	143.3 ± 16.9	45.1 ± 5.6	115.1 ± 9.6	20.9 ± 1.5	49.2 ± 7.2	1.2 ± 0.1	3.0 ± 1.1
NRC402	66.7 ± 5.2	143.7 ± 7.1	73.8 ± 4.9	173.7 ± 10.5	60.2 ± 9.5	137.1 ± 5.0	24.7 ± 2.6	50.0 ± 5.8	1.6 ± 0.1	3.8 ± 0.9
NRC404	99.9 ± 12.3	206.9 ± 17.5	90.9 ± 8.3	220.6 ± 18.1	69.6 ± 16.8	168.9 ± 9.3	37.4 ± 5.6	74.7 ± 10.4	2.6 ± 0.4	5.7 ± 1.3
NRC405	86.6 ± 4.1	181.7 ± 3.3	89.4 ± 5.2	205.6 ± 6.5	62.0 ± 5.4	157.1 ± 10.3	33.3 ± 2.1	64.1 ± 3.6	2.2 ± 0.1	4.7 ± 0.6
NRC500	73.0 ± 3.1	145.5 ± 9.7	77.9 ± 5.4	174.5 ± 10.7	53.8 ± 3.6	137.7 ± 14.5	27.5 ± 2.2	48.8 ± 7.2	2.0 ± 0.1	3.6 ± 1
NRC501	53.3 ± 3.8	129.6 ± 15.1	56.6 ± 4.0	137.4 ± 11.6	47.3 ± 6.0	99.0 ± 16.2	18.2 ± 1.4	49.4 ± 4.9	1.6 ± 0.3	2.9 ± 0.7
NRC600	52.3 ± 7.9	118.5 ± 3.7	55.5 ± 5.9	128.2 ± 8.5	45.8 ± 8.2	96.0 ± 11.9	17.8 ± 2.5	41.3 ± 2.3	1.6 ± 0.3	2.9 ± 2.3
NRC601	54.0 ± 2.8	115.7 ± 8.9	59.3 ± 2.0	124.3 ± 16.8	47.5 ± 3.0	90.3 ± 11.2	17.7 ± 0.9	41.8 ± 4.8	1.6 ± 0.5	2.2 ± 0.7
NRC602	85.1 ± 10.7	178.2 ± 9.7	93.4 ± 7.1	196.6 ± 10.8	68.2 ± 7.1	138.3 ± 25.3	29.5 ± 2.1	64.5 ± 3.1	2.6 ± 0.3	4.1 ± 0.8
NRC700	69.6 ± 11.7	131.1 ± 13.7	81.5 ± 9.0	152.8 ± 9.0	59.4 ± 9.9	105.8 ± 18.5	23.7 ± 3.1	43.2 ± 3.3	2.6 ± 0.3	3.4 ± 0.4
NRC701	54.2 ± 3.6	121.8 ± 6.4	63.9 ± 4.5	129.4 ± 6.7	46.4 ± 3.8	91.7 ± 13.0	19.1 ± 1.1	42.6 ± 2.0	1.9 ± 0.4	2.7 ± 0.8
3R4F	45.1 ± 6.7	85.1 ± 9.1	48.3 ± 6.8	91.8 ± 9.8	35.0 ± 8.8	56.9 ± 8.3	10.9 ± 2.7	23.1 ± 5.0	1.4 ± 0.4	2.0 ± 0.5
ProductCode	**1-Aminonaphthalene(ng/cig)**		**2-Aminonaphthalene(ng/cig)**		**2-Aminobiphenyl(ng/cig)**		**3-Aminobiphenyl(ng/cig)**		**4-Aminobiphenyl(ng/cig)**	

Product Code	o-Toluidine(ng/cig)		m-Toluidine(ng/cig)		p-Toluidine(ng/cig)		2,6-Dimethylaniline(ng/cig)		o-Anisidine (ng/cig)	
	ISO[a]	CI[b]	ISO[a]	CI[b]	ISO[a]	CI[b]	ISO[a]	CI[b]	ISO[a]	CI[b]
	ISO[a]	CI[b]	ISO[a]	CI[b]	ISO[a]	CI[b]	ISO[a]	CI[b]	ISO[a]	CI[b]
NRC100	7.1 ± 2.6	35.3 ± 4.2	3.6 ± 1.7	23.9 ± 2.7	2.4 ± 0.9	9.4 ± 0.8	1.4 ± 0.4	7.8 ± 0.9	1.2 ± 0.5	7.2 ± 0.8
NRC101	7.6 ± 0.8	34.1 ± 1.2	4.0 ± 0.5	23.4 ± 1.4	2.5 ± 0.2	9.8 ± 0.9	1.6 ± 0.1	7.5 ± 1.1	1.3 ± 0.1	6.7 ± 0.7
NRC102	12.5 ± 1.5	34.7 ± 3.8	6.8 ± 1.2	22.4 ± 1.8	4.0 ± 0.5	9.5 ± 0.7	2.4 ± 0.3	7.4 ± 1.5	2.4 ± 0.5	7.0 ± 1.0
NRC103	13.5 ± 0.3	39.5 ± 2.7	7.2 ± 1.2	25.9 ± 2.4	4.3 ± 0.6	10.7 ± 0.7	2.5 ± 0.4	7.8 ± 0.8	2.5 ± 0.6	7.7 ± 1.0
NRC104	27.4 ± 3.6	57.2 ± 8.0	14.4 ± 2.3	36.3 ± 4.4	7.5 ± 0.7	14.7 ± 1.1	3.7 ± 0.4	10.2 ± 0.6	4.6 ± 0.7	11.1 ± 1.0
NRC105	27.2 ± 5.1	52.8 ± 6.2	13.0 ± 3.1	34.2 ± 3.7	7.0 ± 1.1	13.7 ± 1.2	3.4 ± 0.2	9.8 ± 0.9	4.4 ± 0.9	11.0 ± 1.1
NRC200	16.1 ± 2.6	40.8 ± 4.1	8.3 ± 1.5	26.4 ± 2.5	4.7 ± 0.5	10.6 ± 0.6	2.7 ± 0.3	8.3 ± 0.3	2.7 ± 0.4	8.0 ± 0.7
NRC201	15.3 ± 2.1	37.9 ± 6.8	8.3 ± 1.3	24.4 ± 3.9	4.5 ± 0.4	9.9 ± 1.0	2.6 ± 0.1	7.5 ± 1.2	2.6 ± 0.3	6.7 ± 1.4
NRC300	14.6 ± 1.9	37.7 ± 2.0	7.9 ± 0.9	24.1 ± 1.4	4.4 ± 0.4	9.9 ± 0.5	2.5 ± 0.1	7.2 ± 0.6	2.6 ± 0.3	7.2 ± 0.8
NRC301	12.7 ± 0.9	33.6 ± 5.4	6.9 ± 0.2	19.0 ± 2.7	4.2 ± 0.2	10.0 ± 1.0	2.5 ± 0.4	5.3 ± 0.7	2.0 ± 0.3	5.6 ± 0.5
NRC302	23.7 ± 1.4	55.1 ± 3.6	13.9 ± 1.5	32.2 ± 2.5	7.1 ± 0.4	15.3 ± 0.8	3.4 ± 0.2	7.4 ± 0.7	4.1 ± 0.7	9.4 ± 0.8
NRC400	16.0 ± 1.4	41.3 ± 4.7	9.2 ± 1.3	23.7 ± 2.1	4.6 ± 0.4	10.6 ± 0.5	2.7 ± 0.3	6.0 ± 0.6	2.6 ± 0.5	6.7 ± 0.4
NRC401	15.4 ± 1.2	35.8 ± 6.2	8.3 ± 0.5	21.8 ± 3.0	4.6 ± 0.2	11.2 ± 1.2	2.7 ± 0.3	5.5 ± 0.8	2.5 ± 0.3	6.5 ± 0.6
NRC402	19.2 ± 0.8	44.4 ± 5.7	10.7 ± 1.2	25.6 ± 2.1	6.2 ± 0.6	12.4 ± 1.0	3.3 ± 0.3	5.9 ± 0.7	3.6 ± 0.8	7.9 ± 1.0
NRC404	25.5 ± 2.8	55.8 ± 3.5	15.1 ± 1.8	33.9 ± 2.6	7.2 ± 0.7	16.1 ± 1.9	3.7 ± 0.3	7.3 ± 0.6	4.3 ± 0.9	9.5 ± 1.3
NRC405	23.9 ± 0.5	52.7 ± 1.9	15.1 ± 1.1	30.3 ± 1.8	7.2 ± 0.2	14.9 ± 0.8	3.3 ± 0.3	6.9 ± 0.9	4.1 ± 1.1	9.0 ± 0.5
NRC500	19.2 ± 1.4	43.1 ± 2.8	13.2 ± 0.9	26.8 ± 1.1	5.7 ± 0.2	11.4 ± 0.9	3.0 ± 0.1	6.3 ± 0.8	2.9 ± 0.2	7.1 ± 0.2
NRC501	13.9 ± 2.3	30.2 ± 5.9	8.0 ± 0.3	19.3 ± 1.4	4.0 ± 0.2	10.0 ± 1.0	2.1 ± 0.6	5.4 ± 0.7	2.2 ± 0.7	6.0 ± 0.5
NRC600	13.4 ± 3.1	28.8 ± 5.7	7.8 ± 0.6	17.1 ± 1.8	3.7 ± 0.4	8.8 ± 0.4	2.0 ± 0.8	5.5 ± 1.2	1.9 ± 0.7	6.3 ± 1.2
NRC601	13.4 ± 1.5	26.9 ± 4.6	8.2 ± 0.6	17.5 ± 3.1	3.8 ± 0.1	9.0 ± 0.8	1.9 ± 0.6	4.7 ± 0.7	2.0 ± 0.3	6.1 ± 0.7
NRC602	20.1 ± 5.6	42.4 ± 8.7	12.9 ± 1.6	27.5 ± 1.1	5.9 ± 0.4	13.9 ± 0.8	2.8 ± 0.9	6.6 ± 0.7	2.8 ± 0.5	8.4 ± 1.0
NRC700	17.3 ± 4.4	34.8 ± 5.9	12.7 ± 2.0	24.1 ± 1.2	4.7 ± 0.7	10.0 ± 0.7	2.4 ± 0.8	5.1 ± 0.3	2.2 ± 0.6	6.3 ± 0.7
NRC701	14.5 ± 2.2	27.1 ± 5.0	9.1 ± 1.4	19.6 ± 1.3	3.8 ± 0.2	8.8 ± 0.5	1.9 ± 0.6	5.1 ± 1.3	1.7 ± 0.5	6.6 ± 1.1
3R4F	11.2 ± 1.5	21.6 ± 2.8	8.1 ± 1.1	16.4 ± 1.6	2.7 ± 0.2	5.8 ± 0.5	1.9 ± 0.3	4.2 ± 0.8	2.0 ± 0.5	4.3 ± 0.9

Note.

[a]= ISO (35 mL puff volume, 60 sec puff interval, 2 sec puff duration, and filter-tip vent open).

[b]= CI (55 mL puff volume, 30 sec puff interval, 2 sec puff duration, and 100% vent block). Mean ± standard deviation.

Table 5

Mainstream Smoke Deliveries of Carbonyls from SPECTRUM Cigarettes (N = 5)

Product Code	Formaldehyde (μg/cig)		Acetaldehyde (μg/cig)		Acrolein (μg/cig)		Acetone (μg/cig)	
	ISO[a]	CI[b]	ISO[a]	CI[b]	ISO[a]	CI[b]	ISO[a]	CI[b]
NRC100	7.1 ± 1.5	12.0 ± 6.3*	434 ± 164	1684 ± 245	12.3 ± 2.7	91.8 ± 11.3	164 ± 17.1	702 ± 80.5
NRC101	Not detected[c]	10.7 ± 9.5*	348 ± 85	1814 ± 125	8.6 ± 1.9	91.2 ± 20.0	135 ± 16.6	680 ± 43.7
NRC102	Not detected[c]	10.3 ± 7.3*	774 ± 276	1658 ±173	31.8 ± 9.5	82.9 ± 12.0	282 ± 46.8	673 ± 81.0
NRC103	Not detected[c]	14.0 ± 9.6*	819 ± 197	1678 ± 85	35.3 ± 9.9	96.0 ± 17.1	301 ± 54.7	682 ± 12.4
NRC104	7.7 ± 2.9	16.2 ± 7.5	1043 ± 328	1720 ± 193	44.9 ± 10.5	91.4 ± 9.8	341 ± 44.9	628 ± 59.6
NRC105	10.3 ± 5.4	14.1 ± 14.3	1129 ± 358	1710 ± 334	49.2 ± 8.3	93.1 ± 28.0	339 ± 25.8	678 ± 79.6
NRC200	Not detected[c]	9.9 ± 7.7*	935. ± 287	1784±92	38.7 ± 7.9	96.7 ± 21.0	302 ± 60.3	660 ± 44.1
NRC201	Not detected[c]	10.6 ± 4.6*	957 ± 328	1760 ± 270	36.9 ± 2.81	95.9 ± 14.7	327 ± 42.3	661 ± 47.0
NRC300	Not detected[c]	8.12 ± 8.5*	1005 ± 299	1768 ± 173	40.9 ± 11.9	97.2 ± 25.2	311 ± 63.0	675 ± 60.0
NRC301	Not detected[c]	10.0 ± 7.3*	900 ± 288	1800 ± 167	34.5 ± 7.5	99.0 ± 19.2	254 ± 24.3	662 ± 67.2
NRC302	12.7 ± 5.8	19.5 ± 10.6	1173 ± 262	1696 ± 154	51.0 ± 7.8	94.5 ± 16.7	355 ± 38.6	673 ± 69.1
NRC400	Not detected[c]	3.4 ± 2.2	932 ± 108	1794 ± 211	40.8 ± 7.3	85.6 ± 11.7	311 ± 35.5	595 ± 118
NRC401	Not detected[c]	3.6 ± 3.1	899 ± 49	1896 ±2 60	40.0 ± 6.6	90.4 ± 7.5	295 ± 38.3	621 ± 108
NRC402	4.4 ± 2.3	10.0 ± 2.8	1016 ± 106	2004 ± 243	47.0 ± 2.6	93.3 ± 10.6	325 ± 28.5	621 ± 59.2
NRC404	5.7 ± 2.5	14.3 ± 4.0	1096 ± 116	1936 ± 239	58.5 ± 9.9	95.6 ± 13.4	363 ± 51.7	614 ± 87.2
NRC405	6.7 ± 2.1	12.9 ± 6.3	1069 ± 83	1944 ± 290	52.6 ± 3.1	91.4 ± 7.7	348 ± 44.9	603 ± 90.9
NRC500	7.3 ± 3.7	19.7 ± 5.3	1081 ± 107	2024 ± 143	54.4 ± 5.8	96.6 ± 10.5	326 ± 25.7	551 ± 35.0
NRC501	Not detected[c]	11.0 ± 2.9	1037 ± 108	2084 ± 182	46.7 ± 5.7	96.3 ± 7.0	326 ± 40.3	605 ± 48.4
NRC600	4.7 ± 3.0	16.0 ± 3.3	1076 ± 307	2170 ± 257	54.9 ± 6.7	104 ± 1.4	370 ± 90.0	571 ± 49.2
NRC601	8.0 ± 5.7	18.0 ± 5.3	960 ± 163	1970 ± 233	54.1 ± 3.3	101 ± 10.2	293 ± 35.5	529 ± 46.8
NRC602	17.0 ± 5.7	21.7 ± 5.1	1054 ± 240	1988 ± 288	58.2 ± 4.9	94.4 ± 13.6	352 ± 36.2	578 ± 75.5
NRC700	24.5 ± 4.6	41.4 ± 5.9	1033 ± 151	1940 ± 274	62.7 ± 4.6	110 ± 11.2	316 ± 30.4	530 ± 36.8
NRC701	22.3 ± 10.6	45.6 ± 12.4	885 ± 296	1820 ± 274	55.5 ± 10.7	109 ± 8.4	297 ± 55.5	511 ± 24.4
3R4F	20.5 ± 14.9	100.0 ± 19.4	685 ± 198	1858 ± 128	46.0 ± 6.3	142 ± 11.8	261 ± 66.0	633 ± 37.0

[b] = CI (55 mL puff volume, 30 sec puff interval, 2 sec puff duration, and 100% vent block).

[c] = Non-detected, below background value of formaldehyde.

[*] N = 4 due to one replicate being background value. Mean ± standard deviation.