A Comparison of Mainstream and Sidestream Marijuana and Tobacco Cigarette Smoke Produced under Two Machine Smoking Conditions

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The chemical composition of tobacco smoke has been extensively examined, and the presence of known and suspected carcinogens in such smoke has contributed to the link between tobacco smoking and adverse health effects. The consumption of marijuana through smoking remains a reality and, among youth, seems to be increasing. There have been only limited examinations of marijuana smoke, including for cannabinoid content and for tar generation. There have not been extensive studies of the chemistry of marijuana smoke, especially in direct comparison to tobacco smoke. In this study, a systematic comparison of the smoke composition of both mainstream and sidestream smoke from marijuana and tobacco cigarettes prepared in the same way and consumed under two sets of smoking conditions, was undertaken. This study examined the suite of chemicals routinely analyzed in tobacco smoke. As expected, the results showed qualitative similarities with some quantitative differences. In this study, ammonia was found in mainstream marijuana smoke at levels up to 20-fold greater than that found in tobacco. Hydrogen cyanide, NO, NO_x, and some aromatic amines were found in marijuana smoke at concentrations 3–5 times those found in tobacco smoke. Mainstream marijuana smoke contained selected polycyclic aromatic hydrocarbons (PAHs) at concentrations lower than those found in mainstream tobacco smoke, while the reverse was the case for sidestream smoke, with PAHs present at higher concentrations in marijuana smoke. The confirmation of the presence, in both mainstream and sidestream smoke of marijuana cigarettes, of known carcinogens and other chemicals implicated in respiratory diseases is important information for public health and communication of the risk related to exposure to such materials.

Introduction

In 2004, the percentage of young Canadians aged 15–24 years that reported having used marijuana at least once in the previous year was 37%, which was up from 22% in 1994 (*1*). Eight percent of Canadian youth reported using marijuana daily, the vast majority through smoking (*2*). In comparison, the percentage of youth (15–24 years) that smoked tobacco, daily and occasionally combined, was 23%, and the prevalence of daily tobacco use in that age group was 15% in 2004 (*3*). Although the prevalence of tobacco smoking appears to be decreasing among youth, with the percentage of daily or occasional smokers dropping from 32% in 1999 to 23% by 2004 (*3*), that of marijuana use may be increasing.

Marijuana has not been approved as a therapeutic product anywhere in the world but has reportedly been widely used for medical purposes. In Canada, the Medical Marijuana Access Regulations provides a legal means for patients, with the support of their physician, to be authorized to use marijuana for medical purposes. Most of the people who use marijuana for medical purposes use it by the smoking route (*4, 5*).

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Smoke chemistry has been extensively investigated in tobacco (*6–9*), as has the impact of ingredients on smoke chemistry (*10–13*), and the journal Beitrage zur Tabakforshchung has published many papers on smoke chemistry since 1961. However, there are substantially fewer investigations into the chemical characterization of the smoke arising from marijuana cigarettes. Of those few studies, several have concentrated on the determination of cannabinoids in smoke (*14, 15*), an early study examined polycyclic aromatic hydrocarbons (PAHs) in marijuana and tobacco smoke (*16*), while others have focused on the generation of tar from marijuana cigarettes (*17, 18*). Tobacco smoke contains over 4000 identified chemicals, including more than 50 that are known to cause cancer (*6*). Most of the chemicals, including carbon monoxide, benzene, formaldehyde, and hydrogen cyanide, are formed during the combustion of the tobacco. Others, such as lead, tobacco-specific nitrosamines, and nicotine, are found naturally in the tobacco and are released as the tobacco burns. Although tobacco and marijuana smoke have been found to qualitatively contain many of the same carcinogenic chemicals (*16, 19, 20*), there is a lack of studies that examine the comparative chemistry and toxicology of tobacco and marijuana smoked under similar, rigid, and standardized conditions.

Because marijuana and tobacco are both smoked and the emissions contain similar carcinogens (*19*), it has sometimes been assumed that regular marijuana smoking would pose risks for respiratory disease and cancer that are similar to those

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Table 1. Analytes and Health Canada Official Methods Used for Analysis of Mainstream and Sidestream Smoke from Both Tobacco and Marijuana Cigarettes

	Health Canada Official methods	
emission	mainstream	sidestream
ammonia	T-101	T-201
1-aminonaphthalene, 2-aminonaphthalene 3-aminobiphenyl, 4-aminobiphenyl	T-102	T-202
formaldehyde, acetaldehyde, acetone, acrolein, proprionaldehyde, crotonaldehyde, methyl ethyl ketone, and butyraldehyde	T-104	T-204
hydrogen cyanide	T-107	T-205
mercury	T-108	T-206
lead, cadmium, chromium, nickel, arsenic, and selenium	T-109	T-207
NO and NO_x	T-110	T-208
N-nitrosonornicotine (NNN), 4-(*N*-nitorosomethylamino)-1-(3-pyridyl)-1-butanone (NNK), *N*-nitrosonatabine (NAT), and *N*-nitorosoanabasine (NAB)	T-111	T-209
pyridine and quinoline	T-112	T-210
styrene		T-213
pH	T-113	
hydroquinone, resorcinol, catechol, phenol, *m* + *p*-cresol, and *o*-cresol	T-114	T-211
tar and nicotine	T-115	T-212
carbon monoxide		T-214
1,3-butadiene, isoprene, acrylonitrile, benzene, and toluene	T-116	T-213

associated with tobacco. Although the causal relationships between tobacco smoking and respiratory diseases and cancer are now very well-established (*21*), a link between regular marijuana smoking and cancer has not yet been demonstrated (*22, 23*). Furthermore, although marijuana smoking is associated with long-term pulmonary inflammation and injury, epidemiological evidence that marijuana smoking leads to chronic pulmonary disease is inconsistent to date (*24*). It is worth noting that the effort to prove the causal links between tobacco smoke inhalation and disease, including lung cancer, even though smokers, nonsmokers, and former smokers could be readily identified and tracked, required decades of case-control and prospective epidemiological studies and reviews (see the above review by Thun).

Clearly, further information regarding the chemistry of marijuana smoke and information regarding the hazards and risks associated with marijuana smoke exposure are needed. As with tobacco smoking cessation programs, this type of information is necessary to support risk communication strategies for a reduction in marijuana use. Such information is also critical for patients who use marijuana for medical purposes so that they, and their physicians, can better weigh the risks of smoking marijuana with the benefits of alleviating disease symptoms.

The objective of this study is to compare the chemical composition of mainstream and sidestream marijuana and tobacco smoke using standardized products and protocols. While tobacco products require consistency to satisfy consumers, marijuana has no such requirement. The recognized variability of marijuana, arising from point of origin, cultivar, method of cultivation, or a myriad of other factors, requires the standardization of the production of marijuana to the extent possible. To that end, a standardized, quality-controlled marijuana product was manufactured in Canada by Prairie Plant Systems Inc. for Health Canada, which allowed the use of enough product from a single lot to permit cigarette to cigarette consistency. To permit rigorous comparisons between cigarettes made from that marijuana and those made from tobacco, the preparation of the cigarettes, the combustion, the collection of the smoke, and the subsequent analyses were all standardized. This study takes a novel approach by recognizing that tobacco and marijuana cigarettes are not smoked in the same fashion and, hence, includes a modified smoking condition designed to reflect marijuana smoking style and habits. It is acknowledged that the machine smoking conditions employed in this study do not represent actual smoking behavior in an individual or in a population, for either tobacco or marijuana. There is recognition that the standard ISO smoking regime has limitations in terms of product regulation or consumer information (*25*); however, the rigor affforded by the standardized machine approaches used in this study allows the direct comparison of the emissions of one product to the other. The in vitro toxicity of the smoke condensates as well as the cannabinoid profile of the marijuana smoke will be reported separately.

Materials and Methods

The preparation of both the marijuana and the tobacco cigarettes, the combustion of those cigarettes, and the resultant analyses of all mainstream and sidestream smoke were carried out by Labstat International (Kitchener, Ontario). The analyses employed the Health Canada Official Methods listed in Table 1, unless specified otherwise. A commercially available fine-cut tobacco product was used (Players brand). A standardized, quality-controlled, dried marijuana product, made of flowering heads only, reference H55-MS17/338-FH, was obtained from Prairie Plant Systems Inc. (Saskatoon, Canada), which grows the material under contract to Health Canada. All of the marijuana came from the same harvest: #55 from May, 2004. The marijuana plants were grown under controlled conditions according to documented procedures. Upon harvest, flowering heads were dried to a moisture content of approximately 10%, milled at 10 mm, packaged, and irradiated. The marijuana was received in two shipments of 25 pouches each, with each shipment totaling 1 kg of dried marijuana.

Samples of marijuana and fine-cut tobacco were laid out in a monolayer on aluminum trays and conditioned at a temperature of 22 ± 1 °C and relative humidity of 60 ± 3% for a minimum of 48 h (*26*). The conditioned product of about 775 mg was accurately weighed and transferred to the cigarette-rolling device (Nugget, American Thrust Tobacco, LLC, Champlain, NY), and cigarettes were prepared using Players papers, all without filters. All cigarettes (marijuana and tobacco) were stored in sealed plastic bags in advance of smoking. Samples were removed from the bags and conditioned for a minimum of 48 h prior to smoking as required by ISO 3402:1999.

Smoking of marijuana and tobacco cigarettes was carried out on either a Borgwaldt 20 port rotary smoking machine or a Cerulean 20 port linear smoking machine. The smoking parameters and smoking machine specifications that were used are set out in the International Organization for Standardization standard ISO 3308, Routine Analytical Cigarette-Smoking Machine—Definitions and Standard Conditions (*27*). A Borgwaldt single port smoking

Table 2. Averages of Masses Used in Preparation of Cigarettes, TPM Generated and Puff Count Per Cigarette, and ± Coefficients of Variation (%) for Tobacco and Marijuana under Two Smoking Conditions

	ISO (35/2/60)[a]		extreme (70/2/30)[a]	
	tobacco	marijuana	tobacco	marijuana
weight (mg) (±%)	788 ± 2.1	769 ± 1.4	783 ± 3.1	773 ± 1.3
TPM (mg) (±%)	46.9 ± 10.4	47.9 ± 10.5	111 ± 9.7	115 ± 15.4
puff count (±%)	13.0 ± 11.1	14.8 ± 6.6	15.4 ± 15	16.0 ± 14.5
L of mainstream smoke/cig (puff vol × puff no.)	0.455	0.518	1.078	1.12

[a] The numbers in the parentheses refer to the volume of the puff in milliliters, the duration of the puff in seconds, and the interval between puffs in seconds.

machine was employed for the analysis of the NO content of both mainstream and sidestream smoke and in the determination of smoke pH.

Briefly, the standard conditions employed a puff volume of 35 mL, a puff duration of 2 s, and a puff interval of 60 s. These conditions are termed "ISO" throughout. Conditions more reflective of marijuana smoking employed a puff volume of 70 mL, a duration of 2 s, and a 30 s interval. These conditions are referred to as "extreme" and differ from the Health Canada "intense" tobacco smoking conditions, which employ a puff volume of 55 mL.

Both mainstream and sidestream smoke were collected for each type of cigarette under each type of smoking condition. The smoke was analyzed using the Health Canada Official Test Methods as listed in Table 1, the specific details of which can be found on the Health Canada website for tobacco regulations (*28*). For tobacco, the methods were followed as written. For marijuana smoke, there was a need to verify that the tobacco methods would be able to accurately measure the specific analytes, or else alternative methods were also required. The verification of the applicability of the method varied depending on the specific analysis. For example, spiking with standards (laboratory-fortified matrices) was used to ensure the quantifiability of the carbonyls measured using Official Methods T-104 and T-204. This same approach was used for hydrogen cyanide, ammonia, and the phenolics. GC-MS analyses used retention time and goodness of fit against library mass spectra to confirm the applicability of the methods for the aminonaphthalenes, aminobiphenyls, pyridine, quinoline, and styrene as well as for the selected volatiles measured using test protocols T-116 and T-213. In each of the above cases, the verification studies confirmed the applicability of the tobacco methods for use in analysis of marijuana smoke. For certain others, such as pH and carbon monoxide, there was no expectation that the official methods for tobacco would not be suitable for use on marijuana smoke.

The methods normally used for PAH and aza-arene determinations in smoke are based upon that of Gmeiner et al. (*29*) and involve solid-phase extraction followed by GC-MS analysis employing single ion monitoring. Initial investigations on PAHs in mainstream marijuana smoke revealed the potential for interference from some cannabinoids with two of the PAHs, benzo(a)anthracene and chrysene. The determination of those PAHs uses the ion *m*/*z* 228. The cannabinoids also have that fragment as a low-intensity ion. However, because the cannabinoids are present in much greater concentrations than the PAHs, the presence of this ion can compromise the ability to quantify those PAHs accurately. Accordingly, a GC-MS-MS method was developed to allow the quantitation of those two PAHs by filtering on *m*/*z* 228 and monitoring the product ion of 226. For chrysene, this eliminated the problem; for benzo(a)anthracene, the results were acceptable as long as sufficient resolution was maintained to allow splitting of the benzo(a)anthracene−cannabinoid peak.

Results and Discussion

To estimate total particulate matter (TPM) and puff count for representative cigarettes, 30 cigarettes of each type were consumed under each smoking condition. Table 2 shows the average weight of the two types of cigarettes consumed under the two conditions, along with average TPM and puff count. TPM increased about 2.4-fold under the extreme conditions, more reflective of marijuana cigarette consumption.

Table 3. Various Analytes Including Tobacco-Specific Compounds and Heavy Metals Determined in Mainstream Smoke from Tobacco and Marijuana under Two Smoking Conditions[a]

	ISO		extreme	
	tobacco	marijuana	tobacco	marijuana
tar (mg/cig)	38.2 ± 2.2	37.4 ± 4.5	80.3 ± 5.6	103 ± 11*
pH	5.5 ± 0.05	7.21 ± 0.17*	5.47 ± 0.04	7.73 ± 0.10*
NO (μg/cig)	65.7 ± 8.9	296 ± 33*	151 ± 10	685 ± 58*
NOx (μg/cig)	68.2 ± 9.2	302 ± 33*	158 ± 10	693 ± 58*
CO (mg/cig)	20.8 ± 1.9	13.4 ± 1.6*	41.5 ± 4	35.3 ± 2.9*
nicotine (mg/cig)	2.44 ± 0.18	0.005 ± 0.011*	5.2 ± 0.39	0.002−0.007*
ammonia (μg/cig)	35.5 ± 2.4	720 ± 84*	67 ± 9.9	1315 ± 106*
HCN (μg/cig)	208 ± 24	526 ± 46*	320 ± 29	1668 ± 159*
NNN	87.6 ± 4.4	<1.49*	160 ± 15	<1.49*
NAT	71 ± 3.4	<1.87*	125 ± 9	<1.87*
NAB	5.68 ± 0.42	<0.063*	8.26 ± 0.47	0.063−2.00*
NNK	86.7 ± 5.2	<3.72*	158 ± 15	<3.72*
mercury	3.17 ± 0.32	<1.10*	5.35 ± 0.52	3.51 ± 0.31*
cadmium	145 ± 8	6.91 ± 1.34*	284 ± 7	14.6 ± 1.2*
lead	21.1 ± 1.1	3.85−12.8*	43.8 ± 2.9	7.7−25.7*
chromium	5.94−19.8	5.94−19.8	11.9−39.6	11.9−39.6
nickel	6.47−21.6	6.47−21.6	12.9−43.1	<12.9
arsenic	5.49 ± 0.33	1.13−3.75*	12.7 ± 0.9	2.25−7.49*
selenium	2.21−7.37	2.21−7.37	4.42−14.7	4.42−14.7

[a] Values are provided ± standard deviations. For tar, nicotine, and CO, $n = 20$. For all others, $n = 7$. Units are ng/cigarette unless noted differently. *$P < 0.05$ vs tobacco. Values shown with "<" were below the limit of detection; values shown as a range were above the limit of detection but below the limit of quantitation.

As the amount of smoke produced by the combustion of marijuana cigarettes could be different than that produced by tobacco cigarettes, the yields of smoke constituents on a cigarette basis could be skewed. Yields were also calculated on a per liter of smoke basis and were found to not significantly be different from those calculated on a per cigarette basis. Accordingly, all data are presented on a mass per cigarette basis.

The chemicals described in Tables 3−10 are arbitrarily grouped for convenience of presentation. For mainstream tar, nicotine, and carbon monoxide, the numbers shown in Table 3 represent the mean of 20 observations. All other data shown represent the mean of seven observations.

It was surprising to find nicotine in the mainstream and sidestream marijuana smoke (Tables 3 and 4). For mainstream smoke, of the 20 marijuana cigarettes examined under ISO conditions, 16 showed no nicotine and none of those examined under extreme smoking conditions had any evidence of nicotine. As nicotine is present in high concentrations in tobacco, in the range of mg per cigarette, it was concluded that the source of nicotine was cross-contamination from tobacco smoking. The level in mainstream represents about 0.2% of that found in tobacco smoke. This could be problematic for compounds present in very high concentrations in tobacco and known to be present in low concentrations in marijuana. Such cross-contamination could then result in exaggerated results. However, there seems to be no such compound, at least not in these analyses. With the exception of nicotine, and the cannabinoids of course, the two matrices have compounds present in the same order of magnitude, so a contamination of 0.2% would not cause an exaggeration of the determined residue.

Beyond nicotine and the cannabinoids (data not shown), the component with the greatest difference between tobacco and

Table 4. Various Analytes Including Tobacco-Specific Compounds and Heavy Metals Determined in Sidestream Smoke from Tobacco and Marijuana under Two Smoking Conditions[a]

	ISO		extreme	
	tobacco	marijuana	tobacco	marijuana
tar (mg/cig)	24.3 ± 1.8	49.7 ± 2.5*	17.2 ± 1.8	30.8 ± 1.6*
NO (μg/cig)	1101 ± 47	2087 ± 152*	1419 ± 124	2631 ± 241*
NOx (μg/cig)	1172 ± 44	2284 ± 229*	1521 ± 153	2880 ± 323*
CO (mg/cig)	61.7 ± 2.0	54.0 ± 3.7*	61.6 ± 2.9	50.6 ± 3.9*
nicotine (mg/cig)	4.77 ± 0.26	0.065 ± 0.018*	3.11 ± 0.23	0.074 ± 0.029*
ammonia (μg/cig)	5568 ± 322	14270 ± 472*	3919 ± 327	10743 ± 675*
HCN (μg/cig)	83.8 ± 7.8	685 ± 29*	103 ± 10	678 ± 72*
NNN	41 ± 4.8	<0.634*	28 ± 2.0	0.634−2.0*
NAT	17.4 ± 1.4	<2.34*	10.2 ± 1.1	<2.34*
NAB	2.71 ± 0.52	<0.793*	0.79−2.5	<0.793
NNK	92 ± 11.7	<4.65*	61 ± 5.1	<4.65*
mercury	8.32 ± 0.57	<4.40*	6.31 ± 0.61	<4.40*
cadmium	478 ± 19	4.0−13.4*	360 ± 20	4.0−13.4*
lead	34.5−115	<34.5	34.5−115	<34.5
chromium	31.0−103	31.0−103	<31.0	31.0−103
nickel	35.5−118	35.5−118	<35.5	<35.5
arsenic	<11.3	<11.3	<11.3	<11.3
selenium	<17.5	<17.5	<17.5	<17.5

[a] Values are provided ± standard deviations. For tar, nicotine, and CO, $n = 20$. For all others, $n = 7$. Units are ng/cigarette unless noted differently. *$P < 0.05$ vs tobacco. Values shown with "<" were below the limit of detection; values shown as a range were above the limit of detection but below the limit of quantitation.

Table 5. Miscellaneous Organics Determined in Mainstream and Sidestream Smoke from Tobacco and Marijuana under Two Smoking Conditions[a]

	ISO		extreme	
	tobacco	marijuana	tobacco	marijuana
		mainstream		
pyridine	31.1 ± 1.7	34.6 ± 4.3	59 ± 4.9	93.0 ± 8.9*
quinoline	1.31 ± 0.08	1.06 ± 0.26*	2.22 ± 0.22	2.68 ± 0.34*
1,3-butadiene	64.8 ± 2.2	79.5 ± 7.4*	124 ± 7	138 ± 17
isoprene	286 ± 15	74.0 ± 6.5*	540 ± 18	132 ± 19*
acrylonitrile	13 ± 1.2	36.6 ± 4.3*	24 ± 0.9	66.9 ± 9.5*
benzene	62.2 ± 3.5	58.3 ± 5.9	94.6 ± 2.6	84.4 ± 8.9*
toluene	103 ± 6	124 ± 15*	169 ± 3	199 ± 25*
styrene	15 ± 0.6	17.2 ± 2.3*	28.6 ± 2.0	44.7 ± 4.2*
		sidestream		
pyridine	265 ± 11	307 ± 14*	225 ± 9	278 ± 22*
quinoline	9.94 ± 0.92	11.3 ± 0.7*	8.53 ± 0.54	9.82 ± 1.10*
1,3-butadiene	372 ± 12	412 ± 27*	269 ± 13	420 ± 22*
isoprene	1459 ± 82	656 ± 40*	1153 ± 51	614 ± 31*
acrylonitrile	102 ± 4	295 ± 21*	73.8 ± 4.7	273 ± 17*
benzene	290 ± 11	341 ± 12*	203 ± 11	328 ± 18*
toluene	516 ± 20	704 ± 29*	393 ± 32	729 ± 28*
styrene	105 ± 10	162 ± 10*	85.2 ± 10.6	175 ± 9*

[a] Values are provided ± standard deviations; $n = 7$. Units are μg/cigarette. *$P < 0.05$ vs tobacco.

marijuana was ammonia. In marijuana smoke, ammonia was found at levels about 20-fold those in tobacco in mainstream smoke (Table 3) and about 3-fold greater in sidestream smoke (Table 4), although the absolute values were very much greater in sidestream smoke. The amount of ammonia produced during combustion of tobacco has been related to the amount of nitrate fertilizer applied during growth (*30*). The simplest explanation for the very high levels of ammonia found in marijuana smoke may be that the marijuana used for this study contained more nitrate than the tobacco sample. The marijuana plants were grown on soil-less growth medium. All fertilizers were commercially available and consisted of water-soluble hydroponic vegetable fertilizers used for horticulture and contained nitrogen

Table 6. Aromatic Amines Determined in Mainstream and Sidestream Smoke from Tobacco and Marijuana under Two Smoking Conditions[a]

	ISO		extreme	
	tobacco	marijuana	tobacco	marijuana
		mainstream		
1-aminonaphthalene	24.9 ± 2.6	84.4 ± 13.2*	35.1 ± 5.7	178 ± 17*
2-aminonaphthalene	9.38 ± 0.62	33.6 ± 3.5*	12.9 ± 1.2	66.3 ± 6.8*
3-aminobiphenyl	2.22 ± 0.18	9.15 ± 0.63*	3.68 ± 0.44	18.8 ± 1.8*
4-aminobiphenyl	1.56 ± 0.13	6.17 ± 0.44*	2.54 ± 0.17	13.5 ± 1.5*
		sidestream		
1-aminonaphthalene	195 ± 16	305 ± 21*	144 ± 8	266 ± 23*
2-aminonaphthalene	136 ± 7	177 ± 19*	79.4 ± 7.4	139 ± 12*
3-aminobiphenyl	33 ± 2.1	50.4 ± 3.7*	19.7 ± 1.6	40.6 ± 2.4*
4-aminobiphenyl	23.2 ± 1.8	31.2 ± 2.8*	13.9 ± 1.3	27.3 ± 2.2

[a] Values are provided ± standard deviations; $n = 7$. Units are ng/cigarette. *$P < 0.05$ vs tobacco.

Table 7. Selected Carbonyl Compounds Determined in Mainstream and Sidestream Smoke from Tobacco and Marijuana under Two Smoking Conditions[a]

	ISO		extreme	
	tobacco	marijuana	tobacco	marijuana
		mainstream		
formaldehyde	200 ± 28	25.1 ± 2.7*	543 ± 91	66.5 ± 11.8*
acetaldehyde	872 ± 101	448 ± 44*	1555 ± 222	1021 ± 99*
acetone	454 ± 44	237 ± 23*	826 ± 93	514 ± 32*
acrolein	125 ± 13	54.3 ± 4.5*	251 ± 32	148 ± 13*
propionaldehyde	72.1 ± 8.1	32.3 ± 3.2*	97.8 ± 14.4	74.0 ± 6.4*
crotonaldehyde	62.9 ± 7.3	23.1 ± 1.5*	127 ± 17	56.7 ± 7.7*
methyl ethyl ketone	135 ± 16	62.4 ± 5.5*	265 ± 27	140 ± 7*
butyraldehyde	47.1 ± 5.7	46.5 ± 3.8	77.1 ± 10.0	110 ± 8*
		sidestream		
formaldehyde	886 ± 47	383 ± 27*	662 ± 29	202 ± 34*
acetaldehyde	1587 ± 45	1170 ± 69*	1383 ± 37	896 ± 112*
acetone	828 ± 22	566 ± 34*	720 ± 22	405 ± 54*
acrolein	437 ± 10	304 ± 20*	316 ± 12	179 ± 24*
propionaldehyde	121 ± 6	120 ± 6	116 ± 5	93.4 ± 11.7*
crotonaldehyde	106 ± 3	49.9 ± 3.8*	97.5 ± 8.7	42.9 ± 4.7*
methyl ethyl ketone	222 ± 9	160 ± 11*	202 ± 17	116 ± 13*
butyraldehyde	67.1 ± 2.7	173 ± 12*	60.2 ± 1.7	139 ± 13*

[a] Values are provided ± standard deviations; $n = 7$. Units are μg/cigarette. *$P < 0.05$ vs tobacco.

in the form of both nitrate and ammoniacal nitrogen. However, it is not known to what extent the differences in the growing conditions between the marijuana and the tobacco, including the types of fertilizers used, influenced the levels of nitrates in the plants. The temperature of combustion can also influence the production of ammonia. Burning tobacco results in a reduction of nitrate to ammonia, which is released to a greater extent during sidestream smoke formation (*31*), suggesting that lower combustion temperatures favor the production of ammonia. Combustion temperature differences between marijuana and tobacco may have also contributed to the differences in ammonia yield, but this was not verified.

Tobacco-specific nitrosamines were not found in the marijuana smoke (Tables 3 and 4). This result was expected, given that these compounds are derived from nicotine. Arsenic and lead were also noticeably absent from the marijuana smoke, which is consistent with the certificate of analysis provided with the plant material (data not shown). Again, this could be a function of the relatively controlled growth conditions.

NO and NO_x were significantly elevated in the marijuana smoke under both smoking regimes and in mainstream (Table 3) and sidestream smoke (Table 4). A logical explanation would be that these are arising from the nitrate present in the fertilizer and would be consistent with the very high ammonia yields.

Hydrogen cyanide (HCN) was also significantly higher in marijuana smoke, both mainstream and sidestream, with a 5-fold increase relative to tobacco under extreme conditions. HCN forms from protein at temperatures above 700 °C (*32*); smoldering at 600 °C does not produce HCN to the same extent. This is consistent with the mainstream results in that under extreme conditions, HCN was significantly increased. This could be due to higher temperatures or to the temperature being higher for a longer period of time under those conditions. Also consistent was the amount of HCN found in sidestream smoke. The levels were substantially lower than those in mainstream smoke; within the sidestream results, ISO to extreme comparisons showed little differences. If the higher temperature is the key variable, mainstream would have more HCN, which it does, and it would increase under extreme conditions.

The yields of the selected organics shown in Table 5 are consistent with the production of these chemicals varying with temperature. For example, volatile pyridines are higher in sidestream smoke likely because of preferential formation from alkaloids during smoldering (*33*). All of the components in this table are found in greater yields in sidestream smoke. Under extreme conditions, the yields generally drop slightly relative to ISO conditions, reflecting the reduction in volume of sidestream smoke produced. Marijuana smoke did contain elevated levels of acrylonitrile as compared to tobacco.

Table 6 shows that the four aromatic amines examined in the two materials were all significantly, and substantially, elevated in marijuana smoke over tobacco smoke, especially in mainstream smoke but also in sidestream smoke under both smoking conditions. In a study on tobacco pyrolysis to measure effects of temperature, atmosphere, and pH on the generation of specific compounds, it was found that the formation of these four aromatic amines was favored in basic conditions (*34*). In that study, the yields of some 29 chemicals were compared from the pyrolysis of tobacco leaf at pH 2.89 and at pH 7.07. The yield of 1-aminonaphthalene was increased 3-fold in the smoke from the tobacco at the basic pH, with the other three also significantly increased. Interestingly, the marijuana material used in the present study had an average mainstream smoke pH of about 7.5, while the tobacco was more acidic at a pH of about 5.5. These values were consistent with other reported smoke pH values for marijuana and tobacco (*17*). In the examination of the effect of temperature, it was determined that in air, 1-aminonaphthalene yield reached a plateau at about 500 °C, which could favor generation in sidestream smoke. All of the aromatic amines examined in the present study had much higher yields in sidestream smoke for both marijuana and tobacco. There is a hypothesis that increased nitrate from fertilizer use leads to higher pH, higher levels of ammonia, and increased levels of aromatic amines generated through the intermediacy of NH_2 radicals (*30*), and this is consistent with all of the results presented here.

As Table 7 shows, low-molecular weight carbonyls, including formaldehyde and acetaldehyde, were generally found in lower yield in the marijuana smoke as compared to the tobacco smoke. The one exception was butyraldehyde, which was present at higher yields in marijuana smoke. In tobacco smoke, acetaldehyde is thought to arise from the combustion of tobacco polysaccharides, including cellulose (*35*). It has also been shown that levels of formaldehyde in tobacco smoke increase as a direct result of the addition of saccharide to tobacco ingredients (*36*) or from the presence of relatively high levels of sugars produced during the flue-curing process (*11*). The relative reduction of these analytes in marijuana smoke may be related to the use of flowering tops in the preparation of the marijuana cigarettes, as compared to the use of mature leaves of tobacco. The polysaccharide content would likely be different, although this was not verified in this study.

Table 8. Phenolic Compounds Determined in Mainstream and Sidestream Smoke from Tobacco and Marijuana under Two Smoking Conditions[a]

	ISO		extreme	
	tobacco	marijuana	tobacco	marijuana
		mainstream		
hydroquinone	153 ± 12	30.1 ± 2.9*	299 ± 24	71.3 ± 2.9*
resorcinol	2.43 ± 0.21	4.07 ± 0.39*	7.32 ± 0.38	11.8 ± 1.7*
catechol	170 ± 15	63.9 ± 7.3*	402 ± 25	161 ± 19*
phenol	137 ± 11	91.5 ± 10.5*	283 ± 20	265 ± 20
m + *p*-cresols	55.4 ± 3.8	57.8 ± 6.7	114 ± 7	157 ± 12*
o-cresol	25.5 ± 1.9	17.6 ± 1.5*	51.5 ± 3.3	46.8 ± 3.9*
		sidestream		
hydroquinone	135 ± 8	43.5 ± 3.1*	141 ± 15	35.8 ± 2.5*
resorcinol	<1.63	1.63−5.42	1.63−5.42	1.63−5.42
catechol	107 ± 9	69.7 ± 4.1*	91.8 ± 11.6	53.1 ± 4.3*
phenol	264 ± 13	260 ± 11	250 ± 12	235 ± 7*
m + *p*-cresols	64.6 ± 2.5	104 ± 6*	65.6 ± 3.0	100 ± 5*
o-cresol	28.2 ± 1.0	29 ± 1.7	30.4 ± 1.3	39.5 ± 1.6*

[a] Values are provided ± standard deviations; $n = 7$. Units are μg/cigarette. *$P < 0.05$ vs tobacco. Values shown with "<" were below the limit of detection; values shown as a range were above the limit of detection but below the limit of quantitation.

Table 8 presents the results of the analyses of selected phenolic compounds. For mainstream smoke, there was a reasonably consistent increase of several fold for each component under extreme conditions as compared to ISO for both marijuana and tobacco. In a controlled study examining the effects of temperature, atmosphere, and pH on some smoke components during tobacco pyrolysis, Torikai et al. found that increasing the temperature of pyrolysis did increase the production of those phenolics listed in Table 8 (*34*). Comparing marijuana to tobacco, there were generally lower levels of phenolics in mainstream smoke of marijuana, although resorcinol was higher. These slight reductions may support combustion temperature differentials, although the use of pyrolysis studies on tobacco under controlled conditions for comparison to cigarette smoking has been put in question, given the complexity of the latter (*8*).

Tables 9 and 10 present the data for PAHs and aza-arenes from marijuana and tobacco in mainstream and sidestream smoke, respectively. The compounds are presented in order of elution, and the later-eluting compounds generally have higher molecular weights. As described in the Materials and Methods section, a cannabinoid-derived mass at *m*/*z* 228 interfered with the quantitation of several PAHs using the standard method of analysis. Consequently, a GC-MS-MS method was developed for PAH analysis. All of the PAH and aza-arene data presented in Tables 9 and 10 were generated using this technique, and it served to allow unambiguous quantitation of chrysene, but the benzo(a)anthracene analysis continued to require suitable resolution for acceptable measurement.

A comparison of the PAHs in mainstream smoke showed that levels from marijuana were lower than those from tobacco, although the pattern of content was very similar. The only exception was dibenz(a,h)anthracene, which was slightly elevated in marijuana under ISO conditions. Under high temperatures and reduced oxygen, tobacco can undergo a pyrolysis process in which free radical formation is enhanced (*34*), which increases PAH formation. Nitrogen oxides can act as free radical scavengers and can lower PAH formation from pyrolysis (*37*), and the presence of higher levels of nitrate may therefore lower

Table 9. PAHs and Aza-arenes Determined in Mainstream Smoke from Tobacco and Marijuana under Two Smoking Conditions[a]

		ISO		extreme	
no.		tobacco	marijuana	tobacco	marijuana
1	naphthalene	2907 ± 159	2070 ± 290*	4908 ± 456	4459 ± 646
2	1-methylnaphthalene	2789 ± 176	2057 ± 302*	4888 ± 491	4409 ± 604
3	2-methylnaphthalene	2093 ± 137	1292 ± 189*	3666 ± 374	2917 ± 477*
4	acenaphthylene	385 ± 22	235 ± 31*	711 ± 51	459 ± 60*
5	acenaphthene	172 ± 10	91.2 ± 10.2*	309 ± 22	213 ± 48*
6	fluorene	769 ± 42	366 ± 37*	1369 ± 100	659 ± 64*
7	phenanthrene	293 ± 14	273 ± 23	515 ± 32	476 ± 45
8	anthracene	91.8 ± 5.4	70.9 ± 6.7*	162 ± 13	136 ± 9*
9	fluoranthene	96.8 ± 3.7	65.6 ± 6.5*	171 ± 11	117 ± 12*
10	pyrene	88.8 ± 4.3	45.6 ± 4.4*	154 ± 12	82.3 ± 11.2*
11	benzo(a)anthracene	30.5 ± 2.5	26.2 ± 3.4*	52 ± 5.8	43.1 ± 7.9*
12	chrysene	38.8 ± 2.3	26.2 ± 1.4*	61.7 ± 7.4	56.3 ± 7.9
13	benzo(b)fluoranthene	10.8 ± 0.6	7.18 ± 1.12*	21.9 ± 3.1	16.2 ± 3.6*
14	benzo(k)fluoranthene	3.42 ± 0.32	1.52 ± 0.26*	7.45 ± 1.47	4.54 ± 0.96*
15	benzo(e)pyrene	11 ± 0.6	6.15 ± 0.37*	19.2 ± 1.3	12.6 ± 2.7*
16	benzo(a)pyrene	14.3 ± 1.2	8.67 ± 1.12*	25.1 ± 2.5	15.5 ± 2.9*
17	perylene	3.9 ± 0.46	3.72 ± 0.79	10.8 ± 2.3	6.10 ± 0.82*
18	indeno(1,2,3,-cd)pyrene	4.58 ± 0.89	3.60 ± 0.48*	10.1 ± 0.9	8.65 ± 3.11
19	dibenz(a,h)anthracene	1.15 ± 0.21	1.41 ± 0.19*	4.84 ± 1.05	2.83 ± 0.59*
20	benzo(g,h,i)perylene	3.77 ± 0.66	2.56 ± 0.36*	7.17 ± 1.02	6.03 ± 2.34
21	5-methylchrysene	<0.035	<0.035	<0.071	<0.071
22	benzo(b)fluoranthene	11.5 ± 1.4	6.47 ± 0.86*	19.1 ± 1.7	17.6 ± 1.4
23	benzo(j)fluoranthene	5.81 ± 0.44	4.27 ± 0.83*	13.3 ± 1.8	12.2 ± 2.1
24	dibenz(a,h)acridine	<0.314	<0.314	<0.628	<0.628
25	dibenz(a,j)acridine	<0.260	<0.260	<0.519	<0.519
26	7*H*-dibenzo(c,g)carbazole	<0.139	<0.139	<0.278	<0.278
27	dibenz(a,l)pyrene	<0.317	<0.317	<0.634	<0.634
28	dibenz(a,e)pyrene	0.531 ± 0.198	0.156−0.522	<0.313	<0.313
29	dibenz(a,i)pyrene	0.987 ± 0.145	0.164−0.548*	2.55 ± 0.60	<0.329*
30	dibenz(a,h)pyrene	0.177−0.589	<0.177	<0.354	<0.354

[a] Values are provided ± standard deviations; $n = 7$. Units are ng/cigarette. *$P < 0.05$ vs tobacco. Values shown with "<" were below the limit of detection; values shown as a range were above the limit of detection but below the limit of quantitation.

Table 10. PAHs and Aza-arenes Determined in Sidestream Smoke from Tobacco and Marijuana under Two Smoking Conditions[a]

		ISO		extreme	
no.		tobacco	marijuana	tobacco	marijuana
1	naphthalene	6861 ± 419	16748 ± 2396*	10111 ± 758	14398 ± 2614*
2	1-methylnaphthalene	6265 ± 365	14812 ± 1511*	7115 ± 787	11016 ± 2954*
3	2-methylnaphthalene	6513 ± 306	11832 ± 1078*	7137 ± 778	9030 ± 2236
4	acenaphthylene	2684 ± 184	4056 ± 452*	2171 ± 123	2876 ± 571*
5	acenaphthene	960 ± 31	1345 ± 101*	791 ± 51	873 ± 163
6	fluorene	1429 ± 71	1073 ± 72*	1242 ± 56	873 ± 67*
7	phenanthrene	2818 ± 112	4932 ± 306*	2117 ± 98	3113 ± 477*
8	anthracene	755 ± 38	1135 ± 75*	542 ± 26	693 ± 111*
9	fluoranthene	699 ± 26	952 ± 61*	520 ± 24	619 ± 78*
10	pyrene	528 ± 35	609 ± 60*	377 ± 25	398 ± 38
11	benzo(a)anthracene	159 ± 8	245 ± 16*	113 ± 7	170 ± 21*
12	chrysene	401 ± 21	488 ± 28*	291 ± 18	331 ± 27*
13	benzo(b)fluoranthene	98.4 ± 8.4	114 ± 7*	79.8 ± 4.3	80.3 ± 8.0
14	benzo(k)fluoranthene	25.8 ± 4.1	27.3 ± 2.8	19.3 ± 3.1	19.7 ± 2.2
15	benzo(e)pyrene	94.9 ± 6.9	87.9 ± 7.5	72.9 ± 3.8	63.1 ± 6.2*
16	benzo(a)pyrene	91.7 ± 7.1	101 ± 9*	62.7 ± 4.2	69.7 ± 6.3*
17	perylene	23.6 ± 2.9	26.4 ± 4.7	16.4 ± 1.7	19.9 ± 2.7*
18	indeno(1,2,3,-cd)pyrene	41.7 ± 5.7	45.9 ± 6.8	32.8 ± 6.6	27.4 ± 3.3
19	dibenz(a,h)anthracene	13.8 ± 3.1	15.6 ± 3.2	13.9 ± 2.8	10.8 ± 1.2*
20	benzo(g,h,i)perylene	44.7 ± 8.0	41.8 ± 9.6	32.8 ± 7.2	30 ± 5.0
21	5-methylchrysene	<0.354	<0.354	<0.354	<0.354
22	benzo(b)fluoranthene	118 ± 9	102 ± 11*	90.4 ± 5.6	86.7 ± 12.5
23	benzo(j)fluoranthene	102 ± 7	120 ± 16*	72.3 ± 6.2	124 ± 14*
24	dibenz(a,h)acridine	<3.138	<3.138	<3.138	<3.138
25	dibenz(a,j)acridine	<2.597	<2.597	<2.597	<2.597
26	7*H*-dibenzo(c,g)carbazole	<1.389	<1.389	<1.389	<1.389
27	dibenz(a,l)pyrene	<3.172	<3.172	<3.172	<3.172
28	dibenz(a,e)pyrene	<1.565	<1.565	<1.565	<1.565
29	dibenz(a,i)pyrene	<1.644	<1.644	<1.644	<1.644
30	dibenz(a,h)pyrene	<1.768	<1.768	<1.768	<1.768

[a] Values are provided ± standard deviations; $n = 7$. Units are ng/cigarette. *$P < 0.05$ vs tobacco. Values shown with "<" were below the limit of detection.

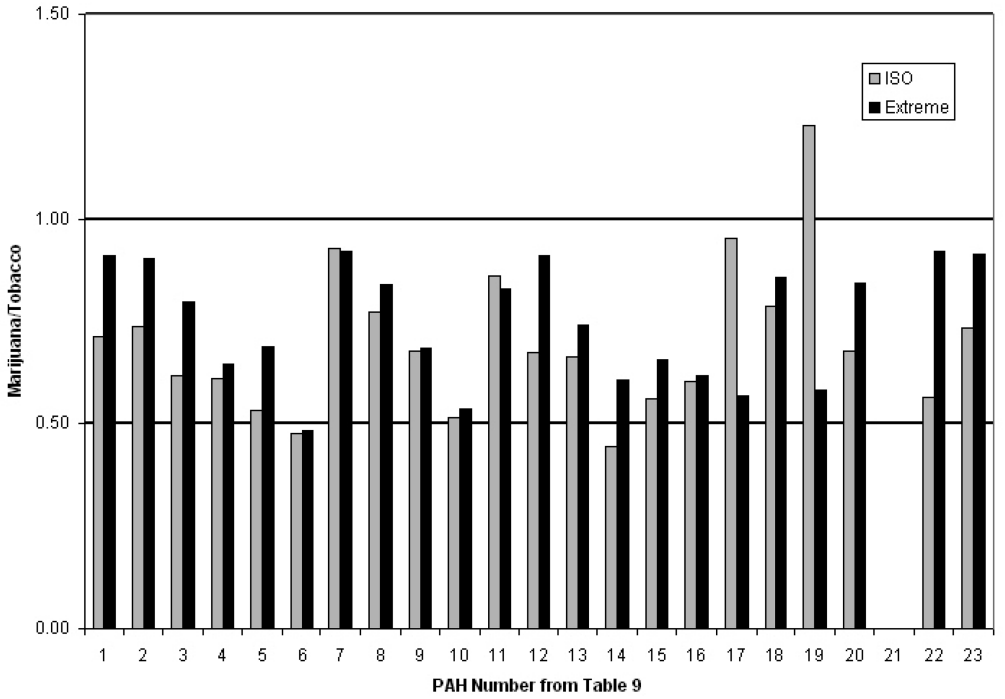

Figure 1. Marijuana to tobacco ratios of PAH analytes in mainstream smoke generated under two smoking conditions.

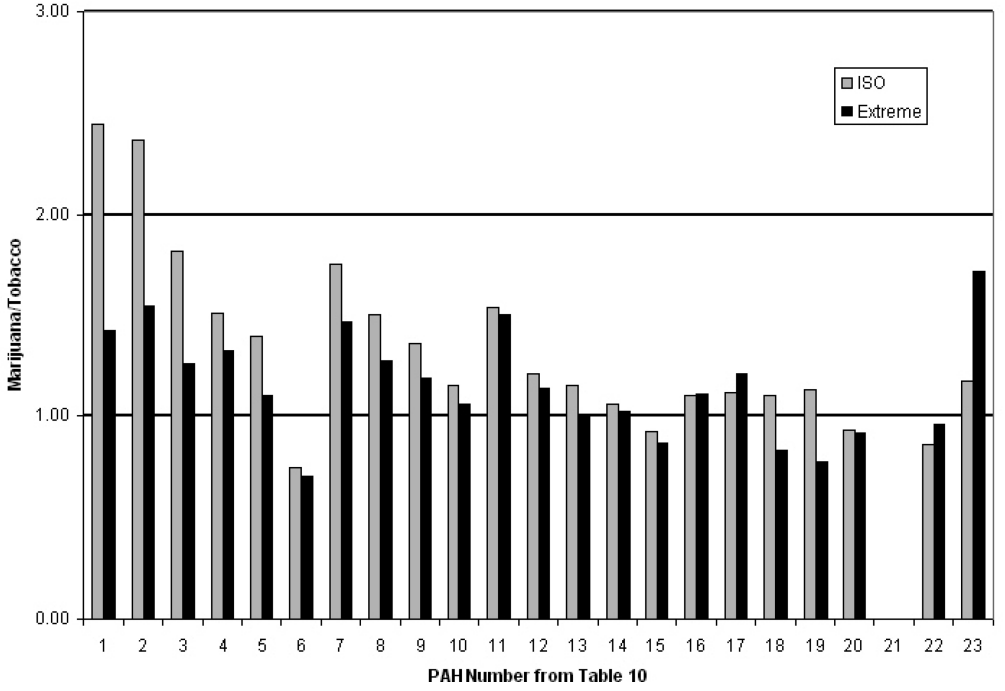

Figure 2. Marijuana to tobacco ratios of PAH analytes in sidestream smoke generated under two smoking conditions.

PAH formation. However, in a study examining the levels of 14 PAHs in commercial tobacco cigarettes, no correlation could be found between nitrate levels and PAH content in the smoke (*38*). The authors concluded that many factors affect the ultimate concentration of PAHs in mainstream smoke.

The sidestream smoke tells a different story from the mainstream, with marijuana showing greater yields of a number of PAHs than those from tobacco. The differences seem to be more pronounced for the lower molecular weight substances as shown in Figures 1 and 2.

The combustion of any plant material will result in a complex mixture of chemicals, the composition and percentages of which depend on a large number of variables. The present study supports previous research (*16, 20*) and found that marijuana smoke contains qualitatively many of the same chemicals as tobacco smoke. This qualitative similarity is more important when assessing the risks for adverse outcomes than are the differences in level of a particular substance, which can change from sample to sample or from one smoking condition to another. That being said, on a quantitative basis, a number of chemicals were present in marijuana smoke at levels that were substantially higher than in tobacco smoke. For example, NO, NO_x, hydrogen cyanide, and aromatic amines were present in marijuana smoke at levels 3−5 times higher than in mainstream tobacco smoke, while ammonia was present at levels 20 times higher than tobacco. Conversely, some compounds such

as PAHs, formaldehyde, and acetaldehyde were found at moderately higher levels in tobacco.

This study focused specifically on the chemical analytes routinely measured in tobacco smoke, and consequently, many compounds were not included for analysis. Future work could include analytes recently identified as potential issues in marijuana smoke. For example, aluminum has been found in high levels in both tobacco and cannabis and has been seen to be biologically available, presenting the potential for aluminum-mediated toxicity (*39*).

Differences in the chemistry of the smoke condensates were observed between mainstream and sidestream smoke. Previous studies have shown that sidestream tobacco smoke contains higher levels of chemicals than mainstream smoke (*40*), and these differences have been largely attributed to variations in pH and combustion temperature (*41*). Differences were also noted in the chemical composition of smoke obtained under the ISO smoking conditions vs under the extreme smoking conditions. Because the chemical composition of smoke is thought to be influenced by the smoking regime (*42*), this finding further demonstrates the importance of selecting an appropriate model when investigating the exposures and potential hazards associated with smoking marijuana or tobacco.

Many of the analytes detected in the smoke condensates are known to be cytotoxic, mutagenic, and/or carcinogenic (IRIS Database, www.epa.gov/iris). In particular, compounds such as PAHs, aromatic amines, and *N*-heterocyclics are thought to be responsible for a significant part of the mutagenic and carcinogenic activity of cigarette smoke condensate (*43, 44*). In a companion paper, we will evaluate the relative in vitro (geno) toxicity of mainstream and sidestream tobacco and marijuana smoke condensates in three different biological systems. Together with the chemistry data, the biological data will enable a better assessment of the relative hazards posed by tobacco and marijuana cigarettes smoked under identical conditions.

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