

Original investigation

Chemical Analysis and Simulated Pyrolysis of Tobacco Heating System 2.2 Compared to Conventional Cigarettes

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Abstract

Introduction: Tobacco Heating System 2.2 (THS 2.2, marketed as IQOS) is a heat-not-burn (HNB) tobacco product that has been successfully introduced to global markets. Despite its expanding market, few independent and systematic researches into THS 2.2 have been carried out to date.

Methods: We tested a comprehensive list of total particulate matter (TPM), water, tar, nicotine, propylene glycol, glycerin, carbon monoxide, volatile organic compounds, aromatic amines, hydrogen cyanide, ammonia, N-nitrosamines, phenol, and polycyclic aromatic hydrocarbon under both ISO and HCl regimes. We also simulated pyrolysis of THS 2.2 heating sticks and made comparisons with conventional cigarette tobacco fillers using comprehensive gas chromatography–mass spectrometry (GC × GC-MS) to determine whether the specially designed ingredients help reduce harmful constituents.

Results: Other than some carbonyls, ammonia, and N-nitrosoanabasine (NAB), the delivered releases from THS 2.2 were at least 80% lower than those from 3R4F. Tar and nicotine remained almost the same as 3R4F. Interestingly, the normalized yield of THS 2.2 to 3R4F under the HCl regime was lower than that under the ISO regime.

Conclusions: THS 2.2 delivered fewer harmful constituents than the conventional cigarette 3R4F. Simulated pyrolysis results showed that the lower temperature instead of specially designed ingredients contributed to the distinct shift. In particular, if smoking machines are involved to evaluate the HNB products, smoking regimes of heat-not-burn tobacco products should be carefully chosen.

Implications: To our knowledge, few independent studies of HNB products have been published. In this paper, a comprehensive list of chemical releases was tested systematically and compared to those from 3R4F. Although THS 2.2 generates lower levels of harmful constituents, the nicotine and tar levels were almost identical to 3R4F. The results should be discussed carefully in the

future when assessing the dual-use with other conventional cigarettes, nicotine dependence of HNB products, etc. This study also suggests that regulatory agencies should pay attention to the smoking regimes that are adopted to evaluate HNB tobacco products.

Introduction

Tobacco use is the leading cause of global preventable morbidity and mortality. In spite of the adverse health effects of tobacco use, many people continue to smoke. CDC (Center for Disease Control and Prevention) and HHS (United States Department of Health and Human Services) have reported that more than 70% of smokers want to quit smoking completely, yet only 6% of smokers are able to successfully quit.^{1,2} Thus, many smokers tend to seek tobacco products that have lower risks. E-cigarettes provide an alternative for smokers as they are generally perceived to be less harmful than conventional cigarettes.³ However, E-cigarette devices do not use real tobacco ingredients and lack the so-called “throat-hit” or authentic tobacco tastes that cigarettes offer, encouraging some people to go back to conventional cigarettes.⁴ In contrast, heat-not-burn (HNB) products taste more like conventional cigarettes while delivering nicotine to consumers. E-cigarettes users have perceived that noncombustible devices are lower-risk than conventional cigarettes, although non-combustible devices like e-cigarettes are nontobacco to this point unlike emerging HNB products. In short, HNB products “are about to reach their boiling point.”⁵

Philip Morris International's (PMI) Tobacco Heating System 2.2 (THS 2.2; marketed as IQOS) is a typical HNB tobacco product. Notably, the markets exhibited a visible trend of increased sales, especially in Japan where THS 2.2 had claimed a cigarette market share of 6.8% as of January 2017.⁶ In contrast to a conventional lit-end cigarette, THS 2.2 is an electrically heated cigarette, which is heated and used in a tobacco-heating device. A consumable cigarette stick remains in constant contact with a thin heating blade that is located inside the tobacco-heating device. During use, the cigarette stick is maintained at a controlled heating temperature so that the cigarette stick remains unburned and at a lower temperature than lit-end cigarettes. PMI has claimed that these electrically heated products reduce high-temperature pyrolysis (thermal decomposition under inert atmospheres) and thus reduce a majority of Harmful and Potentially Harmful Constituents (HPHCs). A burning cigarette is separated into two zones: an oxygen-rich combustion zone and an oxygen-deficient pyrolysis/distillation zone. The majority of cigarette emissions are generated in the endothermic pyrolysis zone by a variety of mechanisms.⁷

PMI submitted an application to the FDA for the iQOS system as a Modified Risk Tobacco Product (MRTP). MRTPs are sold or distributed for use to reduce harm or the risk of tobacco-related disease, defined by the Family Smoking Prevention and Tobacco Control Act of 2009⁸ (FSPTCA). The FSPTCA requires the FDA to issue guidance or regulation on the scientific evidence required for the assessment and ongoing review of an MRTP applicant.

To support the health claims of THS 2.2, PMI has published several peer-reviewed papers.^{9–20} Interestingly, PMI adopted the HCI smoking regime to compare the iQOS emissions with reference cigarettes. Few independent, systematic researches into THS 2.2 have been carried out, however, despite its expanding market. Recently, Auer et al.²¹ compared volatile organic compounds (VOCs), polycyclic aromatic hydrocarbons (PAHs), carbon dioxide, carbon monoxide, nitric oxide and nicotine of iQOS and a commercial cigarette using a revised ISO puffing regime. They found that iQOS contains

similar species of harmful constituents as conventional cigarettes. In addition, smoking behavior of HNB products has not been investigated thoroughly and thus there are yet no standard smoking regimes for HNB. Therefore, the released constituents of HNB products should be monitored comprehensively under different regimes. When these data have been generated, the variability of the harmful constituents across the products, and the potential for the constituents to be reduced, can be evaluated. Furthermore, experiments should be carried out to explain the HNB emissions results, for example, whether the reduced releases of these constituents are the result of HNB methods or other combined effects. It is noteworthy that reduction of harmful constituent emissions cannot be interpreted as equivalent to a proportionate reduction in harm to the user. There is no long-term health data on the health implications of using HNB products. Long-term disease reduction data from conventional cigarette exposure reduction did not show a reducing morbidity risk.^{22,23}

To evaluate the impact of THS 2.2 design changes on the resulting smoke, we analyzed a comprehensive list of chemical constituents both under the International Organization for Standardization (ISO) regime and the Health Canada Intense (HCI) regime. The list included tar, nicotine and carbon monoxide (TNCO), propylene glycol and glycerin (humectants), the World Health Organization (WHO) 9 priority components, and a proportion of harmful and potentially harmful constituents (HPHCs). Tar (tobacco) is the common name of nicotine-free dry particulate matter, which is the portion of the mainstream smoke trapped in the smoke trap after deduction of its water content and nicotine content.²⁴ Because of the heating properties of tobacco-heating devices, we adjusted the smoking experiment procedures of THS 2.2 to meet the requirements of the standard ISO and HCI regimes. We adapted the chemical composition data of 3R4F except propylene glycol and glycerin from Roemer et al.²⁵ In addition, to better explain the reduced HNB emission results, we performed a simulated pyrolysis experiment to confirm whether the reduced constituents are due to the HNB design or the combined effects of a specially processed tobacco filler inside the heating stick. Pyrolysis experiments are a common technique to establish the relationship between tobacco constituents and smoke products.^{7,26–28} We used a pyrolyzer, which simulated the working temperature inside the THS 2.2 heating devices. THS 2.2 and three other commercial tobacco products were heated in the pyrolyzer and the emissions were transferred to comprehensive gas chromatography–mass spectrometry (GC×GC-MS) to compare the differences. GC×GC-MS is a relatively new analytical technique that is quite suitable for detecting unknown compounds in complex mixtures, such as tobacco smoke.

Methods

Chemical Characterization of Mainstream 3R4F and THS 2.2 Emissions

Test Samples

We purchased reference research cigarettes 3R4F from the University of Kentucky (Lexington, KY, USA). The THS 2.2 systems were provided by Philip Morris International (Lausanne, Switzerland).

Mainstream Emission Preparation

Before smoking, the consumable cigarette sticks (THS 2.2) and 3R4F were conditioned at 22°C and 60% relative humidity for at least 48 h following ISO 3402.²⁹ Cigarette smoking was carried out with an SM450 linear smoking machine (Cerulean, England). THS 2.2 uses an automatic instrument for heating the consumable cigarette stick for about 6 min after ignition, which is achieved by pressing a start button: (1) preheating process: the heating blade is heated for 30 s; and (2) smoking process: following preheating, the heating works for approximately 5.5 min. During the working condition, the cigarette stick is controlled in a heating status without combustion, so the consumable stick length remains unchanged after smoking, which made air velocity control inappropriate. Two smoking regimes were adopted: (1) Under the ISO regime, the smoking machine drew a 35 mL puff volume every 60 s with a puff duration of 2 s in combination with no blocking of filter ventilation; and (2) Under the HCl regime, the smoking machine drew a 55 mL puff volume every 30 s with a puff duration of 2 s in combination with 100% blocking of filter ventilation. Because of the fixed heating time, the puff numbers of THS 2.2 under the ISO and HCl regimes were fixed at 6 and 12, respectively.

Determination of Chemical Analytes

Chemical determination was performed according to ISO 4387, ISO 10315, and ISO 8454.^{30–32} Mainstream emissions were collected on a Cambridge glass fiber filter (44 mm diameter). TPM (total particulate matter) and tar levels were determined gravimetrically (measurement by weight). Water was determined by gas chromatography with a thermal conductivity detector and nicotine, propylene glycol and glycerin were determined by gas chromatography with flame ionization detection. CO was determined by nondispersive infrared photometry integrated with the smoking machine, and chemical determination of volatile organic compounds and carbonyls were simultaneously trapped by a sorbent cartridge inside the Cambridge filter without cryogenic impinge and determined by gas chromatography–mass spectrometry and high-performance liquid chromatography, respectively. Aromatic amines were extracted by hydrochloric acid solution and analyzed by gas chromatography–mass spectrometry. Hydrogen Cyanide was extracted by sodium hydroxide and analyzed by continuous flow analyzer. Ammonia was extracted by hydrochloric acid solution and analyzed by ion chromatography. N-nitrosamines were extracted by acetic acid and analyzed by high-performance liquid chromatography. PAH was extracted by hexane and analyzed by gas chromatography–mass spectrometry. See [Supplementary Material](#) for chemical determination method details.

Online Simulated Pyrolysis of THS2.2 and Conventional Cigarettes

Test Samples and Sample Preparation

Apart from THS 2.2, we selected three other tobacco samples for simulated pyrolysis experiments to help explain the reduced emissions results of HNB products: (1) Reconstituted tobacco, also known as tobacco sheet (abbreviated as RECON) was provided by China Tobacco Henan Industrial Corporation. RECON is a type of tobacco product that uses tobacco by-products, such as tobacco dust, stems, and fines. RECON is an important part of conventional cigarette fillers, which introduces a significant number of additives into the cigarette filler blend enhancing the flavor and reducing harshness.³³ From a physical aspect, we found that THS 2.2 heating stick fillers are quite similar to RECON. (2) Two conventional commercialized conventional cigarettes, including Chinese Virginia

Cigarettes (CVS, China Tobacco) from Chinese Marked and Blended Cigarettes (BC, Philip Morris Int.) were adopted instead of reference cigarettes. Because the simulated pyrolysis experiments mainly aimed to discover whether any specially processed tobacco ingredients help reduce the emissions, commercial cigarettes may better represent conventional tobacco filler designs, which may appeal to smokers' tastes. All of the samples were crushed with a rotary cutting mill to pass 80 mesh sieves.

Online Simulative Pyrolysis: Comprehensive Gas Chromatography–Mass Spectrometry

We conducted simulative pyrolysis tests with a Pyroprobe 5200 analytical pyrolyzer (CDS Analytical, Inc., Oxford, PA, USA). In a 25-mm quartz tube (2.0 mm internal diameter) between quartz wool, 1 mg of each sample was placed. The quartz tube was inserted into the pyrolyzer interface, and then pyrolyzed using a Pt filament that coiled the tube. The Pt filament was heated rapidly to 300°C or 350°C (a similar temperature to the heating source inside THS 2.2) and the sample was then held for 60 s under high-purity helium flux during simulative pyrolysis. The volatiles emitted via this fast heating were conducted by helium through a heated transporting tube (280°C, 1 m) to comprehensive gas chromatography–mass spectrometry (GC×GC-MS QP2010 Ultra system, Shimadzu, Inc., Kyoto, Japan). See [Supplementary Material](#) for GC×GC-MS method details. Notably, the simulated pyrolysis of all samples was conducted at a similar heating temperature of THS 2.2, whereas in the chemical characterization experiments the THS 2.2 and the conventional combustible cigarettes were tested in their working temperature respectively, which means that THS 2.2 were heated at a much lower temperature than conventional combustible cigarettes. Shimadzu GC-MS solution software and Zoex GC image software, GC project software, and GC investigator software were used for data analysis and construction of GC×GC chromatograms. For tentative identification of pyrolysis products, all mass spectra were compared to the National Institute of Standard and Technology (NIST) mass spectral library.

Data evaluation

Comprehensive analysis of the large and complex data, however, is extremely difficult, and analyzing the data from multiple samples presents even more complicated challenges. The data comparison method was adopted from Reichenbach et al.,^{34,35} and computed and visualized by GC image and GC investigator software. The informatics for cross-sample analysis improves inter-sample peak matching by aligning the sample chromatogram with a few reliably matched peaks, generating a cumulative chromatogram, and creating a feature vector for cross-sample discriminant analysis. The Fisher ratio analysis and analysis of variance were used to find differences between samples for data comparison, which calculates the difference among the samples using Fisher discriminant analysis (FDR) based on the cumulative chromatograms using a feature template from all samples.

Results

Chemical Characterization of Mainstream Emissions

[Table 1](#) summarizes the yields of basic analytes, carbon monoxide, volatile organic chemicals (VOCs), carbonyls, aromatic amines, hydrogen cyanide, ammonia, N-nitrosamines, phenol, and polycyclic aromatic hydrocarbons (PAH) of 3R4F and THS 2.2 under the ISO and HCl regimes. Among the basic analytes, TNCO includes tar,

nicotine, and carbon monoxide, which legally must be printed on cigarette packs. Under both regimes, THS 2.2 released much less carbon monoxide than 3R4F (reduced by more than 90% on a per-cigarette basis). This result from the HNB device can be rationalized because carbon monoxide mainly comes from incomplete combustion.³⁶ In contrast, tar from THS 2.2 was almost the same as 3R4F, whereas nicotine was slightly lower than that from 3R4F. However, water increased by 1541.67% under ISO regime and 268.08% under HCI regime for THS 2.2 compared to 3R4F. On the contrary, tar decreased slightly by 6.39% under ISO regime and 34.9% under HCI regime. Propylene glycol were not detected in 3R4F mainstream emissions under both regimes. Glycerin increased by 99.72% under

ISO regime and 64.27% under HCI regime for THS 2.2 compared to 3R4F. Because TPM is composed mostly of water, nicotine, and tar (nicotine-free dry particulate matter), the basic analyte results suggest that the major difference in TPM among the test items is water. Except for basic analytes, the determined components almost all come from the FDA's list of HPHCs. Thus, THS 2.2 resulted in lower HPHC levels compared to 3R4F. Except for carbonyls, ammonia, and NAB, the reduction rate is more than 90%. The reduction effect of carbonyls, ammonia, and NAB is relatively less than the other tested HPHCs. Ammonia release was 63.41% less than 3R4F under the HCI regime and formaldehyde and acetaldehyde were 55.80% and 77.34% less than 3R4F under the ISO regime (Table 1).

Table 1. Chemical Characterization of 3R4F and THS 2.2 Under Both Regimes

Analyte	Unit	ISO				HCI				
		per cigarette	3R4F		THS 2.2		3R4F		THS 2.2	
			Mean	Mean	SD	Reduction rate (%)	Mean	Mean	SD	Reduction rate (%)
Basic Analytes										
TPM	mg	9.77	25.70	0.84	-163.05	37.70	55.82	1.10	-48.06	
Water	mg	1.08	17.73	0.51	-1541.67	10.30	37.91	0.77	-268.06	
Nicotine	mg	0.71	0.50	0.03	29.28	1.90	1.35	0.07	28.95	
Tar	mg	7.98	7.47	0.42	6.39	25.50	16.60	0.42	34.90	
Propylene glycol	mg	—	0.23	0.01	—	—	0.63	0.05	—	
Glycerin	mg	0.80	1.59	0.02	-99.72	2.34	3.84	0.12	-64.27	
Carbon monoxide	mg	11.20	0.25	0.06	97.77	32.70	0.52	0.04	98.41	
VOCs	µg	579.20	1.54	0.06	99.7	1318.50	6.77	0.04	99.5	
1,3-butadiene	µg	38.50	NQ*	/	—	76.50	0.45	0.03	99.41	
Isoprene	µg	395.00	0.58	0.06	99.85	863.00	3.02	0.25	99.65	
Acrylonitrile	µg	26.40	NQ	/	—	67.00	0.21	0.01	—	
Benzene	µg	45.70	0.12	0.01	99.74	104.00	0.61	0.04	99.41	
Toluene	µg	73.60	0.84	0.05	98.86	208.00	2.48	0.18	98.81	
Carbonyls	µg	948.80	191.27	0.43	79.8	2899.73	308.24	0.81	89.4	
Formaldehyde	µg	20.00	8.84	0.43	55.80	68.10	21.87	0.81	67.89	
Acetaldehyde	µg	567.00	128.50	9.96	77.34	1534.00	210.00	21.71	86.31	
Acetone	µg	210.00	18.83	0.48	91.03	690.00	26.59	1.17	96.15	
Acrolein	µg	56.70	4.01	0.15	92.94	155.00	6.37	0.32	95.89	
Propionaldehyde	µg	48.40	9.59	0.19	80.18	124.00	11.76	0.38	90.52	
Crotonaldehyde	µg	10.10	2.39	0.09	76.38	43.10	6.42	0.28	85.10	
Butanal	µg	25.60	14.87	0.22	41.92	65.03	18.77	0.53	71.13	
2-Butanone	µg	11.00	4.24	0.46	61.44	220.50	6.46	0.33	97.07	
Aromatic Amines	ng	19.36	NQ	0.01	100.0	38.12	NQ	0.01	100.00	
1-Aminonaphthalene	ng	10.62	NQ	/	—	21.60	NQ	/	—	
2-Aminonaphthalene	ng	5.69	NQ	/	—	10.10	NQ	/	—	
3-Aminobiphenyl	ng	2.04	NQ	/	—	4.18	NQ	/	—	
4-Aminobiphenyl	ng	1.01	NQ	/	—	2.24	NQ	/	—	
Hydrogen Cyanide	µg	70.90	NQ	0.01	100.00	319.00	NQ	0.01	100.00	
HCN	µg	70.90	NQ	/	—	319.00	NQ	/	—	
Ammonia	µg	11.10	2.41	0.44	78.27	28.70	10.50	1.62	63.41	
Ammonia	µg	11.10	2.41	0.44	78.27	28.70	10.50	1.62	63.41	
N-nitrosamines	ng	280.10	17.20	0.32	93.9	794.00	41.50	0.46	94.8	
NNN	ng	92.10	5.00	0.32	94.57	276.00	10.50	0.46	96.20	
NNK	ng	85.50	3.50	0.17	95.91	243.00	7.30	0.34	97.00	
NAT	ng	92.90	6.10	0.42	93.43	251.00	18.10	0.67	92.79	
NAB	ng	9.60	2.60	0.15	72.92	24.00	5.60	0.31	76.67	
Phenol	µg	7.04	NQ	0.01	100.00	14.80	1.20	0.05	95.8	
Phenol	µg	7.04	NQ	/	—	14.80	1.20	0.05	95.8	
PAH	ng	6.73	NQ	0.01	100.00	16.20	NQ	0.01	100.00	
Benzo(a)pyrene (B[a]P)	ng	6.73	NQ	/	—	16.20	NQ	/	—	

*NQ: Not quantified

Ammonia, formaldehyde, and acetaldehyde are listed on the WHO 9 priorities list. The International Agency for Research on Cancer (IARC) classified formaldehyde and acetaldehyde as category 1 and category 2B carcinogens.³⁷ Except NAB, the other TSNAs (NNN, NNK, and NAT) release is over 92% less than 3R4F under both regime. On the contrast, NAB release is only 72% less than 3R4F under both regimes. NNN and NNK are classified as Group 1 by IARC, whereas NAT and NAB are classified as Group 3.³⁷

Simulated Pyrolysis in Working Temperature of THS 2.2

Figure 1 only depicts the four chromatograms of the simulated pyrolysis samples at 350°C because simulated pyrolysis chromatograms at 300°C are similar to those at 350°C. The GC×GC-MS data are represented in a two-dimensional array. Each pixel is color-coded, from cold to hot, to indicate detected compound scale at a specific time. In the simulated pyrolysis GC × GC-MS experiments, thousands of compounds are separated and characterized, providing a rich and useful source of chemical information. The simulated pyrolysis is similar to the real working condition of THS 2.2. Thus, the emissions from simulated pyrolysis by online determination should help explain the real tar levels released by THS 2.2 under real working status. Thus, from the online GC×GC-MS data and mainstream characterization, we could infer that THS 2.2 tar is mainly composed of glycerin (percent response 56.26%) and propylene glycol, followed by some primary decomposition products, such as 1-acetate-1,2,3-propanetriol, formyl acetate, 1-hydroxy-2-propanone, and lactamide (listed in descending order with a percent response larger than 1). Because the high amount of glycerin releases, propylene glycol blob may have been covered by glycerin in the GC×GC-MS chromatogram. It is important to note that all these compounds were identified by comparing

mass spectra of the samples with NIST library mass spectra without further verification or quantification by standard substance. More carefully conducted verification experiments should be performed to figure out the tar constituent of THS 2.2.

All the samples are pyrolyzed in a simulated iQOS working condition, comparing the differences among THS 2.2 (Figure 1a) and the other samples (Figure 1b–d) would help to further understand whether specially designed ingredients help reduce releases. Because the main purpose of simulated pyrolysis is to determine whether the THS 2.2 heating stick fillers generate significantly different chemical constituents compared to conventional tobacco products, we classified three other samples (BC, RECON, and CVS) into a conventional group. First of all, no new released compound was found in comparison to the conventional tobacco products. The FDR one-versus-(the other three) were calculated and labeled as FDR (THS 2.2, others), FDR (BC, others), FDR (RECON, others), and FDR (CVS, others). If the FDR (THS 2.2, others) of one compound is larger than the other three FDR ratios, that means the difference of this compound between THS 2.2 and the conventional tobacco groups is larger than the difference within the conventional tobacco group; that is, this compound emission is significantly different between THS 2.2 and conventional products. Because all the heating conditions are the same, these differences would imply release by a special ingredient in the THS 2.2 heating stick. Also, F value was calculated for all compounds on the cumulative chromatograms from all samples. For compounds that are significantly different ($p < .05$) among the four samples (Supplementary Figure S1 and Supplementary Table S1), the FDR (THS 2.2, others) of only 18 compounds were larger than the other FDR of FDR one-versus-(the other three), which indicates only 18 compounds are significantly different from the conventional tobacco products in scale. Glycerin exhibited an FDR (THS 2.2, others) of 1951.27, whereas the other 17 compounds exhibited FDR

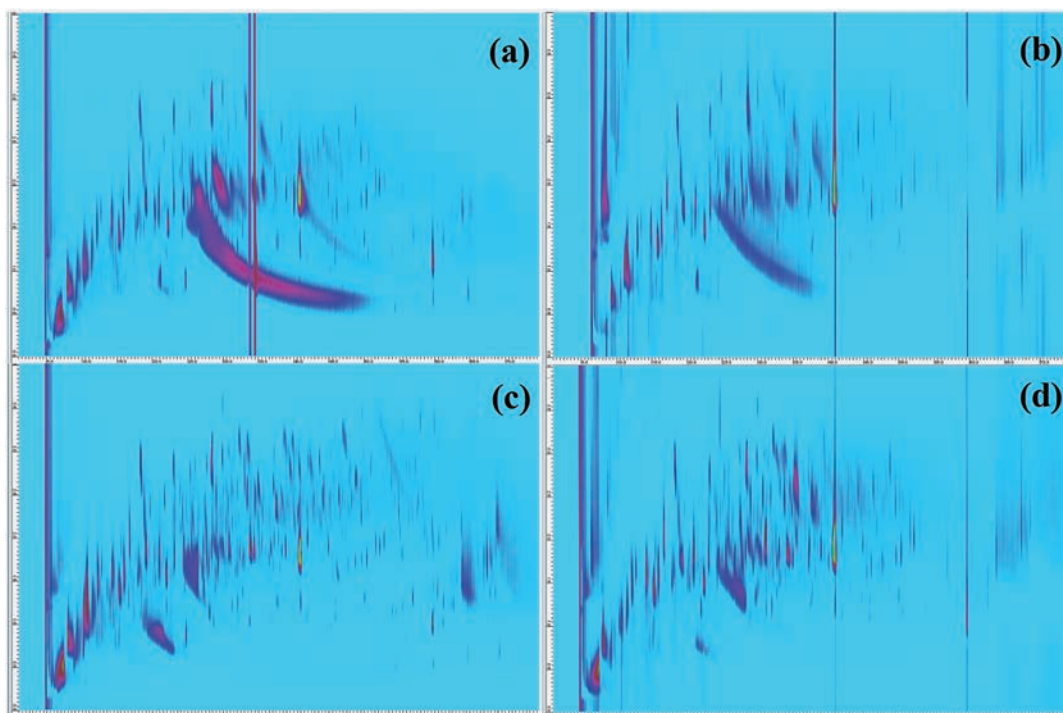


Figure 1. GC×GC-MS color-coded chromatograms of simulated pyrolysis: (a) THS 2.2, (b) BC, (c) RECON, and (d) CVS.

(THS 2.2, others) of between 2.82 and 116.61. This result suggests that the biggest difference is the additional glycerin. The other identified compounds appear to be those such as pyrolysis flavor products, such as Li-mone-6-ol pivalate, and pyrolysis cellulose products, such as Beta. -D-Glucopyranose, and 1,6-anhydro.³⁸ The distinguishing identification number of the 18 compounds was very small relative to the total number of features (more than 1000), indicating that under simulated pyrolysis conditions, IQOS generates similar products as conventional tobacco fillers. Because, IQOS released very similar constituents to conventional cigarettes products when heated to the same temperature, we can conclude that the low temperature of HNB products during use, rather than the ingredients in the heating sticks, contributes to the reducing effects of harmful constituents. The results also showed that iQOS emissions are quite similar to directly heated releases of commercial tobacco products.

Discussion

The chemical characterization results suggest that THS 2.2 releases tar and nicotine yields similar to 3R4F, but much more water than 3R4F. The high-water release may be due to the addition of glycerol and propylene glycol in the THS 2.2 heating sticks. Glycerol and propylene glycol are frequently used tobacco humectants used to absorb atmospheric water and to decrease smoke irritation in the throat. They are also used in the THS 2.2 system or e-cigarettes to produce mainstream emissions. Regulatory agencies should pay attention to similar nicotine levels in THS 2.2 mainstream emissions, which may be designed commercially as an alternative to satisfy smokers.

THS 2.2 delivered more than 90% fewer HPHCs, except for carbonyls, ammonia, and NAB, which were about 50–80% lower. These results may be due to the electronically heated technology. The heating element of THS 2.2 is set at less than 350°C to produce mainstream emissions and a temperature-control adjuster is connected to the heating element. Once the temperature exceeds 350°C, power to the heating element cuts off to avoid overheating. The heating stick was cut and unfolded after the smoking experiment both under the ISO and HCI regimes, and only a few signs of combustion (eg, charcoal) were identified. Thus, for the determined components, the reduction rate was more than 90%, and the results are quite reasonable: (1) carbon monoxide (reduction rate >97.00%) is mostly produced by incomplete combustion; (2) VOCs, aromatic amines, hydrogen cyanide, phenol, and PAH (reduction rate >98%) are mainly produced in high-temperature pyrolysis of carbohydrates and proteins in tobacco^{39–41}; and (3) N-nitrosamines (NNN, NNK, NAT >90%; NAB >70%) are mainly volatilized and transferred from tobacco filler to mainstream emissions, although a portion of NAB could be produced from the thermosynthesis of a tobacco precursor.⁴² Ammonia and carbonyls are also pyrolysis products included in tobacco filler, but our results suggest that at 300°C–350°C, carbohydrates and nitrogen-containing compounds included in tobacco fillers produce a certain number of carbonyls and ammonia. In addition, previous pyrolysis experiments on tobacco precursors have shown that temperature has less effect on ammonia and carbonyls formation.^{43,44} To be clear, the reduction of harmful constituent emissions cannot be interpreted as equivalent to a proportionate reduction in harm to users. The long-term health effects of HNB products in particular should be further evaluated.

We compared our HNB release results with reported E-cigarette aerosols.^{45,46} The testing results of E-cigarettes indicated little or no detectable levels of most HPHCs under normal working conditions. Some carbonyls were quantifiable, but several times lower than

conventional cigarette releases, except in dry puff conditions.^{45–47} E-cigarette emissions may differ by randomly selected parameters (brand, type, flavor, voltage, etc.).⁴⁸ Generally, E-cigarettes were reported lower HPHCs^{45–47} than THS 2.2 from our results (Supplementary Table S2), but similar levels of nicotine.⁴⁹ When the user activated the E-cigarette devices by pushing a button or inhaling, the heating elements raise the E-liquid temperature to 100°C–250°C to generate an aerosolized vapor.⁵⁰ The working temperature of E-cigarettes was lower than that of HNB products. Nicotine was added into some E-liquids products on purpose, but E-liquids do not use tobacco ingredients thus do not contain most of the HPHC precursors in tobacco fillers. In addition, lower working temperature will decrease pyrolysis process that may further decrease HPHC products. We also compared our results to both former independent research and PMI studies of iQOS. As yet, few independent research papers have been published, to the best of our knowledge. Auer et al.²¹ published a short research letter and tested a simpler list of VOCs, PAHs, three inorganic compounds, and nicotine under a revised ISO regime. We reached similar results that THS 2.2 emissions still contain some harmful constituents, just as conventional cigarettes, which also suggested that “some advertising slogans such as heat-not-burn are no substitute for science.”²¹ PMI⁹ tested the THS 2.2 emissions under the HCI regime and showed the similar reducing effects as our results under the HCI regime. However, our results under the ISO regime suggested a “worse” harmful constituent reduction compared to 3R4F. Previous PMI’s series studies^{12–15} of toxicology results both from in vivo and in vitro suggested lower toxic effects than conventional cigarettes. However, only HCI regimes were used to generate emissions for toxicology comparison. We observed smokers’ smoking behavior by smoking behavior machine and found that the puffing parameter varied significantly and individually. No standard HNB product puffing regimes have been published, and our results suggest that puffing regime affects the comparison results between HNB products and conventional cigarettes. Thus, it should be careful when smoking machine is involved in HNB production evaluation.

For further insight into how HNB technology affects the mainstream emissions under the ISO and HCI regimes, Figure 2 depicts the reduction results of HPHCs under the two regimes. The y-axis is the component release ratio of THS 2.2 to 3R4F, which also indicates the normalized yields of THS 2.2 to 3R4F. Figure 2 shows that THS 2.2 HNB technology significantly decreased VOCs, aromatic amines, hydrogen cyanide, phenol, and PAH release, and partially decreased carbonyls, ammonia, and N-nitrosamines (as noted in Table 1). The reduction comparison of HPHCs between the ISO regime and the HCI regime is interesting. Except for ammonia, the normalized yields of most HPHCs under the HCI regime are lower than those under the ISO regime (Figure 2). To further understand the normalized yields of THS 2.2, we applied and compared the ISO and HCI regimes to two samples. In contrast to 3R4F, THS 2.2 emissions would not be eluted because of its unventilated filter under the ISO regime and the higher puff volume would not increase the heating temperature under the HCI regime.⁵¹ To some extent, the different temperature ranges of the conventional cigarette (3R4F) and the HNB product (THS 2.2) may also lead to lower normalized yields of THS 2.2.

We performed further comparisons of smoke chemistry for the 3R4F reference cigarette and THS 2.2 by calculating 3R4F and THS 2.2 yield ratios for HCI and ISO. Yields ratios on a per-cigarette and per-nicotine basis are presented in Table 2. When expressed on a per-cigarette basis, the nicotine ratio of 3R4F is almost the same as THS 2.2 (2.69 versus 2.70), which is expected because THS 2.2 was commercially designed as a cigarette alternative to satisfy smokers’

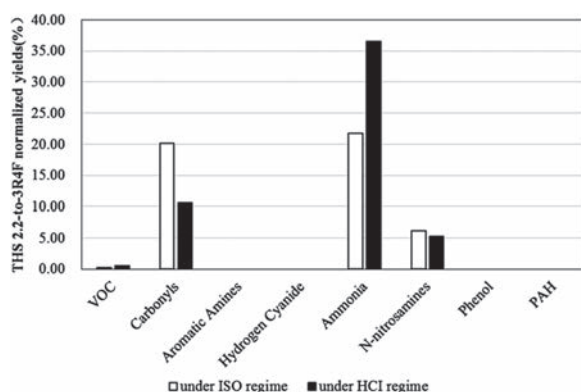


Figure 2. Normalized classified yields of THS 2.2. Comparison under the ISO and HCl regimes.

Table 2. Relative Smoke Basic Analyte Yields HCl-to-ISO Ratio of 3R4F and THS 2.2 on a Per-Cigarette and Per-Nicotine Basis

	HCl-to-ISO Ratio			
	per cigarette		per nicotine	
Basic Analytes	3R4F	THS 2.2	3R4F	THS 2.2
TPM	3.86	2.17	1.44	0.80
Water	9.54	2.14	3.55	0.79
Tar	3.20	2.22	1.19	0.82
Nicotine	2.69	2.70	1.00	1.00
CO	2.92	2.08	1.09	0.77

nicotine addiction. Except for nicotine, the basic analyte yield ratios of 3R4F varied between 2.92 and 9.54, whereas the yield ratio of THS 2.2 is approximately 2 (from 2.08 to 2.22). Interestingly, the puff numbers of THS 2.2 under the HCl regime are exactly two times higher than under the ISO regime (12 versus 6), because of product design, but both have a puff duration of 2 s. These results agree well with our previous analysis that smoking topography affected the THS 2.2 heating condition much less than that of conventional cigarettes. In other words, puff volume is affected much less in the smoke release of the HNB product. Thus, this could explain why the HCl-to-ISO ratio of THS 2.2 per nicotine is less than 1 (Table 2). The results of normalized yields and the HCl-to-ISO ratio comparison strongly suggest that when the use of a smoking machine is involved in comparison with conventional cigarettes, including but not limited to chemical release and toxicology, regulators should pay close attention to the selection of a proper smoking topography. With a rapidly developing market for HNB tobacco products, relevant supervising organizations should reevaluate human smoking behavior and build particular smoking regimes for HNB tobacco products.

Conclusion

The results of this study demonstrate that the majority of mainstream constituents of THS 2.2 were reduced compared to 3R4F. Simulated pyrolysis results suggested that the heat-not-burn condition, which has a much lower pyrolysis temperature than THS 2.2, may cause distinct shifts in the composition of the smoke compared to 3R4F. Some of the chemical constituents (eg, carbonyls and ammonia) from THS 2.2 and 3R4F varied under the two smoking regimes. Thus, more research is needed to evaluate how smoking

behavior influences chemical constituent yields. It is noteworthy that reduction of harmful constituent emissions cannot be interpreted as equivalent to a proportionate harm/risk reduction for smokers. Independent studies, especially into long-term health effects, should be undertaken.

Supplementary Material

Supplementary Figure S1 and Tables S1 and S2 can be found online at <https://academic.oup.com/ntr/>

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Declaration of Interests

The authors declare there is no conflicts of interest regarding the publication of this paper.

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