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Heated Tobacco Products: Volatile Emissions and Their Predicted Impact on Indoor Air Quality

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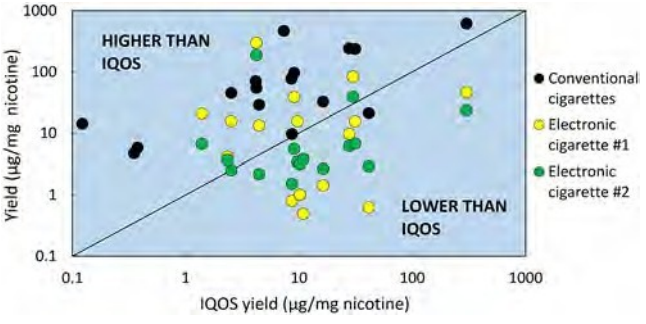
ABSTRACT: This study characterized emissions from IQOS, a heated tobacco product promoted as a less harmful alternative to cigarettes. Consumable tobacco plugs were analyzed by headspace GC/MS to assess the influence of heating temperature on the emission profile. Yields of major chemical constituents increased from 4.1 mg per unit at 180 °C to 6.2 mg at 200 °C, and 10.5 mg at 220 °C. The Health Canada Intense smoking regime was used to operate IQOS in an environmental chamber, quantifying 33 volatile organic compounds in mainstream and sidestream emissions. Aldehydes, nitrogenated species, and aromatic species were found, along with other harmful and potentially harmful compounds. Compared with combustion cigarettes, IQOS yields were in most cases 1−2 orders of magnitude lower. However, yields were closer to, and sometimes higher than electronic cigarettes. Predicted users' daily average intake of benzene, formaldehyde, acetaldehyde and acrolein were 39 μg, 32 μg, 2.2 mg and 71 μg, respectively. Indoor air concentrations were estimated for commonly encountered scenarios, with acrolein levels of concern (over 0.35 μg m^{-3}) derived from IQOS used in homes and public spaces. Heated tobacco products are a weaker indoor pollution source than conventional cigarettes, but their impacts are neither negligible nor yet fully understood.



INTRODUCTION

Over the past few years, disruptive innovations have emerged as alternatives to conventional tobacco products. Electronic cigarettes are being rapidly adopted by millions of users worldwide, and the tobacco industry is developing a new generation of heated tobacco devices. Advocates of this technology, in which tobacco is heated rather than burned (often referred to as "heat-not-burn", or HNB), claim that it is a less harmful alternative to smoking. Earlier versions of these products have been marketed in the US market since the 1990s, but most were discontinued due to poor commercial performance.[1] Innovative, slick heated tobacco platforms are now made possible by the same technical advances that propelled e-cigarettes, such as rapidly rechargeable batteries and compact electronics.

IQOS is the brand name of a heated tobacco device developed by Philip Morris International (PMI) and launched

in more than 40 countries in Asia, Europe, Africa, and South and Central America over the past four years.[2] It has three main components: a consumable tobacco stick (or "heat- stick"), a holder and a charger. Heatsticks are shorter and thinner than conventional cigarettes and are made with reconstituted "cast leaf" tobacco,[3] composed of a finely ground tobacco blend mixed with water, glycerin, guar gum, and cellulose fibers, shaped into thin sheets and rolled up to form a 1 cm long plug. The remaining length (3.5 cm) is occupied by cellulose and polymer filters (Figure S1, Supporting Information). Heatsticks are inserted into the holder, which contains an electronically controlled ceramic blade heater.

Consumers turn on the heater and draw through the filter, in a similar way as in conventional cigarette smoking. Unlike electronic cigarettes, users do not have control of the heating power and duration, which are set by the manufacturer. Once the device is activated, the tobacco stick is heated independently of the frequency and intensity of puffing, generating sidestream emissions that contribute to increasing indoor pollutant levels, as do exhaled mainstream emissions. After 6 min of continuous heating, the heatstick is discarded and the holder battery recharged.[2] The manufacturer claims that by heating tobacco at lower temperatures than conventional cigarettes (below 350 °C) IQOS delivers the desired nicotine doses and organoleptic properties resembling those of cigarette smoking, without combustion, fire, ash, or smoke. An application for consideration as a modified risk tobacco product (MRTP) was filed with the Food and Drug Administration (FDA) in 2017, prior to its release in the USA, and it was still under evaluation at the time of this study. The MRTP classification is applied to products expected to benefit the health of the population as a whole.[4] However, in January 2018, the FDA's Tobacco Products Scientific Advisory Committee established that PMI failed to provide enough evidence to support the claim that this product reduces the risks of tobacco-related diseases.[5]

Several studies have focused on chemical characterization of IQOS mainstream emissions,[6−11] including work carried out by PMI in support of their harm reduction claims.[3,12,13] Overall, results show that emissions from conventional cigarettes are significantly higher than IQOS emissions. When considering the potential impact on the indoor environment, PMI described IQOS as a smoke-free product without any negative effects on indoor air quality.[14] However, a few studies of the chemical composition of IQOS sidestream emissions have reported increased indoor levels of particulate matter and a limited number of volatile compounds.[15−19] This study identified and quantified chemicals released during IQOS operation, including a broad range of volatile organic compounds (VOCs) in mainstream and sidestream emissions. The influence of heating temperature on the emission profile was evaluated. The results were compared with those determined for electronic and conventional cigarettes. By modeling contributions to VOCs concentrations in indoor air under various scenarios, this study also estimated the potential impacts of IQOS emissions on users, as well as the effects on indoor environmental quality.

METHODS

Materials. The IQOS device (Tobacco Heating Device 2.4, Philip Morris Products S.A.) and consumable heatsticks were purchased from a retail tobacco store in France. The IQOS kit included the holder containing a heating blade into which the heatsticks were inserted for consumption (Figure S1), the charger used to recharge the holder after each use, a USB cable with wall adapter, and a set of special brushes and cleaning sticks or swabs to remove residuals remaining after use. The heatsticks, manufactured to be used exclusively with the IQOS device under the brand names HEETS and Marlboro (Philip Morris Products S.A.), were purchased in packs of 20 units each corresponding to three different labels: amber (regular), yellow (light), and blue (mentholated).

High purity compounds were obtained from Sigma-Aldrich for preparation of standards for glycerin, propylene glycol, menthol, acrolein, acetic acid, glycidol, acetol, nicotine, diacetyl

(2,3-butanedione), isoprene, acrylonitrile, *N*-methylforma- mide, *o*-cresol, *p*-cresol, *m*-cresol, benzene, phenol, naphtha- lene, pyridine, pyrrole, 2,3-dimethylpyridine, 3-ethylpyridine, quinoline, 4-ethenylpyridine (as a surrogate for its isomer 3- ethenylpyridine), furfural, 2-furanmethanol, and 1-bromo-4-fluorobenzene. A certified mixture of DNPH (dinitrophenylhy- drazone) derivatives was also obtained from Sigma-Aldrich as standards for analysis of formaldehyde, acetaldehyde, acrolein, acetone, propanal, crotonaldehyde, methacrolein, butanal, 2-butanone, benzaldehyde, *m*-tolualdehyde, and hexaldehyde. Carbonyl-free acetonitrile (Honeywell) and GC grade methanol (Honeywell) were used without further purification. Experimental Setup and Sampling. A laboratory-made 200 L environmental chamber was used to measure main- stream and sidestream emissions. The 56 cm × 56 cm × 64 cm chamber was lined with a polytetrafluoroethylene (PTFE)− coated aluminum film (Bytac, Saint Gobain) to minimize sorption of gases on the walls. Injection and sampling ports were located at the bottom of the front panel. Four 5 cm fans were operated continuously inside the chamber to distribute the air evenly and accelerate mixing. Laboratory compressed air was delivered to the chamber through a HEPA filter (PN 12144, Pall Life Sciences) and an activated carbon bed (PN 12011, Pall Life Sciences). Constant inlet (1000 cm^3 min^{-1}) and outlet (620 cm^3 min^{-1}) air flows were controlled with mass flow controllers (Tylan General) and peristaltic pumps with #16 and 17 tubing (Cole-Parmer MasterFlex L/S). Balance of 380 cm^3 min^{-1} corresponded to chamber leaks due to pressurization. The chamber air change rate of 0.34 h^{-1} was typical for mechanically ventilated homes in the US.[20,21] The air change rate was calculated by measuring tracer gas CO_2 decay in four different locations inside the chamber, as described in the Supporting Information (Figure S2 and Table S1), verifying that the air inside the chamber was well mixed. The IQOS was used inside the chamber according to the manufacturer's instructions, by remotely actuating the start button, and mechanically drawing mainstream emissions through the filter. Heatsticks were consumed following the Health Canada Intense (HCI) smoking protocol, consisting of puff volumes of 55 mL, puff durations of 2 s (1650 cm^3 min^{-1}), and interpuff intervals of 30 s.[22] By design, the heating blade is powered over a 6 min period once the button is activated, generating a total of 12 individual puffs when the HCI protocol is followed. Mainstream emission samples were collected as the heatstick was consumed, and sidestream emissions were assessed by sampling chamber air over the ensuing 3 h period. The experimental setup for volatile carbonyl and VOC sampling is illustrated in Figure S3 (Supporting Information). Only $^1/_4$ in. PTFE tubing and stainless-steel Swagelok connectors were used to collect samples. Blank samples were taken and analyzed for volatile carbonyls and VOCs before using IQOS in the chamber. Volatile carbonyls in mainstream and sidestream emissions were collected onto 2,4-dinitrophenylhydrazine (DNPH)-impregnated silica gel cartridges (Waters Corp.). Mainstream emissions were collected directly from the heatstick onto a DNPH cartridge with a glass syringe, to minimize analyte surface losses. A new cartridge was used for each puff. Sidestream emissions were sampled for volatile carbonyls from the center of the chamber through a DNPH cartridge at 620 cm^3 min^{-1} during IQOS operation and for 3 h after the heatstick was consumed. Volatile organic compounds (VOCs) in mainstream and sidestream emissions were sampled using Carbopack sorbent tubes (Supelco Analytical).

Mainstream emissions were collected onto a sorbent tube connected to a syringe pump drawing air at 40 cm^3 min^{-1}. To keep the total flow as required by the HCI protocol, an additional pump drew the remaining flow (1610 cm^3 min^{-1}) from the heatstick in parallel with the sampling syringe pump. Sidestream VOC emissions were sampled from the center of the chamber through a sorbent tube at 100 cm^3 min^{-1} during IQOS operation and for 3 h after the heatstick was used. An additional peristaltic pump was used to draw air from the chamber at 520 cm^3 min^{-1} to maintain the target air change rate.

Temperature Measurements. The temperature profile during the operation of IQOS was measured by inserting a K- type thermocouple (Testo 922) through the filters up to the inner edge of the tobacco plug. The thermocouple was at approximately 1−2 mm from the heating blade, but not in direct contact. This position captured the temperature of the tobacco that was in the immediate proximity of the heater. After inserting the heatstick inside the device, heating was started and temperature measurements were taken every 10−20 s during the 6 min of operation. The procedure was repeated three times to assess reproducibility.

Chemical Analysis. *Headspace Analysis of Heated Tobacco.* The composition of volatile constituents of three identical mentholated tobacco plugs (blue heatsticks) was determined using headspace gas chromatography with mass- selective detection (HS-GC/MS; Shimadzu HS-20 coupled with QP2010SE). The tobacco content of each heatstick (0.2 g) was transferred into a 20 mL headspace glass vial and incubated for 6 min, the time needed to consume one heatstick, at 180, 200, and 220 °C, respectively. The analytical column (Carbowax 25 m × 0.25 mm, split ratio 20:1) was operated initially at 60 °C for 1 min, followed by a 5 °C min^{-1} ramp to reach 250 °C and held for 6 min. The mass spectrometer source was heated to 200 °C, and signals were detected between mass to charge ratios (m/z) of 33 and 400. Identification of the three major constituents (menthol, glycerin, and nicotine) was carried out with authentic standards. Minor constituents were also identified with standards, or tentatively identified using the NIST MS Standard Reference Database. Quantification was based on calibration curves of authentic standards, which were also used as surrogates for tentatively identified analytes. For the analysis of menthol, glycerin, and nicotine, a split ratio 150:1 was used to avoid saturation of the detector. Reported values are the average of triplicate determinations. Experimental uncertainties were estimated using the standard deviation of those triplicates.

VOCs Analysis in Mainstream and Sidestream Emissions. Analysis and quantification of volatile compounds in main- stream and sidestream emissions were carried out by thermal desorption gas chromatography mass spectrometry (TD-GC/ MS, model 6890/5973, Agilent) using 1-bromo-4-fluoroben- zene as an internal standard.[24] Analytes were identified on the basis of the retention time and mass spectrum of authentic standards. Calibration curves were created for all reported VOCs using those standards. Low-level VOCs detected in the blank measurements did not match with any of the compounds emitted during IQOS operation. Reported values are the average of duplicate determinations. Experimental uncertain- ties were estimated as the absolute difference of those duplicates.

Nicotine mainstream emissions. Nicotine in mainstream emissions could not be quantified using the method described above for VOCs due to losses to the walls of tubing and hardware upstream of sorbent tubes. For that reason, mainstream nicotine emissions were analyzed using an adaptation of the CORESTA (Cooperation Centre for Scientific Research Relative to Tobacco) method No. 22.[25] Mainstream emissions were sampled onto a 47 mm glass fiber filter in a stainless steel holder (Fiberfilm, Pall Life Sciences). The filter was then extracted three times with 5 mL of methanol and sonicated for 10 min. Five microliters of the extract was injected into a Carbopack sorbent tube (Supelco Analytical). Identification and quantification were carried out by TD-GC/MS as detailed above. Triplicate determinations were made for each sample. Experimental uncertainties were estimated using the standard deviation of the replicates.

Modeling Users' Intake and Indoor Air Concentra- tions. *Intake of Mainstream Emissions.* Users' daily intake I_i for each compound i was estimated as a function of the corresponding mainstream emission rate $E_{M,i}$ (yield per heatstick), the retention factor R_i and the number of sticks consumed per day, N, as follows:

$$I_i = E_{M,i} \times R_i \times N \quad (1)$$

The retention factor R_i for each VOC was derived as the product of two quantities: the fraction of each puff effectively inhaled and the fraction of the inhaled compound absorbed in the respiratory system:

$$R_i = (1 - MS) \times R_{R,i} \quad (2)$$

Carbonyl Analysis in Mainstream and Sidestream Emissions. The DNPH cartridges containing mainstream and sidestream emissions were extracted with 2 mL

of carbonyl- free acetonitrile and analyzed by high performance liquid chromatography (HPLC) with UV detection (Agilent 1200), following the EPA TO-11 method.[23] Analytes were identified on the basis of the retention time of authentic standards of dinitrophenylhydrazone derivatives. Calibration curves were generated for quantification of each analyte using those standards for 12 carbonyls. Chamber blank measurements were subtracted from the values obtained for the samples. Reported values are the average of duplicate determinations. Experimental uncertainties were estimated as the absolute difference of those duplicates.

where MS is the fraction of each puff spilled from the mouth and not inhaled and $R_{R,i}$ is the compound-specific respiratory retention during an inhalation/exhalation cycle. In the absence of data describing puffing retention for IQOS, the mean mouth spill value reported for conventional cigarettes (MS = 0.3) was used as a reasonable approximation.[26] Compound-specific $R_{R,i}$ values were taken from the literature for several tobacco-related compounds[27−31] or were predicted by the correlation proposed by St. Charles et al.[26]

Predicted Indoor Air Concentrations of Acrolein Emitted by IQOS. Following a method previously used by our group,[32] two scenarios for simulated indoor environments were devised to predict nonusers' exposure to IQOS emissions: (1) a residential space in which a nonuser lives with a user and (2) bars where IQOS is allowed to be used indoors, as an example of a public space with multiple users. The indoor air concentration of acrolein, a strong respiratory irritant emitted by IQOS, was calculated for each environment using a mass balance equation. The amount of acrolein released into the

indoor environment per heatstick was calculated as the emission rate $E_{acrolein}$, by adding contributions from sidestream and exhaled mainstream emissions, as follows:

$$E_{acrolein} = E_{S,acrolein} + E_{M,acrolein} \times (1 - R_{acrolein}) \quad (3)$$

where $E_{S,acrolein}$ is the sidestream emission rate, $E_{M,acrolein}$ is the mainstream emission rate, and $R_{acrolein}$ is the fraction retained by the user.

These emission rates were used as inputs to calculate indoor air concentrations for residential and public settings as described in the Supporting Information.

RESULTS AND DISCUSSION

Temperature Measurements. The temperature profile inside the tobacco plug is shown in Figure 1. Once heating

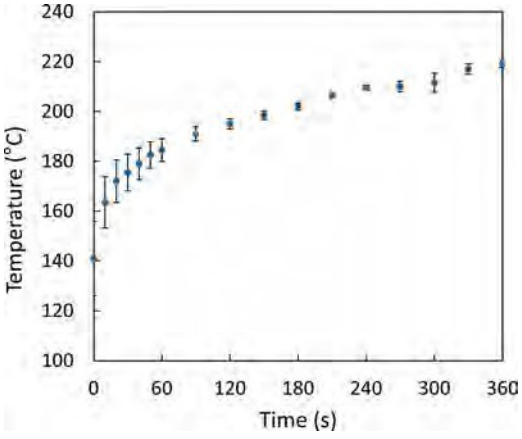


Figure 1. Temperature profile of the tobacco plug over 6 min of operating IQOS.

started, the temperature showed a sharp increase followed by a slower continuous upward trend up to 220 °C at the end of 6 min. The mean temperature during that period was 192 °C. Comparison between used and unused heatsticks suggested that temperature was not homogeneous during the heating process across the tobacco plug. Clear signs of charring and pyrolysis were observed in the portion of tobacco that was in direct contact with the heating blade (Figure S5, Supporting Information). Contrarily, the color of the tobacco farthest from the blade remained almost unchanged compared to an unused heatstick. Auer et al.[33] and Davis at al.[34] expressed concerns about the production and release of harmful constituents by thermal degradation of tobacco.

Headspace Analysis of Tobacco Sticks. Headspace GC/MS analysis of the emissions of tobacco plugs from mentholated IQOS heatsticks led to identification and quantitation of 58 volatile compounds at three different temperatures (180, 200, and 220 °C), listed in Table S2 (Supporting Information). The three incubation temperatures simulated initial, intermediate, and final conditions at the heated tobacco plug. Yields of major chemical constituents increased from 4.1 mg per heatstick at 180 °C to 6.2 mg at 200 °C and 10.5 mg at 220 °C. Menthol, nicotine, and glycerin were the most abundant species. While high levels of nicotine were expected, the two other compounds were present at comparable or higher concentrations. Menthol is the main flavor additive for the blue label heatsticks, and glycerin is the main constituent of the cast-leaf tobacco used to manufacture the sticks.[3] In Table S2, carbonyls and polyols are listed separately, and chemicals listed under the category "other oxygenated compounds" include alcohols, epoxides, oxygenated heterocyclic compounds, carboxylic acids, and multi- functional species. In Figure 2, the yields of menthol, glycerin, and nicotine in milligrams per stick are compared for three different headspace incubation temperatures. For each of these compounds, the yield increased with temperature. While the menthol yield only grew marginally in that temperature range, the nicotine yield almost tripled, and the yield of glycerin at 220 °C was 18 times higher than at 180 °C. Table S2 shows the same tendency for most VOCs, with some species showing significant increases between 200 and 220 °C.

Several carbonyls were found in the headspace analysis of heated tobacco plugs. Acetaldehyde and diacetyl had the highest yields. Acetaldehyde is a known irritant of the respiratory tract and is listed by WHO/IARC as a possible carcinogen to humans (group 2B), and diacetyl has been reported as the cause of a respiratory disease (bronchiolitis obliterans). Its exposure limits are currently under evaluation at the National Institute of Occupational Safety and Health (NIOSH).[35] Other carbonyls found in the headspace included acrolein (strong airways irritant) and glycidol (carcinogen). All these carbonyls have been reported as byproducts of propylene glycol and glycerin thermal decomposition in e-cigarettes.[36,37] The large amount of glycerin in the heatsticks, as well as the presence of its degradation byproducts in IQOS emissions, suggest that pyrolysis of glycerin takes place by mechanisms with strong similarities to those that explain e-

cigarette

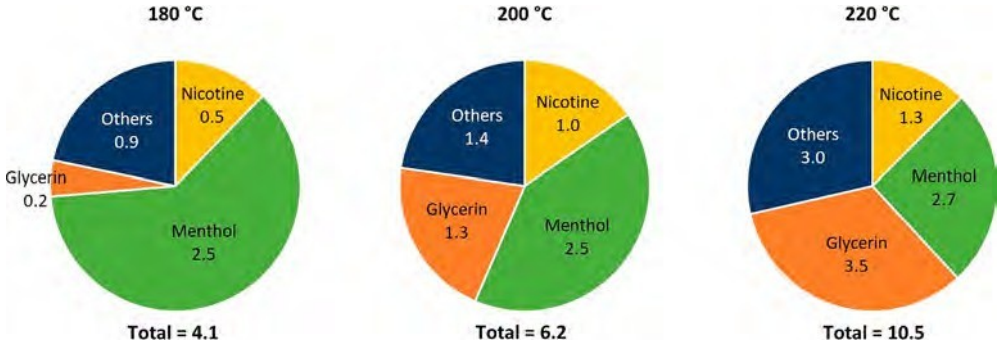


Figure 2. Influence of temperature on major chemical constituents identified in blue label tobacco sticks by headspace analysis. Yields are expressed in milligrams per heatstick.

Table 1. Chemical Constituents Quantified in Mainstream and Sidestream Emissions for Blue, Amber, and Yellow Label Heatsticks[a]

	mainstream emissions (µg per heatstick)			sidestream emissions (µg per heatstick)		
	blue	amber	amber	yellow	blue	yellow
Nitrogenated Compounds						
nicotine	600 ± 140	990 ± 100	702 ± 58	<0.09	<0.09	<0.09
pyridine	2.5 ± 0.3	5.7 ± 0.7	4.0 ± 0.5	0.62 ± 0.08	0.32 ± 0.04	0.57 ± 0.07
3-ethenylpyridine	2.5 ± 2.8	3.1 ± 3.4	1.9 ± 2.1	0.05 ± 0.05	0.03 ± 0.03	0.04 ± 0.05
pyrrole	1.7 ± 0.2	4.7 ± 0.6	2.9 ± 0.4	0.42 ± 0.06	0.26 ± 0.03	0.32 ± 0.04
N-methylformamide	1.1 ± 1.0	ND	0.4 ± 0.3	<0.04	<0.04	<0.04
acrylonitrile	0.2 ± 0.3	0.2 ± 0.2	0.04 ± 0.05	<0.03	<0.03	<0.03
3-ethylpyridine	0.12 ± 0.06	0.05 ± 0.03	ND	<0.04	<0.04	<0.04
2,3-dimethylpyridine	0.03 ± 0.01	0.06 ± 0.03	0.015 ± 0.007	<0.04	<0.04	<0.04
Carbonyls						
acetaldehyde	181 ± 31	151 ± 26	151 ± 26	23.4 ± 5.9	24.2 ± 6.1	18.6 ± 4.7
diacetyl	18.8 ± 3.9	16.4 ± 3.4	16.8 ± 3.5	1.4 ± 0.5	1.4 ± 0.5	1.3 ± 0.5
butanal	24.8 ± 2.2	24.5 ± 2.2	23.0 ± 2.1	2.6 ± 0.9	3.0 ± 1.0	2.3 ± 0.8
acetone	16.7 ± 0.8	16.7 ± 0.8	14.7 ± 0.7	4.3 ± 1.0	3.8 ± 0.9	3.2 ± 0.7
propanal	9.8 ± 1.9	8.1 ± 1.5	7.8 ± 1.5	1.2 ± 0.3	1.2 ± 0.3	1.0 ± 0.3
benzaldehyde	6.6 ± 1.8	5.5 ± 1.6	4.7 ± 1.3	0.4 ± 0.2	0.4 ± 0.2	1.5 ± 0.8
methacrolein	6.1 ± 0.2	5.5 ± 0.2	5.1 ± 0.2	1.0 ± 0.1	1.1 ± 0.1	0.8 ± 0.1
acrolein	5.4 ± 0.7	4.9 ± 0.6	5.3 ± 0.7	0.6 ± 0.3	0.8 ± 0.3	0.7 ± 0.3
crotonaldehyde	5.2 ± 0.6	5.0 ± 0.5	4.9 ± 0.5	0.4 ± 0.2	0.4 ± 0.2	0.3 ± 0.2
formaldehyde	2.52 ± 0.08	2.33 ± 0.07	2.31 ± 0.07	0.9 ± 0.2	1.0 ± 0.2	0.7 ± 0.1
2-butanone	1.5 ± 0.4	1.8 ± 0.5	1.1 ± 0.3	1.5 ± 1.2	1.2 ± 0.9	1.0 ± 0.8
m-tolualdehyde	1.41 ± 0.04	1.89 ± 0.06	1.25 ± 0.04	0.52 ± 0.07	0.52 ± 0.07	0.40 ± 0.05
hexaldehyde	0.8 ± 0.2	0.9 ± 0.1	0.9 ± 0.2	0.2 ± 0.2	0.1 ± 0.1	0.08 ± 0.06
Other Oxygenated Compounds						
acetol (hydroxyacetone)	18.0 ± 0.4	23.7 ± 0.5	19.7 ± 0.4	3.4 ± 1.3	2.4 ± 0.9	1.3 ± 0.5
furfural	11.1 ± 4.5	28 ± 11	17.7 ± 7.1	1.4 ± 0.6	1.0 ± 0.4	1.7 ± 0.7
glycidol	5.8 ± 0.2	7.3 ± 0.2	11.4 ± 0.3	0.10 ± 0.07	0.1 ± 0.1	0.2 ± 0.2
2-furanmethanol	3.1 ± 2.1	6.7 ± 4.6	5.5 ± 3.8	0.7 ± 0.5	0.5 ± 0.4	0.8 ± 0.6
Terpenoids						
isoprene	4.4 ± 0.7	3.7 ± 0.6	3.8 ± 0.6	0.47 ± 0.07	0.8 ± 0.1	0.7 ± 0.1
menthol	670 ± 120	ND	ND	10.5 ± 1.3	ND	ND
Aromatic Compounds						
phenol	5.1 ± 0.2	5.6 ± 0.2	3.1 ± 0.1	0.51 ± 0.08	<0.09	<0.09
p-cresol + *m*-cresol	0.21 ± 0.02	0.19 ± 0.01	0.116 ± 0.008	<0.07	<0.07	<0.07

[a]Mainstream emission samples were collected following HCI smoking protocol over a 6 min period. Sidestream emissions were measured over the ensuing 3 h period. ND: not detected.

emissions of these harmful byproducts. Detection of acetic acid in the headspace analysis further support this hypothesis.

Our headspace analysis has also detected neophytadiene, a diterpene mainly generated during tobacco curing and aging by dehydration of phytol, a metabolite from chlorophyll hydrolysis.[38] Neophytadiene may act as a flavor enhancer and it could be used as additive for e-cigarette liquids.[39] Some authors have reported this compound in conventional cigarettes,[40] while others do not mention it.[41,42] As an unstable diene, neophytadiene is very reactive at high temperatures.[43] Hence, the lower IQOS operation temperatures, compared to conventional cigarettes, could lead to a consistent presence of neophytadiene in its emissions.

Chemical Composition of IQOS Emissions. *Main- stream Emissions.* More than 70 volatile compounds were detected in chromatograms corresponding to IQOS main- stream emissions, from which 33 were identified and

quantified. The composition profile is very similar to that determined by headspace GC/MS analysis of heated tobacco plugs, but significantly more complex than the profiles reported for electronic cigarettes, with more than twice as many chemicals as in e-cigarette emissions.[36] Chemical constituents quantified in mainstream emissions during operation of IQOS are shown in Table 1. These include isoprene, acrylonitrile, cresols, benzene, phenol, naphthalene, acetaldehyde, propanal, acrolein, formaldehyde, 2-butanone, acetone, crotonaldehyde, and quinoline, which are listed by the US FDA as harmful and potentially harmful constituents (HPHCs) of tobacco products and tobacco smoke.[44] These compounds, except for naph- thalene, have been reported by the IQOS manufacturer with comparable mass yields per stick.[12] Other recent independent studies are generally in agreement.[8−11] Nitrogenated com- pounds often used as tobacco smoke markers,[45−47] such as nicotine, pyridine, 2,3-dimethylpyridine, pyrrole, *N*-methyl-

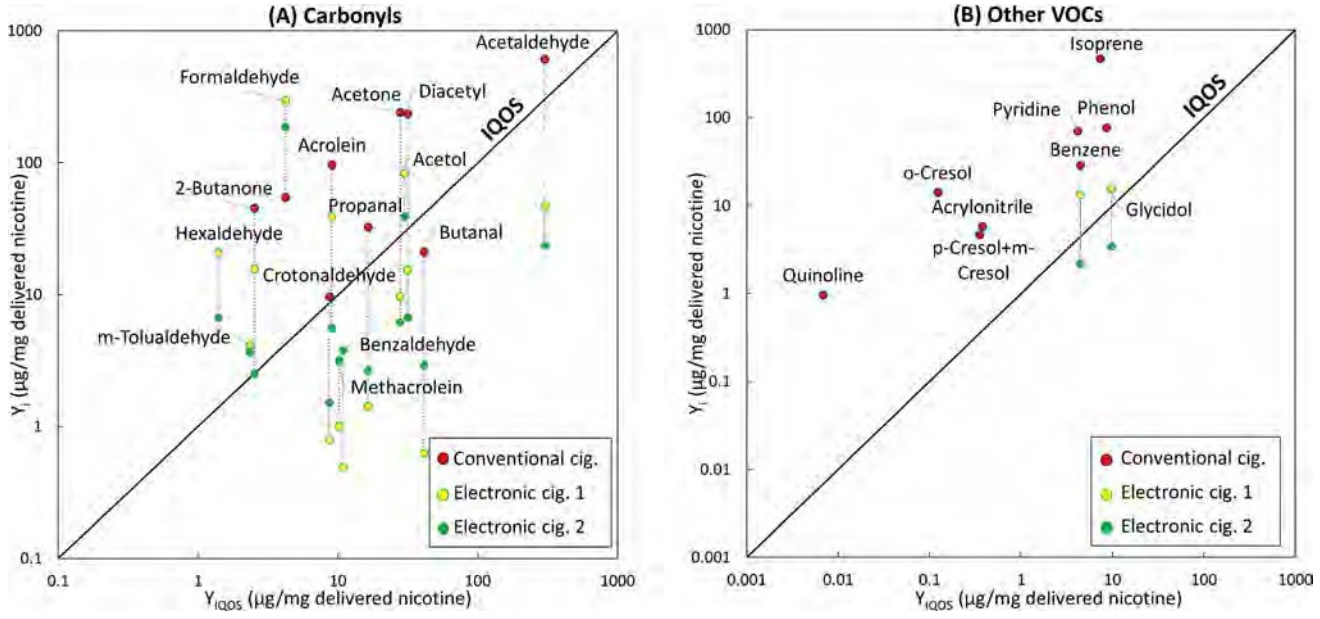


Figure 3. Yield of (A) carbonyls and (B) other VOCs in mainstream emissions of IQOS (*x*-axis), conventional (combustion) cigarettes, and two electronic cigarettes (1 = EGO operated at 3.8 V using CT liquid; 2 = AERO operated at 3.8 V using CT liquid). In all cases, yields were normalized by the amount of nicotine delivered by each device.

formamide, 3-ethylpyridine, and 3-ethenylpyridine, have also been detected in IQOS emissions. Formaldehyde, a common constituent of electronic cigarettes emissions,[36,48,49] has been classified as carcinogenic to humans (group 1) by the International Agency for Research on Cancer (IARC). Furfuryl alcohol, or 2-furanmethanol, has been classified as a possible carcinogen by IARC into group 2B and, along with furfural, is a marker for thermal decomposition of saccharides. Acetol, diacetyl, and glycidol (IARC group 2A probable carcinogen) have also been found in mainstream emissions, at lower concentrations than the tobacco stick analyzed by headspace chromatography. For most of the VOCs, notably oxygenated VOCs, the yield per stick was lower than that determined in the headspace analysis of tobacco plugs between 180 and 220
°C. This is likely because (a) not all the tobacco in the plug reaches the temperatures measured with the thermocouple near the heating blade, and a fraction remains at lower temperatures (Figure S5 Supporting Information), and (b) unlike the headspace analysis, mainstream emissions from the heatstick flow through three different filters that can reduce the amount of each compound that reaches the mouthpiece.

To compare the IQOS mainstream emission profile with those of typical electronic cigarettes and conventional cigarettes, the yield of each compound was expressed in micrograms of compound per milligram of emitted nicotine. Normalizing emissions by the amount of nicotine delivered is
used to account for users' compensatory behavior.[50−52]

Information about electronic cigarette emissions was taken
from our previous work,[36] in which two vaporizers, EGO (eGO CE4 version 2, one-coil, 2.6 Ω, operated at 3.8 V) and AERO (Kangertech Aerotank Mini, two-coil, 2.0 Ω, operated at 3.8 V), were used with Classic Tobacco (CT) flavor e-liquid (Apollo brand). Their emissions were analyzed using similar methods and instrumentation. For conventional cigarettes, average concentrations in mainstream smoke were taken from a recent compilation[53] (except for diacetyl[54]). For both electronic and conventional cigarettes, the yield of each

compound was calculated in microgram of compound per milligram of emitted nicotine and compared with the yield of the same compound in IQOS. In Figure 3, this comparison is shown for carbonyls (Figure 3A) and for other selected VOCs (Figure 3B). The diagonal 1:1 line indicates normalized yields that would be equal to those from IQOS. Thus, the data points above the diagonal represent compounds emitted at higher yields than IQOS, while those below the 1:1 line correspond to compounds emitted with lower yields than IQOS.

Carbonyl emissions from conventional cigarettes were higher than IQOS emissions for all compounds except for butanal and crotonaldehyde, which were similar for IQOS and conventional cigarettes. Typically, cigarette emissions exceeded those of IQOS by 1−2 orders of magnitude. The differences between IQOS and electronic cigarettes emissions were compound dependent. For acetaldehyde, diacetyl, acetone, propanal, benzaldehyde, methacrolein, crotonaldehyde, and butanal, IQOS emissions were higher than electronic cigarettes. Emissions of formaldehyde from IQOS were much lower, and one of the electronic cigarettes showed higher emissions of acrolein than IQOS, while the other one showed a lower value. Electronic cigarettes offer a wide variety of options for users: different designs and the abilities to regulate the power delivered to the coil by adjusting the battery voltage and vape with very different use patterns (e.g., different puffing frequency). These factors can significantly affect the profile of emissions, resulting in differences in the concentrations of chemical constituents. Nevertheless, Figure 3A suggests that, in terms of mainstream emissions, IQOS is more similar to electronic cigarettes than to conventional cigarettes. The same conclusion can be reached from Figure 3B, where the information for other selected VOCs is shown. Isoprene, phenol, pyridine, benzene, acrylonitrile, cresols, and quinoline emissions in conventional cigarettes were significantly higher than IQOS. For electronic cigarettes, only benzene and glycidol data are shown in Figure 3B, supporting the similarities between these devices and IQOS.

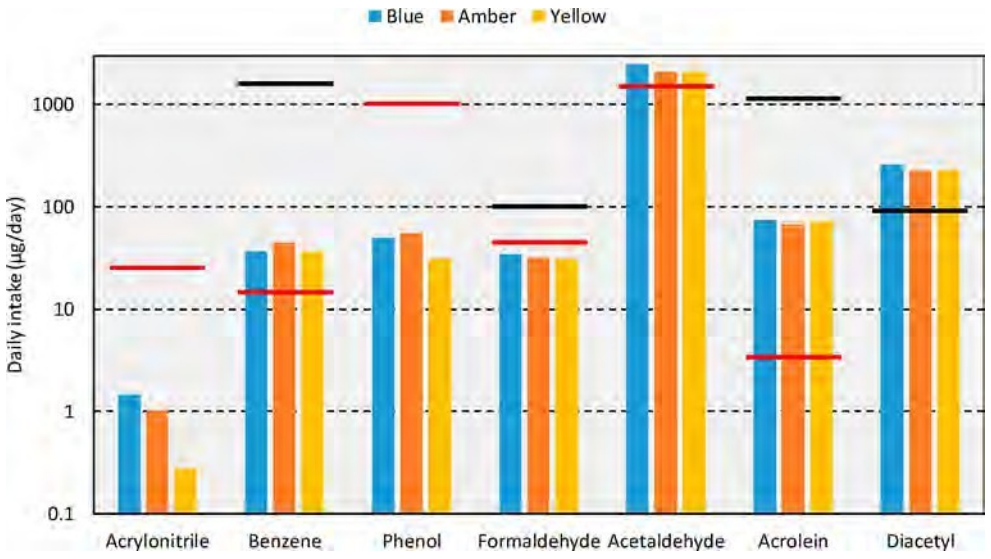


Figure 4. Users' daily intake for blue, amber, and yellow heatsticks. The lines correspond to maximum daily doses derived from OEHHA (red) and NIOSH (black) guidelines.

Sidestream Emissions. More than 100 volatile compounds were detected in chromatograms corresponding to IQOS sidestream emissions, from which 33 were identified and quantified. Table 1 shows data for blue, amber, and yellow label heatsticks, including harmful chemicals in the FDA's HPHC list, compounds also reported by the IQOS manufacturer, and common tobacco smoke markers. Despite being one of the compounds with the highest emission yields, nicotine is detected in chamber air at very low levels due to its strong sorption to chamber walls.[45,46]

Predicted Impacts on Users and Bystanders Exposed Passively. *Users' Intake of Harmful Compounds.* Daily intake of chemicals in IQOS emissions was based on a consumption rate of 20 sticks per day. Figure 4 and Table S3 in the Supporting Information present the estimated intake and compare these values with maximum daily doses derived from NIOSH and OEHHA (California Office of Environmental Health Hazard Assessment) guidelines for exposure limits. For formaldehyde, acetaldehyde, acrolein, diacetyl, and benzene, the predicted daily doses were comparable to those associated with breathing contaminated air at or above recommended limits. The reference exposure levels (RELs) established by NIOSH for an 8 h time-weighted average (TWA) exposure are 0.016 ppm (20 µg m^{-3}) for formaldehyde, 0.1 ppm (230 µg m^{-3}) for acrolein, and 0.1 ppm (320 µg m^{-3}) for benzene.[55] For diacetyl, NIOSH recommends a limit of 5 ppb (18 µg m^{-3}).[35] Assuming a constant breathing rate of 15 m^3 per day, the amounts inhaled during 8 h at NIOSH limits are estimated as 100 µg for formaldehyde, 1.1 mg for acrolein, 1.6 mg for benzene, and 90 µg for diacetyl. OEHHA recommends even lower 8 h RELs for formaldehyde (9 µg m^{-3}), acrolein (0.70 µg m^{-3}), and benzene (3 µg m^{-3}); 300 µg m^{-3} are recommended for acetaldehyde.[56] Using these values, the amounts inhaled during 8 h at OEHHA limits are estimated as 45 µg for formaldehyde, 4 µg for acrolein, 15 µg for benzene, and 1500 µg for acetaldehyde.

For acrolein, benzene, and acetaldehyde daily intake is significantly higher than the OEHHA maximum daily dose. The same applies to diacetyl with respect to levels recommended by NIOSH. For formaldehyde, maximum daily doses are not reached although daily intakes by IQOS

users are close to both OEHHA and NIOSH limits. Air quality guidelines are used solely as a benchmark for comparison with available health-based criteria. This approach, which has been applied previously to evaluate users' intake of e-cigarette emissions,[32] should not be construed as risk assessment.

Potential asthmagenicity was assessed using the asthma hazard prediction model developed by Jarvis et al.[57] A total of 27 compounds were detected in IQOS emissions with an asthma hazard index (AHI) greater than 0.2, as reported in Table S4 (Supporting Information). As a reference, in our previous study of electronic cigarettes,[36] we had detected 11 compounds with AHI > 0.2 (Table S5). Nicotine is an important contributor to the overall asthma hazard of emissions for IQOS and e-cigarettes, and formaldehyde contribution is very significant for e-cigarettes. IQOS data in Table S4 include several nitrogenated tobacco compounds that are predicted to be asthmagenic and are not present in e- cigarette emissions. The AHI analysis provides only a preliminary prediction based on chemical structure and activity relationships, but further evaluation of the respiratory effects of IQOS emissions is required in order to make more conclusive claims.

Predicted Impact on Indoor Air Quality. In order to elucidate the impact of IQOS on indoor air quality, exposure to acrolein was calculated in two case studies for residential and public spaces, for which indoor concentrations were estimated. A residential space where one user consumed 20 heatsticks per day was considered. Figure 5 shows 8 h averaged maximum indoor acrolein concentration for different indoor space volumes and air change rates. The air change rate range presented in the *y*-axis corresponds to typical residential values, and the indoor space volumes in the *x*-axis, to small to midsize indoor spaces. For example, the volume of a typical master bedroom of approximately 20 m^2 (215 sq ft) floor plan is ~50 m^3, and a studio of approximately 45 m^2 (485 sq ft) floor plan is ~115 m^3. For acrolein, the OEHHA 8 h and chronic inhalation RELs are 0.7 and 0.35 μg m^{-3}, respectively. Hence, indoor concentrations above the chronic REL can be reached in small spaces with poor ventilation.

For public spaces, the steady-state indoor concentration of acrolein was estimated for bars that allow the use of IQOS by

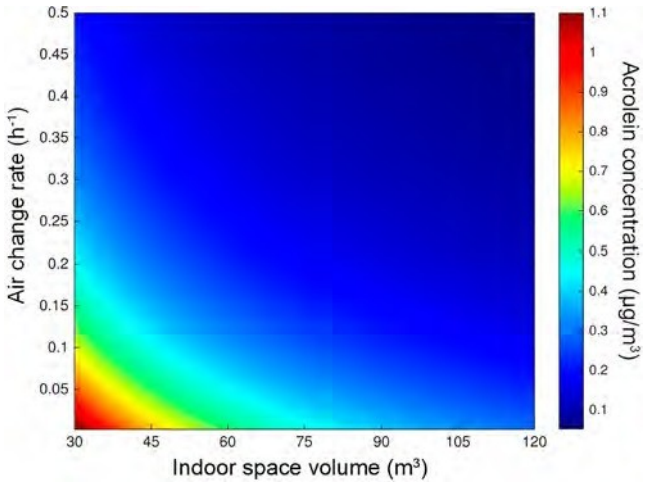


Figure 5. Acrolein concentration in indoor air (μg m^{-3}) from model estimation of IQOS use (average of 20 heatsticks per day) versus air change rate (h^{-1}) and indoor space volume (m^3).

patrons. As previously described in Logue et al.,[32] parameters adapted from a study of 17 bars in Austin, TX,[58] were used to characterize each scenario, including the dimensions of the indoor space, air change rate and average number of simultaneous smokers. Results are shown in Table S6 in the Supporting Information. Indoor concentrations were close to OEHHA chronic inhalation REL (0.35 μg m^{-3}) for several bars and exceeded that level in at least one occasion. These estimations suggest that indoor air quality can be affected in both residential and public spaces, where nonusers could be exposed to potentially hazardous concentrations of carbonyls and other VOCs. These predictions based on a simple box model do not capture inhomogeneous distribution of air pollutants that may lead to higher exposures due to proximity to the source.

Implications. Overall, the predicted impacts of IQOS on users and bystanders are of the same magnitude as those previously reported for electronic cigarettes. While this may represent a lower health risk and a less polluted indoor environment than those associated with conventional cigarettes, the negative impacts are far from being negligible and are not yet fully understood. Several of the compounds detected in IQOS mainstream and sidestream emissions are not listed by FDA as harmful and potentially harmful constituents (HPHCs). Some of those chemicals should be considered in the evaluation of health risks. A recently published review on the incipient IQOS literature highlights the fact that a health risk exposure profile still needs to be developed by independent research.[59]

Considering the effect on indoor air quality, PMI research claims that the use of IQOS has no negative impacts.[14] However, our study has consistently found the presence of several harmful compounds in sidestream and mainstream emissions (a fraction of which is exhaled, contributing to indoor air levels). Detectable indoor concentrations of acrolein, acetaldehyde, and formaldehyde from use of IQOS have also been reported by Ruprecht et al.[16] Using the conditions from that study (room volume of 48 m^3, air change rate of 1.54 h^{-1}, and a maximum of 14 heatsticks consumed in 3 h), the model predicted concentrations of 0.14 μg m^{-3} for formaldehyde, 6.6 μg m^{-3} for acetaldehyde, and 0.19 μg m^{-3} for acrolein. These values are in good agreement with those

reported by Ruprecht et al. for acrolein (0.11 μg m^{-3}) and acetaldehyde (3.5 μg m^{-3}) and are underestimated form- aldehyde levels (2.7 μg m^{-3}). Meisŭtovič-Akhtarieva et al.[19] reported an increase of acetaldehyde concentration. In the conditions of their study (room volume of 30 m^3, air change rate of 0.5 h^{-1}, and one heatstick consumed by one user), similar predicted indoor air concentrations were achieved with our model. For acetaldehyde, the predicted concentration was 2.8 μg m^{-3}, while Meisŭtovič-Akhtarieva et al. reported an average of 3.6 μg m^{-3}. For formaldehyde and 3-ethenylpyr- idine, the predicted concentrations were as low as 0.06 and 0.03 μg m^{-3}, respectively, while the authors report no significant increases compared to background levels of those compounds. Hence, the emission rates determined in this study can be used to predict the contribution of IQOS emissions to indoor pollutant levels under a variety of scenarios.

This study also provides an independent assessment of emissions reported by PMI. After thorough examination of the MRTP application submitted to the US FDA by PMI in 2016, St.Helen et al.[60] pointed out that the IQOS manufacturer identified a total of 114 compounds in mainstream emissions, from which 56 had higher yields than conventional cigarettes, and 58 had lower yields. The latter, referred to as the PMI-58 list, included 40 of the 93 harmful and potentially harmful constituents (HPHCs) listed by the FDA. Our study reports a total of 66 compounds, from which 26 (39%) coincide with those reported by PMI (and 16 of which are in the PMI-58 list), as shown in Figure S7 (Supporting Information). The mainstream emission yields reported in our study are in good agreement with those listed by PMI (Table S7, Supporting Information). Naphthalene, a compound included in FDA's HPHC list, was found in our study but not reported by PMI. Table S7 includes data from other independent studies on IQOS mainstream emissions measured under relatively similar (although not identical) conditions, also showing general agreement in most cases. We found significant coincidences with the emerging literature on IQOS emissions, considering the identity of main constituents in mainstream emissions and their yields per stick. From the large number of compounds found by PMI, this work and other independent studies, several are well-characterized toxicants, but we lack enough toxicological and/or epidemiological information to assess many others.

Considering its novelty and relevance, this work has focused on the impact of exhaled mainstream and sidestream emissions on the indoor environment. Pollutant levels were predicted for a variety of scenarios, contributing to establishing the impacts of IQOS on indoor air quality, in support of policies and practices protecting nonsmokers. While several studies have shown that IQOS emissions are lower than those of conventional cigarettes, few have made a direct comparison with electronic cigarettes, which share with heated tobacco products a common universe of potential consumers. IQOS yields were compared with those of e-cigarettes measured under consistent conditions using similar methodologies. This study also found that emission rates increased with temper- ature in a compound-dependent manner, leading to significant variations in the emission profiles at different temperatures.

Limitations of the study can also be noted. It explored only a subset of conditions and chemical emissions. It excluded particle emission analysis, which has been assessed by other authors.[15−17,19] Predicted health effects are more severe if

aerosols and particulate matter, specially the $PM_{2.5}$ fraction, are taken into consideration. The analytical methods used in this study did not allow to capture the effect of short-lived reactive oxygen species (ROS), which have been identified in the literature.[11] Emissions were quantified only for new devices, without exploring the effect of aging and blade soiling.

In summary, the impact of IQOS is likely lower than that of conventional cigarettes, but not negligible. Current evidence is insufficient to fully assess health effects in users and bystanders.

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The authors declare no competing financial interest.

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