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Brief report
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Brief report

Free-Base and Total Nicotine, Reactive Oxygen Species, and Carbonyl Emissions From IQOS, a Heated Tobacco Product

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Abstract

Introduction: IQOS is an emerging heated tobacco product marketed by Philip Morris International (PMI). Because the tobacco in IQOS is electrically heated and not combusted, PMI claims that it generates significantly lower toxicant levels than combustible cigarettes. To date, a few independent studies have addressed IQOS toxicant emissions, and none have reported reactive oxygen species (ROS), and the form of the nicotine emitted by the device.

Methods: In this study, IQOS aerosol was generated using a custom-made puffing machine. Two puffing regimens were used: Health Canada Intense and ISO. ROS, carbonyl compounds (CCs), and total nicotine and its partitioning between free-base and protonated forms were quantified in the IQOS aerosol by fluorescence, high-performance liquid chromatography, and gas chromatography, respectively. The same toxicants were also quantified in combustible cigarette aerosols for comparison. In addition, propylene glycol and vegetable glycerin were also measured in the IQOS tobacco and aerosol.

Results: IQOS and combustible cigarettes were found to emit similar quantities of total and free-base nicotine. IQOS total ROS (6.26 ± 2.72 nmol H_2O_2/session) and CC emissions (472 ± 19 µg/session) were significant, but 85% and 77% lower than levels emitted by combustible cigarettes.

Conclusions: IQOS emits harmful constituents that are linked to cancer, pulmonary disease, and addiction in cigarette smokers. For a given nicotine intake, inhalation exposure to ROS and CCs from IQOS is likely to be significantly less than that for combustible cigarettes.

Implications: IQOS is PMI's new heated tobacco product. PMI claims that because IQOS heats and does not burn tobacco it generates low toxicant yields. We found that one IQOS stick can emit similar free-base and total nicotine yields as a combustible cigarette. A pack-a-day equivalent user of IQOS may experience significant inhalation exposure of ROS and CCs compared to background air. However, substituting IQOS for combustible cigarettes will likely result in far lower ROS and carbonyl inhalation exposure for a given daily nicotine intake.

Introduction

Philip Morris International recently began marketing the IQOS, a heated tobacco product that uses cigarettes called Heets, which are specially designed tobacco units that consist of reconstituted tobacco, paper, and a filter. The Heets are inserted into a battery-powered device that features a protruding metal heating blade which penetrates into the Heet and heats up the tobacco inside up to 330°C.[1]

Advertised as a reduced harm product in which "the levels of harmful chemicals are significantly reduced compared to cigarette smoke,"[2] IQOS and other heated tobacco products have been described by Philip Morris International officials as central to a growth strategy focused on getting smokers to switch to reduced harm products.[3] To date, independent assessments of non-nicotine toxicant emissions from IQOS found relevant yields of volatile organic compounds, polycyclic aromatic hydrocarbons, phenols, carbon monoxide, and tobacco-specific nitrosamines albeit at generally lower levels than are typical of combustible cigarettes.[1,4–6] In one study, formaldehyde cyanohydrin, a highly toxic chemical that breaks downs into formaldehyde and cyanide, was released from the IQOS polymer filter upon heating.[7] Interestingly, nicotine yields in IQOS were also lower than those of combustible cigarettes.[8]

In this study, we aimed to investigate two aspects of toxicity and nicotine delivery potential not previously reported for IQOS: reactive oxygen species (ROS), and free-base (FB) and protonated nicotine emissions. ROS is a particularly useful assay for screening new tobacco products because ROS-initiated oxidative stress is a trigger for many smoking-related diseases,[9] and because it is a broadband assay that does not require prior knowledge of the chemical species that present the main disease risk to users. FB nicotine was investigated because it may provide a better indicator of a product's abuse potential than does total nicotine. All else being equal, a product with a greater fraction of FB to total nicotine is expected to produce a more rapid and more potent nicotine hit to the user.[10,11] The relative proportion of FB to total nicotine (ie, the sum of FB and protonated forms of nicotine) depends on the pH.[12] We also measured toxic and carcinogenic carbonyl compounds (CCs), which often appear in cigarette-like and greater levels in another modified risk tobacco products: electronic cigarettes. The CC species investigated include the United States Environmental Protection Agency's target aldehyde compounds as well as glyoxal and methyl glyoxal. In addition to studying the aerosol, we characterized the IQOS Heets for humectant content (ie, propylene glycol [PG] and vegetable glycerin [VG]).

Methods

An IQOS kit was purchased from Geneva, Switzerland, in 2017, along with tobacco-flavored, balance-labeled Heets. Prior to sampling, the IQOS device was charged and prepared for use according to the manufacturer's instruction manual. A custom-built digital puffing machine was used to generate aerosol using the Health Canada Intense (HCI) puffing regime (55 mL puff volume, 30-second interpuff interval, 27.5 mL/s flow rate, and 2-second puff duration). The IQOS heater remains active for 6 minutes, after which the battery needs to be recharged; this constraint allows for 12 puffs to be executed for each sampling session. In addition, aerosol was generated from an IQOS using the ISO regime for comparison (35 mL puff volume, 60-second interpuff interval, 17.5 mL/s flow rate, and 2-second puff duration resulting in six puffs). After each sampling session, the IQOS heater was cleaned using the cleaning sticks provided in the kit. For each outcome measure, three Heets were used. The aerosol from all puffs was collected for each Heet for subsequent analyses. For comparison, aerosol was also generated using Marlboro Red combustible cigarettes that were procured in Beirut, Lebanon. Combustible cigarettes samples were analyzed in triplicates. For nicotine and CC determinations, the puffing machine was set up such that the aerosol was drawn through a Gelman type A/E glass fiber filter followed by a 2,4-dinitrophenylhydrazine-coated silica cartridge (H10, volume size 3 mL). The particulate matter collected on the filter was analyzed for nicotine, whereas the cartridge was used to trap and derivatize CC species. When sampling ROS, the smoke exiting the IQOS was first drawn through a 47 mm glass fiber filter and then split into two parallel streams. The first branch was used to trap the ROS using three midget impingers each containing 20 mL dichlorofluorescein solution. This split-flow arrangement was used to reduce the flow through the impingers, and thereby avoid overly vigorous bubbling and subsequent escape of the solvent. A schematic of the setup is shown in Supplementary Figure 1.

Chemical Analysis

Total particulate matter (TPM): TPM was determined by weighing the filter pad and holder before and after each sampling session. *ROS*: ROS in the aerosol particles and vapors were determined separately in the filter pads and midget impinger solution, respectively, using the fluorescence-based technique described in Haddad et al. (2018, under review). Thereafter, 10 mL of 2′,7′-dichlorofluorescein diacetate solution was deacetylated using NaOH (40 mL of 0.01 M), after which the pH was adjusted to 7.2 using a phosphate buffer solution (200 mL of 0.25 mM). Horseradish peroxidase (0.5 U/mL) was added to amplify the fluorescence signal. Fluorescence was measured using a SpectraMax M5 microplate reader against a calibration curve of H_2O_2 (1×10^{-7} to 10^{-6} M). *Carbonyls*: CCs were determined using the method described in Al Rashidi et al.[13] Derivatized CC species were extracted from the 2,4-dinitrophenylhydrazine cartridges in 90/10 (vol/vol) ethanol/acetonitrile and quantified by high-performance liquid chromatography with ultraviolet detection. *Nicotine*: Nicotine in the aerosol was measured by immersing the filter pads in 6 mL water and shaking for 30 minutes. Then, 6 mL toluene was added to extract FB nicotine. The last step was repeated twice to ensure complete extraction. A solution of NaOH (200 µL) was then added to the mixture to convert protonated into FB nicotine. Nicotine was thereafter extracted using toluene. Total nicotine was quantified by summing FB and protonated nicotine. *pH*: Heet tobacco sample (0.3 g) or filter pads were immersed in 6 mL deionized water as reported in El-Hellani et al.[14] The solution pH was measured using a Starter 3100 OHAUS pH-meter. PG and VG: PG and VG were quantified in the tobacco Heets and filter pads by gas chromatography–flame ionization detector in accordance with the method described in El-Hellani et al.[15]The filter and 0.3 g tobacco were dissolved in 4 mL ethyl acetate and sonicated for 30 minutes. A diluted solution (10-fold) was spiked with the internal standard β-citronellol (50 ppm) and injected into chromatography–flame ionization detector for analysis. The quantification was done against a calibration curve of the range 20–315 ppm of standard PG and VG solutions.

Results

A summary of findings is presented in Table 1. Ten of the 11 aldehyde species investigated were found in the IQOS aerosol. ROS and CC emissions from IQOS were generally lower than those found in

Table 1. Summary of Aerosol Toxicant Content. Mean (SD)

	IQOS		Marlboro Red		
Device	ISO	HCI	ISO	HCI	IQOS (previous reports)
TPM (mg/cigarette)	12.93 (0.25)	27.17 (2.08)	10.03 (0.65)	37.5 (2.96)	44–55.85[4,6]
Nicotine (mg/cigarette)	0.77 (0.06)	1.50 (0.2)	0.80 (0.05)	1.80 (0.11)	0.5–1.4[4,6,8]
%FB	13.6 (1.4)	5.7 (2.2)	14.5 (1.9)	5.8 (1.7)	NR
pH	6.66 (0.12)	5.87 (0.17)	6.11 (0.05)	5.69 (0.06)	NR
PG/VG		8/92			14/86[6]
ROS (nmol H_2O_2/cigarette)					
Gas phase	1.93 (0.95)	2.25 (0.74)	22.10 (0.74)		NR
Particle phase	4.34 (1.8)	7.78 (1.46)	24.74 (4.18)		NR
Total	6.26 (2.72)	10.04 (2.12)	46.83 (9.6)		NR
Carbonyls (µg/cigarette)					
Formaldehyde		0.85 (0.28)		3.17 (0.33)	3.2–21.87[1,5,6]
Acetaldehyde		301.46 (15.8)		1059 (9.03)	133–210[1,5,6]
Acetone		48.37 (2.73)		775.6 (28.42)	12–26.59[1,6]
Acrolein		ND		0 (0)	0.9–10.8[1,5,6]
Propionaldehyde		22.25 (0.6)		47.89 (1.04)	7.8–12.8[1,5]
Crotonaldehyde		5.52 (0.55)		40.42 (0.69)	0.7–6.42[1,5,6]
Methacrolein		6.53 (0.37)		85.46 (3.85)	NR
Butyraldehyde		30.73 (1.89)		22.19 (2.91)	NR
Valeraldehyde		20.11 (1.48)		0 (0)	NR
Glyoxal		3.11 (0.18)		0 (0)	NR
Methyl glyoxal		33.51 (1.23)		0 (0)	NR
Sum of carbonyls		472.4 (19.35)		2033 (35.72)	NR

Blank entry = not analyzed, FB = free-base, ND = not detected, NR = not reported, PG = propylene glycol, ROS = reactive oxygen species, TPM = total particulate matter, VG = vegetable glycerin. Puffing regimens used in citations: [1]ISO; [4]HCI; [5]HCI; [6]HCI, ISO; [8]HCI.

combustible cigarettes. There was no significant difference between the ROS levels generated under the ISO and HCI regimes (p = .13). IQOS and combustible cigarettes had similar total nicotine yields and FB fractions (p > .05). HCI puffing regimen generated higher nicotine yield than ISO (p < .05). PG and VG in the Heets and aerosol were found to be equal to 07/93 and 08/92 (PG/VG vol/vol), respectively. Mean (SD) pH in the Heets and aerosol was found to be equal to 5.58 (0.04) and 6.47 (0.55), respectively. ROS were found in the aerosol in both gas and particle phases.

Discussion

ROS are associated with numerous smoking-related diseases in cigarette smokers, including cancer.[9] In this study, we measured and quantified ROS generated from the IQOS, a new tobacco product marketed as a safer alternative to combustible cigarette. In addition, we measured CCs and nicotine yields generated from the IQOS. The fractions of FB and protonated nicotine in the aerosol were also quantified. For comparison, a Marlboro Red combustible cigarette was tested. We found that, under the same regime (ISO), IQOS generated significantly lower levels of ROS relative to the combustible cigarette. Similarly, CCs were present in the IQOS aerosol at lower levels compared to combustible cigarettes. IQOS and combustible cigarettes had nearly identical total nicotine yields and FB fractions under both HCI and ISO puffing regimens.

FB nicotine is widely thought to be responsible for the “kick” or “impact” of tobacco smoke, and a key variable for satisfaction and addiction in smokers.[10] It has also long been connected with throat harshness upon inhalation.[16] Nicotine yields and FB fraction similar to combustible cigarette levels suggest that smokers may experience similar sensory qualities when using IQOS. On the other hand, the comparable nicotine profile of IQOS and combustible cigarette in the aerosol indicates that nonsmokers who use IQOS are at risk for developing addiction.

Our measurements indicated that a cigarette user switching to IQOS will reduce their particulate-ROS intake by 82%, and their gaseous-ROS intake by 90% (Table 2). To put the results into context, we calculated daily inhalation exposures to ROS, formaldehyde (listed by the International Agency for Research on Cancer/World Health Organization [IARC/WHO] as group 1, carcinogenic to humans), and acetaldehyde (IARC/WHO group 2B, possibly carcinogenic to humans, and group 1 when associated with consumption of alcoholic beverages) based on a daily nicotine intake equivalent to one pack of cigarettes (20 cigarettes). For comparison, ambient air particulate and gaseous-ROS concentration measured at urban sites (New York, United States, and Seoul, Korea, respectively) were obtained from Venkatachari et al.[17] and Kang et al.[18]; formaldehyde and acetaldehyde levels measured in urban Savannah, Georgia, United States, were obtained from MacIntosh et al.[19] Daily inhalation exposure was calculated assuming a mean daily inhalation volume of 16 m^3/day.[20] We found that pack-a-day equivalent IQOS users would roughly double their daily formaldehyde and total ROS inhalation exposures, respectively, relative to breathing urban air alone. Exposure to acetaldehyde would be more than 100 times greater than from breathing urban air. On the other hand, obtaining a pack-a-day nicotine intake equivalent from IQOS rather than combustible cigarettes under the conditions studied would result in a reduction in daily intake of formaldehyde and acetaldehyde of 70% and 65%, respectively, and an 85% reduction in ROS (Table2). How differential exposure of these toxicants translates to differential population morbidity and mortality risk is difficult to estimate; indeed risk assessment for novel modified risk tobacco products is an active area of research and concern of regulatory bodies such as the US Food and Drug Administration.[21,22]

Table 2. Estimated Daily Exposure to ROS, Formaldehyde and Acetaldehyde From IQOS and Combustible Cigarette for a Pack-a-Day Smoker

Daily exposure	IQOS	Combustible cigarette	Background air
Particulate-ROS (nmol H_2O_2)	90	500	20[17]
Gaseous-ROS (nmol H_2O_2)	40	450	60[18]
Formaldehyde (mg)	0.02	0.06	0.03[19]
Acetaldehyde (mg)	7	20	0.04[19]

The ISO regimen was used for ROS quantifications, HCI was used for carbonyl measurements.

We note that because of logistical problems with equipment, ROS and CC measurements were conducted using different puffing regimens, whereas nicotine was measured for both the HCI and ISO regimens. Although ideally ROS and CC would also have been measured for both puffing regimens, the data available nonetheless allow for an apples–apples comparison of emissions across the IQOS and combustible cigarette conditions. We also note that, although HCI and ISO have been commonly used for IQOS testing,[1,4–6,8] specific puffing regimens for testing IQOS and other heated tobacco products remain to be developed; human puff topography measurements are needed in this regard.

We conclude that IQOS is capable of delivering at the mouthpiece similar levels and FB fractions of nicotine as combustible cigarettes and therefore has the potential to satisfy nicotine cravings of dependent smokers. For the same reason, it poses a risk of nicotine addition to previously nicotine-naive individuals who use it. On a nicotine-for-nicotine basis, inhalation exposure to ROS and CCs for IQOS is likely considerably lower than for combustible cigarettes, but is likely not zero.

Supplementary Material

Supplementary Figure 1 can be found online at http://www.ntr.oxfordjournals.org

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Declaration of Interests

The authors declare the following competing financial interest(s): AS is a paid consultant in litigation against the tobacco industry and is named on a patent application for a device that measures the puffing behavior of electronic cigarette users.

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