



# Identification of volatile constituents released from IQOS heat-not-burn tobacco HeatSticks using a direct sampling method

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► Additional material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/tobaccocontrol-2019-055521>).

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Received 22 November 2019

Revised 1 April 2020

Accepted 21 April 2020

## ABSTRACT

**Objectives** To identify the chemicals released in I Quit Ordinary Smoking (IQOS) heat-not-burn tobacco aerosol and to assess their potential human health toxicity.

**Methods** The heating temperature window of the IQOS heat-not-burn device was determined using a thermographic camera over a period of 100 s. Qualitative studies were performed using a novel real-time gas chromatograph–mass spectrometer set-up. Aerosols from six tobacco-flavoured IQOS HeatSticks (Amber, Blue, Bronze, Sienna, Turquoise and Yellow) were collected in a 1 mL loop via a manual syringe attached to the sample-out port of the valve. The gas transport line was heated to 200°C in order to prevent the condensation of volatile species. Compound identification was performed using the NIST11 mass spectrometry database library (US National Institute of Standards and Technology), where only chemicals with a match of 70% and above were listed as identifiable.

**Results** The temperature profile of the IQOS device revealed a non-combustive process employed in generating the tobacco aerosol. Real-time qualitative analysis revealed 62 compounds encompassing a broad spectrum of chemicals such as carbonyls, furans and phthalates, which are highly toxic.

**Discussion** Our findings complement the qualitative studies previously performed by Philip Morris International and others via indirect sampling methods. By analysing the aerosols in real time, we have identified a total of 62 compounds, from which only 10 were in common with previous studies. Several identified species such as diacetyl, 2,3-pentanedione, hydroxymethylfurfural and diethylhexyl phthalate are classified as highly toxic, with the latter considered carcinogenic.

## INTRODUCTION

Active and passive exposures to cigarette vapours are serious human health threats, leading to coronary heart diseases, asthma and lung cancer. Based on a recent report submitted by the WHO, around 1.1 billion people are using tobacco products, from which approximately six million die annually due to tobacco-associated disorders.<sup>1</sup> New alternative smoking products (electronic cigarettes and vapourisers) are reaching higher grounds, encompassing 356 million consumers worldwide. However, the death toll provoked by their consumption has increased significantly, reaching 650 000 annually, and it is likely to rise over the coming years.<sup>2</sup>

More countries are now facing difficulties in regulating e-cigarettes, as these novel devices are

becoming popular especially among young people aged between 13 and 15 years old<sup>2,3</sup> and are highly addictive and can cause serious health problems.<sup>4</sup> More than 30 carcinogenic compounds in high concentrations were identified, leading to severe health hazards such as oral, pharyngeal, oesophageal and pancreatic cancers.<sup>5</sup> Cardiovascular death risks and stillbirths were also shown to increase up to four times, signalling real concerns regarding human health safety.<sup>6</sup>

A new class of tobacco products, specifically tobacco heating devices such as I Quit Ordinary Smoking (IQOS), Glo and iFuse, have gained attention after unsuccessful attempts in the late 1980s.<sup>7,8</sup> The market is currently dominated by Philip Morris International (PMI), Neuchâtel, Switzerland, with their flagship product, IQOS. After its launch in 2014 in Italy and Japan, the product is now available in over 52 countries, located mostly in the European Union.<sup>9</sup> The IQOS system includes two distinct components that perform different functions (figure 1): a holder equipped with a heating blade fitting the tobacco stick and reaching temperatures up to 300°C, and an external charger used to recharge the holder after each use.<sup>10</sup>

The IQOS system differs from a normal cigarette in many ways. First, the novel tobacco stick does not contain small-cut tobacco pieces. Instead, the tobacco is grounded and compacted into sheets (termed as cast-lead) to which certain quantities of glycerin, guar gum, cellulose fibres and water are added. Second, the quantity of tobacco found in the IQOS stick is about half of that than in combustible cigarettes. Third, the novel topology of the stick includes a polymer film fitted to cool the aerosol and a low-density cellulose acetate mouthpiece that mimics the shape of a cigarette. The tobacco plug and the polymer-film filter are separated by a hollow acetate tube (figure 2).<sup>10</sup>

Lighting a cigarette generates a self-sustaining combustion process by the interaction of tobacco with oxygen in the air. Between puffs, the cigarette smoulders at temperatures up to 900°C, leading to heat, smoke and ash formation.<sup>10</sup> The smoke released in the form of volatiles and non-volatiles contains a complex aerosol mixture, with more than 8000 compounds being identified in previous studies.<sup>11</sup> In contrast, the IQOS stick is heated, not burned, for a fixed period of approximately 6 min, which allows the smoker to inhale up to 14 puffs.<sup>10</sup> The operating temperature of the system is around 300°C, which delivers heat to the tobacco stick via



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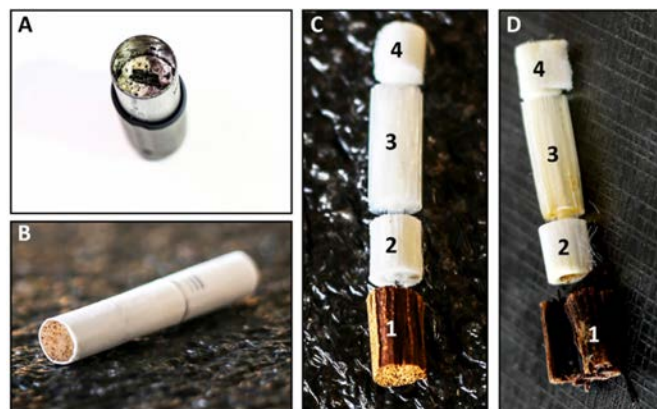
**To cite:** Ilies BD, Moosakutty SP, Kharbatia NM, et al. *Tob Control* Epub ahead of print: [please include Day Month Year]. doi:10.1136/tobaccocontrol-2019-055521



**Figure 1** Two components of the IQOS V.3.0 system. (A) Above view of the IQOS device: (1) holder cap, (2) holder equipped with the heating blade and (3) external charger. (B) Frontal view of the IQOS device. IQOS, I Quit Ordinary Smoking.

a heating blade. Since no combustion takes place, the topology of the stick is retained after usage.<sup>10</sup>

PMI has claimed that heating the tobacco at 300°C generates an aerosol that contains between 90% and 95% less harmful and potentially harmful constituents (HPHCs) than a combustible cigarette.<sup>12</sup> Several studies have been published so far,<sup>12–13</sup> agreeing that the aerosols released by IQOS are less toxic; however, their employed methodology was unsuitable for detecting highly unstable volatile compounds, which can be very toxic. Our findings complement the studies submitted by Schaller *et al*<sup>12</sup> and Ibañez *et al*,<sup>13</sup> with more than 50 new compounds to be added on their list. Among them, diacetyl, 2,3-pentanedione, hydroxymethylfurfural and diethylhexyl phthalate (DEHP) are classified as highly toxic and carcinogenic,<sup>14</sup> revealing the importance of real-time tobacco aerosol analysis, and the urgent need for more sensitive analytical techniques when dealing with highly unstable volatiles.



**Figure 2** (A) Postusage appearance of the heating blade after smoking 10 IQOS tobacco HeatSticks. (B) Frontal view of the tobacco HeatStick. (C) Components of the unsmoked IQOS tobacco HeatStick: (1) tobacco plug, (2) hollow acetate tube separating the tobacco plug and the polymer film fitter, (3) polymer mesh and (4) cellulose acetate mouthpiece. (D) Components of the smoked IQOS tobacco HeatStick with same numbering as in (C). IQOS, I Quit Ordinary Smoking.

## MATERIALS AND METHODS

### Acquisition and storage of IQOS products

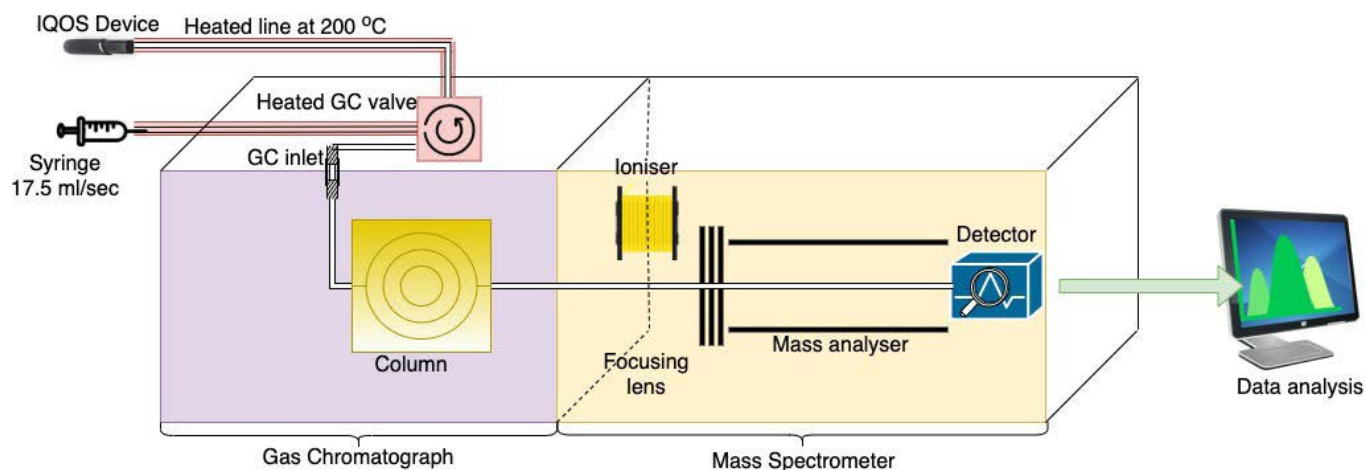
Two IQOS V.3.0 tobacco heating system kits, manufactured by Philip Morris Products S.A. (Switzerland), were purchased from a local vendor in Romania. The kits were sealed and in new condition. The kits were inventoried and stored at 22°C when not in use. Three packs for each of the six different IQOS flavoured HeatSticks (Amber, Blue, Bronze, Sienna, Turquoise and Yellow) were purchased from a local vendor in Romania. Each pack was individually sealed and in new condition. The packs were stored unopened in a dark area at 22°C when not in use.

### Thermal profile of IQOS

The temperature profile of the IQOS device during smoking was captured using a thermographic VarioCAM HD head 640G camera, operating in the long-wave infrared spectra of (7.5–14.0 µm). The experiment was performed at normal room temperature of 20°C and 40% relative humidity. The lens reproduced a scene with a resolution of 640×480 pixels, in the temperature range of −40°C to 1200°C, with a temperature resolution close to ±0.05 K. The emissivity was set to 0.1, and the thermal history was recorded at 500 frames per second for a duration of 100 s.

### Gas chromatograph–mass spectrometer (GC-MS) analyses

Six flavoured IQOS tobacco HeatSticks were analysed in real time using a gas chromatograph with a quadrupole mass spectrometer GC-MS system (Agilent 7890 GC/5975C MSD) (figure 3). The instrument was equipped with a gas sampling valve and an electron ionisation source with ionisation energy of 70 eV. The temperatures of the ion source and mass analyser were set to 230°C and 150°C, respectively. The mass analyser was autotuned according to the manufacturer's manual, and the scan range was set from 20 to 350 Da with a scan speed of 2 scans/s. Chromatographic separation was performed using DB-5MS fused silica capillary column (30 m×0.25 mm I.D. and 0.25 µm film thickness; Agilent J&W Scientific, Folsom, California, USA), chemically bonded with 5% phenyl, 95% methylpolysiloxane cross-linked stationary phase. Helium was used as the carrier gas with a constant flow rate of 1.0 mL/min. The oven programme consisted of two ramping programmes. First, the initial oven temperature was held at 40°C for 5 min, then ramped to 100°C at a rate of 20°C/min. Next, the oven temperature was ramped to 235°C with a rate of 30°C/min and held for 28 min. The temperature of the gas chromatograph inlet port, gas sampling box and transfer line to the MS source were kept at 250°C, 220°C and 320°C, respectively. The gas sample generated from each tobacco HeatStick was withdrawn through a 1 mL loop of the heated valve using a manual syringe attached to the sample-out port of the valve. The line was heated to 200°C using a heating tape, such that the collected smoke would not condense. The GC-MS run analysis was initiated after electrically actuating the valve so that helium carrier gas swept the sample from the loop to a split inlet with a split ratio of 5:1. All the six flavoured IQOS tobacco HeatSticks were tested in triplicate, performing a blank before starting the analysis of each set. Compound identification was performed using the NIST11 mass spectrometry database library (US National Institute of Standards and Technology). Only chemicals with a 70% or higher probability match were listed as identifiable.



**Figure 3** GC-mass spectrometer set-up able to perform real-time gas analysis. GC, gas chromatograph; IQOS, I Quit Ordinary Smoking.

## RESULTS

### Thermal stability of IQOS

The cover of the IQOS holder was removed, such that the thermographic camera could fit inside and monitor the temperature of the heating blade. The operating temperature of the IQOS device was recorded over four different time instances (figure 4). As shown, the device reached 300°C after approximately 30 s.

Furthermore, a temperature profile of IQOS was generated by plotting the temperature evolution over a 2 min time window (figure 5). The temperature rapidly increased from 25°C to 300°C in approximately 10 s. The maximum value of 320°C was recorded after 40 s and then plateaued around 285°C, indicating a non-combustive process.

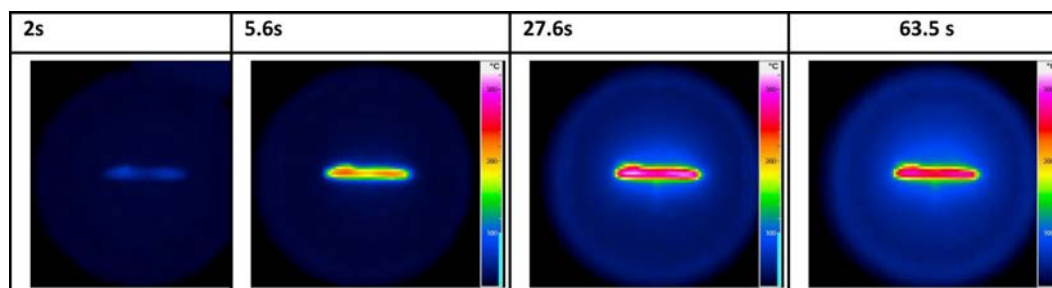
### Identification of toxic constituents from IQOS smoke

E-cigarette solutions and tobacco sticks mainly consist of humectants such as propylene glycol (PG) and glycerol, mixed with various flavours and, optionally, a certain nicotine percentage. Several studies have qualitatively and quantitatively identified a variety of chemical constituents from different e-cigarette liquids.<sup>15 16</sup> However, there are insufficient data regarding the heat-not-burn tobacco sticks and their potential human health hazards.

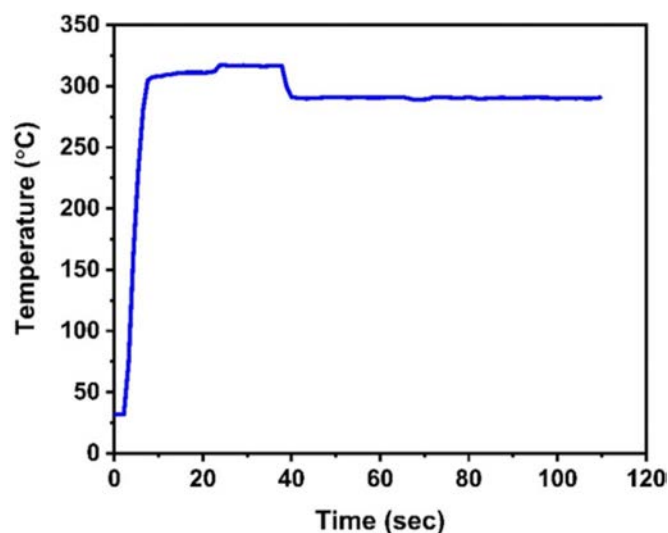
In a recent study, Ibañez *et al*<sup>13</sup> assessed the smoke constituents released by the IQOS tobacco HeatSticks by capturing the volatiles in methanol and analysing them by GC-MS. The chromatogram of the identified chemicals was then compared against that released by a normal combustible cigarette, revealing only a few identifiable peaks with low intensities. Another offline study performed by Schaller *et al*<sup>12</sup> on IQOS aerosols dissolved in methanol identified 112 analytes, covering various chemical classes.

In this study, a total of 62 volatile compounds from six different IQOS tobacco HeatSticks were identified using a real-time GC-MS set-up (table 1). Figure 6 shows a general fingerprint of the chemicals released in the aerosols, up to peak number 49. The rest can be found in the online supplementary material. In the first part of the chromatograms, up to a retention time of 8 min, small carbonyls like propanal, acrolein, 3-methylbutanal, diacetyl and 2,3-pentanedione (peaks 1, 3, 7, 9 and 11) were identified. These are highly toxic compounds, with acrolein (peak 3), diacetyl (peak 9) and 2,3-pentanedione (peak 11) presenting high health risks. Furans, compounds released by the decomposition of the sugar-made cigarette filter, were located at opposite ends of the chromatograms. They were represented by 3-methylfuran (peak 4), as well as hydroxymethylfurfural (peak 50), which was found to exhibit tumorigenic activity in mice. However, the presence of phthalates such as DEHP (peak 61) in the analysed samples is the most pressing concern, as this compound was placed in group 2B by the International Agency for Research on Cancer (IARC).<sup>14</sup>

Schaller *et al*<sup>12</sup> submitted a list of 112 species, from which 99 were found to be organic. In this study, we have identified 62 organic compounds, from which only 10 were common with the ones submitted by Schaller *et al*<sup>12</sup> (figure 6). The difference in the identified species arises from the measurement techniques employed in these studies. Schaller *et al*<sup>12</sup> captured the smoke from a whole IQOS tobacco HeatStick on a Cambridge filter pad, dissolved it in a polar solvent and analysed the solution for its constituents. This method increases the concentration of certain species, making them easier to detect by the mass spectrometer. However, many of the species may be decomposed or transformed due to interactions with the polar solvent and/or



**Figure 4** Heating temperature of the I Quit Ordinary Smoking blade recorded on four different time points.



**Figure 5** Temperature profile of the I Quit Ordinary Smoking V.3.0 device.

oxygen in air. This might be the reason why only 10 compounds were common between our study and Schaller *et al.*<sup>12</sup> In our study, we employed an online technique using 35 mL volume of smoke equating to a puff, from which only 1 mL was used for analysis. This decreases our sensitivity to detect several low concentration compounds using the real-time sampling GC-MS methodology. Therefore, complementary real-time studies must be performed on tobacco aerosols for better characterisation of the aerosol constituents. The identified compounds are found in table 1, and the toxicity of the primary aerosol constituents (nicotine and glycerol), together with that of carbonyls, furans and phthalates, is discussed next.

## DISCUSSION

### Nicotine

The tobacco heat-not-burn systems contain lower amounts of nicotine when compared with combustible cigarettes. Glo and iFuse are two other devices similar to IQOS operating at 250°C and 35°C, respectively. The aerosols released by IQOS contain the highest amounts of nicotine and HPHCs, followed by Glo and iFuse.<sup>17</sup> Leigh *et al.*<sup>18</sup> have shown that tobacco-specific nitrosamines (TSNA), which are carcinogenic by-products formed from nicotine, were significantly higher in IQOS than those found in tank-like e-cigarettes but significantly lower when compared with normal cigarettes except for the nicotine-derived nitrosamine ketone (NNK). In our study, nicotine (peak 38) was identified in all six IQOS samples, exhibiting high intensities, but TSNA were absent. This is probably due to their similar polarity with other compounds that might hinder their detection or due to their low concentrations. Hence, more sensitive instruments such as Orbitrap mass spectrometry should be employed for better separation and identification of the chemical constituents.

### Glycerol

Glycerol (peak 43) is accounted for 50% of the smoke mass released by IQOS and is generally regarded as safe by the US Food and Drug Administration.<sup>19</sup> Several *in vivo* studies using high oral LD<sub>50</sub> doses of glycerol were performed on mice, rabbits, rats and guinea pigs, without showing acute toxic effects.<sup>20</sup> However, a recent study by Sleiman *et al.*<sup>21</sup> has shown a plausible mechanism for thermal degradation of glycerol to glycidol and

**Table 1** List of compounds identified in the released I Quit Ordinary Smoking aerosols

Peak no	Species	Retention time	Match (%)
1	Propanal	2.9	72.7
2	1-Propen-2-ol, acetate	3.09	83.7
3	Acrolein	3.37	71.7
4	3-Methylfuran	3.66	87.2
5	Ethyl acetate	3.89	80.5
6	Methanol	4.12	90.7
7	3-Methylbutanal	4.34	82.4
8	Ethanol	4.91	94.9
9	Diacetyl	5.7	92.0
10	Toluene	6.81	86.6
11	2,3-Pentanedione	7.17	81.0
12	Disulfide, dimethyl	7.35	80.1
13	Hexanal	7.49	81.5
14	2,6-Dimethyl-2-trans-6-octadiene	7.92	85.3
15	2-Propen-1-ol	7.99	88.5
16	Ethinamate	8.3	70.5
17	Phenol, 3-methyl	8.46	77.9
18	B-Myrcene	8.58	87.2
19	Citral	8.68	70.1
20	Pyridine	8.86	83.4
21	D-limonene	8.97	95.2
22	Eucalyptol	9.11	93.8
23	γ-Terpinene	9.413	91.9
24	Styrene	9.5	88.9
25	Bicyclo(4,2,0)octa-1,3,5-triene	9.51	92.4
26	Propanoic acid, 3-methylbutyl ester	9.56	89.2
27	o-Cymene	9.62	92.1
28	Benzene, 1-methyl-3-(1-methylethyl)	9.63	86.7
29	Dimethyl trisulfide	10.47	86.9
30	Acetic acid	10.75	91.8
31	l-Menthone	10.97	85.3
32	Formic acid	11.11	82.1
33	Cyclohexanol, 5-methyl-2-acetate	11.41	92.6
34	1,2-Propanediol	11.46	84.1
35	Propylene glycol	11.47	95.0
36	Cyclohexanol, 5-methyl-2-(1-methylethyl)	11.54	92.4
37	Levomenthol	11.73	93.6
38	Nicotine	12.81	96.2
39	Glycerol 1,2-diacetate	13.35	96.5
40	Pyridine, 3-(3,4-dihydro-2H-pyrrol-5-yl)	14.32	89.7
41	Tricosane	14.37	88.0
42	1,2,3-Propanetriol, 1-acetate	14.41	89.4
43	Glycerol	14.65	89.7
44	Nicotyrine	14.91	82.4
45	Tetracosane	14.95	83.7
46	Docosane, 7-hexyl	15.29	75.4
47	3-Pyridinol	15.35	78.4
48	Octadecanoic acid, 17-methyl, methyl ester	15.42	80.7
49	Hexacosane	15.66	92.9
50	Hydroxymethylfurfural	15.956	76.0
51	9-12-Octadecadienoic acid, ethyl ester	16.04	87.5
52	Heneicosane	16.52	85.2
53	Ethyl 9,12,15-octadecatrienoate	16.68	88.4
54	Tetradecanoic acid	17.75	83.8
55	Dibutyl phthalate	18	90.6

Continued

Table 1 Continued

Peak no	Species	Retention time	Match (%)
56	Pentadecanoic acid	19.29	78.6
57	Hexanedioic acid, bis(2-ethylhexyl) ester	19.76	87.0
58	5,9,13-Pentadecatrien-2-one, 6, 10,14-trimethyl, (E, E)	20.88	80.8
59	n-Hexadecanoic acid	21.23	89.7
60	Diisooctyl phthalate	28.8	85.4
61	Diethylhexyl phthalate (DEHP)	28.85	95.4
62	Diphenyl sulfone	31.59	80.9

Species highlighted in grey were common with the ones identified by Schaller *et al.*<sup>12</sup>

acrolein (peak 3); the latter is a highly carcinogenic compound identified in all the samples, except menthol (turquoise). Wang *et al.*<sup>22</sup> investigated the formation of acrolein from glycerol. For this purpose, a reactor with precisely controlled temperatures was used, and the experiments were performed in the absence of nicotine and flavour additives. Wang *et al.*<sup>22</sup> concluded that acrolein was formed at temperatures exceeding 270°C, with  $0.80 \pm 0.50 \mu\text{g}$  of acrolein detected per milligram of glycerol. The heating temperature of the IQOS device reaches up to 300 °C, which can lead to the formation of acrolein in significant amounts, leading to acute toxicities when inhaled.

### Carbonyls

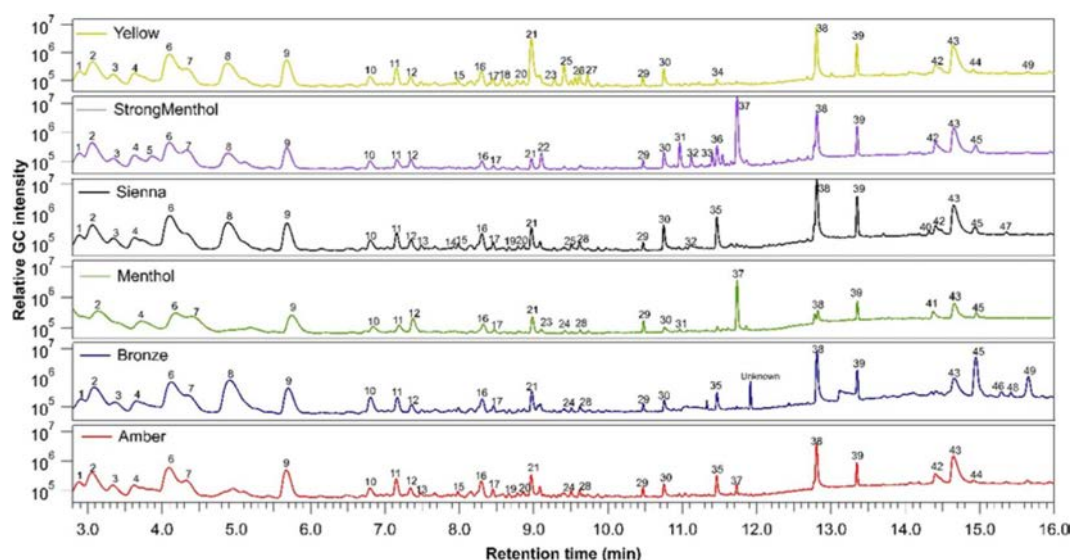
Various carbonyl compounds, including propanal, acrolein, 3-methylbutanal, diacetyl and 2,3-pentanedione (peaks 1, 3, 7, 9 and 11) were identified. Carbonyl compounds are mostly toxic and carcinogenic for human health,<sup>23</sup> with high concentrations being detected even in nicotine-free e-cigarettes.<sup>24</sup> Temperature, airflow and catalytic properties of the metallic heating coils are some of the factors that may contribute to the formation and decomposition of chemical products, leading to various aldehydes and ketones. Moreover, humectants such as PG and glycerol can also contribute to the formation of carbonyls. It was demonstrated that oxidation followed by decomposition of PG

and glycerol could lead to the generation of formaldehyde and acrolein, which are highly carcinogenic.<sup>25–29</sup>

Extremely high concentrations of carbonyls from 51 types of flavoured e-cigarettes were identified in a study by Allen *et al.*<sup>30</sup> From these, diacetyl and 2,3-pentanedione (peaks 9 and 11) were found in concentrations higher than the normal laboratory limits in more than half of the labels. These compounds were also identified in this study, exhibiting high intensities. Diacetyl and its flavouring substitute, 2,3-pentanedione are highly toxic and are often associated with the development of the so-called ‘popcorn lungs’ disease after prolonged exposures. The first toxicity reports regarding 2,3-pentanedione were published in 2010.<sup>31</sup> A follow-up laboratory study by Hubbs *et al.*<sup>32</sup> has shown that prolonged exposure to diacetyl and 2,3-pentanedione can cause airway epithelial damage. Another in vivo study performed by scientists from the National Institute of Environmental Health Sciences identified obliterative bronchiolitis-like changes in rats after prolonged exposures to either diacetyl or 2,3-pentanedione.<sup>33</sup> Induced genetic mutations in the olfactory bulb of the mouse brain were also spotted.<sup>34</sup>

### Furans

The thermal degradation of the sugar-made e-cigarette filter can lead to the formation of furans, a highly toxic class of compounds. We have identified the presence of 3-methylfuran (peak 4) in all the analysed flavours. However, hydroxymethylfurfural (peak 50), a compound known to cause irritations in the human respiratory tract<sup>35</sup> and exhibit tumorigenic activity in mice,<sup>36 37</sup> was identified only in Sienna flavoured HeatSticks. The mechanism responsible for the formation of furans is highly complex, as indicated by Yu and Wu,<sup>38</sup> where the degradation of sugar-made filters is highly influenced by the e-cigarette coil and maximum temperature attained. In a recent study, Soussy *et al.*<sup>39</sup> pointed that e-cigarette users have the same exposure to hydroxymethylfurfural as normal combustible cigarette users, but less than those using waterpipes. Hence, the presence of these toxic compounds especially in flavoured IQOS tobacco sticks calls for more stringent regulation on the apparatus design.



**Figure 6** Chromatograms of the six I Quit Ordinary Smoking flavoured tobacco sticks (Amber, Bronze, Blue/strong menthol, Sienna, Turquoise/menthol and Yellow). GC, gas chromatograph.

## Phthalates

Phthalates are mainly used for binding cosmetics and fragrances, and in fabricating plasticisers and aerosol sprays.<sup>40</sup> Several phthalates were identified in this study, including dibutyl phthalate (peak 55), diisooctyl phthalate (peak 60) and diethylhexyl phthalate (DEHP) (peak 61). Lorz *et al*<sup>41</sup> has shown that phthalates possess oestrogenic and antiandrogenic activities and can cause premature female breast development. One of the most toxic representatives, DEHP is widely used as a plasticiser in the manufacture of polyvinyl chloride products. In cigarettes, it is believed to originate from the packaging material or during the tobacco production steps.<sup>42</sup> Due to its toxicity, this chemical agent was coined by the IARC as 'a possible carcinogen to humans' and placed in group 2B.<sup>14</sup> Davis *et al*<sup>43</sup> showed that IQOS heating blade temperatures can melt the polymer mesh from the tobacco sticks, under both cleaned and uncleaned conditions. The amount of damage to the filter matrix increased with each HeatStick, hence releasing higher concentrations of phthalates after each use. This is particularly worrying due to the carcinogenic nature of these compounds, resulting in serious health hazards.

## Conclusions

In conclusion, a total of 62 volatile compounds (table 1) were identified in all the six flavoured tobacco IQOS HeatSticks, complementing the offline studies submitted by PMI and others. The difference in the identified species arises from the contrasting analytical methodologies, with ours being designed to target volatiles in real time. However, the GC-MS set-up displayed low sensitivities to some compounds and was not able to resolve all isomers. Moreover, compounds beyond a mass of 350 Da could not be analysed due to the imposed limit. Future real-time studies will employ highly sensitive instruments like Orbitrap MS and expand the mass scan range. With this approach, we expect to identify more compounds that may exhibit high toxicity for human health and thereby help improve the tobacco regulatory system. Future work will also focus on quantitative studies on nicotine, humectants (glycerol and propylene glycol) and potential carcinogenic species (carbonyls, furans and phthalates) identified in the GC-MS chromatogram. Quantitative measurements of these studies are relevant for determining the toxicity of the IQOS tobacco sticks.

**Correction notice** The paper has been updated since first published to correct author names and update ORCID iDs.

**Acknowledgements** We thank Mr Javier Ordonez Loza for acquiring the thermal profile of I Quit Ordinary Smoking (IQOS). We thank Ms Raheena Abdurehim for taking pictures of the IQOS device.

**Contributors** BDI: conceived, designed and performed the experiments, and wrote and edited the manuscript. SM: designed and made the figures and edited the manuscript. NK: designed and set up the gas chromatograph–mass spectrometer (GC-MS) experiment and wrote the GC-MS methodology. MS: edited the manuscript.

**Funding** This work was supported by King Abdullah University of Science and Technology with funds awarded to the Clean Combustion Research Center.

**Disclaimer** The content is solely the responsibility of the authors.

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** All data relevant to the study are included in the article or uploaded as supplementary information.

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## What this paper adds

### What is already known on this subject

- Studies conducted by Philip Morris International (PMI) on I Quit Ordinary Smoking (IQOS) smoke have portrayed it as a healthier choice when compared with combustible cigarettes.
- The analytical methodology used in their studies consisted of capturing the released IQOS tobacco smoke in solvents such as water or methanol and analysing them in an offline fashion.

### What important gaps in knowledge exist on this topic

- The analytical technique employed by PMI leads to the rapid decomposition of toxic volatiles due to their reaction with the polar solvents or oxidation when in contact with air.

### What this paper adds

- We have identified 62 compounds, out of which only 10 were in common with the list submitted by the manufacturer, using an online system capable of detecting low-range volatile compounds.
- Identified compounds such as diacetyl, 2,3-pentanedione, hydroxymethylfurfural and diethylhexyl phthalate are toxic and carcinogenic.
- Identification of these unknown harmful volatile compounds shows the importance of measuring heat-not-burn tobacco aerosols in real-time.

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