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Carbonyl emissions from a novel heated tobacco product (IQOS): comparison with an e-cigarette and a tobacco cigarette

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ABSTRACT

Aims To measure carbonyl emissions from a heated tobacco product (IQOS) in comparison with an e-cigarette (Nautilus Mini) and a commercial tobacco cigarette (Marlboro Red). **Design** Regular and menthol variants of the heated tobacco product were tested. A tank-type atomizer was tested with a tobacco-flavoured liquid at 10 and 14 W. Aerosol and smoke were collected in impingers containing 2,4-dinitrophenylhydrazine. Health Canada Intense and two more intense puffing regimens were used. **Setting** Analytical laboratory in Greece. **Measurements** Carbonyl levels in the aerosol and smoke. **Findings** At the Health Canada Intense regimen, heated tobacco products emitted 5.0–6.4 μg/stick formaldehyde, 144.1–176.7 μg/stick acetaldehyde, 10.4–10.8 μg/stick acrolein, 11.0–12.8 μg/stick propionaldehyde and 1.9–2.0 μg/stick crotonaldehyde. Compared with the tobacco cigarette, levels were on average 91.6% lower for formaldehyde, 84.9% lower for acetaldehyde, 90.6% lower for acrolein, 89.0% lower for propionaldehyde and 95.3% lower for crotonaldehyde. The e-cigarette emitted 0.5–1.0 μg/12 puffs formaldehyde, 0.8–1.5 μg/12 puffs acetaldehyde and 0.3–0.4 μg/12 puffs acrolein, but no propionaldehyde and crotonaldehyde. At more intense puffing regimens, formaldehyde was increased in heated tobacco products, but levels were three–fourfold lower compared with the tobacco cigarette. Based on the findings from Health Canada Intense puffing regimen, use of 20 heated tobacco sticks would result in approximately 85% to 95% reduced carbonyl exposure compared with smoking 20 tobacco cigarettes; the respective reduction in exposure from use of 5 g e-cigarette liquid would be 97% to > 99%. **Conclusions** The IQOS heated tobacco product emits substantially lower levels of carbonyls than a commercial tobacco cigarette (Marlboro Red) but higher levels than a Nautilus Mini e-cigarette.

Keywords Carbonyls, electronic cigarettes, harm reduction, heated tobacco products, nicotine, smoking.

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INTRODUCTION

Heated tobacco products (also referred to as heat-not-burn products) have been developed recently and released to the market, after unsuccessful past attempts in the late 1980s [1,2]. Currently, the most widely available product is IQOS (Philip Morris International, Neuchâtel, Switzerland), which was launched in 2014 in Italy and Japan. It is currently available in approximately 30 countries, mainly in Europe, while in May 2017 the manufacturer filed a modified risk tobacco product application to the US Food and Drug Administration for marketing approval in the US [3]. Heated tobacco products function by heating rather than combusting tobacco, using a battery device and controlled heat delivery to the tobacco. Although technically they could be called ‘electronic cigarettes’, this term has long been used for personal vaporizers that generate aerosol by heating nicotine-containing liquid. The temperature generated by IQOS is reported to be 350°C, lower compared to the combustion temperatures reaching 900°C in the cigarette tip [4]. This is expected to result in lower levels of toxic emissions and, as a result, they are marketed as reduced-risk products. Several studies have assessed the chemistry and toxicology of this and other similar products from other manufacturers [5–8]. However, with few exceptions [9–11], all studies have been performed by the manufacturers of the products. Considering the past history of the tobacco industry, it is reasonable to be cautious and it is necessary for independent studies to assess the accuracy of the reported findings and the potential of these products to reduce risk to smokers.

Carbonyls such as formaldehyde, acetaldehyde and acrolein are among the most toxic compounds emitted in tobacco cigarette smoke [12]. They have been linked to respiratory disease, cardiovascular disease and carcinogenesis [12–15]. The main source of carbonyls in tobacco cigarette smoke are carbohydrates present naturally in the tobacco plant and added by the manufacturers as flavourings [16]. Carbohydrates undergo thermal degradation due to the high temperatures in the tip of the tobacco cigarette, resulting in carbonyl emissions [17]. Carbonyls are also emitted from e-cigarettes, another smoking alternative. Several studies have identified carbonyls in the e-cigarette aerosol of both unflavoured [18,19] and flavoured liquids [20,21]. The main source of carbonyls is thermal degradation of propylene glycol and glycerol [22], while one study suggested that flavourings could be a significant source of carbonyls [23]. In general, e-cigarettes emit far lower carbonyl emissions compared to tobacco cigarettes, with some reports of very high emissions being challenged through replication studies [24–27].

Because heated tobacco products are marketed and can be used as alternatives to smoking, it is essential to examine their safety profile compared to tobacco cigarettes. Additionally, it is important for smokers to make informed decisions by knowing the relative risk of heated tobacco products compared to other alternative to smoking products. In that respect, the purpose of this study was to compare carbonyl emissions from a heated tobacco product (IQOS) in comparison with a popular commercial e-cigarette and a tobacco cigarette.

METHODS

Equipment

IQOS equipment (power bank, battery and tobacco sticks, both regular and menthol) were purchased from a tobacco store in Greece. The e-cigarette equipment used for this study was Evic VTC Mini variable wattage battery (Joyetech, Shenzhen, China) and Nautilus Mini atomizer with 1.6 Ohm cotton wick replacement atomizer heads Aspire, Shenzhen, China). The liquid used was Halo Longhorn (Nicopure Labs, Gainesville, FL, USA), a tobacco-flavoured liquid, with 18 mg/ml nicotine concentration. All e-cigarette equipment was purchased from a vapeshop in Greece. A commercially available tobacco cigarette (Marlboro Red; Papastratos-Philip Morris International, Athens, Greece) was obtained from a tobacco shop in Greece.

Aerosol collection and measurements

Products were tested using the Health Canada Intense puffing regimen (PR1: 55-ml puff volume, 2-s puff duration, 3-s interpuff interval) and two more intense regimens (PR2: 80-ml puff volume, 3-s puff duration, 30-s interpuff interval; and PR3: 90-ml puff volume, 3-s puff duration, 25-s interpuff interval). The battery of IQOS lasts for approximately 6 minutes or 14 puffs (whichever comes first), so 12 puffs can be generated with PR1 and PR2 and 14 puffs with PR3. The purpose of the latter puffing regimen was to obtain the maximum number of puffs per tobacco stick from IQOS. The e-cigarette was tested at two power settings, 10 and 14 W. Two experienced daily e-cigarette users (members of the research team) tested the e-cigarette for the generation of dry puffs using the puff duration and the power settings as tested in the laboratory. They verified that both power settings were associated with realistic use conditions.

For aerosol collection, a custom-made, programmable for puff number, duration and volume smoking machine was used. For the e-cigarette, an automatic push mechanism was integrated to the controller in order to push the activation button of the battery device at puff initiation.

For carbonyl emissions, the devices and the tobacco cigarette were attached to a set of two impingers connected in series that contained 35 ml acidified 2,4-dinitrophenylhydrazine (2,4-DNPH) solution. The aerosol from two tobacco cigarettes, two IQOS tobacco sticks and 50 e-cigarette puffs passed through the impingers to trap carbonyls. The number of e-cigarette puffs was chosen to make the method more sensitive to carbonyl detection, and was used in previous studies [18,26,27]. For each product, five aerosol collections per puffing regimen were analysed to improve the level of precision in measurements and reported mean values. For the e-cigarette, one atomizer head was used for every five aerosol collections. The IQOS device was allowed to warm up for 20 s before taking the first puff. The DNPH derivatives of formaldehyde, acetaldehyde, acrolein, propionaldehyde and crotonaldehyde were measured by high performance liquid chromatography, using a previously validated protocol [28]. The limits of detection (LODs) for the method were 0.254 μg/collection for formaldehyde, 0.290 μg/collection for acetaldehyde, 0.395 μg/collection for acrolein, 0.440 μg/collection for propionaldehyde and 0.403 μg/collection for crotonaldehyde.

For nicotine measurements, the devices and the tobacco cigarette were attached to a filter holder containing a 44 mm Cambridge filter for aerosol and smoke collection. The tobacco cigarette was smoked until 35 mm butt length, with the ventilation holes covered. Two tobacco cigarettes were used per collection. The IQOS device was allowed to warm up for 20 s before taking the first puff. After the end of the warm-up period, puffs were obtained until the battery was deactivated (12 puffs for PR1 and PR2 and 14 puffs with PR3). Two IQOS sticks were used per collection, similarly to the number of tobacco cigarettes used. The e-cigarette was attached to the same equipment and 24 puffs were obtained per collection (similar to the puff number of IQOS). For every product, three collections per puffing regimen were analysed in order to obtain a mean value. For the e-cigarette, one atomizer head was used for each triplicate. The samples were analysed for nicotine levels with GC-NPD, using a method validated and described previously [9]. The values were expressed as mg/12 puffs (mg/14 puffs for PR3) for IQOS and e-cigarette and as mg/cigarette for the tobacco cigarette. The mean value of each puffing regimen was used to report carbonyl emissions as amount per mg nicotine yield.

RESULTS

Table 1 presents the levels of carbonyl emissions per unit of tobacco cigarette and IQOS and per 12 (for PR1 and PR2) and 14 (for PR3) e-cigarette puffs. Propionaldehyde and crotonaldehyde were not detected in any of the e-cigarette aerosol samples. All carbonyls were detected > LOQ in all samples of IQOS and tobacco cigarette. At PR1, IQOS products emitted 91.6% [95% confidence interval (CI) = 77.7–105.4%] less formaldehyde, 84.9% (95% CI = 74.5–95.3%) less acetaldehyde, 90.6% (95% CI = 82.0–99.3%) less acrolein, 89.0% (95% CI = 77.9–100.2%) less propionaldehyde and 95.3% (95% CI = 71.9–118.6%) less crotonaldehyde compared to the tobacco cigarette. The e-cigarette emitted 98.9% (95% CI = 85.2–112.5%) less formaldehyde, 99.9% (95% CI = 89.9–109.9%) less acetaldehyde and 99.7% (95% CI = 91.4–108.0%) less acrolein compared to the tobacco cigarette. In comparison with the IQOS products, the e-cigarette tested herein emitted 86.7% (95% CI = 66.5–107.0%) less formaldehyde, 99.3% (95% CI = 86.1–112.4%) less acetaldehyde and 96.7% (95% CI = 78.1–115.2%) less acrolein.

At more intense puffing regimens, minimal differences in carbonyl emissions were observed for IQOS products, with the exception of formaldehyde levels that were increased by three–fourfold at PR3 compared to PR1. The e-cigarette showed four to sevenfold higher carbonyl emissions at PR3 compared to PR1. A 50% increase in acrolein levels was observed at PR3 compared to PR1 for the tobacco cigarette. At PR3, the IQOS products emitted 72.2% (95% CI = 56.7–87.7%) less formaldehyde, 85.5% (95% CI = 77.6–93.4%) less acetaldehyde, 92.7% (95% CI = 84.7–100.7%) less acrolein, 89.2% (95% CI = 80.4–97.9%) less propionaldehyde and 92.2% (95% CI = 78.2–106.2%) less crotonaldehyde than the tobacco cigarette. The e-cigarette emitted 94.9% (95% CI = 80.6–109.1%)

Table 1 Carbonyl emissions per one IQOS stick, 12 e-cigarette puffs (14 puffs at PR3) and one tobacco cigarette. Data presented as mean (standard deviation) from five repetitions.

	Formaldehyde	*Acetaldehyde*	*Acrolein*	*Propionaldehyde*	*Crotonaldehyde*
	μg/stick or μg/12 puffs or μg/cigarette				
PR1					
IQOS regular	6.4 (1.8)	144.1 (23.3)	10.8 (4.0)	12.8 (3.7)	2.0 (0.4)
IQOS menthol	5.0 (1.4)	176.7 (32.6)	10.4 (1.9)	11.0 (2.4)	1.9 (0.2)
E-cigarette 10 W	0.5 (0.2)	0.8 (0.3)	0.3 (0.1)	< LOD	< LOD
E-cigarette 14 W	1.0 (0.2)	1.5 (0.3)	0.4 (0.1)	< LOD	< LOD
Tobacco cigarette	67.2 (14.0)	1062.2 (161.4)	112.7 (14.2)	108.6 (17.9)	41.1 (14.6)
PR2					
IQOS regular	9.1 (3.7)	146.8 (22.3)	8.1 (2.0)	8.8 (4.6)	1.4 (0.5)
IQOS menthol	13.6 (5.3)	187.8 (61.8)	10.6 (6.1)	13.2 (4.0)	2.4 (0.9)
E-cigarette 10 W	2.8 (0.9)	1.9 (0.6)	0.5 (0.3)	< LOD	< LOD
E-cigarette 14 W	3.1 (0.4)	1.9 (03.3)	1.0 (0.1)	< LOD	< LOD
Tobacco cigarette	74.4 (24.2)	1372.9 (191.2)	156.8 (32.1)	113.7 (14.1)	65.7 (9.5)
PR3					
IQOS regular	17.1 (2.4)	165.1 (10.5)	10.4 (1.8)	11.8 (1.5)	3.0 (0.7)
IQOS menthol	22.6 (4.8)	187.1 (13.4)	13.1 (1.2)	13.5 (1.3)	3.3 (0.6)
E-cigarette 10 W[a]	3.6 (1.7)	1.7 (0.4)	0.9 (0.1)	< LOD	< LOD
E-cigarette 14 W[a]	3.7 (6.6)	2.9 (0.6)	1.1 (0.1)	< LOD	< LOD
Tobacco cigarette	71.4 (15.4)	1212.6 (144.2)	160.9 (19.3)	117.1 (15.4)	40.5 (8.6)

IQOS = heated tobacco product; PR = puffing regimen; LOD = limit of detection. [a]μg/14 puffs. PR1: 2-s puff duration, 55-ml puff volume, 30-s interpuff interval; PR2: 3-s puff duration, 80-ml puff volume, 30-s interpuff interval; PR3: 3-s puff duration, 90-ml puff volume, 25-s interpuff interval.

less formaldehyde, 99.8% (95% CI = 92.0–107.6%) less acetaldehyde and 99.4% (95% CI = 91.5–107.3%) less acrolein than the tobacco cigarette. In comparison with the IQOS products, the e-cigarette emitted 81.5% (95% CI = 65.6–97.4%) less formaldehyde levels 98.7% (95% CI = 92.6–104.8%) less acetaldehyde and 91.5% (95% CI = 80.2–102.7%) less acrolein.

The average nicotine yield for IQOS regular and menthol was 1.2 mg at PR1, 1.3 mg at PR2 and 1.6 and 1.7 mg, respectively, at PR3. For the e-cigarette at 10 and 14 W, nicotine yield was 1.1 and 1.6 mg at PR1, 1.7 mg and 2.3 mg at PR2 and 2.2 and 3.1 mg at PR3, respectively. The nicotine yield from the tobacco cigarette was 1.8 mg at PR1, 2.1 mg at PR2 and 2.4 mg at PR3. Table 2 presents the levels of carbonyl emissions per mg of nicotine emission to the aerosol (nicotine yield). At PR1, IQOS products emitted 87.1% (95% CI = 73.0–101.3%) less formaldehyde, 77.0% (95% CI = 66.0–87.9%) less acetaldehyde, 85.7% (95% CI = 76.5–94.9%) less acrolein, 83.3% (95% CI = 71.6–94.9%) less propionaldehyde and 92.8% (95% CI = 69.4–116.1%) less crotonaldehyde per mg nicotine yield than the tobacco cigarette. The e-cigarette emitted 98.5% (95% CI = 84.9–112.2%) less formaldehyde, 99.9% (95% CI = 89.9–109.8%) less acetaldehyde and 99.6% (95% CI = 91.3–107.9%) less acrolein per mg nicotine yield than the tobacco cigarettes. In comparison with the IQOS products, 88.6% (95% CI = 68.6–108.5%) less formaldehyde, 99.4% (95% CI = 86.2–112.5%) less acetaldehyde and 97.0% (95% CI = 78.5–115.6%) less acrolein per mg nicotine yield was emitted from the e-cigarette. At PR3, IQOS products emitted approximately 59.2% (95% CI = 42.7–75.7%) less formaldehyde, 78.6% (95% CI = 70.7–86.6%) less acetaldehyde, 89.3% (95% CI = 81.2–97.3%) less acrolein, 84.1% (95% CI = 75.3–92.9%) less propionaldehyde and 88.5% (95% CI = 74.4–102.5%) less crotonaldehyde than the tobacco cigarette. The e-cigarette emitted approximately 95.1% (95% CI: 80.8–109.4%) less formaldehyde, 99.8% (95% CI: 92.0–107.6%) less acetaldehyde and 99.4% (95% CI = 91.5–107.3%) less acrolein than the tobacco cigarette. In comparison with the IQOS products, 88.0% (95% CI = 73.7–102.4%) less formaldehyde, 99.2% (95% CI = 94.4–104.0%) less acetaldehyde and 94.6% (95% CI = 84.6–104.5%) less acrolein were emitted from the e-cigarette.

Figure 1 presents the percentage reduction in carbonyl exposure from an assumed daily consumption of 20 IQOS sticks and 5 g e-cigarette liquid compared with 20 tobacco cigarettes according to carbonyl emissions at PR1. While it would be reasonable to compare puffs or number of tobacco sticks between IQOS and tobacco cigarettes, the pattern of consumption for e-cigarettes is different. Consumers report e-cigarette consumption as amount of liquid consumed daily [29,30]. The e-cigarette daily consumption assumed herein was similar to a large survey where former smoking

Table 2 Carbonyl emissions per mg nicotine yield for the products tested. Data presented as mean (standard deviation) from five repetitions.

	Formaldehyde	*Acetaldehyde*	*Acrolein*	*Propionaldehyde*	*Crotonaldehyde*
	μg/mg nicotine yield				
PR1					
IQOS regular	5.3 (1.5)	120.1 (19.4)	9.0 (3.3)	10.7 (3.1)	1.6 (0.4)
IQOS menthol	4.1 (1.2)	147.3 (27.2)	8.6 (1.6)	9.2 (2.0)	1.6 (0.2)
E-cigarette 10 W	0.5 (0.2)	0.8 (0.3)	0.3 (0.1)	< LOD	< LOD
E-cigarette 14 W	0.6 (0.2)	0.9 (0.2)	0.3 (0.1)	< LOD	< LOD
Tobacco cigarette	36.7 (7.6)	580.4 (88.3)	61.6 (7.8)	59.4 (9.8)	22.5 (8.0)
PR2					
IQOS regular	7.0 (2.8)	112.9 (17.1)	6.3 (1.5)	6.8 (3.6)	1.1 (0.4)
IQOS menthol	10.4 (4.1)	144.5 (47.5)	8.2 (4.7)	10.2 (3.1)	1.9 (0.7)
E-cigarette 10 W	1.6 (0.5)	1.1 (0.3)	0.3 (0.2)	< LOD	< LOD
E-cigarette 14 W	1.3 (0.2)	0.8 (0.1)	0.4 (0.1)	< LOD	< LOD
Tobacco cigarette	35.9 (11.7)	663.2 (92.4)	75.7 (15.5)	54.9 (6.8)	31.7 (4.6)
PR3					
IQOS regular	10.7 (1.5)	103.2 (6.6)	6.5 (1.1)	7.4 (0.9)	1.9 (0.4)
IQOS menthol	13.3 (2.8)	110.0 (7.9)	7.7 (0.7)	8.0 (0.8)	1.9 (0.4)
E-cigarette 10 W	1.7 (0.8)	0.8 (0.2)	0.4 (0.1)	< LOD	< LOD
E-cigarette 14 W	1.2 (1.2)	0.9 (0.2)	0.4 (0.1)	< LOD	< LOD
Tobacco cigarette	29.4 (6.3)	499.0 (59.3)	66.2 (8.0)	48.2 (6.3)	16.7 (3.5)

IQOS = heated tobacco product; PR = puffing regime; LOD = limit of detection PR1: 2-s puff duration, 55-ml puff volume, 30-s interpuff interval. PR2: 3-s puff duration, 80-ml puff volume, 30-s interpuff interval. PR3: 3-s puff duration, 90-ml puff volume, 25-s interpuff interval.

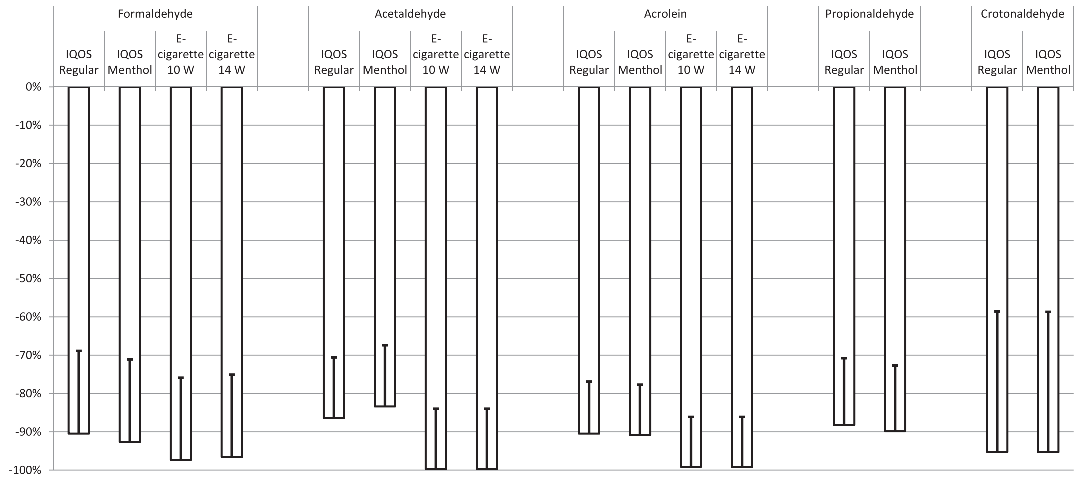

Figure 1 Percentage reduction in exposure to carbonyls from using 20 IQOS (heated tobacco product); sticks and five g e-cigarette liquid compared to 20 tobacco cigarettes at Health Canada Intense puffing regime (PR1, 2-s puff duration, 50-ml puff volume, 30-s interpuff interval). Bars represent mean difference, lines represent lower 95% confidence interval of the difference

vapers reported past consumption of 20 tobacco cigarettes per day [30]. Formaldehyde exposure would be reduced by approximately 90%, acetaldehyde by 85%, acrolein by 90%, propionaldehyde by 90% and crotonaldehyde by 95% from using 20 IQOS compared to smoking 20 tobacco cigarettes. The respective reduction from using 5 g e-cigarette liquid was from 97 to $> 99\%$ for all carbonyls. Supporting information, Fig. S1 shows exposure reductions according to the findings at PR2 and PR3. Smaller reductions were observed for formaldehyde exposure from IQOS use at PR3 (76.0 and 68.4% for IQOS regular and menthol, respectively) while for all other carbonyls reductions were consistently $\geq 85\%$ compared to smoking 20 tobacco cigarettes. For e-cigarettes, reductions were from 92 to $> 99\%$ at both more intense puffing regimens.

DISCUSSION

To the best of our knowledge, this is the first independent (not funded by any commercial entity) study evaluating carbonyl emissions from a heated tobacco product that is currently marketed in many countries in Europe and Asia. The main findings of the study are that IQOS heated tobacco products emit substantially lower carbonyl levels compared to a commercial tobacco cigarette at the 3 tested puffing regimens. The study also evaluated another popular tobacco harm reduction product, a commercial e-cigarette, and found that it emitted lower carbonyl levels than IQOS heated tobacco products.

The safety/risk profile of products that can be used for harm reduction is an essential factor in estimating the public health effects of these products [31]. For smokers, it is particularly important to assess the relative risk of these products compared to tobacco cigarettes, while for non-smokers defining the absolute risk is essential. The study herein showed that both heated tobacco products and e-cigarettes emit carbonyls, but the levels are lower by far compared to tobacco cigarette smoke. Carbonyl levels were higher in the heated tobacco products than the e-cigarette.

Similar levels of carbonyl emissions were reported by the manufacturer of the product [8], and our findings are in agreement with a study findings substantial reduction in biomarkers of acrolein and crotonaldehyde exposure after 5 days of switching from smoking to IQOS use [32]. One study found that the reduction in carbonyl emissions from IQOS compared to tobacco cigarettes was much lower than reported previously by the manufacturer [11]. While that study found lower carbonyl emissions from IQOS compared to the study herein, it reported unusually low emissions from the tobacco cigarette. The present findings on tobacco cigarettes are consistent with the literature data [33], supporting the reliability of the laboratory methods used. Thus, although not harmless, the findings suggest that IQOS products can have a role as harm reduction products if smokers switch to them and stop using combustible cigarettes—although far more testing is required. It is also evident that there is a risk continuum between different product types, with e-cigarettes emitting approximately 10-fold lower carbonyls compared to the heated tobacco products tested, while crotonaldehyde and propionaldehyde were not detected in the e-cigarette aerosol. This is important information for smokers who should have the opportunity to make informed decisions based on the safety profile of each product. It should be noted that the absolute difference in carbonyl emissions between the heated tobacco products and the e-cigarette is low when compared to the difference between these products and tobacco cigarette smoke.

The first priority should be to quit smoking; thus, for smokers unwilling or unable to quit with currently approved methods, it would be reasonable to first try an e-cigarette, and if this is also unsuccessful, to proceed with the use of heated tobacco products in an effort to quit by switching to harm reduction products. However, it should be emphasized that the risk profile of the products in terms of chemical composition does not depend solely upon carbonyl emissions, but on a large array of different compounds that are emitted in tobacco cigarettes and how such levels are compared to the respective levels of the harm reduction products. Thus, more studies are needed, evaluating several other compounds such as aromatic amines, polycyclic aromatic hydrocarbons, heavy metals, tobacco-specific nitrosamines and phenols. The manufacturer of the product has already presented the emission profile for these compounds [8], while limited data exist from independent studies on some toxic compounds [10]. Considering the past experience of tobacco industry science [34,35], it is reasonable to be cautious and emphasize the importance to have independent studies replicating research published by the industry. Until now, this and other independent studies have, for the most part, verified the manufacturer reports [9–11].

This study assessed carbonyl emissions at three different puffing regimens. Although the Health Canada Intense puffing regimen is considered the standard in tobacco cigarette chemistry research, it is currently unknown if it is applicable to heated tobacco product use. It is expected that smokers would want to obtain a similar amount of nicotine from these products as from smoking tobacco cigarettes. Three studies have shown that IQOS delivers approximately 30% lower levels of nicotine to the aerosol compared to a commercial or standardized tobacco cigarette [8–10]. Therefore, it is possible that smokers who switch to IQOS might use more intense puffing patterns. A nicotine pharmacokinetic study showed that peak plasma nicotine levels after single use of IQOS was approximately 30% lower compared to a tobacco cigarette, but similar reductions in urge to smoke were observed with the two products [36]. Another study found similar 24-hour pharmacokinetic profiles for IQOS and tobacco cigarette among Japanese smokers [37]. A randomized, controlled trial of switching from tobacco cigarette to IQOS found that IQOS users took more frequent puffs and had shorter interpuff intervals. To address uncertainty in the puffing regimen representative of IQOS use, two intense puffing patterns were tested herein. No clear pattern of increase in carbonyl emissions at more intense puffing regimens was observed, with the exception of formaldehyde. Additionally, the levels of carbonyl emissions were reported per nicotine yield. This comparison again showed substantial reduction in carbonyl emissions compared to tobacco cigarette, although the reductions observed in IQOS were somewhat lower compared to reporting carbonyl levels per cigarette or IQOS stick. On the contrary, larger reductions were observed for the e-cigarette, especially at 14 W, due to higher nicotine yield. It remains to be seen whether emissions from heated tobacco products should be reported per stick or nicotine yield. For e-cigarettes, however, it is more relevant to report emissions per liquid consumption [27].

There are several limitations to this study. First, it included a very small sample size. Secondly, the study included the assessment of just a few of the harmful and potentially harmful compounds that are found in tobacco cigarette smoke. However, studies on other potential toxins have shown reduced emissions from IQOS compared to tobacco cigarettes, although no comparison with e-cigarettes was performed [8,10]. Thirdly, only one e-cigarette device was tested. While the findings herein are consistent with previous reports using the same new-generation atomizer [19,27,38], studies have shown some variability in carbonyl emissions depending upon the e-cigarette design and product type [19,26]. For example, old-generation atomizers, using silica wicks and coils on the top of the atomizer, emit substantially higher levels of carbonyls compared with new-generation cotton wick atomizers [19]. Few studies reported that carbonyl emissions from e-cigarettes exceeded the levels in tobacco cigarette smoke [23–25]. However, these findings have been questioned with replication studies showing either lower carbonyl emissions or unrealistic testing conditions that created overheating and dry puffs [26,27,38]. A recent systematic review of carbonyl emissions from e-cigarettes identified several methodological issues which could result in reporting findings with questionable clinical context [39].

In conclusion, this small, independently funded study found that IQOS emitted far lower levels of potentially harmful carbonyl emissions than a combustible cigarette, but higher levels than an e-cigarette. Nicotine yield from the heated tobacco products tended to be lower than combustible cigarette and the e-cigarette. Our results are consistent with studies conducted by the manufacturer of the tested products when they compared their products with combustible cigarettes. While the chemicals assessed in this study do not represent all potential harmful constituents, our results suggest that the continuum of risk is highest for combustible cigarette, considerably less for IQOS heat-not-burn product, and even less for the e-cigarette.

Declaration of interests

In the past 36 months, two studies by K.F. were funded by the non-profit association AEMSA and one study was funded by the non-profit association Tennessee Smoke-Free Association. SkyLab-Med is a private analytical laboratory involved mainly in analytical testing of food products, pharmaceuticals and cosmetics, and in the past few years has been involved in the testing of e-cigarette products.

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References

1. Sutherland G., Russell M. A., Stapleton J. A., Feyerabend C. Glycerol particle cigarettes: a less harmful option for chronic smokers. *Thorax* 1993; **48**: 385–7.
2. Stapleton J. A., Russell M. A., Sutherland G., Feyerabend C. Nicotine availability from eclipse tobacco-heating cigarette. *Psychopharmacology (Berl)* 1998; **139**: 288–90.
3. U.S Department of Health and Human Services, US Food and Drug Administration. Philip Morris Products S.A. Modified Risk Tobacco Product (MRTP) Applications. 2017. Available at: https://www.fda.gov/TobaccoProducts/Labeling/MarketingandAdvertising/ucm546281.htm (accessed 18 November 2017) (Archived at http://www.webcitation.org/70ciyR1RH on 3 July 2018).
4. Baker R. Temperature distribution inside a burning cigarette. *Nature* 1974; **247**: 405–6.
5. Jaccard G., Tafin Djoko D., Moennikes O., Jeannet C., Kondylis A., Belushkin M. Comparative assessment of HPHC yields in the tobacco heating system THS2.2 and commercial cigarettes. *Regul Toxicol Pharmacol* 2017; **90**: 1–8.
6. Szostak J., Boué S., Talikka M., Guedj E., Martin F., Phillips B. *et al*. Aerosol from tobacco heating system 2.2 has reduced impact on mouse heart gene expression compared with cigarette smoke. *Food Chem Toxicol* 2017; **101**: 157–67.
7. Forster M., Fiebelkorn S., Yurteri C., Mariner D., Liu C., Wright C. *et al*. Assessment of novel tobacco heating product THP1.0. Part 3: comprehensive chemical characterisation of harmful and potentially harmful aerosol emissions. *Regul Toxicol Pharmacol* 2018; **93**: 14–33.
8. Schaller J. P., Keller D., Poget L., Pratte P., Kaelin E., McHugh D. *et al*. Evaluation of the tobacco heating system 2.2. Part 2: chemical composition, genotoxicity, cytotoxicity, and physical properties of the aerosol. *Regul Toxicol Pharmacol* 2016; **81**: S27–S47.
9. Farsalinos K. E., Yannovits N., Sarri T., Voudris V., Poulas K. Nicotine delivery to the aerosol of a heat-not-burn tobacco product: comparison with a tobacco cigarette and e-cigarettes. *Nicotine Tob Res* 2017; https://doi.org/10.1093/ntr/ntx138.
10. Bekki K., Inaba Y., Uchiyama S., Kunugita N. Comparison of chemicals in mainstream smoke in heat-not-burn tobacco and combustion cigarettes. *J Univ Occup Environ Hygeine* 2017; **39**: 201–7.
11. Auer R., Concha-Lozano N., Jacot-Sadowski I., Cornuz J., Berthet A. Heat-not-burn tobacco cigarettes: smoke by any other name. *JAMA Intern Med* 2017; **177**: 1050–2.
12. Haussmann H. J. Use of hazard indices for a theoretical evaluation of cigarette smoke composition. *Chem Res Toxicol* 2012; **25**: 794–810.
13. Yuan J.-M., Gao Y.-T., Wang R., Chen M., Carmella S. G., Hecht S. S. Urinary levels of volatile organic carcinogen and toxicant biomarkers in relation to lung cancer development in smokers. *Carcinogenesis* 2012; **33**: 804–9.
14. Moretto N., Volpi G., Pastore F., Facchinetti F. Acrolein effects in pulmonary cells: relevance to chronic obstructive pulmonary disease. *Ann NY Acad Sci* 2012; **1259**: 39–46.
15. Beauchamp R. O. Jr., Andjelkovich D. A., Kligerman A. D., Morgan K. T., Heck H. D., Feron V. J. A critical review of the literature on acrolein toxicity. *Crit Rev Toxicol* 1985; **14**: 309–80.
16. Seeman J. I., Dixon M., Haussmann H. J. Acetaldehyde in mainstream tobacco smoke: formation and occurrence in smoke and bioavailability in the smoker. *Chem Res Toxicol* 2002; **15**: 1331–50.
17. Baker R. R., Coburn S., Liu C., Teteh J. Pyrolysis of saccharide tobacco ingredients: a TGA–FTIR investigation. *J Anal Appl Pyrolysis* 2005; **74**: 171–80.
18. Farsalinos K. E., Voudris V., Poulas K. E-cigarettes generate high levels of aldehydes only in ‘dry puff’ conditions. *Addiction* 2015; **110**: 1352–6.
19. Gillman I. G., Kistler K. A., Stewart E. W., Paolantonio A. R. Effect of variable power levels on the yield of total aerosol mass and formation of aldehydes in e-cigarette aerosols. *Regul Toxicol Pharmacol* 2016; **75**: 58–65.
20. Goniewicz M. L., Knysak J., Gawron M., Kosmider L., Sobczak A., Kurek J. *et al*. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control* 2014; **23**: 133–9.
21. Geiss O., Bianchi I., Barrero-Moreno J. Correlation of volatile carbonyl yields emitted by e-cigarettes with the temperature of the heating coil and the perceived sensorial quality of the generated vapours. *Int J Hyg Environ Health* 2016; **219**: 268–77.
22. Bekki K., Uchiyama S., Ohta K., Inaba Y., Nakagome H., Kunugita N. Carbonyl compounds generated from electronic cigarettes. *Int J Environ Res Public Health* 2014; **11**: 11192–200.
23. Khlystov A., Samburova V. Flavoring compounds dominate toxic aldehyde production during E-cigarette vaping. *Environ Sci Technol* 2016; **50**: 13080–5.
24. Sleiman M., Logue J. M., Montesinos V. N., Russell M. L., Litter M. I., Gundel L. A. *et al*. Emissions from electronic cigarettes: key parameters affecting the release of harmful chemicals. *Environ Sci Technol* 2016; **50**: 9644–51.
25. Jensen R. P., Luo W., Pankow J. F., Strongin R. M., Peyton D. H. Hidden formaldehyde in e-cigarette aerosols. *N Engl J Med* 2015; **372**: 392–4.
26. Farsalinos K. E., Voudris V., Spyrou A., Poulas K. E-cigarettes emit very high formaldehyde levels only in conditions that are aversive to users: a replication study under verified realistic use conditions. *Food Chem Toxicol* 2017; **109**: 90–4.
27. Farsalinos K. E., Kistler K. A., Pennington A., Spyrou A., Kouretas D., Gillman G. Aldehyde levels in e-cigarette aerosol: findings from a replication study and from use of a new-generation device. *Food Chem Toxicol* 2017; **111**: 64–70.
28. Cooperation Centre for Scientific Research Relative to Tobacco. CORESTA recommended method no. 75: determination of selected carbonyls in mainstream cigarette smoke by HPLC. 2013. Available at: http://www.coresta.org/Recommended_Methods/CRM_75.pdf (accessed 19 October 2017) (Archived at http://www.webcitation.org/70cjAkjfC on 3 July 2018).
29. Dawkins L., Turner J., Roberts A., Soar K. ‘Vaping’ profiles and preferences: an online survey of electronic cigarette users. *Addiction* 2013; **108**: 1115–25.
30. Farsalinos K. E., Romagna G., Tsiapras D., Kyrzopoulos S., Spyrou A., Voudris V. Impact of flavour variability on electronic cigarette use experience: an internet survey. *Int J Environ Res Public Health* 2013; **10**: 7272–82.
31. Farsalinos K. Electronic cigarettes: an aid in smoking cessation, or a new health hazard? *Ther Adv Respir Dis* 2018; **12**: 1753465817744960. https://doi.org/ 10.1177/1753465817744960.

32. Haziza C., de La Bourdonnaye G., Skiada D., Ancerewicz J., Baker G., Picavet P. *et al*. Evaluation of the tobacco heating system 2.2. Part 8: 5-day randomized reduced exposure clinical study in Poland. *Regul Toxicol Pharmacol* 2016; **81**: S139–50.
33. Counts M. E., Morton M. J., Laffoon S. W., Cox R. H., Lipowicz P. J. Smoke composition and predicting relationships for international commercial cigarettes smoked with three machine-smoking conditions. *Regul Toxicol Pharmacol* 2005; **41**: 185–227.
34. Brandt A. M. Inventing conflicts of interest: a history of tobacco industry tactics. *Am J Public Health* 2012; **102**: 63–71.
35. Hammond D., Collishaw N. E., Callard C. Secret science: tobacco industry research on smoking behaviour and cigarette toxicity. *Lancet* 2006; **367**: 781–7.
36. Picavet P., Haziza C., Lama N., Weitkunat R., Lüdicke F. Comparison of the pharmacokinetics of nicotine following single and *ad libitum* use of a tobacco heating system or combustible cigarettes. *Nicotine Tob Res* 2016; **18**: 557–63.
37. Brossard P., Weitkunat R., Poux V., Lama N., Haziza C., Picavet P. *et al*. Nicotine pharmacokinetic profiles of the tobacco heating system 2.2, cigarettes and nicotine gum in Japanese smokers. *Regul Toxicol Pharmacol* 2017; **89**: 193–9.
38. Farsalinos K. E., Voudris V. Do flavouring compounds contribute to aldehyde emissions in e-cigarettes? *Food Chem Toxicol* 2018; **115**: 212–7.
39. Farsalinos K. E., Gillman G. Carbonyl emissions in E-cigarette aerosol: a systematic review and methodological considerations. *Front Physiol* 2018; **8**: 1119.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 Percent reduction in exposure to carbonyls from using 20 IQOS sticks and 5 g e-cigarette liquid compared to 20 tobacco cigarettes at PR2 (A, 3 s puff duration, 80 mL puff volume, 30 s interpuff interval) and PR3 (B, 3 s puff duration, 90 mL puff volume, 25 s interpuff interval). Bars represent mean difference, lines represent lower 95% confidence interval of the difference.

