From: "James Middleton"
To:

Date: Tuesday, February 28, 2017 09:46AM
Subject: Subm-PHS-PMIre but.pdf

History: This message has been forwarded.

Panel on Health Services Meeting

28 Feb 2017

Dear Hon Members,

Please find self -explanatory information regarding the comments made in the attached letter from Philip Morris tobacco company tabled for today's meeting.

Should you trust the words of convicted racketeers?

http://www.dwlr.com/blog/2011-05-12/rico-convictions-major-tobacco-companies-affirmed

Yours sincerely,

James Middleton

Chairman

http://cleartheair.org.hk

Attachments:

Subm-PHS-PMIrebut.pdf

Philip Morris Facing More Thai Tax Evasion Charges

By **Bryan Koenig** https://www.law360.com/articles/891973/philip-morris-facing-more-thai-tax-evasion-charges

Law360, Washington (February 14, 2017, 6:38 PM EST) -- Philip Morris International Inc. announced a widening Tuesday of the government of Thailand's long-running criminal investigation seeking billions of dollars in potential penalties based on allegations the company deliberately shorted cigarette import prices to avoid full taxation. The charges announced in Philip Morris' annual report with the U.S. Securities and Exchange Commission were filed Jan. 26 and follow charges levied against the company a year earlier. While the January 2016 charges are seeking more than $2 billion in fines purportedly stemming from imports from the Philippines, the new charges cover cigarettes imported from Indonesia, Philip Morris said in the report.

"The government is seeking a fine of approximately THB 19.8 billion (approximately $562 million). The first hearing, which will focus on preliminary procedural matters, is scheduled for April 2017," Philip Morris said in the filing. "PM Thailand disagrees with the allegations and believes that its declared import prices are in compliance with the Customs Valuation Agreement of the [World Trade Organization] and Thai law."

According to the cigarette giant, the Thailand Department of Special Investigation, or DSI, probed Indonesian imports and the subsequent excise taxes and customs duties paid from 2000 through 2003. The late-January charges the public prosecutor filed in Bangkok Criminal Court also targeted a Thai ex-employee, Philip Morris said.

The company stands accused of working with the employee "with the intention to defraud the Thai government" on "under declared import prices of cigarettes" from 780 import entries between January 2002 and July 2003, all to avoid full taxation and duties, according to the filing.

The charges filed last year against Philip Morris (Thailand) Ltd. and seven current and former workers in the same court followed an **investigation** into the period from 2003 to 2007, according to the filing. Those charges cover allegedly "under declared import prices" from 272 entries brought in from the Philippines from July 2003 to June 2006, Philip Morris said.

"The government is seeking a fine of approximately THB 80.8 billion (approximately US$2.29 billion). The case is in the pre-trial evidentiary phase. Trials are scheduled to begin during the last quarter of 2017," the company said. "PM Thailand believes that its declared import prices are in compliance with the Customs Valuation Agreement of the World Trade Organization and Thai law and that the allegations of the public prosecutor are inconsistent with several decisions already taken by Thai Customs and other Thai governmental agencies."

The Thailand charges are not the end of Philip Morris' international tax woes.

Tuesday's filing also discussed a South Korean Board of Audit and Inspection probe into whether inventory changes by cigarette companies like Philip Morris Korea Inc. complied with the country's tax laws in the run up to a Jan. 1, 2015, cigarette tax increase. According to the filing, the audit wrapped up in November with the assessment of underpaid taxes and penalties. In order to avoid "nonpayment financial costs," Philip Morris' Korean affiliate paid the full amount of taxes assessed to the tune of about $185 million, according to the company.

Philip Morris also reported an early 2017 demand for around US$46 million total from other government authorities. The company vowed to appeal the assessments, while noting that the matter has been referred to the public prosecutor, who will investigate the potential for criminal charges against the company and others.

“If the public prosecutor decides to prosecute, it may seek up to three times the underpaid tax for company criminal penalties and up to five times the underpaid tax for individual criminal penalties,” the company said. “PM Korea believes that it has paid cigarette-related taxes in compliance with the South Korean tax laws.”

South Korea’s Ministry of Strategy and Finance has also filed criminal charges against the country’s Philip Morris unit and its managing director, according to the filing, which characterized the charges as allegations that it went over monthly product withdrawal restrictions imposed by the ministry. The public prosecutor will conduct an investigation into that complaint and make a decision about pursuing a case, according to Philip Morris, which noted disagreement with the allegations.

--Editing by Kelly Duncan.

-

Related Articles

Philip Morris Expects Thai Charges Alleging $2B Tax Evasion

By **Dan Prochilo** **Nov 05, 2013**

Philip Morris International Inc. said its Thailand unit likely would face criminal charges over allegations that it underreported the value of cigarette imports to the Asian nation for years and thereby avoided about $2 billion in duties and import taxes, according to a Friday filing with the U.S. Securities and Exchange Commission.

Tobacco firm Philip Morris pleads not guilty to huge Thai tax dodge

PUBLISHED : Tuesday, 26 April, 2016, 3:01am
UPDATED : Tuesday, 26 April, 2016, 3:00am

Agence France-Presse

Tobacco giant Philip Morris on Monday pleaded not guilty to dodging hundreds of millions of dollars in import tax to Thailand, a crime carrying a massive fine of up to US$2.27 billion.

Thai prosecutors accuse the local unit of the company,

which owns the Marlboro and L&M brands, of evading some 20 billion baht (US$568 million) tax by under declaring import prices for cigarettes from the Philippines between 2003 and 2006.

In fact the duty-free end price of the cigarettes was much higher, according to prosecutors.

The company and seven Thai staff pleaded not guilty according to a written statement read out by a judge at a pretrial hearing at a Bangkok court on Monday.

If convicted prosecutors say the company could be fined up to four times of the sum of unpaid tax, while the employees face a maximum of 10 years in jail.

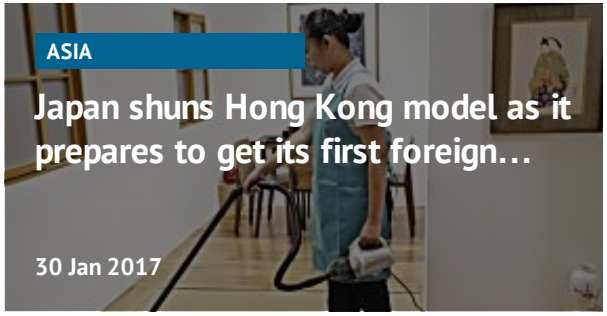
Four foreign executives have also been charged but have left the country in a case that dragged for a decade.

India steps up fight against cigarette firms over prominence of health warnings on packs →

The company "vigorously" denies the "baseless" allegations, Alejandro Paschalides, managing director of Philip Morris Thailand, said after the hearing.

"We would like to encourage the Thai government to reconsider these meritless charges which will harm Thailand's standing in the trade community and ultimately cause damage to the Thai economy and thus the Thai

12 Dec 2016




ASIA 16 Feb 2017


ASIA 25 Feb 2017


ASIA 27 Feb 2017


VIDEO 26 Feb 2017

people," he added in a statement.

The cigarette manufacturer insists that its import valuations complied with World Trade Organization agreements and had been cleared by local Thai customs officials.

> We would like to encourage the Thai government to reconsider these meritless charges which will harm Thailand's standing in the trade community
>
> ALEJANDRO PASCHALIDES, MANAGING DIRECTOR OF PHILIP MORRIS THAILAND

The legal issue has simmered since 2006 under the administration of prime minister Thaksin Shinawatra, shortly before his ousting in a military coup.

Thailand has since been hit by a decade of political instability with frequent government changes and a second coup in 2014.

In 2011, the attorney general at the time recommended against charging the tobacco giant, but the prosecution was restarted two years later.

The next hearing will be in October but the trial is likely to drag out for a number of years.

Environmental Science & Technology

Article

pubs.acs.org/est

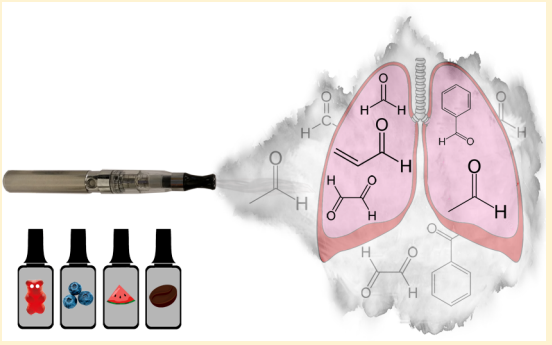
Flavoring Compounds Dominate Toxic Aldehyde Production during E-Cigarette Vaping

Andrey Khlystov* and Vera Samburova

Department of Atmospheric Sciences, Desert Research Institute, Reno, Nevada 89512, United States

Supporting Information

ABSTRACT: The growing popularity of electronic cigarettes (e-cigarettes) raises concerns about the possibility of adverse health effects to primary users and people exposed to e-cigarette vapors. E-Cigarettes offer a very wide variety of flavors, which is one of the main factors that attract new, especially young, users. How flavoring compounds in e-cigarette liquids affect the chemical composition and toxicity of e-cigarette vapors is practically unknown. Although e-cigarettes are marketed as safer alternatives to traditional cigarettes, several studies have demonstrated formation of toxic aldehydes in e-cigarette vapors during vaping. So far, aldehyde formation has been attributed to thermal decomposition of the main components of e-cigarette e-liquids (propylene glycol and glycerol), while the role of flavoring compounds has been ignored. In this study, we have measured several toxic aldehydes produced by three popular brands of e-cigarettes with flavored and unflavored e-liquids. We show that, within the tested e-cigarette brands, thermal decomposition of flavoring compounds dominates formation of aldehydes during vaping, producing levels that exceed occupational safety standards. Production of aldehydes was found to be exponentially dependent on concentration of flavoring compounds. These findings stress the need for a further, thorough investigation of the effect of flavoring compounds on the toxicity of e-cigarettes.



INTRODUCTION

Electronic cigarettes (or e-cigarettes) are battery-operated electronic devices that deliver nicotine or nicotine-free "vapors" to smokers in aerosol form. Since their introduction to the market in 2003, e-cigarettes have been increasing in popularity, especially among the younger population, including school-age children.[1] According to the 2015 report[2] of the National Center for Health Statistics (NCHS), approximately 3.7% adults in the United States use e-cigarettes on a regular basis while 12.6% of adults had tried an e-cigarette. The Adult Tobacco Survey (ATS), prepared by the Centers for Disease Control and Prevention (CDC), reported that the number of adult e-cigarette users doubled between 2010 and 2013,[3] while several studies showed that e-cigarette use is higher among 18−24-year-olds.[3,4] Bunnell et al.[5] reported the number of young e-cigarette users who never smoked before more than tripled (from 79000 to more than 263000) during the period of 2011−2013. According to Singh et al.,[1] in 2015, 25.3% of high school students have regularly used (one or more times per 30 days) any tobacco products (cigarettes, cigars, hookahs, pipes, etc.), with e-cigarettes being the most popular nicotine delivery device (16.0%). A similar pattern was observed among middle school smokers, where e-cigarette user group was dominant, 5.3%.[1] The popularity of e-cigarettes among young people raises serious concerns that e-cigarette usage could cause a future nicotine addiction and facilitate transition to regular cigarettes.

The growing popularity of e-cigarettes could be explained by marketing of these devices as a less harmful or even "healthy" alternative to traditional tobacco products. These claims are based on the assumption that "vapor" produced by "atomization" of e-cigarette liquid (or e-liquid) is harmless, because the e-liquid that is used for vaping is composed mostly of nontoxic components. However, with the exception of ultrasonic brands, e-cigarettes produce vapors using a heating element, which can lead to decomposition of e-liquid constituents. Thermal decomposition does indeed take place, resulting in the production of aldehydes[6−9] and other toxic compounds.[10] Toxic compounds produced by pyrolysis of e-liquid constituents could be the cause of immune and inflammatory response gene suppression in nasal epithelial cells observed in e-cigarette users.[11]

The studies hypothesized that the main source of carbonyl compounds is thermal decomposition of propylene glycol (PG) and/or vegetable glycerin (VG); each serves as a solvent for nicotine and flavoring compounds in e-liquids. Indeed, neat PG and VG were shown to produce aldehydes during vaping, with PG reportedly contributing more to aldehyde production.[6,7] The power and construction of e-cigarettes were also shown to

Received: August 8, 2016
Revised: October 20, 2016
Accepted: October 27, 2016

DOI: 10.1021/acs.est.6b05145
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

have a strong effect on aldehyde emissions.[6,8,9,12] In addition to PG, VG, and nicotine, e-liquids often contain large quantities of flavoring compounds.[13] So far, only two studies have investigated the contribution of flavorings to toxic aldehyde emissions during vaping.[14,15] These studies have investigated direct emission due to evaporation of flavoring compounds, such as benzaldehyde and diacetyl. Thermal decomposition of flavoring compounds and its contribution to the production of aldehydes in e-cigarette vapor have been overlooked so far.

Because the operating temperature of e-cigarettes is sufficient to decompose small molecules, such as PG and VG, it is possible that flavoring compounds could decompose, too. Many flavoring additives are aldehydes,[16] often containing unsaturated bonds. It was demonstrated that thermal decomposition of "chocolate" aldehyde (2-methylbutyraldehyde) leads to formation of formaldehyde, acrolein, and other aldehydes.[17] Another study has shown that unsaturated 2-alkenals and 2,4-alkadienals, while relatively stable in neat form, decompose at 200 °C in the presence of air and/or buffer, producing formaldehyde, acetaldehyde, and other small aldehydes.[18] Flavoring compounds, thus, could be an additional source of toxic aldehydes in e-cigarette emissions, which could explain the recent studies showing that flavorings significantly affect the inhalation toxicity of e-cigarette aerosols.[19,20]

In this study, we have investigated whether flavoring compounds could affect e-cigarette emissions of small, toxic aldehydes, such as formaldehyde, by measuring aldehyde concentrations in aerosols produced by vaping flavored and unflavored liquids.

MATERIALS AND METHODS

We have measured concentrations of 12 aldehydes in e-cigarette aerosols produced by flavored and unflavored liquids. To determine the role of flavoring compounds, in each experiment, we fixed all potentially important parameters that could affect aldehyde production (e-cigarette design, power output, and liquid PG/VG ratio)[6−9,12] and varied only the type and concentration of flavors. Under these conditions, any differences in aldehyde emissions could be due only to differences in the type and concentration of e-liquid flavor.

While comparison between e-cigarette brands was not the aim of this study, we have tested three popular brands of e-cigarettes to investigate whether results are not limited to one e-cigarette brand or construction type. The selected e-cigarette brands were chosen to represent the three most common types of e-cigarette "atomizers": bottom and top coil "clearomizers" and a "cartomizer". Two of the brands were single-coil types, while one was a double-coil type. General characteristics of the three types of e-cigarette devices that were tested in this study are listed in Table 1. The brands were chosen on the basis of ease of availability among the most popular brands to represent the three most common types of e-cigarette "atomizers".

Brand I was a double-bottom coil "clearomizer"; brand II was a single-coil "cartomizer", and brand III was a single-top coil "clearomizer". Though brand I offered a possibility to adjust output voltage (and thus power) between 3.2 and 4.8 V, it was operated at 4 V, the lowest common power setting according to the retailer. Brands II and III have a fixed, manufacturer-set power output. Thus, the possibility of overheating e-liquids during vaping that could lead to excessive aldehyde production (the so-called "dry puff") is excluded. Per the manufacturer's instructions, e-cigarettes were kept horizontal during sampling. Cartridges of brand I and III e-cigarettes were sampled with

Table 1. List of Tested E-Cigarette Devices

	brand I	brand II	brand III
brand	Kangertech eVod Glass[a]	V2 Standard	E-Cig CE4
type	bottom double coil clearomizer	single coil cartomizer	top single coil clearomizer
voltage (V)	4.0[b]	4.2[c]	3.9[d]
resistance (Ω)	1.5	3.4	3.1
power (W)	10.7	5.2	4.9
PG (%)/VG (%)	60/40	80/20	80/20
[nicotine] (mg mL^{-1})	12	18	12

[a]Used with a SmokTech Winder battery. [b]Voltage used for experiments. [c]Manufacturer-set voltage that cannot be modified by the user. [d]Used with a 1100 mAh eGo-T battery, a manufacturer-set voltage that cannot be modified by the user. Voltage and power are nominal values.

fresh coils, whose resistance was verified to be within the manufacturers' specifications, and filled up to two-thirds of their tank capacity. This was done to avoid wick starvation, which could also lead to "dry puff". Brand II was sampled with fresh manufacturer-prefilled cartridges.

E-Cigarette vapor was produced by 4 s, 40 mL controlled "puffs" with a 30 s resting period between each puff. This protocol was adapted to simulate the most common vaping conditions.[14,21] E-Cigarettes were operated according to instructions from the manufacturer and retailer to mimic the most common vaping conditions. The schematic of the sampling setup is given in Figure 1. E-Cigarettes were operated

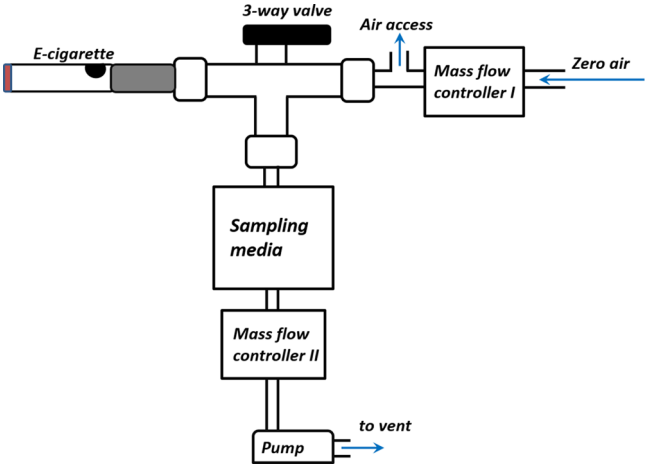


Figure 1. Schematics of the sampling system for e-cigarette emissions. The three-way valve was heated to 40 °C to prevent deposition and/or condensation of gaseous species.

manually to better represent real-life conditions. The operator manually depressed the e-cigarette power button, simultaneously switching a stainless steel three-way valve to sample position. The sample air was drawn by a pump through a mass flow controller (MassTrak 810C-DR-13-V1-S0, Sierra Instruments Inc., 0−50 sccm flow range, 810 ms response time constant) at a rate of 10 mL s^{-1}. The stability of the sample flow was monitored using the mass flow controller display and was checked before and after each experiment using a Gillibrator (Sensodyne, LP). After 4 s, on a signal from an electronic timer, the power button was released and the valve switched to the flush position, during which time the sampling

DOI: 10.1021/acs.est.6b05145
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

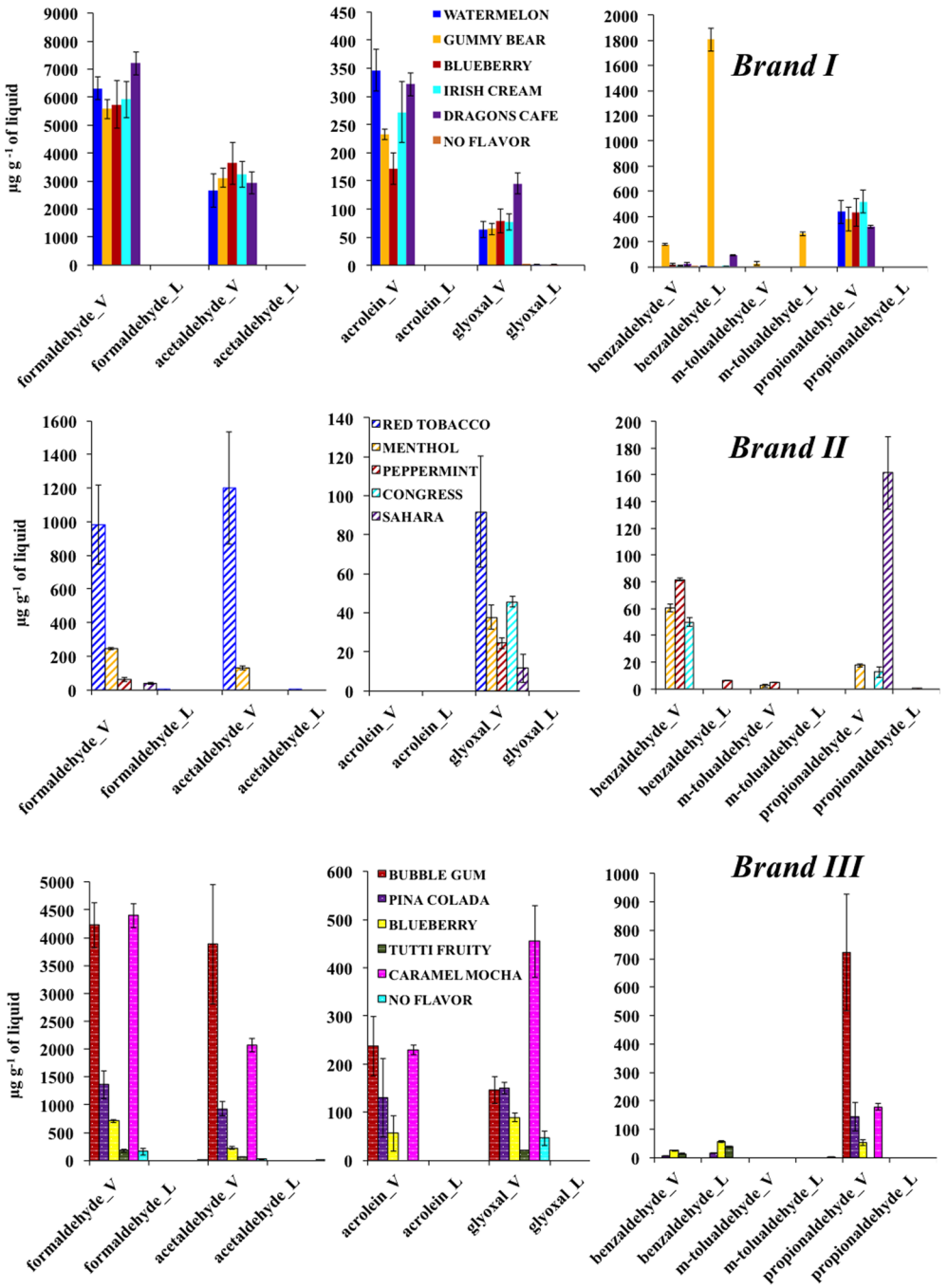


Figure 2. Amounts of aldehydes produced per gram of e-liquid. Error bars represent one standard deviation of triplicate measurements ($N = 3$). "V" designates "vapor" (aerosol), and "L" designates liquid.

line was flushed with zero air. All parts of the sampling system were made of stainless steel and were heated to 40 °C to minimize wall losses.

After 15 warm-up puffs, which are necessary to bring e-cigarette output to steady state,[9] two puffs were sampled directly into 2,4-dinitrophenylhydrazine (DNPH) cartridges (Sep-Pak DNPH-Silica Short Body Cartridges, part WAT047205, Waters, Milford, MA) using the sampling setup presented in Figure 1. All samples were collected in triplicate; i.e., three DNPH cartridges were collected for each liquid. To verify the collection efficiency of DNPH cartridges, several tests were carried out with two cartridges in series. No aldehydes were detected in the second cartridge, indicating quantitative collection of aldehydes. Blank measurements were performed before and after experiments and showed no presence of aldehyde.

Because some aldehydes measured in this study, such as benzaldehyde, could be found as flavoring compounds in liquids and not produced during vaping, we have tested the aldehyde content of liquids. An aliquot (100 μL) of e-liquid was directly run through a DNPH cartridge, which was then extracted in a manner similar to that used for cartridges collected during vaping. Using DNPH cartridges to collect aldehydes from liquids has been reported elsewhere.[12]

Sampled cartridges were eluted with 2 mL of acetonitrile [high-performance liquid chromatography (HPLC) grade,

DOI: 10.1021/acs.est.6b05145
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

EMD Millipore Corp., Billerica, MA] within a few hours of sampling and analyzed with a HPLC system (Waters 2690 Alliance System with a model 996 photodiode array detector) equipped with a Polaris column (C18-A, 3 μm, 100 mm × 2.0 mm HPLC column, Agilent). The following HPLC parameters were used: flow rate of 0.2 mL min^{-1}, injection volume of 2 μL, solvent A of ultrapure water, and solvent B of acetonitrile. The HPLC gradient was as follows: 50% A and 50% B for 10 min, 30% A and 70% B for 8 min, and 100% B for 1 min. The run time was 31 min. The photodiode array detector was operated in the range of 210−400 nm. The detection wavelength was set to 360 nm. Full spectrum readings were used to verify the identity of individual compounds by comparing spectra of individual peaks with the spectra of calibration compounds (DNPH−aldehyde adducts). The HPLC response is calibrated in micrograms per milliliter with a certified calibration mixture purchased from AccuStandard Inc. (New Haven, CT) that contains all 12 DNPH species listed in Table S1. Six-point external calibration was run prior to analysis, and one calibration check was run every 24 h. If the response of an individual compound is more than 10% off, the system is recalibrated, which did not occur during this study. Calibration curves for all aldehydes were linear with R^2 values of >0.99. Recovery rates for 12 standard aldehydes were 94.1−109%. The limit of detection for analyzed free (as opposed to DNPH adducts) aldehydes varied between 0.003 and 0.01 μg mL^{-1} (Table S1). Given the elution volume of 2 mL and the total of two puffs collected per cartridge, this translated into minimal detection limits of 0.003−0.01 μg/puff.

To investigate whether flavoring additives affect aldehyde production during vaping, five flavored e-liquids per each device were tested. In addition to flavored e-liquids, brands I and III were tested with unflavored e-liquids provided by the manufacturers. Brand II did not provide unflavored e-liquids. The relative amount of PG and VG in e-liquids was reported to have an effect on aldehyde production.[6,7,12] To control for this variable, e-liquids for each e-cigarette brand had the same PG/VG ratio. No information about the concentration or composition of flavoring compounds was provided by any of the manufacturers.

To determine whether the concentration of flavoring compounds affects aldehyde production, a series of experiments were performed with Brand III using "bubblegum" e-liquid diluted with the unflavored e-liquid of the same manufacturer and the same PG/VG content; 25, 50, and 75% dilutions were tested in addition to undiluted "bubblegum" and the unflavored e-liquids.

All measured aldehyde concentrations were normalized to the amount of e-liquid consumed. For this purpose, the amount of e-liquid per puff was determined by weighing cartridges before and after each experiment and dividing the weight change by the number of puffs made during each experiment. The liquid consumption per puff is reported in Table S2.

RESULTS

Figure 2 shows aldehyde concentrations detected in e-liquids and in aerosols ("vapors") measured in this study. Among the tested brands, brand I produced the most aldehydes per liquid consumed (Figure 2) and per puff (Table S3) while brand II produced the least. There is anecdotal evidence that bottom coil construction is less prone to dry puffs, yet a bottom coil e-cigarette (brand I) produced the most aldehydes among the tested brands. This reflects the effect of power output on aldehyde production reported by other researchers, as brand I was the most powerful of the three tested brands (Table 1).

While a direct comparison with other studies is difficult because of the differences in e-cigarette construction, power setting, and e-liquid composition, amounts of aldehydes per puff observed in this study (Table S3) are in the range of or higher than those reported elsewhere.[8,9,12,15,22] For example, maximal formaldehyde emissions observed in this study are approximately 2−7 times lower than the steady-state emissions measured by Sleiman et al.,[9] who reported values ranging from 13000 to 48200 ng/mg. In terms of emissions per puff, our formaldehyde data [0.12−50 μg/puff (Table S3)] are comparable to values of 0.05−50 μg/puff reported by Gillman et al.[6] and 30−100 μg/puff reported by Sleiman et al.[9] Several earlier studies have reported significantly lower concentrations. Those studies, however, have used no warm-up puffs. As Sleiman et al. have shown,[9] the first few puffs significantly underestimate the actual emissions. This could be a reason for the low concentrations reported in those studies.

With the exception of benzaldehyde and tolualdehyde, common flavoring compounds, aerosols contained significantly more aldehydes per gram of e-liquid consumed than the liquids used to produce these vapors did. None of the flavored liquids contained formaldehyde, acetaldehyde, or acrolein. Aerosols produced by flavored liquids, however, contained large amounts of these toxic aldehydes. This clearly demonstrates that these aldehydes are formed not by evaporation but by chemical breakdown of e-liquid components. This is consistent with several previous studies.[6,7,9]

Remarkably, there is a significant variation in the amount and relative abundance of individual aldehydes in vapors within each brand. It should be kept in mind that for each e-cigarette brand, the e-cigarette coil construction and power are the same; the e-liquid carrier composition (i.e., the PG/VG ratio) was also kept constant within each brand. These parameters could not explain the observed variations. Thus, the observed variations in emissions of individual aldehydes observed within each brand are not due to pyrolysis of carrier e-liquids (PG and VG). The only variable within one e-cigarette brand is the type of e-liquid flavor. This strongly suggests that flavoring compounds contribute to the production of aldehydes during vaping.

A comparison of aldehyde concentrations found in flavored and unflavored vapors shows that, in fact, decomposition of flavoring compounds dominates production of aldehydes during vaping. Unflavored brand I e-liquid produced detectable amounts of only glyoxal (2.53 ± 1.16 μg/g of e-liquid) and benzaldehyde (6.77 ± 1.05 μg/g of e-liquid); 11 other aldehydes were not detected (ND). In contrast, flavored brand I e-liquids produced large amounts of formaldehyde (5570 ± 330 to 7210 ± 410 μg/g of e-liquid), acetaldehyde (2670 ± 600 to 3640 ± 750 μg/g of e-liquid), acrolein (172 ± 27 to 347 ± 37 μg/g of e-liquid), glyoxal (64.2 ± 14.3 to 146 ± 18 μg/g of liquid), propionaldehyde (320 ± 10 to 518 ± 89 μg/g of e-liquid), and benzaldehyde (ND to 176 ± 7 μg/g of e-liquid). Brand III unflavored e-liquid produced formaldehyde (159 ± 54 μg/g of e-liquid), glyoxal (46.0 ± 14.5 μg/g of liquid), and acetaldehyde (26.9 ± 9.49 μg/g of e-liquid). Brand III flavored e-liquids produced formaldehyde (176 ± 18 to 4400 ± 200 μg/g of e-liquid), acetaldehyde (58.4 ± 1.1 to 3880 ± 1080 μg/g of e-liquid), acrolein (ND to 237 ± 61 μg/g of e-liquid), glyoxal (22.0 ± 3.4 to 455 ± 74 μg/g of e-liquid), propionaldehyde (ND to 722 ± 204 μg/g of e-liquid), and

DOI: 10.1021/acs.est.6b05145
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

benzaldehyde (ND to 58.8 ± 3.2 μg/g of e-liquid). Because unflavored e-liquids produced relatively "clean" vapors, the large amounts of aldehydes found in flavored vapors must be due to pyrolysis of flavoring compounds.

It should be noted that our results do not suggest that PG or VG produces no aldehydes, but that flavoring compounds are responsible for the main part of the emitted toxic aldehydes. Nondetects for unflavored liquids reported in this study are likely due to the small number of puffs that we have used in our measurements. By collecting more puffs per measurement, we could have quantified emissions for unflavored liquids. This quantification, however, is of minor consequence, as the flavored liquids produce significantly more aldehydes than unflavored ones do.

To the best of our knowledge, only two studies have reported emissions from both flavored and unflavored liquids. Kosmider et al.[12] measured both flavored commercially available liquids and liquids containing only PG, VG, water, and nicotine. With the exception of butanal, detectable aldehyde concentrations were found only in flavored liquids. Gillman et al.[6] used 48% (w/w) PG and glycerin with 2% nicotine; it is not clear what the remaining 2% consisted of. For an atomizer that was identical to our brand III e-cigarette, but operated at a higher power setting (5.3 W), they reported formaldehyde emissions of 8.5 ± 8.9 μg/puff. Formaldehyde emissions from unflavored liquid measured in our study are 0.64 ± 0.22 μg/puff. Given the very large uncertainty in the data of Gillman et al. and the sample size (six) used in that study, the difference from our data is not statistically significant.

To provide further proof that flavoring compounds, not the carrier e-liquid (PG and/or VG), dominate production of aldehydes during vaping, we have performed a series of experiments in which a flavored brand III e-liquid ("bubblegum") was diluted with different amounts of the unflavored brand III e-liquid. Amounts per puff of formaldehyde, acetaldehyde, acrolein, and propionaldehyde as a function of the volume fraction of the flavored e-liquid are shown in Figure 3. Aldehyde concentrations increase exponentially with the concentration of flavoring compounds. While the reason for the superlinear relationship is not clear, it emphasizes the dominant effect of flavoring compounds on aldehyde concentration in e-cigarette vapors.

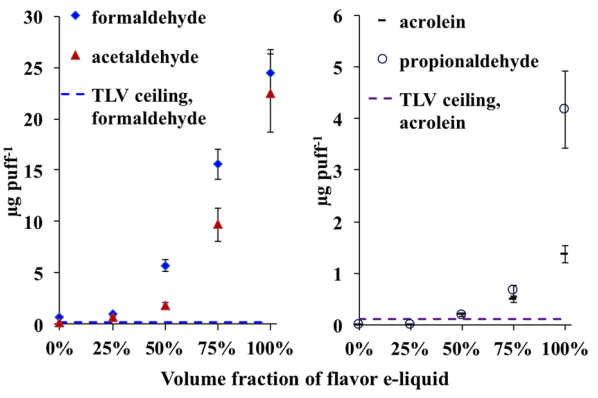


Figure 3. Amounts of formaldehyde, acetaldehyde, acrolein, and propionaldehyde as a function of flavored e-liquid volume fraction after dilution with unflavored e-liquid. Also shown are TLV ceiling levels for formaldehyde and acrolein, assuming each puff is diluted in 500 mL of air (a typical lung tidal volume). Error bars represent one standard deviation of triplicate measurements (N = 3).

It should be stressed that the amount of aldehydes produced by pyrolysis of flavoring compounds is dangerously large. The American Conference of Governmental Industrial Hygienists (ACGIH) establishes Threshold Limit Values (TLVs) for various hazardous chemicals. The ACGIH defines the threshold limit value-ceiling (TLV-C) as the concentration that should not be exceeded during any part of the working exposure,[23] thus representing a limit to instantaneous, not time-averaged, exposure. For formaldehyde, the TLV-C is 0.3 mg m^{-3}, and for acrolein, it is 0.23 mg m^{-3}. To compare exposure to these aldehydes from one puff, we have divided the amount per puff by 500 mL, the average tidal volume of a healthy adult.[24]

All flavored brand I vapors exceeded the ACGIH formaldehyde ceiling level by factors of 190−270 and the acrolein ceiling level by factors of 11−24, depending on the flavor used. Three of five liquids of brand II vapors exceeded the formaldehyde ceiling level by 2.0−13-fold, depending on the e-liquid flavor. No acrolein was detected in brand II vapors. All flavored brand III vapors exceeded the formaldehyde ceiling level by 2.9−66-fold. Four of brand III flavored vapors exceeded the acrolein ceiling by 1.5−6.0-fold, while no acrolein was detected in one of the liquids ("tutti fruity"). In other words, one puff of any of the tested flavored e-cigarette liquids exposes the smoker to unacceptably dangerous levels of these aldehydes, most of which originates from thermal decomposition of flavoring compounds.

In summary, our observations demonstrate that thermal decomposition of flavoring compounds is the main source of aldehydes in vapors produced by e-liquids tested in this study. These results demonstrate the need for a further thorough study of the contribution of flavoring additives to the formation of aldehydes and other toxic compounds in e-cigarette vapors. A study of the thermal behavior of individual flavoring compounds was beyond the scope of this paper and is part of a larger ongoing study, which also includes other decomposition products in addition to aldehydes. The dependence of toxic emissions on flavor concentration in e-liquids is another facet that needs attention. The results of our experiments indicate an exponential dependence of aldehyde emission strength on the concentration of flavoring compounds. For example, by diluting the flavored liquid by a factor of 4 in our experiments, we decreased the acrolein concentration below the TLV-C level (Figure 3). A better understanding of this dependence could offer a way to reduce the toxicity of vapors by controlling concentrations of flavoring compounds in e-liquids.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.6b05145.

Information about detection limits per compound, the average liquid consumption for each of the tested flavors, and a table with aldehyde concentrations per puff for each of the e-cigarette brands and e-liquids tested in this study (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: andrey.khlystov@dri.edu. Phone: +1-775-6747084.

Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.est.6b05145
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

■ ACKNOWLEDGMENTS

This work has been carried out with Desert Research Institute (DRI) internal funding. We thank Anna Cunningham of DRI for technical assistance with chemical analysis of collected samples. We also thank Dr. Marc Pitchford of DRI and Dr. Jeffrey E. Angermann, Dr. Matthew Strickland, and Dr. Lyndsey Darrow of the University of Nevada, Reno (Reno, NV), for their useful suggestions during the preparation of the manuscript.

■ REFERENCES

(1) Singh, T.; Arrazola, R. A.; Corey, C. G.; Husten, C. G.; Neff, L. J.; Homa, D. M.; King, B. A. Tobacco Use Among Middle and High School Students - United States, 2011−2015. *MMWR-Morbidity and Mortality Weekly Report* **2016**, *65*, 361−367.

(2) Schoenborn, C. A.; Gindi, R. M. Electronic Cigarette Use Among Adults: United States, 2014. Report NCHS Data Brief 217; National Center for Health Statistics: Hyattsville, MD, 2015.

(3) King, B. A.; Patel, R.; Nguyen, K. H.; Dube, S. R. Trends in Awareness and Use of Electronic Cigarettes Among US Adults, 2010−2013. *Nicotine Tob. Res.* **2015**, *17*, 219−227.

(4) Duke, J. C.; Lee, Y. O.; Kim, A. E.; Watson, K. A.; Arnold, K. Y.; Nonnemaker, J. M.; Porter, L. Exposure to Electronic Cigarette Television Advertisements Among Youth and Young Adults. *Pediatrics* **2014**, *134*, e29−e36.

(5) Bunnell, R. E.; Agaku, I. T.; Arrazola, R. A.; Apelberg, B. J.; Caraballo, R. S.; Corey, C. G.; Coleman, B. N.; Dube, S. R.; King, B. A. Intentions to Smoke Cigarettes Among Never-Smoking US Middle and High School Electronic Cigarette Users: National Youth Tobacco Survey, 2011−2013. *Nicotine Tob. Res.* **2015**, *17*, 228−235.

(6) 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.

(7) 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*, 392−394.

(8) 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*, 268−277.

(9) Sleiman, M.; Logue, J. M.; Montesinos, V. N.; Russell, M. L.; Litter, M. I.; Gundel, L. A.; Destaillats, H. Emissions from Electronic Cigarettes: Key Parameters Affecting the Release of Harmful Chemicals. *Environ. Sci. Technol.* **2016**, *50*, 9644−9651.

(10) Fromme, H.; Schober, W. Waterpipes and e-cigarettes: Impact of alternative smoking techniques on indoor air quality and health. *Atmos. Environ.* **2015**, *106*, 429−441.

(11) Martin, E.; Clapp, P. W.; Rebuli, M. E.; Pawlak, E. A.; Glista-Baker, E. E.; Benowitz, N. L.; Fry, R. C.; Jaspers, I. E-cigarette use results in suppression of immune and inflammatory-response genes in nasal epithelial cells similar to cigarette smoke. *American Journal of Physiology - Lung Cellular and Molecular Physiology* **2016**, *311*, L135−L144.

(12) Kosmider, L.; Sobczak, A.; Fik, M.; Knysak, J.; Zaciera, M.; Kurek, J.; Goniewicz, M. L. Carbonyl Compounds in Electronic Cigarette Vapors: Effects of Nicotine Solvent and Battery Output Voltage. *Nicotine Tob. Res.* **2014**, *16*, 1319−1326.

(13) Tierney, P. A.; Karpinski, C. D.; Brown, J. E.; Luo, W.; Pankow, J. F. Flavour chemicals in electronic cigarette fluids. *Tobacco Control* **2016**, *25*, e10−e15.

(14) Allen, J. G.; Flanigan, S. S.; LeBlanc, M.; Vallarino, J.; MacNaughton, P.; Stewart, J. H.; Christiani, D. C. Flavoring Chemicals in E-Cigarettes: Diacetyl, 2,3-Pentanedione, and Acetoin in a Sample of 51 Products, Including Fruit-, Candy-, and Cocktail-Flavored E-Cigarettes. *Environ. Health Perspect.* **2016**, *124*, 733−739.

(15) Kosmider, L.; Sobczak, A.; Prokopowicz, A.; Kurek, J.; Zaciera, M.; Knysak, J.; Smith, D.; Goniewicz, M. L. Cherry-flavoured electronic cigarettes expose users to the inhalation irritant, benzaldehyde. *Thorax* **2016**, *71*, 376−377.

(16) Fisher, C.; Scott, T. R. *Food Flavours: Biology and Chemistry*; Information Services, Royal Society of Chemistry: London, 1997.

(17) Rosado-Reyes, C. M.; Tsang, W. Thermal Stability of Larger Carbonyl Compounds: 2-Methylbutyraldehyde. *Int. J. Chem. Kinet.* **2014**, *46*, 285−293.

(18) Zamora, R.; Navarro, J.; Aguilar, I.; Hidalgo, F. Lipid-derived aldehyde degradation under thermal conditions. *Food Chem.* **2015**, *174*, 89−96.

(19) Lerner, C.; Sundar, I.; Yao, H.; Gerloff, J.; Ossip, D.; McIntosh, S.; Robinson, R.; Rahman, I. Vapors Produced by Electronic Cigarettes and E-Juices with Flavorings Induce Toxicity, Oxidative Stress, and Inflammatory Response in Lung Epithelial Cells and in Mouse Lung. *PLoS One* **2015**, *10*, e0116732.

(20) Leigh, N.; Lawton, R.; Hershberger, P.; Goniewicz, M. Flavourings significantly affect inhalation toxicity of aerosol generated from electronic nicotine delivery systems (ENDS). *Tobacco Control* (September 15, 2016).

(21) Dautzenberg, B. Real-Time Characterization of E-Cigarettes Use: The 1 Million Puffs Study. *J. Addict. Res. Ther.* **2015**, *6*, 229.

(22) Goniewicz, M. L.; Knysak, J.; Gawron, M.; Kosmider, L.; Sobczak, A.; Kurek, J.; Prokopowicz, A.; Jablonska-Czapla, M.; Rosik-Dulewska, C.; Havel, C.; Jacob, P.; Benowitz, N. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tobacco Control* **2014**, *23*, 133−139.

(23) ACGIH, TLV Chemical Substances Introduction (http://www.acgih.org/tlv-bei-guidelines/tlv-chemical-substances-introduction), 2016 (accessed August 1, 2016).

(24) Barrett, K. E.; Barman, S. M.; Boitano, S.; Brooks, H. *Ganong's Review of Medical Physiology, Section VII, Pulmonary Function*, 24th ed.; McGraw-Hill: New York, 2012.

DOI: 10.1021/acs.est.6b05145
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

https://eurekalert.org/pub_releases/2017-02/aha-emp021517.php

Public Release: 23-Feb-2017

E-cigarettes may pose the same or higher risk of stroke severity as tobacco smoke

Session A25 - Abstract LB10 in Grand Ballroom B

American Heart Association

Electronic cigarette (e-cigarettes) vaping may pose just as much or even higher risk as smoking tobacco for worsening a stroke, according to a preliminary study in mice presented at the American Heart Association's International Stroke Conference 2017.

Researchers found:

Mice exposed to e-cigarette vapor for 10 days or 30 days had worse stroke outcome and neurological deficits, than those exposed to tobacco smoke.

E-cigarette exposure decreased glucose uptake in the brain. Glucose fuels brain activity.

Both e-Cig and tobacco smoke exposure for 30 days decreased Thrombomodulin (anti-coagulant) levels.

From a brain health perspective, researchers said, electronic-cigarette vaping is not safer than tobacco smoking, and may pose a similar, if not higher risk for stroke severity.

Use of e-cigarettes is a growing health concern in both smoking and nonsmoking populations. Researchers said rigorous studies are needed to investigate the effects of the nicotine exposure via e-cigarettes on brain and stroke outcome.

###

Ali Ehsan Sifat, Graduate Student/Research Assistant, Department of Pharmaceutical Sciences, Texas Tech University Health Sciences Center, Amarillo, Texas.

Additional Resources:

Any available multimedia related to these tips are on the right column of this link
http://newsroom.heart.org/news/isc17-thursday-news-tips?preview=4bf61fdc2bf2161ccff14e2358af048d

Join the AHA/ASA Support Network to talk with others going through similar journeys including depression after stroke.
Quitters Win
Follow news from the American Stroke Association's International Stroke Conference 2017 via Twitter: @HeartNews #ISC17.

Environmental Research 152 (2017) 221–225

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

E-cigarettes as a source of toxic and potentially carcinogenic metals

Catherine Ann Hess[a,b,*], Pablo Olmedo[b], Ana Navas-Acien[b,c], Walter Goessler[d], Joanna E. Cohen[c], Ana Maria Rule[b]

[a] University of California, Berkeley, School of Public Health, Prevention Research Center, 180 Grand Ave., Ste. 1200, Oakland, CA 94612, USA
[b] Department of Environmental Health Sciences, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe St. Baltimore, MD 21205, USA
[c] Institute for Global Tobacco Control, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe St. Baltimore, MD 21205, USA
[d] Karl-Franzens-Universität Graz, Graz, Institute of Chemistry, Unversitätsplatz 1, 8010 Graz, Austria

ARTICLE INFO

Keywords:
Electronic nicotine delivery devices
Carcinogens
Non-cigarette tobacco products

ABSTRACT

Background and aims: The popularity of electronic cigarette devices is growing worldwide. The health impact of e-cigarette use, however, remains unclear. E-cigarettes are marketed as a safer alternative to cigarettes. The aim of this research was the characterization and quantification of toxic metal concentrations in five, nationally popular brands of cig-a-like e-cigarettes.

Methods: We analyzed the cartomizer liquid in 10 cartomizer refills for each of five brands by Inductively Coupled Plasma Mass Spectrometry (ICP-MS).

Results: All of the tested metals (cadmium, chromium, lead, manganese and nickel) were found in the e-liquids analyzed. Across all analyzed brands, mean (SD) concentrations ranged from 4.89 *(0.893)* to 1970 (*1540*) μg/L for lead, 53.9 (*6.95*) to 2110 (*5220*) μg/L for chromium and 58.7 *(22.4)* to 22,600 (*24,400*) μg/L for nickel. Manganese concentrations ranged from 28.7 (*9.79*) to 6910.2 (*12,200*) μg/L. We found marked variability in nickel and chromium concentration within and between brands, which may come from heating elements.

Conclusion: Additional research is needed to evaluate whether e-cigarettes represent a relevant exposure pathway for toxic metals in users.

1. Introduction

E-cigarettes are increasing in popularity in the United States with sales in 2015 exceeding $3.5 billion (Herzog, 2015). There is great controversy surrounding e-cigarettes and some evidence showing that e-cigarettes are not harmless, although less so than cigarettes and may have long-term health implications for the user (Rom et al., 2015; Grana et al., 2014). Many of the active smokers who switch to e-cigarettes, and never smokers who start using them, do so in the belief that these devices are safer than combustible tobacco (Etter and Bullen, 2011; Goniewicz et al., 2013).

Cig-a-likes, the rechargeable or fully disposable devices commonly sold at convenience and liquor stores, are sometimes referred to as "first-generation" devices, implying that these e-cigarettes are waning in popularity (Lechner et al., 2015). We chose to analyze cig-a-likes because as of 2015, cig-a-likes still maintained a strong market share, despite falling in popularity compared to "second-generation" devices (Herzog and Gerberi, 2013). Surveys of e-cigarette users report that 99% of adult users are former or current smokers (Etter and Bullen, 2011; Etter, 2010). Over 80% of e-cigarette users are former tobacco smokers (defined as no longer smoking any tobacco cigarettes) (Etter and Bullen, 2011; Piñeiro et al., 2016). In the US, e-cigarette use is increasing among teenagers who have never used tobacco (McCarthy, 2014, 2015; Wills et al., 2015; Gilreath et al., 2016).

Regulation of e-cigarettes varies across countries although at the time this research was conducted, cig-a-likes were unregulated in the US. Recently however, the US Food and Drug Administration (FDA) has announced new deeming regulations that bring e-cigarettes under the same regulations as tobacco (US Food and Drug Administration). Scheduled to come into effect as of August 2016, the rules require FDA approval for all e-cigarette products which entered the market after 2007. This move may have a substantial impact on the e-cigarette market and could potentially increase the market share of cig-a-like devices in the US, as many of these devices are produced by established tobacco companies who may be better positioned to afford the high cost of FDA product approval than smaller, independent device and e-liquid producers (Yandle et al., 2015). The European Union (EU) has also recently implemented regulations on e-cigarettes (Directive 2014/40/EU). These regulations include new labeling requirements and advertising restrictions.

* Corresponding author at: 180 Grand Avenue, Suite 1200, Oakland, CA 94612, USA.
E-mail address: chess@prev.org (C.A. Hess).

http://dx.doi.org/10.1016/j.envres.2016.09.026
Received 14 June 2016; Received in revised form 27 September 2016; Accepted 29 September 2016
Available online 28 October 2016
0013-9351/

Table 1
Metal concentrations in five commercial brands of cig-a-like e-cigarettes (μg/L).

Brand	N	Cadmium			Chromium			Lead			Manganese			Nickel		
		Mean (SD)	Median	Range	Mean (SD)	Median	Range	Mean (SD)	Median	Range	Mean (SD)	Median	Range	Mean (SD)	Median	Range
Brand A (μg/L)	10	205 (318)	12.40	322–755	2110 (5220)	213	98.6–16,900	1970 (1450)	1630	500–4870	6910 (12,200)	918	541–31,500	22,600 (24,400)	15,400	2040–72,700
Brand B (μg/L)	10	1.17 (1.09)	0.796	0.470-4.11	788 (284)	726	306–1130	58.1 (79.4)	18.5	3.53–218	670 (283)	627	247–1200	13,400 (4540)	13,100	4560–20,500
Brand C (μg/L)	8	1.57 (1.30)	1.17	0.157–4.18	231 (71.6)	205	162–381	5.83 (1.80)	5.15	4.50-9.82	200 (33.9)	187	154–258	463 (132)	491	316–652
Brand D (μg/L)	10	0.982 (0.802)	0.502	0.249–2.23	76.1 (11.0)	75.6	60.2–92.7	4.89 (0.893)	4.98	3.17–5.89	41.50 (13.9)	44.4	11.8–65.5	58.7 (22.4)	58.1	13.7–85.4
Brand E (μg/L)	10	0.415 (0.38)	0.204	0.137–1.23	53.9 (6.95)	56.7	41.5–60.79	93.4 (80.5)	69.3	7.94–233	28.7 (9.79)	26.1	15.5–48.23	114 (49.3)	134	39.3–175
LOD (μg/L)*			0.04			0.1			0.02			0.08			0.1	
Intra-laboratory ICC	48×2		0.965			0.999			0.997			1.000			1.000	
Inter-laboratory ICC	4×2		0.997			0.993			0.997			0.988			0.988	

ICC: intraclass correlation coefficient. The intra-laboratory ICC was calculated from duplicate aliquots from the same e-cigarette liquid sample. Mean concentration was calculated by taking the mean of 2 duplicate samples from the same e-cigarette. The inter-laboratory ICC was calculated from duplicate analyses conducted in a subset of 4 e-cigarette liquid samples conducted at Graz University (Graz, Austria). *LOD are calculated to a 1:20 dilution factor.

Cig-a-like devices work by heating a liquid mixture of propylene glycol, glycerin, nicotine and flavorings. When heated with a metal coil, the mixture is aerosolized into a “vapor”, which is inhaled by the user. The commonly held belief among consumers of e-cigarettes is that they are a safer alternative to cigarettes (Goniewicz et al., 2013; Dockrell et al., 2013; Farsalinos et al., 2014). However, based on investigations including our own, there is strong evidence to suggest that these devices may be a source of toxic chemical exposure for users, particularly substances with known carcinogenic properties (Chervona et al., 2012; Cheng, 2014; Lerner et al., 2015; Tokar et al., 2011; Varlet et al., 2015; Barrington-Trimis et al., 2014).

Very little research has evaluated the potential of e-cigarettes to be a source of toxic metal exposure, including metals with known carcinogenic properties. To date, few published studies have investigated metal concentrations in US e-cigarette brands (Goniewicz et al., 2014; Williams et al., 2013). Goniewicz et al. investigated 12 Polish and British cig-a-like e-cigarettes and identified only nickel, cadmium and lead in cig-a-like aerosol, and in concentrations similar to that of a commercially available nicotine inhaler (Goniewicz et al., 2014). Concentrations ranged from 0.11 to 0.29 μg/e-cigarette (150 puffs) for nickel and 0.03–0.57 μg/e-cigarette for lead. That study did not report chromium or manganese in any brand. Williams et al. analyzed metal concentration in both liquid and aerosol and report the presence of nickel, chromium and lead, but not cadmium (Williams et al., 2013). Reported concentrations were 0.005 μg/10 puffs for nickel, 0.007 μg/10 puffs for chromium and 0.017 μg/10 puffs for lead (Williams et al., 2013).

The aim of this study was to analyze metal concentrations in the liquid of popular brands of e-cigarettes.

2. Materials and methods

We selected five popular brands of rechargeable “cig-a-like” devices available in the United States. The retail environment and sales of cig-a-likes are difficult to determine. Brands increase and decrease in popularity rapidly as cig-a-like manufacturers bring new products to market (Zhu et al., 2014). We chose five brands based on national market share. Three of the brands we tested comprised 71% of the market share of cig-a-likes in 2015 (Craver, 2015). Three of the brands are manufactured by tobacco companies and two are not, but all brands are available nationally in the US at big-box retail outlets, convenience stores, and online. All brands contained nicotine in concentrations of approximately 1.6–1.8 mg/mL, as stated by the manufacturer on the cartridge packaging.

Cartridges from each brand were purchased at retail outlets or online. The liquid from 10 cartridges from each brand were analyzed. For each cartridge, we aimed to obtain enough liquid sample (approximately 400 μL) for two replicates. In the end we had a total of 48 liquid samples instead of 50 because two samples from Brand C did not yield enough liquid for analysis and those two samples were excluded. We only selected one flavor for each brand and flavor choice was determined by retail availability at the time of purchase. We found that total volume of liquid per cartridge varied significantly by brand and ranged from 300 to 600 μL. For this reason we chose not to measure per-cartridge metal content but instead report metal concentrations in μg/L, which allows for consistency in reporting across brands.

The end caps of each cartomizer were removed with standard pliers and the pad, free of the heating coil, was removed from the cartridge using polypropylene forceps. Pads were centrifuged for 10 min at 1540 RCF. Two aliquots of 250 μL were collected from each sample for Brand A, Brand B, Brand D and Brand E, and 150 μL for Brand C and diluted to 5 mL final volume with 1% HNO_3 and 0.5% HCl (Fisher Optima Trace Element Grade) in ultra-pure MilliQ water and vortexed prior to analysis. Cd, Cr, Pb, Mn, and Ni were analyzed using inductively coupled plasma mass spectrometry (ICP-MS, Agilent 7500ce Octopole ICP-MS, Agilent Technologies, Santa Clara, USA). Method limits of detection (MLD) were calculated using procedural blanks and are reported in Table 1. Accuracy was successfully tested using NIST traceable Certified Reference Material TMDW-B (High Purity Standards, Charleston, SC). We estimated the intra-class correlation coefficient (ICC) for the two aliquots from the same sample (intra-laboratory ICC) and given the high reliability (Table 1), we calculated and used in the analysis the mean metal concentration of the two replicates for each e-cigarette liquid sample. We also conducted a duplicate analysis in a random subset of four e-cigarette liquid samples at the Trace Element Laboratory of the Institute of Chemistry Analytical Chemistry, Graz University (Graz, Austria), showing high comparability between laboratories (inter-laboratory ICC, Table 1).

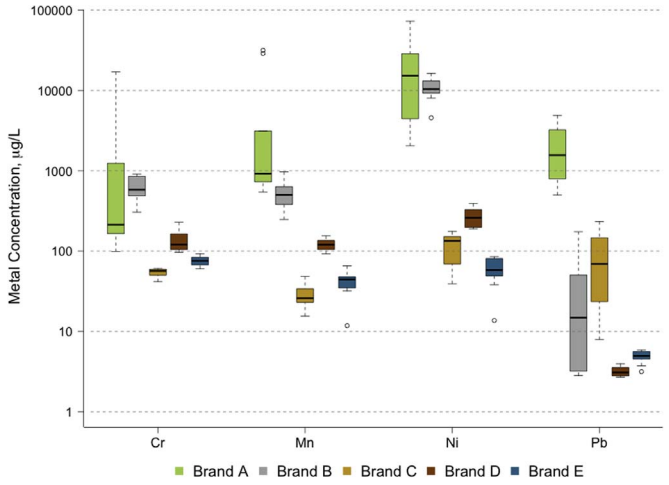


Fig. 1. Distribution of metal concentration within brands. Horizontal lines within boxes indicate medians; boxes, interquartile ranges; error bars, values within 1.5 times the interquartile range; solid circles, outlying data points.

3. Results

We found high levels of metals in the liquids of some brands. Cd, Cr, Pb, Mn and Ni were detected in all liquids analyzed. Metal concentrations per brand are given in Table 1 and Fig. 1 (cadmium was not included in the figure as the concentrations were markedly lower in most brands compared to the other metals). Brand A had the highest mean concentrations of all metals investigated. Brand B had the second highest mean concentrations of Cr, Mn and Ni. Mean (*SD*) Ni concentration in Brand A was 22,600 (*24,400*) µg/L and was nearly 400 times that of the lowest Ni concentration of 58.0 (*22.4*) µg/L measured in liquid from Brand D. Mean Cr concentration in Brand A was 2110 (*5220*) µg/L, 39 times that of the lowest Cr concentration of 53.9 (*6.95*). Mean (*SD*) Mn concentration in Brand A was 6910 *(12,200)* µg/L, 240 times that of the lowest Mn concentration, measured in Brand E. Cd levels were fairly low, except in Brand A. Pb concentrations were fairly low in Brand C and Brand D and highly variable in other brands.

Intra class correlation coefficients were calculated for sample repeats for inter- and intra-laboratory results. ICCs for all elements are >0.96, indicating high reliability of analytical results. Variation in and distribution of metal concentrations within some brands was high, particularly in Brand A for all metals and Brand C and Brand E brands for Pb (Fig. 1).

4. Discussion

This analysis of cig-a-like e-cigarette liquid found marked variability in nickel and chromium, manganese and lead concentrations within and between brands. For cadmium, the concentrations were comparatively low, except for Brand A. To date, few studies have investigated metal concentrations in e-cigarettes liquid. Comparisons with previous studies are difficult because of differences in the type of sample analyzed (e-cigarette liquid vs. aerosol), sampling protocol and reporting methods across studies. We have reported metal concentrations in µg/L, compared to a per-cartridge concentration, in part, because we found variation in total cartridge liquid volume both within and between brands.

The concentrations of nickel, chromium and manganese in some brands warrant further detailed investigation into metal concentrations in e-cigarette liquid and in aerosol. Nickel is a Group 1 carcinogen and has been associated with chronic bronchitis and lung cancer in occupationally exposed populations (ATSDR, 2005; IARC, 2012). In animal models, inhaled nickel can enter the lymphatic system inducing lymph node damage and reducing acquired immunity (ATSDR, 2005). Inhaled chromium has been associated with emphysema and chronic lung infection and reduced lung function in humans (ATSDR, 2012). More generally, nickel is a known respiratory and skin irritant. (Thyssen et al., 2007). It is estimated that the prevalence of nickel contact allergy is approximately 12% in the North American population, with recent evidence that the prevalence is increasing (Admani and Jacob, 2014). Nickel allergy may be higher among younger individuals and women. Nickel allergy is also associated with cigarette smoking, as tobacco is a significant source of nickel (Thyssen et al., 2007). Effects of inhaled nickel can include, rhinitis, chronic sinusitis and bronchitis and allergic asthma. (ATSDR, 2005). Chronic dermal exposure from vaping can occur around the peri-oral area and could potentially result in contact dermatitis from e-cigarettes containing nickel.

Recent research has highlighted the potential harmful effects of even small concentrations of chromium (III), indicating the potential for the oxidization of chromium (III) into carcinogenic chromium (VI) at the cellular level (Wu et al., 2016), There is growing evidence that chromium (III) is genotoxic (Fang et al., 2014), highlighting the importance of measuring total chromium. In our study, we could not measure the valence state of chromium. It is possible that the nickel and chromium concentrations stem from the use of nickel and chromium (nichrome) in the heating elements of most devices (Brown and Cheng, 2014). The origin of lead and manganese is unclear, but it could be present due to contamination during the production of the heating coil. Concerns over the health risks of metals in cig-a-likes have been debated, however the high toxicity of these metals justifies the further study of their concentrations in e-cigarette devices, and are high enough to cause concern for user health (Farsalinos et al., 2015). Lead and manganese, though measured at lower concentrations in our study, are both highly toxic when inhaled. Lead is of particular concern as it affects multiple organs and systems, even at low exposure levels, and inhaled lead is more readily absorbed into the blood stream compared to other routes (ATSDR, 2007). Manganese is a potent neurotoxicant, and exposure to inhaled manganese is associated with neurological symptoms which resemble Parkinson's Disease, tremor, and muscle spasms as well as inflammation of the lungs (Mergler et al., 1999; Han et al., 2009; O'Neal and Zheng, 2015).

Direct translation of these results into a quantified level of exposure for users is complicated and beyond the scope of this paper. Electronic cigarettes do not produce side-stream aerosol in the same way as a tobacco cigarette produces side-stream smoke. Because the aerosol is only generated when the user activates the battery through inhalation, a significant portion of the aerosol generated is inhaled into the lungs. The data presented do show the potential for high concentrations of metals in the aerosols produced across the life of one cartridge. While it is unknown how much of the metal in the liquid is aerosolized, even if only a fraction of these metals were aerosolized and transferred into the lung, the concentrations and the variability presented in this paper warrant caution and additional research. More research is needed to evaluate metal exposure in the generated aerosol, including the relatively high concentrations of toxic metals in some brands of e-cigarettes but not others, and the variability within brands. Research is also needed measuring metal concentrations in biospecimens of e-cigarette users. Limits for inhaled metals are generally set for occupational exposure and measured in mg/m^3 over a set period of time. A user exposed to the total metal concentrations present in these liquids could exceed NIOSH recommended exposure limits as well as the more conservative ATSDR (Agency For Toxic Substances And Disease Registry) Maximum Recommended Limit (MRL) in one cartridge, particularly for nickel, chromium and lead (ATSDR, 2015; NIOSH, 1997).

From a consumer standpoint, the variability in metal concentrations makes it difficult to determine which brands or devices may be

less harmful than others with regards to toxic metal exposure. More critically, from a quality control perspective, high variability within brands and batches makes safety testing of these devices more difficult for both manufacturers and regulatory agencies. We did not analyze the metal heating coil, however previous studies in both the US and Japan have reported nichrome heating coils in cig-a-likes (Williams et al., 2013; Bekki et al., 2014). Additionally, nichrome, along with kanthal, an iron/chromium/aluminum alloy, is among the most commonly used alloys for resistance heating components. When in use, the heating coil comes in direct contact with e-liquid, and at higher temperatures could result in some leaching of the coil metals into the liquid. Given the likelihood that the source of some of these metals are the device components themselves, it appears that the existing screening of the liquid for metals prior to assembly of the device is insufficient. While the concentrations of metals in e-cigarette liquid are higher than would be expected in aerosol, and may be lower than in tobacco, the metals and concentrations reported here indicate that these devices are a source of toxic metal exposure. This exposure may be of particular concern in the case of non-smokers who use e-cigarettes, a demographic which is predominantly adolescents.

This study does have limitations. Firstly, it is difficult to translate these findings into delivered dose estimates. This is primarily due to uncertainty in vaping topography and subsequently, in estimating metals exposure from “typical” vaping behavior. Secondly, we did not quantify nickel or chromium species in cig-a-likes, however this is an important subsequent step in determining more precise health risks associated with the element concentrations reported here.

The implications of these findings are particularly relevant in light of increased regulation of e-cigarette manufacturing. New FDA deeming rules may bring about change and may result in more stringent quality control regarding product constituents as well as greater transparency for consumers. The regulations require that manufacturers of electronic cigarettes and e-liquids submit both ingredient lists, as well as information on harmful or potentially harmful constituents (HPHC), which includes nickel, lead and chromium and cadmium (US Food and Drug Administration). A more thorough investigation of the mechanical components of e-cigarettes is needed, as is greater chemical monitoring of e-cigarette liquids after prolonged contact with the device itself as well as monitoring of the final aerosol. For cig-a-likes, hazard reduction may take the form of a shift away from nichrome heating components and greater scrutiny of the materials used in device components.

Competing interests

None.

Funding

This study was funded by the Institute for Global Tobacco Control, Johns Hopkins School of Public Health (Grant# 118402); NIEHS Training Grant T32ES007141-31A1; NIAAA Training Grant T32-AA014125 and the Alfonso Martín Escudero Foundation.

Contributions

CAH and PO developed and implemented experimental methods and analysis; AR, WG, and ANA contributed to experimental design; CAH conducted data analysis and wrote the manuscript; PO, ANA, AR and JEC contributed to the preparation of the manuscript.

Acknowledgements

The authors thank Maria Grau Pérez for her assistance in preparing the figure for the manuscript.

References

Admani, S., Jacob, S.E., 2014. Allergic contact dermatitis in children: review of the past decade. Curr. Allergy Asthma Rep. 14 (4), 1–11.
ATSDR, 2005. Toxicological profile for Nickel. U.S. Department of Health and Human Services PHS, Atlanta, GA.
ATSDR, 2007. Toxicological Profile for Lead. Department of Health and Human Services, Atlanta, Georgia.
ATSDR, 2012. Toxicological Profile for Chromium. U.S. Department of Health and Human Services, Atlanta, GA.
ATSDR, 2015. Minimal Risk Levels for Hazardous Substances.
Barrington-Trimis, J.L., Samet, J.M., McConnell, R., 2014. Flavorings in electronic cigarettes an unrecognized respiratory health hazard? JAMA 312 (23), 2493–2494.
Bekki, K., Uchiyama, S., Ohta, K., Inaba, Y., Nakagome, H., Kunugita, N., 2014. Carbonyl Compounds generated from electronic cigarettes. Int J. Environ. Res. Public Health 11 (11), 11192.
Brown, C.J., Cheng, J.M., 2014. Electronic cigarettes: product characterisation and design considerations. Tob. Control 23 (Suppl. 2), ii4–ii10.
Cheng, T., 2014. Chemical evaluation of electronic cigarettes. Tob. Control 23, 11–17.
Chervona, Y., Arita, A., Costa, M., 2012. Carcinogenic metals and the epigenome: understanding the effect of nickel, arsenic, and chromium. Metallomics 4 (7).
Craver, R., 2015. Vuse overwhelming e-cig competition. Richmond Times-Dispatch. June 1, 2015.
Directive 2014/40/EU of the European Parliament and of the Council of 3 April 2014 on the approximation of the laws, regulations and administrative provisions of the Member States concerning the manufacture, presentation and sale of tobacco and related products and repealing Directive 2001/37/EC. Official Journal of the European Union. Available at: ⟨http://ec.europa.eu/health/tobacco/docs/dir_201440_en.pdf.⟩ (accessed 27.09.16.).
Dockrell, M., Morrison, R., Bauld, L., McNeill, A., 2013. E-cigarettes: prevalence and attitudes in Great Britain. Nicotine Tob. Res. 15 (10), 1737–1744.
Etter, J., 2010. Electronic cigarettes: a survey of users. BMC Public Health 10, 231.
Etter, J.-F., Bullen, C., 2011. Electronic cigarette: users profile, utilization, satisfaction and perceived efficacy. Addiction 106 (11), 2017–2028.
Fang, Z., Zhao, M., Zhen, H., Chen, L., Shi, P., Huang, Z., 2014. Genotoxicity of tri- and hexavalent chromium compounds and their modes of action on DNA damage. PLoS One 9 (8).
Farsalinos, K.E., Voudris, V., Poulas, K., 2015. Are metals emitted from electronic cigarettes a reason for health concern? A risk-assessment analysis of currently available literature. Int J. Environ. Res. Public Health 12 (5), 5215–5232.
Farsalinos, K.E., Romagna, G., Tsiapras, D., Kyrzopoulos, S., Voudris, V., 2014. Characteristics, perceived side effects and benefits of electronic cigarette use: a worldwide survey of more than 19,000 consumers. Int. J. Environ. Res. Public Health 11 (4), 4356–4373.
Gilreath, T.D., Leventhal, A., Barrington-Trimis, J.L., et al., 2016. Patterns of alternative tobacco product use: emergence of hookah and e-cigarettes as preferred products amongst youth. J. Adolesc. Health 58 (2), 181–185.
Goniewicz, M.L., Lingas, E.O., Hajek, P., 2013. Patterns of electronic cigarette use and user beliefs about their safety and benefits: an Internet survey. Drug Alcohol Rev. 32 (2), 133–140.
Goniewicz, M.L., Knysak, J., Gawron, M., et al., 2014. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. Tob. Control 23 (2), 133–139.
Grana, R., Benowitz, N., Glantz, S.A., 2014. E-Cigarettes a scientific review. Circulation 129 (19), 1972–1986.
Han, J., Lee, J.-S., Choi, D., et al., 2009. Manganese (II) induces chemical hypoxia by inhibiting HIF-prolyl hydroxylase: implication in manganese-induced pulmonary inflammation. Toxicol. Appl. Pharm. 235 (3), 261–267.
Herzog, B., 2015. National association of tobacco outlets E-cig and vape panel: key trends facing the industry. Wells Fargo Securities; April 22, 2015.
Herzog, B., Gerberi, J., 2013. E-cigs revolutionizing the tobacco industry. Wells Fargo Securities LLC, Equity Research Department.
IARC, 2012. Working Group on the Evaluation of Carcinogenic Risk to Humans. Arsenic, metals, fibres and dusts. Lyon (FR). International Agency for Research on Cancer.
Lechner, W.V., Meier, E., Wiener, J.L., et al., 2015. The comparative efficacy of first- versus secondgeneration electronic cigarettes in reducing symptoms of nicotine withdrawal. Addiction 110 (5), 862–867.
Lerner, C.A., Sundar, I.K., Watson, R.M., et al., 2015. Environmental health hazards of e-cigarettes and their components: oxidants and copper in e-cigarette aerosols. Environ. Pollut. 198, 100–107.
McCarthy, M., 2014. Cigarette, alcohol, and illicit drug use down among US teens but e-cigarette use common, survey finds. BMJ 349, 7735.
McCarthy, M., 2015. “Alarming” rise in popularity of e-cigarettes is seen among US teenagers as use triples in a year. BMJ 350, 2083.
Mergler, D., Baldwin, M., Belanger, S., et al., 1999. Manganese neurotoxicity, a continuum of dysfunction: results from a community based study. Neurotoxicology 20 (2–3), 327–342.
NIOSH, 1997. Pocket Guide to Chemical Hazards. US Department of Health and Human Services, Public Health Serivce, Centers for Disease Prevention, National Institute for Occupational Safety and Health, Cincinnati, OH.
O’Neal, S.L., Zheng, W., 2015. Manganese toxicity upon overexposure: a decade in review. Curr. Environ. Health Rep. 2 (3), 315–328.
Piñeiro, B., Correa, J.B., Simmons, V.N., et al., 2016. Gender differences in use and expectancies of e-cigarettes: online survey results. Addict. Behav. 52, 91–97.
Rom, O., Pecorelli, A., Valacchi, G., Reznick, A.Z., 2015. Are E-cigarettes a safe and good alternative to cigarette smoking? Ann. N.Y. Acad. Sci. 1340, 65–74.

Thyssen, J.P., Linneberg, A., Menné, T., Johansen, J.D., 2007. The epidemiology of contact allergy in the general population – prevalence and main findings. Contact Dermat. 57 (5), 287–299.
Tokar, E.J., Benbrahim-Tallaa, L., Waalkes, M.P., 2011. Metal ions in human cancer development. Met. Ions Life Sci. 8, 375–401.
US Food and Drug Administration. Vol 81 FR 28973:28973-29106.
Varlet, V., Farsalinos, K., Augsburger, M., Thomas, A., Etter, J.-F., 2015. Toxicity assessment of refill liquids for electronic cigarettes. Int J. Environ. Res. Public Health 12 (5), 4796.
Williams, M., Villarreal, A., Bozhilov, K., Lin, S., Talbot, P., 2013. Metal and silicate particles including nanoparticles are present in electronic cigarette cartomizer fluid and aerosol. PLoS One 8 (3).
Wills, T.A., Knight, R., Williams, R.J., Pagano, I., Sargent, J.D., 2015. Risk factors for exclusive e-cigarette use and dual e-cigarette use and tobacco use in adolescents. Pediatrics 135 (1), e43–e51.
Wu, L.E., Levina, A., Harris, H.H., et al., 2016. Carcinogenic chromium(VI) compounds formed by intracellular oxidation of chromium(III) dietary supplements by adipocytes. Angew. Chem. Int. Ed. 55 (5), 1742–1745.
Yandle, B., Meiners, R.E., Adler, J.H., Morriss, A.P., 2015. Bootleggers, Baptists, and E-Cigarettes.
Zhu, S.H., Sun, J.Y., Bonnevie, E., et al., 2014. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. Tob. Control 23, 3–9.

Environmental Analytical Chemistry

O'Connell et al., J Environ Anal Chem 2015, 2:5
http://dx.doi.org/10.4172/2380-2391.1000163

Short Communication Open Access

Heated Tobacco Products Create Side-Stream Emissions: Implications for Regulation

Grant O'Connell[1], Peter Wilkinson[1], Kerstin MM Burseg[2], Stephen J Stotesbury[1], John D Pritchard[1]*

[1]*Imperial Tobacco Ltd, 121 Winterstoke Road, Bristol, BS3 2LL, UK*
[2]*Reemtsma Cigarettenfabriken GmbH - Imperial Tobacco Group, Albert-Einstein-Ring 7, D-22761, Hamburg, Germany*

Abstract

A number of tobacco manufacturers are promoting products where the tobacco is reportedly "heated" rather than burned. It has been claimed that certain heated tobacco products produce only mainstream and no side-stream emissions. In this study we investigated these claims for a commercially available heated tobacco product and, by using a simple experimental design, investigated whether the high temperature heating of the tobacco matrix during product activation and use results in the generation of side-stream emissions. By way of comparison, the Nicorette® inhalator and a leading e-cigarette brand were also investigated. Our findings indicated that a large number of different chemical compounds were released into the airspace around the heated tobacco product when switched on and during consumer use indicating the generation of side-stream emissions. As the public health community has concluded there is no safe level of exposure to tobacco-containing product emissions, this would be of concern and warrants further investigation. Based on our data showing side-stream emissions from the tobacco matrix, the use of heated tobacco products in indoor public places should fall under the same regulations as cigarettes.

Keywords: Heated tobacco; Heat-not-burn; E-cigarette; Nicorette; Side-stream emissions; Second-hand smoke; Nicotine; Tobacco

Introduction

It is well known that when tobacco burns, many thousands of chemicals are released from the tobacco matrix and are inhaled by consumers and bystanders [1,2]. It has been stated that the majority of smoking-related diseases are caused not by nicotine but by the generation of harmful or potentially harmful smoke constituents (HPHCs) from the burning of tobacco [3,4]. In response, a number of tobacco manufacturers are promoting products where the tobacco is reportedly "heated" rather than burned in an attempt to reduce HPHC emissions [5-7]. This is not a new concept, as cigarette-based heated tobacco products were first marketed in the USA in the 1980s and proved to be commercially unsuccessful. Heated tobacco products are now being revived and repositioned as an alternative for smokers who may not wish to replace conventional cigarettes with non-tobacco products such as electronic cigarettes (e-cigarettes). While some manufacturers claim heated tobacco products do not produce side-stream emissions, the major component of 'second-hand smoke', this has yet to be independently verified [8-12]. Since the World Health Organisation has stated "*there is no safe level of exposure to second-hand tobacco smoke*" [13] and the British Medical Association (BMA) has stated that "*almost 85 per cent of second-hand smoke is in the form of invisible, odourless gases*" [14], claims of an absence of side-stream emissions from heated tobacco products warrants investigation. To that end, we sought to investigate whether or not side-stream emissions were generated by a commercially available heated tobacco product. For comparative purposes, we also investigated the Nicorette® inhalator and a leading e-cigarette.

Experimental Section

The analytical technique Proton Transfer Reaction-Mass Spectrometry (PTR-MS) was used to sample and analyze for any side-stream emissions released to the airspace around an iQOS heated tobacco product with regular Marlboro *HeatSticks* (manufacturer, Philip Morris International) when activated by the user (but not puffed) and also during product use. Additionally, sampling was conducted for a Nicorette® inhalator (15 mg nicotine replacement aid; manufacturer, McNeil Consumer Healthcare Ltd) and Blu™ closed system e-cigarette (18 mg nicotine; manufacturer, Fontem Ventures B.V.) All products used in this study were used in accordance with manufacturer's instructions and consumed *ad libitum* i.e., there was no pre-defined consumption requirement. For each of the different products, a number of replicate puffs were made and representative data from a single puff is shown. In short, the PTR-MS instrument ionizes volatile organic compounds (VOCs) in the gas phase through their reaction with H_3O^+ to form protonated VOCs ($VOCH^+$) which can then be detected by a mass spectrometer [15]. This process can be run on air samples with or without dilution as normal air gases (e.g., N_2, O_2, CO_2) have a proton affinity less than water and thus are not ionized. Most VOCs have a proton affinity greater than water and therefore are readily ionized and detected [15]. Analyses with PTR-MS can be conducted in real-time and continuously without the need for sample preparation [15]. Airspace analysis was conducted by connecting the PTR-MS inlet to the test chamber and sampling directly. PTR-MS operating conditions were as follows: drift tube voltage, 500 V; drift tube pressure, 2.3 mbar; drift tube temperature, 120°C; drift tube length, 9.3 cm; *E/N* ratio, 130 Td (Townsends; where *E* is electric field and *N* is the number density of the gas in the drift tube; 1 Td=10^{-17} cm^2 V $molecule^{-1}$); inlet temperature, 120°C. The experimental set-up is outlined in Figure 1.

Results and Discussion

Qualitative characterization of side-stream emissions

Following activation of the iQOS heated tobacco product, as per the manufacturer's instructions, a large number of different VOC species across a range of masses were released into the airspace (Figure 2A). This clearly indicates the generation of side-stream emissions when the device is activated but not puffed by the consumer, which

***Corresponding author:** John D Pritchard, Imperial Tobacco Ltd, 121 Winterstoke Road, Bristol, BS3 2LL, UK, Tel: 440117-933-7556; E-mail: john.pritchard@uk.imptob.com

Received October 02, 2015; **Accepted** October 12, 2015; **Published** October 15, 2015

Citation: O'Connell G, Wilkinson P, Burseg KMM, Stotesbury SJ, Pritchard JD (2015) Heated Tobacco Products Create Side-Stream Emissions: Implications for Regulation. J Environ Anal Chem 2: 163. doi:10.4172/2380-2391.1000163

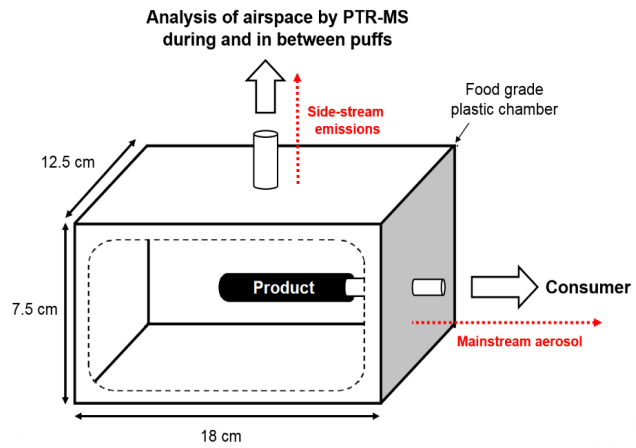


Figure 1: Schematic representation showing experimental set-up and the side-stream emissions capture chamber.

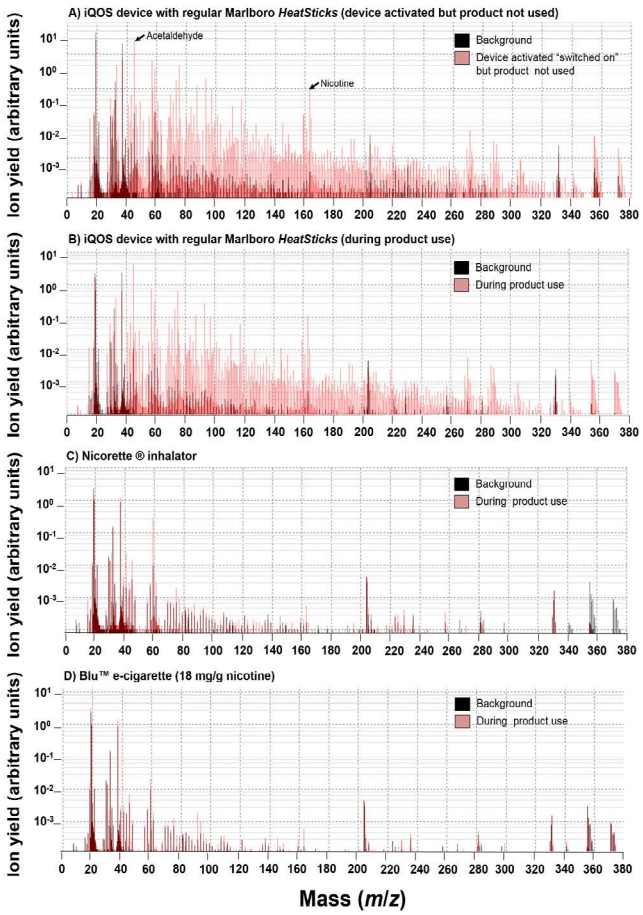


Figure 2: Representative PTR-MS mass spectra of the VOCs released to the airspace for (**A**) iQOS with regular Marlboro *HeatStick* when activated "switched on" but product not actively puffed and (**B**) during consumer use of the iQOS device with regular Marlboro *HeatSticks*; (**C**) during consumer use of the Nicorette® inhalator; and (**D**) during consumer use of the Blu™ e-cigarette. Specific compound (peaks) at *m/z* 45 is protonated acetaldehyde and *m/z* 163 is protonated nicotine and is labelled with arrowheads in (**A**).

would be released into the ambient air, raising potential concerns for bystanders. Furthermore, during active puffing on the heated tobacco product, side-stream emissions are also released (Figure 2B). These chemicals are being released from the high temperature heating of the tobacco matrix in the *HeatSticks*. Given the similarities of the Marlboro branded *HeatStick* used in the iQOS device to a conventional cigarette, the detection of side-stream emissions is perhaps not surprising even though it has been stated that such products produce no side-stream aerosol/smoke [8-12]. Given the findings presented in this pilot study, this requires further investigation.

The PTR-MS mass spectra of the VOCs in the airspace around the Nicorette® inhalator (Figure 2C) and the e-cigarette (Figure 2D) during product use are virtually indistinguishable. Moreover, the Nicorette® inhalator and the e-cigarette profiles are entirely distinct from that of the heated tobacco product, as may be anticipated given these products do not contain tobacco. The Nicorette® inhalator was selected as an appropriate comparator in this study as the UK Medicines and Healthcare products Regulatory Agency (MHRA) has indicated this should be used as a reference product, if manufacturers intend to license e-cigarettes as medicinal products [16].

Future investigations

PTR-MS is a one dimensional technique that characterizes VOCs via their mass; to enable identification of the chemicals in the side-stream emissions from the heated tobacco product it is necessary to further calibrate the machine for identification and quantification of compounds of regulatory interest e.g., HPHCs in tobacco products and tobacco smoke as developed by the US Food and Drug Administration (FDA) [17]. We will therefore determine the identities of the many different VOCs released to the airspace, and by extension to the bystander's breathing space, from the heated tobacco product when activated and used by the consumer. Moreover, it is also conceivable that differences in side-stream emissions may be observed under varying user consumption topographies. Further research in these areas will be informative.

Conclusions

The release of side-stream emissions from heated tobacco products has been observed by PTR-MS using the simple method presented here. These emissions are generated by the high temperature heating of the *HeatSticks* tobacco matrix inserted within the iQOS device.

The public health community has stated that there is no safe level of exposure to tobacco-containing product emissions [13,18], and so the side-stream constituents including nicotine, released during activation and use of the iQOS heated tobacco product can lead to exposure to bystanders; this would be of concern to public health authorities and warrants further investigation.

It is conceivable that based on these findings and the conclusions of public health community regarding tobacco product emissions, the use of heated tobacco products should be included in smoke-free legislation.

Conflicts of Interest

The work in this short communication was supported by Imperial Tobacco Group. Imperial Tobacco Group is the parent company of Fontem Ventures B.V., the manufacturer of the e-cigarette used in this study.

References

1. U.S. Department of Health and Human Services (2014) The health consequences of smoking—50 years of progress: A report of the surgeon general, Atlanta, GA: U.S.
2. U.S. Department of Health and Human Services (2010) How tobacco smoke causes disease: The biology and behavioral basis for smoking-attributable disease: A report of the surgeon general. Atlanta, GA: U.S.

3. UK National Institute for Health and Care Excellence (2013) Tobacco: Harm-reduction approaches to smoking. Public health guidance.
4. http://www.ash.org.uk/files/documents/ASH_715.pdf
5. PMI. Heat-not-burn. Accessed on: 10 August 2015.
6. BAT. Tobacco heating products (2015) Accessed on: 10 August 2015.
7. JTI. It's time to rethink tobacco (2013) Accessed on: 10 August 2015.
8. Frost-Pineda K, Zedler BK, Liang Q, Roethig HJ (2008) Environmental tobacco smoke (ETS) evaluation of a third-generation electrically heated cigarette smoking system (EHCSS). Regulatory toxicology and pharmacology 52: 118-121.
9. Tricke AR, Schorp MK, Urban HJ, Leyden D, Hagedorn HW, et al. (2009) Comparison of environmental tobacco smoke (ETS) concentrations generated by an electrically heated cigarette smoking system and a conventional cigarette. Inhalation toxicology 21: 62-77.
10. Ginglinger GC, Campelos P, Maeder S, Mitova M, Mottier N, et al. (2015) Indoor air chemistry comparative study between conventional cigarette and heat-not-burn technology. In Global Forum on Nicotine, Warsaw, Poland.
11. Ginglinger GC, Campelos P, Maeder S, Mitova M, Mottier N, et al. (2015) Indoor air chemistry comparative study between conventional cigarette and heat-not-burn technology. In Society of Toxicology Annual Meeting, San Diego, California, USA.
12. Ginglinger GC, Maeder S (2015) Indoor air chemistry (IAC) - comparative study between conventional cigarette and heat-not-burn technology. In Society for Research on Nicotine and Tobacco 21st Annual Meeting, Philadelphia, Pennsylvania, USA.
13. WHO (2007) Only 100% smoke-free environments adequately protect from dangers of second-hand smoke. Accessed on: 10 August 2015.
14. BMA (2002) Towards smoke-free public places. British medical association board of science and education and tobacco control resource centre.
15. Ellis AM, Mayhew CA (2014) Background, in proton transfer reaction mass spectrometry: Principles and applications. John Wiley & Sons, Inc., Chi Chester, UK.
16. MHRA (2013) Licensing procedure for electronic cigarettes and other nicotine containing products (NCPS) as medicines.
17. FDA (2012) Harmful and potentially harmful constituents in tobacco products and tobacco smoke; established list. Federal register: 20034-20037.
18. U.S. Department of Health and Human Services (2006) The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. Rockville, MD: U.S.

Citation: O'Connell G, Wilkinson P, Burseg KMM, Stotesbury SJ, Pritchard JD (2015) Heated Tobacco Products Create Side-Stream Emissions: Implications for Regulation. J Environ Anal Chem 2: 163. doi:10.4172/2380-2391.1000163

Real-time analysis of exhaled breath following the use of a range of nicotine delivery products by PTR-MS: proof of concept study

Grant O' Connell[1], Kerstin Burseg[2], Kostiantyn Breiev[3], Stéphane Colard[1,4] and John D. Pritchard[1]

[1] Imperial Tobacco Limited, Winterstoke Road, Bristol, BS3 2LL, UK
[2] Reemtsma Cigarettenfabriken GmbH, Imperial Tobacco Group, Albert Einstein Ring 7, 22761, Hamburg, Germany
[3] IONICON Analytik GmbH, Eduard-Bodem-Gasses 3, 6020 Innsbruck, Austria
[4] SEITA, Imperial Tobacco Group, 48 rue Danton, 45404 Fleury-les-Aubrais, France

Visit our Scientific Research website:
www.imperialtobaccoscience.com

1. Introduction

The analytical technique PTR-MS (Proton Transfer Reaction-Mass Spectrometry) is a sensitive tool for the simultaneous real-time monitoring of volatile organic compounds (VOCs) without sample preparation, with the potential to achieve parts per trillion detection levels.

The technique involves the chemical ionisation, by proton transfer, of a gaseous sample inside a drift tube under an electric field. The proton source is normally protonated water (H_3O^+). The chemical analyte and H_3O^+ ions are introduced into the drift tube, where proton transfer will occur for those VOCs with a greater proton affinity than water. On the basis of proton affinity, normal air gases (e.g. N_2, O_2, CO_2) show no reaction with H_3O^+ but many trace VOCs are readily protonated as shown: $VOC + H_3O^+ \rightarrow VOCH^+ + H_2O$.

After passing through a drift tube to remove cluster ions, VOCs are then detected by the mass spectrometer. The mass spectrometer used in this work is a time-of-flight mass spectrometer that benefits from a mass resolution ($m/\Delta m$) >1000 Da and most significantly is able to observe all mass channels simultaneously.

PTR-MS has many applications in environmental and biological research, food flavour and fragrance science, indoor air quality, security and safety (detection of illicit substances) and in medical diagnostics. The fundamentals of PTR-MS and its applications have been reviewed elsewhere [1, 2].

PTR-MS has been established as a novel tool for a rapid determination of exhaled air profiles. However, no investigations have been carried out into the profile of exhaled air following use of nicotine delivery products as determined by PTR-MS. In this proof of concept study, we aimed to identify and determine the breath concentrations of nicotine following use of a conventional cigarette, a Heat-not-Burn (heated tobacco) device, an electronic vapour product (e-cigarette) and a nicotine inhalator.

2. Experimental setup

The PTR-ToF-MS 8000 used in this investigation has been described elsewhere (IONICON; [3]). As a modification to this original PTR-MS, a heated inlet system (120 °C) was used to prevent condensation and deposition of the analytes and to enable also a qualitative analysis of less volatile compounds. Exhaled air was sampled at a flow rate of 100 sccm (standard cubic centimetre per minute). Spectra were acquired at 0.8 cycle per second and the sampling time per channel in the TOF was 0.1 ns for a mass spectra ranging from m/z 1 to 280. The PTR-MS showed a count rate of the primary ions (H_3O^+ ions) of 6500 counts/s. The length of the drift tube of the PTR-ToF-MS was 9.3 cm, with an applied voltage of 600 V. The usual pressure in the drift tube was 2.2 mbar and the temperature was 120 °C. The ratio E/N (E is electric field and N is the number density of the gas in the drift tube) was at 100 Td (*Townsend*; 1 Td = 10^{-17} V.cm^2) which is the optimal value to avoid analyte fragmentation and to obtain high level of primary ions signal.

The following products were used in this study: conventional cigarette (0.6 mg nicotine [ISO smoking regime]), Heat-not-Burn (heated tobacco; iQOS with regular heatsticks), electronic vapour product (20 mg/mL nicotine Puritane rechargeable e-cigarette) and 15 mg nicotine inhalator (Nicorette® Inhalator). Three volunteers participated in this study and each volunteer used each of the four products. For each of the products tested: five blank breath measurements were taken directly before product use (background control) and following this the volunteer was given the product to use and become familiar with. Following this, the volunteer used the product *ad libitum* five times and exhaled into the PTR-MS each time allowing analysis on a per puff basis. Representative results shown here are the output from a single exhalation event.

To enable the identification and quantification of nicotine in the exhaled breath, the PTR-MS was calibrated with a liquid sample. A liquid calibration unit (LCU) was used to evaporate an aqueous nicotine standard (stock solution, 7.2% [v/v] nicotine in propylene glycol) into a gas stream, resulting in a gas flow containing nicotine at defined concentrations.

3. Identification of nicotine: *m/z* 163

To enable the identification and quantification of nicotine in the exhaled breath, the PTR-ToF-MS was calibrated by directly injecting liquid nicotine standards at a known rate into a dilution air stream. The key assumption of this approach is that the evaporation of the liquid standard into the air stream is complete, which is then homogenized in a mixing chamber. ***Figure 1*** shows the mass spectra of nicotine at *m/z* 163.123; confirming the expected exact mass of protonated nicotine.

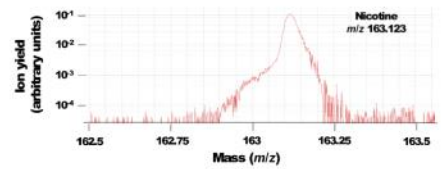


Figure 1 Calibration of PTR-ToF-MS for nicotine. Mass spectra of nicotine at *m/z* 163.123; the expected exact mass of protonated nicotine

4. Comparison of VOCs released in exhaled breath following use of a conventional cigarette, Heat-not-Burn device, electronic vapour product and nicotine inhalator product

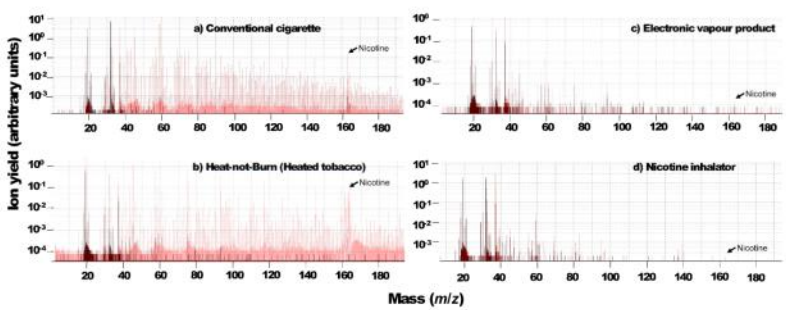


Figure 2 Representative PTR-MS mass spectra of VOCs released in exhaled breath following use of (**a**) a conventional cigarette, (**b**) a Heat-not-Burn [heated tobacco] device, (**c**) an electronic vapour product [e-cigarette] and (**d**) a nicotine inhalator. Black peaks, VOC released in normal exhaled breath (background control); red peaks, VOCs released in exhaled breath following product use. Specific compound (ion trace) at *m/z* 163 is nicotine and is labelled with arrowhead.

Representative data presented in ***Figure 2*** shows mass spectrometric profiles of exhaled breath following a single exhalation event after product use (red) and comparison with blank control breath (black). The peaks on mass 19 and 37 m/z (and their isotopes) represent the reagent ions (H_3O^+) and their clusters. The PTR-MS has been calibrated for nicotine (m/z 163; see arrowheads); all other pink peaks correspond to compounds released following use of the specific nicotine delivery product however their identities remain to be determined in future work

Following use of a conventional cigarette and a Heat-not-Burn product, a large number of different chemicals are released in the exhaled breath, as shown by the red spectra across a range of masses. When focussing specifically on exhaled nicotine, 1150 ppb nicotine were detected in the exhaled breath following use of the conventional cigarette (**a**) and 1840 ppb (parts per billion) nicotine following use of the heated tobacco device (**b**). In contrast, 7 ppb nicotine were detected in the exhaled breath following use of the electronic vapour product (**c**) and 1 ppb nicotine following use of the nicotine inhalator (**d**).

The exhaled breath following use of electronic vapour products appears chemically less complex compared to conventional cigarette and Heat-not-Burn and more similar to that of the nicotine inhalator.

The release of chemicals in the exhaled breath is likely to depend on the user topography (i.e. the way in which each individual uses the product)The components of the exhaled breath will also contribute to the quality of the indoor air, as we reported previously [4].

5. Conclusions & future work

In this study, many more chemical components were detected in the exhaled breath from users of conventional cigarettes and Heat-not-Burn (heated tobacco), compared to users of a simple electronic vapour product and a nicotine inhalator. This is not unexpected given that these are products based on tobacco. Substantially more nicotine was also found in the exhaled breath following use of the tobacco based products.

The large number of chemical species detected in the exhaled breath following use of the heated tobacco product might be indicative that the use of such products has the potential to impact indoor air quality in a similar way to that reported for conventional cigarettes. This is an important area for additional research.

Our proof-of-concept study presented here shows the potential of PTR-MS to be used as a technique to monitor the emissions from a range of nicotine delivery products and quantify released VOCs in real-time under a range of conditions.

PTR-MS mass spectra of complex aerosols, such as exhaled breath, requires careful interpretation, for example to appreciate that some overlap of certain compounds at a single mass-to-charge ratios can arise due to fragmentation.

PTR-MS is a one dimensional technique that characterises compounds only via their mass and is not sufficient for the diagnostic identification of 'unknowns' without prior calibration. Our next step will therefore be to determine the profiles and identities of VOCs in exhaled breath following use of a range of nicotine delivery products by a coupled PTR-MS/GC-MS study.

References

[1] Cappellin *et al.* (2013) PTR-MS in Italy: a multipurpose sensor with applications in environmental, agri-food and health sciences. *Sensors.* 13, 11923-11955.
[2] Schwarz *et al.* (2009) Determining concentration patterns of volatile compounds in exhaled breath by PTR-MS. *J. Breath Res.* 3, 1-15.
[3] IONICON, www.ionicon.com, accessed January 2015.
[4] Colard *et al.* (2015) Electronic cigarettes and indoor air quality: a simple approach to modelling potential bystander exposures to nicotine. *Int. J. Environ. Res. Public Health.* 12, 282-299.

Declaration

This project was supported by Imperial Tobacco Group. The electronic vapour product used in this study was manufactured by Fontem Ventures, a fully owned subsidiary of Imperial Tobacco Group.

PHILIP MORRIS
ASIA LIMITED

BRETT COOPER
GENERAL MANAGER
HONG KONG & MACAU

Telephone: +85 2 2825 1600
Mobile: +85 2 [redacted]
brett.cooper@pmi.com

February 24, 2017

Health Panel
Legislative Council Secretariat
Legislative Council Complex
1 Legislative Council Road
Central
Hong Kong

Dear LegCo Health Panel Chairman,

Views on the proposal to amend the graphic health warnings on packets and retail containers of tobacco products

Philip Morris Asia Limited ("PMAL") appreciates the opportunity to provide our views on the proposal to amend the health warnings on packets and retail containers of tobacco products.

PMAL recognizes the need for the Government to revisit and revise the relevant tobacco control regulation with an aim to reduce the harm caused by cigarette smoking. We believe there are much more effective ways to achieve this than the proposal to amend the health warnings on packets and retail containers of tobacco products being put forward by the Government.

International experience does not support the proposition that increasing the size of health warnings will have a public health benefit. In Thailand, the first country to increase the health warnings size to 85%, the early evidence appears to show the opposite. Cigarette consumption in Thailand continues to increase. In fact, in the first quarter of 2015 (with 85% health warnings) retail cigarette sales increased by 281 million sticks compared to the first quarter of 2014 (with 55% health warnings).

This experience is in line with a 2012 United States court decision which addressed the potential impact on smoking prevalence of health warnings covering 50% of the front and back panels of cigarette packs.[1] Even the US Food and Drug Administration (FDA), which proposed the warnings in question, predicted that increasing health warnings to 50% of the front and back of tobacco packs from the current side panel text warning would have an effect of only 0.088%, which the FDA admitted was "*not statistically distinguishable from zero.*"[2]

[1] *R.J. Reynolds et al. v. FDA*, No. 11-5332 (D.C. Cir. Aug. 24, 2012), *available at* http://www.cadc.uscourts.gov/internet/opinions.nsf/4C0311C78EB11C5785257A64004EBFB5/$file/11-5332-1391191.pdf.
[2] Ibid.

.../cont'd page 2

Canada has required 50% health warnings on the front and back of cigarette packs from 2000, and 75% since 2012. Despite these much stricter requirements than in the United States, in 2014 smoking rates in Canada remained **above** the United States, and smoking prevalence in Canada has fallen no faster than in the United States[3].

Having deliberated over a significant period of time, the European Parliament issued a Directive in 2014 that strikes a sensible balance between the need to communicate to consumers about the health risks of smoking whilst allowing product manufacturers sufficient pack space to display trademarks. In terms of international experience on this matter, DIRECTIVE 2014/40/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL (usually referred to as the EU Tobacco Product Directive or the "EU TPD") is a more balanced position than any arbitrary call to increase health warnings to as large a size as possible. Under the EU TPD:

1. Smoked tobacco products carry a combined (graphic and text) health warning covering 65% of both front and back of the pack, an information message comprising 50% of one side of the pack, and a general warning comprising 50% of the other side of the pack;
2. Member States may exempt smoked tobacco products (other than cigarettes, roll-your-own tobacco and waterpipe tobacco) from the combined health warnings and the information message. Exempted products carry the general warning covering 30% of the most visible surface, and a text warning covering 40% of the next most visible surface; and
3. Tobacco packaging and labelling must not include any information about nicotine, tar or carbon monoxide content of the product.

PMAL recognises the health effects caused by combustible cigarettes, and the best way to avoid the harms of smoking is never to start, or to quit. The smoking incidence in Hong Kong is one of the lowest in the world at about 10%. The introduction of the health warning labels and subsequent size increases has not changed this percentage significantly in the last 10 years. PMAL believes it is time for the Government to consider other avenues to complement the effort, ones that have the potential to address the individual risks and population harm caused by cigarette smoking.

Technological innovation is transforming the tobacco industry with a wide range of non-combustible tobacco products that have been scientifically proven to significantly reduce health risks compared to continued smoking.

In addition to these non-combustible tobacco products, there has been major advancements in evidence to support e-cigarettes and nicotine replacement therapies (NRT's). Earlier this month, Cancer Research UK issued a press release[4] on research funded by them on long term use of e-cigarettes. Dr Lion Shahab, senior lecturer in the department of epidemiology and public health at University College London, and lead author of the publication, said: "Our study adds to existing evidence showing that e-cigarettes and NRT are far safer than smoking, and suggests that there is a very low risk associated with their long-term use."

---

[3]OECD (2017), Daily smokers (indicator): https://data.oecd.org/healthrisk/daily-smokers.htm

[4] http://www.cancerresearchuk.org/about-us/cancer-news/press-release/2017-02-06-e-cigarettes-safer-than-smoking-says-long-term-study

.../cont'd page 3

We strongly believe that if regulated appropriately, i.e. prohibition on sales to minors, restrictions on advertising and marketing, etc. these alternatives to cigarettes have a significant role to play in making Hong Kong smoke-free. Philip Morris International has been, and will continue to be, a driving force in this transformation. Our ambition is to lead a full-scale effort to ensure that non-combustible products ultimately replace cigarettes to the benefit of adult smokers and society.

Yours sincerely,

Brett Cooper