Arsenic species in electronic cigarettes: Determination and potential health risk

Qingqing Liu [1,2], Chengzhi Huang [3], X. Chris Le [4,]*

[1] *Chongqing Key Laboratory of Biomedical Analysis (Southwest University), Chongqing Science & Technology Commission, College of Chemistry and Chemical Engineering, Southwest University, Chongqing 400715, China*
[2] *College of Resources and Environment, Southwest University, Chongqing 400715, China*
[3] *Key Laboratory of Luminescent and Real-Time Analytical System, Chongqing Science and Technology Bureau, College of Pharmaceutical Sciences, Southwest University, Chongqing, 400715, China*
[4] *Department of Laboratory Medicine and Pathology, Faculty of Medicine and Dentistry, University of Alberta, 10-102 Clinical Sciences Building, Edmonton, Alberta T6G 2G3, Canada*

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ABSTRACT

Human exposure to contaminants from electronic cigarettes (e-cigarettes) and the associated health effects are poorly understood. There has been no report on the speciation of arsenic in e-liquid (solution used for e-cigarettes) and aerosols. We report here determination of arsenic species in e-liquids and aerosols generated from vaping the e-liquid. Seventeen e-liquid samples of major brands, purchased from local and online stores in Canada and China, were analyzed for arsenic species using high-performance liquid chromatography and inductively coupled plasma mass spectrometry. Aerosols condensed from vaping the e-liquids were also analyzed and compared for arsenic species. Six arsenic species were detected, including inorganic arsenate (iAs^V), arsenite (iAs^{III}), monomethylarsonic acid (MMA), and three new arsenic species not reported previously. In e-liquids, iAs^{III} was detected in 59%, iAs^V in 94%, and MMA in 47% of the samples. In the condensate of aerosols from vaping the e-liquids, iAs^{III} was detected in 100%, iAs^V in 88%, and MMA in 13% of the samples. Inorganic arsenic species were predominant in e-liquids and aerosols of e-cigarettes. The concentration of iAs^{III} in the condensate of aerosols (median 3.27 μg/kg) was significantly higher than that in the e-liquid (median 1.08 μg/kg) samples. The concentration of inorganic arsenic in the vaping air was approximately 3.4 μg/m^3, which approaches to the permissible exposure limit (10 μg/m^3) set by the United States Occupational Safety and Health Administration (OSHA). According to the Environmental Protection Agency's unit risk factor (4.3 × 10^{-3} per μg/m^3) for inhalation exposure to inorganic arsenic in the air, the estimated excess lung cancer risk from lifetime exposure to inorganic arsenic in the e-cigarette vaping air (3.4 μg/m^3), assuming e-cigarette vaping at 1% of the time, is as high as 1.5 × 10^{-4}. These results raise health concerns over the exposure to arsenic from electronic cigarettes.

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* *Corresponding author.*
   E-mail addresses: chengzhi@swu.edu.cn (C. Huang), xc.le@ualberta.ca (X. Chris Le).

Introduction

The popularity of electronic cigarettes (e-cigarettes) has been booming worldwide since they were first introduced into market in 2004 (Centers for Disease Control and Prevention (CDC), 2016; Gentzke et al., 2019, United States Department of Health and Human Services (HHS), 2016). According to results from National Youth Tobacco Survey, the prevalence of e-cigarette use among high school students increased rapidly from 1.5% in 2011 to 16% in 2015 (CDC, 2017). Though varying widely in design and appearance, e-cigarettes generally operate in a similar manner: a solution known as e-liquid is aerosolized by a heating component, and the generated aerosols vaped through a mouthpiece whereby the users puff. E-liquid typically uses propylene glycol and/or glycerine as a basic ingredient to dissolve nicotine, flavoring chemicals, and other additives (HHS, 2016). Because these ingredients are simpler than the mixture chemicals generated by burning tobacco, e-cigarettes have been regarded as less harmful than the conventional tobacco cigarettes. However, recent studies have suggested many health risks of e-cigarettes, and many studies have reported metals, fine and ultrafine particles, volatile organic compounds (VOCs), aldehydes, carbonyl compounds, endotoxins, flavoring chemicals, and other additives in the e-liquids and/or the generated aerosols (Allen et al., 2016; Bekki et al., 2014; Cheng, 2014; Farsalinos et al., 2015; Fernández et al., 2015; Geiss et al., 2015; Goniewicz et al., 2014; Hess et al., 2017; Hua et al., 2019; Hutzler et al., 2014; Ingebrethsen et al., 2012; Jensen et al., 2015; Kamilari et al., 2018; Klager et al., 2017; Lee et al., 2017, 2019; Melstrom et al., 2017; Pankow et al., 2017; Scungioa et al., 2018; Williams et al., 2013, 2015, 2019a, 2019b; Zhao et al., 2019).

Several recent studies have reported the presence of arsenic in e-cigarettes (Mikheev et al., 2016; Beauval et al., 2016, 2017; Palazzolo et al., 2017; Williams et al., 2017; Olmedo et al., 2018; Song et al., 2018; Zhao et al., 2019). Beauval and co-workers detected on average 1.5 μg/L (2016) and 1.57 μg/L (2017) arsenic in the e-liquids. Mikheev et al. (2016) found 0.01–1 ng arsenic per mg of particulate matter captured on filters of e-cigarettes. Williams et al. (2017) reported that for every 10 puffs of disposable e-cigarettes and e-hookahs, arsenic in the aerosols was in a range of 0.001–0.01 μg. Palazzolo et al. (2017) showed that e-liquids contained (0.08 ± 0.04) μg/L arsenic and the aerosol generated from every 15 puffs on an e-cigarette had 0.002 μg arsenic. Olmedo et al. (2018) found arsenic in 10.7% of e-liquid samples, with a median concentration of 26.7 μg/kg; whereas Song et al. (2018) determined arsenic concentrations in e-liquids ranging from 0.83 to 3.04 μg/kg.

The assessment of arsenic in e-cigarettes to date has mainly focused on total arsenic concentration. None of the previous studies have investigated arsenic species in the e-cigarettes. The toxicity of arsenic is highly dependent on its chemical species, varying by several orders of magnitude in medium lethal dose (LD_{50}) and medium lethal concentration (LC_{50}) values (Charoensuk et al., 2009; Cullen and Reimer, 1989; Moe et al., 2016; Naranmandura et al., 2011; Shen et al., 2013; Styblo et al., 2000). Therefore, an appropriate assessment of potential health risks of arsenic exposure depends on the knowledge of the exact arsenic species and the concentrations of each arsenic species present in the e-liquid and its corresponding aerosol samples.

The aim of the present study was to determine the concentrations of arsenic species in e-cigarettes, including e-liquids and condensed aerosols. E-cigarettes are now in widespread global distribution through convenience stores, tobacco stores, pharmacies, and online retailers. The popularity of brands has varied rapidly since manufacturers continually bring new products to the market (Zhu et al., 2014). On the basis of the monthly sale and market share information of e-cigarettes, we selected representative e-liquids for this study. Seventeen e-liquid samples, which matched with rechargeable USB-like and tank-type e-cigarette devices, were purchased from local stores and online retailers in Canada and China. Quantitative results of individual arsenic species in these representative e-liquid samples and their corresponding aerosol samples generated by vaping the e-liquids provide meaningful information and enable assessment of potential risks from e-cigarettes. This study points to the need for careful characterization and monitoring of toxicologically relevant chemical contaminants in e-cigarettes.

1. Material and methods

1.1. Chemicals

Standard solutions of arsenite (iAs^{III}), arsenate (iAs^{V}), monomethylarsonic acid (MMA), dimethylarsinic acid (DMA), and arsenobetaine (AsB) were prepared from stock solutions of sodium m-arsenite (Aladdin Inc., China), sodium arsenate (Sigma-Aldrich, U.S.A), monosodium acid methane arsonate (Aladdin Inc.), cacodylic acid (Aladdin Inc.), and arsenobetaine (Yuanye Biology Inc., China), respectively. The concentrations of arsenic species were determined by an Agilent 7700 inductively coupled plasma mass spectrometer (ICPMS) (Agilent Technologies, U.S.A) and calibrated by a certified reference material BW30018-1000-N-50 (TMRM Inc., China) containing 1000 mg/L inorganic arsenic. When performing the calibration, a standard solution (Agilent Technologies), containing 10 μg/mL Bi, Ge, In, Li, Sc, Tb, and Y, was used to test the performance and stability of ICPMS. Another certified reference material GSB 07-3171-2014 (HBKC Inc., China) was used to confirm the accuracy of quantitative analyses. Working solution was prepared daily. Methanol and ammonium bicarbonate were purchased from Aladdin Inc. and Sigma-Aldrich, respectively. A certified reference material CRM No.18 human urine, was obtained from National Institute for Environmental Studies, Japan.

1.2. E-cigarette samples

Seventeen e-liquid samples and their detailed information are listed in Appendix Table S1. In Canada, we selected 2 most popular brands of rechargeable USB-like e-cigarette devices and their accompanying e-liquid pod cartridges. These two brands were chosen based on their high market shares. Apart from the rechargeable USB-like devices, we obtained 3 brands
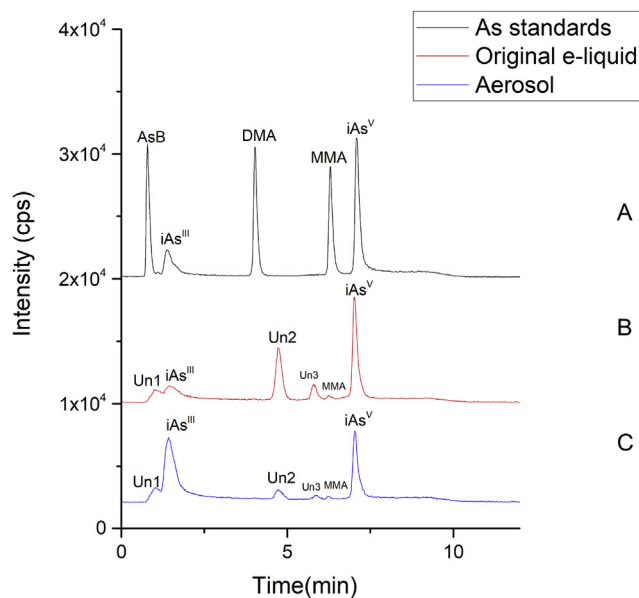
of e-liquid cartridges in 5 flavors for the tank-type devices from two popular e-cigarette stores in Toronto, Canada. In China, 3 brands of e-liquid cartridges in 8 flavors for the tank-type devices were obtained from the largest Chinese online shopping platform. These online brands were chosen according to their monthly sales. The nicotine content in these e-liquid cartridges ranged from 0 to 5%, as stated on the packaging. For the rechargeable USB-like devices, the refilling pods were carefully dissected to get the e-liquid. For the tank-type devices, the e-liquid was squeezed out from the cartridges directly.

1.3. Preparation of aerosol samples

Aerosol samples were generated by vaping 8 e-liquid samples using the tank-type e-cigarette devices, according to the method reported in Olmedo et al. (2016) with some modifications. The condensed aerosol was collected for arsenic speciation analysis. Briefly, a peristaltic pump puffed the e-cigarette to generate the aerosol. The aerosol was condensed through a series of plastic tubing and conical pipette tips. Because the tank-type devices were button-activated and had to be activated repeatedly right before every puff, we built a simple apparatus, which repeatedly pushed the button in a controllable manner to activate repeat puffing. Appendix Figure S1 shows a photograph of the set-up for the generation and collection of aerosol samples. Comparing the weight of the condensed aerosol with the weight of e-liquid vaporized to generate the aerosol, we found that the recovery of e-liquid from the aerosol generation and collection process was 89–102% (Appendix A Section S1 and Table S2). Duplicate experiments were performed with collection of aerosol condensate (0.2–1 mL) generated from of e-liquid. The aerosol condensate samples were analyzed immediately or stored in a −20 °C freezer for subsequent analyses.

1.4. Arsenic speciation analysis

Speciation of arsenic was conducted using an Agilent 1260 series high-performance liquid chromatography (HPLC) system connected with ICPMS. Helium gas was introduced into the collision/reaction cell of the ICPMS to suppress/minimize potential isobaric interference caused by $ArCl^+$. Separation of arsenic species was carried out using a strong anion-exchange column (PRP X110s, Hamilton, USA). Two mobile phases were used: mobile phase A contained 5% methanol in deionized water and mobile phase B contained 60 mmol/L ammonium bicarbonate and 5% methanol in deionized water (pH 8.75). For the gradient elution, the ramping program of mobile phase B started from 0% and increased to 10% in the first 4 min. Then, mobile phase B linearly increased to 100% from the 4th min to the 8th min and returned to 0% in the next 1 min. The column was allowed to equilibrate in this final mobile phase composition for 4 min. The flow rate was 2 mL/min for the entire 13 min. The samples were diluted 2-fold with deionized water and filtered through a 0.45-μm membrane. A 50-μL aliquot of each sample was injected onto the HPLC column for arsenic speciation analysis. A typical chromatogram obtained from the anion-exchange HPLC-ICPMS analysis of 5 arsenic species is shown in Fig. 1A.

Fig. 1 – Chromatograms obtained from anion-exchange HPLC-ICPMS analyses of (A) 5 arsenic species standard mixture solution, (B) an e-liquid sample, and (C) an aerosol condensate sample. The 5 arsenic species standards included AsB, iAs^{III}, DMA, MMA, and iAs^V. MMA, iAs^{III}, iAs^V, and three unknown arsenic species (Un1, Un2, and Un3) were detected in the e-liquid and aerosol condensate samples.

Certified reference material CRM No.18 human urine was used for quality control and was analyzed in parallel with samples. Our replicate analyses of CRM No.18 urine showed the concentration of DMA being 39 ± 4 μg/L, which is consistent with the reference value of 36 ± 9 μg/L DMA. In addition, a standard mixture (containing 1 μg/L of each arsenic species) was repeatedly analyzed between every 10 samples, which showed good stability (CV = 6.0% for AsB, CV = 5.5% for iAs^{III}, CV = 5.1% for DMA, CV = 7.7% for MMA, and CV = 8.2% for iAs^V). Calibration solutions were re-run after every 30 samples. Column recovery was assessed as the ratio of the concentrations of arsenic species determined with and without HPLC separation. It represented the sum of arsenic species determined using HPLC-ICPMS and the total arsenic concentration in the same sample determined using direct ICPMS analysis. Our tests from three samples showed that the column recovery of arsenic species was (89 ± 14)%. The details on the determination of the recovery of arsenic species from the aerosol generation and collectoin process were shown in Appendix A Section S1. The limits of detection (LODs) were determined using the method of US EPA (2011). Briefly, a mixture of five arsenic standards (0.05 μg/L of each arsenic species) was added to a blank e-liquid sample, and this spiked sample was analyzed repeatedly for seven times using the HPLC-ICPMS method. Standard deviations from the seven replicate analyses for each arsenic species, multiplied by the student's t value of 3.143 (for n = 7), in combination with calibration of each arsenic species, gave rise to the LODs for the 5 arsenic species: 0.01 μg/kg for AsB, 0.02 μg/kg for iAs^{III}, 0.01 μg/kg for DMA, 0.01 μg/kg for MMA, and 0.37 μg/kg for

iAs^V. A solution containing 70% propylene glycol and 30% glycerol was used as blank matrix and underwent the same aerosol generating process to evaluate the method blank. The arsenic species in the method blank were close to the LODs.

Because of the high viscosity of the e-liquid, the actual volume of e-liquid was difficult to measure. In the present study, we report the concentration of arsenic in the unit of μg/kg.

1.5. Concentrations of arsenic species in the vaping air

The concentrations of arsenic species in the aerosol condensate ($c_{aerosol}$, μg/kg) was converted to a gas phase concentration (c_{air}, mg/m^3) using Eq. (1) (Olmedo et al., 2018).

$$c_{air} = c_{aerosol} \times \frac{m_{aerosol}}{V_{air}} = c_{aerosol} \times \frac{m_{aersol}}{Q \times t \times N} = c_{aerosol} \times \beta \quad (1)$$

where $m_{aerosol}$ (g) is the mass of the e-liquid analyzed, V_{air} (m^3) is the volume of air in which the e-liquid was totally aerosolized, Q is the flow rate of the pump, t is the puff time, N is the number of puffs required to aerosolize the e-liquid, and β is $\frac{m_{aerosol}}{V_{air}}$, the conversion factor between c_{air} and $c_{aerosol}$. The puff topography used in this experiment was: Q = 250 mL/min, t = 8 sec, inter-puff time S = 9 sec. Under the conditions of this puff topography, the volume of air puffed per minute was equivalent to that generated by an average slow e-cigarette user under the following puff conditions: Q = 1 L/min, t = 4 sec, S = 30 sec (Talih et al., 2016). Approximately 40 puffs were needed to aerosolize an average of 1 g of e-liquid, producing 1.33 × 10^{-3} m^3 aerosol. Thus, β was estimated to be 0.75 kg/m^3.

1.6. Statistical analyses

The mean and standard deviation (SD) of concentrations of arsenic species were reported for each e-liquid and aerosol sample. Median and interquartile range (IQR) were reported for each arsenic species. Wilcoxon signed rank test was used to compare the concentrations of individual arsenic species in the e-liquid samples with that in the aerosol samples. SPSS version 20.0 (IBM Corp, Armonk, NY) was used to conduct the statistical analysis. When necessary, values below the detection limit were substituted by half of the LOD values.

2. Results and discussion

2.1. Arsenic species detected in e-liquids

Fig. 1B shows a representative chromatogram of arsenic species from the HPLC-ICPMS analysis of an e-liquid sample. It reveals the presence of iAs^{III}, iAs^V, MMA, and three new arsenic species (Un1, Un2, and Un3) not reported previously. The concentrations of each of these 6 arsenic species in the 17 e-liquid samples are summarized in Table 1. These results show that iAs^V is present in 94% of samples (16 of 17 samples), iAs^{III} in 59% (10 of 17), and MMA in 47% (8 of 17) samples. The chromatogram also shows the presence of three new arsenic species: Un1 eluting at a retention time of 1.1 min, Un2 eluting at 4.6 min, and Un3 eluting at 5.7 min (Fig. 1B). The retention times of these arsenic species do not match with any of the known arsenic species for which 20 arsenic standards are available to us (Cullen et al., 2016). Although the exact chemical nature of these arsenic species remains to be identified, these are arsenic-containing compounds because the ICPMS detection is set for specifically detecting arsenic. Un1 is detectable in 53% (9 of 17) of samples, Un2 in 82% (14 of 17), and Un3 in 47% (8 of 17) of the e-liquid samples. We also considered the determination of DMA and arsenobetaine, but their concentrations in all 17 e-liquid samples were below the detection limits of 0.01 μg/kg.

Table 1 — The concentrations (μg/kg, mean ± SD, n = 4) of arsenic species in the e-liquid samples.

Sample No.	Un1	iAs^{III}	Un2	Un3	MMA	iAs^V
1	N.D.*	2.56 ± 0.02	N.D.	N.D.	N.D.	2.64 ± 0.43
2	0.88 ± 0.03	1.78 ± 0.03	N.D.	N.D.	0.94 ± 0.17	8.30 ± 1.17
3	N.D.	1.16 ± 0.22	N.D.	N.D.	N.D.	2.28 ± 0.49
4	N.D.	1.08 ± 0.02	1.38 ± 0.01	N.D.	1.10 ± 0.03	1.92 ± 0.17
5	N.D.	1.06 ± 0.09	1.36 ± 0.03	N.D.	0.94 ± 0.03	1.86 ± 0.16
6	0.38 ± 0.06	N.D.	0.63 ± 0.05	0.36 ± 0.02	N.D.	N.D.
7	0.85 ± 0.01	N.D.	1.47 ± 0.14	0.17 ± 0.01	N.D.	1.76 ± 0.09
8	0.90 ± 0.01	2.19 ± 0.02	1.26 ± 0.01	0.30 ± 0.06	N.D.	1.70 ± 0.23
9	0.53 ± 0.03	1.35 ± 0.02	1.55 ± 0.09	0.36 ± 0.04	0.05 ± 0.01	1.64 ± 0.28
10	N.D.	N.D.	1.00 ± 0.04	N.D.	2.28 ± 0.10	3.40 ± 0.23
11	0.66 ± 0.04	N.D.	1.93 ± 0.08	0.35 ± 0.01	N.D.	2.47 ± 0.16
12	0.82 ± 0.03	N.D.	1.23 ± 0.18	0.34 ± 0.03	N.D.	1.71 ± 0.16
13	0.28 ± 0.01	N.D.	0.26 ± 0.01	0.40 ± 0.01	N.D.	2.67 ± 0.09
14	N.D.	2.80 ± 0.09	2.32 ± 0.02	N.D.	1.04 ± 0.03	1.10 ± 0.15
15	N.D.	2.56 ± 0.08	1.20 ± 0.01	N.D.	0.52 ± 0.03	1.62 ± 0.17
16	0.44 ± 0.07	N.D.	0.62 ± 0.03	0.42 ± 0.03	N.D.	0.71 ± 0.09
17	N.D.	4.66 ± 0.05	1.22 ± 0.02	N.D.	0.44 ± 0.02	1.04 ± 0.01
Species Median	0.28	1.08	1.22	N.D.	N.D.	1.76

* N.D. denotes below the detection limit (LOD) of 0.01 μg/kg for AsB, 0.02 μg/kg for iAs^{III}, 0.01 μg/kg for DMA, 0.01 μg/kg for MMA, and 0.37 μg/kg for iAs^V in the e-liquid samples. Un1, Un2, and Un3 were three arsenic species whose chemical structure were not yet identified and eluted at retention time of 1.1 min, 4.6 min, and 5.7 min, respectively. Their detection limits were set as same as the detection limits of the arsenic species that had the closest retention time with them.

2.2. Arsenic species detected in condensates of aerosols

We also determined arsenic species in the condensates of aerosols that were generated by vaping 8 e-liquid samples. A representative chromatogram of arsenic species from the HPLC-ICPMS analysis of a condensed aerosol sample is shown in Fig. 1C. The same six arsenic species, as detected in the e-liquid sample (Fig. 1B), are also detectable in the aerosol samples (Fig. 1C). The concentrations of six arsenic species in the 8 aerosol samples are summarized in Table 2. These results show the presence of iAs^{III}, Un1, and Un2 in 100% samples (8 of 8), iAs^{V} in 88% (7 of 8), Un3 in 75% (6 of 8) samples, and MMA in 13% (1 of 8) samples.

The concentrations of arsenic species in the condensates of aerosols were compared to those in the corresponding original e-liquids. Table 3 presents the median, IQR, detectable ratio, and p-values calculated from the Wilcoxon signed rank test for each detectable arsenic species. The results show that after the e-cigarette vaping, the concentrations of iAs^{III} ($p = 0.012$) were significantly higher than those in the original e-liquid, whereas Un2 ($p = 0.012$) and Un3 ($p = 0.012$) in the aerosol were significantly lower than those in the original e-liquids. The concentrations of Un1 ($p = 0.889$), MMA ($p = 0.317$), and iAs^{V} ($p = 0.063$) had no significant difference between the samples of aerosols and e-liquids.

2.3. Concentration of arsenic in the vaping air

Using Eq. (1), we estimated the concentrations of arsenic species in the vaping air generated from aerosolizing e-liquid samples. The concentrations of iAs^{III} ranged from 0.38 to 3.45 (median 2.45) $\mu g/m^3$. The concentrations of iAs^{V} were from <0.28 to 1.70 (median 0.68) $\mu g/m^3$. Total concentrations of inorganic arsenic species (iAs^{III} and iAs^{V}) ranged from <0.91 to 4.09 (median 3.38) $\mu g/m^3$. The United States Occupational Safety and Health Administration (OSHA) instituted a permissible exposure limit (PEL) at 0.01 mg/m^3 (10 $\mu g/m^3$) for airborne inorganic arsenic averaged over 8 h in the workplace (US NIOSH, 1988). Our study indicates that e-cigarette smokers could inhale inorganic arsenic species (iAs^{III} and iAs^{V}) at an inhalation concentration as high as 4 $\mu g/m^3$, which is nearly half of the permissible exposure limit (10 $\mu g/m^3$) set by OSHA.

2.4. Estimate of cancer risk from inhalation exposure to arsenic

Inhalation exposure to arsenic has been positively associated with the excess lung cancer mortality among smelting workers, e.g., at two smelters in Montana and Washington (Enterline and Marsh, 1982, Lee-Feldstein, 1986). Many epidemiological studies have consistently shown that inhalation

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Table 2 – The concentrations ($\mu g/kg$, mean $\pm$ SD, $n = 4$) of arsenic species in the aerosol condensate samples.

Sample No.	Un1	iAs^{III}	Un2	Un3	MMA	iAs^{V}
6	0.52 ± 0.06	0.84 ± 0.07	0.43 ± 0.01	0.22 ± 0.11	N.D.	N.D.[*]
7	0.62 ± 0.03	4.60 ± 0.19	0.49 ± 0.05	0.08 ± 0.01	N.D.	0.83 ± 0.21
8	1.03 ± 0.16	3.37 ± 0.06	0.47 ± 0.16	N.D.	N.D.	2.08 ± 0.18
9	0.45 ± 0.03	4.55 ± 0.78	0.51 ± 0.20	0.10 ± 0.01	0.06 ± 0.02	0.52 ± 0.01
11	0.71 ± 0.11	4.05 ± 0.84	0.73 ± 0.04	0.11 ± 0.03	N.D.	0.93 ± 0.40
12	0.96 ± 0.08	3.16 ± 0.26	0.34 ± 0.21	N.D.	N.D.	0.88 ± 0.20
13	0.21 ± 0.01	0.50 ± 0.02	0.07 ± 0.01	0.08 ± 0.04	N.D.	2.26 ± 0.12
16	0.34 ± 0.06	0.64 ± 0.36	0.37 ± 0.12	0.23 ± 0.04	N.D.	1.01 ± 0.61
Species median	0.57	3.27	0.45	0.09	N.D.	0.97

[*] N.D. denotes below the detection limit (LOD) of 0.01 $\mu g/kg$ for AsB, 0.02 $\mu g/kg$ for iAs^{III}, 0.01 $\mu g/kg$ for DMA, 0.01 $\mu g/kg$ for MMA, and 0.37 $\mu g/kg$ for iAs^{V} in the e-liquid samples. Un1, Un2, and Un3 were three arsenic species whose chemical structure were not yet identified and eluted at retention time of 1.1 min, 4.6 min, and 5.7 min, respectively. Their detection limits were set as same as the detection limits of the arsenic species that had the closest retention time with them.

Table 3 – Comparison between concentrations of individual arsenic species in the e-liquid samples and in the aerosol condensate samples (n = 8).

Species	E-liquids (median (IQR), $\mu g/kg$)	Detectable ratio in e-liquids	Aerosol (median (IQR), $\mu g/kg$)	Detectable ratio in aerosol	p-values
Un1	0.60 (0.40–0.84)	8/8	0.57 (0.37–0.90)	8/8	0.889
iAs^{III}	N.D.[*] (N.D.-1.02)	4/8	3.27 (0.69–4.43)	8/8	0.012[**]
Un2	1.25 (0.62–1.53)	8/8	0.45 (0.35–0.51)	8/8	0.012[**]
Un3	0.36 (0.31–0.39)	8/8	0.09 (0.02–0.19)	6/8	0.012[**]
MMA	N.D.(N.D.-N.D.)	1/8	N.D.(N.D.-N.D.)	1/8	0.317
iAs^{V}	1.71 (0.94–2.29)	7/8	0.91 (0.60–1.81)	7/8	0.063

[*] N.D. means below the detection limit (LOD) of 0.01 $\mu g/kg$ for AsB, 0.02 $\mu g/kg$ for iAs^{III}, 0.01 $\mu g/kg$ for DMA, 0.01 $\mu g/kg$ for MMA, and 0.37 $\mu g/kg$ for iAs^{V} in the e-liquid samples. Un1, Un2, and Un3 were three arsenic species whose chemical structure were not yet identified and eluted at retention time of 1.1 min, 4.6 min, and 5.7 min, respectively. Their detection limits were set as same as the detection limits of the arsenic species that had the closest retention time with them. When doing the Wilcoxon signed rank test, we used LOD/2 to substitute N.D.;
[**] Statistically significant at $\alpha = 0.05$ level.

exposure to inorganic arsenic increased the risk of lung cancer (Frost et al., 1987; Järup and Pershagen, 1991; Guo, 2004). On the basis of lung cancer risks, the United States Environmental Protection Agency (EPA) derived an inhalation unit risk factor (URF) of 4.3×10^{-3} excess cancer risk associated with a lifetime exposure to 1 μg/m^3 of inorganic arsenic in the air (US EPA, 1986). Our study estimated that the median concentration of inorganic arsenic species in the vaping air was approximately 3.4 μg/m^3. A lifetime inhalation exposure of inorganic arsenic species at 3.4 μg/m^3 would correspond to an excess lung cancer risk of 1.5×10^{-2}. Taking into account that inhalation exposure from e-cigarette may be intermittent, with vaping at 1% of the time inhaling inorganic arsenic species at 3.4 μg/m^3, an excess lung cancer risk would be 1.5×10^{-4}, which is still 150 times higher than the EPA's goal of 1×10^{-6}. Notwithstanding the fact that the linear extrapolation involves large uncertainties and that the inhalation exposure from e-cigarette is intermittent, inhalation of inorganic arsenic from e-cigarette vaping is a serious health concern.

2.5. New arsenic species yet to be fully characterized

The three new arsenic species, Un1 eluting at a retention time of 1.1 min, Un2 at 4.6 min, and Un3 at 5.7 min (Fig. 1B), remain to be fully characterized. Their chromatographic retention times do not match with any of the known arsenic standards available to us (Cullen et al., 2016). Further research to identify these arsenic species is necessary. Methods for sample treatment, pre-concentration of arsenic species, efficient chromatographic separation of arsenic species, in combination with ICPMS and electrospray ionization (ESI) mass spectrometry (MS) detection will be useful for the chemical characterization and identification of new arsenic species (Liu et al., 2018a, 2018b; Peng et al., 2017; Reid et al., 2020). Our previous studies using HPLC separation and simultaneous detection with ICPMS and ESIMS have succeeded in identification of several new arsenic species (Liu et al., 2018; Peng et al., 2017).

It is not known where the arsenic species in e-liquids were originated from. E-liquids typically consists of glycerol, propylene glycol, vegetable glycerin, nicotine, and various flavoring chemicals. Impurities from any of these components could contribute to the detected arsenic species. Inorganic and organic arsenic species of the +3 and + 5 oxidation states have been shown to be present in various food items and biological and environmental media (Foster and Maher, 2016; Kalantzi et al., 2017; Khan and Francesconi, 2016; Popowich et al., 2016; Raab et al., 2013; Sun et al., 2016; Taleshi et al., 2014; Taylor et al., 2017; Thomas and Bradham, 2016; Uppal et al., 2019). Recent findings of arsenolipids in oily materials, e.g., fish oil, may be relevant to further research on arsenic species in e-liquids. Reported arsenolipids include arsenic-containing hydrocarbons, fatty acids, phospholipids, phosphatidylcholines, fatty alcohols, and phosphatidylethanolamines (Khan and Francesconi, 2016; Raab et al., 2013; Taleshi et al., 2014; Taylor et al., 2017). Reversed-phase liquid chromatography in combination with detection of ICPMS and ESIMS will be useful for determining possible presence of these relatively hydrophobic arsenic species (Reid et al., 2020).

3. Conclusions

The present study assessed the concentrations of individual arsenic species in the e-liquid samples used for rechargeable USB-like and tank-type e-cigarettes, representative samples purchased from online and local e-cigarette stores in Canada and China. The total concentrations of arsenic species in the e-liquid samples ranged from 1.37 to 12.4 μg/kg. These values are on the same order of magnitude as those reported by Olmedo et al. (2018) and Song et al. (2018). Six arsenic species were detected in the e-liquid samples and the aerosols generated from the e-liquids. The concentration of iAs^{III} was significantly increased after vaping the e-liquids. The median concentrations of inorganic arsenic in the vaping air was approximately 3.4 μg/m^3. This was compared to the permissible occupational exposure limit of 10 μg/m^3 set by OSHA.

On the basis of the EPA's unit risk factor (4.3×10^{-3}) for inhalation exposure to 1 μg/m^3 of inorganic arsenic in the air, inhalation exposure to 3.4 μg/m^3 of inorganic arsenic in the vaping air would give rise to an excess lifetime lung cancer risk of 1.5×10^{-4}, after taking into account of intermittent vaping at 1% of the time. This increased lung cancer risk is more than 150 times higher than the EPA's goal of one in a million.

Electronic cigarettes have become increasingly consumed worldwide, with popularity among teenagers. As of 2016, the United States Food and Drug Administration (FDA) extended its regulatory power on tobacco products to include electronic cigarettes. The legal status of electronic cigarettes is currently pending in many countries. The arsenic exposure from e-cigarettes is of a particular concern of both customers and regulatory agencies. The present study provides quantitative information on individual arsenic species in e-liquid and aerosols of some of the popular electronic cigarettes on markets. Our findings of inorganic arsenic species in the e-liquids, the estimated concentration of arsenic in the vaping air, and the potential lung cancer risks from the inhalation exposure call for further research and regulatory considerations of e-cigarettes including e-liquids.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jes.2020.01.023.

R E F E R E N C E S

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