

Evidence That Metal Particles in Cannabis Vape Liquids Limit Measurement Reproducibility

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Cite This: *ACS Omega* 2022, 7, 42783–42792



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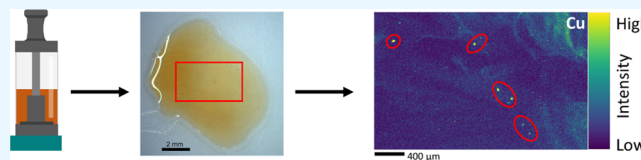


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ABSTRACT: Cannabis vaping involves the vaporization of a cannabis vaping liquid or solid via a vaping accessory such as a vape pen constructed of various metals or other parts. An increasing number of reports advocate for expansion of the testing and regulation of metal contaminants in cannabis vape liquids beyond the metals typically tested such as arsenic, cadmium, mercury, and lead to reflect the possibility of consumers' exposure to other metal contaminants. Metal contaminants may originate not only from the cannabis itself but also from the vape devices in which the cannabis vape liquid is packaged. However, metal analyses of cannabis vape liquids sampled from cannabis vaping devices are challenged by poor precision and reproducibility. Herein, we present data on the metal content of 12 metals in 20 legal and 21 illegal cannabis vape liquids. The lead mass fraction in several illegal samples reached up to $50 \mu\text{g g}^{-1}$. High levels of nickel (max $677 \mu\text{g g}^{-1}$) and zinc (max $426 \mu\text{g g}^{-1}$) were found in illegal samples, whereas the highest copper content ($485 \mu\text{g g}^{-1}$) was measured in legal samples. Significant differences in metal mass fractions were observed in the legal cannabis vape liquid taken from two identical devices, even though the liquid was from the same lot of the same cannabis product. Metal particles in the vape liquids were observed by scanning electron microscopy, and laser ablation inductively coupled plasma mass spectrometry confirmed the presence of copper-, zinc-, lead-, and manganese-bearing particles, metals that are in common alloys that may be used to make vape devices. Colocalized particles containing aluminum, silica, and sodium were also detected. These results suggest that metal particles could be a contributing factor to poor measurement precision and for the first time, to the best of our knowledge, provide evidence of metal particles in cannabis vape liquids contained in unused cannabis vape pens.



INTRODUCTION

Legalization and regulation of cannabis in Canada and at the state level across the United States have led to a wide variety of commercially available cannabis products. Inhalation is still the dominant mode of cannabis consumption; however, the traditional smoking of dried cannabis through combustion has seen a decline, while vaping of cannabis has seen an increase, particularly in young adults who are concerned with the health implications associated with smoking.^{1,2}

Vaping cannabis liquid is a noncombustion process, where a cannabis liquid concentrate is aerosolized upon contact with a resistance-heated element and inhaled through a mouthpiece. The heating element is a metal wire, which vaporizes the vape liquids directly or through a cotton wick soaked in the vape liquid. Newer generation of coils, the so-called ceramic coils, incorporated ceramic as a wicking material, and depending on the design, they are either completely replaced by the cotton wick or used in conjunction with it. There are a large variety of designs on the market that are based on the same vaporization principle; however, the individual components can be made of different metal alloys. The most commonly used heating elements are made of nichrome (Ni, Cr), Ni-plated brass (Cu, Zn), and kanthal (Al, Cr, Fe), whereas other atomizers' metal

components are often made from stainless steel (Cr, Ni, Fe, Mn), and tin (Sn) and lead (Pb) are being used as solders.^{3,4}

In Canada, regulations require that chemical contaminants in cannabis products, such as metals, must be tested for and meet the generally accepted tolerance limits appropriate for the intended use of the cannabis product. These tolerance limits are found in publications referred to in schedule B of the Food and Drugs Act, which is referenced in the Cannabis Regulations.⁵ Most license holders routinely test cannabis for arsenic (As), cadmium (Cd), mercury (Hg), and lead (Pb) to the limits found in the U.S. Pharmacopeia Chapter 232 and European Pharmacopeia Chapter 5.20 (both publications referred to in schedule B of the Food and Drugs Act). The concentration limits used by the industry are typically those found in the European Pharmacopoeia of $0.2 \mu\text{g g}^{-1}$ for As, $0.1 \mu\text{g g}^{-1}$ for Hg, $0.3 \mu\text{g g}^{-1}$ for Cd, and $0.5 \mu\text{g g}^{-1}$ for Pb. These

Received: July 20, 2022

Accepted: October 27, 2022

Published: November 14, 2022



limits correspond to a permitted daily exposure for products where the maximum daily dose of cannabis would not exceed 10 g per day and align with the limits set by other jurisdictions that regulate metals in cannabis vape liquids, such as California⁶ and many other U.S. states. Although these limits are not standard across the industry, an increasing number of U.S. states require testing for heavy metals in cannabis vape liquids, including Colorado, Oregon, Michigan, Maryland, and Florida. The Cannabis Regulations also require that testing for contaminants in cannabis must occur at or after the final step in production where contamination is likely to be introduced or concentrated. Furthermore, the Cannabis Regulations state that any packaging and accessories should not contaminate the cannabis product. While cannabis is a known hyperaccumulator of metals,⁷ the cannabinoid extraction processes are not efficient at metal extraction; thus, the contamination of cannabis vaping products most likely comes from the materials used to make the vaping devices themselves.

Recent studies of metal contaminants in nicotine vape liquids indicate that expanding the number of metals required to be tested may be necessary to reflect the actual risks of vaping.^{4,8} Several publications have shown that the metallic components of vaping devices leach metals into the vaping liquids.^{9,10} The levels of leached metals depend on the metals used in constructing the vaping device components, but the most commonly measured are Pb, Ni, Cu, Zn, Sn, Al, and Cr. While the exact mechanism by which metals in vaping devices may leach into the vaping liquid is not yet fully understood, there is evidence of corrosion of metal components as well as surface cracking in nicotine vaping devices.^{10,11} More importantly, elevated levels of metals have been measured in aerosols produced by nicotine vaping devices, and a recent study by Pappas et al. showed that metal nanoparticles are transported in the generated aerosol and inhaled by the consumer.¹⁰ The most frequent particle size detected was less than 100 nm, a size at which some metal particles exhibit enhanced toxicity. Some vaping devices even emitted over 200,000 Pb-containing particles per 10 puffs. This is concerning as chronic exposure to metals can have serious health consequences and their inhalation can induce a large number of lung pathologies.^{12,13}

In this study, the metal content in cannabis vape liquids from 20 legal and 21 illegal electronic vaping devices was analyzed and possible implications are discussed. Scanning electron microscopy with energy-dispersive X-ray spectroscopy (SEM/EDS) and laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS) were used for *in situ* approaches to identify metal particles within cannabis vape liquids. The data presented are from unused vaping devices and hence represent the baseline levels that the consumer may be exposed to.

MATERIALS AND METHODS

Chemicals and Reagents. Analytical grade nitric acid (HNO₃) (J. T. Baker, VWR) was purified in-house by sub-boiling distillation using high-purity quartz still (duoPUR, Milesone) in class 100 clean room and was used for all sample and standard preparations. Elemental stock standards (1–100 ng g⁻¹) by Inorganic Ventures were obtained from Delta Scientific (Canada) and contained V, Cr, Mn, Co, Ni, Cu, Zn, As, Se, Mo, Cd, Hg, Tl, Pb, Ru, Rh, Pd, Sn, Sb, Te, Hf, Ir, Pt, and Au, which were traceable to NIST-certified reference materials (CRMs). Three certified reference materials (CRMs)

were processed and analyzed as unknowns for quality control purposes. These were trace elements in fuel oil (NIST 1634c) obtained from the National Institute of Standards and Technology and both dogfish liver (DOLT-5)¹⁴ and lobster hepatopancreas (TORT-3)¹⁵ obtained from the National Research Council Canada. Legal cannabis samples were purchased from the Ontario Cannabis Store (www.ocs.ca), and available information on the THC/CBD content, method of extraction, and additives can be found in Table S1. Illegal cannabis samples were provided by the Ontario Provincial Police. Deionized water (> 18 MΩ cm Milli-Q Element, Millipore) was used in all experiments.

Sample Preparation and Analysis by ICP-MS/MS. The cannabis vape liquids were collected from their respective sealed cartridges in one of three ways, where the approach used was dependent upon the manufacturing design: (1) unscrewing the top of the cartridge, (2) using a pipe/glass cutter to carefully remove the top of the cartridge, or (3) carefully break the glass at the top of the cartridge. No visible abrasion of the metal components occurred from opening the cartridges, but glass contamination cannot be excluded for some samples. Once the top of the cartridge was removed, the remainder of the cartridge holding the cannabis vape liquid was inverted and placed in a disposable 5 mL pipette tip, of which the very tip was subsequently placed within a 2 mL glass high-performance liquid chromatography (HPLC) vial. This entire setup was then placed within a 50 mL centrifuge tube to secure it in place. In the rare case where a vape cartridge top could not be removed, general sampling method (3) was employed. Breaking the cartridge glass allowed access to the sample, after which the cannabis vape liquid was transferred to a 2 mL HPLC vial using a syringe or pipette tip. Centrifugation of the vape cartridges was performed at 4000g for 5 min. As viscosity of the cannabis vape liquids varied, cartridges were inspected after every 5 min cycle to determine if additional cycles were required.

Prior to subsampling, the cannabis vape liquid was warmed up in a hot block (Reacti Therm Heating module, Thermo-Fisher) at 60 °C for 30 min and stirred with a pipette tip. Triplicate cannabis vape liquids were digested following a previously described method.¹⁶ An aliquot of approximately 0.1 g was accurately weighed into microwave digestion vessels and digested in 6 mL of concentrated HNO₃ in a microwave digestion system (Multiwave 7000, Anton Paar), using a temperature program of 0–15 min ramp to 200 °C and held at 200 °C for 15 min. After digestion, the samples were transferred into 50 mL vials, evaporated to approximately 0.2 mL, and reconstituted to 2% HNO₃. Three CRMs (NIST 1634c, DOLT-5, and TORT-3) and one method blank were included in each digestion cycle for quality control. Method blanks were carried through the entire sample preparation process and were used for monitoring possible contamination. To test As leaching from HPLC vials during storage and homogenization of the cannabis vape liquids, a blank sample containing DIW adjusted to pH 4.0 to simulate cannabis vape liquid pH was heated at 60 °C for 30 min in the same way as cannabis samples. This blank sample was analyzed directly without digestion.

All samples were analyzed using ICP-MS/MS (Agilent 8900, Agilent Technologies, Santa Clara, CA) configured with the standard sample introduction system consisting of a MicroMist glass concentric nebulizer, a quartz spray chamber, and a quartz torch with a 2.5 mm id injector. The interface was

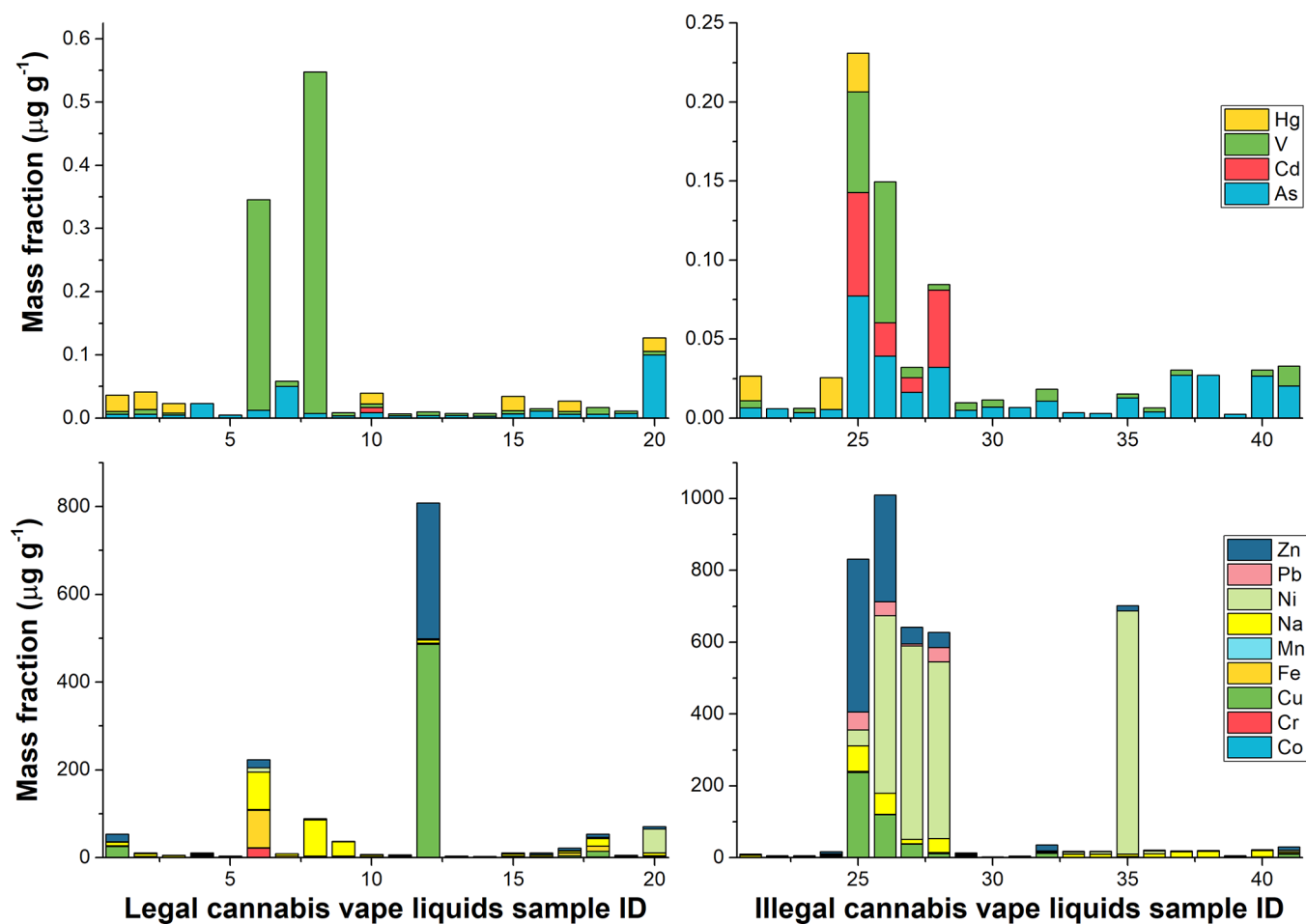


Figure 1. Elemental mass fractions of studied cannabis vape liquids from legally purchased vaping devices (sample IDs 1–20) and illegal vaping devices (sample IDs 21–41).

equipped with a nickel-plated copper sampling cone and a nickel skimmer cone. The instrument was operated in MS/MS mode using H_2 collision gas (4.0 mL min^{-1}) for the detection of ^{63}Cu , ^{64}Zn , and He collision gases (5.0 mL min^{-1}) to detect ^{59}Co , ^{52}Cr , ^{55}Mn , and ^{206}Pb . Oxygen gas (22%) was used as a reaction gas for the detection of ^{75}As (mass shift to m/z 91), ^{111}Cd (on mass), ^{56}Fe (on mass), ^{202}Hg (on mass), ^{23}Na (on mass), ^{60}Ni (on mass), and ^{51}V (mass shift to m/z 67). Optimization for suitable sensitivity and stability with cerium oxide ratios of $< 1\%$ and doubly charged ions ($^{70}\text{Ce}^+ = ^{140}\text{Ce}^{++}$) of $< 2\%$ was performed daily. An online internal standard of yttrium was continuously mixed with calibration standards and samples during the analysis at a concentration of $20 \mu\text{L L}^{-1}$. Monitored yttrium isotope (m/z 89) was used to compensate for possible instrument instability and matrix effects by calculating the ratio between the m/z of an element of interest and internal standard. Quantitation was performed using the external calibration method; quality control samples of low, medium, and high concentrations, as well as blank, were measured every 10 samples. An Agilent SPS 4 autosampler with a cover (Agilent Technologies) was used for sample introduction.

The limits of detection (LODs) were determined by analyzing 11 method blanks and calculating the standard deviation (σ) of their elemental concentrations, which was multiplied by 3. The method limits of detection were

determined as LOD multiplied by a nominal dilution factor of 55.

Electron Scanning Microscopy with Energy-Dispersive X-ray Spectroscopy (SEM/EDS) Analysis. Prior to sampling, the cannabis vape liquid was warmed up in a hot block (Reacti Therm Heating module, ThermoFisher) at 60°C for 30 min and homogenized with a pipette tip. A portion of $15 \mu\text{L}$ of the cannabis vape liquid was placed into the Quantomix QX-102 capsule (El-Mul), which was sealed from the vacuum by a thin electron-transparent membrane cover and immediately placed into the microscope vacuum chamber. A Hitachi SU5000 Schottky field emission scanning electron microscope (SEM) equipped with an Oxford Instruments X-Max³ 80 mm energy-dispersive X-ray (EDX) spectrometer was used for the analysis. The images were taken in high vacuum mode, using an acceleration voltage of 20 kV and detected by both the backscatter and the secondary electron detectors.

Laser Ablation ICP-MS (LA-ICP-MS) Analysis. Prior to sampling, the cannabis vape liquid was warmed up in a hot block (Reacti Therm Heating module, ThermoFisher) at 60°C for 30 min and stirred with a pipette tip. A drop of $50 \mu\text{L}$ of the cannabis vape liquid was placed between two microscope glass slides, which were temporarily pressed together to spread the liquid; then, the glass slides were separated (to create two slides/sample) and stored in falcon tubes prior to analysis. To evaluate whether particles would settle in the liquid prior to analysis, a second set of slides were stored in a falcon tube with

the deposited sample facing downwards. The microscope glass slides were cleaned with 2% HNO₃, followed by methanol.

Element mapping of the cannabis vape liquid was carried out by laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS) at the Geological Survey of Canada, using a Photon Machines/Teledyne Analyte G2 193 nm excimer laser ablation system, with a HelEx two-volume ablation cell, coupled to an Agilent 7700x quadrupole ICP-MS (Agilent Technologies, Santa Clara, CA). The mapping procedure follows a previously published method.¹⁷ The element maps were constructed by translating the sample stage under a focused laser beam to form a series of laser line scans. Laser conditions during the analytical sessions include a fluence of 3.5–4.0 J cm⁻² and a repetition rate of 30 Hz. The spot size and scan speed were set to 6 μm and 24 μm s⁻¹, respectively, such that the sample stage would advance one equivalent spot diameter every 0.25 s. Each analysis began with 20 s of background measurement (gas blank) and was followed with 60 s of washout. The ablation aerosol was transported out of the HelEx cell using 1 L min⁻¹ of helium gas and carried to the ICP-MS through approximately 1 m of 2 mm (inner diameter) Teflon tubing. Prior to entering the ICP-MS, the aerosol and helium gas were mixed with 0.95 L min⁻¹ of argon gas. The ICP-MS was tuned on a NIST-612 glass reference material¹⁸ to achieve > 9000 cps ppm⁻¹ on ¹⁷⁵Lu (50 μm spot, approximately 7 J cm⁻² at 10 Hz) while minimizing the production of oxides (< 0.2% for ThO/Th) and maintaining a U/Th ratio of approximately 1.0. The total duty cycle time to measure all masses on the ICP-MS (in time-resolved analysis mode) was 125 ms. Dwell times for most elements were 5–8 ms in the first experiment (sample 18) but were optimized in the second mapping experiment (sample 21) so that a larger proportion of time was spent measuring Ni, Cu, and Pb (16, 16, and 10 ms, respectively).

The map data were processed using Iolite 4 software following the Trace Element data reduction scheme.¹⁹ Calibration of the signals was achieved by external standardization (i.e., semiquantitative) using line scans of GSE-1G (for Fe)²⁰ and NIST-612 (for all other elements) glass reference materials. A background correction was applied to every line scan using a step-forward baseline subtraction, and instrument drift was accounted for using analyses GSE-1G and NIST-612, which were analyzed every 40 unknowns (every 1–1.5 h). Reference values for GSE-1G and NIST-612 were taken from the online geological and environmental reference material database (GeoREM).²¹

An Olympus SZH10 stereo-microscope at a 1× magnification was used for capturing images of cannabis vape liquid drops after ablation analysis.

RESULTS AND DISCUSSION

Quality Control, Blank Samples, and Limits of Detection. Certified reference materials (NIST 1634c, TORT-3, and DOLT-5) were digested and measured for the total metal content, with each measurement showing good agreement with certified values, with an overall recovery range between 94 and 115%. Metal levels in the blank samples were at or around limits of quantitation values, with negligible contribution to the mass fractions measured in the samples and no carry-over between measured samples was observed. Arsenic leaching from the HPLC vials was below the levels of the blank samples.

Total Metal Concentrations. The content of 20 legally purchased (sample ID 1–20) and 21 illegal (sample ID 21–41) vape devices containing cannabis vape liquids was analyzed for metals routinely tested for in cannabis (As, Cd, Hg, and Pb) and other metals that may leach from the metallic parts of the vaping devices. Figure 1 shows the elemental concentrations found in the 41 vape samples. The concentrations of As, Hg, and Cd in all tested samples were within the generally accepted schedule B publication tolerance limits of 0.2, 0.1, and 0.3 μg g⁻¹, respectively (Table 1), but the concentration of

Table 1. Median (Interquartile Range) of Metal Mass Fractions (ng g⁻¹) in Cannabis Vape Liquids

	legal samples (n = 20)	illegal samples (n = 21)
As	6.18 (4.51–9.52)	7.07 (4.99–26.6)
Cd	7.65 ^a	35.1 (18.3–53.0)
Co	190 (100–250)	190 (130–235)
Cr	294 (85.7–534)	50.0 (30.0–87.5)
Cu	569 (273–3057)	1264 (453–9984)
Fe	1694 (1064–2877)	922 (669–1219)
Hg	21.5 (17.0–24.6)	20.0 (17.8–22.5)
Mn	40.0 (30.0–85.0)	20.0 (10.0–55.0)
Na	4223 (3234–6958)	7020 (2619–15431)
Ni	521 (246–1071)	1759 (579–7215)
Pb	28.1 (11.5–43.9)	88.0 (48.1–1522)
V	5.00 (4.00–7.50)	4.50 (3.00–8.75)
Zn	1532 (518–5451)	2283 (1494–14575)

^aCd mass fraction was above LOD only in one legal cannabis vape pen.

Pb exceeded the tolerance limit of 0.5 μg g⁻¹ in one legal (0.628 μg g⁻¹; Figure 1 and Table S2) and six illegal samples (range 1.52–48.9 μg g⁻¹; Table S3). The mass fractions of measured metals in legal samples varied significantly (Tables 1 and S4), and several samples with a mass fraction of Ni above the established tolerable limit also yielded Cr and/or Cu levels above-established limits. Similarly, illegal samples high in Pb were also measured high for Cu, Ni, and Zn (Table S5).

In general, the mass fractions of Pb in nicotine vape liquids reported in the literature are in sub μg g⁻¹, with one publication reporting in the 1.30–2.56 μg g⁻¹ range.²² In a recently published study of cannabis vape liquids, the highest measured Pb mass fraction was 11 ± 10 μg g⁻¹,⁸ which is comparable with the results reported here.

For the other metals, mass fractions of Zn and Cu are generally in the low μg g⁻¹ range. However, similarly high levels (Zn 454 ± 11 μg g⁻¹ and Cu 903 ± 27 μg g⁻¹) to those observed in the present study were reported in nicotine vape liquids from devices that were analyzed 2 years after the purchase date.⁴ This indicates the high leaching potential of these metals and perhaps a dependency of the measured concentration on the age of the device. Using the packaging date as a proxy to the age of the device, none of the devices analyzed in the present study exceeded 8 months of age. Although Ni is present in several metal alloys used in vaping devices, its reported mass fractions are generally in the low to sub-μg g⁻¹ range in nicotine vape liquids. However, four illegal samples of cannabis vape liquids in the present study yielded Ni mass fractions in the range of 493–677 μg g⁻¹, similar to levels reported by Kubachka et al. in two samples of cannabis vape liquids (102 ± 6 and 477 ± 21 μg g⁻¹).⁸ The levels of Co in several legal and illegal samples are in the same order of

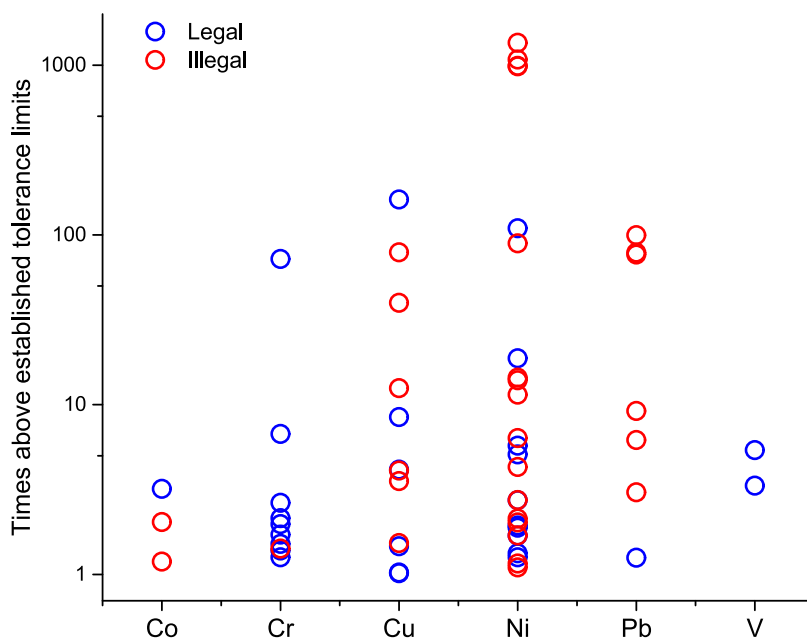


Figure 2. Comparison of the legal versus illegal cannabis vape liquids when the measured mass fractions exceeded established tolerance limits for metals in European Pharmacopoeia general Chapter 5.20 on elemental impurities.

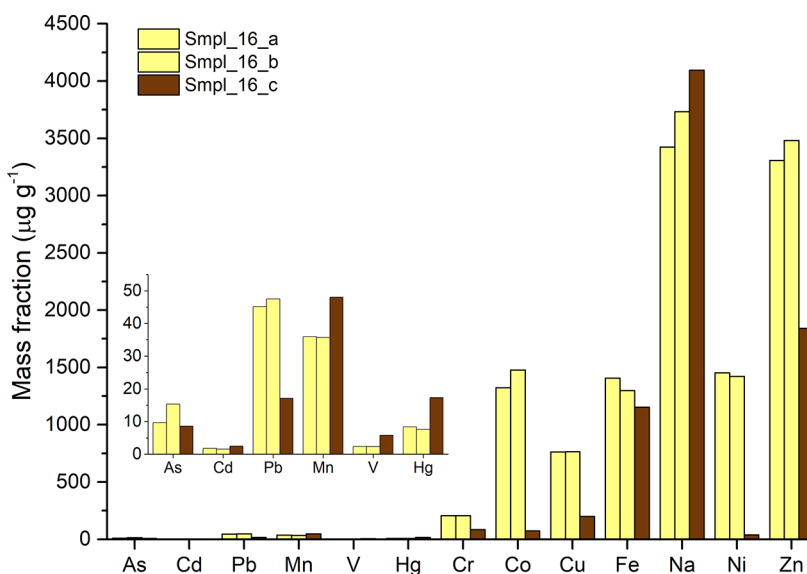


Figure 3. Mass fractions of studied metals in three replicate subsamples of the same legal cannabis vape liquid obtained from two individual vape devices (yellow bar device #1 and brown bar device #2).

magnitude as Ni; however, Co is rarely used in steel alloys and thus generally presents as an impurity. There are only a few publications reporting Co mass fractions in cannabis and nicotine vape liquids, and their levels are comparable to values measured in our study.^{8,23} The source of Co contamination is not clear although few publications identified Co in the mouthpieces, cartridge metal core, or heating wire.²⁴ To the best of our knowledge, the levels of V are reported in only one published study of nicotine vape liquids and are in the low to sub-ng g⁻¹ range.²⁵ However, two legal samples in this study had elevated V mass fractions, with the highest value of 0.54 ± 0.015 µg g⁻¹.

It is evident that some metals present in the cannabis vape liquids can be found in high concentrations. When compared with permitted levels of elemental impurities in inhaled

products established by European Pharmacopoeia, several legal and illegal samples significantly exceeded established tolerance limits (Figure 2). While only a few samples exceeded the limits for Co and V, a large number of samples were above the limits for Cr, Cu, Ni, and Pb. Very often, samples exceeded these limits in more than one measured analyte. The magnitude by which some of the samples exceeded these limits varied between the analytes, with Ni being 900 times above the established limits in several illegal samples. It also seems that some metals may be leaching at a higher rate in cannabis vape liquids than nicotine vape liquids, but with very few publications on cannabis vape liquids currently available, these observations require further validation.

A large number of replicate analyses of the studied cannabis vape liquids exhibited a relative standard deviation (RSD)

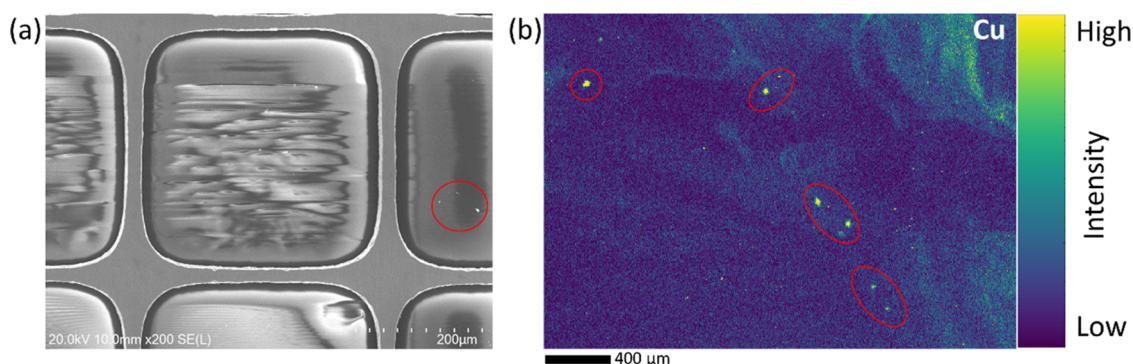


Figure 4. Metal particles in an illegal cannabis vape liquid detected from sample 41 by SEM (a) and elemental map of Cu by LA-ICP-MS with several hotspots depicting Cu-containing particles (b). SEM image also shows distortion on the central grid caused by charging of the polyimide membrane of the QX-102 capsule.

>20% for most of the measured analytes (for $n = 2$, the relative percent difference (RPD) was calculated instead; Table S2). One of the reasons for the observed high RSD (or RPD) could be poor sample homogeneity resulting from the high viscosity of the sample matrix, while another factor that could contribute to high RSD is metal particulate. To reduce the viscosity and improve sample homogeneity, the samples were heated at 60 °C for 30 min and stirred with a pipette tip prior to subsampling. Additionally, the mass fraction of K, which is not present in the metal components of the vaping devices but is present in the matrix of cannabis vape liquids, was measured to serve as an indicator of adequate mixing. A portion of the samples had RSD (or RPD) for K < 20%, and these samples were considered adequately homogenized. However, even within this set of samples, an RSD (or RPD) of > 20% was observed for most of the other measured metals. This indicates that there are factors contributing to low sampling reproducibility other than sample homogeneity. Significant efforts to improve sample mixing were described by Kubachka et al. who reported inconsistencies in RSD reduction for measured metals in cannabis vape liquids.⁸ The authors concluded that despite thorough stirring of the samples the metal homogeneity may be difficult to achieve. These findings support the notion that metal contamination comes from discrete particles that are heterogeneously suspended in the cannabis vaping liquids. The results presented in the section below on scanning electron microscopy further support the source of heterogeneity being metal particulates rather than heterogeneity from sample viscosity.

Additionally, due to limited amounts of some legal cannabis vape liquids (< 0.2 mL), the replicate analysis was done on liquids obtained from two devices purchased at the same time and from the same production lot. As can be seen in Figure 3, their metal composition varied significantly as did their visual appearance (Figure S1), despite coming from the same production lot. The difference in color may be a result of intrabatch heterogeneity of the extract used to make these vape products or the changes to the extract could occur once packaged during shipping and/or storage.

The RSD between two replicates of the device #1 is < 10% for all studied analytes excluding As but increases significantly when the analysis of the second device was added as the third replicate. Specifically, the mass fractions of Cr, Co, Cu, Ni, and Pb were significantly higher in the first device. Cannabis vape liquids are thought to have high acidity and thus, upon prolonged contact of the metal components with the vape

liquids, the metals may leach into the liquid. McDaniel et al. have shown that the amount of leached metals is dependent on temperature and contact time with the metals. In their experiments, identical cannabis vape devices were stored for 3 weeks and 7 months at room temperature and at an elevated temperature of 42 °C.²⁴ Subsequent analysis of the cannabis vape liquids held at the same storage temperature showed a significant increase in mass fractions of Cu, Cr, Ni, and Pb with prolonged storage time. This increase in mass fractions for metals was also observed for increases in temperature when cannabis vape liquids were stored for equivalent amounts of time. Because the rate of the leaching is dependent on the length of the exposure, temperature, vape liquid acidity, and the integrity or physical conditions of the metal components, it is highly probable that the amount of leached metals will differ between individual devices.

Our findings indicate that metal particulates are contributing to high RSD. Several samples exhibited extremely high concentrations of a given analyte in one replicate. For example, the measured concentrations in individual replicates in sample 12 for Cu were 0.213, 0.092, and 1455 $\mu\text{g g}^{-1}$, and for Zn, they were 0.447, 0.363, and 928 $\mu\text{g g}^{-1}$. Adequate homogeneity of the sample containing particulates can be achieved for monodispersed solutions; however, naturally formed particulates are very rarely uniform in size. Therefore, if the cannabis vape liquids contained metal particles of varying sizes, despite their homogeneous distribution within the matrix, their contribution to total metal content will differ between individual sample aliquots. In a recent publication, Pappas et al. analyzed the aerosol from nicotine vape devices by single-particle ICP-MS.¹⁰ The results showed that aerosol from all studied devices contained metal nanoparticles of varying sizes and particle number concentrations. The size ranged between 20 and over 300 nm. Because the analysis was done on the aerosol, the upper size of metal particles may be limited by the transport efficiency of the particles in a specific vaping device. In another study, one puff of aerosol was found to contain approximately 4 million particles cm^{-3} of a size range from 10 nm to 1 μm .²⁶ Thus, it is possible that microsized metal particles are present in the vape liquids, but their transport into the aerosol is device-dependent.

Scanning Electron Microscopy. Applications of scanning electron microscopy with energy-dispersive X-ray spectroscopy (SEM/EDS) are generally focused on solid samples; however, wet scanning electron microscopy (WETSEM) technology enables the analysis of liquids.

Table 2. Elemental Composition of Cannabis Vape Liquid Matrix, Detected Particle, and QX-102 Capsule Matrix

	C %	O %	Cr %	Si %	S %	Fe %	Co %	Mn %	Ni %	Sn %	total %
matrix	100										100
particle	88.03	9.85	0.33			0.81	0.13		0.64	0.21	100
capsule	33.67	4.29	12.88	0.81	0.16	43.14		0.64	4.41		100

The SEM analysis showed the presence of metal particles within cannabis vape liquids (Figure 4a). The elemental composition of these particles was significantly different from the composition of the QX-102 capsule (Table 2), suggesting that the metal particles originate from metal components in contact with the vape liquid while in the device and not the capsule.

Several publications have identified metal particles in the aerosol generated from nicotine vape devices.^{10,26} In these studies, the devices were subjected to several vaping cycles and required heating of the coil to high temperature followed by cooling. It can be hypothesized that this thermal expansion and contraction of metal parts may result in chipping or shedding of metal particles, especially if the surface of the metal parts is already cracked, as demonstrated by the authors. However, the devices in the present study were never used by consumers, which further indicates that other sources than heating coils may be contaminating the cannabis vape liquids. In fact, a recent multielemental analysis of metal particles in the aerosols generated by nicotine vape devices identified the stainless steel aerosol tube and the core of the electrical connector as the most probable source of detected particles in studied devices.¹⁰

It should be noted that the WETSEM technology carried a number of limitations. First, despite the high viscosity of the cannabis vape liquids, the metal particles were free-flowing through the matrix, and considering the high magnification provided by SEM, significant particle mobility during interaction with the electron beam was observed. This made switching to the X-Max^N silicon drift detector challenging because localized particles identified through SEM moved by the time EDS elemental measurements were acquired. Second, although the polyimide polymer membrane should be electron beam transparent, significant charging of the membrane and/or liquid was observed (e.g., see the central portion of Figure 4a). Charging impacted the clarity of the image and the magnification that could be used. Even at low magnification, distortion of the SEM image in the main grid of Figure 4a is caused by charging of the polyimide membrane and/or the cannabis liquid. Despite the distortion, several metal particles are clearly visible, although only at low magnification (Figure 4a). Lastly, because the electron beam only interacts with the immediate surface of a material (an interaction volume of only a few microns), gravitational settling of particles has to be taken into consideration. The apparent loss of particles from the surface of the liquid was observed if the capsule was kept under vacuum for several days and is attributed to particles settling on the bottom of the holder—hence too deep for the electron beam to penetrate.

Laser Ablation Inductively Coupled Plasma Mass Spectrometry. To corroborate the observations by SEM/EDS, a drop of cannabis vape liquid placed on a glass slide was analyzed by laser ablation ICP-MS (LA-ICP-MS). Initial experiments on sample 18 showed the presence of spatially colocalized particles containing Al, Si, and Na (Figure S2), which could indicate shards of glass in the liquid, visible on the transmitted light image (Figure S3). Several vape liquids were

contaminated with glass fragments during opening of the device atomizers. Considering that Al, Si, and Na intensities were localized within very small areas of the sample confirms that they are results of ablation of small glass fragment rather than the glass slide on which the sample was deposited. Ablation of the surface of the glass slide would result in consistently high signals for these elements across the entire map, not isolated clusters of Si, Al, and Na. Hotspots were also observed in the Cu, Pb, Zn, and Mn maps for this sample, with some colocalization between particles (Figure S4). The largest number of particles were observed in the maps for Pb followed by Cu. A small number of Zn and Mn clusters are observed but their signal intensity is similar to, or slightly higher than the matrix, suggesting that they are at the limit of particle size detection. Only large particles would produce signals sufficiently intense to be distinguished from the matrix, which would explain the small number of particles associated with the Zn and Mn maps.

In the subsequent experiment, a drop of illegal cannabis vape liquid sample 41 was kept inverted to limit the time for particle settling prior to analysis. As can be seen from Figure 4b, the elemental map of Cu contains several distinct hotspots, most probably due to Cu-rich particles being present within the sample. Although data for Al, Cu, Co, Cr, Fe, Mn, Na, Ni, Si, and Pb were acquired, none of the other elemental maps contained any hotspots. The Zn map contained small clusters that correlated with Cu but the clusters were only a few pixels wide, thus being difficult to interpret with high certainty. A precise sizing of the metal particles was not an objective of these experiments and is complicated to measure accurately due to the slow washout characteristics of the LA-ICP-MS technique (i.e., the time between ablation of the sample and measurement by ICP-MS), but considering the applied parameters (i.e., an analytical spot size of 6 μm), the imaged particles are approximately in the size range of hundreds of nanometers to tens of micrometers. Interestingly, 8 months after the ablation of cannabis sample 41, distinct streaks have developed around the particles, suggesting that some of the particles were oxidized in the liquid (Figure S5). This is in line with published observations of metal component corrosion exposed to vape liquid.

Similarly to SEM/EDS analysis, gravitational settling of particles may be problematic for LA-ICP-MS analysis. The drop of the vape liquids was approximately 300 μm deep, which provides a suitable depth for nanosized particles to settle, which, in turn, would not be accessible to a laser while ablating the surface of the drop. During the analysis, the laser fluence was kept relatively low (3.98 J cm^{-2}) because the ablation of the drop was causing the dispersion of hydrocarbon matrix within the ablation chamber and ICP-MS introduction parts, in addition to potential displacement of the metal particles at the surface due to disturbance of the surrounding liquid during ablation, despite the liquids not being free-flowing at room temperature. It was observed that the wells created by ablation of the drop's surface were refilled with the matrix after the laser beam changed position. Such movement

of the matrix could shift the location of particles away from the incident beam. Therefore, to stabilize the particles within the vape liquids, a cryogenic laser ablation chamber could be used in future LA-ICP-MS analyses.

Regulatory Considerations and Health Implications.

The current Cannabis Regulations require testing for appropriate chemical contaminants, which could include heavy metals in each lot of cannabis product either before or after it is packaged and labeled as a cannabis product, as long as the testing occurs after the final step where the contaminants could be introduced or concentrated.⁵ Many companies are testing their cannabis vape liquids before they are filled into the vape devices. Published research on nicotine vape liquids suggests that vape liquids are contaminated by the metal components coming from vape devices and there is no reason to believe that the same may not occur with cannabis vape liquids. Therefore, testing of cannabis vape liquids before they are filled into the vaping devices cannot detect metal contamination coming from the storage and operation of such vape devices. Additionally, as previously mentioned, the rate of the leaching is dependent on the length of the exposure, temperature, pH of the vape liquid, and the integrity or physical conditions of the metal components. This raises the question of whether regulatory or commercial testing of metals should be occurring after the device is filled and not before. It also raises the potential issue of additional contamination from metals upon prolonged storage as well as from use of the device due to thermal expansion and contraction, which may compromise the metal vape component materials.

To date, regulators and companies in the cannabis industry in and outside of Canada have focused on the most concerning class of elemental impurities, the class 1 metals (As, Cd, Hg, and Pb). These elements are typically of high concern due to their relative ubiquity in the environment and their inherently high toxicity. However, the range of metals, which were found in cannabis vape liquids and have been known to be present in nicotine vape liquids for some time, is much broader than these four and could also present significant health risks with long-term exposure, especially with inhalation and in particular when the particles are in the nanoscale. The severity of these risks has been acknowledged by establishing maximum acceptable limits within occupational exposure regulations worldwide for these other metals, and limits for these metals in health products can be found in elemental impurity standards published by the ICH, USP, and European Pharmacopoeia. Given this, further consideration may need to be given to potentially expanding the number of metals that are regularly tested for in cannabis vape products, as well as to the timing of this testing. Inhaled metals are rapidly absorbed through the respiratory tract and can be further transported to other organs. In the present study, a large number of cannabis vape liquids contained Ni and Pb significantly above the established tolerance limits. Lungs are particularly susceptible to Ni toxicity, which adverse effects can range from lung inflammatory changes to induced rhinitis and sinusitis or allergic dermatitis.^{27,28} Similarly, only low exposure to inhaled Pb can result in an increased risk of cardiovascular and kidney diseases.^{29,30} Inhalation of Cr and Cu can lead to reduced lung function, increased risk of asthma, respiratory irritation, or chest pain.²⁷ However, the reported presence of nanosized metal particles in the aerosol is also significant. Ultrafine particles can penetrate deeper into the alveolar region than larger particles.³¹ They are also both more reactive and

absorbed more rapidly within the body and thus could be potentially more hazardous. This has been shown in studies on rodents, where exposure to nano Ni-oxide particles caused greater inflammatory lesions in lungs than equivalent exposure to micro Ni-oxide particles.³² Furthermore, short-term exposure to nano Ni caused acute lung inflammation, whereas a long-term exposure lead to chronic lung inflammation and fibrosis.³³ Similarly, CoCr and Cr-oxide nanoparticles caused damage to cultured cells' DNA,³⁴ and inhalation of Cu nanoparticles resulted in pulmonary inflammation in pregnant mice and triggered an immunomodulatory effect in offspring.³⁵ *In vivo* studies have also shown that inhaled nanoparticles can be transported to other organs, where they can cause damage to the liver, kidney, heart, and brain.^{36,37}

Legal cannabis vape products do not typically provide any information on their packaging about the type of heating element and metal parts used, and illegal products may not even have outer packaging, making it extremely difficult to identify the composition of metal components of the device without additional analysis. Several published papers report detailed lists of identified parts after the scrupulous dismantling of different vape devices;^{11,26,38} however, with the increasingly large number of new designs on the market, it is difficult to keep up with component changes. Due to the lack of information on the metal composition of the atomizers, it is also impossible to assess which devices may be safer for the consumer. A recently published metal analysis of aerosols from 50 nicotine vaping devices identified only five devices for which metal concentrations were above the limit of detection for the methods used.³⁹ Although the authors did not have information about the components in the atomizers, the devices resembled ceramic cell cartridge technology. In this type of vaping device, the metal wire of the heating element is replaced by a ceramic heating element, which has a larger surface area and is more suitable for aerosolization of viscous liquids such as cannabis vaping products. The reported results are encouraging with respect to limiting consumers' exposure to toxic metals; however, more research on devices using ceramic heating elements is needed.³⁹

Previous studies showed that significant contamination of nicotine vape liquids occurs when the coil is heated to temperatures between 150 and 250 °C under normal operating conditions.^{9,22} Vaporization of cannabis vape liquids requires a slightly higher temperature range (200–350 °C). However, a recent study showed that in vaping pens with variable temperature and voltage setting, coils can reach a temperature above 600 °C when the tank is sufficiently filled,⁴⁰ which may increase even higher when the amount of the vape liquid is low. This means that under standard operating conditions the vaping devices can (i) induce volatilization of dissolved metals and/or fine metallic particles and (ii) compromise the durability of metal components, which are not designed to be exposed to such high temperatures. Another interesting observation is the correlation between metal contamination and coil change frequency in nondisposable products. Higher metal concentrations were found in the vape liquid and aerosol produced by devices with coils that were changed more than twice a month.⁹ Usually, coil replacement is necessary when the metal wire is coated by a vape liquid residue, which alters the taste of the vaped aerosol. It seems that the coating of the coil over time may in fact reduce the leaching of metals into the vape liquid. Additional research could be focused on the development of coil coating materials, which could serve as a

barrier between metal parts and the vape liquids and reduce leaching of metals from that particular component of the device.

CONCLUSIONS

While it is true that compared to smoking, vaping reduces the exposure of the user to several toxicants and carcinogens such as polycyclic aromatic hydrocarbons, volatiles, and nitrosamines, there is ample evidence of exposure to metals in vape aerosols. The presented data from legally purchased and illegal cannabis vape devices showed mass fractions of Pb above the currently established tolerance limits in several of the vape liquids analyzed, particularly in the illegal samples where Pb concentrations were up to 100 times higher than the limit. Additionally, the measured mass fractions of toxic metals such as Cr, Cu, Ni, and Co, as well as the essential metals Zn and Mn that have known inhalation toxicity, add to the existing evidence that long-term vaping may carry risks to health. More importantly, the use of imaging techniques SEM/EDS and LA-ICP-MS confirmed the presence of metal particles in studied samples. Previous studies suggested that metal particles may be released from the metal coils during the heating cycles to generate aerosols; however, our data showed that metal particles are present in the cannabis vape liquids at the point of purchase, before their actual use. The origin of these particles is unknown.

Further research studies of vape devices are necessary to better understand the composition of the metal parts of the devices as well as other factors that promote leaching of metals into the liquids (e.g., storage temperature, pH). Given the analytical challenges encountered in the present study, further method development is needed for particle detection by SEM-EDS and LA-ICP-MS. While these techniques provided pertinent information about the identification and distribution of metal particles, their full potential could not be utilized due to the physical properties of cannabis vape liquids. Making more information about the metal components of vape device available along with the filling date of the vape device can help support and inform additional research studies and risk assessments. Development of standards for vaping device construction and the materials used could also be considered by standard development organizations to reduce the risks of metals leaching into the vaping liquids.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.2c03797>.

Tables of mass fractions and their RSD for legal and illegal cannabis vape liquids, picture of cannabis vape liquid from two devices, LA-ICP-MS images, and microscopic image of cannabis vape liquids (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

M.J.T. would like to acknowledge Jeff Fraser, Oltion Kodra, and David Kingston for their valuable discussions and inputs in the SEM analysis. Ontario Provincial Police is acknowledged for providing illegal cannabis vape liquid samples.

REFERENCES

- (1) Shiplo, S.; Asbridge, M.; Leatherdale, S. T.; Hammond, D. Medical cannabis use in Canada: vapourization and modes of delivery. *Harm Reduct. J.* **2016**, *13*, No. 30.
- (2) Chadi, N.; Minato, C.; Stanwick, R. Cannabis vaping: Understanding the health risks of a rapidly emerging trend. *Paediatr. Child Health* **2020**, *25*, S16–S20.
- (3) Lynch, J.; Lorenz, L.; Brueggemeyer, J. L.; Lanzarotta, A.; Falconer, T. M.; Wilson, R. A. Simultaneous Temperature Measurements and Aerosol Collection During Vaping for the Analysis of Δ^9 -Tetrahydrocannabinol and Vitamin E Acetate Mixtures in Ceramic Coil Style Cartridges. *Front. Chem.* **2021**, *9*, No. 734793.
- (4) Gray, N.; Halstead, M.; Gonzalez-Jimenez, N.; Valentin-Blasini, L.; Watson, C.; Pappas, R. S. Analysis of toxic metals in liquid from electronic cigarettes. *Int. J. Environ. Res. Public Health* **2019**, *16*, No. 4450.
- (5) Food and Drugs Act (R.S.C., 1985, c. F-27), 1985.
- (6) EFSA. Scientific opinion on the risk for public health related to the presence of mercury and methylmercury in food. *EFSA J.* **2012**, *10*, No. 2985.
- (7) Khan, A. G. Promises and potential of in situ nanophytoremediation strategy to mycorrhizo-remediate heavy metal

- contaminated soils using non-food bioenergy crops (*Vetiver zizanioides* & *Cannabis sativa*). *Int. J. Phytorem.* **2020**, *22*, 900–915.
- (8) Kubachka, K. M.; Wilson, R. A. Elemental Analysis of Tetrahydrocannabinol and Nicotine E-Liquids Related to EVALI. *ACS Omega* **2021**, *6*, 32090–32100.
- (9) Olmedo, P.; Goessler, W.; Tanda, S.; Grau-Perez, M.; Jarmul, S.; Aherrera, A.; Chen, R.; Hilpert, M.; Cohen, J. E.; Navas-Acien, A.; Rule, A. M. Metal concentrations in e-cigarette liquid and aerosol samples: the contribution of metallic coils. *Environ. Health Perspect.* **2018**, *126*, No. 027010.
- (10) Pappas, R. S.; Gray, N.; Halstead, M.; Valentin-Blasini, L.; Watson, C. Toxic metal-containing particles in aerosols from pod-type electronic cigarettes. *J. Anal. Toxicol.* **2021**, *45*, 337–347.
- (11) Wagner, J.; Chen, W.; Vrdoljak, G. Vaping cartridge heating element compositions and evidence of high temperatures. *PLoS One* **2020**, *15*, No. e0240613.
- (12) Pappas, R. S. Toxic elements in tobacco and in cigarette smoke: inflammation and sensitization. *Metallomics* **2011**, *3*, 1181–1198.
- (13) Kelleher, P.; Pacheco, K.; Newman, L. S. Inorganic dust pneumonias: the metal-related parenchymal disorders. *Environ. Health Perspect.* **2000**, *108*, 685–696.
- (14) Yang, L.; Willie, S.; Grinberg, P.; Pihillagawa Gedara, I.; Clancy, V.; Maxwell, P.; McRae, G.; Meija, J.; Mester, Z. *DOLT-5: Dogfish Liver Certified Reference Material for Trace Metals and Other Constituents*; National Research Council of Canada, 2014.
- (15) Willie, S.; Pihillagawa Gedara, I.; Maxwell, P.; Meija, J.; Mester, Z.; Yang, L. *Lobster Hepatopancreas Reference Material for Trace Metals*; National Research Council of Canada, 2013.
- (16) Grinberg, P.; D'Ulivo, L.; Nadeau, K.; Pihillagawa, I. G.; Mihai, O.; LeBlanc, K. L.; Yang, L.; Meija, J.; Mester, Z. Development of low and elevated level multivitamin and mineral supplement certified reference materials: VITA-1 and VITB-1. *Accredit. Qual. Assur.* **2020**, *25*, 201–220.
- (17) Lawley, C. J.; Petts, D. C.; Jackson, S. E.; Zagorevski, A.; Pearson, D. G.; Kjarsgaard, B. A.; Savard, D.; Tschirhart, V. Precious metal mobility during serpentinization and breakdown of base metal sulphide. *Lithos* **2020**, *354–355*, No. 105278.
- (18) Kane, J. S. A history of the development and certification of NIST glass SRMs 610-617. *Geostand. Geoanal. Res.* **1998**, *22*, 7–13.
- (19) Paton, C.; Hellstrom, J.; Paul, B.; Woodhead, J.; Hergt, J. Iolite: Freeware for the visualisation and processing of mass spectrometric data. *J. Anal. At. Spectrom.* **2011**, *26*, 2508–2518.
- (20) Guillong, M.; Hametner, K.; Reusser, E.; Wilson, S. A.; Günther, D. Preliminary characterisation of new glass reference materials (GSA-1G, GSC-1G, GSD-1G and GSE-1G) by laser ablation-inductively coupled plasma-mass spectrometry using 193 nm, 213 nm and 266 nm wavelengths. *Geostand. Geoanal. Res.* **2005**, *29*, 315–331.
- (21) Jochum, K. P.; Nohl, U.; Herwig, K.; Lammel, E.; Stoll, B.; Hofmann, A. W. GeoReM: a new geochemical database for reference materials and isotopic standards. *Geostand. Geoanal. Res.* **2005**, *29*, 333–338.
- (22) Gray, N.; Halstead, M.; Valentin-Blasini, L.; Watson, C.; Pappas, R. S. Toxic Metals in Liquid and Aerosol from Pod-Type Electronic Cigarettes. *J. Anal. Toxicol.* **2022**, *46*, 69–75.
- (23) Medana, C.; Baiocchi, C.; Dal Bello, F.; Aigotti, R.; Sala, C.; Santoro, V.; Gastaldi, D. Analysis of Nicotine Alkaloids and Impurities in Liquids for e-Cigarettes by LC-MS, GC-MS, and ICP-MS. *Curr. Trends Mass Spectrom.* **2016**, 20–28.
- (24) McDaniel, C.; Mallampati, S. R.; Wise, A. Metals in cannabis vaporizer aerosols: sources, possible mechanisms, and exposure profiles. *Chem. Res. Toxicol.* **2021**, *34*, 2331–2342.
- (25) Beauval, N.; Howsam, M.; Antherieu, S.; Allorge, D.; Soyec, M.; Garcon, G.; Goossens, J.-F.; Lo-Guidice, J.-M.; Garat, A. Trace elements in e-liquids-development and validation of an ICP-MS method for the analysis of electronic cigarette refills. *Regul. Toxicol. Pharmacol.* **2016**, *79*, 144–148.
- (26) Williams, M.; Villarreal, A.; Bozhilov, K.; Lin, S.; Talbot, P. Metal and silicate particles including nanoparticles are present in electronic cigarette cartomizer fluid and aerosol. *PLoS One* **2013**, *8*, No. e57987.
- (27) Nordberg, G. F.; Fowler, B. A.; Nordberg, M. *Handbook on the Toxicology of Metals*; Academic Press, 2014.
- (28) Maridet, C.; Atge, B.; Amici, J. M.; Taïeb, A.; Milpied, B. The electronic cigarette: the new source of nickel contact allergy of the 21st century? *Contact Dermatitis* **2015**, *73*, 49–50.
- (29) Lin, J.-L.; Lin-Tan, D.-T.; Li, Y.-J.; Chen, K.-H.; Huang, Y.-L. Low-level environmental exposure to lead and progressive chronic kidney diseases. *Am. J. Med.* **2006**, *119*, 707.e1–707.e9.
- (30) Navas-Acien, A.; Guallar, E.; Silbergeld, E. K.; Rothenberg, S. J. Lead exposure and cardiovascular disease—a systematic review. *Environ. Health Perspect.* **2007**, *115*, 472–482.
- (31) Carvalho, T. C.; Peters, J. I.; Williams, R. O., III Influence of particle size on regional lung deposition—what evidence is there? *Int. J. Pharm.* **2011**, *406*, 1–10.
- (32) Chang, X.; Zhu, A.; Liu, F.; Zou, L.; Su, L.; Liu, S.; Zhou, H.; Sun, Y.; Han, A.; Sun, Y.; et al. Nickel oxide nanoparticles induced pulmonary fibrosis via TGF- β 1 activation in rats. *Hum. Exp. Toxicol.* **2017**, *36*, 802–812.
- (33) Mo, Y.; Jiang, M.; Zhang, Y.; Wan, R.; Li, J.; Zhong, C.-J.; Li, H.; Tang, S.; Zhang, Q. Comparative mouse lung injury by nickel nanoparticles with differential surface modification. *J. Nanobiotechnol.* **2019**, *17*, No. 2.
- (34) Bhabra, G.; Sood, A.; Fisher, B.; Cartwright, L.; Saunders, M.; Evans, W. H.; Surprenant, A.; Lopez-Castejon, G.; Mann, S.; Davis, S. A.; et al. Nanoparticles can cause DNA damage across a cellular barrier. *Nat. Nanotechnol.* **2009**, *4*, 876–883.
- (35) Adamcakova-Dodd, A.; Monick, M. M.; Powers, L. S.; Gibson-Corley, K. N.; Thorne, P. S. Effects of prenatal inhalation exposure to copper nanoparticles on murine dams and offspring. *Part. Fibre Toxicol.* **2015**, *12*, No. 30.
- (36) Takenaka, S.; Karg, E.; Roth, C.; Schulz, H.; Ziesenis, A.; Heinzmann, U.; Schramel, P.; Heyder, J. Pulmonary and systemic distribution of inhaled ultrafine silver particles in rats. *Environ. Health Perspect.* **2001**, *109*, 547–551.
- (37) Terzano, C.; Di Stefano, F.; Conti, V.; Graziani, E.; Petroianni, A. Air pollution ultrafine particles: toxicity beyond the lung. *Eur. Rev. Med. Pharmacol. Sci.* **2010**, *14*, 809–821.
- (38) Williams, M.; Bozhilov, K.; Ghai, S.; Talbot, P. Elements including metals in the atomizer and aerosol of disposable electronic cigarettes and electronic hookahs. *PLoS One* **2017**, *12*, No. e0175430.
- (39) Gonzalez-Jimenez, N.; Gray, N.; Pappas, R. S.; Halstead, M.; Lewis, E.; Valentin-Blasini, L.; Watson, C.; Blount, B. Analysis of Toxic Metals in Aerosols from Devices Associated with Electronic Cigarette, or Vaping, Product Use Associated Lung Injury. *Toxics* **2021**, *9*, No. 240.
- (40) Oar, M. A.; Savage, C. H.; Rufer, E. S.; Rucker, R. P.; Guzman, J. A. Thermography of cannabis extract vaporization cartridge heating coils in temperature- and voltage-controlled systems during a simulated human puff. *PLoS One* **2022**, *17*, No. e0262265.