Chemical Research in Toxicology

pubs.acs.org/crt

Article

Examining Metal Contents in Primary and Secondhand Aerosols Released by Electronic Cigarettes

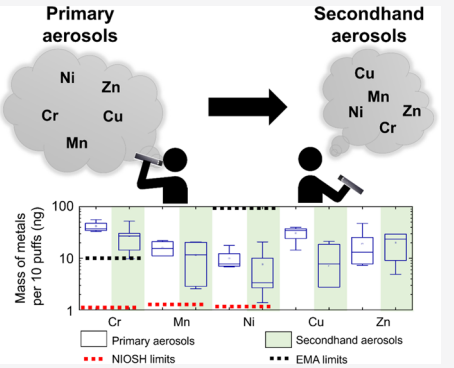
Kashala Fabrice Kapiamba, Weixing Hao, Stephen Adom, Wenyan Liu, Yue-Wern Huang, and Yang Wang*

Cite This: *Chem. Res. Toxicol.* 2022, 35, 954−962

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: The usage of electronic cigarettes (ECs) has surged since their invention two decades ago. However, to date, the health effects of EC aerosol exposure are still not well understood because of insufficient data on the chemical composition of EC aerosols and the corresponding evidence of health risks upon exposure. Herein, we quantified the metals in primary and secondhand aerosols generated by three brands of ECs. By combining aerosol filter sampling and inductively coupled plasma mass spectrometry (ICP-MS), we assessed the mass of metals as a function of EC flavoring, nicotine concentration, device power, puff duration, and aging of the devices. The masses of Cr, Cu, Mn, Ni, Cu, and Zn were consistently high across all brands in the primary and secondhand aerosols, some of which were above the regulated maximum daily intake amount, especially for Cr and Ni with mass (nanograms per 10 puffs) emitted at 117 ± 54 and 50 ± 24 (JUUL), 125 ± 77 and 219 ± 203 (VOOPOO), and 33 ± 10 and 27 ± 2 (Vapor4Life). Our analysis indicates that the metals are predominantly released from the EC liquid, potentially through mechanisms such as bubble bursting or the vaporization of metal−organic compounds. High metal contents were also observed in simulated secondhand aerosols, generally 80−90% of those in primary aerosols. Our findings provide a more detailed understanding of the metal emission characteristics of EC for assessing its health effects and policymaking.



1. INTRODUCTION

The usage of electronic cigarettes (ECs) has been on the rise since their introduction two decades ago. Initially designed to transition tobacco cigarette (TC) quitters, they are believed to have the benefits of reduced toxicants and elimination of secondhand aerosols.[1,2] The aerosols in EC are generated by vaporizing a liquid (EC liquid) containing propylene glycerol (PG) and vegetable glycerin (VG), nicotine, and flavoring agents.[2] Currently, manufacturers of more than 400 identified EC brands claim that EC is a healthier alternative to conventional TCs.[2,3] However, chemical characterization of EC aerosols and EC liquids has revealed relatively high concentrations of nicotine, flavoring chemicals, and organic byproducts, which may lead to health complications in cases of excessive and extended use.[4,5] Moreover, transition and heavy metals, such as As, Cr, Ni, Cu, Sb, Sn, and Zn, were detected in the EC liquids and aerosols.[6,7] These metals can cause oxidative stress leading to various pulmonary and cardiovascular diseases.[8−10]

The metallic species in EC aerosols may have resulted from their working mechanism, which uses excessively heated metal filaments to vaporize the EC liquid. These filaments are generally made of kanthal or nichrome, meaning that metals such as Ag, Al, Cr, Cu, Fe, Ni, and Zn can be expected in EC aerosols. These metals were further observed using scanning electron microscopy (SEM) and energy-dispersive X-ray (EDX) characterization across the atomizers of all ECs investigated.[11] In a study, Zervas et al.[12] observed that the metals in the heated filaments were first transferred into the EC liquid and then into the aerosols. The transfer rate depends on the airflow, nicotine concentration, EC liquid composition, and EC liquid temperature. Furthermore, the smooth surface of the metal filaments showed drastic decay and fissures even within 150 puffs of usage,[13] suggesting that the metal contents in EC liquids can change significantly over time. Considering that metal ions, oxides, and nanoparticles are nonvolatile, it is possible that these species form metal−organic compounds in the EC liquid or they are generated from the bubble fragmentation of the EC liquid.[14] If the transfer of metals into aerosols occurs through the vaporization of the EC liquid, then a change of the metal contents in the EC liquid would result in the variation of the metals detected in the aerosol samples. In an analysis of 56 used EC devices, the correlations

Received: November 30, 2021
Published: April 6, 2022

of metals (Al, Cr, Fe, Mn, Ni, Pb, Sb, Sn, and Zn) between the aerosol samples and tank samples were statistically significant but not for Cd and Cu.[15] One study pointed out that the leaching of metals into the EC liquid may even occur before vaping because of the acidity of some liquids.[16] But the correlation between EC liquid pH (high 6.79 and low 4.02) and metals emitted was not observed,[6] suggesting the possibility of other metal-transfer mechanisms.

Metals may also be directly aerosolized from the surface of the metal filaments owing to their excessive heating, which can reach as high as 1000 °C.[17,18] This finding is supported by operating the EC without the liquid (dry puff).[19] In fact, in gas-phase nanoparticle synthesis, researchers have been using "glowing wire generators" to produce ultrafine metal and metal oxide nanoparticles using a mechanism similar to that of an EC.[20−22] However, for this mechanism, the formation of metal particles was speculated to occur only at the beginning of the EC operation because the real-time size distribution measurements of EC aerosols showed the intense formation of 20 nm aerosols during the first second of the EC puff.[19]

Given the importance of filaments in metal release, studies have also examined the aerosol metal emissions under different heating powers of ECs. The concentrations of metals (such as Cr, Cu, Ni, and Zn) increased by 7−631 times when the power of the filament was increased from 20 to 40 W.[23] The influence of heating power on the EC aerosol properties was also reflected in the aerosol size distributions, where a higher heating power led to larger particles generated for all tested filaments.[24] However, there is still no consensus on how the metal is released into the gas phase, partly because of the limited number of studies examining the mechanism of particle formation in EC operation. Moreover, aerosol sampling techniques also influence the determination of the metal content. Technically, sampling aerosols with filters would guarantee a high collection efficiency across a wide range of aerosol sizes,[25,26] one of the optimal methods for trapping particles. But many of the previous studies use the "bubble-through" method and direct collection approaches, including a novel trap method,[27−31] which involved passing aerosols through an acidic solution; this may be unreliable for inorganic trace analytes in aerosols.

To understand the mechanisms of metal emission and potentially optimize EC designs that minimize such emissions, we conducted a systematic study examining metal release under a wide range of EC configurations. These configurations include power setting, puff duration, EC liquid flavoring and nicotine content, and device aging. If the metals are predominantly released from the EC liquid, the liquid's thermal properties (or compositions) and the device aging (building up of the metal residual) would play a significant role in determining the metal contents. In addition, the metal content would also positively correlate with puff duration, considering that metal release from the EC liquid is a continuous process. However, if metals were directly released from the surface of the heating filament, the metal contents would be dominated by those released at the beginning of the puff, and thus, the metal contents would not depend on puff duration. To estimate the potential environmental impact of metal release from EC usage, we also quantified the metal contents in secondhand EC aerosols using the simulated respiratory system recently developed by our research group and compared those to the primary EC aerosols. The results of this study provide a better understanding of metal emission mechanisms, quantification, and potential toxicological effects of the usage of EC.

2. MATERIALS AND METHODS

2.1. EC Aerosol Sampling and Characterization. The EC aerosols examined in this study included primary aerosols directly generated from EC devices and secondhand aerosols generated from a simulated respiratory system. The primary aerosols were collected using a 37 mm Teflon filter with a 0.3 μm pore size (SKC Ltd., Eighty Four, PA) housed in a filter cassette (Zefon International Ocala, FL) by pulling the airflow through the EC devices. Before the experiments, Teflon filters were soaked overnight in 67−70% nitric acid (Sigma-Aldrich Inc., St. Louis, MO) to remove the pre-existing metal contents. With this pre-treatment method, the metal content in the Teflon filters was below the method limit of detection (MLD). During EC aerosol sampling, the airflow through the Teflon filter was controlled by a mass flow controller (Pneucleus Technologies LLC, Hollis, NH) programmed in LabVIEW to withdraw flow according to the puff profile elaborated in Section 2.3. The secondhand EC aerosols were generated by installing a simulated respiratory system, which mimics the hygroscopic growth and deposition of particles in human lungs,[32] between the EC devices and the Teflon filter. The simulated respiratory system is composed of an array of filter media that yields similar particle deposition efficiencies in the human extrathoracic, tracheobronchial, and alveolar regions under an RH of 90%.[32] The Teflon filters collected the aerosols generated by the simulated respiratory system with a puff profile similar to that of primary EC aerosols.

Thirty puffs of aerosols were collected from both the primary and secondhand EC aerosols. We note that membrane filters may exhibit a flow resistance during aerosol sampling, which may affect the aerosol flow rate. However, according to the reading from the mass flow controllers used in this study, there was no significant flow rate variation. The flow resistance through the filter was below 6 kPa throughout the sample collection of 30 puffs (Figure S1). This is potentially because we used a strong vacuum source and a low targeted flow rate.

2.2. Metal Content Characterization Using ICP-MS. Metals collected on the Teflon filter were digested in 70% nitric acid (Sigma-Aldrich Inc., St. Louis, MO) following the digestion procedure outlined in the Environmental Protection Agency protocol 3050 B.[33] After sample collection, the metal concentrations were quantified using ICP-MS (NexION 350 ICP-MS, PerkinElmer, Waltham, MA). First, we fully optimized the instrument's torch position and ion lenses. Then, a short-term stability test was performed in a standard mode using a 1 μg/L tuning solution to maximize the ion signal and stability. The optimization parameters for the ICP-MS are presented in Table S1.

A certified trace metal quality control standard (QCI-034-1, NSI Lab Solutions, Raleigh, NC) was used as a control for all cation analyses performed in this study. We determined the linearity of the calibration curve by analyzing the standards with six different concentrations (0.1, 0.5, 1, 5, 10, 100, 250 μg/L) five times. The coefficient of determination was 0.996 or higher, and the recovery of each standard level of all analytes ranged from 97.8 to 107.8%. We calculated the method limit of detection (LOD) and defined the limit of quantitation (LOQ) using eqs 1 and 2, respectively.[34,35]

$$\mathrm{LOD} = 3.3 \times \mathrm{SDs} \quad (1)$$

$$\mathrm{LOQ} = 3 \times \mathrm{LOD} \quad (2)$$

where SD is the standard deviation of 10 replicates of blank samples. The blank samples were prepared by digesting unexposed filters as stated in Section 2.1 for actual samples. LOD and LOQ values for metals are expressed in ng per 10 puffs. To ensure the elimination of the high background signal for Zn, we washed the sampler and skimmer cones after a couple of runs, changed the peristaltic pump and autosample tubes, and left the ICP-MS under high-pressure vacuum overnight. All ICP-MS method parameters are tabulated in the Supporting Information (Table S2).

https://doi.org/10.1021/acs.chemrestox.1c00411
Chem. Res. Toxicol. 2022, 35, 954−962

Table 1. Experimental Plan of the Study[a]

task	studied parameter	EC device	EC flavoring	nicotine (mg/mL)	EC power (W)	puff duration (s)	aging effect (puffs)
1	EC device	JUUL, VOOPOO, Vapor4Life	none	0 or default	default	2	0−400
2	EC flavoring	JUUL	menthol classic tobacco Virginia tobacco	0	default	2	0−400
3	nicotine	VOOPOO	none	0, 3, 4.5, 6	default	2	0−400
4	EC power	VOOPOO	none	0	5, 25, 45	2	0−400
5	puff duration	JUUL, VOOPOO	none	0	default	2, 4, 6	0−400
6	aging effect	VOOPOO, Vapor4Life	none	0	default	2	0−400, 400−800, 800−1200
7	secondhand aerosol	JUUL, VOOPOO, Vapor4Life	none	0	default	2	0−400

[a]The default EC power for the VOOPOO, which is a mod system, is 25 W. The JUUL and Vapor4Life devices are pod systems designed with fixed default power settings of over 7 and 10 W, respectively.

2.3. Experimental Plan. Three available EC brands, JUUL (JUUL pods, JUUL Labs), Vapor4Life (XL pen EC, AUTO VAPOR ZEUS KIT, Vapor4Life, Inc.), and VOOPOO (Drag X, Shenzhen Woody Vapes Technology Co., China), were purchased in 2019 and used in this study. The JUUL and Vapor4Life ECs are pod (closed) systems, and VOOPOO EC belongs to the mod (open) system. No specific criteria were employed to choose the brands, although it is worth mentioning that these devices are the most popular among young adolescents, according to a local vape shop. The JUUL (battery and prefilled pod) EC was a rechargeable system that uses a disposable pod that contained 0.7 mL of the EC liquid. The pod could be easily switched, and the device was puff-actuated. Three flavorings of pods, menthol (MT), classic tobacco (CT), and Virginia tobacco (VT), were used for the JUUL EC. The automated Vapor4Life EC comprises a battery (5-V, 900 mAh) and a smileomizer. VOOPOO EC could deliver power between 5 and 60 W and possessed an EC liquid capacity of 4.5 mL. Finally, for comparison with the EC aerosols, the Kentucky 1R6F reference cigarette (Tobacco Research Institute, University of Kentucky, Lexington, KY) was used as a representative of conventional TC.

Thirty puffs of aerosols were collected from EC devices. Several puff profiles for generating the EC aerosols have been reported in the literature. To mention a few, a more recent standard ISO 20768(2018) has been established to define the specific requirement for laboratory smoking machines for aerosol sampling. The main parameters include the pressure drop through the device not exceeding 1000 Pa, for a 3 s puff every 30 s, with a flow rate of 1.09 liter per minute (lpm), all for a puff volume of 55 mL. The standard puff profile for TC aerosol measurements (ISO 3308:2000) uses a puff duration of 2 s, puff volume of 35 mL, and 60 s puff interval.[36] In this study, we used the TC puff flow rate for the EC aerosol sampling. The square-wave puff profile, 2 s puff duration, and 35 mL puff volume can be translated to a puff flow rate of 1.05 lpm. A square-wave puff profile was used because of its ease of control, and the reading of the mass flow controller confirmed that the flow profile is close to a square wave. By integrating the flow reading (Figure S1a), we calculated that the volumes withdrawn from the mass flow controller are 34.2 and 32.4 mL for the 1st and 30th puffs, which have a 2.4 and 7.5% deviation from the targeted puff volume (35 mL). The more significant deviation from the targeted puff volume is due to the increased flow resistance (Figure S1b). Since the puff volume gradually changed from 34.2 to 32.4 mL, we expect that this would result in a 5.0% lower mass of particle collection on the filter over the sampling of 30 puffs. A recent study showed that although the square-wave puff profile may give slightly higher measured aerosol yields, the difference from a bell-shaped puff profile is statistically insignificant.[37] During the measurement of 30 puffs, the pressure drop across the EC devices never exceeded 20 Pa.

Puff topography studies showed that the mean puff durations of EC users range from 1.8 ± 0.9 to 4.16 ± 1.06 s.[38,39] To examine the effect of metal contents on puff duration, we maintained the puff flow rate while keeping the puff duration at 2, 4, and 6 s. To study the effect of aging on metal contents, we used the VOOPOO EC, which contains a digital counter, to record the number of puffs generated by the device since its purchase. EC aerosols generated between the cumulative puff count (number of puffs generated since the first use) 0 and 400, 400 and 800, and 800 and 1200 puffs were collected and analyzed. Table 1 summarizes the experimental plan of this study, which focuses on examining the effects of EC devices, flavorings, nicotine content, power, puff duration, and aging on the metal contents in EC aerosols. Using the simulated respiratory system, we also studied the metal content of the secondhand EC aerosols. Each test was repeated at least four times. The following metals were measured: As, Sn, Fe, Ba, Na, Mg, Al, K, Ca, Pb, Cr, Mn, Ni, Cu, and Zn. The concentrations of some metals were very low (close to or below the detection limits in most cases); therefore, for the rest of this paper, we focused on the last five metals listed above, which were consistently higher in all sampled EC aerosols.

When reporting the metal contents in EC aerosols, we normalized the metal contents to the mass of metals per 10 puffs ($m_{10,i}$, where i stands for the ith metal). To evaluate the potential health effects of these metals, the standard daily inhalation mass limits established by the National Institute for Occupational Safety and Health (NIOSH) were converted into the mass concentration of metals per 10 puffs using the following equation:

$$m_{L,i} = 10\, V_{puff}\, C_i \quad (3)$$

where V_{puff} is the inhaled volume of air per puff, assumed here as the tidal volume (~450 mL), and C_i (mg/m^3) is the regulated maximum limit for the specific metal. The NIOSH established inhalation exposure daily limits for adult workers in the Toxic Substances and Disease Registry, and the limits for Cr and Mn are 0.0001 mg/m^3 and 0.3 μg/m^3, respectively.[40] The NIOSH legal airborne permissible exposure limit (PEL) is 5 mg/m^3 for Zn and 1 mg/m^3 for Cu over an 8 h shift. Then, $m_{10,i}$ and $m_{L,i}$ were compared to examine the potential health effects of the metals. In addition, we considered the minimum risk levels for inhalable Cr (10 ng/day) and Ni (100 ng/day), established by the European Medicines Agency (EMA), and these values are directly compared against $m_{10,i}$. Note that our normalized calculations of the exposure limits were based on the assumption that an adult smoker vapes 100 puffs per day. However, according to a large EC usage monitoring study, an average of 163 puffs per day with a maximum of 235 puffs per day has been reported.[41−43] So, the potential exposure of metal to ENDS smokers and bystanders will be even higher.

2.4. Statistical Analysis. Box plots are used to show the metal content distributions from the ECs. We also showed metal contents associated with nicotine concentration in the EC liquid, flavoring, power, aging, and so on. Statistical significance among groups was assessed based on the Kruskal−Wallis H test followed by Dunn's test;

https://doi.org/10.1021/acs.chemrestox.1c00411
Chem. Res. Toxicol. 2022, 35, 954−962

in all cases, the p-value was set at 0.1. All statistical analyses were performed using the Origin 2021b software package (OriginLab Corporation, MA).

3. RESULTS AND DISCUSSION

3.1. Variability of Metal Contents in Aerosols Generated from Different EC Devices. The concentrations of five metals (Cr, Mn, Cu, Ni, and Zn) were consistently higher in all EC aerosols across all brands. The masses of metals per 10 puffs for all tested brands are shown in Figure 1.

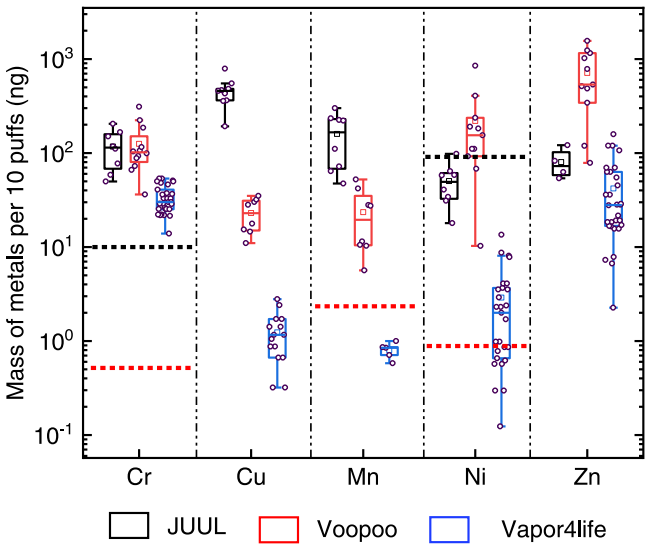


Figure 1. Metal contents measured across different brands of EC devices operated under default conditions. Black and red dashed lines show the normalized maximum regulated intake amount based on the European Medicines Agency (EMA) and NIOSH standards, respectively. Exposure limits of Cu and Zn are higher than the upper limit of the y-axis.

The Vapor4life brand had the lowest average mass of all five metals emitted. The significant ($p < 0.05$) difference in the average metal masses emitted by the Vapor4life brand was between 2 or 3 orders of magnitude compared to the JUUL and VOOPOO brands. For instance, the average mass of Cu and Ni per 10 puffs was 1.3 ± 0.7 and 2.9 ± 3.2 ng for Vapor4life compared to 22.99 ± 9.3 and 240.1 ± 234.9 ng for VOOPOO and 454.5 ± 162.2 and 50.3 ± 24.9 ng for the JUUL, respectively. Moreover, Mn, Ni, and Zn concentrations were significantly higher in JUUL than in VOOPOO ($p < 0.1$). In general, the mod systems were found to generate more metals than pod systems due to the higher heating power of the metal filaments.[29] The difference between JUUL and Vapor4life is likely due to the difference in the filament materials. In a detailed analysis, Omaiye et al.[44] analyzed the anatomy of up to six different popular ECs and revealed that the filaments were mostly made of Elinvar (Ni, Fe, and Cr) (36.4%), nichrome (36.4%), Fe−Cr (18.2%), and Ni (9%). Owing to these varieties, it was not surprising to observe a vast difference in metal concentrations between the pod devices.

It is noteworthy that the metal contents within the same group (sampling conditions) of EC devices also have relatively wide variations. This phenomenon was also observed in a few other studies, as indicated in Table S3. This is likely due to uncertainties in the particle sampling loss. A large fraction of the EC aerosols remained in the liquid form (droplets),[45−47] and we noticed that the EC liquid also built up in the sampling system. Because we avoided sharp turns in the sampling tube to avoid particle loss via impaction, droplet deposition is likely due to gravitational settling. Given the large size of these settled droplets, they may represent a significant fraction of the total aerosol mass. Therefore, the metal contents reported in this study represent the lower limits of actual metal emissions from ECs.

Cr(VI) and Ni detected in EC aerosols appear on the FDA's "harmful and potentially harmful chemicals" list and belong to Group 1 in the International Agency for Research on Cancer (IARC), which is "carcinogenic to humans."[48] Both Cr and its oxides have been found to damage cultured cells.[49] Long-term inhalation of NiO particles in mice has been found to cause oxidative stress and inflammation in the human lung and cardiac tissues.[50,51] As shown in Figure 1, it is evident that the metals contained in the EC aerosols are higher than the regulated limits (NIOSH and EMA) for Cr across all tested brands. It is worth mentioning that Cr(III), which is not carcinogenic, is the likely Cr form in aerosols containing

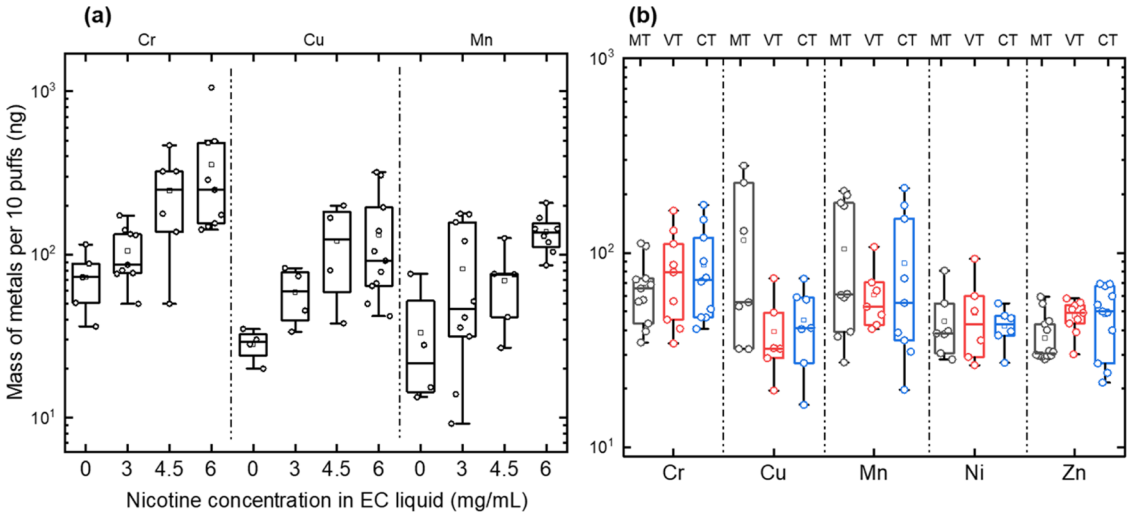


Figure 2. Effects of nicotine concentration (a) and flavorings (b) on metal emissions. Flavorings of menthol (MT), Virginia tobacco (VT), and classic tobacco (CT) are tested.

https://doi.org/10.1021/acs.chemrestox.1c00411
Chem. Res. Toxicol. 2022, 35, 954−962

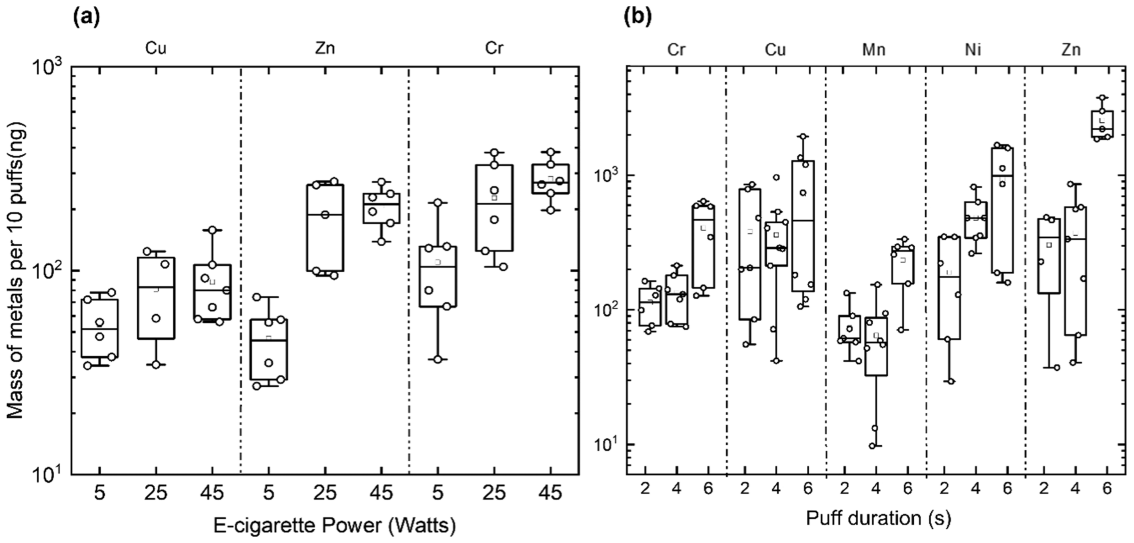


Figure 3. Effects of power setting (a) and puff duration (b) on metal emissions.

corroded metal particles. However, further studies regarding the oxidation state of the metals detected in EC aerosols need to be conducted. For Ni and Mn, only Vapor4Life EC showed lower metal emissions than the daily regulated limit. All three brands showed Cu and Zn emissions under daily maximum exposure limits. Even though high concentrations of Pb and Sn have been reported in EC liquids and aerosols,[52−54] herein, we only detected Pb and Sn in 3 out of 25 samples of VOOPOO and 5 out of 27 samples of Vapor4Life. Pb and Sn concentrations were below LOD for all of the JUUL samples. Furthermore, in the samples where these metals were detected, their contents are below 0.5 and 0.1 ng/puff for Pb and Sn, respectively, which is considerably lower than the other major metal species. Due to the measurement uncertainties, we did not report their concentrations and compared them against the regulated limits. In summary, we observed that several metals, namely, Cr, Ni, and Mn, are emitted in the form of aerosols at levels likely to pose health hazards.

3.2. Effects of Nicotine and Flavorings on Metal Contents. The EC liquid contains many additives that intend to enrich the vaping experience of users. Nicotine and flavorings are the most commonly used additives in ECs. Nicotine content varies significantly across different brands; some of which are even higher than the maximum recommended level of 20 mg/mL in many countries.[55] Appealing flavorings are always used as marketing tools to attract more users. These components change the chemical composition and thermal properties of the EC liquid, which in turn may affect the metal emissions. Figure 2 shows the variation of metals with respect to nicotine content and flavoring.

Figure 2a shows selected metal emissions as a function of nicotine concentration in the EC liquid. The general trend indicates that the average and median mass of the emitted metals increased significantly with nicotine concentration. A Kruskal−Wallis H test showed that there was a statistically significant difference in the mass of metals between EC liquid with 0 and 6 mg/mL nicotine content of Cr ($H = 9.00$, $p < 0.05$), Cu ($H = 8.25$, $p < 0.1$), and Mn ($H = 7.41$, $p < 0.1$). To illustrate, the average mass of Cr per 10 puffs of EC is 78.15 ± 33.0, 105.53 ± 40.6, 246.71 ± 152, and 325.32 ± 294.6 ng under nicotine concentrations of 0, 3, 4.5, and 6.0 mg/mL, respectively. A linear correlation between nicotine content and metal emissions, depicted in Figure S2a, illustrates a significant influence of nicotine content. A study observed that the aerosol's concentration of particles was in the range of 3.26×10^9 to 4.09×10^9 cm^{-3} for nicotine-free EC, while that was in the range of 5.08×10^9 to 5.29×10^9 cm^{-3} for high-nicotine -concentration EC, nearly the double in some cases.[56] Similarly, Talih et al.[57] showed that nicotine concentration in the aerosol was directly proportional to the total mass of particulate matter. Hence, the positive correlation between the metal and nicotine contents indicates that the metal contents were transferred from the EC liquid, which was aerosolized at a higher rate under higher nicotine content. Unlike nicotine, the mass of metals emitted was not affected by the type of flavoring used. The average and median mass of metals were within the same range, as shown in Figure 2b, and not statistically significant up to a p-value less than 0.5, illustrated by circled data, in the correlation analysis in Figure S2b. For instance, the mean masses (ng per 10 puffs) of Cr were 77.24 ± 44.2, 76.36 ± 47, and 107.84 ± 83.5 for MT, VT, and CT, respectively. A similar trend was observed for the other four metals, and all remained above the regulated limits, as shown in Figure 1.

3.3. Effects of EC Power, Puff Duration, and Device Aging on Aerosol Metal Contents. Chemical characterization of aerosols in terms of EC power and puff duration was conducted with all other parameters remaining constant (Table 1). Figure 3 shows the effects of power and puff duration on metal emissions. In general, the metal concentrations tended to increase with increasing power settings (Figure 3a). Statistical analyses showed that Cu emitted with power settings 5, 25, and 45 W were not significantly different ($H = 1.14$, $p < 0.1$). Average masses of both Zn and Cr showed significant increases from 5 to 25 W ($H = 7.50$, $p < 0.05$, and $H = 3.10$, $p < 0.1$, respectively), while only a marginal increase was observed between 25 and 45 W without notable statistical difference ($H = 0.13$, $p < 0.1$, and $H = 1.26$, $p < 0.1$, respectively). Similar observations were reported by Zhao et al.[29] for open-system devices. The increase in metal concentration with power can be attributed to a general increase in aerosol particle concentrations, which has also been shown to be temperature-dependent.[58,59] At higher powers, there is a faster increase in the filament's temperature,

https://doi.org/10.1021/acs.chemrestox.1c00411
Chem. Res. Toxicol. 2022, 35, 954−962

vaporizing a high volume of the EC liquid, thus generating a high concentration of particulates in aerosols. However, a marginal increase in metal emissions was observed when the power was increased from 25 to 45 W, suggesting that most of the power below 25 W has been used to evaporate the EC liquid. The power above 25 W setting may have caused the decomposition of the EC liquid solvent without necessarily affecting the metal emissions.[24,60] Figure 3b shows the effects of puff duration on the metals released from the EC aerosols. Briefly, it can be seen that the metal content increases with puff duration. Notably, the masses of Cr ($H = 4.59$, $p < 0.1$), Zn ($H = 8.08$, $p < 0.1$), and Mn ($H = 7.35$, $p < 0.1$) significantly increased from 4 to 6 s puff sample groups. The mass of Ni only showed a significant increase ($H = 3.69$, $p < 0.1$) from 2 s puff to 6 s puff groups, while there was no significant difference observed for Cu.

Previous studies show that metals can be directly generated from the surface of the filament at the beginning of the EC operation due to the excessive heating process.[19] This was supported by the aerosol size distribution measurements when ECs were operated under the dry puff condition, where a high concentration of 20 nm particles was observed during the first second of the EC operation. However, the overall increase in metal emissions with prolonged puffing indicates that metals are predominantly generated from aerosolized EC liquids. Otherwise, the metal contents should be independent of puff duration. Moreover, the fact that metal contents increase under higher nicotine contents (Figure 2a) also suggests that metals are mainly transferred from the liquid, as liquid properties significantly affect the metal emission. During the EC operation, we observed bubbles being generated from the bulk of the EC liquid (Figure S3). The bursting of these bubbles at the liquid−air interface could break the EC liquid film and directly aerosolize the EC liquid.[61,62] The direct vaporization of the metal−organic compounds is also probable, as these compounds generally have much higher volatility than the metal ions or oxides. However, the determination of the exact chemical composition of these compounds is beyond the scope of this study.

Note that our observation cannot completely rule out the metal generation from the surface of the heated filament. The metal nanoparticles directly emitted from the filament's surface are likely too small,[19] contributing less mass to the total metal content. However, the metal particles released from this mechanism may lead to more severe health effects due to their smaller sizes,[63] and the toxicological effects of these metal nanoparticles need to be examined.

After repetitive and prolonged use of EC, metallic components may degrade, mainly when acidic EC liquids are used, leading to higher concentrations of metals released in the aerosols. Figure 4 shows the effects of metal release on EC aging (VOOPOO). The increase in mass between cycle 1 (0−400 puffs) and cycle 3 (800−1200 puffs) for Cr ($H = 7.60$, $p < 0.1$), Cu ($H = 9.80$, $p < 0.1$), and Mn ($H = 4.80$, $p < 0.1$) are worth mentioning. The average masses (ng) per 10 puffs at, respectively, puff cycles 1 (0−400 puffs), 2 (400−800 puffs), and 3 (800−1200 puffs) of 134.43 ± 78.5, 142.4 ± 108.9, and 227.99 ± 82.14 for Cr; 31.97 ± 23.8, 70.5 ± 31.8, 129.76 ± 113.9 for Cu; and 9.89 ± 6.5, 26.31 ± 10.9 and 33.91 ± 17.7 for Mn were recorded. The increased metal contents with device aging again imply that the metals are first transferred from the filament to the EC liquid and then aerosolized from the EC liquid. The average masses of Zn and Ni did not increase with device aging, as their concentrations were within the same order of magnitude. It is likely that these metals were already aerosolized extensively during the first 400 puffs, as a study found a decrease of 39−43% of Ni in the nichrome wire after only 150 heating cycles.[18]

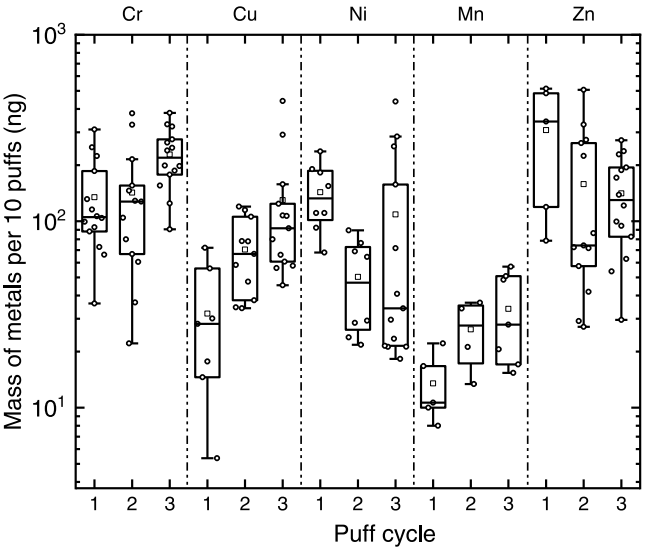


Figure 4. Effect of aging on metal emissions. Puff cycle: 1 (0−400 puffs), 2 (400−800 puffs), and 3 (800−1200 puffs).

3.4. Metal Contents in Secondhand EC Aerosols.

As EC users can generate secondhand aerosols through exhalation, the environmental and health impacts need to be evaluated. Here, we examined the metal contents in secondhand EC aerosols generated from a simulated respiratory system.[32] Figure 5 shows the masses of metals contained in the primary and secondary aerosols per 10 puffs.

Results show that secondhand aerosols from EC contain high concentrations of metals and can thus be of significant concern to bystanders. The average masses of all tested metals from secondhand aerosols were ∼80 to 90% of their corresponding primary aerosol emissions, which agrees with the respiratory deposition efficiencies of submicron aerosols.[64] Moreover, the metals contained in simulated secondhand aerosols are higher than the maximum regulated limits for Cr and Mn across all tested brands (although it was found to be relatively lower in the reference 1R6F TC). The average mass of Ni emissions is higher than the regulated limits for the JUUL, VOOPOO, and 1R6F but lower in the Vaper4life brand. Cu and Zn emissions were under the maximum exposure limits for all of the tested brands based on the usage of 10 puffs. In short, we observed that metals contained in secondhand EC aerosols might pose a potential threat to indoor air quality and the health of nonsmokers. These metals, together with nicotine, carbonyls, and other toxic species,[55,65−67] can lead to various health effects through secondhand EC smoke exposure, which warrants more detailed studies.

4. CONCLUSIONS

This study characterized the metals contained in primary and secondary EC aerosols. EC aerosols were collected on a Teflon filter, and the metal content was quantified using ICP-MS. Several EC parameters were assessed, including EC brands, nicotine content, flavorings, EC power, puff duration, and

https://doi.org/10.1021/acs.chemrestox.1c00411
Chem. Res. Toxicol. 2022, 35, 954−962

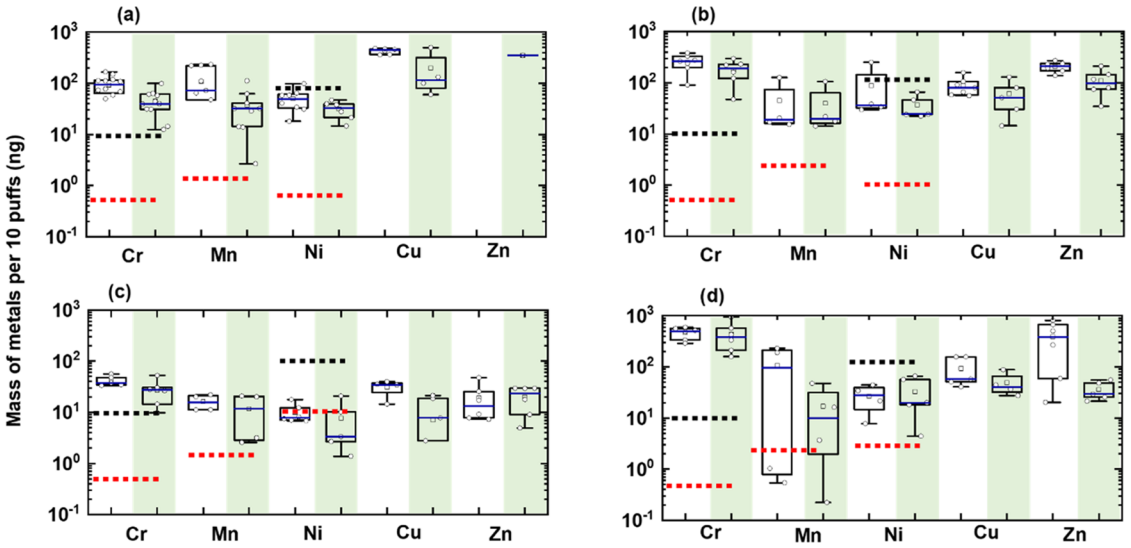


Figure 5. Mass of metals contents normalized to every 10 puffs for primary and secondhand EC aerosols for (a) JUUL, (b) VOOPOO EC, (c) Vapor4Life EC, and (d) 1R6F TC. Unshaded and shaded data represent primary and secondhand cigarette aerosols, respectively. Black and red dashed lines show the normalized maximum regulated intake amount based on EMA and NIOSH standards, respectively. Exposure limits of Cu and Zn are higher than the upper limit of the *y*-axis.

device aging. The data indicated that metal emissions vary tremendously across brands because of the different materials used to make the filament and the mode of operation. We further found that metal emissions increased with nicotine concentration, puff duration, and device power, whereas the flavoring type had no noticeable effect. In addition, a marginal increase in two metal emissions was observed with prolonged EC use. We speculate that the metals are predominantly generated through the aerosolization of the EC liquid, as the metal content positively correlates with nicotine content and puff duration. The contents of some metals in secondhand EC aerosols were above the regulated limits, presenting health risks for nonsmokers.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.chemrestox.1c00411.

ICP-MS method parameters, tabulated metal emissions range, linear correlation between nicotine content (flavoring) in the EC liquid and metal emissions, and bubble bursting picture (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Yang Wang − *Department of Civil, Architectural and Environmental Engineering, Missouri University of Science and Technology, Rolla, Missouri 65409, United States;* orcid.org/0000-0002-0543-0443; Phone: +1-573-341-4597; Email: yangwang@mst.edu

Authors

Kashala Fabrice Kapiamba − *Department of Civil, Architectural and Environmental Engineering, Missouri University of Science and Technology, Rolla, Missouri 65409, United States*

Weixing Hao − *Department of Civil, Architectural and Environmental Engineering, Missouri University of Science and Technology, Rolla, Missouri 65409, United States*

Stephen Adom − *Department of Chemistry and Center for Research in Energy and Environment, Missouri University of Science and Technology, Rolla, Missouri 65409, United States*

Wenyan Liu − *Department of Chemistry and Center for Research in Energy and Environment, Missouri University of Science and Technology, Rolla, Missouri 65409, United States*

Yue-Wern Huang − *Department of Biological Sciences, Missouri University of Science and Technology, Rolla, Missouri 65409, United States;* orcid.org/0000-0003-1957-6459

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.chemrestox.1c00411

Funding

This work was supported by the Center of Biomedical Research at the Missouri University of Science and Technology.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors appreciate the assistance of Ninu Madia from the Center for Research in Energy and Environment at Missouri S&T for her technical support in running the ICP-MS.

■ REFERENCES

(1) Hajek, P.; Phillips-Waller, A.; Przulj, D.; Pesola, F.; Myers Smith, K.; Bisal, N.; Li, J.; Parrott, S.; Sasieni, P.; Dawkins, L.; Ross, L.; Goniewicz, M.; Wu, Q.; McRobbie, H. J. A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. *N. Engl. J. Med.* **2019**, *380*, 629−637.

(2) Grana, R.; Benowitz, N.; Glantz, S. A. E-Cigarettes: A Scientific Review. *Circulation* **2014**, *129*, 1972−1986.

(3) Zhu, S. H.; Sun, J. Y.; Bonnevie, E.; Cummins, S. E.; Gamst, A.; Yin, L.; Lee, M. Four Hundred and Sixty Brands of E-Cigarettes and Counting: Implications for Product Regulation. *Tob. Control* **2014**, *23*, iii3−iii9.

(4) Farsalinos, K.; Lagoumintzis, G. Toxicity Classification of E-Cigarette Flavouring Compounds Based on European Union

Regulation: Analysis of Findings from a Recent Study. *Harm Reduct. J.* **2019**, *16*, 1−8.
(5) Chun, L. F.; Moazed, F.; Calfee, C. S.; Matthay, M. A.; Gotts, J. E. Pulmonary Toxicity of E-Cigarettes. *Am. J. Physiol. − Lung Cell. Mol. Physiol.* **2017**, *313*, L193−L206.
(6) 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.
(7) 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.
(8) Zhao, D.; Aravindakshan, A.; Hilpert, M.; Olmedo, P.; Rule, A. M.; Navas-Acien, A.; Aherrera, A. Metal/Metalloid Levels in Electronic Cigarette Liquids, Aerosols, and Human Biosamples: A Systematic Review. *Environ. Health Perspect.* **2020**, *128*, No. 036001.
(9) Pearce, K.; Gray, N.; Gaur, P.; Jeon, J.; Suarez, A.; Shannahan, J.; Pappas, R. S.; Watson-Wright, C. Toxicological Analysis of Aerosols Derived from Three Electronic Nicotine Delivery Systems Using Normal Human Bronchial Epithelial Cells. *Toxicol. In Vitro* **2020**, *69*, No. 104997.
(10) McAlinden, K. D.; Lu, W.; Eapen, M. S.; Sohal, S. S. Electronic Cigarettes: Modern Instruments for Toxic Lung Delivery and Posing Risk for the Development of Chronic Disease. *Int. J. Biochem. Cell Biol.* **2021**, *137*, No. 106039.
(11) Williams, M.; Bozhilov, K. N.; Talbot, P. Analysis of the Elements and Metals in Multiple Generations of Electronic Cigarette Atomizers. *Environ. Res.* **2019**, *175*, 156−166.
(12) Zervas, E.; Matsouki, N.; Kyriakopoulos, G.; Poulopoulos, S.; Ioannides, T.; Katsaounou, P. Transfer of Metals in the Liquids of Electronic Cigarettes. *Inhal. Toxicol.* **2020**, *32*, 240−248.
(13) Mulder, H. A.; Stewart, J. B.; Blue, I. P.; Krakowiak, R. I.; Patterson, J. L.; Karin, K. N.; Royals, J. M.; DuPont, A. C.; Forsythe, K. E.; Poklis, J. L.; Poklis, A.; Butler, S. N.; Turner, J. B. M. G.; Peace, M. R. Characterization of E-Cigarette Coil Temperature and Toxic Metal Analysis by Infrared Temperature Sensing and Scanning Electron Microscopy−Energy-Dispersive X-Ray. *Inhal. Toxicol.* **2020**, *32*, 447−455.
(14) Talih, S.; Balhas, Z.; Salman, R.; El-Hage, R.; Karaoghlanian, N.; El-Hellani, A.; Baassiri, M.; Jaroudi, E.; Eissenberg, T.; Saliba, N.; Shihadeh, A. Transport Phenomena Governing Nicotine Emissions from Electronic Cigarettes: Model Formulation and Experimental Investigation. *Aerosol Sci. Technol.* **2017**, *51*, 1−11.
(15) 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.
(16) Duell, A. K.; Pankow, J. F.; Peyton, D. H. Free-Base Nicotine Determination in Electronic Cigarette Liquids by 1H NMR Spectroscopy. *Chem. Res. Toxicol.* **2018**, *31*, 431−434.
(17) Chen, W.; Wang, P.; Ito, K.; Fowles, J.; Shusterman, D.; Jaques, P. A.; Kumagai, K. Measurement of Heating Coil Temperature for E-Cigarettes with a "Top-Coil" Clearomizer. *PLoS One* **2018**, *13*, No. e0195925.
(18) Mulder, H. A.; Stewart, J. B.; Blue, I. P.; Krakowiak, R. I.; Patterson, J. L.; Karin, K. N.; Royals, J. M.; DuPont, A. C.; Forsythe, K. E.; Poklis, J. L.; Poklis, A.; Butler, S. N.; Turner, J. B. M. G.; Peace, M. R. Characterization of E-Cigarette Coil Temperature and Toxic Metal Analysis by Infrared Temperature Sensing and Scanning Electron Microscopy−Energy-Dispersive X-Ray. *Inhal. Toxicol.* **2020**, *32*, 447−455.
(19) Mikheev, V. B.; Brinkman, M. C.; Granville, C. A.; Gordon, S. M.; Clark, P. I. Real-Time Measurement of Electronic Cigarette Aerosol Size Distribution and Metals Content Analysis. *Nicotine Tob. Res.* **2016**, *18*, 1895−1902.
(20) Peineke, C.; Attoui, M. B.; Schmidt-Ott, A. Using a Glowing Wire Generator for Production of Charged, Uniformly Sized Nanoparticles at High Concentrations. *J. Aerosol Sci.* **2006**, *37*, 1651−1661.
(21) Khan, A.; Modak, P.; Joshi, M.; Khandare, P.; Koli, A.; Gupta, A.; Anand, S.; Sapra, B. K. Generation of High-Concentration Nanoparticles Using Glowing Wire Technique. *J. Nanopart. Res.* **2014**, *16*, No. 2776.
(22) Fomenko, E.; Altman, I.; Agranovski, I. E. On Anomalous Nanoparticle Size Evolution in Glowing Wire Generator. *Nano-Struct. Nano-Objects* **2021**, *26*, No. 100693.
(23) Lechasseur, A.; Altmejd, S.; Turgeon, N.; Buonanno, G.; Morawska, L.; Brunet, D.; Duchaine, C.; Morissette, M. C. Variations in Coil Temperature/Power and e-Liquid Constituents Change Size and Lung Deposition of Particles Emitted by an Electronic Cigarette. *Physiol. Rep.* **2019**, *7*, No. e14093.
(24) Zhao, J.; Nelson, J.; Dada, O.; Pyrgiotakis, G.; Kavouras, I. G.; Demokritou, P. Assessing Electronic Cigarette Emissions: Linking Physico-Chemical Properties to Product Brand, e-Liquid Flavoring Additives, Operational Voltage and User Puffing Patterns. *Inhal. Toxicol.* **2018**, *30*, 78−88.
(25) 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. *Tob. Control* **2014**, *23*, 133−139.
(26) Margham, J.; McAdam, K.; Forster, M.; Liu, C.; Wright, C.; Mariner, D.; Proctor, C. Chemical Composition of Aerosol from an E-Cigarette: A Quantitative Comparison with Cigarette Smoke. *Chem. Res. Toxicol.* **2016**, *29*, 1662−1678.
(27) Smart, D. J.; Phillips, G. Collecting E-Cigarette Aerosols for in Vitro Applications: A Survey of the Biomedical Literature and Opportunities to Increase the Value of Submerged Cell Culture-Based Assessments. *J. Appl. Toxicol.* **2021**, *41*, 161−174.
(28) Olmedo, P.; Navas-Acien, A.; Hess, C.; Jarmul, S.; Rule, A. A Direct Method for E-Cigarette Aerosol Sample Collection. *Environ. Res.* **2016**, *149*, 151−156.
(29) Zhao, D.; Navas-Acien, A.; Ilievski, V.; Slavkovich, V.; Olmedo, P.; Adria-Mora, B.; Domingo-Relloso, A.; Aherrera, A.; Kleiman, N. J.; Rule, A. M.; Hilpert, M. Metal Concentrations in Electronic Cigarette Aerosol: Effect of Open-System and Closed-System Devices and Power Settings. *Environ. Res.* **2019**, *174*, 125−134.
(30) Zhao, D.; Ilievski, V.; Slavkovich, V.; Olmedo, P.; Domingo-Relloso, A.; Kleiman, N. J.; Navas-Acien, A.; Rule, A. M.; Hilpert, M. Effects of E-Liquid Flavor, Nicotine Content, and Puff Duration on Metal Emissions from Electronic Cigarettes. *Environ. Res.* **2021**, *204*, No. 112270.
(31) Halstead, M.; Gray, N.; Gonzalez-Jimenez, N.; Fresquez, M.; Valentin-Blasini, L.; Watson, C.; Steven Pappas, R. Analysis of Toxic Metals in Electronic Cigarette Aerosols Using a Novel Trap Design. *J. Anal. Toxicol.* **2020**, *44*, 149−155.
(32) Hao, W.; Kapiamba, K. F.; Varuni, A.; Shoaib, U.; Yue-Wern, H.; Wang, Y. A Simulated Respiratory System for Secondhand Smoke Generation and Characterization. *Inhal. Toxicol.*, **2022**, under review.
(33) U.S. Environmental Protection Agency. Method 6020B, Inductively Coupled Plasma−Mass Spectrometry, Revision 2, 33, 2014.
(34) Al-Hakkani, M. F. Guideline of Inductively Coupled Plasma Mass Spectrometry "ICP−MS": Fundamentals, Practices, Determination of the Limits, Quality Control, and Method Validation Parameters. *SN Appl. Sci.* **2019**, *1*, No. 791.
(35) Armbruster, D. A.; Pry, T. Limit of Blank, Limit of Detection and Limit of Quantitation. *Clin. Biochem. Rev.* **2008**, *29*, S49−S52.
(36) International Organization for Standardization (ISO). ISO 3308:2000(E): Routine Analytical Cigarette-Smoking Machine − Definitions and Standard Conditions, 2018.
(37) McAdam, K.; Davis, P.; Ashmore, L.; Eaton, D.; Jakaj, B.; Eldridge, A.; Liu, C. Influence of Machine-Based Puffing Parameters on Aerosol and Smoke Emissions from next Generation Nicotine Inhalation Products. *Regul. Toxicol. Pharmacol.* **2019**, *101*, 156−165.

https://doi.org/10.1021/acs.chemrestox.1c00411
Chem. Res. Toxicol. 2022, 35, 954−962

(38) Spindle, T. R.; Breland, A. B.; Karaoghlanian, N. V.; Shihadeh, A. L.; Eissenberg, T. Preliminary Results of an Examination of Electronic Cigarette User Puff Topography: The Effect of a Mouthpiece-Based Topography Measurement Device on Plasma Nicotine and Subjective Effects. *Nicotine Tob. Res.* **2015**, *17*, 142−149.
(39) Goniewicz, M. L.; Kuma, T.; Gawron, M.; Knysak, J.; Kosmider, L. Nicotine Levels in Electronic Cigarettes. *Nicotine Tob. Res.* **2013**, *15*, 158−166.
(40) Agency for Toxic Substances and Disease Registry (ATSDR). Minimal Risk Levels (MRLs), 2021.
(41) Etter, J. F.; Eissenberg, T. Dependence Levels in Users of Electronic Cigarettes, Nicotine Gums and Tobacco Cigarettes. *Drug Alcohol Depend.* **2015**, *147*, 68−75.
(42) Dawkins, L.; Turner, J.; Roberts, A.; Soar, K. "Vaping" Profiles and Preferences: An Online Survey of Electronic Cigarette Users. *Addiction* **2013**, *108*, 1115−1125.
(43) Dautzenberg, B. Real-Time Characterization of E-Cigarettes Use: The 1 Million Puffs Study. *J. Addict. Res. Ther.* **2015**, *06*, 1−5.
(44) Omaiye, E. E.; Williams, M.; Bozhilov, K. N.; Talbot, P. Design Features and Elemental/Metal Analysis of the Atomizers in Pod-Style Electronic Cigarettes. *PLoS One* **2021**, *16*, No. e0248127.
(45) Sosnowski, T. R.; Kramek-Romanowska, K. Predicted Deposition of E-Cigarette Aerosol in the Human Lungs. *J. Aerosol Med. Pulm. Drug Delivery* **2016**, *29*, 299−309.
(46) Flora, J. W.; Wilkinson, C. T.; Wilkinson, J. W.; Lipowicz, P. J.; Skapars, J. A.; Anderson, A.; Miller, J. H. Method for the Determination of Carbonyl Compounds in E-Cigarette Aerosols. *J. Chromatogr. Sci.* **2017**, *55*, 142−148.
(47) David, G.; Parmentier, E. A.; Taurino, I.; Signorell, R. Tracing the Composition of Single E-Cigarette Aerosol Droplets in Situ by Laser-Trapping and Raman Scattering. *Sci. Rep.* **2020**, *10*, No. 7929.
(48) Agents Classified by the IARC Monographs, Volumes 1−116, 2016, pp 1−36.
(49) DesMarias, T. L.; Costa, M. Mechanisms of Chromium-Induced Toxicity. *Curr. Opin. Toxicol.* **2019**, *14*, 1−7.
(50) Osei, A. D.; Mirbolouk, M.; Orimoloye, O. A.; Dzaye, O.; Uddin, S. M. I.; Benjamin, E. J.; Hall, M. E.; DeFilippis, A. P.; Stokes, A.; Bhatnagar, A.; Nasir, K.; Blaha, M. J. Association Between E-Cigarette Use and Cardiovascular Disease Among Never and Current Combustible-Cigarette Smokers. *Am. J. Med.* **2019**, *132*, 949−954.
(51) Wang, J. B.; Olgin, J. E.; Nah, G.; Vittinghoff, E.; Cataldo, J. K.; Pletcher, M. J.; Marcus, G. M. Cigarette and E-Cigarette Dual Use and Risk of Cardiopulmonary Symptoms in the Health EHeart Study. *PLoS One* **2018**, *13*, No. e0198681.
(52) Dunbar, Z. R.; Das, A.; O'Connor, R. J.; Goniewicz, M. L.; Wei, B.; Travers, M. J. Brief Report: Lead Levels in Selected Electronic Cigarettes from Canada and the United States. *Int. J. Environ. Res. Public Health* **2018**, *15*, No. 154.
(53) Beauval, N.; Antherieu, S.; Soyez, M.; Gengler, N.; Grova, N.; Howsam, M.; Hardy, E. M.; Fischer, M.; Appenzeller, B. M. R.; Goossens, J. F.; Allorge, D.; Garçon, G.; Lo-Guidice, J. M.; Garat, A. Chemical Evaluation of Electronic Cigarettes: Multicomponent Analysis of Liquid Refills and Their Corresponding Aerosols. *J. Anal. Toxicol.* **2017**, *41*, 670−678.
(54) Beauval, N.; Howsam, M.; Antherieu, S.; Allorge, D.; Soyez, M.; Garçon, 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.
(55) Schober, W.; Szendrei, K.; Matzen, W.; Osiander-Fuchs, H.; Heitmann, D.; Schettgen, T.; Jörres, R. A.; Fromme, H. Use of Electronic Cigarettes (e-Cigarettes) Impairs Indoor Air Quality and Increases FeNO Levels of e-Cigarette Consumers. *Int. J. Hyg. Environ. Health* **2014**, *217*, 628−637.
(56) Fuoco, F. C.; Buonanno, G.; Stabile, L.; Vigo, P. Influential Parameters on Particle Concentration and Size Distribution in the Mainstream of E-Cigarettes. *Environ. Pollut.* **2014**, *184*, 523−529.
(57) Talih, S.; Balhas, Z.; Salman, R.; El-hage, R.; Karaoghlanian, N.; El-hellani, A.; Baassiri, M.; Jaroudi, E.; Eissenberg, T.; Shihadeh, A.; Street, B. Transport Phenomena Governing Nicotine Emissions from Electronic Cigarettes: Model Formulation and Experimental Investigation. *Aerosol Sci. Technol.* **2017**, *51*, 1−11.
(58) Floyd, E. L.; Queimado, L.; Wang, J.; Regens, J. L.; Johnson, D. L. Electronic Cigarette Power Affects Count Concentration and Particle Size Distribution of Vaping Aerosol. *PLoS One* **2018**, *13*, No. e0210147.
(59) Lalo, H.; Leclerc, L.; Sorin, J.; Pourchez, J. Aerosol Droplet-Size Distribution and Airborne Nicotine Portioning in Particle and Gas Phases Emitted by Electronic Cigarettes. *Sci. Rep.* **2020**, *10*, No. 21707.
(60) 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.
(61) Resch, F. J.; Darrozes, J. S.; Afeti, G. M. Marine Liquid Aerosol Production from Bursting of Air Bubbles. *J. Geophys. Res.* **1986**, *91*, 1019.
(62) Lhuissier, H.; Villermaux, E. Bursting Bubble Aerosols. *J. Fluid Mech.* **2012**, *696*, 5−44.
(63) Jiang, J.; Oberdörster, G.; Biswas, P. Characterization of Size, Surface Charge, and Agglomeration State of Nanoparticle Dispersions for Toxicological Studies. *J. Nanopart. Res.* **2009**, *11*, 77−89.
(64) Cheng, Y. S. Aerosol Deposition in the Extrathoracic Region. *Aerosol Sci. Technol.* **2003**, *37*, 659−671.
(65) Fernández, E.; Ballbè, M.; Sureda, X.; Fu, M.; Saltó, E.; Martínez-Sánchez, J. M. Particulate Matter from Electronic Cigarettes and Conventional Cigarettes: A Systematic Review and Observational Study. *Curr. Environ. Health Rep.* **2015**, *2*, 423−429.
(66) Czogala, J.; Goniewicz, M. L.; Fidelus, B.; Zielinska-Danch, W.; Travers, M. J.; Sobczak, A. Secondhand Exposure to Vapors from Electronic Cigarettes. *Nicotine Tob. Res.* **2014**, *16*, 655−662.
(67) Tehrani, M. W.; Newmeyer, M. N.; Rule, A. M.; Prasse, C. Characterizing the Chemical Landscape in Commercial E-Cigarette Liquids and Aerosols by Liquid Chromatography−High-Resolution Mass Spectrometry. *Chem. Res. Toxicol.* **2021**, *34*, 2216−2226.

https://doi.org/10.1021/acs.chemrestox.1c00411
Chem. Res. Toxicol. 2022, 35, 954−962