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

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

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

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ABSTRACT

Background and aims: The popularity of electronic cigarette devices is growing worldwide. The health impact of e-cigarette use, however, remains unclear. E-cigarettes are marketed as a safer alternative to cigarettes. The aim of this research was the characterization and quantification of toxic metal concentrations in five, nationally popular brands of cig-a-like e-cigarettes.
Methods: We analyzed the cartomizer liquid in 10 cartomizer refills for each of five brands by Inductively Coupled Plasma Mass Spectrometry (ICP-MS).
Results: All of the tested metals (cadmium, chromium, lead, manganese and nickel) were found in the e-liquids analyzed. Across all analyzed brands, mean (SD) concentrations ranged from 4.89 *(0.893)* to 1970 (*1540*) µg/L for lead, 53.9 (*6.95*) to 2110 (*5220*) µg/L for chromium and 58.7 *(22.4)* to 22,600 (*24,400*) µg/L for nickel. Manganese concentrations ranged from 28.7 (*9.79*) to 6910.2 (*12,200*) µg/L. We found marked variability in nickel and chromium concentration within and between brands, which may come from heating elements.
Conclusion: Additional research is needed to evaluate whether e-cigarettes represent a relevant exposure pathway for toxic metals in users.

1. Introduction

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

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

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

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

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

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

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

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

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

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

2. Materials and methods

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

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

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

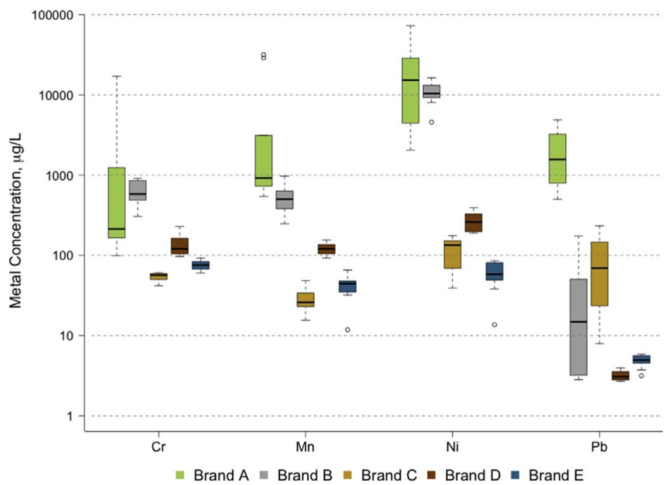

Fig. 1. Distribution of metal concentration within brands. Horizontal lines within boxes indicate medians; boxes, interquartile ranges; error bars, values within 1.5 times the interquartile range; solid circles, outlying data points.

3. Results

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

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

4. Discussion

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

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

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

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

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

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

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

Competing interests

None.

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Contributions

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

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