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Metal/Metalloid Levels in Electronic Cigarette Liquids, Aerosols, and Human Biosamples: A Systematic Review

Di Zhao,[1,2] Atul Aravindakshan,[3]* Markus Hilpert,[1] Pablo Olmedo,[1,3,4] Ana M. Rule,[3] Ana Navas-Acien,[1] and Angela Aherrera[3]*

[1]Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, New York, USA
[2]State Key Laboratory of Pollution Control and Resource Reuse, School of the Environment, Nanjing University, Nanjing, China
[3]Department of Environmental Health and Engineering, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA
[4]Department of Legal Medicine and Toxicology, School of Medicine, University of Granada, Granada, Spain

Background: Electronic cigarettes (e-cigarettes) have become popular, in part because they are perceived as a safer alternative to tobacco cigarettes. An increasing number of studies, however, have found toxic metals/metalloids in e-cigarette emissions.

Objective: We summarized the evidence on metal/metalloid levels in e-cigarette liquid (e-liquid), aerosols, and biosamples of e-cigarette users across e-cigarette device systems to evaluate metal/metalloid exposure levels for e-cigarette users and the potential implications on health outcomes.

Methods: We searched PubMed/TOXLINE, Embase®, and Web of Science for studies on metals/metalloids in e-liquid, e-cigarette aerosols, and biosamples of e-cigarette users. For metal/metalloid levels in e-liquid and aerosol samples, we collected the mean and standard deviation (SD) if these values were reported, derived mean and SD by using automated software to infer them if data were reported in a figure, or calculated the overall mean (mean ± SD) if data were reported only for separate groups. Metal/metalloid levels in e-liquids and aerosols were converted and reported in micrograms per kilogram and nanograms per puff, respectively, for easy comparison.

Results: We identified 24 studies on metals/metalloids in e-liquid, e-cigarette aerosols, and human biosamples of e-cigarette users. Metal/metalloid levels, including aluminum, antimony, arsenic, cadmium, cobalt, chromium, copper, iron, lead, manganese, nickel, selenium, tin, and zinc, were present in e-cigarette samples in the studies reviewed. Twelve studies reported metal/metalloid levels in e-liquids (bottles, cartridges, open wick, and tank), 12 studies reported metal/metalloid levels in e-cigarette aerosols (from cig-a-like and tank devices), and 4 studies reported metal/metalloid levels in human biosamples (urine, saliva, serum, and blood) of e-cigarette users. Metal/metalloid levels showed substantial heterogeneity depending on sample type, source of e-liquid, and device type. Metal/metalloid levels in e-liquid from cartridges or tank/open wicks were higher than those from bottles, possibly due to coil contact. Most metal/metalloid levels found in biosamples of e-cigarette users were similar or higher than levels found in biosamples of conventional cigarette users, and even higher than those found in biosamples of cigar users.

Conclusion: E-cigarettes are a potential source of exposure to metals/metalloids. Differences in collection methods and puffing regimes likely contribute to the variability in metal/metalloid levels across studies, making comparison across studies difficult. Standardized protocols for the quantification of metal/metalloid levels from e-cigarette samples are needed. https://doi.org/10.1289/EHP5686

Introduction

Electronic cigarettes (e-cigarettes) are battery-operated devices that generate aerosols by heating a liquid solution (e-liquid with or without nicotine) with a metal coil (Bansal and Kim 2016; Mishra et al. 2017). The use of e-cigarettes is increasing among both former smokers and young adults who have never smoked due to the perception of safety (Goniewicz et al. 2013) and appealing flavors (Farsalinos et al. 2015; Zare et al. 2018). There is increasing evidence, however, on the toxicity of e-cigarettes to the lungs and other organs and systems (Dinakar and O'Connor 2016; Layden et al. 2019; NASEM 2018). Numerous studies, moreover, have measured elevated levels of toxic organic and inorganic chemicals in e-cigarette liquid (Beauval et al. 2017; Dunbar et al. 2018; Kamilari et al. 2018; Palazzolo et al. 2017; Song et al. 2018) and aerosols (Goniewicz et al. 2014; Klager et al. 2017; Mikheev et al. 2016; Tayyarah and Long 2014; Williams et al. 2013).

The presence of metals and metalloids (e.g., arsenic, chromium, lead, nickel) in e-cigarette aerosols is a major concern, given their serious health effects, including cancer (García-Esquinas et al. 2014; Kuo et al. 2017), cardiovascular disease (Chowdhury et al. 2018; Moon et al. 2012), renal damage (Suwazono et al. 2006), and neurotoxicity (Sankhla et al. 2017). Metals/metalloids may originate from the coil (Farsalinos et al. 2015; Olmedo et al. 2018) and from soldered joints and other parts of the device (Williams et al. 2017). Commonly used coils are made of alloys {e.g., kanthal [iron (Fe), chromium (Cr), and aluminum (Al)], nichrome [nickel (Ni) and Cr], or high-purity metals (e.g., Ni or titanium)} (Farsalinos et al. 2015; Olmedo et al. 2018). Tin (Sn) and other metals are used in soldered joints (Williams et al. 2015). E-liquids may also contain arsenic (As) and other metals/metalloids at varying levels (Beauval et al. 2016; Olmedo et al. 2018; Zhao et al. 2019).

The contribution of e-cigarettes to metal/metalloid exposure is not fully understood, particularly because of the rapidly changing nature of devices and e-liquids. E-cigarettes can be classified into three types: cig-a-like, tank, and pod devices (Williams and Talbot 2019; Williams et al. 2019a; Williams et al. 2019b). Cig-a-likes look similar to conventional cigarettes and have small disposable liquid cartridges. Tanks (clearomizer and mod) have a larger capacity to store refill fluid in comparison with cig-a-likes, and users can change coils and adjust power based on their preference. Most pod devices resemble USB drives; they have small cartridges or pods that are disposable (or refillable in the newest versions). As of 2014, ~7,000 e-liquids were available in the U.S. market with a wide range of flavors, nicotine content, and chemical compositions (Zhu et al. 2014). Device design, e-liquid composition, and operation preferences can affect the metal/metalloid levels that e-cigarettes deliver to users (Williams et al. 2019b; Zhao et al. 2019). To

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*These authors contributed equally to this work.

Address correspondence to Di Zhao, Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, 722 West 168th St., New York, NY, 10032 USA. Email: dz2381@cumc.columbia.edu or Angela Aherrera, Department of Environmental Health and Engineering, Johns Hopkins Bloomberg School of Public Health, 615 N Wolfe St. Baltimore, MD 21205 USA. Email: aaherre2@jhu.edu

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demonstrate internal exposure to toxic metals associated with e-cigarette use, metal/metalloid levels have not only been measured in e-liquids and aerosols but also in human biosamples such as urine (Aherrera et al. 2017; Goniewicz et al. 2018; Jain 2018), saliva (Aherrera et al. 2017), serum (Badea et al. 2018; Jain 2018), and blood (Jain 2018) collected from e-cigarette users.

Reviews on e-cigarettes have summarized e-cigarette development (Cooke et al. 2015; Glasser et al. 2017), their impact on decreasing smoking use (Kalkhoran and Glantz 2016; Rahman et al. 2015), health and physiological effects (Hajek et al. 2014; Pisinger and Døssing 2014; Zucchet et al. 2017), and effects of vaping on indoor air quality (Fernández et al. 2015; Zainol Abidin et al. 2017). Some of these reviews reported on metal levels; in addition, two systematic reviews have specifically evaluated metals/metalloids in cig-a-like cartomizers (Mishra et al. 2017) and in e-cigarette aerosols (Gaur and Agnihotri 2019). Overall, previous reviews reporting on e-cigarette–related metal/metalloid levels focused on aerosols, e-liquids, or human biosamples, separately. Moreover, none of the reviews systematically evaluated metals/metalloids across multiple samples in comparable metrics.

In this systematic review, we included studies that measured metal/metalloid levels in e-liquids (bottle, cartridge, open wick, and tank), e-cigarette aerosols (from cig-a-like and tank), and human biosamples (urine, saliva, serum, and blood) of e-cigarette users. The objective was to summarize the range of metal/metalloid levels across e-cigarette device systems to better understand the metal/metalloid levels e-cigarette users are exposed to and the potential implications on health outcomes.

Methods

Data Sources and Search Strategy

We searched PubMed/TOXLINE, Embase®, and Web of Science through 19 July 2018, using keywords and Mesh terms listed in "Search strategies" in the Supplemental Material. The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines were followed to identify the studies on metals/metalloids in e-cigarette liquid, aerosol, and human biosamples of e-cigarette users with no language restrictions.

Study Selection

Two research groups independently developed search strategies and executed literature searches; three authors (D.Z., A. Aravindakshan, and A. Aherrera) conducted title and abstract screening independently, followed by full text reviews conducted by two authors (D.Z. and A. Aravindakshan) independently, after which both searches were combined. Conflicts regarding manuscripts to include and in the data abstracted by each of the two authors independently were resolved through review of the original manuscripts and consensus with four other authors (A. Aherrera, A.N.-A., A.R., and M.H.).

We included studies published between January 2008 and July 2018. Studies prior to 2008 were excluded because e-cigarettes were introduced in the U.S. market in 2007 (Regan et al. 2013). To be included, studies must have quantified metal/metalloid levels in e-cigarette liquids, e-cigarette aerosols, and/or human biosamples from e-cigarette users. A hand search was conducted after completing the search process in the bibliographic databases, but during the record screening and full text review process, we found three additional papers related to metals in e-cigarettes that met the search criteria. E-liquid was classified as coming from the bottle (with no contact with the heating coil), from cartridges or pods (where the e-liquid is in contact with the coil), and from open wick and tanks (where the e-liquid is in contact with the coil and the samples were often collected after vaping the device). Studies measuring metals/metalloids only in indoor air (reflecting secondhand exposure to e-cigarette aerosols) were excluded from this review (Liu et al. 2017; O'Connell et al. 2015; Oldham et al. 2017; Saffari et al. 2014; Schober et al. 2014). We placed no restriction on the type or generation of e-cigarette device and/or e-liquid, the method of sample collection, or the method of metals/metalloids analysis. Secondary data and reviews were excluded.

Data Extraction

For each study, the following data were collected: citation (author/year), source of e-cigarettes/e-liquids (online, local outlet, manufacturer), device/e-liquid brand, device type (cig-a-likes, tanks, pods), e-liquid container (bottle, cartridge, open wick, tank), e-liquid flavor, nicotine content, puffing protocol, type of coil (nichrome, kanthal, other, not reported), whether the study accounted for background concentration (considered unaccounted for if not mentioned), sample size, analytical methods for metals/metalloids detection, and summary data of metal/metalloid levels. If the information was not available in the published manuscript, we contacted the study authors. For e-liquid and aerosol samples, we collected or derived the mean and standard deviation (SD). For human biosamples, we collected the median and interquartile range (IQR) or the geometric mean (GM) and 95% confidence interval (CI). For studies reporting metal/metalloid summary data both with and without background correction, we abstracted and reported values that accounted for background metal/metalloid levels (subtraction of metal/metalloid levels assessed in blanks or controls to account for interference or external contamination). For nicotine content, if only the volume fraction of nicotine (%) was provided, nicotine density of 1.01 g/ml (Oldham et al. 2018) was used to convert this number into a mass concentration (mg/ml).

Metal/Metalloid Data Synthesis

Several decisions were made in order to report and summarize metal levels in comparable metrics across studies. For studies reporting data in the form of plots (Mikheev et al. 2016; Williams et al. 2015), we used automated software tools to infer the underlying mean (SD) values [Origin (version 9.0; OriginLab Corporation)]. For studies that reported metal/metalloid levels for individual samples but not the mean (SD) (Beauval et al. 2016, 2017), we calculated the mean (SD). If metal/metalloid levels were below the limit of detection (LOD) and the study reported the original data but not the mean (SD), we replaced values below the LOD by $\mathrm{LOD}/\sqrt{2}$ before calculating the mean (SD) (Beauval et al. 2016, 2017; Kamilari et al. 2018; Margham et al. 2016; Song et al. 2018; Tayyarah and Long 2014). For studies reporting the mean (SD) for multiple groups (e.g., by nicotine levels, by different flavors) (Goniewicz et al. 2014; Kamilari et al. 2018; Talio et al. 2015, 2017; Tayyarah and Long 2014), we calculated the weighted mean and total SD to facilitate summary and comparison across studies and device types after confirming there were no major differences across flavors and nicotine levels. The total SD was estimated because it accounts for the SD within the groups as well as among the groups (Sharma 2006). For some studies, there were insufficient data to estimate the SD because only means were reported, with no estimation of variability around those point estimates (Beauval et al. 2017; Dunbar et al. 2018; Margham et al. 2016; Palazzolo et al. 2017; Song et al. 2018; Williams et al. 2013; Williams et al. 2017; Zhao et al. 2018). The study by Olmedo et al. (2018) reported medians instead of means (SDs) in the original publication, but we calculated them directly from the original data. For the study that reported two aerosol size fractions of particulate matter ($PM_{0.1}$ and $PM_{0.1–2.5}$), we kept only the $PM_{0.1}$, because it is likely inhaled deep into the lungs, and metals/metalloids were not detected in the $PM_{0.1–2.5}$ (Zhao et al. 2018).

Most studies of e-liquids reported metals/metalloids in micrograms per kilogram. For easy comparison, for studies reporting e-liquid metal/metalloid levels in micrograms per liter (Beauval et al. 2017; Hess et al. 2017; Palazzolo et al. 2017; Talio et al. 2015, 2017; Zhao et al. 2018) and parts per billion (ppb) (Beauval et al. 2016; Dunbar et al. 2018; Song et al. 2018), those concentrations were converted to micrograms per kilogram, assuming the e-liquid density was $1.16\ \mathrm{g/ml}$ (Sleiman et al. 2016). Most studies of aerosols reported metals/metalloids in ng per puff. For studies reporting aerosol metal/metalloid levels in other units (Beauval et al. 2017; Goniewicz et al. 2014; Mikheev et al. 2016; Olmedo et al. 2018; Palazzolo et al. 2017; Williams et al. 2013, 2015, 2017; Zhao et al. 2018), we converted them to ng per puff. For the study by Mikheev et al. (2016) that reported aerosol metal/metalloid levels in nanograms per milligram of total PM (TPM), we used the average mass of TPM per puff of 2 mg to convert nanograms per milligram TPM to ng per puff. For the study by Olmedo et al. (2018) that reported aerosol metal/metalloid levels in micrograms per kilogram, we first converted micrograms per kilogram to milligrams per cubic meter using the equation described in the original paper ($C_i = \theta_i \times \frac{m_{\mathrm{tot}}}{V_{\mathrm{air}}}$), and then converted milligrams per cubic meter to nanograms per puff using the conversion factor of $6.67 \times 10^{-5}\ \mathrm{m}^3/\mathrm{puff}$ (Olmedo et al. 2018). The study by Zhao et al. (2018) reported aerosol metal/metalloid levels (nanograms per milligram) in PM with an aerodynamic diameter of $\leq 0.1\ \mu\mathrm{m}$ ($\mathrm{PM}_{0.1}$). To facilitate comparison with the other studies, we estimated the mass of metals/metalloids per puff from the total aerosol mass (measured in $\mathrm{PM}_{0.1}$) collected in 10 min divided by the number of puffs (17.65 puffs based on an inter-puff time of 30 s and puff duration of 4 s provided by their study) and multiplied by the metals/metalloids mass fraction (Zhao et al. 2018).

Quality Assessment

We conducted a quality assessment for each study using the QualSyst tool for systematic reviews of quantitative studies (Kmet et al. 2004), which draws upon existing published tools, including instruments developed by Cho and Bero (1994) and Timmer et al. (2003). QualSyst uses a set of 14 criteria for the reporting of study objectives, design, methods, analysis, results, and conclusions to derive a final numerical score and to allow quantitative means of assessing research quality among the different studies. To account for different biases, we adapted this list to include specific items pertinent to e-cigarette devices (device characteristics reported; e-liquid characteristics reported) and elaborate on certain criteria (Table S1), resulting in a total of 17 criteria.

Each criterion on the QualSyst tool is given a score ranging from 0 to 2 (yes or criteria fulfilled = 2, partial or criteria partially fulfilled = 1, no or criteria not reported or conducted = 0). Items that were not applicable to the study design were marked “N/A” and were excluded from the calculation. A summary score for each study was obtained by calculating the total sum and dividing by the total possible sum (Kmet et al. 2004). Rather than being considered as a factor for inclusion criteria, the summary scores were used to categorize articles as strong (>0.80), good (0.71–0.79), adequate (0.50–0.70), or limited (<0.50) in research quality (Lee et al. 2008; Maharaj and Harding 2016).

Results

Study Characteristics

Two research groups developed search strategies independently. The search strategy retrieved a total of 728 individual studies by search A, including 118 duplicates and 320 studies by search B, including 112 duplicates (Figure 1). After abstract and full text review, a total of 24 individual studies met the inclusion criteria, including 3 studies identified through hand search (Badea et al. 2018; Goniewicz et al. 2018; Jain 2018). Of the 21 studies not counting the 3 found through manual search, 14 were identified both by search A and search B, 17 were identified by search A, and 18 were identified by search B. Among those 24 studies, 12 reported data on metals/metalloids in e-liquids [9 from bottle, 4 from cartridges (3 from cig-a-likes and 1 from pod), 1 from an open wick, 1 from both bottles and cartridges, and 1 from the tank after heating]. (The sum of the types of samples is higher than 12 because some studies collected multiple types of samples) (Table 1). Twelve reported data on metals/metalloids in e-cigarette aerosols (8 from cig-a-likes, 3 from tank devices, and 1 from both cig-a-like and tank devices) (Table 2), and 4 reported data on metals/metalloids in human biosamples of e-cigarette users (Table 3).

The number of metals/metalloids analyzed across studies was diverse, and some metals/metalloids (Be, Hg, Si, Tl, and V) were analyzed only in either e-liquid or aerosol in two studies (Table S1; Table S2). We prioritized metals/metalloids that were analyzed in at least three studies: Al, antimony (Sb), As, cadmium (Cd), cobalt (Co), Cr, copper (Cu), Fe, lead (Pb), manganese (Mn), Ni, selenium (Se), Sn, and zinc (Zn). Among these metals/metalloids, Cd and Pb were the most commonly determined in e-liquids, and Cu and Ni were the most commonly determined in aerosols. For easy comparison, metal/metalloid levels in e-liquid and aerosol samples from e-cigarette devices were converted to the same units (micrograms per kilogram and nanograms per puff, respectively). Metal/metalloid levels in e-liquid and aerosol samples before (Table S2; Table S3) and after conversion (Table 4; Table 5) are both provided. We report the mean metal/metalloid levels for e-liquid samples grouped according to the source of the e-liquid (bottle, cartridge, open wick, and tank) and for aerosol samples grouped according to device type (cig-a-likes and tanks; no study reported aerosol metal levels in pods during the search period).

Metal/Metalloid Levels in e-Liquids

Twelve studies published between 2015 and 2018 met the inclusion criteria for the analysis of metals/metalloids in e-liquids (Table 1). E-liquids for metals/metalloids analysis were collected from the bottle (no contact with the heating coils) in 9 studies, from the cartridge (cig-a-likes) in 3 studies, from the pods (JUUL) in one study, from the open wicks in one study, from both bottles and cartridges reported together in one study, and from the tanks after heating the aerosol in one study (the sum of the types of samples is higher than 12 because some studies collected multiple types of samples). E-cigarettes were obtained from the manufacturers, local or online stores, or e-cigarette users. The studies assessed between 1 and 10 e-liquid brands and between 1 and 9 flavors. The reported nicotine levels ranged from 0 to 24 mg/ml. The number of different e-liquid samples in individual containers of different brand, flavor, or nicotine content ranged from 1 to 56, and the total number of samples analyzed for metal concentrations including replicates ranged from 3 to 132. Seven studies used inductively coupled plasma mass spectrometry (ICP-MS) to quantify element levels in e-liquids; others used atomic absorption spectrometry (AAS) (Dunbar et al. 2018), total reflection X-ray fluorescence (Kamilari et al. 2018), molecular fluorescence (Talio et al. 2015; Talio et al. 2017), and sector field inductively coupled plasma mass spectrometry (SF-ICP-MS) (Zhao et al. 2018). Three studies used a mixture solution of propylene glycol and glycerol as blank e-liquids to assess matrix effects (Beauval et al. 2016; Olmedo et al. 2018; Palazzolo et al. 2017); other studies did not report metal/metalloid background correction.

Metal/metalloid levels in e-liquid samples not in contact with the heating coil (bottle) were generally lower than levels in most e-liquid samples collected from cartridges or from open wicks/tanks, which had already been in contact with the coil (Table 4; Figure S1); however, for most metals, mean levels varied between 1 and 3 orders of magnitude across studies even within similar types of e-liquid samples.

Metal/Metalloid Levels in Aerosols of e-Cigarettes

Twelve studies published between 2013 and 2018 met the inclusion criteria for metals/metalloids in e-cigarette aerosols generated by cig-a-likes ($n = 8$), tank devices ($n = 3$), and both cig-a-like and tank devices ($n = 1$) (Table 2). Studies of aerosols are particularly important because these samples reflect the metal/metalloid levels inhaled by the user. E-cigarettes were obtained from the manufacturers, local or online stores, or e-cigarette users. The studies assessed between 1 and 11 device brands. The e-liquids assessed included between 1 and 7 flavors, with nicotine levels ranging from 0 to 45 mg/ml. The puffing protocols to collect the aerosols were widely different, although seven studies used the same puff duration (4 s per puff). The total number of puffs ranged from 4 to 150. Background metal/metalloid levels were used to correct aerosol metal/metalloid levels in all studies except in Lerner et al. (2015). Nine studies used ICP-MS or inductively coupled plasma optical emission spectrometry (ICP-OES), one study used AAS (Lerner et al. 2015), one study used ICP-MS and AAS (Margham et al. 2016), and one used SF-ICP-MS (Zhao et al. 2018) to quantify metal/metalloid levels. The number of different devices evaluated ranged from 1 to 56, and the total number of aerosol samples ranged from 3 to 108.

Studies of aerosol samples showed generally higher metal/metalloid levels in samples from tank devices in comparison with levels in cig-a-likes (Table 5; Figure S2). It is also important to compare metals found in the aerosol samples with those found in e-liquid samples. Al, Fe, Ni, and Zn were found in studies looking at e-liquids and aerosols, whereas Cr, Cu, and Pb were more consistently found in aerosols. Notably, Cd levels were low and even undetectable in both e-liquid and aerosol samples in several studies. Only four studies compared metal/metalloid levels measured in the e-liquid and the corresponding aerosol from the same device (Beauval et al. 2017; Olmedo et al. 2018; Palazzolo et al. 2017; Zhao et al. 2018). These studies allow us to compare changes in metal/metalloid levels before and after the e-liquid is in contact with the device, which can contribute to identifying the source and processes that determine metal/metalloid contamination in e-cigarettes. With the exception of Beauval et al. (2017), where metal/metalloid levels in the aerosol were comparable with those of the e-liquid samples, studies found markedly higher levels in the aerosol than in the e-liquid samples. Zhao et al. (2018) detected Zn only in the e-liquid formulation but found Al, Cu, Fe, Mn, Ni, Pb, and Zn in aerosols. Similarly, Palazzolo et al.

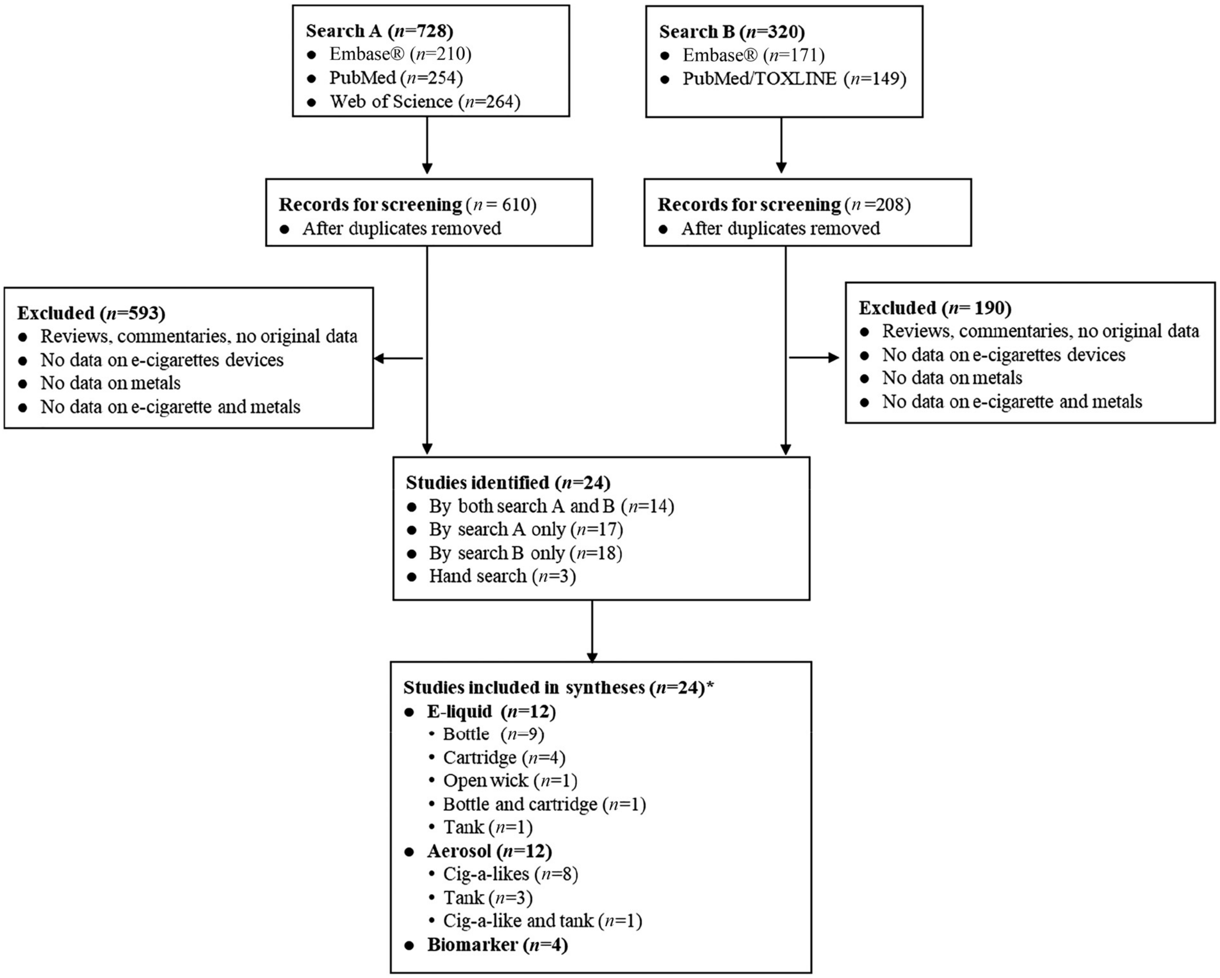

Figure 1. Summary of the search and screening process. *The number of studies in the final box adds to 28 instead of 24 because some studies reported data both for e-liquid and aerosol metal/metalloid levels. Of the 21 studies (not counting the 3 found through manual search), 14 had been identified by both searches, 17 were identified by search A and 18 were identified by search B.

Table 1. Characteristics of studies on metal/metalloid levels in e-liquid samples used in e-cigarette devices.

Ref	Type of e-liquid	Source of e-liquid	E-liquid brand	E-liquid flavor (nicotine mg/ml)	Analytical methods	N e-liquid[a]	N samples[b]	Background correction	Metals measured
Talio et al. 2015	Bottle	Internet	NR	Tobacco, Cappuccino, Ice Min, Tobacco Whinston (0, 11, 12, 18)	Molecular Fluorescence	4	16	NR	Pb[c]
Beauval et al. 2016	Bottle	Manufacturer	NHOSS	Cherry and others (0 or 16)	ICP-MS	54	54	Y	Al,[c] As,[c] Cd, Co,[c] Cr,[c] Cu,[c] Hg,[c] Mn,[c] Ni, Pb, Sb,[c] Tl, V,[c] Zn[c]
Beauval et al. 2017	Bottle	Manufacturer	NHOSS	Unflavored, Tobacco, Mint (0,16)	ICP-MS	6	6	NR	Al,[c] As,[c] Cd, Co,[c] Cr,[c] Cu,[c] Hg, Mn,[c] Ni, Pb, Sb,[c] Tl, V,[c] Zn
Palazzolo et al. 2017	Bottle	Local outlet	7's	Tobacco (24)	ICP-MS	1	4	Y	Al,[c] As,[c] Cd, Cu, Fe,[c] Mn,[c] Ni,[c] Pb, Zn[c]
Talio et al. 2017	Bottle	Online	NR	Tobacco, Cappuccino, Mint (0, 11, 12, 18)	Molecular Fluorescence	4	16	NR	Cd,[c] Ni[c]
Dunbar et al. 2018	Bottle	Canadian or U.S. outlet	Multiple brands[d]	Multiple flavors[e] (6, 12, 18, 24)	AAS	12	36	NR	Pb
Kamilari et al. 2018	Bottle	Market (USA, France, Turkey, Greece)	NR	NR	Total Reflection X-Ray Fluorescence	22	132	NR	As, Cd, Cr,[c] Cu,[c] Ni,[c] Pb[c]
Olmedo et al. 2018	Bottle	Daily e-cig users in MD	NR	NR	ICP-MS	56	56	Y	Al,[c] As,[c] Cd,[c] Co,[c] Cr,[c] Cu,[c] Fe,[c] Mn,[c] Ni,[c] Pb,[c] Sb,[c] Zn[c]
Song et al. 2018	Bottle	Local retails	NR	Tobacco	ICP-MS	3	NR	NR	As,[c] Cd,[c] Cr, Cu, Ni,[c] Pb,[c] Zn
Flora et al. 2016	Cartridge	Indiana and Arizona outlet	MarkTen	Menthol and Classic (15)	ICP-MS	4	12	NR	As, Cd
Hess et al. 2017	Cartridge	U.S. outlet and online	Brand A	NR (1.6–1.8)	ICP-MS	10	20	NR	Cd,[c] Cr,[c] Mn,[c] Ni,[c] Pb[c]
	—	—	Brand B	—	—	10	20	—	—
	—	—	Brand C	—	—	8	16	—	—
	—	—	Brand D	—	—	10	20	—	—
	—	—	Brand E	—	—	10	20	—	
Dunbar et al. 2018	Cartridge (cig-a-like)	Canadian outlet	DUNE	Strawberry (0)	AAS	1	3	NR	Pb
	Cartridge (pod)	U.S. outlet	JUUL	Crème Brulee, Fruit (0)	AAS	2	6	NR	Pb
	Open wick	Canadian or U.S. outlet	EZEE, DUNE, EVO	Fruitalicious, Mint, Grape, Menthol, Berry (0)	AAS	6	18	NR	Pb[c]
Zhao et al. 2018	Bottle, cartridge	Local retails and online	Blu, NJOY	Tobacco (10)	SF-ICPMS	NR	NR	NR	Zn[c]
Olmedo et al. 2018	Tank	Daily e-cig users in MD	NR	NR	ICP-MS	49	49	Y	Al,[c] As,[c] Cd,[c] Co,[c] Cr,[c] Cu,[c] Fe,[c] Mn,[c] Ni,[c] Pb,[c] Sb,[c] Zn[c]

Note: —, no data; AAS, atomic absorption spectrometry; ICP-MS, inductively coupled plasma–mass spectrometry; LOD, limit of detection; LOQ, limit of quantification; MD, Maryland; NR, not reported; Ref, reference; SF-ICP-MS, sector field inductively coupled plasma mass spectrometry.

[a] The number of e-liquid samples means different e-liquids in individual containers of different brands, flavors, or nicotine content.

[b] Total number of samples means all the e-liquid samples analyzed for metal concentration, including replicates.

[c] The mean metal/metalloid concentration was above the LOD.

[d] Multiple brands include Cosmic Fog, Cool Vape, Premium Labs, Blue V, Club, V, Vaper's Knoll, High Caliber, Good E-Juice, House of Vapor.

[e] Multiple flavors include Milk & Honey, Banana Mama, Strawberry, Watermelon, Cola, Menthol, Pina Colada, Bubble Gum, Vanilla.

Table 2. Characteristics of studies of metal/metalloids in aerosol samples collected from e-cigarette devices.

Ref	Device type	Source of e-cigarette	Device brand	E-liquid flavor (nicotine mg/ml)	Type of coil	Puffing protocol	Analytical methods	N devices^a	N samples^b	Background correction	Metals/metalloids measured^c
Williams et al. 2013	Cig-a-likes	Local outlet and online	NR	NR (0)	nichrome	60 puffs, 4.3 s/puff	ICP-OES	1	3	Y	Al,^{c} Cr,^{c} Cu,^{c} Fe,^{c} Mn,^{c} Ni,^{c} Pb,^{c} Si,^{c} Sn,^{c} Zn^c
Goniewicz et al. 2014	Cig-a-likes	Online	Multiple brands^d	Marlboro, regular, trendy, menthol, camel, tobacco (4, 8, 11, 16, 18)	NR	1.8 s/puff, 10 s interval, puff volume of 70 ml, 150 puffs	ICP-MS	12	108	Y	As, Cd,^{c} Cr, Cu, Mn, Ni,^{c} Pb,^{c} Se, Zn
Tayyarah and Long 2014	Cig-a-likes	Manufacturers	Blu, SKYCIG	Tobacco, menthol, cherry (16, 18, 24)	NR	99 puffs, 55 ml/puff, 2 puffs/min	ICP-MS	5	19	Y	As, Be, Cd, Cr,^{c} Hg, Mn, Ni, Pb, Se, Sn
Lerner et al. 2015	Cig-a-likes	E-cigarette users	Blu	Tobacco (16)	NR	4 puffs, 4 s/puff	AAS	1	4	N	Cu^c
Williams et al. 2015	Cig-a-likes	Local outlet and online	4 brands (name NR)	NR	nichrome	60 puffs, 4.3 s/puff	ICP-OES	4	12	Y	Cr,^{c} Cu,^{c} Ni,^{c} Sn,^{c} Zn^c
Margham et al. 2016	Cig-a-likes	NR	Vype	Tobacco (18.6)	nichrome	puff volumes of 55 cm^3, puff duration 3 s, twice/min	ICP-MS, AAS	1	5	Y	As, Be, Cd, Cr,^{c} Cu,^{c} Fe,^{c} Hg, Ni, Pb, Se, Sn, Zn^c
Mikheev et al. 2016	Cig-a-likes	NR	Blu	Tobacco, menthol, cherry, java jolt, peach, colada, vanilla (0, 12–16)	NR	17.5 ml/s, 75 puffs, 4.3 s/puff, 60-s interval	ICP-MS	1	42	Y	As,^{c} Cr,^{c} Cu,^{c} Ni,^{c} Sb,^{c} Sn,^{c} Zn^c
Williams et al. 2017	Cig-a-likes	Local outlet and online	Multiple brands^e	Multiple flavors^f (12.5, 18, 24, 45)	nichrome	4.3 s/puff every 5 mins, 60 puffs	ICP-OES	6	18	Y	Al^c, As^c, Cu,^{c} Fe,^{c} Ni,^{c} Sb,^{c} Se,^{c} Si,^{c} Sn,^{c} Zn^c
Beauval et al. 2017	Tank	Manufacturer	NHOSS	Unflavored, Tobacco, Mint (0, 16)	NR	55 ml puff longer than 3 s, 12/min	ICP-MS	1	18	Y	As, Cd^c, Cr^c, Pb,^{c} Sb^c
Palazzolo et al. 2017	Tank	Local outlet	Triple 3 eGo	Tobacco (24)	NR	400 ml/puff, volume: 33.6 ml, 45 puffs, 5 s/puff, 10-s interval	ICP-MS	1	8	Y	Al,^{c} As,^{c} Cd, Cu, Fe,^{c} Mn, Ni,^{c} Pb, Zn^c
Olmedo et al. 2018	Tank	Daily e-cigarette users in Maryland	NR	NR	Kanthal or others	Puff volume of 66.67 ml, 4 s/puff, puff interval 30 s, 1 l/min	ICP-MS	56	56	Y	Al,^{c} As,^{c} Cd,^{c} Cr,^{c} Cu,^{c} Fe,^{c} Mn,^{c} Ni,^{c} Pb,^{c} Sb,^{c} Sn,^{c} Zn^c
Zhao et al. 2018	Cig-a-likes, Tank	Local retails and online	Blu, NJOY	Tobacco (10)	NR	30 l/min for 10 min, 3.7 V, puff volume of 55 ml, 4 s/puff, puff interval 30 s.	SF-ICP-MS	NR	NR	Y	Al,^{c} Cu,^{c} Fe,^{c} Mn,^{c} Ni,^{c} Pb,^{c} Zn^c

Note: AAS, atomic absorption spectrometry; ICP-MS, inductively coupled plasma–mass spectrometry; ICP-OES, inductively coupled plasma optical emission spectrometry; LOD, limit of detection; LOQ, limit of quantification; NQ, not quantifiable; NR, not reported; Ref, reference; SF-ICP-MS, sector field inductively coupled plasma mass spectrometry.

[a] The number of devices means all the devices used to collect aerosols.

[b] Total number of samples means all the aerosol samples analyzed for metal concentration including replicates.

[c] The mean metal/metalloid was above the LOD.

[d] Multiple brands include Joye, Janty, DSE, Trendy, Nicore, Mild, Ecis, Dekang, Intellicig, Colinss, Premium.

[e] Multiple brands include Blucig, Mistic, NJOY King, Square 82, V2 Cig, Vype.

[f] Multiple flavors include Tobacco, Menthol, Traditional, Original Red, Red, Classic Regular.

Table 3. Characteristics of studies and metal/metalloid levels in human biosamples from e-cigarette users.

Ref	Aherrera et al. 2017[a]				Badea et al. 2018[b]	Goniewicz et al. 2018[c]	Jain 2018[d]		
Human biosample	Urine	Urine-creatinine	Saliva	Exhaled breath condensate (EBC)	Serum	Urine	Blood	Urine	Serum
Unit	μg/l	μg/g creatinine	μg/l	μg/l	μg/l	μg/g creatinine	μg/l	μg/l	μg/l
N	64	64	63	64	34	247	23	14	14
Summary statistics[e]									
Ag	—	—	—	—	0.2 (0.1, 0.5)	—	—	—	—
As	—	—	—	—	0.2 (0.1, 0.3)	—	—	3.2 (0.8, 13.4)	—
Ba	—	—	—	—	2.5 (1.9, 3.1)	—	—	0.9 (0.3, 2.5)	—
Be	—	—	—	—	0.3 (0.3, 0.3)	0.01 (0.01, 0.01)	—	—	—
Cd	—	—	—	—	0.03 (0.0, 0.0)	0.19 (0.17, 0.23)	—	—	—
Co	—	—	—	—	0.3 (0.2, 0.4)	0.58 (0.52, 0.64)	—	0.3 (0.2, 0.6)	—
Cr	0.5 (0.4, 0.8)	0.4 (0.3, 0.5)	1.5 (0.8, 2.9)	0.3 (0.3, 0.7)	—	—	—	—	—
Cu	—	—	—	—	892 (799, 958)	—	—	—	106 (70.7, 160)
Fe	—	—	—	—	1151 (888, 1515)	—	—	—	—
Hg	—	—	—	—	0.5 (0.5, 0.5)	—	—	—	—
Mn	—	—	—	—	0.8 (0.6, 1.0)	0.14 (0.12, 0.16)	10.3 (8.7, 12.2)	—	—
Mo	—	—	—	—	0.6 (0.4, 0.9)	—	—	31.3 (14.6, 67.2)	—
Ni	0.9 (0.6, 1.6)	0.7 (0.4, 1.4)	2.3 (1.0, 4.9)	1.3 (0.9, 1.9)	7.0 (3.9, 10.0)	—	—	—	—
Pb	—	—	—	—	2.2 (1.0, 3.5)	0.43 (0.38, 0.49)	—	—	—
Pd	—	—	—	—	0.01 (0.0, 0.0)	—	—	—	—
Sb	—	—	—	—	1.2 (1.1, 1.6)	—	—	0.04 (0.02, 0.08)	—
Se	—	—	—	—	88.0 (79.6, 95.0)	—	186 (163, 211)	—	131 (108, 160)
Sn	—	—	—	—	5.4 (4.9, 6.6)	—	—	0.4 (0.04, 3.1)	—
Sr	—	—	—	—	23.2 (20.0, 29.1)	119 (101, 140)	—	114 (38.5, 337)	—
Th	—	—	—	—	0.01 (0.0, 0.1)	—	—	—	—
Tl	—	—	—	—	0.03 (0.0, 0.0)	0.17 (0.15, 0.19)	—	0.1 (0.03, 0.3)	—
U	—	—	—	—	0.01 (0.0, 0.0)	0.007 (0.006, 0.008)	—	0 (0, 0.02)	—
V	—	—	—	—	0.3 (0.2, 0.3)	—	—	—	—
W	—	—	—	—	—	—	—	0.02 (0, 0.1)	—
Zn	—	—	—	—	871 (781, 1008)	—	—	—	60.9 (39.1, 95)

Note: All four studies used inductively coupled plasma–mass spectrometry (ICP-MS) as the analytical method. —, not measured; Ref, reference.

[a] 64 participants from Baltimore, Maryland (5 cig-a-likes, 59 mod).

[b] 150 Romanian participants (58 nonsmokers, 58 conventional cigarette smokers, 34 e-cigarette users).

[c] 5,105 U.S. adults (247 e-cigarette users, 2,411 cigarette smokers, 792 dual users, and 1,655 never tobacco users) of the Population Assessment of Tobacco and Health Study (PATH 2013–2014).

[d] U.S. adult users from (cigars, cigarettes, and e-cigarettes users) the 2013–2014 National Health and Nutrition Examination Survey (NHANES).

[e] Median (IQR) for Aherrera et al. 2017 and Badea et al. 2018; GM (95% confidence interval) for Goniewicz et al. 2018 and Jain 2018.

Table 4. Metal/metalloid [standard deviation (SD)] levels (micrograms per milligram) in e-liquid samples collected from e-cigarette devices.

Ref	Type of e-liquid	Al[a]	As	Cd	Co	Cr	Cu	Fe	Mn	Ni	Pb	Sb	Zn
Talio et al. 2015	Bottle	—	—	—	—	—	—	—	—	—	0.8 (0.9)	—	—
Beauval et al. 2016	Bottle	11.1 (2.8)	1.0 (0.6)	<0.3 (LOQ)	0.2 (0.1)	6.2 (1.1)	12.6 (2.2)	—	1.7 (1.4)	<13.8 (LOQ)	<0.9 (LOQ)	6.2 (27.1)	130 (47.8)
Beauval et al. 2017	Bottle	10.0 (1.5)	0.8 (0.4)	<0.3 (LOQ)	0.1 (0.08)	4.5 (1.1)	16.3 (6.7)	—	1.6 (0.9)	<13.8 (LOQ)	<0.9 (LOQ)	1.2 (0.1)	<172 (LOQ)
Palazzolo et al. 2017	Bottle	6.6 (0.4)	0.07 (0.03)	<0.009 (LOD)	—	—	<0.009 (LOD)	3.5 (0.2)	0.1 (0.005)	0.1 (0.006)	<0.009 (LOD)	—	0.4 (0.03)
Talio et al. 2017	Bottle	—	—	12.6 (4.0)	—	—	—	—	—	14.5 (6.8)	—	—	—
Dunbar et al. 2018	Bottle	—	—	—	—	—	—	—	—	—	<7.8 (LOQ)	—	—
Kamilari et al. 2018	Bottle	—	<1.0 (LOD)	<25.0 (LOD)	—	8.4 (55.5)	9.5 (47.3)	—	—	4.7 (27)	2.2 (10.3)	—	—
Olmedo et al. 2018	Bottle	15.0 (11.7)	3.6 (10.3)	0.07 (0.000)	0.2 (0.3)	1.6 (2.2)	20.0 (38.1)	65.2 (102)	6.2 (20.7)	28.9 (43.8)	1.04 (1.94)	0.9 (3.7)	41.3 (137)
Song et al. 2018	Bottle	—	1.9	0.7	—	NR	NR	—	—	3	10.5	—	NR
Flora et al, 2016	Cartridge	—	<430 (LOQ)	<220 (LOQ)	—	—	—	—	—	—	—	—	—
Hess et al. 2017[b]	Cartridge	—	—	176 (273)	—	1815 (4489)	—	—	5943 (10492)	19436 (20984)	1694 (1247)	—	—
		—	—	1.0 (0.9)	—	678 (244)	—	—	576 (243)	11524 (3904)	50 (68.3)	—	—
		—	—	1.4 (1.1)	—	199 (61.6)	—	—	172 (29.2)	398 (114)	5.0 (1.5)	—	—
		—	—	0.8 (0.7)	—	65.4 (9.5)	—	—	35.7 (12.0)	50.5 (19.3)	4.2 (0.8)	—	—
		—	—	0.4 (0.3)	—	46.4 (6.0)	—	—	24.7 (8.4)	98 (42.4)	80.3 (69.2)	—	—
Dunbar et al. 2018	Cartridge (cig-a-like)	—	—	—	—	—	—	—	—	—	<7.8 (LOQ)	—	—
	Cartridge (pod)	—	—	—	—	—	—	—	—	—	<7.8 (LOQ)	—	—
	Open wick	—	—	—	—	—	—	—	—	—	202	—	—
Zhao et al. 2018	Bottle, cartridge	—	—	—	—	—	—	—	—	—	—	—	220
Olmedo et al. 2018	Tank	101 (176)	4.2 (11.6)	0.4 (1.0)	10.8 (17.1)	214 (346)	1990 (5550)	1880 (3860)	124 (247)	2510 (8160)	517 (1520)	3.6 (7.5)	3250 (9640)

Note: —, not measured; LOD, limit of detection; LOQ, limit of quantification; NR, not reported; Ref, reference.

[a] All metal concentrations were reported as mean (SD). The study by Palazzolo et al. (2017) reported the mean (standard error) instead of the SD. The studies by Flora et al. (2016) and Zhao et al. (2018) did not report the SD or any other measure of variability. We calculated mean and SD for individual samples by Beauval et al. (2016) and Beauval et al. (2017). We calculated the weighted mean and total SD for multiple groups by Talio et al. (2015), Talio et al. (2017), and Kamilari et al. (2018). The study by Olmedo et al. (2018) did not report means (SDs) in the original publication, but we calculated them directly from the original data.

[b] Metal levels reported by Hess et al. (2017) were not combined because they are highly variable across five brands of e-cigarette devices.

(2017) found higher Al, As, Ni, and Zn in aerosols in comparison with the liquids before aerosolization. Olmedo et al. (2018) reported markedly higher metal/metalloid levels in the aerosols, with Pb and Zn aerosol levels 25 times higher, and Cr, Ni, and Sn levels 6 times higher than levels in the bottle samples. Still higher metal/metalloid levels were found in the remaining e-liquids from the tank after vaping, with Cr, Cu, Ni, Pb, and Zn aerosol levels being more than 35 times higher than levels in the bottles.

Metal/Metalloid Levels in Biosamples of e-Cigarette Users

Four studies reported metal/metalloid levels in biosamples of e-cigarette users (Table 3). Aherrera et al. (2017) recruited 64 daily e-cigarette users from Maryland in the United States (5 users of cig-a-like devices and 59 users of mod devices), including 50 sole e-cigarette users who had never smoked before or had quit smoking at least 3 months prior and 14 dual users (users of both e-cigarettes and cigarettes) who smoked traditional cigarettes at least weekly. Badea et al. (2018) recruited 34 e-cigarette users (device type not reported) who were former smokers, 58 nonsmokers, and 58 conventional smokers from Brasov, Romania. All e-cigarette participants in this study were sole e-cigarette users (dual users of e-cigarettes and traditional cigarettes were excluded from the study). Goniewicz et al. (2018) used data of 5,105 U.S. adults (247 e-cigarettes–only users, 2,411 cigarette-only smokers, 792 dual users, and 1655 never tobacco users) from the Population Assessment of Tobacco and Health Study in the United States (PATH 2013–2014). Jain (2018) used data from cigars, cigarettes, and e-cigarettes users from the 2013–2014 National Health and Nutrition Examination Survey (NHANES) in the United States (23 e-cigarette–only users, 417 conventional cigarette-only users, and 43 cigar-only users). All studies used ICP-MS for metal/metalloid analysis. The number of e-cigarette users across the four studies ranged from 23 to 247.

Three studies reported metal/metalloid levels in urine in micrograms per liter (Aherrera et al. 2017; Jain 2018) and in micrograms per gram creatinine (Goniewicz et al. 2018; Jain 2018). Most metals/metalloids (As, Ba, Be, Cd, Cr, Mn, Mo, Ni, Pb, Sb, Sn, and W) were reported in only one study. Four metals/metalloids (Co, Sr, Tl, and U) were reported in two studies, although in different units. In PATH and NHANES, no statistically significant differences were found in the urinary Ba, Be, Co, Mo, Mn, Sb, Sn, and Tl levels of e-cigarette users and cigarette smokers (Goniewicz et al. 2018; Jain 2018) (Table S4), except urinary Sr levels, which were higher among e-cigarette users in comparison with cigarette smokers and cigar users (Jain 2018), and urinary Cd levels, which were significantly lower in e-cigarette users (Goniewicz et al. 2018). Neither PATH nor NHANES has measured Ni or Cr.

Among studies reporting metal/metalloid levels in serum ($n = 2$) (Badea et al. 2018; Jain 2018), most metals/metalloids (Ag, As, Ba, Be, Cd, Co, Fe, Hg, Mn, Mo, Ni, Pb, Pd, Sb, Sn, Sr, Th, Tl, U, and V) were reported in only one study. Both studies reported Cu, Se, and Zn in the serum of e-cigarette users. In NHANES, serum Cu and Se were higher in e-cigarette users in comparison with both cigar and cigarette users in adjusted models, even though the results were not statistically significant (Jain 2018). In e-cigarette users from Romania, levels of Ag, Se, and V were higher among e-cigarette users in comparison with levels found among nonusers and cigarette smokers (Badea et al. 2018).

One study reported Cr and Ni in urine, saliva, and exhaled breath condensate (EBC) (micrograms per liter) of e-cigarette users (Aherrera et al. 2017). This study is the only one correlating measures of metals/metalloids reported in the aerosol of the e-cigarette devices used by the users with metal/metalloid levels in urine, saliva, and EBC. In comparison with the lowest tertile, participants in the two highest tertiles of aerosol Ni showed 16%

Table 5. Metal/metalloid mean (standard deviation) levels in aerosol samples (nanograms per puff) collected from e-cigarette devices.

Ref	Device type	Al^a	As	Cd	Cr	Cu	Fe	Mn	Ni	Pb	Sb	Se	Sn	Zn
Williams et al. 2013	Cig-a-likes	39.4	—	—	0.7	20.3	52	0.2	0.5	1.7	—	—	3.7	5.8
Goniewicz et al. 2014	Cig-a-likes	—	<LOD (0.10)	0.6 (0.6)	<LOD (0.01)	<LOD (0.06)	—	<LOD (0.03)	1.2 (0.8)	0.6 (1.1)	—	<LOD (0.04)		<LOD (0.18)
Tayyarah and Long 2014	Cig-a-likes	—	<1.4 (LOQ)	<1.4 (LOQ)	1.4	—	—	<1.3 (LOQ)	<1.4 (LOQ)	<1.4 (LOQ)	—	<1.4 (LOQ)	<1.4 (LOQ)	—
Lerner et al. 2015	Cig-a-likes	—	—	—	—	117 (83.6)	—	—	—	—	—	—	—	—
Williams et al. 2015	Cig-a-likes	—	—	—	0.6 (0.5)	8.9 (10.2)	—	—	2.0 (3.7)	—	—	—	88.6 (322)	3.8 (6.2)
Margham et al. 2016	Cig-a-likes	—	0.2 (NQ)	<0.2 (LOD)	0.4	1.9	4.2	—	0.6 (NQ)	<0.5 (LOD)	—	<0.08 (LOD)	<0.6 (LOD)	12.3
Mikheev et al. 2016	Cig-a-likes	—	0.14 (0.02, 1.0)	—	4.0 (0.16, 9.2)	1.2 (0.08, 12.6)	—	—	0.3 (0.1, 13.5)	—	0.3 (0.06, 1.1)	—	0.1 (0.04, 180)	6.2 (3.2, 105.6)
Williams et al. 2017	Cig-a-likes	1.3	0.6	—	—	8	0.8	—	0.4	—	0.7	5.3	2.9	3.6
Beauval et al. 2017	Tank	—	<0.7 (LOQ)	0.1	7	—	—	—	—	2.7	0.7	—	—	—
Palazzolo et al. 2017	Tank	290	0.13	<LOD	—	<LOD	0.07	<LOD	14.5	<LOD	—	—	—	61.9
Olmedo et al. 2018	Tank	0.02 (0.05)	0.004 (0.01)	0.0001 (0.003)	0.07 (0.27)	0.05 (0.12)	0.39 (1.33)	0.01 (0.02)	0.32 (1.06)	0.08 (0.27)	0.002 (0.004)	—	0.02 (0.06)	0.54 (0.88)
Zhao et al, 2018	Cig-a-likes, Tank	0.98	—	—	—	0.98	0.44	0.01	0.05	0.21	—	—	—	0.65

Note: —, not measured; LOD, limit of detection; LOQ, limit of quantification; NR, not reported; Ref, reference.

[a] All metal concentrations were reported as mean [standard deviation (SD)]. The studies by Williams et al. (2013), Margham et al. (2016), Williams et al. (2017), Palazzolo et al. (2017), and Zhao et al. (2018) did not report the SD or any other measure of variability. The metal concentrations by Mikheev et al. (2016) and Williams et al. (2015) were derived using an automated program from the figure. The mean and SD were calculated for individual samples by Beauval et al. (2017). The study by Olmedo et al. (2018) did not report means (SDs) in the original publication, but we calculated them directly from the original data. We calculate the weighted mean and total SD for multiple groups by Goniewicz et al. (2014) and Tayyarah and Long (2014).

and 72% higher urinary Ni (p-trend 0.03), and 202% and 321% higher saliva Ni (*p*-trend 0.01), whereas no association was found with EBC (adjusted for sociodemographic). For aerosol Cr, the corresponding comparison showed 98% and 193% higher saliva Cr (*p*-trend 0.02), with no association with EBC. In NHANES, e-cigarette users had significantly higher blood Mn levels in comparison with levels in cigar users in adjusted models (*p*-trend 0.02) (Jain 2018).

E-cigarette use behaviors may influence metal/metalloid exposure because e-cigarette users who changed their heating coils more frequently and consumed more e-liquid per week were associated with higher urinary Ni levels (Aherrera et al. 2017), and being a "daily" e-cigarette user (vs. being a "some days" user) was associated with having significantly higher urinary Pb and Sr levels (Goniewicz et al. 2018).

Quality Assessment

Overall, the majority of studies were ranked as "strong" (71%) in research quality, whereas fewer were ranked as either "good" (18%) or "adequate" (11%). None of the studies were "limited" (score <0.50) in research quality. The studies ranked as "good" or "adequate" lacked or had an incomplete report of important aspects of the study protocols in the published manuscript, such as estimates of variance for the main results (Song et al. 2018; Flora et al. 2016; Zhao et al. 2018; Williams et al. 2013; Mikheev et al. 2016), information on limits of detection or quantification (Song et al. 2018; Zhao et al. 2018; Williams et al. 2013; Lerner et al. 2015; Mikheev et al. 2016), report of blanks and background correction (Song et al. 2018; Flora et al. 2016; Zhao et al. 2018; Lerner et al. 2015; Badea et al. 2018), laboratory quality control (Song et al. 2018; Flora et al. 2016; Williams et al. 2013; Lerner et al. 2015; Mikheev et al. 2016), and measures of central tendency (Song et al. 2018; Flora et al. 2016; Zhao et al. 2018; Mikheev et al. 2016). This assessment demonstrates the need to standardize the reporting of vaping conditions in the study of e-cigarette contaminants.

Discussion

Numerous metals/metalloids—Al, Sb, As, Cd, Co, Cr, Cu, Fe, Pb, Mn, Ni, Se, Sn, and Zn—were present in e-cigarette samples in the studies reviewed. For most metals/metalloids, levels were heterogeneous according to sample (e-liquid, aerosol), source of the sample (bottle, cartridge, open wick tank), and device type (cig-a-likes and tank). Studies of biosamples support the hypothesis that e-cigarettes are a source of metals/metalloids because most metal/metalloid biosample levels, with the exception of Cd, were similar or even higher in e-cigarette users in comparison with conventional cigarette users, and higher in comparison with cigar users. The direct comparison of metal/metalloid aerosol levels to human biosample levels (Aherrera et al. 2017) also provides direct support for the hypothesis that aerosol metals/metalloids are inhaled and absorbed by the e-cigarette user.

In comparison with conventional cigarettes, e-cigarette aerosols may result in less exposure to Cd but not to other toxic metals/metalloids found in tobacco. In the United States, the highest metal/metalloid levels in mainstream smoke of conventional cigarettes were for Cd (<5.0–80 ng/cigarette), followed by Pb (<5.0–23 ng/cigarette), whereas other metal/metalloid levels were markedly lower (As, Co, Cr, Mn, Ni) or undetectable (Ni, Cr) (Pappas et al. 2014). In cig-a-like devices, such as Blu® e-cigarettes, Lerner et al. (2015) measured Cu levels, which were 6.1 times higher than those previously measured in conventional smoke (Stohs et al., 1997); in tank devices, aerosol levels of Cr and Ni were higher than, and Pb and Zn levels were similar to, levels measured from conventional cigarette smoke (Olmedo et al. 2018).

As indicated, most e-liquids sampled from cartridges or from tanks or open wicks that were in contact with the coil had higher metal/metalloid levels in comparison with levels in e-liquids sampled from the bottle. Numerous studies have shown that e-liquids in contact with heating coils like nichrome or kanthal (Olmedo et al. 2018; Palazzolo et al. 2017; Williams et al. 2013, 2015, 2017; Zhao et al. 2018) facilitate leaching of metals/metalloids into the liquid present in the tank or cartomizer. A recently published study showed that metals (Cu, Ag, Ni, Si, Ca, Al, Mn, Zn, and Sn) were used in various device components, such as thick wires, wicks, sheaths, and joints (Williams et al. 2019a). These device components may also transfer metals/metalloids into the e-liquid because the presence of brass clamps and copper wires with silver coatings have been associated with higher Zn, Cu, Ag, and Al in the aerosol (Williams et al. 2013, 2017). Furthermore, the presence of soldered joints of poor quality or with signs of fraying were associated with higher Sn levels (Williams et al. 2013, 2015, 2017), emphasizing that poor manufacturing techniques (Loewenstein and Middlekauff 2017) make a notable contribution to potential metal impurities that may reach the user. The e-cigarette user's vaping regimen, which includes modifications in voltage, resistance, temperature, and puff duration, may also play a role in the degradation of the heating coils and other metal elements, and in turn modify the aerosol composition and degree of metal/metalloid exposure, although few studies have evaluated their contribution.

Inhaled metals/metalloids are rapidly absorbed through the respiratory tract (Nordberg et al. 2007; Henry et al. 2019), and those that were detected in the studies in this review have been associated with serious adverse health effects. For instance, the lung is the most sensitive target of Ni toxicity, and lung inflammatory changes have been observed at the lowest adverse effect levels (ATSDR 2005a). Inhaled Ni exposure is also related to induced rhinitis and sinusitis in humans (Nordberg 2007). Several cases of Ni induced allergic dermatitis have been related to e-cigarette use (Maridet et al. 2015; Ormerod and Stone 2017). In a recent study, 89%–100% of aerosol samples of tank devices ($n = 54$) exceeded the minimum risk levels for Ni inhalation (Zhao et al. 2019). No study, however, has measured the chemical form of Ni in the aerosols. Ni speciation could contribute to determining the health implications of Ni exposure from e-cigarette use. Ni and Cr are established inhalation carcinogens (IARC 2012a, 2012b) and have also been associated with decreased lung function, increased risk of asthma, bronchitis (Nordberg 2007), and cardiovascular disease (Nigra et al. 2016). Although total Cr is reported in these studies, there is concern regarding Cr (III)'s carcinogenic potential due to the possible oxidation of Cr (III) to Cr (VI) within the oxygen-rich environment of lungs (U.S. EPA 2000). Pb, which requires only low levels of exposure to result in health effects (Lin et al. 2006), is associated with increased risk of cardiovascular and kidney disease and is a major neurotoxicant, particularly for children and the aging population (Fadrowski et al. 2010; Navas-Acien et al. 2007). Several studies have reported that exposure to secondhand smoke increases blood Pb levels in U.S. children (Apostolou et al. 2012; Mannino et al. 2003); considering the relatively high levels of Pb in e-cigarette aerosols, increased blood Pb levels in young adults who use e-cigarettes is possible. Mn, which is an essential nutrient through ingestion, has been linked to an irreversible Parkinson's-like disease known as manganism if inhaled (Aschner et al. 2005). Cu is known to cause respiratory irritation, coughing, sneezing, chest pain, and runny nose through inhalation (U.S. DHHS 2004). In an *in vitro* study, exposure of human lung fibroblasts to Cu nanoparticles from e-cigarette aerosols increased mitochondrial oxidative stress and DNA fragmentation (Lerner et al. 2016). Exposure to Al at high levels can lead to impaired lung function and fibrosis as well as decreased performance in motor and cognitive function (U.S. DHHS 2008). Fe was shown to be associated with metal fume fever, siderosis, and fibrosis in a study of 78 iron and steel workers (Johnson et al. 1985), whereas Zn can cause chest pain, dyspnea, metal fume fever, and shortness of breath (ATSDR 2005b). Last, As is highly toxic to numerous organs and body systems, and exposure to inorganic As is associated with cancer and cardiovascular disease (Saint-Jacques et al. 2014; Moon et al. 2012). In addition, As was detected in e-liquids at varying levels (Beauval et al. 2016; Olmedo et al. 2018; Zhao et al. 2019). The sources of As and strategies to eliminate As in e-liquids must be investigated. The health effects of metals/metalloids through inhalation have been studied, mostly in occupational settings. Although the exposure pattern in occupational settings might be different from that of chronic e-cigarette exposure, Olmedo et al. (2018) reported that close to 50% or more of the aerosol samples from daily e-cigarette users exceeded current health-based limit levels for Cr, Mn, Ni, and Pb.

This systematic review has several limitations. A major issue was the differing puffing protocols from varied puff counts, puff length (s per puff), and the puff volume across all studies ranging from 13–70 ml. Other studies reported their findings using graphics (box plots, bar graphs, pie charts), which provided rough estimations as opposed to exact values. Some studies reported only means, which limited our analysis in the spread of data. Background correction after measuring blanks was sometimes missing or unclear, particularly in studies measuring metal/metalloid levels in aerosols. We recommend reporting blank or control-corrected metal/metalloid levels. Particularly for human biosample studies, some had a small sample size, lacked a control group, and based their analysis of e-cigarette use on one question, without sufficient information on the frequency of use or the type of device. Notwithstanding these limitations, this review has several strengths. To our knowledge, ours is the first systematic review *a*) to analyze metal/metalloid levels in e-liquids, aerosols, and human biosamples in such detail, *b*) to compare across studies standardizing units as much as possible, and *c*) to conduct a quality assessment of each research study. We strove to include all information presented to identify the metals/metalloids of concern, the devices and sources of e-liquids that give off relatively higher metal/metalloid levels, and the levels that can be compared with conventional cigarettes. Last, this review has identified the need for standardization both in the methodology of the experiments, such as puffing protocols and accounting for background contamination, and in the reporting of the findings (units, measures of central tendency, and variability) because that standardization would aid in more straightforward comparisons in future e-cigarette studies than are currently feasible.

Overall, the evidence available consistently supports that e-cigarettes are a major concern for exposure to toxic metals/metalloids. Substantial heterogeneity exists across products and, in particular, across e-liquids that are in contact with the heating coil. There is also evidence that aerosols have higher metal/metalloid levels than the unused e-liquids have. These findings indicate that higher metal/metalloid levels in aerosol samples are, at least in part, due to the metal/metalloid components of the devices. Although the studies included in this review found lower Cd levels in human biosamples of e-cigarette users than those found in conventional cigarette and cigar users, most other metal/metalloid levels were similar or even higher in e-cigarette users. Manufacturing procedures could constitute a major contribution to potential metal impurities and could influence metal/metalloid release during vaping. Regulation is needed to inform e-cigarette users of possible metal/metalloid exposure through vaping as well as to prevent metal/metalloid exposure during e-cigarette use.

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