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Health Effects of Trace Metals in Electronic Cigarette Aerosols—a Systematic Review

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Abstract
Electronic cigarettes (ECs) are essentially nicotine delivery devices that mimic the appearance of a conventional cigarette (CC). Lately, they have been marketed as tools for quitting smoking. Even though they are promoted as safe alternatives to CC, they are not devoid of hazardous components. Literature reveals that the EC aerosols and e-liquids are a potential source of elements that induce and promote development of chronic conditions. These include trace metals which are leached from their core assembly. Some of these metals like nickel, chromium, cadmium, tin, aluminum, and lead are potential carcinogens. They have been associated with fatal conditions like lung and sinonasal cancer. Besides, they may have adverse effects on oral tissues like periodontal ligament and mucosa where they may trigger chronic periodontitis and oral cancer. However, there is only trivial evidence related to health hazards of metals released from ECs. With this background, the present review first focuses on the structure of the ECs followed by an appraisal of the data from experimental studies about the metals released in EC aerosols and their associated health hazards.

Keywords Chromium · Cadmium · Electronic cigarettes · Health · Lead · Nickel · Trace metals · Vaping

Introduction

Electronic cigarettes (ECs) also called as e-cigarettes, e-cig, electronic vaping device, or personal vaporizer or vaping are essential nicotine delivery devices proposed for long-term smokers or individuals who wish to quit smoking [1]. They were developed and patented in 2003 in Beijing, China, and then launched in Europe and the USA in 2006 [2, 3]. They were marketed as "cheaper and safer smokeless alternative" to traditional cigarettes [1]. In 2014, the US National Health Interview Survey (NHIS) reported that among the 146 million working adults, 3.8% (5.5 million) used ECs [4, 5]. The usage was high among the male, non-Hispanic whites, aged 18–24 years, with an annual household income of less than $35,000 [5].

The EC is an electronic nicotine delivery device that mimics the appearance of a conventional cigarette (CC) [5]. It consists of a battery, a heating element, and a liquid-containing cartridge. The liquids are vaporized by the heating element. Even though ECs are claimed to be safe, the FDA has reported that their cartridges and solutions contain nitrosamines, diethylene glycol, heavy metals, and other contaminants potentially harmful to humans [6]. As they deliver nicotine and chemicals with established adverse effects on humans, their promotion as a safe alternative to CC or as a smoking cessation device is questionable [6].

Several trace metals including aluminum (Al), arsenic (As), cadmium (Cd), chromium (Cr), copper (Cu), iron (Fe), manganese (Mn), nickel (Ni), lead (Pb), and zinc (Zn) are released from ECs [7]. Their concentration is higher in the aerosolized e-liquids as compared to the non-aerosolized forms. Moreover, the concentration of some of these metals was higher in EC aerosol when compared to conventional tobacco smoke [8]. For instance, the levels of Ni and Cr have been found to be very high in aerosols due to their leaching from the core assembly [9]. It was proposed that these metals could be trapped in

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respiratory tissues and could induce pathologies [10]. Additionally, their increased concentration in body fluids may induce systemic and oral conditions.

As the manufacturing process for e-liquids is not standardized, there is a heightened risk that carcinogenic substances may be included. A recent study showed that 10 to 81% of the nicotine (about 2.1 to 15.1 mg) from the cartridges was vaporized [2, 11]. Although precise data regarding EC-induced carcinomas is not available, the elevated levels of nicotine and heavy metals heighten the risk of cancer.

There is immense data related to harmful health effects of carbon monoxide, nicotine, tar, irritants, and other noxious gases present in the conventional tobacco smoke. However, those due to heavy metals and other toxic elements in tobacco smoke are not sufficiently emphasized. Nevertheless, literature reveals that tobacco smoking influences the concentrations of several elements like Al, As, Cd, Cr, Cu, Pb, Mn, Hg, Ni, Po, Se, and Zn in the organs [12]. It is a substantial source of these hazardous elements, not only to the current smoker but also to the passive smokers and non-smokers. Their adverse effects on the fetus through maternal smoking, and on infants through parental smoking, are of special concern.

As the concentration of metals is elevated in EC aerosol when compared to CC smoke, it may be inferred that chronic long-term exposure to these metals, through inhalation of EC smoke, may have a negative impact on humans [8]. Unfortunately, there is insufficient data evaluating these effects. Therefore, the ECs which were introduced as a “healthy alternative” to conventional smoking contain e-liquids supplemented with nicotine, and heavy metals released from the core assembly and liquid vaporization [13]. They may pose health risks similar to conventional tobacco consumption. With this background, the aim of the present work is to first provide an overview of the ECs followed by an insight into the plausible adverse health effects of trace metals released in their aerosol.

Structure of Electronic Cigarettes and Plausible Sources of Trace and Toxic Elements in Electronic Cigarettes

As already stated, the EC has three basic components: a battery, a heating element, and a liquid-containing cartridge (Fig. 1). The secondary parts include an airflow sensor, a microchip for controlling the heating element, and a light-

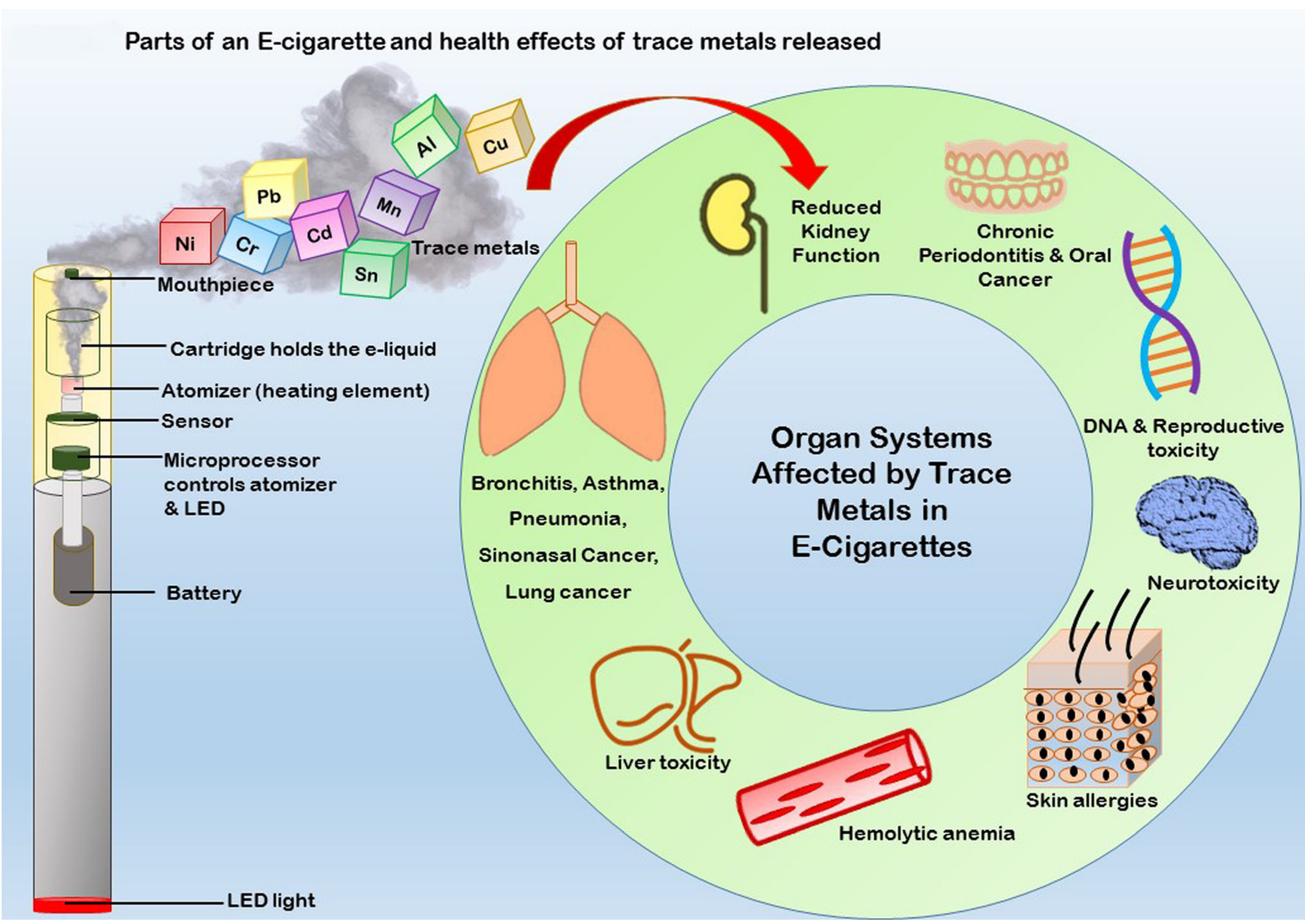

Fig. 1 Parts of an e-cigarette and health effects of trace metals released

emitting diode at the tip that simulates a burning cigarette [14]. The air holes in the devices control the pressure drop and facilitate the air flow required for puffing. The batteries in ECs may be activated automatically through inhalation or manually by pressing the activating button.

The structure of ECs has undergone tremendous change since their introduction in 2003. This includes changes in their size, nicotine concentrations, e-liquid composition, the atomizer, and the type of batteries. There are three generations of ECs [15]. The second- and third-generation devices allow user customization, which influences aerosol production, nicotine delivery, and risk associated with the use of the product [15].

There are three stages in aerosol production [14]. These include preprocessing, aerosol generation, and postprocessing. During the first stage, the e-liquid is transported to the aerosol generator either by capillary action, through a wick, or by mechanically controlled pumps, nozzles, and diaphragms. Other methods of transport include fluid jet, micromesh, microetched screen, or electro-permeable membranes [14]. Some ECs utilize micropumps on microelectro-mechanical systems to deliver predetermined quantities and combinations of e-liquids to an aerosol generator [14]. In some customizable forms, the user may directly drip the liquid onto the heating element before puffing.

In the second stage, aerosol is generated when the e-liquid contacts the heated element [14]. An ultrasonic generator produces aerosol by mechanical dispersion. The final stage includes aerosol processing, as it travels through the central air passage to the consumer [14]. If the aerosol temperature is low, condensation may occur on the inner surface of the passage. These condensed droplets are either removed or reprocessed into aerosol.

Due to the structure and design of ECs, involving a large number of metal components in conjunction with cyclic temperature changes, some metallic compounds may be delivered to the aerosol from the atomizer, batteries, or e-liquids. Studies have reported the presence of metals in EC aerosol at levels higher than that in CC smoke [9, 16, 17]. Various structural components of ECs that may contribute metal particles in aerosols are as follows.

Atomizer

The atomizer is a chamber consisting of a resistance wire encircling the wicking device that draws in the fluid. The smoke is generated through the activation of atomizer by the sensing device. Subsequently, the resistance wire is heated up, and e-liquid vapors are released, which are inhaled by the user. This part of ECs has undergone numerous modifications resulting in the development of "cartomizers" (cartridge plus atomizer), which are a combination of e-liquid distribution system, the wick, and heating element [15, 18]. The second- and third-generation ECs are also called "clearomizers," "tankomizers," or "carotanks," as they can hold several milliliters of fluid in refillable reservoirs [18].

The quantity and quality of aerosol, including the concentration of metals, is dependent on the material of the heating element, its inherent resistance, voltage applied, and temperature. The latter even influences the size of the particles and their generation rate. Warmer air can hold greater quantity of e-liquid per unit volume. The heating element is customarily made of nichrome (an alloy of Ni and Cr) or a combination of nichrome and Kanthal (an alloy of Fe, Cr, and Al) [8]. Therefore, Ni and Cr are most often leached from this unit. Additionally, metals like Cu, Ag, Zn, Sn, Pb, Ca, Mg, Fe, and Al may also be released from the other components of ECs. Their detailed analysis is discussed in a later section.

Batteries

The ECs may be powered by a permanent rechargeable battery or a non-rechargeable battery or a user-replaceable battery [14]. These batteries include metals like Ni-Cd, Ni metal-hydride, lithium (Li) alkaline, Li-polymer, and Li-Mn [14]. These metals may leach into the aerosol from batteries.

E-Liquid

The cartridge can be filled with different e-liquid solutions. They are vaporized by the heating element, and the cigarette is consumed by inhaling the aerosol mist [2]. This simulates the act of real tobacco smoking. The diluents in e-liquid vaporize upon heating. The most common chemicals used are propylene glycol and vegetable or aqueous glycerin, in the ratio of 4:1 [2]. Besides, flavors are added to improve the taste of the liquid. Nicotine is added to propylene glycol in concentrations up to 70 mg/mL [2]. Although propylene glycol is a safe, colorless, and odorless food additive, nicotine is very harmful to both general and oral health.

Metals like Cd, Cr, Pb, Mn, and Ni have been identified in the e-liquids. The nicotine in e-liquids is derived from *Nicotiana tabacum* (cultivated tobacco), a potent bioaccumulator [19, 20]. It absorbs pollutants including the heavy metals from the immediate growing environment. Therefore, Pb may be introduced into the e-liquids during the extraction of nicotine from tobacco leaves [19]. Furthermore, heating coil, wick, and other internal components of ECs may introduce Pb into the e-liquid [9, 21].

The packaging and design of ECs is an important contributor to metal exposure [19]. This was commonly seen in the disposable electronic nicotine delivery system (ENDS) with open-wick designs. Here, the e-liquid was deposited on a fabric pad tightly packed inside the device. Further, it maintained a continuous direct contact with the heating element. Conversely, in the cartridge designs, the liquid is encased in an interchangeable metal chamber. It contacts the chamber but not the heating element. Moreover, the e-liquid may be available as refill solutions packaged in glass or plastic bottles. Therefore, unless the e-liquid was removed from these containers, they could not be contaminated by the metallic components [19].

When activated, the heating coil directly contacts the e-liquid. Higher temperatures may cause leaching of the coil metals into the liquid. Therefore, mere screening of liquids for metals prior to the assembly of the device is insufficient. It is imperative that the design characteristics as well as the formulation of e-liquids be standardized to avoid metallic contamination. Additionally, standard protocols have to be followed in the experimental trials, as determination of metals in aerosols may be affected by the method of collection, the brand of e-liquid (commercially prepared or home brewed), as well as the EC [21]. The following section would describe evidence related to trace metals in EC aerosols and their health effects.

Evidence on the Release of Trace Metals from Electronic Cigarettes

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed to identify the research publications on trace metals associated with ECs and their influence on general and oral health. The databases searched were Medline (PubMed), Scopus, and Web of Science. A combination of keywords like "metals" AND "electronic cigarette" OR "e-cigarette" OR "electrically heated cigarette" OR "ENDS and cigarette" OR "electronic nicotine delivery system" OR "electronic nicotine delivery device" OR "e-liquid" OR "Vaping" AND "health" was used. They were verified in the titles, abstracts, or keywords during the initial search. It resulted in a total of 95 articles (Fig. 2). The data was screened for duplicates which resulted in 61 articles wherein the titles and abstracts were read. The eligibility criteria included free full-text original studies related to the trace metals in ECs and their influence on oral and general health. Only articles in English language were included. Any kind of recommendations, expert statements, reviews, technical reports, and non-original papers was excluded. This resulted in 16 original research articles of which three were excluded due to non-availability of free full text. Full texts of 13 original studies were evaluated. One study was excluded as it did not mention the trace metals evaluated in e-liquid or its aerosol. Finally, full texts of 12 studies were included in the review [8–10, 19, 21–28]. Their salient features, metals evaluated, and results and conclusions were recorded (Table 1). The level of metals in EC aerosols was recorded separately. These concentrations were converted into nanograms/10 puffs, wherever possible, for the ease of comparison of results between the studies [7] (Table 2).

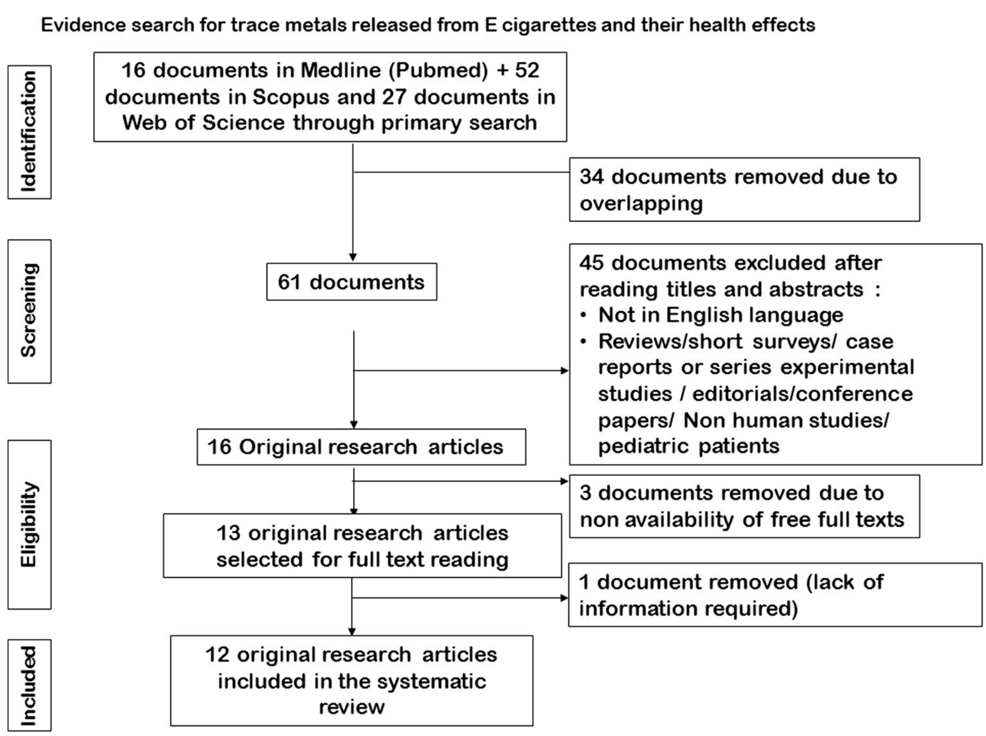

Fig. 2 Evidence search for trace metals released from e-cigarettes and their health effects

Table 1 Salient features of the studies included in the review

Author	Aim of the study and salient features	Results	Metals reported in e-vapors	Conclusion
Williams M et al., 2013 [9]	• The study tested the hypothesis that EC aerosol contains metals derived from various components in EC Salient features: • Cartomizer contents and aerosols were analyzed using light and electron microscopy, cytotoxicity testing, X-ray microanalysis, particle counting, and inductively coupled plasma optical emission spectrometry	Metals in various components of ECs • Filament: Ni-Cr wire coupled to Cu wire • 4 Sn solder joints attached wires to each other and coupled Cu/Ag wire to air tube and mouthpiece • Fibers in two cartomizers → Cu (green deposits) • Centrifugation of fibers resulted in large pellets containing Sn • Cartridge fluid and outer fiber were positive for Sn Cartomizer fluid with Sn particles → cytotoxic to human pulmonary fibroblasts The aerosol contained • Particles > 1 μm: Sn, Ag, Fe, Ni, Al • Silicate and nanoparticles (< 100 nm) of Sn, Cr, and Ni • 9 out of 11 elements in EC aerosol were ≥ corresponding concentrations in conventional cigarette smoke	• Sn • Ag • Fe • Ni • Al • Cr	• Many metals in EC aerosol cause respiratory distress • The presence of metal and silicate particles in aerosol suggests a need for improved quality in EC design and manufacture • Further studies required to evaluate the impact of EC aerosol on health
Schober W et al., 2014 [10]	• Conducted an exposure assessment of EC aerosols to determine the particulate matter, particle number concentrations, volatile organic compounds, polycyclic aromatic hydrocarbons, carbonyls, and metals • 9 volunteers smoked ECs (with and without nicotine) in 6 vaping sessions in a thoroughly ventilated room for 2 h • Levels of EC pollutants in indoor air, fractional nitric oxide, and urinary metabolite profile of subjects were measured • Components of e-liquids were analyzed	• The gas phase showed the presence of 1,2-propanediol, glycerine, and nicotine, and high concentrations of particulate matter (mean 197 g/m^3) • Concentration of carcinogenic polycyclic aromatic hydrocarbons in indoor air increased by 20% (147 ng/m^3) • Al = 2.4-fold increase (median particle number concentrations = 48,620 to 88,386 $particles/cm^3$ • Fractional nitric oxide increased in 7 of 9 individuals • Nicotine content of liquids was 1.2-fold higher than claimed by the manufacturer	• Al	• ECs are a potential source of hazardous pollutants • The ultrafine particles of 1,2-propanediol vapor could be deposited in the lung, and aerosolized nicotine may stimulate release inflammatory signaling molecule nitric oxide upon inhalation • ECs and nicotine liquids should be officially regulated and labeled with appropriate warnings
Goniewicz ML et al., 2014 [22]	Screened the EC vapors for the presence of 4 groups of toxic and carcinogenic compounds: • Carbonyls • Volatile organic compounds • Nitrosamines • Heavy metals Salient features: • Vapors were generated from 12 brands of ECs and the reference product, the medicinal nicotine inhaler, in controlled conditions using a modified smoking machine • Selected toxic compounds were extracted from vapors into a solid or liquid phase and analyzed with chromatographic and spectroscopy methods	• EC vapors contained toxic substances which were about 9 to 450 times lower than the conventional cigarette smoke • Among the 12 metals analyzed, Cd, Ni, and Pb were present in all EC vapors • These metals were detected in trace amounts in medicinal nicotine inhaler and blank samples	• Cd • Ni • Pb	• ECs may substantially reduce exposure to selected tobacco-specific toxicants, but further research is warranted
Williams M et al., 2015 [23]	• Measured the amounts of Sn, Cu, Zn, Sn, Ni, and Cr in EC aerosol from 4 brands • Identified the sources of these metals by examining the elemental composition of the atomizer components	• All filaments were made of Ni and Cr • Thick wires of Cu were coated with either Sn or Ag. They were joined to each other by Sn solder, brazing, or brass clamps	• Sn • Cu • Cr • Ni • Zn	• Sn and other unwanted metals may be removed from EC aerosol by altering designs and using materials of suitable quality

Table 1 (continued)

Author	Aim of the study and salient features	Results	Metals reported in e-vapors	Conclusion
	Salient features: • ECs were dissected and cartomizers examined microscopically; its elemental composition was determined using integrated energy-dispersive X-ray microanalysis • Concentrations of Sn, Cu, Zn, Ag, Ni, and Cr in the aerosol were determined for each brand using inductively coupled plasma optical emission spectroscopy	• Sn was produced in aerosol due to friable solder joints, coating on Cu wires • Sn was reduced in aerosol by coating the thick wires with Ag and by placing stable solder joints outside the atomizing chamber; using brass clamps or brazing for joining the wires also helped in reducing the Sn content	• Ag	
Lerner CA et al., 2015 [24]	• Investigated materials that contribute to tobacco waste and environmental pollution • Oxidants/ROS associated with EC aerosols, aerosol particle size distribution, and Cu levels were assessed • Evaluate oxidants/ROS-induced toxicity when inhaling ENDS/EC aerosols Salient features: • Semi-quantitative methods were used to detect oxidant reactivity in disposable components of ENDS/ECs (batteries and cartomizers)	• Levels of ROS from used and unused cartomizer components were not significantly different; i.e., both were a potential source of oxidants • EC batteries showed ROS reactivity similar to cartomizers and used conventional cigarette filters • ROS produced by EC and within the ENDS aerosols traveled distance equal to that from the mouth to the lung • 50% of the particles by mass in EC were of submicron size (< 1 μm in diameter) • Cu was detected in EC aerosol	• Cu	• The presence of potentially cytotoxic metal and oxidants from EC and its components raises concern regarding the safety of their use and disposal of EC waste products into the environment
Mikheev VB et al., 2016 [25]	• Measured the particle size and distribution of aerosols generated by different ECs ("cigar likes" and "tank-style") • The metal content of the EC aerosol was determined, and the preliminary assessment of nicotine's influence on aerosol size and concentration was performed Salient features: • A real-time, high-resolution aerosol differential mobility spectrometer was used to monitor the evolution of aerosol size and concentration during puff development • Particles generated by ECs were immediately analyzed	• EC aerosols showed bimodal particle size distribution (nanoparticles of 11–25 nm and submicron particles of 96–175 nm count median diameter, respectively) • Concentration of particles ranged from 107 to 108 particles/cm^3 • "Dry puff" tests with no EC liquid revealed the presence of nanoparticles Analysis of the bulk aerosol on the filter showed the presence of metals (As, Cr, Ni, Cu, Sb, Sn, and Zn with varied levels across the nicotine- and non-nicotine-containing flavors) • Filters showed Cu, Cr, and Pb contamination	• Cr • Ni • Zn • Cu • As • Sb • Sn	• ECs generated high concentrations of nanoparticles of metals which could have toxicological impact
Williams M et al., 2017 [8]	• Determined the quantity of 36 inorganic chemical elements in aerosols from disposable ECs and electronic hookahs (EHs) • Examined the influence of puffing topography and the source of elements released in aerosols Salient features: • The chemical elements and their concentrations in EC/EH aerosols were analyzed in the disassembled atomizers	• 35 out of 36 elements were detected in EC/EH aerosols, while only 15 in conventional tobacco smoke Metals in various components: • Filament: Ni and Cr • Thick wire: Cu coated with Ag • Brass clamp: Cu and Zn • Solder joints: Sn and Pb (in EH) • Wick and sheath: Si, O, Ca, Mg, and Al • Concentration of elements/metals in EC aerosols varied within and between the brands; a total concentration of elements/metals in aerosol ranged from 1.778 to 7.257 μg/10 puffs • Metals in EC aerosol: Ca, Cu, Sn, K. B, and Zn • Si was a dominant element in aerosols of both EC and conventional cigarette across all brands	• Ca • Cu • Sn • K • B • Zn • Ni	• The EC/EH aerosols contained a mixture of elements (including heavy metals) with concentrations significantly higher than those in conventional cigarette smoke

Table 1 (continued)

Author	Aim of the study and salient features	Results	Metals reported in e-vapors	Conclusion
		• Pb was present in EH only (0.165 ± 0.048 μg/10 puffs) • Total element concentration decreased at the higher air flow rate • The relative amount of elements in the first and last 60 puffs were different		
Beauval N et al., 2017 [26]	• Developed and validated analytical procedures for multicomponent analysis of 6 e-liquid refills and their resultant aerosols • The results were compared to conventional tobacco smoke Salient features: • Utilized gas chromatography, high and ultra-performance liquid chromatography, inductively coupled plasma with mass spectrometry, and ultraviolet and flame ionization detection method to identify the main constituents in e-liquids as well as identify multiple potentially harmful components	E-liquid aerosols showed • Trace elements ($\leq$`3.4 pg/mL puff) which were less than conventional cigarette smoke • Quantifiable concentrations of Al, Co, Mn, Ni, Cd, Cr, and Sb • Pb (due to contamination by smoking machine) • Cr from nichrome wires in EC • Cd, As, Pb, and thallium were quantified in conventional tobacco smoke (1.02 pg/mL puff for thallium to 44.98 pg/mL puff for Cd)	• Cd • Cr • Sb • Pb	• Metals like Cr are carcinogenic • Further studies are required to explore its carcinogenic potential in EC users
Hess CA et al., 2017 [27]	The study involved characterization and quantification of toxic metals in e-liquids of 5 EC brands Salient features: • Inductively coupled plasma with mass spectrometry was utilized to analyze cartomizer liquid in 10 cartomizer refills for each of the 5 brands • 5 metals were tested: Cd, Cr, Pb, Mn, and Ni	• The e-liquid tested positive for Pb, Cr, Ni, and Mn • Source of Ni and Cr was leached from nichrome-heating elements and showed marked variability within and between brands • Low Cd concentrations	–	• Additional research is required to evaluate the role of EC as a source of toxic metals to the users
Palazzolo DL et al., 2016 [21]	• Investigated the presence of trace metals in the EC aerosol which could potentially impact respiratory tissues and induce pathology • Utilized peristaltic pumps and mixed cellulose ester membranes to collect and trap EC-generated aerosol Salient features: • Peristaltic pumps were used to generate and transport aerosol onto mixed cellulose ester membranes to mimic trapping of metals • Following metals were captured and analyzed: Al, As, Cd, Cu, Fe, Mn, Ni, Pb, and Zn • The presence of trace metals on unexposed membranes and on membranes exposed to mainstream smoke and in e-liquid before aerosolization and untouched by the EC device was determined • All metals were quantified using inductively coupled plasma with mass spectrometry (ICP-MS) • The EC core assembly was analyzed using scanning electron microscopy that included elemental analysis	• The amount of trace metals generated in EC aerosol was lower than that of the traditional mainstream smoke • Ni was significantly higher on membranes exposed to aerosol • Contents of Al, As, Fe, Mn, and Zn were higher on membranes exposed to cigarette smoke • The contents of all metals except Fe were negligible in e-liquids before aerosolization compared to amounts in aerosolized forms • The core assembly revealed traces of Al, Fe, Ni, and Zn • Only Ni (from the core assembly) was higher in EC-generated aerosol	MCE membranes exposed to aerosol: similar to controls • Ni	• The amount of trace metals from EC aerosols was lower than that from traditional mainstream smoke • Only Ni from the core assembly was higher than controls
Dunbar ZR et al., 2018 [19]	• Utilized a novel graphite furnace technology to compare the concentration of Pb between commercially available e-liquids in the USA and Canada	• Pb was present in open-wick ENDS devices • In bottled e-liquids, no quantifiable levels of lead were detected	–	• Quantifiable levels of Pb are present in certain disposable ECs • The design of ENDS devices may contribute to Pb exposure

Table 1 (continued)

Author	Aim of the study and salient features	Results	Metals reported in e-vapors	Conclusion
	Salient features: • Nicotine-free disposable ENDS devices ($n = 11$) and bottled refill solutions ($n = 12$) that contained nicotine were purchased between 2015 and 2017 • E-liquids extracted from the disposable products and individual containers were analyzed for lead content by graphite furnace using atomic absorption detection			• Pb testing should be incorporated into future chemical analyses of ENDS devices
Olmedo P et al., 2018 [28]	• Investigated the transfer of metals from the heating coil to the e-liquid in the EC tank and the generated aerosol • 56 EC devices were sampled • Metals were reported as mass fractions (μg/kg) in liquids and converted to mass concentrations (mg/m^3) for aerosols	• Median metal concentrations were higher in samples from the aerosol and tank • Aerosol mass concentrations for Cr, Mn, Ni, and Pb exceeded the current health-based limits	• Al • Cr • Ni • Pb • Zn • Mn • Fe • Cu • Sb • Sn • Cd • As	• ECs are a potential source of toxic heavy metals like Cr, Ni, and Pb and metals that are toxic when inhaled (Mn and Zn) • Coil contact induced e-liquid contamination

Table 2 Concentration of metals in EC aerosols and method of estimation

Author	Concentration of metal in EC aerosol as reported	Concentration of metal in EC aerosol in ng/10 puffs	Method of estimation
Williams M et al., 2013 [9]	• Na = 4.18 μg/10 puffs • B = 3.83 μg/10 puffs • Si = 2.24 μg/10 puffs • Ca = 1.03 μg/10 puffs • Fe = 0.52 μg/10 puffs • Al = 0.394 μg/10 puffs • K = 0.292 μg/10 puffs • S = 0.221 μg/10 puffs • Cu = 0.203 μg/10 puffs • Mg = 0.066 μg/10 puffs • Zn = 0.058 μg/10 puffs • Sn = 0.037 μg/10 puffs • Pb = 0.017 μg/10 puffs • Ba = 0.012 μg/10 puffs • Zi = 0.007 μg/10 puffs • Cr = 0.007 μg/10 puffs • Ni = 0.005 μg/10 puffs • Mn = 0.002 μg/10 puffs	• Na = 4180 ng/10 puffs • B = 3830 ng/10 puffs • Si = 2240 ng/10 puffs • Ca = 1030 ng/10 puffs • Fe = 520 ng/10 puffs • Al = 394 ng/10 puffs • K = 292 ng/10 puffs • S = 221 ng/10 puffs • Cu = 203 ng/10 puffs • Mg = 66 ng/10 puffs • Zn = 58 ng/10 puffs • Sn = 37 ng/10 puffs • Pb = 17 ng/10 puffs • Ba = 12 ng/10 puffs • Zi = 7 ng/10 puffs • Cr = 7 ng/10 puffs • Ni = 5 ng/10 puffs • Mn = 2 ng/10 puffs	• Inductively coupled plasma optical emission spectrometry (ICP-OES)

Table 2 (continued)

Author	Concentration of metal in EC aerosol as reported	Concentration of metal in EC aerosol in ng/10 puffs	Method of estimation
	• Ti = 0.002 μg/10 puffs • Li = 0.008 μg/10 puffs	• Ti = 2 ng/10 puffs • Li = 8 ng/10 puffs	
Goniewicz ML et al., 2014 [22]	The content of metals per 1 EC was as follows: • Cd = 0.01 to 0.22 μg/150 puffs • Ni = 0.11 to 0.29 μg/150 puffs • Pb = 0.03 to 0.57 μg/150 puffs	The content of metals per 1 EC was as follows: • Cd = 0.66 to 14.6 ng/10 puffs • Ni = 7.33 to 19.3 ng/10 puffs • Pb = 2 to 38 ng/10 puffs	• Inductively coupled plasma with mass spectrometry (ICP-MS)
Lerner CA et al., 2015 [24]	• Cu = 24.3 to 224.7 ng/puff	• Cu = 243 to 2247 ng/10 puffs	• Atomic absorption
Williams M et al., 2015 [23]	• Sn (brand A) = < 6 μg/10 puffs • Cu • Zn • Ag • Cr • Ni < 0.2 μg/10 puffs	• Sn (brand A) = < 6000 ng/10 puffs • Cu • Zn • Ag • Cr • Ni < 200 ng/10 puffs	• ICP-OES
Palazzolo DL et al., 2016 [21]	MCE membranes exposed to aerosol: • Al = 1.2 ± 0.2 μg/45 puffs • As = 0.050 ± 0.002/45 puffs • Cd = 0.047 ± 0.003 μg/45 puffs • Cu = 0.05 ± 0.01/45 puffs • Fe = 0.001 ± 0.001/45 puffs • Mn = 0.16 ± 0.04/45 puffs • Ni = 0.024 ± 0.004 μg/45 puffs • Pb = 0.014 ± 0.006/45 puffs • Zn = 0.09 ± 0.02/45 puffs	MCE membranes exposed to aerosol: • Al = 266 ± 40 ng/10 puffs • As = 11 ± 0.44 ng/10 puffs • Cd = 10 ± 0.6 ng/10 puffs • Cu = 11 ± 2 ng/10 puffs • Fe = 0.22 ± 0.22 ng/10 puffs • Mn = 35 ± 8.8 ng/10 puffs • Ni = 5.33 ± 0.88 ng/10 puffs • Pb = 3.11 ± 1.33 ng/10 puffs • Zn = 20 ± 4 ng/10 puffs	• ICP-MS
Williams M et al., 2017 [8]	• Ca = 0.480 μg/10 puffs • Cu = 0.072 μg/10 puffs • Sn = 0.036 μg/10 puffs • K = 0.151 μg/10 puffs • B = 0.052 μg/10 puffs • Zn = 0.079 μg/10 puffs • Ni = 0.005 μg/10 puffs	• Ca = 480 ng/10 puffs • Cu = 72 ng/10 puffs • Sn = 36 ng/10 puffs • K = 151 ng/10 puffs • B = 52 ng/10 puffs • Zn = 79 ng/10 puffs • Ni = 5 ng/10 puffs	• ICP-OES

The method used for estimating the levels of metals was also noted.

Results

About 12 studies were included in the review. They were all experimental research that simulated the EC smoking. These studies analyzed an array of metals in EC aerosols, ranging from potentially toxic heavy metals like Ni, Cd, Cr, Mn, Pb, As, B, Sn, Ba, Al, Zr, Ti, Ag, and Li to metals which may not have adverse health effects in low concentrations like Ca, K, Zn, Fe, Na, Mg, and Cu. Additionally, Si was also identified in a study [8]. The salient features of these studies may be summarized as follows.

Sampling of EC Aerosol

The sampling methods for EC aerosols varied in different studies. For instance, in a study, e-vapors were generated with a smoking machine and the Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) approach was used for mimicking the vaping (55 mL puff over 3 s, twice a minute) [26]. E-vapors were collected from 96 puffs of ECs. Another study imitated conditions reflecting the actual manner of ECs to generate the aerosol. Results of inhalation topography measurement among 10 "e-smokers" who regularly used ECs (> 1 month) were used [22]. The testing procedures used averaged puffing conditions, i.e., puff duration (1.8 s), intervals between puffs (10 s), puff volume (70 mL), and the number of puffs taken in one puffing session as 15. A total of 150 puffs were taken from each EC in a 10 series of 15 puffs with an interval of 5 min between the series. Each EC was tested three times on three following days after batteries were recharged during nights. Vapors were visible during the full 150 puffs taken from each tested product. The metals were collected through absorption into the indoor air in gas washing bottles containing methanol. Their quantization was done with inductively coupled plasma with mass spectrometry (ICP-MS) technique.

Method for Detection

The studies utilized either ICP-MS or inductively coupled plasma optical emission spectrometry (ICP-OES) to quantify the metals released in the aerosols (Table 2) [8, 9, 21–23]. One study used atomic absorptiometry for analysis [24].

Metals Analyzed

Most of the studies showed the presence of Ni, Cr, Pb, Sn, Al, Cd, and Cu [8–10, 19, 21–23, 25–27]. Relatively small levels of other metals like As, Fe, and Zn were reported [8–10, 21, 23, 25–27]. The presence of Ni in EC aerosol was reported in nine studies [8–10, 21–23, 25, 27, 28]. Its levels varied between 5 and 7.33 ng/10 puffs [9, 22]. Cr was reported in six studies [9, 10, 21, 25, 26, 28] with levels ranging from 7 to < 200 ng/10 puffs in two studies [9, 23]. Pb with levels ranging from 2 to 38 ng/10 puffs was reported in six studies [9, 19, 21, 22, 26, 27]. Likewise, Al was reported in about five studies in concentrations ranging from 266 to 394 ng/10 puffs [9, 10, 21, 26, 28]. Cd was reported in four studies with levels ranging from 0.66 to 14.6 ng/10 puffs [21, 22, 26, 28]. Sn was reported in six studies [8–10, 23, 25, 28] with a concentration ranging from 36 to < 6000 ng/10 puffs in three studies [8, 9, 23]. Cu was observed in eight studies [8–10, 18, 21, 24, 25, 28] with levels ranging from 11 to 2247 ng/10 puffs in two studies [21, 24]. Similarly, Mn was reported in four studies [9, 10, 21, 28] at a concentration of 2 to 35 ng/10 puffs in two studies [9, 21].

Source of Metals in Electronic Cigarettes

About five studies investigated the sources of metals in aerosols from ECs [8, 9, 23, 26, 27]. One study investigated metal substrates in different components of atomizer [8]. It was reported that metals like Ni and Cr were released from the nichrome filament [8, 9, 23, 26, 27], Cu and Ag from the thick wire [8, 9, 23], Cu and Zn from the brass clamp, Sn and Pb from solder joints, and Si, oxygen, Ca, Mg, and Al from the wick and sheath [8, 9]. The elemental analysis of the core assembly revealed the presence of trace metals, especially Al, Fe, Ni, and Zn [21]. EC batteries and cartomizer were reported as sources of Cu in one study [24].

High levels of Sn were reported to be released from friable solder joints and Cu wires coated with Sn [8, 23]. In one study, Sn was reported in the pellets derived from the centrifugation of the outer and inner fibers of the cartomizer [8]. Sn "whiskers" (microscopic, conductive crystals that emanate spontaneously from pure Sn) were present on the solder joints and on wires near the joints. Centrifugation of outer and inner fibers of cartomizer produced large pellets of white and black Sn, respectively. The black pellets contained tin oxide, which is usually produced when the metal is heated. Therefore, its deposition near the filament actually confirmed its source. Additionally, green coloration was observed in some cartomizer fibers. These were mainly Cu particles that migrated from the solder or the large wire. The authors concluded that Sn in the centrifuged pellets percolated from the solder joints or from the solder that escaped into the cartomizers during manufacturing or presale testing. They suggested that as the solder joints were Pb free, they were more fragile and susceptible to cyclic temperature changes. Small amounts of Ni and Cr from the nichrome wire, Ag from the coatings on Cu wire, and Fe from the mouthpiece and/or metallic base at the battery interface were also reported. Besides, silicate beads from the fiberglass wick were found in the aerosol. The elemental analysis of wick showed the presence of silicon, Ca, Al, and Mg. Furthermore, boron, which is used for the manufacture of glass wick, was also reported.

An earlier detailed analysis of the core assembly by the same authors revealed that the inner and outer surfaces of the casing comprised of Fe and Mn [9]. The core tip consisted of Ni, Cu, and Zn. The upper core was composed of Si while Zn and Pb were present in the gasket. The fabric material contained high percentages of Cu and Ni. The outer and inner surfaces of the woven tube comprised primarily of Si, Sn, and Al. The upper and lower halves of the core were coated with Ag, with underlying metal compositions of Ni and Cu. The wick fibers within the surrounding resistance coil consisted mainly of Si while the coil filament around the wick fibers contained high quantities of Ni, with less amounts of Si and Mn. The weld joint connecting the coil with the thick extension wire was made up of high amounts of Ni and some Si. The thick extension wire beyond the weld joint consisted of Ni with minimal amounts of Cu. The juncture of thick extension wire, coil, and weld joint contained mainly Ni (53%) and Cr (18%). The levels of the latter were beyond the acceptable threshold of 5%.

Quantifiable levels of Pb were reported in the open-wick ENDS devices in another study, and it was suggested that the design characteristics of ECs were responsible for its presence [19]. Furthermore, the direct contact between the coil and e-liquid was reported as a cause in another study [28].

Some studies compared the metals in different components of various EC brands [9, 23]. For instance, a study reported that for most brands (BluCig, NJOY King, Mistic, V2 Cigs, Luxury Lites, Smooth, Tsunami, and Imperial Hookah), the filament comprised of Ni and Cr [9]. In one brand (Square 82), the filament mainly consisted of Cr, Fe, and Al (Kanthal) along with Mo, Ti, and Cu. Brands like Vype and Starbuzz had Fe, Cr, and Ni in their filaments. The thick wire was made of Cu coated with Ag in the brand BluCig while in NJOY King, Tsunami, and Starbuzz, these wires comprised of Cu and Ni coated with Ag. In the brand Smooth, the Cu wire was coated with Sn. The thick wire and filaments were joined with either clamps or solder. In five brands (BluCig, NJOY King, Mistic, Vype, and Starbuzz), these wires were joined by Cu/Zn (brass) clamps, while in other brands (Square 82, V2 Cigs, Luxury Lites, Smooth, Tsunami, and Imperial Hookah), they were joined with a solder, predominantly made of Sn. The electronic hookahs contained both Sn and Pb in their solder joints, and Pb was detected in their aerosols. The joints between the thick wire and battery were made of Sn solder in all brands, except in Luxury Lites and Imperial Hookah, where Pb was present. The sheaths comprised of Si, oxygen, Ca, Al, and Mg in all the brands.

A similar work was reported by these authors in which they compared four brands of ECs [23]. Although the names of the brands were not revealed, three brands (A, B, and C) had a cartomizer while one brand (D) was a disposable device. Aerosol from brand A had high levels of Sn. Further analysis of this brand revealed that Sn concentrations varied by approximately 30-fold between its cartomizers. Therefore, two cartomizers (A1 and A2), representing the high and low end ranges for Sn, in brand A, were analyzed. The thin wires in both the cartomizers were made of Ni and Cr while the thick Cu wire was coated with Ag. The clamps joining the two wires in cartomizer A1 comprised mainly of Cu while in A2, they contained Ni with some Cu and Zn. In brand A, the thick wire was attached to the air tube via Sn solder joints. The fibers in cartomizer A1 were coated with Sn and Cu. It was suggested that unstable solder joints were a source of Sn in the cartomizer of brand A. The basic design of the cartomizers in brands B, C, and D was similar to that of brand A. The thin wire was made of nichrome. It coiled around a loop of thick wire, made of Cu, coated with Ag in brand B and Sn in brand C. In all the three brands, the thin and thick wires made of Ni and Cr were crimped together inside a metal casing. The thick Cu wire was coated with Ag. The joints between the thick and thin wires in brand B comprised of Sn solder, and those in brand C are mainly of Cu and Cr while in brand D, they were joined together by a Cu-Zn alloy (brass) clamp. In cartomizers from brand B, the thick wire was joined to the air tube and mouthpiece by Sn solder. However, in brand D, they were attached directly to the battery by the Sn solders.

Concentrations of Metals in Conventional Cigarette Smoke and Electronic Cigarette Aerosol

About 10 studies compared metals among different brands of ECs [8, 9, 19, 21–27] while five studies included comparison of their levels between the CC smoke and EC aerosol [8, 9, 22, 24, 26].

The CC smoke is a substantial source of hazardous metals not only to the smoker but also to the passive non-smokers [29]. Smoking alters metal homeostasis in the body, resulting in a number of diseases. Metals like Al, Cd, Cr, Cu, Pb, Mn, Hg, Se, and vanadium have been reported in cigarette smoke. It is generally accepted that Cd and Pb concentrations in CCs range from 1 to 3 μg/g and from 1 to 2 μg/g, respectively [29–31]. In filter cigarettes, the Cd and Pb concentrations were about 1.7 and 2.4 μg/g, respectively [31]. On an average, cigarettes contain 1–2 μg of Cd and a person smoking 20 cigarettes/day may inhale up to 1 μg of Cd/day [29].

As already stated, tobacco grown in soils with higher available Cd and Pb may show their increased levels in the tobacco lamina. Therefore, cigarette brands with similar tar measure could yield different levels of heavy metals, depending on the growth conditions of tobacco. This was seen in a study evaluating levels of heavy metals in 20 popular cigarette brands, in Saudi Arabia [29]. The levels of Cd inhaled from smoking one pack (20 cigarettes) of different brands were about 1.40–2.70 μg. This value was very close to cigarettes from the

United Kingdom (UK) (1.32–2.64 μg) and Korea (1.54–3.08 μg). However, the amount of Pb inhaled from these brands was four times higher when compared with the UK and Korean cigarettes. It was suggested these variations could be attributed to the metal content in the soil, type of tobacco, growth conditions, and tobacco treatment process.

Likewise, in another study, the levels of As, Cd, Cr, Ni, and Pb were estimated in cigarettes obtained from adult smokers participating in the 2009 wave of the International Tobacco Control (ITC) United States Survey [32]. Differences in the metal concentrations between different cigarette brands were attributed to the source of tobacco. For Ni, significant pairwise differences were seen between Philip Morris USA (PMUSA) and R. J. Reynolds (RJR) brands as well as between these and other brands. The RJR brand had higher levels of Cr than any other brand. However, the levels of As, Cd, and Pb did not differ significantly across the brands.

In the studies included in the present review, the concentration of metals in EC aerosols varied within and between the brands. Further, differences were present when EC aerosols were compared to CC smoke. For instance, a comparative analysis of metals in the aerosols of branded ECs (Vype, BluCig, NJOY King, Square 82, Mistic, and V2 Cigs), disposable electronic hookahs, and CCs (Marlboro Red cigarettes) revealed an inter- and intrabrand variation in the levels, despite similar design characteristics of ECs [8]. Their total concentration in the aerosol ranged from 1.778 μg/10 puffs (BluCig) to 7.257 μg/10 puffs (Vype). Metals like Ca, Cu, Sn, K, B, and Zn were present in concentrations > 0.01 μg/10 puffs in EC aerosols. When these concentrations were compared to mainstream smoke from conventional branded cigarette (Marlboro Red), 15 elements were found in CC smoke as opposed to 35 in EC aerosol. Surprisingly, Pb was not detected in the branded CC. However, it was present in the two brands of electronic hookahs. Twelve of these elements (K, iridium, Zr, tungsten, lanthanum, Ba, indium, vanadium, Cr, Mo, Mn, Ti) were present in seven brands of ECs but were not significantly different from the CCs. Further, 16 elements (silicon, Ca, Na, Cum Mg, Sn, Pb, Zn, B, Se, Al, Fe, germanium, Sb, Ni, Sr) were present in most of the brands of ECs, except for Pb which was present only in two brands. In some EC brands, these elements were significantly higher than in the branded CC. Greater inter- and intrabrand variability was seen in the elemental composition of ECs than the branded CCs.

Another study examined vapors generated from 12 brands of ECs (11 Polish and 1 British). They identified only Ni, Cd, and Pb in EC aerosols. Their concentrations were similar to those of a commercially available nicotine inhaler (Nicorette) [22]. The concentrations of Ni ranged from 0.11 to 0.29 μg/EC (150 puffs) while Pb ranged from 0.03 to 0.57 μg/EC. However, Cr or Mn was not reported in any brand.

An evaluation of four brands of ECs (three with cartomizer and one disposable device) for the presence of Sn, Cu, Zn, Ag, Ni, and Cr in their aerosols revealed that, except for Sn, concentrations of all the metals were generally below 0.20 μg/10 puffs [23]. Sn was not detected in the aerosol of two brands (C and D). The levels of Cu, Zn, and Sn differed significantly within the ECs of the same brands, purchased at different times, within 2 years. Cu concentrations were higher in brands B and D than in brand A. Cr and Ni were either not detected (brand C) or were negligible (brand D). The concentration of Sn in brands B and D ranged from 0 to 0.036 μg/10 puffs, while in brand A, the levels were 100 to 1000 times that of the other three brands. Interestingly, the levels of Sn varied within the cartomizers of brand A (range = 0.398 to 11.3 μg/10 puffs).

A study compared the oxidant activity between branded ECs (BluCig ECs, eGO Vision® Spinner) and CCs (Marlboro 100s, Kentucky 3R4F). It revealed that the disposable components of ENDS (batteries and cartomizers) and CC filters harbored oxidative properties [24]. The oxidants were present inside the cartomizer and outside an EC puff. The amount of Cu in branded EC aerosols was 116.79 ± 83.59 ng/puff (range from 24.3 to 224.7 ng/puff). It was about 6.1 times higher than that reported for CC smoke.

Furthermore, a study evaluated the particle size generated by three branded non-refillable ECs (NJOY King, V2 Cigs, and BluCig brands) [25]. A standard CC (Kentucky 3R4F) enabled comparison of aerosol size distributions between ECs and combustible tobacco products. Significant variations in the levels of As, Cr, Ni, Cu, Sb, Sn, and Zn were reported across the nicotine- and non-nicotine-containing ECs. The EC aerosols exhibited a bimodal particle size distribution, i.e., nanoparticles (11–25 nm count median diameter) and submicron particles (96–175 nm count median diameter). Each mode had comparable concentrations (10^7–10^8 particles/cm^3). The ECs generated high concentrations of nanoparticles, and at high dilution, their fraction increased but the submicron fraction decreased. This behavior was different from the CC where at both low and high dilutions, most of the particles remained in the submicron range. It was suggested that even though the mass of nanoparticles was small, their toxicological impact could be significant. Moreover, the toxic chemicals attached to the small nanoparticles could produce greater adverse health effects than when attached to larger submicron particles.

Likewise, about six e-liquid refills (NHOSS® brand) and their resultant vapor emissions were compared to tobacco smoke in a study [26]. Two flavored e-liquids (chlorophyll mint and blond flavor without nicotine or with 16 mg/mL nicotine) and a “control” e-liquid (unbranded, flavorless, containing a mixture of propylene glycol/glycerol, without nicotine or with 16 mg/mL of nicotine) were analyzed. Quantifiable concentrations of Al, Co, Mn, Ni, and Pb were found in several e-vapor samples in both the test and controls. Only increased concentrations of Cd, Cr, and Sb were seen in some e-vapors. Heavy metals like As, Cd, Pb, and Ti were quantified in branded CC smoke (Kentucky 3R4F).

Furthermore, the metal emanation from cartomizer liquid was analyzed in a recent work that characterized and quantified toxic metal concentrations in five popular brands of cig-a-like ECs in the USA [27]. The evaluation of cartomizer liquid in 10 cartomizer refills for five brands revealed the presence of Cd, Cr, Pb, Mn, and Ni. Brand A had the highest mean concentrations of all the metals. In brand A, the mean Ni concentration was nearly 400 times that of brand D (lowest Ni concentration). Likewise, the mean Cr concentration in brand A was 39 times, and the mean Mn concentration was 240 times that of the lowest Cr and Mn concentrations (brand E). Cd levels were fairly low, except in brand A, while Pb concentrations, although low in brands C and D, were highly variable in other brands. It was suggested that the source of Ni and Cr was nichrome-heating elements while Pb and Mn were plausibly present due to contamination of the heating coil during manufacturing.

Similar analysis of metal release from branded e-liquids and their comparison with the branded CC smoke showed that the concentrations of Al, As, Cd, Cu, Fe, Mn, Ni, Pb, and Zn in e-liquid (μg/L) were higher than those in the tobacco and paper of CC (Marlboro brand) [21]. Although the content of As in the e-liquid was quite low, it was below the detection limit in tobacco and paper.

Additionally, the e-liquids may be a source of Pb as was reported in the analysis of branded e-liquids of different packaging and product designs (11 nicotine-free disposable devices and 12 bottled refill solutions containing nicotine), commercially available in the USA and Canada [19]. It was observed that none of the bottled e-liquids contained quantifiable levels of Pb. However, Pb was present in certain disposable EC devices.

The above data shows that further research is required to evaluate metal exposure in the generated aerosol. There was high variability in the levels of metals within the products manufactured at different times in the same brands as well as between the brands. Significant differences were also reported when EC aerosols were compared to CC smoke. Their concentration was more in the EC aerosols which could be related to differences in the design characteristics. Besides, non-standardization of e-liquid compositions and lack of strict protocols to evaluate the aerosols may also be responsible for these variations. Therefore, it is difficult to determine which brands or devices may be less harmful than others with regard to toxic metal exposure.

Diseases Caused by Electronic Cigarettes

EC aerosols have been associated with diseases like bronchial asthma, diabetes, kidney, and cardiovascular problems, and they are hazardous during pregnancy [33–38] (Fig. 1). There is very little awareness regarding the health issues related to ECs despite their growing popularity. A recent study involving 35,904 high school students in South Korea investigated the association between EC use and asthma [33]. It was found that the prevalence of asthma in "current EC users," "former EC users," and "never EC users" was 3.9, 2.2, and 1.7%, respectively. The odds for asthma in current EC user was very high when compared to non-EC users. It was concluded that EC usage was strongly associated with asthma. Besides, ECs have been shown to increase glycated hemoglobin levels in e-smokers with no history of diabetes [34, 35]. This is mainly related to nicotine present in both CCs and ECs. Studies have shown that nicotine adversely affects the blood sugar levels [39]. There is also a negative impact of ECs on the cardiovascular system. The ECs increase arterial stiffness, blood pressure, and heart rate in humans [36]. They increase the endothelial progenitor cells (EPCs) within the first hour of using one EC [40]. Elevated EPCs signify damage to the inner lining of blood vessels. The EPC levels may return to normal within 24 h of usage. Additionally, the e-liquids have been demonstrated to be nephrotoxic in rats [37]. Reduced levels of uric acid and urea but increased oxidative stress (reduced superoxide dismutase and catalase activities) were reported in rats exposed to these liquids [37]. Many renal collecting ducts showed signs of damage. It was concluded that e-liquids altered the anti-oxidant defense mechanisms and promoted minor changes in renal function parameters. ECs have been reported to be unsafe during pregnancy owing to nicotine and other chemical constituents [38].

The health effects of various components of ECs were discussed in a recent work which suggested that factors like climate conditions, air flow, room size, number of users in the vicinity, type and age of systems being used, battery voltage, puff length, interval between puffs, and user characteristics (e.g., age, gender, experience, health status) may contribute to inhalation effects of ECs [41]. Additionally, particle size may affect the site and pulmonary absorption [41, 42]. Components like glycol and glycerol vapors, which are known upper airway irritants, may dry the mucous membranes and eyes [41, 43]. Furthermore, ECs may be associated with an increased risk of nicotine toxicity due to its high availability in the cartridges [41]. An acute exposure to ECs or EC aerosol may result in mouth and throat irritation and dry cough at initial use, decrease in fractional exhaled nitric oxide (FeNO), and increase in the respiratory impedance and respiratory flow resistance similar to cigarette use [41].

The following section would describe the health issues related to inhalation of toxic metals reported in EC aerosols.

Evidence on Adverse Health Effects of Trace Metals in Electronic Cigarette Aerosols

The results from the experimental studies included in this review show that EC aerosol is a concoction of potentially toxic trace metals. The main source of these metals is the core assembly. Further, the solder joints and composition of the e-liquids before aerosolization also influence the type and concentration of metals released [19, 21, 26, 27] (Table 1). One study reported a difference in the levels of trace metals between nicotine- and non-nicotine-based ECs [25]. The concentration of metals released in EC aerosols was reported to be expressed in nanograms/10 puffs for the ease of comparison [7] (Table 2). However, due to the difference in the units in which the concentrations were reported in various studies, this conversion was applied only for six studies [8, 9, 21–24].

Some of these metals (Ni, Cr, Cd, Pb, Al, Sn, Cu, and Mn) have numerous negative influences on human health. They produce direct effects on vital organs like the lungs, liver, kidney, and brain and indirectly lead to immunologic, neurologic, reproductive, developmental, and carcinogenic effects (Fig. 1, Table 3). These may be acute or chronic, depending upon the duration of exposure.

Unlike the conventional tobacco smoking, studies reporting the direct health effects of trace metals in EC aerosols are negligible. Therefore, the following section would describe the general evidence related to the influence of some of these heavy metals (Ni, Cr, Cd, Pb, Cu, Al, Sn, and Mn), on systemic and oral health (Fig. 1, Table 3).

Table 3 Adverse health effects of trace metals in e-cigarettes

Metal	Source of the metal in EC [Ref]	Adverse health effects
Nickel	Filament [8, 9, 21, 23, 27] E-liquid [27]	Exposure to high levels of nickel • Lung, nasal, and paranasal cancers • Kidney toxicity, genotoxicity, hematoxocity, neurotoxicity, reproductive toxicity • Changes in heart rate • Oxidative stress • Nickel dermatitis
Chromium	Filament [8, 9, 23, 26, 27]	Short-term effects on • Respiratory system: shortness of breath, coughing, wheezing • Gastrointestinal system: abdominal pain, vomiting, and hemorrhage Chronic long-term inhalation: • Respiratory system: perforations and ulcerations of the septum, bronchitis, decreased pulmonary function, pneumonia, asthma, nasal itching, soreness, lung cancer • Negative impact on the liver, kidney, immune systems, and blood • Complications during pregnancy and childbirth
Lead	E-liquid [19, 27]	• Children: impaired cognition, reduced growth, low birth weight, slowed postnatal neurobehavioral development, and developmental defects • Adults: slowed nerve conduction in peripheral nerves, hearing loss, decreased sperm count, spontaneous abortions, anemia, hypertension, carcinogenesis
Aluminum	Wick and sheath [8] Core assembly [21]	• Slow bone growth in infants • Mental impairments • Degenerative brain diseases (Alzheimer's and Parkinson's) • Microcytic anemia • Osteomalacia
Cadmium	E-liquid [22, 26]	Short-term effects: • Bronchial and pulmonary irritations • Acute exposure: impairment of the lung Long-term effects: • Inhalation and ingestion: accumulation in the kidneys and negative impact on the liver, lung, bone, immune system, blood, and nervous system • Itai-itai disease (cadmium poisoning due to mining in Toyama, Japan) • Lung cancer
Tin	Solder joints [8] Cartridge fluid and outer fibers [9]	• Anemia • Stannosis
Copper	Thick wire [8, 9, 23] Brass clamp [8] Filters [25]	• Irritation of the nasal mucous membranes, eyes, upper respiratory tract, metallic taste, nausea • Acute copper poisoning: liver injury, methemoglobinemia, hemolytic anemia, epigastric pain, headache, nausea, dizziness, vomiting and diarrhea, tachycardia, respiratory difficulty, massive gastrointestinal bleeding, liver and kidney failure, and death • Chronic overexposure: damage to the liver and kidneys, anemia
Manganese	E-liquid [27]	• Neurological problems, impaired pulmonary function, pneumonia, and cough

Influence of Trace Metals in Electronic Cigarette Aerosol on Systemic Health

Nickel

The exposure to Ni, based on duration, may be classified as acute (1 day), subchronic (10–100 days), and chronic (> 100 days) [44]. Its exposure limit varies between 0.015 and 1.5×10^6 ng/m^3 while the indoor air levels after 2 h of vaping may range between 8.1 and 356 ng/m^3 [7, 10]. This shows that chronic long-term inhalation of Ni from EC aerosol may damage the lungs, liver, and kidneys in a manner similar to drinking water contaminated with Ni or inhalation as seen in refinery workers [44, 45]. Even though the exposure to Ni through chronic EC smoking is trivial when compared to refinery fumes, its effects on the lungs cannot be annulled completely. Furthermore, the second hand aerosols may have adverse effects on other individuals, for instance the children [10].

Many studies have suggested a close relationship between Ni exposure and lung and sinonasal cancer [46]. It was suggested that in workers exposed to Ni at concentrations of ≥ 15 mg/m^3, the risk of sinonasal cancer was higher than that of lung cancer. Additionally, a dose-dependent gradient for both Ni oxide and soluble Ni was reported. The risk was multiplied in workers who were heavy smokers [47]. This association between occupational Ni exposure and sinonasal cancer has been seen in Swedish battery workers, Finnish Cu/Ni smelter workers, and Clydach refiners [48–50].

The inhalation of Ni causes chronic active inflammation in the lungs, leading to alveolar epithelium hyperplasia, fibrosis, bronchiolization, alveolar proteinosis, and atrophy of the nasal olfactory epithelium [44, 51]. The Ni carcinogenicity has also been related to genetic and/or epigenetic factors which may be direct (e.g., conformational changes) or indirect (e.g., generation of oxygen radicals) [44]. Furthermore, it causes significant oxidative stress in the lung tissue. This was revealed by increased levels of lipid peroxides with simultaneous reduction of superoxide dismutase, catalase, and glutathione peroxidase enzymes in the lungs [44, 52].

The Ni toxicity may affect the genes, blood, and nervous and reproductive systems [44]. The genetic abnormalities are mainly related to DNA damage (DNA strand breaks and cross-links, infidelity of DNA replication, inhibition of DNA repair, and the helical transition of B-DNA to Z-DNA) by binding to DNA and nuclear proteins [53]. It is immunotoxic as it suppresses natural killer cells and interferon production [54]. Besides, Ni ion may produce systemic allergic reactions by oxidizing to a low molecular weight protein called hapten. The latter modifies the native protein configuration. It is recognized as a non-self-antigen by the hapten-specific T cells which trigger the immune reaction [44, 55]. A study reported a significant increase in the levels of immunoglobulin (Ig)G, IgA, and IgM after Ni exposure [56]. Further, increased levels of other serum proteins, involved in cell-mediated immunity like α1-antitrypsin, α2-macroglobulin, and ceruloplasmin, have also been reported [56]. Both Ni and Cr depress the circulating antibody response to viral antigens [44]. Neurological signs like lethargy, ataxia, and reproductive toxicity, leading to spontaneous abortions and testicular degeneration, have also been reported [44].

Chromium

The presence of Cr in EC smoke, although not widely interpreted, is definitely a health concern. There was a very wide range of Cr in EC aerosol as reported in the studies included in the present review [9, 10, 23, 25, 26, 28]. The general effects of Cr inhalation are mentioned in Table 3. Cr can exist in several oxidation states, although only the trivalent, Cr(III), and hexavalent, Cr(VI), forms are common in the natural environment [12]. The levels of Cr in mainstream cigarette smoke range from 0.0002 to 0.5 mg/cigarette [57]. In smokers, its concentration in the lung tissue may be about 4.3 mg/kg (dry weight) as compared to 1.3 mg/kg in non-smokers [58]. Accumulation of Cr in the lung tissue has been directly correlated with duration of smoking, age, and smoking time [58]. Its concentrations have been reported to be significantly higher in all five lobes of smokers' lungs when compared to non-smokers [59]. The Cr(VI) is recognized by the International Agency for Research on Cancer (IARC) as a group 1 carcinogen [57]. It induces DNA damage (single-strand breaks) and has potential cell-transforming effects [12]. It may cause ulceration, chronic rhinitis and pharyngitis, impaired lung function, and emphysema.

Lead

As already stated, exposure to Pb may occur through inhalation of tobacco smoke including the EC aerosol. Pb is a major neurocognitive and kidney toxicant for children at a relatively low concentration (10 μg/dL) [60, 61]. It is present in both mainstream (exhaled by the smoker) and sidestream (from the burning cigarette) smoke, including the gas phase [60]. A study reported that from 1988 to 1994, the US children exposed to second hand smoke had increased blood Pb levels [62]. The latter was directly correlated to serum cotinine levels and the number of smokers at home. Furthermore, children living in urban areas or young adults of low socioeconomic status had high Pb exposure. The second hand smoke exposure is an "unrecognized" source of relatively small particles of Pb which are more easily absorbed in the bronchial-alveolar region [60, 63, 64]. In the present review, one study reported the presence of Pb in the open-wick ENDS devices [19] while another study reported e-liquid to be the major source of Pb in EC aerosols [27].

The various health effects of Pb in tobacco smoke are given in Table 3. Its effect on the nervous system has been explained here. The neurotoxic effects of Pb may range from alteration of nerve conduction velocity to encephalopathy [65–67]. The symptoms may worsen to paralysis, convulsions, delirium, coma, or death.

The nervous system is affected through a combination of mechanisms, direct or indirect. It may directly alter the development of the system. This involves disruption of vital molecules during neuronal migration and differentiation or an interference with synapse formation (mediated by a reduction in neuronal sialic acid production) or a premature differentiation of glial cells [65]. Besides, Pb may substitute for Ca and Zn in the central nervous system [65]. This inappropriately triggers the processes dependent on calmodulin [66]. It further interferes with the neurotransmitter release, energy metabolism (by activating protein kinase C), and Na^+/K^+ ATPase enzyme system in the cell membranes [66, 68, 69]. Additionally, it accelerates the mitochondrial self-destruction and primes its apoptosis by inhibiting the Ca release [66, 70]. The indirect effects result from interference with other body systems; for instance, Pb exposure causes hypertension and impairs the renal and thyroid function [66].

A study in the present review reported that the design of ECs was a major source of Pb in aerosols [19]. Therefore, it is imperative to incorporate Pb testing during chemical analyses of EC devices.

Aluminum

The higher permissible limit for Al in the work environment is 10^7 ng/m^3 [7]. This level can be easily reached in smoking rooms or rooms with poor ventilation. After inhalation, Al accumulates in the kidneys, brain, lungs, liver, and thyroid. It competes with Ca for absorption and affects the skeletal mineralization. A study evaluated indoor levels of Al due to EC vaping [10]. It involved six vaping sessions by nine volunteers who consumed ECs in a thoroughly ventilated room for 2 h. The authors reported a 2.4-fold increase in the concentration of Al after 2 h of vaping [10]. The levels reached to 483 ng/m^3 from the initial 203 ng/m^3. The Al content of tobacco is about 0.37% by weight [71]. Al whether actively (drawn) or passively inhaled accumulates significantly in surrogate lung fluids and causes respiratory, neurological, and other smoking-related diseases [71]. The various health effects of Al are listed in Table 3.

Cadmium

Cigarette smoke is one of the major sources of airborne Cd [12]. Smokers have twice the amount of Cd in their bodies as compared to non-smokers. A single cigarette contains about 1–3 μg of Cd [29]. Approximately 40 to 60% of the Cd inhaled from cigarette smoke passes through the lungs and body. Therefore, for every 20 cigarettes smoked, approximately 2–4 μg of Cd is inhaled by the smoker and approximately a microgram spreads into the environment [29]. Since Cd was present in EC aerosols at levels very close to those observed in urban and industrial areas, it may pose a health issue [21, 22, 26, 28].

Its health effects include alteration of immune response at very low concentrations (0.1–10 μM). Cd inhibits the production of IgE in a concentration-dependent manner [72]. Further, an exposure for more than 24 h diminishes the activated B cells paralleled by a concomitant decrease in their viability and proliferation [72]. Therefore, Cd may be both immunotoxic and immunomodulatory.

Tin

In the present review, two studies extensively evaluated the sources of Sn in EC aerosol and strategies to reduce its levels by changing the design characteristics [9, 23]. The authors suggested that Sn in EC was mainly emitted from the metal coating the thick Cu wires or the solder joints. It was trapped in the Poly-Fil fibers of the cartomizer. They revealed that both large-sized (> 500 nm) and nanometer-sized (< 0.1 mm) Sn and Ni particles were present in the aerosol. Besides, the coarse particles (> 1 mm) also included Ag, Fe, Al, and silicate and nanoparticles of Cr. Its concentration varied between and within the brands of EC. It was suggested that Sn could be reduced in aerosol by coating the thick wires with Ag and placing stable Sn solder joints outside the atomizing chamber. Further, joining the wires with brass clamps or brazing was more beneficial rather than soldering wires [23]. Changing the design was considered ideal to reduce leaching of Sn into the EC aerosol. The cartomizer fluid with Sn particles inhibited both attachment and proliferation of human pulmonary fibroblasts in a dose-dependent manner in this study [9]. This shows that Sn in EC aerosols can affect the lung tissue.

Exposure to Sn(IV) oxide dust and fumes for more than 3 years results in benign pneumoconiosis called stannosis [73]. Furthermore, animal studies have shown that Sn may cause anemia as indicated by decreased hematocrit, total erythrocyte, and hemoglobin levels [74]. This was related to the negative influence of Sn on Fe and Cu metabolism. It reduced their levels in the blood, leading to anemia.

Copper

In one study, the main source of Cu was the thick wires in the cartomizer [9]. Another study detected the presence of Cu and reactive oxygen species in the EC aerosol [24].

Cu is essential at low concentrations. However, inhaled Cu is a respiratory irritant which causes alveolar migration of macrophages, eosinophilia, and formation of histiocytic and non-caseating granulomas [75, 76]. Furthermore, pulmonary fibrosis and fibrohyaline nodules may be formed. In animal studies, Cu strongly induced pulmonary inflammation than other transition metals [77]. It is an active oxidation-reduction (redox) metal that has been determined at a significantly higher concentration in the blood of smokers [78]. However, the influence of Cu inhaled from EC aerosol is yet to be investigated.

Manganese

Mn in EC smoke was reported in four studies [9, 10, 21, 28]. The Mn(II) complexes have been reported in CC smoke [76, 79]. It is proposed that the Mn oxides oxidize Cr(III) to Cr(VI) and potentiate Cr toxicity [80]. Compounds of Mn may induce or exacerbate asthma. Besides, Mn(II) has been associated with pulmonary inflammation in rats [76, 77]. Like Cu, further research is required to verify the adverse health effects of Mn in EC aerosol.

Influence of Trace Metals in Electronic Cigarette Aerosols on Oral Health

Even though there is immense literature describing the potential harmful effects of conventional tobacco smoking on oral health, the influence of ECs on oral tissues has received very little attention. This is highly unusual as the EC aerosols first contact the oral tissues when they are most concentrated. Likewise, the heavy metals present in them may produce both direct and indirect effects in oral cavity.

The oral tissues most likely to be affected are periodontal ligament and oral epithelium. The role of CC smoke in promoting chronic periodontitis and oral cancer is well established. However, there is negligible evidence on the role of ECs on oral tissues.

A study demonstrated that ECs with flavorings increased the oxidative/carbonyl stress and inflammatory cytokine release in human periodontal ligament fibroblasts, human gingival epithelium progenitors pooled (HGEPp), and epigingival 3D epithelium [81]. Furthermore, increased levels of prostaglandin E2 and cycloxygenase-2 were demonstrated. They upregulated the receptor for advanced glycation end products (RAGEs) through EC-mediated carbonyl stress in the gingival epithelium. They even increased DNA damage along with histone deacetylase 2 (HDAC2) reduction via RAGE-dependent mechanisms in the gingival epithelium. This suggests that increased oxidative stress, pro-inflammatory, and pro-senescence responses are induced by ECs that deregulate repair in periodontal ligament cells. Further, the menthol derivatives in e-liquids reduced the fibroblastic proliferation [81].

Another study investigating the effects of EC vapor on human gingival epithelial cells demonstrated altered morphology of cells from small cuboidal to large undefined shapes [82]. Both single and multiple exposures led to bulky morphology with large faint nuclei and enlarged cytoplasm. It also increased L-lactate dehydrogenase (LDH) activity in the targeted cells, specifically with repeated exposures. The percentage of apoptotic/necrotic epithelial cells was also increased. This was attributed to over activity of the caspase-3 pathway. These morphological and functional changes in gingival cells could enhance progression of oral cancer.

Specific metals like Ni, Pb, and Cr are more concentrated in EC aerosol than in burnt tobacco [14]. Therefore, they are highly likely to influence the gingival epithelium, periodontal ligament, and oral mucosa. Unfortunately, this area has not been explored. However, their adverse effects on oral tissues when released from the CCs have been widely demonstrated. For instance, a study reported that cigarette smoke was a major source of Cd [83]. Chronic low levels of Cd were linked to decreased bone mineral density and osteoporosis [84]. It was suggested that Cd increased the serum concentration of cross-linked telopeptide of type 1 collagen (a marker of bone resorption) and decreased the activity of serum alkaline phosphatase (a marker of bone formation) [85]. This disturbed the normal bone metabolism and enhanced the levels of inflammatory mediators (prostanoids, cytokines, MMPs, and prostaglandin E2) in osteoblasts. It even caused Ca release from cells at very low concentrations. Therefore, Cd might disturb alveolar bone remodeling in periodontal disease, favoring the resorption [83].

Another study compared toxic heavy metal accumulation in the supragingival dental calculus of smokers and non-smokers [86]. It was found that the levels of metals like As, Cd, Pb, Mn, and vanadium were significantly higher in the dental calculus of smokers than non-smokers. Their overexpression was significantly correlated to chronic tobacco smoke exposure. Similarly, accumulation of Cd and Pb has been reported in the teeth of smokers [87]. As already stated, these metals are carcinogenic and may trigger oral cancer by impairing pathways for the anti-oxidative metabolism, Ca-dependent apoptotic cell death, stimulating free radical production (damages DNA and cell membranes), and inducing oxidative stress. Another study evaluated the concentrations of As, Cd, Cr, and Ni in healthy and tumor tissues of patients with head and neck cancer [88]. Their levels were about 1.3 to 3.4 times higher in tumor tissues than in healthy tissues. As and Cd levels were also significantly higher than those of non-smokers.

The elevated levels of serum Cd and Pb have been significantly associated with chronic periodontitis in studies on Korean and American populations [89, 90]. It was suggested that Cd altered bone remodeling and apoptosis due to intracellular induction of reactive oxygen species while Pb promoted periodontal inflammation.

Besides, Ni has been associated with oral cancer [91]. Although this association was seen with Ni present in soil, water, and air, the linkage between Ni from inhaled EC aerosol and oral cancer is yet to be investigated.

Albeit, there is scant data on the amount of metals aerosolized in the ECs and their health effects; even if a fraction of these metals were vaporized and transferred into the lungs, they could produce health issues [44, 51]. Unfortunately, the limits for inhaled metals are generally set for occupational exposure and measured in milligrams/cubic meter over a set period of time [92]. An EC user exposed to these metals through aerosols may not exceed the National Institute for Occupational Safety and Health (NIOSH) recommended exposure limits as well as the Agency for Toxic Substances and Disease Registry (ATSDR) maximum recommended limit. Therefore, further research, specifically involving the bio-specimens of EC users, is desirable. This would help in determining the permissible levels of exposure to these metals from ECs.

Comparison of Harmful Effects of Conventional Cigarettes and Electronic Cigarettes

The results from the present review suggest that the concentration of metals in EC aerosols may be more than that in CC smoke [8]. This is related to the fact that ECs are an assembly of numerous metallic components which are highly susceptible to cyclic temperature changes. Besides, ECs increase the risk of nicotine toxicity due to its high concentrations in the cartridges. The exposure levels of nicotine from EC usage may vary due to the difference in aerosolization, inaccurate product labeling, and inconsistent nicotine delivery during the product use [41]. The e-liquids obtained in retail stores and via the Internet may contain about 14.8 to 87.2 mg/mL of nicotine which may differ from the declared levels by about 50% [5, 41, 93]. Even the FDA has found nicotine levels ranging from 26.8 to 43.2 μg nicotine/100 mL puff in branded ECs [41].

Recent studies suggest that the adolescents and first-time users are attracted to ECs because they are considered to be less harmful [94]. However, various chemical substances and ultrafine particles like metals known to be toxic/carcinogenic may cause respiratory and heart distress. They have been identified in EC aerosols, cartridges, refill liquids, and environmental emissions.

Overall, the existing studies provide certain insights about ECs, but critical information gaps remain. These are mainly related to device designs, chemical substance release, effects of carrier solvents and additives, aerosol generation, aerosol physical properties, and the chemical profiles of EC emissions. Although the evaluations of other EC components have not found serious health effects, it is difficult to accept these facts due to limited data and lack of standardized testing methods. Moreover, as CCs have been used for more than a century, there are many more CC than EC users worldwide. Therefore, far more information is available about the harmful effects of CCs. This makes it difficult to suggest that ECs have less product-specific mortality/morbidity. Finally, it is questionable to suggest ECs as smoking cessation devices as they are associated with health risks.

Conclusion

It is clearly evident from the studies included in the review that the ECs are a source of hazardous trace metals. The exposure limits to these metals may be easily exceeded due to prolonged indoor vaping in poorly ventilated rooms or through passive inhalation. As EC aerosols are a major source of toxic heavy metals, marketing the ECs as a safe alternative to CCs is debatable. It is imperative to reconsider their design characteristics and composition of e-liquids to minimize the associated health hazards.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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