Review on metallic components released due to the use of electronic cigarettes

Vinit K. Mishra[1], Ki-Hyun Kim[2†], Pallabi Samaddar[2], Sandeep Kumar[3†], M. L. Aggarwal[1], K. M. Chacko[1]

[1]Shriram Institute for Industrial Research, 19 University Road, Delhi-7, India
[2]Atmospheric Environment and Air Quality Management Lab, Department of Civil and Environmental Engineering, Hanyang University, Seoul 04763, Republic of Korea
[3]Department of Bio and Nano Technology, Guru Jambheshwar University of Science and Technology, Hisar-Haryana 125001, India

ABSTRACT

The use of electronic cigarettes (ECs) is recognized as a source of many pollutants, just like conventional cigarettes (CCs). The analysis of EC aerosol samples has confirmed the presence of various metallic species. Most of these metals originate from various parts of the cartomizer, e.g., solder joints, wires, and silicate beads. The metal concentration levels in EC samples were shown to be generally two to four orders of magnitude lower than those of CCs. However, the use of ECs can still pose significant human health hazards as consumers are exposed to the toxicity of those metals and many other hazardous pollutants released simultaneously via the vaping of ECs. The review also describes the detection and quantification of various metals in ECs and CCs. This review was carried out to assess the level of metal species released from ECs and to suggest proper guidelines to control consumer exposure.

Keywords: Conventional cigarettes, Electronic cigarettes, Health impact, Metals, Vaping

1. Introduction

During the 20th century, it has been estimated that the use of tobacco products contributed to the deaths of more than 100 million persons worldwide [1]. As such, it has been a more significant cause of human death (each year) than many well-known diseases, like HIV/AIDS, tuberculosis, and malaria. By 2030, the death toll due to tobacco products is expected to exceed eight million people a year. Unless proper regulation is taken, tobacco causes deaths of one billion people during last hundred years [1]. Statistical report inferred that one-third to one-half of lifetime tobacco users tend to die an average of 14 years earlier compared to nonsmokers [2, 3]. Unless smokers want to suffer the harmful consequences due to continued smoking, the only option is to quit.

In an effort to reduce concerns associated with such issues, tobacco harm reduction (THR) products with much safer sources of nicotine have been introduced with the goal of reducing smoking-related diseases [4]. Electronic cigarettes (ECs) are one of the latest products for THR [5, 6]. At present time ECs have been gaining increasing popularity with smokers globally for variety of reasons. General assumption is that EC helps quit smoking, reduce cigarette consumption, alleviate tobacco withdrawal symptoms, and prolong smoking with less health risks. Consumers also prefer several different nicotine strengths. Among them non-nicotine liquids is very popular with a countless list of flavors. This assortment is one of the characteristic features that distinguish ECs from any other THR product. As such, ECs have become an integral part of the smoking industry, while relatively little is known about their human health impact and associated issues. Quality control used in EC manufacturing or the toxic effects of their components is also very lesser studied area [7].

ECs are powered by a lithium-ion rechargeable battery designed to vaporize nicotine or other components for inhalation [8]. Puffing on an EC activates the battery to heat liquid containing humectants (propylene glycol (PG) and/or vegetable glycerin (VG)) either with or without flavors and nicotine. Early models of ECs were separately equipped with atomizers for heating and cartridges for holding fluid [7]. As the structure of ECs has developed in this way that the atomizer and cartridge have been linked jointly into a single unit known as "cartomizer" [9].

The popularity of ECs has grown both in the young and in adults despite many warnings regarding their safety and overall impact on public health. To address such problems, many efforts have been made to accurately assess the levels of various pollutants released via the vaping of ECs. For instance, we have recently provided a comprehensive review on the experimental approaches to quantify various hazardous substances released via smoking of ECs including volatile organic compounds, carbonyls, nicotine, TSNA, PAH, phthalate, PG, VG, and metal [10]. However, the emphasis of such review work was generally placed on the approaches used for the determination of the gaseous pollutants with the aid of chromatographic methods. Likewise, not enough importance has been paid to the existence of heavy metals and trace elements in ECs. For regulatory purposes, it is, however, important to properly document the health hazard of each toxic component. The present work therefore aimed to provide a review on the up-to-date knowledge regarding the metal concentration levels released during use of ECs.

2. Methodology

The literature search was mainly conducted using online references through PubMed, EMBASE, Scopus, Google, and Google Scholar of articles published through Feb 2017. In addition, data from the authors own libraries were used, including textbooks and hard copies of journals. Original articles, book chapters, and scientific reports were also selected as references.

As the metal levels in ECs have been reported in many different units in different studies, all the values were converted into ng/10 puffs (for ECs) to simulate a parallel comparison for conventional cigarette (CC) results, generally reported in terms of ng/cigarette (for CCs). Since the units of measurement were different in the case of ECs and CCs, it was important to convert all of the data into comparable units for comparative analysis among studies. The assumptions made for the conversions were as follows:

1) The complete burning of one CC was considered to involve approximately 10 puffs [11].

2) The weight of one CC was considered to be one gram; subsequently, values reported as emissions per gram were considered equivalent to the metal concentration levels in 10 puffs. For example, a metal concentration reported in mg/g or ng/g was considered to be equivalent to the emissions from one CC or 10 puffs of a CC.

3) In many documents, the metal concentration levels from ECs have been reported as ng/10 puffs. A few publications have also used ng/150 puffs, which were converted into ng/10 puffs.

2.1. Sampling of EC Metals

The methods for sampling EC aerosols are diverse among the published studies, with some studies not providing full descriptions regarding such information, such as Williams et al. [11]. Here, we describe some procedures used for the collection and analysis of metals in EC aerosols using representative case studies.

Schober et al. [12] recruited nine adult volunteers (20-30 years old men having mean age: 24.7 ± 4.2 y; height: 173-198 cm; weight:

63-85 kg) for partaking in their study. Three of these men first consumed a nicotine-free EC followed by a nicotinic EC for two hours in each vaping session. During the vaping session, air samples were accumulated with 47-mm quartz fiber filters (Pieper, Bad Zwischenahn, Germany) using a medium volume sampler equipped with a $PM_{2.5}$ sampler as the sample inlet. This device operated at a constant flow of 2.3 m^3/h over a 2-h sampling period, which is equivalent to the conditions of EC vaping. Firstly, the filters (from the same production lot) were analyzed for heavy metal blank values. Closed-vessel microwave decomposition of the filter samples was done afterward by using nitric acid and hydrogen peroxide. Metals were analyzed using inductively coupled plasma-mass spectrometry (ICP-MS).

Goniewicz et al. [13] also used 10 "e-smokers," who were regular EC smoker for longer than one month. All testing methods were conducted using the same average puffing conditions like: 1.8-s puff duration, 10-s interval puff break, 70-mL puff volume, and 15 puffs taken in each puffing session. In each case, 150 total puffs were taken from each EC in 10 series of 15 puffs with intervals between the series (5 min each). Each EC was analyzed three times on three subsequent days after the batteries had been recharged over the night. A fresh cartridge was placed in the ECs each day for testing. Vapor generation was visible during the full 150 puffs taken from each product tested. The metals were collected through absorption into the indoor air in gas washing bottles containing methanol. Their quantization was carried out with an ICP-MS technique. All methods used by Goniewicz et al. [13] were corroborated according to the International Conference on Harmonisation Guideline Q2(R1) [14].

2.2. Instrumental Analysis of EC and CC Smoke

As shown in Table 1, different authors have used separate instruments for the analysis of EC and CC smoke samples due to the unique operating principles and quality assurance procedures (e.g., detection limits).

2.2.1. ICP-OES

Inductively coupled plasma-optical emission spectrometry (ICP-OES), is a multi-elemental technique dependent on excited species in which the composition of elements samples can be analyzed using plasma and a spectrometer under vacuum condition. In ICP-OES, plasma is generated at the end of a quartz torch by a water-cooled induction coil. A high-frequency alternate current flows through the mentioned coil [15]. An alternate magnetic field is induced consequently, which further accelerates electrons in a circular trajectory. Due to collisions between the argon atoms and the electron ionization, plasma is generated at 6,000-7,000 K. This temperature increases upto 10,000 K at the induction zone.

The quartz torch is invariably horizontal, but it can also be operated vertically (side-on viewing) to allow axial measurement (end-on viewing). The former (radial ICP) is more robust and resistant to the matrix, but it is less sensitive (relative to the axial ICP). Both systems are capable of analysis of metals at ppm (mg/L) levels. An axial system can also be used to generate data at the ppb (μg/L) level, although ICP-MS is a preferable option for detection in these low-ppb regions (as shown below).

Table 1. Instrumentation Used for the Analysis of Metals in ECs and CCs and Their Detection Limits

S. No.	Metal	Electronic Cigarettes			Conventional Cigarettes		
		Detection limit	Detection system	References	Detection limit	Detection system	Reference
1	Aluminum (Al)	10 mg/L	ICP-OES	[11]	0.1 ng/g	INAA**	[18]
		0.1 mg/L	ICP-MS	[12]			
2	Arsenic (As)	0.1 mg/L	ICP-MS	[12]	0.1 mg/L	ICP-MS	[24]
					150 ng/g	X-ray fluorescence (XRF)	[20]
3	Cadmium (CDC)	0.1 mg/L	ICP-MS	[13]	0.1 mg/L	ICP-MS	[23]
		0.1 mg/L	ICP-MS	[12]	0.1 mg/L	ICP-MS	[24]
					240 ng/g	X-ray fluorescence (XRF)	[20]
4	Chromium (Cr)	5 mg/L	ICP-OES	[11]	0.1 mg/L	ICP-MS	[31]
		0.1 mg/L	ICP-MS	[12]	310 ng/g	X-ray fluorescence (XRF)	[20]
5	Copper (Cu)	5 mg/L	ICP-OES	[11]	0.1 mg/L	ICP-MS	[27]
		0.1 mg/L	ICP-MS	[12]			
6	Manganese (Mn)	5 mg/L	ICP-OES	[11]	0.005 mg/L	AAS	[28]
		0.1 mg/L	ICP-MS	[12]			[29]
7	Nickel (Ni)	5 mg/L	ICP-OES	[11]	1.1 ppb	INAA**	[19]
		0.1 mg/J	ICP-MS	[13]	140 ng/g	X-ray fluorescence (XRF)	[20]
8	Lead (Pb)	50 mg/L	ICP-OES	[11]	0.1 ng/g	INAA**	[19]
		0.1 mg/L	ICP-MS	[13]	0.1 mg/L	ICP-MS	[24]
					190 ng/g	X-ray fluorescence (XRF)	[20]
9	Vanadium (V)	0.1 mg/L	ICP-MS	[12]	0.1 mg/L	AAS	[32]
10	Tin (Sn)	0.1 mg/L	ICP-MS	[11]			
11	Zinc (Zn)	5 mg/L	ICP-OES	[11]	200 ppb	INAA**	[19]
		0.1 mg/L	ICP-MS	[12]			

Williams et al. [11] relied on an ICP-OES system for the analysis of EC smoke. The detection limits of that system for different elements are presented in Table 1. The detection limit (mg/L) for most of the elements, such as Ni, Cu, Mn, Cr, and Zn, was 5, though those of Al (10) and Pb (50) were higher.

2.2.2. ICP-MS

Inductively coupled plasma-mass-spectrometry (ICP-MS) is generally employed to determine low concentrations (range: ppb = parts per billion $\sim \mu g/L$) and ultra-low concentrations of elements (range: ppt = parts per trillion $\sim$ ng/L). When atomic species are forced through a plasma source, they become ionized and are sorted by mass. ICP-MS technique has some advantages over other common techniques like atomic absorption spectroscopy [16] or ICP-OES due to several reasons. Advantages of ICP-MS include extremely low detection limits, wide range of linearity, and possible detection of isotopic compositions of elements. The ICP-MS technique exhibits multi-element character and a high sample throughput, like ICP-OES. It also has highly sensitive detection ability. However, the occurrence of spectral and non-spectral interference and its high cost both are two demerits of this technique.

Similar to ICP-OES, the sample solution in ICP-MS is introduced through peristaltic pump. Nebulization is taken place in a spray chamber, and the resulting aerosol is injected into an argon plasma at 6,000-8,000 K. The sample is desolvated for atomization and ionization within plasma torch. Only a small amount of the ions produced in the plasma further penetrate to the mass spectrometer.

A mass spectrometer (MS) is generally composed by an interface (in particular, a "sampler cone" and a skimmer cone) into which a small amount of the free ions induced by the plasma are transmitted. The ions migrate from an extremely high temperature and atmospheric pressure to a compartment at room temperature at a high vacuum (< 0.001 Pa). Electrostatic lenses are used to focus (positive) the entry of ions to the true mass-spectrometer. The true mass spectrometer in the GI device has a quadrupole which consists four metal rods. These metal rods accelerate the separation of ions according to mass by following resonance stability. An electron multiplier (a specific type of detector) is also needed to enhance the signal from one colliding ion into a measurable pulse. Contrary to ICP-OES, the detection limit of ICP-MS is 0.1 mg/L for almost all the elements listed in the present review.

2.2.3. Instrumental neutron activation analysis (INAA)

Neutron activation analysis (NAA) is generally applied for quantitative multi-element analysis of major, minor, trace, and rare elements in a wide variety of matrices. Preliminary step of such analysis

is associated with the irradiation of a sample with neutrons in a nuclear reactor or other neutron source. A gamma-ray spectroscopy system is an assembly of a detector (and a high-voltage power supply for the detector), pre-amplifier, spectroscopy amplifier, analog-to-digital converter, multi-channel analyzer, and an output device. Radioactive nuclides are generated while samples are subjected to a neutron flux. intensity of gamma rays are compared with the intensity emitted by a standard nuclide which further allows the quantitative measure of the unknown concentrations of the various nuclides [17].

Next, a sample is presented to the detector (Ge in the case of gamma-ray analysis). In order to minimize thermal noise, the detector is maintained at cryogenic temperatures (liquid nitrogen, temperature = 77 K). Samples in solid form are the matrix of choice for the INAA technique, while liquid samples can be analyzed with certain precautions. Although virtually any material can be examined, technical limitations are mainly produced due to the chemistry of the matrix.

An important advantage of INAA analysis is that the common sample matrices constitute elements - H, C, O, N, P, and Si - that rarely form radioactive isotopes. Hence, most sample matrices appear to be transparent in order to facilitate the detection of target species, while also enhancing the sensitivity with the least interference. As a result, the technique can be applied on a non-destructive basis without the need for any sample preparation other than size reduction or drying in some cases. Moreover, this technique requires only small amounts of sample material, such as 100-200 mg, as long as reagent or laboratory contamination is minimal (no need for sample pretreatment such as digestion or dissolution). The detection limit for INAA analysis was reported as 0.1 ng/g [18, 19].

2.2.4. X-ray fluorescence (XRF)

The principle of XRF analysis involves tracing the behaviors of atoms when they interact with X-ray radiation. A XRF spectrometer works as follows: When some of the energy is scattered during sample illumination by an intense X-ray beam, other components are absorbed by the sample. Such illumination of the primary X-ray beam is said to be excitation. The excited sample emits X-rays along a spectrum of wavelengths in compliance with the types of atoms. Caruso et al. [20] used XRF for the analysis of metals in the smoke of CCs; the reported detection limits were seen in a moderately narrow range of 140 ng/g (for Ni) - 310 ng/g (for Cr).

3. A Comparison of Concentration Levels of Metals in ECs and CCs

The concentration levels of metals released due to the consumption of ECs are listed in Table 2 in reference to those of CCs. In most studies, the levels of elements in ECs were shown to be two to four orders of magnitude lower than those of CCs. However, the trends for the elemental concentration levels are reversed in certain cases [11, 21]. According to Williams et al. [11], the metal composition of EC aerosol was measured across different particle fractions.

The results showed that coarse particles (> 1 mm) were comprised of tin, silver, iron, nickel, aluminum, and silicate, while nanoparticles (< 0.1 mm) were dominated by tin, chromium, and nickel. Accordingly, the concentration levels of 11 common elements were compared between ECs and CCs. Concentrations of nine of 11 elements in EC aerosols were higher than or comparable to those of CCs: (1) relative enhancement in EC: Na, Fe, Al, and Ni (n = 4); (2) comparable range for both: Cu, Mg, Pb, Cr, and Mn (n = 5); and (3) relative depletion in EC: K and Z (n = 2). As found from the silicate beads and fiberglass wick used in SEM and EDS analyses, S, Ca, Al, and Mg were among the most abundant elements in EC aerosol [11]. These authors indicated that the primary source of the metals was the filaments inside the EC cartomizer. An exposure study that included participants who consumed EC for 2 h in a café showed only a 2.4-fold increase in aluminum during vaping activity as compared to that of CCs (482.5 vs. 203.0 ng/m^3) [12]. Saffari et al. [21] reported a 10-fold decrease in the total exposure to particulate elements (such as B, K, Zn, and Pb) in ECs compared to CCs when measured inside a room; however, a few metals (such as Ni, Ti, Cr, and Ag) produced higher emission rates from ECs than they did from CCs.

The concentrations of two rare-earth elements (lanthanum and cerium) are usually found at elevated levels in CC smoke; however, their concentrations in EC smoke did not exhibit any increase but instead were in the range of typical outdoor air levels below 0.5 and 1 ng/m^3, respectively [22]. Moreover, in the case of potentially carcinogenic elements, such as Cd, As, and Tl, there were no significant increases in ECs.

In Table 2, the remarkable enrichment of several metals (Al, Cd, Cu, and Mn) was observed in CCs relative to ECs (e.g., by two to four orders of magnitude). In the case of six other metals (As, Cr, Ni, Pb, V, and Zn), this difference was moderately reduced to one to two orders of magnitude. The maximum level of Cd reported in ECs was 14.67 ng/10 puffs [13], while it was 1 μg/cigarette for CCs [23]. According to Piadé et al. [24], the average amount of Cd in CCs was 25.9 ng/cigarette, which is comparable to that of ECs. Cigarette smoking has been suggested as the most significant route of human exposure to Cd [25]. The mean Cd content in the blood of smokers with an average age of 30 years (~ 2.67 mg/L) was 1.9 times higher than that of non-smokers (~ 1.37 mg/L) [26]. The level of Cu in ECs was found to vary between 13.1-190 ng/10 puffs [11, 12], while the amount was 156 mg/cigarette in the case of CCs [27]. In contrast, the concentrations of Cu in CCs and ECs were close to each other (~ 0.2 mg/10 puffs) [11].

The concentration levels of Mn in EC were in the range of 2-84 ng/10 puffs puffs [11, 12], while those of CCs varied in the range of 155-400 mg/cigarette [28, 29]. In contrast, the levels of As in CCs were three to ten times higher than those of ECs [12, 24, 30]. The maximum level of As in CCs was 170 ng/10 puffs [20], which is approximately 100 times higher than that in ECs [12]. The level of Cr in ECs varied between 7-655 ng/10 puffs in different samples puffs [11, 12], while its amount in CCs ranged widely between 0.2-2,350 ng/cigarette [20, 31]. For Ni, the concentration level in ECs varied between 2-356 ng/10 puffs [11-13, 21], while its CC counterparts had a much larger range of 78-5,000 ng/CC [19, 20]. The concentration of Pb in ECs varied between

Table 2. Summary of Reported Elemental Concentration Levels in ECs and CCs

S. No.	Metal		EC		CC		
		Raw data	Converted to ng/10 puffs	Ref.	Raw data	Converted to ng/10 puffs	Ref.
1	Al	0.394 (μg/10 puffs)	394	[11]	699-1,200 μg/g	699,000-1200,000	[18]
		351-709 (ng/m^3)	-	[12]			
2	As	0.2-1.7 (ng/m^3)	-	[12]	3.75-43.8 (avg. ~3.81) ng/cigarette	3.75-43.8 (avg 3.81)	[24]
					0.17 μg/g	170	[20]
					7.5-14.5 ng/cigarette	7.5-14.5	[30]
3	Cd	0.01 mg to 0.22 mg (150 puffs)	0.67-14.67	[13]	0.5 and 1.5 μg/g	500-1,500	[23]
		0.1-1.2 (ng/m^3)	-	[12]	1.59-299 (avg. 25.9) ng/cigarette	1.59-299 (avg. 25.9)	[24]
					0.86 μg/g	860	[20]
4	Cr	0.007 (μg/10 puffs)	7	[11]	0.0002-0.5 μg/cigarette	0.2-500	[31]
		65.3-655 (ng/m^3)	-	[12]	2.35 μg/g	2,350	[20]
		28.10 (ng/h)	-	[21]	ND	ND	[21]
5	Cu	0.19 (μg/10 puffs)	190	[11]	156 μg/g	156,000	[27]
		13.1-127 (ng/m^3)	13.1-127	[12]			
6	Mn	0.002 (μg/10 puffs)	2	[11]	155-400 μg/L	155,000-400,000	[28, 29]
		5-84 (ng/m^3)	-	[12]			
7	Ni	0.002 (μg/10 puffs)	2	[11]	0.078 μg/g and 5 μg/g	78-5,000	[19]
		0.11-0.29 μg (150 puffs)	7.33-19.33	[13]	2.21 μg/g	2,210	[20]
		8.1-356 (ng/m^3)	-	[12]			
		130.5 (ng/ h)	-	[21]	36.39 (ng/h)	-	[21]
8	Pb	0.017 (μg/10 puffs)	17	[11]	1.2 μg/cigarette	1,200	[19]
		0.03-0.57 μg (150 puffs)	2-38	[13]	12.8-221 (19.4) ng/cigarette	12.8-221 (avg. 19.4)	[24]
		3-10.9 (ng/m^3)	-	[12]	0.44 μg/g	440	[20]
9	V	10 (ng/m^3)	-	[12]	0.49-5.33 μg/g	490-5,330	[32]
10	Zn	0.058 (μg/10 puffs)	58*	[11]	24 μg/g	24,000	[19]
		500 (ng/m^3)	-	[12]			

2-17 ng/10 puffs [11, 13], while Pb was at much higher levels of 12.8-1,200 ng/CC [19, 24]. The concentration level of V in EC was observed as 10 ng/10 puffs [12] compared to the 490-5,330 ng/cigarette [32]. In the case of Zn, the EC level was 58-500 ng/10 puffs [11, 12], while that of CC was 24 mg/cigarette [19].

According to these comparative analogies, the concentration levels of various metals were generally higher in CCs than they were in ECs. Therefore, crossing the threshold limits for various metals indoors is possible either inside "EC smoking rooms" or when there is heavy and frequent use of ECs indoors. Although the metal concentration levels are much lower in ECs than in CCs, the effect of long-term exposure to low-dose EC smoke must be further evaluated to learn more about its impact. The unregulated use of ECs may cause health hazard for both direct and passive smokers. Consequently, caution must be taken to set appropriate rules and regulations for the production and use of ECs.

4. Health Impact of Metals Released from EC Smoking

Exposure to metals due to cigarette smoke has the potential to cause a myriad of human health effects, ranging from cardiovascular and pulmonary inflammation to cancer and damage of vital organs. Metals have both acute and chronic health impacts; recommended health limits have been established, as summarized in Table 2.

Note that no recommended exposure limits have been set for metals released during cigarette smoking indoors. Such regulation guidelines exist only under limited conditions, such as industrial work zones as exposure limits for various targets. The recommended exposure limits (RELs) of metals set by various regulatory agencies along with their acute and chronic health impacts are summarized in Table 2. The National Institute for Occupational

Table 3. Summary of the Exposure Limits and Acute and Chronic Health Impacts of Elements Released from ECs and CC Smoke*

S. No.	Element	NIOSH-REL.*	OSHA- PEL.**	ACGIH-TLV***	Exposure	Outcome	Causality determination
1	Al	$10\ 10^6$ ng/m^3	$15\ 10^6$ ng/m^3	NE****	Short-term / Acute	Irritation of the skin and eyes	Causal
						Metal fume fever (flulike complaints including fever, chills, nausea, fatigue, muscle aches, and joint pain)	Causal
						Immunological and lymphoreticular effects	Causal
					Long-term / Chronic	Pulmonary fibrosis and poor pulmonary function	Causal
						Death	Causal
						Finger clubbing, joint pain	Suggestive
						Enlargement of the thyroid	Suggestive
						Food poisoning	Causal
						Nausea, vomiting	Causal
2	Cd	$0.01\ 10^6$ ng/m^3	$5\ 103$ ng/m^3	$0.01\ 10^6$ ng/m^3	Short-term / Acute	Abdominal cramps and pain, diarrhea	Causal
						Death	Causal
						Renal and hepatic toxicity	Causal
					Long-term / Chronic	High blood pressure, liver and kidney damage, and anemia	Causal
						Bone demineralization	Causal
						Lung cancer	Causal
						"Itai-itai" or ouch-ouch disease (osteoporosis, renal dysfunction, anemia, and low blood pressure)	Causal
3	Cu	$1\ 10^6$ ng/m^3	$0.1\ 10^6$ ng/m^3	$0.2\ 10^6$ ng/m^3	Short-term / Acute	Gastrointestinal distress, nausea, vomiting, and/or abdominal pain	Causal
						Liver damage (necrosis, fibrosis, abnormal biomarkers of liver damage)	Causal
					Long-term / Chronic	Liver and kidney damage, anemia, immunotoxicity, and developmental toxicity	Causal
						Coughing, sneezing, runny nose, pulmonary fibrosis, and increased vascularity of the nasal mucosa	Causal
						Cancer	Causal
4	Mn	$0.1\ 10^6$ ng/m^3	$5\ 10^6$ ng/m^3	$0.2\ 10^6$ ng/m^3	Short-term / Acute	Neurological problems (inorganic forms)	Causal
						Increased susceptibility to pneumonia	Suggestive
					Long-term / Chronic	Impaired pulmonary function, pneumonia, cough	Causal
						Respiratory effects	Causal
						Neurological, neuropsychiatric symptoms	Causal
						Reproductive and developmental issues	Suggestive
5	As	$0.002\ 10^6$ ng/m^3	$0.01\ 10^6$ ng/m^3	$0.01\ 10^6$ ng/m^3	Short-term / Acute	Increased susceptibility to pneumonia	Causal
					Long-term / Chronic	Cerebral edema, acute lung injury [12], acute respiratory distress syndrome (ARDS), frank respiratory failure, hepatitis, hemolytic anemia, and renal failure	Causal
						Peripheral/motor neuropathy	Causal
						Bone marrow suppression	Causal
						Skin changes, both malignant and nonmalignant, hypertension, diabetes mellitus, peripheral vascular disease ("Blackfoot disease"), and cancers of the lung, liver, bladder, or skin.	Causal

S. No.	Element	NIOSH-REL [*]	OSHA-PEL [**]	ACGIH-TLV [***]	Exposure	Outcome	Causality determination
6	Cr	$0.2\ 10^3$ ng/m^3	$5.0\ 10^3$ ng/m^3	$0.05\ 10^6$ ng/m^3	Short-term / Acute	Bronchial and pulmonary irritation and impairment of lung function	Causal
					Long-term / Chronic	Kidney disease	Causal
						Bronchiolitis and emphysema	Causal
						Decreased birthweight	Suggestive
						Lung cancer	Causal
7	Ni	$0.015\ 10^6$ ng/m^3	$1\ 10^6$ ng/m^3	$1.5\ 10^6$ ng/m^3	Short-term / Acute	Nausea, vomiting, cough, pneumonia, and death	Causal
						Visual disturbance, headache, giddiness	Causal
						Abdominal discomfort	Causal
						Death	Causal
					Long-term / Chronic	Lung fibrosis, cancer of the lungs, nose, sinuses, throat, and stomach.	Causal
						Contact dermatitis	Causal
						Death	Causal
						Cardiovascular and kidney diseases	Causal
						Mutagenicity, genotoxicity	Suggestive
8	Pb	$0.05\ 10^6$ ng/m^3	$0.05\ 10^6$ ng/m^3	$0.05\ 10^6$ ng/m^3	Short-term / Acute	Cardiovascular morbidity	Suggestive
						Vomiting, diarrhea, and constipation	Causal
						Body and stomach pain	Causal
						Poor muscle coordination	Causal
					Long-term / Chronic	Lung fibrosis, cancer of the lungs, nose, sinuses, throat, and stomach	Causal
						Contact dermatitis	Causal
						Death	Causal
						Cardiovascular and kidney diseases	Causal
						Mutagenicity, genotoxicity	Suggestive
9	V	$0.05\ 10^6$ ng/m^3	NE	NE	Short-term / Acute	Airway irritation (e.g., coughing, wheezing, sore throat)	Causal
					Long-term / Chronic	Lung lesions including alveolar/bronchiolar hyperplasia, inflammation, and fibrosis	Causal (in animals)
						Restrictive impairments in lung function and respiratory distress (rapid respiration, difficulty breathing)	Causal
						Alveolar/bronchiolar adenoma or carcinoma	Causal
10	Zn	$5\ 10^6$ ng/m^3	$5\ 10^6$ ng/m^3	$2\ 10^6$ ng/m^3	Short-term / Acute	Fever, nausea	Causal
						Death	Inadequate
					Long-term / Chronic	Copper deficiency	Causal
						Neurological issues	Suggestive
						Gastric erosion	Causal
						Anemia, pancreas damage, reduced immune function	Causal
						Decreased levels of high-density lipoprotein (HDL) cholesterol	Suggestive

* All the data were taken from the Agency for Toxic Substance and Disease Registry (http://www.atsdr.cdc.gov/toxprofiles)

* National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit (REL)

** OSHA-PEL: Occupational Safety and Health Administration permissible exposure limits

*** American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) (2008)

**** NE: Not established

Safety and Health (NIOSH) evaluated all available medical, biological, engineering, chemical, and trade information relevant to such hazards. RELs are intended to limit exposure to hazardous substances in workplace air to protect the health of workers. In the development of RELs and other recommendations for such purposes, the NIOSH transmitted its recommendations to Occupational Safety and Health Administration [33] for use in developing legally enforceable standards (UW-Madison, WI, United States). OSHA set enforceable permissible exposure limits (PELs) to protect workers against the health effects of exposure to hazardous substances, including limits on the airborne concentrations of hazardous chemicals in the air. Most OSHA PELs are 8-hour time-weighted averages (TWA). For more than 75 years, the American Conference of Governmental Industrial Hygienists (ACGIH) has been a well-respected organization for the industrial hygiene and occupational and environmental health and safety industry.

The comparison of reported metal concentration levels in EC (Table 3) can be achieved by comparing it against various recommended guideline values (Table 3). The threshold limits can be violated in the case of CCs, particularly in smoking rooms or less ventilated rooms where more than one smoker resides. The threshold limits of ECs can also be violated in smoking rooms but are much less likely to be exceeded in domestic environments.

For estimation of indoor exposure levels due to EC vaping, Schober et al. [12] performed six vaping sessions in which nine volunteers consumed ECs in a thoroughly ventilated room for two hours. They analyzed the levels of various pollutants, including metals, inside the room. These authors reported a 2.4-fold increase in the concentration level of Al after two hours of vaping, which increased to 483 ng/m^3 from the initial level of 203 ng/m^3. In comparison, the permissible limit in the work environment, which is usually set much higher in anticipation of higher concentration levels, is 10^7 ng/m^3. Such levels can be reached in designated smoking rooms or rooms with poor ventilation. After inhalation, Al accumulates in the kidneys, brain, lungs, liver, and thyroid, where it competes with Ca for absorption and affects skeletal mineralization (Table 3). Hence, in infants, this type of exposure can slow bone growth. Animal studies have also indicated the possible role of Al exposure in mental impairments [34]. Aluminum is also linked to degenerative brain diseases, such as Alzheimer's and Parkinson's [35]. In addition, Al plays a causal role in the development of microcytic anemia and osteomalacia and can also potentiate inflammatory and oxidative events [36].

The reported Cd levels ranged from 0.1-1.2 ng/m^3, which are also far lower than the prescribed workplace permissible limit ($\sim 10^4$ ng/m^3). The Cd levels in the blood and kidney were consistently higher in smokers than in nonsmokers [19]. Cd is known to cause renal and hepatic toxicity and lung cancer. It can also cause "Itai-itai" or "ouch-ouch" disease, which is known to have a combination of different effects, including osteoporosis, renal dysfunction, anemia, and low blood pressure [37].

The exposure limit of Cu varies between 0.1-1 10^6 ng/m^3, while observed levels inside a room (after two hours of vaping) ranged from 13.1-127 ng/m^3 [12]. Cu toxicity includes gastrointestinal distress, liver and kidney damage, and carcinogenicity [19]. In contrast, the exposure limit for Mn varies between 0.1-5 10^6 ng/m^3, while the observed levels inside a room after two hours of vaping ranged between 13.1-127 ng/m^3 [12]. The health effects of Mn in humans include neurological problems, impaired pulmonary function, pneumonia, and cough [19].

The exposure limit for Ni varies between 0.015-1.5 10^6 ng/m^3, while the observed concentration levels inside a room after two hours of vaping were 8.1-356 ng/m^3. As such, the Ni levels released from vaping may be approaching this guideline value. Note that Ni has the potential to cause a variety of adverse human health effects; the most important and frequent are nickel allergy in the form of contact dermatitis, lung fibrosis, cardiovascular and kidney diseases, and lung and nasal cancers [19]. The effect of Cr is generally exerted on the respiratory system and kidneys, while long-term exposure can lead to lung cancer [19].

The permissible limit for Pb in work environments is 5 10^4 ng/m^3, while its level in EC smoke was reported to be 10.9 ng/m^3 [12]. Pb can affect almost every organ in the body. The main target of Pb toxicity is the nervous system in both adults and children [19]. It can also cause weakness in the fingers, wrists, or ankles. Exposure to Pb is also known to cause anemia and hypertension, particularly in middle-aged and older people. Exposure to high levels of Pb can severely damage the brain and kidneys in adults or children and ultimately lead to death. In pregnant women, high-levels of Pb exposure can cause miscarriage, while they can affect sperm production in men.

The concentration of Zn from EC smoke was observed at 500 ng/m^3 in ECs, while its recommended exposure limit is 5 10^6 ng/m^3 [12]. Compared to several other metal ions, Zn is relatively harmless. Only exposure to high doses has acute toxic effects. Long-term, high-dose Zn supplementation is known to interfere with the uptake of copper. One organ where Zn is prominently involved in cell death is the brain, and the cytotoxicity produced as a result of ischemia or trauma involves the accumulation of free Zn [16].

As evidenced by the above discussion, exposure limits can be exceeded when many smokers are using ECs indoors. Similarly, regular EC smokers will experience accumulated exposure, which might lead to health complications related to heavy metal exposure. Because of the variety of toxic heavy metals in EC smoke and their numerous negative health effects, the metal content in EC components should be reduced.

5. Regulation of ECs

The increasing use of ECs has caused many public health experts, medical societies, large health organizations, and policymakers to exercise caution when proposing new regulations regarding availability to children and teenagers. The World Health Organization (WHO) Study group on Tobacco Product Regulation classified ECs as electronic nicotine delivery systems; current regulation of the EC has not been sufficient [38]. The tobacco authority of the United States Food and Drug Administration (US FDA) has proposed that ECs be covered as additional products that meet the legal definition of a tobacco product [39]. As per the

new findings released by the US Centers for Disease Control and Prevention [2] on September 6, 2013. The use of ECs by children and teenagers has more than doubled in the past two years. The nicotine at the levels present in e-liquid can be toxic to infants and children. Child-safe or child-resistant packaging, child safety locks (such as those present on cigarette lighters), and proper instruction on the safe handling of e-liquid can help mitigate some of these risks [40]. According to a recent Wells Fargo prediction analysis conducted by Mangan [41], EC consumption could surpass that of CCs within the next decade. As is clear from the discussion above, ECs are not reliably safe and can have harmful impacts on both active and passive smokers. Most importantly, across the globe, ECs are not subject to safe manufacturing and quality standards.

As shown in Table 2, the concentration levels of metals reported from cigarette products in different studies were remarkably different. The levels in a few studies, such as Williams et al. [11], were comparable between EC and CCs. However, most of the studies showed two to four orders of magnitude higher levels in CCs. The difference in metal levels also indicates that the emission levels vary greatly across product brands. Unlike CCs, the sources of metals in ECs are not only the refill solution, but also the actual cigarette assembly, such as solder joints, wires, and silicate beads. Therefore, the lack of regulation in the manufacturing process of EC components should be addressed to reduce exposure to toxic materials (such as metals), which would otherwise lead to their emission in the form of an aerosol. Implementation of quality control procedures on the design and manufacturing process of ECs should also be addressed to prevent exposure to non-desirable material in ECs (and e-liquids).

Considering all of these aspects, regulations for the manufacture, availability, and use of ECs in public places must be promulgated to control both first- and second-hand exposure. Implementation of quality control in the manufacturing protocols of ECs would also further minimize the risk associated with metal release from these devices and should be developed to improve the safety and associated health effects of ECs.

6. Conclusions

The presence of metals and silicate particles in EC aerosols demonstrates the need for more stringent quality control of the design and manufacturing processes for ECs and calls for more detailed studies on the health impacts on both passive and active smokers. Although many studies have reported the presence of greatly reduced levels of metals in ECs, this decrease does not suggest that ECs are a safer product. Because metals tend to accumulate in the body over time, the risk of long-term exposure due to EC smoking should be carefully evaluated. Moreover, the popularity of ECs appears to be associated with the fact that they can be used in many smoke-free areas; they also possess a price merit and are perceived as being less harmful than CCs. The presence of toxic metals below the threshold limit does not necessarily guarantee that no ill health effects will result from the use of ECs (100-200 daily inhalations) on a long-term basis. As such,

the potential for harmful effects may accumulate over decades, as with CCs. Further, the presence of different metals below the official threshold-limit values may accumulate in a synergistic way to result in a substantial combined impact of various toxic metals.

Based on all of these considerations, regulations for ECs with respect to manufacture, sales, and use in public places must be promulgated to control both first- and secondhand exposure. Implementation of strict quality control protocols on the manufacture of ECs, which is currently lacking, would further minimize the emission of metals due to the use of these devices and also improve their negative health effects. Further, comprehensive research on EC is urgently needed in order to ensure that decisions of regulators, healthcare providers, and consumers are based on science.

Acknowledgements

References

1. WHO. WHO report on the global tobacco epidemic: The MPOWER package World Health Organization; 2008.
2. CDC. Smoking-attributable mortality, years of potential life lost, and productivity losses--United States, 2000-2004. *MMWR Morb. Mortal. Wkly. Rep* 2008;57:1226-1228.
3. WHO. WHO report on the global tobacco epidemic, 2013: Enforcing bans on tobacco advertising, promotion and sponsorship. World Health Organization; 2013.
4. Rodu B, Godshall WT. Tobacco harm reduction: An alternative cessation strategy for inveterate smokers. *Harm Reduct. J.* 2006;3:1-23.
5. CASAA, 2013. Results of web-based survey (Cigarettes Consumer Advocates for Smoke-free Alternatives Association) [Internet]. Survey Monkey website; c2013 [cited 10 Feb 2017]. Available from: http://casaa.org/.
6. Polosa R, Rodu B, Caponnetto P, Maglia M, Raciti C. A fresh look at tobacco harm reduction: The case for the electronic cigarette. *Harm Reduct. J.* 2013;10:1-11.
7. Trtchounian A, Talbot P. Electronic nicotine delivery systems: Is there a need for regulation? *Tob. Control* 2011;20:47-52.
8. Hon L. A non-smokable electronic spray cigarette. *Canada Patent CA* 2005;2518174.
9. Williams M, Talbot P. Variability among electronic cigarettes in the pressure drop, airflow rate, and aerosol production. *Nicotine Tob. Res.* 2011;13:1276-1283.
10. Bansal V, Kim KH. Review on quantitation methods for hazardous pollutants released by e-cigarette (EC) smoking. *Trends. Analyt. Chem.* 2016;78:120-133.
11. Williams M, Villarreal A, Bozhilov K, Lin S, Talbot P. Metal

and silicate particles including nanoparticles are present in electronic cigarette cartomizer fluid and aerosol. *PLoS ONE* 2013;8:e57987.

12. Schober W, Szendrei K, Matzen W, et al. Use of electronic cigarettes (e-cigarettes) impairs indoor air quality and increases FeNO levels of e-cigarette consumers. *Int. J. Hyg. Environ. Health* 2014;217:628-637.

13. Goniewicz ML, Knysak J, Gawron M, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob. Control* 2013;23:133-139.

14. ICH. Technical requirements for registration of pharmaceuticals for human use. Topic Q2 (R1): Validation of analytical procedures: Text and methodology, International Conference on Harmonization, Geneva, Switzerland; 2005.

15. Hou X, Amais RS, Jones BT, Donati GL. Inductively coupled plasma optical emission spectrometry. Encyclopedia of Analytical Chemistry. John Wiley & Sons, Ltd; 2010.

16. Plum LM, Rink L, Haase H. The essential toxin: Impact of zinc on human health. *Int. J. Environ. Res. Public Health* 2010;7:1342-1365.

17. Siddappa K, Ganesh, Balakrishna KM. Neutron and gamma activation analyses using microtron facility. Trends in NDE Science & Technology; Proceedings of the 14th World Conference on Non-Destructive Testing; 8-13 December 1996; New Delhi. p. 389-392.

18. Iskander FY, Bauer TL, Klein DE. Determination of 28 elements in American cigarette tobacco by neutron-activation analysis. *Analyst* 1986;111:107-109.

19. Chiba M, Masironi R. Toxic and trace elements in tobacco and tobacco smoke. *Bull. World Health Organ.* 1992;70:269-275.

20. Caruso RV, O'Connor RJ, Stephens WE, Cummings KM, Fong GT. Toxic metal concentrations in cigarettes obtained from US smokers in 2009: Results from the International Tobacco Control (ITC) United States survey cohort. *Int. J. Environ. Res. Public Health* 2013;11:202-217.

21. Saffari A, Daher N, Ruprecht A, et al. Particulate metals and organic compounds from electronic and tobacco-containing cigarettes: Comparison of emission rates and secondhand exposure. *Environ. Sci. Process. Impacts* 2014;16:2259-2267.

22. Böhlandt A, Schierl R, Diemer J, et al. High concentrations of cadmium, cerium and lanthanum in indoor air due to environmental tobacco smoke. *Sci. Total Environ.* 2012;414:738-741.

23. Satarug S, Moore MR. Adverse health effects of chronic exposure to low-level cadmium in foodstuffs and cigarette smoke. *Environ. Health Perspect.* 2004;112:1099-1103.

24. Piadé J-J, Jaccard G, Dolka C, Belushkin M, Wajrock S. Differences in cadmium transfer from tobacco to cigarette smoke, compared to arsenic or lead. *Toxicol. Rep.* 2015;2:12-26.

25. Friberg L. "Cadmium" Annual Review of Public Health; 1983.

p. 367-373.

26. Mortada WI, Sobh MA, El-Defrawy MM. The exposure to cadmium, lead and mercury from smoking and its impact on renal integrity. *Med. Sci. Monit. Basic Res.* 2004;10:CR112-CR116.

27. Bárány E, Bergdahl IA, Bratteby L-E, et al. Trace elements in blood and serum of Swedish adolescents: Relation to gender, age, residential area, and socioeconomic status. *Environ. Res.* 2002;89:72-84.

28. Díaz C, López F, Henríquez P, Rodríguez E, Serra-Majem L. Serum manganese concentrations in a representative sample of the Canarian population. *Biol. Trace Elem. Res.* 2001;80:43-51.

29. Pleban P, Pearson KH. Determination of manganese in whole blood and serum. *Clin. Chem.* 1979;25:1915-1918.

30. Pappas RS, Fresquez MR, Martone N, Watson CH. Toxic metal concentrations in mainstream smoke from cigarettes available in the USA. *J. Anal. Toxicol.* 2014;38:204-211.

31. Smith C, Livingston S, Doolittle D. An international literature survey of "IARC Group I carcinogens" reported in mainstream cigarette smoke. *Food Chem. Toxicol.* 1997;35:1107-1130.

32. Adachi A, Asai K, Koyama Y, Matsumoto Y, Kobayashi T. Vanadium content of cigarettes. *Bull. Environ. Contam. Toxicol.* 1998;61:276-280.

33. OSHA. Table Z-1 limits for air contaminants, United States Department of Labor, Occupational Safety and Health Standards; 2013.

34. Kumar V, Gill KD. Aluminium neurotoxicity: Neurobehavioural and oxidative aspects. *Arch. Toxicol.* 2009;83:965-978.

35. Brenner S. Aluminum may mediate Alzheimer's disease through liver toxicity, with aberrant hepatic synthesis of ceruloplasmin and ATPase7B, the resultant excess free copper causing brain oxidation, beta-amyloid aggregation and Alzheimer disease. *Med. Hypotheses* 2013;80:326-327.

36. Gupta VB, Anitha S, Hegde M, et al. Aluminium in Alzheimer's disease: Are we still at a crossroad? *Cell. Mol. Life Sci.* 2005;62:143-158.

37. Inaba T, Kobayashi E, Suwazono Y, et al. Estimation of cumulative cadmium intake causing Itai–itai disease. *Toxicol. Lett.* 2005;159:192-201.

38. WHO. WHO Study Group on Tobacco Product Regulation. Report on the scientific basis of tobacco product regulation: 3rd report of a WHO study group. WHO Technical Report Series; 2009.

39. FDA. Deeming–Extending authorities to additional tobacco products (Food Drug Administration); 2014.

40. Brown CJ, Cheng JM. Electronic cigarettes: Product characterisation and design considerations. *Tob. Control* 2014;23:ii4-ii10.

41. Mangan D. E-cigarette sales are smoking hot, set to hit $1.7 billion. CNBC Healthcare; 2013.