TOX/2018/15

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT)

Potential toxicological risks from electronic nicotine (or non-nicotine) delivery systems (e-cigarettes). Paper 2: Exposure to metals present in the aerosol of electronic nicotine (or non-nicotine) delivery systems

Background

1. During a horizon-scanning exercise at the COT meeting in February 2016, the Committee considered the subject of the possible human health effects of electronic nicotine delivery systems or electronic non-nicotine delivery systems (E(N)NDS or e-cigarettes) as a potential item for review. Members considered that this was a topic that should be evaluated by the COT. It was decided that a full systematic review would not be an efficient way to proceed, and the Committee recommended a more focussed review of three key areas: additives, nitrosamines produced by E(N)NDS, and secondary exposure to exhaled products.

2. A scoping document (TOX/2016/25) reviewing these three areas was discussed by the Committee in July 2016, with the aim to set priorities for more in-depth reviews. From these discussions, a number of areas were agreed for further consideration. These were:

- the composition of particles
- bystander exposure to key analytes
- effects of long term inhalation of the main constituents and emissions
- the situation regarding flavourings (exposure, thermal products, toxicity on inhalation)
- exposure to metals from the device components

3. The Committee agreed that further discussion papers should be prepared to address the above questions. A first paper on characterisation of the aerosol droplet particle fraction was discussed at the COT meeting in December 2017. This second paper addresses potential exposure to metal particles present in the particulate fraction of E(N)NDS aerosols.

Introduction

4. E(N)NDS are battery-powered devices containing a liquid (E(N)NDS liquid or ‘e-liquid’). The E(N)NDS liquid is heated on use to produce an aerosol that is inhaled by the user (‘puffing’, ‘vaping’). E(N)NDS were first introduced commercially in China in 2004 and subsequently in the EU (2005) and USA (2007) as nicotine-delivery

devices (Bansal and Kim 2016). The main constituent parts of an E(N)NDS device are a mouthpiece, cartridge (tank) containing E(N)NDS liquid, a heating element/atomizer, a microprocessor, a battery, and sometimes an LED light. Commercially available devices are sometimes categorised as first, second, or third generation. First-generation devices look like conventional cigarettes and thus are termed 'cigalikes'. Initial models comprised three principal parts; a lithium-ion battery, a cartridge and an atomizer. However, more recent models mostly consist of a battery connected to a 'cartomizer' (cartridge/atomizer combined), which may be replaceable, but is not refillable. Second-generation E(N)NDS are larger and have less resemblance to tobacco cigarettes. They often resemble pens or laser pointers (hence the name, 'vape pens'). They have a high-capacity rechargeable lithium-ion battery and a refillable atomizer (sometimes referred to as a 'clearomizer'). Third-generation models ('advanced personal vapers', 'mods') are also refillable, have very-high-capacity lithium-ion batteries and are highly customisable (different coil options, power settings, tank sizes). In addition, highly advanced 'fourth generation' E(N)NDS (innovative regulated mods) are now being described[1].

5. E(N)NDS liquid normally comprises a base material of propylene glycol (PG), with or without glycerol (generally referred to as vegetable glycerine, VG), plus water and optional ingredients such as nicotine and flavourings.

6. Several detailed analyses of E(N)NDS liquids have been reported, and this area has been reviewed in TOX/2016/25 and in several publications (Cheng 2014, Famele et al. 2015, Bansal and Kim 2016). Some constituents that have been identified include PG, VG, water, nicotine, carbonyls, volatile organic compound (VOCs), tobacco-specific nitrosamines (TSNAs), polycyclic aromatic hydrocarbons (PAHs), metals, ethanol, ethylene glycol, di-ethylene glycol, flavouring compounds, flavour enhancers, sweeteners, and phenolics (see paper TOX/2018/16). In addition, studies have investigated the composition of the E(N)NDS 'vape' product (aerosol) (see, for example, Goniewicz et al. (2014); Margham et al. (2016)). This 'aerosol' in fact comprises two major parts – the gas phase (vapour) and a particulate phase of suspended liquid droplets. Several techniques have been used to sample and analyse these components and this is an area that is still in development (see the recent review by Bansal and Kim (2016)). Components of the vapour phase include VOCs and carbonyls. The particulate phase comprises droplets that are formed when components within the E(N)NDS liquid are heated and vaporise, then condense back into liquid aerosol as the gas cools (see paper TOX/2017/49). In addition, solid particles such as metal nanoparticles, derived from the E(N)NDS device or E(N)NDS liquid, may be present, which is the focus of this paper.

7. A literature search was carried out (Annex A) and studies that reported potential exposure to metals/inorganic elements from E(N)NDS aerosols were retrieved. The following narrative reviews the relevant papers, and the possible

[1] see, http://ecigclopedia.com/the-4-generations-of-electronic-cigarettes/ (accessed 18/12/17)

sources of these elements in E(N)NDS devices and/or E(N)NDS liquids. The studies reported are also summarised in Table A (Annex B).

Investigation of E(N)NDS device components and relation to the aerosol produced

8. E(N)NDS contain metal components in the structure of the device, which may include resistive wire heating filaments (e.g. nickel-chromium), wire couplings, solder joints, and silver coatings.

9. Williams and colleagues reported a series of studies in which they investigated the structural components of E(N)NDS devices by disassembling the devices and assessing how the components observed may correlate with the presence of metal particles in aerosols produced from these devices.

10. In a first report, Williams et al. (2013) disassembled cartomizers from a US 'leading brand' of E(N)NDS, purchased over a two-year period (brand not stated, all the same non-nicotine product type), and analysed the individual components by methods including scanning electron microscopy (SEM), electron dispersion X-ray spectroscopy (EDS), transmission electron microscopy (TEM), particle counting and sizing (CPC/SMPS), and inductively coupled plasma optical emission spectrometry (ICP-OES). Dissected cartomizers comprised:

- a mouthpiece, mostly composed of iron, chromium, and manganese (i.e. stainless steel) with a white silica gasket
- a wick (probably fibreglass)
- two thick wires – copper coated with silver, with many small particles on the surface
- one thin wire (the filament, wound around the wick) with numerous nickel and chromium particles on the surface (nichrome)
- a nickel air tube
- four poorly formed solder joints connected at one end to the thin filament and at the other to the mouthpiece; these solder joints comprised mostly tin (including the formation of tin crystals, or 'whiskers') plus a small amount of copper
- inner and outer dense fibres (Poly-fil) (**Figure 1**).

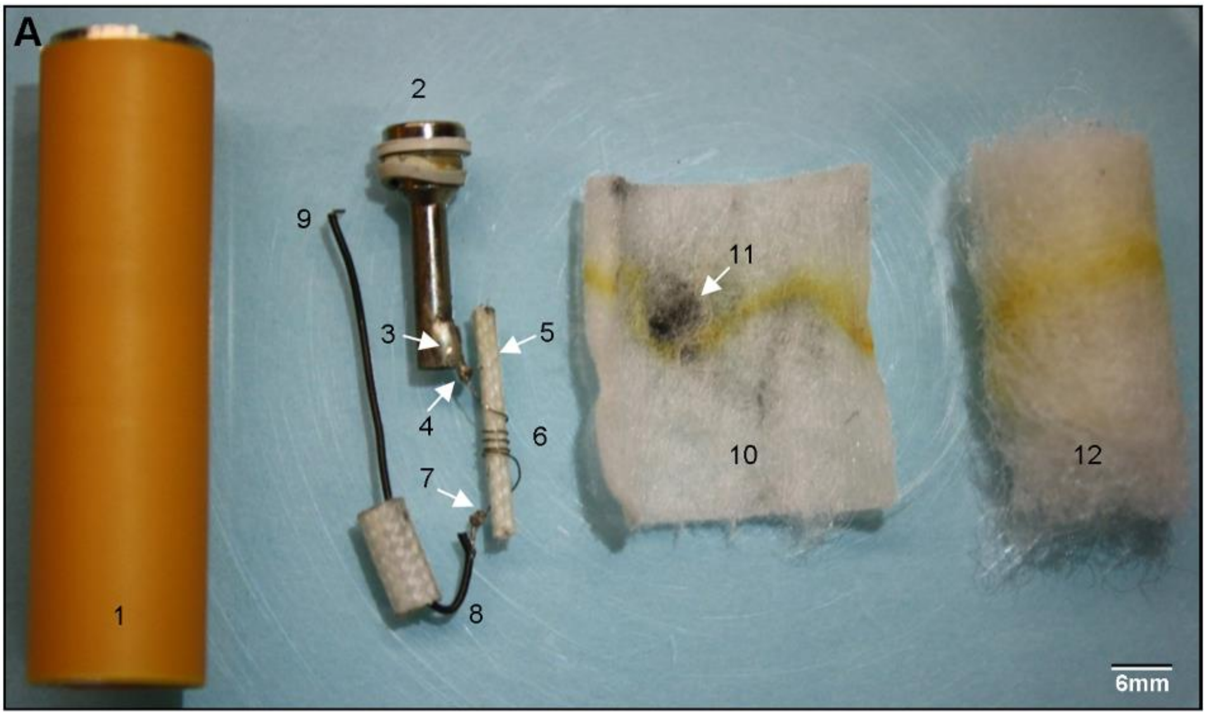

Figure 1. Cartomizer anatomy. (A) A dissected cartomizer. 1 = mouthpiece, 2 = air tube, 3 = solder joint between air tube and thick wire, 4 = solder joint between thick wire and filament, 5 = wick, 6 = filament, 7 = solder joint between the filament and thick wire, 8 = thick wire, 9 = solder joint where the thick wire would attach to the mouthpiece, 10 = inner fibers, 11 = black area on inner fibers, 12 = outer fibers with yellow electrophoretic band. (B) solder joint between the filament and thick wire. Boxed area is shown at higher magnification in the lower insert and contains tin whiskers. (E–H) Images of fiber types, (E, F) inner fibers, and (G, H) outer fibers. (E, G) black deposits on fibers and (F, H) green coloration on both sets of fibers. doi:10.1371/journal.pone.0057987.g001

Figure 1 Components of a disassembled cartomizer-type E(N)NDS

Reproduction of Figure 1 from Williams et al. (2013) PLoS ONE, 8(3): e57987

11. Aerosol produced from these cartomizers and analysed by SEM/EDS and TEM contained elements in two broad size ranges, with the majority in the < 100 nm range. SEM/EDS analysis in the range 1–20 µm revealed predominantly particles of tin, silver, nickel, and aluminium, but also iron, cerium, lanthanum, bismuth, and zinc, and numerous round particles of various sizes containing mainly silicon with lesser amounts of magnesium, aluminium, and calcium. These silicate beads were considered to originate from the fibreglass wick, which was reported to have small, round, smooth-surfaced particles on its surface of a similar size, appearance and elemental composition as the silicate beads in the aerosol. Analysis by TEM/EDS (< 100 nm) indicated the presence of tin, chromium, and nickel nanoparticles. In comparison with reported data for metals in conventional cigarette (CC) smoke, aluminium, iron, nickel and sodium, levels were higher in E(N)NDS aerosol, while copper, chromium, lead, magnesium, and manganese levels were in the same range (**Table 1**).

Table 1 Elemental abundance in E(N)NDS aerosol and comparison with values reported for CC smoke.

	Aluminium	Barium	Boron	Calcium	Chromium	Copper
E(N)NDS	0.394	0.012	3.83	1.03	0.007	0.203
CC[2]	0.22				0.004-0.5	0.19
	Iron	**Lead**	**Lithium**	**Magnesium**	**Manganese**	**Nickel**
E(N)NDS	0.52	0.017	0.008	0.066	0.002	0.005
CC	0.042	0.017-0.14		0.070	0.003	0.000073-0.003
	Potassium	**Silicon**	**Sodium**	**Strontium**	**Sulphur**	**Tin**
E(N)NDS	0.292	2.24	4.18	0.006	0.221	0.037
CC						
	Titanium	**Zinc**	**Zirconium**			
E(N)NDS	0.002	0.058	0.007			
CC		0.12-11.9				

Values are in µg/10 puffs.

Adapted from Table 1 of Williams et al. (2013) PLoS ONE, 8(3): e57987

12. Williams et al. (2015) extended these studies to similarly investigate four ‘popular’ US brands of E(N)NDS purchased over a period of five years (brands not stated; 3 cartomizers [labelled A, B, C], and 1 disposable [D]). In this study they used ICP-OES to evaluate levels of tin, copper, zinc, silver, nickel, and chromium in aerosol produced from ‘fresh’ E(N)NDS units and related the findings to the structure of the apparatus. Measured levels varied widely, both within and between brands. Values for individual metals were generally below 0.20 µg/10 puffs, except for tin, for which the aerosol from one cartomizer (Brand A) contained > 3 µg/10 puffs (Figure 2).

[2] Values for CC were obtained from various literature sources for one CC, as detailed in Table 1 of Williams et al., 2013

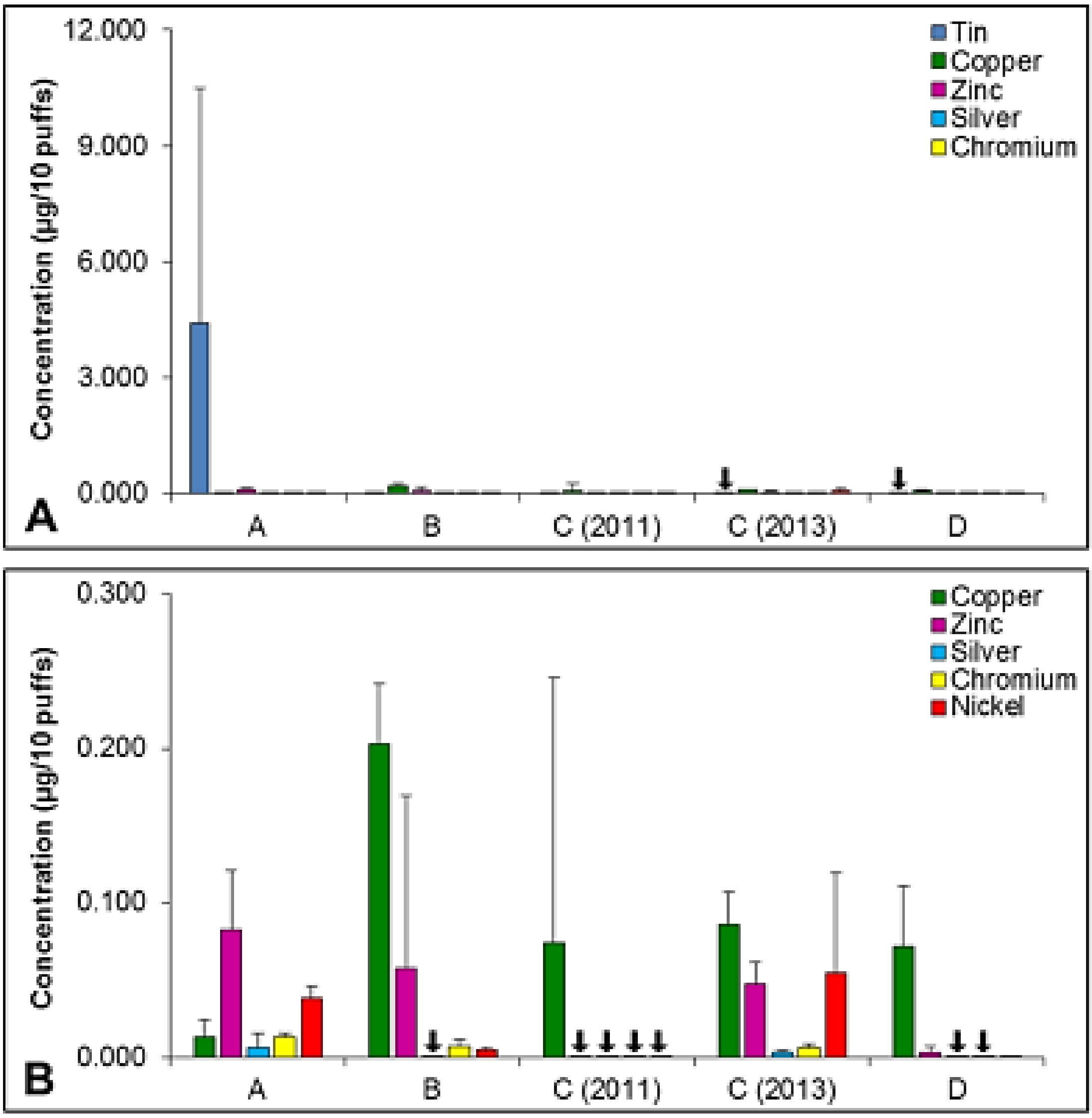

Figure 2 Total concentration of metals in aerosol of four brands of E(N)NDS.

(A) Total concentration of six metals (tin, copper, zinc, silver, chromium, nickel); (B) Total concentration of five metals (copper, zinc, silver, chromium, nickel).

Each bar is the average ± standard deviation of three cartomizers. Black arrows indicate samples that were below the LOQ.

Reproduction of Figure 1 from Williams et al. (2015) PLoS ONE 10(9): e0138933.

13. E(N)NDS devices were investigated to evaluate whether structure and design differences underlay the differences in the presence of metals in the aerosols (**Table 2**). All four devices showed similar overall designs, but with some variations. In all cases, filaments were made of nickel/chromium. Thick wires were copper coated with silver, or in one case, with tin, and wires were joined with either tin solder, brazing[3] or brass (copper/zinc) clamps. Element levels in aerosol in some cases showed substantial variation within and between brands. The highest levels were observed for tin in Brand A (but with a 30-fold variation between cartomizers of this

[3] Brazing is a metal-joining process in which two or more metal items are joined together by melting and flowing a filler metal into the joint, the filler metal having a lower melting point than the adjoining metal

brand). Investigators implicated friable tin solder joints present in these devices as being the cause of the high levels of tin in the aerosol. Tin coating on copper wires was also suggested to contribute to tin in the aerosol. The authors made suggestions for cartomizer design that could reduce the levels of tin or other metals in the aerosol produced by the E(N)NDS device.

Table 2 Summary of elements in E(N)NDS wires and joints

Brand	Thin Filament	Thick Wire	Wire toWire Joint	Wire to Air Tube/Mouthpiece/Battery Joint
A	Nickel, Chromium	Copper, Silver Coated	Zinc, Copper Clamp	Tin Solder
A1	Nickel, Chromium	Copper, Silver Coated	Zinc, Copper Clamp	Tin Solder
A2	Nickel, Chromium	Copper, Silver Coated	Nickel, Zinc, Copper Clamp	Tin Solder
B	Nickel, Chromium	Copper, Silver Coated	Tin Solder	Tin Solder
C (2011)	Nickel, Chromium	Copper, Tin Coated	Chromium and Copper Braze	Organic Glue
C (2013)	Nickel, Chromium	Copper, Silver Coated	Zinc and Copper Clamp	Organic Glue
D	Nickel, Chromium	Copper, Silver Coated	Zinc and Copper Clamp	Tin Solder

doi:10.1371/journal.pone.0138933.t001

Reproduction of Table 1 from Williams et al. (2015) PLoS ONE 10(9): e0138933.

14. Williams et al. (2017) then evaluated eleven E(N)NDS devices (six disposable 'e-cigarettes' (ECs) and five disposable 'e-hookahs' (EHs)) by assessing the disassembled devices, measuring levels of 36 elements, both in the device components and in the aerosol produced, and comparing with a reference CC (Marlboro Red). Inspection of the disassembled devices showed similar structures in all E(N)NDS devices; the compositions of the individual components for the different device brands are summarised in **Table 3**. The majority of the devices had a nichrome (nickel/chromium) filament, thick wire made of copper coated with silver, brass-clamp (copper/zinc) and/or tin-solder joints, and wick/sheath composed primarily of silicon. Lead was present in the solder joints of two brands. The wick and sheath were described as 'made of finely woven silicate glass beads with minor sodium, potassium, calcium and magnesium (fiberglass) that can easily break when handled.'

Table 3 Elemental composition of the atomizer of E(N)NDS devices.

Brand	Thin Filament	Thick Wire	Wire to Wire Joint	Wire to Battery Joint	Wick	Sheath
BluCig	Chromium,Nickel	Copper, Silver Coated	Copper, Zinc Clamp	Tin Solder	Silicon, Oxygen and Silicon, Oxygen, Magnesium, Calcium, Aluminum	Silicon, Oxygen, Magnesium, Calcium, Aluminum
Mistic	Chromium,Nickel[a]	Copper, Silver Coated[a]	Copper, Zinc Clamp[a]	Tin Solder[a]	Silicon, Oxygen, Magnesium, Calcium, Aluminum	Silicon, Oxygen, Magnesium, Calcium, Aluminum
NJOY King	Chromium,Nickel	Copper, Nickel, Silver Coated	Copper,Zinc Clamp	Tin Solder	Silicon, Oxygen	Silicon, Oxygen, Calcium[b]
Square 82	Chromium, Copper, Aluminum, Titanium, Molybdenum, Iron	Copper, Silver Coated	Tin, Calcium Solder	Tin Solder	Silicon, Oxygen	Silicon, Oxygen, Magnesium, Calcium, Aluminum
V2 Cigs	Chromium,Nickel	Copper, Silver Coated	Tin Solder	Tin Solder	Silicon, Oxygen	Silicon, Oxygen, Magnesium, Calcium, Aluminum
Vype	Chromium,Nickel, Iron	Copper, Silver Coated	Copper, Zinc Clamp	Tin Solder	Silicon, Oxygen	Silicon, Oxygen, Magnesium, Calcium, Aluminum,
Imperial Hookah	Chromium,Nickel	Copper, Silver Coated	Tin, Lead Solder	Tin, Lead Solder and Organic glue	Silicon, Oxygen	Silicon, Oxygen, Magnesium, Calcium, Aluminum
Luxury Lites	Chromium,Nickel	Copper, Silver Coated	Tin, Lead Solder	Tin, Lead Solder	Silicon, Oxygen, Calcium, Aluminum	Silicon, Oxygen, Magnesium, Calcium, Aluminum, Sodium
Smooth	Chromium, Nickel	Copper, Tin Coated	Tin Solder	Tin Solder	Silicon, Oxygen	Silicon, Oxygen, Magnesium, Calcium, Aluminum, Sodium
Starbuzz	Chromium, Nickel, Iron	Copper, Nickel, Silver Coated	Copper, Zinc Clamp	Tin Solder	Silicon, Oxygen	Silicon, Oxygen, Magnesium, Calcium, Aluminum
Tsunami	Chromium,Nickel	Copper, Nickel, Silver Coated	Tin Solder	Tin Solder	Silicon, Oxygen	Silicon, Oxygen, Magnesium, Calcium, Aluminum

[a]Data presented in Williams et al 2015 PlosOne.
[b]Elemental maps of silicon, oxygen, and calcium were generated, magnesium and aluminum were also in the spectrum.

https://doi.org/10.1371/journal.pone.0175430.t002

Reproduction of Table 2 from Williams et al. (2017) PLoS ONE 12(4): e0175430.

15. ICP-OES analysis of aerosols for content of 36 elements (subtracted against levels measured in room air) showed that total concentrations varied from approximately 1.8–7.3 µg/10 puffs across different E(N)NDS brands, and approximately 1.5–4.3 µg/10 puffs for the CC, depending on puffing protocol. As reported in other studies, a substantial variation in levels of individual elements was observed both between and within E(N)NDS brands. A total of 31 elements were identified across the spectrum of the 11 E(N)NDS aerosols at levels ≥ 0.001 µg/10 puffs, with 17 elements detected in one or more brands at levels > 0.01 µg/10 puffs. Five elements were not detected (bismuth, cadmium, iridium, palladium, titanium). Individual elements identified are summarised in Table 4, below, and levels for individual E(N)NDS are shown in the figures attached at Annex C.

16. Silicon was the principal element identified in the aerosols of all E(N)NDS brands (> 50% by total mass; range, 0.094–6.835 µg/10 puffs), which the authors assumed was derived from fragments of the sheath and wick (fibreglass). Blackened wicks adjacent to filaments were noted on dissection of used devices. The authors proposed that further work is needed to determine the potential health effects of the silicate fibreglass inhaled in E(N)NDS aerosols.

17. Other prominent elements included: copper (detected in 8 brands; range 0.009–0.194 µg/10 puffs[4]), probably derived from the thick wires and brass clamps; tin (8 brands; range 0.016–0.245 µg/10 puffs), presumed to come from the solder joints; zinc (9 brands; range, 0.003–0.079[5] µg/10 puffs), presumed to come from the brass clamps; sodium (3 brands; range, 0.106–0.387 µg/10 puffs), magnesium (7 brands; range, 0.002–0.049 µg/10 puffs), and calcium (8 brands; range, 0.073–0.791 µg/10 puffs), presumed to come from the sheath and wick. Similar to observations in other studies, low levels of nickel were detected in aerosols from seven of the eleven brands (range, 0.002–0.005 µg/10 puffs), presumably derived from the nichrome filament. Chromium was detected in two brands; the levels reported are unclear, but appear to be around 0.001 µg/10 puffs[6].

18. Lead was observed in the solder joints and also in the corresponding aerosol of two EHs (range, 0.007–0.165 µg/10 puffs).

Table 4 Inorganic elements identified in aerosol samples from 11 brands of E(N)NDS.

	Al	**Sb**	**As**	**Ba**	**B**	**Ca**	**Cr**	**Co**	**Cu**	**Ge**	**In**	**Fe**	**La**	**Pb**	**Mg**	**Mn**
N 0.001-0.01 µg/10 puffs	3	4	2	5	1		2	1	1	1	2	5	3	1	3	3
N > 0.01 µg/10 puffs	4				4	8			7	2		3		1	4	
	Hg	**Mo**	**Ni**	**K**	**Rb**	**Se**	**Si**	**Ag**	**Na***	**Sr**	**Sn**	**W**	**V**	**Zn**	**Zr**	
N 0.001-0.01 µg/10 puffs	1	2	9		1	1		1	1	8		2	4	1	3	
N > 0.01 µg/10 puffs				7	1	4	11		2		8	1		8	4	

N, number of brands in which the element was detected at this level. Measurements were made by ICP-OES and subtracted for levels of the elements in room air.
Al, aluminium; Sb, antimony; As, arsenic; Ba, barium; B, boron; Ca, calcium; Cr, chromium; Co, cobalt; Cu, copper; Ge, germanium; In, indium; Fe, iron; La, lanthanum; Pb, lead; Mg, magnesium; Mn, manganese; Hg, mercury; Mo, molybdenum; Ni, nickel; K, potassium; Rb, rubidium; Se, selenium; Si, silicon; Ag, silver; Na, sodium; Sr, strontium; Sn, tin; W, tungsten; V, vanadium; Zn, zinc; Zr, zirconium.
*only tested for six brands. Bi, Cd, Ir, Pd, Ti were not detected.
Data[7] are taken from Table 3 of Williams et al. (2017) PLoS ONE 12(4): e0175430

[4] In the Discussion section, Williams et al. (2017) describe copper measurements in the range 0.044–0.610 µg/10 puffs. However, these values are not consistent with those presented in Figures 2, 3, and 4 of the Results section of this publication.

[5] In the Discussion section, Williams et al. (2017) describe zinc measurements in the range 0.003–0.048 µg/10 puffs. However, these values are not consistent with those presented in Figures 2, 3, and 4 of the Results section of this publication.

[6] Data from Williams et al. (2017) Supplementary figure S2.

[7] In some cases the values listed in Table 4 are different from those described in paragraphs 16 and 17. This is due to reporting inconsistencies between Figures 2, 3, 4, Table 3 and the text in the publication of Williams et al. (2017).

Measurements of metals in E(N)NDS aerosol

19. A number of other groups have carried out studies to investigate the potential presence of metals in the aerosol produced by E(N)NDS devices. Most collected mainstream aerosol produced on E(N)NDS use, although some others have analysed the air in rooms or chambers where E(N)NDS use has taken place.

Mainstream aerosol

20. Evaluation of several metals (arsenic, barium, cadmium, chromium, cobalt, copper, lead, manganese, nickel, rubidium, selenium, silver, strontium, thallium, vanadium, zinc) in aerosol produced from 12 E(N)NDS brands (11 from Poland and 1 from the UK, of which 10 cartridge and 2 cartomizer) by liquid-phase extraction and inductively coupled plasma mass spectrometry (ICP-MS) indicated the presence of cadmium, nickel, and lead (Goniewicz et al. 2014). These elements were also identified in a commercially obtained nicotine inhaler and in blank samples. The values reported are summarised in Table 5.

Table 5 Levels of cadmium , nickel, and lead in aerosol generated from commercially available E(N)NDS.

	Level measured (µg/150 puffs)				
	Range of mean values across 12 E(N)NDS devices	Commercially available nicotine inhaler	Blank sample[8]	LOD	LOQ
Cd	0.01-0.22	0.03	0.02	0.04	0.120
Ni	0.11-0.29	0.19	0.17	0.024	0.072
Pb	0.03-0.57[9]	0.04	0.02	0.036	0.107

Summary of data reported in Goniewicz et al. (2014).
Cd, cadmium; Pb, lead; nickel.

21. Farsalinos, Voudris and Poulas (2015) used the data reported for 12 E(N)NDS by Goniewicz et al. (2014) plus data for one E(N)NDS reported by Williams et al. (2013) to perform a preliminary risk assessment for exposure to metals from E(N)NDS aerosol. Intakes of each identified metal for individual E(N)NDS were estimated, assuming a daily consumption of approximately 6 g E(N)NDS liquid[10], which would be equivalent to 1200 puffs. These values were compared with regulatory safety limits, where identified, namely permissible daily exposure (PDE) levels for chronic inhalational medicines from the United States Pharmacopeia (USP) (cadmium, chromium, copper, lead, nickel), minimum risk levels (MRL) from the US

[8] It is not clear from the report what 'blank sample' refers to, although a commentary on this study by Farsalinos et al. (2015) states that it was 'collection of air from the environment'.
[9] Only one of the 12 ECs produced aerosol with a lead level > 0.1 µg/150 puffs.
[10] Calculated by Farsalinos et al. (2015) using data from previous publications, as follows: average E(N)NDS liquid consumption, 3 g/day; approximately 5 mg E(N)NDS liquid/puff; uncertainty factor of 2 for inter-individual variability

Agency for Toxic Substances and Disease Registry (ATSDR) (manganese), or recommended exposure limits (REL) from the US National Institute of Occupational Health and Safety (NIOSH) (aluminium, barium, iron, tin, titanium, zinc, zirconium). (Table 6).

22. Of note, estimated intakes of cadmium would in some cases be close to the inhalational medicine PDE, and in one case (EC06 from the study of Goniewicz et al. (2014)) the PDE value for cadmium would be exceeded (1.6 µg/day from 1200 E(N)NDS puffs vs. 1.5 µg/day PDE). It is also notable that lead was identified in all products and although the range of observed values varied widely, in one case the level measured was close to the inhalational product PDE (4.4 µg/day from 1200 puffs from EC08 in the study of Goniewicz et al. (2014) vs. 5 µg/day PDE).

23. From their risk assessment, Farsalinos et al. (2015) concluded that, overall, levels of metals emitted in E(N)NDS aerosols are unlikely to be of substantial concern for adverse health effects for smokers switching to E(N)NDS from CC. However variation between products indicates that product quality should be improved to further reduce any unnecessary exposure to metals.

Table 6 Estimated exposure to metals from E(N)NDS aerosol use in comparison with US regulatory safety limits.

			Daily exposure estimated from 1200 puffs (µg)[1]												
			Goniewicz et al. (2014)												Williams et al. (2013)
Metal	US Regulatory safety limit (µg/day)		EC01	EC02	EC03	EC04	EC05	EC06	EC07	EC08	EC09	EC10	EC11	EC12	
Aluminium	41 500	REL	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	47.28
Barium	4150	REL	0	0	0	0	0	0	0	0	0	0	0	0	1.44
Cadmium	1.5	PDE	1.2	1.04	1.04	0	0.16	1.6	0	0.48	0	1.2	0.08	0	NM
Chromium	25	PDE	0	0	0	0	0	0	0	0	0	0	0	0	0.84
Copper	70	PDE	0	0	0	0	0	0	0	0	0	0	0	0	24.36
Iron	41 500	REL	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	62.4
Lead	5	PDE	0.32	0.32	0.4	0.08	0.24	0.08	0.16	4.4	0.56	0.32	0.16	0.08	2.04
Manganese	6	MRL	0	0	0	0	0	0	0	0	0	0	0	0	0.24
Nickel	1.5	PDE	0.88	0.96	0.32	0	0	0	0.48	0.72	0.16	0	0	0	0.6
Tin	16,600	REL	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	4.44
Titanium	2490	REL	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	0.24
Zinc	41,500	REL	0	0	0	0	0	0	0	0	0	0	0	0	6.96
Zirconium	41,500	REL	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	0.84

[1] subtracted for blank values, except for data from Williams et al. (2013). NM, not measured.

Data summarised from Table 1 of Farsalinos et al. (2015)

24. Tayyarah and Long (2014) reported that levels of metals (beryllium, cadmium, chromium, cobalt, lead, magnesium, mercury, nickel, selenium, tin) in aerosols from 'blu' E(N)NDS (2 disposable and 1 refillable), produced under a Health Canada-type puffing protocol, collected on filter pads, and analysed by ICP-MS, were below the limit of quantitation (LOQ) (which was 4 ng/puff for all metals except 0.8 ng/puff for Hg). Similar analysis of two rechargeable 'SKYCIGs' also showed all metals below the LOQ (which, in these analyses, was 0.06 ng/puff for all metals except 0.01 ng/puff for Hg), except for Cr which was detected at around 0.1 ng/puff.

25. Margham et al. (2016) performed a full evaluation of components, including 13 metals, in the aerosol from a Vype ePen E(N)NDS, which has a disposable cartomizer component containing a nichrome (80% nickel/ 20% chromium) wire heating coil. In this analysis, beryllium, cadmium, cobalt, lead, mercury, selenium, and tin were below the limit of detection (LOD), arsenic and nickel were below the LOQ, and chromium, copper, iron, and zinc were measured at quantifiable levels. Iron and zinc levels were, however, similar in air/blank samples. Copper levels in E(N)NDS aerosol (1.89 ng/puff) were approximately double those measured in air/blank (0.937 ng/puff), but there was high variability between individual measurements. For chromium, the authors commented that it was difficult to discern whether levels were genuinely higher in E(N)NDS aerosol (mean 0.399 ng/puff, variable individual measurements, around or below the LOQ) than blank/air (0.293 ng/puff; reported as being above the LOD but below the LOQ), although there was an indication that this may be the case and thus the possible presence of chromium in E(N)NDS aerosol may warrant further investigation.

26. A mean copper level of 116.79 ± 83.59 ng/puff (range, 24.3–224.7 ng/puff) was measured in a 4 s puff from a 'Blu' cigarette after collection on a methyl-cellulose filter and analysis by atomic absorption spectrometry (AAS) (Lerner et al. 2015). This was significantly higher than the copper level measured on a blank filter (which appears, from the figure presented in the report, to be approximately 5 ng/puff).

27. Mikheev et al. (2016) estimated that metal content accounts for around 10 ng/mg total particulate mass (TPM) measured in aerosol from 'blu cigalike' E(N)NDS (0–1.6% nicotine, various flavours), and would thus account for around 10% of the estimated 100 ng/mg nanoparticle fraction of the TPM, however the authors themselves state that this is a 'rough assessment'. Antimony, arsenic, chromium, copper, nickel, tin, and zinc were detected, but measurements varied widely (by orders of magnitude) between samples of the same flavour and nicotine content. Authors considered the variability may be due to factors such as E(N)NDS manufacturing inconsistencies (wire resistance, precision of application of the solder), variation in E(N)NDS liquid delivery rates, battery voltage, and heating temperature. Beryllium, cadmium, cobalt, lead, and selenium were not detected.

28. Lee et al. (2017) reported an analysis of the components of aerosol produced by V2 cigalike cartomizer devices (1.8% nicotine; tobacco, menthol flavours). The report stated that of 48 elements analysed by X-ray fluorescence spectrometry, trace amounts of barium, chlorine, indium, and silicon were detected in some samples, with the other elements being below the LOD. However, data were not presented.

Bystander air

29. A small number of reports have described studies that analysed the levels of metals/inorganic elements present in ambient air in rooms where E(N)NDS use has taken place.

30. Schober et al. (2014) carried out studies to evaluate potential emissions from E(N)NDS use in a simulated 'café-like setting' (environmentally controlled room). Three adult volunteers, who were not regular CC or E(N)NDS users, vaped E(N)NDS (tobacco flavour, with/without 18 mg/mL nicotine, refillable tank-system E(N)NDS device) for periods of around 2 h in a 45 m^3 room. Room air was monitored approximately 1 m from the E(N)NDS users, at a height of 1 m. The levels of 24 elements, collected on quartz filter pads, were measured by ICP-MS and compared with background levels measured on the day before the first vaping session. Values were reported for three different E(N)NDS liquids, each with and without nicotine. Overall, E(N)NDS use was associated with a 2.4-fold increase for aluminium (482.5 ± 158.6 ng/m^3 vs. 203.0 ng/m^3), with no significant changes in levels of other metals, such as arsenic, cadmium, cerium, lanthanum, and thallium. However, there seems to be a wide variation in the individual levels measured, both before and after E(N)NDS use.

31. In other studies, the levels of various metals in room air where E(N)NDS aerosol had been produced ((Oldham et al. 2017); arsenic, cadmium, chromium, nickel) or E(N)NDS use had occurred ((O'Connell et al. 2015); 18 elements); ((Liu et al. 2017); arsenic, cadmium, chromium, nickel) were either below the LOD of the methods used or did not increase during E(N)NDS product use.

Are the metals in E(N)NDS aerosols derived from E(N)NDS liquids?

32. Some studies have analysed E(N)NDS liquids to determine whether or not these are likely to be the source of the metals detected in E(N)NDS aerosols.

33. Beauval et al. (2015) developed an ICP-MS method for measuring 15 different trace elements (aluminium, antimony, arsenic, beryllium, cadmium, chromium, cobalt, copper, lead, manganese, mercury, nickel, thallium, vanadium, zinc) in E(N)NDS liquids, and validated the method on a total of 54 samples of E(N)NDS liquids from one brand, purchased in 20 mL plastic bottles in France. The LOQ was ≤ 4 ppb for all except nickel (16 ppb), copper (20 ppb), and zinc (200 ppb). For the majority of E(N)NDS liquid samples, levels of trace elements were at or below the LOQ. However, some cherry-flavoured E(N)NDS liquids showed higher levels of

antimony and zinc (approximately 200 or 100 ppb antimony; 300 or 500 ppb zinc, respectively, with or without nicotine). The authors thus raised the possibility that flavour components of E(N)NDS liquids may represent a source of trace element contamination.

34. Hess et al. (2017) analysed metal (cadmium, chromium, lead, manganese, nickel) concentrations in approximately ten E(N)NDS liquid samples, extracted by centrifugation of pads taken from inside the cartomizers of five different brands of rechargeable cigalike E(N)NDS that are commercially available in the US (1.6–1.8 mg/mL nicotine; various flavours). ICP-MS was used for the analysis. Metal concentrations varied substantially between brands, with one brand ('Brand A') having the highest mean concentrations of all metals. Mean values per brand were in the ranges of 0.145–205 µg/L (cadmium), 53.9–2110 µg/L (chromium), 4.89–1970 µg/L (lead), 28.7–6910 µg/L (manganese), and 58.7–22 600 µg/L (nickel). Variation in and distribution of metal concentrations within some brands was also high (particularly for brand A), with distributions in many cases skewed by a small number of very high concentrations, and median values often much lower than means. The authors highlighted the presence of nickel, manganese, and chromium (speciation of the latter not determined) as being of potential cause for concern, although they noted that quantification, in terms of extrapolating levels of exposure via aerosols for users from levels measured in E(N)NDS liquids, was not possible.

35. As well as investigations of E(N)NDS liquids per se, a number of studies have looked at whether there is a correlation between the levels of metals detected in E(N)NDS liquids and the aerosols produced from them.

36. A report by Kim et al. (2017) suggested that metal contamination of E(N)NDS liquid (and hence the aerosol produced) may become an issue as E(N)NDS devices 'age'. These authors developed a reference E(N)NDS liquid containing PG, VG, and nicotine for analytical studies. ICP-OES analysis[11] showed that levels of eight metals (cadmium, chromium, cobalt, copper, lead, manganese, nickel, palladium) were below the LOD (1 ppb) in both the E(N)NDS liquid and aerosol produced when using a new E(N)NDS tank device. However, aerosol produced from the device after 20 h of use (over a 4-month period) contained detectable levels of lead (0.097 mg/L[12]), and manganese (0.001 mg/L), and visual inspection indicated collection of residue on the heating element.

37. Palazzolo et al. (2017) reported that aerosol from a Triple 3 eGo 'clearomizer' E(N)NDS with a tobacco-flavoured, 24 mg/mL-nicotine E(N)NDS liquid contained

[11] It may be noted that the collection method used in this study (bubbling aerosol through 'gas washers'), although often used, can be highly inefficient for capturing aerosols, and thus the concentrations of metals reported may be an underestimate of true concentrations.
[12] Assuming that the values reported are mg per litre of deionised water in which the aerosol was collected prior to ICP-OES analysis, given that 150 puffs were collected in 30 mL, this would extrapolate to approximately 0.02 µg/puff, or approximately 0.2 µg/10 puffs, for lead.

substantial amounts of nickel, which were not derived from the E(N)NDS liquid but presumed to be from the structure of the E(N)NDS device. This study reported levels of nine trace metals (aluminium, arsenic, cadmium, copper, iron, lead, manganese, nickel, zinc) in E(N)NDS liquid and the aerosol produced from it. Metals in E(N)NDS liquid (tested prior to introduction of the liquid into the E(N)NDS device) were determined by ICP-MS. For aerosol, 45 x 5 s puffs were collected on a mixed cellulose ester filter pad, the levels of individual metals were determined by SEM/EDS, and compared with 'naive' (0 puffs) filter pads as the negative control. Mean values for metals in E(N)NDS liquid were (µg/L): aluminium, 7.7; arsenic, 0.8; cadmium, < LOD; copper, < LOD; iron, 4.2; lead, < LOD; manganese, 0.159; nickel, 0.161; zinc, 0.51. Filter-pad analysis showed no significant differences in levels of individual metals on naive filter pads and those exposed to 45 E(N)NDS puffs, except for nickel, which was significantly higher in E(N)NDS-exposed filter pads (0.024 µg E(N)NDS vs. 0.005 µg naive). Taking into account an estimated 3% recovery of E(N)NDS liquid on the filter pad, the exposure to nickel from 15 puffs of E(N)NDS (which was considered to be equivalent to smoking 1 CC) was estimated as 0.217 µg[13], and extrapolating from levels measured in E(N)NDS liquid, it was considered that this would not be derived from the E(N)NDS liquid itself. The core assembly of the E(N)NDS device was evaluated by SEM/EDS and percentage metal compositions for individual device components are detailed in the report. Extrapolating from the nickel values measured in E(N)NDS aerosol, the authors suggested that use of this E(N)NDS device at a level equivalent to smoking one pack of CC per day (i.e. 300 puffs/day of E(N)NDS aerosol) could lead to an estimated nickel inhalation exposure of 4 µg. This would be equivalent to 25% of the US Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL[14]). They expressed concern that E(N)NDS devices containing nickel may lead to a significant amount of exposure to Ni in the aerosol produced, noting in particular that newer, temperature-controlled devices use coils that are 99% nickel.

38. Olmedo et al. (2018) reported that levels of metals measured in E(N)NDS aerosol and tank-residue samples were higher than those in 'naïve' E(N)NDS liquids analysed before introduction into the devices. A total of 56 users of E(N)NDS tank-style ('3rd generation', 'mods') devices provided their E(N)NDS device and a sample of their usual refill liquid in its dispenser. ICP-MS analysis was used to measure the levels of 15 metals (aluminium, antimony, arsenic, cadmium, chromium, copper, iron, lead manganese, nickel, tin, titanium, tungsten, uranium, zinc) in: 1] the new E(N)NDS liquid ('dispenser') (n=56), 2] aerosol produced from puffing 0.2-0.5 ml of this liquid (30-50 four-second puffs) and collected in a 1.5 ml centrifuge tube (n=56), 3] residual liquid in the tank after aerosol production (n=49). Values were reported as mass fractions (µg/kg) for liquids, and subsequently converted to mg/m^3 for aerosols [mass fraction x (total sample weight/total air volume used to produce the sample)].

[13] However, this value is likely to be an overestimate, as 3% capture on the filter is likely to be an underestimate, not accounting for effects such as evaporation and non-collection of volatile materials.
[14] 17 µg, based on ventilation of 7 L/min for 8 h, with a PEL of 0.5 µg/L.

The 30-50 puffs of E(N)NDS liquid was considered to represent daily consumption. Blank E(N)NDS liquids (70% PG/30% VG) were processed in a similar manner, as controls. The following measurements/evaluations were reported (full details can be found in the published paper attached at Annex D):

- The percentages of samples in which each metal was detected, and the LODs (which ranged from 0.1-5.0 µg/kg)
- Median metal concentrations in dispenser, aerosol, and tank
- Ratios of metals in aerosol/dispenser and tank/dispenser; p-values for paired tests were all significant, except for iron in aerosol
- Within-metal concentration correlations for dispenser, aerosol, and tank
- Metal concentrations in dispenser, aerosol, and tank, as a function of voltage (tertiles of low, medium, high voltage device use, as reported by the individual users)
- Median (and range) calculated daily exposure from aerosol vs. identified regulatory guidance values: for nickel, chromium, lead, and manganese.

39. Four metals (arsenic, titanium, uranium, and tungsten) that were identified in < 20% of dispenser, aerosol[15], and tank samples were excluded from the further analyses. For the other 11 metals, the percentages of samples in which the metal was detected ranged from 0.0% for cadmium to 92.9% for zinc in the dispenser, 30.4% for cadmium to 100% for tin in the aerosol, and 55.1% for cadmium to 100% for chromium, copper, iron, lead, nickel, tin, and zinc in tank liquid (Table 1, Olmedo et al., 2018). Comparison of median levels in dispenser, aerosol, and tank (Table 2, Olmedo et al., 2018) showed:

- dispenser < aerosol < tank (aluminium, chromium, nickel)
- dispenser < aerosol ≈ tank (lead, zinc)
- dispenser < aerosol << tank (antimony, copper, manganese, tin)
- dispenser (not detected) < aerosol (30% detection) < tank (cadmium).

40. Paired analyses (aerosol/dispenser and tank/dispenser) indicated significant correlations in all cases[16], with aerosol/dispenser ratios ranging from 1.60 (cadmium) to 29.5 (zinc) and tank/dispenser ratios ranging from 2.30 (cadmium) to 116 (lead) (Table 3, Olmedo et al., 2018). Spearman's within-metal correlations between dispenser and aerosol were statistically significant for antimony, iron, manganese, and tin; between dispenser and tank for antimony, aluminium, and manganese; between aerosol and tank for 9 metals (all 11 evaluated, except cadmium and copper) (Table 4, Olmedo et al., 2018).

41. Evaluations showed no association of device voltage with dispenser and aerosol metal concentrations, but there was a correlation between voltage tertile and

[15] except that tungsten was identified in 42.9% of aerosol samples
[16] except for iron in aerosol vs. tank liquid (ratio, 1.93, p=0.41)

presence of aluminium, iron, and manganese in tank samples (highest in the intermediate voltage tertile) (Table 5, Olmedo et al., 2018). In aerosol samples, levels of aluminium, chromium, and manganese were significantly higher in aerosol samples from users who changed the coils more than twice per month compared to less frequently (Table 7, Olmedo et al., 2018).

42. For four metals (chromium, lead, manganese, nickel), median (and range) concentrations estimated in the E(N)NDS aerosol were compared with published health-based guidance values (Table 8, Olmedo et al., 2018). Authors concluded that: between 46% (for CR(III)) or 68% (for Cr(VI)) of aerosol samples would exceed ATSDR MRLs for chromium; 48% would exceed the US-EPA National Ambient Air Quality Standard (NAAQS) for lead; 14% would exceed the ATSDR MRL for manganese, and 75% would exceed the the US-EPA reference concentration (RfC) for manganese[17]; 57% would exceed the ATSDR chronic MRL for nickel. These are summarised in Table 7. However, it is important to note that the comparisons are of the aerosol sample concentrations with ambient air concentration guidance values.

Table 7 Comparison of metal concentrations measured in E(N)NDS aerosols with US regulatory and health-based limits, adapted from Table 8 of Olmedo et al. (2018)

	Chromium	Lead	Manganese	Nickel
Aerosol Median (mg/m^3)	8.46×10^{-5}	1.06×10^{-4}	1.97×10^{-5}	4.44×10^{-4}
Aerosol Range (mg/m^3)	7.97×10^{-7} to 2:95 $\times 10^{-2}$	1.49×10^{-6} to 2.75×10^{-2}	1.39×10^{-6} to 1.42×10^{-3}	4.35×10^{-6} to 1.12×10^{-1}
US NAAQS (Regulatory limit) (mg/m^3)		1.5×10^{-4} 1.5×10^{-3} (for non-attainment areas)		
US ATSDR inhalation MRL (mg/m^3)	5.00×10^{-6} (CrVI in mists) (intermediate and chronic value) 1.00×10^{-4} (soluble CrIII) (intermediate value)		3.00×10^{-4} (intermediate value)	2×10^{-4} (intermediate value)
US EPA inhalation RfC (mg/m^3)			6.00×10^{-6} [18] 5×10^{-5} [19]	

[17] Although it is unclear where the US-EPA inhalation reference concentration for manganese cited by Olmedo et al. (2018) is obtained from (see subsequent footnotes)

[18] Value cited by Olmedo et al. (2018)

[19] Value cited on EPA/IRIS website (see: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0373_summary.pdf, accessed 07/03/18)

43. A report by Saffari et al. (2014) concluded that although some elements (boron, lanthanum, nickel, potassium, silver, zinc) were present at higher levels in room air during E(N)NDS use compared with air sampled on a terrace outside the same building, evaluation of the E(N)NDS liquids used suggested that they were not likely to be the source of the metals identified in the indoor air (Saffari et al. 2014).

Biomarkers of exposure

44. One study was identified that investigated internal biomarkers of exposure to nickel and chromium in E(N)NDS users. Aherrera et al. (2017) reported some correlations between levels of nickel and chromium in E(N)NDS aerosols and used E(N)NDS liquid (i.e. residing in the device after use) with levels in biospecimens (saliva, urine, exhaled breath) in a group of approximately 50 E(N)NDS users. Higher aerosol and tank nickel were associated with higher nickel and chromium levels in saliva. There was also a positive correlation of aerosol nickel concentration with urinary nickel levels. No correlations were observed between biomarker levels and levels of these metals in unused E(N)NDS liquids, leading the authors to conclude that the sources of these metals to which E(N)NDS users are exposed are derived from the heating coil, not the E(N)NDS liquid. Some self-reported parameters of E(N)NDS use also indicated correlation with Ni levels in E(N)NDS user biospecimens, such as shorter time to first E(N)NDS use after waking, more frequent changing of the heating coil, preferred voltage, and higher volume of E(N)NDS liquid used.

Summary

45. E(N)NDS contain metal components in the structure of the device, which may include resistive wire heating filaments, wire couplings, solder joints, and silver coatings. In most cases, the filament is composed of nickel and chromium, although other metals are present in some devices. Thick wire usually consists of copper (but sometimes copper/nickel) coated with silver (sometimes tin). Joints may be brass (copper/zinc) or solder, which is mostly tin, but in some cases has also been found to contain lead. Insulating sheaths generally contain silicon, calcium, aluminium, and magnesium, and the wick is usually made of fibreglass containing silicon.

46. Overall, the concentrations of metals in E(N)NDS aerosols have been observed to vary widely (by several orders of magnitude) both between and within brands. Reasons for this may include structural aspects of the E(N)NDS device (including manufacturing inconsistencies, variations in wire resistance and battery voltage, and E(N)NDS liquid delivery rate), puffing protocols, variation in E(N)NDS liquid components, and changes occurring with use and storage of products. Studies published to date have mostly investigated first- or second-generation E(N)NDS devices.

47. There is also variability in the findings between studies. A principal source of this variability is likely to be the methods used to extrapolate from the amount of metals captured on the filter to the amount of metals present in the aerosol, with potential for both over- and under-estimation depending on how capture efficiency is corrected for. Additionally, in many cases the reported measurements are around the LOD/LOQ for the detection method used, though the values of the LOD/LOQ are not always provided.

48. Williams et al. (2017) reported a total metal concentration in E(N)NDS aerosol varying in the range of approximately 1.8-7.3 µg/10 puffs for a range of 12 different E(N)NDS products, while Mikheev et al. (2016) reported total metal concentration as a proportion of total particulate matter (TPM), at around 10 ng/mg TPM. Reported values vary according to factors such as puffing parameters and flow rates.

49. The principal inorganic element identified in E(N)NDS aerosols is silicon, which was reported by Williams et al. (2017) to account for > 50% of the total elemental content by weight, with the highest level measured being 6.8 µg/10 puffs in aerosol from a disposable E(N)NDS. This was assumed to be derived from the sheath and wick, which is made of fibreglass (silicate glass bead threads woven with small amounts of sodium, potassium, calcium, magnesium), and which breaks easily. Williams et al. (2017) proposed that further work is needed to determine the potential health effects of the silicate fibreglass inhaled in E(N)NDS aerosols.

50. Other elements of note that have been identified in E(N)NDS aerosols include:

- Copper. A mean level of 1.17 µg/10 puffs (range 0.24-2.25 µg/10 puffs) was measured in cartomizer aerosol by Lerner et al. (2015). Williams et al. (2017) detected copper at levels above 0.01 µg/10 puffs in aerosols from 7 of 11 brands of disposable E(N)NDS, with a highest level at 0.194 µg/10 puffs. Copper is thought to be derived from the thick wire and brass clamps.

- Tin. Williams et al. (2017) detected tin at levels above 0.01 µg/10 puffs in 8 of 11 brands of E(N)NDS tested, with the highest value at 0.245 µg/10 puffs. A prior study by the same group detected very high levels of tin in aerosol from one E(N)NDS brand, although values varied widely between different cartomizers tested from the same brand (0.4–11.3 µg/10 puffs) (Williams et al. 2015). Tin is presumed to derive from the tin solder joints in the E(N)NDS device.

- Calcium, magnesium, and sodium, which are presumed to be derived from the sheath and wick, and zinc probably from the brass clamps. These elements were often detected at levels above 0.01 µg/10 puffs.

- Nickel and chromium. A number of studies have reported the detection of low levels of nickel and chromium in E(N)NDS aerosols, which is considered to result from the nichrome heating element.

  - Williams et al. (2017) detected low levels (0.002–0.005 µg/10 puffs) of nickel in aerosol from 7 of 11 of the E(N)NDS devices tested. Goniewicz et al. (2014) reported nickel levels that ranged from 0.007–0.02 µg/10 puffs for aerosol from 12 cartomizer-type E(N)NDS, although similar levels appear to have been measured in blank samples and in a commercially available nicotine inhaler. Palazzolo et al. (2017) estimated a much higher nickel content, around 0.145 µg/10 puffs, for aerosol collected from a 'clearomizer' E(N)NDS, although this value had been adjusted to account for an estimated low level (3%) of collection on the filter pad (the initial reading was 0.024 µg nickel collected on a filter from 45 puffs, with a background level of 0.005 µg on the control filter). Palazzolo and colleagues suggested that the high nickel content observed in their study may reflect a different structure of the clearomizer device tested as compared with other studies, which have generally looked at cartridge-type E(N)NDS. They suggested that this may become more of a problem with the introduction of new-generation, temperature-controlled devices which use coils made of 99% nickel.

  - Williams et al. (2013) reported 0.007 µg/10 puffs chromium in aerosol from a US-brand cartomizer, and Williams et al. (2017) reported the detection of low levels (which appear to be in the range of around 0.001 µg/10 puffs) of chromium in aerosol from 2 of 11 E(N)NDS brands tested. Margham et al. (2016) measured chromium levels of approximately 0.004 µg/10 puffs, which was around the LOQ of the study, but was slightly higher than observed in blank samples. However, in many cases chromium has not been identified in E(N)NDS aerosols tested.

  - One study found that biomarkers of nickel and chromium exposure in saliva and/or urine appeared to correlate with levels in aerosol and with some self-reported indicators of E(N)NDS use level (Aherrera et al. 2017).

- Lead. In some cases, lead has been observed in E(N)NDS aerosol, and in some studies this has been correlated with the presence of lead in solder joints. Williams et al. (2017) found that 2 of 11 devices had solder joints containing lead, and this correlated with lead in the aerosols produced (0.007-0.165 µg/10 puffs), despite the fact that the use of lead in solder is banned in many countries where E(N)NDS are produced. Goniewicz et al. (2014)

identified lead in aerosol from all 12 E(N)NDS devices tested, with a range of 0.002–0.038 µg/10 puffs, although in all but one case, the levels were below the LOQ (0.007 µg/10 puffs) and low levels of lead (0.0013 µg/10 puffs) were also detected in blank samples. One study showed lead in aerosol produced from an E(N)NDS device after several hours of use but not when it was new, suggesting an effect of aging. However, several studies have not identified lead in E(N)NDS aerosols tested.

51. In general, reports suggest that metals were derived from the E(N)NDS device rather than the E(N)NDS liquid *per se*. However, metals may leach into the E(N)NDS liquid stored in the tank, and Aherrera et al. (2017) concluded that exposure may be higher in E(N)NDS users who use higher amounts of E(N)NDS liquid. Hess et al. (2017) detected cadmium, chromium, lead, magnesium, and nickel in E(N)NDS liquids from cartomizer brands, which may be a result of storage of the E(N)NDS liquid in contact with metallic components of the device.

Conclusion

52. Metals have been detected in E(N)NDS aerosols. These elements appear to be derived from the E(N)NDS device structure itself rather than from the E(N)NDS liquid, although they may leach into E(N)NDS liquid during storage.

53. As different E(N)NDS devices do not all use the same materials, the presence and quantity of the different metals in E(N)NDS aerosol is likely to be related to the materials used in the construction of the particular device, and possibly also the build quality.

54. The principal element identified in E(N)NDS aerosol is silicon, which is presumed to originate from the fibreglass sheath and wick. The presence of aluminium, calcium, magnesium, and sodium are also assumed to be derived from the sheath and wick. Other metals that have been measured at substantial levels in E(N)NDS aerosols include copper and zinc, from the thick wire and brass clamps, and tin, presumed to be from the solder. Other metals of concern that have been detected, although infrequently and generally at low levels, include chromium, nickel, and lead.

55. In general, studies report very wide variations in the ranges of measurements observed, both between and within brands. A principal source of variability between studies is likely to be the methods used to extrapolate from the amount of metals captured on the filter to the amount of metals present in the aerosol, with potential for both over- and under-estimation depending on how capture efficiency is corrected for. In many cases, the reported measurements are around the LOD/LOQ for the detection method used, though the values of the LOD/LOQ are not always provided. In addition, the conduct/reporting of experimental controls is often unclear.

Questions for the Committee

56. Members are asked to consider the paper and in particular:

    i. Based on the evidence presented, can any conclusions be drawn with respect to potential for exposure to metals from E(N)NDS devices and fluids?

    ii. Are there any uncertainties or evidence gaps which should be highlighted to support an assessment of the potential toxicological risks arising from metals in the E(N)NDS aerosol?

    iii. Are there any other aspects of this paper that should be captured when a COT statement on E(N)NDS is prepared?

NCET at WRc/IEH-C under contract supporting the PHE COT Secretariat
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Abbreviations

AAS	Atomic absorption spectrometry
CC	Conventional cigarette
CPC	Condensation Particle Counter
EDS	Electron dispersion X-ray spectroscopy
EH	e-hookah
E(N)NDS	Electronic nicotine (or non-nicotine) delivery system
ICP-MS	Inductively coupled plasma mass spectrometry
ICP-OES	Inductively coupled plasma optical emission spectrometry
LOD	Limit of detection
LOQ	Limit of quantitation
MRL	Minimum risk level
PAH	Polycyclic aromatic hydrocarbon
PDE	Permissible daily exposure
PG	Propylene glycol
REL	Recommended exposure limit
SEM	Scanning electron microscopy
SMPS	Scanning Mobility Particle Sizer
TSNA	Tobacco-specific nitrosamine
TEM	Transmission electron microscopy
TPM	Total particulate mass
VG	Vegetable glycerine
VOC	Volatile organic compound

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COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT)

Potential toxicological risks from electronic nicotine (or non-nicotine) delivery systems (e-cigarettes). Paper 2: Exposure to metals present in the aerosol of E(N)NDS

Details of Literature search carried out by NCET at WRc/IEH-C

The subsequent literature search was performed by NCET at WRc/IEH-C under contract to PHE on 05/10/17 using the following search terms in PubMed, Scopus and Web of Science. Search terms used were:

- e-cigarette OR electronic cigarette OR e-cig

AND

- aerosol OR vapor/vapour

AND

- particle OR particulate OR droplet OR metal OR element

YEAR 2010 to date

Total no. of papers retrieved (for screening) = 169

Inclusion criteria

Papers were selected if they contained relevant information on the (eventual) presence of metals in the E(N)NDS aerosol

For completion, the reference lists of selected papers were examined for further relevant publications, and additional searches were carried out as considered appropriate (e.g. authors publishing in the field were searched directly in PubMed..)

Total no. of papers for further evaluation = 20

Update search

An update search, to check for any more recent papers, was conducted on 12/03/2018 using Scopus and PubMed with the following search terms:

Scopus:

(TITLE-ABS-KEY (e-cig* OR "electronic cigarette*") AND TITLE-ABS-KEY (metal OR element)) AND PUBYEAR > 2016; 37 refs.

PubMed:

((e-Cig*[Title/Abstract] OR "electronic cigarette*"[Title/Abstract]) AND (metal[Title/Abstract] OR element[Title/Abstract]) Filters: Publication date from 2017/01/01 to 2018/12/31: 11 refs

Total no. of papers retrieved (for screening) = 41 refs.

39 refs were either not relevant based on the inclusion criteria above, were reviews or commentaries on the subject, or were already included in the COT paper;

Total no. of papers for further evaluation = 2 refs.

Olmedo et al. (2018) has been included in this paper.

Jain (2018)[20] is in press and will be considered for inclusion in a future paper, but the abstract is attached at this annex. It is not being made publicly available for copyright reasons.

NCET at WRc/IEH-C under contract supporting the PHE COT Secretariat
March 2018

[20] Jain (2018) Concentrations of selected metals in blood, serum and urine among US adult exclusive users of cigarettes, cigars and electronic cigarettes. Toxicological and Environmental Chemistry. DOI: 10.1080/02772248.2018.1426764

TOX/2018/15 - Annex B

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT)

Potential toxicological risks from electronic nicotine (or non-nicotine) delivery systems (e-cigarettes). Paper 2: Exposure to metals present in the aerosol of E(N)NDS

Table A: Summary of studies of the presence of metals and inorganic elements in E(N)NDS devices, E(N)NDS liquids and E(N)NDS aerosols.

NCET at WRc/IEH-C under contract supporting the PHE COT Secretariat
February 2018

Table A. Investigations of the presence of metals in E(N)NDS aerosols.

<table>
<tr><th>Authors</th><th>Investigation</th><th>E(N)NDS models / brands tested</th><th>Experimental details / detection methods</th><th>Results</th><th>Comment</th></tr>
<tr>
<td>Williams et al. (2013)</td>
<td>Analysis of E(N)NDS device structure and elemental content of aerosol</td>
<td>Cartomizers from one company;
0 mg/mL nicotine;
Purchased over a period of two years

Comparisons with CC (published values)</td>
<td>Dissection and analysis (SEM, EDS) of the cartomizer (22 samples). Centrifugation to pellet the inner and outer fibres and analysis by SEM/EDS.
Analysis of aerosol (4.3 s puffs) (compared with room air) by: pin stub and SEM, or formvar-coated copper grid and TEM; EDS (energy dispersive X-ray spectroscopy); particle counting and sizing by Condensation particle counter (CPC)/SMPS (scanning mobility particle sizer); ICP-OES</td>
<td><u>Cartomizer structure</u>
Dissected cartomizers comprised: A mouthpiece – iron, chromium, and manganese (stainless steel); a wick, probably fibreglass; two thick wires – copper coated with silver; one thin wire (the filament) – nichrome (nickel/chromium); an air tube – nickel; a white gasket – silicon; four solder joints – mostly tin (including the formation of tin ‘whiskers’), also copper; inner dense fibres and outer dense fibres (Poly-fil).
Pelleted inner and outer fibres contained mainly tin, with small amounts of copper and nickel
<u>Aerosol</u>
Two broad size distribution peaks (<100 nm; 100-1000 nm); Aerosol contained particles:
> 1 µm including tin, silver, nickel, aluminium, silicon
< 100 nm including tin, chromium, nickel (these nanoparticles were not identified in room air)
<u>Elemental abundances in E(N)NDS aerosol and in CC smoke (µg/10 puffs) were:</u>
<table>
<tr><td></td><td>Aluminium</td><td>Barium</td><td>Boron</td><td>Calcium</td><td>Chromium</td><td>Copper</td></tr>
<tr><td>E(N)NDS</td><td>0.394</td><td>0.012</td><td>3.83</td><td>1.03</td><td>0.007</td><td>0.203</td></tr>
<tr><td>CC[21]</td><td>0.22</td><td></td><td></td><td></td><td>0.004-0.5</td><td>0.19</td></tr>
<tr><td></td><td>Iron</td><td>Lead</td><td>Lithium</td><td>Magnesium</td><td>Manganese</td><td>Nickel</td></tr>
<tr><td>E(N)NDS</td><td>0.52</td><td>0.017</td><td>0.008</td><td>0.066</td><td>0.002</td><td>0.005</td></tr>
<tr><td>CC</td><td>0.042</td><td>0.017-0.14</td><td></td><td>0.070</td><td>0.003</td><td>0.000073-0.003</td></tr>
<tr><td></td><td>Potassium</td><td>Silicon</td><td>Sodium</td><td>Strontium</td><td>Sulphur</td><td>Tin</td></tr>
<tr><td>E(N)NDS</td><td>0.292</td><td>2.24</td><td>4.18</td><td>0.006</td><td>0.221</td><td>0.037</td></tr>
<tr><td>CC</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>Titanium</td><td>Zinc</td><td>Zirconium</td><td></td><td></td><td></td></tr>
<tr><td>E(N)NDS</td><td>0.002</td><td>0.058</td><td>0.007</td><td></td><td></td><td></td></tr>
<tr><td>CC</td><td></td><td>0.12-11.9</td><td></td><td></td><td></td><td></td></tr>
</table>
[1]Values for CC were obtained from various literature sources for one CC, as detailed in Table 1 of Williams et al., 2013
(Particles identified in room air were described as ‘mainly calcium, potassium, silicon, aluminium and sodium’, but the levels of individual elements measured were not reported).</td>
<td>In cartomizer E(N)NDS aerosol: chromium, tin, nickel nanoparticles were present; sodium, iron, aluminium, nickel levels were higher than those reported for CC smoke; copper, magnesium, lead, chromium, manganese levels were in the same range as those reported for CC smoke

Authors concluded that there is a requirement for improved quality control in E(N)NDS design and manufacture.</td>
</tr>
</table>

[21] Values for CC were obtained from various literature sources for one CC, as detailed in Table 1 of Williams et al., 2013

<table>
<tr><th>Authors</th><th>Investigation</th><th>E(N)NDS models / brands tested</th><th>Experimental details / detection methods</th><th>Results</th><th>Comment</th></tr>
<tr>
<td>Goniewicz et al. (2014)</td>
<td>Analysis of metal content in E(N)NDS aerosol</td>
<td>12 commercially available E(N)NDS brands (11 from Poland, 1 from the UK; 10 ‘cartridge’, 2 ‘cartomizer’);

Nicotine inhaler (Nicorette® 10 mg)</td>
<td>150 x 70 mL puffs; liquid-phase extraction

Quantitation of metals (arsenic, barium, cadmium, chromium, cobalt, copper, lead, manganese, nickel, rubidium, selenium, silver, strontium, thallium, vanadium, zinc) by ICP-MS</td>
<td><u>Aerosol</u>
Nickel and lead were identified in all aerosol samples, and cadmium in all but one sample, but also in the nicotine inhaler aerosol and in blank samples.

<table>
<tr><td colspan="6">Metal concentration measured in µg / 150puffs</td></tr>
<tr><td></td><td>LOD</td><td>LOQ</td><td>Blank sample[1]</td><td>Nicorette inhaler</td><td>E(N)NDS range[2]</td></tr>
<tr><td>Cadmium</td><td>0.04</td><td>0.12</td><td>0.02</td><td>0.03</td><td>0.01-0.22</td></tr>
<tr><td>Nickel</td><td>0.024</td><td>0.072</td><td>0.17</td><td>0.19</td><td>0.11-0.29</td></tr>
<tr><td>Lead</td><td>0.036</td><td>0.107</td><td>0.02</td><td>0.04</td><td>0.03-0.57</td></tr>
</table>
[1] Blank sample – it is unclear what this refers to (although, in reviewing this report, Farsalinos et al. (2015) states that this refers to ‘collection of air from the environment’

[2] E(N)NDS – range over 12 different E(N)NDS</td>
<td>Nickel, lead, and cadmium were detected in E(N)NDS aerosol, but also in blank controls.</td>
</tr>
</table>

Authors	**Investigation**	**E(N)NDS models / brands tested**	**Experimental details / detection methods**	**Results**	**Comment**
Saffari et al. (2014)	Comparison of indoor air during E(N)NDS use with outdoor air in the vicinity of the same building	Elips Serie C, tank system, Ovale Europe E(N)NDS liquid (PG, glycerol, aroma, water, with or without 16 mg/mL nicotine)	A volunteer smoked CC or used E(N)NDS in a 48m^3 room (1 puff/min for periods of 7 min, with 3 min intervals) Approximately 1.3 mL E(N)NDS liquid consumed per hour Inorganic elements collected on quartz filters and analysed by ICP-MS Inorganic elements in E(N)NDS liquids measured by ICP-MS	Results were presented relative to measurements in outdoor air on a terrace adjacent to the building where the indoor experiments were conducted. Some metals had higher average levels measured in the indoor than outdoor air (boron, lanthanum, nickel, potassium, silver, zinc). Modelling suggested that the amount of E(N)NDS liquid vaporised during the experiments was not sufficient to be the unique source of these metals measured in the room air.	Levels of some metals (e.g. nickel, silver) were higher in room air where E(N)NDS use was taking place than in air outside the same building. Levels in E(N)NDS liquids were estimated to be too low to be the source of the metals in the indoor air.

Authors	Investigation	E(N)NDS models / brands tested	Experimental details / detection methods	Results	Comment
Schober et al. (2014)	Evaluation of levels of inorganic elements in room air associated with E(N)NDS use	E(N)NDS device comprising a rechargeable lithium-ion battery, electronic circuit, vaporiser, mouthpiece and refillable tank) 3x Red Kiwi (Seevetal, Germany) tobacco-flavour E(N)NDS liquids, each with or without 18 mg/mL nicotine	Aluminium, antimony, arsenic, bismuth, cadmium, calcium, cerium, chromium, cobalt, copper, iron, lanthanum, lead, magnesium, manganese, molybdenum, nickel, potassium, sodium, thallium, tin, titanium, vanadium, zinc collected on quartz filter pads and measured by ICP-MS Measurements of room air also made prior to E(N)NDS use	2.4-fold increase in aluminium levels measured in room air after E(N)NDS use. Wide variation between measurements reported for each metal.	The authors concluded that E(N)NDS use was associated with a 2.4-fold increase in aluminium level in room air.

Authors	Investigation	E(N)NDS models / brands tested	Experimental details / detection methods	Results	Comment
Tayyarah et al. (2014)	Evaluation of E(N)NDS liquid and aerosol components	5 E(N)NDS products (blu or SKYCIG, disposable or rechargeable); 16-24 mg/unit nicotine 3 CC (Marlboro, Lambert & Butler original and menthol)	Health Canada intense puffing regime Quantification of metals collected on filter pads (beryllium, cadmium, chromium, cobalt, lead, magnesium, mercury, nickel, selenium, tin) by ICP-MS	<u>Aerosol</u> LOQ: analysis of 'blu' E(N)NDS, 4 ng/puff for all except mercury at 0.8 ng/puff analysis of 'SKYCIG' E(N)NDS, 0.06 ng/puff for all except mercury, at 0.01 ng/puff Metals in E(N)NDS aerosol: All values below the LOQ, except chromium around 0.1 ng/puff in SKYCIGs	Most metals at or below the limit of quantitation. Low levels of chromium in SKYCIG aerosol.
Beauval et al. (2015)	Developed and validated an analytical method for quantitation of trace elements in E(N)NDS liquids	NHOSS® (Innova, Bondues, France) 27 E(N)NDS liquids obtained in 20 mL plastic bottles (<65% PG, <35%VG, +/- different flavourings) each +/- 16 g/L nicotine	Analysis of 15 trace elements (aluminium, arsenic, beryllium, cadmium, chromium, cobalt, copper, lead, manganese, mercury, nickel, thallium, tin, vanadium, zinc) in E(N)NDS liquid by ICP-MS	<u>E(N)NDS liquid</u> Lower limit of quantitation (LOQ) ≤ 4 ppb for all trace elements except nickel (16 ppb), copper (20 ppb), zinc (200 ppb) Most trace element concentrations in most samples were around or below the LOQ Some cherry-flavoured samples had significantly higher amounts of antimony and zinc (with or without nicotine, approximately 200 or 100 ppb antimony; 300 or 500 ppb zinc, respectively)	Authors concluded that flavour components may be a source of trace element contamination in E(N)NDS liquids.

Authors	Investigation	E(N)NDS models / brands tested	Experimental details / detection methods	Results	Comment
Farsalinos et al. (2015)	Risk assessment of E(N)NDS aerosol metal exposure based on published data	13 E(N)NDS, as reported by Goniewicz et al. (2014) (12 brands) and Williams et al. (2013) (1 brand)	Estimation of intake of individual metals based on consumption of 6 g E(N)NDS liquid/day (1200 puffs of aerosol) Comparison with existing regulatory safety limits where identified	See Table 6 of main paper for full results All estimated intakes were below the identified safety limits except for one brand, EC06 from the study of Goniewicz et al., 2014, for which the United States Pharmacopeia (USP) permissible daily exposure (PDE) for cadmium would be exceeded (estimated intake, 1.6 µg/day from 1200 puffs vs. 1.5 µg/day PDE).	Authors concluded that, overall, levels of metals emitted from E(N)NDS aerosols are unlikely to be of substantial concern for health effects for smokers switching from CC to E(N)NDS, however there is a wide variation between products and product quality should be improved.
Lerner et al. (2015)	Study of oxidants in E(N)NDS (measured aerosol size distribution and levels of copper)	Rechargeable Blu (cartomizer)	4 s puff; Collection on methyl-cellulose filter and determination of Cu by atomic absorption spectrometry (AAS); Blank = filter not exposed to aerosol	Mean copper level 116.79 ± 83.59 ng/puff (range, 24.3–224.7) (4 s puff) (mean copper in blank control appears to be around 5 ng/puff)	A level of copper around 120 ng/puff was observed in E(N)NDS aerosol, which was significantly higher than that on a control filter not exposed to E(N)NDS aerosol.

Authors	Investigation	E(N)NDS models / brands tested	Experimental details / detection methods	Results	Comment
O'Connell et al. (2015)	Evaluation of indoor air before, during, and after E(N)NDS use	Puritane 16 mg/g disposable original-flavoured E(N)NDS (closed system) E(N)NDS liquid: 67% PG, 30% glycerol, 1.6% nicotine + flavourings)	38.5 m^3 room (office) Analysis of ambient air before, during, and after a 165 min session of *ad libitum* E(N)NDS use by three participants at an average puff rate of 3.2 puffs//min (across all users). Analysis of aluminium, antimony, arsenic, barium, beryllium, calcium, chromium, cobalt, copper, lead, manganese, mercury, nickel, phosphorus, selenium, silver, thallium, zinc Elements collected on MCE filters and analysed by ICP-OES	All measurements (before, during, and after E(N)NDS use) were below the LOD (range, 1.0–2.0 µg/m^3, depending on the element)	E(N)NDS use at around 3.2 puffs/min in a small room did not appear to alter ambient air levels of several inorganic elements.

Authors	**Investigation**	**E(N)NDS models / brands tested**	**Experimental details / detection methods**	**Results**	**Comment**
Williams et al. (2015)	Analysis of Sn, Cu, Zn, Ag, Ni, Cr in E(N)NDS aerosol and structural analysis of E(N)NDS devices	4 'popular' brands of E(N)NDS available in the US (3 cartomizer; 1 disposable) Comparison with room air	4.3 s puffs; Analysis of chromium, copper, nickel, silver, tin, zinc in aerosol by ICP-OES; Subtracted for blank room air samples Dissection of E(N)NDS devices and analysis by SEM/EDS	Levels mostly in the range of < LOD – 0.2 µg/10 puffs, except for a high level of tin (> 3 µg/10 puffs) in aerosol from 1 E(N)NDS brand Measured levels varied widely within and between brands	Measured levels of metals in E(N)NDS aerosols varied widely within and between brands Authors concluded that poor-quality solder joints made of tin may be responsible for higher levels of tin in aerosol from some E(N)NDS brands
Margham et al. (2016)	Analysis of components of E(N)NDS aerosols, comparison with levels in CC smoke	Vype ePen (rechargeable battery + cartomizer) with Blended Tobacco flavour E(N)NDS liquid (+1.8% nicotine), used at 3.6 V Ky3R4F CC	CORESTA (E(N)NDS) or Health Canada Intense (CC) puffing regime arsenic, beryllium, cadmium, chromium, cobalt, copper, iron, lead nickel, selenium, tin, zinc analysed by ICP-MS Mercury analysed by AAS	<u>Aerosol</u> Below LOD: E(N)NDS: beryllium, cadmium, cobalt, lead, mercury, selenium, tin CC: beryllium, cobalt, tin Below LOQ: E(N)NDS: arsenic, nickel CC: chromium, nickel, selenium Quantified: E(N)NDS: chromium, copper, iron, zinc CC: arsenic, copper, iron, zinc In E(N)NDS aerosol: For zinc and iron, quantified levels did not differ substantially from those in the air blank; copper levels (mean 1.89 ng/puff) were approximately 2x air/blank, but with high variability; chromium (mean 0.399 ng/puff) was around the LOQ and may have been higher than levels in air/blank (generally below LOQ)	Authors concluded that chromium emissions in the E(N)NDS aerosol (mean, 0.399 ng/puff) were possibly higher than those in the air/blank and in CC smoke.

Authors	Investigation	E(N)NDS models / brands tested	Experimental details / detection methods	Results	Comment
Mikheev et al. (2016)	Measurement of metals content in E(N)NDS aerosol	Blu disposable cigalikes (0–1.6% nicotine, various flavours)	4.3 s puffs; collection on quartz fibre filters, total particulate matter (TPM) determined gravimetrically; samples analysed by ICP-MS; control = blank filters	Antimony, arsenic, chromium, copper, nickel, tin, and zinc detected, but levels varied widely (by orders of magnitude) between samples, including those of same flavour/nicotine content Beryllium, cadmium, cobalt, lead, and selenium not detected Metals content was calculated as around 10 ng/mg of total particulate mass (TPM)	Authors commented that the wide variation in metal content measurements between samples of equivalent flavour/nicotine content may be due to manufacturing inconsistencies and/or variation in E(N)NDS device functioning.
Aherrera et al. (2017)	Assessment of biomarkers of chromium and nickel exposure in saliva, urine, and exhaled breath of E(N)NDS users; correlation with levels of chromium and nickel in E(N)NDS liquids and aerosol, and with variables of E(N)NDS use	64 E(N)NDS users (50 E(N)NDS only; 14 E(N)NDS + CC) in Maryland, USA, of whom 5 used cigalikes (1st generation), and 59 used 2nd or 3rd generation E(N)NDS	Self-reported E(N)NDS use patterns (E(N)NDS liquid consumed per week; time to first vape in the morning; heating coil; preferred voltage; number of coil changes per month; E(N)NDS liquid nicotine concentration)	Geometric mean ratios (GMR) and 95% CI were computed using linear regression models on log-transformed metal levels, compared between tertiles for the different variables. Models were adjusted for age, sex, race, E(N)NDS and CC use characteristics <u>Nickel</u> *E(N)NDS use characteristics*: Increased urinary, saliva, and EBC nickel associated with increased E(N)NDS liquid consumption (significant for 2nd tertile only). Increased urinary nickel associated with vaping within 15 minutes of waking, changing coil ≥ 3 times per month *E(N)NDS liquid/aerosol characteristics* No association between nickel levels in pre-use E(N)NDS liquids and all nickel biomarker levels Positive association between nickel in urine and saliva with nickel in E(N)NDS aerosol and in used E(N)NDS liquid	Results indicated a possible correlation between nickel and chromium levels in E(N)NDS aerosol and used (but not pre-use) E(N)NDS liquid with levels of chromium and nickel biomarkers in users. Some usage parameters were

Authors	Investigation	E(N)NDS models / brands tested	Experimental details / detection methods	Results	Comment
	characteristics		Chromium and nickel analysis of: 1. ‘naive’ E(N)NDS liquid 2. E(N)NDS liquid remaining in device after use 3. aerosol by ICP-MS Analysis of chromium and nickel in saliva, urine, and exhaled breath condensate (EBC) biospecimens by ICP-MS	<u>Chromium</u> *E(N)NDS use characteristics*: Non-significant trend towards higher biomarker chromium levels with higher E(N)NDS liquid consumption. *E(N)NDS liquid/aerosol characteristics* No association between chromium levels in pre-use E(N)NDS liquids and all chromium biomarker levels. Positive association between chromium in saliva with chromium in E(N)NDS aerosol and in used E(N)NDS liquid.	also correlated with chromium and nickel biomarkers in E(N)NDS users. Authors concluded that the main source of nickel and chromium exposure during E(N)NDS use is likely to be from the heating coil rather than the E(N)NDS liquid. They postulated that use of larger volumes of E(N)NDS liquid may exacerbate this problem by facilitating more transfer of metals from the heating coil into the E(N)NDS liquid.

<table>
<tr><th>Authors</th><th>Investigation</th><th>E(N)NDS models / brands tested</th><th>Experimental details / detection methods</th><th>Results</th><th>Comment</th></tr>
<tr><td>Hess et al. (2017)</td><td>Analysis of metal concentrations in E(N)NDS liquid</td><td>5 brands of rechargeable ‘cigalikes’, commercially available in the US, containing nicotine (1.6–1.8 mg/mL), random flavours selected

Up to 10 cartridges from each brand</td><td>Cadmium, chromium, lead, manganese, nickel concentration in cartomizer E(N)NDS liquid analysed by ICP-MS</td><td>All metals were identified in all (48) E(N)NDS liquid samples.

Cadmium levels were much lower than other metals.

There was a wide variation in levels of the metals both across and within brands. One brand had the highest mean concentration of each individual metal tested.

<table><tr><th>Metal</th><th>Range of mean concentrations by brand, µg/L (SD)</th></tr><tr><td>Lead</td><td>4.89 (0.893)–1970 (1540)</td></tr><tr><td>Chromium</td><td>53.9 (6.95)–2110 (5220)</td></tr><tr><td>Nickel</td><td>58.7 (22.4)–22 600 (24 400)</td></tr><tr><td>Manganese</td><td>28.7 (9.79)–6910 (12 200)</td></tr><tr><td>Cadmium</td><td>0.145 (0.38)–205 (318)</td></tr></table></td><td>The concentrations of chromium, manganese, and nickel were highlighted by the authors as being of concern.</td></tr>
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Kim et al. (2017)	Development and analysis of a reference E(N)NDS liquid for analytical studies Evaluation of the levels of 8 metals (cadmium, chromium, cobalt, copper, lead, manganese, nickel, palladium) in aerosol generated from new and used (20 h over 4 months) E(N)NDS device	Vivi-Nova Tank system (new or used for approximately 20 h over 4 months)	4 s puff, 50 mL puff volume 15 (750 mL) or 150 (7.5 L) puffs of aerosol collected in 30 mL water Analysis of 8 metals in E(N)NDS liquid and collected aerosol by ICP-OES (cadmium, chromium, cobalt, copper, lead, manganese, nickel, palladium)	LOD for all metals: 1 ppb E(N)NDS liquid: all metals below LOD Aerosol produced using new E(N)NDS tank system: all metals below LOD Aerosol produced from used E(N)NDS tank system: 2 metals detected; lead, 0.097 ± 0.003 mg/L; manganese 0.001 ± 0.000 mg/L (presumed to be the concentration in the 30 mL collection fluid, from 150 puffs) Accumulation of residue on the heating element in the used E(N)NDS device	E(N)NDS liquid and new E(N)NDS device produced aerosol in which metals were below the LOD. However, after 20 h use, the aerosol from the same device contained detectable levels of lead and manganese.
Lee et al. (2017)	Analysis of E(N)NDS aerosol content	E(N)NDS V2 'cigalike' cartomizer devices; 1.8% nicotine; tobacco flavour or menthol flavour	Collection on teflon filters 48 trace elements (aluminium, antimony, arsenic, barium, bromine, cadmium, caesium, calcium, cerium, chlorine,	Trace levels of silicon, chlorine, barium, indium identified. Levels were stated to vary with flavour and puffing time, but values were not reported. All other elements below the LOD (data not reported)	Trace levels of silicon, chlorine, barium, indium detected in E(N)NDS aerosol.

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			chromium, cobalt, copper, europium, gallium, germanium, gold, indium, iron, lanthanum, lead, magnesium, manganese, mercury, molybdenum, nickel, niobium, palladium, phosphorus, potassium, rubidium, samarium, scandium, selenium, silicon, silver, sodium, strontium, sulphur, terbium, thallium, tin, titanium, tungsten, vanadium, yttrium, zinc, zirconium) analysed by X-ray fluorescence spectrometry in 1:72 dilution aerosol		

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Liu et al. (2017)	Evaluation of room air (exposure chamber) during E(N)NDS product use	MarkTen 2.5% nicotine Classic (Group I); Prototype GreenSmoke 2.4% nicotine (Group II); Compact Ego RBC Tank device with participant's own E(N)NDS liquid (nicotine 5.92-23.9 mg/mL) (Group III); CC (participant's own brand) (Group IV) 9 or 10 users per group	114 m^3 exposure chamber Product use (5 s puff, 30 s interval, x10) every 30 min for 4 h; or *ad libitum* Control = room air before product use Trace elements (chromium, nickel, cadmium, arsenic) collected on quartz filters at 1700 mL/min flow-rate during product use, and analysed by ICP-MS	LOQ for all 4 trace elements, 0.12 µg/m^3 Levels of arsenic and cadmium were below the LOQ for all measurements (control air and all groups) No statistical difference between control air and test-group air in measured levels of chromium or nickel, except that chromium levels were lower after Group II product use than in control air.	cadmium, arsenic below LOD (0.12 µg/m^3) in all samples. No significant increase in chromium or nickel levels with E(N)NDS or CC use.

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Oldham et al. (2017)	Sampling of chemical constituents in room air with E(N)NDS use	MarkTen Classic EVP (Nu Mark LLC); 1.5% nicotine by weight	25.5 m^3 room (unused office); 30 puffs every 60 mins, over 180 min by machine smoking Arsenic, cadmium, chromium, nickel collected on quartz filters, and analysed by ICP-MS	All metals were below the limit of detection, which varied between approximately 0.3 and 3.9 µg/m^3 (in each case, the same value for all 4 metals), depending on the volume of air sampled in the collection	Arsenic, cadmium, chromium, nickel were not detected in room air in which E(N)NDS aerosol was produced (30 puffs per 60 min)
Palazzolo et al. (2017)	Evaluation of trace elements in E(N)NDS aerosol and E(N)NDS liquid. Investigation of the physical components of the E(N)NDS device.	Triple 3 eGo 'clearomizer' E(N)NDS; tobacco flavour E(N)NDS liquid with 24 mg/mL nicotine	SEM analysis of core E(N)NDS device structure 5 s puffs; Collection of aerosol on mixed cellulose ester (MCE) membrane, and quantification of 9 trace elements (aluminium, arsenic, cadmium, copper, iron, lead manganese,	<u>E(N)NDS device</u> The elemental composition of core assembly was described. <u>E(N)NDS liquid</u> Levels of metals in E(N)NDS liquid were very low <u>Aerosol/smoke</u> Nickel collected from 45 puffs (1 membrane): E(N)NDS, 0.024 µg Filter control, 0.005 µg Exposure to nickel from E(N)NDS aerosol was calculated as 0.217 µg/ 15 puffs, after adjusting for filter background and approximately 3% E(N)NDS liquid recovery on the filter membrane. Other trace elements were not significantly higher than controls	Nickel was detected in the aerosol produced from a cartomizer E(N)NDS device. Authors concluded that as levels of nickel in the E(N)NDS liquid used were low, the nickel in the aerosol was assumed to derive from the E(N)NDS device, not the E(N)NDS liquid. They considered

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			nickel, zinc) on the membrane by SEM/EDS Quantification of these 9 elements in ‘pure’ E(N)NDS liquid (i.e. before introduction into the E(N)NDS device) by ICP-MS. 5 s puff, 45 puffs per MCE filter; negative control for aerosol experiments was ‘naive' filter (0 puffs)		that the use of nickel in E(N)NDS devices should be minimised on the basis of potential health concerns related to exposure to nickel from the E(N)NDS aerosol product.

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Williams et al. (2017)	Quantification of 36 elements in aerosol from 11 brands of E(N)NDS (e-cigarette, EC or e-hookah, EH[22]); correlation with device structure/ components	6 disposable ECs (Vype, BluCig, NJOY King, Square 82, Mistic, V2 Cig) 5 disposable EHs (Starbuzz, Imperial Hookah, Luxury Lites, Smooth, Tsunami) Marlboro Red CC	Evaluation of disassembled device components Analysis of EC/EH components by SEM/EDS Analysis of aerosol/smoke samples by ICP-OES Subtracted for concentrations in room air	35 elements were identified in EC/EH aerosol; 15 elements were identified in CC smoke <u>Total content of inorganic elements</u> EC/EH: 1.778–7.257 µg/10 puffs (range over 11 different brands) CC: 1.532–4.259 µg/10 puffs (range for one brand with 2 different puffing protocols) <u>Individual elements detected (EC/EH)</u> Aluminium, antimony, arsenic, barium, boron, chromium, cobalt, copper, germanium, indium, iron, lanthanum, lead, magnesium, manganese, mercury, molybdenum, nickel, rubidium, selenium, silver, sodium, strontium, tungsten, vanadium, zinc, zirconium (0.001–0.01 µg/10 puffs) Aluminium, boron, calcium, copper, germanium, iron, lead, manganese, potassium, rubidium, selenium, silicon, sodium, tin, tungsten, zinc, zirconium (> 0.01 µg/10 puffs)	> 50% mass of inorganic elements in EC/EH aerosol was silicon, presumably from the fibreglass wick Calcium, copper, potassium, tin, and zinc were identified at levels > 0.01 µg/10 puffs in several brands Low levels of nickel (up to 0.005 µg/10 puffs) were detected in aerosol from 9 brands Lead was identified in the solder and corresponding aerosol from 2 brands of EH (highest level, 0.165 µg/10 puffs)

[22] E-hookah (similar in structure and use to an EC)

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Olmedo et al. (2018)	Evaluation of metals in dispenser (i.e. ‘tank-naïve’) refill liquids, aerosols produced from tank-style E(N)NDS devices, and liquid remaining in the tank after use	56 users own E(N)NDS tank-style devices (> 20 brands); Evaluation of: - liquid refill before introduction to the E(N)NDS tank (‘dispenser’); - aerosols produced (‘aerosol’); - liquid remaining in tank after use (‘tank’)	Evaluation of 15 metals by ICP-MS: aluminium, antimony, arsenic, cadmium, chromium, copper, iron, lead manganese, nickel, tin, titanium, tungsten, uranium, zinc	Arsenic, titanium, uranium, and tungsten were detected in < 20% of refill, tank, and aerosol samples (except tungsten, in 21% of aerosols) and so were excluded from further investigations. For the remaining 11 metals, % ranges (no. of samples positive) detected: <u>Dispenser E(N)NDS liquid</u> 0.0% for cadmium to 92.9% for zinc <u>Aerosol</u> 30.4% for cadmium to 100% for tin <u>Remaining tank E(N)NDS liquid</u> 55.1% for cadmium to 100% for chromium, copper, iron, nickel, lead, tin, and zinc Overall, concentrations of individual metals showed an increase: dispenser < aerosol < tank. For details and statistical comparisons, see Tables 1-8 in the published report of Olmedo et al. (2018) [attached at Annex D]	Authors concluded that E(N)NDS are a source of exposure to metals that are toxic or may be toxic when inhaled: chromium, lead, manganese, nickel, zinc. They concluded that higher concentrations in tank and aerosol samples compared with dispenser liquid indicates the device coil as the likely source of the metal contamination.

TOX/2018/15 - Annex C

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT)

Potential toxicological risks from electronic nicotine (or non-nicotine) delivery systems (e-cigarettes). Paper 2: Exposure to metals present in the aerosol of E(N)NDS

Concentrations of elements in E(N)NDS (e-cigarette (EC) and e-hookah (EH)) aerosols and conventional cigarette (CC) smoke. (Reproduction of Figures 2, 3, and 4 from the report of (Williams et al. 2017)).

NCET at WRc/IEH-C under contract supporting the PHE COT Secretariat
February 2018

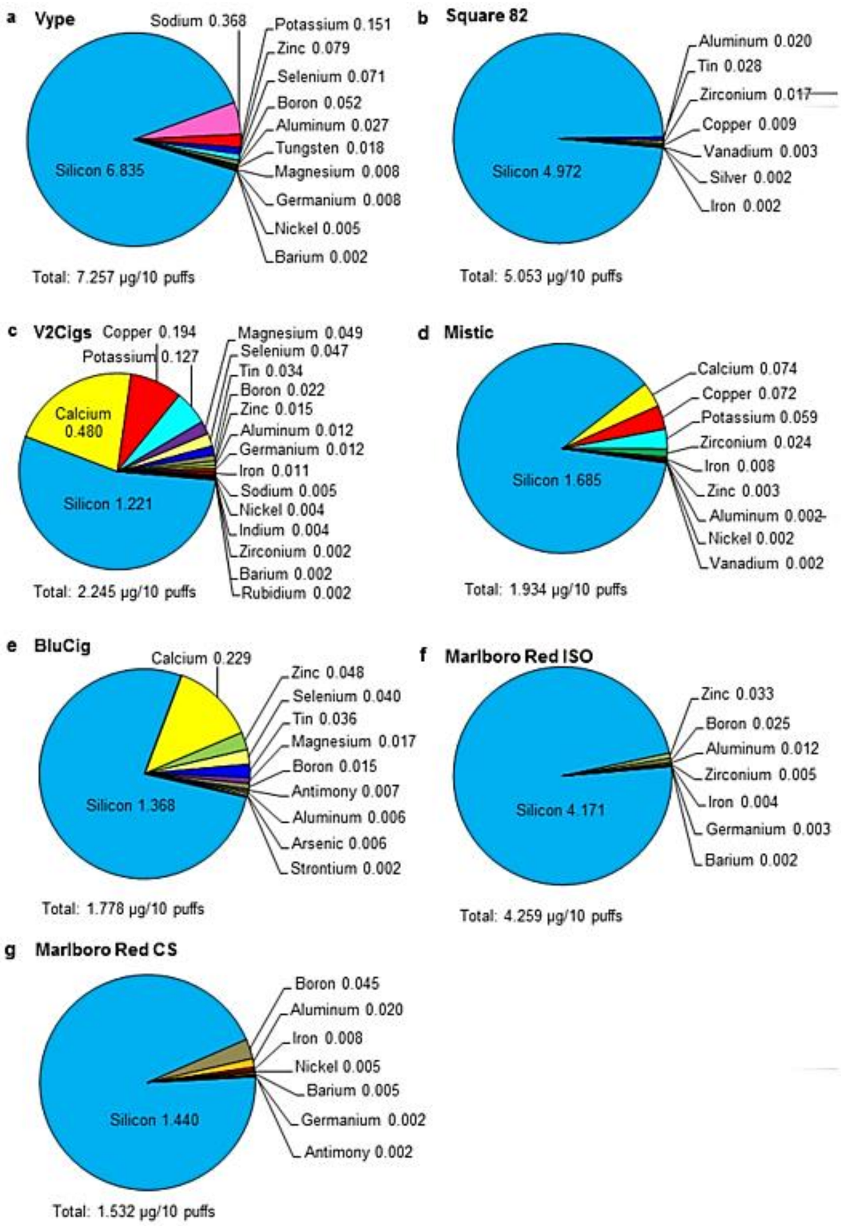

Fig 2. Concentration of elements in disposable EC aerosol (first 60 puffs) and in Marlboro Red cigarette smoke. The concentration of elements in aerosols from (A) Vype, (B) Square 82, (C) V2 Cigs, (D) Mistic, (E) BluCig, and in smoke from (F) Marlboro Red ISO, and (G) Marlboro Red CS are shown in the pie charts as a percentage of the total concentration of elements for each brand. The total concentration of all elements is given for each brand in µg/10 puffs beneath each pie chart. Numbers adjacent to each element are concentrations in µg/10 puffs for that element. For each brand, all concentrations are the average of three aerosol samples from three different ECs, and only elements that were higher than or equal to 0.002 µg/10 puffs are presented in this figure.

Reproduced from Williams et al 2017. PLoS ONE 12(4): e0175430

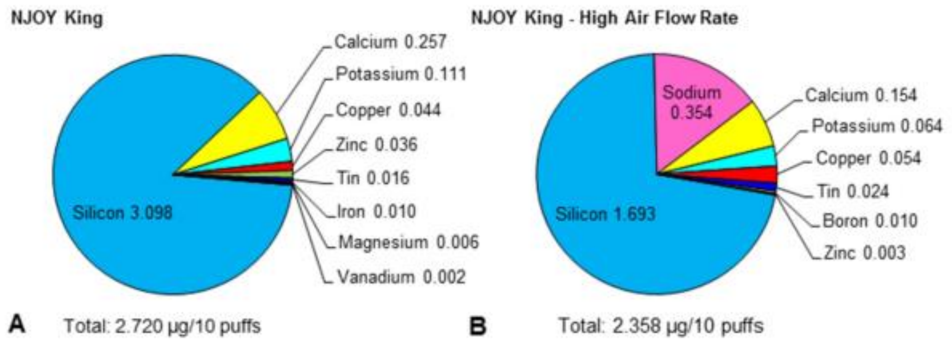

Fig 3. Elemental analysis of disposable ECs at low and high air-flow rates. The concentrations of elements in the aerosol of NJOY King were measured at low (A) and high (B) air-flow rates, and are shown for each element in the pie charts as the percentage of the total concentration of all elements. Sodium was not measured in the aerosol from NJOY King puffed at a low air-flow rate. The total concentration of all elements is given at the bottom of each pie chart. Numbers adjacent to each element are concentrations in µg/10 puffs for that element. All concentrations are the average of three aerosol samples from three different ECs, and only elements that were higher than or equal to 0.002 µg/10 puffs are presented in this figure.

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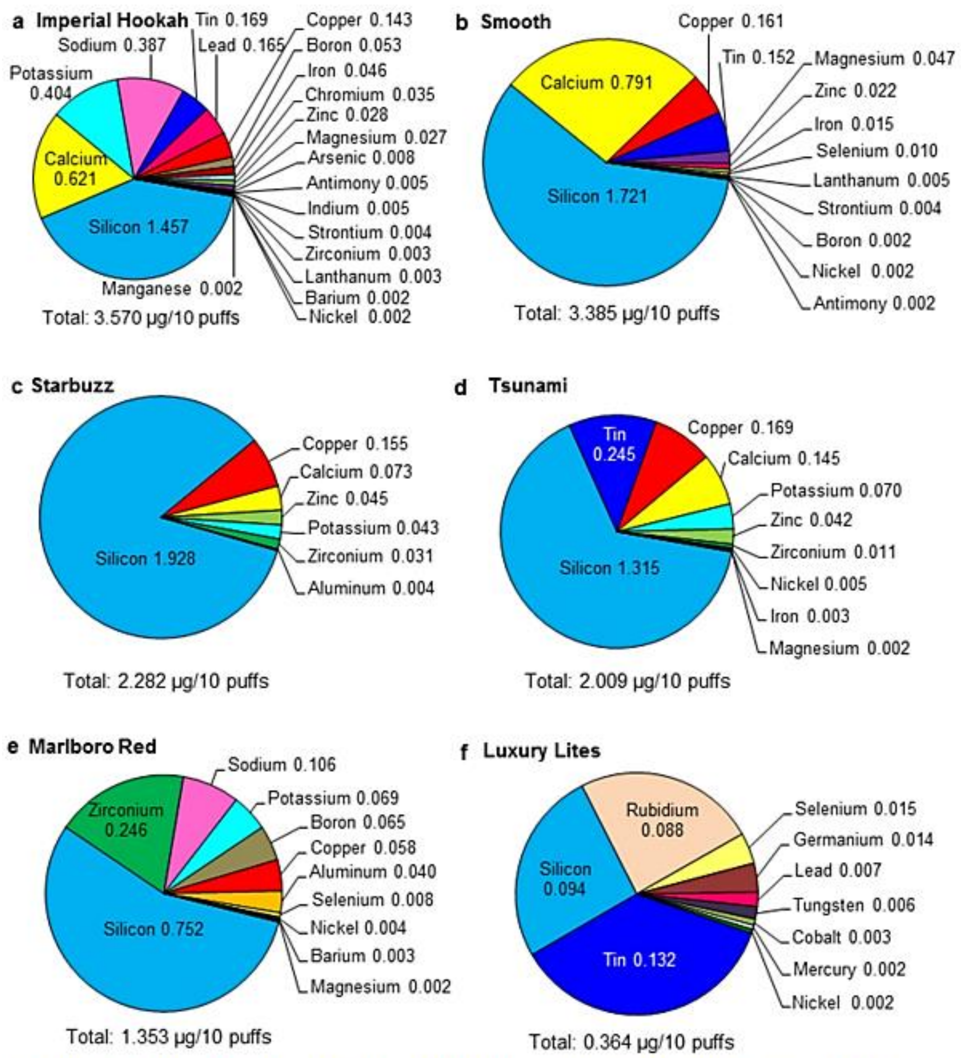

Fig 4. Concentration of elements in disposable EH aerosol and Marlboro Red cigarette smoke. The concentration of elements in the aerosols of (A) Imperial Hookah, (B) Smooth, (C) Starbuzz (D) Tsunami, and in smoke from (E) Marlboro Red ISO and (F) Marlboro Red CS are presented in each pie chart as a percentage of total element/metal concentration. The total concentration of all elements is given in µg/10 puffs at the bottom of each figure for each brand. Numbers adjacent to each element are concentrations in µg/10 puffs for that element. All concentrations presented are the average of three samples, and only elements higher than or equal to 0.002 µg/10 puffs are presented in this figure.

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TOX/2018/15 - Annex D

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT)

Potential toxicological risks from electronic nicotine (or non-nicotine) delivery systems (e-cigarettes). Paper 2: Exposure to metals present in the aerosol of E(N)NDS

Olmedo, P., W. Goessler, S. Tanda, M. Grau-Perez, S. Jarmul, A. Aherrera, R. Chen, M. Hilpert, J. E. Cohen, A. Navas-Acien & A. M. Rule (2018) Metal Concentrations in e-Cigarette Liquid and Aerosol Samples: The Contribution of Metallic Coils. Environ Health Perspect, 126, 027010

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