TOX/2018/16

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). Preparation for further discussion papers

Background

1. After discussing a scoping document (TOX/2016/25) on electronic nicotine delivery systems and electronic non-nicotine delivery systems (E(N)NDS) in July 2016, the COT established the following areas as priorities for more in-depth reviews:

- 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

2. The Committee agreed that further discussion papers should be prepared to address the above questions. A paper (TOX/2017/49) on characterisation of the aerosol particle fraction was discussed in December 2017 and a paper on exposure to metals from E(N)NDS use will presented alongside this one at the March 2018 COT meeting (TOX/2018/15).

3. To support the Secretariat in preparing the upcoming papers, this paper outlines the available data on constituents of E(N)NDS liquids and aerosols, and provides literature searches on potential genotoxicity or carcinogenicity associated with E(N)NDS to determine whether advice should be sought from COM and COC on these areas respectively. Suggestions for papers to support the Committees evaluation in addition to the priority topics given above are outlined at the end of the paper. Questions for the Committee to consider are given in paragraphs 15, 21 and 25.

Summary of data on the constituents of electronic nicotine (or non-nicotine) delivery systems liquids and aerosols

4. To facilitate determining the scope of the paper assessing inhalation effects of the main constituents and emissions, a literature search was carried out (Annex A) and studies that evaluated the chemical constituents of E(N)NDS were retrieved. Data from such studies are summarised in this report. A short overview is given below and study data on E(N)NDS liquids and aerosol/vapour are presented in Tables 1 and 2 of Annex B, respectively. Studies that solely investigated metals or flavourants have not been included as these areas will be addressed in separate papers.

E(N)NDS liquids (Table 1, Annex B)

5. The principal components (often in the range of 90-95% of the mass) of most E(N)NDS liquids are the solvents, propylene glycol (PG) and glycerine (vegetable glycerine, VG, glycerol), which can be present in ratios ranging from 0:100 to 100:0 (Pellegrino et al. 2012, Hahn et al. 2014, Schober et al. 2014, Tayyarah and Long 2014, Geiss et al. 2015, Han et al. 2016, Sleiman et al. 2016, Etter and Bugey 2017, Peace et al. 2017). Other common additives are water, nicotine, and flavourants.

6. Nicotine concentrations stated on product labels are generally in the range of up to 20 mg/mL, although products with higher nicotine concentrations may be available in some countries. In the UK, the Tobacco and Related Products Regulations 2016 states that “nicotine-containing liquid which is presented for retail sale in an electronic cigarette or refill container must not contain nicotine in excess of 20 milligrams per millilitre” (Part 6, section 36(4)). Several investigations have found that nicotine concentrations do not always correlate well with levels stated on the label (Hadwiger et al. 2010, Trehy et al. 2011, Davis et al. 2015, Han et al. 2016, Peace et al. 2016, Sleiman et al. 2016, Cheah et al. 2014).

7. E(N)NDS liquids with many thousands of unique flavours have been listed. Many of the flavouring additives are substances that are established as generally recognised as safe (GRAS) for ingestion, although in most cases the safety of these compounds when heated and inhaled is unknown (reviewed in (CDC 2016)). This will be reviewed further in a later discussion paper as part of this series.

8. Some studies have reported the presence of contaminants and impurities in E(N)NDS liquids, often at low or trace levels (reviewed by CDC (2016), Breland et al. (2017)). One group reported the detection of substantial levels of ethylene glycol (mean, 10%; range up to 76%) in some E(N)NDS liquids (Hutzler et al. 2014, Hahn et al. 2014), although others have found that ethylene glycol is not detectable (Kavvalakis et al. 2015, Han et al. 2016, Peace et al. 2016, Etter and Bugey 2017) or present only at low levels, below maximum residual limits permissible in foods and pharmaceuticals[1] (Varlet et al. 2015). The nicotine in E(N)NDS liquids is usually

[1] 1 mg/g (FDA); 620 µg/g (US Pharmacopeia Convention in 2007) (cited by Varlet et al., 2015)

derived from tobacco plants and may contain contaminants, including minor tobacco alkaloids (reported levels at approximately 1-2% of the nicotine content in one study) (Etter, Zather and Svensson 2013, Lisko et al. 2015, Flora et al. 2016, Han et al. 2016, Sleiman et al. 2016) and tobacco-specific nitrosamines (TSNAs) (maximum values reported, approximately 60 ng/mL NNN, 10 ng/mL NNK, 11 ng/mL NAB, 62 ng/mL NAT) (Kim and Shin 2013, Farsalinos et al. 2015a, Han et al. 2016). One report described the presence of low levels of diethyl phthalate (DEP) (up to 1745 mg/L) and diethylhexyl phthalate (DEHP) (up to 82 mg/L) in some E(N)NDS liquids (Oh and Shin 2015). Ethanol, which may be present as a solvent in flavourants, has also been detected (Sleiman et al. 2016, Poklis, Wolf and Peace 2017). Analysis of some E(N)NDS liquids has identified other active compounds, for example a weight-loss drug (Hadwiger et al. 2010) and a synthetic cannabinoid (Peace et al. 2017, Poklis et al. 2017). Several studies have reported E(N)NDS liquid samples that are not true-to-label.

Aerosol (Table 2, Annex B)

9. Aerosol is produced by heating of the E(N)NDS liquid within the E(N)NDS device. VG and PG have different physical properties (for example, VG has a higher boiling point) and this may affect factors such as the temperature at which the aerosol is produced and the size-distribution properties of the particles, which will affect the region of deposition in the airway (see TOX/2017/49 for further detail on particle characteristics and deposition).

10. Thermal decomposition of E(N)NDS liquids during aerosol production may lead to the production of degradation products, for example carbonyl compounds such as formaldehyde, acetaldehyde, and acrolein, with levels reported ranging widely (from a few ng to > 20 µg per puff) (Uchiyama et al. 2013, Goniewicz et al. 2014, Hutzler et al. 2014, Kosmider et al. 2014, Geiss et al. 2015, Herrington and Myers 2015). Di-aldehydes, glyoxal and methylglyoxal, have also been detected (maximum levels reported, 4.3 and 5.8 µg/puff, respectively) (Uchiyama et al. 2013, Uchiyama et al. 2016). The extent to which thermal breakdown occurs is likely to be related to user behaviour (puffing parameters) and the operating characteristics of the E(N)NDS device, such as battery output and heating-coil resistance, which affect the temperature attained (Jensen et al. 2015, Sleiman et al. 2016, Uchiyama et al. 2016, Ogunwale et al. 2017). For example, formaldehyde emission levels in the range of approximately 80-100 µg/puff have been reported using variable-voltage devices on very high settings (in the range of 5.0 V or 15 W) (Ogunwale et al. 2017, Sleiman et al. 2016), although emission levels reported from use at lower voltage/power settings are generally much lower than this. It has also been suggested that standard methods of analysis underestimate the levels of formaldehyde produced (Salamanca et al. 2017). This is currently an area of active investigation and debate, with some commentators asserting that carbonyl production only occurs during ‘dry puffing’ (i.e. in the absence of E(N)NDS liquid), which would be avoided by E(N)NDS users due to the disagreeable experience (Farsalinos et al. 2017, Farsalinos et al. 2018). The method by which the E(N)NDS

liquid is applied to the heating coil has been reported to affect levels of degradation products in the aerosol. In most E(N)NDS apparatus, liquid is drawn to the coil through a wick. However, some newer devices allow 'direct dripping' of liquid onto the heating element, which appears to be associated with substantially increased levels of carbonyl emissions (Talih et al. 2016).

11. Reported proportions of nicotine emitted from E(N)NDS liquids to aerosols on puffing vary, and this also likely depends on a combination of device characteristics, puffing behaviour, and the overall composition of the E(N)NDS liquid (Talih et al. 2016).

12. Some studies have reported the detection of volatile organic compounds (VOCs), e.g. benzene or toluene, and polycyclic aromatic hydrocarbons (PAHs) in E(N)NDS emissions, although generally at very low levels (Goniewicz et al. 2014, Tayyarah and Long 2014, Margham et al. 2016, Lee et al. 2017).

13. The presence of low levels of metal particles derived from the E(N)NDS device itself in the aerosol has also been reported and this aspect has been reviewed separately in TOX/2018/15. The presence of flavouring compounds in E(N)NDS liquids/aerosols will be summarised in a future paper.

Scope of future paper on inhalation toxicity of main constituents and emissions

14. Following the scoping paper presented in 2016, the Committee considered that a review of the effects of long term inhalation of the main constituents and emissions should be undertaken as part of this work. It is currently anticipated that the following substances will be included, as well as papers investigating the toxicity of the aerosol as a whole:

- Propylene glycol (PG)
- Vegetable glycerine (VG, glycerol)

Questions for the Committee

15. Members are asked for any general comments on this summary of the constituents of E(N)NDS liquids and aerosols, including the data in Tables 1 and 2, Annex B, and in particular:

i. Are there any other key constituents or emissions from E(N)NDS, beyond those listed in paragraph 14, which should be included in the future COT review paper on inhalation toxicity of the main constituents and emissions?

Literature searches on genotoxicity and carcinogenicity

16. To provide information to help in assessing whether this topic should be referred for review by the Committee on Mutagenicity (COM) and Committee on Carcinogenicity (COC), a preliminary search of the published literature on E(N)NDS relating to these areas has been undertaken. Search details are described below.

Search strategy

17. Two searches were carried out in both SCOPUS and PubMed. Search terms in each database are as follows:

- Genotoxicity

  Scopus

  (TITLE-ABS-KEY ("e-cig*" OR "electronic cigarette*" OR "electronic nicotine delivery system*") AND TITLE-ABS-KEY (genotox* OR mutagen* OR "genetic tox")): 30 refs.

  PubMed

  ((("e-cig*" [Title/Abstract] OR "electronic cigarette*" [Title/Abstract] OR "electronic nicotine delivery system*"[Title/Abstract])) AND (genotox* [Title/Abstract] OR mutagen* [Title/Abstract] OR "genetic tox*"[Title/Abstract])) AND english[Language]: 12 refs.

- Carcinogenicity

  Scopus

  (TITLE-ABS-KEY ("e-cig*" OR "electronic cigarette*" OR "electronic nicotine delivery system*") AND TITLE-ABS-KEY (carcin*)): 145 refs.

  PubMed

  ((((("e-cig*" [Title/Abstract] OR "electronic cigarette*" [Title/Abstract] OR "electronic nicotine delivery system*"[Title/Abstract])) AND (carcin* [Title/Abstract]))) AND english[Language]: 38 refs.

Results

18. Genotoxicity: A total of 32 references were retrieved. A list of titles is given in Annex C.

19. Carcinogenicity: A total of 153 references were retrieved. A list of titles is given in Annex D.

20. To note these lists have not been further screened or assessed for relevance. If it is determined that COM and/or COC should be approached to assess the available literature, a more structured search and screening process would be undertaken.

Questions for the Committee

21. Given the output from these preliminary literature searches, do Members wish to refer the potential genotoxic and/or carcinogenic risks from electronic nicotine (and non-nicotine) delivery systems for evaluation by the COM and/or COC, respectively?

Suggestions for further papers to support the COT evaluation of E(N)NDS

22. The Secretariat notes that in parallel with the paper on bystander exposure to key analytes or constituents of the E(N)NDS aerosol, a paper on user exposure to the same constituents could be helpful. These exposure papers would then complement the paper on toxicity of the constituents of the E(N)NDS liquid and aerosol.

23. This topic area is seeing a number of authoritative reviews being published. The Secretariat is keeping these under review and, where relevant, ensuring evidence raised in these is captured in the Committee's discussion papers. To provide an overview of the documents available when the Committee prepares its draft statement, the Secretariat plans to provide an information paper alongside this summarising the available authoritative reviews.

24. In the COT statement on heated tobacco products[2], it was noted that it would be of interest to compare the risks from these products with those of E(N)NDS, which would be borne in mind during the COT E(N)NDS review. Where data are available in E(N)NDS papers on heated tobacco products, these can be included in the upcoming Committee discussion papers.

Questions for the Committee

25. Members are asked for any comments they have on the proposed papers and in particular:

i. Do Members have any further aspects which are high priority that should be added to the papers to be prepared for this topic?

ii. Do Members have any views on how to consider comparing risks of E(N)NDS with those of heated tobacco products?

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[2] https://cot.food.gov.uk/cotstatements/cotstatementsyrs/cot-statements-2017/statement-on-heat-not-burn-tobacco-products

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Abbreviations/Glossary

DEP:	diethyl phthalate
DEHP:	diethylhexyl phthalate
E(N)NDS:	electronic (non) nicotine delivery system
FDA:	US Food and Drug Administration
GRAS:	generally recognised as safe
NAB:	N-nitrosoanabasine
NAT:	N-nitrosoanatabine
NNK:	4-(methylnitrosamino)1-(3-pyridyl)-1-butanone, [nicotine-derived nitrosamine ketone]
NNN:	N-nitrosonornicotine
PAH:	polycyclic aromatic hydrocarbon
PG:	propylene glycol
TSNA:	tobacco-specific nitrosamine
VG:	vegetable glycerine
VOC:	volatile organic compound

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Potential toxicological risks from electronic nicotine (or non-nicotine) delivery systems (e-cigarettes). Preparation for further discussion papers

Details of literature search on constituents of E(N)NDS liquids and aerosols carried out by NCET at WRc/IEH-C

Literature searches were 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, from 2005 to present.

Search terms used were:

- e-cigarette OR electronic cigarette OR e-cig

AND

- constituents OR additives

In addition, manual searches of literature resources relating to this area (e.g. general reviews and commentaries on E(N)NDS; reviews on E(N)NDS constituents; publications by authoritative bodies) were searched for additional publications of relevance and original citations were obtained.

From such searches, a total of 42 papers were selected.

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Tables reporting constituents in E(N)NDS liquids and aerosols

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Table 1. Reported constituents of E(N)NDS liquids.

Reference	E(N)NDS product	Solvent	Solvent-related contaminants or impurities	Nicotine and tobacco alkaloids	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
Hadwiger et al. (2010)	E(N)NDS and/or E(N)NDS liquids advertised as containing E-Cialis (tadalafil) (erectile dysfunction drug) or E-rimonabant (weight-loss drug)			Nicotine identified in cartridges labelled as non-nicotine			Products contained amino-tadalafil (not tadalafil) or ribonamant	
Trehy et al. (2011)	Refill cartridges and refill solutions (NJOY, Smoking Everywhere, CIXI)			Nicotine contents varied substantially from label - less or more than stated, including presence in products labelled as nicotine-free Nicotine-related impurities; Cotinine: <LOD Myosmine: <LOQ–0.08 mg/cartridge Anatabine: <LOD–0.82 mg/cartridge Anabasine: <LOD–0.21 mg/cartridge b-nicotyrine: <LOD–0.06 mg/cartridge				

Reference	E(N)NDS product	Solvent	Solvent-related contaminants or impurities	Nicotine and tobacco alkaloids	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
Pellegrino et al. (2012)	Aria device; with and without nicotine	PG, 66% VG, 24%		Nicotine: 0.25% in device labelled as with nicotine		Methyl pyrazine; 2,3-dimethyl pyrazine; 5-methyl-2-furaldehyde; 1-hydroxy-2-propanone; β-damascon; 2,5-dimethyl pyrazine; 3-hydroxy-2-methyl-4-pyranone (maltol); 2,3,5,6-tetramethyl pyrazine (total <1%)		
Etter et al. (2013)	20 samples of 10 brands of refill liquids, worldwide	PG + VG (19 samples) VG only (1 sample)	Ethylene glycol and diethylene glycol were not detected	Nicotine contents reasonably close to label-stated values Nicotine-degradation products were present at levels between 0–4.4% of sample nicotine content (generally 1–2%), including cis-N-oxide, trans-N-oxide, myosmine, anatabine, and anabasine				

Reference	E(N)NDS product	Solvent	Solvent-related contaminants or impurities	Nicotine and tobacco alkaloids	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
Kim and Shin (2013)	105 E(N)NDS liquids from 11 brands purchased in Korea, 2012				Mean (range; frequency of detection) in ng/mL NNN: 4.06 (0.34–60.08; 65%) NNK: 1.71 (0.22–9.85; 89%) NAB: 0.90 (0.11–11.1; 75%) NAT: 12.99 (0.09–62.19; 93%)			
Lim and Shin (2013)	225 E(N)NDS liquids obtained from 17 retail outlets in the Republic of Korea		Concentration mean (range); Formaldehyde: 2.16 (0.02–10.09) mg/L [detected in 207/225 samples] Acetaldehyde: 4.98 (0.10–15.63 mg/L [detected in all samples] Acrolein: not detected in all samples					

Reference	E(N)NDS product	Solvent	Solvent-related contaminants or impurities	Nicotine and tobacco alkaloids	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
Cheah et al. (2014)	20 E(N)NDS cartridges obtained from samples seized by Singapore authorities (where the sale of E(N)NDS products is prohibited)	PG: range 0–1320 mg/cartridge VG: range 32.2–1020 mg/cartridge		17/20 cartridges contained nicotine, including 4 cartridges labelled as nicotine free 16/20 samples contained nicotine at a concentration that did not correspond to that stated on the label Nicotine range: 0–15.3 mg/cartridge				
Hahn et al. (2014)	54 e-liquids, Germany, labelled as without or with (6-54 mg/mL) nicotine	Mean (range) per 100 g e-liquid); PG: 57 g (0.4–98 g) VG: 37 g (0.3–95 g) Estimated mean exposure per day: 14.5 mg/kg bw (PG), 9.0 mg/kg bw (VG)	Per 100 g e-liquid; Ethylene glycol: 10 g (mean); 5 g (median) (91% positive samples) 1,3-propanediol: 0.6 g (mean), 0 g (median) (13% positive samples)	Mean nicotine concentration: 11 mg/mL Estimated mean nicotine exposure per day: 0.38 mg/kg bw		Thujone, ethyl vanillin		MOEs calculated based on BMD/NOAELs used in monographs of national and international risk assessment bodies: nicotine (< 0.1), ethylene glycol (< 100), PG (between 100-1000), others (> 1000)

Reference	E(N)NDS product	Solvent	Solvent-related contaminants or impurities	Nicotine and tobacco alkaloids	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
Hutzler et al. (2014)	28 e-liquids from Germany, 10 of which were labelled as free of nicotine	Present in all e-liquids	Ethylene glycol identified in 13/28 e-liquids (range, 1-76%) Trace levels (in the range of 1 µg or less) of formaldehyde, acetaldehyde, and propionaldehyde identified in 5 non-nicotine e-liquids at room temperature; Levels increased 10- to 20-fold on heating e-liquid to 150 ^{o}C e.g. for one sample, acetaldehyde increased from 0.5 to 348 g/mL	<u>Nicotine range</u> 0.1-15 µg/mL in 7/10 E(N)NDS liquids labelled non-nicotine; 0.1-324 µg/mL in 16/18 E(N)NDS liquids for which nicotine content was not specified on the label		141 flavour substances detected, including known allergens		7/10 e-liquids labelled as nicotine-free contained nicotine (0.1-15 µg)
Schober et al. (2014)	Refillable tank system 3 tobacco-flavour e-liquids, each with and without 18 mg/mL nicotine	Present in all e-liquids at approximately 500,000 mg/L each		Nicotine levels in the range around; 21-23 mg/mL in e-liquids labelled containing nicotine; Not detected in e-liquids labelled as nicotine-free	Negative for NNN, NAT, NAB, NNK	Some known sensitising chemicals identified		

Reference	E(N)NDS product	Solvent	Solvent-related contaminants or impurities	Nicotine and tobacco alkaloids	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
Tayyarah and Long (2014)	3x blu eCigs (disposable), 2x SKYCIG (rechargeable), 18-24 mg/mL nicotine	VG+PG ≥75%		≈ 2% nicotine		< 7% flavours		
Davis et al. (2015)	71 E(N)NDS liquids purchased in the US from the internet or in local shops			Nicotine levels varied by more than ±10% in 35/54 E(N)NDS liquids labelled as containing nicotine No nicotine was detected in E(N)NDS liquids labelled as nicotine-free Of 5 E(N)NDS liquids that did not have a nicotine specification, 3 contained no nicotine, whilst 2 contained levels > 100 mg/mL				Nicotine content varied from label and between batches of the same product
Farsalinos et al. (2015a)	eGO + tank atomizer 3 tobacco-flavour E(N)NDS liquids purchased in Greece, 18 mg/mL nicotine				NNN: 7.7 ng/g (1 E(N)NDS liquid) NAB: 1.2–2.3 ng/g (3 E(N)NDS liquids) NAT, NNK: <LOD			

Reference	E(N)NDS product	Solvent	Solvent-related contaminants or impurities	Nicotine and tobacco alkaloids	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
Farsalinos et al. (2015b)	159 E(N)NDS liquids from 36 manufacturers retailed in France, Germany, Greece, Italy, Poland, and United Kingdom; selected on the basis of likelihood to have sweet flavours; purchased by internet					Diacetyl: median, 29 µg/mL; IQR, 10–170 µg/mL (110 samples, of which 32 concentrated flavours and 78 E(N)NDS liquid refills) Acetyl propionyl: median, 44 µg/mL; IQR, 7–172 µg/mL (53 samples, of which 10 concentrated flavours and 43 E(N)NDS liquid refills)		
Geiss et al. (2015)	2x second generation E(N)NDS (1 atomiser; 1 cartomizer) 2 e-liquids, each with 0, 9, and 18 mg/mL nicotine, various flavours: 1 PG/VG 1 VG only	PG approximately 500 mg/mL (45%) in PG/VG e-liquid VG approximately 500 mg/mL in PG/VG e-liquid; 1000 mg/mL in VG-only e-liquid		Measured nicotine levels were: <LOD, approximately 10 mg/mL, and approximately 20 mg/mL in E(N)NDS liquids labelled 0, 9, and 18 mg/mL, respectively		Various flavouring chemicals used in foods identified		Significant differences in levels noted between batches of e-liquid

Reference	E(N)NDS product	Solvent	Solvent-related contaminants or impurities	Nicotine and tobacco alkaloids	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
Herrington and Myers (2015)	4x E(N)NDS (first generation)							Evaluation by GC-MS; 1 e-liquid contained > 60 compounds, the identity of many of these was not determined by the method used
Kavvalakis et al. (2015)	263 e-liquids from 13 companies purchased in Greece during 2011-2013		Diethylene glycol was not detected	Measured nicotine concentrations correlated reasonably well with label	Nitrosamines were not detected	Various flavour compounds detected, ranging from 30.4% of samples containing cyclo-pentenolone to 5.3% of samples containing 3,4-dimethoxy-benzaldehyde	PAHs were not detected	

Reference	E(N)NDS product	Solvent	Solvent-related contaminants or impurities	Nicotine and tobacco alkaloids	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
Laugesen (2015)	14 brands imported to New Zealand, purchased in 2013, with labelled nicotine concentrations ranging from 16–18.6 mg/mL (except 1 sample labelled as zero-nicotine, 1 as 11 mg/mL and 1 as 14.5 mg/mL). Including cigalikes, disposables, and cartomisers, but not mods			Mean nicotine concentration for samples labelled as >14 mg/mL nicotine: 18.1 mg/mL (range 5–46 mg/mL)				

Reference	E(N)NDS product	Solvent	Solvent-related contaminants or impurities	Nicotine and tobacco alkaloids	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
Lisko et al. (2015)	36 e-liquids from 4 manufacturers, purchased online in the US			Higher nicotine content was generally associated with higher pH of the e-liquid Minor tobacco alkaloids were identified in all nicotine-containing E(N)NDS liquids. The highest determined levels were: Nornicotine: 6.3-48.2 µg/g myosmine: 8.7-62.7 µg/g anabasine: 21.2-152 µg/g anatabine: 63.1-485 µg/g isonicoteine: 2.4-20.7 µg/g		Commonly present flavours were eucalyptol, pulegone, and menthol		Derivation of minor tobacco alkaloids not known: they may be present as impurities or as a result of e-liquid oxidation
Oh and Shin (2015)	105 E(N)NDS liquids from 11 E(N)NDS brands purchased in the Republic of Korea, 2012						Diethyl phthalate and diethylhexyl phthalate were detected in the ranges of 0.01-1745.20 mg/L (47.6% detection frequency) and 0.06-81.89 mg/L (79.1% detection frequency).	

Reference	E(N)NDS product	Solvent	Solvent-related contaminants or impurities	Nicotine and tobacco alkaloids	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
							Triethylene glycol, tetraethylene glycol and pentaethylene glycol in the ranges of 0.1-19.3 mg/L (10.5% detection frequency), 0.1-30.1 mg/L (12.4% detection frequency) and 0.1-24.9 mg/L (6.7% detection frequency) in the same samples. cis-3-Hexene-1-ol, methyl cinnamate and dodecane in the ranges of 0.03-3267.46 mg/L (70.5% detection frequency), 4.41-637.54 mg/L (6.7% detection frequency) and 0.01-639.96 mg/L (47.6% detection frequency).	

Reference	E(N)NDS product	Solvent	Solvent-related contaminants or impurities	Nicotine and tobacco alkaloids	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
Varlet et al. (2015)	42 e-liquid samples from 14 brands, purchased by internet in 2013, 0-36 mg/mL nicotine, carrier = VG or PG or VG/PG		Diethylene glycol: all samples <4 µg/g Ethylene glycol: < 10 µg/g in 29/32 tested samples;67 µg/g highest level identified Formaldehyde: 0.1-9.0 µg/g (all samples) Acetaldehyde: 0.05-10.2 µg/g (all samples) Acrolein: 0.18-1.03 µg/g (3 products) Propionaldehyde: 0.043-0.261 µg/g (17 samples) Butyraldehyde: 0.077-1.03 µg/g (8 samples) Crotonaldehyde: 0.053-0.067 µg/g (2 samples) Benzaldehyde: 0.035-305 µg/g (30 samples) Isovaleraldehyde: 1.09-1.54 µg/g (4 samples) *O*-tolualdehyde: 0.043 µg/g (1 sample)		Levels of TSNAs were < LOD (1 µg/g) in all samples	Hydrocarbons were detected in 5/42 samples, described mostly as terpenic compounds (e.g. limonene) which were probably used as flavouring agents	Microbiological tests were negative Ethanol < 3.7 mg/g in all samples The following solvents were detected in 1 or a small number of samples: 1,3-butadiene, acetone, 1-propanol, 3-hydroxy-2-butanone, 2-methylpropyl acetate, methyl, 2-methyl butyrate, 2,3-butanedione, cyclohexane, 3-methylbutanal, 2-methyl-1,3-dioxane, 1-butanol, ethylpropanoate, 1,1-dioxyethane Ethyl acetate was present in several samples, generally at <100 µg/g (maximum 253 µg/g)	Authors commented on the e-liquids from the perspective of potential toxicity from ingestion

Reference	E(N)NDS product	Solvent	Solvent-related contaminants or impurities	Nicotine and tobacco alkaloids	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
			m- + *p*-tolualdehyde: 0.069 µg/g (1 sample) Hexaldehyde: 0.036-0.532 µg/g (12 samples) Valeraldehyde and 2,5-dimethylbenzaldehyde < LOD					
Flora et al. (2016)	4x MarkTen brand E(N)NDS produced in 2014, 1.5% nicotine			Nicotine-N-oxides: 11-19 µg/g Cotinine: <LOQ-9.4 µg/g Nornicotine: 14-31 µg/g Myosmine: 7.4-13 µg/g Anatabine, anabasine, b-nicotyrine: <LOQ	NNK, < LOQ NNN, not detected		Arsenic, cadmium not detected	
Han et al. (2016)	55 E(N)NDS liquids from 17 brands purchased in China	Range: VG+PG, 80-97%, of which PG, 40-80% (except 1 sample < 5%) VG, 10-50%	Diethylene glycol – not detected 2.99% triethylene glycol detected in one sample formaldehyde: 0.31-17.22 µg/g acetaldehyde: 0.036-15.61 µg/g acetone: 0.080-1254.42 µg/g	0–36.10 mg/mL; range of variation from level stated on label, -0.67–+64.27% [3 samples labelled non-nicotine contained low levels of nicotine]	NNK: 5.56–6.88 ng/mL NAT: 0.93–3.80 ng/mL NAB: 0.51–2.27 ng/mL NNN: not detected	Menthol, 0.42-2.70%	<u>Phenols</u> p-dihydroxybenzene: 0.10 µg/g o-dihydroxybenzene: 0.39-0.45 µg/g phenol: 0.080-1.23 µg/g m(p)-cresol: 0.040-0.43 µg/g o-cresol: 0.070-4.31 µg/g	Major ingredients identified in some samples that were not included on label ingredients list were triethylene glycol and menthol Tobacco-derived compounds were present

Reference	E(N)NDS product	Solvent	Solvent-related contaminants or impurities	Nicotine and tobacco alkaloids	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
			propionic aldehyde: 0.12-7.73 µg/g butyraldehyde: 0.13-7.30 µg/g acrolein, crotonaldehyde, and 2-butanone: not detected	Minor alkaloids, 0–0.43 mg/mL solanesol: 0.060–49.26 µg/g			11/15 VOCs “Among the 15 VOCs analysed, 11 were detected in samples; the compounds not detected were 2-propenenitrile, chloroform, dicyclopenta-diene, and tetrahydrofuran. The concentration ranges of the 11 compounds were: 0.39~31.85 µg/g for m(p)-xylene (this name represents two positional isomers; we failed to separate m-xylene and p-xylene), 0.11~13.20 µg/g for benzene, 0.25~3.42 µg/g for 2,5-dimethylfuran, 0.10~16.09 µg/g for toluene, 0.13~17.31 µg/g for o-xylene,	with varying levels and detection frequencies

Reference	E(N)NDS product	Solvent	Solvent-related contaminants or impurities	Nicotine and tobacco alkaloids	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
							0.11~11.43 µg/g for ethylbenzene, 0.04~8.56 µg/g for styrene, 1.25~4.38 µg/g for benzaldehyde, 0.61~1.65 µg/g for 2-methylfuran, and 0.56 µg/g for 1,3-pentadiene." [Han et al., 2016] Very low levels (ng/g) of 16/34 PAHs evaluated	
Peace et al. (2016)	27 commercial e-liquids (6-22 mg/mL nicotine) manufactured in the US	17 within 10% of label-stated proportions; 4 > 10% difference from label; 6 not stated on label	No other glycols detected	Nicotine concentrations ranged from 45–131% of label-stated concentration; 18 samples had > 10% variance; 9 samples had > 20% variance		8 flavourants were identified (benzaldehyde, carvone, ethyl homovanillate, methyl anthranilate, methyl salicylate/vanillin and ethyl vanillin)		Nicotine concentrations often vary from those stated on the label of e-liquids

Reference	E(N)NDS product	Solvent	Solvent-related contaminants or impurities	Nicotine and tobacco alkaloids	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
Sleiman et al. (2016)	eGO CE4 (single coil); Kangertech Aerotank mini (dual coil) With Vision Spinner II battery, variable voltage 3.3-4.8 V 3 E(N)NDS liquids (18-24 mg/mL nicotine)	PG: range 441-531 mg/mL VG: range 414-470 mg/mL	Propylene oxide (suggested to be an impurity of PG): 4.2-6.7 mg/mL Acetol (hydroxyl-acetone) (suggested to be a PG decomposition product): 4.1-7.7 mg/mL Trace levels of formaldehyde, acetaldehyde, and acetone (3 E(N)NDS liquids); acrolein (1 E(N)NDS liquid)	Nicotine range: 20.4-32.1 mg/mL Nicotyrine detected		Vanillin, ketones and alcohols, terpenoids	Ethanol: 135-245 mg/mL (presumed to be a solvent for the flavourings)	Authors conclude that: Propylene oxide, a respiratory and eye irritant and possible carcinogen, is likely to be present in E(N)NDS liquids as an impurity of PG
Etter and Bugey (2017)	18 samples from 11 brands of E(N)NDS liquid, purchased from websites in US, UK, France, and Switzerland in 2013	14/17 samples tested contained PG; median content 650 mg/mL PG, 17/17 samples tested contained VG; median content 407 mg/mL	Ethylene glycol < LOD Diethylene glycol < LOD	Median nicotine content: 19.6 mg/mL Range, 15.5-52.0 mg/mL; -7.8% – +30% of label-stated values; 82% of samples within 10% of label-stated range Anabasine <LOD			median pH 9.1; range 8.1-9.9	Measurements were relatively similar when a duplicate batch of the same products, ordered 4 months later, was tested

Reference	E(N)NDS product	Solvent	Solvent-related contaminants or impurities	Nicotine and tobacco alkaloids	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
Peace et al. (2017)	3 E(N)NDS liquids 'Blueberry B juice', 'Regular B juice', Vampire B juice' purchased online (contents not labelled)	PG/VG ratios, 72:26; 52:48, 43:57				Ethyl isovalerate, ethyl 3-hydroxy-butanoate, linalool, amyl isobutyrate, folione, raspberry ketone and raspberry ketone PG; 5-hydroxymethyl furfural, ethyl phenyl acetate, and triethyl citrate; ethyl butanoate, ethyl maltol, isovanillin, hydrocinnamic acid, peach lactone	Apart from PG, VG and flavourants, the main ingredients identified were: MDMB-FUBINACA (a synthetic cannabinoid) (level not stated) ethanol (17.6–24.6%, w/v)	Unlabelled E(N)NDS liquids purchased from a website contained a synthetic cannabinoid as the main active ingredient

Reference	E(N)NDS product	Solvent	Solvent-related contaminants or impurities	Nicotine and tobacco alkaloids	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
Poklis et al. (2017)	56 E(N)NDS liquids purchased in the US via internet, either with no labelled ingredients, or variously labelled as containing one or more of: PG, VG, flavours, nicotine, vitamins, caffeine, melatonin, natural kratom extract, blue lotus, *Nepeta cataria*, Erythroxylum catuaba, Tumera diffusa, Lepidium meyens, Passiflora incarmata, Amapola Papaver, *Artemisia absinthium*						Ethanol was detected in 55 E(N)NDS liquids in the range 0.07–206 mg/mL Three samples (with no labelled ingredients) contained the cannobino-mimetic drug, MDMB-Fubinaca One E(N)NDS liquid ('Blue Lotus Flower Extract') contained the psychoactive alkaloids, apomorphine and nuciferine, which are found in the blue lotus flower (Measured concentrations of detected substances were only reported for ethanol)	

Table 2. Reported constituents of E(N)NDS aerosol/vapour.

Reference	E(N)NDS product	Solvent	Nicotine and tobacco alkaloids	Carbonyl compounds	Volatile organic compounds (VOC)	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
Trehy et al. (2011)	Simulated smoking with one brand of refill cartridge		Per 30 x 100 mL puffs: Nicotine: 50–292 µg anatabine: <LOQ (14 µg) Cotinine, myosmine, anabasine, b-nicotyrine: <LOD						
Pellegrino et al. (2012)	Aria, with and without nicotine	PG, 1650 mg/m^3 Glycerine, 600 mg/m^3 (approximate values)	6.21 mg/m^3 (for the E(N)NDS device labelled as containing nicotine)				(as listed in Table 1)	Maximum aerosol temperature, 43 ^{o}C	

Reference	E(N)NDS product	Solvent	Nicotine and tobacco alkaloids	Carbonyl compounds	Volatile organic compounds (VOC)	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
Uchiyama et al. (2013)	13 first-generation brands sold in Japan			Formaldehyde: 140 µg/10 puffs acetaldehyde: 120 µg/10 puffs acrolein: 33 µg/10 puffs propanal: 46 µg/10 puffs glyoxal: 23 µg/10 puffs methylglyoxal: 21 µg/10 puffs					High variability in levels measured, both within and between brands. Presence of glyoxal and methylgly-oxal noted as being specific to E(N)NDS aerosol
Czogala et al. (2014)	3 brands from Poland (1x cartomizer, 2x pen/ cartridge) with nicotine; sampling 1-h steady state emissions in a 39m^3 exposure chamber		Mean 1-h nicotine concentration : 2.51 µg/m^3 (0.82–6.23)		Toluene detected in chamber at same level before and after E(N)NDS use No other VOCs detected			Change in CO concentra-tion not detected	

Reference	E(N)NDS product	Solvent	Nicotine and tobacco alkaloids	Carbonyl compounds	Volatile organic compounds (VOC)	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
Goniewicz et al. (2014)	12 brands (11 from Poland, 1 from UK) with 16-18 mg/mL nicotine (first generation?)			Formaldehyde: 2.0-56.1 µg/150 puffs; acetaldehyde: 1.1-13.6 µg/150 puffs; acrolein: 0.7-41.9 µg/150 puffs	toluene: 0.2–6.3 µg/150 puffs m,p-xylene: 0.1–0.2 µg/150 puffs	NNN: 0.8–4.3 ng/150 puffs NNK: 1.1–28.3 ng/150 puffs		Cadmium: 0.01–0.22 µg/150 puffs Nickel: 0.11–0.29 µg/150 puffs Lead: 0.03-0.57 µg/150 puffs	4/15 carbonyl compounds detected in most E(N)NDS 2/11 VOCs detected in most E(N)NDS 2/2 TSNAs identified in 9/12 E(N)NDS m,p-xylene and metals also detected in nicotine inhaler and blank samples
Hutzler et al. (2014)	First-generation E(N)NDS device			Formaldehyde: 200 µg/150 puffs acetaldehyde: 300 µg/150 puffs acrolein: 100 µg/150 puffs propionaldehyde: 30 µg/150 puffs					Presence of aldehydes initially low and increased during use until the liquid reservoir was empty
Kosmider et al. (2014)	eGO-3, clearomizer, with variable voltage (3.2-			10 commercial E(N)NDS liquids Formaldehyde: 49–59 ng/15 puffs (4 samples)					Formalde-hyde, acet-aldehyde, acetone,

<table>
<tr><th>Reference</th><th>E(N)NDS product</th><th>Solvent</th><th>Nicotine and tobacco alkaloids</th><th>Carbonyl compounds</th><th>Volatile organic compounds (VOC)</th><th>Tobacco-specific nitrosamines (TSNA)</th><th>Flavourants</th><th>Others</th><th>Author comments</th></tr>
<tr><td></td><td>4.8 V) (second generation)

10 E(N)NDS liquids with nicotine (18-24 mg/mL) and flavour;

PG/ 1.8% nicotine/ water (no flavour)

1:1 PG/VG / 1.8%nicotine/ water (no flavour)

VG/ 1.8% nicotine/ water (no flavour)</td><td></td><td></td><td>acetaldehyde: 20–107 ng/15 puffs (8 samples)

acetone: 59–296 ng/15 puffs (8 samples)

butanal: 15–185 ng/15 puffs (8 samples)

benzaldehyde: 21–46 ng/15 puffs (3 samples)

crotonaldehyde: 53 ng/15 puffs (1 sample)

isovaleric aldehyde: 33–47 ng/15 puffs (3 samples)

m-methybenzaldehyde: 39–94 ng/15 puffs (5 samples)

<u>3 E(N)NDS liquids without flavour</u>
(ng/15 puffs)<table><tr><td></td><td></td><td>3.2V</td><td>4.8V</td></tr><tr><td>Form-alde-hyde</td><td>VG</td><td>0.02</td><td>0.15</td></tr><tr><td></td><td>VG/ PG</td><td>0.13</td><td>27.0</td></tr><tr><td></td><td>PG</td><td>0.53</td><td>17.6</td></tr><tr><td>Acet-alde-hyde</td><td>VG</td><td>0.17</td><td>1.24</td></tr><tr><td></td><td>VG/</td><td>0.43</td><td>1.73</td></tr></table></td><td></td><td></td><td></td><td></td><td>butanal detected in most samples; Crotonalde-hyde detected in 1 sample; acrolein not detected

Increased battery voltage resulted in increased levels of carbonyls in aerosol</td></tr>
</table>

Reference	E(N)NDS product	Solvent	Nicotine and tobacco alkaloids	Carbonyl compounds	Volatile organic compounds (VOC)	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
				<table><tr><td></td><td>PG</td><td></td><td></td></tr><tr><td></td><td>PG</td><td>0.41</td><td>4.23</td></tr><tr><td>Ace-tone</td><td>VG</td><td>0.34</td><td>1.43</td></tr><tr><td></td><td>VG/ PG</td><td>0.73</td><td>7.59</td></tr><tr><td></td><td>PG</td><td>1.68</td><td>3.94</td></tr></table>					
Tayyarah and Long (2014)	3x blu eCigs (disposable), 2x SKYCIG (rechargeable), 18-24 mg/mL nicotine			Total carbonyls <1 µg/puff Formaldehyde, acetaldehyde, propionaldehyde, crotonaldehyde, MEK, butyraldehyde: <LOQ values Acrolein: 0.19 µg/puff (1 product) propionaldehyde: 0.11 µg/puff (1 product)	< 0.08 µg/puff (<LOQ)	Mostly <LOD NAT: 0.20 ng/puff (1 sample)		PAA < 0.00014 µg/puff (<LOD) PAH: (<0.0016 µg/puff)	Levels of HPHCs in E(N)NDS aerosol were much lower than in CC smoke
Farsalinos et al. (2015a)	eGO + tank atomizer 3 tobacco-flavour E(N)NDS liquids purchased in Greece, 18 mg/mL nicotine	E(N)NDS liquid consumption 336–515 mg/100 puffs				NNN, NAT, NAB, NNK: <LOD			Low levels of TSNAs in E(N)NDS liquids were not observed in aerosol

Reference	E(N)NDS product	Solvent	Nicotine and tobacco alkaloids	Carbonyl compounds	Volatile organic compounds (VOC)	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
Geiss et al. (2015)	2x second generation E(N)NDS (1 atomiser; 1 cartomiser) 2 E(N)NDS liquids, each with 0, 9, and 18 mg/mL nicotine, various flavours: 1 PG/VG 1 VG only	Estimated lung concentration from 1 puff: 160 (PG) and 220 (VG) mg/m^3 for PG/VG E(N)NDS liquid; 460 mg/m^3 for VG-only E(N)NDS liquid	18 mg/mL E(N)NDS liquid estimated to produce approx 0.5 mg nicotine in aerosol of 1 CC equivalent	VG-only E(N)NDS liquid produced higher levels of carbonyls (specifically acrolein and acetaldehyde) than PG/VG E(N)NDS liquid. For 9 mg/mL nicotine E(N)NDS liquids, Formaldehyde: 19.6–23.5 ng/puff Acetaldehyde: 8.1–39.9 ng/puff Acetone: 2.7–8.8 ng/puff Acrolein: 0.5–13.5 ng/puff Propanal: 0.9–4.9 ng/puff					Results for nicotine were inconsistent, perhaps due to difficulties in consistency of aerosol production from the E(N)NDS devices
Herrington and Myers (2015)	4x E(N)NDS (first generation) PG/VG E(N)NDS liquids with 12-18 mg/mL nicotine			Acrolein: 0.12–0.6 µg/puff (levels of formaldehyde and acetaldehyde not reported)					Formalde-hyde, acet-aldehyde, acrolein and siloxanes were identified in aerosols but not E(N)NDS liquid Acrolein concentra-tion considered to be in same range as in CC smoke

Reference	E(N)NDS product	Solvent	Nicotine and tobacco alkaloids	Carbonyl compounds	Volatile organic compounds (VOC)	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
Jensen et al. (2015)	Tank system, commercial E(N)NDS liquid with nicotine, variable voltage (5-11 mg E(N)NDS liquid consumed produced 2-6 mg collected)			Formaldehyde (as formaldehyde-releasing agents): 3.3 V: not detected 5.0 V: 380 ng/10 puffs			Several common flavouring chemicals were identified		Authors calculated a daily intake at high voltage of 14.4±3.3 mg formalde-hyde from 3 ml E(N)NDS liquid, which is equivalent to the intake from 1 pack of 20 CC

Reference	E(N)NDS product	Solvent	Nicotine and tobacco alkaloids	Carbonyl compounds	Volatile organic compounds (VOC)	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
Laugesen (2015)	14 brands imported to New Zealand, purchased in 2013, with labelled nicotine concentra-tions ranging from 16–18.6 mg/mL (except 1 sample labelled as zero-nicotine, 1 as 11 mg/mL and 1 as 14.5 mg/mL). Including cigalikes, disposables, and cartomisers, but not mods.		Mean nicotine per 70 mL puff for samples labelled >14 mg/mL nicotine: 43 µg/puff (range 18–93 µg/puff)	Aldehydes (per litre of aerosol): Formaldehyde: mean 1.07 µg/L (range 0.48–2.50 µg/L) Acetaldehyde: mean 0.81 µg/L (range 0.58–1.52 µg/L) Acrolein: mean 1.06 µg/L (range 0.13–3.58 µg/L)					
Flora et al. (2016)	4x MarkTen brand E(N)NDS produced in 2014, 1.5% nicotine		29 µg/puff	Formaldehyde: 0.090-0.33 µg/puff Acetaldehyde: < LOQ (0.71 µg/puff) Acrolein, crotonaldehyde: not detected	Acrylonitrile, benzene, 1,3-butadiene, isoprene, toluene: not detected	NNK, NNN: <LOQ (40 ng/device)		Ammonia: <LOQ (10 µg/device) Aromatic amines, Benz[*a*]pyrene, CO: not detected	

Reference	E(N)NDS product	Solvent	Nicotine and tobacco alkaloids	Carbonyl compounds	Volatile organic compounds (VOC)	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
Margham et al. (2016)	Vype ePen (closed modular system with cartomizer, operated at 3.6 V) 'Blended Tobacco' E(N)NDS liquid (25%PG, 48%VG, 25% water, 1.86% nicotine, tobacco flavour)	PG: 0.709 mg/puff VG: 1.579 mg/puff	Nicotine: 0.032 mg/puff Myosmine: 27.37 ng/puff Cotinine: 10.84 ng/puff	Formaldehyde: 0.122 µg/puff Acetaldehyde: 0.106 µg/puff Acrolein: 0.070 µg/puff Glyoxal: 0.056 µg/puff Methylglyoxal: 0.046 µg/puff		NNN: 0.054 ng/puff (NNK, NAT, NDMA: <LOQ; NAB: <LOD)		Allyl alcohol: 5.365 ng/puff Chrysene (PAH): 0.011 ng/puff Ni: <LOQ Cr: 0.399 ng/puff (around LOQ)	Of 150 compounds evaluated; 104 <LOD; 9 <LOQ; 21 equivalent to laboratory background; 16 generated from E(N)NDS device

<table>
<tr><th>Reference</th><th>E(N)NDS product</th><th>Solvent</th><th>Nicotine and tobacco alkaloids</th><th>Carbonyl compounds</th><th>Volatile organic compounds (VOC)</th><th>Tobacco-specific nitrosamines (TSNA)</th><th>Flavourants</th><th>Others</th><th>Author comments</th></tr>
<tr>
<td>Sleiman et al. (2016)</td>
<td>eGO CE4 (single coil); Kangertech AEROTANK mini (dual coil)

With Vision Spinner II battery, variable voltage 3.3-4.8 V

3 E(N)NDS liquids (18-24 mg/mL nicotine</td>
<td>Liquid consumed: 3.7 mg/puff (3.3 V), 7.5 mg/puff (4.8 V)</td>
<td>Nicotyrine mean: 3.1 µg/puff (EGO, 3.8 V)</td>
<td>Mean emissions (EGO) (µg/puff) with one selected E(N)NDS liquid

<table>
<tr><td>Voltage (V) →</td><td>3.3</td><td>3.8</td><td>4.3</td><td>4.8</td></tr>
<tr><td>Emission (µg/puff) ↓</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Formaldehyde</td><td>53</td><td>45.7</td><td>35.0</td><td>97</td></tr>
<tr><td>Acetaldehyde</td><td>10</td><td>9.2</td><td>31.8</td><td>50</td></tr>
<tr><td>Acrolein</td><td>3</td><td>8.5</td><td>15.8</td><td>21.5</td></tr>
<tr><td>Glycidol</td><td></td><td>2.1</td><td></td><td></td></tr>
<tr><td>Acetol</td><td></td><td>7.6</td><td></td><td></td></tr>
<tr><td>Diacetyl</td><td></td><td>2.2</td><td></td><td></td></tr>
</table>
</td>
<td></td><td></td><td></td><td></td>
<td>Higher temperature and emissions from single-coil device

Substantial increase in aldehyde production at higher voltages

Increased aldehyde production with device aging</td>
</tr>
</table>

Reference	E(N)NDS product	Solvent	Nicotine and tobacco alkaloids	Carbonyl compounds	Volatile organic compounds (VOC)	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
Talih et al. (2016)	NHALER 510 Atomizer with ego-T battery (3.4 V) PG-based E(N)NDS liquid, with flavour and 0 or 18 mg/mL nicotine E(N)NDS use by "direct dripping" of E(N)NDS liquid (dripping every 2, 3, or 4 puffs)	49% of the E(N)NDS liquid evaporated was collected on the filter pad	Range of mean nicotine levels measured with 2, 3, or 4 puff inter-drip interval: 0.74–1.03 mg/15 puffs	Range of mean levels measured with 2, 3, or 4 puff inter-drip interval: Total aldehydes: 399–1873 µg/15 puffs Formaldehyde: 20-88 µg/15 puffs Acetaldehyde: 270-1172 µg/15 puffs propionaldehyde: 52-315 µg/15 puffs valeraldehyde: 29-92 µg/15 puffs Acrolein, methacrolein, and butyraldehyde: < LOQ Crotonaldehyde: < LOD					Maximum coil temperature was 340 °C during puff 4 Authors concluded that volatile aldehyde emission from E(N)NDS use can vary from negligible to levels similar to those emitted in CC smoke, depending on operating characteris-tics.
Uchiyama et al. (2016)	10 brands of second generation E(N)NDS sold in Japan E(N)NDS liquids with or without nicotine	PG VG esters		Compounds identified (numbers in brackets indicate the highest mean value for an individual brand, with measurement performed at 30 puffs). The highest mean total carbonyl compound production was 350 µg/10 puffs, from brand D. As gas and particulate matter formaldehyde (120 µg/10 puffs, brand D)					A detailed summary of the amounts of individual carbonyl compounds produced by each of the 10 E(N)NDS/E(N)NDS liquids is given in Table 2 of the

Reference	E(N)NDS product	Solvent	Nicotine and tobacco alkaloids	Carbonyl compounds	Volatile organic compounds (VOC)	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
				<u>Mainly as gas</u> acetaldehyde (73 µg/10 puffs, brand D) acetone (15 µg/10 puffs, brand E) acrolein (24 µg/10 puffs, brand D) propanal (20 µg/10 puffs, brand E) acetol (7.3 µg/10 puffs, brand D) <u>Mainly as particulate matter</u> glyoxal (43 µg/10 puffs D) methyl glyoxal (58 µg/10 puffs) In tests with one brand (E), the production of carbonyls was very low until a critical puff-number (around 10-15 puffs, depending on other variables) was passed – however, there was still adequate E(N)NDS liquid present in the reservoir at this point Production of carbonyls increased with applied voltage (from 3.2 to 4.8 V) in tests with one brand (D).					publication. A very high inter- and intra-brand variability was noted. Authors suggested that a 'hotspot' may develop in the E(N)NDS device during use, at which point carbonyl production rapidly increases

Reference	E(N)NDS product	Solvent	Nicotine and tobacco alkaloids	Carbonyl compounds	Volatile organic compounds (VOC)	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
Farsalinos et al. (2017)	CE4 top coil atomizer, Innokin iTaste VV V3.0 variable voltage battery device and Halo Caf e Mocha liquid with 6 mg/mL nicotine concentration (intended to replicate the test materials used by Jensen et al., 2015)	Liquid consumption: 3.3 V: 3.0 mg/puff 5.0 V: 8.0 mg/puff		<u>Formaldehyde (µg/10 puffs)</u> 3.3V: 3.4 µg/10 puffs 4.0 V: 19.8 µg/10 puffs 5.0 V: 718 µg/10 puffs					Experienced E(N)NDS users recognised the occurrence of 'dry puffs' at E(N)NDS use ≥ 4.0 V
Lee et al. (2017)	V2 'cigalike' cartomizer devices; 1.8% nicotine; tobacco flavour or menthol flavour; collected in a dilution chamber (1:172 dilution)		Mean and median concentra-tions of nicotine in the range of 1–3.5 µg/m^3	Low levels of acetaldehyde or acetone detected; others <LOD	Low levels of ethanol, acetonitrile, isopropyl alcohol, benzene, toluene detected; 13 other VOCs <LOD				

Reference	E(N)NDS product	Solvent	Nicotine and tobacco alkaloids	Carbonyl compounds	Volatile organic compounds (VOC)	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
Ogunwale et al. (2017)	first generation blu e-cigarette + 4 cartridges (16 mg/mL nicotine) purchased online; Newer-generation EVOD2/KangerTech + iTasteVV V3.0 battery + 3 E(N)NDS liquids (6 mg/mL) purchased in-store			<u>First-generation device (4.6 W power output)</u> Formaldehyde: 0.18–0.62 µg/10 puffs acetaldehyde: 0.15–0.57 µg/10 puffs acrolein: 0.02–0.24 µg/10 puffs acetone: 1.29–6.21 µg/10 puffs <u>Newer-generation device (9.1 W power output)</u> Formaldehyde: 8.2–40.04 µg/10 puffs acetaldehyde: 13.3–63.1 µg/10 puffs acrolein: 1.6–5.8 µg/10 puffs acetone: 1.3–12.5 µg/10 puffs - In tests of 1 E(N)NDS liquid, emissions of aldehydes from one increased with increasing power output <u>Maximum aldehyde emissions at 16.6 W</u> Formaldehyde: 820 µg/10 puffs acetaldehyde: 532 µg/10 puffs acrolein: 16 µg/10 puffs acetone: 809 µg/10 puffs propionaldehyde: 18 µg/10 puffs butyraldehyde: 14 µg/10 puffs Formaldehyde hemiacetals were detected at higher power outputs from the newer-generation device					Used a new method to measure free aldehydes + aldehyde hemiacetals

Reference	E(N)NDS product	Solvent	Nicotine and tobacco alkaloids	Carbonyl compounds	Volatile organic compounds (VOC)	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
Salamanca et al. (2017)	KangerTech Pro Tank II 'glassomizer', 10 W and 15 W battery settings E(N)NDS liquid 1:1 PG/VG			Product yield per mg E(N)NDS liquid: Gaseous formaldehyde 1.20 µg (10 W) 4.43 µg (15 W) Hemiacetal isomers of PG and VG (1a-d) in aerosol 16.75 µg (10W) 65.70 µg (15 W)					Authors conclude that analyses of E(N)NDS product based on standard methods (DNPH cartridges or impinges) substantially underesti-mates the presence of formalde-hyde due to the inability of these methods to collect hemiacetal intermedi-ates in the particulate phase.

Reference	E(N)NDS product	Solvent	Nicotine and tobacco alkaloids	Carbonyl compounds	Volatile organic compounds (VOC)	Tobacco-specific nitrosamines (TSNA)	Flavourants	Others	Author comments
Farsalinos et al. (2018)	CE4v2 atomizers with eGo-type variable battery, at 3.8 V and 4.8 V; Nautilus Mini atomizer with EVIC VTC Mini variable-wattage battery device, at 9.0 W and 13.5 W Apollo Classic Tobacco liquid (50:50 PG/VG ; 18 mg/mL nicotine) or an equivalent liquid without flavouring (the latter for Nautilus Mini only)	CE4v2 used 5.2 and 7.0 mg E(N)NDS liquid per puff, at 3.8 and 4.8 V, respectively; Nautilus Mini used 8.0 and 16.6 mg flavoured E(N)NDS liquid per puff at 9 and 13.5 W, respectively Nautilus Mini used 8.5 and 21.0 mg unflavoured E(N)NDS liquid per puff at 9 and 13.5 W, respectively		Mean aldehyde emissions (µg/g E(N)NDS liquid) <u>CE4v2, 3.8 and 4.8 V</u> Formaldehyde: 797 and 4260 µg/g Acetaldehyde: 321 and 2156 µg/g Acrolein: 69 and 624 µg/g <u>Nautilus mini, 9.0 and 13.5 W (flavoured liquid)</u>; Formaldehyde: 16.7 and 16.5 µg/g Acetaldehyde: 9.6 and 10.3 µg/g Acrolein: 8.6 and 11.7 µg/g <u>Nautilus mini, 9.0 and 13.5 W (unflavoured liquid)</u>; Formaldehyde: 13.5 and 9.9 µg/g Acetaldehyde: 3.2 and 1.8 µg/g Acrolein: 4.1 and 1.8 µg/g					CE4v2 generated dry puffs at 3.8 V and 4.8 V; Nautilus Mini did not generate dry puffs

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