

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

Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes). Follow up to Paper 13: Tabulation of user exposure data.

Background

1. The COT is reviewing the potential toxicity of electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS) (collectively abbreviated to E(N)NDS). As part of this review, a discussion paper summarising data on estimated levels of some constituents to which users of E(N)NDS may be exposed was discussed at the July 2019 COT meeting ([TOX/2019/39](#)). During this discussion, Members requested for the user exposure data to be tabulated. This current paper presents two tables which summarise lowest and highest reported ranges in E(N)NDS aerosols for the main constituents, nicotine, propylene glycol (PG) and glycerol, and for the degradation products, formaldehyde, acetaldehyde and acrolein.

Introduction

2. In [TOX/2019/39](#), levels of constituents measured in E(N)NDS aerosols were tabulated per study and per individual chemical, based on data from studies that had been reviewed in previous COT discussion papers on this topic ([TOX/2017/49](#), [TOX/2018/15](#), [TOX/2018/16](#)). The full, tabulated data set over all studies can be viewed in Tables 2–6 of [TOX/2019/39](#). The evidence base for this current paper was limited to studies that had been reported in the previous COT papers on this topic, and which were collated in [TOX/2019/39](#). Additional data from more recent publications was not sought.

3. Given the wide range of study protocols and methods of data analysis and reporting, it was not possible to integrate or combine data from the different studies. For example, studies have variously reported data from the evaluation of one or several different E(N)NDS products (devices and/or e-liquid formulations). Results have been reported in different ways, such as individual data points; average or range of results for a product type (testing one or more different product samples – e.g. different cartridges); average or range of averages over a range of different product types; and results ranging over different test conditions. The scope of this current paper is thus limited to a summary of data on:

- Lowest levels of each chemical reported in E(N)NDS aerosols (Table 1)

- Average and/or range of values (if available) from the relevant study reporting the highest average level of each individual chemical (Table 2).

4. In each case, a brief explanation of the study methodology is given for context. As most studies have reported concentrations as mg/puff, calculations are also provided to show the estimated equivalent concentration of the chemical in the aerosol *per se* (mg/m³) as an indicator of the magnitude of local exposure concentration in the respiratory tract. The conversion from mg/puff to mg/m³ is calculated based on reported mass measured per puff (or group of puffs) and the puff volume specified in the study methodology. Calculations of overall daily exposure (mg/kg bw/day), based on the assumption of an average E(N)NDS user taking 272–338 puffs per day (see [TOX/2019/39](#)), are also provided for nicotine.

Tables of data

Table 1. Lowest reported levels.

Chemical	Study	Basis of value reported	Lowest reported level [equivalent concentration in aerosol calculated for this report]
Nicotine	Baassiri et al. (2017) 67 mL puff; Second-generation tank system used with PG/glycerol mixtures at ratios ranging from 0/100 to 100/0, and containing 18 mg/mL nicotine	15-puff collection. Mean value from measurements made using 0:100 PG:glycerol base. (The amount of nicotine delivered gradually increased with increasing % PG in the mixture, to a maximum mean value of 0.387 mg/puff with 100:0 PG:glycerol)	0.0087 mg/puff [129 mg/m ³] For a 70 kg user taking 272 puffs/day, average daily exposure would be: 0.034 mg/kg bw/day For a 70 kg user taking 338 puffs/day, average daily exposure would be: 0.042 mg/kg bw/day
PG	Pellegrino et al. (2012) 2 x Italian-brand E(N)NDS (liquids contained 66% PG; > 24% glycerol; 0 or 0.25% nicotine	Aerosol collected from 16 aspirations of each E(N)NDS product. Results reported as concentration of analyte in aerosol.	1650–1660 mg/m ³
Glycerol	Pellegrino et al. (2012) 2 x Italian-brand E(N)NDS (liquids contained 66% PG; > 24% glycerol; 0 or 0.25% nicotine	Aerosol collected from 16 aspirations of each E(N)NDS product. Results reported as concentration of analyte in aerosol.	580–610 mg/m ³
Formaldehyde	Kosmider et al. (2014) eGo-3 clearomizer device (2.4 Ω heating element; 900 mAh battery, 3.4 V) 10 commercial e-liquids with carrier of either PG only, PG/glycerol, or glycerol only; 18-24 mg/mL nicotine; and flavourings 70 mL puff	Mean of 3 replicate 15-puff fractions, results reported for each individual e-liquid	Not detected (2 of 10 e-liquids)

Chemical	Study	Basis of value reported	Lowest reported level [equivalent concentration in aerosol calculated for this report]
Acetaldehyde	<p>Kosmider et al. (2014)</p> <p>eGo-3 clearomizer device (2.4 Ω heating element; 900 mAh battery, 3.4 V)</p> <p>10 commercial e-liquids with carrier of either PG only, PG/glycerol, or glycerol only; 18–24 mg/mL nicotine; and flavourings</p> <p>70 mL puff</p>	Mean of 3 replicate 15-puff fractions, results reported for each individual e-liquid	Not detected (2 of 10 e-liquids)
Acrolein	<p>Kosmider et al. (2014)</p> <p>eGo-3 clearomizer device (2.4 Ω heating element; 900 mAh battery, 3.4 V)</p> <p>10 commercial e-liquids with carrier of either PG only, PG/glycerol, or glycerol only; 18–24 mg/mL nicotine; and flavourings</p> <p>70 mL puff</p>	Mean of 3 replicate 15-puff fractions, results reported for each individual e-liquid	Not detected (9 of 10 e-liquids)

Table 2. Average and/or range in studies reporting highest values for each chemical.

Chemical	Study reporting highest average level of chemical in aerosol	Study - average level for chemical [conversion to equivalent concentration in aerosol for this report] - basis of value reported	Study - range of levels for chemical [conversion to equivalent concentration in aerosol for this report] - basis of value reported	Summary of average (range) of calculated concentration in aerosol (mg/m ³)
Nicotine	Laugesen (2015) 70 cm ³ puff; 11 different ENDS brand products (7 cigalikes, 2 refillable clearomisers (RC), 1 cartomiser rechargeable from bottle (CB), 1 disposable); 14.5–23 mg/mL nicotine (label), 11.5–27.4 mg/mL nicotine (measured); 60-puff collection	0.043 mg/puff [614 mg/m ³] - mean level measured over the 11 products	0.018 mg/puff [257 mg/m ³] (CB product with measured nicotine content of 16.3 mg/mL) to 0.093 mg/puff [1329 mg/m ³] (RC product with measured nicotine content of 15.2 mg/mL) - individual measurements from 2 different products	614 (257–1329) For a 70 kg user taking 272 puffs/day, average (range) daily exposure would be: 0.167 (0.07-0.361) mg/kg bw/day For a 70 kg user taking 338 puffs/day, average (range) daily exposure would be: 0.208 (0.087-0.449) mg/kg bw/day
Propylene glycol (Option 1 - study reporting highest mass per puff)	Margham et al. (2016) 55 cm ³ puff; E-pen with disposable cartomizer; 'blended tobacco' flavour e-liquid containing 25% PG, 48.14% glycerol, 25% water, 1.86% nicotine, <1% flavourings	0.709 mg/puff [12,890 mg/m ³] - mean of 5 replicates from 1 test product	0.667 mg/puff [12,127 mg/m ³] (puffs 1–100 of product collected) to 0.751 mg/puff [13,655 mg/m ³] (puffs 101–200 of product collected) - mean level of replicates from 1 st and 2 nd 100-puff collections	12,890 (12,127–13,655)

Chemical	Study reporting highest average level of chemical in aerosol	Study - average level for chemical [conversion to equivalent concentration in aerosol for this report] - basis of value reported	Study - range of levels for chemical [conversion to equivalent concentration in aerosol for this report] - basis of value reported	Summary of average (range) of calculated concentration in aerosol (mg/m ³)
Propylene glycol (Option 2 – study leading to highest calculated concentration in aerosol)	Kienhuis et al. (2015) 35 cm ³ puff; 4 x disposable shisha pens (2 strawberry, 1 apple, 1 grape flavour); e-liquids contained 54%/46% PG/glycerol; < 1% flavours and other trace components; no nicotine	0.7 mg/puff [20,000 mg/m ³] - Analysis of collection from sample of 4–10 puffs (depending on flavour). Result described in the narrative text as an overall value for 'average' mg/puff.	No additional data reported.	20,000
Glycerol	Margham et al. (2016) 55 cm ³ puff; E-pen with disposable cartomizer; 'blended tobacco' flavour e-liquid containing 25% PG, 48.14% glycerol, 25% water, 1.86% nicotine, <1% flavourings	1.579 mg/puff [28,709 mg/m ³] - mean of 5 replicates from 1 test product	1.53 mg/puff [27,818 mg/m ³] (puffs 1–100 of product collected) to 1.63 mg/puff [29,636 mg/m ³] (puffs 101–200 of product collected) - mean level of 5 replicates from 1 st and 2 nd 100-puff collections	28,709 (27,818–29,636)

Chemical	Study reporting highest average level of chemical in aerosol	Study - average level for chemical [conversion to equivalent concentration in aerosol for this report] - basis of value reported	Study - range of levels for chemical [conversion to equivalent concentration in aerosol for this report] - basis of value reported	Summary of average (range) of calculated concentration in aerosol (mg/m ³)
Formaldehyde	Sleiman et al. (2016) 50 cm ³ puff; eGO CE4 (single coil); Kangertech AEROTANK mini (dual coil) with Vision spinner II batter, variable voltage, 3.3-4.8 V; liquid containing 50/50 PG/glycerol, 18 mg/mL nicotine, classic tobacco flavour	0.053 mg/puff at 3.3 V, 0.0457 mg/puff at 3.8 V, 0.035 mg/puff at 4.3 V, 0.097 mg/puff [1940 mg/m ³] at 4.8 V - mean of duplicate sampling measurements made at each voltage (1–5 puffs collected per sample) Note. The cells to the right in this row use the 4.8V data as a higher end estimate	0.093 mg/puff [1860 mg/m ³] to 0.101 mg/puff [2020 mg/m ³] - individual, duplicate measurements made at 4.8 V (1–5 puffs collected per sample)	1940 (1860–2020)
Acetaldehyde	Sleiman et al. (2016) 50 cm ³ puff; eGO CE4 (single coil); Kangertech AEROTANK mini (dual coil) with Vision spinner II batter, variable voltage, 3.3-4.8 V; liquid containing 50/50 PG/glycerol, 18 mg/mL nicotine, classic tobacco flavour	0.010 mg/puff at 3.3 V 0.0092 mg/puff at 3.8 V 0.0318 mg/puff at 4.3 V 0.050 mg/puff [1000 mg/m ³] at 4.8 V - mean of duplicate sampling measurements made at each voltage (1–5 puffs collected per sample) Note. The cells to the right in this row use the 4.8V data as a higher end estimate	0.048 mg/puff [872 mg/m ³] to 0.052 mg/puff [1040 mg/m ³] - individual, duplicate measurements made at 4.8 V (1–5 puffs collected per sample)	1000 (872–1040)

Chemical	Study reporting highest average level of chemical in aerosol	Study - average level for chemical [conversion to equivalent concentration in aerosol for this report] - basis of value reported	Study - range of levels for chemical [conversion to equivalent concentration in aerosol for this report] - basis of value reported	Summary of average (range) of calculated concentration in aerosol (mg/m ³)
Acrolein	Sleiman et al. (2016) 50 cm ³ puff; eGO CE4 (single coil); Kangertech AEROTANK mini (dual coil) with Vision spinner II batter, variable voltage, 3.3-4.8 V; liquid containing 50/50 PG/glycerol, 18 mg/mL nicotine, classic tobacco flavour	0.003 mg/puff at 3.3 V 0.0085 mg/puff at 3.8 V 0.0158 mg/puff at 4.3 V 0.0215 [420 mg/m ³] at 4.8 V - mean of duplicate sampling measurements made at each voltage (1–5 puffs collected per sample) Note. The cells to the right in this row use the 4.8V data as a higher end estimate	0.020 mg/puff [391 mg/m ³] to 0.023 mg/puff [449 mg/m ³] - individual, duplicate measurements made at 4.8 V (1–5 puffs collected per sample)	420 (391–449)

Risk assessments

5. In the following paragraphs, data on established guideline values are taken from [TOX/2019/39](#), where more detailed descriptions can be found.

Nicotine

6. A risk assessment for nicotine is not included here as this will be presented in the accompanying paper, TOX/2019/59.

Propylene glycol

7. The following guideline values have been reported for inhalation exposure to PG:

- From discussions at the July 2018 COT meeting ([TOX/2018/23](#)), the Committee established an HBGV for continuous exposure to PG of 2.9 mg/m³, based on nasal haemorrhaging in rats.
- UK workplace exposure limits (WELs) for long-term exposure to PG (8 h time-weighted average (TWA)) are 150 ppm, or 474 mg/m³, for total vapour + particulates, and 10 mg/m³ for particulates alone (HSE 2011). No short term WELs are available.
- The Dutch Expert Committee on Occupational Standards 8-h TWA (vapour + aerosol) for PG is 50 mg/m³, based on increased numbers of goblet cells in rats, with a recommendation that health-based occupational exposure limits for inhalable and respirable dust should be applied to aerosols of PG (HCN 2007).
- The German Committee on Indoor Guide Values health precaution guide value (RW I, guideline value I) for PG is 0.06 mg/m³, calculated from a health hazard guide value (RW II, guideline value II) of 0.6 mg/m³, based on nasal haemorrhage in rats (Umweltbundesamtes 2017).
- The ATSDR intermediate-duration minimum risk level (MRL) ¹ for PG is 0.009 ppm [0.028 mg/m³], based on nasal haemorrhaging in rats (ATSDR 1997).

8. The upper range of exposure concentrations for PG in E(N)NDS aerosols, as summarised in Table 2 (12,890–20,000 mg/m³), exceeds the COT HBGV by approximately 5000-fold, the UK 8-h TWA by approximately 30-fold, the Dutch

¹ ATSDR MRLs: acute-duration (≤ 14 days), intermediate-duration (15–365 days), chronic-duration (≥ 365 days)

Expert Committee 8-h TWA by approximately 300-fold, the German RW I value by approximately 300,000-fold, and the ATSDR intermediate-duration MRL by approximately 600,000-fold. However, it is difficult to make direct comparisons, given that exposure to E(N)NDS aerosols by users would be expected to occur as a limited number of puffs of a few seconds duration throughout the day.

Glycerol

9. The following guideline values have been reported for inhalation exposure to glycerol:

- From discussions at the July 2018 COT meeting ([TOX/2018/23](#)), the Committee established an HBGV for continuous exposure to glycerol of 11.8 mg/m³, based on lack of adverse effects in a rat study.
- The UK workplace long-term WEL for glycerol (glycerin) mist is 10 mg/m³ TWA (HSE 2011). No short term WELs are available.
- DFG in Germany set a maximum workplace concentration (MAK value) of 200 mg/m³ based on a lack of adverse effects in a rat study (Hartwig 2017).

10. The upper range of exposure concentrations for glycerol in E(N)NDS aerosols, as summarised in Table 2 (27,818–29,636 mg/m³), exceeds the COT HBGV by approximately 2500-fold, the UK WEL by approximately 3000-fold, and the DFG MAK by approximately 150-fold. However, it is difficult to make direct comparisons, given that exposure to E(N)NDS aerosols by users would be expected to occur as a limited number of puffs of a few seconds duration throughout the day.

Formaldehyde

11. The following guideline values have been reported for inhalation exposure to formaldehyde.

- WELs. UK WEL of 2.5 mg/m³ for long-term (8 h TWA) and short-term (15 min STEL) exposure (HSE 2018). European Commission Scientific Committee on Occupational Exposure Limits (SCOEL) Limit Value of 0.3 ppm [0.37 mg/m³] (8 h TWA) with a STEL of 0.6 ppm [0.74 mg/m³] (SCOEL 2016). WELs reported for 16 individual EU countries, as summarised by SCOEL (2016), were in the range of 0.15–2.5 mg/m³ (8 h TWA) and 0.37–2.5 mg/m³ (15 min STEL).
- WHO short-term (30 min average concentration) guideline for formaldehyde in indoor air of 0.1 mg/m³, based on sensory irritation in the general population. WHO considered that the short-term (30 min) guideline of 0.1 mg/m³ would also prevent long-term health effects, including cancer (WHO 2010).

- ATSDR. Acute inhalation MRL of 0.04 ppm [0.05 mg/m³], based on nasal and eye irritation in humans. Intermediate-duration inhalation MRL of 0.03 ppm [0.037 mg/m³], based on nasopharyngeal irritation in monkeys. Chronic inhalation MRL of 0.008 ppm [0.01 mg/m³], based on clinical symptoms of mild irritation of the eyes and upper respiratory tract and mild damage to the nasal epithelium observed in workers exposed long term (ATSDR 1999).
- US EPA quantitative estimate of carcinogenic risk from inhalation exposure to formaldehyde of 1.3×10^{-5} per $\mu\text{g}/\text{m}^3$ (EPA 1989).

12. The upper range of exposure concentrations for formaldehyde in E(N)NDS aerosols, as summarised in Table 2 (1860–2020 mg/m³), exceeds the UK WELs (8 h TWA and 15 min STEL) by approximately 800-fold, the WHO short-term indoor air guideline by approximately 20,000-fold, and the ATSDR acute, intermediate, and chronic inhalation MRLs by approximately 40,000-fold, 50,000-fold, and 200,000-fold, respectively. However, it is difficult to make direct comparisons, given that exposure to E(N)NDS aerosols by users would be expected to occur as a limited number of puffs of a few seconds duration throughout the day. In addition, it is debated whether the high levels of carbonyl degradation products detected in E(N)NDS aerosols under some experimental conditions would occur during normal use of E(N)NDS products by users.

Acetaldehyde

13. The following guideline values have been reported for inhalation exposure to acetaldehyde.

- UK WELs of 37 mg/m³ for long-term exposure (8 h TWA) and 92 mg/m³ for short-term exposure (15 min STEL) (HSE 2018).
- Health Canada tolerable concentration (TC) of 0.39 mg/m³, based on nasal olfactory lesions in rats. Health Canada calculated a tumorigenic concentration with 5% response (TC₀₅) of 86 mg/m³ with a lower 95% confidence limit (TCL₀₅) of 28 mg/m³ for inhalation of acetaldehyde (Health-Canada 2000a).
- US EPA reference concentration (RfC) of 0.009 mg/m³, based on degeneration of the olfactory epithelium in rats. The EPA quantitative estimate of carcinogenic risk from inhalation exposure to acetaldehyde is 2.2×10^{-6} per $\mu\text{g}/\text{m}^3$ (EPA 1988).

14. The upper range of exposure concentrations for acetaldehyde in E(N)NDS aerosols, as summarised in Table 2 (872–1040 mg/m³), exceeds the UK WELs by approximately 25-fold (8 h TWA) and 10-fold (15 min STEL), the Health Canada TC by approximately 2500-fold, and the US EPA RfC by approximately 100,000-fold. However, it is difficult to make direct comparisons, given that exposure to E(N)NDS

aerosols by users would be expected to occur as a limited number of puffs of a few seconds duration throughout the day. In addition, it is debated whether the high levels of carbonyl degradation products detected in E(N)NDS aerosols under some experimental conditions would occur during normal use of E(N)NDS products by users.

Acrolein

15. The following guideline values have been reported for inhalation exposure to acrolein.

- UK WELs of 0.05 mg/m³ for long-term exposure (8 h TWA) and 0.12 mg/m³ for short-term exposure (15 min STEL) (HSE 2018).
- Health Canada and WHO TC of 0.0004 mg/m³, based on non-neoplastic lesions in the nasal respiratory epithelium in rats (Health-Canada 2000b, WHO 2002).
- US EPA RfC of 0.00002 mg/m³, based on nasal lesions in rats (EPA 2003).

16. The upper ranges of exposure concentrations for acrolein in E(N)NDS aerosols, as summarised in Table 2 (391–449 mg/m³), exceed the UK WELs by 8400-fold (8 h TWA) and 3500-fold (15 min STEL), the Health Canada and WHO TC by approximately one million-fold, and the US EPA RfC by approximately 20 million-fold. However, it is difficult to make direct comparisons, given that exposure to E(N)NDS aerosols by users would be expected to occur as a limited number of puffs of a few seconds duration throughout the day. In addition, it is debated whether the high levels of carbonyl degradation products detected in E(N)NDS aerosols under some experimental conditions would occur during normal use of E(N)NDS products by users.

Summary

17. At the July 2019 COT meeting during discussions of paper [TOX/2019/39](#), the Committee requested that the data on exposure levels to main emissions in E(N)NDS aerosols be presented in tabular form, to aid in evaluating average and ranges of levels to which users may be exposed. As noted in previous COT discussion papers on this topic, it is difficult to compare data across studies, due to the variability in study protocols and reporting. Thus, studies from the previous papers reporting the lowest and highest average levels of emissions of major constituents (nicotine, PG, glycerol, formaldehyde, acetaldehyde and acrolein) were identified, and data from these studies are summarised in Tables 1 and 2 of this report.

18. Risk assessments for PG, glycerol, formaldehyde, acetaldehyde, and acrolein, as originally reported in [TOX/2019/39](#), were limited to comparisons of

estimated exposure concentrations of chemicals in E(N)NDS aerosols with guideline values for inhalation exposure.

19. For all chemicals evaluated, the aerosol concentrations estimated from analytical studies reporting highest emissions of these chemicals into E(N)NDS aerosols exceeded published guideline values for exposure to these chemicals via inhalation. However, the validity of the comparisons between concentrations estimated in E(N)NDS aerosols and the inhalation guideline values identified may be limited, as the guideline values have been set based on continuous exposures (a minimum of at least 15 min for STEL) to these chemicals in ambient air, while exposure from E(N)NDS aerosol would be expected to be limited to short puffs lasting for only a small number of seconds, with an average user taking around 300 puffs per day. The assessments carried out here are based on chemical concentration in E(N)NDS aerosol *per se* and do not attempt to estimate fractions that would reach different levels of the respiratory tract.

20. Another complicating factor is the potential difference between levels of chemicals emitted into E(N)NDS aerosol under conditions of machine puffing compared with real-life puffing by users. This is of particular relevance in relation to studies that have reported high levels of carbonyl degradation products in E(N)NDS aerosols produced by machine puffing, which some commentators suggest would not occur during real-life use due to the unpleasant 'dry-puffing' experience (reviewed by Farsalinos & Gillman 2017). In addition, individual puffing styles are reported to vary widely between different users, and this would also be likely to impact the composition of the aerosol produced on puffing.

Questions for the Committee

21. Members are invited to comment on the information provided in this paper and to consider the following questions:

- i. Is the Committee able to draw any conclusions from the data presented regarding potential adverse health effects to users from exposure to E(N)NDS aerosols?
- ii. Are there any particular 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
October 2019**

Abbreviations

ADI	Acceptable daily intake
AOEL	Acceptable operator exposure level
ARfD	Acute reference dose
ATSDR	US Agency for Toxic Substances and Disease Registry
CC	Conventional cigarette
COT	Committee on Toxicity
EFSA	European Food Safety Authority
E(N)NDS	Electronic nicotine (or non-nicotine) delivery system
ENDS	Electronic nicotine delivery system
ENNDS	Electronic non-nicotine delivery system
EPA	US Environmental Protection Agency
EU	European Union
HBGV	Health-based guidance value
MOE	Margin of exposure
MRL	Minimum risk level
PG	Propylene glycol
RfC	Reference concentration
SCOEL	European Commission Scientific Committee on Occupational Exposure Limits
STEL	Short-term exposure limit
TC	Tolerable concentration
TC05	Tumorigenic concentration with 5% response
TCL05	Lower 95% confidence limit of the TC05
TWA	Time-weighted average
WEL	Workplace exposure limit
WHO	World Health Organization

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