TOX/2020/29

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). Updated risk assessments for exposure of users to propylene glycol (PG) and glycerol from inhalation of E(N)NDS aerosols.

Introduction

1. During 2018 and 2019, the COT reviewed the potential toxicological risks from electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS) (collectively abbreviated to E(N)NDS). A draft statement reflecting the Committee's discussions and conclusions on this topic has been agreed by the Committee except for sections on propylene glycol (PG) and glycerol.

2. The Committee has considered several discussion papers on aspects of relevance to assessing adverse health effects to humans associated with use of E(N)NDS products. Topic areas included the constituents that may be present in E(N)NDS products and the aerosols emitted from them, and toxicological information on some of the principal or commonly identified constituents, including assessments of potential risk to users and bystanders associated with exposure to E(N)NDS emissions.

3. The principal constituents of most e-liquids are the solvents, propylene glycol (PG) and glycerol, which generally comprise 90% or more of the mass, and are present in ratios ranging from 0:100 to 100:0. During evaluation of the potential for adverse health effects associated with long-term inhalation of aerosols of PG and/or glycerol, the Committee encountered some specific issues related to the unique exposure pattern associated with use of E(N)NDS – i.e. intermittent exposure to high concentrations of aerosol for very short time-periods ('puffs') throughout waking hours.

4. Input on this aspect has been sought from external experts, and is provided in Annex A. Data gathered during the COT review of E(N)NDS were used to establish models for potential distribution and deposition of aerosol particles in the human respiratory tract. These modelling data were applied in calculating human equivalent concentrations (HEC) corresponding to concentrations of PG and of glycerol used in rat inhalation toxicity studies. The calculated HEC values were then used, along with data on concentrations of PG and glycerol measured in analytical studies of

E(N)NDS aerosols, to carry out risk assessments of potential adverse health effects to E(N)NDS users from long-term inhalation exposure to PG and glycerol.

5. The following paper presents a brief overview of the risk assessments for E(N)NDS-user exposure to PG and glycerol, as previously conducted by the COT, followed by a narrative of the proposals for updating these risk assessments. A more detailed breakdown of the methodology and calculations underlying the updated risk assessments is presented at Annex A. Proposed amendments to the relevant sections of the COT draft statement on E(N)NDS, based on the updated risk assessments for user exposure to PG and glycerol, are presented at Annex B.

Evidence base and previous COT risk assessments for E(N)NDS-user exposure to PG and glycerol

Toxicological database

6. The toxicity of PG and of glycerol, within a context of relevance to use in E(N)NDS products, was evaluated by COT (see discussion papers TOX/2018/19 and TOX/2018/23). Systemic toxicity was considered to be extremely low for both compounds, but the Committee considered that there was a possibility for local adverse effects on the respiratory tract. Human data were considered to be inadequate for risk assessment purposes, but 13-week rat inhalation studies were available for PG (Suber et al. 1989) and glycerol (Renne et al. 1992). In each case, rats were exposed nose-only 6 h/day, 5 days/week to aerosol of the substance of interest. Further details of these studies can be found in TOX/2018/23.

7. For PG, from the study of Suber et al. (1989), the Committee considered that the key adverse endpoint was nasal haemorrhage. This effect was seen at all PG concentrations tested in the study (160, 1010, 2180 mg/m^3), and a lowest observed adverse concentration (LOAEC) of 160 mg/m^3 was identified. The Committee considered that although human E(N)NDS users would not vape through the nose, the route of exposure could be considered to be of equivocal relevance, and the LOAEC of 160 mg/m^3 could be used to protect against potential irritant effects on the larynx as the first site of contact in the respiratory tract from E(N)NDS use. In calculating a health-based guidance value (HBGV), application of an uncertainty factor (UF) of 10 for toxico-dynamic variation (3 for inter-species, 3 for intra-species) was considered appropriate as the effects of concern were a local irritant effect at the site of contact and thus toxico-kinetic factors would not be of consideration. Given that nasal haemorrhage was observed at 160 mg/m^3 in the absence of other pathological findings at this exposure concentration, the use of a LOAEC to no observed adverse effect concentration (NOAEC) adjustment factor was not considered to be necessary. This was supported by the evaluation of The Dutch Expert Committee on Occupational Standards, which established a health-based occupational exposure limit for PG using data from the study of Suber et al. (1989), based on a NOAEC of 160 mg/m^3 for increased numbers of goblet cells in the medium and high dose groups only (HCN 2007). Based on the LOAEC of 160 mg/m^3 for nasal haemorrhage, with adjustment of x5.6 (6 h/d, 5 d/wk) for continuous

exposure and applying the UF of 10, the COT previously established an HBGV for continuous exposure to PG in air of 2.9 mg/m^3.

8. For glycerol, the study of Renne et al. (1992) indicated effects of mild-to-moderate squamous metaplasia in the epiglottis at all three test concentrations (33, 167, 662 mg/m^3). These effects were considered by the Committee to be minimal and not of toxicological relevance, thus the top dose of 662 mg/m^3 used in the study could be considered a NOAEC. Based on the NOAEC of 662 mg/m^3, with adjustment of x5.6 (6 h/d, 5 d/wk) for continuous exposure and applying a UF of 10, the COT previously established an HBGV for continuous exposure to glycerol in air of 11.8 mg/m^3.

Exposure data

9. Three studies were included in TOX/2019/39 that measured levels of PG and of glycerol in E(N)NDS aerosols produced by machine puffing under controlled experimental conditions. Data are tabulated below (Table 1).

Table 1. Mass or concentration of PG and glycerol measured in analytical studies of E(N)NDS aerosols.

Ref.	Test product(s)	PG	Glycerol	Comment
Pellegrino et al. (2012)	2 x Italian-brand E(N)NDS (liquids contained 66% PG; >24% glycerol; 0 or 0.25% nicotine	1650–1660 mg/m^3	580–610 mg/m^3	Reported as concentration in aerosol
Kienhuis et al. (2015)	4 x disposable shisha pens (liquids contained 54%/46% PG/glycerol; < 1% flavours and other trace components; no nicotine)	0.7 mg per 35 cm^3 puff [20,000 mg/m^3]	0.6 mg per 35 cm^3 puff [17,143 mg/m^3]	Reported as mg/puff [conversion to mg/m^3 in aerosol for COT evaluation]
Margham et al. (2016)	Vype ePen (cartomizer) with 'blended tobacco' e-liquid (liquids contained 25% PG; 48.14% glycerol; 25% water; 1.86% nicotine, <1% flavourings)	0.709 mg per 55 cm^3 puff [12,890 mg/m^3]	1.579 mg per 55 cm^3 puff [28,709 mg/m^3]	Reported as mg/puff [conversion to mg/m^3 in aerosol for COT evaluation]

COT risk assessment to date

10. The highest concentration of PG reported in aerosol (20,000 mg/m^3, Kienhuis et al. 2015) exceeds the COT HBGV of 2.9 mg/m^3 by approximately 5000-fold. The Committee's current assessment in the draft of the statement on E(N)NDS is that "The possibility of adverse health effects for users from long-term exposure to PG from E(N)NDS use cannot be excluded. However, the assessment is limited as the likely scenario in which users would be sporadically exposed to short bursts of high concentrations of PG aerosol from E(N)NDS is very different from the continuous exposure scenario on which the HBGV is based".

11. The highest concentration of glycerol reported in aerosol (28,709 mg/m^3, Margham et al. 2016) exceeds the COT HBGV of 11.8 mg/m^3 by approximately 2500-fold. The Committee's current assessment in the draft of the statement on E(N)NDS is that "The possibility of adverse health effects from long-term exposure of users to glycerol from E(N)NDS use cannot be excluded. However, the assessment is limited as the likely exposure scenario in which users would be exposed to short bursts of high concentrations of glycerol aerosol from E(N)NDS is very different from the continuous exposure scenario on which the HBGV is based".

Updated risk assessments for PG and glycerol exposure for E(N)NDS users based on alternative modelling approaches (see Annex A for full details)

12. Using default breathing assumptions from (EPA 1994), along with data on number of puffs from Dawkins et al. (2018) (see TOX/2019/39), and aerosol particle information from the Suber et al. (1989) and Renne (1992) studies for PG and glycerol, and Pratte, Cosandey and Goujon-Ginglinger (2016) for E(N)NDS aerosols (see TOX/2017/49), multiple-path particle dosimetry (MPPD) modelling was undertaken. This allowed determination of the deposition fraction in the human airways.

13. In contrast to the rat, deposition in humans was highest in tracheobronchial and pulmonary regions, both for the particle sizes used in the Suber et al. (1989) and Renne et al. (1992) studies and the particles observed in E(N)NDS, see table in Annex A. Therefore, subsequent calculations were performed based on this segment of the human airway.

Calculation of human equivalent concentrations (HECs) for E(N)NDS aerosol from rat study data

14. The points of departure (PODs) identified from rat studies (LOAEC or NOAEC) were adjusted to estimated daily human exposure ($LOAEC_{adj}$ or $NOAEC_{adj}$), taking into account the duration of exposure in rat studies, and estimated time of total daily exposure to inhaled E(N)NDS aerosol for a human user taking an average of 300 puffs per day (see Annex A for calculations).

15. Adjustment was then made from $LOAEC_{adj}$ or $NOAEC_{adj}$ to human equivalent concentration (HEC) for E(N)NDS aerosol, taking into account the dosimetry described above for differences between rats and humans, and differences due to aerosol particle size characteristics (see Annex A for calculations).

16. The stages of these conversions are summarised in Table 2, below.

Table 2. Calculation of HEC values for PG and glycerol.

Carrier	NOAEC or LOAEC (mg/L)	$NOAEC_{adj}$ or $LOAEC_{adj}$ (mg/L)	HEC (mg/L)
PG	0.16 (LOAEC)	2.26 ($LOAEC_{adj}$)	1.65
Glycerol	0.662 (NOAEC)	9.33 ($NOAEC_{adj}$)	6.82

Calculation of exposure concentrations for PG and glycerol from E(N)NDS aerosol

17. From the exposure data assessed by the Committee (see TOX/2019/39), the mass of PG in 1 puff of aerosol of 0.7 mg Margham et al. (2016) and Kienhuis et al. (2015) was used to calculate exposure. Similarly, for glycerol 1.6 mg/puff from Margham et al. (2016) was used. These values were used to estimate a single puff concentration using the tidal volume of a human breath, and the average daily concentration using the number of puffs per day from Dawkins et al. (2018) and the daily human tidal volume.

18. Calculated values are shown in Table 3, below.

Table 3. Single puff and average daily concentrations for exposure of E(N)NDS users to PG and glycerol.

Carrier	Single puff concentration (mg/L)	Average daily concentration (mg/L)
PG	0.83	0.011
Glycerol	1.90	0.025

Calculation of margins of exposure

19. Margin of exposure (MOE) values were then calculated from the data in Table 2 and Table 3. Results are summarised in Table 4, below.

Table 4. MOE calculations for potential exposure of E(N)NDS users to PG and glycerol.

Carrier and Scenario	MOE calculation (HEC/exposure concentration)	MOE
PG – Single puff concentration	1.65/0.83	1.99
PG – Average daily concentration	1.65/0.011	150
Glycerol – Single puff concentration	6.82/1.90	3.59
Glycerol – Average daily concentration	6.82/0.025	273

Risk Assessment illustration

20. Utilising the HEC values and the uncertainty factors of 10 for both PG and glycerol previously agreed by the COT (see paragraphs 7 and 8), along with the single puff and average daily concentrations, the Risk21 plot in Figure 1 was generated.

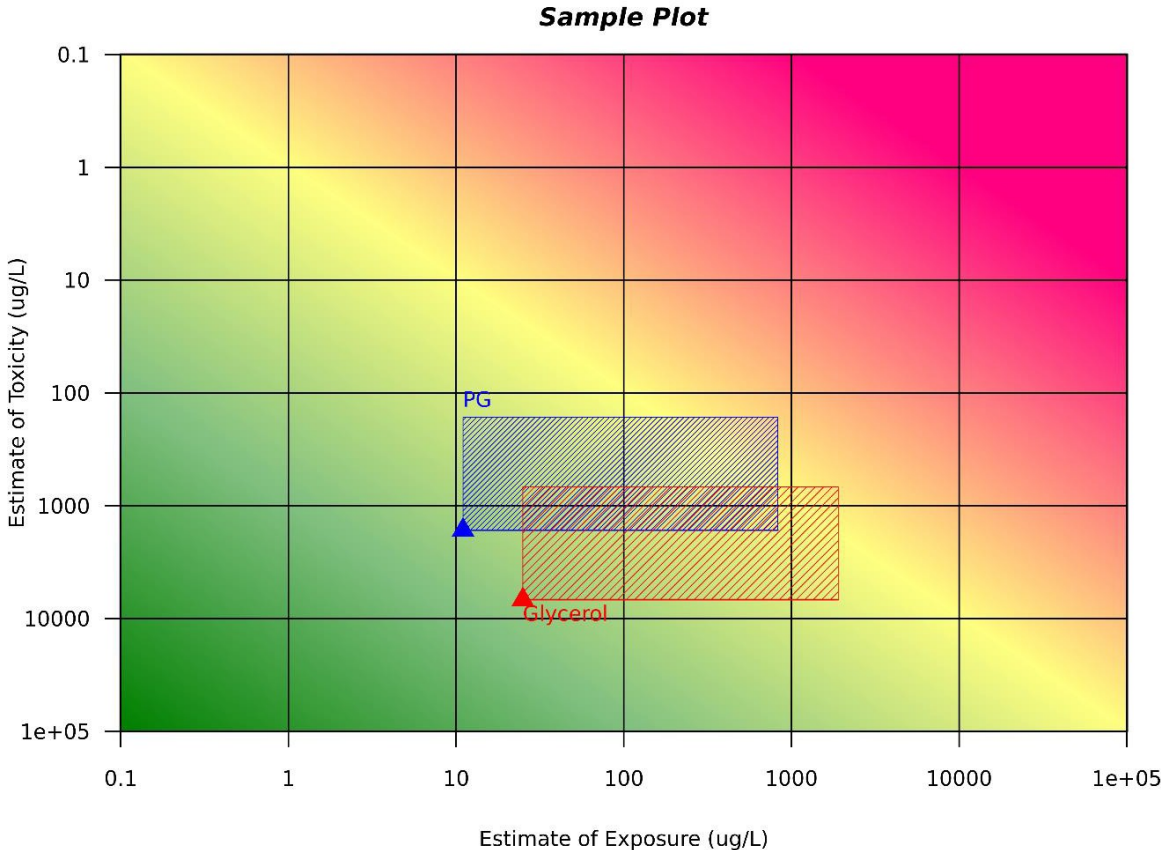

Figure 1. Risk21 plot

Updated sections in the COT draft statement on E(N)NDS

21. Following from the new modelling for exposure of E(N)NDS users to PG and glycerol, as described in paragraphs 12 – 20 above, modifications to the paragraphs relating to PG and glycerol in the draft COT statement on E(N)NDS are suggested. These relevant sections, with proposed modifications, are presented at Annex B.

Summary and conclusions

22. Based on the updated risk assessment, for PG and glycerol, MOE values of 1.99 and 3.59, respectively, were calculated based on the maximum estimated concentration in aerosol to which the user would be exposed during inhalation of 1 puff of product. Alternatively, based on averaged exposure over 1 day, assuming 300 puffs per day, MOE values for PG and glycerol are 150 and 273, respectively.

23. These MOE values and the illustration in the Risk21 plot support the conclusion that although adverse health effects for users from long-term exposure of E(N)NDS users to PG or glycerol cannot be ruled out, the data present in the evidence base available to the Committee do not indicate that inhalation exposure of users to PG or glycerol from E(N)NDS aerosols is of particular cause for concern.

Questions

24. Members are invited to consider the information provided above and in Annex A and Annex B, and in particular:

- Do Members have any comments on the updated approach detailed in Annex A taken to assess potential risk of adverse health effects to E(N)NDS users from long-term inhalation exposure to PG or glycerol?
- Do Members have an opinion on the level of risk associated with the estimated exposures as illustrated by the calculated MOE values?
- Do Members agree that the calculations provided support the conclusion that long-term exposure of users to PG and glycerol from E(N)NDS is likely to be of low concern, based on the evidence base currently available.
- Do Members have any comments on the amended version of the sections relating to risk assessment and conclusions for user exposure to PG and glycerol in the COT statement on E(N)NDS, as provided at Annex B?

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Abbreviations

E(N)NDS	Electronic nicotine (or non-nicotine) delivery system
ENDS	Electronic nicotine delivery system
ENNDS	Electronic non-nicotine delivery system
GSD	Geometric standard deviation
HBGV	Health-based guidance value
HEC	Human equivalent concentration
LOAEC	Lowest observed adverse effect concentration
MMAD	Median mass aerodynamic diameter
MOE	Margin of exposure
MPPD	Multiple-path particle dosimetry
NOAEC	No observed adverse effect concentration
P	Pulmonary
PG	Propylene glycol
POD	Point of departure
TB	Tracheobronchial
UF	Uncertainty factor

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