TOX/2019/47

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 12: Calculation of a health-based guidance value for inhalation exposure to nicotine based on the study of Lindgren et al. (1999).

Introduction

1. As part of the review on the potential toxicity of electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS) (collectively abbreviated to E(N)NDS), the COT has been reviewing potential toxicity of exposure to nicotine from these products.

2. At the July 2019 COT meeting, a review of toxicological data on nicotine was discussed (TOX/2019/38). A study by Lindgren et al. (1999) was noted which had evaluated changes in heart-rate and electroencephalogram (EEG) parameters in subjects given intravenous (i.v.) infusions of nicotine. The European Food Safety Authority (EFSA) had used the heart-rate data from this study as a basis to calculate a health-based guidance value (HBGV) for oral exposure to nicotine. During discussions, Members requested more information on the EEG findings, and for these data to be used as a basis to calculate an HBGV for nicotine. This current paper presents a summary of the report by Lindgren et al. (1999) (attached at Annex A), followed by a proposed calculation for an HBGV for inhalation exposure to nicotine based on the EEG data.

Lindgren et al. (1999)

3. Lindgren et al. (1999) conducted a single-blind, placebo-controlled crossover study with the aim to establish a dose-response relationship between intravenously (i.v.) administered nicotine and quantitative EEG measures and parameters of the auditory oddball P300[1]. The 14 participants (8 males, 6 females; 20–48 y) were all healthy regular smokers of conventional cigarettes (CC), smoking an average of 19 CC per day (1.1 mg nicotine yield per CC).

[1] P300 measures an event-related potential (ERP) component elicited in the process of decision making. In the oddball test, the subject is presented with a stream of regular stimuli interspersed with rare 'oddball' stimuli. In this study, tones of 2 different frequencies were presented through earphones, and the subject was asked to press a button on a response-pad whenever the rare 'oddball' tone was heard.

4. Subjects abstained from nicotine for ≥ 12 h before test sessions, confirmed by plasma nicotine level < 4.0 ng/mL. Caffeine was excluded from the diet.

5. Nicotine was administered during separate test sessions, at doses of 0, 3.5, 7.0, 14.0, and 28.0 µg/kg bw, by i.v. infusion over a 10-min period. The dose range was selected to represent systemic nicotine exposure over a range of low- to high-nicotine CC. Heart rate and EEG (6 segments) were recorded and auditory oddball task analyses (for analysis of event-related potentials) were conducted at baseline (prior to i.v. infusion) and at intervals through to 130 min after the start of i.v. infusion. Venous blood samples were also taken at intervals during this time period. Analyses were based on repeated measures ANOVA (5 nicotine doses X 11 time points X 4 quadrants for quantitative EEG, 5 nicotine doses X 7 time points for data from the oddball task, 5 nicotine doses X 11 time points for plasma nicotine and heart rate).

6. Plasma nicotine concentrations increased in a time- and dose-dependent manner. Results for mean plasma nicotine concentration over time are shown graphically in Fig. 1 of the publication (see Annex A).

7. Nicotine infusions were associated with increased heart-rate in a dose- and time-dependent manner. Results for mean plasma nicotine concentration and heart rate over time are shown graphically in Fig. 1 of the publication (see Annex A). In the narrative text, the authors described the heart rate acceleration as ‘pronounced’ after infusion of the 14.0 and 28.0 µg/kg nicotine doses.

8. EEG data are summarised in Table 2 of the publication and are shown graphically in Fig. 2 (see Annex A). Linear, dose-related decreases of delta and theta power were recorded, consistent with increased arousal. The nicotine X time point interaction was significant for theta power, but not for delta power. Nicotine increased $alpha_2$ power and alpha peak frequency in a significant, linear dose-response pattern, with a significant nicotine X time point interaction[2]. There were no significant changes in $alpha_1$, beta, and auditory oddball P300 parameters, except for a significant interaction of nicotine X time point for beta power.

9. Authors concluded that the arousing effect associated with nicotine infusion was marked in delta and theta bands, with a somewhat weaker relationship with $alpha_2$. They also highlighted the point that, as no non-smoking controls were included in the study, the results were ambiguous as to whether the arousal effect observed was a reversal of abstinence-related sedation or an ‘absolute’ arousal increase.

Calculation of a health-based guidance value for nicotine from Lindgren study

10. An HBGV for nicotine is calculated below, based on acute effects on EEG in regular CC smokers in the study of Lindgren et al. (1999). The lowest observed effect

[2] In the narrative of the ‘Discussion’ section of the report, authors commented that “$Alpha_2$ power increased markedly at the higher nicotine doses, 14.0 and 28.0 µg/kg, as did the dominant alpha frequency”.

level (LOEL) is estimated from data presented in Fig. 2 of the publication (see Annex A), in combination with information in the narrative text.

- Point of departure (PoD) = 0.0035 mg/kg bw (LOEL[3] for decreased delta and theta power on EEG, indicative of effects of arousal).
- Adjustment of 0.55 for bioavailability (extrapolation from i.v. to inhalation route[4]).
- As the LOEL would be considered to be close to the NOEL, an overall UF of 10 to account for human variability and extrapolation from LOEL to NOEL[5].
- HBGV = 0.00064 mg/kg bw.

HBGVs established by other authoritative bodies

11. European Food Safety Authority (EFSA) established a value of 0.0008 mg/kg bw/day for the acute reference dose (ARfD) and acceptable daily intake (ADI) for oral exposure to nicotine in food (dried mushrooms), based on a lowest observed adverse effect level (LOAEL) of 0.0035 mg/kg bw for increased heart rate frequency in human CC smokers exposed to nicotine by i.v. infusion, from the study of Lindgren et al. (1999), described above. A UF of 4.4 was applied (10 for human variability and 0.44 for extrapolation from i.v. to oral route) (EFSA 2009).

12. A draft assessment report (DAR) for the European Union (EU) peer review process for pesticides proposed a value of 0.0001 mg/kg bw/day for the ARfD, ADI, and systemic acceptable operator exposure level (AOEL) for exposure to nicotine as a fumigation formulation, based on a LOAEL of 0.01 mg/kg bw/day for clinical signs of toxicity in children exposed dermally, from the report of Woolf et al. (1997). A UF of 100 was applied (10 for intra-species variability and 10 for use of a limited data set) (UK-DAR 2007).

13. The United States Environmental Protection Agency (US EPA) determined a no observed adverse effect level (NOAEL) of 1.25 mg/kg bw/day based on a study by Yuen et al. (1995), in which hepatotoxicity was reported at the higher dose in rats given nicotine (54 and 108 µmol/L) in drinking water for 10 days. EPA considered that a margin of exposure (MOE) of 1000 (10 for inter-species extrapolation, 10 for intra-species variability, 10 for database uncertainty) would be protective of human health in use of nicotine by operators as an indoor pesticide spray (EPA 2008).

[3] The lowest dose tested
[4] see TOX/2019/38 for details
[5] EFSA applied an overall UF of 10 for human variability and extrapolation from LOAEL to NOAEL in calculating an HBGV based on heart-rate data from this study, noting that "The LOAEL is considered to be close to the NOAEL and the overall uncertainty factor of 10 would be sufficient to cover not only human variability but the extrapolation from the LOAEL to NOAEL for the pharmacological effect observed at the LOAEL."

14. A summary of published values for points of departure (PoD) is given in Table 1, below.

Table 1. Published POD values for nicotine toxicity.

Agency and/or publication	Data source	Species	Endpoint	Exposure	PoD, type	PoD, value	Adjustment factors	HBGV, mg/kg bw (/day); [route of exposure to which HBGV applies]
EFSA EFSA (2009)	Lindgren et al. (1999)	Human	Heart rate frequency	i.v. infusion over 10 min	LOAEL	0.0035 mg/kg bw	0.44 (i.v. to oral), 10 (human variability) Total UF = 44	0.0008 mg/kg bw (ARfD), 0.0008 mg/kg bw/day (ADI) [oral intake from ingestion of wild mushrooms]
DAR for EU peer review process for pesticides UK-DAR (2007)	Woolf et al. (1997)	Human	Clinical signs of toxicity in children	Dermal patches	LOEL	0.01 mg/kg bw/day	10 (intra-species variability), 10 (estimated LOEL based on a poor data set) Total UF = 100	0.0001 mg/kg bw/day (ADI), 0.0001 mg/kg bw/day (ARfD), 0.0001 mg/kg bw/day (AOEL) [use as a fumigation formulation on vegetables grown in glasshouses]

Agency and/or publication	Data source	Species	Endpoint	Exposure	PoD, type	PoD, value	Adjustment factors	HBGV, mg/kg bw (/day); [route of exposure to which HBGV applies]
U.S. EPA EPA (2008)	Yuen et al. (1995)	Rat	Pathological changes in the liver	Drinking water	NOAEL	1.25 mg/kg bw/day	10 (inter-species extrapolation), 10 (intra-species variability), 10 (database uncertainty) Total MOE = 1000	0.00125 mg/kg bw/day (protective of human health using MOE approach) [use as a pesticide, in the format of smoke-generating canisters, on ornamental plants in greenhouses]
Published risk assessment Baumung et al. (2016)	Benowitz and Henningfield (1994)	Human	Addiction	Chronic CC use	Threshold	0.07 mg/kg bw		
	Modelling by Baumung et al. (2016) based on data from Woolf et al. (1997)	Human	Clinical signs of toxicity in children	Dermal patches	$BMDL_{10}$	0.004 mg/kg bw		
	Lachenmeier and Rehm (2015)	Various animal species	Mortality	Various	LD_{50}	3 mg/kg bw		
	Modelling by Baumung et al. (2016) based on data from Yuen et al. (1995)	Rat	Liver: fatty change	Drinking water	$BMDL_{10}$	0.27 mg/kg bw		

Agency and/or publication	Data source	Species	Endpoint	Exposure	PoD, type	PoD, value	Adjustment factors	HBGV, mg/kg bw (/day); [route of exposure to which HBGV applies]
	Modelling by Baumung et al. (2016) based on data from Yuen et al. (1995)	Rat	Liver: focal necrosis	Drinking water	$BMDL_{10}$	0.24 mg/kg bw		
	Modelling by Baumung et al. (2016) based on data from Yuen et al. (1995)	Rat	Liver: dark cell change	Drinking water	$BMDL_{10}$	0.21 mg/kg bw		

Questions for the Committee

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

    i. Is the proposed calculation, based on EEG findings indicating effects of arousal in nicotine-abstinent regular CC smokers, suitable for establishing an HBGV for ENDS users and/or for bystanders exposed to nicotine from ENDS products?

    ii. Alternatively, do Members consider that any of the evaluations carried out by other authoritative bodies are useful for setting a guidance value for exposure of users and/or bystanders to nicotine from ENDS products?

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Abbreviations/Glossary

ADI	Acceptable daily intake
AOEL	Acceptable operator exposure level
ARfD	Acute reference dose
CC	Conventional cigarette
EEG	Electroencephalogram
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
EU	European Union
HBGV	Health-based guidance value
i.v.	Intravenous
LOAEL	Lowest observed adverse effect level
LOEL	Lowest observed effect level
MOE	Margin of exposure
NOAEL	No observed adverse effect level
NOEL	No observed effect level
PoD	Point of departure
UF	Uncertainty factor
US EPA	United States Environmental Protection Agency

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Full-text reference of Lindgren et al. (1999).

Lindgren, M, Molander L, Verbaan C, Lunell E, Rosen I (1999). Electroencephalographic effects of intravenous nicotine – a dose-response study. Psycopharmacology (Berl), 145, 342-350.

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