# Nicotine safety in the context of e-cigarette use and tobacco dependence

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#### Disclosure

- Consultant for public sector : EC SCENIHR, INSERM (France), Ministry of Health, writer of a Newsletter for smoking cessation specialists (SFT)
- Consulting for pharmaceutical industry : J&J, Pfizer, Novartis, Pierre Fabre
- Consulting for tobacco industry : never
- Consulting for e-cigarette industry : NJOY



## Why do people smoke ?

- "It is nicotine that people cannot easily do without, not tobacco."
- "It is not so much the efficacy of new nicotine delivery systems as temporary aids to cessation, but their potential as long-term alternatives to tobacco that makes the virtual elimination of tobacco a realistic future target."

British Journal of Addiction (1991) 86, 653-658

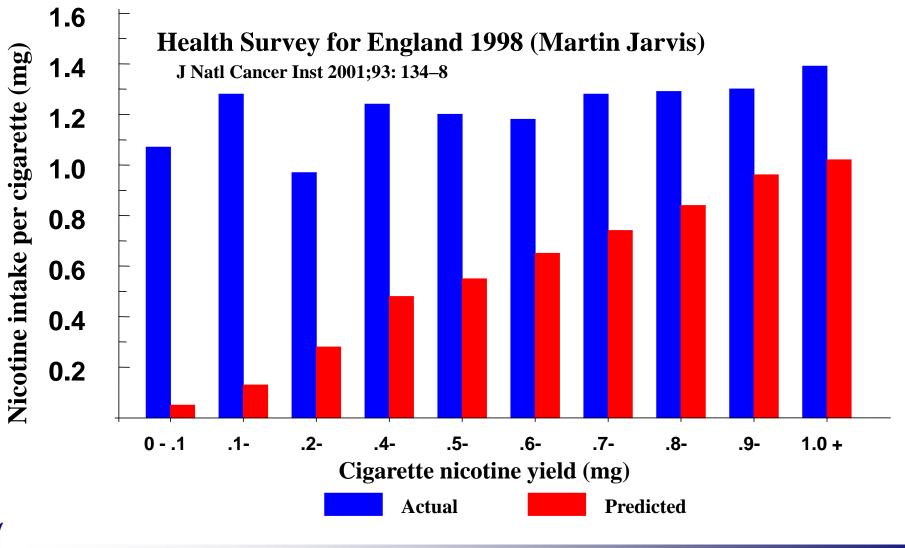
#### The future of nicotine replacement

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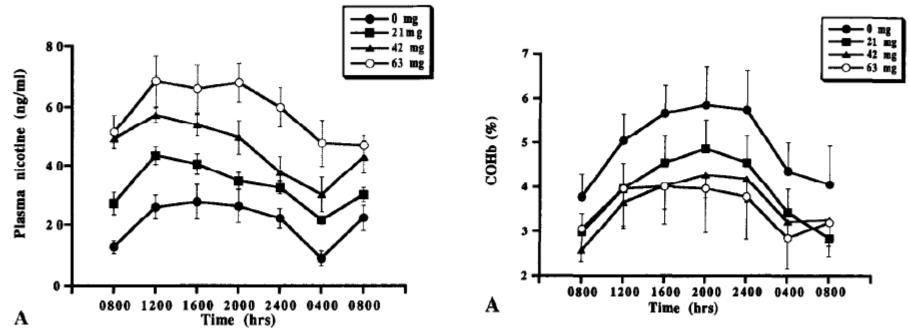


## Predicted and actual nicotine intakes per cigarette smoked by nominal nicotine yield





#### Nicotine users know how to self-titrate



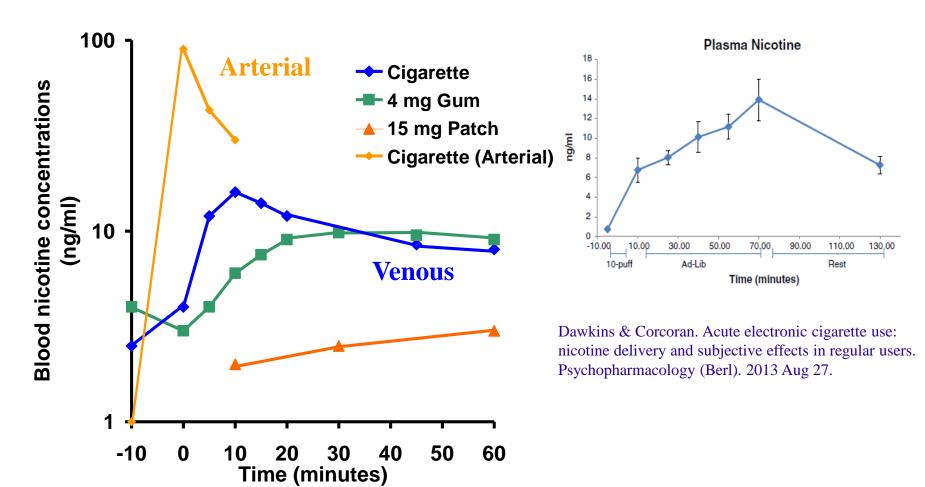
Patch dose	Cigarettes smoked <sup>a</sup>	$\Delta AUC$ nicotine <sup>b</sup>	Nicotine intake from $cigarettes^a$	Nicotine intake per cigarette <sup><math>a</math></sup>	AUC COHba
mg/24 h		ng/ml*hr	mg	mg	$\% \cdot hr$
0	$17.2 \pm 2.4$	$500 \pm 95^{\circ}$	$35.9 \pm 4.0^{\circ}$	$2.5\pm0.5$	$129 \pm 16$
21	$16.2 \pm 2.1$	$417 \pm 73$	$30.4 \pm 3.9$	$2.2\pm0.3$	$101 \pm 13^{d}$
42	$15.5 \pm 1.4$	$334 \pm 53$	$27.4 \pm 4.4$	$1.9\pm0.3$	$92\pm11^d$
63	$12.7 \pm 1.3$	$276 \pm 45^{c}$	$20.7 \pm 3.1^{c}$	$1.6\pm0.3$	$93\pm20^d$

1. Zevin S, Jacob P 3rd, Benowitz NL. Dose-related cardiovascular and endocrine effects of transdermal nicotine. Clin Pharmacol Ther. 1998 Jul;64(1):87-95.

2. Benowitz NL, Zevin S, Jacob P 3rd. Suppression of nicotine intake during ad libitum cigarette smoking by high-dose transdermal nicotine. J Pharmacol Exp Ther. 1998 Dec;287(3):958-62.



### Speed of delivery is critical



Adapted from Henningfield, N Engl J Med. 1995;333:1196-1203



#### **Nicotine vs. Tobacco Dependence**

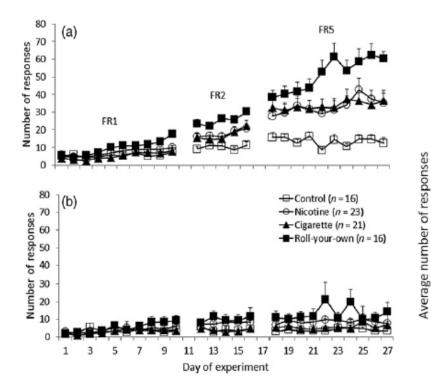
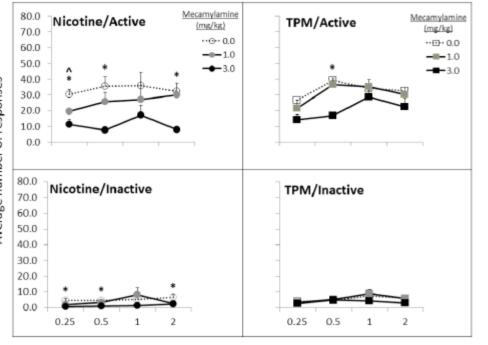


Figure I Self-administration on a fixed ratio (FR) schedule. Data points represent the average number of total responses produced by the nicotine, cigarette tobacco particulate matter (TPM) and roll-your-own TPM groups (FR1, days 1-10, FR2 days 12-16, FR5 days 18-27) on the active (a) or inactive (b) levers during daily 2-hour sessions (+SEM)

#### Brennan KA et al. Addict Biol. 2013





Proportion of training dose

Brennan KA et al. Current Psychopharmacology, 2013, Volume 2, No. 2

## Why do people smoke ?

- People smoke for nicotine +/- other compounds (MAOIs, acetaldehyde...), but die from combustion products.
- Vapers vape for pure nicotine, without combustion products, but still some impurities.
- Is it safe ? Is it less addictive ?





#### Safety concerns about nicotine

• Standard textbooks, databases, and safety sheets consistently state that the lethal dose for adults is 60 mg or less (30–60 mg), leading to safety warnings that ingestion of five cigarettes or 10 ml of a diluted nicotine-containing solution could kill an adult.

Archives of Toxicology© The Author(s) 201310.1007/s00204-013-1127-0 Guest Editorial

#### How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century

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#### Nicotine lethal dose

- A 60 mg lethal dose = oral LD50 of around 0.8 mg/kg, considerably smaller than LD50 in mice (3.3 mg/kg) or rats (50 mg/kg) !
- Smoking a cigarette = 2 mg of nicotine uptake, which gives arterial plasma concentrations of about 30 ng/ml.<sup>1</sup>
- Based on 20 % oral bioavailability of nicotine (and linear kinetics), 60 mg would give rise to a plasma concentration of about 180 ng/ml (= 0.18 mg/L).<sup>2</sup>
- Several reports of much higher nicotine administration (1500 mg) have shown non-fatal issues, suggesting a conservative lower limit of lethal nicotine blood concentrations of about 2 mg/L, corresponding to 4 mg/L plasma.<sup>3</sup>
- This is about 20-fold higher than that caused by intake of 60 mg nicotine.
- So the lower limit causing fatal outcomes is 0.5–1 g of ingested nicotine (oral LD50 of 6.5–13 mg/kg, agreeing well with nicotine toxicity in dogs, which exhibit responses to nicotine similar to humans. <sup>4</sup>

 Gourlay SG, Benowitz NL. Arteriovenous differences in plasma concentration of nicotine and catecholamines and related cardiovascular effects after smoking, nicotine nasal spray, and intravenous nicotine. Clin Pharmacol Ther. 1997;62:453-463.
Hukkanen J, Jacob P 3rd, Benowitz NL. Metabolism and disposition kinetics of nicotine. Pharmacol Rev. 2005 Mar;57:79-115.
Solarino B, Rosenbaum F, Riesselmann B, Buschmann CT, Tsokos M. Death due to ingestion of nicotine-containing solution: case report and review of the literature. Forensic Sci Int. 2010 Feb 25;195(1-3):e19-22.

4. Matsushima D, Prevo ME, Gorsline J. Absorption and adverse effects following topical and oral administration of three transdermal nicotine products to dogs. J Pharm Sci. 1995;84:365-369.



#### Nicotine lethal dose

- On ten cases of children ingesting tobacco cigarettes. Ingestion of 0.5-1 mg/kg produced symptoms of salivation and vomiting within 30 min. Ingesting of 3-6 mg/kg produced salivation, vomiting, diarrhea, tachypnea, tachycardia, and hypertension within 30 min; depressed respiration and cardiac arrhythmia within 40 min; and convulsions within 60 min after ingestion. Within 5 days all children recovered with no complications. <sup>1</sup>
- On 51 cases of children aged 5 months to 9 years who accidently ingested cigarettes or nicotine polacrilex gum, no fatalities observed. Severe toxicity (limb jerking and unresponsiveness) was seen with doses ≥ 1.4 mg/kg; minor toxic symptoms were seen at doses < 1 mg/kg. Most common symptoms were nausea, vomiting, and diarrhea.</li>
- One death-report of 2-year old after drinking e-liquid ? No definitive answer further reported. <sup>3</sup>

 Malizia E, Andreucci G, Alfani F, Smeriglio M, Nicholai P. Acute intoxication with nicotine alkaloids and cannabinoids in children from ingestion of cigarettes. Hum Toxicol. 1983 Apr;2(2):315-6.
Smolinske SC, Spoerke DG, Spiller SK, Wruk KM, Kulig K, Rumack BH. Cigarette and nicotine chewing gum toxicity in children. Hum Toxicol. 1988 Jan;7(1):27-31.

3. http://www.timesofisrael.com/police-investigating-toddler-death-from-nicotine-overdose/



#### Long-term effects of inhaled nicotine

- Effect on the rat of long-term (two years) inhalation of nicotine.
- The rats breathed in a chamber with nicotine at a concentration giving twice the plasma concentration found in heavy smokers. Nicotine was given for 20h a day, five days a week during a two-year period.
- Could not find any increase in mortality, in atherosclerosis or frequency of tumours in these rats compared with controls. Particularly, there was no microscopic or macroscopic lung tumours nor any increase in pulmonary neuroendocrine cells.
- Throughout the study, however, the body weight of the nicotine exposed rats was reduced as compared with controls.

1. Waldum HL, Nilsen OG, Nilsen T, Rørvik H, Syversen V, Sanvik AK, Haugen OA, Torp SH, Brenna E. Long-term effects of inhaled nicotine. Life Sci. 1996;58(16):1339-46.



### Health risks of pure nicotine

- A recent study (Knezevich et al. 2013) showed that nitrosamines (NNN) can be formed from nornicotine in human saliva. However the levels produced vary individually<sup>1</sup>, and the risks from pure nicotine (not from tobacco) appear to be small, and nicotine has not been shown to be carcinogenic in animals.<sup>2</sup>
- Data from snus (low in nitrosamines) use in Sweden are also reassuring, there is no evidence of an increased cancer risk among Swedish snus users (but there is some indication that US snuff which has higher levels of nitrosamines, can increase this risk).<sup>2</sup>
- Another mechanism via stimulation of nAChRs could regulate release lung tumour growth factors, but this seems to occur only at high CO<sub>2</sub> as seen in COPD, and desensitisation of nAChRs with chronic nicotine could suppress tumour growth.<sup>2</sup>

 Knezevich A, Muzic J, Hatsukami DK, Hecht SS, Stepanov I. Nornicotine nitrosation in saliva and its relation to endogenous synthesis of N'-nitrosonornicotine in humans. Nicotine Tob Res. 2013 Feb;15(2):591-5.
Benowitz NL. Nicotine safety and toxicity, Oxford University Press, 1998.



#### Health risks of e-cigarette vapour

• e-cigarette vapours contain some toxic substances. The levels of the toxicants are **9-450 times lower** than in cigarette smoke and, comparable with trace amounts found in a nicotine inhalator (Formaldehyde, Acetaldehyde, Cd, Ni, Pb).<sup>1</sup>

Toxic compound	Conventional cigarette (µg in mainstream smoke) <sup>35</sup>	Electronic cigarette (µg per 15 puffs)	Average ratio (conventional vs electronic cigarette	
Formaldehyde	1.6-52	0.20-5.61	9	
Acetaldehyde	52-140	0.11-1.36	450	
Acrolein	2.4-62	0.07-4.19	15	
Toluene	8.3-70	0.02-0.63	120	
NNN	0.005-0.19	0.00008-0.00043	380	
NNK	0.012-0.11	0.00011-0.00283	40	

NNK, N'-nitrosonomicotine (NNN) and 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone; NNN, N'-nitrosonomicotine.

1. Goniewicz ML, Knysak J, Gawron M, Kosmider L, Sobczak A, Kurek J, Prokopowicz A, Jablonska-Czapla M, Rosik-Dulewska C, Havel C, Jacob P 3rd, Benowitz N. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. Tob Control. 2013 Mar 6. [Epub ahead of print]



## Is pure nicotine less addictive ?

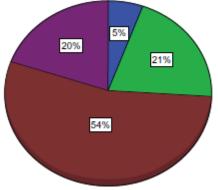
- Vapers tend to lower the nicotine concentration of their e-liquid with time. In one study (n=111), the median score of the 100-point visual analogue scale question about cigarette dependence was 83 (77–89), while for EC dependence it was 59 (49–66). EC dependence was significantly lower P<0.001). <sup>1</sup>
- In an internet survey in 1347 e-cigarette users, among ex-smokers (74% of the sample), 'time to first vape' was significantly longer than 'time to first cigarette' ( $t_{1104} = 11.16$ , P < 0.001) suggesting a lower level of dependence to ecigarettes.<sup>2</sup>



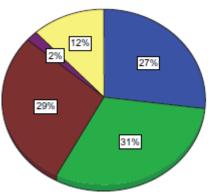
0–5 mg/mL 6–10 ma/mL

> 1–15 mg/mL 6–20 ma/mL

•20 mg/mL







Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V. Evaluating nicotine levels selection and patterns of electronic cigarette use in a group of "vapers" who had achieved complete substitution of smoking. Subst Abuse. 2013 Sep 3;7:139-46.
Dawkins L, Turner J, Roberts A, Soar K. 'Vaping' profiles and preferences: an online survey of electronic cigarette users. Addiction. 2013 Jun;108(6):1115-25.



#### Conclusions

- People smoke for nicotine, but other compounds may play a role in addictiveness.
- Smokers are able to self-titrate nicotine on a puff by puff basis. There is no concerns of nicotine overdosing in e-cigarette users.
- Nicotine lethal dose has been overestimated. Regulators should take it into account.
- Long-term use of pure nicotine has not been shown to pose health problems in animals.
- The health risks from pure nicotine in humans appear to be small if any.
- Pure nicotine use, as with e-cigarettes, seems less addictive than when smoked in tobacco, and is considerably less harmful.



