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.”


The future of nicotine replacement

MICHAEL A. H. RUSSELL

ICRF Health Behaviour Unit, Institute of Psychiatry, 101 Denmark Hill, London SE5 8AF, UK
Predicted and actual nicotine intakes per cigarette smoked by nominal nicotine yield

Health Survey for England 1998 (Martin Jarvis)
Nicotine users know how to self-titraxe


Speed of delivery is critical

Blood nicotine concentrations (ng/ml)

-10 0 10 20 30 40 50 60
Time (minutes)

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

Nicotine vs. Tobacco Dependence

Figure 1 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

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.

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

Bernd Mayer¹ -
(1) Department of Pharmacology and Toxicology, Karl-Franzens University Graz, Univ.-Platz 2, 8010 Graz, Austria
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. ¹
- 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). ²
- 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. ³
- 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. ⁴

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. ¹

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.

One death-report of 2-year old after drinking e-liquid? No definitive answer further reported. ³

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.

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, and the risks from pure nicotine (not from tobacco) appear to be small, and nicotine has not been shown to be carcinogenic in animals.

- 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).

- Another mechanism via stimulation of nAChRs could regulate release lung tumour growth factors, but this seems to occur only at high CO₂ as seen in COPD, and desensitisation of nAChRs with chronic nicotine could suppress tumour growth.

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).¹

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

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). ¹

- 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’ (t₁₁₀₄ = 11.16, P < 0.001) suggesting a lower level of dependence to e-cigarettes. ²

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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 concern 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.