



EST 1892

**Response to the Canadian Consultation on Proposed Concentration of Nicotine
in Vaping Products Regulation**

Professor Lynne Dawkins¹, Dr Sharon Cox^{1,2} and Dr Catherine Kimber¹

¹Centre for Addictive Behaviours Research, London South Bank University (LSBU)

²Department of Behavioural Science and Health, University College London (UCL)

As established nicotine and tobacco researchers, we strongly recommend against ***limiting nicotine concentrations in e-liquids to 20 mg/mL***. We base our recommendation on 1) extensive research which demonstrates that lowering nicotine e-liquid concentrations can increase puffing intensity and exposure to potentially harmful chemicals; 2) evidence that higher nicotine levels can increase quit rates among smokers and 3) a lack of robust long-term evidence that youth nicotine vaping causes smoking.

1. Our research and others have shown that use of lower nicotine concentration e-liquid is associated with more intensive puffing, higher e-liquid consumption and greater exposure to carcinogens. We have demonstrated this effect both in the lab and under real world conditions in our Cancer Research UK (CRUK) funded research described below:

- In our first study (Dawkins et al., 2016), eleven experienced vapers completed 60 minutes of *ad libitum* vaping under low (6 mg/mL) and high (24 mg/mL) nicotine e-liquid conditions in two separate sessions in a laboratory setting. We measured puff number, puff duration and volume of liquid consumed. Number of puffs was significantly higher, and puff duration significantly longer, in the low compared with the high nicotine concentration condition, resulting in a doubling of e-liquid consumed. Our results suggest that, like tobacco smokers, when switching to lower nicotine concentrations, vapers engage in “compensatory puffing” in an attempt to obtain a satisfactory and optimal level of nicotine. Similar findings have been reported in Belgian vapers (Smets et al., 2019).
- We subsequently replicated this effect of compensatory puffing in a group of 20 vapers in a real-world setting (allowing them to take the device home and use as normal for 4-weeks) (Dawkins et al., 2018). Participants increased their daily puff number and puff duration and consumed more liquid a day in the low versus high nicotine condition and this compensatory behavior persisted for several days (Cox et al., 2021). This was particularly pronounced when power setting (voltage) was fixed. Despite the more intensive puffing with the lower nicotine concentration e-liquid, nicotine craving and withdrawal symptoms were higher, and overall satisfaction was lower, in the low nicotine e-liquid condition.

- In the same study we also measured urinary levels of formate, a metabolite of the known human carcinogen, formaldehyde. Formate levels were significantly higher when participants used a low nicotine concentration e-liquid with increased power, suggesting an increase in toxicant exposure.
- We have also replicated the puffing patterns obtained from our participants in the Dawkins et al. (2016) study (described above) using a smoking machine to generate e-cigarette aerosol in the lab. Formaldehyde, acetaldehyde and acetone levels were significantly higher in aerosols from the 6mg/mL compared with 24mg/mL puffing regimen (Kosmider et al., 2017). The same was observed based on our real-world puffing patterns from the 20 vapers in the CRUK-funded study (Kosmider et al., 2020). Based on those data, in an estimation of cancer risk associated with compensatory behaviour, our simulation suggests a 2-fold increase in cancer risk when switching from high to low nicotine e-liquid (Kosmider et al., 2020). It should be noted however, that this still remains orders of magnitude lower than the cancer risk associated with tobacco smoking.

Together, these findings suggest that, when vapers switch to a lower nicotine concentration e-liquid, they engage in compensatory puffing, taking more puffs per day and increasing their puff duration. This, in turn is associated with higher levels of exposure to carcinogens (formaldehyde, acetaldehyde and acetone). Our data therefore suggest that reducing nicotine content in e-liquid may not have the desired harm-minimization effect. **The proposed cap on nicotine concentration at 20 mg/mL may therefore have the unintended consequence of encouraging use of lower nicotine concentration e-liquid in turn, increasing exposure to carbonyl compounds through compensatory puffing.**

2. Reducing nicotine levels in e-liquids may reduce the effectiveness of vaping products for dependent and disadvantaged smokers who need high nicotine levels in order to switch successfully.

- The Action on Smoking and Health (2020) survey in Great Britain showed that 80% of current smokers who had tried and discontinued using an e-cigarette, and 61% of dual users (i.e. who smoked and vaped), found them less satisfying than smoking. This suggests that for many smokers, products available in Great Britain (where regulation imposes a 20mg/mL cap on nicotine concentrations) are insufficient for reducing nicotine craving and promoting smoking abstinence. If smokers cannot obtain the nicotine levels they need from e-cigarettes, they become more vulnerable to increased craving for tobacco cigarettes and are more likely to maintain smoking.
- Moreover, the greatest burden of smoking-related death and disease falls on those who are most disadvantaged in society (ASH, 2016; Leventhal et al. 2019): the poorest (Thirlway et al., 2019); those with other addictions or a mental health diagnosis (Glasheen et al., 2014; McClove et al., 2010; Richardson et al., 2019) and those experiencing homelessness (Soar et al., 2020). Smoking prevalence rates remain

exceptionally high among these groups (up to 4 times higher than national averages) and nicotine dependence is high. High nicotine dependence and low socioeconomic status are predictive of poorer smoking cessation outcomes (Foulds et al., 2006; Glasheen et al., 2014; McClave et al., 2010; Richardson et al., 2019). Many have tried traditional approaches to stop smoking and failed. Higher nicotine concentrations are likely necessary to adequately reduce craving and promote smoking cessation among the most disadvantaged in society.

- Indeed, it is well established that higher dose Nicotine Replacement Therapy (NRT) products (patch and gum) increase the chances of successfully stopping smoking (Lindson et al., 2019; Przulj et al., 2018). Emerging evidence from the e-cigarette field reveals similar findings. In a recent study of 24 highly dependent smokers, only the Juul 59mg/mL nicotine concentration was comparable to tobacco smoking in reducing cigarette craving. The 18mg/mL concentration was associated with inadequate craving relief (Goldenson et al., 2021). Higher strength Juul pods (59mg/mL) have also been associated with an impressive 40% quit rate at 12 weeks among heavy smokers with schizophrenia (Caponnetto, 2019)

The above findings suggest that higher nicotine concentrations in e-liquids may be necessary to adequately address craving relief in smokers highly dependent on nicotine and to reduce persistent high rates of smoking among the most disadvantaged groups in society.

3. There is no compelling evidence that youth nicotine vaping causes smoking and there is more likely to be a diversion away from smoking

- Although many studies report a strong association between e-cigarette use among never smokers and later smoking (Berry et al., 2019; McCabe et al., 2018; Klein, 2018), whether later smoking is *caused* by vaping is debateable. Detailed examination of the studies claiming to have found a gateway effect showed that all had fundamental weaknesses, primarily uncorrected confounding (Chan et al., 2020; Lee et al., 2019) (which is probably an insurmountable challenge in any observational study).
- In a recent review of e-cigarettes and gateway effects (2017), Etter concluded that: *“Available data are compatible with a common liability model in which people who are liable to use nicotine are more likely to use both e-cigarettes and cigarettes”*. Others have echoed this view that other factors such as genetics, propensity to risk taking, family and peer influence contribute to both vaping and smoking (Gartner, 2017; Khouja et al., 2020).
- Population trends also support a common liability explanation. Despite the sharp increase in adolescent vaping in Canada and the US, there has not been an increase in adolescent smoking. In fact, there has been an accelerated decline in youth smoking coinciding with the rise in youth vaping in the US (Levy et al., 2019). Similarly, corrected statistics from the International Tobacco Control Policy Evaluation Project (ITC) Youth Tobacco and Vaping Survey show that past 30-day youth smoking prevalence

decreased in Canada between 2017 and 2018 from 10.7% to 10% (Hammond et al., 2020).

- There is also evidence that vaping can be a gateway *from* smoking for young people. A recent time-series analysis (Selya & Foxon, 2021) concluded that: “A *simulation model shows that a substantial diversion effect is needed to explain observed nicotine use trends among US adolescents*”. Likewise, an analysis of US data using propensity score matching found that initial e-cigarette users were *less likely* than others with similar propensity to initiate smoking (Shahab, Beard & Brown, 2020). Reasons for vaping may also be important; in a sample of 3,994 young English adults, although vaping for curiosity or to reduce smoking, were associated with an increase in smoking one year later, vaping to quit smoking was associated with a lower likelihood of smoking (Khouja, Taylor & Munafò, 2020).

Overall, the above studies suggests that the association between smoking and vaping are more likely to be due to common liabilities and, vaping can also be an ‘exit’ gateway from smoking. Nevertheless, evidence is still emerging and whilst no firm conclusions can be drawn at present, it is reassuring to observe that regular use of e-cigarettes among never smokers is rare.

Given the continued reduction in youth smoking and evidence that higher nicotine concentrations can both minimize harmful compensatory puffing and increase quit rates, a proposition to limit nicotine e-liquid concentrations in Canada seems premature. The 20mg/mL limit on nicotine e-liquid concentrations imposed by the EU Tobacco Products Directive was negotiated in 2013, before relevant evidence was available. Now, in 2021, there is burgeoning evidence available upon which Health Canada can make a balanced and informed decision. Following the arbitrary decision of the EU to reduce nicotine in e-cigarettes, the far safer product, could reduce the ‘diversion’ effect from smoking for both adult and youth smokers and encourage existing vapers to use more e-liquid – at an increased financial cost and possibly to their health.

References

Action on Smoking and Health (ASH) UK. Use of e-cigarettes (vapes) among adults in Great Britain Summary of key findings. 2020;(October):1–17. Available from:

<https://ash.org.uk/information-and-resources/fact-sheets/statistical/use-of-e-cigarettes-among-adults-in-great-britain-2020/>

Action on Smoking and Health (ASH) UK. ASH Briefing : Health inequalities and smoking Key points What are health inequalities ? [Internet]. 2016 [cited 2020 Jul 29]. Available from:

<https://ash.org.uk/information-and-resources/briefings/ash-briefing-health-inequalities-and-smoking/>

Berry KM, Fetterman JL, Benjamin EJ, Bhatnagar A, Barrington-Trimis JL, Leventhal AM, et al. Association of Electronic Cigarette Use With Subsequent Initiation of Tobacco Cigarettes in US Youths. *JAMA Netw open*. 2019;2(2):e187794.

Caponnetto P, Polosa R, Robson D, Bauld L. Tobacco smoking, related harm and motivation to quit smoking in people with schizophrenia spectrum disorders. Vol. 8, Health Psychology Research. 2020. p. 5–21.

Caponnetto, P (2019) Electronic cigarettes for smokers with schizophrenia spectrum disorders. PhD thesis. Available from: <https://dspace.stir.ac.uk/bitstream/1893/30671/1/Phd%20Thesis%20Definitive%2022.01.2020.docx.pdf>

Chan GCK, Stjepanović D, Lim C, et al. Gateway or common liability? A systematic review and meta-analysis of studies of adolescent e-cigarette use and future smoking initiation [Internet]. *Addiction*. 2020 [cited 2020 Dec 4];add.15246.

Cox S, Goniewicz ML, Kosmider L, McRobbie H, Kimber CF, Dawkins L. The time course of compensatory puffing with an electronic cigarette: Secondary analysis of real-world puffing data with high and low nicotine concentration under fixed and adjustable power settings. *Nicotine Tob Res* [Internet]. 2021 Jan 23 [cited 2021 Feb 17]; Available from: <https://academic.oup.com/ntr/advance-article/doi/10.1093/ntr/ntab013/6114004>

Dawkins, L. E., Kimber, C. F., Doig, M., Feyerabend, C., & Corcoran, O. Self-titration by experienced e-cigarette users: blood nicotine delivery and subjective effects. *Psychopharmacology*, 2016; 233(15–16), 2933–2941. <https://doi.org/10.1007/s00213-016-4338-2>

Dawkins, L. E., Cox, S., Goniewicz, M. L., McRobbie, H., Kimber, C. F., Doig, M., & Kosmider, L. “Real-world” compensatory behaviour with low nicotine concentration e-liquid: subjective effects and nicotine, acrolein and formaldehyde exposure. *Addiction*, 2018; 113: 1874-1882. doi: 10.1111/add.14271; <https://rdcu.be/0LbY>

Foulds J, Gandhi KK, Steinberg MB, Richardson DL, Williams JM, Burke M V., et al. Factors associated with quitting smoking at a tobacco dependence treatment clinic. *Am J Health Behav*. 2006;30(4):400–12.

Gartner CE. E-cigarettes and youth smoking: be alert but not alarmed. *Tob Control* [Internet]. 2017;tobaccocontrol-2017-054002. Available from: <http://tobaccocontrol.bmj.com/lookup/doi/10.1136/tobaccocontrol-2017-054002>

Glasheen C, Hedden SL, Forman-Hoffman VL, Colpe LJ. Cigarette smoking behaviors among adults with serious mental illness in a nationally representative sample. *Ann Epidemiol* [Internet]. 2014;24(10):776–80. Available from: <http://dx.doi.org/10.1016/j.annepidem.2014.07.009>

Goldenson NI, Fearon, IM, Buchhalter AB, Heningfield JE. An Open-Label, Randomised, Controlled, Crossover Study to Assess Nicotine Pharmacokinetics and Subjective Effects of the JUUL System with Three Nicotine Concentrations Relative to Combustible Cigarettes in Adult Smokers, *Nicotine & Tobacco Research*, 2021;, ntab001, <https://doi.org/10.1093/ntr/ntab001>

Hammond David, Reid Jessica L, Rynard Vicki L, Fong Geoffrey T, Cummings K Michael, McNeill Ann et al. Correction to: Prevalence of vaping and smoking among adolescents in Canada, England, and the United States: repeat national cross sectional surveys. *BMJ* 2020; 370 doi: <https://doi.org/10.1136/bmj.m2579> (Published 10 July 2020)

Klein JD. E-Cigarettes: A 1-Way Street to Traditional Smoking and Nicotine Addiction for Youth. 2018; Available from: <http://pediatrics.aappublications.org/content/141/1/e20172850>

Khouja, J. N., Suddell, S. F., Peters, S. E., Taylor, A. E., & Munafò, M. R. Is e-cigarette use in non-smoking young adults associated with later smoking? A systematic review and meta-analysis. *Tobacco Control*, Published Online First: 10 March 2020. doi: 10.1136/tobaccocontrol-2019-055433.

Kośmider, L., Kimber, C. F., Kurek, J., Corcoran, O., & Dawkins, L. E. Compensatory Puffing With Lower Nicotine Concentration E-liquids Increases Carbonyl Exposure in E-cigarette Aerosols. *Nicotine and Tobacco Research* 2018; 20 (8): 998-1003. doi: 10.1093/ntr/ntx162

Kosmider, L., Cox, S., Zaciera, M., Kurek, J., Goniewicz, M., McRobbie, H., Kimber, C. & Dawkins, L. Daily exposure to formaldehyde and acetaldehyde and potential health risk associated with use of high and low nicotine e-liquid concentrations. *Scientific Reports* 2020; 10: 6546 <https://doi.org/10.1038/s41598-020-63292-1>

Lee PN, Coombs KJ, Afolalu EF. Considerations related to vaping as a possible gateway into cigarette smoking: An analytical review. *F1000Research* 2019;

Leventhal AM, Bello MS, Galstyan E, Higgins ST, Barrington-Trimis JL. Association of Cumulative Socioeconomic and Health-Related Disadvantage With Disparities in Smoking Prevalence in the United States, 2008 to 2017 Supplemental content. *JAMA Intern Med* [Internet]. 2019;179(6):777–85. Available from: <https://jamanetwork.com/>

Levy DT, Warner KE, Michael Cummings K, et al. Examining the relationship of vaping to smoking initiation among US youth and young adults: A reality check. *Tob Control* 2019; Nov;28(6):629-635. doi: 10.1136/tobaccocontrol-2018-054446.

Lindson N, Chepkin SC, Ye W, Fanshawe TR, Bullen C, Hartmann-Boyce J. Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Reviews* 2019, Issue 4. Art. No.: CD013308. DOI: 10.1002/14651858.CD013308. Accessed 11 February 2021.

McCabe SE, West BT, McCabe V V. Associations between early onset of e-cigarette use and cigarette smoking and other substance use among us adolescents: A national study. *Nicotine Tob Res.* 2018;20(8):923–30.

McClave AK, McKnight-Eily LR, Davis SP, Dube SR. Smoking Characteristics of Adults With Selected Lifetime Mental Illnesses: Results From the 2007 National Health Interview Survey. *Am J Public Health* [Internet]. 2010 Dec 1;100(12):2464–72. Available from: <https://doi.org/10.2105/AJPH.2009.188136>

Przulj D, Wehbe L, McRobbie H, Hajek P. Progressive nicotine patch dosing prior to quitting smoking: Feasibility, safety, and effects during the pre-quit and post-quit periods. *Addiction* [Internet]. 2018; Available from: <http://doi.wiley.com/10.1111/add.14483>

Richardson S, McNeill A, Brose LS. Smoking and quitting behaviours by mental health conditions in Great Britain (1993–2014). *Addict Behav.* 2019; Mar;90:14-19. doi: 10.1016/j.addbeh.2018.10.011

Shahab L, Beard E, Brown J. Association of initial e-cigarette and other tobacco product use with subsequent cigarette smoking in adolescents: a cross-sectional, matched control study. *Tob Control* 2020 0:tobaccocontrol-2019-055283.

Smets J, Baeyens F, Chaumont M, Adriaens K, Van Gucht D. When Less is More: Vaping Low-Nicotine vs. High-Nicotine E-Liquid is Compensated by Increased Wattage and Higher Liquid

Consumption. Int J Environ Res Public Health. 2019 Feb 28;16(5):723. doi: 10.3390/ijerph16050723

Soar, K., Dawkins, L., Robson, D. and Cox, S. Smoking amongst adults experiencing homelessness: a systematic review of prevalence rates, interventions and the barriers and facilitators to quitting and staying quit. Journal of Smoking Cessation 2020; 15 (2): 94-108. <https://doi.org/10.1017/jsc.2020.11>

Thirlway, Frances, Bauld, Linda, McNeill, Ann, et al. Tobacco smoking and vulnerable groups: Overcoming the barriers to harm reduction [Internet]. Vol. 90, Addictive Behaviors. 2019 [cited 2021 Jan 29]. p. 134–5. Available from: <http://eprints.whiterose.ac.uk/139065/>

Acknowledgements

With thanks to Cancer Research UK (CRUK) for funding the work described in 1) above. Grant reference: C50878/A21130