

## Letter

# Nicotine Flux: A Potentially Important Tool For Regulating Electronic Cigarettes

Thomas Eissenberg PhD<sup>1</sup>, Alan Shihadeh SCD<sup>1,2</sup>

<sup>1</sup>Center for the Study of Tobacco Products, Department of Psychology, College of Humanities and Sciences, Virginia Commonwealth University, Richmond, VA; <sup>2</sup>Aerosol Research Laboratory, Faculty of Engineering and Architecture, American University of Beirut, Beirut, Lebanon

Corresponding Author: Thomas Eissenberg, PhD, Center for the Study of Tobacco Products, Department of Psychology, College of Humanities and Sciences, Virginia Commonwealth University, PO Box 980205, Richmond, VA 23298, USA.

Telephone: 804-827-4617; Fax: 804-828-7862; E-mail: [teissenb@vcu.edu](mailto:teissenb@vcu.edu)

We thank Drs. Farsalinos, Voudris, and Le Houezec for their recent correspondence<sup>1</sup> regarding our proposal that electronic cigarette (ECIG) regulation can be aided by attention to nicotine flux, defined as the nicotine emitted per puff second by a given design under given use conditions.<sup>2</sup> In this reply, we note that we agree with several of the issues raised in their letter, find that existing data do not support others, and describe how, based on their correspondence<sup>1</sup> and our published work,<sup>2</sup> we all are in support of nicotine flux as an important regulatory tool.

We agree, as originally presented in our commentary,<sup>2</sup> that there is great variability in ECIG design and performance and that regulation based on a single factor (e.g., liquid nicotine concentration) is unwise. We also agree that nicotine can induce pleasure (or positive reinforcement) and that this drug-induced subjective experience is an important factor in maintaining tobacco cigarette smoking,<sup>3</sup> as is nicotine-induced avoidance or suppression of aversive abstinence symptoms (negative reinforcement; e.g., Eissenberg<sup>4</sup>). We agree that the positive and negative reinforcing effects of nicotine are likely critical factors in those cases where ECIGs have substituted for cigarette smoking in former smokers.<sup>5</sup> If we set aside any of our concerns about the health risks of long-term ECIG use in former cigarette smokers, we agree that maximizing the positive and negative reinforcing characteristics of ECIGs for smokers is an important regulatory goal, so that any available ECIG is reinforcing enough upon first usage that a cigarette smoker substitutes, immediately and completely, the purportedly less lethal ECIG in place of the more lethal tobacco cigarette. We tried to make very clear in our commentary that regulating ECIGs based on nicotine flux will help prevent the marketing of device/liquid combinations that, under a wide range of user behaviors, are unable to deliver nicotine effectively and thus do not allow for this immediate and complete substitution. Finally, one of our most important areas of agreement is that nicotine-induced positive reinforcement should not be a contributing factor in initiation of ECIG use by people who are otherwise nicotine-naïve because ECIG use may be associated with as-yet-unknown disease risk.

Where the extant data do not support the text of the correspondence is in regard to two inter-related topics: the ability of ECIGs to deliver nicotine and the attention paid to positive reinforcement in relation to tobacco use. With regard to ECIG-induced nicotine delivery, the data that we have published are very clear: some ECIGs are capable of delivering to the user cigarette-like doses of nicotine with cigarette-like rapidity.<sup>6</sup> That is, we observed increases in plasma nicotine concentration in 15 experienced ECIG users who had taken 10 puffs from their preferred ECIG using their preferred liquid that rose from a baseline mean of 2.4 ng/ml (*SEM* = 0.2) to 19.2 ng/ml (*SEM* = 2.3) immediately after the 10th puff (Spindle et al.<sup>6</sup>; see also Vansickel and Eissenberg<sup>7</sup> for increases of lesser magnitude but similar rapidity). By way of comparison, when 32 experienced tobacco cigarette smokers took 10 puffs from their preferred brand of tobacco cigarette, their mean plasma nicotine concentration rose from a baseline of 2.1 ng/ml to 18.8 ng/ml immediately after the 10th puff.<sup>8</sup> Indeed, as reported at the 2014 annual meeting of the European chapter of the Society for Research on Nicotine and Tobacco, preliminary results from 10 nicotine-experienced participants suggest that 10 puffs from an ECIG (3.3V battery, 1.5  $\Omega$  dual coil cartomizer) loaded with 1 ml of 26 mg/ml liquid can raise plasma nicotine concentration from 5.4 ng/ml (*SEM* = 1.5) to 34.7 ng/ml (*SEM* = 8.4) immediately after the 10th puff.<sup>9</sup> Thus, some device/liquid combinations on the market today are capable of surpassing the nicotine dose seen with a tobacco cigarette, and plasma concentrations rise with a rapidity that, based on data to date, equals that of a tobacco cigarette. At least in regard to dose, these data from human participants are in accord with nicotine yield data we also have reported previously.<sup>10</sup> If ECIGs continue to improve in their ability to deliver large nicotine doses, there is cause for concern regarding toxicity for the user. We tried to make very clear in our commentary that regulating ECIGs based on nicotine flux will help prevent the marketing of device/liquid combinations that, under plausible conditions of user behavior, are able to deliver nicotine at far greater doses than a tobacco cigarette.

With regard to positive reinforcement, these effects have long been a concern among researchers studying drug abuse generally,<sup>11</sup> nicotine specifically,<sup>12–14</sup> and novel tobacco products more recently.<sup>15</sup> There is no need here to elaborate on this extensive literature, except to say that a primary concern in assessing the abuse liability of a novel drug compound with central nervous system effects is to determine the extent to which it may support misuse and dependence, especially among drug-naïve individuals who use the drug for the first time.<sup>11</sup> As noted in our commentary: “... a product of unknown risk that induces drug dependence in previously drug-naïve individuals is a legitimate public health concern.”<sup>2</sup> While we highlighted that more work will be needed to relate nicotine flux to subjective effect (i.e., positive reinforcement and abuse liability), we remain convinced that nicotine flux may be a valuable tool in helping prevent the marketing of device/liquid combinations that, under plausible conditions of user behavior, could lead to the initiation of ECIG use in nicotine-naïve individuals that we and Farsalinos et al.<sup>1</sup> are eager to avoid.

Overall, we believe that Farsalinos et al.<sup>1</sup> are in agreement with our position that, assuming safety of long-term ECIG use, nicotine flux can be used as means to avoid the marketing of devices that are unable to deliver nicotine effectively enough to help tobacco smokers quit their lethal tobacco cigarettes. Where we may disagree is in the use of nicotine flux to avoid the potential for toxicity and/or high abuse liability of ECIGs. This use of nicotine flux increasingly may become relevant as this product category continues to evolve, especially if new device/liquid combinations deliver ever higher doses of nicotine, increasing the risk of toxicity and/or likelihood of abuse/dependence in otherwise nicotine-naïve individuals. We agree that education, regulation of advertising, and prohibition of promotion to nonsmoking youth will all play a role in avoiding these negative outcomes.<sup>1</sup> Of course, all of these interventions have been applied to tobacco cigarettes, and youth continue to initiate smoking at the rate of 3,200/day in the United States.<sup>16</sup> We suggest nicotine flux as a complementary approach to these and whatever additional interventions are supported by subsequent data regarding ECIG risk (e.g., restricted access based on age and/or smoking status). With careful empirical work, a flux range may be identified such that, when nicotine-naïve individuals try an ECIG for the first time, they do not experience nicotine-mediated effects that induce them to continue.

We conclude this response by addressing an issue raised by Farsalinos et al.<sup>1</sup> that goes far beyond the use of nicotine flux as a regulatory tool. They write “However, this raises an important ethical issue: should a product, which is probably beneficial for a part of the population (smokers), be restricted (which could result in reduced efficacy as a smoking substitute) because some other parts of the population (non-smokers) decide to *voluntarily* adopt its use and expose themselves to a new (even minor) risk?” (emphasis in the original). This statement raises several concerns. First, there is a paucity of objectively verified empirical evidence that ECIGs have a net beneficial effect for smokers over the long term, and we await more research investigating this important point. Second, we did not mean to imply that restricting nicotine flux (or other product features) could result in reduced efficacy of ECIGs as tobacco cigarette substitutes. Indeed, our vision of empirically based tobacco product regulation involves research aimed at investigating policy effect, to ensure that the benefit to public health is maximized. Finally, while we agree with the idea that ECIGs pose an ethical issue, we disagree with this framing of it. If, as Farsalinos et al.<sup>1</sup> posit—and as the tobacco industry long has argued

disingenuously<sup>17</sup>—the problem is one of voluntarily choosing to use a dependence-producing product, then smokers have made that same voluntary choice already, when they chose to smoke tobacco cigarettes. We do not accept this reasoning but, if others do, then we argue that there is no ethical justification to privilege one set of volunteers (smokers) over another (nonsmokers). A balance must be found such that there is equity for both groups. That balance may involve something other than unrestricted access to products with high abuse liability that may jeopardize the health of nonsmokers and may, in fact, be unnecessary for the health of smokers (i.e., products of lower abuse liability may substitute for tobacco cigarettes effectively). Importantly, this idea of taking into account both individual and public health has been incorporated into legislation in the United States that concerns tobacco product regulation.<sup>18</sup> One potential equitable solution—likely to be challenged by the burgeoning ECIG industry that now includes the tobacco industry itself—might involve restricting sales of ECIG products that contain nicotine to those individuals who are already dependent on the drug. In short, we believe that the correct framing of the important ethical issue to which Farsalinos et al.<sup>1</sup> allude is: “Under what conditions is the for-profit manufacture and sale of a product of unknown toxicity to be allowed when that product has been designed to contain, yield, and deliver dependence-supporting doses of a highly addictive drug?” While our commentary did not address this larger question, we believe that it is a sound starting point for an evidence-based regulatory process driven not by profit but rather by concern for the health of all.

## Funding

The work of TE and AS is supported, in part, by the National Institute on Drug Abuse of the National Institutes of Health under Award Number P50DA036105 and the Center for Tobacco Products of the US Food and Drug Administration. The content of this letter is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the US Food and Drug Administration.

## Declaration of Interests

*None declared.*

## References

1. Farsalinos K, Voudris V, Le Houezec J. Risks of attempting to regulate nicotine flux in electronic cigarettes. *Nicotine Tob Res.* In press.
2. Shihadeh A, Eissenberg T. Electronic cigarette effectiveness and abuse liability: predicting and regulating “nicotine flux” [published online ahead of print September 1, 2014]. *Nicotine Tob Res.* doi:10.1093/ntr/ntu175
3. Glautier S. Measures and models of nicotine dependence: positive reinforcement. *Addiction.* 2004;99(suppl 1):30–50.
4. Eissenberg T. Measuring the emergence of tobacco dependence: the contribution of negative reinforcement models. *Addiction.* 2004;99(suppl 1):5–29.
5. Caponnetto P, Polosa R, Russo C, Leotta C, Campagna D. Successful smoking cessation with electronic cigarettes in smokers with a documented history of recurring relapses: a case series. *J Med Case Rep.* 2011;5:585.
6. Spindle T, Breland A, Karaoghlanian N, Shihadeh AL, Eissenberg T. Preliminary results of an examination of electronic cigarette user puff topography: the effect of a mouthpiece-based topography measurement device on plasma nicotine and subjective effects [published online ahead of print September 19, 2014]. *Nicotine Tob Res.* doi:10.1093/ntr/ntu186

7. Vansickel AR, Eissenberg T. Electronic cigarettes: effective nicotine delivery after acute administration. *Nicotine Tob Res.* 2013;15:267–270.
8. Vansickel AR, Cobb CO, Weaver MF, Eissenberg TE. A clinical laboratory model for evaluating the acute effects of electronic “cigarettes”: nicotine delivery profile and cardiovascular and subjective effects. *Cancer Epidemiol Biomarkers Prev.* 2010;19(8):1945–1953.
9. Eissenberg T. Acute effects of electronic cigarettes in adults: nicotine delivery and puff topography. Paper presented at the 15th Annual Meeting of the Society for Research on Nicotine and Tobacco – Europe, Santiago de Compostela, Spain, September 18; 2014.
10. Talih S, Balhas Z, Eissenberg T, et al. Effects of user puff topography, device voltage, and liquid nicotine concentration on electronic cigarette nicotine yield: measurements and model predictions [published online ahead of print September 3, 2014]. *Nicotine Tob Res.* doi:10.1093/ntn/ntu174
11. Balster RL, Bigelow GE. Guidelines and methodological reviews concerning drug abuse liability assessment. *Drug Alcohol Depend.* 2003;70:S13–S40.
12. Houtsmuller EJ, Fant RV, Eissenberg TE, Henningfield JE, Stitzer ML. Flavor improvement does not increase abuse liability of nicotine chewing gum. *Pharmacol Biochem Behav.* 2002;72:559–568.
13. Houtsmuller EJ, Henningfield JE, Stitzer ML. Subjective effects of the nicotine lozenge: assessment of abuse liability. *Psychopharmacology (Berl).* 2003;167:20–27.
14. Schuh KJ, Schuh LM, Henningfield JE, Stitzer ML. Nicotine nasal spray and vapor inhaler: abuse liability assessment. *Psychopharmacology (Berl).* 1997;130:352–361.
15. Carter LP, Stitzer ML, Henningfield JE, O'Connor RJ, Cummings KM, Hatsukami DK. Abuse liability assessment of tobacco products including potential reduced exposure products. *Cancer Epidemiol Biomarkers Prev.* 2009;18:3241–3262.
16. US Department of Health and Human Services. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General.* Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.
17. Henningfield JE, Rose CA, Zeller M. Tobacco industry litigation position on addiction: continued dependence on past views. *Tob Control.* 2006;15(suppl 4):iv27–iv36.
18. Family Smoking Prevention and Tobacco Control Act (FSPTCA) of 2009, HR 1256, 111th Cong., 2010.