

## Letter

# Risks of Attempting to Regulate Nicotine Flux in Electronic Cigarettes

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In their recent analysis, Shihadeh and Eissenberg<sup>1</sup> support that by regulating nicotine flux in electronic cigarettes (ECs) could be a valuable tool in the regulatory process that would increase effectiveness and reduce the chance for abuse liability. Herein, we present the view that such a regulation could endanger the effectiveness of e-cigarettes as smoking substitutes.

## Nicotine Delivery From Tobacco Cigarettes

Although tobacco cigarettes deliver 1–3 mg of nicotine (from about 14 mg in each rod), the levels of daily nicotine intake may vary considerably between users. This is partly attributed to a substantial variability in nicotine intake per cigarette caused by different smoking intensity.<sup>2</sup> It is also possible to smoke more than one cigarette consecutively, further avoiding the limitation of the tobacco cigarette rod standardized design. Therefore, smokers can adjust cigarette use based on personal needs, while it is extremely unlikely for smoking to cause nicotine intoxication or overdose.

## Nicotine Delivery From ECs

Electronic cigarettes differ remarkably from tobacco cigarettes in terms of nicotine delivery. There is no standardized unit of consumption. Consumers usually report their daily consumption in milliliters of liquid,<sup>3</sup> which cannot be directly compared with daily cigarette consumption. The variability in equipment design and potential, and the range of nicotine content in EC liquids provide consumers with the ability to adjust use patterns and nicotine intake. Surveys of dedicated EC users (which were all former smokers) have shown that high nicotine levels are important especially for the initiation of EC use.<sup>3,4</sup> Although nicotine delivery to the aerosol can be similar or higher than tobacco cigarettes,<sup>5,6</sup> clinical studies of EC use have shown that the nicotine absorption potential is significantly lower compared with tobacco cigarettes, even when new generation devices are used.<sup>7</sup> This is mostly attributed to the low speed of nicotine absorption, and clearly indicates that nicotine intoxication is highly unlikely when ECs are used as intended. Therefore, despite the ability to adjust use patterns, ECs are currently not as efficient as tobacco cigarettes in nicotine delivery.

We propose that the comparison between ECs and tobacco cigarettes would be similar to comparing, respectively a car with a large

selection of powerful (in selected cases) engines (i.e., nicotine delivery to the aerosol) but very heavy structure (i.e., reduced rate of absorption for a given nicotine content per puff), with a car with less variability and lower-powered engines but very lightweight structure. With current technology, overall performance (i.e., nicotine delivery to the bloodstream) is definitely in favor of the tobacco cigarette, and smokers may be unable to adequately satisfy their nicotine cravings with EC use despite the ability to adjust use patterns.

## The Pleasure Factor in EC Use

It is physiologically plausible to support that nicotine induces pleasure and reduces anxiety in smokers.<sup>8</sup> The pleasure factor has been largely neglected and marginalized by the tobacco control movement which is usually following the pathology paradigm framework for nicotine use.<sup>9</sup> Perceived pleasure should not be a reason for anyone to initiate smoking (due to exposure to known risks for health damage) or EC use (due to exposure to yet unknown, although evidently much lower than smoking, risk). However, it should be considered and evaluated when discussing about smoking substitution. Surveys indicate that pleasure could be a potential reason for smokers to choose and maintain long-term EC use.<sup>3,10</sup> This is probably one of the main reasons for the enormous variability of different flavors available in EC liquids,<sup>10</sup> and could explain the variability of devices with different characteristics, design, and properties. The recent development and marketing of atomizers with adjustable airflow probably reflects the different preferences by users, and the effort of manufacturers to create products which can be customized based on self-preference. Since the main objective should always be elimination of smoking, the pleasure effect could be an advantage of ECs over other products which should be welcomed if it contributes to smoking reduction or cessation. Further studies are needed to examine this aspect.

## Is There a Need to Regulate Nicotine Flux in ECs?

Based on the evidence presented above, and with current technological evolution, it is our opinion that regulating nicotine flux in ECs, in terms of restricting usage patterns (e.g., restrict puff duration or apply a minimum interpuff interval), is unnecessary. It carries the potential risk of reducing ECs' efficacy as smoking substitutes, while it provides no benefit in terms of safety. There is already the example

of regulatory decisions by the European Union, which defined an upper limit of 20 mg/ml nicotine concentration in EC liquids ([http://ec.europa.eu/health/tobacco/docs/dir\\_201440\\_en.pdf](http://ec.europa.eu/health/tobacco/docs/dir_201440_en.pdf)) based on information about potential nicotine delivery to the aerosol.<sup>6</sup> They failed to recognize that both effectiveness and abuse liability are determined by nicotine absorption (speed and amount delivered to the blood stream) rather than nicotine delivery to the aerosol. As a result, it is possible that such a restriction could exclude some smokers from effectively using ECs as smoking substitutes.

Research on nicotine flux could become an essential tool in the development of more effective EC products and in informing consumers about the characteristics of each device so that they make appropriate choices. There are two options for ECs development: (a) using higher nicotine concentration in liquid and (b) improving the absorption rate. The former results in intense (and, for many users, unbearable) throat irritation (“throat hit”), added to the irritation induced by the humectants in the aerosol (propylene glycol and glycerol). The latter may occur from adjusting use behavior (e.g., taking longer and deeper puffs, although this may make the use tiring), adjusting power delivery (which leads to more liquid consumption and aerosol production per given puff duration) and reformulating EC liquids in order to deliver and deposit nicotine more effectively into the lungs. It is possible that improvement in nicotine delivery efficacy could make ECs more addictive. This is not a concern for smokers (who are already nicotine-dependent) but for nonsmokers who may adopt EC use. 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 (nonsmokers) decide to *voluntarily* adopt its use and expose themselves to a new (even minor) risk? Measures such as proper education, regulation of advertising, and prohibition of promotion and sales to nonsmoking youth could effectively ensure that ECs will not be used by nonsmokers without restricting their potential to substitute smoking.

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