

Nicotine content in electronic cigarettes

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This report has been prepared by the signed physicians, Dr Konstantinos Farsalinos and Dr Giorgio Romagna, after a request from Electronic Cigarette Associations' Alliance (ECAA). It is based on scientific studies and data, and provides evidence on the comparative levels of nicotine in tobacco cigarettes and electronic cigarette liquid. The authors declare no conflict of interest. They have received no financial compensation for this report and they have no financial relation with ECAA or any other electronic cigarette association. Additionally, they have no financial interest in the electronic cigarette industry.

Recently, the European Commission published a new Tobacco Products Directive proposal (hereafter TPD) [1], stating that only nicotine-containing products with nicotine levels less than 2mg or nicotine concentration less than 4mg/ml can be sold as consumer products. This decision was based on the nicotine content of medicinal products (Nicotine Replacement Therapies, NRTs) for smoking cessation. It should be mentioned that this decision has no scientific basis, since it compares two incomparable product categories (NRTs and electronic cigarettes) that have different mode of use, different applications and different characteristics. It is somewhat arbitrary to compare a pharmaceutical method for smoking cessation with a product that is used as an alternative-to-smoking habit. NRTs provide nicotine to users, as a means to stop smoking. However, their effects in smoking cessation are extremely disappointing; they have a success rate of 6.75% at 6 months when combined with regular behavioural support and monitoring, with rates probably being much lower if used alone [2]. Additionally, NRTs are marketed in forms that can lead to uncontrollable use. For example, it is extremely easy for the user to take as many nicotine gums as he wants at the same time, or use as many nicotine patches as he wants, thus absorbing higher levels of nicotine. Contrary to all these, the electronic cigarette is used (and can be successful in smoking cessation) because it provides

pleasure to the users. Pleasure that is maybe less compared to tobacco cigarettes but enough to keep them off smoking or significantly reduce cigarette consumption. Moreover, it deals with both the chemical and the behavioural addiction to smoking, and this is a unique feature of this product. Finally, electronic cigarette liquids are not used in their original format; they are evaporated by the device, and the rate of evaporation is the most limiting factor in the amount of vapour production and nicotine delivery. Unlike NRTs, it is impossible to use them in an uncontrollable way because the limitations in evaporation rate imposed by the device prevent this. Considering the fact that electronic cigarettes are marketed only for smokers that want to use them as an alternative habit, it seems logical that the nicotine delivery potential of electronic cigarettes should be compared with tobacco cigarettes.

The issue of nicotine content that should be present in electronic cigarettes is quite complex. The most important factor is nicotine absorption. Obviously, the higher the rate of nicotine absorption is, the lower the nicotine level that should be present in the liquid. Two studies have shown that nicotine absorption from electronic cigarettes is significantly lower compared to tobacco cigarettes. A study by Vansickel and coworkers [\[3\]](#) showed that nicotine levels in plasma did not increase in smokers who were asked to use an electronic cigarette with 1.8% nicotine content (Figure 1). In comparison, a significant rise was observed when they smoked their own-brand tobacco cigarette. Additionally, the characteristic early peak in plasma nicotine level that is observed immediately after smoking tobacco cigarette (known as “nicotine boost”) was not observed after electronic cigarette use (Figure 1). This was clinically validated by the stability of heart rate after electronic cigarette use, compared to the rise observed after cigarette smoking. Another study by Bullen and coworkers [\[4\]](#) found that plasma nicotine levels after using the electronic cigarette (with 1.6% nicotine content) were 10 times lower compared to post-smoking a tobacco cigarette. Peak plasma nicotine level was only 1.3ng/ml after electronic cigarette use, compared to 2.1ng/ml after using a nicotine inhaler (NRT) and 13.4ng/ml after smoking a regular cigarette. Both studies were performed in smokers that had no experience with the electronic cigarette. It has been suggested that there is a learning curve and nicotine levels might increase to higher levels in experienced users of the electronic cigarette. However, a clinical study by Farsalinos and coworkers [\[5\]](#) (European Society of Cardiology 2012 annual congress, submitted for publication) found only

slight elevation in diastolic blood pressure of experienced electronic cigarette users after using the device ad lib for 7 minutes (with 0.9% nicotine content), while smokers had significant elevations in both systolic and diastolic blood pressure, and in heart rate. Since we know that nicotine is responsible for all hemodynamic effects (through activation of the sympathetic nervous system), this finding represents clinical evidence that nicotine levels are lower after electronic cigarette use, even in experienced users, compared to smokers after smoking. In conclusion, there is substantial evidence that electronic cigarette use results in lower and slower nicotine absorption compared to tobacco cigarette.

Another important issue is the definition of nicotine content in tobacco cigarettes. Nicotine content displayed in packaging information is not a measure of the level present in the tobacco cigarette but is the level measured in the smoke after smoking the cigarette according to FTC/ISO protocol (that is, 35ml puff lasting 2 seconds and making one puff every 60 seconds). Most researchers agree that this definition significantly underestimates the true level of nicotine delivered to the smoker, because the ISO protocol does not represent the true smoking patterns of smokers because they usually take deeper and more frequent puffs. Djordjevic and coworkers [6] found that in reality smokers received 2.5 times more nicotine when they smoked compared to what was predicted if they smoked according to ISO standard. Additionally, they received 2.6 times more tar and two-fold higher levels of nitrosamines and polycyclic aromatic hydrocarbons. They concluded that FTC/ISO protocol underestimates nicotine and carcinogen doses in smokers. Hammond and coworkers [7] estimated that FTC/ISO protocol underestimated by two- to four-fold the amount of nicotine delivered to the smoker. Thus, nicotine content information displayed on cigarette packaging is misleading and far lower than the true amount delivered to the smoker.

Electronic cigarette use pattern and liquid consumption have not been systematically studied yet. Therefore, we decide to test these characteristics as part of a research protocol examining the effects of electronic cigarettes on the cardiovascular system. We recruited 35 experienced electronic cigarette users, aged 39 ± 5 years. All participants were ex-smokers who had been using the electronic cigarette daily for more than 1 month (mean duration of use: 4.3 ± 2.9 months) and reported daily consumption of 4.9 ± 2.4 ml liquid. They were asymptomatic and

healthy, and had normal physical examination, blood pressure, resting electrocardiogram and echocardiogram. After an 8-hour period of abstinence from using the device, we asked them to use a commercially-available electronic cigarette for 5 minutes intensively, taking care to make at least one puff every 30 seconds. The liquid used had a nicotine content of 0.9% (9mg/ml concentration). Five minutes is the average time needed for smokers to smoke one tobacco cigarette. By definition, due to the 8-hour abstinence, participants would use the electronic cigarette more intensively than usually. Moreover, the recruitment of experienced users meant that they used the device more intensively compared to novice users. In order to measure the liquid consumption we weighted the liquid-containing atomizer, using a precision scale, before they started and after they finished using the electronic cigarette for the 5-minutes period. The amount of liquid consumed was $59 \pm 18\text{mg}$. The specific gravity of electronic cigarette liquids is usually more than 1.1, so the volume consumed was estimated to be $0.054 \pm 0.016\text{ml}$. It correlated with the amount of daily liquid consumption reported by the participants (Pearson correlation $r = 0.543$, $P = 0.001$). It should be emphasized that this was the consumption from using a liquid with 9mg nicotine per ml, and, similarly to tobacco cigarettes, we expect that consumption would be significantly lower if users were given a higher nicotine-content liquid.

According to the above-mentioned measurements, we can estimate the maximum nicotine concentration of liquids that would be comparable to the maximum allowable nicotine content in tobacco cigarettes (1mg nicotine per cigarette). Although we have explained that nicotine absorption from electronic cigarettes is lower compared to smoking tobacco cigarettes and that the nicotine content displayed on cigarette packaging is lower than what smokers receive in real situations, we will examine the worst-case scenario for electronic cigarettes: we will assume that nicotine absorption is similar to smoking and that the amount of nicotine obtained from smoking is that derived from FTC/ISO protocol. Our test has shown that for the same time that a smoker consumes one tobacco cigarette, an electronic cigarette user consumes on average 0.054ml of liquid. Considering that 1mg of nicotine is the maximum allowable amount of nicotine delivered per cigarette, the electronic cigarette liquid nicotine concentration needed to deliver 1mg of nicotine is 18.5mg per ml of liquid. This is a level far higher than that proposed by European

Commission. Additionally, it must be emphasized that this is the amount derived when we compare very light (and virtually unrealistic) tobacco cigarette use with intensive electronic cigarette use. Moreover, it is based on the assumption that nicotine is similarly absorbed from tobacco and electronic cigarette, although we have evidence that this is not the case and that electronic cigarette use leads to far lower nicotine absorption. Therefore, according to the worst-case scenario for electronic cigarettes, 1.85% nicotine content in liquids (18.5mg per ml) is similar to 1mg nicotine per cigarette. In realistic and pragmatic terms, the comparative level of nicotine should be significantly higher than 1.85%, probably in the region of 2.4% or even more.

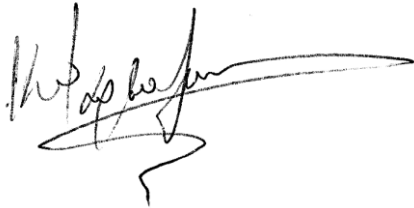
Cigarette smoking exposes the person to more than 4000 chemicals. At least 50 substances are categorized as carcinogenic according to World Health Organization. Every puff of cigarette smoke administers 1000 trillion free radicals to the smoker [\[8\]](#). Until now, all studies (laboratory chemical, toxicological and clinical) have found that electronic cigarettes are, by far, safer alternatives to smoking. Electronic cigarettes are marketed for the smokers who cannot quit smoking with currently-approved medical methods. Unfortunately, this is the majority, since the most effective medications have long-term success rate of less than 20% [\[9\]](#). Commonly, smokers start using the electronic cigarette with liquids containing at least 1.8% nicotine, otherwise the success rate in smoking cessation is significantly compromised. Undoubtedly, regulation should be implemented to make sure that only quality products are available for the users. Safety labeling should also be imposed, but the risk involves only accidental ingestion; it is extremely unlikely that liquids can cause nicotine intoxication when used in vapor form. Even considering the case of accidental ingestion, according to the 2010 report of the American Association of Poison Control Centers' National Poison Data System, from 8,788 cases of reported accidental exposure to tobacco or other nicotine-containing products, electronic cigarettes were involved in only 30 cases. No case developed major adverse health effects or death [\[10\]](#).

In reality, the proposal of the European Commission represents a ban on the sales of electronic cigarette, depriving users of a safer alternative. This might lead to the development of a black market, and more importantly, electronic cigarette users may have to take legal action in order to protect their health. We are certain that the

European Commission and European Parliament understand their responsibility and ethical duty towards the smokers, and they will decide wisely and based on scientific facts.

Thank you

Dr Konstantinos Farsalinos

A handwritten signature in black ink, appearing to read 'Konstantinos Farsalinos', with a long horizontal stroke extending to the right.

Dr Giorgio Romagna

A handwritten signature in black ink, appearing to read 'Giorgio Romagna', with a long horizontal stroke extending to the right.

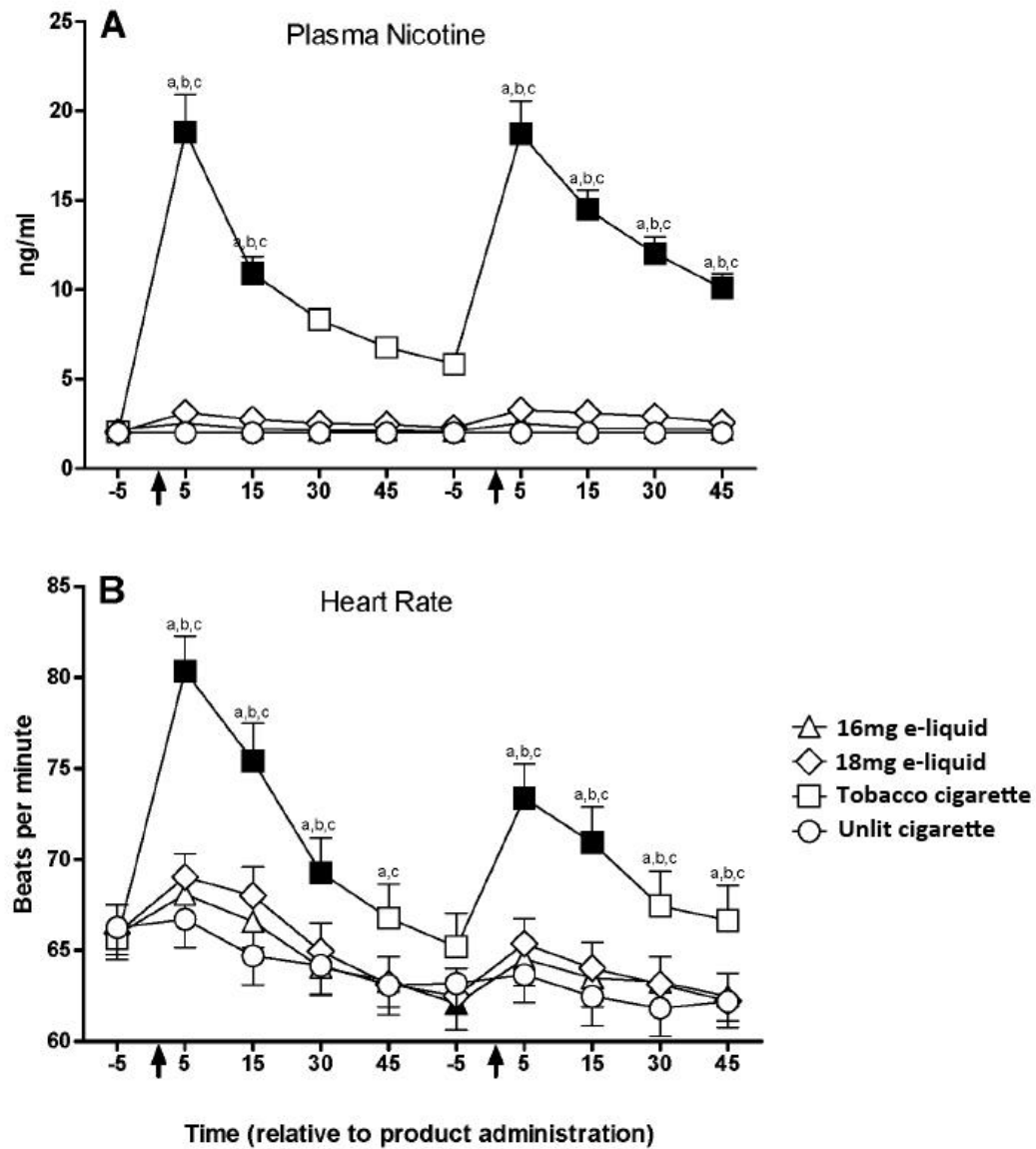


Figure 1. Mean data for nicotine blood plasma (panel A) and heart rate (panel B), as a function of condition and time. Adapted from reference 3.

References

1. European Commission. Proposal for a directive of the European Parliament and of the Council on the approximation of the laws, regulations, and administrative provisions of the Member States concerning the manufacture, presentation and sale of tobacco and related products. http://ec.europa.eu/health/tobacco/docs/com_2012_788_en.pdf accessed 03-02-2013.
2. Moore D, Aveyard P, Connock M, Wang D, Fry-Smith A, Barton P. Effectiveness and safety of nicotine replacement therapy assisted reduction to stop smoking: systematic review and meta-analysis. *BMJ* 2009;338:b1024.
3. Vansickel AR, Cobb CO, Weaver MF, Eissenberg TE. A clinical and laboratory model for evaluating the acute effects of electronic “cigarettes”: nicotine delivery profile and cardiovascular and subjective effects. *Cancer Epidemiol Biomarkers Prev* 2010;19:1945-1953.
4. Bullen C, McRobbie H, Thornley S, Glover M, Lin R, Laugesen M. Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. *Tob Control* 2010;19:98-103.
5. Farsalinos K, Tsiapras D, Kyrzopoulos S, Avramidou E, Vassilopoulou D, Voudris V. Acute effects of using an electronic nicotine-delivery device (e-cigarette) on myocardial function: comparison with the effects of regular cigarettes. *European Heart Journal* 2012;33(Suppl):203.
6. Djordjevic MV, Stellman SD, Zang E. Doses of nicotine and lung carcinogens delivered to cigarette smokers. *J Natl Cancer Inst* 2000;92:106-111.
7. Hammond D, Fong GT, Cummings M, O'Connor RJ, Giovino GA, McNeill A. Cigarette yields and human exposure: a comparison of alternative testing regimens. *Cancer Epidemiol Biomarkers Prev* 2006;15:1495-1501.

8. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease. An update. J Am Coll Cardiol 2004;43:1731-1737.
9. Rigotti NA, Pipe AL, Benowitz NL, Arteaga C, Garza D, Tonstad S. Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: a randomized trial. Circulation 2010;121:221-229.
10. Bronstein AC, Spyker DA, Cantilena LR, Green JL, Rumack BH, Dart RC. 2010 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 28th annual report. Clinical Toxicology 2011;49:910-941.