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Effects of User Puff Topography, Device Voltage, and Liquid Nicotine Concentration on Electronic Cigarette Nicotine Yield: Measurements and Model Predictions

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ABSTRACT

Introduction: Some electronic cigarette (ECIG) users attain tobacco cigarette-like plasma nicotine concentrations, while others do not. Understanding the factors that influence ECIG aerosol nicotine delivery is relevant to regulation, including product labeling and abuse liability. These factors may include user puff topography, ECIG liquid composition, and ECIG design features. This study addresses how these factors can influence ECIG nicotine yield.

Methods: Aerosols were machine generated with one type of ECIG cartridge (V4L Cool Cart) using 5 distinct puff profiles representing a tobacco cigarette smoker (2s puff duration-33 mL/s puff velocity), a slow average ECIG user (4s-17ml/s), a fast average user (4s-33ml/s), a slow extreme user (8s-17ml/s), and a fast extreme user (8s-33ml/sec). Output voltage (3.3-5.2V, or 3.0–7.5W) and e-liquid nicotine concentration (18-36mg/mL labeled concentration) were varied. A theoretical model was also developed to simulate the ECIG aerosol production process and provide insight into the empirical observations.

Results: Nicotine yields from 15 puffs varied by more than 50-fold across conditions. Experienced ECIG user profiles (longer puffs) resulted in higher nicotine yields relative to the tobacco smoker (shorter puffs). Puff velocity had no effect on nicotine yield. Higher nicotine concentration and higher voltages resulted in higher nicotine yields. These results were predicted well by the theoretical model (R^2=0.99).

Conclusions: Depending on puff conditions and product features, 15 puffs from an ECIG can provide far less or far more nicotine than a single tobacco cigarette. ECIG emissions can be predicted using physical principles, with knowledge of puff topography and a few ECIG device design parameters.

INTRODUCTION

Awareness and use of electronic cigarettes (ECIGs) is growing worldwide, as indexed by internet searches (Ayers, Ribisl, & Brownstein, 2011) and nationally representative surveys (Adkison et al., 2013; CDC, 2013). While ECIG designs vary widely, their common defining feature is an electrically powered heating element that vaporizes a liquid that usually contains nicotine. Ostensibly free of many of the toxicants associated with tobacco combustion, the resulting vapors condense to form an aerosol that is inhaled by the user through the mouth end of the device. Though the mixture exiting the ECIG mouthpiece is commonly referred to as a "vapor", it is more correctly termed an "aerosol mist"—a system of liquid droplets suspended in a gas or gas mixture (Hinds, 1999).

The apparent popularity of these products likely is attributable to a variety of factors, including marketing (Noel, Rees, & Connolly, 2011), their availability in appealing flavors (Farsalinos et al., 2013; Grana & Ling, 2014), perceptions that they are less lethal than tobacco cigarettes (Henningfield & Zaatari, 2010), and their ability to deliver nicotine (Dawkins & Corcoran, 2014; Vansickel & Eissenberg, 2013), a psychomotor stimulant that supports dependence (USDHHS, 1988). While some commentators speculate that ECIGs promise reduced tobacco-caused disease and death in cigarette smokers (Goniewicz et al., 2013; Westenberger, 2009), others speculate that daily, long-term use of these novel products imperils users with adverse health consequences, including nicotine dependence in individuals who were not nicotine-experienced prior to their ECIG use (Grana, Benowitz, & Glantz, 2014).

Critical to this debate is understanding nicotine delivery to ECIG users. Studies have reported mixed results with regard to the ability of ECIGs to deliver nicotine systemically. ECIG-naïve cigarette smokers were found to attain negligible levels of plasma nicotine when using ECIGs (Bullen et al., 2010; Eissenberg, 2010; Vansickel, Cobb, Weaver, & Eissenberg, 2010), whereas experienced ECIG users were able to achieve plasma nicotine concentrations approaching those attained by tobacco smokers

(Vancsickel & Eissenberg, 2013). Because plasma nicotine levels are related to the amount of nicotine inhaled, understanding the factors that influence mainstream nicotine emissions from ECIGs is important for understanding nicotine delivery, and ultimately, for addressing questions of safety and effectiveness.

One factor that likely influences ECIG nicotine and other toxicant emissions is the puffing behavior of the user. The study of "puff topography" parameters (e.g., puff volume, puff velocity, inter-puff interval) has long been important in understanding the toxicant content of tobacco smoke (Djordjevic, Stellman, & Zang, 2000; Katurji, Daher, Sheheitli, Saleh, & Shihadeh, 2010; Maziak et al., 2011; Shihadeh, 2003; Shihadeh & Saleh, 2005; Shihadeh & Azar, 2006; Zacny & Stitzer, 1996) and the toxicant delivery to tobacco smokers (Shihadeh & Eissenberg, 2011; USDHHS, 1988). With electronic cigarettes, differences in topography may help explain the fact that sometimes these products deliver nicotine and sometimes they do not (Dawkins & Corcoran, 2014; Eissenberg, 2010; Vansickel & Eissenberg, 2012). Indeed, two studies have used observational methods to examine ECIG user puff topography, and both suggest that experienced ECIG users take longer puffs (e.g., approximately 4 seconds, on average) than tobacco cigarette smokers, approximately 2 seconds, on average: Farsalinos, Romagna, Tsiapras, Kyrzopoulos, & Voudris, 2013; and Hua, Yip, & Talbot, 2011. In extreme cases, puff durations as long as 8 seconds have been observed (Hua, et al., 2011). While puff duration is important, other parameters are also relevant, including puff velocity throughout the puff. Taken together with duration, puff velocity determines puff volume which predicts nicotine delivery in cigarette smokers (Zacny & Stitzer, 1996). The average puff velocity of tobacco cigarette smokers is generally 29-38 ml/s (Djordjevic et al., 2000; Eissenberg, Adams, Riggins, & Likness, 1999; Kleykamp, Jennings, Sams, Weaver, & Eissenberg, 2008) though experienced ECIG users may draw lower puff velocities (Spindle, Breland, Shihadeh & Eissenberg, 2014, under review). To date, no study has examined the combined influence of puff duration and velocity on nicotine yield in electronic cigarette aerosol.

Another factor that likely influences ECIG toxicant emissions involves device operating and design characteristics. ECIGs vary considerably in terms of power source voltage, heating element resistance, and other design features. For example, so-called variable voltage devices allow the user to control the power input, with marketed products ranging from 2.9 to 6.0 volts (e.g., http://www.provape.com/provari-variable-voltage-ecig-s/36.htm#). The electrical power input – which is proportional to the square of the voltage and inversely proportional to the heater resistance – influences the temperature at which the aerosol is produced, and this in turn may influence nicotine and other toxicant emissions. Few studies have looked at the effect of varying puff topography and/or device output voltage on toxicant emissions. In one recent study, carbonyl compounds measured in ECIG aerosol from 13 different nicotine solutions at 3.2 and 4.8V were compared: solvent and output voltage significantly affect the amount of carbonyls in the aerosol (Kosmider et al., 2014). Prior studies have also explored the toxicant emissions produced from different brands of ECIGs but few have varied voltage systematically (see Kosmider et al., 2014), and none have explored the influence of user topography. Goniewicz et al. (2012) measured the nicotine yield in aerosols generated from 16 different ECIG brands using an average puffing condition based on topography measurements of 10 ECIG users (1.8 s puff duration, 70mL puff volume) and found that the nicotine yield in 15 puffs ranged from 0.025 – 0.77 mg, which is lower than the dose inhaled in one conventional cigarette (Goniewicz, Kuma, Gawron, Knysak, & Kosmider, 2012). Using a 2 s puff duration, 100 ml/puff protocol, Trehy et al. (2011) investigated three different brands of ECIGs and reported nicotine yields ranging from 0 to 43.2 µg nicotine per 100 mL puff.

The purpose of the current study was to examine the influence of user puff topography (duration, puff velocity) and device power source voltage on nicotine yield, and to demonstrate the feasibility of predicting the effects of these variables by modeling the underlying physical phenomena mathematically. Because liquids of varying nicotine concentrations are available, we also included an examination of this factor. Taken together, these data will be useful for informing test methods for regulatory action, and for developing a framework in which physical principles can be invoked to guide empirical investigation of ECIG performance and thereby facilitate evaluation of products in this rapidly evolving product category.

The ECIG aerosol production process

A common ECIG configuration comprises an electrical heating element (a.k.a. "atomizer") combined with a cartridge that contains nicotine liquid. This heater/cartridge combination is called a "cartomizer". A cartomizer (Figure S1) typically contains a metallic electrical heating coil that is wound around a central wick; the coil is activated either by pressing a button or by an automatic puff sensor. The wick is saturated with the so called "juice" or "e-liquid", which is typically composed of a solution of propylene glycol (PG), vegetable glycerin (VG), flavorants, and nicotine. Nicotine concentrations in commercially available products usually range from 0-36 mg/ml. A textile sheath envelops the coil-wick assembly. The sheath in turn is surrounded by a fibrous wool-like material that is soaked in liquid and that serves as a reservoir for the wick. The wool, sheath, heating coil, and wick are all packaged in a cylindrical metal case with dimensions similar to those of a cigarette filter.

When a user draws a puff, air is drawn into the cartomizer through the bottom of the assembly. The air passes over the heated coil, and carries away the e-liquid vapors as well as thermal energy from the coil/wick assembly. As the hot, vapor-laden air continues traveling through the cartridge beyond the heater assembly across a transfer tube, it cools and vapors begin to condense to form liquid droplets, likely with a diameter in the 120-165 nm range (Fuoco, Buonanno, Stabile, & Vigo, 2014) . As with tobacco smoke, the condensed droplets scatter light and thereby render the aerosol plume visible.

A battery usually powers the heater within the cartomizer, typically via an electric circuit that regulates the output voltage, allows recharging, and allows electrical current to flow to the cartomizer during a puff. ECIG batteries are available in a wide variety of energy storage and current draw capacities. Similarly, ECIG heater coils are available in a range of resistances and geometries. Combined with the fact that puff topography varies widely across individuals and devices, ECIG aerosols can be produced under a very wide range of conditions. These variations may result in nicotine yields that are far greater or far less than those of a typical cigarette.

MATERIALS & METHODS

ECIG cartridges

Forty-six V4L Cool Cart cartomizers, of which thirty-four were labeled as having a nicotine concentration of 18mg/mL and twelve of 36mg/mL, were procured from an internet vendor in the USA. The resistance of these cartomizers was measured using a standard laboratory Ohmmeter and found to be 3.6 ± 0.16 Ohms (mean ±SD) at 22 deg C. Four of the above cartridges exhibited erratic resistances indicating a faulty internal electrical connection and were therefore excluded from the study. Liquid from three randomly selected V4L Cool Cart cartridges, for each of the two nicotine concentration mentioned above, were extracted and analyzed for nicotine and found to be 8.53 ±0.71 and 15.73 ±1.21 mg/mL, respectively.

Aerosol generation and sampling

A custom-designed digital puff production machine at the American University of Beirut was used to generate ECIG aerosol. Puff durations were chosen to approximate that of a typical cigarette smoker (2 s; (Farsalinos et al., 2013; Hua et al., 2011), an experienced ECIG user taking an average length puff (4 s; (Farsalinos et al., 2013; Hua et al., 2011); and an experienced ECIG user taking a puff of the more extreme length observed (8s; (Hua et al., 2011). Puff velocity was chosen to approximate that observed in tobacco cigarette smokers (33 ml/sec; (Djordjevic et al., 2000; Eissenberg et al., 1999; Kleykamp et al., 2008), but because experienced ECIG users may puff more slowly (Spindle et al., 2014) we also examined the effects of a lower velocity (17 ml/s). As Table 1 shows, puff duration and velocity were combined to yield 5 distinct puff profiles representing a tobacco cigarette smoker (2 s, 33 ml/s), an average ECIG user using low flow (4 s, 17 ml/sec) an average ECIG user using a high flow (4 s, 17 ml/s), an extreme ECIG user using low flow (8 s, 17 ml/sec), and an extreme ECIG user using a high flow (8 s, 33 ml/sec). Each of these 5 combinations was tested at voltages representing lower (3.3 V) and higher (5.2 V) voltage devices available on the U.S. market, resulting in 3.0 and 7.5 Watt electrical power input, respectively. All conditions described were tested using a medium strength e-liquid nicotine concentration (labeled as 18 mg/mL). To examine the effect of nicotine concentration in the e-liquid, two of the above profiles (average and extreme) were repeated at a high nicotine level (labeled as 36 mg/mL).

For each experimental condition, three sets of samples were generated for nicotine determinations. The conditions tested for the high nicotine concentration were generated from six sets of samples. All profiles tested at the lower voltage setting (3.3 V, 3.0 W) and both voltage settings for the tobacco smoker profile were generated by drawing 15 puffs from 3 different randomly selected cartomizers. However, to avoid overloading the filter pad (described below), the profiles tested at the remaining conditions were generated by drawing 5 puffs; the results were thereafter multiplied by 3 for consistency.

For each experiment, the mouth end of the ECIG cartridge was connected by a 5 cm long Tygon® tube (ID) to a polycarbonate filter holder that contained a Gelman Type A/E 47 mm glass fiber filter. The filter holder terminated in another 5 cm long Tygon® tube (ID). In preliminary experiments, we found that losses in the tubing connecting the ECIG cartridge to the filter pad were negligible.

For repeatability, the ECIG cartridge voltage was controlled using a regulated laboratory DC power supply (0.01V resolution). We note that while regulated ECIG battery units are commonly used, many

ECIG battery units do not employ voltage regulators, and therefore allow the supplied voltage to decay as the battery is drained. This study did not attempt to investigate effects of battery drain with unregulated voltage ECIG designs.

Chemical analysis

Total particulate matter (TPM) was determined gravimetrically by weighing the filter pad and holder before and after each sampling session. Nicotine was determined by sonicating the filter pad in 6 mL of ethyl acetate for 30 min at ambient temperature, and analyzing an aliquot of the resulting solution by GC-MS. An extracted calibration curve with concentrations ranging from 1-20 ppm was used to interpret the resulting chromatograms. Spiked filter assays of nicotine in PG solution showed recoveries of 90%.

Mathematical modeling and numerical simulation

A mathematical model was developed to simulate the ECIG vaporization process under various conditions. The modeling effort was focused on determining the evaporated mass of nicotine and liquid in the vicinity of the cartomizer heating element. Because a fraction of these aerosols likely re-condense on the internal surfaces of the cartomizer and therefore do not exit the mouthpiece, the evaporated mass represents a theoretical upper limit, or "potential mass" emitted from a given puffing session. Nonetheless, the potential nicotine mass can be a useful metric for regulators who need to understand how puffing behavior, ECIG liquid composition, and ECIG design parameters interact, and to predict the maximum amount of nicotine that theoretically could be obtained from a given ECIG design/puff topography/liquid composition combination.

Starting from first principles of energy and mass conservation, the relevant heat and mass transfer rate equations, ideal solution/ideal gas equations, and boundary layer approximations for the flow field in the vicinity of the ECIG heating element, we computed the transient temperature, evaporation rate, and nicotine concentration in the aerosol produced during each puff, accounting for cartomizer cooling during the interpuff intervals by natural convection to the surrounding air.

Other than puff topography (puff duration, velocity, interpuff interval, number of puffs) and electrical power input, the model requires specification of air flow tube geometry, heater element dimensions (diameter, length) and mass, and the geometric properties of the components of the atomizer (air inlet diameter of the atomizer, distance of inlet from heater coil), all of which were obtained readily by reverse engineering the V4L cartomizer. Thermodynamic and transport kinetic properties of air, PG, VG, and nicotine were taken from literature and are given in the online supplementary materials (Table S1). The composition of the V4L liquid vehicle was assumed to be 80/20 PG/VG, in accordance with the manufacturer's specifications. The nicotine concentration values input to the mathematical model were assumed to be equal to those measured by analysis of the cartomizer liquids.

The model results in a series of coupled differential equations, which are solved numerically in the Matlab® computing environment using a time-explicit algorithm, in increments of 0.01 ms. Results were checked for independence of time increment.

Statistical methods

Student's t test and analysis of variance (ANOVA) were used for comparisons between TPM and nicotine values obtained by varying user puff topography (velocity, puff duration), ECIG design features (voltage) and liquid content (nicotine concentration).

RESULTS

Measured yields

TPM and nicotine yields (mean ±SD) generated from the 5 ECIG user profiles are provided in Table 1. TPM yield ranged by more than 30-fold while nicotine yield ranged by more than 50-fold across conditions. Voltage and puff duration had a significant impact on TPM and nicotine yield under all conditions, nicotine concentration had no significant effect on TPM, but had an effect on nicotine yield, while puff velocity had no effect under any condition, (p values obtained by varying the puff velocity, for the average experienced smoker at low and high voltages, are less than 0.97 and 0.12 respectively; for the case of the extreme experienced smoker, $p < 0.58$ at low voltage and 0.56, at high voltage).

Figure 1 shows the effect of varying puff profile and device voltage on nicotine yield. Increasing the puff duration resulted in systematically higher nicotine delivery. Increasing the voltage resulted in higher nicotine yields across all conditions ($p < 0.05$). Increasing the e-liquid nicotine strength, from 8.53 to 15.73 mg/mL, did not have an effect on TPM ($p < 0.34$, average experienced user and $p < 0.95$, extreme experienced user), but resulted in higher nicotine delivery for both average and extreme users ($p < 0.05$).

Mathematical model

The mathematical model was used to predict potential nicotine mass emissions for the twelve experimental conditions listed in Table 1. The computed potential nicotine and the measured nicotine yield were strongly correlated, resulting in $R^2 = 0.99$, with a slope of 0.42 (Figure S2).

DISCUSSION

The primary purpose of this study was to explore systematically the influence of puff topography, ECIG device design, and liquid nicotine content on nicotine yield of the resulting ECIG aerosol, while also developing a mathematical model that would predict how other configurations of these variables might influence nicotine yield. Clearly, puff velocity does not influence nicotine yield, while puff duration, device voltage, and liquid nicotine concentration do. Moreover, the influence of these variables can be modeled effectively. Determining which factors do and do not influence the nicotine and other toxicant yield of existing ECIGs helps to understand ECIG user behavior and the ECIG marketplace today, and has clear regulatory implications for the future. Perhaps more important, the mathematical model presented here could, with further refinement, help predict the nicotine yield of ECIG designs that may not yet exist now but might in the future. Each of these issues is discussed below.

The observation that puff topography influences ECIG aerosol nicotine yield is relevant to understanding ECIG use as well as methods for regulating the nicotine intake of ECIG users. In terms of understanding ECIG use, previous reports suggest that experienced ECIG users take longer duration puffs than do cigarette smokers smoking cigarettes (Hua et al., 2011) or using ECIGs for the first time (Farsalinos et al., 2013). The current results help to explain these findings, as longer puffs lead to greater nicotine yield in ECIG aerosol. The fact that puff velocity does not influence nicotine yield may explain why ECIG user puff topography is associated with velocities that are less than those of cigarette smokers (Spindle et al., 2014). That is, while a high velocity puff increases combustion rate and therefore increases the rate at which nicotine is converted from the leaf to the smoke in a tobacco cigarette, it does not increase the rate at which nicotine is emitted from an ECIG. Experienced ECIG users may have learned with practice that the greater effort associated with higher velocity does not influence nicotine-mediated subjective effects. They therefore no longer expend the energy to produce the high velocity puffs observed in cigarette smokers.

The influences of puff duration and velocity on nicotine yield can be understood by examining the structure of an ECIG puff, computed using our theoretical model. Figure 2 illustrates the computed V4L cartomizer heater coil temperature, mass transfer coefficient, and nicotine saturation vapor pressure (P_{sat}) during two consecutive puffs, at two different puff velocities. As shown, when a puff commences and the heater coil is activated the coil temperature (panel a) rises for some time (the "transient" phase), until it attains a steady state temperature, at which time the electrical power input is balanced exactly by the thermal energy transferred out of the heater. Thus increasing puff duration results in a larger proportion of the puffing time spent in the relatively high-temperature steady-state phase.

Higher temperatures, in turn, result in a higher nicotine evaporation rate (panel b), due mainly to the higher P_{sat} (panel b). This picture is corroborated by the measured nicotine emitted per puff second, the "nicotine flux". In Table 1 it can be seen that longer puff durations lead to higher nicotine fluxes when all else is held constant. Therefore longer puff durations result in greater nicotine yields, and greater fluxes. The same will be true for yields of other volatile constituents of the liquid.

The effect of puff velocity on nicotine yield is more complex, and requires recognition of the fact that nicotine evaporation rate is proportional to the product of P_{sat}, and the mass transfer coefficient, h. The latter describes the ability of the flowing air to scavenge nicotine vapor from the heater surface, and this ability increases with puff velocity. Although h increases with puff velocity, heater temperature decreases with puff velocity, resulting in lower P_{sat}. In the relevant flow regimes characteristic of ECIGs, it turns out that the increased h is offset almost exactly by the decreased P_{sat}, resulting in a null effect of puff velocity on nicotine evaporation rate (panel b), and therefore a null effect on nicotine yield. While nicotine yield is not affected by puff velocity, we caution that the same may not be true for other toxicants (e.g. formaldehyde) that form through temperature-dependent chemical reactions in the heater.

In terms of regulation, nicotine yield, in addition to other variables such as nicotine delivery, liquid flavor, and aerosol production, may all be key features that determine the effects of ECIGs in tobacco cigarette smokers as well as in tobacco-naïve individuals. This report is the first to address nicotine yield in a controlled and systematic manner; to our knowledge controlled, systematic exploration of the importance of delivery, flavor, and aerosol production in ECIG effects has not yet been reported. In the absence of that information, we suggest here that controlling the nicotine yield in ECIG aerosol may be critical to limiting the likelihood that ECIGs are used by individuals who are not current tobacco cigarette users (e.g., tobacco naïve youth; tobacco-free former smokers). For these individuals, the availability of a device that provides a cigarette-like dose of nicotine easily may increase the chances of their becoming nicotine dependent when they otherwise would not. The current results suggest regulatory action that might limit this possibility: ECIGs might contain electronics that do not allow puffs that exceed a certain duration, and that require a pre-set interval of time to elapse between puffs so that the duration limit could not be easily overcome with a series of puffs that are performed rapidly in succession. Future study will help determine the range of duration values (in combination with other ECIG-specific factors) that might help limit abuse liability; the current study suggests that puff duration, and not puff velocity, is a variable that could be regulated to limit ECIG aerosol nicotine yield. Further study is also necessary to relate nicotine yield in ECIG aerosol to nicotine delivery to the user, as indexed by plasma nicotine concentration, and this relationship may be critical in guiding ECIG regulation empirically.

The observation that device design characteristics (in this case, voltage) and the nicotine concentration of ECIG liquids influence ECIG aerosol nicotine yield also is relevant to understanding ECIG use as well as informing regulation. With respect to use, many experienced ECIG users report that they initiated ECIG use with so-called "cigalikes": disposable ECIGs that are similar in appearance to a tobacco cigarette (McQueen, Tower, & Sumner, 2011). These experienced users subsequently switched to a non-disposable product that, among other features, is often equipped with a higher voltage power source (McQueen et al., 2011). This transition may reflect the failure of "cigalikes" to deliver nicotine in doses that resemble those delivered by a tobacco cigarette (Nides, Leischow, Bhatter, & Simmons, 2014; Vansickel, Cobb, Weaver, & Eissenberg, 2010). Indeed, the availability of ECIG devices that allow the user to manipulate the voltage delivered to the heating element may indicate that users have learned that nicotine-induced effects are mediated by this device feature. Similarly, the availability of liquids with a wide range of nicotine concentrations (0-36 mg/mL) suggests that ECIG users may be interested in manipulating nicotine intake. Regulators should be aware that ECIG aerosol nicotine yield is likely a function of electrical power, which in turn is a function of device voltage and resistance in addition to liquid nicotine concentration. Further study is necessary to determine how these and other variables interact to influence ECIG acceptability, abuse liability, and toxicity.

The mathematical model is perhaps the most important outcome of the current study. This model demonstrates that the influence of product design and use characteristics on nicotine yield can be predicted remarkably well, as evidenced by the high correlation between measured yields and computed potential mass (Figure S2) over a wide range of conditions. Mathematical modeling can thus provide an additional tool for ECIG product regulation, and can be used to help identify rapidly any potentially problematic products or product combinations currently on the market, as well as those proposed in the future.

This study has some important limitations. First, it was conducted using one ECIG model; other models and brands may use different design features that may alter the emissions. Moreover, this study did not examine the effect of varying the e-liquid PG/VG ratio; prior studies have shown that manipulating the ratio affects the nicotine and carbonyl yields (Kosmider, Sobczak, Knysak, & Goniewicz, 2014; Kosmider et al., 2014). However, our main intention was not to investigate performance variation across products, but rather to illustrate the wide range of possible nicotine yields attainable even from a relatively constrained basis set. Our results show that even for a single ECIG brand, a single PG/VG ratio, and only 5 different user profiles, a 50-fold change in nicotine delivery is possible; a span that ranges from negligible amounts to several cigarettes worth. If a larger number of brands and products are examined, the span can only widen. From a regulatory perspective, this finding highlights the need for developing a robust mathematical model that reliably can predict nicotine yield for any circumstance.

A second limitation of this study is that we did not measure toxicant emissions other than nicotine. We therefore caution against extrapolating the current results to other toxicants. For example, while puff velocity did not influence nicotine yields, it did affect the predicted heater coil temperature, and therefore may influence in situ toxicant formation reactions and resulting yields (e.g. carbonyls). More research is needed to characterize effects of puff topography and device features on non-nicotine toxicant emissions.

Third, we did not vary the nicotine concentration systematically. For the two cases examined we found that increasing the nicotine concentration increased nicotine yield, as predicted by the theoretical model (Figure S2). Theoretically, for the highly dilute nicotine concentration conditions relevant to ECIG liquids nicotine yield will always be directly proportional to the nicotine concentration, all else being equal; in this study we found that increasing the nicotine concentration by a factor of 1.8 resulted in an increase in yield of 1.5±0.5 (mean±95% confidence interval). On the other hand, we also note that by manipulating puff duration and/or battery voltage, a user can obtain a nicotine yield in 15 puffs similar to that obtained from a conventional cigarette, for either nicotine concentration tested in this study. Indeed, in a study which did not control for these factors, nicotine concentration had little relation to nicotine yield (Gonoweicz et al., 2014). This observation highlights the importance of accounting for the overlapping influences of the many factors underlying nicotine yield in ECIG aerosol when measures are taken to minimize abuse liability and potential toxicity.

CONCLUSIONS

Previous reports on ECIG nicotine delivery to blood have mixed results. Some reports suggest that ECIGs deliver a considerable amount of nicotine (Vansickel & Eissenberg, 2012), while other reports do not Bullen et al., 2010; Eissenberg, 2010; Vansickel et al. 2010). It has been hypothesized that these mixed results derived from variations in user experience and device type (Farsalinos et al., 2014; Vansickel & Eissenberg, 2012), factors which, as this study has shown, likely affect the amount of nicotine obtained from the mouth end of an ECIG. Depending on user puff topography and operating conditions, we have found that a given ECIG product can provide far less or far more nicotine than a single combustible cigarette. Experienced ECIG users may extract higher nicotine doses by drawing relatively low velocity, long duration puffs in comparison to conventional tobacco cigarette smokers. ECIG design features also affect nicotine yield; increasing the battery voltage output and liquid nicotine concentration increases the nicotine yield. That these influences are predicted well by a mathematical model of the relevant physics highlights how engineering analysis can inform our understanding of human behavior in the self-administration of nicotine using an ECIG. It also indicates that mathematical modeling may provide a practical way for regulators to identify combinations of factors that would result in a mandated nicotine yield. In addition, it may help identify combinations that would produce ineffective or unsafe levels of nicotine, and regulators could instruct manufacturers accordingly.

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DECLATION OF INTERESTS

The authors have no conflicts of interest to report.

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FIGURE LEGENDS

Figure S1: Anatomy of a typical ECIG cartridge.

Figure 1: Effect of user profile and device voltage on aerosol nicotine yield from 15 puffs. The profiles represent: a typical tobacco cigarette smoker (2 s puff duration, 33 ml/s puff velocity) and experienced ECIG users with 4s ("average") or 8s ("extreme") puff durations and slow (17 ml/s) or fast (33 ml/s) puff velocities. Error bars indicate 95% confidence intervals.

Figure S2: Predicted potential nicotine yield vs. measured nicotine yield for all conditions.

Figure 2: ECIG temperature (T), nicotine flux, nicotine saturation pressure (P_{sat}), and mass transfer coefficient (h) during and between puffs, as predicted by the mathematical model (condition shown for two – 8 second puffs). Panel a illustrates the transient nature of the temperature during a puff. Panel b illustrates the effect of puff velocity on the computed variables.

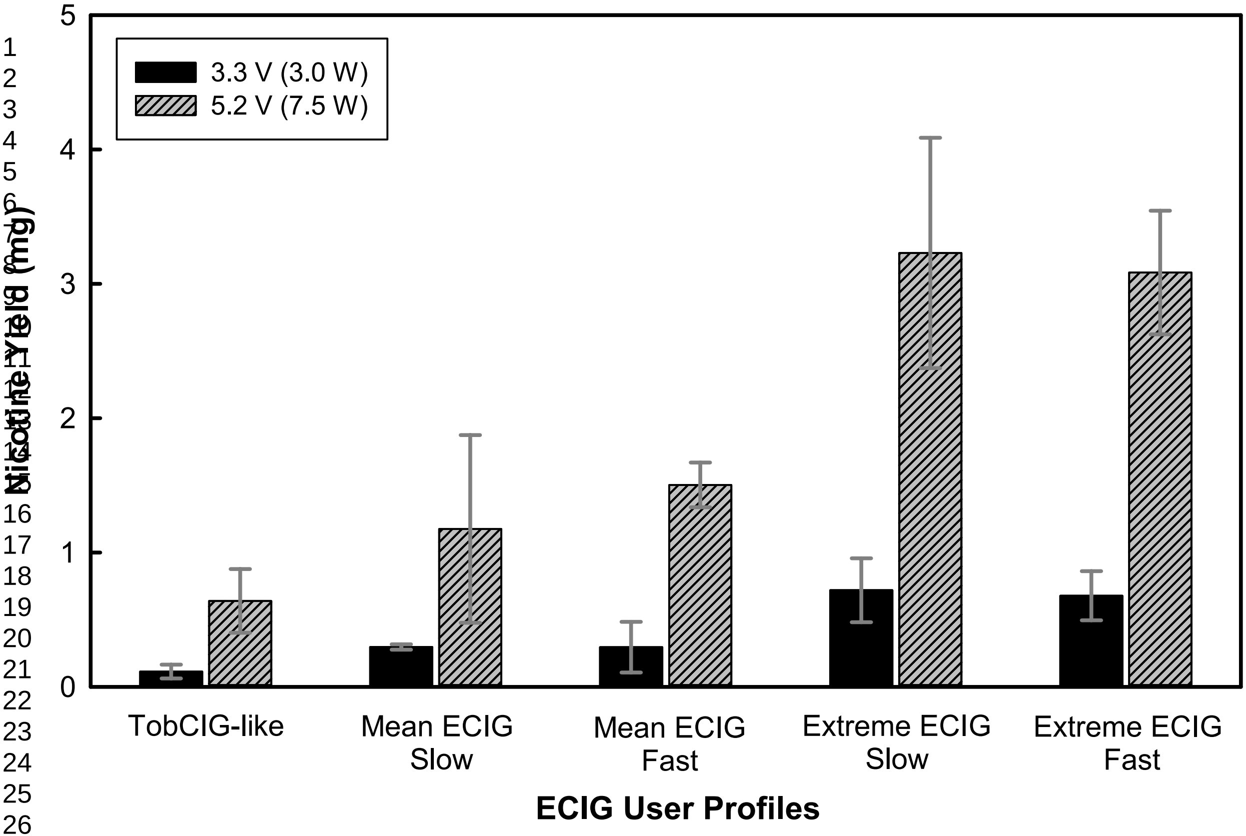
TABLE LEGENDS

Table 1: Measured TPM and nicotine yields in 15 ECIG puffs (mean ±SD) for several user puffing profiles. The profiles represent a typical tobacco cigarette smoker and experienced ECIG users using 4s ("average") or 8s ("extreme") puff durations and slow (17ml/s) and fast (33 ml/s). Each profile was tested under two voltage conditions (3.3 and 5.2 V). All conditions were tested using an 8.53 mg/mL nicotine concentration liquid. The average and extreme (slow) conditions were also tested using a 15.73 mg/mL nicotine concentration liquid.

Table S1: Thermo-physical properties of propylene glycol, vegetable glycerin, and nicotine. Values of M, the molecular weight in kg/mol; Tb , the normal boiling point in K; ΔHvap , the specific latent heat of vaporization in J/kg; s, the surface tension in N/m; ρ, the density in kg/m^3; cp , the specific heat capacity in J/kg.K; μ , the viscosity in N.s/m2; v, the kinematic viscosity in m^2/s; k, the conductivity in W/m.K; Vm, the molar volume in m^3/mol; Ts , the temperature of the heating element in K; Ps , the vapor pressure in bar; D, the diffusivity in air in m^2/s .

Table 1: Measured TPM and nicotine yields in 15 ECIG puffs (mean±SD) for several user puffing profiles. Also listed is the nicotine flux, the mass of nicotine emitted per puff second. The profiles represent a typical tobacco cigarette smoker and experienced ECIG users using 4s (“average”) or 8s (“extreme”) puff durations and slow (17ml/s) and fast (33 ml/s). Each profile was tested under two voltage conditions (3.3 and 5.2 V, 3.0 and 7.5 W respectively). All conditions were tested using an 8.53 mg/mL nicotine concentration liquid. The average and extreme (slow) conditions were also tested using a 15.73 mg/mL nicotine concentration liquid.

Profile	Puff Duration (s)	Puff Velocity (mL/s)	Puff Volume (mL)	Voltage (V)	Measured Nic. Conc. (mg/mL)	TPM (mg)	Nicotine Yield (mg)	Nicotine Flux (µg/s)
Tobacco cigarette smoker	2	33	66	3.3	8.53	9.07 ±2.3	0.11 ±0.02	3.8 ±0.69
Average experienced ECIG (slow)	4	17	68	3.3	8.53	29.4 ±0.9	0.30 ±0.01	4.9 ±0.13
Average experienced ECIG (fast)	4	33	132	3.3	8.53	29.6 ±6.4	0.29 ±0.08	4.9 ±1.3
Extreme experienced ECIG (slow)	8	17	136	3.3	8.53	70.5 ±13.0	0.72 ±0.10	6.0 ±0.80
Extreme experienced ECIG (fast)	8	33	264	3.3	8.53	68.8 ±6.7	0.68 ±0.07	5.6 ±0.61
Tobacco cigarette smoker	2	33	66	5.2	8.53	64.9 ±9.8	0.64 ±0.10	21 ±3.2
Average experienced ECIG (slow)	4	17	68	5.2	8.53	128.3 ±23.1	1.18 ±0.28	20. ±4.7
Average experienced ECIG (fast)	4	33	132	5.2	8.53	152.7 ±13.6	1.50 ±0.07	25 ±1.1
Extreme experienced ECIG (slow)	8	17	136	5.2	8.53	312.6 ±32.9	3.23 ±0.34	27 ±2.9
Extreme experienced ECIG (fast)	8	33	264	5.2	8.53	333.2 ±34.0	3.09 ±0.19	26 ±1.5
Average experienced ECIG (slow)	4	17	68	3.3	15.73	32.7 ±7.4	0.48 ±0.13	8.0 ±2.1
Extreme experienced ECIG (slow)	8	17	136	5.2	15.73	314.0 ±29.4	4.70 ±1.00	39 ±7.0



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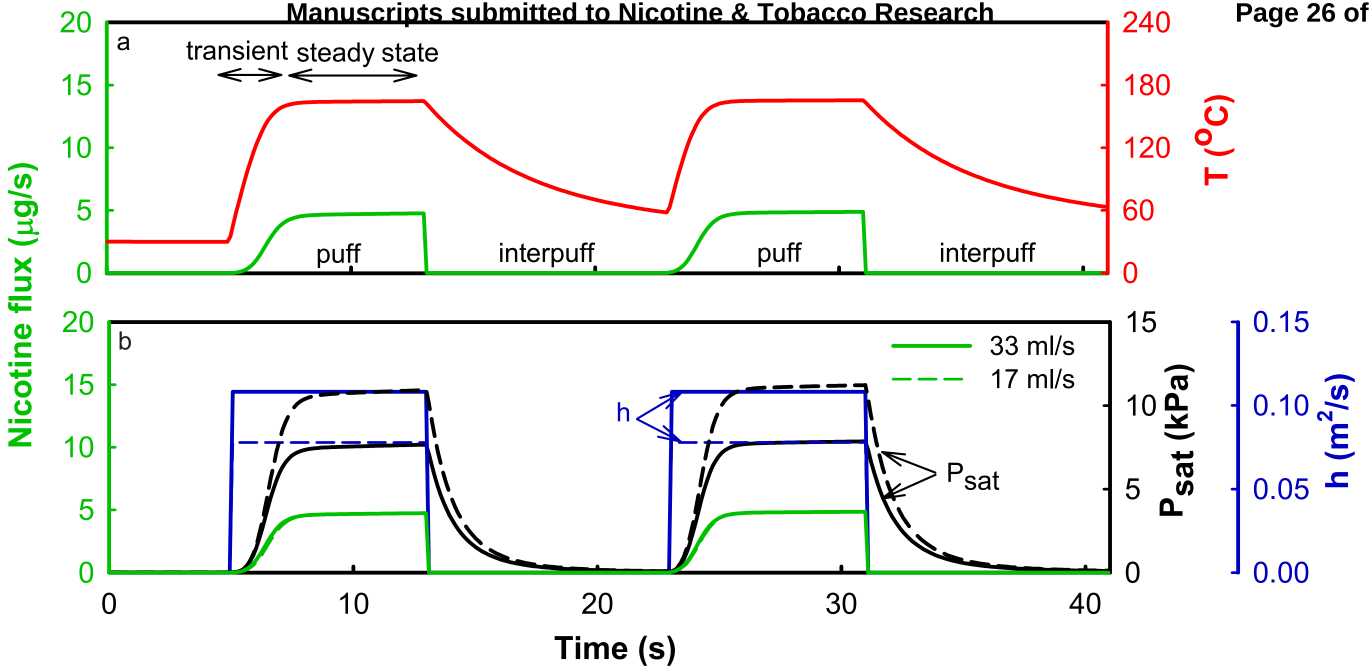

Figure 2: ECIG temperature (T), nicotine flux, nicotine saturation pressure (Psat), and mass transfer coefficient (h) during and between puffs, as predicted by the mathematical model (condition shown for two - 8 second puffs). Panel a illustrates the transient nature of the temperature during a puff. Panel b illustrates the effect of puff velocity on the computed variables.

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Air $\mathbf{M_{air} = 28.97 \times 10^{-3}}$ $\rho_{air} = 0.995,\ c_p = 1.009 \times 10^3, \mu = 208.2 \times 10^{-7}, v = 20.92 \times 10^{-6}\ k = 30 \times 10^3$ (1) $\mathbf{V_{m_{air}} = \frac{M_{air}}{\rho_{air}}}$
Propylene Glycol $M_{PG} = 76.09 \times 10^{-3}, T_b = 461.3\ ,\ \Delta Hvap\ = 914 \times 10^3$ (2), $s = 36 \times 10^{-3}$ (3) $\rho_{PG} = 1.036 \times 10^3,\ c_p = 2.5 \times 10^3$ (3), $\log_{10} P_s = A - \frac{B}{T_s + C}$ (A = 6.07936, B = 2692.187, C = -17.94) (4) $\mathbf{V_{m_{PG}} = \frac{M_{PG}}{\rho_{PG}}\ , D = \frac{0.001 \times 10^{-19/2} \times {T_s}^{1.75} \times \sqrt[2]{\left(\frac{M_{air}+M_{PG}}{M_{air} \times M_{PG}}\right)}}{P \times \left(\sqrt[3]{V_{m_{air}}} + \sqrt[3]{V_{m_{PG}}}\right)^2}}$ **(5)**
Vegetable Glycerin $M_{VG} = 92.09 \times 10^{-3}, T_b = 563.15,\ \Delta Hvap\ = 974 \times 10^3$ (2), $s = 64 \times 10^{-3}$ (6) $\rho_{VG} = 1.261 \times 10^3,\ c_p = 2.37 \times 10^3$ (7), $\log_{10} P_s = A - \frac{B}{T_s + C}$ (A = 3.93737, B = 1411.531, C = -200.566) (8) $\mathbf{V_{m_{VG}} = \frac{M_{VG}}{\rho_{VG}}\ , D = \frac{0.001 \times 10^{-19/2} \times {T_s}^{1.75} \times \sqrt[2]{\left(\frac{M_{air}+M_{VG}}{M_{air} \times M_{VG}}\right)}}{P \times \left(\sqrt[3]{V_{m_{air}}} + \sqrt[3]{V_{m_{VG}}}\right)^2}}$ **(5)**
Nicotine $M_{nic} = 162.2 \times 10^{-3}, T_b = 520.15,\ s = 38.61 \times 10^{-3}$ (9) $\rho_{nic} = 1.01 \times 10^3$(9), $\log_{10} P_s = A - \frac{B}{T_s + C}$ (A = 3.60721, B = 1433.766, C = -121.387) (10) $\mathbf{V_{m_{nic}} = \frac{M_{nic}}{\rho_{nic}}, D = \frac{0.001 \times 10^{-19/2} \times {T_s}^{1.75} \times \sqrt[2]{\left(\frac{M_{air}+M_{nic}}{M_{air} \times M_{nic}}\right)}}{P \times \left(\sqrt[3]{V_{m_{air}}} + \sqrt[3]{V_{m_{nic}}}\right)^2}}$ **(5)**

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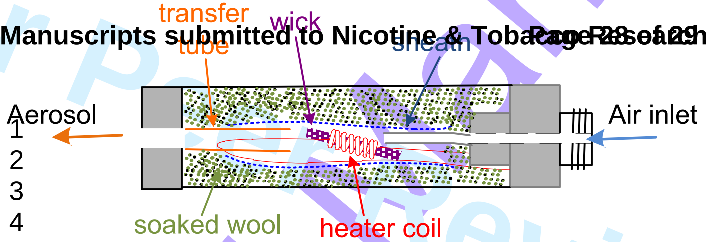

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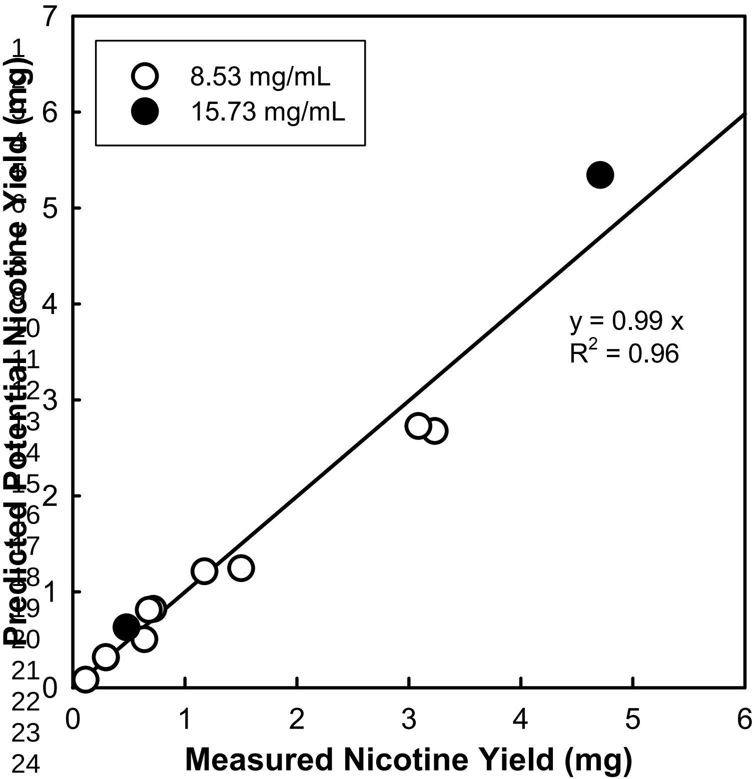

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