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Influence of nicotine form and nicotine flux on puffing behavior and mouth-level exposure to nicotine from electronic nicotine delivery systems☆

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ABSTRACT

Background: Nicotine form (freebase/protonated) and nicotine flux (rate at which nicotine is emitted) are two factors that can affect the dose of nicotine inhaled by individuals using electronic nicotine delivery systems (ENDS) because they can influence puffing behavior. The nicotine dose for each puff also is directly proportional to nicotine flux (i.e., dose/puff=nicotine flux*puff duration). This study examines the effect of nicotine form and flux on puffing parameters and mouth-level nicotine exposure.

Methods: Thirty-two dual ENDS and combustible cigarette participants completed five visits that differed by nicotine form (freebase or protonated) and nicotine flux (14 or 35 μg/sec); a zero-nicotine condition was a negative control. Participants used a Subox Mini C ENDS, powered at 20 W, during a 10-puff directed bout (B1) followed by a one-hour *ad libitum* bout (B2). Puffing parameters and mouth-level nicotine exposure were assessed using the American University of Beirut REALTIME instrument.

Results: Relative to protonated nicotine, freebase nicotine was associated with lower total puff duration (puff duration*number of puffs), lower flow rate in B1, lower liquid consumption, and lower mouth-level nicotine exposure. Increasing nicotine flux from 14 to 35 μg/sec was associated with lower total puff duration in both bouts, as well as lower liquid consumption. Increasing nicotine flux was associated with higher mouth-level nicotine exposure in B1 only.

Conclusion: ENDS with protonated nicotine may enhance nicotine exposure by promoting longer puffing and thus greater dose delivered. This work highlights the importance of accounting for interactions between nicotine form and flux when considering nicotine regulation for ENDS.

1. Introduction

ENDS use in the U.S. has increased rapidly in the last decade, including among youth (Dai and Leventhal, 2019). According to the National Youth Tobacco Survey (NYTS), approximately 2.5 million U.S. adolescents used ENDS in 2022. The widespread adoption by ENDS manufacturers of protonated (salt) nicotine liquids (Duell et al., 2019) has been associated with the rapid increase in the number of young ENDS consumers (Glantz et al., 2022; Pierce et al., 2022). Nicotine salt products are found to be more appealing than freebase nicotine products

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among both ever and never consumers of combustible cigarettes (Leventhal et al., 2021), which suggests that the presence of protonated nicotine in the market might facilitate the transition for individuals looking to switch from smoking. On the other hand, some studies have found that a degree of throat harshness (e.g., that stemming from freebase nicotine) may make ENDS more desirable for established combustible cigarette consumers seeking to switch (Dautzenberg et al., 2016; Etter, 2016).

Variables that impact the chemosensory attributes of tobacco aerosols can influence puffing behavior (Robinson et al., 2018; St.Helen et al., 2018; Voos et al., 2020). Two key ENDS variables that influence chemosensory attributes are liquid nicotine concentration (mg/mL) and nicotine form (i.e., protonated vs. freebase). Nicotine activates the gustatory pathways and generally is associated with bitterness and throat harshness (Dahl et al., 1997). Individuals vary their puffing behavior to modulate harshness (Pullicin et al., 2020) and to modulate nicotine delivery (Dawkins et al., 2018, 2016; Hiler et al., 2017). Because of the palatability of protonated nicotine (Leventhal et al., 2021), individuals may take longer puffs and, in the process, inhale more nicotine, which may facilitate and increase nicotine dependence.

Nicotine dose per puff is directly proportional to the product of puff duration and nicotine flux (μg/sec). Flux is an ENDS performance metric that encompasses product design, electrical characteristics, and liquid composition variables (Talih et al., 2016). To the extent that sensory cues influence puffing behavior, they also influence how much nicotine is consumed. With combustible cigarettes, individuals adjust their behavior almost instantaneously while puffing in response to sensory feedback (Ayya et al., 1995), which indicates that sensory feedback can influence dose through a mechanism other than nicotine satiation because nicotine typically does not reach the brain until after a puff is completed (Rees et al., 2012).

In summary, understanding the influence of nicotine flux and form on puffing behavior is central to assessing nicotine dose, product dependence and its regulation. To date, one study investigated the influence of nicotine form on puffing behavior, using an in-home paradigm where participants used their own ENDS. The study found no differences in puffing parameters and appeal between protonated and freebase nicotine liquids (Pauwels et al., 2023). The focus of the current study was to investigate the influence of nicotine form and nicotine flux on puffing topography and mouth-level exposure to nicotine during directed and ad lib ENDS use sessions in a controlled clinical laboratory study.

2. Methods

2.1. Participants and recruitment

This study was approved by the Institutional Review Board at the American University of Beirut (AUB). Written, informed consent was obtained from each participant and all participants were financially compensated for their time. Participants were recruited via flyers distributed at AUB and through social media channels. Eligible participants were healthy, above 18 years of age, and individuals who used both ENDS and combustible cigarettes. Smoking status was confirmed via an initial screening questionnaire. Participants were classified as dual consumers of ENDS and combustible cigarettes if they reported daily use of ENDS (≥3 mg/mL nicotine) or cigarettes (any frequency) AND someday use (≥3 days/week) of the other product, either ENDS (≥3 mg/mL nicotine) or cigarettes (any frequency). We targeted dual consumers in the study design to include individuals who are likely more accustomed to the harshness of freebase nicotine and other smoke components (Leventhal et al., 2021), and who likely are capable of inhaling the aerosols produced across all conditions of this study.

Participants were excluded from the study if they reported any history of chronic disease or uncontrolled psychiatric condition, history of or active cardiovascular disease, low/high blood pressure, seizures, regular use of a prescription medication (except vitamins/birth control), and past month use of cocaine, opioids, benzodiazepines, or methamphetamines. Individuals who report using marijuana >15/30 days were also excluded, as were women who were breast-feeding or pregnant at screening. Participants intending to quit tobacco/nicotine use in the next 30 days were excluded and referred to cessation treatment.

2.2. Study design and procedure

After providing informed consent, participants attended the lab for a total of 5 sessions. Prior to each session, participants were required to abstain from tobacco/nicotine for ≥12 h. Participants were instructed to arrive at the scheduled study sessions one hour early for an observation period, during which the use of any nicotine/tobacco product was not permitted. Pre-session combustible tobacco abstinence was verified using expired air CO ≤10 ppm, as in Breland et al. (2002) (BreathCO monitor, Vitalagraph). During their initial visit to the lab, participants submitted photos of their ENDS device and liquid and answered survey questions about their ENDS/cigarette use. In the absence of reported nicotine strength and form, these details were obtained from online sources.

Participants completed five sessions at AUB's Clinical Aerosol Technology Lab (CATLAB), each lasting ~3.5 hours. During each session, participants were seated in a lounge chair and were allowed to use their smartphones and laptops. They were offered ad lib access to drinking water while seated. Sessions differed by nicotine flux and/or form and included two different nicotine fluxes (14 or 35 μg/sec) combined with two ratios of nicotine form (100% freebase or 100% protonated), as well as a condition in which no nicotine was administered (0-nicotine condition). Session order was determined by Latin square, and all sessions were administered double-blind. Following a one-hour observation period, participants underwent a 10-puff directed ENDS-use bout (with 30 sec interpuff interval). One hour after the first bout, participants completed a second bout, during which they were instructed that they could puff on the ENDS for 60 min ad libitum.

2.3. ENDS devices and liquids

For all sessions, participants used a Kangertech Subox Mini C ENDS (SSOC nichrome 0.5Ω) powered at 20 W by a Lost Vape Paranormal DNA 250 C Mod. Liquids were prepared from analytical grade propylene glycol (PG) (≥99.5%, CAS 57–55–6), vegetable glycerin (VG) (99.0–101.0%, CAS 56–81–5), nicotine (≥99%, CAS number 54–11–5) and benzoic acid (≥99.5%, CAS 65–85–0) that were procured from Sigma Aldrich. Five solutions were prepared, including a 30/70 PG/VG solution with no nicotine, and four solutions containing entirely freebase or protonated nicotine, each using 4 and 10 mg/mL nicotine concentrations at 30/70 PG/VG ratio. The protonated nicotine solutions were prepared by adding standard solutions of benzoic acid to freebase nicotine as 1:1 mol ratio. To verify the nicotine fluxes, standard vaping sessions of 15 4-sec puffs, 10 sec interpuff interval, and 8LPM were used to generate aerosol using the AUB Aerosol Lab Vaping Instrument (ALVIN; Talih et al. 2020), from the Subox Mini C ENDS powered at 20 W and filled with 4 and 10 mg/mL nicotine concentration liquids with a 30/70 PG/VG ratio. The resulting nicotine emissions were collected and quantified. The nicotine fluxes (nicotine yield divided by the total puff duration) were found to be equal to 14(SD=2.3)μg/sec for the 4 mg/mL nicotine liquid (N=32), and 35(SD=4.6)μg/sec for the 10 mg/mL nicotine concentration liquid (N=32). We note that 14 and 35 μg/sec are within the range of reported nicotine fluxes for commercial ENDS, which exhibit a mean of 29(SD=23)μg/sec, ranging from 3.7 to 110 μg/sec (El Hourani et al., 2022).

Because we previously found that manufacturing differences across nominally identical devices can influence emissions (Talih et al., 2023), a stringent device conditioning protocol was used to reduce nicotine flux variability. Before every session, the tank was fitted with a coil head and

filled with the appropriate liquid (depending on which flux/form condition was scheduled). Then, 15 4-sec puffs at 8LPM (liter per minute) flow rate and 20 W power were generated using ALVIN. The mass of liquid consumed was measured using the pre-post weight of the device. The coil heads were retained and used during the study if the mass of liquid consumed was found to be within a predetermined range. The average mass of liquid consumed across the retained coils was found to be equal to 333(SD=26)mg, with a relative standard deviation equal to 7.8% (N=160).

2.4. Outcome measures and analysis

During each session, the ENDS device was attached to the real-time in-situ sampling device (REALTIME; (Katurji et al., 2010)). The REALTIME unobtrusively samples 5% of the aerosol flow exiting the ENDS mouthpiece during each puff for subsequent chemical assays; the device also records puffing topography (puff volume, flow rate, duration, interpuff interval)(Katurji et al., 2010). We note that the REALTIME sampling mouthpiece uses a similar overall geometry as the eTop ENDS puff topography instrument. The eTop mouthpiece has been previously shown not to influence puff topography, nicotine delivery or acute subjective effects of ENDS use in a clinical setting (Felicione et al., 2020; Spindle et al., 2015).

Aerosol samples collected using REALTIME were analyzed for nicotine and carbonyl emissions to assess mouth-level exposure for each individual participant (Fig. 1). Liquid consumption for each session was determined by pre- and post-weighing the ENDS device. Nicotine was determined by extracting the REALTIME filter pads in an ethyl-acetate solvent and analyzing the solution by GC-MS, as in El-Hellani et al. (2016) We note that one sample was eliminated from the nicotine analysis due to liquid leakage from the tank when we were disassembling the tank from the battery.

2.5. Statistical analysis

All analyses were conducted using SPSS software version 29.0 (IBM, Armonk, NY, USA). We first described for each condition (control, protonated/14, protonated/35, freebase/14, freebase/35) the means of all the outcome variables of interest. Then, we conducted for each outcome (puff duration, number of puffs, total puff duration, liquid consumption, and nicotine yield), linear mixed models (LMMs) taking into account the repeated assessments per subject across 4 visits (with an unstructured correlation) and having each of flux and form as fixed effects. In addition, we conducted a LMM with a five-level independent fixed variable for the 5 conditions of interest (4 flux/form and the control settings) in order to examine and visualize differences in puff duration, number of puffs (B2 only), amount of liquid consumed, and mouth-level nicotine exposure; post-hoc comparisons were made using the Bonferroni correction to control for multiple comparisons; we report results that were significant both at the 0.05 level and with adjustment for multiple comparisons. Statistical significance was $p<0.05$.

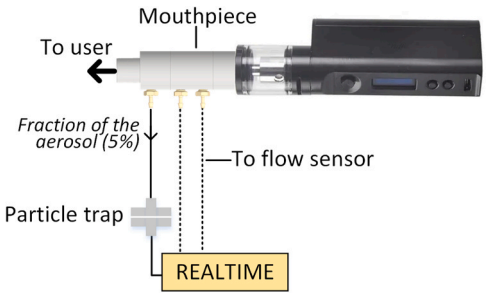

Fig. 1. Schematic of the setup using REALTIME, which was used to sample a fraction of the generated aerosol for off-line chemical analysis of nicotine and record puff topography parameters.

3. Results

Thirty-two participants were enrolled in this study. Participants had a mean age of 24(SD=6) years, ranging from 18 to 42 years. Of these, 23 (72%) were male and 9(28%) were female. All participants met the CO threshold confirming smoking abstinence. The average CO level at baseline was 3 ppm (SD=2 ppm). Fifteen participants (47%) reported their usual nicotine strength, and none reported their nicotine form. The average history of use of any tobacco product among the participants was 6.2(SD=6) years. The average nicotine strength used by the participants was 4%(SD=1.6%). All liquids were salt based. Table 1 summarizes the puff topography parameters, liquid consumed, and mouth-level exposure to nicotine obtained by varying nicotine form and nicotine flux for the 10-puff directed and one-hour ad lib bouts.

Adjusting for nicotine form, greater nicotine flux resulted in significantly reduced puff duration, puff number (B2), flow rate, and liquid consumed. For the 10-puff directed bout, greater nicotine flux resulted in greater mouth-level nicotine exposure. Adjusting for nicotine flux, the freebase nicotine condition resulted in significantly shorter puff duration, shorter total puff duration, reduced liquid consumption, and reduced mouth-level nicotine exposure. For the 10-puff directed bout, freebase nicotine also resulted in lower flow rate. See Table S1 for details.

The zero nicotine flux condition resulted in higher puff duration compared to all other conditions in bout 1 ($p<0.05$) and bout 2 ($p<0.05$), except for protonated/14 ($p=0.16$), as well as higher number of puffs compared to the 35 μg/sec for both nicotine forms (B2: protonated ($p=0.01$); freebase ($p=0.01$)), and higher liquid consumption compared to the 35 μg/sec in both forms (B1: protonated ($p=0.007$); freebase ($p<0.001$); B2: protonated ($p=0.004$); freebase($p<0.001$)) and compared to freebase/14 in bout 2 only ($p=0.014$) (Figs. 2 and 3).

4. Discussion

In this study we sought to test how ENDS nicotine form and flux influence puffing behavior and mouth-level exposure to nicotine. Experienced ENDS consumers were recruited for five clinical laboratory visits which differed by nicotine flux and nicotine form. Each visit involved a 10-puff directed bout followed by 1-hour ad lib use. We measured puffing topography, ENDS liquid consumed, and mouth-level nicotine exposure for each use session. We found that nicotine form and flux strongly influenced puffing behavior in directed and ad lib use sessions. In particular, freebase nicotine reduced puff duration, liquid consumption, and mouth-level nicotine exposure relative to protonated nicotine. In addition, we found that increasing nicotine flux from 14 to 35 μg/sec resulted in lower puff duration, lower number of puffs during ad lib bouts, lower flow rate, lower liquid consumption in both bouts, and greater mouth-level nicotine exposure in bout 1. We also found that, in general, the zero-nicotine liquid condition resulted in higher puff duration, number of puffs, and liquid consumption compared to all other conditions.

Importantly, the longer puffs observed with protonated nicotine liquids resulted in significantly greater mouth-level nicotine exposure. To date, the impact of nicotine form on nicotine delivery from ENDS had not been addressed by industry-independent researchers. While this study found that protonated nicotine liquids resulted in greater mouth-level nicotine exposure than freebase liquids, systemic nicotine uptake is also a function of inhalation depth and formulation-dependent aerosol heat and mass transfer phenomena in the airways. We caution that the relationship between mouth-level nicotine exposure and systemic exposure is not addressed in this study.

In addition, we found that while increasing nicotine flux resulted in greater mouth-level nicotine exposure in the directed bouts, increasing nicotine flux did not significantly increase mouth-level nicotine

Table 1
Puff topography, liquid consumed, and mouth-level nicotine exposure (average(standard deviation)) for N=32 participants who completed five laboratory visits in which they were provided ENDS products that varied by nicotine flux and form. Bout 1 consisted of 10 directed puffs, while Bout 2 consisted of one hour of ad lib use. For all conditions, a puff topography measurement and aerosol sampling system was connected to the ENDS device during use.

Bout		Nicotine Form	NA	Freebase		Protonated	
		Nicotine flux (μg/sec)	**0**	**14**	**35**	**14**	**35**
B1 (directed)	Puff topography	Puff Duration (sec)	3.96(2.04)	2.65(1.12)	1.83(0.639)	3.16(1.53)	2.63(1.09)
		Number of Puffs	9.84(0.92)	10.1(0.246)	10(0.309)	10.2(0.448)	10(0.309)
		Total puff duration (sec)	38.8(20.3)	26.8(11.2)	18.3(6.46)	31.9(15.5)	26.4(10.8)
		Interpuff Interval (sec)	31.1(3.01)	30.4(1.74)	30.7(1.41)	30.8(1.33)	31(1.16)
		Flow Rate (LPM)	10.1(3.56)	8.43(2.89)	7.38(2.53)	8.9(3.02)	9.08(3.92)
	Liquid consumed (mg)		188(170)	110(91.4)	48.4(39.1)	137(132)	96.9(75.2)
	Mouth-level nicotine exposure (mg)		0.0121(0.0389)	0.119(0.149)	0.138(0.174)	0.259(0.303)	0.44(0.46)
B2 (ad lib)	Puff topography	Puff Duration (sec)	2.73(1.11)	2.04(0.76)	1.51(0.714)	2.33(0.934)	2.15(0.77)
		Number of Puffs	59.1(38.7)	49.9(41.8)	34.2(36.8)	58.2(36.9)	41.9(25.4)
		Total puff duration (sec)	172(128)	115(121)	58.4(72)	150(137)	95.9(71.1)
		Interpuff Interval (sec)	111(169)	153(285)	160(183)	68.4(40.6)	207(525)
		Flow Rate (LPM)	9.31(3.89)	7.96(3.24)	6.51(2.82)	8.42(3.99)	8.28(4.15)
	Liquid consumed (mg)		825(795)	488(647)	227(374)	682(912)	399(339)
	Mouth-level nicotine exposure (mg)		0.055(0.1)	0.786(1.26)	0.864(1.8)	1.5(2.28)	2.05(2.3)

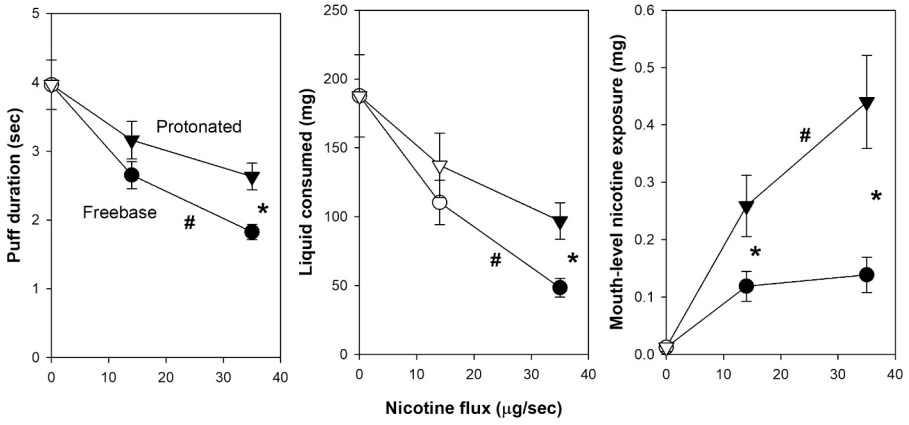

Fig. 2. Mean±SEM outcome measures for Bout 1 (10-puffs directed). Filled symbols indicate significant difference from the 0 nicotine condition, asterisks (*) indicate significant difference between the protonated and freebase nicotine conditions at the shown nicotine flux, and pound (#) symbols indicate significant difference between the 14 and 35 μg/sec nicotine flux condition at the shown nicotine form.

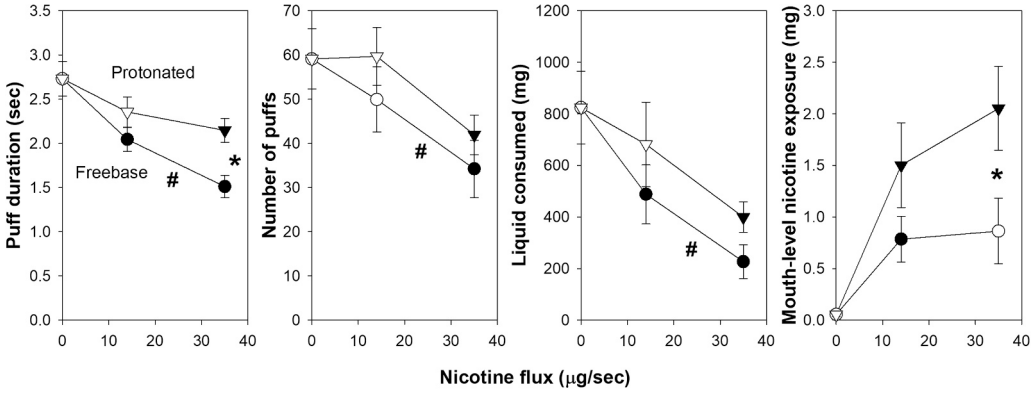

Fig. 3. Mean±SEM outcome measures for Bout 2 (ad lib). Filled symbols indicate significant difference from the 0 nicotine condition, asterisks (*) indicate significant difference between the protonated and freebase nicotine conditions at the shown nicotine flux, and pound (#) symbols indicate significant difference between the 14 and 35 μg/sec nicotine flux condition at the shown nicotine form.

exposure in the ad lib bouts, particularly for freebase nicotine. The effect of increasing nicotine flux with freebase nicotine was canceled out by a decrease in total puff duration, resulting in no net increase in mouth-level nicotine exposure. However, whether individuals would maintain a lower puff duration or gradually adjust upward with time remains to be investigated in future studies.

To date, few studies have addressed the impact of ENDS nicotine form on behavior. In one study that used an in-home paradigm where participants had their normal ENDS devices filled with either protonated or freebase nicotine on separate days, no differences were observed in appeal, harshness, or puffing parameters (Pauwels et al., 2023). In contrast, a clinical study found that during directed puffing sessions that

differed by flavor and nicotine form, protonated nicotine increased the perception of appeal, sweetness and smoothness and decreased the perception of bitterness compared to freebase nicotine, particularly among individuals who never used combustible cigarettes (Leventhal et al., 2021). In the current study, we found that freebase nicotine liquids elicited shorter puffs compared to protonated nicotine, supporting the notion that nicotine formulation influences behavior. We are uncertain why this study yielded different results compared to that by Pauwels et al. (2023). One possible explanation is that, in the study by Pauwels et al. (2023), participants had a trial day with the liquid-filled ENDS before the 15 min online session in which their vaping patterns were recorded. The trial day might have accustomed them to the aerosol's sensory effects and resulted in similar puffing patterns across the protonated and freebase nicotine conditions. On the other hand, in our study we found that even during the ad lib 60-minute use session, the puff topography differences across conditions were maintained.

One limitation of this study is that we manipulated nicotine flux by modifying nicotine concentration only. Flux can also be varied by changing the electrical power delivered to the ENDS coil. That nuance is important because ENDS nicotine concentration may play a direct role in sensory feedback independent of flux; the degree to which nicotine concentration versus nicotine flux influences puffing behavior remains to be studied. Therefore, manipulating nicotine flux by modifying other parameters (e.g., electrical power) might result in different effects of nicotine flux on puffing parameters. Another limitation is that we did not use flavored liquids. ENDS liquids are generally flavored, although flavorless products are now being marketed (Vapeloft, 2023). The use of flavored versus unflavored liquids could potentially alter the puffing behavior of individuals, as also noted by Felicione et al. (2020). While using flavors would have been more representative of ENDS use, by using flavorless liquids we eliminated a potential confounder and focused on the core question: does nicotine form influence puffing behavior? Additionally, while some flavorants and cooling agents can temper the puffing behavior differences observed across freebase and protonated nicotine liquids, e.g., by masking harshness, it is unlikely they would entirely negate the impact of protonation on puffing behavior and mouth-level nicotine exposure. As previously reported by Leventhal et al. (2021) the impact of nicotine formulation on sensory attributes was in general consistent across a range of 10 flavors (Leventhal et al., 2021). In addition, while ENDS liquids in the U.S. often contain varying ratios of freebase to protonated nicotine, we used 100% freebase and 100% protonated in this study to isolate the effects of each form. Finally, while we found that nicotine flux and form influence puffing behavior and mouth-level nicotine exposure, how flux and form influence systemic nicotine delivery kinetics and long-term dependance are open questions that need to be addressed in future industry-independent studies on pharmacokinetics and subjective effects related to dependency.

5. Conclusion

We found that ENDS with protonated nicotine elicit longer puffs and greater mouth-level exposure to nicotine. We also found that greater nicotine flux resulted in shorter puffs in both directed and ad lib bouts, fewer puffs in the ad lib bouts, and greater mouth-level nicotine exposure in the directed bouts only. This work highlights the importance of taking into consideration interactions between nicotine form and flux when considering nicotine regulation for ENDS. Research is needed on how these interactions might be leveraged to produce a regulatory strategy that reduces nicotine dependency risks for nicotine-naïve individuals while providing an acceptable alternative for established combustible cigarette consumers.

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Nareg Karaoghlanian: Methodology, Resources, Software, Supervision, Writing – review & editing. **Farid Talih:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Stephen Baldassari:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Writing – review & editing. **Najat Saliba:** Investigation, Methodology, Resources, Writing – review & editing. **Martine Elbejjani:** Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – review & editing. **Thomas Eissenberg:** Conceptualization, Investigation, Methodology, Project administration, Writing – review & editing. **Ahmad El-Hellani:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing. **Soha Talih:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Alan Shihadeh:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. **Eliana Hanna:** Investigation, Methodology, Supervision, Writing – review & editing, Project administration. **Rola Salman:** Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. **Sally Salam:** Methodology, Resources, Validation, Writing – review & editing. **Rachel El-Hage:** Investigation, Methodology, Resources, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following competing financial interest: Drs. Shihadeh and Eissenberg are paid consultants in litigation against the tobacco industry and the ENDS industry and are named on one patent for a device that measures the puffing behavior of ENDS consumers and on a patent application for a smoking cessation intervention. Dr. Eissenberg is also named on another patent application for a smartphone app that determines ENDS device and liquid characteristics.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2023.111052.

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