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Nicotine flux and pharmacokinetics-based considerations for early assessment of nicotine delivery systems

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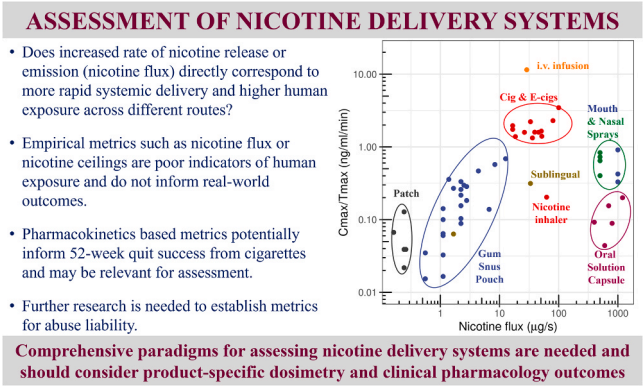
HIGHLIGHTS

- Nicotine flux or nominal nicotine dose alone are poor indicators of human exposure.
- Pharmacokinetics based metric ($\frac{C_{max}}{T_{max}}$) informs 52 week-quit success from cigarettes.
- *In vitro* and *in silico* methods could enable scientific assessment of nicotine delivery systems.
- Further research is needed to establish appropriate metrics for abuse liability.

GRAPHICAL ABSTRACT



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ABSTRACT

In the past few years, technological advancements enabled the development of novel electronic nicotine delivery systems (ENDS). Several empirical measures such as "nicotine flux" are being proposed to evaluate the abuse liability potential of these products. We explored the applicability of nicotine flux for clinical nicotine pharmacokinetics (PK) and 52-week quit success from cigarettes for a wide range of existing nicotine delivery systems. We found that the differences in nicotine flux for various nicotine delivery systems are not related to changes in PK, as nicotine flux does not capture key physiological properties such as nicotine absorption rate. Further, the 52-week quit success and abuse liability potential of nicotine nasal sprays (high nicotine flux product), and nicotine inhalers (nicotine flux similar to ENDS) are low, suggesting that nicotine flux is a poor metric for the assessment of nicotine delivery systems. PK indices are more dependable for characterizing nicotine delivery systems, and a nicotine plasma $\frac{C_{max}}{T_{max}} > 1$ could improve 52-week quit success from cigarettes. However, a single metric may be inadequate to fully assess the abuse liability potential of nicotine delivery systems and needs to be further studied. A combination of *in vitro* and *in silico* approaches could potentially address the factors influencing the inhaled aerosol dosimetry and resulting PK of nicotine to provide early insights for ENDS assessments. Further research is required to understand nicotine dosimetry and PK for *ad libitum*

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product use, and abuse liability indicators of nicotine delivery systems. This commentary is intended to (1) highlight the need to think beyond a single empirical metric such as nicotine flux, (2) suggest potential PK-based metrics, (3) suggest the use of *in vitro* and *in silico* tools to obtain early insights into inhaled aerosol dosimetry for ENDS, and (4) emphasize the importance of considering comprehensive clinical pharmacology outcomes to evaluate nicotine delivery systems.

1. Introduction

While nicotine is addictive and not risk free, it is delivered through a range of products with different risk profiles, the most harmful of which is cigarettes. In 2019, it was estimated that 1.14 billion adults were currently smoking, and 200 million years of disability-adjusted life were attributable to smoking tobacco (GBD, 2019 Tobacco Collaborators, 2021). The best option to reduce health risks is to quit all tobacco and nicotine use, but complete cessation is challenging as cigarette smoking is conditioned through positive and negative reinforcement mechanisms. The positive reinforcements are driven by mechanisms such as nicotine-driven pleasure, smoking ritual, taste, and sensation (Henningfield and Keenan, 1993). The negative reinforcement relates to alleviation of withdrawal symptoms (Henningfield and Keenan, 1993).

Several pharmacological nicotine replacement therapies (NRTs) such as patches, gums, sprays, and lozenges have been introduced as cessation therapies, but many of these products do not meaningfully impact smoking cessation at a population level due to low adherence and reach (i.e., very few people who smoke use these products) (Rosen et al., 2021). For people who do not quit and continue to smoke, switching entirely to scientifically substantiated products that do not combust tobacco has the potential to present less harm than continued smoking. This concept—referred to as tobacco harm reduction—is complementary to efforts to prevent smoking initiation and encourage cessation. Tobacco harm reduction in a population depends on two factors: a nicotine delivery system that delivers significantly lower levels of harmful chemical constituents and a complete shift from cigarettes to these new products (Abrams et al., 2018; Hatsukami and Carroll, 2020). Several scientific bodies have determined that nicotine delivery systems such as electronic nicotine delivery systems (ENDS), which use nicotine-containing e-liquids, produce far lower levels of harmful and potentially harmful constituents than cigarettes (McNeill et al., 2022; National Academies of Sciences Engineering Medicine, 2018; New Zealand Ministry of Heath, 2023); therefore, they could play a key role in tobacco harm reduction.

Recent technological advances have enabled the development of several novel inhalation-based nicotine delivery systems (Fearon et al., 2018). As a result, regulatory agencies are adopting different approaches to lay out guidelines for limiting their uptake among non-smoking or adolescent populations and the potential risk of nicotine poisoning, while ensuring they remain acceptable for adults who use nicotine-containing products. For example, the European Union's Tobacco Products Directive restricted the e-liquid nicotine concentration to 20 mg/mL stating "This concentration allows for a delivery of nicotine that is comparable to the permitted dose of nicotine derived from a standard cigarette during the time needed to smoke such a cigarette" (European Union Tobacco Products Directive, 2014), while Canadian authorities set the limit to 66 mg/mL based on the toxicological assessment of nicotine (Canada Minister of Justice, 2019). In the United Kingdom, ENDS liquid is restricted to 20 mg/mL with a removable cartridge volume of 2 mL and a refill container volume of 10 mL (Medicines and Healthcare products Regulatory Agency, 2016). In New Zealand, the strength of free-base nicotine in a vaping substance must not exceed 20 mg/mL, the strength of nicotine salt in a vaping substance must not exceed 50 mg/mL, and the total nicotine content in a container of a vaping substance sold at retail must not exceed 1800 mg, whether it is free-base nicotine or nicotine salts (New Zealand Ministry of Health, 2021). The regulations for nicotine level in ENDS are mostly derived from empirical calculations (European Union Tobacco Products Directive, 2014; Shihadeh and Eissenberg, 2015).

While a dose metric should be measurable and expressed in relevant units, it also needs to have a causal relationship to exposure and biological responses (Phalen et al., 2010). In 2015, "nicotine flux"—a metric that describes the amount of nicotine emitted from a delivery system over the duration of use—was initially proposed as a regulatory tool to determine nicotine levels that could enable switching to ENDS without higher-than-necessary abuse liability (Shihadeh and Eissenberg, 2015). Nicotine flux concept has been applied to other nicotine delivery systems such as patches and gums (El Hourani et al., 2023), and is being evaluated in ongoing clinical studies (ClinicalTrials.gov: NCT05430334; NCT04332926). However, it must be noted that the abuse liability of nicotine delivery systems is considered to be an aggregated likelihood of repeated use (indicated by PK, drug effects, and reinforcement), and the consequences of use (impacting functioning, physical dependence, adverse effects) (WHO, 2021). The goal of this work was to analyze if an increase in nicotine flux corresponds to a subsequent rapid rise in systemic exposure (PK) along with differential product acceptance and abuse liability outcomes.

This commentary provides perspective on the applicability of nicotine flux for human exposure-response and highlights the importance of clinical pharmacology-related paradigms for assessment of nicotine delivery systems. Data selection was limited to studies that reported product characterization to enable the determination of nicotine flux and PK measurements. The data obtained from the literature, corresponding references, and additional exploration are provided as Supplementary Information.

2. Nicotine flux and nicotine concentration limits

Fundamentally, flux represents the quantity (in this case, mass) passing through a surface area in time ($\mu g m^{-2} s^{-1}$), but for the assessment of nicotine delivery systems, a simplified empirical metric termed as "nicotine flux" was used for a head-to-head comparison of products administered by different routes (El Hourani et al., 2023; Shihadeh and Eissenberg, 2015). The nicotine flux is defined as nicotine dose per product unit over usage time as in Eq. (1) (El Hourani et al., 2023).

$$Nicotine\ Flux\left(\frac{\mu g}{s}\right) = \frac{Nicotine\ dose(\mu g) for\ unit\ product}{usage\ time(s)} \quad (1)$$

The usage time for inhaled nicotine systems is given by the puff duration multiplied by number of puffs, while for nicotine delivery systems administered by other routes, the usage time is duration of application or use (El Hourani et al., 2023). It is extremely importantly to note that the nicotine dose from Eq. (1) can be the nominal, emitted, or applied dose for a unit product (Tepper et al., 2016). El Hourani and colleagues (El Hourani et al., 2023) selected emitted dose for inhaled nicotine delivery systems and nominal dose for nicotine delivery systems administered by other routes. The influence of nicotine dose and product usage time on nicotine flux for products administered by different routes is shown in Fig. 1. A nicotine dose of 1–2 mg could be delivered with a wide range of nicotine flux when administered by different routes such as buccal, sublingual, intravenous infusion, inhalation, or nasal delivery (Fig. 1a and S1). Nasal and mouth sprays have the highest nicotine flux as the dose is administered in 1–2 s. This is followed by inhalation products with a cumulative puffing time of ~30 s, oral and gum products used for ~30–60 min, and nicotine patches applied for 18–24 h.

Under this conceptual framework, nicotine flux is inversely proportional to the duration of product usage (Fig. 1b and S2) and is the major parameter influencing nicotine flux for products administered by different routes. While modulation of nicotine flux and therefore total nicotine delivery for non-inhalable products could be minimal as subjects cannot typically vary the release profile or emission kinetics of nicotine from a given product (e.g., nicotine patch), nicotine delivery with inhalable products is more variable and subject to adaptation. For example, an increase in the puffing time from 2 s to 4 s (due to variability in *ad libitum* product use i.e., similar puff volume but different flow rate) will lower nicotine flux by 50% for the same product, making it a less reliable empirical metric for assessment of inhaled nicotine delivery systems (e.g., ENDS).

Nicotine flux solely relies on the dose and duration of delivery to characterize the nicotine delivery systems (El Hourani et al., 2023; Shihadeh and Eissenberg, 2015). However, this empirical metric does not translate to *in vivo* exposures as it does not consider the most important factor: the rate of absorption of nicotine from the tissue barrier into systemic circulation, which will influence the systemic nicotine delivery kinetics (i.e., PK). For example, using a product with the same nicotine flux via intranasal or transdermal administration routes will result in completely different systemic exposure (PK) profiles because of the lower rate of nicotine absorption from the dermal route compared to the nasal route. The lower nicotine absorption rate from the dermal route allows application of larger doses or use of products with a higher nicotine flux, as they provide in slower systemic delivery of nicotine compared to application of an equivalent dose or nicotine flux product to the lower respiratory tract, which could increase risk due to higher nicotine absorption rate. Conversely, intravenous infusion of nicotine is not impacted by the rate of absorption across tissue barrier but is solely driven by the dose and duration of infusion (i.e., nicotine flux). Although intravenous infusion provides the most rapid systemic delivery, its nicotine flux (28.8 μg/s) is smaller than for nasal or mouth sprays (~500 μg/s) (Fig. 2). For this reason, a head-to-head comparison of nicotine delivery systems administered by different routes solely based on nicotine flux is challenging because fundamental parameters that influence nicotine exposure (PK) are not considered and any proposed empirical metric needs to be interpreted with caution.

Nicotine flux for inhaled nicotine delivery systems was proposed to account for the influence of nicotine delivery from ENDS based on formulation and device characteristics and performance. Mathematical models of nicotine flux are also thought to account for characteristics that contribute to actual nicotine emissions, including formulation (nicotine concentration, propylene glycol/vegetable glycerin ratio, volatility of other ingredients/flavorings), device characteristics (coil size and battery power), and puff duration (Talih et al., 2017). Assuming these parameters are sufficient for describing the amount of nicotine delivered and absorbed, a hypothetical nicotine flux ceiling of 25–65 μg/s (Shihadeh and Eissenberg, 2015) that was further refined to 80 μg/s (mimicking the average cigarette flux) was proposed as a temporary ceiling limit for inhaled nicotine delivery systems (ENDS) until further investigations are performed (El Hourani et al., 2023). However, inhalation-based nicotine delivery systems with nicotine flux <80 μg/s and favorable bioavailability (i.e., aerosol particle sizes, aerosol evolution, and formulations with various mixtures) could mimic the PK of products with nicotine flux >80 μg/s based on the regional deposition and absorption in the respiratory tract (Kolli et al., 2023). Products with similar nicotine flux, such as Nicorette® inhalers and ENDS, would yield different systemic exposures (Fig. 2, S1-S6) due to fundamental differences in product parameters related to formulations, aerosol physicochemical properties, regional airway deposition patterns, and absorption rates (Kolli et al., 2019). Finally, ENDS with high nicotine flux that have varied aerosol physicochemical properties and inhalation patterns might have a similar systemic PK of nicotine as a low nicotine flux product (Goldenson et al., 2022). For these reasons, single empirical metrics such as nicotine flux are poor regulatory tools for nicotine delivery systems because they cannot consider fundamental properties related to device characterization, emitted/inhaled aerosol characterization, and systemic exposure (PK).

Single empirical metrics such as nicotine flux do not consider the interaction between a subject and the delivery system such as ENDS. Do and colleagues (Do et al., 2022) recently reported a positive correlation between nicotine flux and the ENDS dependence scale, but they did not determine whether an increase in nicotine flux resulted in higher systemic nicotine concentrations during an *ad libitum* inhalation regimen. Benowitz and colleagues found subjects consuming cigarettes with 2× higher nicotine-content (i.e., 2× nicotine flux) did not have a 2× increase in total blood nicotine exposure (*AUC*, area under curve) because subjects smoked less intensively compared to their usual brand or low-nicotine cigarettes (Benowitz et al., 1982). Subjects also had lower carboxyhemoglobin levels after consumption of 2× higher nicotine-containing cigarette compared to low-nicotine cigarettes (Benowitz et al., 1982), suggesting that they titrated their smoking patterns to obtain desired nicotine levels. Therefore, a product with higher nicotine flux does not necessarily translate into a dose-dependent increase in systemic exposure or higher consumption of nicotine. A similar observation was reported by Goldenson and colleagues for ENDS, where systemic nicotine concentrations did not increase with higher e-liquid nicotine concentrations (Goldenson et al., 2022). However, depending on the design of the nicotine delivery system and

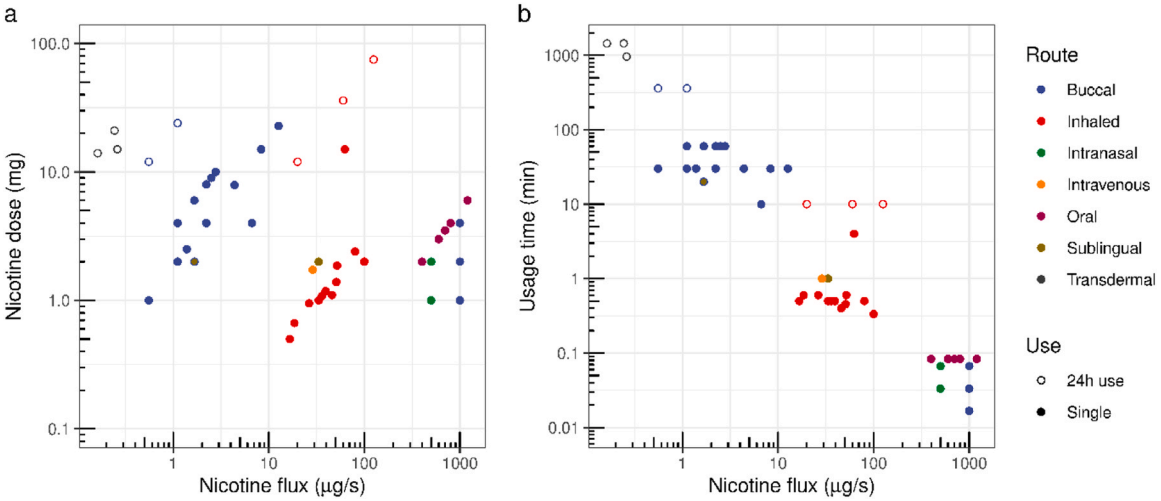

Fig. 1. Influence of (a) nicotine dose and (b) product usage time on nicotine flux for products administered by different administration routes.

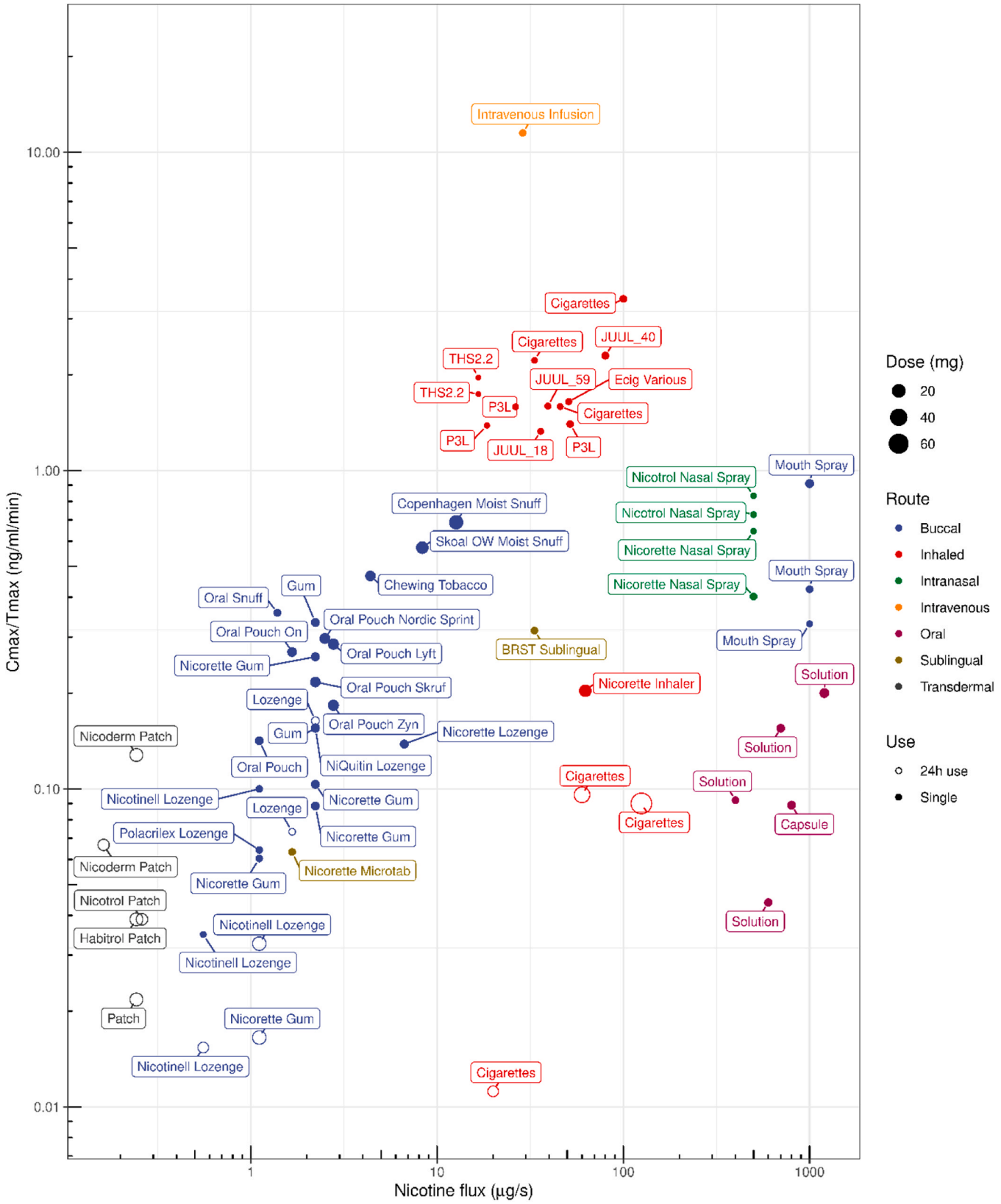

Fig. 2. Nicotine flux and pharmacokinetic parameter ($\frac{C_{max}}{T_{max}}$) calculated based on plasma concentrations for various nicotine-containing products delivered by different routes; data were obtained from multiple sources as listed in the Supplementary Information.

nicotine levels in the formulation, subjects can titrate their desired nicotine levels from low-nicotine flux products during *ad libitum* use, leading to varied exposure (Dawkins et al., 2016). Nicotine flux may be an appealing regulatory target for newer tobacco products because it is relatively easy to measure, but the relationship between nicotine concentration or rate of emissions and actual human nicotine uptake is complex.

3. PK indices

Nicotine PK is influenced by the kinetics of nicotine release (emitted dose) from a nicotine delivery system, consumption patterns (inhaled and deposited dose), and ADME (absorption, distribution, metabolism, and elimination) (Kolli et al., 2019). Absorption of nicotine from the lower respiratory tract into systemic circulation is rapid compared to the nasal, buccal, gastrointestinal tract, and transdermal routes (Benowitz et al., 2009). While nicotine flux is characteristic to a specific product unit and does not change under given use conditions, the resulting PK indices (e.g., maximum plasma concentration [C_{max}], time to reach C_{max} [T_{max}], and $\frac{C_{max}}{T_{max}}$) for overall systemic exposure resulting from using one or several units of product (*ad libitum*) in a day are vastly different (Fig. 2, S3, and S4). For single-unit product use, the most relevant PK parameter that captures the product-specific metric is the rate of systemic nicotine delivery given by $\frac{C_{max}}{T_{max}}$ (ng/mL/min). Unlike nicotine flux, which describes the rate of nicotine release from a unit product, the PK metric $\frac{C_{max}}{T_{max}}$ indicates the rate of rise in plasma nicotine concentration. Despite having the highest nicotine flux, nasal and mouth sprays are slowly absorbed into systemic circulation compared to inhaled products (Fig. 2). The $\frac{C_{max}}{T_{max}}$ is lowest for transdermal route and highest for intravenous infusion and inhaled products, with intravenous infusion being the potential upper ceiling (Fig. 2). All inhaled products absorbed from the lower respiratory tract tend to have a $\frac{C_{max}}{T_{max}} > 1$ ng/mL/min, while products absorbed from other regions tend to have a $\frac{C_{max}}{T_{max}} <$ 1 ng/mL/min. The steady-state 24-h PK for cigarettes mimicking daily *ad libitum* use has a lower $\frac{C_{max}}{T_{max}}$ value (Fig. 2) and provided the basis for nicotine patch development; however, it does not fully capture the C_{max} for inter-product use. Hence, both the single-product PK that informs characteristics of a specific product unit and the data obtained from realistic daily *ad libitum* use should be used for future evaluation of nicotine delivery systems. In light of these considerations, clinical PK-based metrics for nicotine delivery systems administered by different routes will likely be more relevant.

4. Relationship between nicotine flux, PK indices, product acceptance, abuse liability, and tobacco harm reduction

Nicotine nasal sprays have a high nicotine flux and theoretically enable direct delivery of nicotine to the brain. Based on this, sprays should have the highest abuse liability potential, but clinical studies have shown low abuse liability and limited clinical success (Blöndal et al., 1997; Schuh et al., 1997). Nicotine inhalers with nicotine flux similar to ENDS have low abuse liability, suggesting that nicotine flux may not be a reliable metric for abuse liability assessment. In reality, inhalation products that deliver nicotine to the lower respiratory tract enable rapid systemic delivery ($\frac{C_{max}}{T_{max}} > 1$) and therefore have a higher potential for abuse liability (Fig. 2) (Allain et al., 2015). However, subjects who smoke very lightly or tobacco chippers (consuming ≤5 cigarettes per day) use cigarettes ($\frac{C_{max}}{T_{max}} > 1$) without developing dependence (Shiffman, 1989), and products such as chewing tobacco and oral snuff with a $\frac{C_{max}}{T_{max}} < 1$ are also prone to misuse (Henningfield and Keenan, 1993). This makes $\frac{C_{max}}{T_{max}}$ alone a poor PK indicator for abuse liability. However, it must also be noted that all NRTs such as nicotine patch, nicotine gum, Nicorette® inhaler, and Nicorette® nasal sprays with no abuse liability have a $\frac{C_{max}}{T_{max}} < 1$. Recent studies have described partial systemic exposure (pAUC, a specific portion of the total AUC) as a PK parameter to evaluate the abuse liability of drugs (Zhao et al., 2021), which could apply to a head-to-head comparison of nicotine delivery systems, but the utility for evaluating real-world *ad libitum* use across different products and routes needs to be explored. More importantly, a closer look at the nicotine PK from smoking cigarettes (Feyerabend et al., 1985) and different consumption patterns underscores the need to consider advanced metrics such as frequency-dependent exposure-responses during *ad libitum* use (Allain et al., 2015; Schulthess et al., 2018). According to the Tobacco Product Regulation study group at the World Health Organization, the abuse liability or potential for misuse of a drug (and its delivery system) is considered to be linked to PK, drug properties, and reinforcement value for repeated use (WHO, 2021). Hence, deriving a PK-based metric for abuse liability is complex as it is influenced by several parameters (e.g., smoking ritual, product taste, frequency of use, pharmacological properties of nicotine, etc.).

Alongside reduced toxic exposure, product acceptance to enable complete transition away from smoking is the most important parameter that determines the utility of nicotine delivery systems from a public health perspective. Nicotine plays a crucial role in helping subjects who smoke to switch to NRTs or less harmful tobacco products and therefore promotes tobacco harm reduction. Numerous clinical trials have evaluated the long-term quit success of various nicotine delivery systems (Table S1). In most randomized clinical trials (RCTs), up to 5% of participating subjects quit cigarettes using a placebo, while the use of nicotine patches or gum resulted in ~10% 52-week quit success (Fig. 3). In addition, studies have shown that gum and patch use did not prevent subjects from reverting to cigarettes (Rosen et al., 2021). An RCT evaluating nicotine nasal spray reported, 25% quitting success in the treatment group compared to 17% in the placebo group, probably due to the additional cessation support meetings (Blöndal et al., 1997). Although clinical studies have found NRTs to be somewhat effective for quitting smoking, long-term general population studies have found NRTs to be far less effective due to low uptake, low adherence, and high rates of return among subjects who used to smoke (Rosen et al., 2021).

Establishing metrics that potentially relate and inform acceptance of nicotine delivery systems by subjects who continue to smoke for future development of NRTs or less harmful tobacco products could be beneficial. Nicotine inhalers and ENDS with similar ranges of nicotine flux are not strongly associated with 52-week quit success from cigarettes (Fig. 3a), rendering assessments using nicotine flux ineffective. A change in nicotine flux by several orders of magnitude (from patch to mouth spray) did not meaningfully improve the association with 52-week quit success based on real-world outcomes (Fig. 3a) and is therefore unlikely to be an indicator for product acceptance. In comparison, inhalation-based nicotine delivery systems such as ENDS potentially delivering a $\frac{C_{max}}{T_{max}} > 1$ have a 52-week quit success of 18% (Fig. 3b), and among the 52-week abstinence group, 80% of subjects using ENDS were likely to continue use compared to 9% for nicotine patches (Hajek et al., 2019). Furthermore, the number of subjects who quit smoking and switched to ENDS were higher than NRT groups in both studies that offered additional cessation support and those that did not (Hartmann-Boyce et al., 2021). While nicotine flux is not significantly associated with 52-week quit success making it a poor predictor, $\frac{Cmax}{Tmax}$ has a significant association making it a more relevant metric for further consideration.

The systemic nicotine delivery rate was proposed to play a critical role in decreasing abuse liability potential vs. optimizing therapeutic effects (i.e., alleviation of craving and withdrawal symptoms) (De Aquino et al., 2022; Jensen et al., 2020). In humans, a nicotine delivery rate of 16.8 and 6.67 μg/s (IV infusion of 1 mg in 1 and 2.5 min, respectively) produced robust positive subjective effects (i.e., greater pleasure and stimulation) and alleviated smoking urges (De Aquino et al., 2022; Jensen et al., 2020). While a nicotine delivery rate of 3.36 μg/s (IV infusion of 1 mg in 5 min) only alleviated smoking urges, a

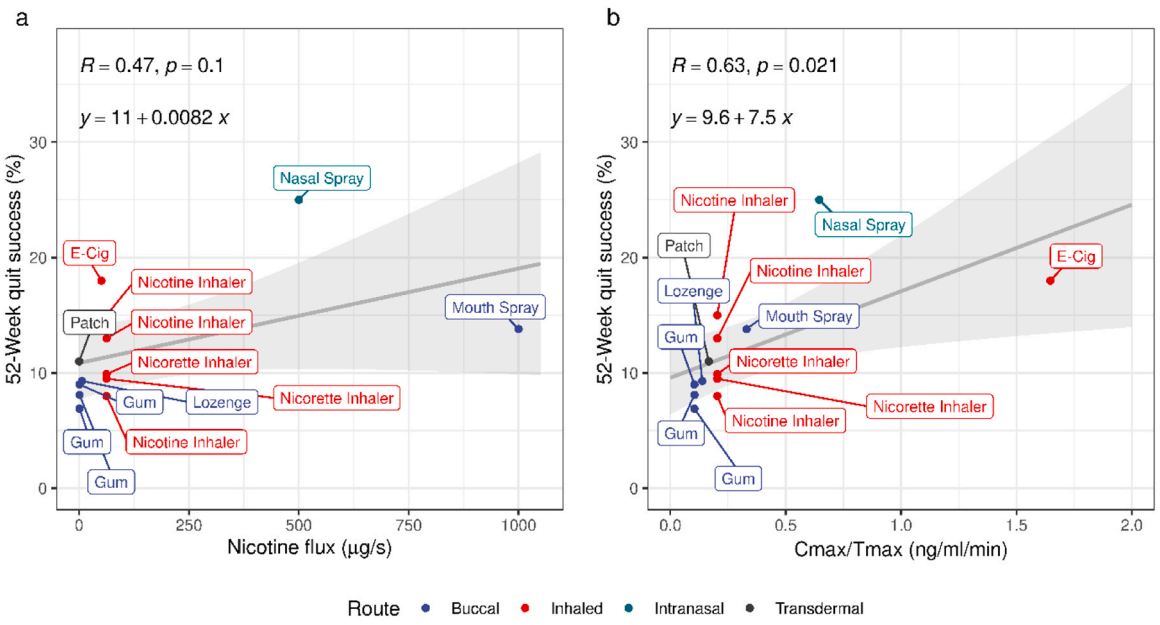

Fig. 3. Association of (a) nicotine flux and (b) the pharmacokinetic parameter ($\frac{C_{max}}{T_{max}}$) of various nicotine-containing products on 52-week quit success from combustible cigarette smoking. The shaded region is the 95% confidence interval for predictions of the linear model (solid line); data were obtained from multiple sources as listed in the Supplementary Information.

nicotine delivery rate of 1.68 µg/s (IV infusion of 1 mg in 10 min) is reported to be least effective in alleviating smoking urges (Jensen et al., 2020). The low delivery rates of NRTs result in lack of reinforcement and showed no association of alleviation of smoking urges to delivery rates (Jensen et al., 2020), thus resulting in poor 52-week quit success from cigarettes. While the precise delivery rates of nicotine linked to abuse liability are not known, high delivery rates may cause aversion (Goodwin et al., 2015). In this context, systematic research is needed to establish the nicotine delivery rate required to maintain therapeutic effects with optimal reinforcement properties to promote long-term smoking cessation. In addition to nicotine delivery rate, alternative metrics such as plasma pAUC and rise of plasma nicotine within a pre-defined time (e.g., 5 min) towards reinforcement needs to be further explored. Next, products that enable rapid systemic nicotine uptake ($\frac{C_{max}}{T_{max}} > 1$) will potentially have a greater reinforcement value, whereas those with slower and more prolonged delivery ($\frac{C_{max}}{T_{max}} < 1$) will have less reinforcement value (Figs. 2, 3b). As acceptance of novel nicotine delivery systems is necessary for those who do not quit all tobacco and nicotine use, products with $\frac{C_{max}}{T_{max}} > 1$, which have a potential for abuse liability, are more likely to transition subjects away from cigarettes. This should be evaluated, as such products could improve 52-week quit success rates from cigarettes.

It is important to note that we identified only a limited number of studies (Table S1) that reported all the information needed for calculating nicotine flux and PK indices. The PK indices for inhaled products determined using arterial plasma concentrations are potentially relevant and will yield higher $\frac{C_{max}}{T_{max}}$ ratios, but not all studies performed these measurements. A meta-analysis of RCT data was not performed to account for the placebo effect or additional cessation support. Also, the 52-week quit success was compared to nicotine flux and pharmacometrics indices from single-product use rather than *ad libitum* use, for which no information is available. Hence, RCTs are needed for clinical pharmacology-based assessment of nicotine delivery systems; they should evaluate the PK alongside measures of product acceptance, use patterns, abuse liability, and long-term quit success from cigarettes. Several such RCTs evaluating multiple nicotine delivery systems across a wide range of conditions should be performed to identify key inhaled aerosol dosimetry parameters that could eventually be linked to abuse liability potential.

5. Early considerations for inhaled aerosol dosimetry and PK of nicotine

Assessment of the potential abuse liability of ENDS requires reliable estimation of the exposure patterns, inhaled dose, and resulting PK. A list of significant factors influencing the inhaled aerosol dosimetry and PK of nicotine from ENDS is provided in Table 1. As discussed above, a single factor (e.g., nicotine concentration in e-liquid) or a combination of two parameters such as emitted dose and duration of puffing (i.e., nicotine flux) are poor metrics of the exposure-response resulting from ENDS. A comprehensive methodology considering interplay between all the factors outlined in Table 1 could better predict the resulting inhaled exposure to nicotine from ENDS.

A combination of *in vitro* and *in silico* approaches could potentially address the factors influencing the inhaled aerosol dosimetry and resulting PK of nicotine to provide early insights into determining exposures from ENDS. *In vitro* performance of inhaled nicotine delivery systems could be performed by chemical characterization of the emitted aerosol, measuring aerosol particle size distribution, assessing aerosol deposition for varied inhalation patterns using human relevant mouth-throat models under physiologically relevant conditions (e.g., temperature and humidity), and emitted dose estimation (including fine particles and gas phase) (Forbes et al., 2015; Phalen et al., 2021). Depending on the chemical composition, inhaled aerosols significantly evolve (e.g., modulating the particle sizes and partitioning between gas-liquid phases) along the respiratory tract, leading to varied aerosol deposition patterns that could be evaluated using 3D airway casts (Asgari et al., 2019). Such *in vitro* aerosol characterization could be used for estimating inhaled aerosol dosimetry using publicly available aerosol deposition models such as Multiple Path Particle Dosimetry (Anjilvel and Asgharian, 1995), International Commission on Radiological Protection (IRCP, 1994) (developed for non-evolving solid-particle aerosols), custom models for evolving aerosol (Asgharian et al., 2018), or more detailed computational fluid dynamics codes (e.g., *AeroSolved* (Philip Morris Products SA)) used to verify and validate assumptions made for aerosol deposition in the upper respiratory tract. The transport

Table 1
List of major factors influencing dose and PK for inhalation-based nicotine delivery systems.

Factors	Description
Device, nicotine concentration, and formulation of e-liquid	Open- and closed-tank designed devices with various specifications (e.g., device power) are coupled to formulations containing different levels of nicotine, propylene glycol/vegetable glycerin, weak acids, etc. (Etter and Bugey, 2017; St Helen et al., 2016). These systems can deliver very different amounts of nicotine (St Helen et al., 2016).
Nicotine levels in emitted aerosol (nicotine flux)	Depending on nicotine formulation, device, and *ad libitum* usage (i.e., puffing topography and number of puffs), the emitted amount of nicotine per puff and overall consumption will be different (St Helen et al., 2016; Talih et al., 2014).
Aerosol particle size distribution and phase (gas-liquid) partitioning	Different ENDS and formulations will emit aerosols of varied particle size distributions and phase partitioning which influence the airway deposition and delivered dose of nicotine (Asgharian et al., 2018; Baassiri et al., 2017; Stefaniak et al., 2022).
pH of e-liquids	The pH of e-liquids ranges between 4.78 and 9.60 (Stepanov and Fujioka, 2015). pH influences the levels of unprotonated form and regional deposition by modulating the aerosol evolutionary processes such as gas-liquid partitioning of nicotine (Pankow, 2001; Sperry et al., 2023). The unprotonated form of nicotine is rapidly absorbed into systemic circulation and influences nicotine PK (Benowitz, et al., 2009).
Inhalation topography	Inhalation topography for ENDS is different from combustible cigarettes (Lee et al., 2015). Depending on the concentration of nicotine and e-liquid formulation, puffing and inhalation topographies can vary (Talih et al., 2014).
Aerosol deposition in airways	Inhaled aerosols evolve (i.e., compound selective evaporation/condensation) during transport and lead to differential regional deposition in the airways (Asgharian et al., 2018; Kolli et al., 2019). The formulation, physicochemical properties of the aerosol mixtures (such as aerosol particle sizes and phase partitioning), inhalation topography, and airway morphology will influence aerosol deposition (Kolli et al., 2019).
Nicotine PK	The systemic delivery of nicotine depends on formulation, regional deposition and absorption kinetics, the population level difference in nicotine consumption patterns, metabolism, and elimination (Kolli et al., 2023; St Helen et al., 2016).

ENDS, electronic nicotine delivery systems.

kinetics of nicotine from emitted aerosol of different formulations may be evaluated using 3D human airway cultures at the air-liquid interface (Silva et al., 2023). The emitted aerosol characteristics (pH, nicotine-free base, nicotine salts, solubility, etc.), inhaled aerosol dosimetry, and *in vitro* bioavailability and transport kinetics can be integrated into existing commercially available inhalation-based PBPK models to estimate nicotine PK (Kolli et al., 2019). *In silico* tools integrating aerosol dosimetry and PBPK are in development to support the estimation of nicotine dosimetry and PK predictions (Asgharian et al., 2022; Kolli et al., 2023; Rostami et al., 2022; Schroeter et al., 2018), and research is ongoing to improve and integrate existing contributions. These *in silico* tools may enable prediction of PK metrics for various formulations and consumption patterns across different populations. Such predictions of human nicotine exposure resulting from a single, *ad libitum* use of a nicotine delivery system could be relevant for comparing PK indices such as C_{max}, T_{max}, *AUC*, *pAUC*, and $\frac{C_{max}}{T_{max}}$ to responses such as product acceptance and abuse liability assessments.

6. Conclusion

Product acceptance and abuse liability of nicotine delivery systems are critical parameters to be evaluated. Single empirical metrics such as nicotine flux or nicotine ceilings solely cannot accurately estimate the nicotine exposure (PK) and thus, the abuse liability potential of nicotine delivery systems. Furthermore, the preliminary empirical metrics to evaluate nicotine delivery systems are insufficient from pharmaceutical product characterization and clinical pharmacology perspectives. Empirical metrics such as nicotine flux need to be further complemented with relevant parameters–potentially based on route of administration–for more reliable estimation of resulting human exposure (PK). Next, PK indices such as $\frac{C_{max}}{T_{max}}$ conceptualized as rate of rise in plasma nicotine levels could inform 52-week quit success from cigarettes. Hence, NRTs and reduced-risk products with a $\frac{C_{max}}{T_{max}} > 1$ could play a significant role in tobacco harm reduction and should be clinically evaluated. However like nicotine flux, $\frac{C_{max}}{T_{max}}$ alone may be insufficient to identify abuse liability potential of nicotine containing products and needs to be further evaluated. The current situation highlights the need to develop comprehensive paradigms to assess nicotine delivery systems. A preliminary set of empirical descriptions for evaluation of nicotine delivery systems to inform product-specific dosimetry based on *in vitro* experimentation and *in silico* PK predictions could be developed to translate exposure-responses. For example, chemical characterization of the formulation, measuring dissolution rate, particle size, solubility, and permeation could be relevant for buccal nicotine delivery systems. For nasal sprays and inhaled nicotine delivery systems, it could be useful to measuring aerosol particle size distribution, aerosol deposition for varied inhalation patterns, spray pattern, plume geometry, emitted dose (or nicotine flux), and emitted aerosol chemical characterization (Forbes et al., 2015; Phalen et al., 2021). Furthermore, extensive toxicity testing to ensure product safety is of paramount importance as potential products containing a wide variety of chemical mixtures and approved solely based on lower nicotine flux levels—but delivering other harmful chemicals—could lead to e-cigarette, or vaping, product use-associated lung injury (Blount et al., 2020). Finally, there is a need for RCTs that perform clinical pharmacology-based assessments of nicotine delivery systems by evaluating the PK (US Food and Drug Administration, 2011) along with long-term product acceptance, abuse liability, frequency of product use, and quit success from cigarettes. Future proposals, and policies drafted should consider comprehensive product-specific dosimetry and clinical pharmacology outcomes of nicotine delivery systems.

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CRediT authorship contribution statement

Ondrej Koumal: Writing – review & editing. **Jed E. Rose:** Writing – review & editing. **Marco Esposito:** Conceptualization. **Arkadiusz K. Kuczaj:** Writing – review & editing. **Emilija Veljkovic:** Writing – review & editing, Project administration, Conceptualization. **Florian Calvino-Martin:** Writing – review & editing, Conceptualization. **Aditya R. Kolli:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Manuel C. Peitsch:** Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Aditya R. Kolli reports financial support was provided by Philip Morris International. Jed E. Rose reports a relationship with Philip Morris International that includes: funding grants. Aditya R. Kolli, Emilija Veljkovic, Florian Calvino-Martin, Arkadiusz K. Kuczaj, Marco Esposito, and Ondrej Koumalare employees of Philip Morris International. Manuel C. Peitsch was an employee of Philip Morris International when this work was performed. Jed E. Rose discloses research support from Foundation for a Smoke-Free World, Philip Morris International, Altria, Embera Neurotherapeutics, Inc., Otsuka Pharmaceutical, and JUUL Labs; consulting with Revive Pharmaceuticals; and consulting and patent purchase agreements with Philip Morris International.

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Appendix A. Supporting information

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