Comparison of nicotine emissions rate, 'nicotine flux', from heated, electronic and combustible tobacco products: data, trends and recommendations for regulation

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ABSTRACT

Introduction Tobacco smoking is a major cause of disease and premature death worldwide. While nicotine is recognised as the main addictive component in tobacco smoke, the total nicotine amount emitted (nicotine yield) and the rate of nicotine emission per second ('nicotine flux') contribute to the abuse liability of a given product. These variables can be regulated for public health ends and conveniently so for electronic cigarettes or electronic nicotine delivery systems (ENDS).

Methods In this study we computed nicotine flux from previously reported values of yield and puff topography for a wide range of tobacco products.

Results We found that nicotine flux varied widely across tobacco products, from less than 0.1 µg/s to more than 100 µg/s, and that since 2015 the upper limit of the ENDS nicotine flux range has risen significantly and is now approaching that of combustible cigarettes. We also found that products that differ in nicotine flux may exhibit similar nicotine yields due to differences in user puffing behavior. Nicotine flux is a tool that can be used to regulate nicotine emissions of tobacco products, including ENDS.

INTRODUCTION

Despite decades of tobacco control efforts, tobacco smoking remains one of the leading causes of premature death globally, estimated at 8 million deaths per year, and a major threat to public health.[1] The psychomotor stimulant nicotine is the main addictive agent in tobacco smoke and, without it, tobacco consumption would not be sustained.[2 3] As with other abused drugs, the dose and the speed at which nicotine reaches brain are critical to producing the addictive character of tobacco smoking.[4] In principle, more rapid delivery and greater dose result in greater reinforcement and greater abuse liability.[5] One reason combustible cigarettes are addictive is that inhaled tobacco smoke delivers nicotine to the brain in seconds, more rapidly even than intravenous nicotine delivery.[6] Historically, nicotine yield has served as the metric for characterising the amount of nicotine emitted by different combustible cigarette products.[7] Yield is defined as the mass of nicotine emitted through the mouth end of a tobacco product per unit of consumption (eg, milligrams of nicotine per cigarette; mg/cig). The rate at which nicotine is delivered, the yield per unit time, is referred to as the 'nicotine flux' (mg/s or µg/s).[8] Because combustible cigarettes a made in a standard size and are consumed in roughly 5 min, nicotine yield and nicotine flux are closely coupled with combustible cigarettes—a cigarette with a high yield will also have a high flux.

However, with electronic nicotine delivery systems (ENDS) and other products whose use patterns vary widely, the yield and the flux are not coupled closely. A product may have low yield and high flux (eg, the one-puff 'dokha'[9]) or vice versa (eg, nicotine patch). Typically, an ENDS product is consumed during multiple use sessions spanning a period of one to several days, depending on such factors as the size of the reservoir containing the nicotine solution and the electrical power of the device. Therefore, the nicotine yield of the product per unit sold may not be relevant to the yield obtained during a single use session. For example, a single JUUL pod emits roughly the same amount of nicotine as an entire pack of cigarettes but is unlikely to be consumed entirely in a single-use session.[10] Even the notion of a use session for an ENDS product may be difficult to define. Does taking a single puff just before entering an office building constitute a 'session'? Nicotine patches, too, can deliver a dose of nicotine over a day that is comparable with a pack of cigarettes. Clearly, a comparison of the yield of a JUUL pod, a nicotine patch and a cigarette stick has little value because the consumption patterns differ greatly; as a regulatory target, yield is not a useful construct. Nicotine flux, however, allows comparisons across products and product classes because it normalises nicotine emission by time. In doing so, flux also highlights the key factor of speed of delivery: nicotine flux is the theoretical upper limit of the rate at which nicotine can reach the brain. As we have discussed elsewhere,[11] to be enforceable a flux standard implies that only closed systems will be allowed on the market.

Figure 1 illustrates by analogy the relationship between nicotine flux, liquid nicotine concentration, device power, time and nicotine yield for ENDS products. The large tank can be thought of as the liquid reservoir of an ENDS product, while the small container can be considered the mouth of the user. The nicotine concentration of the liquid in the tank was prepared by dissolving a given mass, m, of nicotine (mg) in a given volume, V, of liquid (mL), resulting in a liquid nicotine concentration $C=m/V$

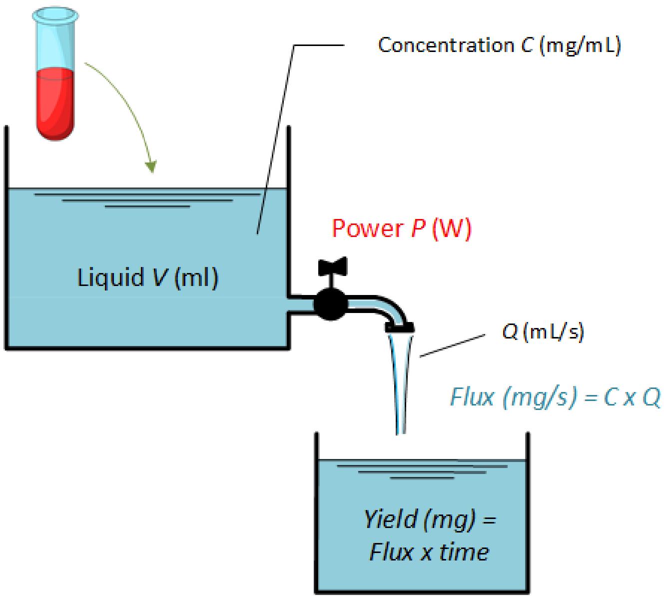

Figure 1 Relationship between liquid nicotine concentration, device power, flux (nicotine emission rate) and yield for an ends device by analogy to a reservoir emptying into a container through a valve and tap assembly. In this analogy, the electrical power of the ENDS device determines the degree to which the tap is open during a puff; greater power means a more open valve. ENDS, electronic nicotine delivery systems.

(mg/mL). When a puff is executed, the rate at which liquid is aerosolised by the ENDS device (ie, in the form of an inhalable aerosol) and delivered to the mouth of the user is represented by opening the tap, allowing the flow to commence at some rate Q (mL/s). The nicotine flux is the product of the nicotine concentration C and the volume flow rate Q. To a close first approximation, Q is directly proportional to the power (P, Watts); greater power translates to a more open tap in figure 1. As a result, nicotine flux is directly proportional to the product of C and P. Finally, the amount of nicotine collected from the tap while the valve was open is the yield, which is simply the product of the flux and time.

In this study, we sought to estimate nicotine flux for a wide range of tobacco products to provide a base against which a potential ENDS product regulation could be considered. To date, extant EU and proposed US regulations have focused exclusively on limiting liquid nicotine concentration,[12 13] an approach that, counter to the stated aims of those regulations, constrains neither yield nor flux and therefore does not constrain exposure (ie, nicotine dose inhaled by the user).

METHODS

Nicotine flux can be computed from published reports on tobacco product yields as the ratio of the yield to the cumulative puffing time of an inhaled tobacco product (eg, a cigarette or pipe) or as the ratio of the yield to the cumulative time of use of a product that emits nicotine continuously (eg, a nicotine patch).

For inhaled products, we searched the Scopus database using the following Boolean expression: ("nicotine" OR "nicotine yield") AND ("flow rate" OR "puff duration" OR "interpuff interval" OR "puff volume" OR "topography"). The search resulted in 651 documents, of which 39 reported values of nicotine yield, puff duration, and number of puffs; these 39 documents were retained for analysis.

The nicotine flux was computed as:

$$Nicotine\ flux\ \left(\frac{\mu g}{s}\right) = 1000 * \frac{Nicotine\ yield\ \left(\frac{mg}{unit}\right)}{Total\ puffnumber\left(\frac{puffs}{unit}\right) * puff\ duration\ \left(\frac{s}{puff}\right)}$$

For patch and gum products, we computed the flux as:

$$Nicotine\ flux\ \left(\frac{\mu g}{s}\right) = 1000 * \frac{Nicotine\ dose\ \left(\frac{mg}{unit}\right)}{Total\ time\ of\ consumption\ \left(\frac{s}{unit}\right)}$$

where the time of consumption was taken as 24 hours for patches and 30 min for gum. The dose was taken as that provided by the manufacturer assuming complete release of nicotine during the time of product consumption.

Average (SD) of nicotine fluxes for each tobacco product were determined to compare different products. A simple linear regression was used to test the correlation between year of publication versus nicotine flux. Statistical significance was taken as $p<0.05$.

RESULTS

Published data were available to compute nicotine flux for approximately 90 products, spanning the categories of cigarettes, cigarillos, small cigars, waterpipes, ENDS, heated tobacco products, patches and nicotine gum. Online supplemental table S1 lists the results obtained for tobacco products that were machine smoked by mimicking human puffing patterns or by standard machine smoking regimens (eg, Canadian Intense, ISO). The nicotine flux across products ranged four orders of magnitude, from less than 0.1 µg/s to more than 100 µg/s, with the low end of the spectrum populated exclusively by nicotine patch and gum products and very low nicotine cigarettes and products above 100 µg/s consisting exclusively of conventional combustible cigarettes. The results are summarised in table 1.

We also found a significant increase in reported flux over time (figure 2) for ENDS products (4.5 µg/s/year; $p<0.001$). Whereas prior to 2018, no publications reported products with a flux exceeding 40 ug/s; from 2019 onwards, nearly 40% of the tested products exceeded a flux of 60 µg/s. The upper quartile flux for ENDS products in a given year also increased significantly at a mean rate of 9.5 µg/s/year ($p<0.001$).

Table 1 Computed nicotine flux by tobacco product category

Product	N	Year span	Flux (µg/s) Mean (SD)	Range
Combustible cigarettes	27	1988–2020	79(32)	29–140
ENDS	52	2015–2021	29(23)	3.7–110
Heated tobacco products	14	2018–2020	31(18)	5.8–58
Waterpipe	8	2003–2019	11 (5.6)	5.8–20
Cigars/cigarillos	9	1976–2018	62(35)	12–110
Roll your own	3	1985–2014	69(28)	52–100
Bidi	2	1988–2003	60 (6.8)	55–64
Kretek	3	2014	47(16)	29–60
Nicotine patch and gum products	4	2018–2019	0.4 (0.48)	0.08–1.1
Very low nicotine cigarettes	1	2019	1.7(-)	–

N indicates the number of products reported, while year span indicates years of publication for the studies included.
ENDS, electronic nicotine delivery systems.

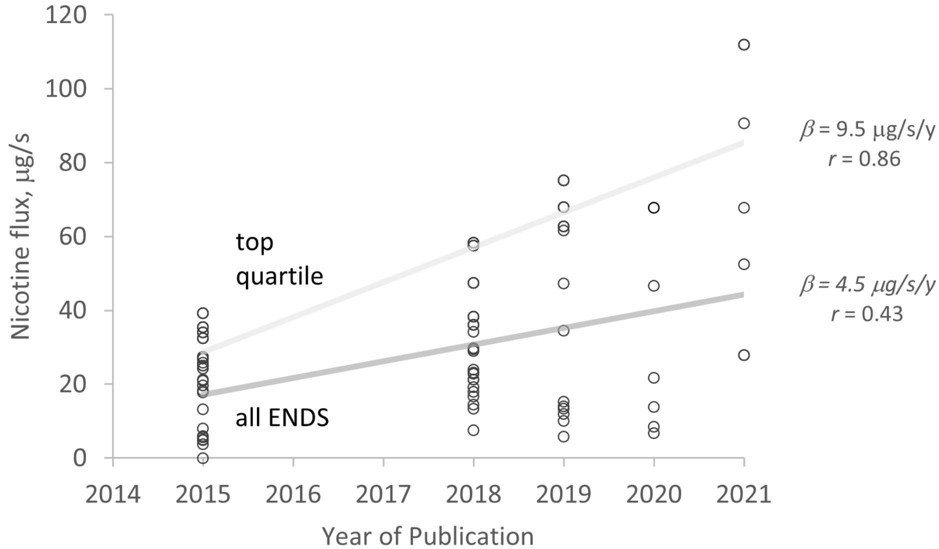

Figure 2 Reported nicotine flux of ENDS products by year of manuscript publication (p<0.001 for both regression lines). ENDS, electronic nicotine delivery systems.

DISCUSSION

Nicotine flux is a performance metric that describes the acute nicotine throughput of a tobacco product, the net outcome of the interactions between numerous product design and operating variables. While nicotine flux represents the rate at which nicotine can enter the human body, and therefore the theoretical limit of the rate of delivery to the brain, the rate is mediated by other factors that influence the pharmacokinetics of nicotine delivery. For inhaled products, these factors include such things as the particle size distribution and freebase-to-protonated nicotine ratio of the aerosol. In this study, we sought to document nicotine flux from a range of tobacco products whose yields and puffing parameters had been reported in the literature. One limitation of this study is that products studied by previous researchers may not represent well the sales-weighted average of each category. A second limitation is that reported smoking machine studies may not have always used representative puffing parameters (eg, puff velocity, duration or interpuff interval), biasing nicotine yield and, therefore, the computed flux. The most accurate analytical determinations of nicotine emissions are made using puffing conditions appropriate to the product in question; for example, users of large sub-Ohm ENDS devices typically draw up to an order of magnitude greater flow rate than a user of a small pod-based device.

We found that for inhalable tobacco products, combustible cigarettes exhibited the greatest average nicotine flux, while waterpipes exhibited the greatest nicotine yield per session. Overall, nicotine patches had the greatest yields but also, owing to the long duration of use per unit, the lowest fluxes. These findings underscore the limitations of nicotine yield as a regulatory construct for tobacco products that vary widely; in these cases, greater yield was associated with *lower* abuse liability.

We also found significant variability in flux within and across product categories, as illustrated in figure 3. While ENDS generally exhibited nicotine fluxes lower than those of combustible cigarettes, reports from 2018 onwards began revealing ENDS products whose fluxes were equivalent to combustible cigarettes. Importantly, the 110 µg/s maximum flux reported to date for an ENDS product does not represent an intrinsic physical limit. With products available over the counter today, an ENDS user can readily access a liquid/device combination whose flux exceeds any value yet reported. For example, based on the mathematical model of Talih *et al*,[14] a device operating at 60 W with an EU-compliant 20 mg/mL nicotine concentration liquid can produce a flux of approximately 240 µg/s, roughly double the maximum reported for any combustible cigarette.

The current regulatory environment therefore allows marketing ENDS products whose nicotine emission rate exceeds that of the high abuse liability combustible cigarette. Combined with emerging evidence that the convenience of ENDS use leads to far more frequent nicotine administration throughout the day than for combustible cigarettes,[15–17] the availability of high-flux ENDS products may portend greater population-wide nicotine dependence than was present prior to the advent of ENDS, if this outcome has not already been realised. Empirical data on the relationship between flux, acute delivery and dependence is too thin to evaluate this hypothesis at present; such data are urgently needed. Of note, Do *et al*[18] recently reported an association between nicotine flux and dependence scores in a pilot study of experienced users of pod-based devices.

Given the approximate doubling of ENDS nicotine flux from 2015 to 2020, policy makers may not have the leeway to wait for a definitive evidence base to emerge and may find it prudent

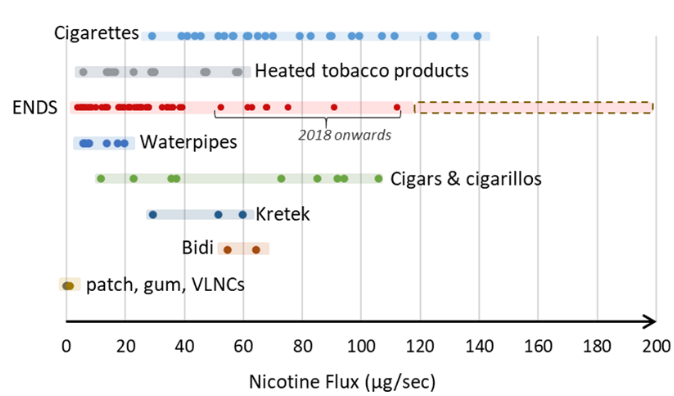

Figure 3 Nicotine flux ranges across tobacco products. The dashed line for ENDS represents the capacity of current over-the-counter products to exceed values reported to date. ENDS, electronic nicotine delivery systems.

to regulate flux in the interim. There is little reason to suspect that exceeding the nicotine flux of combustible cigarettes is necessary to improve public health. With this starting point, an upper limit on ENDS nicotine flux could be, at most, 140 µg/s (see table 1). However, given the greater convenience and greater use frequency observed in ENDS users, this upper limit, if applied to ENDS, may still lead to greater population-level nicotine dependence. For this reason, one potential approach is to use the mean observed for combustible cigarette flux (ie, approximately 80 mg/sec, see table 1) as a temporary ceiling for over-the-counter ENDS products, with further adjustments informed by empirical investigations aimed at understanding the abuse liability of ENDS products across populations of particular interest (eg, nicotine naïve individuals and former smokers at risk for relapse). Of course, if empirical work demonstrates that higher flux ENDS are safe and effective for smoking cessation, these products can be made available to cigarette smokers in a manner that does not risk the health of nicotine-naïve individuals (eg, restricted access rather than over-the-counter availability). An additional concern is that ENDS aerosols contain varying concentrations of toxicants such as carbonyl species. Thus, minimising the amount of inhaled aerosol may be desirable because it can reduce user exposure to harmful toxicants. From this perspective, to the extent that a user seeks to attain a given nicotine intake, too low a nicotine flux can, perversely, increase non-nicotine toxicant exposure because it may drive more prolonged puffing bouts.

Policymakers interested in reducing nicotine dependence at the population level would do well to address nicotine flux as a regulatory target and avoid the mistake of using inappropriate proxies (eg, liquid nicotine concentration) that cannot, by themselves, be used to control the nicotine dose inhaled by ENDS users.

What this paper adds

- ⇒ To date, tobacco product regulation aimed at nicotine abuse liability has been hampered by reliance on metrics that are not relevant to many tobacco products.
- ⇒ Nicotine flux, the amount of nicotine emitted per unit time, is a metric of abuse liability that can be deployed across a diverse range of tobacco products, including those that are inhaled, chewed or applied to the skin.
- ⇒ Nicotine flux across products varies from less than 0.1 µg/s to more than 100 µg/s, and for electronic cigarettes has been rising at an average rate of 5 µg/s/year since 2015.

Contributors The idea for this report was developed at a meeting of the Center for the Study of Tobacco Products (CSTP) Nicotine Flux Work Group in Lisbon, Portugal, 25–27 October 2019, thus all CSTP Nicotine Flux Work Group members are listed as collaborators and the work group name is included in the author list. MH and AS prepared the first draft of the manuscript and performed data analysis and figure preparation. The manuscript was finalised with input from ST and TE. Study guarantor: AS.

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Competing interests TE and AS are paid consultants in litigation against the tobacco industry and also the electronic cigarette industry and are named on one patent for a device that measures the puffing behaviour of electronic cigarette users. TE is also named on a patent for a smartphone app that determines electronic cigarette device and liquid characteristics.

Patient consent for publication Not applicable.

Ethics approval This study does not involve human participants.

Provenance and peer review Not commissioned; externally peer reviewed.

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COMPARISON OF NICOTINE EMISSIONS RATE, "NICOTINE FLUX", FROM HEATED, ELECTRONIC, AND COMBUSTIBLE TOBACCO PRODUCTS: DATA, TRENDS, AND RECOMMENDATIONS FOR REGULATION

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SUPPLEMENTAL MATERIAL

Table S1. Summary of the nicotine yield and flux of various tobacco products and the corresponding puffing topography parameters.
* Average puff number under ISO smoking regime was used.

Tobacco Product	*Brand*	*Puff Number*	*Puff duration (s)*	*Nicotine Yield (mg/unit)*	*Nicotine Flux (μg/s)*	*Reference*	*Year of Publication*
Cigarettes	*Maintained nicotine cigarette*	15	2	2.7	90.0	[1]	1988
	Middle tar cigarette	15	2	2.9	96.7		
	Low tar cigarette	14	2.5	1.8	51.4		
	Regular-yield brands (9-15 mg ISO tar)	11.5	1.4	2	124.2	[2]	2006
	Matinee extra mild (4 mg ISO tar)	13.4	1.6	1.5	70.0		
	Own brand (female smokers)	13.5	1.33	1.92	106.9	[3]	2007
	Own brand (male smokers)	12	1.48	2.2	123.9		
	Kent (non-menthol cigarette)	14.4	1.17	0.9	53.4	[4]	2017
	Benson & Hedges Light (menthol cigarette)	15.1	1.23	1.05	56.5		
	Marlboro red	12.2	1.68	2.54	123.9	[5]	2020
	Lucky Strike	10.7	1.8	1.3	67.5	[6]	2018
	Lucky Strike Menthol	10	2	1.3	65.0		
	Lucky Strike	16.6	1.6	1.5	56.5	[7]	2020
	Low-yield cigarettes (<=0.8 mg of nicotine/cigarette)	12.7	1.5	1.7	89.2	[8]	2000
	Medium-yield cigarettes (0.9–1.2 mg of nicotine/cigarette)	12.1	1.5	2.39	131.7		
	2R4F	9.5	2	0.829	43.6	[9]	2014
	1R6F	8.0	2	0.73	45.6	[10]	2018
	1R6F	8.4	2	2.34	139.3		
	3R4F	9.0	2	0.74	41.1		
	3R4F	10.7	2	2.38	111.2		
	Regular-yield brands (9-15 mg ISO tar)	9	2	1.1	61.1	[2]	2006
		12.1	2	2.4	99.2		
	Low-yield cigarettes (<=0.8 mg of nicotine/cigarette)	9	2	0.7	38.9	[8]	2000
	Medium-yield cigarettes (0.9–1.2 mg of nicotine/cigarette)	9	2	1.11	61.7		
	Marlboro Ultra Smooth	7.2	2	0.42	29.2	[11]	2006
		6.9	2	1.09	79.0		
	Marlboro Regular	12	2	1.99	82.9	[12]	2018
VLNC	VLN King	9*	2	0.03	1.7	[13]	2019
Roll Your Own Cigarettes	Average of 13 brands	12.4	2	1.3	52.4	[14]	1985
	Average of 11 brands	9.42	2	1.90	100.8	[15]	2014
	Average of 517 cigarettes made by 26 regular users	12.3	2	1.30	52.8	[16]	1998
Tobacco Heating Products	glo with Bright Tobacco Kent Neostiks	11.6	1.8	0.3	14.4	[6]	2018
	glo with mentholated Intensely Fresh Kent Neostiks	10	1.8	0.3	16.7		
	iQOS with Essence tobacco HeatStick	10.55	1.8	0.9	47.4		
	glo with Bright Tobacco Kent Neostiks	15.4	1.6	0.34	13.8	[7]	2020
	iQOS with Essence tobacco HeatStick	15	1.4	0.98	46.7		

	carbon-based Eclipse	25	2	2.36	47.2	[17]	2019
	Glo with Bright Tobacco Kent Neostiks	8	2	0.462	28.9	[18]	2018
	Glo with mentholated Intensely Fresh Kent Neostiks	8	2	0.365	22.8		
	Unspecified Heat not Burn Device	12	2	1.4	58.3	[12]	2018
	Unspecified Heat not Burn Device with Mentholated flavor	12	2	1.38	57.5		
	Unspecified Heat not Burn Device	12	4	1.41	29.4		
	Unspecified Heat not Burn Device with Mentholated flavor	12	4	1.43	29.8		
	Carbon-based Eclipse	12	2	0.14	5.8	[17]	2019
	Carbon-based Eclipse	18.3	2	0.56	15.3		
Electronic Nicotine Delivery Systems	*Volish, eGo-3 (nicotine concentration 18 mg/ml; liquid composition: Propylene glycol, nicotine, vanillin, linalool, flavorings)*	15	2.8	1.06	25.2	[19]	2015
	Volish, eGo-3 (nicotine concentration 18 mg/ml; liquid composition: Propylene glycol, glycerin, nicotine, ethanol, flavorings)	15	2.8	1.15	27.4		
	Volish, eGo-3 (nicotine concentration 24 mg/ml; liquid composition: Glycerin, nicotine, propylene glycol, linalool, vanillin, flavorings)	15	2.8	1.05	25.0		
	Volish, eGo-3 (nicotine concentration 22 mg/ml; liquid composition: Glycerin, propylene glycol, nicotine, flavorings)	15	2.8	1.43	34.0		
	Volish, eGo-3 (nicotine concentration 12 mg/ml; liquid composition: Glycerin, propylene glycol, nicotine, flavorings)	15	2.8	0.88	21.0		
	Volish, eGo-3 (nicotine concentration 16 mg/ml; liquid composition: Glycerin, propylene glycol, nicotine, flavorings)	15	2.8	1.02	24.3		
	Volish, eGo-3 (nicotine concentration 25 mg/ml; liquid composition: Glycerin, propylene glycol, nicotine, ethanol, flavorings)	15	2.8	1.36	32.4		
	Volish, eGo-3 (nicotine concentration 28 mg/ml; liquid composition: Glycerin, propylene glycol, nicotine, ethanol, malic acid, flavorings)	15	2.8	1.49	35.5		
	Volish, eGo-3 (nicotine concentration 11 mg/ml; liquid composition: Glycerin, nicotine, menthol, vanillin, aromatic oils, vanilla)	15	2.8	0.77	18.3		
	Blu Cigs (Tobacco-flavored cartomizers with nicotine concentration of 16 mg/ml)	33	2.75	1.2	13.2	[20]	2015
	V2 Cigs (Tobacco-flavored cartomizers with nicotine concentration of 18 mg/ml)	31	2.54	1.4	17.8		
	Lab Assembled ECIG 6 W (E-liquid concentration range 6-18 mg/ml)	57	4.6	3.5	13.3	[21]	2018
	Lab Assembled ECIG 10 W (E-liquid concentration range 6-18 mg/ml)	46	3.8	4.2	24.0		
	KangerTech Mini ProTank with own flavor (E-liquid nicotine concentration range 1.6-16.7 mg/ml and PG/VG ratio range of 69/31-5/95)	106	4.3	3.4	7.5	[22]	2018
	KangerTech Mini ProTank with strawberry flavored e-liquid (E-liquid nicotine concentration 19.9 mg/ml and PG/VG ratio of 40/60)	73	3.2	5.4	23.1		
	KangerTech Mini ProTank with Tobacco flavored e-liquid (E-liquid nicotine concentration 19.3 mg/ml and PG/VG ratio of 44/56)	69	2.8	4.1	21.2		
	Vype with 'Twilight Tobacco' flavored e-liquid (E-liquid nicotine concentration 5 mg/ml and PG/VG ratio of 40/60)	61.1	1.45	0.75	8.5	[7]	2020
	Vapour 2 cigs (E-liquid nicotine concentration 20 mg/ml and PG/VG ratio of 50/50)	12	2	0.46	19.2	[12]	2018
		12	4	0.86	17.9		
	eGo style, Epsilon (E-liquid nicotine concentration 20 mg/ml and PG/VG ratio of 50/50)	12	2	0.51	21.3		
		12	4	1.73	36.0		

	EVIC VTC Mini battery with Nautilus Mini atomizer (E-liquid nicotine concentration 20 mg/ml and PG/VG ratio of 50/50)	12	2	0.82	34.2		
		12	4	1.84	38.3		
Electronic Nicotine Delivery Systems	Vype Disposable Regular	1	3	0.04	13.3	[17]	2019
		1	5	0.06	12.0		
	Intellicig XL	1	3	0.03	10.0		
		1	5	0.07	14.0		
	V4L CoolCart cartomizers (8.53 mg/ml nicotine concentration)	2	15	0.11	3.7	[23]	2015
		4	15	0.30	5.0		
		4	15	0.29	4.8		
		8	15	0.72	6.0		
		8	15	0.68	5.7		
		2	15	0.64	21.3		
		4	15	1.18	19.7		
		4	15	1.50	25.0		
		8	15	3.23	26.9		
		8	15	3.09	25.8		
	V4L CoolCart cartomizers (15.73 mg/ml nicotine concentration)	4	15	0.48	8.0	[23]	2015
		8	15	4.7	39.2		
	JUUL US - Tobacco flavor (65 mg/ml nicotine concentration)	15	4	1.3	21.7	[24]	2020
	JUUL UK - Tobacco flavor (19 mg/ml nicotine concentration)	15	4	0.4	6.7		
	JUUL US - Tobacco flavor (69 mg/ml nicotine concentration)	15	4	2.07	34.5	[25]	2019
	JUUL US - Tobacco flavor	1	2.5	0.157	62.8	[26]	2019
	JUUL US – Crème brulee flavor	1	2.5	0.170	68.0		
	JUUL US – Fruit punch flavor	1	2.5	0.154	61.6		
	JUUL US - Mint flavor	1	2.5	0.188	75.2		
	JUUL US – Tobacco flavor (69.8 mg/ml nicotine concentration)	15	4	1.67	27.8	[27]	2021
	Ezzy Oval – Berry Cool flavor (53.8 mg/m nicotine concentration)	15	4	4.07	67.8		
	Ezzy Oval – Mango Lychee flavor (75.4 mg/m nicotine concentration)	15	4	5.44	90.7		
	Hyde – Cherry lemonade flavor (86.9 mg/m nicotine concentration)	15	4	3.15	52.5		
	Puff Bar – Banana ice flavor (83.4 mg/m nicotine concentration)	15	4	6.72	112.0		
	SEA – Mint flavor (54.3 mg/m nicotine concentration)	15	4	1.67	27.8		
Waterpipes	-	77.7	3.6	1.6	5.8	[28]	2016
	-	290	2.9	5	5.9	[29]	2018
	-	220	2.8	4.8	7.8	[30]	2010
	-	105	2.6	5.4	19.8	[31]	2019
	-	171	2.6	2.96	6.7	[32]	2005
	-	100	3.0	2.25	7.5	[33]	2003
	-	171	2.6	6.06	13.6	[34]	2008
	-	171	2.6	7.75	17.4	[35]	2011
Cigarillos	*Black & Mild*	23.1	2.8	2.3	35.6	[36]	2018
Small Cigars	*Winchester*	9.8	2	1.8	91.8	[36]	2018
	Average values of 8 commercially available small cigars in the US	16.6	2	1.24	37.3	[10]	2018
		16.5	2	3.49	105.8		

	Little cigars with cigar wrapper (average of 5 brands)	8.5	2	1.60	94.1	[37]	1976
	Little cigars with paper wrapper (average of 5 brands)	9.4	2	1.60	85.1		
	Average of 10 brands	14.4	2	2.1	72.9	[14]	1985
Large Cigars	Average of 5 brands	70.3	1.5	2.4	22.8	[37]	1976
	Average of 6 brands	108	1.5	1.9	11.7	[14]	1985
Kretek	Sampoerna	12.6	2	0.74	29.4	[9]	2014
	Garam	17.3	2	1.78	51.4		
	Kretek-R	14.4	2	1.72	59.7		
Bidi	Average of 21 brands	21	2	2.70	64.3	[38]	2003
	Average of 24 brands	17	2	1.86	54.7	[39]	1998
Nicotine Patch	NiQuitin Clear 7 mg	-	24 hrs	7	0.08	[40]	2019
	NiQuitin Clear 14 mg		24 hrs	14	0.16		
	NiQuitin Clear 21 mg		24 hrs	21	0.24		
Nicotine Gum	Zonnic 2mg	-	30 min	2	1.11	[41, 42]	2018/2020

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