

Nicotine delivery and cigarette equivalents from vaping a JUULpod

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ABSTRACT

With patented nicotine salt technology, JUUL dominates the e-cigarette market. We reviewed studies of JUUL's nicotine pharmacokinetic profile and studies quantifying nicotine in a JUULpod, emitted in the aerosol and absorbed by users. Examined in eight studies, JUUL's peak nicotine levels were half to three-quarters that of a combustible cigarette in industry-conducted studies with JUUL-naïve users, while comparable to or greater than combustible cigarettes in independent studies of experienced e-cigarette users. JUUL Labs reports each 5% (nicotine-by-weight) cartridge contains approximately 40 mg nicotine per pod and is 'approximately equivalent to about 1 pack of cigarettes.' In five independent studies, nicotine in the liquid in a JUULpod ranged from 39.3 to 48.3 mg. Seven studies measured nicotine delivery via vaping-machine generated aerosols, varying in puffing regimes and equipment. One study estimated 68% transfer efficiency to the aerosol, measuring 28.8 mg nicotine per JUULpod. The other studies reported nicotine values ranging from 72 to 164 µg/puff. At 200 puffs, this is 14.4–32.8 mg of nicotine per pod with equivalence to 13–30 cigarettes. A study measuring nicotine levels in JUUL users during a 5-day controlled switch found equivalence to 18 cigarettes. One JUULpod appears capable of delivering the nicotine equivalent to smoking about a pack of cigarettes, with variability. In JUUL-naïve smokers, JUUL's nicotine boost was lower than that of combustible cigarettes; while in experienced users, JUUL was comparable. Minimising harshness and adaptive to user experience, JUUL's design facilitates initiation to a high nicotine, and ultimately, highly addictive vaping product.

INTRODUCTION

Promoted with viral social media marketing, JUUL's sleek design, ease of use, and patented nicotine salt technology enabled its quick dominance of the electronic cigarette (e-cigarette) market and unmatched speed as a start-up to reach a US\$10 billion valuation (ie, decacorn status). Resembling a USB flash drive, the thin, rectangular JUUL device consists of an aluminium shell, a battery, a magnet (for the USB-charger), a circuit board, an LED light and a pressure sensor. The JUUL device is used with plastic disposable cartridges, called JUULpods, which contain the e-liquid that gets transformed into an inhalable aerosol. In the JUULpod is a small metal chimney housed over a tiny Nichrome coil (1.6 Ω) wrapped around a silica wick that absorbs flavoured nicotine liquid for vaporisation.¹ Liquid ingredients in a JUULpod are propylene glycol, vegetable glycerin, nicotine as benzoate salt and flavours. The JUULpod nicotine levels and flavours

available in the USA have changed over time due to regulatory pressure, and available nicotine levels and flavours differ by country.

The original JUULpod nicotine strength was 5%, and that level has been the focus of most research to date. The 3% strength was released in summer 2018, and JUULpods of 2% or lower strength are available for sale only outside of the USA, mostly in countries that prohibit over-the-counter sales of e-cigarettes with higher nicotine concentrations. Notably, there is evidence of modifications to the wick of some European JUULpods, resulting in increased aerosol creation and higher nicotine delivery per puff, approximating that of the 5% US strength versions.² JUUL employees' nickname for the modified JUULpods is said to be 'Turbo.'³

JUUL's rapid uptake in the USA has raised public health interest in quantifying nicotine delivery and absorption among JUUL users. An understanding of JUUL's nicotine delivery is sought by clinicians adapting dosing of nicotine replacement therapy for clients using the product alone or in dual use with cigarettes and wanting to quit, by parents and public health educators informing young people of the harms of use, and by researchers seeking a common metric and method to compare nicotine intake from JUUL to conventional smoking. From a regulatory perspective, nicotine delivery levels of the product relative to combustible cigarettes also is of interest to the US Food and Drug Administration (FDA) when considering JUUL's abuse liability and potential for uptake among youth and for helping adults transition exclusively away from combustible cigarettes.⁴ A Google search of 'how much nicotine in JUUL pods compared to cigarettes' produced 27.4 million results (searched 18 January 2021). A Google trend analysis of 'nicotine JUUL cigarette' indicated searches peaked in November 2018, when JUUL's US market share reached 75% of closed system e-cigarettes and when JUUL announced halting US retailer supplies of their crème brulee, cool cucumber, and fruity flavoured pods due to concerns about escalating e-cigarette use among youth.⁵

Widely disseminated prevention educational materials equate JUULpod nicotine delivery to two packs of cigarettes,⁶ while the packaging of a JUULpod 5% strength cartridge indicates, with some notable hesitancy, 'approximately equivalent to about 1 pack of cigarettes.' Studies have sought to quantify the amount of nicotine emitted from a JUUL or absorbed by users of the product. Our aim was to review the methods and consolidate the findings.

To provide a basis of understanding, we first briefly review nicotine pharmacology as it relates



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to nicotine dependence, and then summarise the studies to date that have examined JUUL nicotine pharmacokinetics (PK) and delivery, with consideration of variation in study methodologies, and with comparison to nicotine delivery via traditional combustible cigarettes. Studies were identified via searches in PubMed and review of the JUUL Labs website. Search terms were 'JUUL' with 'nicotine delivery', 'nicotine concentration,' or 'pharmacokinetic.' We reviewed the included studies' reference lists and searched for 'JUUL' in the programme of the 2020 annual meeting of the Society for Research on Nicotine and Tobacco. When details were missing, we reached out to study investigators. We close with consideration of public health impacts and regulatory actions.

NICOTINE PHARMACOLOGY

Nicotine, an alkaloid extracted from tobacco plants, is the dependence-forming constituent in JUUL and in combustible cigarettes. Nicotine use results in rewarding effects on mood, cognition, stress and anxiety, facilitated by release of various neurotransmitters (ie, dopamine, norepinephrine, acetylcholine, glutamate, serotonin, GABA, endorphins).⁷ Nicotine exposure causes dopamine release and, with prolonged use, upregulation of nicotinic cholinergic receptors (nAChRs) in the brain. Dopamine release accounts for much of the rewarding effect of nicotine use, while upregulation of nAChRs is believed to contribute to the development of tolerance and physical dependence.⁸

The speed at which nicotine reaches the brain influences a tobacco product's abuse liability.⁸ Nicotine reaches the brain most quickly via the lungs and arterial blood. The modern-day US combustible cigarette, through a shift from air curing to predominantly flue curing of tobacco, has been designed to be inhalable (pH 5.5–6), delivering nicotine to the brain within only 15–20s.⁹ Rapid delivery not only results in higher nicotine concentrations reaching the brain, but also rapid reinforcement of behaviour and the ability for minute-to-minute dose titration.

Rapid delivery also results in high arterial levels of nicotine, which counteract the effects of tolerance and allows users to maintain nicotine's psychological effects throughout the day. Nicotine levels rise in the blood over 4–6 hours, plateau throughout the day, then decline overnight.⁸ Although nicotine has a relatively short half-life, with an average of 2 hours, regular daily smoking results in constant exposure to nicotine.⁸ Constant nicotine exposure results in high risk of developing dependence symptoms, including tolerance and withdrawal.

JUUL'S NICOTINE SALT TECHNOLOGY

JUUL's patented nicotine salt technology delivers high nicotine aerosol into the lungs. The nicotine content of early-generation e-cigarettes was limited by the use of free-based nicotine. Nicotine in free base (unprotonated) form (pH 7–9) is harsh to inhale.¹⁰ Hence, nicotine levels were kept relatively low to remain palatable. This changed when JUUL Labs implemented a nicotine salt technology that uses benzoic acid to produce an e-liquid with acidic pH (5.5), comparable to that of cigarette smoke, thereby minimising harshness and irritation with inhalation.¹⁰ According to JUUL Labs, this creates a satisfying e-cigarette for adult smokers seeking to switch from smoking to vaping. It also facilitates initiation to a higher nicotine, and hence more addictive vaping product, among novice young users.

Irritation with inhalation is a deterrent to smoking among nicotine-naïve individuals, including adolescents.¹¹ In a 1974 meeting, RJ Reynolds senior scientists discussed cigarettes for beginning smokers, noting that such a cigarette should be 'low

in irritation and possibly contain added flavours to make it easier for those who never smoked before to acquire the taste for it more quickly.'¹² A 1987 internal Brown and Williamson Research, Development and Engineering memo noted that a successful cigarette for 'starters' would provide 'a low tobacco taste... low impact and irritation... low tobacco aftertaste, (and) if it's a menthol product, it should have a low amount.'¹³ The smooth nicotine delivery of JUUL is likely a factor in its popularity with adolescents.^{14 15} The additive menthol also may suppress respiratory irritation and increase nicotine intake, with measured JUULpod aerosol menthol levels of 5.3 ppm for fruit medley, which is not labelled as mentholated; 7.5 ppm for cool cucumber; 63 ppm for classic menthol; and 70 ppm for cool mint.¹⁵ Presumably flavours contribute to the abuse liability of tobacco products, particularly in the experimentation stage.¹⁶ In our review, when reported, we identify the JUULpod flavours tested, though few studies were powered for statistical comparisons by flavour.

PK studies of JUUL

Clinical PK studies examine the dynamic process of drug uptake by the body. We identified eight PK studies of JUUL, seven with crossover designs that compared to combustible cigarettes (table 1). PK parameters include: (1) time at which the highest nicotine concentration occurred in plasma (T_{max}); (2) the highest drug concentration observed in plasma (C_{max}) and (3) estimated area under the plasma nicotine concentration-time curve from 0 to # minutes (AUC; with minutes indicated for each study).¹⁷ In seven of the studies, nicotine concentrations in the intermediate postuse blood samples were corrected for baseline levels and may be referred to as 'nicotine boost,' which is a measure of the absorbed dose of nicotine.¹⁸ Earlier research with combustible cigarettes found that smokers regulate their intake to achieve a constant nicotine blood level. A nicotine boost of 10 ng/mL per cigarette is suitably rapid for positive reinforcing effects¹⁹; whereas, nicotine patches and gum predominantly provide negative reinforcement via alleviation of withdrawal.²⁰ For comparing JUUL to combustible cigarettes, we also calculated JUUL-to-cigarette ratios for C_{max} and AUC.

Five of the eight studies were conducted by JUUL Labs; three were non-industry-supported investigations. At the time of this review, all three of the non-industry supported investigations, and two of the five industry-conducted studies had been published in the peer-reviewed literature. In the studies conducted by JUUL, participants were recruited to be smokers; two of the JUUL studies specified participants were JUUL-naïve^{21 22} and a third was conducted in New Zealand, where JUUL was not commercially available.²³ The studies reported providing instruction and initial practice with the JUUL product; the New Zealand study provided training on the device and the study specific inhalation technique (per author correspondence). In contrast, the three independent studies were conducted with experienced e-cigarette users. All the studies evaluated the 5% JUULpod strength; three studies also evaluated lower strength JUULpods for comparison (1.5%–3%) with lower nicotine concentration values measured.^{22 24 25}

Across the eight studies, T_{max} was comparable for JUUL and combustible cigarettes, if not slightly shorter for JUUL. That is, JUUL's time to maximum nicotine concentration in plasma appears similar to that of cigarettes, indicating rapid delivery and suggesting high abuse potential.

For the 5% JUULpods, nicotine boost ranged from much less to greater than a combustible cigarette. Variability in C_{max} and

Table 1 JUUL (vs combustible cigarette when available) nicotine pharmacokinetics

Author, year, product, flavour and protocol	Sample (N)	# puffs or time (mins)	Tmax (mins)	Cmax baseline adj (ng/mL)	Cmax ratio (JUUL/Cig)	AUC _{time} baseline adj (ng.hour/mL)	AUC ratio (JUUL/Cig)
Wynne 2018* ²³	N=24 smokers					15 min	
JUUL Virginia tob. fixed		10	6.5±3.8	15.4±6.9	77%	2.4±1.0	86%
New Zealand Pall Mall fixed		10	7.5±3.6	20.1±12.1		2.8±1.2	
JUUL Virginia tob. ad lib		4.5 min	5.5±2.4	18.8±10.7	81%	2.6±1.3	76%
New Zealand Pall Mall ad lib		4.5 min	6.8±3.3	23.2±16.0		3.4±1.8	
Yingst 2019 ⁴³	N=5 JUUL users†					--	--
JUUL mango, menthol fixed		30	8.4±1.7	31.0±8.7	--	--	--
Hajek 2020 ⁴⁴	N=20 dual users†					30 min	
JUUL Virginia tob. ad lib		5 min	4 (2–6) ^{Md}	20.4±15.0	106%	5.1±2.9	98%
Cigarettes usual brand ad lib		5 min	6 (4–8) ^{Md}	19.2±17.6		5.2±3.1	
Goldenson 2020* ²¹	N=66 smokers without prior JUUL use					30 min	
JUUL Virginia tob. fixed		10	6	7.5	58%	2.5±1.2	54%
JUUL mint fixed		10	6	7.4	57%	2.5±1.3	54%
JUUL crème fixed		10	6	5.7	44%	1.9±1.1	41%
JUUL mango fixed		10	6	7.7	60%	2.7±1.2	59%
Cigarettes usual brand fixed		10	6	12.9		4.6±2.3	
Buchhalter 2020* ⁴⁵	N=25 smokers					60 min	
JUUL Virginia tob. fixed		10	5.2±1.9	14.2±7.3	67%	5.0±2.2	65%
Marlboro Red standard		10	6.7±5.1	21.2±11.7		7.7±3.6	
JUUL Virginia tob. ad lib		4.5 min	4.9±2.2	17.4±10.0	62%	5.8±2.7	59%
Marlboro Red cigarettes ad lib		4.5 min	5.8±1.4	27.9±19.6		9.8±5.7	
Goldenson 2020 ^{25*}	N=24 smokers					60 min	
5% JUUL Virginia tob. fixed		10	6.2±2.4	10.6±5.6	60%	5.2±1.5	58%
1.5% JUUL Virginia tob. fixed		10	6.3±1.6	3.8±2.3	22%	1.8±0.6	20%
Cigarettes usual brand fixed		10	7.8±5.0	17.6±8.7		8.9±2.7	
5% JUUL Virginia tob. ad lib		5 min	6.4±2.0	8.8±3.2	42%	4.8±1.5	49%
1.5% JUUL ^{EU} tobacco ad lib		5 min	6.5±2.2	3.8±1.8	18%	1.9±0.7	20%
Cigarettes usual brand ad lib		5 min	6.7±1.7	20.9±11.3		9.7±3.5	
Goldenson 2020* ²²	N=146 smokers without prior JUUL use					60 min	
5% JUUL four flavours‡ ad lib		5 min	6.2 ^{Md}	9.9±8.3	46%	4.5±3.1	45%
3% JUUL four flavours‡ ad lib		5 min	6.0 ^{Md}	7.4±6.9	34%	3.3±2.4	33%
Cigarettes usual brand ad lib		5 min	6.2 ^{Md}	21.7±13.6		10.0±4.8	
Phillips-Waller 2020 ²⁴	N=18 dual users†					30 min§	
5% JUUL Virginia tob. ad lib		5 min	4 (2–6) ^{Md}	21.1 (9.9–36.3) ^{Md}	164%	11.9±5.8	109%
1.7% JUUL ^{EU} Golden tob. ad lib		5 min	6 (4–8) ^{Md}	3.8 (2.5–7.5) ^{Md}	29%	2.6±1.0	24%
Cigarettes usual brand ad lib		5 min	5 (4–8) ^{Md}	12.9 (8.0–35.6) ^{Md}		10.8±7.0	

All tested JUULpods are 5% strength and US products, unless otherwise indicated.

*Industry-funded study.

†Participants abstained from smoking and vaping overnight or longer prior to participating.

‡Flavours tested: Mango, Cool Mint, Menthol, Virginia Tobacco.

§Not baseline adjusted and calculated on n=14 because blood samples not collected for 4 of the 18 participants.

AUC, area under the curve; Md, median, interquartile range reported.

AUC values was observed by funder type (industry vs independent), participant familiarity with e-cigarettes, and sampling protocols (fixed vs ad libitum), and may relate to product modifications made in the USA over time.²⁶ Among industry-funded studies of JUUL-naïve users, JUUL's Cmax and AUC were half to three-fourths that of combustible cigarettes. A recent independent trial reporting plasma nicotine concentration following 10 puffs in 13 JUUL-naïve users similarly found half the nicotine delivery relative to combustible cigarettes.²⁷ The investigators called for research in experienced JUUL users.

Higher JUUL Cmax and AUC values, close to or greater than cigarette smoking, were reported in independent studies, with experienced e-cigarette users. JUUL's Cmax and AUC values also approached that of cigarettes in Wynne *et al*'s industry-funded study presented in early 2018,²³ which pretrained participants in the study inhalation technique for JUUL. The study used New Zealand Pall Mall cigarettes as the comparator, known for higher nicotine machine yields than US cigarettes,²⁸ and may have tested an earlier JUUL device.²⁶ Despite the variability in

timeframes and sampling, all three non-industry studies and four of the five JUUL-funded studies calculated the nicotine boost for 5% JUULpods at 10 ng/mL or higher, which based on prior research on combustible cigarettes,¹⁸ and consistent with JUUL's market success, is suitably rapid for positive reinforcing effects.

In addition to the PK profiles, Wynne *et al*²³ reported no significant differences after using JUUL vs smoking New Zealand Pall Malls on any of 11 measures of subjective experience (eg, satisfaction, cigarette craving reduction) in the 10-puff session or ad libitum conditions (ie, 22 comparisons). In contrast, Goldenson *et al* reported less liking, intent-to-use, satisfaction and enjoyment for JUUL relative to combustible cigarettes, though ratings were higher than nicotine gum, and this was in a sample recruited as naïve to JUUL.²¹ This latter study was the only one reporting PK values separately by JUULpod flavour.²¹ Lower Cmax values were found for crème compared with the other JUUL flavours, which the investigators attributed to a lower mass of e-liquid consumed (55%–66% on average), and hence lower nicotine exposure.

Another study examined JUUL puff topography.²⁹ In two 60 min ad libitum sessions, 30 experienced JUUL users aged 18–24 vaped their preferred JUULpod flavour or JUUL classic tobacco flavour in the lab. Most (73%) preferred mint, 20% mango and 7% other. JUUL puff topography parameters averaged 3 s puff duration, 40 mL puff volume, 111 s interpuff interval and 38 total puffs, with no significant differences by JUULpod flavour condition. The mean nicotine boost was 9.5 ± 1.5 ng/mL for preferred JUULpod flavour and 8.9 ± 1.4 ng/mL for classic tobacco flavour, a non-significant difference.

How much nicotine is in a JUULpod?

The typical cigarette contains about 10–15 mg of nicotine, of which 1 to 1.5 mg (10%) is absorbed by the smoker on average.⁹ JUUL Labs reports each 5% JUULpod contains about 0.7 mL with 5% nicotine by weight, or approximately 40 mg per pod based on 59 mg/mL.³⁰ In five separate studies of the 5% strength JUULpods, the average nicotine concentration (mg/mL) in the pod fluid was reported as: 56.2,³¹ 59.6,¹⁰ 61.6,³² 60.9¹⁴ and 69.¹ Based on these reported concentrations, given the volume of a JUULpod is 0.7 mL (or 0.77 g), the amount of nicotine in a pod ranges from 39.3 to 48.3 mg. One study reported nicotine concentration by flavour, ranging from 58 mg/mL for classic menthol to 62 mg/mL for mango.¹⁰ The same study reported nicotine concentrations in 3% strength JUULpods: 35 mg/mL for both Virginia tobacco and mint. Not all nicotine contained in a pod is delivered to a user. Assessing the amount delivered to an actual user is a more involved process.

Measuring nicotine delivery via the JUUL device

Nicotine delivery to the user can be estimated by measuring nicotine in vaping-machine generated aerosols or by measurement of levels of nicotine and/or metabolites in urine or blood in a person following use. Seven separate studies, conducted to quantify the amount of nicotine in the aerosol generated by JUUL devices, varied in their puffing regimes (ie, puff volume, duration, interval) and the equipment used to generate and capture the aerosol (see table 2).

Machine protocol puff durations ranged from 2 to 4.3 s, puff volumes from 55 to 100 mL and the interpuff interval from 10

to 60 s. For analysing nicotine levels in combustible cigarette smoke, the US Federal Trade Commission's machine protocol was 2 s, 35 mL puffs every minute until a certain point was reached along the length of the cigarette (ie, filter overwrap plus 3 mm). Yet, in the combustible cigarette literature, there also is some variability in puffing protocols.³³

Estimated nicotine delivery based on machine vaping of JUUL

Among the seven studies measuring nicotine delivery via vaping-machine generated aerosols, one reported the aerosol nicotine concentration at 41.2 mg/mL or 28.8 mg per JUULpod,¹⁴ with an estimated 68% transfer efficiency for nicotine from pod (60.9 mg/mL unvaped) to the aerosol. The other six studies reported nicotine $\mu\text{g/puff}$ values of: 72,² 83,³¹ 87,³⁴ 114,¹⁵ 137¹ and 164.³⁵ The latter study reported variability in nicotine in aerosol emissions by JUULpod flavour: 154 $\mu\text{g/puff}$ for fruit medley, 157 $\mu\text{g/puff}$ for tobacco, 170 $\mu\text{g/puff}$ for cr me brulee and 188 $\mu\text{g/puff}$ for mint.³⁵

With variation anticipated depending on puff topography, JUUL's website has indicated that each JUULpod offers about 200 puffs.³⁶ Using a standard puffing protocol of 55 mL over 3 s, an independent analysis found an average mass loss of 4.4 mg per puff.¹⁰ In 0.7 mL, which is equivalent to 0.826 g, this would be 188 puffs. If we assume JUUL's 200 puffs per pod, for the six studies reviewed, this would be: 14.4 mg,² 16.6 mg,³¹ 17.4 mg,³⁴ 22.8 mg,¹⁵ 27.4 mg¹ and 32.8 mg³⁵ of nicotine delivery possible per pod.

What is the cigarette nicotine equivalent of vaping a 5%-strength JUULpod?

Estimates of cigarette equivalents for vaping one 5% JUULpod, based on vaping machine studies, range from 13 to 30 cigarettes (table 2). Contributing to the variability are differences observed by JUULpod flavour, puff protocols (especially puff volume), and data collection and analytical methods. For the seven studies reviewed, the correlation between puff volume and measured nicotine per puff was $r=0.61$. Omaiye¹⁴ reported, 'during aerosol production, JUULpods did not perform uniformly on the vaping machine, and some pods did not work at all,' which

Table 2 Studies reporting on nicotine delivery from a 5% strength JUULpod via a JUUL device using machine sampling

Study and flavours tested	Puff		Inter Puff Interval	# of puffs	Device	Nicotine			
	Volume	Duration				mg in the e-liquid per pod	μg per puff	If 200 puffs per pod*	Marlboro Red filtered cigarette equivalents†
Mallock 2020 ² Virginia tobacco	55 mL	3 s	30 s	20	Standard linear smoking machine designed for e-cigarettes	--	72 μg	14.4 mg	13
Talih 2020 ³⁴ Tobacco	67 mL	4 s	10 s	15	AUB Aerosol Lab Vaping Instrument	45.5 mg	87 μg	17.4 mg	16
Talih 2019 ¹ Tobacco	67 mL	4 s	10 s	15	AUB Aerosol Lab Vaping Instrument	48.0 mg	137 μg	27.4 mg	25
Goniewicz 2019 ³¹ Unspecified flavour	70 mL	2 s	10 s	10	'Smoking machine'	39.3 mg	83 μg	16.6 mg	15
Reilly 2019 ³⁵ Fruit medley, mint, tobacco, cr�me brulee	75 mL	2.5 s	30 s	10	Human Puff Profile Cigarette Smoking Machine (CH Technologies, NJ)	--	164 μg	32.8 mg	30
Erythropel 2019 ¹⁵ Eight flavours‡	79 mL	2.8 s	30 s	20	Custom-built vaping machine, liquid nitrogen-chilled traps	--	114 μg	22.8 mg	21
Omaiye 2019 ¹⁴ Eight flavours‡	100 mL	4.3 s	60 s	¼ of pod	Cole-Parmer Masterflex L/S peristaltic pump	42.6 mg	144 μg	28.8 mg	26

*The JUUL website FAQ has indicated that each JUULpod offers about 200 puffs.³⁶

†Per FTC testing protocol, Marlboro Red filtered 100 mm hard pack cigarette delivers 1.1 mg nicotine per cigarette.⁴⁶ A more recent study reported Marlboro Red filtered regular 79 mm cigarette delivers 1.04 mg nicotine.⁴⁷ Used here is the 1.1 mg nicotine value for 100 mm Marlboro Red hard pack cigarettes. Values rounded.

‡Flavours tested: Cr me Brulee, Fruit Medley, Mango, Cool Cucumber, Cool Mint, Classic Menthol, Classic Tobacco, Virginia Tobacco
FAQ, Frequently Asked Questions; FTC, Federal Trade Commission.

may explain some of the variance observed within and between studies. Talih also reported wide variability in the yields between their studies with no apparent design, electrical, or construction differences between the devices (per author correspondence). In defining nicotine pack equivalents, variability would be further introduced if a range was used for the nicotine uptake from a cigarette (ie, 1 to 1.5 mg per stick).

User behaviour also is likely to introduce variability. A limitation with the studies above is that standardised puffing protocols do not reflect how most users inhale the product over the course of a day.²⁹ For example, in the PK studies reviewed earlier, using a standardised puffing protocol, there was marked variation in plasma nicotine levels, presumably reflecting different extents of inhalation and/or retention of aerosol.³⁷

Under extended use, yet still controlled conditions, JUUL investigators Jay *et al*³⁸ recruited 90 daily smokers naïve to JUUL and observed them on a research unit for 5 days, randomised to one of six conditions (n=15 per condition) with ad libitum use of: JUUL Virginia tobacco, mango, mint or crème flavour; their usual cigarette brand; or abstinence. Total nicotine equivalents were measured in 24-hour urine collections at day -1 and day 5. At days 4–5 (ie, after several days of use), those randomised to their usual cigarette brand smoked on average 19.3 cigarettes per day with an average of 19.0 mg of nicotine equivalents measured in urine over 24 hours; while those randomised to JUUL averaged 18.3 mg of nicotine equivalents measured over 24 hours when consuming slightly more than one pod per day (0.79 g e-liquid used on average, with an estimated 0.77 g weight per JUULpod). This study by JUUL suggests that a 5% JUULpod is on average equivalent to smoking 18 cigarettes. Variation was observed in 24-hour measured nicotine by JUULpod flavour, with the mean percent change at day 5 versus baseline showing +26% gain among those randomised to usual brand of cigarettes, +25% for JUUL mango; +15% for crème, +3% for mint and -7% for Virginia tobacco; all far higher than the decline observed among those randomised to the abstinence condition (-96%).

CONCLUSION

JUUL contains nicotine in the form of benzoate salt, which results in an acidic pH and allows for high nicotine levels to be rapidly inhaled and absorbed into the bloodstream, with less irritation, relative to the freebase nicotine that has traditionally been used in other e-cigarettes.³⁹ This innovation allows for inhalation of liquids with higher nicotine concentrations, may enhance nicotine delivery and could potentially increase the likelihood that adult smokers are able to transition completely from conventional cigarettes. JUUL's appealing flavours, now limited in the USA to tobacco and menthol, coupled with the speed and efficiency with which JUUL is able to deliver nicotine to the user, also may increase the potential for initiation and dependence among young people. In JUUL-naïve users, the nicotine boost of 5% JUULpods was half to three-quarters that of a combustible cigarette; while in experienced or trained e-cigarette users, JUUL's nicotine delivery was comparable to a combustible cigarette. Minimising harshness and adaptive to user experience, JUUL's design facilitates initiation to a high nicotine, and ultimately, more addictive vaping product. While estimates vary by study design, vaping machine and human studies suggest that the nicotine in one JUULpod delivers the equivalent to smoking about a pack of cigarettes (ie, 20 cigarettes), consistent with the JUULpod cartridge pack labelling, although with notable variability. Despite reports of 'turbo-charged' European JUULpods,²

What this paper adds

- ▶ JUUL's patented nicotine salt technology allows for high nicotine levels to be rapidly inhaled and absorbed into the bloodstream.
- ▶ JUUL's domination of the US e-cigarette market has raised public health interest in quantifying nicotine delivery and absorption among JUUL users.
- ▶ We reviewed studies of JUUL's nicotine pharmacokinetic profile and studies quantifying nicotine in a JUULpod, emitted in the aerosol, and absorbed by users, and with comparison to nicotine delivery via traditional combustible cigarettes.
- ▶ One JUULpod appears capable of delivering the nicotine equivalent to smoking about a pack of cigarettes, with product and user variability.
- ▶ Minimizing harshness and adaptive to user experience, JUUL's design facilitates initiation to a high nicotine, and ultimately, highly addictive vaping product.

the European JUUL products tested in the two PK studies reviewed here delivered much less nicotine to users than the US 5% JUULpods.^{24 25}

Lack of uniformity observed in the JUUL product challenges computations, including measured differences in nicotine content for the same flavours and between different flavours as well as reported product failures. Data limitations also include variability in testing protocols and use of standardised protocols that may not reflect real-world behaviour. The one identified study of JUUL puff topography,²⁹ with no difference found by preferred versus tobacco flavour, found an average puff duration of 3 s, which is consistent with machine testing protocols, while the average puff volume of 40 mL was lower than machine testing values (55–100 mL). Prior research has shown puff duration influences nicotine delivery.⁴⁰ For the seven machine testing studies reviewed here, puff volume explained 37% of the variability in nicotine measured per puff. The puff topography study was of ad libitum use over 60 min, while the PK studies provided participants 4.5–10 min to use JUUL, followed by a period of abstinence. Determining the optimal puffing paradigm to study a particular device and in consideration of device by user interactions is challenging. Research with Blu e-cigarettes, for example, observed puff topography with ad libitum use in one's natural environment to vary tremendously across vapers leading the investigators to recommend a range of parameters be used in machine testing studies.⁴¹

Six of the 19 identified studies were funded by JUUL Labs, four of which have not yet undergone peer review. More independently funded research is needed. As JUUL Labs complies with the FDA's deferred regulatory review and provides PK data for PMTA review (which notably stands for premarket tobacco applications) we anticipate more data will become available, though still not publicly for some time. Regulatory decision making on e-cigarette products will weigh the relative risks and benefits to the population.⁴² Conclusions from this review are rough equivalency between JUULpods and combustible cigarettes in terms of nicotine delivery.

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Competing interests JJP and NB have served as expert witnesses against the tobacco companies in lawsuits for which they have received fees for the work. They have also provided consultation to pharmaceutical and technology companies that make medications and other treatments for quitting smoking.

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