

Adaptation of ENDS Device Measurements into Puffing Topography Variables and Clinical Implications *

by

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SUMMARY

Some next generation electronic nicotine delivery systems (ENDS) are capable of providing measurements of selected device parameters related to classical puffing topography variables (e.g., number of puffs, puff duration, etc.) and estimated aerosol mass. The JUUL2[®] System can provide some of this information via a mobile phone application. A laboratory study was used to compare and translate selected device measurements into classical puffing topography variables for the breath activated JUUL2[®] device. The sensitivity of the pressure sensors that activate the device were determined using 7 flowrates in a pressure-flow testing apparatus using 30 JUUL2[®] devices. The JUUL2[®] device tracks activation duration as a proxy for puff duration. Comparison of puff duration from a puffing machine to device activation duration was performed using three different puffing regimens for 15 JUUL2[®] devices with a tobacco and menthol formulation. An ISO 20768 square wave, sine wave, and gap wave puffing regimens were used. The gap wave was created from the ISO 20768 square wave puffing regimen with a 0.5-s gap in the middle of the 3-s puff (gap puffing regimen with a 2.5-s puff duration), and all puff regimens were 3 seconds in duration. For each puffing regimen, the gravimetrically deter-

mined device mass loss and aerosol collected mass was compared to the estimate of generated aerosol mass provided by the JUUL2[®] device. Pressure-flow testing demonstrated that device activation occurred at a pressure drop of 95–150 Pa, which corresponded to a flowrate of 7.5–10 cm³/s. The duration of JUUL2[®] device's activation averaged 95% and 76.4% of the 3-s puff duration of the square wave and sine wave regimens, respectively. For the gap wave regimen, the JUUL2[®] activation duration averaged 91% of the 2.5-s puffing regimen. There were small but statistically significant differences in device activation duration between the Virginia Tobacco and Menthol formulations using the square wave and gap wave puffing regimen. For a few puffs, the JUUL2[®] device recorded two activations, rather than one, with the incidence more pronounced for the sine wave than the square wave puffing regimen. A simple algorithm was developed that combined split device activations so that they perfectly matched puff counts during the square wave and sine wave puffing regimens. For each formulation (tobacco and menthol) and puffing regimen, there was a different correlation between the estimated aerosol mass from the JUUL2[®] device and the gravimetrically measured device mass loss. When puffing regimens were combined for each flavor, there was good correlation between measured device mass loss or aerosol

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collected mass and the estimated aerosol mass from the JUUL2[®] device. In conclusion, selected JUUL2[®] device measured parameters can be translated into classical puffing topography variables (i.e., number of puffs and puff duration), as well as provide an estimated aerosol mass generated by the JUUL2 System. [Contrib. Tob. Nicotine Res. 34 (2025) 40–49]

KEYWORDS

Topography; Electronic nicotine delivery systems; ENDS; puffing regimen

ZUSAMMENFASSUNG

Einige elektronische Zigaretten (ENDS) der nächsten Generation sind in der Lage, Messungen ausgewählter Geräteparameter im Zusammenhang mit den klassischen Topographievariablen (z.B. Anzahl der Züge, Dauer der Züge usw.) und der geschätzten Aerosolmasse zu liefern. Das JUUL2[®]-System kann einige dieser Informationen über eine Smartphone-App bereitstellen. In einer Laborstudie wurden ausgewählte Messwerte für das durch den Zug aktivierte JUUL2[®]-Gerät verglichen und in klassische Zugtopographie-Variablen übersetzt. Die Empfindlichkeit der Drucksensoren, die das Gerät aktivieren, mittel eines Druck/Fluss-Testgeräts bei 7 Fließgeschwindigkeiten mit 30 JUUL2[®]-Geräten bestimmt. Stellvertretend für die Zugdauer diente die Aktivierungszeit des JUUL2[®]-Systems. Der Vergleich der Zugdauer einer Vapingmaschine mit der Aktivierungsdauer des Geräts wurde mit drei verschiedenen Zugprofilen an 15 JUUL2[®]-Geräten durchgeführt, jeweils mit tabak- und mentholhaltigen Liquids. Es wurden ein Rechteckprofil nach ISO 20768, ein Sinusprofil und ein Rechteckprofil, das unterbrochen wurde (Gap-Profil), im Test verwendet; alle Züge hatten eine Dauer von 3 Sekunden. Das Gap-Profil wurde aus dem ISO 20768-Rechteckprofil mit einer Zudauer von 3 Sekunden und einer Unterbrechung von 0,5 Sekunden in der Mitte des Zuges erzeugt. Bei allen Tests wurden der gravimetrisch ermittelte Massenverlust des Geräts und die gesammelte Aerosolmasse mit der vom JUUL2[®]-Gerät geschätzten erzeugten Aerosolmasse verglichen. Druck-Fluss-Tests zeigten, dass das Gerät bei einem Druckabfall von 95–150 Pa aktiviert wurde, was einer Fließgeschwindigkeit von 7,5–10 cm³/Sekunde entsprach. Die Aktivierungsdauer des JUUL2[®]-Geräts betrug im Durchschnitt 95% (beim Rechteckprofil) bzw. 76,4% (beim Sinusprofil) der 3 Sekunden dauernden Zugphase. Bei Gap-Profil betrug die Aktivierungsdauer des JUUL2[®]-Gerätes durchschnittlich 91% der 2,5-Sekunden-Zugphase. Es zeigten sich geringe, aber statistisch signifikante Unterschiede in der Aktivierungsdauer des Geräts zwischen den Virginia Tabak- und Menthol-Liquids, die mit dem Rechteck- und dem Gap-Profil verwendet wurden. Bei einigen wenigen Zügen zeichnete das JUUL2[®]-Gerät zwei Aktivierungen statt einer auf, wobei die Häufigkeit beim Sinusprofil ausgeprägter war als beim Rechteckprofil. Es wurde ein einfacher Algorithmus entwickelt, der die geteilten Aktivierungen des Geräts so kombinierte, dass sie perfekt mit der Anzahl

der Züge bei rechteckigem und sinusförmigen Profil übereinstimmten. Für die beiden Liquids (Tabak und Menthol) und jeden Zugmodus zeigte sich eine unterschiedliche Korrelation zwischen der vom JUUL2[®]-Gerät geschätzten Aerosolmasse und dem gravimetrisch gemessenen Masseverlust des Geräts. Bei der Kombination von Zugversuchen für jedes Aroma ergab sich eine gute Korrelation zwischen dem gemessenen Masseverlust des Geräts bzw. der gesammelten Aerosolmasse und der geschätzten Aerosolmasse des JUUL2[®]-Geräts. Zusammenfassend lässt sich sagen, dass die ausgewählten, vom JUUL2[®]-Gerät gemessenen Parameter in klassische Topographievariablen (d.h. Anzahl und Dauer der Züge) übersetzt werden und eine geschätzte Aerosolmasse liefern können. [Contrib. Tob. Nicotine Res. 34 (2025) 40–49]

RESUME

Certains systèmes électroniques d'administration de nicotine (ENDS) de nouvelle génération sont capables de fournir des mesures de certains paramètres de l'appareil liés aux variables topographiques classiques de la bouffée (par exemple, le nombre de bouffées, leur durée, etc.) et à la masse estimée de l'aérosol. Le système JUUL2[®] peut fournir certaines de ces informations via une application pour téléphone portable. Une étude en laboratoire a permis de comparer et de traduire certaines mesures de l'appareil en variables topographiques classiques de la bouffée pour l'appareil JUUL2[®] activé par la respiration. La sensibilité des capteurs de pression qui activent l'appareil a été déterminée à l'aide de 7 débits dans un appareil de test pression-débit utilisant 30 appareils JUUL2[®]. Le dispositif JUUL2[®] enregistre la durée d'activation comme une approximation de la durée de la bouffée. Une comparaison entre la durée des bouffées tirées d'un appareil à bouffées et la durée d'activation de l'appareil a été effectuée à l'aide de trois régimes de bouffées différents pour 15 appareils JUUL2[®] avec une formulation de tabac et de menthol. Des régimes de bouffée à onde carrée ISO 20768, à onde sinusoïdale et à onde discontinue ont été utilisés. L'onde creuse a été créée à partir du schéma de bouffée ISO 20768 à onde carrée avec un écart de 0,5 seconde au milieu de la bouffée de 3 secondes (schéma de bouffée creuse avec une durée de bouffée de 2,5 secondes), et tous les schémas de bouffée ont été d'une durée de 3 secondes. Pour chaque régime de bouffées, la perte de masse déterminée par gravimétrie et la masse d'aérosol recueillie ont été comparées à l'estimation de la masse d'aérosol générée fournie par l'appareil JUUL2[®]. Les tests de pression et de débit ont montré que l'activation du dispositif se produisait à une chute de pression de 95 à 150 Pa, ce qui correspondait à un débit de 7,5 à 10 cm³/s. La durée de l'activation du JUUL2[®] correspondait en moyenne à 95% et à 76,4% de la durée de la bouffée de 3 secondes pour les régimes d'ondes carrées et d'ondes sinusoïdales, respectivement. Dans le cas du régime d'ondes discontinues, la durée d'activation du JUUL2[®] correspondait en moyenne à 91% de la durée de bouffée de 2,5 secondes du régime d'ondes carrées. Il y avait des différences faibles, mais statistiquement significatives dans la durée d'activation de l'appareil entre les formulations Virginia Tobacco et Menthol en utilisant le

régime de bouffées à ondes carrées et à ondes discontinues. Pour quelques bouffées, l'appareil JUUL2® a enregistré deux activations au lieu d'une, l'incidence étant plus prononcée pour le régime de bouffées à ondes sinusoïdales que pour le régime de bouffées à ondes carrées. Un algorithme simple a été mis au point pour combiner les activations fractionnées de l'appareil de manière à ce qu'elles correspondent parfaitement au nombre de bouffées pendant les régimes de bouffées à ondes carrées et à ondes sinusoïdales. Pour chaque formulation (tabac et menthol) et chaque régime de bouffées, la corrélation entre la masse d'aérosol estimée par le JUUL2® et la perte de masse mesurée par gravimétrie était différente. Lorsque les régimes de bouffées étaient combinés pour chaque arôme, il y avait une bonne corrélation entre la perte de masse mesurée par l'appareil ou la masse d'aérosol collectée et la masse d'aérosol estimée par l'appareil JUUL2®. En conclusion, certains paramètres mesurés par l'appareil JUUL2® peuvent être traduits en variables topographiques classiques de bouffée (c'est-à-dire le nombre de bouffées et la durée des bouffées) et fournir une estimation de la masse d'aérosol générée par le système JUUL2®. [Contrib. Tob. Nicotine Res. 34 (2025) 40–49]

INTRODUCTION

Puffing topography attempts to quantify the intensity of tobacco product use in a common set of terminology and variables (e.g., number of puffs, puff duration, puff volume, interpuff interval, etc.). However, with each new type of inhaled tobacco product, the importance of certain variables changes and some of the terminology needs to be redefined based upon the specific type of product (e.g., cigarettes, heat-not-burn, and electronic nicotine delivery systems (ENDS), etc.). As noted in a recent review of puffing topography (1), the variability in ENDS products preclude use of some of the puff topography variables that have been historically used for cigarettes. For example, because cigarettes are relatively homogenous the number of cigarettes smoked/day provide a relatively good estimate of product use intensity (1, 2). This doesn't necessarily apply to ENDS since depending on the e-liquid storage capacity of the ENDS device and the per-puff aerosol mass generated, a single pod or tank full of e-liquid can last throughout a single day or several days.

A recent review of puffing topography provided the advantages and disadvantages of two common methods that have been used to measure puffing topography variables, video recording and use of specialized add-on devices (Clinical Research Support System – CReSS handheld devices and SODIM Smoking Puff Analyzer Mobile Device – SPA-M from Körber Technologies GmbH, Germany, wireless portable use monitor – wPUM™ from the Rochester Institute of Technology; note these devices do not interface with the ENDS product electronics) (1). A similar specialized add-on device for open tank systems provided results similar to a CReSS device in a comparative clinical trial (3, 4). All of these specialized add-on devices use one or more pressure sensors to detect a puff, meaning that within each specialized add-on device there is a minimum pressure difference (pressure drop) required to trigger puff

recording. This pressure drop threshold also means that each specialized add-on device will not recognize some part of each human puff that is below the minimum pressure difference, resulting in underestimation of puff duration and volume (5). These specialized add-on devices may also change the users' behavior. In recent work (6), it was found that the measured topography variables may be influenced by use of one of these specialized add-on devices, CReSS pocket, which echoes concerns regarding use of these specialized add-on devices that date from the 1980s (7). Two recently published studies reported topography variables being directly measured by the ENDS device (8, 9). These two studies used the Joyetech® eVic™ Supreme ENDS device but did not provide any data on the minimum pressure drop required to trigger puff recording nor the accuracy of the measured number of puffs or puff duration reported. FARSALINOS *et al.* (10) used the same ENDS device in a clinical trial and provided data verifying number of puffs using manual counting and puff duration using video recording. UNDERLY *et al.* (11) described a novel Product Use and Behavior (PUB) device that was designed specifically for the Vuse Solo® ENDS. It is placed between the battery and e-liquid cartridge to record various topography parameters (e.g., puff number, puff duration, interpuff interval, etc.) based upon measurement of battery voltage. This data is transferred daily via Bluetooth app connection to a smart phone. Finally, KOLACZYK AND JIANG (12) described incorporating a pressure sensor and photometric monitoring of aerosol concentration to monitor puff topography variables within an existing ENDS product, Aspire® Nautilus Prime X.

It is important to realize that every one of the above-mentioned measurement techniques is measuring a unique aspect of human puff topography and comparison among these different measurement techniques are likely to result in small differences in the measured human topography variables. For example, use of different criteria when evaluating the video recording for the beginning and ending of puffing (e.g., duration of the light-emitting diode if present on the device and visible, when the device is inserted and removed from the mouth, change in cheek shape, abdominal volume change, etc.) will create variability in puff duration measurements. Although, this variability can be reduced by using the same criteria with two independent evaluators, it will still be different from puff duration as measured by specialized add-on devices (e.g., CReSS pocket, SPA-M, and wPUM™) or ENDS devices that use a pressure drop threshold to measure puff duration. By design, a pressure drop threshold omits a certain part of a human puff profile (i.e., beginning and ending parts that are below the pressure drop threshold), but has to be balanced against the incidence of phantom or false puffs due to normal daily events that exceed the pressure drop threshold (e.g., pod insertion and removal, rapid movement of the device when no puff is taken, being dropped, or tossed onto a counter/surface, or ambient pressure changes due to riding in an elevator, etc.). Incorporation of a pressure sensor and photometer into an existing ENDS device (12), would only measure the duration of aerosol production of the ENDS device, once the e-liquid is heated sufficiently to produce an aerosol and the photometer's threshold value is exceeded. Similar to a

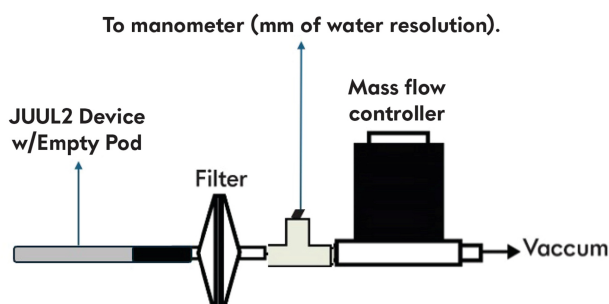


Figure 1. Diagram of the flowrate versus pressure-drop measurement apparatus.

pressure drop threshold, photometers also have a threshold and therefore will omit a small duration of aerosol production at the beginning and end of a puff. BLANK *et al.* (13), found statistically significantly longer puff durations in 30 subjects when measured via video camera compared to the CReSS add-on-device. Based upon these measurement differences described above, the shortest puff duration is likely to occur when duration of aerosol output is measured.

In addition to the Joyetech eVic Supreme, the PUB device, and the modified Aspire Nautilus Prime X, some of the next generation ENDS products also are capable of providing measurements of selected device parameters. The selected device parameters include device activation duration (duration of battery current to heater), counting number of device activations and an estimate of aerosol mass produced by each puff (or device activation). It is measurement of these selected device parameters, their translation into standardized puffing topography parameters (i.e., puff duration and number of puffs) and the estimated aerosol mass that is the focus of this laboratory study for the JUUL2® System.

MATERIALS AND METHODS

All testing was performed at the Juul Labs Regulatory Chemistry Laboratory in Durham, North Carolina, which is an ISO 17025 accredited facility. The JUUL2® System consists of a JUUL2® device and a single use JUUL2® pod (1.2 mL volume). A total of 30 commercial JUUL2® devices obtained from finished goods inventory were used in this laboratory study. For the first part of the laboratory study an empty pod was used in each of the 30 JUUL2® devices. For the second part of the laboratory study, 15 of the 30 JUUL2® devices were used with pods filled with either Virginia Tobacco (18 mg/mL nicotine) and the other 15 JUUL2® devices were used with pods filled with Polar Menthol (18 mg/mL nicotine) e-liquids. Both the Virginia Tobacco and Polar Menthol e-liquids contain United States Pharmacopeia compliant propylene glycol, glycerin, and nicotine along with proprietary flavors. A single lot of Virginia Tobacco (18 mg/mL nicotine) and Polar Menthol (18 mg/mL nicotine) e-liquid-filled pods from finished goods inventory were used and all e-liquid filled pods used were approximately 16 months post manufacture and were within their shelf-life period of 18 months. For both parts of the laboratory study all devices were fully charged prior

to use and for the second part of the study the JUUL2® devices with pods were oriented 45 degrees to gravity for testing. The study was conducted in a controlled temperature 22 ± 2 °C and humidity $60 \pm 5\%$ relative humidity laboratory environment.

In the first part of the laboratory study, different flowrates were set using a mass-flow controller (Allicat, MC-20SLPM-D-DB9M/5M, 5IN, Tucson, AZ, USA) that was connected to a digital manometer (Bonoutil® 522, Hangzhou, Zhejiang, China), which was protected from any aerosol generation by a Cambridge filter pad (Performance Systematix Inc., acquired by Selig Group, Grand Rapids, MI, USA) (Figure 1). The inherent pressure-drop of this test system (without the JUUL2® system attached) was determined at each flowrate and was subtracted from the pressure-drop value measured when a JUUL2® device with empty pod were attached. Each of the JUUL2® devices with an empty pod were attached to the Cambridge filter pad holder using a labyrinth seal and the mass-flow controller was set to one of the following flowrates: 0.3, 0.45, 0.6, 0.75, 1.0, 1.25, and 1.5 standard L/min (note these standard flowrates translate to 5, 7.5, 10.0, 12.5, 16.7, 20.8, and 25.0 standard cm³/s). At each flowrate an empty pod was inserted into the JUUL2® device, the mass flow controller was used to set the desired flowrate, a reading from the digital manometer was recorded, flow was stopped using the mass flow controller and the pod was removed. Two replicate measurements per flowrate for each JUUL2® device were performed with the first replicate starting at 0.3 L/min and finishing at 1.5 L/min and the second replicate starting at 1.5 L/min and finishing at 0.3 L/min. Because the JUUL2® device activation stops after six seconds the average of the first six seconds of the digital manometer readings was used to correlate to the maximum draw strength reported in the JUUL2® device logs to determine whether the flowrate triggered device activation. The number of pressure versus flow replicate measurements that didn't trigger device activation were also recorded.

In the second part of the laboratory study the 30 JUUL2® devices were randomly divided into two equal groups. One group of JUUL2® devices was used with Virginia Tobacco (18 mg/mL nicotine) pods and the second group of JUUL2® devices was used with Polar Menthol (18 mg/mL nicotine) pods. For each group three puffing regimens were used:

- an ISO 20768 square wave profile (13) (hereafter called square wave),
- a sine wave profile (55 mL puff volume over 3 s with an interpuff interval of 30 s),
- and a gap wave consisting of a square wave (14) with a 0.5-s gap starting at 1.4 s (Figure 2).

The gap was created using a three-way solenoid valve (Parker/71315, New Britain, CT, USA) placed between the piston and JUUL2® devices with one way vented to atmosphere that was controlled with a pressure switch (SMC/ZSE30A-NO1-P, Noblesville, IN, USA) and a calibrated digital timer (Eaton Moeller/Easy 621-DC-TC, Cologne, Germany). Each group of JUUL2® devices were puffed in groups of five devices simultaneously using a 20-port SM450 RH linear smoking machine (Cerulean, Milton Keynes, UK). The first five ports were programmed for the square wave puff profile (14), ports 6–10 were -

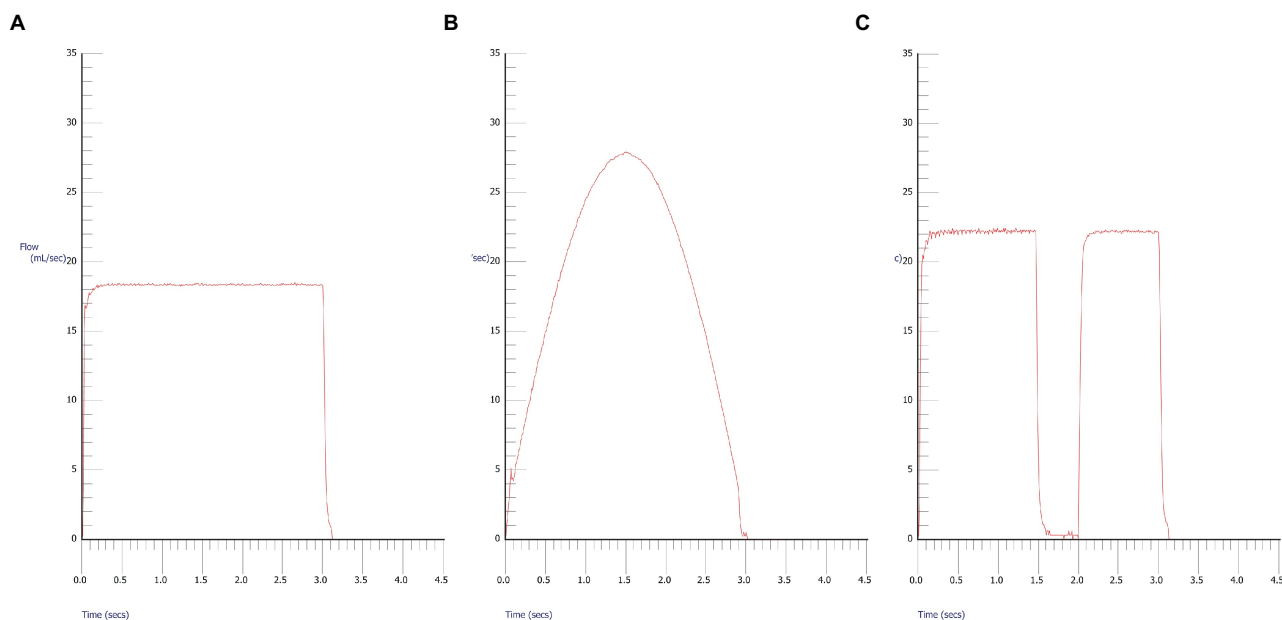


Figure 2. Three puffing regimens using a square wave (A), sine wave (B) and gap wave (C). All puff profiles were 55 mL in volume with the square and sine wave using that volume over 3 seconds while the gap profile was over 2.5 seconds.

programmed for the sine wave puff profile and ports 11–15 were programmed for the gap wave puffing profile. Prior to puffing JUUL2[®] devices, the puffing profile on each port was verified using a calibrated puff profiler (Cerulean VFA450RH, Milton Keynes, UK) designed for use with the SM450 RH linear puffing machine (Cerulean, Milton Keynes, UK). Each group of JUUL2[®] devices were rotated among these 15 ports. At each rotation, the JUUL2[®] devices were fully charged, and a new pod was inserted (Virginia Tobacco 18 mg/mL nicotine or Polar Menthol 18 mg/mL nicotine). For each puff profile, a total of 50 puffs from each JUUL2[®] device/pod combination were performed in 10 puffs/block with each block separated by a 2-min rest period. JUUL2[®] devices with pods were weighed at the beginning and after conclusion of the 50 puffs (called device mass loss), as was the filter collecting all of the aerosol mass generated from each JUUL2[®] device/pod combination (called aerosol collected mass). These gravimetric estimates of aerosol mass produced were compared to aerosol mass estimate from the JUUL2[®] device (i.e., the sum of estimated aerosol mass from the JUUL2[®] device for all device activations) provided in the JUUL2[®] device logs. This estimate mass is based upon a thermal model where e-liquid parameters are determined experimentally (e.g., latent heat of vaporization of the liquid, specific heat of the liquid in use, heat losses to the environment, etc.), which enables an estimation of the power required to vaporize an amount of e-liquid and therefore how much e-liquid was vaporized.

To assess if there were differences in device activation duration between the formulations (Virginia Tobacco *versus* Polar Menthol) for the same puffing regimen, a Z-test was performed ($N = 15$ devices). Analysis of variance was used to see if device activation duration was influenced by order of puffing regimens tested. In the analysis of variance devices 1–5 were coded as order 1, devices 6–10 coded as order 2, and devices 11–15 coded as order 3. These analyses were conducted in SAS (version 9.4) using a $p < 0.05$

as the criterion for statistical significance. Correlations of estimated aerosol mass provided by the JUUL2[®] device *versus* gravimetric measurements of device mass loss and aerosol collected mass between the two tested formulations were performed using linear regression in Microsoft Excel (Version 2405; June 11, 2024).

RESULTS

The mean flowrate *versus* pressure-drop curve for all 30 JUUL2[®] devices was very consistent (Figure 3). The estimated pressure-drop when device activation occurred was between 95 and 150 Pa, which corresponded to a flowrate of 7.5 and 10 cm³/s (Figure 3). As noted in the tabulation of missed device activations, there was some variability among the 30 JUUL2[®] devices tested (Table 1). It was also noted that pod insertion and removal frequently resulted in the JUUL2[®] device recording a puff of very short duration with zero estimated aerosol mass.

For the square wave puffing regimen, the duration of JUUL2[®] device's activation averaged 95% (Table 2) of the 3 second puff duration with a small but statistically signifi-

Table 1. Percent of device actuation occurrences as a function of flowrate and pressure-drop measurements.

Flowrate setting (cm ³ /s)	Pressure-drop (Pascal)			Percent of missing device activations
	Mean	SD	N	
5	47	7.3	2	100
7.5	92	12.8	2	100
10	151	14.9	2	18.3
12.5	227	29.5	2	5.0
16.7	380	36.3	2	3.3
20.8	539	51.9	2	5.0
25.0	727	48.7	2	0

N = number of replicate measurements; SD = standard deviation

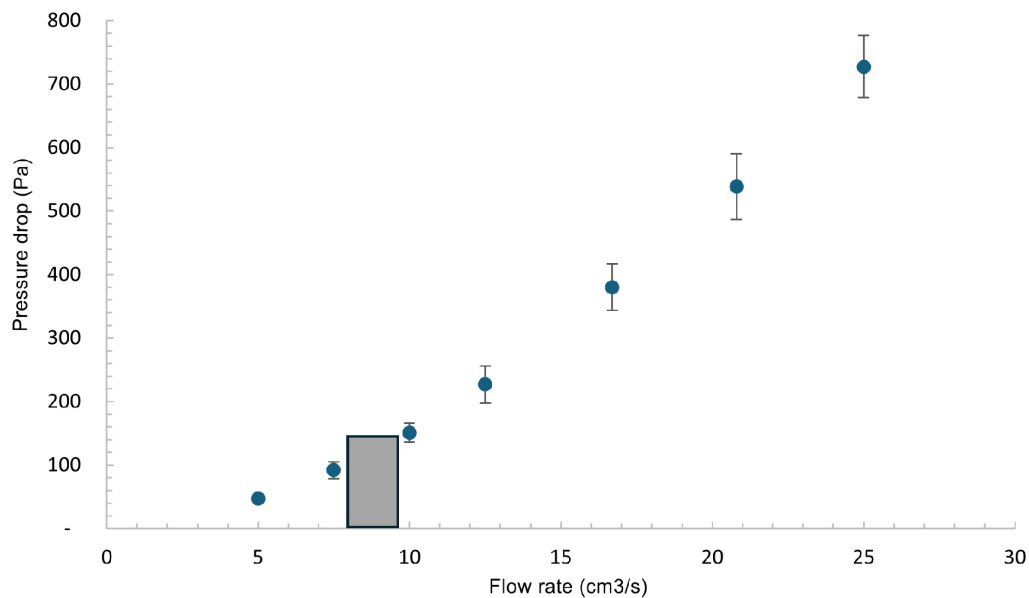


Figure 3. Mean (SD) pressure-drop measurement of the 30 JUUL2® devices. Standard deviation values for some data points are within the data point. The dark vertical rectangle is the estimated pressure-drop required for device activation.

cant difference between the Virginia Tobacco (94.8%) and Polar Menthol (96.0%) formulations ($p = 0.0227$). Statistical analysis indicated testing order did influence ($p < 0.00001$) percentage of the device activation duration for both Virginia Tobacco and Polar Menthol pods using the square wave puffing regimen. For the sine wave puffing regimen, the duration of the JUUL2® device's

Table 2. Summary of duration of device activation for three puffing regimens.

Device number	Mean percent of puff duration ^a					
	Virginia Tobacco			Polar Menthol		
	Square	Sine	Gap	Square	Sine	Gap
1	95.0	76.1	91.3	95.1	76.1	92.0
2	95.4	77.2	90.0	95.8	73.5	90.1
3	95.9	77.2	90.9	95.5	76.1	90.8
4	95.5	74.5	92.3	96.5	77.4	93.3
5	96.1	76.6	90.4	96.8	75.9	92.7
6	91.3	74.6	88.3	95.4	77.4	91.9
7	95.9	73.8	86.9	96.6	76.6	91.1
8	95.5	78.9	89.1	95.8	76.6	90.2
9	97.1	77.4	92.5	96.2	76.9	92.8
10	97.0	76.2	89.7	95.7	77.1	92.8
11	93.8	76.3	90.4	96.8	78.1	93.3
12	93.0	76.8	89.1	95.5	78.2	92.1
13	92.4	75.4	88.2	96.8	78.2	93.1
14	94.6	74.6	91.2	95.8	77.1	92.1
15	93.8	77.6	90.3	95.4	75.5	91.5
Mean	94.8	76.2	90.0	96.0	76.7	92.0
SD	1.6	1.4	1.5	0.6	1.2	1.0

SD = Standard Deviation

^a Square and sine wave puff duration = 3 seconds and for the gap wave puff duration = 2.5 seconds. Each value is the mean of 50 puffs.

activation averaged 76.4% of the 3-s puff showing that more of the sine wave compared to the square wave was below the 95–150 Pa pressure-drop required for device activation (Table 2). No statistically significant differences were noted between percent of the 3-s puff that device activation occurred for Virginia Tobacco (76.4%) and Polar Menthol (76.7%) formulations ($p = 0.3084$) and there was no order of testing influence on the percent of the 3-s puff that device activation constituted. For the gap wave puffing regimen, the duration of the JUUL2® device's activation averaged 91% of the 2.5-s puff duration (Table 2). There was a small but statistically significant difference in the percent of the 2.5 second puff device activation between pods with Virginia Tobacco (90.0%) *versus* Polar Menthol (92.0%) formulations ($p = 0.0004$). There was also a statistically significant ($p = 0.0428$) effect of testing order on percentage of the device activation duration using Virginia Tobacco, but not Polar Menthol formulations for the gap wave puffing regimen.

In the square wave puffing regimen testing, approximately 1% of the device activations were anomalous in that they were split into two activations when only a single puff was taken on the SM450 RH linear smoking machine port. The percent of device activations split into two activations increased to approximately 4% for the sine wave puffing regimen testing and decreased to approximately 1.8% for the gap wave regimen. No meaningful differences were found between the Virginia Tobacco and Polar Menthol pods. These anomalies didn't affect device activation duration measurements as the device activation duration of both activations were manually combined into a single duration. The 50-puff mean device mass loss and aerosol collected mass measurements were different between the Virginia Tobacco and Polar Menthol filled pods, such that mass loss was greater for the Polar menthol pods. However, there was little difference in the estimated aerosol mass from the JUUL2® System for the two formulations (Table 3).

Table 3. Summary of average measured device mass loss, aerosol collected mass, and estimated aerosol mass from the JUUL2® system.

Puffing regimen	50 Puff collection mean mass ± standard deviation (mg) (N = 15)					
	Virginia Tobacco			Polar Menthol		
	Device mass loss	Aerosol collected mass	Estimated aerosol mass	Device/pod mass loss	Aerosol collected mass	Estimated aerosol mass
Square	466.6 ± 22.7	474.2 ± 22.1	408.0 ± 20.7	526.8 ± 30.1	532.1 ± 30.3	402.1 ± 35.0
Sine	362.8 ± 15.4	371.3 ± 15.9	308.6 ± 13.2	441.3 ± 19.1	448.5 ± 19.4	349.4 ± 9.7
Gap	330.6 ± 25.1	335.8 ± 25.4	304.0 ± 9.6	399.2 ± 24.0	404.0 ± 24.4	338.3 ± 6.9

Association of the measured device mass loss and aerosol collected mass for pods with Virginia Tobacco 18 mg/mL e-liquid to the JUUL2® device estimated aerosol mass was different for each puffing regimen ([Supplemental Figures 2 and 3](#)). The correlation coefficient comparing the JUUL2® device estimated aerosol mass from Virginia Tobacco 18 mg/mL pods and both measured device mass loss and aerosol collected mass using data from all puffing regimens was very good (Figure 4). The correlation coefficient of the measured device mass loss and aerosol collected mass for pods with Polar Menthol 18 mg/mL nicotine e-liquid to the JUUL2® device estimated aerosol mass were also different for each puffing regimen ([Supplemental Figures 5 and 6](#)). The correlation coefficient comparing the JUUL2® device estimated aerosol mass for Polar Menthol 18 mg/mL pods and both measured device mass

loss and aerosol collected mass using data from all puffing regimens was good (Figure 5), but less than the correlation coefficient found for Virginia Tobacco 18 mg/mL pods.

DISCUSSION

Based upon results of this laboratory study, it is possible to translate selected device parameters provided by the JUUL2® System into clinically relevant standardized puffing topography parameters (i.e., puff duration and number of puffs), as well as, estimated aerosol mass, with some caveats. For example, duration of device activation provided by the JUUL2® System is sensitive enough to be used as a surrogate for puff duration with the following caveats: it requires a minimum pressure drop of 95-150 Pa

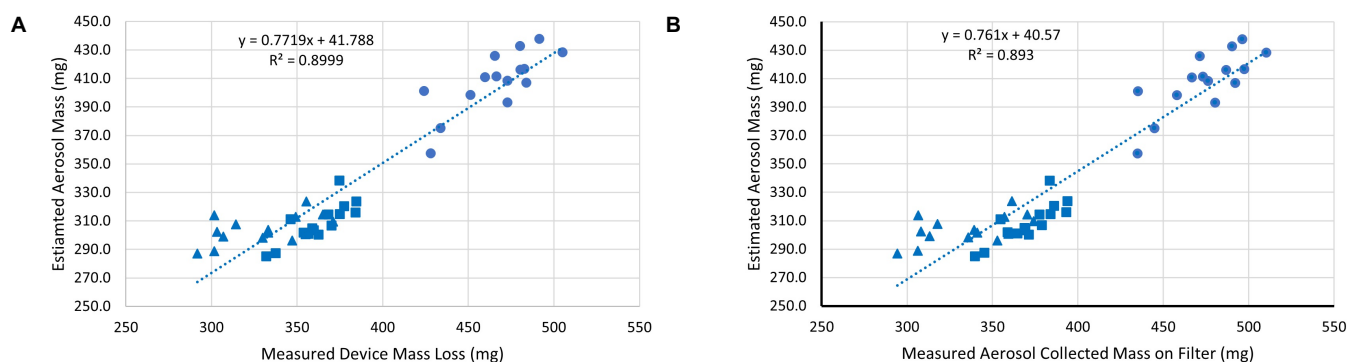


Figure 4. Correlation of laboratory measured device mass loss versus estimated aerosol mass (A) and aerosol collected mass versus estimated aerosol mass (B) from the JUUL2® device for square wave (circles), sine wave (squares), and gap wave (triangles) puffing profile for Virginia Tobacco pods.

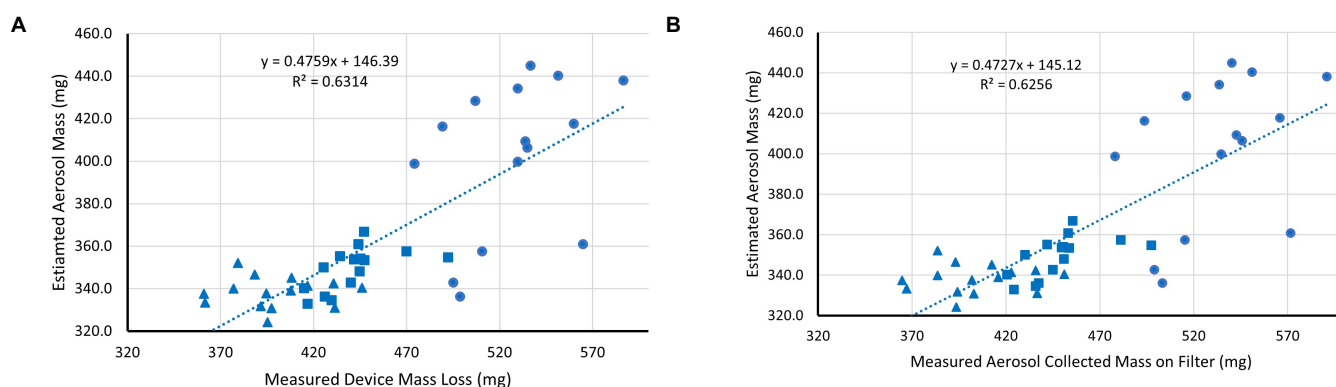


Figure 5. Correlation of laboratory measured device mass loss versus estimated aerosol mass (A) and aerosol collected mass versus estimated aerosol mass (B) from the JUUL2® device for square wave (circles), sine wave (squares), and gap wave (triangles) puffing profile for Polar Menthol pods.

and it has a maximum activation duration of 6 seconds meaning aerosol is no longer produced after 6 seconds because battery current to the heater is turned off. The minimum pressure drop means that the part of the human puff that is below this pressure (95–150 Pa) will not be included (beginning and end of puff) in the estimate of puff duration represented by device activation duration. Our laboratory study demonstrated this is a function of puff shape when puff volume and duration are held constant, with a sine wave only representing on average 76.4% and a square wave puff of equal volume representing on average 95% of the 3 second puff duration.

However, puff volume and duration are just as important, and the three variables are all inter-related in human topography. Using the pressure drop of 95–150 Pa and a 3 s-sine wave puff profile, the effect of different puff volumes ranging from 25 mL to 100 mL resulted in predicted device activation durations (puff duration) from 1.4–1.8 s for the 25 mL-puff volume to 2.8 s for the 100 mL-puff volume (Supplemental Figures 4–8). A similar relationship has been published for the CReSSmicro™ add-on device and would be expected for all breath activated devices (5). The clinical implication is that depending on the puff shape, volume, and duration estimate provided by the JUUL2® device, the puff duration estimate will need to be multiplied by a factor between 1.05 (square wave with 55 mL puff volume) and 2.00 (sine wave with 25 mL puff volume) to correspond to the actual duration of a human puff in classical topography terms.

The number of device activations can be used as a surrogate for number of puffs with the following caveat: because of the sensitivity of the JUUL2® System, sometimes a single puff is split into two puffs with the frequency seeming to increase as the puff profile becomes more complex (e.g., more similar to human puffing) meaning that puffs with short durations (e.g., ≤ 0.5 s) should be combined with the appropriate parent puff (11). The challenge of false or phantom puffs and splitting puffs have been previously reported for CReSSmicro™ and SPA-M add-on devices (5, 15). The differences between the device mass loss and aerosol collect mass measurements are likely due to the hygroscopicity of the aerosol collected on the filter (e.g., propylene glycol and glycerin at the laboratory relative humidity) (16, 17). Finally, the estimated aerosol mass provided by the JUUL2® System correlated with the measured device mass loss and aerosol-collected mass better when data from all puffing regimens was combined *versus* comparing each individual puffing regimen for Virginia Tobacco 18 mg/mL pods. However, for Polar Menthol 18 mg/mL pods the correlation when puffing regimen data was combined was better for only two of the three puffing regimens and equivalent to third puffing regimen. More importantly, the JUUL2® device had a higher correlation with a wider range of device mass loss measured in a clinical trial (18). These results are consistent with previous work that found a specialized add-on device used for open tank systems provided similar estimates of nicotine consumption to those using device mass loss as a surrogate and correlated well with nicotine area-under-the-curve values under *ad libitum* use measured in a small clinical trial (3, 4).

To test translation of these selected JUUL2® device parameters into standardized puffing topography parameters, a simple algorithm was constructed and the JUUL2® device logs from this laboratory study were evaluated using the simple algorithm. The algorithm was designed to combine device activations (puffs) if they were less than 0.5 seconds in duration or within 1.5 seconds of each other (end of one to beginning of another) and if the subsequent device activation (total puff duration) did not exceed 4.3 seconds. If the combined device activations exceeded 4.3 seconds, the device activations (puffs) were kept separate. In processing the device logs for the square wave puffing profile using this algorithm, the percent of puff duration for the 15 devices with Virginia Tobacco and Polar Menthol formulation were 96.1% and 96.1%, respectively. When device logs were processed for the sine wave puffing profile, the percent of puff duration for the 15 devices with Virginia Tobacco and Polar Menthol formulation were 76.9% and 77.3%, respectively. For both the square wave and sine wave puff profiles the simple algorithm resulted in slight improvements in percent of puff duration. More importantly, the number of device activations exactly matched the number of puffs from the SM450 puffing machine, with no anomalous device activations noted for the square and sine wave puffing profiles. This suggests that algorithm-processed device logs can be used as an approximation to traditional topography measures, subject to the caveats noted above. The gap wave regimen device logs were not tested since there was an intentional 0.5-s gap between the two portions of the gap wave regimen.

The flowrate between 7.5 and 10 cm³/s resulting in the pressure drop required to activate the JUUL2® device of 95 and 150 Pa (0.96–1.53 cm water) is approximately half of the flowrate reported for the CReSSmicro™ add-on device of 20 cm³/s (5). It is similar to the lowest flowrate (10 cm³/s) used to evaluate the CReSS Pocket and SPA-M add-on devices (15) and calibrate the second generation wPUM™ add-on device (19). The flowrate between 7.5 and 10 cm³/s resulting in the pressure drop threshold required for JUUL2® device activation is also similar to the minimum flow rate (8.33 cm³/s) required to activate puffing for the Vuse Solo ENDS product (20) used in the PUB add-on device (11). Using a 3-s square wave puffing profile, the JUUL2® device activation duration was 95% or only 150 milliseconds different from the actual puff duration. In comparison the CReSS Pocket and SPA-M add-on devices with three different e-cigarettes were generally $\pm 10\%$ of the actual puff duration with the CReSS Pocket add-on device in some cases being up to 18% shorter (15), while the puff duration accuracy for the wPUM™ add-on device is ± 100 microseconds (19). Using a 55 mL-puff volume in a sine wave profile the CReSS Micro add-on device measured on average only 66.5% of the puff duration compared to an average 76.4% for the JUUL2® System without the simple algorithm and 77.1% using the simple algorithm. Using a bell-shaped puffing profile the CReSS Pocket add-on device puff duration was up to 22% less than the actual puff duration while the SPA-M add-on device was within $\pm 10\%$ of the actual puff duration (15).

Several publications have indicated challenges with topography data, noting that it should be reviewed for accuracy prior to analysis (5, 11, 15). OLDHAM *et al.* (5)

noted a significant number of false puffs when the sensitivity setting of the CReSS Mirco device was increased, precluding device testing using this setting. MIKHEEV *et al.* (15) described numerous recording anomalies including various lengths of data signal dropouts and data storage limitations with the CReSS Pocket device and single puffs being split into multiple puffs by the SPA-M device. UNDERLY *et al.* (11) described analyzing downloaded topography data for false puffs that were defined as puffs with less than 0.5 seconds and removing these false puffs from further analysis. HILER *et al.* (21) described combining puffs that were separated by less than 0.1 s and any puffs less than 0.3 s were deleted when analyzing data from a custom-built topography device. The JUUL2[®] laboratory testing was limited so no data storage limitations were encountered. Use of a square, sine, and gap wave puffing regimens resulted in the JUUL2[®] System splitting a small percentage of single puffs into two puffs, which based upon the previously reported work (5, 11, 15) and sensitivity of the JUUL2[®] device, was not surprising. A simple post-processing algorithm completely solved this anomaly for the square and sine wave puffing profiles. Our laboratory study has several limitations including that only three puffing regimens were used and only one puff volume was used (55 mL) with each puffing regimen. The use of only three puffing regimens will not capture the variability of human puffing topography and may not be representative of human ENDS puffing topography. Although the square wave has been reported as the most representative of ENDS topography in a natural setting (22), there is not universal agreement on what puff profile is the most representative of human topography. PRASAD *et al.* (23) tested various ENDS devices and concluded that differing device characteristics (e.g., more powerful batteries, aerosolization technology, etc.) influence user puffing topography such that the values obtained from one product may not apply to others. Use of a single puff volume limited the range of the correlation of measured device pod mass loss and collected aerosol mass to the JUUL2[®] estimated aerosol mass resulting in potentially lower correlation coefficients than were seen with a wider range of measured device mass loss or aerosol collected mass reported in a recent clinical trial (18). A further limitation in this comparison is that use of a filter to estimate the aerosol mass neglected gas phase constituents that were not collected. Another limitation was testing 5 devices in a puffing regimen simultaneously rather than using a more complex randomization scheme. Although this simplified the laboratory testing approach, potentially reduced laboratory errors and reduced laboratory testing time, in some cases order of puffing regimen testing was found to be a statistically significant factor in JUUL2[®] device activation duration. Finally, due to our use of only one lot of Virginia Tobacco and Polar Menthol filled pods in this work, conclusions regarding their differences should be interpreted with caution. In conclusion, our laboratory study demonstrated that selected JUUL2[®] device measured parameters can be translated into classical puffing topography variables (i.e., number of puffs and puff duration), and can provide an estimated aerosol mass generated by the JUUL2[®] System.

SUPPLEMENTARY INFORMATION

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AUTHOR CONTRIBUTIONS

MJO: Conceptualization, study design, data analysis, wrote original draft, reviewing, editing and approval of final manuscript.

DKC: Conceptualization, study design, project administration, reviewing, editing and approval of final manuscript.

QL: Study design, statistical analysis, reviewing, editing and approval of final manuscript.

NF: Data acquisition and analysis, project administration, reviewing, editing and approval of final manuscript.

BS: Data curation and analysis, project administration, reviewing, editing and approval of final manuscript.

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IGG: Conceptualization, funding, study design, reviewing, editing and approval of final manuscript.

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CONFLICTS OF INTEREST

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