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## ▶ To cite this version:

Jérémie Pourchez, Sandrine Parisse, Gwendoline Sarry, Sophie Perinel-Ragey, Jean-Michel Vergnon, et al.. Impact of power level and refill liquid composition on the aerosol output and particle size distribution generated by a new-generation e-cigarette device. Aerosol Science and Technology, 2018, 52 (4), pp.359 - 369. 10.1080/02786826.2017.1422857 . hal-01899515

**HAL Id: hal-01899515**

**https://hal.science/hal-01899515v1**

Submitted on 19 Oct 2018

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**Impact of power level and refill liquid composition on the aerosol output and particle size distribution generated by a new-generation e-cigarette device**

**Jérémie Pourchez**[1] , **Sandrine Parisse**[2,3], **Gwendoline Sarry**[1], **Sophie Perinel-Ragey**[2,4] , **Jean-Michel Vergnon**[2,5], **Anthony Clotagatide**[2,3], **Nathalie Prévôt**[2,3].

[1] Univ Lyon, IMT Mines Saint-Etienne, Centre CIS, INSERM, SainBioSE, F - 42023 Saint-Etienne, France. .

[2] Univ Lyon, Univ Jean Monnet, INSERM, SainBioSE, F - 42023 Saint-Etienne, France

[3] CHU Saint-Etienne, Department of Nuclear Medicine, Saint-Etienne, F-42055, France.

[4] CHU Saint-Etienne, Medical-Surgical Intensive Care Unit, Saint-Etienne, F-42055, France.

[5] CHU Saint-Etienne, Department of Chest Diseases and Thoracic Oncology, Saint-Etienne, F-42055, France.

*Corresponding author: Jérémie POURCHEZ

École Nationale Supérieure des Mines de Saint-Etienne

158 cours Fauriel, CS 62362

42023 Saint-Etienne Cedex 2. FRANCE.

Email address: pourchez@emse.fr - Telephone number: +33477420180

**Abstract**

The new high-power Electronic Nicotine Delivery System (ENDS) can generate aerosols with higher nicotine concentrations than older ENDS . Aerosol particle sizes affect deposition patterns and then plasma nicotine levels in vapers. Consequently, understanding the factors influencing particle size distribution of high-power ENDS is relevant to assess their performance in terms of nicotine delivery. The particle size distribution and the aerosol output (aerosol mass) were measured using cascade impactors. The effects of the refill liquid composition (80% PG/20% VG *vs.* 80% VG/20% PG; PG refers to propylene glycol and VG to vegetable glycerin) and the power level of the battery (from 7 W to 22 W) were investigated. The aerosol output increases significantly with the power level following a logarithmic law. The PG/VG ratio also has an impact on the aerosol output. The higher the VG content in the refill liquid, the higher is the aerosol output. Besides, particle size distribution is positively related to the power level, following linear correlations between the mass median aerodynamic diameter (MMAD) and the power level in the range of 7-22 W. A moderate impact of the PG/VG ratio on size distribution is equally observed. Changes in the power level allow the transition between a dominant mode with MMAD from 613 nm to 949 nm. We demonstrated that the power level can strongly change the aerodynamic properties of high-power ENDS, especially at high voltage. Associated with the aerosol nicotine level assessment, MMAD could be determined as a means for comparing ENDS devices and nicotine delivery.

**Key-words**

Electronic cigarettes, smoking cessation, ENDS, aerosol, MMAD, cascade impactor

## INTRODUCTION

Electronic cigarettes or electronic nicotine delivery systems (ENDS) have recently exploded onto the smoking cessation scene as a newer way to deliver nicotine. Although the primary marketing focus is the use of ENDS as an alternative nicotine source, ENDS are used by some as a new nicotine replacement therapy (NRT) (Breland et al. 2014). By delivering aerosol nicotine, the ENDS devices have the potential to serve as a substitute for smoking cigarettes and thus as a harm reduction tool. While vaping may not be harmless, ENDS have demonstrated a much more favorable toxicological profile than cigarettes since most of the chemicals causing smoking-related disease are absent (Public health England 2015). Indeed, contrary to smoking cigarettes, ENDS do not contain tobacco and deliver nicotine-containing aerosol without any combustion.

ENDS, in all their shapes and technical designs, have already been present on the market for a decade. Basically, ENDS are battery-powered personal vaporizers. The main components are a mouthpiece, a tank for the refill liquid, a heating element, a battery and sometimes a microprocessor. The physical principle common to all ENDS is a small heating element that vaporizes a refill liquid to generate an aerosol (called “vape”). This refill liquid (called “e-liquid”) contains nicotine, humectants (such as glycerol and propylene glycol) and in the vast majority of cases, other ingredients in small quantities (water, ethanol, flavorings, etc.) (Breland et al. 2014). Since its emergence in the 2000s and throughout its relatively short history, the ENDS industry has continuously evolved. New technologies were quickly developed, thanks to various innovations and technological breakthroughs. Thus, many products have constantly been brought to market. These rapid developments in manufacturing induce a great variability of ENDS in terms of power source voltage, heating element resistance, and other technical features.

ENDS typically fall into at least three categories, from small cigarette-like devices (first-generation) to new-generation devices including high-capacity batteries with electronic circuits that provide high energy to a refillable atomizer (second- and third-generation). The third-generation of ENDS (also called advanced personal vaporizers**)** has only recently appeared. These devices encompass a wide variety of product types and brands. They have stronger batteries, variable setting features and tank-type atomizers. The tank-type atomizers consist of a chamber that contains the refill liquid and a wick-coil head. These devices generally incorporate control hardware that lets the user modify the voltage and/or wattage of the battery.

A new trend emerging in the ENDS users (called "vapers") community consists of using variable voltage/wattage ENDS associated with regulated mods (*i.e.*, modified parts in the frame of the concept of rebuildable atomizers) to apply high energy. Recently, a study underlined specific features when "*v*aping" at high voltage (Farsalinos et al. 2016). High-power ENDS can deliver high levels of aerosol nicotine (Farsalinos et al. 2016). This newer technology of ENDS can generate at high voltage aerosol nicotine in a much wider range of concentrations (2.72-10.61 mg of nicotine/20 puffs) than older ENDS devices using cartomizers (1.01-3.01 mg of nicotine/20 puffs) but also tobacco cigarettes (1.76-2.20 mg of nicotine/cigarette). Thus, high-power ENDS could be a promising technology to raise nicotine absorption and plasma nicotine levels. To relate exposure to biological effects (such as nicotine absorption), it is crucial to assess the deposition pattern of inhaled particles (Pichelstorfer et al. 2016). Many parameters are needed (*e.g.*, aerodynamic diameter, composition of the particles, composition of the vapor phase, parameters of the mixture such as vapor pressure, surface tension, activity coefficient, etc.) to obtain a proper description of the deposition of the dynamic aerosols in the respiratory tract. In particular, the accurate determination of the particle size distribution is essential to predict aerosol deposition

(Sosnowski and Kramek-Romanowska 2016). However, aerodynamic features of the aerosol generated by high-power ENDS remain poorly known. Against this background, this work describes the impact of power level and refill liquid composition on aerosol features generated by recent high-power ENDS. Aerosol features were assessed in terms of Mass Median Aerodynamic Diameter (MMAD), Count Median Aerodynamic Diameter (CMAD), and aerosol output (*i.e.*, the mass of airborne refill liquid per volume of aerosol generated by the ENDS). The purpose of this work is to remedy the lack of studies addressing:

(i) The impact of the aerosol dilution ratio (from 0 to 6) prior to particle size distribution measurement.

(ii) The effects of two propylene glycol (PG)/vegetable glycerin (VG) ratios (80% + 20% *vs.* 20% + 80%) on particle size distribution and aerosol output.

(iii) The influence of the power level of the battery (from 7 W to 22 W) on particle size distribution and aerosol output.

## METHODS

### Materials and experimental design

A recent technology of high-power ENDS was used (purchased in March 2016 from a local store and online distributor). This ENDS device was made up of a variable lithium-ion battery (iStick 30W, Eleaf) and an atomizer (GS Air, Eleaf). Under the support of a 2200 mAh battery capacity, the battery produces performance between 2 V-8 V (or 5 W-30 W). The atomizer emphasizes a dual-coil atomizer head. The main technical features of the atomizer are a refill liquid capacity of 2.5 mL, a voltage in the 3.5 V-5.5 V range, a wattage in the 8 W-20 W range and a resistance of 1.5 ohm. A thread-adjustable air inflow allows the changing of the airflow resistance by adjusting the tightness of the screw. Prior to performing experiments, batteries were fully charged. In addition, the maximum air inflow position was fixed, and the electrical resistance of the atomizer was checked at 1.5 ± 1 ohm. Atomizers were regularly changed to avoid bias and to avoid using a degraded and/or dirty coil. All combinations of vaping parameters allow the limitation of the overheating of the refill liquid (*i.e.*, the so-called "dry puff phenomenon"). Because it results in a strong unpleasant taste, the dry puff phenomenon can easily be detected by vapers and avoided in real life practice by reducing the power levels and the puff duration (Farsalinos et al. 2015b).

Two different compositions of refill liquid were used corresponding to 80% propylene glycol (PG) + 20% vegetable glycerin (VG), noted as 80PG/20VG, and 20% PG + 80% VG, noted as 20PG/80VG. These formulations were prepared in the laboratory from commercial solutions available on the market to do the refill liquid oneself (100-VG and 100-PG base, A&L, France). The refill liquids used for this study were nicotine-free and flavor-free to exhibit only the impact of the PG/VG ratio on the aerodynamic features. The rationale in selecting the compositions of the refill liquid (80/20 and 20/80) and the power level of the ENDS battery (from 7 to 22 W) is to cover a wide range including the most popular parameter

combinations used by vapers. Finally, although the nominal capacity of the tank-type atomizer is 2.5 mL, the atomizer was filled with 2 mL of the prepared solution to avoid potential overfilling. For all measurements, the ambient conditions were as follows: temperature of 23 ± 2 °C, relative humidity from 45% to 75%, pressure from 86.0 kPa to 106.0 kPa.

**Particle size distribution (mass distribution and MMAD): experimental conditions using a high flow rate and measuring aerosol aged for a few seconds**

Aerosol particle sizing was defined in terms of Mass Median Aerodynamic Diameter (MMAD). Our objective was to compare two measurement strategies (mass distribution *vs.* count distribution using the same cascade impactor design) to examine the impact of experimental biases due to particle evaporation (because of high dilution ratios) or particle coagulation (because of long residence times between aerosol sampling and measurement). The DLPI setup was used (Dekati Low-Pressure Impactor; Dekati Ltd., Finland) to quantify the mass distribution and MMAD. In cascade impactors, the aerosolized particles are impacted on different stages depending on their inertia related to their aerodynamic diameter. This device operates with an air flow of 10 $L \cdot min^{-1}$ and allows the collection of nebulized particles from 7 nm to 10 µm in 12 size fractions. The DLPI design consists of a 12-stage cascade low pressure impactor leading to the determination of gravimetric size distribution. An in-house interface was developed to reproducibly introduce a puff that was well-controlled for duration and volume into the inlet of the impactor. Based on the work of Bertholon et al. (Bertholon et al. 2013), our interface was composed of a 3-L syringe (Hans-Rudolph, USA) acting as a reservoir during the puffing and connected to the DLPI cascade impactor and the ENDS (Figure 1). Aerosol sampling was carried out considering a 4-s puff (with a flow rate of 500 mL/s) and various dilution ratios from 0 to 6 (*e.g.*, a dilution ratio of 1.5 corresponds to 2 L of aerosol generated by the ENDS diluted in 1 L of ambient air initially present in the 3-L

syringe). At the end of the 4-s puff duration, the volume of aerosol contained in the syringe was injected into the DLPI setup using the 10 $L \cdot min^{-1}$ flow rate of the cascade impactor without any other air dilution. However, the main drawback of this protocol is having a very disparate flow rate (500 mL/s) compared to the more usual flow rate (10-50 mL/s) used by vapers in real-life practice. The main advantage of using this high flow rate is to obtain a significant mass of aerosol during a short sample residence time to be able to determine the aerosol mass distribution, thanks to the size-fractionation through the DLPI setup. We must keep in mind that the ENDS aerosol is highly dynamic and unstable, showing a half-life limited to approximately 15-30 seconds, depending on the devices tested (Bertholon et al. 2013). Four aerosol dilution ratios (from 0 to 6) applied during the sampling step were tested to investigate their impact on changes in the particle size distribution.

According to European standard method NF EN 13544-1, the MMAD of nebulized particles was determined by tracing the cumulative curve of mass *vs.* size. The cumulative mass was obtained using a gravimetric method consisting of weighing each DLPI stage after the experiments using an electronic precision balance (Adventurer Pro, OHAUS, USA). The MMAD was interpolated from the particle size distribution curve by noting the particle size at which the line crosses the 50 % mark. The geometric standard deviation (*i.e.*, GSD) should be calculated only if the aerosol was log-normally distributed. The calculation of GSD was performed by noting the particle size X at which the line crosses the 84.13 % mark and the particle size Y at which the line crosses the 15.87 % mark. Then, the GSD was calculated from the equation $X/Y^{0.5}$.

**Particle size distribution (count distribution, CMAD and resulting calculated MMAD): experimental conditions using a low flow rate and freshly generated aerosol**

The second measurement strategy used the ELPI set-up (Dekati Ltd., Finland). This sizing technique allows the quantification of the count distribution of the aerosol generated by high-power ENDS using the same cascade impactor used by the DLPI setup. Thus, as in the DLPI, the ELPI allows the collection of nebulized particles from 7 nm to 10 µm into 12 size fractions and operates with an air flow of 10 $L \cdot min^{-1}$ (Järvinen et al. 2014). The ELPI operating principle can be divided into three major parts: particle charging in a unipolar corona charger, size classification in a DLPI cascade impactor and then electrical detection with sensitive electrometers. Finally, the induced current of the impacted particles is measured and related to the aerodynamic cut-off diameter of the impactor stage. The results can be expressed by means of number concentrations to calculate the CMAD. Aerosol sampling was carried out considering a 3-s puff (with a flow rate of 20 mL/s) without aerosol dilution. An in-house interface was designed for puffing (Figure 2). Puffs were performed using a 60-mL syringe connected to the ENDS. This syringe was also connected to the ELPI *via* a metal United States Pharmacopeia (USP)-like artificial throat and a PTFE mouthpiece adaptor. The USP throat (height, 112 mm; width, 42 mm; internal diameter, 19 mm) was a 90° bent metal pipe with a uniform cross section with slight contractions at the inlet and a small diffuser at the outlet. The ELPI V4.0 software recorded current *vs.* time data. Experiments were performed in triplicate. Finally, CMAD and cumulative particle number distributions *vs.* aerodynamic diameter were obtained. Furthermore, the MMAD was calculated from count distribution. For log-normal distribution, the known relationship holds: $MMAD = CMAD\ exp^{3\,(\log(GSD))^2}$ (Prévôt et al. 2017).

**Aerosol output measurement**

The aerosol output is the total mass of aerosol generated by the ENDS. The aerosol output can be measured by collecting the aerosolized refill liquid that leaves the ENDS on filters or stages of the cascade impactor. In this study, the aerosol output was expressed as mg of

airborne refill liquid per liter of aerosol generated by the ENDS. Explicitly, the aerosol output was simply calculated by summing the mass of airborne refill liquid collected on the 12 stages of the DLPI for a given volume of aerosol generated by the ENDS.

## RESULTS

### Impact of the aerosol dilution ratio on MMAD using the DLPI measurement strategy (*i.e.*, a high flow rate and aerosol aged for a few seconds )

To investigate the impact of the aerosol dilution ratio during the sampling step on the particle size distribution, only the results obtained for the power level fixed at 13 W and the formulation 20PG/80VG are highlighted (Table 1 with lines in gray, Figures 3 and 4). A unimodal distribution was observed for all experimental conditions resulting in GSD from 1.45 ± 0.01 to 1.60 ± 0.05 (Table 1 with lines in gray). Particle sizes measured in the stage impactor patterns ranged from 0.382 µm to 2.39 µm. A significant impact of the dilution ratio on the MMAD and the aerosol output was shown. The impactor stage cutoff values resulted in 0.96 ± 0.4 µm of MMAD for no dilution, to 0.71 ± 0.2 µm of MMAD for a dilution ratio of 6 (Table 1 with lines in gray; see also Figure 3). A linear correlation ($y=-0.04x+0.98$, $R^2=0.96$; Figure 3) between the MMAD and the value of the dilution ratio of the aerosol generated by the ENDS was clearly observed. This decrease in both the aerosol output and the MMAD could be due to a rise in the evaporation process when the dilution ratio increases. Nevertheless, it is impossible to exclude the possibility that there is also a contribution by coagulation (higher dilution rate means less coagulation) in a given set of experimental conditions. In addition, without dilution, the aerosol output was notably lower compared to a dilution ratio of 1.5 (13.2. ± 1.0 mg/L *vs.* 18.0 ± 1.2 mg/L). All things considered, the dilution ratio of 1.5 during the sampling step appeared to be the best compromise to obtain high

aerosol output with, at the same time, unchanged MMAD compared to an ENDS aerosol that was not diluted.

**Impact of the power level on aerosol output using the DLPI measurement strategy (*i.e.*, high flow rate and aerosol aged for a few seconds )**

Figure 5 presents the aerosol output as a function of the power level of the ENDS battery ranging from 7 W to 22 W. Unsurprisingly, the power level of the ENDS appeared to be a very important parameter playing on the aerosol output generated by ENDS. As a matter of fact, a logarithmic law seems to be quite satisfactory to predict the rise of the aerosol output when the power of the battery increases (Figure 5). Second, the impact of the refill liquid composition was also demonstrated. For a given power level of the battery, a higher aerosol output was noticed using the formulation with higher VG content compared to the formulation with higher PG content (*e.g.*, at 16 W, 15.0 ± 1.7 mg/L for 80PG/20VG *vs.* 21.5 ± 1.5 mg/L for 80VG/20PG, $p = 0.0172$ (Mann-Whitney test), Figure 5).

**Impact of the power level on the particle size distribution using the DLPI measurement strategy (*i.e.*, high flow rate and aerosol aged for a few seconds)**

Figure 6 shows the impactor-collected data by means of frequency mass distribution (cumulative mass distribution available in Figures 7 and 8). Six levels of ENDS power and two formulations were investigated. Table 1 provides the particle size summary for all experimental conditions. The findings present a gradual transition of a dominant mode distributed mainly from 613 nm at 7 W to 949 nm at 22 W (Figure 6). This behavior was observed for the two VG/PG ratios studied. However, the transition from 613 nm to 949 nm seems to occur at a lower power level for the 20PG/80VG formulation compared with the 80PG/20VG formulation (*i.e.*, 10 W for 20PG/80VG *vs.* 17 W/19 W for 80PG/20VG, Figure

6). As a result, a slight increase in the MMAD was noticed when the power level rises (Table 1, see also Figure 9). A linear correlation highlighting the rise of MMAD as a function of the power level was clearly evident for the 20PG/80VG formulation (y=0.02+0.61, $R^2$=0.97; Figure 9). By contrast, two linear correlations were observed (y=0.007+0.77, $R^2$=0.95, in the range of 7-17 W; y=0.05+0.01, $R^2$=0.99, in the range of 17-22 W; Figure 9) for the 80PG/20VG formulation with a transition at 17 W. This power level at 17 W also corresponds to the transition of a dominant mode centered on 613 nm to 949 nm for the 80PG/20VG formulation.

**Impact of the power level on the particle size distribution using the ELPI measurement strategy (*i.e.*, flow rate similar to the flow rate that vapers use in real-life practice and freshly generated aerosol)**

Considering our experimental conditions (choice of ENDS device and vaping parameters such as the power range of the battery, the resistance of the atomizer, the air flow resistance adjusted on the device using the tightness of the screw), we observed that ELPI could be used for CMAD measurement of the ENDS aerosol. Our data showed a maximum count aerosol concentration measured for each puff in the range of $1.5.10^6$ to $3.10^6$ particles per cc. The maximum number concentration for each stage of the ELPI is always significantly lower than the maximum count aerosol concentration above $10^5$ particles per cc between stages 8 and 5 (*i.e.*, $D_{50}$ in the 0.26 µm-1 µm] range) and lower than the maximum count aerosol concentration above $10^6$ particles per cc for an aerodynamic diameter lower than 0.26 µm.

For real-life conditions used by vapers (fresh aerosol and realistic flow rate), the cumulative particle number distribution was measured for the 80PG/20VG formulation and 20PG/80VG formulation (Table 2, Figure 10). In good concordance with the observations made using mass distribution data obtained with the DLPI setup for an aerosol aged for a few seconds and a

high flow rate, a gradual transition of a dominant mode distributed mainly from 480 nm to 760 nm was shown when the power level rises from 7 to 22 W. A rise in the CMAD was observed between 7 and 22 W, both for the 80PG/20VG formulation and the 20PG/80VG formulation: from 0.69 ± 0.03 µm to 1.32 ± 0.06 µm and from 0.95 ± 0.05 µm to 1.28 ± 0.07 µm, respectively. To summarize, the main point is that the PG-dominant e-liquid generates smaller particles at low wattage compared to the VG-dominant e-liquid, but they converge at 22 W.

In addition, the MMAD can also be calculated from these particle number distribution data. Unsurprisingly, a rise in the calculated MMAD was also observed between 7 and 22 W, both for the 80PG/20VG formulation and the 20PG/80VG formulation, from 0.86 ± 0.04 µm to 1.52 ± 0.07 µm and from 1.21 ± 0.06 µm to 1.50 ± 0.08 µm, respectively. However, although the same tendency was clearly observed (*i.e.*, a rise of MMAD when the power increases) whatever the measurement strategy used, DLPI measurements lead to lower MMAD compared to ELPI measurements when measuring freshly generated aerosol with a realistic flow rate compared to real-life conditions. For the conditions at 13 W with a dilution ratio of 1.5, the DLPI measurements showed an MMAD of 0.92 ± 0.02 µm and 0.86 ± 0.01 µm for the 80PG/20VG formulation and the 20PG/80VG formulation, respectively. For the same power level conditions, the ELPI measurement showed an MMAD of 1.26 µm ± 0.07 and 1.27 ± 0.03 µm for the 80PG/20VG formulation and the 20PG/80VG formulation, respectively.

Finally, in contrast with the mass distribution data, the count distribution data allow the detection of a population lower than 100 nm, corresponding to approximately 10 % of the particle distribution count (Figure 10). The results allow us to distinguish that this population lower than 100 nm tends to disappear at high power levels (*e.g.*, 8.4 ± 3.5 % of the count

distribution is lower than 120 nm at 7 W *vs.* 4.3 ± 1.1 % at 22 W for the 20PG/80VG formulation; 8.6 ± 2.4 % of the count distribution is lower than 120 nm at 7 W *vs.* 0.35 ± 0.15 % at 22 W for the 80PG/20VG formulation; Figure 10).

## DISCUSSION

Determination of the particle size distribution for the ENDS aerosol is an experimental challenge because of the high hygroscopicity and volatile nature of the particulate matter (composed largely of propylene glycol, glycerin and water). These obstacles seriously complicate accurate characterizations of ENDS aerosol measurements. Sizing techniques requiring a high degree of aerosol dilution are expected to result in significant particle evaporation and then to induce potential bias with the alteration of the particle size distribution from that provided to the vaper. For example, particle evaporation during electrical mobility measurements can be the cause of the indication of artificially small particle sizes (Ingebrethsen et al. 2012). In addition, the ENDS aerosol exhibits a dynamic behavior after puffing and during inhalation. Both the particle size distribution and the particle number concentration are expected to evolve because the aerosol is subject to condensational growth, particulate matter evaporation, coagulation and particle deposition. In this study, we compared two different measurement strategies using the following: realistic or unrealistic high flow rates to generate the ENDS aerosol, the count or mass distribution to assess aerosol sizing, and analyzing fresh aerosol or aerosol aged for a few seconds. A specific advantage of the cascade impactor is that a very high dilution of the aerosol is not required before the size measurement. As a result, potential artifacts from very important particulate matter evaporation during the aerosol sampling are quite limited compared to other aerosol sizing techniques. Nevertheless, other sizing techniques could also be applied using no or low sample dilution (Mikheev et al. 2016; Cabot et al. 2013; Ingebrethsen et al. 2012).

For example, Ingebrethsen *et al.* (Ingebrethsen et al. 2012) used not only electrical mobility but also a spectral transmission method as well that does not require a dilution.

The consistency of the results obtained and the data interpretation should be discussed. Few studies have been devoted to aerosol features generated by ENDS. In addition, results found in the literature, using various types and brands of ENDS, are often contradictory.

(i) Some papers have focused on aerosol mass by avoiding the phase transition. Particle diameters of an average mass appeared in the 500-1000 nm range when inertial sizing techniques such as cascade impaction were used (487 nm to 631 nm for Alderman *et al.* (Alderman et al. 2015), from 600 to 650 nm for Bertholon *et al.* (Bertholon et al. 2013), from 600 to 800 nm for Kane and Rusyniak (Kane and Rusyniak 2015) and 1.03 µm for Lerner *et al*. (Lerner et al. 2015)). Sosnowski and Kramek-Romanowska (Sosnowski and Kramek-Romanowska 2016) found a mass median diameter of droplets emitted from ENDS at 410 nm when an optical technique such as laser diffraction was used.

(ii) Some papers have focused on the number of particles by avoiding severe coagulation. Particle diameters of an average count appeared in the 30-200 nm range when electrical mobility analyzers were used (186-198 nm for Sahu *et al.* (Sahu et al. 2013), 120-180 nm for Zhang *et al.* (Zhang et al. 2013), 120-165 nm for Fuoco *et al.* (Fuoco et al. 2014), 107-165 nm for Manigrasso *et al*. (Manigrasso et al. 2015) and 18-29 nm for Zhao *et al.* (Zhao et al. 2016)).

To summarize, regarding the measurement of ENDS particle size distributions, there are typically two different approaches. The first approach consists mainly of avoiding coagulation by applying a relatively high dilution rate while suffering from phase transition. A second approach consists mainly of avoiding phase transition by not diluting the aerosol while suffering from coagulation. We support the conclusion that both well-defined approaches

cannot tell the whole story. In our study, we compared the results obtained with two different measurement strategies using the same design for the cascade impactor. Based on both DLPI and ELPI setup measurements, the findings obtained are consistent with cascade impactor data devoted to ENDS aerosols previously published (Alderman et al. 2015; Kane and Rusyniak 2015; Bertholon et al. 2013). Indeed, using the DLPI setup, we obtained MMAD in the 0.71-1.19 µm range with the same brand of ENDS and by varying the power level and the refill liquid composition. In addition, the results obtained using the ELPI measurement strategy showed higher MMAD compared to the DLPI measurement strategy. This difference can be explained by at least 3 factors:

- The dilution of the aerosol generated by ENDS during the sampling step (dilution ratio of 1.5 for the DLPI measurements *vs.* no dilution for the ELPI measurements in real-life conditions).
- The flow rate used to generate the aerosol (extremely high flow rate of 500 mL/s for the DLPI measurements *vs.* 20 mL/s for the ELPI measurements under real-life conditions). One assumption can be that the high flow rate used to generate the aerosol for the DLPI measurements led to more evaporation compared to the realistic flow rate. The use of an extremely high flow rate (500 mL/s) compared to a more realistic flow rate (approximately 20 mL/s) used by vapers in real-life practice remains an important drawback of the DLPI measurement strategy. Indeed, our findings showed that a high flow rate can affect the particle size distribution.
- The aging time (*i.e.*, the sample residence duration in the syringe acting as a reservoir), which is longer for the DLPI measurements (approximately 10 s including the puff duration with the 3-L syringe) compared to the ELPI measurements (approximately 4 s including the 3-s puff duration with the 60-mL syringe). Regarding the dynamic behavior of the ENDS aerosol, the fact that the DLPI measurement

strategy induces the analysis of an aerosol aged for a few seconds compared to freshly generated aerosol for the ELPI measurement strategy can partially explain our results since the evaporation process can be involved during the duration of the sampling procedure using the DLPI setup, which analyzed the aerosol that had aged for a few seconds.

This work demonstrated that the DLPI cascade impactor can be used to measure the particle size distribution under controlled conditions. However, two competing processes may operate simultaneously, making DLPI data analysis very difficult. On the one hand, the high flow rate results in aerosol dilution and is therefore most likely to lead to the partial evaporation. On the other hand, long sample residence time (above 10 s) may lead to coagulation as well. Summarizing, the proposed method and results obtained do not allow us to conclude without ambiguity what the "true" ENDS aerosol size is. As a consequence, the DLPI procedure may be used for inter-comparison of ENDS devices (to compare ENDS brands, to test several power levels of a given ENDS technology, to define the impact of the refill liquid composition, etc.). Thus, the data related to particle size distribution produced in that way do not serve as a proper input for estimating a quantitative deposition in the human lung. Nevertheless, our results suggest that the frequency mass distribution changes according to power levels are not that dramatic (Figure 6), so it should not result in a meaningful effect of power levels on particle deposition in the respiratory tract. We support the conclusion that the methodology proposed to quantify parameters of the aerosol generated by an ENDS device is highly welcomed. All things considered, whatever the measurement strategy used, the same tendency and the same order of magnitude were observed considering MMAD change with vaping parameters. Indeed, it is still quite unknown how the MMAD is affected by the power level of the ENDS devices or the composition of the refill liquid. In a recent study, Zhao *et al.* (Zhao et al. 2016) measured both mainstream aerosols and the heating coil temperature to

study the effects of the ENDS design parameters and the puff topography. These authors proved that the peak heating coil temperature and the CMD increased with longer puff duration and lower puff flow rate. Even if a better knowledge of the puff topography on the aerosol features were noticed, the impact of the power level was not examined. In our study, we demonstrated that the aerosol output rose significantly when the power level increased, following a logarithmic law. Our findings are in good accordance with the literature (Talih et al. 2015; Kosmider et al. 2014). In addition, these results are consistent with empirical evidence and especially from vapers who aim for the largest aerosol production, commonly referred to as "cloud chasers". Second, particle size distribution was related positively to the power level following linear correlations.

Several studies using older technologies for the atomizer have demonstrated that plasma nicotine levels are lower when using ENDS compared to smoking tobacco cigarettes (Farsalinos et al. 2014, 2015a; Hajek et al. 2015; Dawkins and Corcoran 2014; Bullen et al. 2010). Farsalinos *et al.* (Farsalinos et al. 2016) recently investigated the potential of high-power ENDS in nicotine delivery from the refill liquid to the aerosol. These authors demonstrated that nicotine delivery was enhanced significantly with the new generation of atomizers, especially at high power levels. Some tank-type atomizers appeared to exceed tobacco cigarettes in nicotine delivery, due mainly to different design characteristics of the atomizer and the power delivery potential of the battery. The high levels of nicotine in the aerosol from high-power ENDS could enhance nicotine absorption. Our findings proved that even if the aerosol output of high-power ENDS increases at a high voltage (perfectly in accordance with the high nicotine delivery observed by Farsalinos *et al.* (Farsalinos et al. 2016)), this rise in aerosol output is also accompanied by an increase in the MMAD. This change in aerodynamic behavior can significantly impact aerosol deposition within the respiratory tract and ultimately nicotine absorption and plasma nicotine levels.

At present, high-power ENDS could satisfy the nicotine craving of vapers without the need to do prolonged and/or frequent puffs. However, this point cannot be simply assessed only by determining aerosol nicotine level per puff. Indeed, due to the rise of MMAD occurring at high voltage, the efficiency of the nicotine absorption can be impacted. The rate of nebulization and droplet size are well known to be critical factors in achieving nebulizer performance (Boe et al. 2001). These critical factors were assessed according to standards using cascade impactors in the case of drug delivery to the lung (*e.g.*, NF EN 13544-1 used in this study). However, specifically, the DLPI device equipment does not meet current regulatory guidelines, contrary to other inertial sizing techniques such as the Andersen Cascade Impactor (ACI) and Next Generation Impactor (NGI). We assumed that when addressing ENDS testing, combined approaches associating first the assessment of aerosol nicotine delivery (as proposed by Farsalinos *et al.* (Farsalinos et al. 2016), and second, the measurement of aerodynamic features (based on particle size distribution and MMAD determination using cascade impactors) should be carried out for inter-comparison of ENDS devices.

**CONCLUSIONS**

Focusing on recent high-power ENDS, the impact of the PG/VG ratio and the power level of the battery on aerosol features was determined. This work demonstrated that:

(i) The aerosol output significantly rose when the power level increased following a logarithmic law. The PG/VG ratio had an impact on the aerosol output. The higher the VG content in the refill liquid formulation, the higher was the mass of refill liquid found in the aerosol generated.

(ii) The mass and count size distribution were positively related to the power level, following linear correlations between MMAD and the power level in the range of 7-22 W. A moderate impact of the PG/VG ratio was observed. Changes in the

power level allow the transition between a dominant mode centered on 613 nm of MMAD to a mode centered on 949 nm of MMAD.

These findings provide a better understanding of how high-power ENDS generates particles. The protocol designed by Farsalinos *et al.* (Farsalinos et al. 2016) to measure nicotine delivery to the aerosol and the protocol designed in this work to measure MMAD (based on the standard applied to medical nebulizers) could be combined to serve for inter-comparison of ENDS devices.

**FUNDING**

There is no source of support for this study (grants, gifts, equipment or drugs) to declare.

**DECLARATION OF INTERESTS**

The authors are independent from the tobacco industry and declare no financial relationships with any organizations that might have an interest in the submitted work. Specifically, we do not have a source of support to declare from the company that sells the electronic cigarettes used for the submitted work.

**AUTHOR CONTRIBUTIONS**

Conceived and designed the experiments: JP and NP.

Performed the experiments: JP SP GS AC and NP.

Analyzed the data: JP SP GS SPR JMV AC NP.

Contributed reagents/materials/analysis tools: SP AC NP.

Wrote the paper: JP. All authors reviewed and approved the manuscript.

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Table 1: Summary of the size distribution and the aerosol output data. Experiments were performed in triplicate. MMAD refers to the Mass Median Aerodynamic Diameter. GSD refers to the Geometric Standard Deviation. The aerosol output refers to the mass of airborne refill liquid by volume of aerosol generated by the ENDS. Gray lines correspond to the impact of the dilution ratio on the main aerosol features (power level was fixed at 13 W, 20PG/80VG).

| | | **Formulation at 20PG/80VG** | | |
|---|---|---|---|---|
| **Power Level (W)** | **Dilution Ratio** | MMAD (µm) | GSD | Aerosol Output (mg/L) |
| 7 | 1.5 | 0.78 ± 0.01 | 1.62 ± 0.20 | 4.3 ± 0.5 |
| 10 | 1.5 | 0.82 ± 0.05 | 1.50 ± 0.05 | 9.7 ± 0.7 |
| 13 | 0 | 0.96 ± 0.04 | 1.45 ± 0.01 | 13.2 ± 1.0 |
| 13 | 1.5 | 0.92 ± 0.02 | 1.50 ± 0.03 | 18.0 ± 1.2 |
| 13 | 3 | 0.88 ± 0.04 | 1.60 ± 0.05 | 12.7 ± 1.5 |
| 13 | 6 | 0.71 ± 0.02 | 1.57 ± 0.14 | 9.1 ± 1.7 |
| 16 | 1.5 | 0.95 ± 0.02 | 1.45 ± 0.02 | 21.5 ± 1.5 |
| 19 | 1.5 | 1.07 ± 0.05 | 1.50 ± 0.05 | 21.0 ± 2.7 |
| 22 | 1.5 | 1.10 ± 0.06 | 1.53 ± 0.05 | 23.2 ± 1.3 |
| | | **Formulation at 80PG/20VG** | | |
| **Power Level (W)** | **Dilution Ratio** | MMAD (µm) | GSD of the Mass Distribution | Aerosol Output (mg/L) |
| 7 | 1.5 | 0.81 ± 0.04 | 1.53 ± 0.04 | 5.0 ± 0.2 |
| 10 | 1.5 | 0.84 ± 0.02 | 1.60 ± 0.13 | 6.7 ± 0.9 |
| 13 | 1.5 | 0.86 ± 0.01 | 1.50 ± 0.03 | 14.0 ± 2.2 |
| 16 | 1.5 | 0.87 ± 0.03 | 1.53 ± 0.02 | 15.0 ± 1.7 |
| 19 | 1.5 | 1.02 ± 0.05 | 1.58 ± 0.06 | 19.5 ± 2.9 |
| 22 | 1.5 | 1.19 ± 0.05 | 1.50 ± 0.05 | 18.6 ± 1 |

Table 2: Summary of the count distribution data. Experiments were performed in triplicate (fresh aerosol, realistic flow rate compared to vapers). CMAD refers to the Count Median Aerodynamic Diameter. GSD refers to the Geometric Standard Deviation. The MMAD was calculated from the count distribution. For log-normal distribution, the known relationship holds: MMAD = CMAD exp [3 (log (GSD))$^2$].

| | **Formulation at 20PG/80VG** | | |
|---|---|---|---|
| **Power Level (W)** | CMAD (µm) | GSD | Calculated MMAD (µm) |
| 7 | 0.95 ± 0.05 | 1.93 | 1.21 ± 0.06 |
| 13 | 1.09 ± 0.06 | 1.65 | 1.26 ± 0.07 |
| 22 | 1.28 ± 0.07 | 1.70 | 1.50 ± 0.08 |
| | **Formulation at 80PG/20VG** | | |
| **Power Level (W)** | CMAD (µm) | GSD | Calculated MMAD (µm) |
| 7 | 0.69 ± 0.03 | 1.88 | 0.86 ± 0.04 |
| 13 | 1.12 ± 0.02 | 1.60 | 1.27 ± 0.03 |
| 22 | 1.32 ± 0.06 | 1.65 | 1.52 ± 0.07 |

FIGURE CAPTIONS:

Figure 1: Scheme of the experimental setup for the mass sizing distribution of the aerosol generated by ENDS (DLPI measurement strategy).

Figure 2: Scheme of the experimental setup for the count sizing distribution of aerosol generated by ENDS (ELPI measurement strategy).

Figure 3: Impact of different dilution ratios of the aerosol generated by the ENDS on the MMAD. The ENDS power level was fixed at 13 W, and the formulation of the refill liquid was 20PG/80VG. Experiments were performed in triplicate.

Figure 4: Impact of the dilution ratios during the sampling step on the aerosol output. The ENDS power level was fixed at 13 W, and the formulation of the refill liquid was 20PG/80VG. Experiments were performed in triplicate.

Figure 5: Impact of the power level of the ENDS battery on the aerosol output. Dilution ratio fixed at 1.5. Experiments were performed in triplicate.

Figure 6: DLPI Impactor-collected data. Impact of the power level on the frequency mass distribution for the 80PG/20VG formulation (Figure 6A) and for the 20PG/80VG formulation (Figure 6B). Experiments were performed in triplicate with an aerosol dilution ratio of 1.5. Five power levels ranging from 7 W to 22 W were tested, but only 3 power levels are used to illustrate trends.

Figure 7: DLPI Impactor-collected data for the 80PG/20VG formulation. Impact of the power level on the cumulative mass distribution. Experiments were performed in triplicate with a dilution ratio of 1.5.

Figure 8: DLPI Impactor-collected data for the 20PG/80VG formulation. Impact of the power level on the cumulative mass distribution. Experiments were performed in triplicate with a dilution ratio of 1.5.

Figure 9: Impact of the power level of the ENDS battery on the MMAD. Dilution ratio fixed at 1.5. Experiments were performed in triplicate.

Figure 10: ELPI Impactor-collected data. Impact of the power level on the cumulative count distribution of the 80PG/20VG formulation (Figure 10A) and the 20PG/80VG formulation (Figure 10B). Experiments were performed in triplicate with a dilution ratio of 1.5 (fresh aerosol, realistic flow rate used compared to vapers).