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Aerosol deposition doses in the human respiratory tree of electronic cigarette smokers

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A B S T R A C T

Aerosols from eight e-cigarettes at different nicotine levels and flavoring were characterized as particle number size distributions in the range 5.6–560 nm by FMPS and CPC. Results were used to provide dosimetry estimates applying the MMPD model.

Particle number concentrations varied between 3.26×10^9 and 4.09×10^9 part cm^{-3} for e-liquids without nicotine and between 5.08×10^9 and 5.29×10^9 part cm^{-3} for e-liquids with nicotine. No flavor effects were detected on particle concentration data. Particle size distributions were unimodal with modes between 107–165 nm and 165–255 nm, for number and volume metrics, respectively.

Averagely, 6.25×10^{10} particles were deposited in respiratory tree after a single puff. Highest deposition densities and mean layer thickness of e-cigarette liquid on the lung epithelium were estimated at lobar bronchi.

Our study shows that e-cigarette aerosol is source of high particle dose in respiratory system, from 23% to 35% of the daily dose of a no-smoking individual.

1. Introduction

Tobacco use has been recognized as the leading preventable cause of death in the world (WHO, 2008), being responsible of many deadly diseases, including cardiovascular diseases, chronic obstructive pulmonary diseases, and different types of cancers, in particular lung cancer (U.S. Department of Health and Human Services (2010)).

Recently, Electronic Nicotine Delivery Systems (ENDs), known as electronic cigarettes (e-cigarettes), have been widely commercialized as they are claimed to be a less harmful alternative to conventional tobacco cigarettes even if this hypothesis has not yet confirmed by scientific studies (Riker et al., 2012). E-liquid is a water-based nicotine solution containing propylene glycol, vegetable glycerine, water, and flavors. Liquids with different nicotine contents are commercialized (ranging from 0 to 36 mg mL^{-1}) (Flouris et al., 2013).

E-cigarettes are claimed to help smokers quit and to reduce the harmful effects of second-hand smoke (Etter, 2010). The sudden commercial success of e-cigarettes was not contemporarily supported by proper regulations as well as research activities concerning possible health effects (Gornall, 2012). Limited and not definitive studies are available only on short-term use effects (McCauley et al., 2012; Vardavas et al., 2012; Goniewicz et al., 2014; Hua et al., 2013; Marini et al., 2014), whereas data on long-term use are completely lacking. More studies are available on the possible health effects due to the components of the solution when they are considered separately. Nicotine is recognized as powerfully addictive drug with a rapid onset of action also affecting the peripheral and central nervous systems (Slotkin, 2004; Dani and Bertrand, 2007). Other components also affect human health. Bahl et al. (2012) reported cytotoxic effects of the solutions used in the e-cigarettes not addressable to the nicotine but to the concentration of chemicals employed as flavors. McCauley et al. (2012) reported the negative effects of glycerine-based solution inhalation on a woman affected by lipoid pneumonia. As regards propylene glycol, even if the European Union approved it as food additive (EC, 2008), its inhalation was recognized to increase the risk of developing asthma (Choi et al., 2010). Moreover, Wieslander et al. (2011) detected upper airway irritation in non-asthmatic subjects (e.g.

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lower airway obstruction, cough, and mild dyspnoea) due to the acute exposure to propylene glycol.

Studies aimed to characterize the e-cigarette-generated aerosol were also performed both in terms of particle chemical composition as well as particle number concentrations and size distributions (Trehy et al., 2011; Ingebrethsen et al., 2012; Schripp et al., 2012; Williams et al., 2013; Zhang et al., 2013; Fuoco et al., 2014). E-cigarettes are recognized as a new source of volatile compounds and sub-micrometric particles leading to possible high exposure of e-cigarette smokers. Particle number concentrations in the 10^9 part $\times$ cm^{-3} range were measured in the mainstream of e-cigarette aerosols.

At the best authors' knowledge, studies addressing the doses of particles from e-cigarettes deposited in the human respiratory system are still lacking. Therefore, the aim of this study is to give a contribution to fill the gap between source emission and related health effects providing dosimetry data useful to estimate both acute and long-term effects of the aerosols delivered by such devices. To this purpose, the mainstream aerosol dimensional characterization was performed and the corresponding deposited particle doses in the different airway generations were evaluated through a multiple-path particle dosimetry model based on stochastic morphometric lung description.

Since aerosol deriving from e-cigarette liquids is mainly made of droplets that are expected to dissolve as they reach the lung epithelium, not only number but also volume metric was considered. The mean layer thickness of the e-cigarette liquids on the lung epithelium was compared with the thickness of the surfactant film that covers both the alveolar and the bronchial regions. This is meaningful information because the lung surfactant is the first barrier encountered by inhaled noxious agents, and its damage leads to severe respiratory problems (Hamm et al., 1996; Hohlfeld et al., 1997; Stephanova et al., 2007).

2. Materials and methods

2.1. Experimental apparatus

A rechargeable e-cigarette model made up of a tank system was used (major details are reported in Fuoco et al., 2014). Eight different e-liquids in terms of nicotine content and flavor were tested. Concerning the flavor, liquid can be classified as: tobacco flavor (Liquid 1 and Liquid 4), e-juice flavor (Liquid 2), and herb flavor (Liquid 3). As regard the nicotine content, two nicotine concentration levels were tested for each liquid: zero (0 mg mL^{-1}) and high (14 or 18 mg mL^{-1}) nicotine concentration level. A summary of the e-liquid tested is reported in Table 1.

Measurements were performed in the European Accredited (EA) Laboratory of Industrial Measurements (LAMI) at the University of Cassino and Southern Lazio, Italy, where thermo-hygrometric conditions were continuously monitored, in order to guarantee temperature and relative humidity values equal to 20 ± 1 °C and 50 ± 10%, respectively.

Measurements of total particle number concentrations and particle size distributions were carried out for each e-liquid through a Condensation Particle Counter (CPC 3775, TSI Inc.) and a Fast Mobility Particle Sizer spectrometer (FMPS 3091, TSI Inc.), respectively. The CPC 3775 measures particle total number concentration down to 4 nm in diameter with a one-second-time resolution. It was calibrated, before the experimental campaigns, by the European Accredited Laboratory at the University of Cassino and Southern Lazio through comparison with a TSI 3068B Aerosol Electrometer using NaCl particles generated through a Sub-micrometer Aerosol Generator (TSI 3940) (Stabile et al., 2013).

The FMPS 3091 is able to measure particles size distribution in the range 5.6–560 nm through the electrical mobility technique. Particle classification and counting are performed simultaneously through several aerosol electrometers able to count particles of different sizes with a 1-s time resolution (Johnson et al., 2004).

Due to the possible high particle number concentration expected in the e-cigarette mainstream aerosol under investigation, the aerosol was diluted before entering the measuring section. To this end, a thermodilution system (two-step dilution), made up of a rotating disk thermodiluter, RDTD (model 379020, Matter Engineering AG, Hueglin et al., 1997) and a thermal conditioner (model 379030, Matter Engineering AG, Burtscher, 2005) was used. It is able to ensure a proper sample conditioning during the measurement of number distributions and total concentrations of particles emitted by the e-cigarettes, as hereinafter described. In Fig. 1 a detailed scheme of the experimental apparatus used to characterize the cigarette-generated mainstream aerosols is reported.

Table 1
List of the e-liquids investigated in this study.

E-liquid	Flavor	Nicotine concentration
Liquid 1	Tobacco: Selene	0 and 14 mg mL^{-1}
Liquid 2	e-juice: Strawberry	0 and 12 mg mL^{-1}
Liquid 3	Herb: Menthol	0 and 18 mg mL^{-1}
Liquid 4	Tobacco: Camel	0 and 18 mg mL^{-1}

2.2. Aerosol sampling

Aerosol measurements were carried out considering 2-s puff profiles. Each puff profile was performed considering four consecutive puffs with a 30-s inter puff interval. The first puff was considered a “warm up” puff as it could lead to possible errors when e-cigarettes were tested, as also reported in Ingebrethsen et al. (2012). Puffs were performed connecting the aerosol sampling line to the cigarette itself. In particular, a time-controlled switch valve was used to generate a 2-s puff (and an inter puff interval): when it was closed the room air was sampled, whereas it was opened for 2 s to perform the puff. Batteries of the e-cigarettes were fully charged prior to performing experiments.

The puffs were performed straightly connecting measurement instrument tubing to the e-cigarette mouthpiece. Before entering the measurement section (CPC or FMPS), the aerosol was flown into the thermodilution system in order to prevent measurement artifacts likely happening in the sampling process. In fact, aerosol generated by e-cigarettes was expected highly concentrated and made up of volatile gaseous compounds that could easily condense when sampled, thus significantly changing the particle number distribution and concentration under investigation (Hueglin et al., 1997; Burtscher, 2005; Holmes, 2007; Buonanno et al., 2012a). The thermodilution was performed at 37 °C in order to simulate the respiratory system temperature, whereas aerosol sampling flow rates for CPC and FMPS were set at 1.5 L min^{-1} and 10 L min^{-1}, respectively. Thus, dilution ratios equal to 1:1000 and 1:880 were chosen for CPC and FMPS, respectively, to avoid over-range measurements.

After the thermodilution process, the aerosol was flown to the CPC or the FMPS depending on whether particle number concentrations or size distributions were measured. Since the long path experienced by the aerosol before entering the CPC or FMPS, a diffusion loss correction was applied to estimate the particle losses onto the inner surface of the connecting tubing. In particular, the method proposed in Gormley and Kennedy (1949) was applied; further details about diffusion loss correction evaluation are reported in Buonanno et al. (2011a). Despite the 5.6–560 nm FMPS measurement range, particle distribution data in the range from