Measurements of electronic cigarette-generated particles for the evaluation of lung cancer risk of active and passive users

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\textbf{ABSTRACT}

Electronic cigarettes (ECs) are perceived to be safer than traditional tobacco cigarettes because of the absence of combustion processes. The use of these devices, however, exposes the users (“vapers”) and passive “vapers” to possible high concentration of fine and ultrafine particles (UFPs) which can deliver toxic and carcinogenic compounds. In the present work, an experimental campaign was carried out using dedicated instrumentation in order to characterize both the aerosol emitted from ECs and the exposure to second hand EC smoke in a typical indoor microenvironment in terms of particle number and surface area concentrations. Thus, the potential carcinogenic effects due to the inhalation of EC-generated aerosol was evaluated by means of an ad-hoc Excess Lifetime Cancer Risk (ELCR) model able to take into account for the contribution of both sub-micron and super-micron particles, referring to the particle surface area, evaluated on the basis of their solid core only, by heating the aerosol at 300 °C. To this end, literature data of toxic compounds deposited on EC-generated particles (both with and without nicotine) and typical smoking behaviours of male and female Italian vapers were considered. The results showed that the particle number concentrations in EC mainstream aerosol (2.23–2.34×10\textsuperscript{8} part. cm\textsuperscript{-3}, mode at 34 nm) are higher than that in mainstream smoke of traditional cigarettes, while surface area concentrations in mainstream EC aerosol (2.48–3.35×10\textsuperscript{10} nm\textsuperscript{2} cm\textsuperscript{-3}, at 300 °C) are lower than that in traditional mainstream cigarettes smoke. The corresponding ELCR value of mainstream EC aerosol (6.11–7.26×10\textsuperscript{-6}) is 5 orders of magnitude lower than that of mainstream traditional cigarettes smoke, and also lower than the guideline values defined by EPA and WHO. Particle number concentrations equal to 6.30–9.08×10\textsuperscript{3} part. cm\textsuperscript{-3} with bi-modal distribution (at 30 nm and 90 nm) and surface area concentrations of 5.16–5.90×10\textsuperscript{7} nm\textsuperscript{2} cm\textsuperscript{-3} (at 300 °C), respectively, were measured in second-hand aerosol of ECs, leading to extremely low values of ELCR due to the exposure to second-hand EC aerosol (1.24–2.70×10\textsuperscript{-8}).

\section{1. Introduction}

The use of electronic cigarettes (e-cigs or ECs from now on) is continuously growing because they are perceived as a safer and healthier alternative to classical combustion-based cigarettes (Farsalinos, Romagna, Tsiapras, Kyrozopoulos, & Voudris, 2014; Goniewicz, Lingas, & Hajek, 2013). Some recent estimations report that the number of electronic cigarette users all over the world is...
more than 10 million (Schoenborn & Grindi, 2015). The e-cigs are mainly composed of a mouthpiece, a liquid tank, a heating resistance and a battery. There are many e-cig types on the market, but they all work on the same operating principle, which could be described as follows: by inhaling from the mouthpiece, the user activates the electric heater through a sensor, and the liquid contained in the tank is vaporized in a fine mist of liquid droplets.

Because of the absence of tobacco leaf combustion, the e-cigs are expected to produce less harmful compounds, as the e-cig liquid formally contain only propylene glycol, vegetable glycerine, flavourings and nicotine if provided. In fact, in a recent study the long-term e-cigarette use was found to be associated with substantially reduced levels of carcinogens and toxins with respect to traditional cigarettes smoking (Shahab, Goniewicz, & Blount, 2017). The use of these devices, however, exposes the users to high concentrations of fine and ultrafine particles (UFPs, particles with diameter less than 100 nm) that could deliver toxic compounds which may be formed when the liquid comes in contact with the heating coil or already contained in the liquid itself. As found in recent papers, the exposure level in terms of UFP number concentration of mainstream aerosol can reach $10^9$ part. cm$^{-3}$ (Fuoco, Buonanno, Stabile, & Vigo, 2014), while some discrepancies were reported in literature about particle sizes, ranging from 24 to 36 nm (Schober et al., 2014) to 250–450 nm (Ingebrethsen, Cole, & Alderman, 2012). Deposited doses in the respiratory apparatus and passive exposure to sub-micrometric particles were evaluated in recent papers of (Manigrasso, Guerriero, & Avino, 2015; Manigrasso, Vitali, Protano, & Avino, 2017; Protano, Manigrasso, Avino, Sernia, & Vitali, 2016), who found that particle concentrations released by traditional cigarettes resulted four-times higher than those released by electronic and heat-not-burn devices. In addition, different toxic compounds such as metals and tobacco-specific nitrosamines (NNN-NNK), deposited on the aerosol particles, were found in some recent investigations. Using specifically designed smoking machines, Mikheev, Brinkman, Granville, Gordon, and Clark (2016), Goniewicz et al. (2014) and Farsalinos, Gillman, Poulas, and Voudris (2015) found significant amounts of As, Cr, Ni and Cd, as well as NNN and NNK in the mainstream aerosol from e-cigs, while Schober et al. (2014) found the presence of As, Cd, Cr and Ni in the aerosol emitted from e-cigs during vaping sessions of smokers in controlled environments (rooms). The presence of these compounds on particles with very small diameters, which are able to deeply penetrate and settle in the human respiratory apparatus, may cause adverse health effects. Airborne particles, in fact, were recently classified as carcinogenic to humans (IARC Group 1 carcinogenic) by the International Agency for Research on Cancer (IARC) (International Agency for Research on Cancer, 2013).

In the last few years, the e-cigs were subjected to specific legislative frameworks, which differ between countries. The European Union (EU) recently implemented regulations concerning labelling and advertising requirements for electronic cigarettes by the Directive 2014/40/EU (European Parliament, 2014), while in the US the e-cigs are subjected to the same legislation of tobacco from a recent US Food and Drug Administration (FDA) regulation (US Food and Drug Administration, 2016).

In the present work, a risk-assessment model has been applied to evaluate the potential carcinogenic effects of aerosol from electronic cigarettes by estimating the probability of cancer incidence in a population of individuals for a specific lifetime. To this end, the original Excess Lifetime Cancer Risk (ELCR) model developed by Sze-To, Wu, Chao, Wan, and Chan (2012) has been modified in order to consider the contribution of both ultrafine and coarse particles emitted from e-cigarettes. The same modified risk assessment model was successfully applied in estimating the excess of lung cancer risk for traditional cigarettes smokers (Stabile, Buonanno, Picco, & Scungio, 2017), for Italian population (Buonanno, Giovino, Morawska, & Stabile, 2015) and for people living nearby an incinerator plant in Italy (Scungio, Buonanno, Stabile, & Picco, 2016). In the authors knowledge, the ELCR model was applied for the first time in the present paper for the evaluation of the risk due to the use of electronic cigarettes.

In order to evaluate the ELCR for e-cig aerosol inhalation, data of particle concentrations and sizes were collected by means of specifically designed experimental campaign, while data of PM, heavy metals and tobacco-specific nitrosamines were selected from available literature. Two scenarios were considered: exposure to mainstream aerosol (considering data collected directly from EC mouthpiece) and second hand aerosol exposure (considering data collected in a room occupied by users vaping in controlled conditions), reproducing the same smoking patterns (puffs per e-cig and puff time) for both the cases.

2. Material and methods

In order to estimate the extra cancer risk (ELCR) due to the use of e-cigs, the risk model adopted in the present work requires the following steps: (i) obtaining data of the emitted particulate matter in terms of number, surface area and mass concentration as well as particle size distribution; (ii) identifying and quantifying the hazardous compounds contained on the emitted particles and (iii) evaluating the dose-response characteristics of each compound.

2.1. Characteristics of the emitted particulate matter

2.1.1. Experimental apparatus

The characteristics of the emitted e-cig aerosol in terms of number and surface area concentrations, as well as size distributions, were obtained through a dedicated experimental campaign performed in the period September-November 2016 at the European Accredited (EA) Laboratory of Industrial Measurements (LAMI) of the University of Cassino and Southern Lazio (Cassino, Italy). For the measurements, the following instrumentation was used:

- Condensation Particle Counter (CPC model 3775, TSI Inc.) able to measure total particle number concentration down to 4 nm in diameter with a one-second time resolution;
- Fast Mobility Particle Sizer spectrometer (FMPS model 3091, TSI Inc.) able to measure particles size distribution and total concentration in the range 5.6–560 nm through an electrical mobility technique with a one-second time resolution;
thermo-dilution system made up of a Rotating Disk Thermodiluter (RDTD model 379020, Matter Engineering AG) and a Thermal Conditioner Air Supply (model 379030, Matter Engineering AG);

- flow meter (model 4410, TSI Inc.) to measure the flow rates in the sampling line connecting the e-cigs to the instruments.

Before the measurements, the CPC was calibrated by comparison with a TSI 3068B Aerosol Electrometer, using NaCl particles generated through a Submicrometer Aerosol Generator (model 3940, TSI Inc.) (Buonanno, Dell’Isola, Stabile, & Viola, 2009; Stabile, Trassierra, Dell’Agli, & Buonanno, 2013). Small artificial particle modes, resulting from measurement artefacts due to particle evaporation during high aerosol dilutions, were corrected in order to avoid overestimation of the particle number concentrations (Fuoco et al., 2014).

2.1.2. Measurements of particle characteristics in the mainstream aerosol

In Fig. 1 the scheme of the experimental apparatus is reported. A new (unused) rechargeable e-cig filled with a mint-flavoured liquid with two levels of nicotine (0 mg ml\(^{-1}\), and 12 mg ml\(^{-1}\)) was used. The e-cig has been cleaned with deionized water after each test in order to avoid liquid contamination and fully charged before each experiment.

For the measurements of the mainstream aerosol, the EC was connected to the measurement line by means of a time-controlled switch valve. In order to avoid measurement artefacts due to the highly concentrated aerosols, that can lead to the nucleation of new particles or the growth of existing ones from the condensation of volatile gaseous compounds, a thermo-dilution system was used (Burtscher, 2005; Hueglin, Scherrer, & Burtscher, 1997). Through the thermo-dilution system, the aerosol was flown at 37 °C in order to simulate the respiratory apparatus temperature, and 300 °C in order to evaluate the volatility of the particles. The aerosol from the ECs mouthpiece was sampled from the thermo-dilution system at a fixed flow rate of 1 l min\(^{-1}\), with a 2 s puff and 30 s inter-puff profile. Flow rates were checked through the Flow meter TSI 4410. After the dilution process, the aerosol was sampled by the CPC (at flow rate of 1.5 l min\(^{-1}\)) or the FMPS (at flow rate of 10 l min\(^{-1}\)) depending on whether particle number concentrations or size distributions were measured. The CPC and FMPS measurements were not performed simultaneously, while 10 measurements for each liquid and for each instrument were made (10 measurements for CPC and 10 measurements for FMPS, replicated using liquid with and without nicotine).

2.1.3. Measurements of particle characteristics in the second-hand aerosol

In order to measure the second-hand aerosol exposure, measurements were performed in a 40 m\(^3\) naturally ventilated room whose air exchange rate (AER) has been calculated by means of a CO\(_2\) decay test performed on the basis of the procedure proposed by He, Morawska, Hitchins, and Gilbert (2004) using a Testo - Ambient CO\(_2\) probe, and burning incense sticks inside the room. Five AER measurements were performed and the resulting average AER was 0.2 h\(^{-1}\): this value represents the typical ventilation rate of an Italian naturally ventilated building (d’Ambrosio Alfano, Dell’Isola, Ficco, & Tassini, 2012; Stabile, Dell’Isola et al., 2016). The CPC and the FMPS have been placed inside the room, sampling the ambient air for the entire duration of the vaping session at 1.5 l min\(^{-1}\) and 10 l min\(^{-1}\), respectively. The room was occupied by one user performing a vaping session of 10 min (corresponding to the duration of two traditional cigarettes) at puff rate varying from 0.7 to 1.5 puffs min\(^{-1}\). The instrumentation was placed in different position and at different distances from the source (vaper) in order to take into account the spatial variability of the particle concentration inside the room.

The particle diffusion loss onto the inner surface of the tubing was corrected applying the method proposed by Gormley and Kennedy (1949). Finally, assuming as spherical the particle cores on the basis of the findings reported by Johnson et al. (2014), the surface area concentrations were evaluated from the above-mentioned particle number distributions.
2.2. Literature analysis for IARC Group 1 carcinogenic compounds data

The identification and quantification of the hazardous compounds deposited on the emitted particles were assessed from data available in literature at the time of writing. It should be pointed out, anyway, that the literature is characterized by inconsistent and contradictory data since an harmonized measurement methodology is still missing. The most evident discrepancies are relative to types and operating parameters of e-cigs, environmental conditions, puffing protocol etc. (Allen et al., 2016; Jensen, Luo, Pankow, Strongin, & Peyton, 2015; Kosmider et al., 2014). In the light of that, the data of hazardous compounds used in the present work were taken from a limited number of papers reporting methodology and measurement conditions similar that reported in Section 2.1 (direct sampling from the EC for mainstream aerosol and ambient sampling for second-hand aerosol).

In Table 1 the hazardous compounds measured in emission from e-cigs and in second-hand aerosol are reported. The values of PM10 and Cd for second-hand aerosol were used in order to obtain TPM and Cd concentration of mainstream aerosol without nicotine, since these values were not available in literature at the time of writing. Finally, it should be pointed out that also the PM10 and TPM data are obtained by the literature survey, as showed in Table 1, and not measured through the experimental campaign.

2.3. Dose-response characteristics evaluation

On the basis of particle number, mass and surface area concentration data, the doses received by a vaper expressed as sum of surface area ($\delta_S$, alveolar and tracheobronchial contributions) and PM10 ($\delta_{PM10}$) were evaluated as:

$$\delta_S = \sum_{D=1}^{10\mu\text{m}} DF_{Alv+TB}(D) \frac{dS}{d\log D} dD$$

$$\delta_{PM10} = \sum_{D=1}^{10\mu\text{m}} DF_{Alv+TB}(D) \frac{dM}{d\log D} dD$$

where $dS/d\log D$ and $dM/d\log D$ are the particle surface area and mass concentrations of a certain particle diameter ($D$), and $DF_{Alv+TB}$ represents the deposition fraction in the alveolar and tracheobronchial regions of the lungs, as a function of the particle diameter ($D$), adapted from the International Commission on Radiological Protection (1994), and considered for adults in sitting activity, males and females (tidal volume of 0.54 m$^3$ h$^{-1}$ for male and 0.39 m$^3$ h$^{-1}$ for female).

The relationship between dose and response is defined, in terms of compound mass, by the U.S. Environmental Protection Agency (2005) as cancer slope factor (SF). SF represents the increase of the risk (in percent) to develop cancer due to the exposure to a given dose of a toxicant (expressed as mg of toxicant per kg of body weight) every day for a lifetime (conventionally assumed to be 70 years). The SF values for the Group 1 carcinogenic compounds is provided by the Office of Environmental Health Hazard Assessment (2009) and are reported in Table 2.

SFs for particle phase PAHs are not reported because they were not found in e-cig aerosols (Saffari et al., 2014), while unquantifiable or below LOD levels of dioxins/furans were observed in measurements of Margham et al. (2016). The contribution of PAHs and dioxins/furans to the ELCR was then not evaluated.

Table 1
Hazardous compounds measured in the mainstream aerosol (MS) and second-hand aerosol (SH) of ECs, as found in scientific literature.

<table>
<thead>
<tr>
<th>Substance with nicotine</th>
<th>Substance without nicotine</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AsMS [ng puff$^{-1}$]</td>
<td>0.1282</td>
<td>Mikheev et al. (2016)</td>
</tr>
<tr>
<td>NMS [ng puff$^{-1}$]</td>
<td>0.3994</td>
<td>Mikheev et al. (2016)</td>
</tr>
<tr>
<td>As [ng puff$^{-1}$]</td>
<td>1.2333</td>
<td>Williams, To, Bozhilov, and Talbot (2015)</td>
</tr>
<tr>
<td>N [ng puff$^{-1}$]</td>
<td>–</td>
<td>Goniewicz et al. (2014)</td>
</tr>
<tr>
<td>CdMS [ng puff$^{-1}$]</td>
<td>0.6424</td>
<td>Goniewicz et al. (2014)</td>
</tr>
<tr>
<td>NNNMS [ng puff$^{-1}$]</td>
<td>0.0136</td>
<td>Goniewicz et al. (2014)</td>
</tr>
<tr>
<td>NNKMS [ng puff$^{-1}$]</td>
<td>0.2247</td>
<td>Farsalinos et al. (2015)</td>
</tr>
<tr>
<td>TPMMS [mg puff$^{-1}$]</td>
<td>0.0587</td>
<td>Farsalinos et al. (2015)</td>
</tr>
<tr>
<td>TPM [ng puff$^{-1}$]</td>
<td>1.2333</td>
<td>Williams, To, Bozhilov, and Talbot (2015)</td>
</tr>
<tr>
<td>CdSH [ng m$^{-3}$]</td>
<td>31.27</td>
<td>Gillman, Kislner, Stewart, and Paolantonio (2016)</td>
</tr>
<tr>
<td>PM10SH [µg m$^{-3}$]</td>
<td>11.76</td>
<td>Zhao, Pyrgiotakis, and Demokritou (2016)</td>
</tr>
</tbody>
</table>

Table 2
Carcinogenic characteristics of the main IARC Group 1 pollutants in the e-cig aerosol.

<table>
<thead>
<tr>
<th>As</th>
<th>Cd</th>
<th>Ni</th>
<th>NNN</th>
<th>NNK</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF, - inhalation unit risk EPA (kg d mg$^{-1}$)</td>
<td>$1.51 \times 10^4$</td>
<td>$6.30 \times 10^3$</td>
<td>$9.10 \times 10^{-1}$</td>
<td>$1.40 \times 10^0$</td>
</tr>
</tbody>
</table>
Table 3  
Average data of human smoking patterns as reported by (Zacny & Sitzer, 1988) used as reference values for ECs vapers.

<table>
<thead>
<tr>
<th>Puff volume, ( V_{\text{pu}} ) (cm³)</th>
<th>Puffs per cigarette, ( N_{\text{cf}} )</th>
<th>Puff time, ( t_{\text{pf}} ) (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>42.5 ± 9.3</td>
<td>11.5 ± 2.2</td>
<td>1.8 ± 0.4</td>
</tr>
</tbody>
</table>

2.4. Lung cancer risk assessment for direct vaping and second-hand aerosol exposure

The contribution of both sub-micron and super-micron particles in the ELCR calculation was addressed by modifying the original model of Sze-To et al. (2012) by using two different particle metrics: surface area and PM10. Since the particles emitted by electronic cigarettes are mainly composed by liquid droplets with a solid core, in order to correctly evaluate the surface area contribution to the ELCR, the aerosol was conditioned at 300 °C by means of the thermo-dilution system reported in Section 2.1.1, referring the surface area only to the solid core of the particles.

The contribution of each pollutant is evaluated on mass-based cancer potency, so the particle surface area-based cancer potency was referred to the mass by using a coefficient, \( \epsilon_{fi} \), to correlate the particle surface area-based cancer potency of the pollutant to the typically used mass-based SF. The ELCR equation for each pollutant for 70 years is:

\[
ELCR_i = \frac{SF_i \cdot m_{i-\text{EC}}}{BW \cdot PM10_{\text{EC}}} \cdot \left( \epsilon_{fi} \cdot \delta_S + \delta_{\text{PM10}} \right)
\]  

where \( ELCR_i \) is the excess lifetime cancer risk of the i-th pollutant, \( SF_i \) is the inhalation slope factor used to describe the mass-based cancer potency of the i-th pollutant, \( BW \) is the body weight, \( m_{i-\text{EC}} \) is the mass concentration of the i-th pollutant condensed on the aerosol particles, \( PM10_{\text{EC}} \) is the PM10 concentration, \( \delta_S \) and \( \delta_{\text{PM10}} \) are the particle surface area and PM10 deposited doses. The total ELCR was then calculated as the sum of the \( ELCR_i \) for each pollutant. The \( \epsilon_{fi} \) coefficient has a value of \( 6.60 \times 10^{-13} \) mg nm⁻², obtained experimentally by Sze-To et al. (2012) through risk assessment for heavy duty emission exposure. As reported by Sze-To et al. (2012), since the \( \epsilon_{fi} \) coefficient depends mainly on the physical size of the particles, it can be used for different types of particulate matter, and then it was used without other simplifying assumptions in the present study.

The ELCR for the exposure scenario corresponding to the direct inhalation of the aerosol from EC is obtained considering data of smoking habits for traditional cigarettes: smoking patterns (Table 3) and cigarette consumption for Italian adults (Table 4). The ELCR for an Italian vapor was then calculated as:

\[
ELCR = ELCR_{i-puf} \cdot N_{\text{pu}} \cdot N_{\text{EC}}(Y_{\text{start}} - Y_{\text{quit}})/70
\]  

where \( ELCR_{i-puf} \) represents the ELCR per puff per single day, obtained by multiplying \( \delta_S \) and \( \delta_{\text{PM10}} \) in Eq. (3) by the puff volume, \( V_{\text{pu}} \), \( N_{\text{pu}} \) is the puff number per e-cigarette, \( N_{\text{EC}} \) is the number of e-cigarette smoked per day, \( Y_{\text{start}} \) and \( Y_{\text{quit}} \) are the ages of start and end of smoking, respectively. Average data of cigarette smoking among Italian adults, reported in Table 5, were obtained from the Italian statistical and opinion research company named DOXA on 2015 (http://www.iss.it/binary/fumo4/cont/Doxa_2015.pdf).

As regards the exposure scenario of people inhaling second-hand aerosol, the ELCR was evaluated directly from Eq. (3). In this case, the same SFs used for mainstream aerosol were considered, while the particle number concentrations and size distributions inside the room were evaluated from the trends measured during the vaping session following three steps: (i) background concentrations inside the room before vaping; (ii) measurements of the above described particle characteristics throughout the duration of the vaping session; (iii) further after-vaping measurements in order to evaluate the particle concentration decay. The particle number concentration and size distribution considered are those corresponding to the median values for the whole duration of the experiment. For each test, three measurements were performed using the instrumentation reported in Section 2.1.1. For the PM10 concentration in the room, the values reported in Table 1 were considered. Finally, the exposure time was evaluated considering the smoking patterns reported in Tables 3 and 4.

The ELCR for both the direct inhalation and second-hand aerosol exposure, was evaluated as the most probable value through a Monte Carlo method (Hammersley & Handscomb, 1964) applied by varying the input data of the model between the available or measured values (hazardous compound concentrations, particle number and size distributions, surface area, PM10, vaping patterns and ECs consumption).

Table 4  
Data on cigarette smoking among Italian adults, used as reference values for ECs vapers.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Cigarette consumption, ( N_{\text{cf}} ) (cigarette day⁻¹)</th>
<th>Age of starting smoking, ( Y_{\text{start}} ) (years old)</th>
<th>Age of quitting smoking, ( Y_{\text{quit}} ) (years old)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>14.1</td>
<td>17.0</td>
<td>42.4</td>
</tr>
<tr>
<td>Female</td>
<td>31.8</td>
<td>19.1</td>
<td>42.3</td>
</tr>
</tbody>
</table>
3. Results and discussions

3.1. Particle emission characteristics

In Table 5 the particle characteristics in terms of number and surface area concentrations (average and standard deviation values) are reported for mainstream and second-hand aerosol.

As shown, average number concentrations of $2.23 \times 10^8$ and $2.34 \times 10^8$ part. cm$^{-3}$ were measured in the mainstream aerosol for ECs with and without nicotine, and of $6.30 \times 10^3$ and $9.08 \times 10^3$ part. cm$^{-3}$ in the second-hand aerosol for ECs with and without nicotine, respectively. From the data showed in the Table it can be seen that particle number and surface area concentrations are higher in e-cigs with nicotine, in both mainstream and second-hand aerosol. The values of particle number concentrations in the mainstream aerosol are one order of magnitude lower than that measured for e-cigs by Fuoco et al. (2014) in similar conditions, due to the different liquid used. The values of surface area concentration, instead, were found equal to $5.22 \times 10^5$ and $6.99 \times 10^5$ µm$^2$ cm$^{-3}$ in the mainstream aerosol with and without nicotine, and equal to $5.90 \times 10^1$ and $3.51 \times 10^1$ µm$^2$ cm$^{-3}$ in second-hand aerosol with and without nicotine, respectively.

In Figs. 2 and 3, the particle number distributions are shown for mainstream and second-hand aerosol of ECs with and without nicotine, at 37 °C and 300 °C. As can be seen, the particles are characterized by mode values at 37 °C of about 34 nm for mainstream aerosol. For second-hand aerosol at 37 °C, instead, bi-modal distributions were observed, with the main mode at about 30 nm and the secondary one at about 90 nm. It is evident from the analysis of Figs. 2 and 3 that the mainstream aerosol emitted from ECs results composed by a large number of volatile droplets: passing from 37 °C to 300 °C, the mode of mainstream aerosol results decreased of about 24 nm, while the particle concentration decreases of about 30%. The decrease of the mode and number concentration is also observable in second-hand aerosol but in this case the differences between 37 °C and 300 °C, are less evident.

<table>
<thead>
<tr>
<th></th>
<th>With nicotine</th>
<th>Without nicotine</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N_{MS}$, 37 °C (part. cm$^{-3}$)</td>
<td>$2.34 \pm 0.8 \times 10^8$</td>
<td>$2.23 \pm 0.5 \times 10^8$</td>
</tr>
<tr>
<td>$N_{MS}$, 300 °C (part. cm$^{-3}$)</td>
<td>$7.02 \pm 0.8 \times 10^7$</td>
<td>$6.23 \pm 0.5 \times 10^7$</td>
</tr>
<tr>
<td>$S_{AMS}$, 37 °C (nm$^2$ cm$^{-3}$)</td>
<td>$5.22 \pm 1.5 \times 10^{11}$</td>
<td>$6.99 \pm 0.8 \times 10^{11}$</td>
</tr>
<tr>
<td>$S_{AMS}$, 300 °C (nm$^2$ cm$^{-3}$)</td>
<td>$3.35 \pm 1.5 \times 10^{10}$</td>
<td>$2.48 \pm 0.8 \times 10^{10}$</td>
</tr>
<tr>
<td>$N_{SH}$, 37 °C (part. cm$^{-3}$)</td>
<td>$9.08 \pm 0.2 \times 10^7$</td>
<td>$6.30 \pm 1.3 \times 10^7$</td>
</tr>
<tr>
<td>$N_{SH}$, 300 °C (part. cm$^{-3}$)</td>
<td>$8.92 \pm 0.2 \times 10^7$</td>
<td>$5.97 \pm 1.3 \times 10^7$</td>
</tr>
<tr>
<td>$S_{ASH}$, 37 °C (nm$^2$ cm$^{-3}$)</td>
<td>$5.90 \pm 1.4 \times 10^7$</td>
<td>$5.16 \pm 0.8 \times 10^7$</td>
</tr>
<tr>
<td>$S_{ASH}$, 300 °C (nm$^2$ cm$^{-3}$)</td>
<td>$5.32 \pm 1.4 \times 10^7$</td>
<td>$3.51 \pm 0.8 \times 10^7$</td>
</tr>
</tbody>
</table>

Fig. 2. Particle size distributions measured in the mainstream aerosol of electronic cigarettes with and without nicotine at 37 °C and 300 °C.
By referring to the mainstream aerosol at 37 °C only, the comparison of traditional cigarettes with respect to ECs shows that the latter are characterized by lower number concentration, surface area concentration and mode, as resumed in Table 6 considering the data for traditional cigarettes proposed by Stabile et al. (2017).

3.2. Particle doses

In Table 7 the particle surface area daily doses (alveolar and tracheobronchial, calculated referring to the solid cores only, at 300 °C) and PM$_{10}$ daily doses received by vapers for mainstream aerosol and second-hand aerosol are reported. As regards the surface area doses, they result higher for ECs with nicotine with respect to ECs without nicotine in both mainstream and second-hand aerosol, as expected, while the PM$_{10}$ doses result comparable. As a general remark, both the daily doses in terms of surface area and PM$_{10}$ result higher for male.

As a comparison, daily surface area doses equal to $1.13 \times 10^5$ mm$^2$ day$^{-1}$ and $8.85 \times 10^4$ mm$^2$ day$^{-1}$ (most probable values) were measured by Fuoco et al. (2017) in mainstream smoke for male and female, respectively, while a dose of $8.18 \times 10^2$ mm$^2$ day$^{-1}$ was reported as the most probable for second-hand smoke in indoor/home environment by the same authors, which results higher than that measured in the present paper.

**Fig. 3.** Particle size distributions measured in the second-hand aerosol of electronic cigarettes with and without nicotine at 37 °C and 300 °C.

### Table 6

Comparison between traditional cigarettes and electronic cigarettes in terms of emitted particle number (N) and surface area (SA) in the mainstream smoke/aerosol (values for traditional cigarettes displayed as minimum – maximum; values for ECs displayed as without nicotine – with nicotine). Data for traditional cigarettes as showed in Stabile et al. (2017).

<table>
<thead>
<tr>
<th></th>
<th>Traditional cigarettes</th>
<th>Electronic cigarettes (37 °C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (part. cm$^{-3}$)</td>
<td>$2.9 \times 10^8$–$6.1 \times 10^8$</td>
<td>$2.23 \times 10^8$–$2.34 \times 10^8$</td>
</tr>
<tr>
<td>SA (µm$^2$ cm$^{-3}$)</td>
<td>$6.2 \times 10^7$–$2.2 \times 10^8$</td>
<td>$5.22 \times 10^5$–$6.99 \times 10^5$</td>
</tr>
<tr>
<td>Mode (nm)</td>
<td>184–212</td>
<td>34</td>
</tr>
</tbody>
</table>

### Table 7

Particle surface area (SA) and PM$_{10}$ daily doses received by vapers from mainstream aerosol (MS) and second-hand aerosol (SH) (mpv = most probable value), for male (M) and female (F). Puff number and exposure time as showed in Tables 3 and 4.

<table>
<thead>
<tr>
<th></th>
<th>$\delta_{SA}$ M mpv (mm$^2$ day$^{-1}$)</th>
<th>$\delta_{SA}$ F mpv (mm$^2$ day$^{-1}$)</th>
<th>$\delta_{PM10}$ M mpv (mg day$^{-1}$)</th>
<th>$\delta_{PM10}$ F mpv (mg day$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS with nicotine</td>
<td>$8.72 \times 10^1$</td>
<td>$6.68 \times 10^1$</td>
<td>384</td>
<td>293</td>
</tr>
<tr>
<td>MS without nicotine</td>
<td>$5.69 \times 10^1$</td>
<td>$4.35 \times 10^1$</td>
<td>387</td>
<td>292</td>
</tr>
<tr>
<td>SH with nicotine</td>
<td>$6.65 \times 10^0$</td>
<td>$6.02 \times 10^0$</td>
<td>$1.78 \times 10^{-2}$</td>
<td>$1.61 \times 10^{-2}$</td>
</tr>
<tr>
<td>SH without nicotine</td>
<td>$4.17 \times 10^0$</td>
<td>$3.77 \times 10^0$</td>
<td>$5.31 \times 10^{-2}$</td>
<td>$5.40 \times 10^{-2}$</td>
</tr>
</tbody>
</table>
Table 8
Comparison between traditional cigarettes and electronic cigarettes in terms of received particle doses in the mainstream aerosol (values for traditional cigarettes displayed as minimum – maximum; values for ECs displayed as most probable value), for male (M) and female (F); liquid with nicotine.

<table>
<thead>
<tr>
<th></th>
<th>Traditional cigarettes</th>
<th>Electronic cigarettes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (mm$^2$ puff$^{-1}$)</td>
<td>M (mm$^2$ puff$^{-1}$)</td>
</tr>
<tr>
<td>SA</td>
<td>$5.6 \times 10^{-6}$ - $1.1 \times 10^3$</td>
<td>$5.42 \times 10^{-1}$</td>
</tr>
<tr>
<td>SA, F (mm$^2$ puff$^{-1}$)</td>
<td>$4.5 \times 10^{-6}$ - $9.3 \times 10^2$</td>
<td>$4.93 \times 10^{-1}$</td>
</tr>
<tr>
<td>PM$_{10}$, M (mg puff$^{-1}$)</td>
<td>$3.4 \times 10^{-2}$ - $6.3 \times 10^{-2}$</td>
<td>$2.4 \times 10^0$</td>
</tr>
<tr>
<td>PM$_{10}$, F (mg puff$^{-1}$)</td>
<td>$3.4 \times 10^{-2}$ - $5.6 \times 10^{-2}$</td>
<td>$2.17 \times 10^0$</td>
</tr>
</tbody>
</table>

Table 9
ELCR for mainstream aerosol (MS) and second-hand aerosol (SH) (mpv = most probable value), for male (M) and female (F).

<table>
<thead>
<tr>
<th></th>
<th>ELCR$_{SA}$ M mpv</th>
<th>ELCR$_{SA}$ F mpv</th>
<th>ELCR$<em>{PM</em>{10}}$ M mpv</th>
<th>ELCR$<em>{PM</em>{10}}$ F mpv</th>
<th>ELCR$_{TOT}$ M mpv</th>
<th>ELCR$_{TOT}$ F mpv</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS with nicotine</td>
<td>$3.75 \times 10^{-6}$</td>
<td>$3.25 \times 10^{-6}$</td>
<td>$3.51 \times 10^{-6}$</td>
<td>$3.03 \times 10^{-6}$</td>
<td>$7.26 \times 10^{-6}$</td>
<td>$6.28 \times 10^{-6}$</td>
</tr>
<tr>
<td>MS without nicotine</td>
<td>$2.92 \times 10^{-6}$</td>
<td>$2.52 \times 10^{-6}$</td>
<td>$4.21 \times 10^{-6}$</td>
<td>$3.59 \times 10^{-6}$</td>
<td>$7.13 \times 10^{-6}$</td>
<td>$6.11 \times 10^{-6}$</td>
</tr>
<tr>
<td>SH with nicotine</td>
<td>$2.69 \times 10^{-8}$</td>
<td>$2.61 \times 10^{-8}$</td>
<td>$1.10 \times 10^{-10}$</td>
<td>$1.06 \times 10^{-10}$</td>
<td>$2.70 \times 10^{-8}$</td>
<td>$2.62 \times 10^{-8}$</td>
</tr>
<tr>
<td>SH without nicotine</td>
<td>$1.27 \times 10^{-8}$</td>
<td>$1.22 \times 10^{-8}$</td>
<td>$2.42 \times 10^{-10}$</td>
<td>$2.38 \times 10^{-10}$</td>
<td>$1.29 \times 10^{-8}$</td>
<td>$1.24 \times 10^{-8}$</td>
</tr>
</tbody>
</table>

In Table 8 the doses per puff in terms of surface area and PM$_{10}$ in the mainstream aerosol are resumed (data for traditional cigarettes taken from Stabile et al., 2017). As can be seen, the doses per puff in terms of surface area result 3 orders of magnitude higher for traditional cigarettes, while the PM$_{10}$ doses for electronic cigarettes result higher than those of traditional cigarettes.

As a comparison, the dose in terms of surface area received by people exposed to particles emitted from a 40 min-long 3D printing process in a 40 m$^3$ room with natural ventilation is equal to 200 mm$^2$ (Stabile & Scungio, 2016), which is a dose one order of magnitude higher than that received daily from mainstream aerosol of EC and two orders of magnitude higher than that received daily from second-hand EC aerosol exposure. In addition, the daily average surface area dose received by adults in Australia was found to be of the order of 500 mm$^2$ (Buonanno, Morawska, Stabile, Wang, & Giovinco, 2012).

3.3. ELCR for typical vapers

In this section the Excess Lifetime Cancer Risk is reported for typical Italian vapers referring to the mainstream aerosol, and for people exposed to second-hand aerosol. As reported in Section 2.4, the risk calculation was performed on the basis of the actual traditional smoking habits (number of ECs per day, pu) for males and females, and referring only to the solid core of the particles in order to correctly take into account the contribution of surface area. In Table 10 the ELCR total values and the single contributions of surface area and PM$_{10}$ for mainstream aerosol and second-hand aerosol, respectively, are reported. The ELCRs are displayed as most probable values, obtained from the Monte Carlo simulation. The ELCR values for mainstream aerosol with and without nicotine were found equal to $7.26 \times 10^{-6}$ and $7.13 \times 10^{-6}$ for male, and to $6.28 \times 10^{-6}$ and $6.11 \times 10^{-6}$ for female, respectively, corresponding to a lung cancer incidence of 0.6 new cases over 100 000 population. For second-hand aerosol with and without nicotine, the ELCR values were found equal to $2.70 \times 10^{-8}$ and $1.29 \times 10^{-8}$ for male, and to $2.62 \times 10^{-8}$ and $1.24 \times 10^{-8}$ for female, respectively.

To the mainstream aerosol results lower if compared to Italian traditional cigarettes smoking population (2–6 $\times 10^{-1}$ as shown by Stabile et al., 2017), while the ELCR for second-hand aerosol corresponds to 0.001–0.003 extra cases over 100 000 population.

As shown in Table 9, there are about two orders of magnitude of difference between ELCR associated to mainstream and second-hand aerosol, while the risk for ECs with nicotine results higher than that for ECs without nicotine. In addition, the risk for female results slightly lower than that for male. The higher values of ELCR for aerosol with nicotine is due to the presence of NNK and NNN (not found in ECs without nicotine). Referring to the second-hand aerosol exposure, even if the PM$_{10}$ concentration was found higher in aerosol without nicotine (see Table 1), its contribution on the total ELCR (ELCR$_{PM_{10}}$ in the above Tables) is limited because it results about two orders of magnitude lower than that of surface area. Looking at the data for traditional cigarettes of Stabile et al. (2017), the difference between the contributions of SA and PM$_{10}$ to the total ELCR was found of about 4 orders of magnitude.

Table 10
Contribution to ELCR by pollutants (reported as most probable values and averaged between males and females) for ECs with and without nicotine and for traditional cigarettes.

<table>
<thead>
<tr>
<th></th>
<th>As (%)</th>
<th>Cd (%)</th>
<th>Ni (%)</th>
<th>NNK (%)</th>
<th>NNN (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECs with nicotine</td>
<td>20.2</td>
<td>42.4</td>
<td>7.8</td>
<td>27.9</td>
<td>1.7</td>
</tr>
<tr>
<td>ECs without nicotine</td>
<td>21.2</td>
<td>63.9</td>
<td>14.9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Traditional cigarettes</td>
<td>2–4</td>
<td>0–17</td>
<td>0</td>
<td>69–88</td>
<td>8–9</td>
</tr>
</tbody>
</table>
(2.41–5.56 × 10⁻¹ for SA and 2.39–4.95 × 10⁻⁵ for PM₁₀).

In Table 10 the contribution of each considered hazardous compound to the total calculated ELCR is reported. As shown, the greatest contribution is provided by Cadmium in both aerosol with and without nicotine (42.4% and 63.9%, respectively), while significant contribution of NNK was also found for ECs with nicotine. As shown in Table 10, there is no contribution of Ni to the ELCR of traditional cigarettes, which on the contrary, determine a significant contribution for the ELCR of e-cig aerosol. For traditional cigarettes, in addition, the greatest contribution is provided by NNK (69–88%), while the contribution of heavy metals results lower with respect to electronic cigarettes.

Finally, the ELCR evaluated for the mainstream aerosol of ECs results lower to the target limit reported by EPA and WHO. WHO, in fact, reports an ELCR of 1 × 10⁻⁵ as target value (Commission on Environmental Health, 1996), while EPA considers a target risk range of 10⁻⁶ to 10⁻⁴ to be “safe and protective of public health” but “even risks slightly greater than 1 × 10⁻⁴ may be considered adequately protective” under specific conditions (EPA, 1991b).

4. Conclusions

In the present paper, an experimental campaign was carried out in order to measure the characteristics of electronic cigarettes aerosol and evaluate its carcinogenic effects on active and passive vapers. To this end, aerosol particle number and surface area concentrations were measured by means of a condensation particle counter (CPC 3775, TSI Inc.) and a fast mobility particle sizer (FMPS 3091, TSI Inc.) for mainstream and second-hand aerosol, while data of particle mass (PM₁₀) and toxic compounds (IARC Group 1 carcinogenic) deposited on particle surface were assessed through an extensive literature analysis. Two different sampling temperature were considered (37 °C and 300 °C) in order to take into account the volatility of the emitted liquid particles and correctly consider the contribution of surface area. Based on the measured and literature data, particle surface area and PM₁₀ doses received by vapers exposed to mainstream and second-hand aerosol were evaluated on daily basis and per single puff. In addition, the excess lifetime cancer risk (ELCR) was evaluated for both the exposure scenarios (mainstream and second-hand aerosol) considering typical smoking patterns available for traditional Italian cigarettes users.

From the analysis of the measured data, it was found that e-cig users are in general exposed to almost the same particle number concentrations as traditional cigarettes smokers, but the corresponding surface area concentration is higher for traditional cigarettes because of their higher particle mode. The presence of nicotine in the electronic cigarette leads to an increase in particle number and surface area concentrations, consequently the daily doses in terms of surface area result higher with respect to ECs without nicotine. Considering the doses per puff, traditional cigarettes are characterized by higher values in terms of surface area, while looking at the PM₁₀ doses per puff of ECs, they result higher than that for traditional cigarettes. The difference between mainstream aerosol and second-hand aerosol is of about 5 orders of magnitude for number concentration (at 37 °C) and 3 orders of magnitude for surface area concentration (at 300 °C).

The use of electronic cigarettes as an alternative to traditional cigarettes, in the described conditions and considering typical habits for Italian smokers, reduces the risk to get lung cancer from about 4 × 10⁻¹ to about 7 × 10⁻⁶ (40,000 additional cases versus 0.7 additional cases over a population of 100,000). The exposure to second-hand aerosol, instead, determines a negligible increment of lung cancer cases (0.001–0.003 new cases over a population of 100,000). Higher risks are associated to ECs with nicotine due to the presence of NNN and NNK. In particular, NNK, As and Cd are the main contributors to the total ELCR for ECs with nicotine, while for ECs without nicotine, the main contributor is Cd.

Finally, the extra risk of develop lung cancer due to the mainstream EC aerosol exposure is lower than the limit values proposed by EPA and WHO, leading to the conclusion that electronic cigarettes are safer than traditional cigarettes, under the conditions described in this paper, while the variability in exposure and risk estimates due to the use of electronic cigarettes and liquids different than those here analyzed will be addressed in future development of the paper.

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Us Food and Drug Administration (2016). Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Restrictions on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products. 81 FR 288973, pp. 134.


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Luca Stabile earned his PhD degree in 2010 at the University of Cassino defending the thesis “Airborne particle characterization for human exposure assessment”. He is currently researcher at the Department of Civil and Mechanical Engineering of the University of Cassino (Italy). His research is focused on particle measurement issues both from a metrological and exposure assessment point of view. He carried out several experimental analyses aimed to evaluate the emission of different particle sources and the related exposures and doses of people in different micro-environments. He also performed studies and projects in the area of the waste treatment and management.

Giorgio Buonanno is a Professor of thermodynamics at the Department of Engineering of the university of Naples “Parthenope”. He is also Adjunct professor at the Department of Civil and Mechanical Engineering of the University of Cassino (Italy), at the Queensland University of Technology, (Brisbane, Australia) and at the research group POLARIS (University Milano Bicocca, Italy). His research involves several aspects of the aerosol characterization from the particle emission of sources to the estimation of the particle doses and related risks.