Waterpipes and e-cigarettes: Impact of alternative smoking techniques on indoor air quality and health

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Waterpipes and e-cigarettes: Impact of alternative smoking techniques on indoor air quality and health

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HIGHLIGHTS
• Waterpipe (WP) smoking and E-cigarette has increased in the last years.
• WP smoke is responsible for various adverse effects in humans.
• E-cigarettes vapers can be exposed to substantial amounts of harmful substances.
• More research on the safety of e-cigarettes is needed.

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ABSTRACT
Waterpipe (WP) smoking is growing as an alternative to cigarette smoking, especially in younger age groups. E-cigarette use has also increased in recent years. A majority of smokers mistakenly believe that WP smoking is a social entertainment practice that leads to more social behavior and relaxation and that this type of smoking is safe or less harmful and less addictive than cigarette smoking. In reality, WP smokers are exposed to hundreds of toxic substances that include known carcinogens. High exposures to carbon monoxide and nicotine are major health threats. Persons exposed to secondhand WP smoke are also at risk. There is growing evidence that WP smoke causes adverse effects on the pulmonary and cardiovascular systems and is responsible for cancer.

E-cigarettes are marketed as a smokeless and safe way to inhale nicotine without being exposed to the many toxic components of tobacco cigarettes, and as an aid to smoking cessation. In fact, consumers (vapers) and secondhand vapers can be exposed to substantial amounts of VOC, PAH or other potentially harmful substances. Of major health concern is the inhalation of fine and ultrafine particles formed from supersaturated 1,2-propanediol vapor. Such particles can be deposited in the deeper parts of the lung and may harm the respiratory system or increase the risk of acquiring asthma. More research on the safety of e-cigarettes needs to be conducted to ensure a high level of public health protection in the long-term.

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1. Introduction
It has been well documented in the last few decades that tobacco smoking is related to diverse major health threats that result in approximately 440,000 deaths each year in the US alone. The cost is approximately $157 billion in annual health-related economic losses as well as more than 5.6 million years of potential life lost each year (e.g., US-DHHS, 2006). There is convincing evidence from numerous experimental and epidemiological studies that environmental tobacco smoke (ETS), often referred to as “secondhand smoke”, causes an increase in lung cancer and cardiovascular diseases and is responsible for other severe health effects, such as bronchial asthma, middle ear infections, sudden infant death syndrome (SIDS), pre-term delivery, and low birth weight. Consequently, ETS has been classified as a human carcinogen by diverse scientific organizations (IARC, 2004; US-DHHS, 2006; US-DHHS, 2010). ETS is a complex mixture of thousands of gaseous substances and particles that comprise the combustion products of tobacco and of charcoal as well as the smoke exhaled by the smoker (NRC, 1986). The ETS composition varies depending on the heat of combustion, the tobacco content, the additives that are present, and the type of filter material. Reducing the health effects attributed to smoking is an important public health initiative. Despite general efforts, we have observed few changes in the use of tobacco-related products as well as the development of new smoking techniques in western countries. Waterpipe smoking has
increased as an alternative to cigarette smoking, especially in younger age groups (WHO, 2005). E-cigarettes use has also increased in recent years. This increased usage necessitates an investigation of whether these techniques cause harmful exposure situations or adverse health effects. It is important to ensure that these techniques are not harmful and that they do not undermine the smoking prevention and cessation efforts of the last few decades.

Apart from possible health risks to users, our paper focuses on the concentrations of combustion and vapor products that are emitted or formed during the smoking of waterpipes or vaping e-cigarettes indoors and on the exposures of users and of persons unintentionally exposed to secondhand smoke. In addition to the characterization of external exposure, the determination of the body burden of the target substances or their urinary metabolites is an accurate method of obtaining important information to use in a risk assessment (Angerer et al., 2011). We focused predominantly on nicotine and its transformation products, cotinine and trans-3-nicotine, because mercapturic acids are metabolites of the highly reactive components of tobacco smoke (Schettgen et al., 2008). Moreover, carboxyhemoglobin (COHb) in blood and exhaled carbon monoxide (eCO) are easy, reliable and immediately available biomarkers that are related to exposure to carbon monoxide (CO) and that have been consistently used in numerous studies (e.g., Prockop and Chichkova, 2007; Jarvis et al., 2008).

The aim of the present paper was to summarize in detail the recent data on exposure to WP smoking and e-cigarette vapor, especially in indoor environments. Moreover, the known health effects based on currently available toxicological or epidemiological data are discussed. We used the results of various Medline and Web of Science inquiries to obtain an overview of the current scientific literature. We also included papers presented at conferences; reports from governmental, scientific and other institutions; and where possible, unpublished reports and other gray literature.

2. Waterpipe smoking

Waterpipe (WP) smoking is a traditional practice with roots in ancient India that is most popular in Middle Eastern and South Asian countries. The WP is known by many names, such as the oriental pipe, arghileh, narghileh, narguila, hookah, shisha, chicha, gozah, and ghalyan. Traditionally, unsweetened and unflavored nicotine-rich tobaccos named jurak, ajami, and tumbak were smoked (Kushikowsky et al., 2005). Today, 5–20 g of maassel (or muassel) is used, which consists of ~30% tobacco and ~70% honey or molasses. Maassel is flavored with additives such as apple, mango, mint, cappuccino, etc. The nicotine concentrations in the tobacco (maassel) vary between 1.8 and 6.3 mg/g (Hadidi and Mohammed, 2004). In a typical WP, charcoal heats the tobacco; the charcoal is separated from the tobacco by aluminum foil. When the smoker draws air through the mouthpiece of the hose, charcoal-heated air becomes smoke and passes through a bowl filled with water before being inhaled by the user (Maziak et al., 2011). A scheme of a typical WP is shown in Fig. 1. During a WP smoking session, smokers are exposed to more smoke over a longer period of time than in cigarette smoking because of the longer duration of such a session and because of the higher respiratory volume inhaled.

2.1. Occurrence

Traditionally, WP smoking is common in Mediterranean and Arabian countries. A recent review stated that in the Eastern Mediterranean region, 5–15% of adults are currently WP smokers and 63% have smoked a WP (Akl et al., 2011). The BREATHE study performed by interviewing 65,154 persons over 40 years old by telephone about their smoking habits found an average prevalence of WP smoking of 2% (maximum: 5.7%) in 10 countries in the Middle East and North Africa (Khattap et al., 2012). A survey of 13 middle-income countries around the world that enrolled adults who were >15 years old from a total of 288,800 households found a daily prevalence between 0.3% and 11% among men and from 0 to 0.3% among women (Morton et al., 2013). Higher prevalences of WP smoking of 9–15% and 6–28% were observed with pupils and university students, respectively (Akl et al., 2011). Up to 66% and 46% of these persons had smoked a WP.

Current WP smoking has been observed in 16.7% of Arab Americans and in 11.3% of non-Arab youth 14–18 years of age (n: 2782) in the Midwest USA (Weglicki et al., 2007, 2008). A logistic regression showed that students were 11 times more likely to be current WP smokers if they currently smoked cigarettes; if one or more family members smoked WP in the home, the youth were 6.3 times more likely to be current WP smokers. In Michigan, in a total of 1455 high school students, 8% of the Arab Americans regularly used a WP, as did 3% of the non-Arab subjects (Rice et al.,
A study of 1671 mostly Arab-American teens in Michigan found that 27% had used a WP (Rice et al., 2006). Significant predictors of WP use were having friends who smoke, having a sibling who smokes, and having easy access to tobacco. This study also showed that WP use was a strong predictor of cigarette smoking. In Canada, 23% of 18- to 24-year-old 10th graders reported WP use in the previous year (Dugas et al., 2010). In a survey of 143 people who were mostly college students, the daily WP use was 3% or 13% of the participants in 2 US cities (Ward et al., 2007). In a 2008–2009 National College Health Assessment that enrolled 100,891 students who were 18–26 years old, 9% reported current WP smoking (Primack et al., 2013). Users of WP cafés and Internet forums in the US reported 19% and 41% daily and weekly WP use, respectively (Smith-Simone et al., 2008b). These results were confirmed by another US cross-sectional internet-based survey of university students (Eisenberg et al., 2008). More recent studies performed in California, North Carolina, and Florida found current WP percentages between 10% and 17% (Sutfin et al., 2011; Barnett et al., 2013; Nuzzo et al., 2013). Among military recruits, Ward et al. (2006) reported WP use of only 0.3%. In a first report of the prevalence in an Arabic-speaking Australian population, 11.4% of the participants used a WP (Carroll et al., 2008).

The situation in Europe has not been well documented, but there are indications that WPs have become more common in recent years (Baska et al., 2008; Jensen et al., 2010). A cross-sectional survey of 937 British students showed that 38% had recent years (Baska et al., 2008; Jensen et al., 2010). A cross-

## 2.2. Concentrations of the constituents in mainstream smoke and sidestream smoke

Some studies have characterized the constituents of the mainstream smoke (MS) from WPs and showed that higher levels of metals (e.g., arsenic, nickel, cobalt, chromium and lead), carbon monoxide, “tar”, total particulate matter, nicotine, polycyclic aromatic hydrocarbons, and phenols were observed compared with cigarette smoke (Shihadeh et al., 2003; Monn et al., 2007; Shihadeh and Saleh, 2005; Sepetdjian et al., 2008; Monzer et al., 2008; Sepetdjian et al., 2013). Additionally, additives such as vanillin, ethyl vanillin, and benzylalcohol, which are known contact allergens, were found in waterpipe MS (e.g., 3192 μg of vanillin/water-

Concerning the concentrations of particles in the MS, one study observed high ultrafine particle concentrations of 70–105 particles per liter with a median diameter of 40 nm (Monn et al., 2007). In sidestream smoke (SS), high average ultrafine particle emissions of 3.99–10^12 particles per WP were found after 4 repeated WP smoking sessions (Daher et al., 2010). The peak of the particle diameter distribution was 37.9 nm in this study. Using a smoking machine protocol, the carbonylic compounds in MS were analyzed by two groups (Al Rashidi et al., 2008; Schubert et al., 2012b). During one WP session and the smoking of five different tobaccos, formaldehyde and acetaldehyde levels from 55.6 to 111 μg and from 136 to 397 μg were detected, respectively, compared with values of 21 μg and 587 μg from a 2RAF reference cigarette (Schubert et al., 2012b). Al Rashidi et al. (2008) found somewhat higher concentrations of 630 μg of formaldehyde and 2520 μg of acetaldehyde in the MS per session. The effect of filtration by the water in the bowl was investigated by Schubert et al. (2011a, 2012a, 2012b). With aromatic amines and 5-(hydroxymethyl)-2-furaldehyde, the retention in the water was low; however, with other furanic compounds and with carbonyls, the filtration was more efficient, reaching reduction rates of 65% for formaldehyde and 75% for acetaldehyde, for example.

Daher et al. (2010) compared SS and MS while a WP was smoked in a Teflon-coated chamber of 1 m^3 that was operated with an air exchange rate of 1.5 volumes per hour. They concluded that the SS of a single WP session has approximately four times the carcinogenic PAH, four times the volatile aldehydes, and 30 times the CO of a single cigarette. Additionally, including the exhaled MS and given a habitual smoking rate of 2 cigarettes per hour, during a typical 1-h session, a WP smoker most likely generates carcinogens and toxicants equivalent to those of 2–10 cigarette smokers.

## 2.3. Impact of WP smoking on indoor air quality

### 2.3.1. Particulate matter

The results of studies performed in the US, Canada, Germany, Pakistan, and Syria have presented data on particulate matter in indoor spaces. In Syria, the concentration of WP smoke was quantified using a continuously operating aerosol monitor (Maziak et al., 2008b). In this study, the PM_{2.5} and PM_{10} levels were measured during a laboratory session (room space: 34 m^3) in which 20 individuals each used a WP and 20 others each smoked a cigarette. The mean PM_{2.5} background concentration and the mean PM_{2.5} level during WP smoking were 48 and 264 μg/m^3, respectively, with a maximum value of 908 μg/m^3. Cigarette smoking led to similar average concentrations in the test room. In a second study in Aleppo, Syria, the same group found a mean PM_{2.5} value of 464 μg/m^3 (range: 56–1389 μg/m^3) in 40 hospitality venues and a significant relation with smoker density, which was measured as the number of cigarettes or WPs per 100 m^2 (Maziak et al., 2008a). However, a mixed exposure was described; thus, the contribution...
from WP smoking alone could not be determined. In Pakistan, the PM$_{2.5}$ level was measured in 39 WP bars, and a mean value of 1745 µg/m$^3$ was found, whereas in cigarette-smoking venues, a value of 689 µg/m$^3$ was observed. A positive correlation was found between the PM levels and smoker density. Two studies were performed in the US, one in 28 commercial venues in Virginia in 2011 (Cobb et al., 2013), and the other in 10 WP lounges in Oregon in 2010 (Fiala et al., 2012). In the first study, in the 17 WP cafes in which smoking was allowed, a mean PM$_{2.5}$ of 374 µg/m$^3$ (range: 13–1733 µg/m$^3$) was observed, whereas in the non-smoking section, the mean was only 123 µg/m$^3$ (range: 16–823 µg/m$^3$). Overall, they found that the indoor air quality in the WP cafes was poorer than that in rooms with cigarette smoke by an average factor of 3.2. In Oregon, the PM$_{2.5}$ concentrations ranged from 67 to 750 µg/m$^3$, with a mean of 198 µg/m$^3$. In Canada, Zhang et al. (2013a) studied 12 WP cafes in Toronto in 2012. The mean PM$_{2.5}$ level was 1419 µg/m$^3$ (range: 5–17,221 µg/m$^3$), an average of 69 times higher than the ambient level. After adjusting for various influencing factors, the PM$_{2.5}$ levels increased with the number of active WPs in the room. An additional study in Canada investigated 6 venues in Edmonton, with PM$_{2.5}$ levels from 14 to 430 µg/m$^3$ (mean: 264 µg/m$^3$) (Hammal et al., 2013). In Germany, the PM$_{2.5}$ level was analyzed in 8 WP cafes in Berlin in 2007 (BÄK Bg, 2007). A measurement time of 30–60 min in each location resulted in mean PM$_{2.5}$ levels between 51 and 2727 µg/m$^3$ (range: 30–4253 µg/m$^3$). In a second German study, the PM in a typical ventilated room was measured while a shisha was smoked (Fromme et al., 2009). A mean PM$_{2.5}$ value of 406 µg/m$^3$ (range: 79–1057 µg/m$^3$) was measured. Furthermore, the particle number concentration (PNC) reached a high mean value of 319,000 particles/cm$^3$, and the peak of the electrical mobility diameters occurred at 18 nm. Fig. 2 and Fig. 3 illustrate the indoor concentrations during such a shisha session as a function of time.

In indoor environments, a 24-h mass-related mean guideline value of 25 µg/m$^3$ of PM$_{2.5}$ was recommended by the WHO to protect against peaks in pollution that would lead to substantial excess morbidity or mortality (WHO, 2006). This guideline value was obviously exceeded by the exposures observed when smoking a WP. There is growing evidence of the health effects of ultrafine particles on humans, but no recommendations for this fraction are provided by any scientific institution at present (WHO, 2010).

Nevertheless, the particle number concentrations during WP smoking are high compared with those of a non-smoking indoor environment.

### 2.3.2. Carbon monoxide (CO)

Data on the indoor air concentrations of CO are very limited. El-Nachef and Hammond (2008) observed mean concentrations of 18–26 ppm (range: 31–40 ppm) in a residence hall in which 7–10 subjects smoked WPs for 60 min on 3 evenings in 2006. Comparable levels were found in a German study in which 4 persons smoked a WP in a typical ventilated room for 4 h (Fromme et al., 2009) (Fig. 2). In this study, the mean value was 48 ppm, with a range from 0 to 68 ppm. In Canada, 6 and 12 WP cafes were investigated in Edmonton and Toronto, respectively (Hammal et al., 2013; Zhang et al., 2013a). The mean levels (range) found in these studies were 6.7 ppm (1.9–11.4 ppm) and 17.7 ppm (0–120 ppm), respectively. In indoor spaces, guideline values of 30 ppm for 1 h and 9 ppm for 8 h were recommended based on an acute exposure-related reduction in exercise tolerance and an increase in the symptoms of ischemic heart disease (WHO, 2010). These values were supported by the proposed guidelines of the European Commission’s INDEX project (EC, 2005). It is obvious that the use of WPs in indoor spaces could exceed the guidelines and be a significant health threat.

### 2.3.3. Polycyclic aromatic hydrocarbons (PAH)

During the incomplete combustion of organic materials, several PAH are produced. Indoor WP smoking is expected to be a source of these PAH. It is well known that exposure to PAH is higher in the homes of smokers than in the homes of non-smokers and is higher in public places where smoking is allowed than in places where smoking is prohibited (Fromme et al., 2004; Repace et al., 2006; Bolte et al., 2008). For example, with cigarette smoke, Repace et al. (2006) found a mean of 65.1 ng/m$^3$ in 7 pubs in Delaware, and Bolte et al. (2008) found means of 215 ng/m$^3$ and 260 ng/m$^3$ in
German restaurants and bars, respectively. The data on PAH exposure during WP smoking are limited. In a typical ventilated room, Fromme et al. (2009) observed levels of PAH that were classified as probable human carcinogens (B2) by the US-EPA of 4.9 ng/m³ and, for all PAH, 270 ng/m³ during a 4-h WP session, compared with levels in a control room of 1.9 ng/m³ and 140 ng/m³, respectively. The highest differences were found for naphthalene.

There is sufficient evidence that some PAH, including benzo[a]pyrene (B[a]P), are genotoxic. Therefore, no threshold can be determined, and all indoor exposures are considered relevant to health. Based on epidemiological data from studies of cook-oven workers, the unit risk of B[a]P as an indicator of PAH in ambient air was estimated to be 8.7×10⁻⁵ per ng/m³. The corresponding concentrations for lifetime exposure to B[a]P of approximately 0.12 ng/m³ and 0.012 ng/m³ produced excess lifetime cancer risks of 1 per 100,000 and 1 per 1,000,000, respectively (WHO, 2010).

The concentration of 0.61 ng/m³ observed in the Fromme et al. (2009) study indicates that the risks from indoor WP use must be reduced.

2.3.4. Nicotine and volatile organic compounds (VOC)

The most recent study that investigated nicotine in indoor air was performed in 12 WP cafés in Toronto in 2012 (Zhang et al., 2012a). A mean level of 3.3 μg/m³ (range: 0.2–7.9 μg/m³) was found. Similar results were reported in a study of cigarette smoke in 46 indoor areas in hospitality venues in 8 European countries in 2009 and in 2011 (López et al., 2012). In this study, the median value was 3.7 μg/m³. Park et al. (2013) observed comparable concentrations with a mean indoor nicotine concentration in air of 2.9 μg/m³ at monitoring sites that had evidence of active smoking in 20 restaurants and entertainment venues in Korea in 2009. Bolte et al. (2008) reported higher mean levels of 21.3 and 53.7 μg/m³ in German restaurants and bars in 2005-2006, respectively. Factors such as room characteristics, ventilation, and the density of active smokers can result in higher nicotine levels. In a single room in which a WP was smoked for over 4 h, 18 μg/m³ of nicotine was measured (Fromme et al., 2009). Little information on VOC in WP venues is available. Only Fromme et al. (2009) reported that higher levels of benzene (15.0 vs. 0.11 μg/m³) and total volatile organic compounds (TVOC) (1800 vs. 730 μg/m³) were found in a room in which a WP was smoked compared with a control day. Nevertheless, it is well known that tobacco smoking in indoor spaces enhances the levels of VOC in the air. For example, in 56 hospitality venues in Spain, a mean benzene level of 3.7 μg/m³ was found, whereas outdoors, only 0.9 μg/m³ was observed (Alonso et al., 2010). In Germany, levels of 8.9 μg/m³ and 8.1 μg/m³ were found in restaurants and bars with cigarette smoke (Bolte et al., 2008).

2.4. Body burden

2.4.1. Nicotine/cotinine

Neergaard et al. (2007) reviewed the published literature on WP use to estimate the daily nicotine exposure of adult WP smokers. They summarized that the daily use of a WP produced a 24-h urinary cotinine level of 785 μg/l, which indicates a nicotine absorption rate equivalent to that of smoking 10 cigarettes per day.

Plasma nicotine concentrations were analyzed for the first time in 14 male habitual WP smokers who smoked 20 g of muassel for a period of 45 min (Shafagoj et al., 2002). The plasma nicotine concentration rose from 1.1 μg/l at the baseline to a maximum of 60.3 μg/l at the end of smoking and then fell to 31 μg/l and 70 μg/l after 25 min and 3 h, respectively. In a second experiment, 16 healthy subjects smoked 12.5 g of flavored tobacco for 30–60 min (Jacob et al., 2011). The plasma nicotine concentrations peaked at approximately 45 min, with an average of 8.4 μg/l. Among the WP-only smokers, there was a significant correlation between the number of puffs taken from the WP and the maximum plasma nicotine concentration. The authors stated that the WP users had a systemic dose that was equivalent to the dose from smoking 2 to 3 cigarettes. Additionally, Maziak et al. (2011) measured the nicotine levels of 61 WP smokers before and after the use of a WP. Before the experiment, the users abstained for at least 24 h. The mean pre- and post-levels of plasma nicotine were 3.1 μg/l and 15.7 μg/l, respectively. In an experiment with 54 participants who each smoked a WP or a cigarette for 43.3 min or 61 min, respectively, the mean peak plasma nicotine concentrations were 9.8 μg/l and 9.4 μg/l, respectively (Cobb et al., 2011). In Germany, the blood nicotine levels of 10 WP users who smoked 5 g of flavored tobacco in one session increased to 11.4 μg/l (Schubert et al., 2011b). The results of nicotine and cotinine concentrations in urine samples are given in Table 1.

Extremely high concentrations of cotinine were found in investigations of 16 participants in Lebanon and 10 WP smokers in India, with mean values of 6080 and 2379 μg/l, respectively (Macaron et al., 1997; Behera et al., 2003). In both studies, no significant differences in the mean urinary cotinine and (only in India) nicotine levels were found between the cigarette smokers and the WP smokers. Somewhat lower concentrations were observed in studies from Saudi Arabia and Kuwait (Al Saleh et al., 2000; Al Mutairi et al., 2006) and in studies of one single WP session from Jordan and Germany (Shafagoj et al., 2002; Schubert et al., 2011b). Overall, these studies showed a wide range of nicotine and cotinine excretion levels that could be explained by differences in smoking behavior, such as smoking frequency and the type and amount of tobacco used. The investigations carried out in Saudi Arabia, India

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Mean concentrations (μg/L) of cotinine and nicotine in urine samples.</th>
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<tbody>
<tr>
<td><strong>Cotinine</strong></td>
<td><strong>Reference</strong></td>
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<td></td>
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<tr>
<td>Macaron et al., 1997</td>
<td>15m, 1f</td>
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<td>Al Saleh et al., 2000</td>
<td>14m</td>
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<td>Shafagoj et al., 2002</td>
<td>9m, 15f</td>
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<td>Behera et al., 2003</td>
<td>8m, 2f</td>
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<tr>
<td>Al Mutairi et al., 2006</td>
<td>8m, 5f</td>
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<tr>
<td>Schubert et al., 2011b</td>
<td>10</td>
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<tr>
<td><strong>Nicotine</strong></td>
<td><strong>Reference</strong></td>
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<td>Shafagoj et al., 2002</td>
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<td>Behera et al., 2003</td>
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<tr>
<td>Al Mutairi et al., 2006</td>
<td>8m, 6f</td>
</tr>
<tr>
<td>Jacob et al., 2011</td>
<td>13</td>
</tr>
</tbody>
</table>

m: male; f: female.

* Estimated using a 24-h urine volume of 1500 ml.
* μg/24 h.
* Mean of maximum.
and Kuwait found significantly lower cotinine concentrations in non-smokers compared with WP smokers, with mean levels of 4.1 μg/l vs. 580 μg/l, 7.3 μg/l vs. 2379 μg/l, and <100 μg/l vs. 678 μg/l (Al Saleh et al., 2000; Behera et al., 2003; Al Mutairi et al., 2006), respectively.

2.4.2. Mercapturic acids

Only in the study of Fromme et al. (2009) were urine samples from four active WP smokers characterized before and after a 4-h smoking session (data not published). Specific biomarkers of benzene (S-PMMA), 1,3-butadiene (MHBMA), and acrolein (3-HPMA) were found after WP smoking, and concentrations of 2.4 μg/g of creatinine, 7.8 μg/g of creatinine, and 400 μg/g of creatinine, respectively, were observed. The difference between the two time points reached a factor of 12.1, 2.5, and 2.4, respectively, which indicates that the WP smokers were exposed to carcinogenic substances. The levels of these mercapturic acids that were found after the session are consistent with the findings of other studies, in which higher concentrations were found in cigarette smokers (Scherer et al., 2007; Carmella et al., 2007; Schettgen et al., 2008, 2010; Ding et al., 2009). These preliminary results for mercapturic acids in urine prove that there is a significant uptake of human carcinogens due to WP smoking that is comparable with that in cigarette smokers. These parameters should be integrated into further biomonitoring studies.

2.4.3. Exhaled CO (eCO)

Four studies were conducted under laboratory conditions in Jordan (Shafagoj et al., 2002), one in the US (El-Nachef and Hammond, 2008), and two in Syria (Ward et al., 2007; Maziak et al., 2009). In Jordan, Shafagoj et al. (2002) studied 18 male habitual WP smokers who had smoked for the previous 3.3 years with at least three sessions per week and an average of 20 g of tobacco per session. In the US study, 27 students smoked WPs containing 10 g of tobacco each in a 60-min smoking session, and five additional students were passively exposed. In one of the Syrian studies, 11 volunteers were exposed to smoke, whereas in the second, pre- and post-exposure data were obtained from 56 WP users who consumed an average of 4.1 g of tobacco. Three of these studies reported similar concentrations after the WP session that ranged from 36 to 38 ppm. Shafagoj et al. (2002) found a somewhat lower post-exposure level of 16 ppm. The baseline readings in all of these studies were in the range from 2.0 to 5.6 ppm. Among the five passively exposed subjects in the US study, no increase in the eCO levels was observed after exposure (El-Nachef and Hammond, 2008).

Three other studies reported results under more natural conditions. In the first, 15 regular WP smokers were observed in a study conducted in a WP café located in downtown Beirut (Bacha et al., 2007). All the participants used the same type of tobacco. The mean concentration after smoking was 38 ppm. In the second study, 63 people smoking in WP cafés in the UK participated in a survey with measurements taken before and after smoking (Jackson and Aveyard, 2008). The mean pre-smoking eCO concentration was 5.1 ppm, and the mean concentration after WP smoking was 37.4 ppm. An additional field study of 173 patrons of WP cafés and 198 patrons of traditional bars that was conducted in 2009 in the US indicated that the patrons of WP cafés had significantly higher eCO levels (mean: 30.8 ppm vs. 8.9 ppm) (Barnett et al., 2011). In conclusion, WP smokers are exposed to high concentrations of CO. This is true to a lesser extent with subjects who are passively exposed to WP smoke.

2.4.4. Carboxyhemoglobin (COHb)

Within half an hour after smoking for 15 min, 26 subjects who smoked 15–30 g of tobacco had a mean COHb level of 8.8% (range: 6.5–13.9%) (Zahran et al., 1982). In a second study from the same group, the COHb level was determined in 1832 male Saudi Arabian volunteers after each smoked a WP for 10–40 min (Zahran et al., 1985). In this study, the mean COHb level of 10.1% was distinctly different from the levels in the cigarette smokers (6.5%) and non-smokers (1.6%). For the WP smokers, a linear relation was found between the number of WPs smoked per day and the amount of COHb saturation. In a third study from Saudi Arabia, 186 WP smokers were investigated (Al-Fayez et al., 1989). Depending on the age of the smoker, the mean COHb of light (1 head/day) and heavy (>2 head/day) smokers varied from 6.7 to 9.6% and from 13.8 to 20.3%, respectively. Findings from a study conducted in Germany, in which ten WP users smoked a single pipe, showed a mean COHb level of 17.1% (maximum: 32%) after the session (Schubert et al., 2011).

The high COHb levels found in WP users can be compared with guideline levels. The most recent German biological tolerance level for COHb in the workplace is 5%, and this should not be exceeded after the work shift (AGS, 2006). Long-term exposure to levels above this limit is related to headaches, fatigue, dizziness, nausea, and disturbances in mental performance. The ACGIH (2000) has recommended 3.5% COHb as a Biological Exposure Index (BEI). For risk-assessment purposes, it should be considered that, in contrast with the general population, the working population normally consists of individuals who are presumably healthy and under permanent medical supervision. However, individuals with cardiovascular impairments and pulmonary diseases have a higher risk of severe symptoms and require additional safety controls.

2.4.5. Tobacco-specific nitrosamines

During an experiment, 16 healthy subjects smoked 12.5 g of flavored tobacco for 30–60 min, and urine samples were taken for 12–24 h (Jacob et al., 2011). The tobacco-specific 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) level increased significantly from an average baseline value of 1.2 pg/ml, had a peak on the order of 5–20 pg/ml, and then declined slowly, consistent with its long half-life of 10–18 days. In a study in Syria, the NNAL levels in the first morning urine samples of 23 exclusive and habitual cigarette smokers and 24 exclusive and habitual male WP smokers were analyzed and had geometric means of 46.8 pg/ml (27.6–79.3 pg/ml) and 10.7 pg/ml (5.0–22.6 pg/ml), respectively (Ali et al., 2013). Compared with 28 non-smokers, the levels in WP users were 5–10 times greater (geometric mean: 0.7 pg/ml). In a second study, the urine samples of 13 male exclusive cigarette smokers and 11 male exclusive WP smokers were analyzed (Radwan et al., 2013). Higher levels of NNAL were found in smokers of either cigarettes or WPs, with ranges of 0.78–2.58 pmol/ml and 0.21–1.71 pmol/ml, respectively (Radwan et al., 2013). In non-smoking wives, the level of 0.04 pmol/ml (range: 0.01–0.60 pmol/ml) was significantly lower.

2.5. Summary of health effects

2.5.1. Acute health effects

The most important issue regarding the acute toxicity of WP smoke is the effects due to the high CO concentration during a smoking session. Cases of CO poisoning have been reported worldwide. In Singapore, a 19-year-old man had neurological symptoms including retrograde amnesia and dizziness 4 h after smoking a WP (Lin et al., 2005). His COHb level was 27.8%. Enhag et al. (2011) reported two cases from Sweden. In the first, a 15-year-old girl who had smoked a WP over three consecutive days was dizzy, had a headache, and became unconscious 1 h after the last WP session. In the emergency room, she was confused, answered questions with delay, and complained of a headache.
Two hours and 40 min after the smoking session, her COHb level was 21%. In the second case, a 28-year-old man felt dizzy and cold after the session and thereafter became unconscious. Arziman et al. (2011) reported a series of five patients with WP-induced CO poisoning in Turkey. The subjects had general neurological complaints, such as headaches, nausea, vomiting, and vertigo. In the UK, 12 persons brought to an emergency department with signs of CO intoxication had COHb levels from 7.3% to 23% after an event in a poorly ventilated room (Clarke et al., 2012). In Germany, the National Notification System for Poisoning Incidents at the Federal Institute for Risk Assessment listed 70 cases of CO poisoning that were related to the use of a WP (Hahn et al., 2014). In addition to these cases, it is highly probable that the real extent of poisoning is underreported due to the generality of the symptoms.

Although the health effects of WP use are not well evaluated at present, but studies have shown short-term effects on the cardiovascular system (Al-Kubati et al., 2006; Blank et al., 2011; Hakim et al., 2011) and on pulmonary function (Al-Fayez et al., 1998; Kiter et al., 2000) as well as on changes in oxidative and inflammatory markers in the lung (Khabour et al., 2012). A recent review of the effects on lung function based on the results of six cross-sectional studies, all with methodological limitations, concluded that WP smoking has statistically significant negative effects on the forced expiratory volume (FEV1) (Raad et al., 2011).

2.5.2. Long-term health effects

The evidence summarized in a systemic review showed that WP smoking was significantly associated with lung cancer, respiratory illness, low birth-weight, and periodontal disease (Akl et al., 2010). Smoking was significantly associated with bladder cancer, nasopharyngeal cancer, esophageal cancer, oral dysplasia or infertility, but important associations cannot be excluded. Additionally, in a population-based cohort study in Iran, in which 928 randomly selected healthy subjects were followed for 10 years, WP use was seen as a risk factor of gastric cancer as well as of precancerous lesions (Sadjadi et al., 2014). These epidemiological findings were supported by the higher levels of micronuclei found in the buccal mucosal cells of WP smokers compared with those of non-smokers (El-Setouhy et al., 2008) and by the significantly increased frequencies of sister chromatid exchanges in human lymphocytes in 50 WP smokers compared with 18 heavy cigarette smokers (Khabour et al., 2011). Moreover, WP smokers have significantly more DNA damage as found using a chromosomal aberration assay than non-smokers (Alsatri et al., 2012). Nevertheless, the quality of the evidence from the available epidemiological studies was low; thus, high-quality studies are needed (Ald et al., 2010).

3. E-cigarette vaping

First developed in China in 2003, electronic nicotine delivery systems also known as electronic cigarettes or e-cigarettes have spread globally and show a fast growing market share. E-cigarettes are battery-powered devices resembling cigarettes that consist of a liquid-containing cartridge and a vaporization chamber. With each puff, the microelectrical circuit of the e-cigarette is activated and a small amount of liquid is aerosolized to produce a respirable vapor (Fig. 4). Therefore, e-cigarettes are marketed as a smokeless and safe way to inhale nicotine without being exposed to the many toxic components of tobacco cigarettes, and as an aid to smoking cessation (Bullen et al., 2010; Gray, 2014; Kuschner et al., 2011). Despite their growing popularity, to date only limited data is available on the safety of e-cigarettes for both users (vapers) and passive vapers (Eiter et al., 2011). Consumers usually do not have valid information on the chemical content of nicotine solutions or on their health risk, and the release of potentially harmful substances from the liquids into the indoor environment is mostly unknown. This section provides an overview of the current knowledge on the chemical and aerosol exposure by e-cigarette consumption and evaluates the impact of vaping on indoor air quality in terms of potential health effects.

3.1. Occurrence

Marketed since 2004 as an alternative to nicotine delivery and advertised as a valid means to smoking cessation, the e-cigarette have become widely available globally, particularly over the Internet. A systematic review of the literature published between 2006 and 2013 revealed that e-cigarette awareness increased from 16% to 58%, and use increased from 1% to 6% (Pepper and Brewer, 2013). The majority of users were current or former smokers. Common reasons for using e-cigarettes were quitting smoking and using a product that is healthier than traditional cigarettes. The International Tobacco Control Four-Country Survey performed by interviewing 5939 current and former smokers in Canada (n: 1581), the United States (US; n: 1520), the United Kingdom (UK; n: 1325), and Australia (n: 1513) found that 46.6% of all respondents were aware of e-cigarettes (US: 73%, UK: 54%, Canada: 40%, Australia: 20%), 7.6% had tried e-cigarettes (16% of those aware of e-cigarettes), and 2.9% were current users (39% of triers) (Adkison et al., 2013). Prevalence of trying e-cigarettes was higher among younger, non-daily smokers with a high income and among those who perceived e-cigarettes as less harmful than conventional cigarettes. Current use was higher among both non-daily and heavy (>20 cigarettes per day) smokers. A representative cross-sectional US survey of 1836 current or recently former adult smokers found that 38% of the smokers had tried an alternative tobacco product, most frequently e-cigarettes (Popova and Ling, 2013). Alternative tobacco product use was associated with having made a quit attempt, and those intending to quit were significantly more likely to have tried and to currently use the products than were smokers with no intentions to quit. Use was not associated with successful quit attempts. Interest in future use of alternative tobacco products was low, except for e-cigarettes. In another US survey among 6307 adults, 40.2% had heard of e-cigarettes, with awareness highest among current smokers. Utilization was higher among current smokers (11.4%) than in the total population (3.4%), with 2.0% of former smokers and 0.8% of never-smokers ever using e-cigarettes (Pearson et al., 2012). A Web-based survey performed by interviewing 4444 US college students in North Carolina found an average prevalence of e-cigarette use of 4.9%, with 1.5% reporting past month use (Sutfin et al., 2013). Although e-cigarette use was more common among conventional cigarette smokers, 12% of ever e-cigarette users had never smoked a conventional cigarette.

A European survey that was carried out by the TNS Opinion & Social network in the 27 Member States of the EU found that of the
26,751 respondents, 69% have heard of e-cigarettes (TNS Opinion and Social, 2012). However, the level of awareness varies considerably between Member States. The highest levels of self-reported familiarity are observed in Finland (92%), Greece (90%), and Latvia (88%). Conversely, only 34% of respondents in Sweden and 47% in Ireland are familiar with e-cigarettes. Overall, 7% of EU citizens have tried e-cigarettes. However, the regular use of these products remains rare and most respondents have only tried them. About 2% of respondents in Denmark, Greece and Romania use or have used e-cigarettes on a daily basis followed by 1% of respondents in 13 other EU Member States including Germany. 3% of respondents in Poland and Romania report that they use or have used them occasionally. Around 1 respondent in 10 in Bulgaria (11%), Latvia (10%), Denmark (9%), Poland (9%) and the Czech Republic (9%) report they have tried e-cigarettes once or twice. Some differences in recognition levels for e-cigarettes can be observed between the socio-economic groups: Males are more likely than females to say they have heard of e-cigarettes, but are not more likely to know what they are. Lower levels of recognition are observed in the oldest age group and consequently among retired respondents. The 15–24 age group shows a high level of recognition of e-cigarettes.

3.2. E-cigarette solutions (liquids)

Main ingredients of e-cigarette solutions are usually 1,2-propanediol and glycerine to produce the vapor (Cheah et al., 2014; Schober et al., 2014). Moreover, nicotine and different flavorings (e.g. hazelnut, forest fruits, cherry) may be added in various concentrations to the liquid (Cobb and Abrams, 2011). Rarely, the cartridges may also contain active pharmaceutical ingredients such as rimonabant for the purpose of losing weight and reducing smoking addiction, and taladafil for the purpose of increasing sexual capacity. Analyses of these cartridges revealed the presence of amino-tadalafil and not tadalafil, and the presence of an oxidative product of rimonabant, as well as rimonabant (Hadwiger et al., 2010), although the amount of either of these substances that is able to transfer from liquid to vapor is low (Trehy et al., 2014). The nicotine content of e-cigarette solutions roughly differs between 8.5 and 22.2 mg/ml depending on the brand (Cameron et al., 2014), but can show high inconsistencies with the product labeling, along with misleading information (Cheah et al., 2014; Goniewicz et al., 2013). In particular, liquids labeled as nicotine-free have been found to contain low levels of nicotine or nicotine related impurities, some of which are known to be harmful to humans, including anabasine, anatabine, myosmine, and β-nicotyrine (FDA, 2009; Trehy et al., 2011). Diethylene glycol, a potentially lethal organic compound and an ingredient in anti-freeze (Schep et al., 2009), was found in one cartridge (approximately 1%), while tobacco-specific nitrosamines (TSNA) which are strong human carcinogens were detected in several liquid samples (FDA, 2009; Goniewicz et al., 2014; Kim and Shin, 2013). However, the TSNA levels of these liquids represented only a small fraction (0.008 μg per e-cigarette cartridge) of what is typically found in traditional cigarettes (6.3 μg per full flavor cigarette) (Stepanov et al., 2006). Moreover, recent analyses of cartridge fluids also confirmed the presence of tin particles and tin whiskers (Williams et al., 2013) as well as small amounts of sensitizing chemicals including benzylalcohol, t-limone, menthol and vanillin (Schober et al., 2014).

Liquids are freely available via the Internet and not subjected to official quality control. Thus, the risk of contaminations due to lack of certified manufacturing sites and external surveillance is of major concern to health care authorities worldwide (FDA, 2009). Moreover, some users refill their own cartridges, which may be dangerous because it involves dealing with potentially toxic concentrations of nicotine. Upon dermal contact or ingestion nicotine readily passes into the bloodstream and induces the release of several neurotransmitters in the central nervous system (Tweed et al., 2012). At toxic doses it cause death by respiratory paralysis (Katzung, 2006). Based on internationally accepted data (IPCS, 1991), the fatal dose of nicotine in adults is estimated at 30–60 mg while for young children it is estimated only 10 mg. However, a recent analysis given by Mayer (2014) questions the common view on lethal doses of nicotine and suggests minor toxicity in most cases (e.g. vomiting, nausea, tachycardia). On the other hand, the amount of nicotine in refill bottles (up to 7 g) poses a greater toxicity or fatality risk in children if ingested orally or absorbed transdermally (Cameron et al., 2014). Exposure data for children, e.g. regarding transdermal nicotine patches or gums or other forms of nicotine application (Davies et al., 2001; Smolinske et al., 1988; Wain and Martin, 2004; Woolf et al., 1997), suggest that only -0.1 mg/kg are safe and 0.2 mg/kg may be sufficient to cause at least clinical symptoms. This is particularly concerning as nicotine solutions come in flavors and colors attractive to young children and are often not sold in child-safe containers.

Treichouman and Talbot (2011) evaluated five brands of e-cigarettes and found that fluid leaked out of most cartridges, that the labeling of cartridges was poor and that most packs lacked warning information about potential risks. These findings clearly indicate that nicotine containing liquids should be officially regulated and labeled with appropriate warnings on health risks, particularly toxicity in children.

3.3. Impact of vaping on indoor air quality

E-cigarettes are electronic devices that provide doses of nicotine and other additives to the user in an aerosol. In contrast to conventional smoking, the released compounds are not generated from a combustion process as a smoke but by direct evaporation as a mist, which is only released during puffing when energy is imparted and not in the periods between single puffs. Unlike real cigarettes, e-cigarettes do not produce secondary or side-stream emissions, and so only primary (inhaled) and tertiary vapor (exhaled) have been studied. In general, exposure levels of e-cigarette aerosols differ with the composition of the applied liquid, the type of e-cigarette in use, length of the puff, and the interval between the puffs.

3.3.1. Nicotine and volatile organic compounds (VOC)

A recent study by Schober et al. (2014) showed that vaping impairs indoor air quality by the release of high amounts of VOC. A distinct increase versus control was found for 1,2-propanediol (mean ± SD, 199.2 ± 93.2 vs. <0.04 μg/m³), glycerine (72.7 ± 6.9 vs. <0.04 μg/m³) and nicotine (2.2 ± 1.7 vs. <0.04 μg/m³). Formaldehyde, benzene and the pyrolysis products acrolein and acetone did not exceed background levels. Indoor concentrations of the sensitizing chemicals vanillin and benzylalcohol were only slightly increased in comparison to control values (0.3 ± 0.2 vs. <0.04 μg/m³; 5 ± 3 vs. 4 μg/m³). Czogala et al. (2014) measured selected airborne markers of secondhand exposure to e-cigarette pollutants in an exposure chamber. The study showed that e-cigarettes are a source of secondhand exposure to nicotine but not to tobacco-specific combustion products. The air concentrations of nicotine emitted by various brands of e-cigarettes ranged from 0.82 to 6.23 μg/m³. In comparison, the average concentration of nicotine resulting from tobacco cigarettes was 10-fold higher than from e-cigarettes (31.6 ± 6.9 vs. 3.3 ± 2.5 μg/m³). Schipp et al. (2013) analyzed the VOC composition directly in the breath gas of one exhaled e-cigarette puff. Prominent components in the gas-phase were 1,2-propanediol, 1,2,3-propanetriol, diacetin, flavors, and traces of nicotine. Formaldehyde was not detected. Goniewicz et al.
liquids by generic e-cigarettes and assessed the indoor air concentrations of which are usually elevated by conventional tobacco smoking. The rare-earth elements lanthanum and cerium, the concentrations of which were the focus of this study with subjects who consumed e-cigarettes for 2 h in a café-like environment. They found that the e-cigarette aerosol contains metals derived from various components in e-cigarettes. The aerosol generated on a smoking machine contained particles >1 μm comprised of tin, silver, iron, nickel, aluminum, and silicate and nanoparticles (<100 nm) of tin, chromium and nickel. The concentrations of nine of eleven elements in the e-cigarette aerosol were higher than or equal to the corresponding concentrations in tobacco cigarette smoke. The authors indicated that the primary source of these trace metals was the e-cigarette cartomizer. An exposure study with subjects who consumed e-cigarettes for 2 h in a café-like environment showed only a 2.4-fold increase of aluminum during vaping activity (482.5 vs. 203.0 ng/m³) (Schober et al., 2014). The rare-earth elements lanthanum and cerium, the concentrations of which are usually elevated by conventional tobacco smoking (Böhlandt et al., 2012), exhibited no increase and were in the range of outdoor air levels of below 0.5 ng/m³ and 1 ng/m³, respectively. No significant increase was also observed for the toxic and potentially carcinogenic elements cadmium, arsenic and thallium.

3.3.3. Metals/elements
Williams et al. (2013) tested the hypothesis that the e-cigarette aerosol contains metals derived from various components in e-cigarettes. The aerosol generated on a smoking machine contained particles >1 μm comprised of tin, silver, iron, nickel, aluminum, and silicate and nanoparticles (<100 nm) of tin, chromium and nickel. The concentrations of nine of eleven elements in the e-cigarette aerosol were higher than or equal to the corresponding concentrations in tobacco cigarette smoke. The authors indicated that the primary source of these trace metals was the e-cigarette cartomizer. An exposure study with subjects who consumed e-cigarettes for 2 h in a café-like environment showed only a 2.4-fold increase of aluminum during vaping activity (482.5 vs. 203.0 ng/m³) (Schober et al., 2014). The rare-earth elements lanthanum and cerium, the concentrations of which are usually elevated by conventional tobacco smoking (Böhlandt et al., 2012), exhibited no increase and were in the range of outdoor air levels of below 0.5 ng/m³ and 1 ng/m³, respectively. No significant increase was also observed for the toxic and potentially carcinogenic elements cadmium, arsenic and thallium.

3.3.4. Particulate matter (PM)
In contrast to conventional smoking, particles related to vaping activity are not generated from a combustion process, but by direct evaporation. Due to this different operation principle, e-cigarette particles differ substantially in chemical composition and size distribution from that of tobacco cigarettes. Airborne particles of e-cigarettes are assumed to be formed from supersaturated 1,2-propanediol vapor. Schripp et al. (2013) measured the e-cigarette aerosol in an 8 m³ test chamber and found a bimodal size distribution, with one maximum at 30 nm and one in the range of 100 nm. During the ongoing experiment, the ultrafine mode increased. The study also investigated the effect of particle aging at different temperatures and confirmed the shrinking of the particles due to evaporation. Pellegrino et al. (2012) compared PM emissions of an e-cigarette with that of a conventional cigarette and showed that fine and ultrafine PM emissions were higher for the conventional versus the e-cigarette (PM₁₀: 922 vs. 52 μg/m³; PMₐ: 80 vs. 14 μg/m³). Schober et al. (2014) observed high concentrations of PM₂.₅ (mean 197 μg/m³) during vaping activity. Particle number concentrations (PNC) ranged from 48,620 to 88,386 particles/cm³ (median) with peaks between 24 and 36 nm. For comparison, the particle size distribution of a conventional filter cigarette peaks at 100 nm and shows a higher total number concentration (Schripp et al., 2013). However, in vitro studies suggested that e-cigarette aerosol particle size and distribution in the respiratory system is similar to conventional cigarette smoke (Zhang et al., 2013b). Analogous results were also found by Fuoco et al. (2014) in their study on the physical characterization of the e-cigarette mainstream aerosol. PNC (4.39 ± 0.42 × 10⁶ particles/cm³) and distribution modes (120–165 nm), averaged across different e-cigarettes and liquids, were measured equal and were comparable to those of the conventional cigarette smoke. Because of the high vapor pressure of 1,2-propanediol, the dynamics of the e-cigarette aerosol is fast (Verkuylen, 2004). Bertholon et al. (2013) showed that the half-life of 1,2-propanediol droplets in ambient air is around 10 s, which is 100 times less than with cigarette smoke. This is caused by the rapid revaporization of the droplets at the ambient temperature. The effect was also confirmed by Ingebrethsen et al. (2012), who measured the particle size distribution of e-cigarette aerosols in an undiluted state and after high dilution. The undiluted aerosols were found to have particle diameters in the range of 250–450 nm and PNC of 10⁶ particles/cm³. After dilution very small particle diameters in the range of 50 nm were observed, which probably resulted from almost complete evaporation of the e-cigarette aerosol particles. 1,2-Propanediol is not acutely toxic and there is also no evidence of genotoxic or carcinogenic action of 1,2-propanediol in humans (Montanu et al., 2010; Werley et al., 2011). However, it cannot be deduced from this, that long-term inhalation of fine and ultrafine 1,2-propanediol droplets must be completely safe. Such particles are assumed to be deposited in the deeper parts of the lung and may cause respiratory irritations (Wieslander et al., 2001) or can increase the risk of acquiring asthma (Choi et al., 2010). Moreover, it has been shown, that the size distribution of e-cigarette particles may change within the lung and lead to the exhalation of even smaller particles (Schripp et al., 2013).

3.4. Budy burden

3.4.1. Nicotine/cotinine
Two studies provide preliminary data on nicotine absorption and carving relief by several e-cigarette products (Bullen et al., 2010; Eissenberg, 2010). Both studies were consistent in finding that nicotine absorption did not mimic tobacco cigarettes. Eissenberg found no significant increase in plasma nicotine by either of two product brands. Bullen et al. documented somewhat higher nicotine levels than Eissenberg, but these were far lower than those produced by cigarette smoking (1.3 ng/ml vs. 13.4 ng/ml) and lower than those typically produced by nicotine replacement medicines for smoking cessation (Henningfield et al., 2009). Bullen et al. did not find significant relief of tobacco withdrawal, but both investigators found some degree of carving relief.
In a recent study by Dawkins and Corcoran (2014) plasma nicotine concentration of 14 e-cigarette users rose significantly from a mean of 0.74 ng/ml at baseline to 6.77 ng/ml 10 min after 10 puffs, reaching a mean maximum of 13.91 ng/ml by the end of a 1-h vaping period. Tobacco-related withdrawal symptoms and urge to smoke were significantly reduced; direct positive effects were strongly endorsed, and there was very low reporting of adverse effects. It has also been reported that cotinine in the saliva (Etter and Bullen, 2011) and serum (Flouris et al., 2013) of e-cigarette users is significantly elevated to levels commonly found in cigarette smokers. Schober et al. (2014) characterized urine samples from nine e-cigarette users before and after a 2-h vaping session. On average, vaping e-cigarettes with nicotine resulted in a significant increase of urinary nicotine and cotinine, but not 3-OH-cotinine levels. Interestingly, 3-HPMA, the mercapturic acid metabolite of acrolein, was elevated in all subjects irrespective of the nicotine content of the aerosolized liquid. In e-cigarette solutions, glycerine is used to improve mist generation, but if heated to 280 °C acrolein can be formed. Acrolein is a strong irritant for the skin, eyes, and nasal passages and is commonly associated with the risk of lung cancer (Feng et al., 2006). Nicotine-free vaping had no impact on all urinary metabolite levels measured in this study.

3.5. Summary of health effects

3.5.1. Acute health effects

There are few data on adverse physiologic effects after short-term use of e-cigarettes (Vardavas et al., 2012). Using an e-cigarette and liquids containing <10% nicotine for only 5 min led to an immediate decrease in FeNO and an increase in airway resistance. In a similar study by Marinii et al. (2014), the authors also observed an immediate reduction of exhaled nitric oxide after short-term vaping. This effect may be attributed to nicotine and/or 1,2-propanediol that is capable of causing acute ocular and upper airway irritations in healthy individuals (Wieslander et al., 2001). Recently, a case report even described the occurrence of exogenous lipid pneumonia due to inhalation of glycerine present in e-cigarette solutions (McCauley et al., 2012). A second case study reported that a 20-year-old previously healthy man was found to develop acute eosinophilic pneumonia after vaping an e-cigarette. He was treated with antibiotics and steroids and his symptoms improved (Thota and Latham, 2014). Inconsistencies between actual and labeled nicotine levels of the liquids (see above), and hence deliveries, could be a reason why some e-cigarette consumers reported adverse reactions such as mouth and throat irritation, vertigo, headache, and nausea (Barbeau et al., 2013; Etter, 2010; Hua et al., 2013). Two other studies conducted on 37 and 32 subjects also found a series of acute effects after e-cigarette use such as cough, sore throat, eye irritation and an increase in airways resistance and heart rate (Gennimata et al., 2012; Valaki et al., 2012). The investigators concluded that vaping may harm the respiratory system. Consistently, physiologic effects in consumers were also suggested by the increase of FeNO after vaping nicotine-containing liquids (Schober et al., 2014). Whether such effects also occur in passive vapers, is uncertain. Recent data on leukocyte populations in the blood and parameters of conventional spirometry did not indicate alterations induced by passive or even active vaping of e-cigarettes (Flouris et al., 2013, 2012) but these measures are not likely to be the most sensitive markers.

3.5.2. Long-term health effects

Currently, literature on potential health risks of e-cigarette consumption is sparse, and studies investigating long-term effects are completely lacking. However, the available studies indicate that e-cigarettes mark a new source for chemical and aerosol exposure in the indoor environment. There is growing evidence that vaping impairs indoor air quality by the release of substantial amounts of VOC, PAH and other potentially harmful substances. Further research is strongly needed to address particularly the issue of long-term effects of exposure to fine and ultrafine particles formed from supersaturated 1,2-propanediol. This is relevant because e-cigarettes are used by many consumers in order to facilitate withdrawal from cigarette smoking, and secondhand exposure can also occur among vulnerable populations, including children, pregnant women, and people with cardiovascular impairments. It is obvious, that more research on the safety of e-cigarettes needs to be conducted, and that more stringent quality control should be implemented in order to ensure a high level of health protection for both consumers and secondhand vapers in the long-term.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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Al-Mutairi, S.S., Shihab-Eldeen, A.A., Mojiminiyi, O.A., Alwar, A.A., 2005. Comparison of patterns of use, tobacco smoke contamination in public premises: significant because e-cigarettes are used by many consumers in order to facilitate withdrawal from cigarette smoking, and secondhand exposure can also occur among vulnerable populations, including children, pregnant women, and people with cardiovascular impairments. It is obvious, that more research on the safety of e-cigarettes needs to be conducted, and that more stringent quality control should be implemented in order to ensure a high level of health protection for both consumers and secondhand vapers in the long-term.


