International Journal of Hygiene and Environmental Health xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

# Systemic absorption of nicotine following acute secondhand exposure to electronic cigarette aerosol in a realistic social setting

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ARTICLE INFO

*Keywords:*
Nicotine
E-cigarette
Secondhand
Aerosol
Cotinine

ABSTRACT

Evidence suggests exposure of nicotine-containing e-cigarette aerosol to nonusers leads to systemic absorption of nicotine. However, no studies have examined acute secondhand exposures that occur in public settings. Here, we measured the serum, saliva and urine of nonusers pre- and post-exposure to nicotine via e-cigarette aerosol. Secondarily, we recorded factors affecting the exposure.

Six nonusers of nicotine-containing products were exposed to secondhand aerosol from ad libitum e-cigarette use by three e-cigarette users for 2 h during two separate sessions (disposables, tank-style). Pre-exposure (baseline) and post-exposure peak levels (Cmax) of cotinine were measured in nonusers' serum, saliva, and urine over a 6-hour follow-up, plus a saliva sample the following morning. We also measured solution consumption, nicotine concentration, and pH, along with use behavior.

Baseline cotinine levels were higher than typical for the US population (median serum session one = 0.089 ng/ml; session two = 0.052 ng/ml). Systemic absorption of nicotine occurred in nonusers with baselines indicative of no/low tobacco exposure, but not in nonusers with elevated baselines. Median changes in cotinine for disposable exposure were 0.007 ng/ml serum, 0.033 ng/ml saliva, and 0.316 ng/mg creatinine in urine. For tank-style exposure they were 0.041 ng/ml serum, 0.060 ng/ml saliva, and 0.948 ng/mg creatinine in urine. Finally, we measured substantial differences in solution nicotine concentrations, pH, use behavior and consumption.

Our data show that although exposures may vary considerably, nonusers can systemically absorb nicotine following acute exposure to secondhand e-cigarette aerosol. This can particularly affect sensitive subpopulations, such as children and women of reproductive age.

## 1. Introduction

Studies show a dramatic increase in experimentation and use of electronic cigarettes among US adults and youth (Arrazola et al., 2014; Giovenco et al., 2014; King et al., 2015). One area of particular concern to the public health community is nonusers' exposure to the contents of e-cigarette aerosol, particularly sensitive subpopulations such as children, the developing fetus and pregnant women. In addition to nicotine, e-cigarettes' aerosols can contain heavy metals, ultrafine particles, and cancer-causing agents like acrolein (Goniewicz et al., 2013a; McAuley et al., 2012; Pellegrino et al., 2012; Schober et al., 2013; Schripp et al., 2013). The aerosol of e-cigarettes can also contain propylene glycol (PG) or vegetable glycerin (VG) and flavorings. The health effects of chronic inhalation of these substances are currently unknown. Moreover, fundamental questions remain about what compounds to measure, how best to measure them, and how best to describe the variable effects of e-cigarette solutions, uses, and devices when assessing health threats from e-cigarettes.

Most e-cigarettes deliver aerosolized nicotine, which raises concerns for nonusers about the potential for acute poisonings, developmental and reproductive toxicity, and addiction (Chatham-Stephens et al., 2014; England et al., 2015; U.S. Department of Health and Human

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https://doi.org/10.1016/j.ijheh.2018.05.003
Received 18 January 2018; Received in revised form 27 April 2018; Accepted 15 May 2018
1438-4639/ Published by Elsevier GmbH.

Services, Printed with corrections, January 2014). Studies have measured nicotine in air following e-cigarette aerosol generation (Czogala et al., 2013; Schripp et al., 2013), and Flouris and colleagues exposed never-smokers to machine-generated e-cigarette aerosol in an exposure chamber for a single hour and measured serum cotinine concentrations immediately after the exposure and an hour later (Flouris et al., 2013). Although the values were not published, cotinine concentrations in the never-smokers passively exposed to e-cigarette aerosol were significantly higher than in a control group. Similarly, Ballbe and colleagues measured urine and salivary cotinine in nonusers who lived with exclusive e-cigarette users (n = 5) and found significantly higher levels of cotinine in these nonusers compared to nonusers living in homes where no smoker or e-cigarette user was living (n = 24), both in urine and saliva (p-values 0.008 and 0.003, respectively) (Ballbe et al., 2014).

However, these studies did not simulate realistic short-term exposures that occur in social or public settings, nor did they describe the factors affecting the exposures. To address this gap in the scientific literature, we examined acute secondhand nicotine exposure to nonusers by using three habitual e-cigarette users (active users) vaping ad libitum in a room co-occupied by six nonusers for two hours. The number of e-cigarette users for each exposure represented a plausible number of users in a physical space comparable to public spaces such as bars or restaurants, or to a private space such as a household room. We also accounted for other sources of nicotine exposure and the extent to which certain factors, such as solution and device characteristics, as well as how the e-cigarette users used their device (use behavior) might affect exposure.

## 2. Methods

### 2.1. General procedure and setting

Both sessions were conducted in a 6.10mX3.35 m X 2.57 m or 52.6m$^3$ (20′x11′X8′5″ or 1858ft$^3$) room kept at 26 °C (78.8 °F). The room was equipped with furnishings covered in fabric materials that allowed the aerosol to deposit on and recirculate from surfaces more commonly found in living and social quarters. The room was cleaned of background nicotine contamination before each exposure session by including wiping down hard surfaces and pre-washing fabric materials. Each participant wore a clean surgical top to prevent contamination from their clothes and to limit dermal absorption. The door and windows remained closed during the sessions. Room air ventilation measurements (~5 air changes per hour), layout of the exposure room, and air nicotine concentrations for each nonuser were previously published in Melstrom, et al. (Melstrom et al., 2017). A 2-hour time length was chosen as a realistic duration for how long a member of the public who does not use nicotine-containing products might be exposed to e-cigarette aerosol in a social setting. All participants were allowed to perform normal activities during the sessions. In addition, because of the several different types of e-cigarette products now available, including first generation e-cigarettes (i.e., disposable, cig-a-like) and second generation tank systems (Fig. 1), we conducted two separate exposure sessions to account for e-cigarettes' market diversity. During the first session, the active users used first generation e-cigarettes and tank-style second generation e-cigarettes during the second. Except for the type of e-cigarette used, both sessions were conducted identically. All participants were present for both sessions. On each study day, within 2 h prior to the 2-hour exposure, the following were obtained from the nonusers: blood, urine, and saliva samples; blood pressure; pulse; expired carbon monoxide and self-reported symptoms.

Before and following each exposure, the masses of the e-cigarette products were measured to determine the amount of e-cigarette solution used during the exposure. The amount of nicotine consumed could then be calculated by converting the mass of solution consumed into volume by dividing the mass of solution by either the specific density of PG (1.032 g/cm$^3$) or of VG (1.261 g/cm$^3$) or, if the solution was a blend, by estimating it to be a 50:50 ratio and averaging the specific density to 1.147 g/cm$^3$. The volume could then be multiplied by the measured nicotine concentration to yield mass of nicotine consumed during the exposure.


**Fig. 1.** Electronic cigarettes used: first generation disposable e-cigarette (A) and second generation tank-style e-cigarette (B)*.

After each 2-hour exposure, the active users were discharged, and the nonusers monitored for an additional 6 h for collection of biological samples. Finally, the unused e-cigarette cartridges and solutions were collected and sent to the Centers for Disease Control and Prevention (CDC) for analysis of pH and nicotine concentrations, where the latter analysis was performed in a manner that aligned with the method described in Stanfill et al (Stanfill et al., 2009). Analysis of pH was performed as previously described with minor modifications.(U.S. federal register, 1999) Using the measured pH values, $pKa_{nicotine} = 8.02$ (Rumble, 2017) and the Henderson-Hasselbalch equation pH = pKa + log10([Base]/[Acid]), the percentage of nicotine in the unionized, or free-base, form was calculated.

### 2.2. Participants

Inclusion criteria for both nonusers and active users: male or non-pregnant, non-breastfeeding female; 21–55 years; healthy-by-history; able to commit to both sessions. Specific criteria for nonusers: never-users of combustible tobacco products (never smoked more than 100 cigarettes in their lifetime), no use in the past year of non-combustible tobacco products (eg, smokeless tobacco) or nicotine replacement therapies. Nonusers agreed to abstain from exposure to secondhand tobacco smoke or e-cigarette aerosol for 6 days before each exposure. However, they must have had a history of tolerating exposure to secondhand tobacco smoke to establish that they were assuming no more risk by study participation than they had previously assumed without incident. At the screening visit and before each session, nonusers were given an exhaled carbon monoxide breath test and a spot urinalysis. They were required to have an expired carbon monoxide level < 6 ppm, an undetectable measured urine cotinine concentration (NicAlert, Nymox Pharmaceutical Corporation, Hasbrouck Heights, New Jersey), and for females, a negative pregnancy test (Sure-Vue, Fisher Scientific, Waltham, Massachusetts). Specific criteria for active users: having used an e-cigarette for more than 6 months, having used both a tank-style and a first generation e-cigarette, and currently using a tank-style at least 5 times per day with at least 18 mg/ml concentrated nicotine solution.

Exclusion criteria included: having respiratory symptoms on study days; having chronic obstructive pulmonary disease; having had a stroke; having cancer within the past 5 years; having tuberculosis by history or chronic cough; having cardiac disease; having asthma or severe allergic rhinitis; having allergy or hypersensitivity to nicotine or a component of e-cigarette solution, including PG and VG; having hypertension (blood pressure > 150/95 after 5 min rest or by history); showing obvious intoxication or positive drug screen for cocaine, amphetamines, methamphetamine, or opiates (One Step Drug of Abuse