

## Research Article

Benzene Uptake in Hookah Smokers and Non-smokers  
Attending Hookah Social Events: Regulatory Implications

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## Abstract

**Background:** Benzene is a human hematotoxicant and a leukemogen that causes lymphohematopoietic cancers, especially acute myelogenous leukemia. We investigated uptake of benzene in hookah smokers and non-smokers attending hookah social events in naturalistic settings where hookah tobacco was smoked exclusively.

**Methods:** We quantified *S*-phenylmercapturic acid (SPMA), a metabolite of benzene, in the urine of 105 hookah smokers and 103 non-smokers. Participants provided spot urine samples the morning of and the morning after attending an indoor hookah-only smoking social event at a hookah lounge or in a private home.

**Results:** Urinary SPMA levels in hookah smokers increased significantly following a hookah social event ( $P < 0.001$ ). This increase was 4.2 times higher after hookah lounge events ( $P < 0.001$ ) and 1.9 times higher after home events ( $P = 0.003$ ). In non-smokers, urinary SPMA levels increased 2.6 times after hookah lounge events ( $P = 0.055$ ); however, similar urinary SPMA levels were detected before and after home events, possibly indicating chronic exposure to benzene ( $P = 0.933$ ).

**Conclusions:** Our data provide the first evidence for uptake of benzene in hookah smokers and non-smokers exposed to hookah tobacco secondhand smoke at social events in private homes compared with their counterparts in hookah lounges. Hookah tobacco smoke is a source of benzene exposure, a risk factor for leukemia.

**Impact:** Because there is no safe level of exposure to benzene, our results call for interventions to reduce or prevent hookah tobacco use, regulatory actions to limit hookah-related exposure to toxicants including benzene, initiate labeling of hookah-related products, and include hookah smoking in clean indoor air legislation. *Cancer Epidemiol Biomarkers Prev*; 23(12); 1–17. ©2014 AACR.

## Introduction

Tobacco use, the leading global preventable cause of mortality, is responsible for the death of about 6 million people worldwide each year (1, 2). Hookah smoking, also known as waterpipe, is a tobacco use method in which smoke passes through a partially filled water jar (3). Burning charcoal heats the hookah tobacco which produces the smoke that the user inhales. The most popular hookah tobacco is *Moassel*, which is sweetened

and flavored tobacco (3–6). *Moassel* contains about 30% tobacco fermented with molasses and fruits mixed with glycerin and flavoring chemical substances (3–6). The increase in the popularity of hookah tobacco smoking has been reported around the world (7, 8). In the United States, in 2013, 26.6% of male and 23.2% of female college students nationally reported ever using hookah (9). Among middle- and high school students, the National Youth Tobacco Survey in 2011 showed that 8.1% of males and 6.6% of females nationally ever used hookah (10). This is alarming because hookah tobacco smoking has been associated with increased risk for lung and oral cancers, coronary heart disease, and pulmonary disease (11–13).

Hookah smoking is often practiced in social settings (14). Hookah smokers may smoke alone or in groups of two or more per hookah (15). Hookah smokers and their non-smoker friends and/or family members gather around a hookah or several hookahs during lengthy social sessions (14, 16). Non-smokers may enjoy the social occasion in which hookah smoking is an inclusive activity (14). Hookah tobacco users smoke in hookah lounges and in private homes (14, 17, 18).

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A hookah lounge is a commercial venue that offers its patrons the opportunity to smoke tobacco using a hookah. These venues may also offer food, alcohol, free internet access, dancing, and live music (19). Hookah lounges are opening at an increasing rate in the United States (20). Owners of hookah lounges often advertise via the internet alluding to an atmosphere that is pleasurable, relaxed, and entertaining, indicating at times that hookah smoking is safer than cigarette smoking (19). However, studies have shown that patrons of hookah lounges are exposed to indoor air quality levels considered hazardous to human health (15, 21, 22). High mean levels of fine particulate matter (PM<sub>2.5</sub>) pollution, a marker for tobacco smoke, were detected in indoor hookah smoking venues in the United States, Canada, and Pakistan (374  $\mu\text{g}/\text{m}^3$ , 1,419  $\mu\text{g}/\text{m}^3$ , and up to 1,745  $\mu\text{g}/\text{m}^3$ , respectively; refs. 15, 21, 22). These PM<sub>2.5</sub> concentrations were well above the Environmental Protection Agency (EPA) guidelines for air quality standards that identified that average annual levels in excess of 12  $\mu\text{g}/\text{m}^3$ , or daily exposure in excess of 35  $\mu\text{g}/\text{m}^3$ , pose health risks (23).

Private homes represent another social setting where hookah tobacco smoking takes place (3, 17), (18, 24). In the United States, 43.4% to 79.0% of hookah-smoking university students surveyed reported smoking hookah at home or in their dormitory (17, 24). Hookah tobacco smoking inside homes is hazardous to human health, including the non-smokers who live in these homes (18). In a recent study, we provided the first evidence for uptake of nicotine and the tobacco-specific lung carcinogen 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in children living in homes of hookah smokers; we also detected high levels of nicotine contamination on household surfaces of living rooms and bedrooms in these homes (18). Thus, hookah tobacco smokers and the non-smokers who live or socialize with them are at risk for potential exposure to a combination of hookah tobacco smoke and emissions from hookah charcoal combustion.

Benzene, a tobacco and charcoal toxic constituent, has been quantified in cigarette and hookah tobacco smoke, and has been assessed as the predominant aromatic compound emitted from glowing charcoal (25–29). Scientific evidence has established that benzene is a human hematotoxicant and a leukemogen that causes lymphohematopoietic cancers, especially acute myelogenous leukemia (30–33). The World Health Organization's (WHO) International Agency for Research on Cancer (IARC) and the U.S. National Toxicology Program classified benzene as a Group 1 carcinogen (34, 35). The WHO reported that benzene is carcinogenic to humans, and no safe level of exposure can be recommended (36).

Benzene exposure occurs mostly through inhalation; however, it must be metabolized to become carcinogenic (33, 36, 37). Benzene is metabolically activated to the reactive species benzene oxide which in turn reacts with glutathione, catalyzed by glutathione *S*-transferases, and undergoes further metabolism to be excreted in the urine as *S*-phenylmercapturic acid (SPMA; ref. 38). Benzene expo-

sure can be monitored by SPMA, a minor metabolite of benzene and a highly specific urinary biomarker (39, 40). Only 0.11% (0.05%–0.26%) of inhaled benzene is metabolized to SPMA, which has a short half-life; mean ranges from 9 to 13 hours (39–41). Cigarette smoking is regarded as a source of benzene intake and an established risk factor for adult acute myelogenous leukemia (42–49). Cigarette smokers have elevated excretion of SPMA, as much as ten times higher than non-smokers (50). In the United States, about half of the total national exposure to benzene comes from cigarette smoke (35). Although research has been focusing on cigarette smoking, the prevalence of hookah tobacco smoking has been increasing (7–10). A recent crossover study conducted on a clinical research ward demonstrated that exposure to benzene when smoking hookah tobacco was 2.5 times higher than when smoking cigarettes, probably because burning hookah charcoal is a major source of benzene [SPMA: geometric mean (GM) = 1.73  $\mu\text{g}/24\text{ h}$  vs. 0.695  $\mu\text{g}/24\text{ h}$ ,  $P = 0.03$ , respectively; ref. 51]. Exposure to benzene in hookah tobacco smokers may be a potential risk factor for leukemia. There is a need for studies on the uptake of benzene in hookah smokers and non-smokers exposed exclusively to hookah tobacco secondhand smoke (SHS) in social settings.

The WHO reported that active and passive exposure to tobacco smoke is a significant source of exposure to benzene (36). To our knowledge, this is the first study that measured SPMA in the urine of hookah smokers and non-smokers before and after an indoor hookah-only smoking social event in private homes comparing them with their counterparts at hookah lounges.

## Materials and Methods

### Study design

A pre and post group comparison design was used. Trained research assistants (RAs) collected data from a convenience sample ( $N = 208$ ) comprised of hookah smokers ( $n = 105$ ) and non-smokers ( $n = 103$ ) exposed exclusively to hookah tobacco SHS at hookah lounges or in private homes in San Diego County, California. Data were collected between 2009 and 2011 and included tobacco use, demographics, hookah smoking session observation, and two urine samples per participant. Study participants received \$75 as an incentive. Procedures were approved by the San Diego State University Institutional Review Board.

### Inclusion criteria

Eligible participants were 18 years or older, hookah smokers, or non-smokers. Hookah smokers were eligible if they had smoked exclusively hookah tobacco and had not used any other tobacco product in the past 30 days. Non-smokers were eligible if they had not been exposed to SHS from any tobacco product other than hookah tobacco in the past 30 days.

### Recruitment, screening, and consent

Participants were recruited from the community via intercept brief screening interviews. Hookah smokers

were asked to recruit their non-smoker friends and/or relatives. Participants were assigned to either a hookah lounge event or a home event based on their preference in addition to responding "almost always" to a screening form question asking about the usual location of attending hookah events in the past 6 months. Qualified persons were invited to our research center for group training on data collection. During training, participants provided an informed consent and completed a Tobacco Use History questionnaire, which included past and current hookah use, other tobacco products use, smoking rules in homes, health history, and demographics. Participants were then provided with two coded urine cups and study activities check lists. Participants chose the day of the social gathering at a hookah lounge or at a home of a hookah smoker participant. NicAlert, a commercial semiquantitative instant saliva cotinine test, was used to validate non-smoking status, and as a bogus pipeline technique (52–54). Non-smoking participants were informed about the purpose of the NicAlert test during the informed consent process.

### Hookah events

Participants in groups of 6 to 12, comprised of hookah smokers and non-smokers, spent an average of three consecutive hours indoors either in a hookah lounge (hookah smoker:  $n = 55$ ; non-smoker:  $n = 53$ ) or in a private home (hookah smoker:  $n = 50$ ; non-smoker:  $n = 50$ ) anytime between the hours of 7 pm and 1 am where hookah tobacco was exclusively smoked. To observe any evidence of other tobacco use during the hookah events, and answer any questions the participants may have had, two hookah smoker RAs were present during the entire event at hookah lounges and homes where the hookah social events occurred. Hookah smokers were asked to smoke as they usually do. Non-smokers were asked to perform the activities that they usually do when socializing with hookah smokers. During the hookah social event, hookah smokers counted the number of hookah heads they smoked. A hookah head was defined as one hookah tobacco serving equivalent to 10 to 20 g of hookah tobacco (55). Using cell phones, every 30 minutes for a total of 3 hours, every participant recorded the number of active hookah heads being smoked by other hookah smokers with the first count starting at point of entry to the hookah lounge or home. An active hookah head was defined as a hookah head being smoked (a hookah smoker holding the hookah hose). Following the hookah event, all participants completed a Hookah Event Observation form. On the basis of this form, we calculated the average number of hookah heads smoked by the smoker participants and by others during hookah events.

### Biologic measures

Two first-void spot urine samples were provided by participants, the morning of the hookah event day and the following morning, to measure urinary biomarkers of carcinogens and toxicants. Participants stored the urine

samples in the freezer section of their refrigerator until pickup or drop off within 12 hours. Urine samples were then transferred frozen to our research center laboratory. Participants who opted to drop off urine samples were given coolers and ice packs during the group training for the transfer of frozen samples. Urine samples were aliquoted and stored in a freezer ( $-20^{\circ}\text{C}$ ), then sent frozen in dry ice to two laboratories. The Masonic Cancer Center, University of Minnesota laboratory conducted urinary analyses for SPMA by LC-APCI-MS/MS-SRM with a limit of detection (LOD) of 0.03 pmol/mL as previously described (56). San Diego State University Laboratory conducted urinary analyses for creatinine by LC-MS/MS that was linear from 0.3 to 1,000 mg/dl (see supplementary Data for details on creatinine analyses).

### Statistical analysis

The following analyses were conducted: Wilcoxon signed-rank tests to identify differences in SPMA levels before and after hookah events; Mann-Whitney  $U$  tests to identify differences in pre to post hookah event change in SPMA levels, by location of hookah event and by hookah use pattern; Pearson correlation coefficients to determine associations of change in SPMA levels with time spent at events, with number of hookah heads smoked by (i) the participant and (ii) other hookah smokers; and independent  $t$  tests or  $\chi^2$  tests where applicable to identify differences in demographics by smoking status. Uncorrected (pmol/mL) and creatinine-corrected (pmol/mg creatinine) arithmetic means and SDs, GMs and 95% confidence intervals (CI), medians and 5th and 95th percentiles, and minimum and maximum levels were computed for SPMA. Because SPMA is a minor metabolite and exposure to benzene is generally low, there were 114 samples below the LOD out of 410 samples: 38 in non-smokers at home, 51 in non-smokers at lounge, 10 in smokers at home, and 15 in smokers at lounge; and there was one interference value. We excluded the interference value and replaced the nondetectable values of SPMA with the LOD of SPMA divided by 2 ( $0.03 \text{ pmol/mL}/2 = 0.015 \text{ pmol/mL}$ ). All statistical tests were two-tailed with an  $\alpha$  level of 0.05 and were conducted using SPSS version 21 and Stata version 11. Monthly and occasional hookah smokers were combined and renamed occasional hookah smokers. Creatinine-corrected SPMA data are discussed below. Throughout the remainder of the article, location of hookah event refers to either a hookah lounge or a private home; "pmol/mg creatinine" is referred to as "pmol/mg"; "indoor hookah-only smoking social events" are referred to as "hookah events," "hookah lounge events," or "home events"; and "hookah tobacco smoking" is referred to as "hookah smoking."

### Results

Hookah smokers were younger than non-smokers, had more close friends who were current hookah smokers, were more likely to allow hookah smoking inside their

homes, and to live with at least one hookah smoker. Hookah smokers were daily (19.1%), weekly (43.8%), monthly (25.7%), or occasional (11.4%) smokers who exclusively smoked flavored hookah tobacco, *Moassel*. Hookah smokers and non-smokers did not differ significantly by gender, racial/ethnic makeup, or body mass index (Table 1).

Daily hookah smokers at hookah lounges smoked more hookah heads than their counterparts in homes (median, 10 hookah heads vs. 2 hookah heads,  $P = 0.005$ , respectively; Table 2). No significant difference was found in number of hookah heads smoked by location of hookah event among weekly or occasional smokers. Daily hookah smokers smoked more hookah heads than weekly ( $P = 0.021$ ) or occasional ( $P = 0.010$ ) hookah smokers at hookah lounges; however, no significant difference was found between groups in home events. Among hookah smokers overall, pre to post event change in SPMA levels was positively correlated with number of hookah heads smoked by participants at hookah lounge events ( $r = 0.287$ ,  $P = 0.043$ ); the correlation was not significant for home events ( $P = 0.568$ ).

Number of hookah heads smoked by hookah smokers other than the participants during the hookah events was higher in hookah lounges than in homes (median, 81 hookah heads vs. 21 hookah heads;  $P < 0.001$ , respectively). In all hookah events, pre to post event change in SPMA levels in hookah smokers was positively correlated with number of hookah heads smoked by others at the event ( $r = 0.277$ ,  $P = 0.006$ ). When split by location, change in SPMA levels in hookah smokers showed a stronger positive correlation with number of hookah heads smoked by others in home events ( $r = 0.455$ ,  $P = 0.002$ ); the correlation was not significant for hookah lounge events ( $P = 0.110$ ).

There was no significant difference between hookah smokers and non-smokers in time spent at hookah events (Table 2). The majority of hookah smokers [77.1% (81 of 105)] and non-smokers [71.8% (74 of 103)] spent 180 minutes (3 hours) at the hookah event (Fig. 1). Pre to post event change in SPMA levels was not correlated with time spent at the event among hookah smokers (lounge:  $P = 0.978$ ; home:  $P = 0.345$ ) or non-smokers (lounge:  $P = 0.588$ ; home:  $P = 0.297$ ).

### Exposure to benzene

Urinary SPMA levels for hookah smokers and non-smokers in both uncorrected and creatinine-corrected values before and after a hookah event are presented in Table 3. Detection of urinary SPMA increased from 82% to 94% of the samples among hookah smokers overall, compared with an increase from 53% to 60% of the samples among non-smokers pre to post hookah event. Urinary SPMA was detected in 100% of post event samples among daily hookah smokers.

In hookah smokers, urinary SPMA levels after a hookah event ranged from nondetectable to 9.42 pmol/mg. Overall, urinary SPMA levels in hookah smokers increased 2.7 times after hookah event (median, from 0.23 pmol/mg to

0.62 pmol/mg,  $P < 0.001$ ). Daily, weekly, and occasional hookah smokers had significantly higher levels of urinary SPMA than non-smokers pre and post hookah events. In daily hookah smokers, urinary SPMA levels after hookah event were 8.5 times higher than those found in non-smokers (median, 1.28 pmol/mg vs. 0.15 pmol/mg,  $P < 0.001$ , respectively). Urinary SPMA levels before hookah event for occasional smokers were higher than those of weekly smokers. About half of the hookah smoker participants overall (53 of 102) reported smoking the day before the study hookah event.

In non-smokers, urinary SPMA levels after a hookah event ranged from nondetectable to 4.77 pmol/mg. Urinary SPMA levels did not change significantly in non-smokers overall after hookah event (median, from 0.08 pmol/mg to 0.15 pmol/mg,  $P = 0.206$ ). Non-smokers were hookah smokers' friends or relatives, and were likely exposed to hookah tobacco smoke before the study. About half (47.5%) of the non-smokers reported at least one of their four closest friends currently smoked hookah, 13.3% lived with one or more hookah smoker, and more than one third (38.8%) reported that hookah smoking was allowed inside their homes (Table 1).

### Exposure to benzene by location of event

Urinary SPMA levels for hookah smokers and non-smokers in both uncorrected and creatinine-corrected values before and after a hookah event by location of event are presented in Tables 4 and 5. Among all hookah smokers, pre to post event change in SPMA levels was significantly higher for hookah lounge events compared with home events ( $P = 0.034$ ); urinary SPMA levels increased 4.2 times after hookah lounge events (median, from 0.20 pmol/mg to 0.83 pmol/mg,  $P < 0.001$ ), and increased 1.9 times after home events (median, from 0.32 pmol/mg to 0.60 pmol/mg,  $P = 0.003$ ). The highest increase in urinary SPMA levels was found in daily hookah smokers at hookah lounge events; SPMA levels were 14.2 times higher after event (median, from 0.25 pmol/mg to 3.56 pmol/mg,  $P = 0.043$ ).

In daily hookah smokers, urinary SPMA levels were 27.4 times higher than in non-smokers after hookah lounge events (median, 3.56 pmol/mg vs. 0.13 pmol/mg,  $P < 0.001$ ) and 7.8 times higher after home events (median, 1.24 pmol/mg vs. 0.16 pmol/mg,  $P < 0.001$ ), respectively. For occasional smokers at home events ( $n = 9$ ), urinary SPMA levels before event were higher than after event (median, 0.51 pmol/mg vs. 0.19 pmol/mg,  $P = 0.139$ ); four of 9 lived with a hookah smoker, and 2 smokers had relatively high SPMA levels before event (2.25 pmol/mL and 2.38 pmol/mL) compared with after event (nondetectable and 0.92 pmol/mL) of whom one smoked at a hookah party the day before the study event and one was a beach lifeguard.

In non-smokers, urinary SPMA did not change significantly after home events (median, from 0.14 pmol/mg to 0.16 pmol/mg,  $P = 0.993$ ); however, it did increase 2.6 times after hookah lounge events approaching

**Table 1.** Characteristics of hookah smokers and non-smokers ( $N = 208$ )<sup>a</sup>

|  | Hookah smokers<br>( $n = 105$ ) | Non-smokers<br>( $n = 103$ ) | $P^b$            |
|--|---------------------------------|------------------------------|------------------|
|  | $n$ (%)                         | $n$ (%)                      |                  |
| Age (years)  |                                 |                              |                  |
| Mean ( $\pm$ SD)   | 26.9 ( $\pm$ 10.5)              | 32.0 ( $\pm$ 12.0)           | <b>0.001</b>     |
| Median (minimum–maximum)   | 22 (18–61)                      | 28 (18–67)                   |                  |
| Gender   |                                 |                              |                  |
| Male   | 57 (54.3)                       | 49 (47.6)                    | 0.333            |
| Female   | 48 (45.7)                       | 54 (52.4)                    |                  |
| Race/ethnicity   |                                 |                              |                  |
| Arab American  | 52 (50.5)                       | 40 (38.8)                    | 0.179            |
| White, Caucasian   | 18 (17.5)                       | 25 (24.3)                    |                  |
| Mexican, Hispanic, or Latino   | 8 (7.8)                         | 13 (12.6)                    |                  |
| Black or African American  | 2 (1.9)                         | 6 (5.8)                      |                  |
| Other  | 23 (22.3)                       | 19 (18.5)                    |                  |
| Body mass index (BMI; kg/m <sup>2</sup> )  |                                 |                              |                  |
| <25 normal   | 51 (48.6)                       | 43 (41.8)                    | 0.499            |
| $\geq$ 25 overweight   | 39 (37.1)                       | 40 (38.8)                    |                  |
| $\geq$ 30 obese  | 15 (14.3)                       | 20 (19.4)                    |                  |
| Do you currently smoke hookah?   |                                 |                              |                  |
| Daily (at least once each day)   | 20 (19.1)                       | 0 (0.0)                      |                  |
| Weekly (at least once each week but less than daily)                                       | 46 (43.8)                       | 0 (0.0)                      |                  |
| Monthly (at least once each month but less than weekly)                                    | 27 (25.7)                       | 0 (0.0)                      |                  |
| Occasionally (at least once a year but less than monthly)                                  | 12 (11.4)                       | 0 (0.0)                      |                  |
| Type of hookah tobacco currently smoke   |                                 |                              |                  |
| Flavored   | 100 (100.0)                     | 0 (0.0)                      |                  |
| Unflavored   | 0 (0.0)                         | 0 (0.0)                      |                  |
| Owns a hookah at home  |                                 |                              |                  |
| Yes  | 76 (73.8)                       | 6 (7.0)                      | <b>&lt;0.001</b> |
| No   | 27 (26.2)                       | 95 (93.0)                    |                  |
| Number of your four closest friends who currently smoke hookah                             |                                 |                              |                  |
| 0  | 9 (9.2)                         | 42 (52.5)                    | <b>&lt;0.001</b> |
| 1  | 6 (6.1)                         | 17 (21.2)                    |                  |
| 2  | 19 (19.4)                       | 7 (8.8)                      |                  |
| 3  | 15 (15.3)                       | 6 (7.5)                      |                  |
| 4  | 49 (50.0)                       | 8 (10.0)                     |                  |
| Number of people residing in your home who currently smoke hookah, including yourself      |                                 |                              |                  |
| 0  | 6 (6.2)                         | 78 (86.7)                    | <b>&lt;0.001</b> |
| 1  | 40 (41.2)                       | 7 (7.8)                      |                  |
| 2  | 29 (29.9)                       | 3 (3.3)                      |                  |
| $\geq$ 3   | 22 (22.7)                       | 2 (2.2)                      |                  |
| Home hookah smoking restriction  |                                 |                              |                  |
| Allowed everywhere   | 22 (22.0)                       | 3 (3.1)                      | <b>&lt;0.001</b> |
| Allowed special guest/certain location   | 64 (64.0)                       | 35 (35.7)                    |                  |
| Not allowed anywhere   | 14 (14.0)                       | 60 (61.2)                    |                  |
| In the past 30 days, how many days did people smoke hookah around you inside your home?    |                                 |                              |                  |
| At least one day   | 49 (46.7)                       | 12 (13.3)                    | <b>&lt;0.001</b> |
| Not at all   | 56 (53.3)                       | 89 (86.7)                    |                  |
| In the past 30 days, how many days did people smoke hookah around you inside other places? |                                 |                              |                  |
| At least one day   | 75 (75.0)                       | 11 (11.3)                    | <b>&lt;0.001</b> |
| Not at all   | 25 (25.0)                       | 86 (88.7)                    |                  |

NOTE: Significant levels are shown in bold.

<sup>a</sup>Due to missing values, numbers of categories of some variables do not sum to the total sample size.<sup>b</sup> $P$  Smokers vs. non-smokers:  $P$  values were derived from Mann–Whitney  $U$  tests; two-tailed  $\alpha$  level  $P < 0.05$ .

**Table 2.** Number of hookah heads smoked by participants and by others during an indoor hookah-only social event

|  | Hookah smokers by location of event              |                                   |                          | <i>P</i> <sup>b</sup> |
|--|--|-----------------------------------|--------------------------|-----------------------|
|  | Hookah smokers<br>( <i>n</i> = 105) <sup>a</sup> | Hookah lounge<br>( <i>n</i> = 55) | Home<br>( <i>n</i> = 50) |                       |
| Number of hookah heads <sup>c</sup> smoked during an indoor hookah-only social event | <i>n</i> (%)                                     | <i>n</i> (%)                      | <i>n</i> (%)             |                       |
| One hookah head  | 26 (26.8)  | 10 (19.2)                         | 16 (35.6)                | <b>0.025</b>          |
| Two hookah heads   | 26 (26.8)  | 15 (28.9)                         | 11 (24.4)                |                       |
| Three hookah heads   | 24 (24.7)  | 9 (17.3)                          | 15 (33.3)                |                       |
| Four or more hookah heads  | 21 (21.7)  | 18 (34.6)                         | 3 (6.7)                  |                       |
| Did you share the hookah with anyone?  |  |                                   |                          |                       |
| Yes  | 92 (92.9)  | 50 (92.6)                         | 42 (93.3)                | 0.887                 |
| No   | 7 (7.1)  | 4 (7.4)                           | 3 (6.7)                  |                       |
| Number of hookah heads smoked by participants  |  |                                   |                          |                       |
| All hookah smokers ( <i>n</i> = 105)   |  |                                   |                          |                       |
| Mean (±SD)   | 3.26 (±3.32)                                     | 3.67 (±3.42)                      | 2.78 (±3.17)             | <b>0.025</b>          |
| GM (95% CI)  | 2.39 (2.07–2.77)                                 | 2.75 (2.24–3.37)                  | 2.04 (1.65–2.51)         |                       |
| Median (5–95 percentile)   | 2 (1–12)   | 3 (1–10)                          | 2 (1–13)                 |                       |
| (Minimum–maximum)  | (1–19)   | (1–19)                            | (1–16)                   |                       |
| Daily hookah smokers ( <i>n</i> = 20)  |  |                                   |                          |                       |
| Mean (±SD)   | 4.06 (±4.98)                                     | 9.6 (±6.58)                       | 1.75 (±0.75)             | <b>0.005</b>          |
| GM (95% CI)  | 2.52 (1.57–4.04)                                 | 7.44 (2.51–22.11)                 | 1.60 (1.21–2.12)         |                       |
| Median (5–95 percentile)   | 2 (1–19)   | 10 (2–19)                         | 2 (1–3)                  |                       |
| (Minimum–maximum)  | (1–19)   | (2–19)                            | (1–3)                    |                       |
| Weekly hookah smokers ( <i>n</i> = 46)   |  |                                   |                          |                       |
| Mean (±SD)   | 3.16 (±3.02)                                     | 3.42 (±2.82)                      | 2.96 (±3.21)             | 0.332                 |
| GM (95% CI)  | 2.32 (1.84–2.93)                                 | 2.55 (1.74–3.73)                  | 2.16 (1.59–2.94)         |                       |
| Median (5–95 percentile)   | 2 (1–10)   | 3 (1–10)                          | 2 (1–13)                 |                       |
| (Minimum–maximum)  | (1–13)   | (1–10)                            | (1–13)                   |                       |
| Occasional hookah smokers ( <i>n</i> = 39)   |  |                                   |                          |                       |
| Mean (±SD)   | 3.00 (±2.72)                                     | 2.79 (±1.76)                      | 3.67 (±4.72)             | 0.755                 |
| GM (95% CI)  | 2.42 (1.97–2.96)                                 | 2.42 (1.98–2.97)                  | 2.40 (1.22–4.69)         |                       |
| Median (5–95 percentile)   | 2 (1–10)   | 2 (1–5)                           | 3 (1–16)                 |                       |
| (Minimum–maximum)  | (1–16)   | (1–10)                            | (1–16)                   |                       |
| <i>P</i> <sup>d</sup> daily vs. weekly   | 0.926  | <b>0.021</b>                      | 0.198                    |                       |
| <i>P</i> <sup>e</sup> daily vs. occasionally   | 0.604  | <b>0.010</b>                      | 0.203                    |                       |
| <i>P</i> <sup>f</sup> weekly vs. occasionally  | 0.728  | 0.764                             | 0.717                    |                       |
| Time spent at hookah events by smokers (minutes)                                     |  |                                   |                          |                       |
| Mean (±SD)   | 183.1 (±13.01)                                   | 181.9 (±7.49)                     | 184.6 (±17.49)           | 0.419                 |
| GM (95% CI)  | 182.7 (180.1–185.3)                              | 181.8 (179.8–183.7)               | 183.8 (178.6–189.2)      |                       |
| Median (5–95 percentile)   | 180.0 (175–210)                                  | 180.0 (175–200)                   | 180.0 (180–226)          |                       |
| (Minimum–maximum)  | (120–240)  | (165–215)                         | (120–240)                |                       |
| Time spent at hookah events by non-smokers (minutes)                                 |  |                                   |                          |                       |
| Mean (±SD)   | 182.5 (±12.74)                                   | 182.0 (±15.21)                    | 183.1 (±9.60)            | 0.683                 |
| GM (95% CI)  | 182.0 (179.5–184.4)                              | 181.2 (177.1–185.2)               | 182.8 (180.1–185.4)      |                       |
| Median (5–95 percentile)   | 180.0 (180–205)                                  | 180.0 (175–205)                   | 180.0 (180–200)          |                       |
| (Minimum–maximum)  | (97–240)   | (97–205)                          | (180–240)                |                       |
| <i>P</i> <sup>g</sup> smokers vs. non-smokers  | 0.328  | 0.228                             | 0.908                    |                       |
| Number of hookah heads smoked by others <sup>h</sup>                                 |  |                                   |                          |                       |
| Mean (±SD)   | 63.99 (±53.77)                                   | 94.99 (±53.18)                    | 27.85 (±23.30)           | <b>&lt;0.001</b>      |
| GM (95% CI)  | 43.17 (37.73–49.40)                              | 80.90 (72.16–90.70)               | 20.75 (17.72–24.30)      |                       |
| Median (5–95 percentile)   | 54 (7–185)                                       | 81 (28–207)                       | 21 (6–78)                |                       |
| (Minimum–maximum)  | (6–238)  | (15–238)                          | (6–78)                   |                       |

NOTE: Significant levels are shown in bold.

<sup>a</sup>Due to missing values, numbers of categories of some variables do not sum to the total sample size.<sup>b</sup>*P* Hookah lounge vs. home.<sup>c</sup>A hookah head was defined as one hookah tobacco serving (10–20 g tobacco).<sup>b,d,e,f,g</sup>*P* values were derived from Mann–Whitney *U* tests; two-tailed  $\alpha$  level *P* < 0.05.<sup>h</sup>Using cell phones, every 30 minutes for 3 hours, participants recorded the number of active hookah heads being smoked by others during the hookah event with first count starting at point of entry to the hookah lounge or home hookah event.

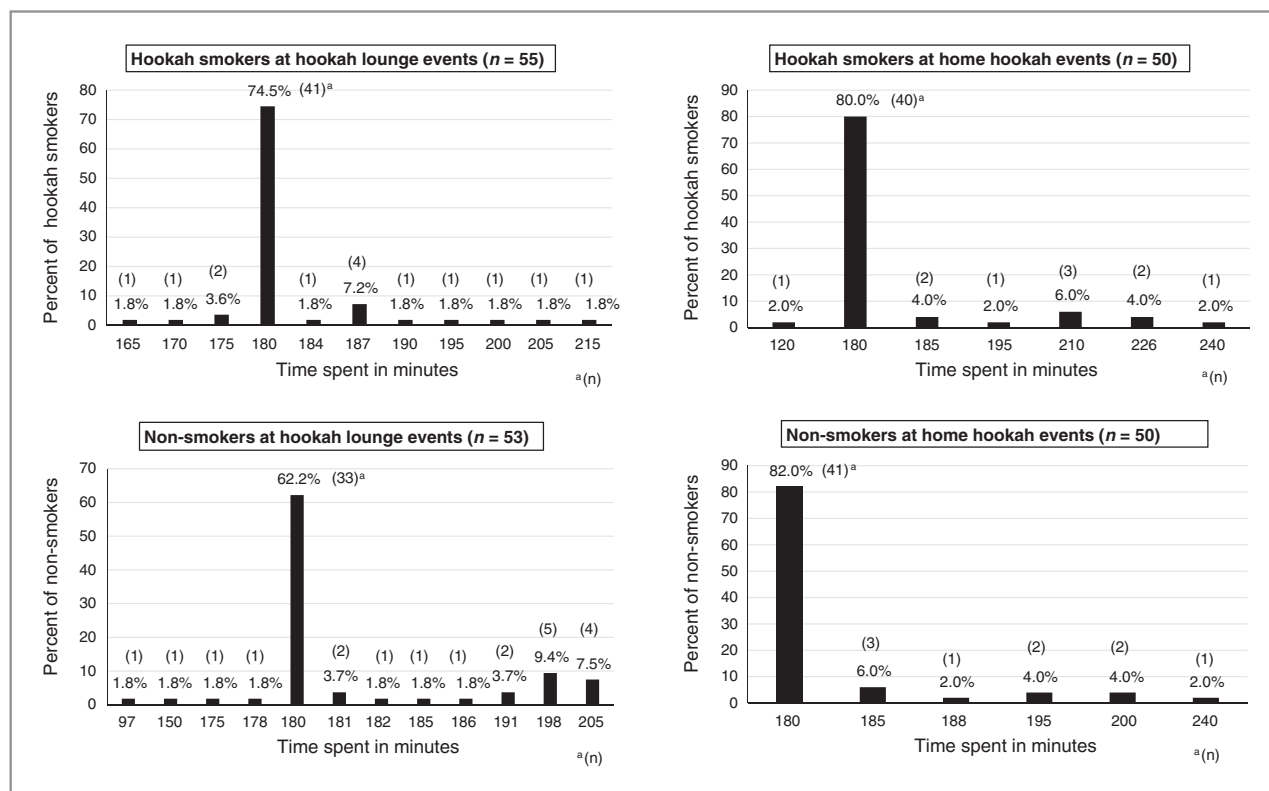


Figure 1. Time spent at hookah events.

significance (median, from 0.05 pmol/mg to 0.13 pmol/mg,  $P = 0.055$ ).

## Discussion

This is the first study to investigate uptake of benzene, a leukemogen, in hookah smokers and non-smokers exposed exclusively to hookah tobacco smoke in indoor hookah smoking social events in private homes compared with their counterparts at hookah lounges. Our results demonstrated higher exposures to benzene in hookah smokers overall after hookah events compared with before hookah events in hookah lounges and in private homes (Fig. 2). Change in SPMA levels in daily and weekly hookah smokers after a hookah event were significantly higher than in non-smokers (Table 3). These results suggest that hookah tobacco smoking may be a risk factor for leukemia. Although leukemia may result from chronic multiple and interacting environmental and genetic components, it is recommended that exposure to benzene should be minimized (36, 39, 40).

In a health risk context, the U.S. EPA estimates that carcinogenic risk from inhalation of benzene is increased by  $1 \times 10^{-5}$  after chronic exposure to  $2.9 \mu\text{g}/\text{m}^3$  benzene (40). This corresponds to mean  $\pm$  SD SPMA values of about  $2.9 \pm 2.9$  pmol/mg. We found that the percentage of hookah smokers who had SPMA values above 2.9 pmol/mg increased after hookah event from 4% to 13%, and for non-smokers increased from 1% to 3%.

Compared with the general population and cigarette smokers, the mean urinary SPMA levels in our study population of hookah smokers ranging from 1.04 to 2.53 pmol/mL (Table 3) were higher than the average urinary benzene concentrations for the non-smoking general population [0.10 to 0.25  $\mu\text{g}/\text{L}$  (0.42 to 1.0 pmol/mL)], and comparable with cigarette smokers [0.20 to 0.80  $\mu\text{g}/\text{L}$  (0.84 to 3.3 pmol/mL)] as indicated in a review of biomonitoring data for benzene exposure (40).

A recent study reported a significant increase in the excretion of SPMA after smoking hookah tobacco in a hookah lounge (57). When including all smoking participants, the urinary SPMA levels were somewhat higher than observed in our study, showing a preexposure GM excretion of 0.75 pmol/mg versus 0.18 pmol/mg and a postexposure excretion of 1.42 pmol/mg versus 0.62 pmol/mg, respectively. However, the overall trend is similar in both studies, showing a 1.9-fold increase compared with our findings of a 3.4-fold increase in the SPMA GMs after smoking hookah in a hookah lounge.

Comparisons between studies on hookah smoking in naturalistic settings should be evaluated with care taking into consideration factors that may influence SPMA levels in study populations, such as air pollution. For example, mean ambient air levels of benzene are reported to range from 0.6 to 0.7  $\mu\text{g}/\text{m}^3$  in rural settings and 0.3 to 3.9  $\mu\text{g}/\text{m}^3$  in urban settings (40). A study in non-smokers showed a clear increase in mean  $\pm$  SD SPMA from rural residents

**Table 3.** Urinary levels of SPMA<sup>a</sup> in adult ( $\geq 18$  years) hookah smokers ( $n = 105$ ) and non-smokers ( $n = 103$ ) before and after an indoor hookah-only social event ( $N = 208$ )

|   | Hookah-only social event<br>( $N = 208$ )<br>pmol/mL <sup>b</sup> |                           |                    |                  | Hookah-only social event<br>( $N = 208$ )<br>pmol/mg creatinine <sup>c</sup> |                           |                    |                  |
|---|---|---------------------------|--------------------|------------------|--|---------------------------|--------------------|------------------|
|   | Pre event   | Post event                | Ratio <sup>d</sup> | $P^e$            | Pre event  | Post event                | Ratio <sup>d</sup> | $P^e$            |
| All hookah smokers ( $n = 105$ )        |   |                           |                    |                  |  |                           |                    |                  |
| M ( $\pm$ SD) <sup>f</sup>              | 0.60 $\pm$ 0.83   | 1.49 $\pm$ 2.03           |                    | <b>&lt;0.001</b> | 0.59 $\pm$ 1.10  | 1.42 $\pm$ 2.03           |                    | <b>&lt;0.001</b> |
| GM (95% CI) <sup>g</sup>                | 0.20 (0.15–0.30)  | 0.60 (0.44–0.81)          | 3.0                |                  | 0.22 (0.16–0.29)   | 0.60 (0.45–0.79)          | 2.7                |                  |
| Median (5–95 percentile)                | 0.20 (0.02–2.20)  | 0.79 (0.02–5.69)          | 4.0                |                  | 0.23 (0.02–1.68)   | 0.62 (0.06–6.12)          | 2.7                |                  |
| (Minimum–maximum)                       | (0.02–4.57)   | (0.02–10.6)               |                    |                  | (0.02–9.30)  | (0.02–9.42)               |                    |                  |
| % above LOD (Freq/ $n$ ) <sup>h,i</sup> | 82% (84/103) <sup>j</sup>   | 94% (98/104) <sup>j</sup> |                    |                  | 82% (84/103) <sup>j</sup>  | 94% (98/104) <sup>j</sup> |                    |                  |
| Daily hookah smokers ( $n = 20$ )       |   |                           |                    |                  |  |                           |                    |                  |
| M ( $\pm$ SD)                           | 1.17 $\pm$ 1.25   | 2.53 $\pm$ 2.72           |                    | <b>0.004</b>     | 1.22 $\pm$ 2.09  | 2.43 $\pm$ 2.76           |                    | <b>0.002</b>     |
| GM (95% CI)                             | 0.50 (0.23–1.11)  | 1.51 (0.93–2.44)          | 3.0                |                  | 0.41 (0.18–0.94)   | 1.50 (0.95–2.36)          | 3.7                |                  |
| Median (5–95 percentile)                | 0.82 (0.02–4.18)  | 1.17 (0.36–8.17)          | 1.4                |                  | 0.48 (0.02–6.38)   | 1.28 (0.45–9.32)          | 2.7                |                  |
| (Minimum–maximum)                       | (0.02–4.57)   | (0.32–8.44)               |                    |                  | (0.02–9.30)  | (0.30–9.42)               |                    |                  |
| % above LOD (Freq/ $n$ )                | 90% (18/20)   | 100% (20/20)              |                    |                  | 90% (18/20)  | 100% (20/20)              |                    |                  |
| Weekly hookah smokers ( $n = 46$ )      |   |                           |                    |                  |  |                           |                    |                  |
| M ( $\pm$ SD)                           | 0.37 $\pm$ 0.53   | 1.42 $\pm$ 2.10           |                    | <b>&lt;0.001</b> | 0.35 $\pm$ 0.57  | 1.31 $\pm$ 1.79           |                    | <b>&lt;0.001</b> |
| GM (95% CI)                             | 0.12 (0.07–0.20)  | 0.53 (0.33–0.85)          | 4.4                |                  | 0.14 (0.09–0.22)   | 0.57 (0.37–0.87)          | 4.0                |                  |
| Median (5–95 percentile)                | 0.16 (0.02–1.64)  | 0.53 (0.02–4.82)          | 3.3                |                  | 0.18 (0.02–1.33)   | 0.51 (0.11–5.31)          | 2.8                |                  |
| (Minimum–maximum)                       | (0.02–2.05)   | (0.02–10.6)               |                    |                  | (0.02–3.34)  | (0.02–7.10)               |                    |                  |
| % above LOD (Freq/ $n$ )                | 70% (32/46)   | 94% (43/46)               |                    |                  | 70% (32/46)  | 94% (43/46)               |                    |                  |
| Occasional hookah smokers ( $n = 39$ )  |   |                           |                    |                  |  |                           |                    |                  |
| M ( $\pm$ SD)                           | 0.58 $\pm$ 0.72   | 1.04 $\pm$ 1.23           |                    | 0.073            | 0.53 $\pm$ 0.66  | 1.02 $\pm$ 1.73           |                    | 0.120            |
| GM (95% CI)                             | 0.24 (0.14–0.40)  | 0.42 (0.25–0.71)          | 1.8                |                  | 0.25 (0.16–0.40)   | 0.40 (0.24–0.65)          | 1.6                |                  |
| Median (5–95 percentile)                | 0.30 (0.02–2.38)  | 0.52 (0.02–3.56)          | 1.7                |                  | 0.23 (0.02–1.68)   | 0.48 (0.02–5.82)          | 2.1                |                  |
| (Minimum–maximum)                       | (0.02–2.86)   | (0.02–5.28)               |                    |                  | (0.02–3.24)  | (0.02–9.05)               |                    |                  |
| % above LOD (Freq/ $n$ )                | 92% (34/37) <sup>j</sup>  | 92% (35/38) <sup>j</sup>  |                    |                  | 92% (34/37) <sup>j</sup>   | 92% (35/38) <sup>j</sup>  |                    |                  |
| Non-smokers ( $n = 103$ )               |   |                           |                    |                  |  |                           |                    |                  |
| M ( $\pm$ SD)                           | 0.32 $\pm$ 0.74   | 0.34 $\pm$ 0.69           |                    | 0.629            | 0.28 $\pm$ 0.54  | 0.37 $\pm$ 0.73           |                    | 0.206            |
| GM (95% CI)                             | 0.07 (0.05–0.10)  | 0.09 (0.07–0.13)          | 1.3                |                  | 0.08 (0.06–0.11)   | 0.12 (0.09–0.17)          | 1.5                |                  |
| Median (5–95 percentile)                | 0.05 (0.02–1.39)  | 0.12 (0.02–1.54)          | 2.4                |                  | 0.08 (0.02–1.21)   | 0.15 (0.02–1.26)          | 1.9                |                  |
| (Minimum–maximum)                       | (0.02–4.50)   | (0.02–4.78)               |                    |                  | (0.02–3.16)  | (0.02–4.77)               |                    |                  |
| % above LOD (Freq/ $n$ )                | 53% (53/101) <sup>j</sup>   | 60% (61/102) <sup>j</sup> |                    |                  | 53% (53/101) <sup>j</sup>  | 60% (61/102) <sup>j</sup> |                    |                  |
|   | $P^k$   | $P^k$                     | $P^L$              |                  | $P^k$  | $P^k$                     | $P^L$              |                  |
| Daily vs. weekly                        | <b>0.002</b>  | <b>0.020</b>              | 0.521              |                  | <b>0.011</b>   | <b>0.005</b>              | 0.387              |                  |
| Daily vs. occasional                    | 0.076   | <b>0.007</b>              | 0.097              |                  | 0.181  | <b>0.001</b>              | <b>0.042</b>       |                  |
| Daily vs. non-smoker                    | <b>&lt;0.001</b>  | <b>&lt;0.001</b>          | <b>&lt;0.001</b>   |                  | <b>&lt;0.001</b>   | <b>&lt;0.001</b>          | <b>&lt;0.001</b>   |                  |
| Weekly vs. occasional                   | 0.076   | 0.532                     | 0.077              |                  | 0.105  | 0.285                     | 0.066              |                  |
| Weekly vs. non-smoker                   | 0.074   | <b>&lt;0.001</b>          | <b>&lt;0.001</b>   |                  | <b>0.047</b>   | <b>&lt;0.001</b>          | <b>&lt;0.001</b>   |                  |
| Occasional vs. non-smoker               | <b>&lt;0.001</b>  | <b>&lt;0.001</b>          | 0.090              |                  | <b>&lt;0.001</b>   | <b>&lt;0.001</b>          | 0.241              |                  |

NOTE: Significant levels are shown in bold.

<sup>a</sup>SPMA = S-Phenylmercapturic acid, a metabolite of benzene.<sup>b,c</sup>SPMA values presented are uncorrected (pmol/mL) and corrected with creatinine (pmol/mg).<sup>d</sup>Ratio = ratio of post to pre hookah event SPMA GMs and medians.<sup>e</sup> $P$  hookah events: pre vs. post event;  $P$  values were derived from Wilcoxon signed-rank tests; two-tailed  $\alpha$  level  $P < 0.05$ .<sup>f</sup>M ( $\pm$ SD) = arithmetic mean and SD.<sup>g</sup>GM (95% CI) = geometric mean and 95% confidence interval.<sup>h</sup>% above LOD = percentage of urine samples above the limit of detection: SPMA LOD = 0.03 pmol/mL. All SPMA values and percentages are rounded up.<sup>i</sup>Freq/ $n$  = frequency of samples with levels above the LOD/ $n$  size of samples per group.<sup>j</sup>Missing values due to interference ( $n = 1$ ) or missing urine samples ( $n = 4$ ).<sup>k</sup> $P$  SPMA levels by smoking frequency status.<sup>L</sup> $P$  Pre to post event change in SPMA levels by smoking frequency status;  $P$  values were derived from Mann–Whitney  $U$  tests; two-tailed  $\alpha$  level  $P < 0.05$ . Nondetectable values of SPMA were replaced with (LOD/2 = 0.015 pmol/mL).



**Table 4.** Urinary levels of SPMA<sup>a</sup> in hookah smokers and non-smokers ( $\geq 18$  years) pre and post hookah-only social events in hookah lounge versus home ( $N = 208$ )

|  | Hookah lounge<br>(n = 108)<br>pmol/mL |                    |                    | Hookah-only social event<br>(n = 100)<br>pmol/mL |                    |                    | P <sup>c</sup> | Ratio <sup>b</sup> | P <sup>d</sup> | P <sup>e</sup> | P <sup>f</sup> |
|--|---------------------------------------|--------------------|--------------------|--|--------------------|--------------------|----------------|--------------------|----------------|----------------|----------------|
|  | Pre event                             | Post event         | Ratio <sup>b</sup> | Pre event  | Post event         | Ratio <sup>b</sup> |                |                    |                |                |                |
| All hookah smokers (n = 105)                   |                                       |                    |                    |  |                    |                    |                |                    |                |                |                |
| M ( $\pm$ SD) <sup>g</sup>                     | 0.47 ( $\pm$ 0.81)                    | 1.75 ( $\pm$ 2.27) |                    | 0.71 ( $\pm$ 0.84)                               | 1.21 ( $\pm$ 1.72) |                    | <0.001         | 4.6                | 0.030          | 0.059          | 0.023          |
| GM (95% CI) <sup>h</sup>                       | 0.15 (0.09–0.24)                      | 0.69 (0.45–1.08)   |                    | 0.28 (0.18–0.45)                                 | 0.51 (0.33–0.78)   |                    |                | 4.6                |                |                |                |
| Median (5–95 percentile)                       | 0.19 (0.02–2.04)                      | 1.11 (0.02–7.91)   |                    | 0.34 (0.02–2.25)                                 | 0.58 (0.02–5.07)   |                    |                | 5.8                |                |                |                |
| (Minimum–maximum)                              | (0.02–4.57)                           | (0.02–10.60)       |                    | (0.02–3.80)                                      | (0.02–8.44)        |                    |                |                    |                |                |                |
| % above LOD <sup>i</sup> (Freq/n) <sup>j</sup> | 77% (41/53)                           | 94% (51/54)        |                    | 86% (43/50)                                      | 94% (47/50)        |                    |                |                    |                |                |                |
| Daily hookah smokers                           |                                       |                    |                    |  |                    |                    |                |                    |                |                |                |
| M ( $\pm$ SD)                                  | 1.34 ( $\pm$ 1.92)                    | 4.09 ( $\pm$ 3.29) |                    | 1.11 ( $\pm$ 1.03)                               | 2.01 ( $\pm$ 2.41) |                    | 0.043          | 6.7                | 0.047          | 0.896          | 0.032          |
| GM (95% CI)                                    | 0.44 (0.05–4.28)                      | 2.93 (0.88–9.70)   |                    | 0.53 (0.21–1.34)                                 | 1.21 (0.70–2.09)   |                    |                | 6.7                |                |                |                |
| Median (5–95 percentile)                       | 0.26 (0.04–4.57)                      | 3.09 (1.02–7.91)   |                    | 0.89 (0.02–3.80)                                 | 1.06 (0.32–8.44)   |                    |                | 11.9               |                |                |                |
| (Minimum–maximum)                              | (0.04–4.57)                           | (1.02–7.91)        |                    | (0.02–3.80)                                      | (0.32–8.44)        |                    |                |                    |                |                |                |
| % above LOD (Freq/n)                           | 100% (5/5)                            | 100% (5/5)         |                    | 87% (13/15)                                      | 100% (15/15)       |                    |                |                    |                |                |                |
| Weekly hookah smokers                          |                                       |                    |                    |  |                    |                    |                |                    |                |                |                |
| M ( $\pm$ SD)                                  | 0.33 ( $\pm$ 0.57)                    | 1.86 ( $\pm$ 2.78) |                    | 0.40 ( $\pm$ 0.50)                               | 1.07 ( $\pm$ 1.34) |                    | 0.002          | 8.4                | 0.019          | 0.141          | 0.150          |
| GM (95% CI)                                    | 0.08 (0.03–0.18)                      | 0.67 (0.31–1.44)   |                    | 0.17 (0.09–0.31)                                 | 0.44 (0.23–0.84)   |                    |                | 8.4                |                |                |                |
| Median (5–95 percentile)                       | 0.07 (0.02–1.84)                      | 0.82 (0.06–9.36)   |                    | 0.19 (0.02–1.29)                                 | 0.53 (0.02–4.04)   |                    |                | 11.7               |                |                |                |
| (Minimum–maximum)                              | (0.02–2.04)                           | (0.02–10.60)       |                    | (0.02–2.05)                                      | (0.02–4.82)        |                    |                |                    |                |                |                |
| % above LOD (Freq/n)                           | 55% (11/20)                           | 95% (19/20)        |                    | 81% (21/26)                                      | 92% (24/26)        |                    |                |                    |                |                |                |
| Occasional hookah smokers                      |                                       |                    |                    |  |                    |                    |                |                    |                |                |                |
| M ( $\pm$ SD)                                  | 0.46 ( $\pm$ 0.58)                    | 1.27 ( $\pm$ 1.32) |                    | 0.96 ( $\pm$ 0.97)                               | 0.29 ( $\pm$ 0.28) |                    | 0.003          | 2.8                | 0.139          | 0.128          | 0.011          |
| GM (95% CI)                                    | 0.20 (0.11–0.36)                      | 0.55 (0.30–1.03)   |                    | 0.44 (0.14–1.39)                                 | 0.18 (0.07–0.44)   |                    |                | 2.8                |                |                |                |
| Median (5–95 percentile)                       | 0.30 (0.02–1.09)                      | 1.05 (0.02–3.56)   |                    | 0.68 (0.08–2.38)                                 | 0.21 (0.02–0.92)   |                    |                | 3.5                |                |                |                |
| (Minimum–maximum)                              | (0.02–2.86)                           | (0.02–5.28)        |                    | (0.08–2.38)                                      | (0.02–0.92)        |                    |                |                    |                |                |                |
| % above LOD (Freq/n)                           | 89% (25/28)                           | 93% (27/29)        |                    | 100% (9/9)                                       | 89% (8/9)          |                    |                |                    |                |                |                |
| Non-smokers (n = 103)                          |                                       |                    |                    |  |                    |                    |                |                    |                |                |                |
| M ( $\pm$ SD)                                  | 0.22 ( $\pm$ 0.65)                    | 0.36 ( $\pm$ 0.79) |                    | 0.43 ( $\pm$ 0.82)                               | 0.33 ( $\pm$ 0.58) |                    | 0.062          | 2.0                | 0.285          | 0.040          | 0.059          |
| GM (95% CI)                                    | 0.05 (0.03–0.08)                      | 0.10 (0.07–0.16)   |                    | 0.10 (0.06–0.17)                                 | 0.10 (0.06–0.15)   |                    |                | 2.0                |                |                |                |
| Median (5–95 percentile)                       | 0.02 (0.02–0.93)                      | 0.13 (0.02–1.54)   |                    | 0.12 (0.02–2.19)                                 | 0.12 (0.02–1.60)   |                    |                | 6.5                |                |                |                |
| (Minimum–maximum)                              | (0.02–4.50)                           | (0.02–4.78)        |                    | (0.02–4.37)                                      | (0.02–2.90)        |                    |                |                    |                |                |                |
| % above LOD (Freq/n)                           | 46% (24/52)                           | 56% (29/52)        |                    | 59% (29/49)                                      | 64% (32/50)        |                    |                |                    |                |                |                |

(Continued on the following page)

**Table 4.** Urinary levels of SPMA<sup>a</sup> in hookah smokers and non-smokers ( $\geq 18$  years) pre and post hookah-only social events in hookah lounge versus home ( $N = 208$ ) (Cont'd)

|                           | Hookah lounge<br>(n = 108)<br>pmol/mL |                              |                                      | Home<br>Hookah-only social event<br>(n = 100)<br>pmol/mL |                              |                                      | P <sup>f</sup> |
|---------------------------|---------------------------------------|------------------------------|--------------------------------------|--|------------------------------|--------------------------------------|----------------|
|                           | Pre event<br>P <sup>k</sup>           | Post event<br>P <sup>k</sup> | Ratio <sup>b</sup><br>P <sup>L</sup> | Pre event<br>P <sup>k</sup>                              | Post event<br>P <sup>k</sup> | Ratio <sup>b</sup><br>P <sup>L</sup> |                |
| Daily vs. weekly          | 0.082                                 | 0.103                        | 0.135                                | <b>0.017</b>   | <b>0.051</b>                 | 0.787                                |                |
| Daily vs. occasional      | 0.451                                 | <b>0.039</b>                 | <b>0.027</b>                         | 0.743  | < <b>0.001</b>               | <b>0.022</b>                         |                |
| Daily vs. non-smoker      | <b>0.012</b>                          | < <b>0.001</b>               | <b>0.001</b>                         | <b>0.003</b>   | < <b>0.001</b>               | <b>0.011</b>                         |                |
| Weekly vs. occasional     | 0.065                                 | 0.745                        | 0.149                                | 0.186  | 0.089                        | <b>0.010</b>                         |                |
| Weekly vs. non-smoker     | 0.346                                 | < <b>0.001</b>               | <b>0.002</b>                         | 0.297  | < <b>0.001</b>               | <b>0.007</b>                         |                |
| Occasional vs. non-smoker | < <b>0.001</b>                        | < <b>0.001</b>               | <b>0.025</b>                         | <b>0.029</b>   | 0.247                        | 0.209                                |                |

<sup>a</sup>SPMA = S-Phenylmercapturic acid, a metabolite of benzene, in pmol/mL.

<sup>b</sup>Ratio = ratio of post to pre hookah event SPMA GMs and medians.

<sup>c</sup>P Hookah lounge: pre vs. post event; P Home: pre vs. post event.

<sup>d</sup>P values were derived from Wilcoxon signed-rank tests; two-tailed  $\alpha$  level  $P < 0.05$ .

<sup>e</sup>P pre event: hookah lounge vs. home.

<sup>f</sup>P change in SPMA hookah lounge vs. home.

<sup>g</sup>P values were derived from Mann-Whitney  $U$  tests; two-tailed  $\alpha$  level  $P < 0.05$ .

<sup>h</sup>M ( $\pm$ SD) = arithmetic mean and SD.

<sup>i</sup>GM (95% CI) = geometric mean and 95% confidence interval. All SPMA values and percentages are rounded up.

<sup>j</sup>% above LOD = percentage of urine samples above the limit of detection: SPMA LOD = 0.03 pmol/mL.

<sup>k</sup>Freq/n = frequency of samples with levels above the LOD/n size of samples per group; nondetectable values of SPMA were replaced with (LOD/2 = 0.015 pmol/mL).

<sup>l</sup>P SPMA levels by smoking frequency status.

<sup>m</sup>P pre to post event change in SPMA levels by smoking frequency status; P significant levels are shown in bold.

**Table 5.** Creatinine-corrected urinary levels of SPMA<sup>a</sup> in hookah smokers and non-smokers ( $\geq 18$  years) pre and post hookah-only social events in hookah lounge versus home ( $N = 208$ )

| Creatinine-corrected SPMA values                   | Hookah lounge<br>Hookah-only social event ( $n = 108$ )<br>pmol/mg creatinine |                    |                    | Home<br>Hookah-only social event ( $n = 100$ )<br>pmol/mg creatinine |                    |                    |
|--|---|--------------------|--------------------|--|--------------------|--------------------|
|  | Pre event   | Post event         | Ratio <sup>b</sup> | Pre event  | Post event         | Ratio <sup>b</sup> |
| All hookah smokers ( $n = 105$ )                   |   |                    |                    |  |                    |                    |
| M ( $\pm$ SD) <sup>g</sup>                         | 0.43 ( $\pm$ 0.61)  | 1.56 ( $\pm$ 2.03) |                    | 0.75 ( $\pm$ 1.44)   | 1.27 ( $\pm$ 2.05) |                    |
| GM (95% CI) <sup>h</sup>                           | 0.18 (0.12–0.27)  | 0.62 (0.40–0.96)   | 3.4                | 0.26 (0.17–0.41)   | 0.58 (0.40–0.83)   | 2.2                |
| Median (5–95 percentile)                           | 0.20 (0.02–1.62)  | 0.83 (0.03–6.12)   | 4.2                | 0.32 (0.02–3.34)   | 0.60 (0.11–7.10)   | 1.9                |
| (Minimum–maximum)                                  | (0.02–3.24)   | (0.02–9.05)        |                    | (0.02–9.30)  | (0.02–9.42)        |                    |
| % above LOD <sup>i</sup> (Freq/ $n$ ) <sup>j</sup> | 77% (41/53)   | 94% (51/54)        |                    | 86% (43/50)  | 94% (47/50)        |                    |
| Daily hookah smokers                               |   |                    |                    |  |                    |                    |
| M ( $\pm$ SD)                                      | 0.59 ( $\pm$ 0.81)  | 3.05 ( $\pm$ 2.25) |                    | 1.43 ( $\pm$ 2.36)   | 2.22 ( $\pm$ 2.95) |                    |
| GM (95% CI)  | 0.29 (0.05–1.58)  | 2.26 (0.71–7.22)   | 7.8                | 0.47 (0.17–1.32)   | 1.30 (0.76–2.24)   | 2.8                |
| Median (5–95 percentile)                           | 0.25 (0.05–2.02)  | 3.56 (0.80–6.12)   | 14.2               | 0.49 (0.02–9.30)   | 1.24 (0.30–9.42)   | 2.5                |
| (Minimum–maximum)                                  | (0.05–2.02)   | (0.80–6.12)        |                    | (0.02–9.30)  | (0.30–9.42)        |                    |
| % above LOD (Freq/ $n$ )                           | 100% (5/5)  | 100% (5/5)         |                    | 87% (13/15)  | 100% (15/15)       |                    |
| Weekly hookah smokers                              |   |                    |                    |  |                    |                    |
| M ( $\pm$ SD)                                      | 0.29 ( $\pm$ 0.41)  | 1.62 ( $\pm$ 2.05) |                    | 0.40 ( $\pm$ 0.67)   | 1.08 ( $\pm$ 1.56) |                    |
| GM (95% CI)  | 0.11 (0.05–0.23)  | 0.60 (0.26–1.36)   | 5.5                | 0.17 (0.10–0.31)   | 0.55 (0.35–0.87)   | 3.2                |
| Median (5–95 percentile)                           | 0.18 (0.02–1.29)  | 0.48 (0.03–5.81)   | 2.7                | 0.19 (0.02–1.33)   | 0.52 (0.13–4.38)   | 2.7                |
| (Minimum–maximum)                                  | (0.02–1.58)   | (0.02–6.30)        |                    | (0.02–3.34)  | (0.11–7.10)        |                    |
| % above LOD (Freq/ $n$ )                           | 55% (11/20)   | 95% (19/20)        |                    | 81% (21/26)  | 92% (24/26)        |                    |
| Occasional hookah smokers                          |   |                    |                    |  |                    |                    |
| M ( $\pm$ SD)                                      | 0.51 ( $\pm$ 0.68)  | 1.26 ( $\pm$ 1.92) |                    | 0.62 ( $\pm$ 0.59)   | 0.25 ( $\pm$ 0.20) |                    |
| GM (95% CI)  | 0.23 (0.14–0.39)  | 0.51 (0.28–0.92)   | 2.2                | 0.34 (0.13–0.93)   | 0.17 (0.08–0.38)   | 0.5                |
| Median (5–95 percentile)                           | 0.21 (0.02–1.62)  | 0.91 (0.03–5.82)   | 4.3                | 0.51 (0.06–1.68)   | 0.19 (0.02–0.62)   | 0.4                |
| (Minimum–maximum)                                  | (0.02–3.24)   | (0.02–9.05)        |                    | (0.06–1.68)  | (0.02–0.62)        |                    |
| % above LOD (Freq/ $n$ )                           | 89% (25/28)   | 93% (27/29)        |                    | 100% (9/9)   | 89% (8/9)          |                    |
| Non-smokers ( $n = 103$ )                          |   |                    |                    |  |                    |                    |
| M ( $\pm$ SD)                                      | 0.19 ( $\pm$ 0.46)  | 0.38 ( $\pm$ 0.82) |                    | 0.37 ( $\pm$ 0.59)   | 0.36 ( $\pm$ 0.62) |                    |
| GM (95% CI)  | 0.06 (0.04–0.09)  | 0.09 (0.06–0.15)   | 1.5                | 0.11 (0.07–0.19)   | 0.12 (0.07–0.20)   | 1.1                |
| Median (5–95 percentile)                           | 0.05 (0.02–0.64)  | 0.13 (0.02–1.26)   | 2.6                | 0.14 (0.02–1.81)   | 0.16 (0.02–1.49)   | 1.1                |
| (Minimum–maximum)                                  | (0.02–3.16)   | (0.02–4.77)        |                    | (0.02–2.89)  | (0.02–3.84)        |                    |
| % above LOD (Freq/ $n$ )                           | 46% (24/52)   | 56% (29/52)        |                    | 59% (29/49)  | 64% (32/50)        |                    |

(Continued on the following page)

**Table 5.** Creatinine-corrected urinary levels of SPMA<sup>a</sup> in hookah smokers and non-smokers ( $\geq 18$  years) pre and post hookah-only social events in hookah lounge versus home ( $N = 208$ ) (Cont'd)

| Creatinine-corrected SPMA values | Hookah lounge event ( $n = 108$ ) pmol/mg creatinine |                  |                    | Home Hookah-only social event ( $n = 100$ ) pmol/mg creatinine |                    |                    |
|----------------------------------|--|------------------|--------------------|--|--------------------|--------------------|
|                                  | Pre event  | Post event       | Ratio <sup>b</sup> | Pre event  | Post event         | Ratio <sup>b</sup> |
| Daily vs. weekly                 | $P^k$ 0.277  | $P^k$ 0.089      | $P^L$ 0.135        | $P^k$ <b>0.026</b>   | $P^k$ <b>0.016</b> | $P^L$ 0.705        |
| Daily vs. occasional             | 0.802  | <b>0.076</b>     | <b>0.031</b>       | 0.571  | <b>&lt;0.001</b>   | <b>0.006</b>       |
| Daily vs. non-smoker             | <b>0.034</b>   | <b>0.001</b>     | <b>0.001</b>       | <b>0.011</b>   | <b>&lt;0.001</b>   | <b>0.014</b>       |
| Weekly vs. occasional            | 0.132  | 0.823            | 0.228              | 0.213  | 0.021              | <b>0.002</b>       |
| Weekly vs. non-smoker            | 0.105  | <b>&lt;0.001</b> | <b>0.001</b>       | 0.361  | <b>&lt;0.001</b>   | <b>0.007</b>       |
| Occasional vs. non-smoker        | <b>&lt;0.001</b>                                     | <b>&lt;0.001</b> | 0.086              | 0.080  | 0.643              | 0.201              |

<sup>a</sup>SPMA = S-Phenylmercapturic acid, a metabolite of benzene, in pmol/mL.<sup>b</sup>Ratio = ratio of post to pre hookah event SPMA GMs and medians.<sup>c</sup> $P$  Hookah lounge: pre vs. post event;  $P$  Home: pre vs. post event.<sup>d</sup> $P$  values were derived from Wilcoxon signed-rank tests; two-tailed  $\alpha$  level  $P < 0.05$ .<sup>e</sup> $P$  pre event: hookah lounge vs. home.<sup>f</sup> $P$  change in SPMA hookah lounge vs. home.<sup>g</sup> $P$  values were derived from Mann-Whitney  $U$  tests; two-tailed  $\alpha$  level  $P < 0.05$ .<sup>h</sup>GM ( $\pm$ SD) = arithmetic mean and SD.<sup>i</sup>% above LOD = percentage of urine samples above the limit of detection: SPMA LOD = 0.03 pmol/mL.<sup>j</sup>Freq/ $n$  = frequency of samples with levels above the LOD/ $n$  size of samples per group; nondetectable values of SPMA were replaced with (LOD/2 = 0.015 pmol/mL).<sup>k</sup> $P$  SPMA levels by smoking frequency status.<sup>l</sup> $P$  pre to post event change in SPMA levels by smoking frequency status;  $P$  significant levels are shown in bold.

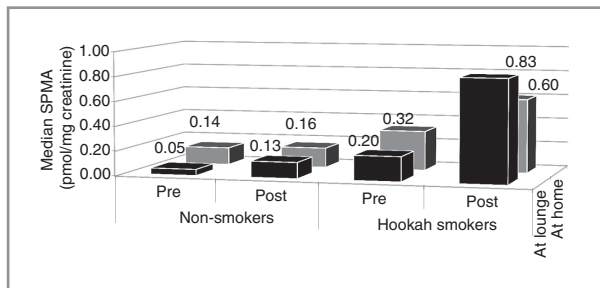


Figure 2. Urinary SPMA levels before and after hookah social events.

( $0.16 \pm 0.71$  pmol/mg) to suburban residents ( $0.42 \pm 0.46$  pmol/mg) to urban residents ( $1.25 \pm 1.59$  pmol/mg) to taxi drivers ( $2.30 \pm 1.88$  pmol/mg; ref. 58). Other factors may include ventilation in lounges or homes, type of hookah tobacco and coal used, reported exposure to SHS from various tobacco products, and occupational exposure.

In hookah lounges, our results showed that hookah smokers overall reported smoking more hookah heads than their counterparts at home events. Daily hookah smokers in hookah lounges reported smoking the highest number of hookah heads, and had the highest pre to post change in SPMA levels.

Besides the relatively high number of hookah heads smoked by hookah smokers during the hookah lounge events, participants were at risk for exposure to hookah tobacco SHS from other hookah smoker patrons. During the hookah event at hookah lounges, participants were exposed to an alarmingly high number of hookah heads (median, 81 hookah heads). After hookah lounge event, urinary SPMA levels increased 4.2 times among hookah smokers and increased 2.6 times among non-smokers (Table 4). Four studies have shown that indoor air quality levels in hookah lounges are hazardous to human health focusing on air nicotine, PM 2.5, and ambient carbon monoxide (CO); however, benzene levels were not measured in these studies (15, 21), (22, 59). Future studies aiming to assess the quality of indoor air in hookah lounges are encouraged to include benzene as a constituent of hookah tobacco SHS.

Hookah lounges continue to be exempt from clean indoor air legislation (20). Many cities and states in the United States have exemptions that allow hookah lounges to remain in operation despite the passage of clean indoor air legislation, such as operating as a generic tobacco retail establishment (19, 20). Current smoke-free air legislation should take into consideration hookah tobacco smoke and reconsider exemptions that encourage the proliferation of hookah lounges.

In contrast to beliefs that hookah tobacco is a less harmful form of tobacco, probably due to the sweet aroma and the passage of smoke through water before inhalation, the Centers for Disease Control and Prevention reported that hookah smoking is not a safe alternative to smoking cigarettes (60, 61). Studies also demonstrated that mainstream and sidestream hookah tobacco

smoke contain toxic and carcinogenic chemicals, such as polycyclic aromatic hydrocarbons (PAH), tobacco-specific nitrosamines, volatile aldehydes, phenols, heavy metals, CO, tar, nicotine, and ultrafine particles (27), (62–69). Only one study reported benzene levels in hookah tobacco smoke (27). The experiment was performed in a  $57 \text{ m}^3$  room on two dates with no smoking on the first date and hookah smoking for 4 hours on the second date (27). When comparing the 4-hour sampling periods, benzene level increased from  $0.11 \mu\text{g}/\text{m}^3$  to  $15.0 \mu\text{g}/\text{m}^3$ , a level well above the average outdoor ambient air concentration of benzene in the United States ( $0.9 \mu\text{g}/\text{m}^3$ ) as indicated by data collected by the U.S. EPA from 22 urban nationwide monitoring sites (27, 40). Research is needed to quantify benzene in hookah tobacco smoke generated in naturalistic settings, such as hookah lounges and home settings where hookah smoking is practiced.

In addition to inhaling toxicants and carcinogens found in the hookah tobacco smoke, hookah smokers and non-smokers who socialize with hookah smokers also inhale large quantities of charcoal combustion-generated toxic and carcinogenic emissions. Hookah tobacco is generally moist and does not burn in a self-sustaining manner, as with cigarettes (55, 70, 71). Therefore, burning charcoal is placed on top of the tobacco covered with perforated aluminum foil at the start of a use session, and is replaced one or more times during the smoking session (55, 71). The IARC reported that charcoal emissions are carcinogenic to humans, and benzene is one of its chemical constituents (72). Three studies have reported that charcoal used for hookah tobacco smoking contributed to quantities of CO and PAHs in mainstream hookah smoke; however, these studies did not quantify benzene in hookah charcoal emission (55, 70, 71).

Our findings confirm concerns about the lack of regulation on labeling of hookah tobacco and charcoal products, thereby misleading consumers (73, 74). Packages of hookah tobacco portray large images of fruits, and quote misleading false ingredients statements, for example "0.0% tar" and "0.05% nicotine" (74). Such labels may mask the adverse health consequences of smoking and create a false impression that hookah tobacco products are less harmful than other tobacco products (73–75). Packages of charcoal, a unique toxicant source in hookah smoking, contain misleading statements as well, such as "environmentally friendly," "natural," or "smokeless, odorless, and free of chemicals" (73, 74). In hookah lounges, customers are served hookah already packed with tobacco, and therefore are possibly not aware of health warnings that are displayed on the hookah tobacco packages (76). Regulations are needed to require hookah lounge owners to display health warnings on the harms of smoking hookah tobacco in their venues and on the hookah tobacco menus that are provided to their customers.

This study also addressed exposure to hookah tobacco SHS among non-smokers. SHS, a by-product of tobacco

smoking, is an indoor toxic air contaminant and contains human carcinogens (61, 77, 78). The WHO reported that there are no known safe levels of exposure to SHS in general and to benzene in particular (36, 61, 79). Our results showed that urinary SPMA levels in non-smokers before home events were 2.8 times higher than those found in their counterparts before hookah lounge events (median, 0.14 pmol/mg vs. 0.05 pmol/mg,  $P = 0.051$ , respectively); and there was no significant change in urinary SPMA levels in non-smokers after home events (median, 0.14 pmol/mg vs. 0.16 pmol/mg,  $P = 0.933$ , respectively; Table 4).  $\chi^2$  tests showed that our non-smoker participants in home events were exposed to hookah tobacco smoke before the study more than their counterparts in hookah lounges. They were more likely to allow hookah smoking at their homes (53.1% ( $n = 26$ ) vs. 24.5% ( $n = 12$ ),  $P = 0.004$ ), live with hookah smokers (22.9% ( $n = 11$ ) vs. 2.4% ( $n = 1$ ),  $P = 0.004$ ), and have at least one hookah smoker friend (50% ( $n = 25$ ) vs. 25.5% ( $n = 13$ ),  $P = 0.011$ ).

Our findings suggest that non-smokers who prefer home hookah events may be chronically exposed to benzene in their homes, and the potential long-term adverse health effects of benzene exposure are a concern. Our results call for longitudinal and experimental studies to determine the extent of cumulative exposure over time and the extent to which such exposure can be reduced or prevented. Such studies guided by our results and our previous research will inform regulatory actions to limit toxicants, including benzene in hookah tobacco and charcoal products, and call to action for the implementation of voluntary smoke-free home rules (80–82). In the interim, health providers need to include hookah tobacco smoking as a health hazard in their health risk behavior screenings to tailor primary preventive measures to limit exposure to hookah tobacco smoke in all settings including the home.

On April 24, 2014, the FDA took the first step to regulate hookah tobacco (83). The FDA proposed rules to require the manufacturers of hookah tobacco to disclose to the FDA their products' ingredients and to report harmful and potentially harmful constituents (83, 84). To date, however, the FDA did not address banning the use of flavorings in flavored hookah tobacco products, nor the internet advertising and sale of these products. Our results call for the FDA to develop additional regulations addressing such issues that make hookah tobacco appealing and accessible.

### Limitations and recommendations

Generalizability of this study is limited by convenience sampling. All hookah social events were indoors, most of the hookah smokers (92.9%) shared hookah with other smokers, and we had only 5 daily hookah smoker participants attending a hookah lounge event out of a total of 105 hookah smoker participants. Research is needed with larger sample sizes per frequency of smoking, taking into consideration indoor versus outdoor

smoking, and sharing versus not sharing hookah to enable a more rigorous assessment of benzene exposure from hookah tobacco smoking. Though hookah events may end in the early evening hours, a spot urine sample was not collected until the morning after the hookah event. Because of the short half-life of SPMA, future efforts are needed to collect spot urine samples from all voids between the end of a hookah event until the first morning void.

Homes with cigarette smokers have been found to have higher indoor air concentrations of benzene than homes without smokers during fall and winter (85). It is important that future studies measure indoor air benzene contamination in hookah lounges and in homes where hookah tobacco smoking takes place and also investigate the prevalence of leukemia among persons with a history of hookah tobacco smoking.

### Conclusion

Our data provide evidence that hookah smokers and non-smokers exposed to hookah tobacco smoke in social events in hookah lounges and in private homes are at risk of exposure to benzene. Our results call for regulatory actions to limit toxicants, including benzene, in hookah tobacco and charcoal products, examination of hookah-related products labeling, inclusion of hookah smoking in clean indoor air legislation, and clinical trials to investigate and limit exposure to this form of charcoal-heated tobacco use. Meanwhile, health professionals need to raise public awareness that hookah tobacco smoke is a source of benzene exposure, a risk factor for leukemia.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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## Benzene Uptake in Hookah Smokers and Non-smokers Attending Hookah Social Events: Regulatory Implications

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