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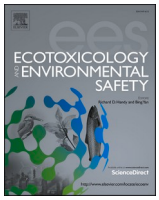

Use of urinary hippuric acid and *o*-/*p*-/*m*-methyl hippuric acid to evaluate surgical smoke exposure in operating room healthcare personnel

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ABSTRACT

Toluene and xylene are common components of surgical smoke, whereas hippuric acid (HA) and methylhippuric acid (MHA) are the products of toluene and xylene metabolism in humans, respectively. HA and MHA can be used as indicators to evaluate the exposure hazards of toluene and xylene. In this study, we used liquid chromatography tandem mass spectrometry (LC-MS/MS) to simultaneously analyze the HA, *o*-/*m*-/*p*-MHA, and creatinine contents in the urine of healthcare personnel. Concentrations of HA and *o*-/*m*-/*p*-MHAs were normalized to those of creatinine and used to analyze urine samples of 160 operating room (OR) healthcare personnel, including administrative staff, surgical nurses, nurse anesthetists, and surgeons. The results showed that the five analytes could be accurately separated and exhibited good linearity ($r > 0.9992$). The rate of recovery was between 86% and 106%, and the relative standard deviation was less than 5%. Urine from administrative staff presented the highest median concentration of hippuric acid (0.25 g/g creatinine); this was significantly higher than that found in the urine of surgeons (0.15 g/g). The concentrations of urinary *o*-/*m*-/*p*-MHAs in surgical nurses were higher than those in administrative staff, nurse anesthetists, and surgeons. Furthermore, the type, sex, and age of healthcare personnel were associated with changes in urine HA and *o*-/*m*-/*p*-MHA concentrations. Healthcare personnel should be aware of the risk of exposure to surgical smoke.

1. Introduction

Electrosurgical instruments such as lasers, electrosurgical units, and ultrasonic devices are used to cut human tissue and induce hemostasis during surgery; this leads to immediate release of visible and odorous surgical smoke (Ulmer, 2008). Surgical smoke is composed of 95% moisture and 5% of particulate matter or chemical substances (Ulmer, 2008). These particulates include blood (Ott et al., 1998; Heinsohn and Jewett, 1993; Jewett et al., 1992), cell debris (Fletcher et al., 1999; Nduka et al., 1998), viruses (Taravella et al., 1999; Kwak et al., 2016), and bacteria (McKinley and Ludlow, 1994; Capizzi et al., 1998), whereas the chemical substances include benzene (Zhao et al., 2013; U.S. DHHS, 1988), toluene (Zhao et al., 2013; Al Sahaf et al., 2007; Lin et al., 2010; Fitzgerald et al., 2012), xylene (Choi et al., 2014), cyclohexanone (Al

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Sahaf et al., 2007), acrylonitrile (Zhao et al., 2013; Barrett and Garber, 2003), and furfural (Barrett and Garber, 2003). Owing to the presence of these components, exposure to surgical smoke may endanger the health of operating room (OR) healthcare personnel. Approximately 50,000 OR healthcare personnel are exposed to surgical smoke every year in the United States (OSHA, 2012).

Previous studies have primarily focused on assessing the chemical components of surgical smoke and changes in their concentrations. However, a few studies have evaluated the effects of electrocautery machine usage on the quality of air in the OR and the risk of exposing healthcare personnel to surgical smoke. Le Moual et al. (2013) found that the risk of developing severe persistent asthma was 2.48-times higher among nursing staff working in ORs than among administrative staff; surgeons (117×10^{-6}) and anesthetists (270×10^{-6}) had increased 70-year lifetime cancer risks due to exposure to polycyclic aromatic hydrocarbons at levels exceeding the safety level recommended by the World Health Organization (WHO; 1×10^{-6}), implying that 1 out of 1,000,000 individuals may develop cancer due to polycyclic aromatic hydrocarbons (Tseng et al., 2014). Therefore, it is imperative to evaluate the exposure risk of healthcare personnel to surgical smoke. A few studies have investigated the correlation between surgical smoke exposure and changes in biomarker concentrations in humans. Dobrogowski et al. (2014) showed that urinary concentrations of benzene and toluene in patients after laparoscopic cholecystectomy were higher than those before the procedure. Cheng et al. (2019) found that the concentrations of benzene and toluene in breath specimens from healthcare personnel were slightly higher following breast and abdominal surgery than the concentrations before surgery. Furthermore, the exhaled *m-/p*-xylene concentrations of medical staff after breast surgery were slightly higher than those before surgery (Cheng et al., 2019).

Human or animal exposure to toluene may cause central nervous system damage, sore throat, dizziness, headache, and upper respiratory tract and eye irritation (DHHS ATSDR, 2017). The American Conference of Governmental Industrial Hygienists (ACGIH) reported that humans inhale 70 ppm of toluene over 2 h; toluene can be metabolized and has a half-life of 0.5–2.7 days. Of the total quantity of inhaled toluene, 15–20% is excreted through exhalation, whereas the remaining 80% is converted to HA and excreted via urine after 7 h (ACGIH, 2013). Cytochrome P450 enzymes catalyze the conversion of toluene to benzyl alcohol and a few types of phenols in the liver. Benzyl alcohol is then converted to benzoic acid, which rapidly interacts with glycine and is excreted via urine in the form of HA (ACGIH, 1997). According to the recommendations of the ACGIH, the permissible exposure limit of urinary HA in workers after 1 day is 1.6 g/g creatinine (ACGIH, 2007). In addition to toluene exposure, urinary HA concentrations are affected by sex (Siqueira and Paiva, 2002), intake of salicylic acid-containing drugs (Pacifici et al., 1991), and intake of foods containing high amounts of benzoic acid, such as plums (Villanueva et al., 1994).

Xylene, which is composed of three isomers (*m-/p-/o*-xylenes), can be quickly absorbed through the skin and mucous membranes, leading to acute irritation or chronic central nervous system and auditory system toxicity (Kandyala et al., 2010). Human exposure to 14 ppm of xylene for 8 h per day may lead to symptoms such as memory loss and anxiety (Uchida et al., 1993). Xylene is absorbed by the human body and oxidized to form methylbenzoic acids, which are subsequently conjugated with glycine to form MHA and then eliminated through urine (DHHS ATSDR, 2007). The ACGIH recommends that urinary MHA levels in workers once off-duty should be less than 1.5 g/g creatinine (ACGIH, 2007). Additionally, creatinine is a by-product of muscle metabolism, and is produced by the catabolism of phosphocreatine and mainly excreted through the kidneys. Urinary solute concentrations are easily affected by water reabsorption in the kidney; therefore, the creatinine concentration in urine is usually used to normalize the urinary concentration of metabolites (Fernández-Fernández et al., 2015).

A few studies have explored the correlation between exposure to toluene and xylene in surgical smoke and the concentrations of their respective biomarkers, HA and MHAs. The purpose of this study was to establish an analytical method to measure the concentrations of urinary metabolites (such as HA and MHAs) and to compare their concentrations among different healthcare personnel working in ORs.

2. Materials and methods

2.1. Chemicals

Creatinine, creatinine-d_3, and *o*-MHA standards were obtained from Toronto Research Chemicals Inc. (North York, Canada); *m*-MHA and *p*-MHA standards were purchased from Sigma-Aldrich Co. (St. Louis, USA), and the HA standard was purchased from Chem Service Inc. (West Chester, USA). Creatinine, *o*-MHA, *m*-MHA, and *p*-MHA were dissolved in 50% methanol at a concentration of 1000 μg/mL. Next, creatinine and HA were diluted to 100 μg/mL, whereas *o*-MHA, *m*-MHA, and *p*-MHA were diluted to 10 μg/mL, using 50% methanol. Creatinine-d_3 was dissolved in 50% methanol, and 1 μg/mL creatinine-d_3 was used as the internal standard. The standard solution was diluted to the concentration levels determined using the calibration curves (including 10 ng/mL internal standard) with 2% acetonitrile. The range of the calibration curves was 5–2000 ng/mL for creatinine, 20–2000 ng/mL for HA, and 5–200 ng/mL for *o*-MHA, *m*-MHA, and *p*-MHA.

2.2. Urine specimen collection

For this cross-sectional study, we recruited 160 OR healthcare personnel from the Linkuo Chang Gung Memorial Hospital in Taiwan, who had worked for at least 3 months and were not pregnant. Of these, 120 healthcare personnel from the orthopedic, colorectal, and trauma ORs (20 surgeons, 20 nurse anesthetists, and 80 surgical nurses) comprised the surgical smoke exposure group, whereas 40 administrative nurses who did not work in areas exposed to surgical smoke constituted the surgical smoke non-exposure group. Based on the half-life of toluene as reported by the ACGIH (2013), 10 mL samples of mid-stream urine were collected from the participants and immediately stored at − 80 °C after they had worked for at least three consecutive days.

2.3. Sample preparation

2.3.1. Pretreatment of o-MHA, m-MHA, and p-MHA samples

After thawing, the urine samples were centrifuged at 2100*g* and 15 °C for 3 min. Then, 990 μL of the supernatant was mixed thoroughly with 10 μL of the internal standard (1 μg/mL creatinine-d_3) and passed through a 0.22-μm nylon filter before LC-MS/MS analysis.

2.3.2. Pretreatment of creatinine and HA samples

An aliquot of 2 mL of 100% acetonitrile was mixed with 1 mL of the supernatant for protein precipitation. Then, deionized water was added to a final volume of 10 mL. The solution was centrifuged at 2100*g* for 3 min at 15 °C, and 10 μL of the supernatant was mixed with 980 μL of deionized water and 10 μL of the internal standard (1 μg/mL creatinine-d_3). After filtration using a 0.22-μm nylon filter, the samples were analyzed by LC-MS/MS.

2.3.3. LC-MS/MS analysis

The system included a Waters Acquity UPLC equipped with a pump, column compartment, autosampler, and Waters TQS mass spectrometer (Waters, Milford, MA, USA), operated in the electrospray ion (ESI) mode. A Kinetex Biphenyl (100 Å, 1.7 μm, 2.1 × 100 mm) column was used for analysis and maintained at 25 °C with a flow rate of 0.3 mL/min and an injection volume of 3 μL. The mobile phase consisted of 5% (A) and 100% (B) methanol, both containing 0.01% formic acid. The linear gradient conditions were as follows: 16% B (0–13.0 min), 16–99% B (13.0–13.5 min), 99% B (13.5–15.5 min), 99–16% B (15.5–16.0 min),

and 16% B (16.0–19.0 min). The ESI parameters were set as follows: capillary voltage, 3.0 kV; desolvation temperature, 200 °C; source temperature, 150 °C; desolvation gas flow, 400 L/h; cone gas flow, 150 L/h; and nebulizer gas flow, 7.0 bar. All MS/MS data for the analytes were collected in the multiple reaction monitoring (MRM) mode, using MassLynx v4.1 software. The urine concentrations of HA and MHAs were normalized to urinary creatinine concentrations and presented as g/g creatinine and μg/g creatinine, respectively.

2.4. Questionnaire

On the day of urine collection, a questionnaire was used to collect basic data and lifestyle information from the participants for the previous 3 days; these data were used as a reference to analyze changes in the urine concentrations of HA and *o*-/*m*-/*p*-MHAs. Basic data collected included sex, age, education level, job category, task in the OR, working hours, job tenure, and current residence information, whereas lifestyle information included transportation to work, eating habits, intake of salicylic acid-containing drugs, and smoking and drinking habits.

2.5. Statistical analysis

All data were analyzed using SPSS version 23.0 (SPSS, Chicago, USA), and the significance level was set at 0.05. GraphPad Prism 7.0 software (GraphPad Software, San Diego, CA, USA) was used to prepare figures. The *chi*-square test was used to identify differences between groups for categorical variables. The Mann–Whitney U and Kruskal–Wallis tests were used to analyze group differences between continuous variables. A simple linear regression analysis was used to evaluate the association between HA and *o*-/*p*-/*m*-MHA concentrations in the urine and factors including healthcare personnel group, sex, age, job tenure, working hours, and bus use.

3. Results

3.1. Analysis of urine concentrations of creatinine, HA, and o-/m-/p-MHAs

First, we established a platform to analyze creatinine, HA, and *o*-/*m*-/*p*-MHA concentrations in human urine, and examined the concentration distributions of toluene and xylene metabolites in the urine (i.e., HA and *o*-/*m*-/*p*-MHAs) of OR workers. Individual compounds were detected using tandem mass spectrometry in the MRM mode. The optimized MRM conditions are shown in Table 1; creatinine and creatinine-d_3 were analyzed in the positive mode, whereas the other analytes were analyzed in the negative mode. The three isomers, *o*-/*m*-/*p*-MHAs, which have the same quantitative (192 > 91 *m*/*z*) and qualitative (192 > 148 *m*/*z*) ion pairs, could be separated based on their different retention times (Fig. 1). Table 2 shows that five urinary metabolites could be efficiently separated within 14 min, with a coefficient of correlation (*r*) greater than 0.9992. The retention times of creatinine, HA, and *o*-, *m*-, and *p*-MHAs were 0.79, 4.23, 6.56, 11.38, and 12.05 min, respectively. The rate of HA and *o*-/*m*-/*p*-MHA recovery in urine samples ranged from 86% to 106%, and the average relative standard deviation was less than 5%.

3.2. Participant characteristics

As shown on Table 3, 95% of the administrative staff and nurse anesthetists and 89% of surgical nurses were female. Conversely, all the surgeons were male. The median ages of the administrative staff (48 years) and nurse anesthetists (49 years) were significantly higher than those of the surgeons (31 years, $P < 0.01$) and surgical nurses (34.0 years, $P < 0.01$). Overall, 70% of the administrative staff, 90% of the nurse anesthetists, 100% of the surgical nurses, and 100% of the surgeons were educated above the university degree level. The job tenures of the administrative staff (20.5 years) and nurse anesthetists (26 years, $P < 0.01$) were significantly higher than those of the surgeons (3.1 years, $P < 0.01$) and surgical nurses (10.5 years, $P < 0.01$). The median working hours for OR personnel were 8–8.7 h/day. Furthermore, 42.5% of the administrative staff, 40% of the nurse anesthetists, 20% of the surgical nurses, and 10% of the surgeons commuted by bus, with a significant statistical difference among the four groups ($P = 0.041$). Regarding eating habits, only 12.5% of surgeons, 3% of surgical nurses, and 20% of administrative staff did not frequently eat soy products, meat products, minced fish products, chili sauce, jam, succade, cheese products, or pickles. Moreover, 100% of surgeons, nurse anesthetists, and surgical nurses and 95% of the administrative staff were non-smokers. The remaining 5% of the administrative staff were former smokers. With regard to alcohol consumption, 35% of surgeons, 10% of nurse anesthetists, 15% of surgical nurses, and 12.5% of administrative staff had consumed an alcoholic drink within 3 days prior to sample collection. Meanwhile, 25% of surgeons, 20% of nurse anesthetists, 10% of surgical nurses, and 25% of administrative staff had not consumed soft drinks within 3 days prior to urine sample collection; 17.5% of administrative staff, 9% of surgical nurses, and 20% of nurse anesthetists took salicylic acid preparations.

3.3. Urine HA and o-/m-/p-MHA concentrations of OR staff

Fig. 2 shows the distribution of HA and *o*-/*m*-/*p*-MHA in the urine samples of OR staff. The median concentration of HA (0.25 g/g creatinine) in the urine of administrative staff was significantly higher than that in the urine of surgeons (HA: 0.15 g/g creatinine, $P < 0.01$) and surgical nurses (HA: 0.18 g/g creatinine, $P < 0.01$).

The median concentrations of *o*-MHA (nurse anesthetists: 300.07 μg/g creatinine, $P < 0.01$; surgeons: 215.59 μg/g creatinine, $P < 0.01$; surgical nurses: 921.50 μg/g creatinine, $P < 0.01$), *m*-MHA (nurse anesthetists: 1078.67 μg/g creatinine, $P < 0.01$; surgeons: 785.52 μg/g creatinine, $P < 0.01$; surgical nurses: 3392.14 μg/g creatinine, $P < 0.01$), and *p*-MHA (nurse anesthetists: 490.77 μg/g creatinine, $P < 0.01$; surgeons: 353.94 μg/g creatinine, $P < 0.01$; surgical nurses:

Table 1
Optimized MRM transition and parameters for the analysis of creatinine, creatinine-d_3, hippuric acid, and *o*-, *m*-, and *p*-methylhippuric acids.

Compound	ESI	Quantitative ion pair			Qualitative ion pair		
		Parent ions (*m*/*z*) > Product ions (*m*/*z*)	Cone voltage (V)	Collision energy (eV)	Parent ions (*m*/*z*) > Product ions (*m*/*z*)	Cone voltage (V)	Collision energy (eV)
Creatinine	+	114 > 44	34	30	114 > 86	34	20
Creatinine-d_3	+	117 > 47	44	25	117 > 89	44	15
Hippuric acid	–	178 > 134	10	20	178 > 77	10	30
o-Methylhippuric acid	–	192 > 91	10	16	192 > 148	10	12
m-Methylhippuric acid	–	192 > 91	4	16	192 > 148	4	12
p-Methylhippuric acid	–	192 > 91	2	16	192 > 148	2	12

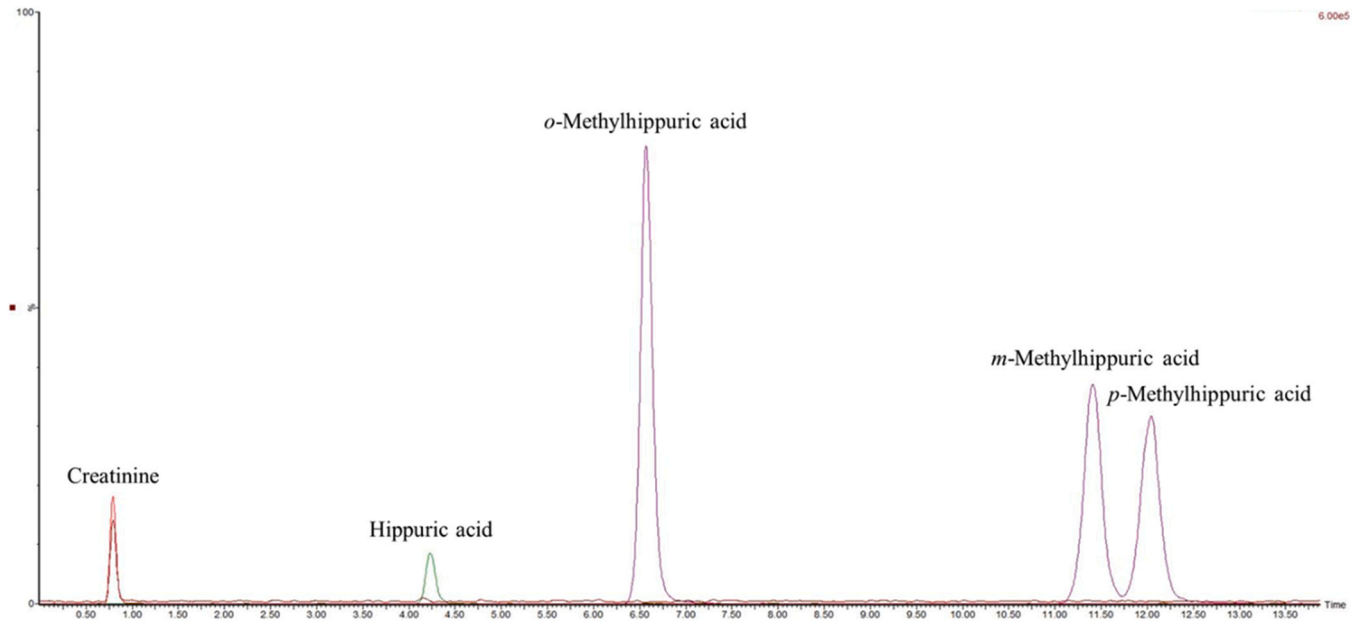

Fig. 1. LC-MS/MS analysis of creatinine, hippuric acid, and *o*-/*m*-/*p*-MHAs.

Table 2
Calibration curves of creatinine, hippuric acid, and *o*-, *m*-, and *p*-methylhippuric acids.

Compound	Retention time (min)	Calibration range (ng/mL)	*r*	Linear equation
Creatinine	0.79	5–2000	0.9996	y = 0.306x + 0.059
Hippuric acid	4.23	20–2000	0.9993	y = 28.910x – 173.434
o-Methylhippuric acid	6.56	5–200	0.9999	y = 326.912x – 227.504
m-Methylhippuric acid	11.38	5–200	0.9992	y = 199.817x – 102.167
p-Methylhippuric acid	12.05	5–200	0.9993	y = 221.263x – 121.411

1517.31 μg/g creatinine, $P < 0.01$) in the urine of all surgical staff were significantly higher than those in the urine of administrative staff (*o*-MHA: 38.61 μg/g creatinine; *m*-MHA: 85.25 μg/g creatinine; *p*-MHA: 37.13 μg/g creatinine). No significant differences in urinary *o*-/*m*-/*p*-MHA levels were found between the nurse anesthetists and surgeons.

Table 4 shows that surgical nurses had significantly lower HA urine concentrations (beta coefficient [β] = − 0.101, 95% confidence interval [CI] of $\beta = -0.192$ to − 0.010, $P = 0.03$) and higher *o*-MHA ($\beta = 1170.135$, 95% CI of $\beta = 881.695$–1458.574, $P < 0.001$), *m*-MHA ($\beta = 4341.092$, 95% CI of $\beta = 3281.189$–5400.995, $P < 0.001$), and *p*-MHA ($\beta = 1945.916$, 95% CI of $\beta = 1471.250$–2420.581, $P < 0.001$) concentrations than administrative staff. Nurse anesthetists had higher urinary *o*-MHA ($\beta = 441.865$, 95% CI of $\beta = 33.951$–849.780, $P = 0.034$), *m*-MHA ($\beta = 1624.049$, 95% CI of $\beta = 125.120$–3122.978, $P = 0.034$), and *p*-MHA ($\beta = 742.139$, 95% CI of $\beta = 70.861$–1413.417, $P = 0.03$) concentrations than administrative staff. Higher urinary *o*-/*m*-/*p*-MHA concentrations (*o*-MHA: $\beta = 404.161$, 95% CI of $\beta = 53.993$–754.328, $P = 0.024$; *m*-MHA: $\beta = 1475.406$, 95% CI of $\beta = 184.529$–2766.282, $P = 0.025$; *p*-MHA: $\beta = 660.181$, 95% CI of $\beta = 82.181$–1238.182, $P = 0.025$) were positively associated with female sex. Age ($\beta = 0.004$, 95% CI of $\beta = 0.001$–0.008, $P = 0.01$) and job tenure ($\beta = 0.004$, 95% CI of $\beta = 0.001$–0.008, $P = 0.01$) were positively associated with urinary HA concentrations. However, age was negatively associated with urinary *o*-/*m*-/*p*-MHA concentrations (*o*-MHA: $\beta = -15.605$, 95% CI of $\beta = -28.589$ to − 2.620, $P = 0.019$; *m*-MHA: $\beta = -58.495$, 95% CI of $\beta = -106.318$ to − 10.672, $P = 0.017$; *p*-MHA: $\beta = -26.184$, 95% CI of $\beta = -47.597$ to − 4.771, $P = 0.017$) of OR healthcare personnel.

4. Discussion

To the best of our knowledge, only a few studies have evaluated the effects of surgical smoke exposure on human health. A study in Poland revealed that the concentrations of benzene and toluene in the urine of patients were higher after abdominal cholecystectomy than before surgery (Dobrogowski et al., 2014). A study in Taiwan showed that the concentrations of sevoflurane, dimethyl sulfide, and methyl methacrylate in breath samples from OR healthcare personnel in different departments were higher after surgery than before surgery (Cheng et al., 2019).

These results suggest that volatile organic compounds and their metabolites can be detected in urine and breath samples after exposure to surgical smoke. However, whether this exposure is hazardous to human health has not yet been confirmed. Metabolites such as HA and MHA are produced after exposure to toluene and xylene, respectively (ACGIH, 2013; Engström et al., 1978), and a positive correlation has been reported between concentrations of urinary *o*-/*m*-/*p*-MHAs and low-dose xylene exposure (< 15 ppm) (Jacobson and McLean, 2003). However, to the best of our knowledge, no study has evaluated the concentrations of HA and MHAs in the urine of OR healthcare personnel. We found that HA concentrations in the urine of administrative staff (0.04–1.58 g/g creatinine), nurse anesthetists (0.02–0.44 g/g creatinine), surgeons (0.03–1.54 g/g creatinine), and surgical nurses (0.01–1.15 g/g creatinine) were all lower than the maximum value recommended by the ACGIH (< 1.6 g/g creatinine) (ACGIH, 2007). Furthermore, the total concentrations of *o*-/*m*-/*p*-MHAs in the urine of administrative staff (7.92×10^{-5} to 1.05×10^{-3} g/g creatinine), nurse anesthetists (2.68×10^{-4} to 1.74×10^{-2} g/g creatinine), surgeons (7.15×10^{-4} to 4.66×10^{-3} g/g creatinine), and surgical nurses (1.34×10^{-3} to 3.37×10^{-2} g/g creatinine) were lower than the maximum value recommended by the ACGIH (< 1.5 g/g creatinine). The concentrations of these metabolites in the urine of OR healthcare personnel were below the maximum values recommended by the ACGIH; however, the effects of long-term exposure to low concentrations of toluene and xylene in ORs need to be further evaluated.

To date, a few studies have investigated the effects of long-term

Table 3
Sociodemographic characteristics and habits of OR healthcare personnel.

Variable	Administrative staff		Nurse anesthetist		Surgeon		Surgical nurse		*P* value
	(n = 40)		(n = 20)		(n = 20)		(n = 80)		
Personal characteristics									
Sex, n (%)									< 0.001
Female	38	(95)	19	(95)	0	(0)	71	(89)	
Male	2	(5)	1	(5)	20	(100)	9	(11)	
Age (year)	48	(39–54)	49	(43–54)	31	(30–33)†,‡	34	(26–41)†,‡	< 0.001
Education level, n (%)									< 0.001
≥ University degree	28	(70)	18	(90)	25	(100)	80	(100)	
< University degree	12	(30)	2	(10)	0	(0)	0	(0)	
Job tenure, years	20.5	(10.8–25.3)	26.0	(19.9–33.5)	3.1	(1.9–5.0)†,‡	10.5	(3.8–20.0)†,‡,§	< 0.001
Working hours, h/day	8	(8–8)	8.7	(8–9.3)	8.5	(7.3–12)	8.0	(6.4–9.3)	0.056
Habits									
Transportation, n (%)									
Motorcycle	12	(30)	4	(20)	3	(15)	27	(26)	0.308
Car	16	(40)	4	(20)	9	(45)	21	(20)	0.151
Bus	17	(42.5)	8	(40)	2	(10)	21	(20)	0.041
Mass rapid transit	0	(0)	1	(5)	2	(10)	7	(7)	0.256
Bicycle	0	(0)	0	(0)	1	(5)	1	(1)	0.386
On foot	6	(15)	5	(25)	6	(30)	28	(32)	0.144
Wearing mask, n (%)									0.008
No	16	(40)	13	(65)	17	(85)	47	(59)	
Yes	24	(60)	7	(35)	3	(15)	33	(41)	
Dietary intake, n (%)									
Soy product	17	(42.5)	13	(65)	12	(60)	47	(25)	0.264
Meat product	13	(32.5)	5	(25)	8	(40)	31	(16)	0.645
Minced fish product	12	(30)	2	(10)	4	(20)	27	(14)	0.146
Chili sauce	13	(32.5)	8	(40)	5	(25)	24	(13)	0.762
Jam	7	(53.85)	5	(25)	0	(0)	12	(6)	0.151
Succade	6	(15)	3	(15)	1	(5)	14	(7)	0.581
Cheese product	12	(30)	5	(25)	7	(35)	21	(11)	0.856
Pickles	6	(15)	2	(10)	2	(10)	7	(4)	0.773
None of the above	5	(12.5)	0	(0)	4	(20)	6	(3)	0.138
Soft drink consumption, n (%)									
Tea	17	(42.5)	11	(55)	9	(45)	45	(39)	0.484
Coffee	21	(50)	11	(55)	11	(55)	42	(37)	0.995
Juice	4	(10)	2	(10)	2	(10)	8	(7)	1.000
Carbonated soft drink	2	(5)	0	(0)	3	(15)	8	(7)	0.277
None of the above	10	(25)	4	(20)	5	(25)	12	(10)	0.532
Use of salicylic acid preparations, n (%)									0.105
No	33	(82.5)	16	(80)	20	(100)	73	(91)	
Yes	7	(17.5)	4	(20)	0	(0)	7	(9)	
Smoking, n (%)									0.071
No	40	(100)	20	(100)	19	(95)	80	(100)	
Yes	0	(0)	0	(0)	0	(0)	0	(0)	
Former	0	(0)	0	(0)	1	(5)	0	(0)	
Alcohol consumption, n (%)									0.100
No	35	(87.5)	18	(90)	13	(65)	68	(85)	
Yes	5	(12.5)	2	(10)	7	(35)	12	(15)	
Former	0	(0)	0	(0)	0	(0)	0	(0)	

Data are presented as n (%) or median (25–75 percentiles). †: compared to administrative staff, $P < 0.01$; ‡: compared to nurse anesthetist, $P < 0.01$; §: compared to surgeon, $P < 0.01$.

exposure to low concentrations of toluene and xylene on human health. A study in Korea (Yoon et al., 2010) showed that the concentrations of HA and MHA in the urine of people aged over 60 years with a history of long-term exposure to low concentrations of volatile organic compounds indoors (toluene: 11.18 μg/m^3, xylene: 5.24 μg/m^3) and outdoors (toluene: 6.20 μg/m^3, xylene: 2.84 μg/m^3) changed positively, and that exposure to low concentrations of toluene and xylene was negatively associated with lung function. A study in China (Chen et al., 2011) showed that the air concentrations of benzene, toluene, and xylene in buses were 21.3–106.4, 53.5–26.0, and 46.9–234.8 μg/m^3, respectively, whereas the age and mileage of the buses were associated with changes in the concentrations of benzene, toluene, and xylene.

We found that the concentrations of HA in the urine of administrative staff were significantly higher than those in the urine of both surgeons and surgical nurses. This finding may be explained by the high proportion of OR administrative staff who commute by bus (42.5%) and are exposed to air pollutants during travel. Additionally, the *o*-/*m*-/*p*-MHA concentrations in the urine of surgical nurses were higher than those in the urine of administrative staff, nurse anesthetists, and surgeons. To reduce the exposure of healthcare personnel to surgical smoke, it is recommended to use a local smoke exhaust system, strictly control overall ventilation in the OR, and provide appropriate personal protective equipment.

This study has a few limitations. The number of participants included in this study was relatively small; therefore, future studies with a larger sample size are recommended. Another limitation of this study is that exposure to toluene and xylene was from surgical smoke as well as from indoor and outdoor air pollutants. Although a questionnaire was used to collect information regarding the participants' means of transportation, some confounding factors such as commute time and the correct manner of wearing masks could not be measured in practice.

5. Conclusions

In this study, we successfully established a quantitative method to analyze HA and *o*-/*m*-/*p*-MHA levels in urine samples. The results

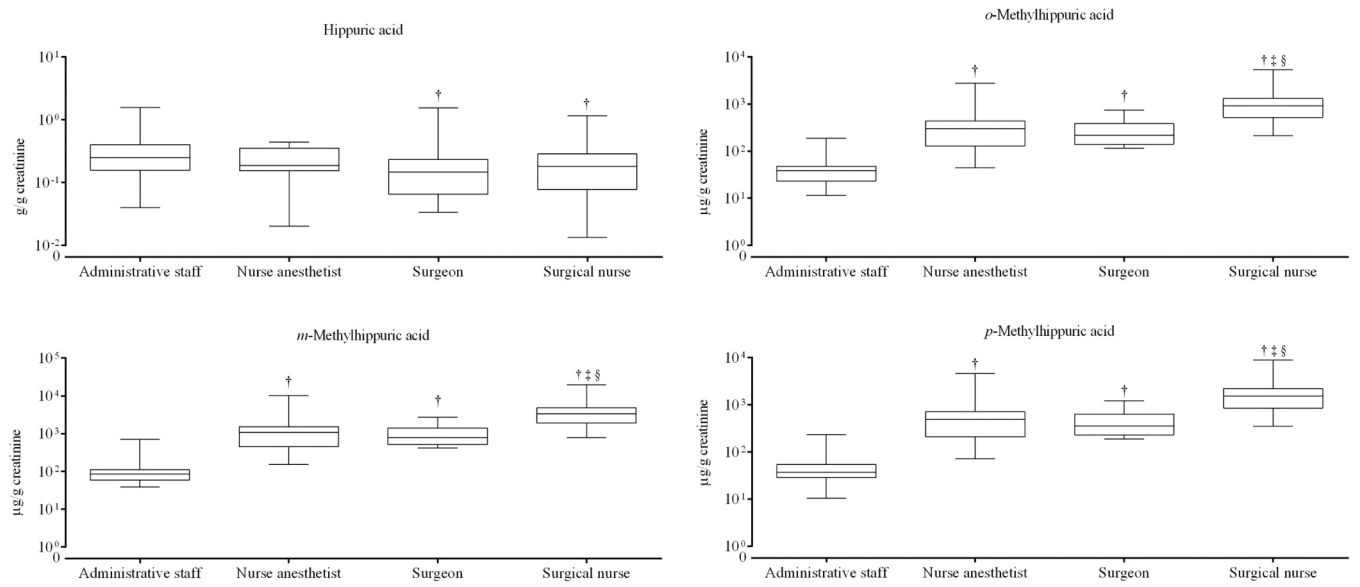

Fig. 2. Distribution of hippuric and *o*-/*m*-/*p*-methylhippuric acids in the urine of operating room healthcare personnel. †: compared to administrative staff, $P < 0.01$; ‡: compared to nurse anesthetists, $P < 0.01$; §: compared to surgeons, $P < 0.01$. Box-and-whisker plots show the minimum, 25th percentile, median, 75th percentile, and maximum values.

Table 4
Associations between sociodemographic characteristics and urinary concentrations of hippuric acid and methylhippuric acid in OR healthcare personnel.

Independent variable	β	(95% CI of β)	P	Independent variable	β	(95% CI of β)	P
Hippuric acid, g/g creatinine				–*m*-Methylhippuric acid, μg/g creatinine			
Sex	0.064	(− 0.029, 0.158)	0.174	Sex	1475.406	(184.529, 2766.282)	0.025
Age, years	0.004	(0.001, 0.008)	0.010	Age, years	− 58.495	(− 106.318, − 10.672)	0.017
Job tenure, years	0.004	(0.001, 0.008)	0.010	Job tenure, years	− 18.107	(− 66.311, 30.097)	0.459
Working hours, h/day	− 0.014	(− 0.032, 0.004)	0.134	Working hours, h/day	116.795	(− 136.492, 370.082)	0.364
Healthcare personnel group				Healthcare personnel group			
Administrative staff	Reference group			Administrative staff	Reference group		
Nurse anesthetist	− 0.101	(− 0.229, 0.027)	0.122	Nurse anesthetist	1624.049	(125.120, 3122.978)	0.034
Surgeon	− 0.103	(− 0.231, 0.026)	0.117	Surgeon	930.375	(− 568.554, 2429.304)	0.222
Surgical nurse	− 0.101	(− 0.192, − 0.010)	0.030	Surgical nurse	4341.092	(3281.189, 5400.995)	< 0.001
Bus user	0.034	(− 0.048, 0.116)	0.412	Bus user	− 454.902	(− 1597.464, 687.661)	0.433
–*o*-Methylhippuric acid, μg/g creatinine				–*p*-Methylhippuric acid, μg/g creatinine			
Sex	404.161	(53.993, 754.328)	0.024	Sex	660.181	(82.181, 1238.182)	0.025
Age, years	− 15.605	(− 28.589, − 2.620)	0.019	Age, years	− 26.184	(− 47.597, − 4.771)	0.017
Job tenure, years	− 4.687	(− 17.769, 8.395)	0.480	Job tenure, years	− 8.052	(− 29.636, 13.531)	0.462
Working hours, h/day	31.433	(− 37.298, 100.165)	0.368	Working hours, h/day	52.520	(− 60.886, 165.927)	0.362
Healthcare personnel group				Healthcare personnel group			
Administrative staff	Reference group			Administrative staff	Reference group		
Nurse anesthetist	441.865	(33.951, 849.780)	0.034	Nurse anesthetist	742.139	(70.861, 1413.417)	0.030
Surgeon	245.258	(− 162.656, 653.173)	0.237	Surgeon	422.258	(− 249.020, 1093.536)	0.216
Surgical nurse	1170.135	(881.695, 1458.574)	< 0.001	Surgical nurse	1945.916	(1471.250, 2420.581)	< 0.001
Bus user	− 121.711	(− 431.759, 188.337)	0.439	Bus user	− 205.870	(− 717.429, 305.689)	0.428

Sex: reference group = male; bus user: reference group = no.

showed that the concentration of HA in the urine of administrative staff was higher than that in the urine of surgeons and surgical nurses. Surgical nurses had the highest urinary *o*-MHA, *m*-MHA, and *p*-MHA concentrations, followed by nurse anesthetists and surgeons, whereas administrative nurses had the lowest urinary concentrations of *o*-MHA, *m*-MHA, and *p*-MHA. The type of healthcare personnel, sex, age, and job tenure were all found to affect the concentration of urinary toluene and xylene metabolites.

CRediT authorship contribution statement

Chun-Hui Chiu: Formal analysis, Methodology, Visualization, Writing - original draft. **Chi-Tsung Chen**: Formal analysis, Investigation, Visualization, Writing - original draft. **Ming-Huei Cheng**: Investigation, Writing - review & editing. **Li-Heng Pao**: Writing - review & editing. **Chi Wang**: Investigation. **Gwo-Hwa Wan**: Conceptualization, Methodology, Project administration, Funding acquisition, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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