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OCCUPATIONAL EXPOSURE TO TOLUENE AMONG AUTOMOTIVE PART INDUSTRIAL WORKERS IN EASTERN THAILAND

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ABSTRACT

To determine the exposure levels and factors related to toluene exposure, 154 workers from five automotive part industries using toluene in the production process were monitored, using a combination of environmental and biological sampling. The results showed that toluene concentration in the production areas was 19-fold greater than that of office areas. The levels of personal toluene exposure in painting and mixing workers were significantly higher than production workers ($P < 0.05$), and higher than those in office areas ($P < 0.001$). The average urinary hippuric acid (HA) level in process workers was comparable with levels observed in office workers and much lower than the biological exposure index (BEI). Exposed levels were significantly influenced by working position, their use of chemical protective clothing, helmet and respirator, and some personal hygiene's for chemical safety. Levels of toluene and HA detected in our study indicated low risk of toluene exposure. Urinary HA might be insufficient as an estimator of low toluene exposed workers, probably due to the reduced use of aromatics, i.e., toluene. Our results gave support to the argument for not using HA as an internal dose biomarker for low toluene exposures in some workplaces related to solvents including automotive part industry.

Keywords: Toluene, hippuric acid, and automotive part industry.

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INTRODUCTION

Toluene is a chemical substance extensively used in industrial applications including the automobile part industry (Moriguchi *et al*., 2006). Inhalation of low concentration of toluene induces a persistent deficit in spatial learning and memory in humans (Win-Shwe and Fujimaki, 2010; Yu *et al*., 2004). Although toluene is not known to be carcinogenic for humans or laboratory animals, it produces genotoxic effects and has been classified as a possible reproductive toxicant (risk phase R63-possible risk to unborn child) (IARC, 2012; HPA, 2007). Toluene is taken up mainly by inhalation and metabolized to benzoic acid, then conjugated with glycine to form hippuric acid (HA). Studies of urinary metabolites in toluene-exposed humans have identified HA as the major metabolite (Angerer *et al*., 1998; Alvarez-Leite *et al*., 1999). Determination of HA concentrations has been accepted as a helpful for monitoring workers exposed to toluene (ACGIH, 2009).

The biological monitoring of toluene exposure, complementary to air monitoring, can be used to better assess personal uptake related to body burden, to estimate the internal dose for all exposure routes, and to evaluate the efficiency of protective measures. Currently, the automotive industry is fast growing, increasing the production capacity and thus putting more workers at risk of toluene exposure. Monitoring of chemical exposure in the workplace is necessary for health risk evaluation, as an integral part of strategies to improve conditions of occupational health and safety. The aim of this study was to evaluate the concentration of toluene exposure and to identify personal factors and safety behavior of workers in the working environment that influenced on the personal exposure.

MATERIALS AND METHODS

Sampling sites and study population

Selection criteria of sampling location was based on industry location, type of industry and production process using toluene, and other factors including the consent of plant manager and workers to conduct the research. Data were collected from 154 employees in five automotive part industries located in industrial estate, Eastern Thailand. All 77 exposed subjects worked in the production process used toluene, whereas 77 control subjects were officers who were randomly selected by matching age with those in the exposed group. All workers were healthy, 18-45 years old volunteer and had to work in this factory at least one year. To avoid the interference, we advised subjects not to consume preservative foods before collecting urine specimen. Factors taken into account for exclusion included consuming of preserved food within the previous 24 hours and chronically taking any medicines. A consent form was signed and then workers were asked to answer a questionnaire which gave information related to their personal and work history, health history, types of food consumed, drug ingestion, and personal hygiene and safety. The Ethic Review Committees for Research on Human Subjects, Burapha University approved this study.

Determination of toluene in air samples

Air samplings were carried out in August – September 2012. Personal and area air sampling of toluene was conducted by using Carbopack B™ packed into the stainless steel tube, which was set in the respiratory zone. The tubes were precleaned before each sampling period by heating under a stream of ultra high purity helium for removing any contaminating species trapped on the adsorbent bed. Individual toluene exposure was monitored by attaching diffusive sampler near the breathing zone of study subjects. For ambient air sampling, samplers were hung on poles or walls at a height of approximately 160 cm off the ground. Sampling time was 8 hours, after which the sample cartridge was sealed, transported to the laboratory and stored at -10 ^{O}C until analysis. Sample tubes were loaded into a Gas Chromatography System and heated to 200 ^{O}C to desorb toluene. The desorbed toluene gases were transferred via a heated line to the gas chromatography (Agilent Technology, 7890A Series) where they were separated in a capillary column (300 mm x 0.25 mm, 2.5 μm by Agilent technology) and detected with a flame ionization detector. The limit of detection of toluene was 0.94 $\mu g/m^3$. The coefficient value of toluene determination (r^2) was 0.9954.

Determination of urinary hippuric acid

Urine samples from each subject were collected in bottles after working time and stored in a cooling box until they were returned to the laboratory. Then they were frozen at 4 ^{O}C without preservative until analysis.

Urine samples were thawed at room temperature for 15 min, and then centrifuged at 14,000 rpm for 10 min. The supernatant (10 μL) was injected into the HPLC (Agilent Technologies, 1200 series) with a Ultra Aqueous C18 column (Agilent TC-C18, 4.6 mm i.d. x 250 mm, 5 μm packing material) equipped with a UV detector (210 nm) (Ogata and Tagachi, 1988). The mobile phase was 10 mM KH_2PO_4 (adjust to a pH 3.0 with phosphoric acid) / tetrahydrofuran (93.5:6.5 v/v) with a flow rate 1.2 mL/min under isocratic condition. The column temperature was 25^{o}C. The calibration curves were prepared by diluting standard hippuric acid with mobile phase over the concentration range of 0-2,000 μg/mL. Standard curves were consistently linear with R^2 > 0.999. Limit of detection (LOD) for hippuric acid analysis was 1.000 mg/L. The value of toluene metabolite in urine samples was also expressed as creatinine ratio. Urinary creatinine was analyzed using a Roche Diagnostic kit with Cobas 6000 automated system.

Statistical analyses

Data were analyzed using the Statistical Package for the Social Sciences (SPSS Inc Version 17). Exposure levels for toluene, and urinary biomarker were presented as mean $\pm$ SD and compared between the exposed and control groups by using Independent T-test. A Pearson correlation was used to evaluate the association between levels of personal toluene exposure and urinary HA. Multiple linear regressions were used to analyze factors affecting toluene exposure. A P-value $\leq$ 0.05 was considered statistically significant.

RESULTS

General characteristics of workers

Of the 154 study workers, 66 (42.86%) were male and 88 (57.14%) were female. The exposed workers had mean age of 29.30 years whereas the control workers had mean age of 28.31 years. The working hour per day among the exposure workers was found to be slightly higher than the control group. Smoking and drinking behavior of the production workers were found to be significantly higher than those of the office workers. The general characteristics of workers are summarized in Table 1.

Ambient air levels of toluene in the working area

During the sampling period, the average temperature was about 28 ^{O}C and the average relative humidity ranged between 68 – 84 %. The levels of toluene measured in the production areas were 19-fold greater than that of the office areas. Levels of toluene in the painting area were 26-fold higher than the office area and were approximately 3.5-fold greater than the production area. There was no significant different between levels of toluene in the process area using toluene and the office area (Table 2).

Levels of toluene exposure and its metabolite

The exposure level of toluene in working ambient was low with a mean of 0.57 mg/m^3 and the maximum toluene in air on an individual basis was 2.84 mg/m^3. The levels of personal toluene exposure in production workers were significantly lower than painting and mixing workers (P < 0.05) and lower than those in the office areas (P < 0.001). The average urinary HA level in process workers was 0.44 g/g creatinine, which was comparable with levels observed in office workers. However, a significant difference of HA for non-corrected creatinine was found between process workers and control group (Table 3). None of exposed workers was exposed to a toluene level higher than the threshold limit value for 8-hour time weight average (TLV-TWA) of 75 mg/m^3 for air sample and 1.6 g/g creatinine for urinary HA (ACGIH, 2009). The level of individual exposure showed no significant association with urinary HA which expressed as creatinine ratio (r_S = 0.3072, p > 0.05).

Table 1. Basic characteristics of workers expressed as mean ± SD, (min-max).

Personal information	Officers (n = 77)	Processing workers (n=77)	*P*-value*
Age (yrs)	28.31 ± 5.70 (18-42)	29.30 ± 6.19 (19-45)	NS
Length of work in this factory (yrs)	3.36 ± 2.79 (1-20)	5.57 ± 4.32 (1-20)	NS
Working hour per day	8.21 ± 1.22 (8-12)	8.33 ± 1.89 (8-12)	NS
Overtime working hour per week	10.32 ± 6.80 (0-36)	12.56 ± 7.05 (0-31)	NS
Smoking†	3 (3.90)	18 (23.38)	0.000
Alcohol drinking†	37 (48.05)	56 (72.73)	0.002
Coffee/tea drinking†	23 (29.87)	33 (42.86)	NS
Drinking of soft drinks†	28 (36.36)	31 (40.26)	NS

†Values are expressed as number (%).
*Difference from officers, NS: not significant.

Table 2. Levels of toluene in the working areas.

Working areas	Number of sampling point	Levels of toluene (mg/m^3)
Office	5	0.02 ± 0.02 0.01 (0.001 – 0.084)
Production area using toluene	16	0.38 ± 0.17 0.15 (0.02 – 2.84)
• Processing and cleaning product area	6	0.15 ± 0.06 0.07 (0.03 – 0.43)
• Painting and mixing area	10	0.52 ± 0.27 0.18 (0.02 – 2.84)

Values were expressed as mean ± SD, median (min-max).

Table 3. Levels of toluene exposure and urinary metabolite in the automotive industrial workers.

Workers	Individual exposure (mg/m^3)	Levels of hippuric acid	
		(g/g creatinine)	(g/L)
Officers	-	0.41 ± 0.04 [77] 0.28 (0.004 – 1.39)	0.25 ± 0.03 [77] 0.15 (0.001 – 1.01)
Production workers	0.57 ± 0.08††† 0.29 (0.001–2.84) [76]	0.44 ± 0.05 0.27 (0.03–2.10) [77]	0.75 ± 0.10*** 0.38 (0.01 – 4.33) [77]
Processing and cleaning product workers	0.37 ± 0.02††† 0.02 (0.001–1.38) [25]	0.42 ± 0.09 0.27 (0.03–2.01) [25]	0.57 ± 0.12* 0.35 (0.01 – 2.35) [25]
Painting and mixing workers	0.66 ± 0.03††† 0.36 (0.001–2.84) [51]	0.45 ± 0.06 0.30 (0.03–2.10) [52]	0.84 ± 0.13*** 0.42 (0.03–4.33) [52]

Values were expressed as mean ± SD [n], median (min-max).
*, *** Significant difference from officers (control group) at $p< 0.05$ and 0.001, respectively.
†††Significant difference from office area (control group) at $p< 0.001$.

Factors influencing the exposure of workers

The influencing factors on the exposure of workers interesting in this study included personal characteristics and consuming behaviors (Table 1), safety behaviors in chemical work (Table 4) and using of personal protective equipments (PPE). Personal hygiene of workers in chemical work is shown in Table 4. Most of them (~90%) always washed hands and wore cleaned clothing. Approximately 42% of workers always changed protective clothing after working with solvents. A few of them (2.6%) always teased and talked while working with solvents, whereas all the rest (81.8%) did not. About using of PPE, most workers (~70%) always wore PPE including protective clothing, helmet, respirator, chemical protective gloves, and safety shoes. Approximately 90% of them rarely wore chemical protective goggles. Only painting workers (~10%) always wore chemical protective goggles (data not shown).

Table 4. Safety behavior in chemical work.

Behavior	Number	Percentage
Changing protective clothing after working with solvents		
Never	29	37.66
Sometimes	16	20.78
Always	32	41.56
Wearing cleaned clothing		
Never	4	5.19
Always	73	94.81
Washing hands before eating		
Never	1	1.30
Sometimes	3	3.90
Always	73	94.80
Washing hands after finishing work		
Never	5	6.49
Sometimes	3	3.90
Always	69	89.61
Teasing while working with solvents		
Never	63	81.82
Sometimes	12	15.58
Always	2	2.60

The evaluation of the possible effecting factors on the exposure measurement is shown in Table 5. Exposure levels of toluene were significantly influenced by working position, using of protective clothing and respirator, and some personal hygiene's including washing before eating, changing clothes after working with solvents. The results indicated that painting and mixing workers had higher toluene exposure level than processing and cleaning workers. Workers always wearing chemical protective clothing had lower exposure level, whereas those always wearing respiratory had higher level. Those who always changed protective clothing after working with solvents had higher exposure level than those who did not. The uses of PPE such as, protective clothing and chemical protective helmet appeared to have lower exposure of toluene. Drinking of soft drinks also affected on urinary HA levels.

DISCUSSION

Toluene was chosen for this study due to its great use in the automotive part industry. In this study, occupational exposure to toluene might be considered low, as the mean airborne and urinary concentration found for each of them were much lower than the TLVs and BEIs. In comparison with other risk groups, toluene exposure of workers in automotive part industry (0.57 mg/m^3) was lower than those reported in tape manufacture workers (7.15 mg/m^3; Inoue *et al.*, 2008), vehicle repair workers (10 mg/m^3; Wilson *et al.*, 2007), lacquer-ware manufacture workers (57.57 mg/m^3; Tanaka *et al.*, 2003), and shoe making industrial workers (Nijem *et al.*, 2001).

Normally, urine density from the same person may vary depending on physiological conditions such as perspiration, water intake, etc. (Kawai *et al.*, 2010). In this study, we used creatinine concentration for urine correction which desired for better evaluation of analyte levels in the samples. However, the present observation showed that correction for urine density did not improve the correlation coefficient. The average HA levels corrected for creatinine were shown to be similar in production workers and officers. This may be explained by the fact that HA is a common component of urine. Some similar findings on high basal value of HA in office workers as control group were reported (Roma-Torres *et al.*, 2006; Wiwanitkit *et al*, 2002). Comparison with previous studies disclosed that HA correlated with individual toluene exposure when the exposure was intense (e.g., 10 ppm (or 37.63 mg/m^3) or above), but no longer proportional to air-borne toluene when the exposure was low, e.g., 2 ppm or 7.53 mg/m^3 (Inoue *et al.*, 2008; Ukai *et al.*, 2007; Kawai *et al.*, 2007). Due to inherent methodological limitation, we did not evaluate other exposure biomarkers for toluene. Future investigation of other reliable urinary biomarkers of toluene (i.e., urinary toluene, *o*-cresol) should include more accurate means of exposure assessment. However, this study established reference value in non-occupationally toluene exposed subjects (officers) which was fundamental for interpreting biomonitoring results.

Table 5. Multiple regression models of variables effects on log-transformed exposure of toluene

Variables	No. (%)	Coefficient	95% Confident Interval		*P*-value1	*P*-value2
Individual toluene exposure						
Working position						0.003**
Processing and cleaning products	25(32.5)	0				
Painting and mixing	52(67.5)	0.4605566	0.1447097	0.7764034	0.005*	
Wearing of protective clothing						0.002**
Never	15(19.5)	0				
Sometimes	12(15.6)	-0.4804663	-1.108809	0.1478767	0.131	
Always	50(64.9)	-0.6056070	-1.097967	-0.113247	0.017*	
Wearing of respirator						0.012*
Never	4(5.2)	0				
Sometime	19(24.7)	0.7183639	-0.104224	1.540952	0.086	
Always	54(70.1)	0.9224286	0.1657728	1.679084	0.018*	
Washing hands before eating						0.021*
Never	1(1.3)	0				
Sometimes	3(3.9)	0.1507855	-1.363577	1.665148	0.843	
Always	73(94.8)	-0.7016657	-0.617715	2.021047	0.292	
Changing cloths after working with solvents						0.03*
Never	29(37.7)	0				
Sometimes	16(20.8)	0.1850687	-0.6717493	1.0418870	0.667	
Always	32(41.5)	0.2944815	-0.0610774	0.6500404	0.103	
Urinary hippuric acid						
Drinking of soft drinks						0.006**
No	59(76.6)	0				
Yes	18(23.4)	-0.4136143	-0.7317308	-0.0723958	0.060	
Wearing of protective clothing						0.044*
Never	15(19.5)	0				
Sometimes	12(15.6)	-0.2655197	-0.101612	0.6326514	0.154	
Always	50(64.9)	-0.2718572	0.019554	0.5241604	0.035*	
Wearing of chemical protective helmet						0.014*
Never						
Sometimes	14(18.2)	0				
Always	10(13.0)	-0.0894882	-0.4553794	0.276403	0.627	
	53(68.8)	-0.2929843	-0.5560256	-0.0299429	0.030*	

*, ** Significant difference at $P < 0.05$ and 0.005, respectively

Since 2010, urinary HA has not been used to monitor toluene exposure during medical examination, according to the American Conference of Governmental Industrial Hygienists (ACGIH) recommendation, whereas it is still used widely in most workplaces that used solvent in the process for assessing personal uptake of toluene, and accepted by the Ministry of Labor, Thailand. Every worker exposed to toluene including painting, mixing and cleaning product worker need for determination of proper urinary metabolite toluene at least once a year. Our results gave support to the argument for not using HA as an internal dose biomarker for toluene exposures at these low air concentration levels for some solvent workplaces including automotive part industry.

In this study, smoking and alcohol drinking did not confound the exposure-excretion relation of toluene although there were significant differences in those percentages between exposed and control group (Table 1). This is in agreement with the previous observation that these two social habits, either separately or combined, do not influence urinary HA levels (Wiwanitkit *et al*., 2002; Alvarez-Leite *et al*., 1999). Consumption of soft drinks was associated with urinary HA levels. This finding was in contrast to some previous report, which indicated levels of sodium benzoate in processed food including soft drinks did not show a correlation with urinary, HA excretion (Villanueva *et al*., 1994). Coffee and tea do not represent a significant factor influencing toluene exposure. On the other hand, they reported that the consumption of coffee and/or tea can result in the elevation of HA concentration (Munaka *et al*., 2009). Other benzoic acid liberators in certain foods and used in food preservatives also influences to increase HA level (Ogawa *et al*., 2011; Mulder *et al*., 2005).

Considering sex and age, they were not also found to be responsible for a significant effect on levels of toluene and HA. These findings agreed with the report of Takeuchi *et al*. (2002) who found no significant influence of sex and age in low-level exposure to toluene. Workers using respirator and changing clothes immediately after working with solvents had higher exposure level than those having no personal hygiene. It was possible that there was no cleaning respirator before reuse or delayed changing clothes, which would tend to increase amount of exposure. Wearing protective suits may enhanced dermal penetrate of vapor (Jone *et al*., 2003); however, the results indicated that use of protective clothes corresponded to lower exposure of toluene. Although the personal protective equipments were distributed to these workers, the high urinary HA can be observed (0.44 g/g cr) compared to those studies in Thai police working close to urban traffic (0.0007 g/g cr; Wiwanitkit *et al*., 2008), and in Thai press workers (0.00037 g/g cr; Wiwanitkit *et al*., 2002). In addition, some employees working in the process used toluene had no report of a biological monitoring of toluene exposure.

Levels of toluene and HA detected in our study indicated low risk of toluene exposure for the exposed workers, probably due to the reduced use of aromatics (i.e., toluene), but prevalence in use of alcohols, ketone and esters. In addition, subjects recruited in our study worked in the large enterprise in Industrial Estate, which has a growing concern with the deployment of measures regarding occupational hygiene followed by standard regulation of Ministry of Labor. However, many studies investigated the degree of exposure to organic solvents and related genotoxic although these exposure levels were low (de Oliveira *et al*., 2011; Roma-Torres *et al*., 2006). Shih *et al* (2011) also found that continuous exposure to low levels of toluene (0.43 $\pm$ 0.26 g/g Cr), as comparable with levels observed in our study, may be associated with nerve dysfunction and sub-clinical haematological damage. Due to these considerations and the complex multi-composition of solvents in the workplace, long time average are needed to evaluate the health risks and further studies focusing on the systemic health effect of toluene exposure are suggested.

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