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ORIGINAL ARTICLE

Urinary Hippuric Acid and Toluene Levels in Workers of Printing Factories in Thailand

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ABSTRACT

The aims of this study were to determine hippuric acid and toluene in urine samples, airborne toluene levels, health effects, and to describe any correlation between specimen samples. Seventy-five printing workers exposed to toluene at work (exposed group), and 60 nonexposed people (control group) were studied. Study participants were selected from same factories in the different positions. Urine samples were collected at the end of a shift and analyzed for hippuric acid, toluene in urine, and airborne toluene by using Gas Chromatograph (GC). The median of the 75 airborne toluene levels was 11.16 ppm (range, 3.72-68.83 ppm). The median of the urinary hippuric acid level was 200 mg/g creatinine (range, 78-1870 mg/g creatinine), and toluene in urine was 13 µg/L (range, 11-58 µg/L). A statistically significant positive correlation was found among airborne toluene exposure, hippuric acid levels, and urinary toluene levels ($r= 0.713$, $P<0.001$, and $r= 0.738$, $P<0.001$, respectively) and the relationship between toluene in urine levels and hippuric acid levels was significant ($r=0.578$, $P<0.001$). Workers with health effects were exposed to significantly higher toluene levels than those who did not ($P < 0.05$). Improvements in working conditions and occupational health education are required at these workplaces.

KEYWORDS: *Adverse health effects, Hippuric acid, Printing workers, Urinary toluene*

INTRODUCTION

Toluene is an aromatic compound which is widely used in many products, such as a solvent in paints, thinners, coatings, correction fluid, and many consumer products. The International Agency for Research on Cancer classified toluene as a category 3 carcinogen [1]. That is not classifiable as a carcinogen for humans.

Toluene can enter the body through 3 pathways; inhalation, ingestion, and dermal absorption [2]. It is metabolized by mixed-function oxidase enzyme reactions into benzoic and hippuric acid prior to excretion into the urine, eliminated within 12 hours after exposure [3-4]. Additionally, other sources of background hippuric acid are fruit, green coffee beans and other benzoic acid liberators [5-6].

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The measurement of toluene in urine is particularly useful for biological monitoring, due to being non-invasive and easy to sample [7].

Toluene targets and acts on the central nerve system (CNS). Low or moderate levels of exposure to toluene by inhalation may be related to many symptoms, including fatigue, sleepiness, headaches, and nausea. However, CNS depression and death have occurred at higher levels of exposure [3]. CNS depression has been reported to occur in chronic abusers exposed to high levels of toluene. Drowsiness, ataxia, tremors, cerebral atrophy, nystagmus (involuntary eye movements), impaired speech, hearing, and vision may occur in workers who have high exposure to high levels of toluene in their work. [8]. The Occupational Safety and Health Administration (OSHA) has determined the acceptable level of occupational exposure to

toluene for people in the workplace. The Permissible Exposure Limit (PEL) of 200 ppm is considered an acceptable level of exposure as a time-weighted average for an 8-hour workday [9]. ACGIH [10], recommends that toluene in workplace air should not exceed 20 ppm (average levels over 8 hours). In Thailand, the health hazard of printing factories has not been well assessed. Most of printing workers are occupationally exposed to solvent in the working process, but little is known about their adverse health effects.

The aims of this study were to investigate the occupational exposure of printing workers to airborne toluene, to determine their urinary toluene and hippuric acid levels, to describe the workers' hygiene behaviors and adverse health effects, and to make clear whether urinary toluene and hippuric acid are useful indices for assessing the printing workers' exposures to toluene.

MATERIALS AND METHODS

Study site and study subjects: In this cross-sectional study, data were collected during March- June 2015 by purposive sampling from 75 printing workers (49 males and 26 females) worked in 16 printing factories and were exposed to toluene for at least 1 year. Data were also collected from a control group of nonexposed subjects (60 persons) who worked in the same factories but had no exposure to toluene or other chemicals (35 office workers, and 25 drivers, respectively).

Inclusion criteria for this study were printing workers who worked in the printing process, aged ≥ 20 yr. The non-exposed control group was matched to exposed subjects by age and sex.

Samples collection: Information was collected by questionnaires. General information on the printing workers was also collected by face-to-face interview and by walkthrough survey in the area of the factories. Urine samples of the 135 participants were collected at the end of shift.

Questionnaires: Detailed information was shown in the questionnaires including general characteristics, occupational lifestyles, personal protective equipment, personal hygiene of the exposed group, and adverse health effects. The study focused on the health effects and acute symptoms that occurred during the preceding 6 months. Interview results were confirmed by direct observation.

Airborne toluene collection: Personal passive dosimeters (TK-200; Zambelli, Bolona, Italy) were used for examining the workers exposure to toluene during working. Each sampling period lasting 8 hours.

Urine collection: Spot urine samples were collected at the end of shift after 2 days exposure. Urine samples were collected in polyethylene bottles for creatinine testing and they were stored at -20 °C until analysis.

Laboratory analysis: A) Analytical methods: Toluene in environmental air samples and urinary toluene and hippuric acid levels were analyzed by a Gas Chromatograph (GC) (Model GC-148; Shimadzu, Tokyo, Japan).

B) Determination of toluene concentration in the breathing zone air: The time-weight average (TWA) exposure of each worker to toluene was measured by a diffusive sampler with carbon cloth (Toyobo Co., Osaka, Japan). After exposure, the carbon cloth toluene extract was measured by flame ionization detection gas-liquid chromatography technique (Model GC-148; Shimadzu, Tokyo, Japan) using a DB-1 capillary column (30 m - 0.53 mm inner diameter; J&W Scientific, Folsom, CA, USA).

C) Determination of Urinary hippuric acid levels: Urinary hippuric acid was performed according to method of Kongtip et al [11]. One mL of urine mix with 1 mL distilled water and acidified with 0.5M HCl then extracted with 3 mL ethyl acetate. Sample was evaporated to dryness and the residue reconstituted with derivatizing reagent and left in oven at 60 ºC for 45 min. Solution was extracted with 1 mL chloroform and add 2 mL distilled water. Kinetic Jaffe colorimetric method was used for determined the urinary creatinine concentration [12].

D) Determination of urinary toluene levels: Urine samples were analyzed within a few days with periodical vortexing for 2 h before analysis. Two mL of headspace was injected onto a 0.5 mL loop of the gas chromatograph [13]. Toluene (99.9%) and sodium chloride were used. Stock solutions of each of the above organic compounds were prepared in methanol (Mallinckrodt Baker Inc., Phillipsburg, USA) at a concentration of 1000 mg L^{-1}, and stored at 4 ºC in sealed amber vial until use. Gas-liquid chromatography technique using a DB^{-1} capillary column (30 m - 0.53 mm inner diameter; J&W Scientific) and flame ionization detector with an oven temperature of 200 ^{o}C, injector and detector temperature of 250 ^{o}C and a helium flow rate of 10 mL/min. Calibration curves were obtained spiking blank urine samples with six different concentrations of each solvent (5 replicates per concentration), toluene between 92 and 560 µg L^{-1} when CAR-PDMS fibers were used.

RESULTS

The participants in this study were mostly male; (nonexposed (80.0%) and exposed subjects (69.3%). Mean (SEM) aged of nonexposed subjects

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and exposed subjects were 33.21 ± 11.01 yr and 34.01 ± 9.15, respectively. Duration of work in exposed subjects was 9.04 ± 2.15 years. More nonexposed participants smoked cigarettes and drank alcoholic beverage than did the exposed (Table 1).

This study shows a correlation between airborne toluene levels and hippuric acid levels. The relationship between these variables was significant (r= 0.713, P<0.001) (Fig.1.). The relationship between airborne toluene levels and urinary toluene levels was significant (r= 0.738, P<0.001) (Fig.2.) There was a significant relationship between urinary toluene and hippuric acid levels (r=0.578, P<0.001) (Fig.3.), respectively.

The median (range) of airborne toluene levels that the printing workers were exposed to was 11.16 ppm (3.72-68.83 ppm). The median of urinary hippuric acid levels of the exposed and nonexposed was significantly different (P<0.001). The median of urinary hippuric acid levels of the exposed workers was 200 mg/g creatinine (range, 78-1870 mg/g creatinine). The median of urinary toluene levels of the exposed and nonexposed was significantly different (P<0.001). The median of urinary toluene levels of the exposed workers was 13 µg/L (range, 11-58 µg/L) (Table 2).

Table 1. Characteristics of exposed and non-exposed subjects

Items	Non-exposure subjects (n=60)	Exposure subjects (n=75)
Sex		
Male	48(80.0)	52(69.3)
Female	12(20.0)	23(30.7)
Age (yr) (mean ± SEM)	33.21 ± 11.01	34.01 ± 9.15
Duration of work (years) (mean ± SEM)	-	9.04 ± 2.15
Smoking cigarettes		
Yes	47(62.7)	35(46.7)
No	28(37.3)	40(53.3)
Consuming alcohol		
Yes	52(69.3)	43 (57.3)
No	23(30.7)	32 (42.7)

Table 2. Concentration levels of toluene in air and its urinary biomarkers

Biomarkers of exposure	Median	Interquartile range	Range (min-max)	*P* value
Air borne toluene levels (ppm)	11.16	16.48	3.72-68.83	
Hippuric acid (mg/g creatinine)				<0.001*
Nonexposed subjects (n=60)	28.00	260.00	58-344	
Exposed workers (n=75)	200.00	700.00	78-1870	
Toluene in urine (µg/L)				<0.001*
Nonexposed subjects (n=60)	3.00	7.00	nd-8.10	
Exposed workers (n=75)	13.00	14.00	11.00-58.00	

*Significantly associated at P value of <0.05.

The median of hippuric acid level and the characteristics of the exposed group (including cigarette smoking, positions, duration of work, and using mask during work) had significant differences, at P=0.031, P<0.001, P=0.002, and P<0.001, respectively. It was found that the median toluene in urine level and consuming alcohol, positions, duration of work, using mask during work, washing hands after work, also had significant differences, at P=0.006, P<0.001, P<0.001, P<0.001, and P=0.012, respectively (Table 3).

The exposed group of printing workers showed adverse health effects. These included: 45.3% reported irritation of the nose, eyes and throat, 33.3% reported fatigue, 28.0% reported downiness, 21.3% reported headache, and 13.3% reported nausea. The printing workers who had symptoms of irritation of the nose, eyes and throat , fatigue, downiness, headache, and nausea, had significantly higher expose to airborne toluene than those who did not have symptoms (P<0.001 for all) (Table 4).

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Table 3. Comparison between hippuric acid levels, urinary toluene levels, and characteristics of exposed group

Items	n=75	Hippuric acid (mg/g creatinine)		*P*-value	Toluene in urine (µg/L)		*P*-value
		Median	Interquartite range (min-max)		Median	Interquartite range (min-max)	
Sex							
Male	52(69.3)	302	890(10-1871	0.086	14.50	18.75(1.5-58)	0.073
Female	23(30.7)	123	200(102-1210)		12.00	9.10(2-33)	
Smoking cigarettes							
Yes	35(46.7)	305	550(105-1770)	0.031*	15.00	12.01(1-52)	0.582
No	40(53.3)	200	892(10-184)		9.03	13.75(2-33)	
Consuming alcohol							
Yes	43 (57.3)	310	807(10-1820)	0.101	15.10	18.02(2-58)	0.006*
No	32 (42.7)	154	275(108-1870)		11.58	2(1-58)	
Positions							
Officer workers	35(60.0)	32	257(50-321)	0.001*	10.05	14.58(2-34)	0.001*
Drivers	25(40.0)	12	28(2-35)		8.02	12.05(1-33)	
Printing workers	75 (100)	200	700(10-1870)		13.0	14.00(11-58)	
Duration of work (years)							
≤5	43(57.3)	123	215(105-1504)	0.002*	12.04	5(1-39)	0.001*
>5	32(42.7)	650	1075(10-1870)		24.80	21(10-58)	
Cotton mask during work							
Sometimes	25(33.3)	810	1000(102-1870)	0.001*	29	19(10-58)	0.001*
Always	40(66.7)	116.50	209(12-1508)		11.8	5(1-33)	
Washed hands after worked							
Sometimes	30(40.0)	355	1025(10-1827)	0.232	20	20.50(10-58)	0.012*
Always	45(60.0)	205	300(100-1871)		12.5	7.8(1-57.5)	
Gloves							
Sometimes	28(37.3)	208	410(10-1870)	0.181	12.75	13.50(1-58)	0.406
Always	47(62.7)	321	725(101-1501)		14.5	15.5(9-39)	
Apron							
Sometimes	57(76.0)	200	550(10-1860)	0.343	13.5	15.80(1-58)	0.489
Always	18(24.0)	305	850(104-1450)		14.50	15.0(10-39)	
Eat or drank during work							
Sometimes	35(46.7)	145	705(10-1870)	0.661	15	20.5(1-58)	0.729
Always	40(53.3)	250	612.5(100-1505)		13.5	12.5(2-34)	

*Significantly associated at P value of <0.05.

Table 4. Comparison between airborne toluene levels, and adverse health effects of exposed group

Items	n=75	Air borne toluene levels (ppm)		*P*-value
		Median	Interquartite range (min-max)	
Headache				
Yes	16(21.3)	35.21	16.08(7.71-68.83)	0.001*
No	29(78.7)	8.5	8.77(3.72-32.95)	
Downiness				
Yes	21(28.0)	32.42	18.21(7.44-68.83)	0.001*
No	54(72.0)	8.5	8.65(3.72-32.01)	
Fatigue				
Yes	25(33.3)	25.7	27.93(7.40-68.83)	0.001*
No	50(66.7)	8.2	8.24(3.7-30.12)	
Memory loss				
Yes	35(46.7)	18.57	29.93(5.40-38.89)	0.061
No	40(53.3)	16.90	26.24(16.7-68.83)	
Nausea				
Yes	10(13.3)	20.7	29.93(9.40-68.83)	0.001*
No	65(86.7)	9.2	9.24(3.7-28.12)	
Irritation of the nose, eyes and throat				
Yes	34(45.3)	22.60	22.59(4.7-68.83)	0.001*
No	41(54.7)	8.50	8.84(3.7-39.65)	

*Significantly associated at P value of <0.05.

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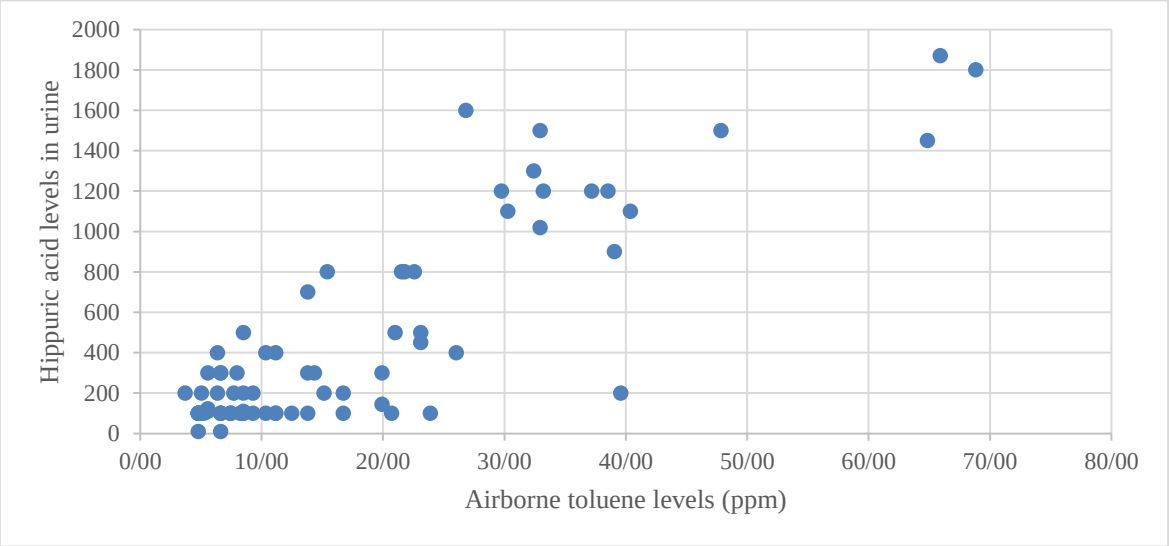

Fig.1. The correlation plot of airborne toluene levels (personal sampling) versus printing workers' hippuric acid levels

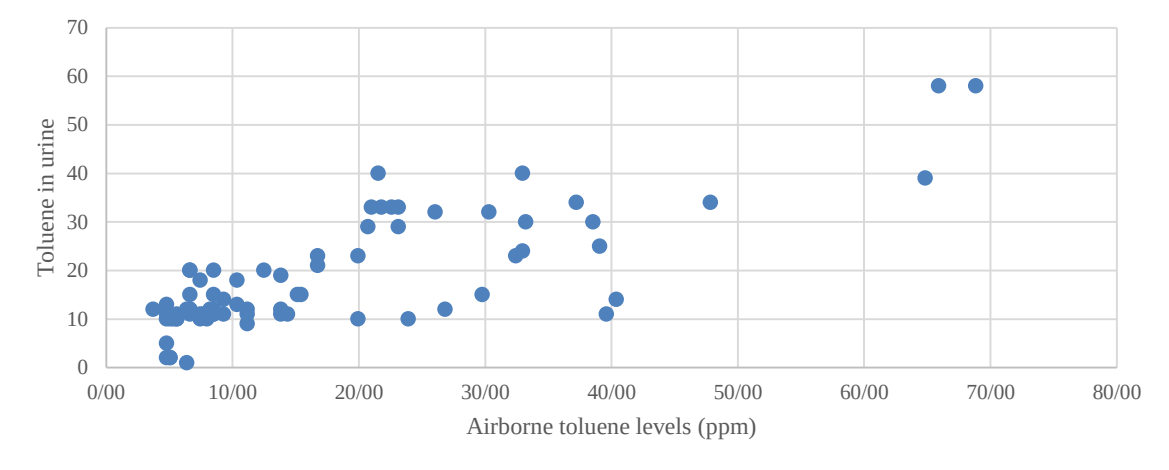

Fig.2. The correlation plot of airborne toluene levels (personal sampling) versus printing workers' urinary toluene level

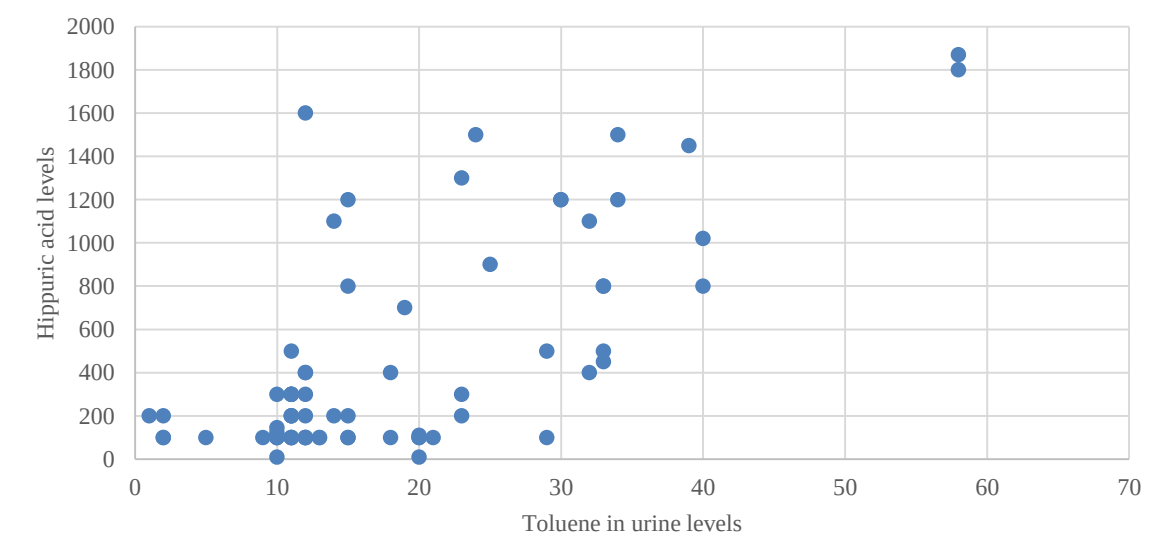

Fig.3. The correlation plot of toluene in urine levels (personal sampling) versus printing workers' hippuric acid levels

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DISCUSSION

Toluene air monitoring is useful to evaluate the occupational exposure to toluene. In this study, the mean airborne toluene level in the breathing zone was 11.16 ppm (range, 3.72-68.83 ppm). The time weight average (TWA) of all airborne toluene levels was less than 200 ppm that it is the Permissible Exposure Limit recommended by OSHA. On the other hand, obtained TWA was 33% higher than 20 ppm, the ACGIH-TLV [10]. When lowering the TWA value of toluene to 50-100 ppm, the toxic effects were still observable. However, when the TWA value for toluene was lowered to 50 ppm -100 ppm it still showed toxic effects. [14]. This supported by Eller et al. [15], where the risk of chronic effects on the central nervous system. Occurred at concentration as low as 20 ppm.

This study showed a correlation between airborne toluene levels and hippuric acid levels. This result is supported with another study [16], where the levels of hippuric acid in blood plasma and hippuric acid in urine were significantly correlated. This study presents a correlation between airborne toluene and toluene in urine. This study is supported by Daniell et al. [17], who presented a good correlation between airborne toluene levels and its metabolites in urine. This is also supported by Kawai et al. [18], who reported the relationship between the levels of toluene in urine and airborne toluene in the working environment.

Controlling the levels of airborne solvents in the working environment, improving safe practices, and using the personal protective equipment by workers can reduce the toxic effect of toluene. Most of printing workers had hippuric acid levels that did not exceeded the accepted safe standard (1600 mg/g creatinine), biological exposure index (BEI) recommended by the ACGIH [10]. Three printing workers (4%) had hippuric acid levels up to 1870 mg/g creatinine (range, 78-1870 mg/g creatinine).

Hippuric acid levels in urine have generally been used as a biomarker of exposure to toluene due to its short half-life. However, Hippuric acid levels correlate best to acute exposure situations [19]. In addition, most printing workers had toluene in urine which did not exceed the BEI standard at 30 µg/L, recommended by ACGIH [10]. Fifteen printing workers (20%) had urinary toluene level up to 58 µg/L (range, 11.00-58.00 µg/L). The printing workers who had hippuric acid > 1600 mg/g creatinine and toluene in urine >30 µg/L were workers that sometimes used PPEs such as mask or gloves, and had poor personal hygiene practices. This result is supported by Rogers [20], who reported the risk of toxic exposure can be reduced by implementation of appropriate behavior. In addition, an artist who did not wear PPE (mask and gloves) was exposed to paint solvents in the process [21]. Inappropriate working conditions during work were related to neuropsychological symptoms between two different groups of furniture workers [22].

The adverse health effects reported by printing workers were; irritation of the nose, eyes and throat, fatigue, downiness, headache, and nausea. This study was supported by many studies that reported neuropsychological symptoms such as mild headache, fatigue, and cognitive disorders on the workers who worked in a furniture factory [21-24]. These effects on health can cause mental and emotional disorders [25-26].

Exposed subjects showed symptoms of irritation of the nose, eyes and throat, fatigue, downiness, headache, and nausea. This result is supported by Chouaniere et al. [27], who conducted a study in two printing plants. Exposure to toluene 25 ppm and 40 ppm can cause the effects on psychomotor performance or neurotoxic symptoms. Zupaniet et al. [28], reported the exposure to 45.1 ppm (range, 34.2-57.9 ppm) toluene during worker's life with a mean current concentration of 24.7 ppm can affect the psychomotor performance. Tanaka et al. [29], reported the concentration of toluene in air of 15.3 ppm - 31.4 ppm was significantly the central nervous, and autonomic nervous systems. In a group of workers, the symptoms prevalence in the exposed workers was higher than that of for the non-exposed group.

CONCLUSION

Printing workers are exposed to toluene. Urine is a biological matrix to assess biomarkers. Thus, printing workers with high levels of hippuric acid and urinary toluene are at increased risk of developing adverse health symptoms. However, although urine sampling is more convenient and less invasive than blood sampling to screen for toluene exposure [30], there may be situations in which blood sampling for toluene is more useful. In addition, it is recommended the increasing of workers awareness of occupational hazards and motivating them to use PPEs in the workplace. Risk assessment and management techniques was suitable and effective to assess risk and offer solutions [31].

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