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Original Research

BENZENE EXPOSURE ANALYSIS IN INFORMAL SHOE INDUSTRY WORKERS IN SUKAJAYA VILLAGE, WEST JAVA VIA LEUKOCYTE COUNT AND S-PHENYLMERCAPTURIC ACID MEASUREMENT IN URINE

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ABSTRACT
Background: Benzene is a hematotoxic and carcinogenic compound contained in the glue used in the shoe industry. This compound has been suspected of causing decreased leukocyte counts, which is one of the blood cell production disorders. Benzene exposure can be determined by measuring the concentration of S-phenylmercapturic acid (S-PMA) in urine.
Objective: This study was conducted to determine the association between S-PMA urine concentration and the leukocyte count of shoe industry workers.
Methods: The study design was cross sectional and the data were collected by conducting interviews, analyzing urine samples for S-PMA concentrations, and conducting blood examinations. Chi square and multiple logistic regression were used for the analysis.
Results: The results showed there were no concentrations of S-PMA in urine that exceeded the Biological Exposure Index (BEI) value (≤25 µg/g creatinine). Higher S-PMA concentrations in this study show a higher risk of decreased leukocyte counts. When controlling for age, duration of work, history of infection, Body Mass Index (BMI), smoking, occupation, and exercise, workers with high S-PMA urine concentration were found to be at higher risk of a decreased leukocyte count.
Conclusion: Although S-PMA urine concentrations were still below BEI values, workers with higher S-PMA urine concentration were more at risk of leukocyte counts of < 5.0 x 10^3/µL. The decrease in the minimum BEI S-PMA limit value was lower than the current standard may need to be considered.

Keywords: benzene, S-phenylmercapturic acid, leukocyte, shoe workers

BACKGROUND

Benzene is a volatile chemical solvent and is widely used in the glue/adhesive industry (Nugraha, 2017). It is carcinogenic and is especially known to cause acute myeloid leukemia. It is also hematotoxic and can cause anemia, leukopenia, thrombocytopenia, pancytopenia, and aplastic anemia (Santos, Tavora, Koide, & Caldas, 2013). Leukocytes play a role in the body's defense system, so disruption to their production and a decrease in their levels can negatively affect the body's ability to ward off disease (Santos et al., 2013).

S-phenylmercapturic acid (S-PMA) concentration in urine is considered to be the most sensitive, specific, and reliable method for measuring benzene exposure (Farmer et al., 2005; Perbellini, Veronese, & Princivalle,

2002; Santos et al., 2013). Sukajaya Village is one of the largest shoe producers in the informal industry in West Java (Ekasari & Arminsih, 2019). The production process in Sukajaya Village is still simple and conducted without regard to occupational safety and health. For example, no one uses personal protective equipment, there are no routine health checks, and the majority of production takes place in workers' residences. This simple and unsafe production process may increase the risk of health problems due to benzene exposure. Therefore, this study was conducted to determine benzene exposure through examination of S-PMA urine biomarkers and the number of leukocytes in shoe workers.

METHODS

Study Design and Sample

This study used a cross-sectional research design. The entire population consisted of informal shoe industry workers in Sukajaya Village, while the samples were workers who fulfilled the inclusion and exclusion criteria. The inclusion criteria were that workers must be male and aged over 17 years and that they must have been working for at least one year in the informal shoe industry. The exclusion criteria were workers who were unwilling to be interviewed, those who were ill, and those with creatinine levels in urine of less than 0.3 g/L or more than 3 g/L. The total number of samples in this study was 71.

Instrument

S-PMA urine concentration was measured and routine blood tests to obtain leukocyte counts were conducted. Height and weight were also measured and interviews conducted to obtain confounding variables such as age, total number of years worked, and daily work duration, body mass index (BMI), history of infection, alcohol consumption, and smoking habits as independent variables.

Data Analysis

Data were analyzed using Chi square and multiple logistic regression analysis.

Ethical Considerations

Etchical approval was obtained from The Research and Community Engagement Ethical Committee Faculty of Public Health University of Indonesia with number: 222/H2.F10/ PPM.00.02/2018.

RESULTS

In Table 1 below, it is shown that the average S-PMA concentration was 1.55 µg/gr creatinine, with the lowest concentration at 0.018 µg/gr creatinine and the highest at 10.245 µg/gr creatinine. The average leukocyte count was 6.6 $x10^3/\mu L$, with the lowest count at 4.4 $x10^3/\mu L$ and the highest at 9.8 $x10^3/\mu L$.

Table 1 consist of the variables of age, work duration, and work period. The youngest sample in the study was 18 years old and the oldest was 56 years old, so the average age was 30. The shortest work duration was 7 hours per day and the longest was 16 hours per day, making the average work duration 11.2 hours per day. The average work period was 6.97 years, with the shortest work period being one year and the longest 25 years. The average BMI was 21.47 kg/m^2, with the lowest BMI at 15.83 kg/m^2 and the highest at 36.58 kg/m^2.

Table 1 Descriptive Distribution of S-PMA Concentration, Leukocyte Count, Age, Work Duration and Period, and Body Mass Index (BMI) of Informal Shoe Industry Workers 2018 (n = 71)

Variables	Mean	Median	Deviation Standard	Min–Max
S-PMA Concentration (µg/gr creatinine)	1.55	0.67	2.2	0.018–10.245
Leukocyte Count ($x10^3/\mu L$)	6.6	6.4	1.45	4.4–9.8
Age (year)	30.01	29	7.98	18–56
Daily work duration (hour)	11.2	11	1.9	7–16
Total number of years worked (year)	6.97	5	5.77	1–25
BMI	21.47	21.24	3.66	15.83–36.58

Bivariate Analysis

The numerical variables in this study were S-PMA concentration, total number of years worked, and daily work duration. They were changed into categorical form according to median value because, except for BMI and leukocyte count, they were not normally distributed. The BMI was based on the World Health Organization standard value (normal BMI = 18.5–24.99 kg/m^2). Meanwhile, the leukocyte count variable was divided into two categories according to the normal value defined by previous study (Dharma, Immanuel, & Wirawan, 1983). The normal group comprised workers with 5–10 x 10^3/µL, while the abnormal group comprised those with less than < 5 x 10^3/µL. Workers in the high S-PMA concentration group had the highest risk of a leukocyte count of (Odds Ratio (OR) = 1.13). Statistically, there was no significant relationship between S-PMA concentration and leukocyte count (as shown in Table 2). As with the independent variable, the covariate variables showed no significant relationship with leukocyte count. Nevertheless, for certain variables, such as history of infection, BMI, work duration, type of work, smoking status, and alcohol consumption, there was a high risk of leukocyte count decline. This is shown through the OR value for the variables (Table 2).

Table 2 Relationship between S-PMA Concentration and Leukocyte Count in Informal Shoe Industry Workers Based on Its Characteristics in Sukajaya Village 2018 (n = 71)

Variable	Leukocyte Count				Total		OR (95% CI)	P-value
	< 5 x10^3/µL		5–10 x10^3/µL					
	n	%	n	%	n	%		
S-PMA (µg/gr creatinine)								
Very High	2	11.1	16	88,9	18	100	1.07 (0.13–8.56)	0.952
High	2	10.5	17	89.5	19	100	1.13 (0.1–49.06)	0.906
Medium	2	11.8	15	82.2	17	100	1.00 (0.12–8.05)	1.000
Low	2	11.8	15	88.2	17	100	(standard)	
Age								
> 29 years	2	5.9	32	94.1	34	100	0. 32 (0.06–1.72)	0.264
18–29 years	6	16.2	31	83.8	37	100		
Total number of years worked								
> 5 years	3	9.4	29	90.6	32	100	0.70 (0.15–3.20)	0.722
1–5 years	5	12.8	34	87.2	39	100		
History Infection								
Yes	5	20.8	19	79.2	24	100	3.86 (0.84–17.81)	0.11
No	3	6.4	44	93.6	47	100		
BMI								
Abnormal	3	13.6	19	86.4	22	100	1.39(0.30–6.41)	0.696
Normal	5	10.2	44	89.8	49	100		
Daily Work Duration								
> 11 hours	5	14.7	29	85.3	34	100	1.95 (0.43–8.89)	0.467
≤ 11 hours	3	8.1	34	91.9	37	100		
Exercise Habit								
Not Routine	2	9.5	19	90.5	21	100	0.77 (0.14–4.17)	1
Routine	6	12	44	88	50	100		
Type of Work								
Gluing	6	12	44	88	50	100	1.29 (0.24–7.00)	1
Not Gluing	2	9.5	19	90.5	21	100		
Smoking Status								
Active Smoker	7	12.3	50	87.7	57	100	1.82 (0.25–16.14)	1
Secondhand Smoker	1	7.1	13	92.9	14	100		
Alcohol Consumption								
Yes	4	12.5	28	87.5	32	100	1.25 (0.28–5.50)	1
No	4	10.3	35	89.7	39	100		

Multivariate Analysis

In the multivariate analysis, the initial modeling was carried out on all variables with the assumption that all variables were risk factors for a decreased leukocyte count. The final modeling showed that after controlling for total number of years worked, type of work, exercise habits, smoking habits, daily work duration BMI, age, and history of infection, workers with high S-PMA concentrations (0.67–1.83 µg/g creatinine) had a 2.26 times higher risk of decreased leukocyte counts than workers with low S-PMA concentrations (Table 3).

Table 3 Final Model of S-PMA Concentration and Leukocyte Count in Informal Shoe Industry Workers Based on Its Characteristics in Sukajaya Village 2018 (n = 71)

Variable	Coefficient B	OR adjusted	95% CI		P-value
			Lower	Upper	
S-PMA Concentration (µg/gr creatinine)					
Very High (1.84–10.245)	0.722	2.06	0.12	34.95	0.617
High (0.67–1.83)	0.817	2.26	0.14	36.47	0.565
Medium (0.199–0.66)	0.033	1.03	0.064	16.62	0.982
Low (0.018–0.198)	Standard				
Total number of years worked (> 5 years)	-0.348	0.71	0.12	3.97	0.693
Type of Work (Gluing)	0.674	1.96	0.19	19.73	0.567
Exercise Habit (No)	0.515	1.67	0.22	12.80	0.620
Smoking Status (Active)	0.730	2.07	0.17	25.48	0.568
Daily Work Duration (> 11 hours)	0.558	1.75	0.33	9.25	0.512
BMI (Abnormal)	0.863	2.37	0.36	15.47	0.367
Age (> 29 years)	-1.657	0.19	0.027	1.35	0.097
History of Infection (Yes)	1.671	5.32	0.90	31.29	0.064
Constanta	0.516	1.67			0.775

DISCUSSIONS

The results of this study showed no significant difference in leukocyte count in workers with high S-PMA concentrations. This may be due to the fact that there were no workers with S-PMA concentrations exceeding the Biological Exposure Indices (BEI). These results were similar to those in a study conducted by Jothery & Tareq (2017) on workers at refueling stations, in which no significant difference was found between the leukocyte counts of workers exposed to greater and smaller amounts of benzene (al Jothery & Al-hassnwi, 2017). Similar results also emerged in a study conducted by Haen & Oginawati (2009) in the Cibaduyut industrial area. These showed no significant association between benzene exposure and leukocyte count (Haen & Oginawati, 2011).

A decrease in blood component can occur after two days of benzene exposure at a concentration of more than 60 ppm (Wilbur, Wohlers, Paikoff, Keith, & Faroon, 2008). Swaen & Twisk (2010) found no significant differences in the number of blood cells between the exposed and the exposure (benzene concentration < 0.5 ppm, 0.5–1 ppm, and > 1 ppm) (Swaen et al., 2010). The level of benzene concentration in the air at which hematological effects begin to emerge is still the subject of debate, although more than five studies have found effects beginning at concentrations of 5 to 10 ppm, with no effects arising at lower concentrations (Arnold et al., 2013).

Another reason the relationship between S-PMA concentration and leukocyte count was not significant is that, based on secondary data from measurements of air benzene carried out together with this study, the concentration of air benzene in the workplace was below the threshold limit value of the American Conference of Governmental Industrial Hygienists ACGIH (0.5 ppm). Therefore, the

hematototoxic effect did not arise. Future research with cohort design needs to be conducted to observe the emergence of hematotoxic effects and reaching a response dose.

The personal susceptibility factor also needs to be taken into account when considering the reason for the non-significant relationship found between the concentration of S-PMA and number of leukocytes in this study. Human susceptibility to benzene toxicity differs per person (Santos et al., 2013). Therefore, research related to susceptibility biomarkers. Research conducted in the petrochemical industry in Texas found that the average number of leukocytes was relatively similar to those found in this study, which was 6.75 x10^3/mm^3 (Tsai et al., 2004)

From the results of the above analysis, it can generally be observed that workers with higher S-PMA concentrations had an increased risk of reduced leokocyte counts. However, the risk was not very different between those with a moderate concentration of S-PMA (0.199-0.198 µg/g creatinine) and those with a low concentration (0.018-0.198 µg/g creatinine).

Likewise, the risk of a reduction in the number of leukocytes increases when S-PMA concentration is controlled by age, total number of years worked, BMI, daily work duration, history of infection, type of work, exercise habits, and smoking habits. These were confounding variables that influence the relationship between S-PMA concentration and leukocyte count.

Age was a confounding variable in this research because the average number of leukocytes in the older age group was lower than in the younger age group. The younger the age of the workers, the higher the number of leukocytes (McGrath, Hitchcock, & van Assendelft, 1982). However, the statistical analysis showed that age has a weak relationship with leukocyte decline. This is because older workers usually work for a shorter length of time and have a lower workload compared to younger workers, so the risk of exposure to benzene is lower. The theory of the relationship between age and leukocyte count was thus not applicable in this research.

On the other hand, BMI was also a confounding variable because an increase in weight was associated with a reduction in the excretion of benzene that was not metabolized. Increased BMI causes a decrease in benzene excretion so benzene accumulates in the body due to its lipophilic nature. This situation could increase the effects of hematotoxic benzene, one of which is a reduction in the number of leukocytes (Barbieri, Violante, Sabatini, Graziosi, & Mattioli, 2008).

A history of infection in workers can also cause a reduction in the number of leukocytes. While leukocytes usually increase in bacterial infections, especially pyogenic bacteria, inflammation, and tissue necrosis, they decrease in viral infections such as hepatitis, HIV, influenza, bacterecular bacterial infections, and typhus/paratyphus (Mehta & Hoffbrand, 2006).

Several types of exercises can also increase the number of leukocytes, especially long and/or high intensity exercises (Nieman, 2000). Physical exercise can increase the number of blood components, especially erythrocytes and oxidative stress, which can stimulate leukocyte activity so that the number of leukocytes increase (Ekasari & Arminsih, 2019). On the other hand, in this research, exercise habit had low risk of leukocyte count. This is because workers did exercise routines once a week with an average duration of two hours, rather than long and/or high intensity exercise. The most common sport was futsal.

Alcohol consumption was another confounding variable in this research. The workers studied consumed alcohol only occasionally, at a certain time, and at most once a month. The amounts were also low, namely one glass or one can of alcohol, whereas the toxic effects of alcohol depend on the dose and duration of consumption (Rajamurugan et al., 2012).

Cigarette smoking is one source of occupational benzene exposure to glue in the shoe industry and can increase the amount of benzene inhalation by an average of 720 µg/day (16 cigarettes/day x 45 µg/cigarette) (Fustinoni et al., 2005). Gordon, Wallace, Brinkman, Callahan, and Kenny (2002) found that the amount of benzene in the exhalation of smokers was 10–20 times higher than in non-smokers. In passive smokers, cigarette smoke could be a significant source of benzene exposure, while in active smokers 90% of exposure to benzene comes from cigarettes.

Furthermore, in a study conducted by Lan et al. (2004) on 250 shoe industry workers exposed to benzene, workers who worked on the bottom of the shoe, using a lot of glue, had a lower leukocyte count compared to workers who were focused on other parts of the shoe (Barbieri et al., 2008). This was because some glues use benzene as a solvent.

S-PMA concentration was also affected by how long in total workers had worked in benzene-contaminated workplaces and how long they worked there per day. In research conducted by Dosemeci et al. (1996) on benzene exposure in workers in China, it was found that the risk of developing benzene poisoning increased depending on how long they had been working. Those who had worked less than five years had a relative risk (RR) of 1.0, those who had worked for five–nine years an RR value of 1.3, those who had worked for 10–19 years an RR value of 1.6 and those who had worked for more than 20 years, an RR value of 2.7.

CONCLUSION

After the variables of age, work period, work duration, BMI, infection history, type of work, exercise habits, and smoking habits were controlled for, it was found that workers with very high S-PMA concentrations were more at risk of having a leukocyte count of less than 5.0 x 10^3/µL compared to workers with low concentrations of S-PMA (2.06; 0.12–34.95). Workers with high S-PMA concentrations were 2.26 times more at risk of decreased leukocyte counts than workers with low S-PMA concentrations (2.26; 0.14–36.47). Finally, workers with average S-PMA concentrations had the same risk as those with low S-PMA concentrations (1.03; 0.064–16.62).

Recommendations arising from this research are that workers need to take care of their health by not smoking, not consuming alcohol, exercising regularly, resting sufficiently, and not working for excessive amounts of time per day. In the future, cohort research using both quantitative and qualitative methods should also be conducted to determine the dose of response. Finally, it is also important to conduct research on genetic polymorphism or susceptibility biomarkers.

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Declaration of Conflicting Interest
No conflict of interest in this study.

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