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Airborne Benzene Concentrations Increase Trans, Trans-Muconic Acid (tt-MA) Levels and Liver Function in Workers in The Manufacturing Industry

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ABSTRACT

The use of benzene as a solvent in the manufacturing industry can be dangerous because it is volatile, toxic, and carcinogenic. Exposure to benzene occurs through inhalation of the chemical in the air, which can enter the human body through the respiratory system. The levels of trans, trans-Muconic Acid (tt-MA), which is used to metabolize benzene, can be affected by the amount of exposure to the chemical. This study aims to determine the differences in exposure to benzene in the air by measuring the tt-MA indicators and liver function of workers in the manufacturing industry. This research uses an observational and cross-sectional approach, with a population of 158 employees from both administration and production units. The sample size for the study is 16 respondents, selected using the consecutive sampling technique. The research instrument uses a questionnaire and examines urine samples using the in-house method. Blood samples are examined using IFCC 37 C. The data is processed using the independent-sample t-test and Pearson correlation. The results show that the level of benzene in the air is below the threshold of 0.5 ppm. However, there is a significant difference in the results of tt-MA and SGOT ($p<0.05$), while the levels of SGPT ($p>0.05$) show no significant differences. In conclusion, there are differences in the tt-MA and SGOT exposure levels between workers in the production and toxicity units, while SGPT does not show significant differences. It is recommended that the industry maximizes the use of local exhaust ventilation and prohibits smoking.

Keywords: Benzene; tt-MA; liver function; manufacturing industry

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INTRODUCTION

The industrial growth in Indonesia is advancing rapidly. In tandem with this progress, it becomes imperative to implement controls to ensure the working environment is in harmony, ultimately enhancing work productivity. One of the industries significantly contributing to both domestic and international needs is the chemical and adhesive manufacturing sector. Manufacturing industries often employ benzene as a solvent in their processes. Benzene, known for its easy evaporation, is commonly used as a solvent in various manufacturing applications[1]. The existence of benzene in the air can give rise to various problems, including waste concerns, air pollution, and adverse effects on workers' health due to benzene's volatile nature in the air. Moreover, benzene is a toxic substance and becomes carcinogenic when exposed for an extended period at high concentrations[2]

Material Safety Data Sheet (MSDS) on Gasoline Products by HESS Company in 2007 states that benzene compound results from the gasoline group with a concentration range of 0.1% - 4.9%. The gasoline group has a flashpoint of -43°C, indicating easy evaporation into the air at 27°C. Benzene is easily evaporative and slightly soluble in water. The presence of benzene sources in the vicinity of humans makes it easier to be exposed to benzene vapors [3]. Workers in industries that produce or use benzene as a production component may be exposed to the highest levels of exposure [4].

The American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) for the maximum allowable benzene concentration in the workplace is 0.5 ppm. In 1997, benzene was classified as a confirmed human carcinogen (A1 = Confirmed Human Carcinogen). The National Institute for Occupational Safety and Health (NIOSH) set the Recommended Exposure Limit (REL) for a working day (8 hours) in 2005 at 0.1 ppm. According to the Minister of Manpower and Transmigration Regulation Number 13 of 2011, which regulates the Threshold Limit Values for physical and chemical factors in the workplace, the maximum allowed benzene concentration is 0.5 ppm[5]. Chronic exposure to benzene leads to a reduction in the formation of hemoglobin in the blood [6]. Benzene can also be distributed to the bone marrow and disrupt the formation of hemoglobin, thus individuals exposed to benzene are likely to experience a decrease in hemoglobin formation in the spinal bone marrow [2].

The liver is the primary organ for the metabolism of benzene, producing various metabolites [3]. Benzene is distributed into the bloodstream through the alveoli throughout the human body and is temporarily stored in adipose tissue and bone marrow. It is then transformed into metabolites in the liver and bone marrow[7]. Approximately 48 hours after exposure to benzene, most metabolites will be excreted in the urine [6]. The higher the concentration of benzene in the air, the more it will affect the levels of SGOT and SGPT [8].

Biological markers that can be used as indicators of benzene exposure, according to WHO, state that benzene compounds can be detected through respiratory breath results: benzene in blood, benzene in urine, phenol in urine, catechol in urine, hydroquinone in urine, 1,2,4 trihydroxy. Benzene in urine contains phenylmercapturic acid and trans, trans-Muconic Acid (tt-MA). Exposure to benzene entering

the body through inhalation can be identified by trans, trans-Muconic Acid (tt-MA) present in urine as a biological indicator [9]. Therefore, trans, trans-Muconic Acid (tt-MA) is a minor metabolite resulting from benzene compounds that can be used as a biological marker for individuals exposed to benzene in the body [3]

This study aims to analyze the impact of airborne benzene exposure using the indicator trans, trans-Muconic Acid (tt-MA) and needs to be carried out to detect benzene exposure in workers more accurately. Therefore, the research hypothesis is that there is a difference in benzene levels in the air with red blood cells, liver function, and tt-MA in the urine of manufacturing industry employees.

METHOD

This research adopts an observational approach with a cross-sectional design to analyze the relationship and differences in the levels of Trans Trans-Muconic Acid (TMA) in the urine and liver function of workers in the manufacturing industry. The study is conducted in the manufacturing industry, specifically in the painting production unit, where workers are at risk of exposure to benzene contained in the paint used as a solvent. The research population includes all employees in the manufacturing industry, both in administration and production units. The total number of employees is 158, with 58 individuals in four production units and 16 in administration. Research respondents are selected based on inclusion criteria, such as not having metabolic diseases, being permanent employees, not taking medication in the last two weeks, and willingness to participate. The research instrument involves a questionnaire, as well as urine and blood sample collection from the respondents. Consecutive sampling is employed as the sampling technique, and the sample size is determined using the mean equation:

$$n = \frac{2.\sigma^2(Z_\alpha + Z_\beta).^2}{(\mu_1 - \mu_2)^2}$$

The mean value was obtained for the tt-MA levels in administrative workers (229.96 ± 127.80) as the control group and in operator workers (480.74 ± 219.65) as the case group [10]. the sample size consists of 8 individuals in the unexposed to benzene group (administration) and eight individuals in each production unit (painting). The total sample size is 16 individuals for both groups.

Examination of airborne benzene uses the NIOSH Analytical testing method. Levels of benzene in urine (tt-MA) are assessed using an in-house method, while liver function is examined using the IFCC 37 C method. Parametric Independent-Samples T-test and non-parametric Mann-Whitney Test are utilized to determine differences in tt-MA levels between production unit workers and administrative unit workers.

RESULTS

The measurement results for Benzene in the Production Unit (Painting) yielded 0.0098 BDS, while the benzene level in the office was found to be 0.0001 DBS, indicating that the levels are still within a

safe range. The Occupational Exposure Limit (OEL) is 0.5 BDS/ppm of air in the workplace, according to the Indonesian Ministry of Manpower Regulation No. 5 of 2018. Therefore, indoor benzene levels are considered safe.

Table 1. Testing Results for Air Quality of Benzene and Working Climate in Administrative and Production Spaces

Air Quality Parameters	Location	
	Administration Room *(Office)*	Production Room *(Painting)*
Benzene	0,0001 BDS	0,0098 BDS
Temperature	27,5 °C	30,1 °C
Humadity	67,6 %	58,4 %
Air Pressure	93,2 kPA	93,2 kPA

Based on the Mann-Whitney test, Table 2 shows that the levels of SGPT and Independent-2 Sample t-Test obtained statistical test results indicate a significant difference in tt-MA and SGOT levels between workers in the production unit and workers in the administrative unit. The correlation test results indicate a significant relationship between the high levels of benzene in the air and the increased tt-MA in workers in the production unit (painting).

Table 2. Testing Differences and the Impact of Benzene Exposure in the Air on tt-MA Levels and Liver Function in Manufacturing Workers

Variable	Workers in the administrative space Mean ± SD	Workers in the production space Mean ± SD	t-test *p-Value*	Correlation p-Value
tt-MA	22,7 ± 1,2	25,3 ± 2,9	0,001*	0,004*
SGOT	19,9 ± 3,6	25,2 ± 8,5	0,033*	0,123
SGPT	22,9 ± 7,8	38,6 ± 25,1	0,247	0,113

*p<0,05 = signifikan

DISCUSSION

The measurement of benzene in the air in the manufacturing industry revealed that the concentration of benzene in the air is still within normal conditions, specifically 0.0002 DBS, using the NIOSH Analytical testing method. Based on the test results, there is no significant difference in the concentration of benzene compounds in the air between the production and administrative spaces. This is attributed to the use of local ventilation assistance in the production area during the painting process. Throughout the painting process, local ventilation is activated to prevent pollutants from spreading into the air.

Benzene is classified as a Group 1 carcinogen (IARC Group 1) and a mutagen that can contaminate animals and humans through various routes, including inhalation and oral and dermal exposure, based on evidence that it causes leukemia[11]. However, the primary route of benzene exposure in the workplace is through inhalation [12] .

The results of the examination of Trans Trans-Muconic Acid (tt-MA) levels in both groups showed a highly significant result with a p-value < 0.001. The characteristics of tt-MA levels based on

the exposed group had an average of 331.5 µg/creatin, while the unexposed group had an average of 106.6 µg/creatin. The results indicate that the production unit group experienced an increase in tt-MA levels, followed by an increase in airborne benzene levels. In the exposed group, two workers had tt-MA levels exceeding the Biological Exposure Indices (BEI) set by ACGIH (500/µg/creatin), while 16 respondents were still within the safe limits. The high-risk factors for tt-MA in urine in the production unit include factors such as working period and smoking behavior [13].

Benzene present in the body can be eliminated by being excreted, primarily through respiration, with benzene being mainly excreted through urine. As metabolites, especially phenolic conjugates and glucuronate and sulfate acids, will be exhaled into the air in the same compound form. Absorbed benzene can be excreted through the metabolism of phenol and muconic acid found in the urine in the form of conjugates such as sulfate and glucuronide [14].

Indicated after exposure to benzene compounds in the workplace environment at 100 cm3/m3, the amount = phenol 13.2%; quinol 10.2%; t,t muconic acid, catechin 1.9%; 1.6% cathejol, and 0.5% 1,2,4-Benzenetriol, originating from total absorption released through urine after work. The ratio of absorbed benzene to exhaled benzene is 8-17%. A small amount of benzene is also detected in the urine[15].

Approximately 12-50% of absorbed benzene remains unchanged through respiration, and less than 1% is excreted through urine. The average amount of phenol excreted is around 30% of the absorbed benzene compound. If there is no metabolic reaction with benzene, the process is reversible, and benzene is eliminated through the respiratory system[16].

Toxicity of benzene after exposure through inhalation/exhalation at high concentrations (3000ppm in 5 minutes) or ingestion for 30-60 minutes will affect the central nervous system. Exposure to moderate concentrations of benzene compounds can cause dizziness, nausea, headaches, instability, and a burning sensation in the eyes. Prolonged exposure to benzene can result in tremors, shortness of breath, loss of consciousness, coma, and even death[17].

The compound trans,trans-muconic acid is the oxidation product of muconaldehyde (MUC) compound. Muconaldehyde is a six-carbon chain diene, and dialdehyde compound believed to cause benzene toxicity in the bone marrow[10]. Urinary Tt-MA can serve as a sensitive and specific indicator in biological examinations, especially in low-level benzene exposure [18,9,19]. tt-MA present in urine can detect benzene exposure as low as 0.1 ppm [3].

The results of liver function tests (SGPT and SGOT) show the most significant difference in SGOT levels with a p-value <0.033, while SGPT levels do not show a significant difference. The metabolic pathway and biochemical interactions that occur in the body involve various biochemical reactions. Benzene is first oxidized to benzene oxide in the liver by cytochrome P-450-dependent monooxygenase. After this reaction, enzymatic and non-enzymatic reactions will form several secondary metabolites[6].

Similar research revealed a significant increase in liver enzymes (SGPT and SGOT) among the exposed group compared to the group not exposed to benzene [20,21]. Workers with a benzene exposure duration ≤ 8 hours/day account for 70%, while those with > 8 hours/day account for 30%. Measurement results exceed the normal limits, with SGOT values at 15% and SGPT at 30%[8].

The liver is the main organ for metabolizing benzene. Benzene can be neutralized in two stages. In the first stage, benzene is oxidized by cytochrome P450 2E1, forming benzene oxide. Then, in the second stage, reactive electrophilic intermediates occur, and benzene oxide is metabolized through three pathways[17]. The liver is the primary organ for the transformation and metabolism of toxins; hence, liver damage can occur, making it susceptible to benzene [22]. Prolonged exposure to organic solvents such as benzene, toluene, and xylene is a risk factor for liver cancer [23].

Benzene is distributed throughout the body via the bloodstream. Its lipophilic nature (high solubility in oil rather than water) allows it to accumulate in adipose tissue. A study indicated that workers who died due to high-concentration benzene exposure had 0.38 mg of benzene in the blood, 1.38 mg in the brain, and 0.26 mg in liver tissue. Another study on pregnant rats exposed to 2000 ppm benzene vapor for 10 minutes found that benzene and its metabolites were present in fatty tissues such as adipose tissue, brain, liver, and kidneys. Additionally, they were detected in the fetus and placenta. Exposure to benzene for 6 hours can be detected in the blood and spinal cord, with benzene metabolites such as catechol, hydroquinone, and phenol [24-25]

CONCLUSION AND RECOMMENDATION

The levels of benzene in the air have been measured and found to be below 0.5 ppm, which is considered safe. However, there were significant differences observed in the levels of tt-MA and SGOT between workers in the production and administrative units, while SGPT levels did not show any significant differences. To ensure the safety of workers in the production unit, it is recommended that they follow the Standard Operating Procedures (SOP), which includes using local exhaust ventilation as a control measure for exposure sources, wearing personal protective equipment (PPE) like respirator masks and refraining from smoking.

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