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ASSOCIATION BETWEEN BLOOD LEAD LEVELS AND HEME SYNTHESIS PROCESS IN PAINT INDUSTRY WORKERS

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ABSTRACT

Blood lead levels and delta-aminolevulinic acid dehydratase (ALAD) activity are considered biomarkers of lead exposure and lead toxicity respectively. The inhibition of ALAD can cause in accumulation of ALA in urine and also inhibit the heme synthesis pathway that plays a role in hemoglobin production. The present study was designed to investigate the association between the BLLs and the heme synthesis process, which is detected by the accumulation of urinary ALA (ALA-U) and decreasing hemoglobin, in paint industry workers from Indonesia. A total of 52 paint industry workers participated in this study. The sample collection was conducted using cross-sectional design. Blood lead was measured using ICP-MS and ALA-U was measured using spectrophotometer method. Mean blood lead was 4.213±1.6 µg/L; and 17 workers (32.7%) crossed the recommended level of 5 µg/L. Mean urinary ALA level was 3.712±2.5 mg/L; and 11 workers (11.54%) crossed the normal level of 6 mg/L but still classified as acceptable. Mean hemoglobin level was 15.273±1.03 g/L. The correlation between the BLL and ALA-U was found to be positive but not significant. Meanwhile, the correlation between the ALA-U and the hemoglobin levels was found to be negative but also not significant. This study implies that the occupational exposure of lead in paint industry has not reached a limit that significantly disrupts the heme synthesis. However, the lead exposure in occupational air is recommended to be monitored because there is indication of an increase in ALA-U and decrease in hemoglobin due to increase in BLLs.

KEYWORDS *blood lead levels; delta-aminolevulinic acid; heme synthesis; hemoglobin; occupational exposure; paint industry workers*

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INTRODUCTION

In 2015, 73% of the total 120 paint products circulating in Indonesian market was found to contain more than 90 ppm lead, of which 39% contained quite high concentrations of lead, even exceeding 10,000 ppm (Ismawati et al., 2021). This shows that lead-based paints are still widely sold in Indonesia. Lead is most commonly used in solvent-based paints. Lead compounds are also commonly added to make paint pigments that are opaquer. In addition, lead compounds are also often added to enamel paint as desiccant (Clark et al., 2009). In adults, lead exposure is usually related to occupational exposure where the inhalation route is the most common route of exposure occurring in the working environment (Dongre, 2020). In paint industry, lead can be contained in particulate matter or vapor from the paint that is produced and inhaled by the workers who do not use PPE. Other than inhalation, the occupational exposure of lead can happen through dermal absorption. Even though dermal is not the significant portal of entry, dermal contact has a role in transferring lead to the industry workers that use lead material.

Exposure and toxicity monitoring of lead in humans can be done by monitoring the biomarkers. Blood lead levels (BLL) is the most widely used lead exposure biomarker (Sakai, 2000). Meanwhile, for toxic effects monitoring, the widely used effect biomarker for lead is the activity of enzyme delta-aminolevulinic dehydratase (ALAD) (Jangid et al., 2012). OSHA (2012) conducted a study related to the inhibition of the heme synthesis process in the form inhibition of the delta-ALAD enzyme on the incidence of anemia. From that study, it was found that there was a negative pathophysiological effect on BLL of more than 40 μg/dL. ALAD is one of the enzyme which catalyzes the condensation of two ALA (aminolevulinic acid) to form monopyrolle porphobilinogen (PBG) (Kelada et al., 2001). When BLL exceeds 20 μg/dL, 50% of ALAD activity will be inhibited (Philip & Gerson, 1994). The study conducted by Jangid, *et al.* in [5] also gave the result about significantly lower ALAD activity in line with increasing BLL where the BLL was also negatively correlated with blood ALAD ($r = -0.425$, p-value < 0.001, $N = 250$).

Heme synthesis is a biosynthetic process involving eight steps of enzymatic pathway that produces a heme product which has a role in stimulating the synthesis of red blood cells and hemoglobin. Heme is an essential prosthetic group in proteins that plays an important role as sub-cellular components to carry out various biological function such as hemoglobin and myoglobin (Yuan et al., 2016). The heme synthesis happens mainly in the bone marrow by erythrocytes and in the liver by hepatocytes. ALAD is the second enzyme that plays a role in the heme synthesis pathway (La-Llave-Leon et al., 2017).

Lead inhibition of ALAD activity impacts the accumulation of ALA which is associated with the oxidative damage through the damage in formation of reactive oxygen species (ROS) such as superoxide, hydroxyl radicals, and hydrogen peroxide. High ALA content in the blood then will be eliminated with the urine (La-

Llave-Leon et al., 2017). Based on these mechanisms, lead exposure in humans has the potential to cause excessive concentrations of ALA in urine (ALA-U). Inhibition of ALAD enzyme activity also has various physical effects beyond the production of ROS. Inhibition of ALAD will result in obstacles to the heme biosynthesis pathway (Monteiro et al., 1985). Without properly functioning heme, the erythrocytes cannot carry enough oxygen to the other body issues, especially the brain which requires large amount of oxygen.

The accumulation of ALA molecules is also harmful to the body. ALA can accumulate in nerve tissue, bloodstream, heart, liver, kidney, spleen, muscle, and adipose tissue. Accumulation of ALA in bloodstream means that ALA can be distributed to all other parts of the body and these molecules can enter the central nervous system including penetrating the blood brain barrier which can cause interference in synaptic transmission (Monteiro et al., 1985). The disruption occurs through competition for presynaptic GABA receptors. Based on the background described, the objective of this study is to investigate the association between the blood lead level and the heme synthesis process observed by the accumulation of ALA in the urine and decrease in hemoglobin count in paint industry workers in Indonesia.

Several have shown indications of inhibition in heme synthesis pathways caused by exposure of lead at certain level and the impact it has on human's health. Thus, further research is needed regarding the community groups that potentially receive lead exposure. One of these community groups is workers in paint industry, especially in Indonesia, sees that there are still many paint products sold in Indonesian market containing high levels of lead. Therefore, this study aims to investigae the association between the occupational lead exposure detected by blood lead levels and the heme synthesis pathways observed by the accumulation of ALA in the urine and decrease in hemoglobin count in Indonesian paint industry workers.

RESEARCH METHOD

Research Subject And Location

The research was conducted in three paint industries located in three different cities in Indonesia. Furthermore, these three industries will be mentioned as Industry A, Industry B, and Industry C. The research subjects were taken from the population which was all workers in the paint industries. The selection of the subjects was carried out based on non-probability sampling technique, namely purposive sampling with the inclusion criteria being male, aged 25 – 50 years old, had worked in the industry for at least 2 years, and were willing to sign the informed consent, and the exclusion criteria namely workers residing around or near landfill area and/or industrial area. The total number of subjects participating in this study were 52 subjects. The methods involving human research subjects had been reviewed and approved by the Padjadjaran University Research Ethic Commission through the document number 1066/UN6.KEP/EC/2022.

Sample Collection

The data collection was carried out through interviews and questionnaires to obtain general information, workers' characteristics and habits, as well as other information such as working time and period. To determine the BLL, the blood samples were taken from the workers by the medical personnel of Prodia Clinic Laboratory using the IV (intra venous) blood collection method to provide more accurate quantification of body burden. Then, urine samples were also taken from the workers to check the urinary ALA (ALA-U) and the creatinine levels. The urine samples were placed in 30 ml plastic urine pot.

Blood Samples Analysis

The blood samples analysis was done by Prodia Clinic Laboratory. From the existing blood samples, the blood lead levels were measured using the ICP-MS method. Then, the hematological parameter which is hemoglobin is also counted using a hematology analyzer.

Measurement of Urinary ALA (ALA -U)

The measurement of ALA-U levels was carried out at ITB's Environmental Engineering Industrial Hygiene and Toxicology Laboratory using the spectrophotometer method. The method used is a spectrophotometric method developed by Tomokuni and Ogata (1972) which uses a modified Erhlich's reagent, and the color development will be measured at 553 nm wavelength.

Statistical Analysis

The descriptive statistics were used to describe the subjects' characteristics, and biomarkers of lead exposure and effects. Statistical tests with Pearson's correlation were used to determine the association between the BLL and ALA-U levels detected in workers. Then, to determine the factors that are significantly related to the exposure and response biomarker which are the categorical variables, non-parametric statistical analysis using Kruskal Wallis and Mann Whitney U tests will be performed. The degree of confidence used in this study is 95% with the margin of error of 0.05. The statistical analysis was performed using SPSS 22 software.

RESULT AND DISCUSSION

Subjects' Characteristics

The research was conducted in 3 paint industries located in 3 different cities with 52 research subjects participating in this study. 20 subjects were from Industry A, 12 subjects were from Industry B, and 20 subjects were from Industry C. In line with the inclusion criteria, the research subjects were 25 – 50 years old with the average of 34 years old. Each subject had worked in each industry for 2.5 – 29 years with the average of 11 years. Table 1 and Table 2 summarizes the workers' characteristics and habits that potentially affect the BLL.

Table 1. Main characteristics of the studied subjects (n = 52). SD: standard deviation.

Variables	Mean ± SD	Range
Age (years)	33.67±5.39	26-50
Working period (years)	10.61±4.79	2.5-29
Body weight (kg)	75.81±14.05	50-105
Body height (cm)	170.04±5.59	161-185

Table 2. Categorization of the workers' characteristics and habits.

No	Variables	Categories	N
1	Workplace	A	20
		B	12
		C	20
2	Working activities	Paint production	35
		Logistic	10
		Non-paint production	7
3	PPE usage	Never	3
		Sometimes	11
		Always	38
4	Smoking habit	Smoking	25
		Non-smoking	27
5	Daily vehicle used	Opened vehicle (motorcycle, walking, etc.)	46
		Closed vehicle (car, shuttle bus, etc.)35	6

Blood Lead Levels (BLLs)

The exposure biomarker measurements were performed to measure the subject's exposure to a toxicant. The exposure biomarker used in this study was BLL. The results of the BLL measurement were expressed in µg/L units which shows the mass of lead compared to a unit volume of the blood analyzed with ICP-MS method. The results of blood lead levels are shown in Table 3. The results of the workers' BLL showed the average concentration value of 4.219±1.6 µg/L and in the range of 1.4-8.1 µg/L. Based on the references from UCSF Health, the normal BLL value for adults is <10 µg/L (UCSF, 2023). Meanwhile, according to several other institutions, the limit value of BLL that does not require monitoring for adults is <5 µg/L (CPDH, 2021; WHO, 2023). The BLL distribution of all workers is shown in Figure 1.

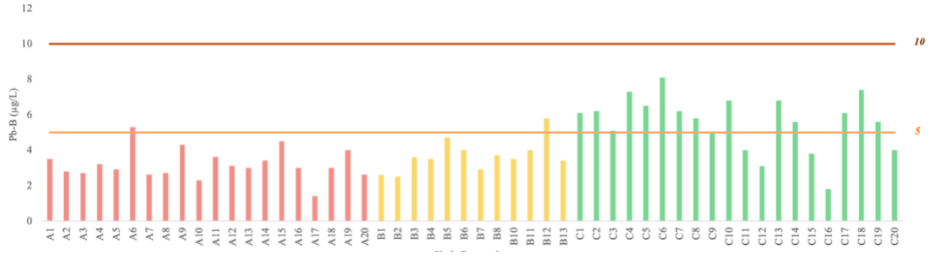


Figure 1. BLL levels distribution for all workers.

From Figure 1, there were no workers whose BLL exceeded the normal adult BLL value (≥10 μg/L). However, there is one worker from Industry A, one worker from Industry B, and fifteen workers from Industry C who have BLL higher than 5 μg/L. Even though these values are still within the normal levels of BLL, blood lead levels monitoring is highly suggested.

Table 3. Descriptive summary of BLL, ALA-U, and hemoglobin counts.

Parameters	BLL (μg/L)	ALA-U (mg/L)	Hemoglobin (g/dL)
MIN	1.4	0.476	13.4
Q1	3	1.758	14.6
MEDIAN	3.75	3.158	15.5
Q3	5.6	5.273	15.825
MAX	8.1	10.266	18.1
MEAN	4.219	3.712	15.273
STD	1.6	2.5	1.04

Factors Affecting The Blood Lead Levels

Since the research was conducted using a cross-sectional study design, the exposure biomarker of lead was taken at the same time as the effect biomarker so that the biomarker data obtained reflected the current concentration of lead in the blood of the workers. However, the BLL detected surely has variations and is influenced by other factor such as the working activities, the habit of using PPE (masks) at work, smoking habits, and the type of vehicle used daily.

For the factors consist of 3 categories, the statistical test will be conducted using the Kruskal Wallis test method. Meanwhile, for the factors consist of 2 categories, the statistical test will be conducted using the Mann Whitney U test method. The significance of each factor is summarized in Table 4.

The factors which gave the p-value < 0.05 are workplace and PPE usage, so those two factors have a significant influence on the workers' BLL. To determine in which categories the differences are significant, a post hoc test using Mann Whitney U will be carried out on those two factors. The post hoc test results are shown in Table 4

Table 4. Significance results of each factor on the workers' BLL

No	Variables	Categories	N	p-value (Sig.)
1	Workplace	A	20	**0.000**
		B	12	
		C	20	
2	Working activities	Paint production	35	0.245
		Logistic	10	
		Non-paint production	7	
3	PPE usage (mask)	Never	3	**0.01**
		Sometimes	11	
		Always	38	
4	Smoking habit	Smoking	25	0.384

No	Variables	Categories	N	p-value (Sig.)
5	Daily vehicle used	Non-smoking	27	0.302
		Opened vehicle (motorcycle, walking, etc.)	46	
		Closed vehicle (car, shuttle bus, etc.)35	6	

Table 5. Posts hoc test results

No	Variables	H_0	p-value (Sig.)
1	Workplace	μA = μB	0.133
		μA = μC	**0.00**
		μB = μC	**0.001**
3	PPE usage (mask)	μNever = μSometimes	0.221
		μNever = μAlways	**0.02**
		μSometimes = μAlways	**0.031**

Based on the post hoc test results, a significant difference in BLL concentration was found in between the workers who worked in Industry A and Industry C (p-value = 0.00) and in between the workers who worked in Industry B and C (p-value = 0.001). It is obtained that the average concentration of the workers' BLL in Industry A, Industry B, and Industry C are 3.195 μg/L, 3.683 μg/L, and 5.565 μg/L respectively. The maximum BLL was found in Industry C, which was 8.1 μg/L, and the minimum BLL was found in Industry A, which was 1.4 μg/L. Thus, it can be concluded that the BLL of the workers from Industry C is significantly higher than the BLL of the workers from Industry A and Industry B.

Then, it was also found that there was also a significant difference in the average of BLL between the workers who did not use PPE (mask) (p-value = 0.02) and the workers who always used PPE (mask) at work (p-value = 0.02), and between the workers who use PPE (mask) sometimes and the workers who always used PPE (mask) at work (p-value = 0.031). Thus, the BLL detected on the workers who always use PPE (mask) while working is significantly lower than the BLL detected on the workers who occasionally or do not use masks at all while working. Similar result was also stated by Santosa (2022) where the automobile painting workers who never or rarely use mask at work have a higher risk of receiving lead exposure than the workers who always wear mask at work.

Urinary ALA (ALA-U) Levels

In this study, the effect biomarker of lead exposure on workers was viewed from the inhibition of ALAD enzyme which can be seen through the accumulation of ALA molecules in the workers' urine. The concentration of ALA-U in workers' urine is expressed in mg/L unit and analyzed using the spectrophotometer method. The measuring results of the ALA-U levels are summarized in Table 3. The ALA-U levels of the workers is in the range of 0.476-10.266 mg/L. The reference values for measuring the ALA-U levels were obtained from a medical study by Malady

(1968) as well as the research published by Kalahasthi and Barman (2018). ALA-U levels less than 6 mg/L is considered as the normal value, while ALA-U in the range of 6-20 mg/L is considered higher than normal but still classified as acceptable, and ALA-U levels greater than 20 mg/L is classified as excessive and dangerous. The distribution of the workers' ALA-U levels is shown in Figure 2.

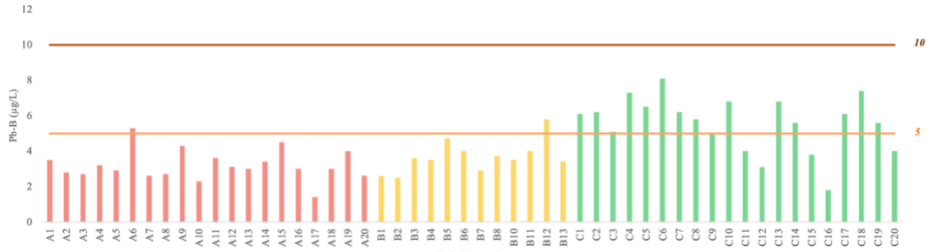


Figure 2. ALA-U levels distribution for all workers

Based on Figure 2, there are 11 workers who have ALA-U levels greater than 6 mg/L, which are one worker from Industry A, four workers from Industry B, and six workers from Industry C. Even though those values are greater than 6 mg/L and exceeding the normal limit, but those values have not exceeded 20 mg/L, so it still classified as acceptable.

Correlation of BLL and ALA-U

The correlation analysis will be carried out to determine the association between the lead exposure dose represented by the BLL and the effect caused by the exposure represented by the ALA-U levels. The association of those two variables is tested using Pearson's correlation. According to Hudak, *et al* (1992), the clinical relevance of the ALA-U variable adjusted with the subjects' creatinine through the logarithmic equation (ALA-U/log creatinine) proved to be better at detecting lead exposure, especially for BLL exceeding 2.5 µmol/L as evidenced in 483 male workers exposed to lead. Urine creatinine itself is a specimen that describes the kidney function condition of the workers. Kidney function of each different subject can certainly affect the elimination of ALA molecules through urine. From there, this study will also carry out the correlation analysis to see the association between the BLL and the ALA-U/log creatinine using the Pearson's correlation. The correlation analysis results are shown in Table 6.

Table 6. Pearson's correlation results between BLL and ALA-U levels

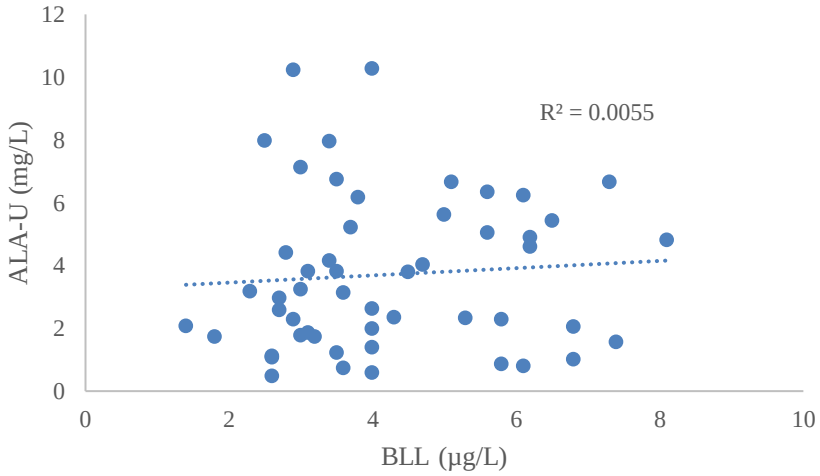
Correlation	BLL – ALA-U	BLL – ALA-U/log creatinine
r (correlation coefficient)	0.074	0.032
p-value (sig.)	0.4	0.412

Based on Table 6, the correlation coefficient for the association between the BLL and the urinary ALA levels have positive values, which means the association between those variables is a positive correlation. It shows the tendency of the existing data that the increasing value of BLL is in line with the increasing value in ALA-U levels. Nonetheless, the value of r (correlation coefficient) for the correlation of those variables are quite small and close to zero. The p-value for both BLL vs ALA-U and BLL vs ALA-U/log creatinine are greater than 0.05. Thus,

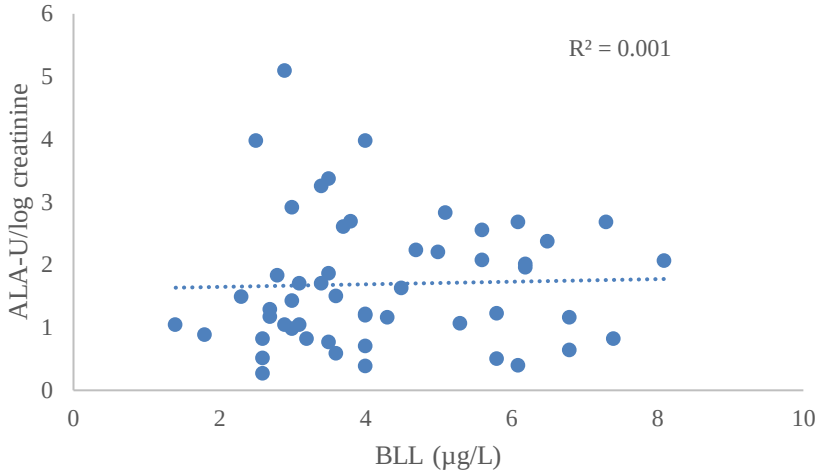
there are no significant correlations among the BLL, ALA-U, and ALA-U/log creatinine.

Lead is a strong inhibitor of ALAD enzyme where lead can interact and join the ALAD enzyme sulfhydryl group (Brody, 1999) and replace the Zn on the metal binding site of the enzyme. This mechanism can interfere with the binding interaction between the ALAD enzyme and the substrate (Cardoso et al., 2017). Lead inhibition on ALAD activity will result in ALA accumulation in blood plasma and urine even at BLL < 10 µg/dL [23]. ALA can accumulate in nerve tissue, blood, heart, liver, kidney, spleen, muscle, and adipose tissue (Monteiro et al., 1985). This causes urinary ALA to be less sensitive than ALAD activity in blood (La-Llave-Leon et al., 2017) in evaluating BLL because not all accumulated ALA molecules are eliminated with urine.

In addition, research by Jangid, *et al.* (2012) suggested that significant decreased in ALAD happened in the research subjects who had BLL in the range of 20-40 µg/dL. Meanwhile, in this study there were no subjects with BLL exceeded 10 µg/dL. Therefore, it is possible that the exposure has not reached the dose and concentration which causes a significant difference between the workers who receive the higher dose and those who receive the lower dose.



(a)



(b)

Figure 3. Regression of blood lead levels and (a) ALA-U levels; (b) ALA-U/log creatinine

Hemoglobin Levels

Hemoglobin is an oxygen-binding protein found in red blood cells that transports oxygen from the lungs to the body tissues. The two main components of hemoglobin synthesis are globin production and heme synthesis (Farid et al., 2019). The measurement of hemoglobin in this study was carried out to see whether the lead exposure, which is thought to result in inhibition of the heme synthesis process, will have an impact on the hemoglobin synthesis process by observing the hemoglobin levels in the workers' blood. The results of the hemoglobin levels are summarized in Table 3. The distribution of the workers' hemoglobin level is shown in Figure 4.

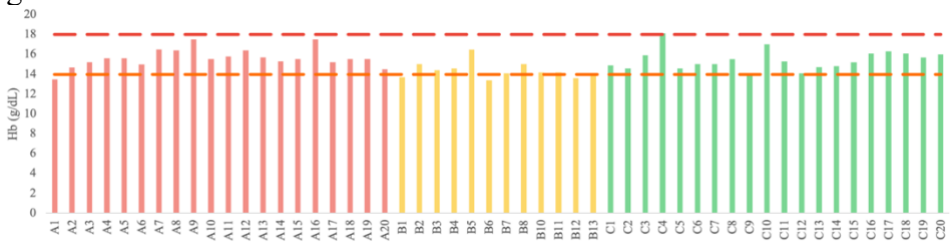


Figure 4. Henoglobin levels distribution for all workers

The hemoglobin levels measurement in the workers' blood showed the average of 15.273 ± 1.04 g/dL. The normal level of hemoglobin in the blood for adult males is 14-18 g/dL (Walker et al., 1990). Based on Figure 4, there is one worker from Industry A and 3 workers from Industry B who have a hemoglobin level less than the reference value.

Correlation of ALA-U and Hemoglobin Levels

The effect of lead exposure on the heme synthesis process is the accumulation of ALA due to inactivation of the ALAD enzyme which functions to catalyze the condensation of two ALA molecules into PBG (Fowler, 2016). Therefore, to see whether there is an effect of lead exposure on hemoglobin due to the inhibition of

the heme synthesis process, which is thought to occur, the correlation analysis will be carried out between the ALA-U levels and the hemoglobin levels. The correlation analysis will be carried out using Pearson's correlation test. The correlation analysis results for those variables are shown in Table 7.

Table 7. Pearson's correlation results between ALA-U and hemoglobin levels

Correlation	ALA-U - hemoglobin
r (correlation coefficient)	-0.095
p-value (sig.)	0.252

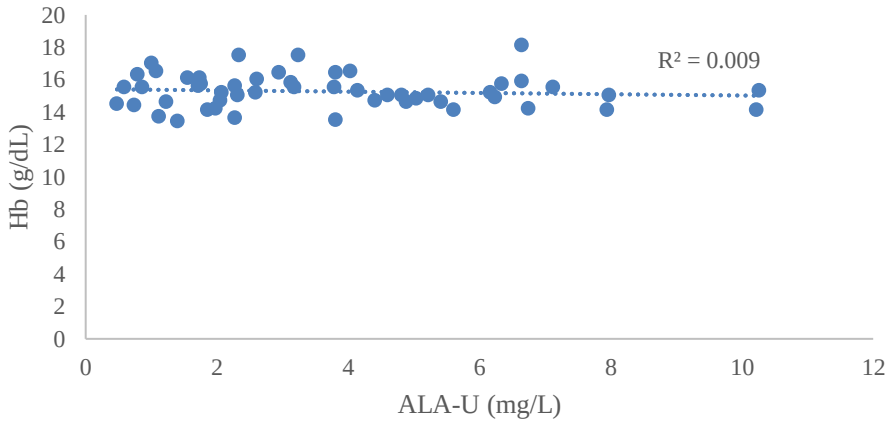


Figure 5. Regression of ALA-U and hemoglobin levels

The correlation coefficient (r) obtained from the Pearson's correlation test is a negative value. It means the correlation between ALA-U and hemoglobin levels is negative (not in the same direction) or there is a tendency in the existing data that the increasing ALA-U is in line with the decreasing in hemoglobin levels. However, the value of the correlation coefficient is quite small (close to zero). The p-value was also greater than 0.05 which means there was no significant correlation between ALA-U levels and hemoglobin levels.

Lead can inhibit the body's ability to produce hemoglobin by interfering with several enzymatic pathways that play a role in the heme synthesis pathway. EPA estimates that the threshold of BLL which results in decreasing hemoglobin for adult workers is 50 µg/dL (Abadin et al., 2007). In this study, there were no workers whose BLL reached the value of 50 µg/dL and all workers had the ALA-U levels that were still at the acceptable levels so that lead exposure and inhibition of heme synthesis that occurred might not have reached the dose or concentration which led to significant differences between the workers who received the high exposure and those who receive lower exposure. According to Monteiro, *et al*. (1985), when the inactivation of ALAD enzyme occurs, ALA molecules are not only accumulated and eliminated through urine. However, ALA molecules can also accumulate in other tissues and organs.

CONCLUSION

Based on the research results, the lead exposure detected in the biomarker, which is BLL, has a positive correlation with the urinary ALA (ALA-U) levels. It illustrates the tendency of increasing BLL is in line with increasing ALA-U, which means the ALA molecules fail to be condensed into PBG by the ALAD enzyme. However, the correlation obtained is not significant (p-value > 0.05). Then, the increase in ALA-U levels indicating the inhibition of ALAD enzyme activity also tends to be followed by the decrease in hemoglobin levels in this study. However, the correlation obtained is also not significant (p-value = 0.252). Therefore, the results of this study suggest that the lead exposure received by the paint industry workers still has not reached the level that can significantly indicate the difference between the exposed and the non-exposed group in terms of the heme synthesis process and the exposure level has not reached the concentration that causes significantly observable effects. Therefore, the results of this study suggest that the lead exposure received by the paint industry workers still has not reached the level that can significantly indicate the difference between the exposed and the non-exposed group in terms of the heme synthesis process and the exposure level has not reached the concentration that causes significantly observable effects.

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