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RELATIONSHIP BETWEEN LEAD EXPOSURE AND GENOTOXIC EFFECT IN PAINT INDUSTRY WORKERS

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KEYWORDS
DNA damage; occupational lead exposure; paint industry workers; PbB

ABSTRACT
Lead-based paint is a main source of lead exposure to paint industry workers and causes an imbalance of Reactive Oxygen Species (ROS) and antioxidants, causing a genotoxic effect. Pb in the blood (PbB) level and DNA damage are frequently used as exposure and effect biomarker of lead. The purpose of this study to determine the relationship between PbB level and DNA damage due to occupational lead exposure in paint industry workers. The research design uses a cross-sectional epidemiological study involving 52 workers from three paint manufacturers in Indonesia. Blood samples were taken for PbB analysis using ICP-MS, while DNA damage was analyzed using the Comet Assay method. The PbB average obtained was 4.36±1.60 µg.dL^{-1}, where 17 workers (32.69%) exceeded the safe limit value of PbB (5 µg.dL^{-1}). Meanwhile, the influential factors of PbB are the working period and alcohol consumption (p=0.029). The level of DNA damage was represented as Tail DNA (%), and the average was 9.62±0.19 %. All respondents in this study were categorized as under low damage (Class 2). There was no significant relationship between PbB and Tail DNA (%) and has a negative correlation (p=0.878; r=-0.022). The study concludes that there was no difference in Tail DNA (%) between PbB ≥ 5 µg.dL^{-1} and PbB < 5 µg.dL^{-1} (p=0.876). It means that lead exposure in this finding has not reached a level that can significantly cause DNA damage. However, it is necessary to monitor PbB levels in workers to minimize genotoxic or other effects.

INTRODUCTION

Lead (Pb) is a xenobiotic that is widely distributed and highly persistent (Singh et al., 2018). Lead (Pb) characteristics are low melting point, ductility, high malleability, corrosion resistance, and low cost. These functions made it widely used in various industrial sectors, which can accumulate in the environment and cause serious health problems for humans (Sangeetha and Umamaheswari, 2020). IARC classifies lead as a class 2A carcinogenic substance, in which the agent is possibly carcinogenic to humans (O'Connor et al., 2018). It is also unnecessary for human health, and harmful to the human body (Wani et al., 2015).

Lead-based paints are the primary source of lead poisoning in the industrial environment (Abdollahi et al., 1996). Occupational environments lead to higher lead levels in the occupational area, so there can be more opportunities for lead exposure (Singh et al., 2018). Paint products may contain lead when the paint's raw materials are contaminated with lead during the mixing process or cross-contamination from other products in the same industry. Paint manufacturers add Pb to paint to be a pigment, dryer, or anti-corrosion, however, the lead compound most often added to paint is pigment (Brosché et al., 2014) for improve colors such

as lead chromate ($PbCrO_4$) for yellow pigments and lead carbonate ($PbCO_3$) for white pigments. Also, it is protective, which makes the paint last longer, increases paint adhesion to the surface, and can make the paint layer remains strong but remains flexible and resists cracking longer (O'Connor et al., 2018).

The issue of lead-based paint has attracted the attention of international organizations and non-governmental organizations (NGOs). The International Community, led by UNEP and WHO, is actively supporting the global elimination of lead-based paints by 2020 due to its severe health risks. However, lead-based paints are still widely produced and used in developing countries, including Indonesia (O'Connor et al., 2018). Based on Ismawati et al. (2021), lead-based paints in Indonesia are still widely manufactured and sold. Of 120 samples tested, 39% have lead concentrations above 10,000 ppm. The threshold of Pb in paints (dry) is 600 ppm (Badan Standarisasi Nasional, 2014). IPEN recommends 90 ppm as a safe and achievable concentration of lead in paints worldwide (Brosché et al., 2014).

The pathway for lead to enter the body can be through air, food, or drink (Wani et al., 2015). Meanwhile, the routes of absorption of lead are through ingestion, inhalation, or the skin. Exposure to lead occurs mainly through gastrointestinal (GI) tracts and the respiratory system (Sangeetha and Umamaheswari, 2020). However, the dermal route is not significant in the general population, but dermal exposure most likely occurs in persons working with lead-containing materials. Although inorganic Pb exposure to the dermal route is rarely studied because it contributes little to absorption (Wani et al., 2015), several absorption kinetics parameters, such as Kp and diffusion rate, are produced to be used as a risk assessment for the work environment. The study produced Kp of 10^{-7} – 10^{-5} $cm.hour^{-1}$ and diffusion rate ranges of 10^{-7} - 10^{-4} $mg.cm^{-2}.hour^{-1}$ obtained from animal and human skins (Niemeier et al., 2022). After absorption, lead accumulates in the blood, soft tissues, and bone, and the lead's half-life in these parts is 35 days, 40 days, and 20-30 years respectively (Sangeetha and Umamaheswari, 2020).

Blood is commonly used as a biomarker because it is relatively easy to collect and is one of the pathways through which most chemicals and their metabolites travel within the body (Paustenbach and Galbraith, 2006). The concentration of lead in the blood (PbB) is an indication of Pb absorption. It is the best parameter to be used as a biological marker to evaluate lead exposure (La-Llave-León et al., 2017). While any measurable effect or response biomarkers, such as biomonitoring of enzymes in the blood, indicate organ damage, microscopic and subcellular levels (Timbrell, J. 2002). Lead toxicity can affect organ systems, induce various biochemical, physiological, and genetic dysfunctions as well as cause damaging effects, such as DNA damage (genotoxicity) (Singh et al., 2018).

Individuals exposed to the paint experienced increased levels of DNA damage (Cassini et al., 2011). It occurs due to changes in the basic structure of DNA which affect the physical-chemical properties of DNA which then affect the interpretation and transmission of genetic information (Juan et al., 2021). Occupational exposure to lead is associated with DNA damage that can measure using Comet Assay, a rapid, sensitive method suitable for biomonitoring studies (Olewińska et al., 2010). This method is widely used because it can detect DNA damage sensitively by measuring and analyzing DNA damage in lymphocyte cells. The damage can be in the form of a single strand break (SSB) or a double strand break (DSB) in opposite positions. The degree of DNA damage was determined by the proportion of cells with comets (Danadevi et al., 2003).

The major mechanism of Pb toxicity is lead can induced oxidative stress (Collin et al., 2022) which describe as an imbalance between the generation of Reactive Oxygen Species (ROS) and the ability of antioxidants. Pb is capable of inhibiting the activities of antioxidant

enzymes by interacting with a functional sulfhydryl (SH) group in antioxidant enzymes, such as δ-aminolaevulinic acid dehydrase (δ-ALAD), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glucose-6-phosphate dehydrogenase (G6PD), resulting increase Reactive Oxygen Species (ROS) production and decreased antioxidants (Hemmaphan and Bordeerat, 2022) which can cause damage to cellular biomolecules (include lipids, proteins, and DNA) (Juan et al., 2021).

Reactive Oxygen Species (ROS) are the typical by-products of the electron transport chain (ETC) during cellular respiration in aerobic organisms and are additionally derived from catabolic oxidases, anabolic processes, and peroxisomal metabolism. However, in excess, ROS species can cause a total of approximately 100 different oxidative base lesions and 2-deoxyribose modifications. The most reactive of ROS is OH radical (-OH) produced as a by-product of Fenton's reactions of H_2O_2 with Fe^{2+} can damage DNA. Another biologically significant and major oxidative base lesion formed from hydroxylation of the C-8 residue of guanine is the saturated imidazole ring 7,8 dihydro-8-oxo guanine (8-oxo-G). 8-oxo-guanine pairs incorrectly with adenine instead of cytosine, thereby adding to the overall mutational load, and is further oxidized to other deleterious secondary DNA lesions because of its low oxidation potential. Besides attacking DNA bases, ROS radicals can also compromise the DNA backbone causing an estimated 2300 single-strand breaks per cell per hour (Chatterjee and Walker, 2017).

Continuous oxidative stress can cause severe molecular and cellular changes that can lead to cell death (Singh et al., 2018). Moreover, any resulting damage, if not repaired, will lead to mutations and possibly disease (Lodish, 2004). Pb replaces calcium and zinc in enzymes involved in DNA processing and repair, resulting in increased genotoxicity when combined with other DNA-damaging agents such as tobacco smoke or UV A. Interestingly, abnormal DNA repair capacity was reported in lead-exposed workers (Hemmaphan and Bordeerat, 2022)

Based on this mechanism, it is necessary to evaluate the genotoxic effect in the form of DNA damage using comet assay on workers in the paint industry in Indonesia, because the genotoxic effects of paint industry workers in Indonesia have never been reported. The purpose of this study was to investigate the relationship between blood Pb (PbB) levels and DNA damage in workers of occupational exposure to lead in the paint industry in Indonesia.

RESEARCH METHOD

Research Design

The research design used an observational epidemiological study type cross-sectional to determine exposure and effects at one time quantitatively. Sampling was taken from 52 paint industry workers who are in three different locations in Indonesia, namely Industry A, Industry B, and Industry C. The kind of sampling technique used is non-probability sampling, namely purposive sampling. The selection of respondents is not random, but by setting inclusion criteria, including, males, aged 25-50 years, and willing to sign informed consent, while the exclusion criteria were not living near landfills and or industrial areas.

The respondents were divided into two groups based on exposure, the exposed groups and the controls groups. The groups in contact with lead-containing materials were included as the exposed group, while the group that had indirect contact with lead-containing materials was included as the unexposed group or as a control. The sample size in this research refers to NIOSH Occupational Exposure Sampling Strategy Manual (Leidel et al., 1997). This research has been reviewed and approved by the Padjadjaran University Research Ethics Commission with document number 1066/UN6.KEP/EC/2022.

Data Collection

Primary data collection is in the form of blood sampling and interviews with respondents. Blood collection was carried out by a phlebotomy-certified health professional from Prodia Clinic Laboratory and stored in a trace element Na-Heparin tube (Royal Blue-Top). As much as 6 mL samples of blood were preserved in an ice box for PbB analysis later. Meanwhile, 2 mL of blood was collected in a vacutainer tube then the sample was preserved in an ice box for DNA damage analysis later. Meanwhile, interviews were conducted to determine the characteristics of respondents.

Measurement of Pb in Blood and DNA Damage

Pb Level in Blood (PbB) was analyzed using the ICP-MS methods in Prodia Clinic Laboratory, while DNA damage was measured using the Alkaline Comet Assay according to the method of Singh et al., (1988) with some modifications in the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada. It uses horizontal submarine electrophoresis 300 mA; 50V. DNA damage was analyzed using ImageJ software for evaluating 50 cells per slide.

Statistical Analysis

Statistical analysis in this research used SPSS 22 software. The confidence interval used was 95%, with an error of 5%. Descriptive statistics are used to describe the characteristics of the respondents, PbB values, and DNA damage (%Tail DNA). The non-parametric comparison test used was Kruskal Wallis and Mann Whitney U to determine the factors that influence PbB. Then the Rank Spearman test was used to determine the correlation between PbB and DNA damage.

RESULTS AND DISCUSSIONS

Characteristics of Research Subjects

This research was conducted on 52 respondents from three paint industries in different locations in Indonesia. The number of respondents involved in each of the industries A, B, and C are 20, 12, and 20 respondents respectively. The interval aged of workers was 25-50 years with an average of 34 years. The working periods variable also varies among respondents, 2.5-29 years with an average of 11 years. Each subject has worked in their respective industries for 2.5 – 29 years with an average of 11 years. Table 1 summarizes the characteristics of the subjects participating in this study, while Table 2 summarizes the classifications of worker characteristics and habits, which will be evaluated for their effect on either PbB levels or DNA damage.

Table 1. Main characteristics of research subjects (n=52).

Variables	Min.	Max.	Mean ± SD
Ages (Years)	26	50	33.67±5.39
Working Periods (Years)	2.5	29	10.61±4.79
Body Weight (kg)	50	105	75.81±14.05

Table 2. Classifications of characteristics and habits of all respondents

No	Factors	Classifications	N
1	Ages	26-35 (years)	35 (67.0%)
		36-55 (years)	17 (33.0%)
2	Industry	A	20 (38.5%)
		B	12 (23.0%)

No	Factors	Classifications	N
	Locations	C	20 (38.5%)
3	Group of Exposures	Exposed group	35 (67.0%)
		Control group	17 (33.0%)
4	Working Periods	<10 years	19 (36.5%)
		≥10 years	33 (63.5%)
5	Smoking Habits	Smoking	25 (48.1%)
		Non-smoking	27 (51.9%)
6	Alcohol consumptions	Yes	5 (10.0%)
		No	47 (90.0%)

Blood Pb (PbB) Levels

Exposure biomarkers are one of the important parameters in toxicology to evaluate lead exposure, which indicates a measure of the interaction between biological systems and lead. Thus, exposure can be roughly determined by measuring the dose, but it cannot be assumed that all doses are absorbed. Therefore, the estimation of exposure is the concentration of chemicals in the blood lead level (PbB) as an exposure biomarker. The result of PbB measurements was expressed in µg.dL^{-1} units, showing the mass of lead in 100 mL of blood from ICP-MS measuring. The result of the PbB value is shown in Table 3.

Table 3. Descriptive summary of PbB

Parameters	PbB (µg.dL^{-1})
Min	1.40
Median	4.00
Max	8.10
Mean ± SD	4.36 ± 1.60

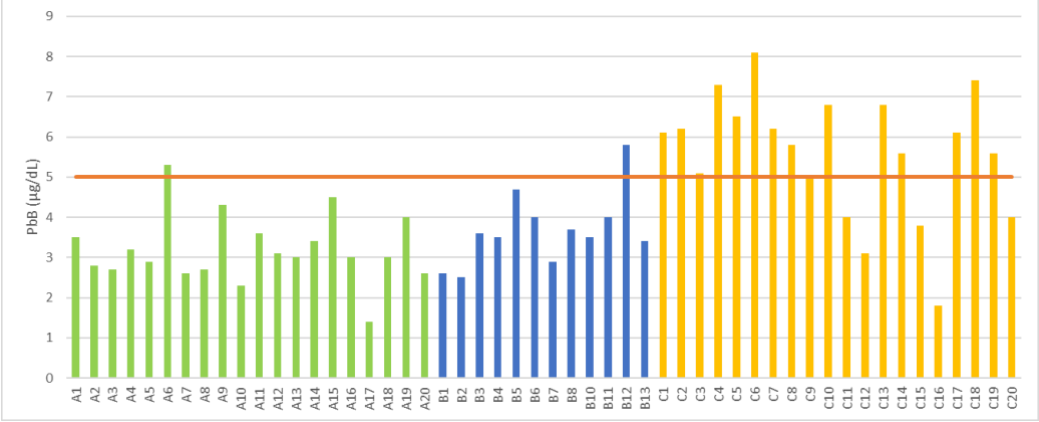

Figure 1. Distributions of Pb in the blood (PbB) level's in all respondents

Based on Table 3., the PbB average of all respondents in three industries was 4.36±1.60 µg.dL^{-1}, where 17 respondents (32.69%) exceeded the safe limit value of PbB, 15 of 17 respondents from industry C, one from industry A, and industry B, respectively, shown at Figure 1. According to the *Centre for Disease Control* (CDC) guidelines, the acceptable range for adult blood lead (PbB) levels is 10 µg.dL^{-1}, whereas based on NIOSH, the maximum value of PbB was 5 µg.dL^{-1} (Singh, et al. 2020). The PbB average of each Industry A, B, and C was 3.2±1.4 µg.dL^{-1}, 3.68±0.87 µg.dL^{-1} and 5.57±1.57 µg.dL^{-1} respectively. However, respondents of Industry C also have the largest PbB concentration range (1.80-8.10 µg.dL^{-1}) and have the

largest average PbB value. The Kruskal-Wallis test was used to find out the average difference between the three industries.

The PbB values in Industry C have significantly larger than in Industry A and B (p<0.05), as shown in Table 4., while the box plot of these industries is shown in Figure 2. The high presence of PbB levels in Industry C's respondents is thought to be due to exposure to lead obtained from lead-based paints that exceed the limit value. Based on a study conducted by Ismawati et al. (2021), industry C uses Pb in paints of more than 600 ppm, and for example, the lead content in the paint for the yellow color was 14,000 ppm, which means it is far from the quality standards set by SNI 8011-2014. Based on the California Department of Public Health, if the PbB value was 5-9 µg.dL^{-1}, it is necessary to identify a history of potential sources of lead exposure in the workplace and minimize contact with lead, as well as monitor these PbB levels, by carrying out inspections PbB levels every three months until the PbB value is less than 5 µg.dL^{-1} (Grandjean et al., 1981).

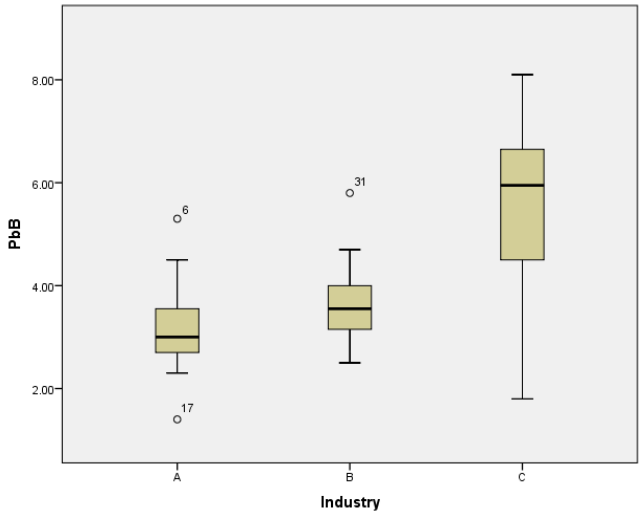

Figure 2. Box plot of PbB value based on industry location

Besides industry locations, several confounding factors will be analyzed for their effect on biomarkers of lead exposure (PbB). The confounding factors that have been evaluated for their significance on blood lead levels are exposure groups, working periods, smoking habits, and alcohol consumption. These factors were also evaluated using the Kruskal Wallis to find out the differences in the three factors while using Mann-Whitney U for two factors as a post hoc test. The statistical test results of these factors are presented in Table 4.

Table 4. Statistical test results of several factors that influence PbB

No.	Factors	Categories	N	*p*-value
1	Industry Locations	A	20 (38.5%)	**0.000***
		B	12 (23.0%)	
		C	20 (38.5%)	
2	Exposure Groups	Exposed Groups	35 (67.0%)	0.441
		Controls	17 (33.0%)	
3	Working Periods	<10 years	19 (36.5%)	**0.017***
		≥10 years	33 (63.5%)	
4	Smoking Habits	Smoking	25 (48.1%)	0.384
		Non-smoking	27 (51.9%)	

No.	Factors	Categories	N	*p*-value
5	Alcohol consumption	Yes	5 (10.0%)	**0.029***
		No	47 (90.0%)	

*p-value is statistically significant ($p<0.05$)

Factors that gave a significance p <0.05 besides industrial locations are working periods and habits of consuming alcohol. So, working periods and alcohol consumption can affect the Pb in blood (PbB) levels. This study is similar to Batra et al. (2020) studies that the concentration of Pb in the blood increases with years of exposure ($p<0.05$) and there was a positive correlation between working periods and PbB (p-value=0.016; r=0.333). Therefore, we conclude that the longer the duration of Pb exposure, the higher the level of lead in the blood (PbB).

For the alcohol consumption factors, this study is similar to Grandjean et al. (1981) that PbB detected in workers who are consuming alcohol is higher than in workers who don't consume alcohol, and also there was a positive correlation between alcohol consumption and PbB (*p*-value=0.031; r=0.300). The significance value of the study was $p<0.05$, which means that it is statistically significant, that people who consume alcohol have increased blood lead levels. Moreover, daily consumption of 13.5 mL of pure ethanol per day can contribute 0.5-1.0 µg leads.100 mL^{-1} of blood. Meanwhile, this study's exposure groups and smoking habits were not significant to PbB values ($p> 0.05$).

DNA Damage

DNA damage as effect biomarkers of lead is a change in the basic structure of DNA that does not replicate on its own when DNA is replicated. DNA damage can be in the form of chemical additions or disruptions to DNA bases (creating abnormal nucleotides or nucleotide fragments) or breaks in one or both strands of DNA (Bernstein & Nfonsam, 2013), which can be detected using Alkaline Comet Assay methods. One of the most used parameters to describe DNA damage is the Tail DNA (%) which represents the fluorescence intensity relative to the head and tail of DNA. The average Tail DNA (%) of all respondents was 9.62±0.19 %. Based on Figure 3, all respondents in this research are categorized as low damage (Class 2) (Pereira et al., 2010).

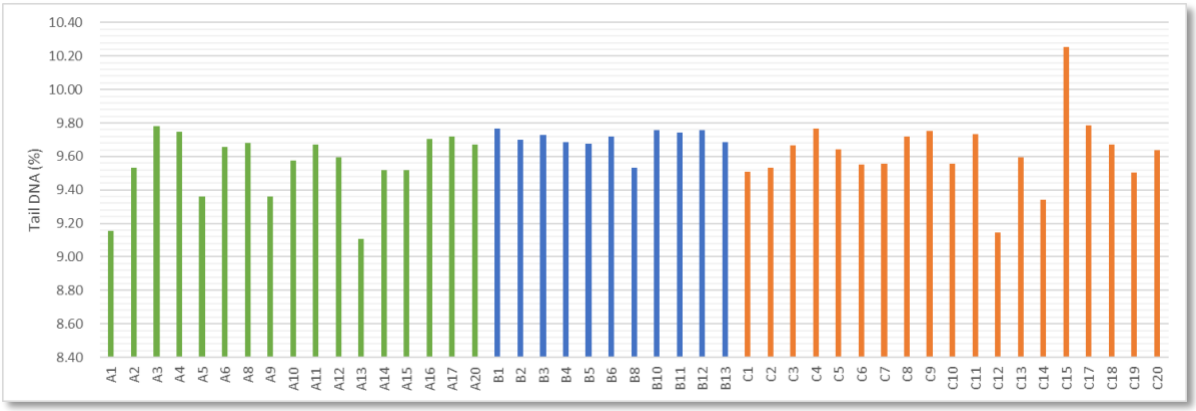

Figure 3. Distributions of Tail DNA's (%) worker

Table 5. Descriptive summary of DNA Tail (%)

Parameters	%Tail DNA
Min	9.11
Median	9.67
Max	10.25
Mean	9.62
SD	0.19

Mann Whitney U test was also used for evaluating the significance between two category PbB values, divided by two groups based on safety value according to NIOSH, PbB < 5 µg.dL^{-1} and PbB ≥ 5 µg.dL^{-1} shown in Figure 4. Moreover, they had no significant differences (p=0.876) between the two PbB levels groups, it shown in Table 6. This study contrasts with Kalaayathi et al. (2013), there was a statistically significant relationship between the Comet parameters and lead level groups in respondents (p <0.05). The differences were due to larger PbB values, and the groups were classified between PbB ≥ 10 µg.dL^{-1} and PbB <10 µg.dL^{-1}. Whereas in this study, it had not yet reached the PbB value for causing significant effects in DNA damage.

Table 6. Tail DNA (%) of the two groups based on PbB values

Parameters	PbB (µg/dL)	n	Min.	Max.	Mean	SD	*p*-value
Tail DNA(%)	<5	35	8.96	10.25	9.60	0.22	
	≥5	17	8.96	10.25	9.61	0.22	**0.876**

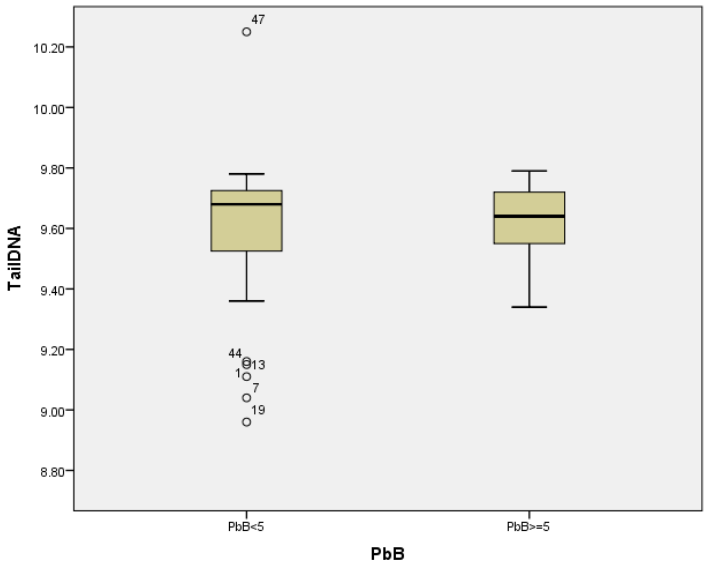

Figure 4. Box plot of Tail DNAs respondents based on PbB value

We used the Rank Spearman method to find out the correlation between PbB and Tail DNA (%). Based on Figure 5, there was no significant relationship between PbB and Tail DNA (%), and it has a negative correlation (p>0.05; r=-0.022). In contrast to research conducted by (Batra et al., 2020), there was a significant relationship and a positive correlation between PbB levels and Tail DNA (%) (p<0.05). The contrasts could be due to different values in this research and differences in subject research and occupational exposure. Batra et al. study involved building construction workers, painters, motor garage workers, tinting and painting workers, and battery workers involved in removing Pb electrodes, smelting, recycling Pb

batteries, and manufacturing and assembling Pb acid storage batteries. Furthermore, the range of lead levels in the exposed group was much larger (38.03 ± 12.92) µg.dL^{-1} than in this study, and Batra et al. were able to identify the cause of DNA damage in the form of Tail DNA (%) of (14.80 ± 1.31)%.

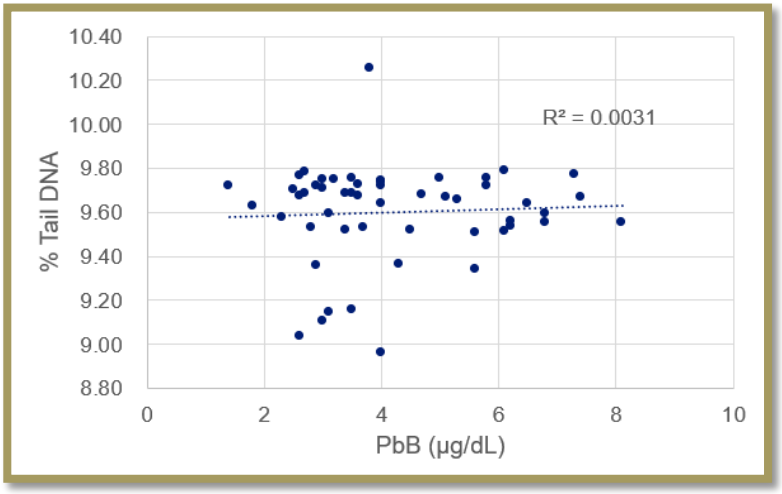

Figure 5. Correlation between PbB and % Tail DNA

According to a study by Dobrakowski et al. (2017), lead exposure to workers results in blood lead levels (PbB) of more than 20 µg/dL can significantly increase DNA damage. It means that the lead exposure in this finding has not reached a level that can significantly cause DNA damage. In addition, the human body contains DNA repair machinery that plays an important role in protecting cells from DNA damage produced by exposure to carcinogens and cytotoxic agents, as well as heavy metals (Hemmaphan and Bordeerat, 2022).

Table 7. Statistical test results of several factors that influence DNA Tail (%)

No	Factors	Categories	N	*p*-value
1	Ages	26-35 (years)	35 (67.0%)	0.464
		36-55 (years)	17 (33.0%)	
2	Groups of Exposure	Exposure	20 (38.5%)	0.114
		Control	12 (23.0%)	0.114
3	Working Periods	<10 years	20 (38.5%)	0.985
		≥10 years	35 (67.0%)	
4	Smoking Habits	Smoking	17 (33.0%)	0.627
		Non-smoking	19 (36.5%)	
5	Alcohol consumption	Yes	33 (63.5%)	0.449
		No	25 (48.1%)	

*p-value is statistically significant ($p<0.05$)

Several factors affecting DNA Tail (%) have been evaluated statistically. They have been evaluated for their significance to DNA Tail (%). These factors include age, groups of exposure, working periods, smoking habits, and alcohol consumption. These factors were also evaluated using the Mann-Whitney U test. The statistical test results of these factors are presented in Table 7. Factors of age, groups of exposure, working periods, smoking habits, and alcohol consumption in this research do not influence the Tail DNA (%) ($p>0.05$). ROS accumulation can cause DNA damage, not only caused by Pb and these factors, but ROS is

also produced by ionizing radiation and UV radiation, and also metabolic processes as well as various drugs and xenobiotics (Juan et al., 2021). So further research must be monitored for ROS accumulation, for example using 8-oxoG as a biomarker for oxidative DNA damage.

CONCLUSIONS

From the results of the study, it can be concluded that: (1) The concentration of Pb in the blood (PbB) of respondents from the paint industry was 4.36±1.60 µg.dL^{-1}. As many as 17 workers (32.69%) have exceeded the safe limit value of PbB, therefore is necessary to monitor blood lead levels in workers periodically, (2) factors affecting PbB value are industry locations, working periods, and alcohol consumption, (3) the result of DNA damage in respondents of this research is categorized as low damage, and (4) there is no relationship between blood Pb levels (PbB) and DNA damage (% Tail DNA) in respondents because the PbB levels obtained have not caused any observed effects. However, it is necessary to monitor blood lead levels in workers due to lead exposure.

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