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# The Effects of Heavy Metal Contamination on Liver Function in a Rat Model

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## Abstract

**Background:** Mining activities in South Kalimantan have been widely associated with the emergence of various health issues caused by heavy metal contamination in the water. Previous studies have demonstrated that the presence of heavy metals has an impact on physiological alterations inside many organs, notably the liver.

**Objective**: The study aimed to determine the impact of liver damage from heavy metals such as lead (Pb), cadmium (Cd), mercury (Hg), and the combination of the three in a rat model.

**Methods:** Our research used the a true experiment laboratory method with a post-test group design. Twenty-five male white rats (Rattus norvegicus), aged 2–6 months and weighing 250–300 grams, were assigned to the control and treatment groups. Treatment groups were administered orally with water contaminated with heavy Pb, Cd, and Hg metals for 28 days. The serum markers of liver damage were then measured.

**Results**: The levels of transaminase enzymes (AST and ALT) in the heavy metal-exposed group were increased compared to the control group. However, the increase was not statistically significant ($p = 0.247$; $p = 0.349$, respectively). The group exposed to Hg exhibited the highest levels of AST and ALT compared to the other groups.

**Conclusion**: Heavy metal exposure raises transaminase enzyme levels, indicating liver damage. Hg exhibited the most significant transaminase value increase of all heavy metals, indicating its highest potential for liver toxicity.

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## INTRODUCTION

Environmental pollution, primarily caused by heavy metals, substantially threatens the environment and human health. Heavy metal pollution is one of the significant environ-mental issues in developing countries, including Indonesia. It has been proposed that mining activities in South Kalimantan have contributed to a detrimental impact on public health through heavy metal contamination in the water. The Barito River, the longest river in South Kalimantan that flows through Banjar-masin, Martapura, and other cities, has exhibited signs of pollution caused by heavy metals in both its water and the organisms inhabiting it. Heavy metals reportedly found in the Barito River Basin include lead (Pb), cadmium (Cd), and mercury (Hg).[1–3] The impact of Martapura River water contamination as part of the Barito River watershed on organs has been studied in the liver, four kidneys, five and testes[4] of rat models.

Heavy metals, while benefiting human life, can also be toxic to human health. Due to their nature, they are difficult to degrade and can potentially induce adverse environmental and public health impacts.[6] Several studies have reported the relationship between heavy metals and health disorders, including metabolic syndrome, seven carcinogenic and non-carcinogenic diseases, and eight hepatic function disorders. The liver is the largest glandular organ with a vital role in glucose and lipid metabolism, helping the digestive process, absorbing fats and fat-soluble vitamins, and detoxifying the body against toxic substances. Metabolic disruption related to hepatic function can cause lipid metabolism disorders known as dyslipidemia. Based on Global Health Observatory (GHO) data from the World Health Organization (WHO), dyslipide-mia in 2008 was 37% in males and 40% in females. Dyslipidemia is estimated to cause approximately 2.6 million and 29.7 million deaths and morbidities, respectively.[9]

High-toxicity heavy metals, such as Pb, Cd, and Hg, can cause oxidative stress in the liver. The presence of free radicals is one of the factors that contribute to liver disorders. If the liver is highly exposed to heavy metals, abnormalities in liver function will be detected in high levels of alanine transaminase (ALT) and aspartate transaminase (AST). Previous studies have shown that increased levels of AST and AST are caused by Pb exposure.[10,11] However, research on the impact of the types of heavy metals on liver damage is currently scarce. This research is vital to provide insights into the effect of heavy metals on subsequent health problems, especially hepatic-related disorders so that it can be prevented early.

## METHODS

This type of research is a true experimental research conducted at the BVET Banjarbaru and Pathology Clinic ULM. The independent variable in this study was heavy metal conta-mination water, while the dependent variable was transaminase enzyme levels (AST and ALT). Making a solution, each heavy metal derived from dry powder is previously dissolved with DSA rules to form a homogeneous solution.

Our research used a true experimental design with a post-test with control groups. Twenty-five male white rats (*Rattus norvegicus*), aged 2-6 months and weighing 250-300 grams, were the


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research subjects. Before treatment, the rats were acclimatized for one week in separate cages to provide optimal physical and psychological conditions. The subjects were then randomly assigned into five groups: control group (C), given distilled water *ad libitum*, and treatment group (P), given heavy metal contaminated water orally. Treatment of water contaminated with heavy metals was given of Pb (P1; 0, 01 mg/l = 0.006 mg/kgBW), Cd (P2; 0.003 mg/l = 0.018 mg/kgBW), Hg (P3; 0.001 mg/l = 0.0006 mg/kgBW), and combination of Pb, Cd, and Hg (P4; 0.006 mg/kgBW; 0.018 mg/kgBW; 0.0006 mg/kg BW, respectively). All groups were given treatments for 28 days. On the 29$^{th}$ day, the rats were euthanized. Serum ALT and AST levels were examined using the enzymatic kinetic method (IFCC reference procedures). This study has received ethical approval from The Ethical Committee of Health Medical Study Medical Faculty, University of Lambung Mangkurat No. 125/KEPK-FK ULM/EC/VI/2023.

Using the Shapiro-Wilk test, a normality test was carried out to determine the normality of data distribution. Comparing each treatment group, the data were analyzed using the one-way analysis of variance (ANOVA), followed by Post - hoc LSD analysis (Tukey test). The results of serum liver enzymes (AST & ALT) were expressed as units/liter (U/l). Statistical analysis was performed using SPSS software, v. 27 (IBM, Chicago, IL, USA). A p-value < 0.05 was considered statistically significant.

## RESULTS

Changes in liver function biomarkers (AST and ALT) by heavy metals are presented in Table 1. The rats in the groups that were exposed to mercury (P3) had higher levels of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) compared to the rats in the remaining groups. We found an increase in both AST and ALT observed in the treatment groups (P1, P2, and P3) compared to the control group. However, we could not observe any statistical differences between each group.

## DISCUSSION

The results of our study suggest a possible association between heavy metal exposure in the treatment group and higher levels of transaminase enzymes (AST and ALT) compared to the control group. The group exposed to mercury (Hg) exhibited the most significant elevation in transaminase levels compared to all other groups. However, the one-way ANOVA analysis test revealed p-values of 0.247 and 0.349 for AST and ALT, respectively.

Table 1. Transaminase Enzyme Levels of Control and Treatment Groups

| Groups | AST Level | *P value* | ALT Level | *P value* |
|---|---|---|---|---|
| C | 219.4 ± 54.33 | | 99.6 ±5.03 | |
| P1 | 227.2 ±47.67 | 0.248 | 106.4 ±16.13 | 0.349 |
| P2 | 265 ±54.16 | | 107.4 ±17.10 | |
| P3 | 307.4 ±112.42 | | 122.8 ±27.74 | |
| P4 | 287.6 ±38.86 | | 111.2 ±13.97 | |

Note: * p < 0.05, a compared with control group
*Source: Yuliana et al, 2023.*


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These results indicate no statistically significant difference in transaminase enzyme levels between the control and treatment groups.

The liver is the largest gland in the body, located on the right side at the top of the abdominal cavity. It has several vital functions, including phagocytosis, synthesis of plasma components (albumin, fibrinogen, prothrombin, and heparin), protein, fat, and carbohydrate metabolism. Additionally, it plays a crucial role in detoxifying harmful substances within the body, producing bile, and serving as a storage site for various substances, including minerals (such as copper and iron), vitamins A, D, K, B12, glycogen, and certain non-eliminable toxins like the Dichlorodiphenyltrichloroethane (DDT) pesticide. The liver can be impaired due to several factors, such as alcohol consumption, cigarette smoking, viral infections, genetic predisposition, muscular injury, drugs, and exposure to heavy metals.[12]

Assessment of liver function can be done through the measurement of enzyme activity, including transaminase. Transaminase enzymes include alanine transaminase (ALT), also known as serum glutamate pyruvate transferase (SGPT), and aspartate transaminase (AST), also referred to as serum glutamate oxaloacetate transferase (SGOT).[13] ALT is an enzyme predominantly present in hepatocytes or liver cells and utilized as a reliable diagnostic marker for hepatocellular injury. A small amount of this enzyme is also found in heart muscle, kidneys, and skeletal muscle. In acute liver parenchymal damage, serum ALT levels are generally higher than AST. The reverse pattern is usually observed in chronic processes. ALT activity in the liver is about 3,000 times greater than serum activity. In cases of hepatocellular injury or death, the release of ALT from damaged liver cells increases serum levels.[14–16] Since serum ALT levels increase in hepatocellular injury, serum ALT levels can effectively identify and monitor the progression of ongoing liver disorders.[13]

AST (aspartate aminotransferase) is an enzyme primarily found in the heart and liver, while moderate concentrations are found in the skeletal muscle, kidneys, and pancreas. In cellular injury, large amounts of AST are released into circulation. In liver disease, the levels will increase tenfold and remain high for a long time. In chronic hepatocellular injury, ALT is more often elevated than AST. However, as fibrosis progresses, ALT activity usually decreases, and the ratio of AST to ALT decreases. Both serum ALT and AST are generally measured photometrically or spectrophotometrically, semi-automatically using a photometer or spectrophotometer, or automatically using a chemistry analyzer.[17]

As an organ, the liver exhibits a high susceptibility to the impact of various chemicals and is the main target organ for the toxic effects of chemicals (toxicants). The liver can exhibit signs of impairment due to exposure to toxic heavy metals in the circulatory system, leading to liver disease. According to Palar (2004), the mechanisms underlying the toxicity of heavy metals in organisms can be classified into three distinct categories: a) blockage and obstruction of essential biomolecular groups for metabolic processes; b) replacement of essential metal ions contained in related molecules; and c) alteration of the shape (conformation) of the active site of biomolecules.[18] Previous studies have shown that in rats, heavy metal treatment


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resulted in cellular degeneration, vacuolation, inflammation, and necrosis of the liver. The mechanisms underlying these changes were thought to be caused by downregulated expression of Bcl2 and Caspase-3 upregulation in the liver cells.[19]

Heavy metals inhibit enzymes in humans by interacting with sulfide groups like disulfide (-S-S) and sulfhydryl (-SH). Heavy metals have a strong affinity for sulfide groups, leading to their binding with these groups inside the bloodstream. For example, the enzyme D-aminolevulinic acid hydratase (ALAD) utilizes lead (Pb) as a cofactor in place of zinc (Zn). Heavy metals can also exhibit toxicity upon their interaction with intracellular components. Lipophilic heavy metals, such as methyl mercury, can enter cellular via traversing the cell membrane. The entry of heavy metals into cells can harm organelles, such as the endoplasmic reticulum (ER), which houses enzymes. Cadmium (Cd) impedes the functioning of microsomal enzymes found in the endoplasmic reticulum (ER), hence causing disruptions to the overall structure of the ER.[20]

According to Markowitz, M. (2000), the level and duration of exposure and the chemical form of heavy metals influence their toxicity. Heavy metals have bioaccumulative and biomagnifying properties. Thus, the higher and more prolonged exposure to heavy metals, the higher the concentration in organisms, including humans, the greater the toxic effect. Chemical form affects heavy metal toxicity. For example, mercury in the form of HgCl2 is more harmful than mercury (HgCl). This toxicity is caused by the divalent form being more soluble than the monovalent form. Inorganic mercury, such as HgCl and HgCl2, is known as a kidney toxicant, while organic mercury, such as methyl mercury, is a central nervous system toxicant.[21]

Some heavy metals can bind to proteins because of their high affinity for Sulfide groups. Methionine (meth) and cysteine (Cys) proteins and amino acids bind heavy metals efficiently. Lead, bismuth, and mercury-selenium are heavy metals that can create metal-protein complexes. Cadmium (Cd) and some metals, such as copper (Cu) and zinc (Zn), can combine with metallothionein, a low-molecular-weight protein. In renal tubular cells, the release of Cd2+ by the Cd metallothionein complex is associated with a higher toxicity level than the Cd complex.[21]

Our study incorporates safe heavy metal exposure from bottled water, as per the Indonesian National Standard (SNI) 2009, with a 28-day subchronic exposure duration under Indonesian Food and Drug Monitoring Agency (BPOM) rules. The transaminase enzyme levels in a rat model tended to increase following the oral injection of heavy metals Pb, Cd, and Hg once a day over a subchronic period. Our study aligns with one by Karina, Berata, and Setiasih (2023), who looked at the effects of Pb exposure to heavy metal at concentrations of 0.5, 1.0, and 2.0 ppm on transaminase enzyme levels and histopathological lesions in the livers of rats. They found that, compared to controls, all lesions except fatty degeneration lesions showed significant congestion and necrosis.[11]

Lead (Pb) in the body is mainly bound to the SH group of protein molecules, inhibiting the activity of enzyme systems. Pb interferes with the Hemoglobin (Hb) synthesis system. Following a series of other events, it undergoes a reaction with Fe to form hem, which serves as

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the principal constituent of Hb. The enzymes involved in hem formation that are most susceptible to Pb are δ-aminolevulinic acid dehydratase (ALAD) and hem synthase (HS). Enzymes that are less sensitive to Pb are δ-aminolevulinic acid synthetase (ALAS), uroporphyrinogen decarboxylase (UROD), and coproporphyrinogen oxidase (COPROD). Inhibition of Hb synthesis results in anemia. Pb molecules in the body attach to the ALAD enzyme's active group, forming porphobilinogen and stopping the activity. Due to Pb metal contamination, poisoning can increase ALAD levels in blood and urine, protoporphyrin levels in red blood cells, shorten red blood cell life, reduce the number of red blood cells and reticulocytes, and increase Fe metal content in blood plasma. Pb2+ can replace Ca2+ in bone tissue.[18,22,23]

The heavy metal exposure study to Cd matches the findings of Ratnanigsih (2003), who reported statistically significant alterations in AST and ALT levels over eight weeks.[24] Concerning exposure, it has been observed that Hg can accumulate in the kidneys, brain, liver, and fetus. Research on rabbits with 28.8 mg/m3 Hg vapor resulted in severe damage to various organs, including the kidneys, liver, brain, heart, lungs, and colon.[25] However, Fiati Kenston (2008) discovered no significant variations in liver function or damage after exposing rats to a heavy metal mixture containing zinc (Zn), copper (Cu), manganese (Mn), chromium (Cr), nickel (Ni), cadmium (Cd), lead (Pb), and mercury (Hg) with doses of 215, 464 or 1000 mg per kg body weight (but).[26] In the case of Cadmium (Cd), the cellular toxicity generated in different target organs results in the disruption of metalloenzymes, modification of protein thiols, inhibition of energy metabolism, alteration of DNA and membrane structure and function, and the induction of excessive oxidative damage, ultimately leading to hepatocellular integrity impairment. [27]

The results of research on the impact of Hg on humans have also been carried out by Y. Kristianingsih et al. (2017). Most participants did not engage in gold processing activities and had resided in Lebaksitu village for over ten years. Overall, 77.9% of respondents had blood mercury above the average threshold set by the WHO at ten µg/l. Elevated ALT levels were experienced by 25% of respondents. However, the study did not reveal a statistically significant association between blood mercury levels and ALT levels. It is important to note that confounding variables such as age and duration of stay impacted blood mercury levels.[28] The level of 8-hydroxy-2'-deoxyguanosine (8-OHdG), a biomarker of oxidative DNA damage, was significantly higher in urine samples from people living in mercury-contaminated areas. Glutathione (GSH) concentrations, total protein thiols, glutathione peroxidase, and superoxide dismutase activities were also higher in mercury-exposed groups. Mercury induces this process via the PI3K-activated Akt pathway or oxidative stress. Additionally, methylmercury can cause apoptosis and oxidative stress-induced cell death.[27]

Our study results demonstrated that Pb, Cd, Hg, and their combinations lead to an elevation in transaminase enzyme levels compared to control. However, the increase in transaminase enzyme levels is not statistically significant. This may be related to the bioaccumulation of heavy metals in the body in experimental ani-

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mals, which is relatively short (28 days/subchronic administration), and the dose given uses a safe dose for consumption in mineral drinking water, according to SNI. Bioaccumulation is an increase in the concentration of chemicals in the body of living things over a long period compared to the levels of chemicals in nature. Excessive levels cause heavy metals to be unable to metabolize and cannot undergo biotransformation to other compounds. Form other compounds so that eventually it can damage the organs of living things, especially the liver and kidneys [10,18]

Our study follows the statement of Markowitz (2000), which states that the level and duration of exposure can affect heavy metal toxicity.[21] The exposure to Hg causes an increase in transaminase enzyme levels, which were also higher than exposure to Pb, Cd, or if given in combination. The observed outcome aligns with the chemical and physical properties of Hg, which has the highest toxicity level compared to cadmium (Cd), zinc (Zn), lead (Pb), chrome (Cr), nickel (Ni), and cobalt (Co). Based on the grouping of toxic power, Hg, Cd, and Pb are included in the metal group with high poisonous power. The order of metal toxicity from the most harmful to humans is Hg2+ > Cd2+ > Ag2+ > Ni2+ > Pb2+ > As2+ > Cr2+ Sn2+ > Zn2+.[18]

## CONCLUSION

Exposure to heavy metals has been found to elevate the levels of transaminase enzymes, suggesting the occurrence of hepatic injury. Hg exposure has the highest AST and ALT values of all single heavy metal exposure groups (Pb, Cd, and the three combinations), which indicates Hg is potentially more toxic to the liver than Pb, Cd, and the three metals combined. Even when government rules limit their intake, the public must be aware of food and beverage contamination from heavy metals, including Pb, Cd, and Hg. This work aims to guide future research endeavors in identifying potential antioxidant therapy candidates rooted in local wisdom, to mitigate the adverse effects of heavy metal toxicity-induced reactive oxygen species (ROS) damage.

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