The Seybold Report

ISSN 1533-9211

EVALUATING THE NEUROTOXIC IMPACT OF MERCURY EXPOSURE IN THE ARTISANAL AND SMALL-SCALE GOLD MINING IN SOUTH SUMATRA, INDONESIA

RA. HOETARY TIRTA AMALLIA [1], POEDJI LOEKITOWATI HARIANI [2], EDDY IBRAHIM [3] and IRFANNUDDIN [4]

[1] Doctoral Program of Environmental Science, Postgraduate, Universitas Sriwijaya, Jalan Padang Selasa, Palembang, Indralaya, Indonesia, Biology Study Program, Faculty of Science and Technology, Universitas Islam Negeri Raden Fatah Palembang , Jalan KM 3, Palembang, Indonesia.
[2,3,4] Doctoral Program of Environmental Science, Postgraduate, Universitas Sriwijaya, Jalan Padang Selasa, Palembang, Indralaya, Indonesia.
Email: [1]hoetary_uin@radenfatah.ac.id, [2]puji_lukitowati@mipa.unsri.ac.id, [3]eddyibrahim@ft.unsri.ac.id, [4]irfan.md@unsri.ac.id

Abstract

The artisanal and small-scale gold mining (ASGM) within residential areas becomes one of the sources of mercury contamination in the environment, which has neurotoxic effects on humans, such as dementia. This has garnered significant global interest, and based on a survey conducted by the United States Geological, that around 16 million people are employed in the small-scale mining and processing of gold, primarily in countries such as Ghana, Ecuador, and Indonesia. In this study, a biomedical scientific method was adopted to explore the correlation between neurotoxic effects on cognitive functioning and the magnitude of mercury exposure. The findings of this research showed a direct relationship between the concentration of mercury in hair and the levels of Amyloid-beta (Aβ) 40. Higher levels of mercury in hair are linked to increased levels of Aβ 40 in plasma. Furthermore, there is an inverse association between plasma Aβ 40 levels and the MoCA-Ina score. ASGM processing has become a matter of worldwide concern due to the potential neurotoxic impacts caused by heavy metal contamination, especially mercury, in the resulting tailing waste. The presence of mercury can lead to cognitive impairments of a dimensional type within the local community residing in those regions.

Keywords: Neurotoxic Impact, Mercury, Exposure, Small-Scale Gold Mining, Indonesia.

1. INTRODUCTION

Dementia is one of the most common neurodegenerative diseases in the elderly. Early symptoms of dementia include episodic deficits, difficulty remembering things for a long time, and progressive impairment in declarative and non-declarative memory. When entering the next phase of dementia, a person with dementia will experience changes in behavior due to loss or reduction of cognitive function. And these changes in behaviour can interfere with their daily lives. These symptoms can finally be diagnosed clinically as Alzheimer's disease [1–4]. Many factors can cause neurodegenerative diseases such as the presence of comorbid diseases such as diabetes, and cardiovascular. In addition, obesity, stress levels, brain injuries, cerebrovascular accidents, Huntington's disease, and the human immunodeficiency virus can also affect cognitive function [5–9]. But now several studies have proven that impaired cognitive function or dementia is neurotoxic effects resulting from exposure to some heavy metals especially mercury. The case of mercury poisoning which first became the center of

ISSN 1533-9211

world attention was the case in Minamata Bay, Japan and is currently receiving special attention by WHO [10–14]. Mercury can be sourced from anthropogenic activities or natural processes. [15, 16]. In recent years, mercury has received increasing attention from the world as a pollutant originating from the tailings of ASGM processing 1,350 tons of mercury per year are released into the environment [17,18]. Mercury can enter the human body through three exposure routes, namely inhalation, ingestion, and absorption through the skin. However, food chain factors and skin absorption are the dominant factors for mercury entry into the body. The mechanism of exposure to mercury through the skin can be through two routes, namely transdermal which is transportation through the epidermal layer and transappendageal which is transportation through sweat glands, sebaceous glands and hair follicles [19–22].Great concern about the impact on people living in ASGM processing locations has been discussed internationally by United Nations Environment Programme (UNEP) with the aim of reducing the risk to human health from Hg releases, as well as increasing global public knowledge about Hg emissions which have actually been discussed in the Minimata Convention. The Minamata case is the case most widely known to the world due to mercury pollution which was then discussed in the Minamata Convention and signed in October 2013 where the convention aims to control the global release of Hg into the environment [23].

Based on the laboratory tests are known that Pollution Load Index (PLI) in the village of Sukamenang is 4492.027119 that Sukamenag Village is included in the extremely polluted category. This is a critical point that will be discussed in this research where this research will review how much mercury accumulates in the hair of residents living in Sukamenag Village which will be linked to the cognitive function of the population by assessing the MoCa Ina number and analyzing beta amyloid 40 in blood plasma. which is a biomarker for diagnosing cognitive impairment or dementia with an accuracy of about 90% [24–27]. So, this study aims to see whether the cognitive impairment that occurs in the people of Sukamenang Village is a neurotoxic effect from mercury used in processing gold ore at that location.

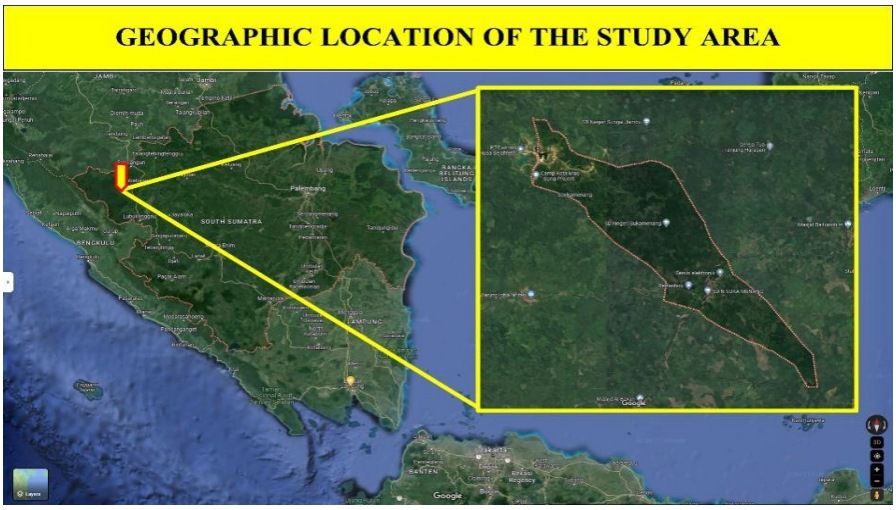

Figure 1: Location of Sukamenang, Musi Rawas Utara Regency, South Sumatra, Indonesia

The Seybold Report
ISSN 1533-9211

2. METHODS

2.1. Design and Study Site

The total sample in this study was 92 population samples consisting of 46 people from case areas, namely ASGM processing areas that use mercury and 46 people as controls, namely residents from areas that do not have ASGM and do not contaminate with mercury. Both case areas and control areas, the population sampled was the same age, sex and all samples did not have congenital diseases. For age criteria, those included in the sample category of this study were residents aged 35-60 years and living in the village. Determination of population age criteria in sampling because diffuse amyloid plaques in plasma will only appear in the late teens, and pathologically Tau protein will only appear after the age of 35 years [28]. This Sukamenang Village is located in Musi Rawas Utara Regency, South Sumatra, Indonesia (Figure 1).

2.2. Measurement

Examination of mercury levels in hair using the ICP-MS metal method. The concentrations of standard solutions, test solutions, and blank solutions were measured using ICP-MS. Samples were weighed as much as 0.5–1.5 grams and added HNO_3. Before being destroyed, the sample is allowed to stand for 15 minutes, then the vessel is closed and digested in a microwave digester. After being destroyed, the sample is cooled first. Then the cold sample is put into a 50 mL volumetric flask. Rinse the vessel with double-distilled water quantitatively, combine the rinse results with the results of the digestion in a 50 mL volumetric flask. Then added internal standards of a mixture of Ge, In, Bi, Rh 10 mg/L and diluted with double-distilled water up to the tera mark. Filter the solution with a 0.20 µm syringe filter. Measure the intensity of the test solution in the Hg Analyte MS ICP system with internal standard Bi [29].

Diagnosis of dementia as an effect neurotoxic exposure to mercurymeasured using MoCA-Ina and measurement of beta amyloid 40 levels in the blood plasma of the population. MoCA-Ina is a tool in the form of a questionnaire and has been patented to help diagnose a person's cognitive function by value96% sensitivity and 95% specificity in detecting cognitive impairment [30–32]. MoCA is a test that contains 30 questions that must be completed in 10 minutes.

The parameters tested consist of aspects of short-term detail memory recall (5points), visuo-spatial ability by drawing a clock (3 points), duplicating a three-dimensional cube (1 point), executive function tested using a follow-order test (1 point), a phonemic fluency task (1 point), and two verbal abstraction items (2 points), attention, concentration, and working memory were tested using a concentration task (1 point), a serial subtraction task (3 points), and a memory task that required the test taker to remember a series of numbers forward and backward (1 point each). Language is tested by identifying three types of animals that are easy to recognize (lion, camel, rhino; 3 points), repeating 2 complex sentences (2 points), finally orientation to time and place as well (6 points) [30].

The Seybold Report
ISSN 1533-9211

The interpretation of the results obtained from the MoCA-Ina score or points is that if less than 26 points indicate that the patient has cognitive impairment [33].Furthermore, for the amyloid 40 beta test in the patient's blood plasma using the reagent CEA864Hu 96 Immunosorbent Test Kit linked to the enzyme For Amyloid Beta Peptide Species Organisms 1-40 (Ab1-40). . The plasma used is plasma with the addition of EDTA or heparin as an anticoagulant. Samples were centrifuged for 15 minutes at 1000 rpm for 30 minutes. Plasma can be preserved by freezing at -20°C and avoiding repeated freezing or thawing cycles. This test uses a competitive inhibition enzyme immunoassay technique.

Monoclonal antibodies specific to Ab1-40 were pre-coated onto microplates. A competitive inhibition reaction was launched between biotin labelled Ab1-40 and non-labelled Ab1-40 (Standard or sample) with pre-coated antibodies specific for Ab1-40. After incubation, unbound conjugates were washed thoroughly. Next, avidin conjugated with Horseradish Peroxidase (HRP) was added to each well of the microplate and incubated. The amount of bound HRP conjugate is inversely proportional to the concentration of Ab1-40 in the sample. After the addition of the substrate solution, the intensity of the color developed was inversely proportional to the concentration of Ab1-40 in the sample.

2.3. Informed Consent Statement

Information on the population that was used as the subject of this study was conveyed when conducting a location survey at the beginning of the study. All residents or research subjects have read and understood and are willing to participate in this research and the operational standards carried out in this research are in accordance with applicable regulations and ethical guidelines.

2.4. Ethics

This research has received ethical approval from the health research committee of the Health Polytechnic of the Palembang Ministry of Health. This study was guided by 7 WHO and CIOMS 2016 standards where the residents who were sampled in this study voluntarily and there was no therapy that could affect and change the lives of the participants in this study. All examination results will be notified to them and also explained to them that this research is only for academic purposes.

2.5. Data Analysis

In accordance with the purpose of this study was to see whether the cognitive impairment that occurred in the people of Sukamenang Village was a neurotoxic effect from the mercury used in processing gold ore at that location, so the data was included in three different tests.

To test the appearance of amyloid beta in each regional group, the test was used Independent Sample T-Test because both groups are normally distributed. And to see the difference in MoCA-Ina values or points in each group, the Mann-Whitney test was used because one group was not normally distributed. Finally, to assess the relationship between mercury accumulation in hair and dementia, which was seen from MoCA-Ina points and Amyloid beta levels, the Chi-Square test was carried out.

The Seybold Report
ISSN 1533-9211

3. RESULTS

3.1. Mercury Concentration in Hair

To assess the level of mercury exposure in residents in ASGM areas, identification of the value of mercury accumulation in hair was carried out, which is a biomarker to assess the level of mercury accumulation in humans by comparing population groups exposed to mercury from ASGM industries and residents not exposed to mercury shows in Figure 2. Residents living in ASGM areas have an average concentration of mercury in their hair of 6.14 Ppm which is categorized as high because it exceeds the permissible threshold value of 2 Ppm. For control areas, namely residents who live in areas free from sources of mercury pollution, the concentration of mercury in the hair of the population is very small, namely 1.3 ppm and is considered safe because it does not exceed the threshold value.

Figure 2: Mercury Concentration in Hair between Groups of Mercury Contaminated Areas (Gold ore Processing Industry Areas) and Mercury Not Polluted Areas (Areas That Do Not Have Gold Ore Processing Industries)

Table 1: Analysis of the Relationship of Mercury Contamination in the Environment with Mercury Concentrations in the Hair of the Residents

Variable	Category	Mercury Levels in Hair			*p*-value	
		High	Low	Total	Chi Square	Risk Estimates
Mercury Concentration in People's Hair	Gold Ore Processing Area	32	14	46	0.000	32.7 (8,680-123,658)
	Areas That Do Not Have Gold Ore Processing	3	43	46		

Correlation test was conducted to see the relationship between mercury accumulation in the hair of residents and the environment where they live is shows in the Table 1. The results of

The Seybold Report
ISSN 1533-9211

this test show the p-value of 0.000 is less than alpha 5% (0.05), which means that the concentration of mercury in the environment where you live has an influence on the concentration of mercury that accumulates in the hair of people living in that area. The odds ratio in the Table 1 is 32.7. This shows that residents who live in small-scale gold ore processing industrial areas have a 32 times greater risk of exposure to mercury compared to residents who do not live in small-scale gold ore processing industrial areas. This is also clearly reflected in the distribution of mercury levels in hair. The number of residents with high levels of mercury is more in small-scale gold ore processing areas compared to control areas.

3.2. Correlation Between Mercury Concentration in Hair and Amyloid-beta (Aβ) 40 Value in Plasma

To assess the relationship between cognitive impairment as a result of mercury exposure, an Independent Samples Test was conducted to see the relationship between mercury concentrations in hair and amyloid beta 40 values in blood plasma (Figure 3). Beta Amyloid 40 plasma is a biomarker from human blood specimens that is used to diagnose cognitive impairment of the dementia type. The test results determined a p-value of 0.004, meaning that there was a significant relationship between the concentration of mercury in the hair of the population and the level of beta amyloid 40 in the blood plasma of the population. In the graph below it is known that the correlation has a positive pattern where the graph line goes straight up. This means that the higher the mercury concentration in the hair, the higher the Amyloid-beta (Aβ) 40 value in the blood plasma of the population in the ASGM area.

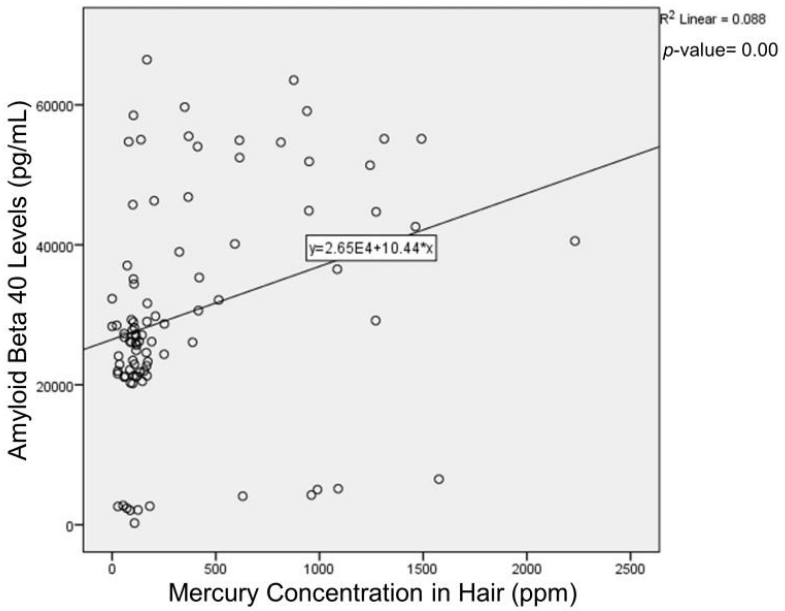

Figure 3: Correlation Diagram between Mercury Concentration in Hair and Amyloid-beta (Aβ) 40 Value in Plasma

ISSN 1533-9211

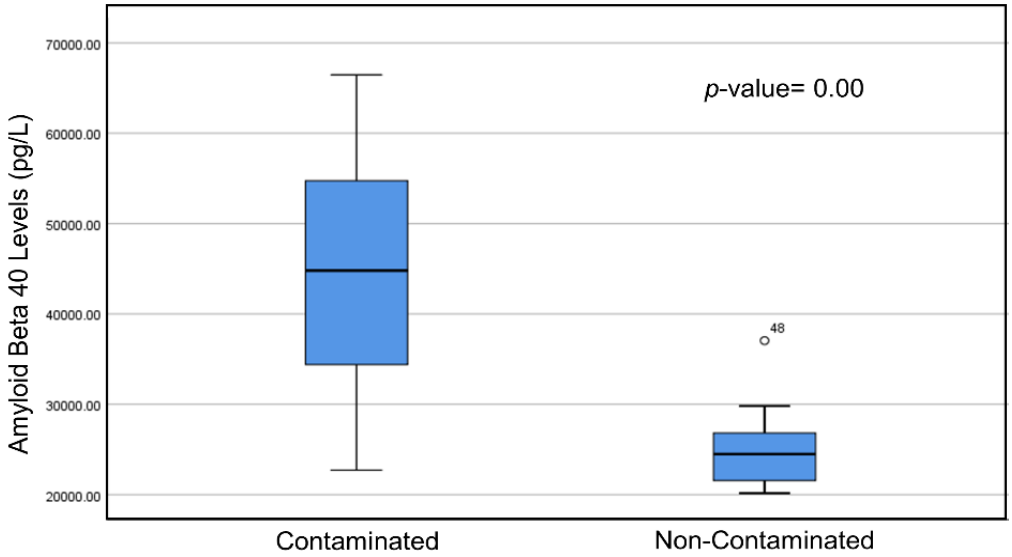

Figure 4: Description of Amyloid-beta (Aβ) 40 Concentration between Residents of Contaminated and Non-Contaminated Areas

Further tests were carried out to compare the two sample groups. The first group is a group of residents from ASGM areas where mercury concentrations in the environment are high. The second group is residents who live not in ASGM areas and where there is no mercury content in their environment shows in the Figure 4. This test aims to reinforce previous results that it is true that ASGM is a major factor in the occurrence of cognitive impairment in the population without any other factors. The graph above shows that there is a significant difference between the Amyloid-beta (Aβ) 40 values between polluted and non-contaminated areas of mercury. Compared to the control area, residents of Sukamenang Village have an average Amyloid-beta (Aβ) value of 40, twice that of the control area. In mercury-contaminated areas, the minimum value of Amyloid-beta (Aβ) 40 was 22.71 pg/L and the maximum value was 66.46 pg/mL with a mean of 44.35 pg/mL and a median of 44.8 pg/mL. Whereas in areas not polluted by mercury, the minimum value of Amyloid-beta (Aβ) 40 was 20.168 pg/L and the maximum value was 37.04 pg/L with a mean of 24.67 pg/mL and a median of 24.480 pg/mL.

3.3. Correlation of Amyloid-beta (Aβ) 40 Levels and Moca Ina Score for Diagnosing Dementia Type Cognitive Disorder.

In this study, the researchers considered it necessary to carry out a test that compared the concentration of Amyloid-beta (Aβ) 40 and the Moca Ina score to confirm the diagnosis of dementia-type cognitive impairment in the treatment group (Figure 5). The results of this test show the valuep value 0.000 which meansthere is a significant relationship between concentrations Amyloid-beta (Aβ) 40 blood plasma of residents of ASGM areas with MoCA-Ina points. In the graph below, you can see a straight downward line pattern, which means that the correlation formed is a negative correlation. This means that the higher the concentration of Amyloid-beta (Aβ) 40 at the population's blood plasma the lower the MoCA-Ina points obtained by the population.

ISSN 1533-9211

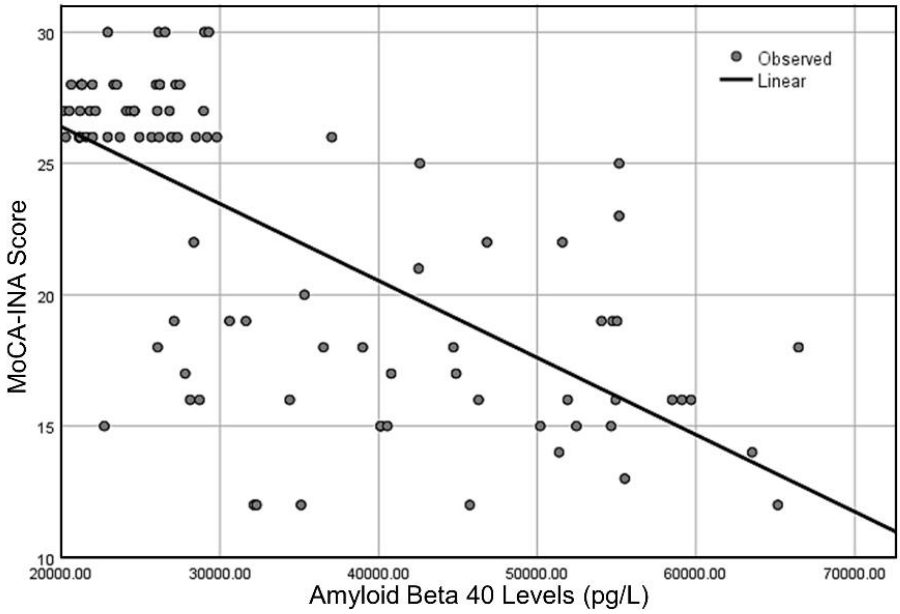

Figure 5: Correlation between Amyloid-beta (Aβ) 40 Levels and MoCA-Ina Score

4. DISCUSSION

Amyloid-beta (Aβ) 40 plasma is a biomarker for diagnosing cognitive disorders in a person [34,35]. Beta amyloid (Ab) 40 is the result of the breakdown of CTF99 (C-99), where this CTF99 will be truncated and turned into 2 versions, namely Ab40 and Ab42. Amyloid-beta (Aβ) 40 will be metabolized and some will form plaques. Ab40 production will be faster and more formed in patients with dementia or syndromes characterized by decreased cognition,[36]. And if the Ab 40 concentration increases by more than 5 pg/mL, this will increase or have an association with a worsening of a person's cognitive status which will later become dementia [37,38].

In this study we try to prove that mercury pollution in the environment as a result of ASGM tailings waste can cause neurotoxic effects on the people living in the area. The results of this study can be used as a valid reference or source of information both locally and internationally and can also be used as a basis for policy making for local governments regarding the existence of ASGM in the midst of community settlements.

This is because the results of this study show with certainty that ASGM in residential areas is a source of mercury contamination in the population resulting in bioaccumulation of mercury in the population's bodies. The bioaccumulation of mercury in the population's body causes the population to experience cognitive impairment of the dementia type. This cognitive disorder can even occur at the age of under 60 years as indicated by the high plasma amyloid (Ab) 40 value of the population's blood and low MoCA-Ina points.

The Seybold Report
ISSN 1533-9211

Neuritic plaques or senile plaques will form in direct proportion to the valuebeta amyloid (Ab) 40and this shows the pathology of Alzheimer's type dementia[39]. The data above illustrates that an increase in beta amyloid 40 levels in residents in Sukamenang Village, Karang Jaya District, North Musi Rawas Regency where there is ASGM in residential areas can be triggered by mercury accumulating in the population's bodies. Mercury can inhibit thiol sensitive enzymes such as tubulin, creatine kinase and glutamine synthetase quickly so that it can affect the metabolism of axonal structures and tubulin release occurs. Tubulin release can result in formation Neurofibrillary Tangles (NFT) and Protein Tau which can result in hyper-phosphorylation and increased production of β-amyloid protein which can aggregate into senile plaques [40].

Many theories and studies say that one of the most dangerous toxic effects of mercury is that it can attack the human nervous system [10,41]. Juhan Azhar in 2020 revealed that even the slightest level of mercury in the atmosphere over a long period of time would still be harmful to humans. And from the results of his research it has been revealed that mercury is very influential in the beta amyloid deposition pathway and the formation of tau tangles [42]. Even since 2007 it has been found that patients suffering from Alzheimer's disease (AD) have higher levels of mercury in the brain tissue and blood of patients [43]. Cognitive disorders such as dementia are one result of damage to the nervous system from the toxic effects of mercury. In this study it has been proven that people living in gold ore processing areas have high levels of mercury in their hair and can be said to have cognitive impairment type dementia based on screening conducted either from MoCA-Ina points or plasma amyloid beta values in the population's blood.

This cannot be considered as a local case only or only in Indonesia. This needs great attention globally because almost all cities in the world have the same or even greater potential. Many countries have a ASGM. Based on a survey by the United States Geological Agency, it is estimated that there are 16 million small-scale artisanal gold miners working as miners or small-scale gold ore processors, especially in global countries such as Ghana, Ecuador and Indonesia. More than 19 million people in more than 70 countries in the world use mercury in ASGM so that mercury pollution becomes a global issue [44]. Mercury pollution due from ASGM in Ghana is of major concern because there is a very significant increase in the amount of mercury in the water, soil and sediments in the area which can be a public health hazard [45]. In addition, in the sediments of the watershed of southern Zimbabwe where there is processing and small-scale gold ore mining, mercury concentrations of 6 µg/kg to 1541 µg/kg were detected [46].

5. CONCLUSIONS

The main cause of mercury poisoning primarily stems from anthropogenic pollution in the environment, with ASGM activities being one significant contributor. In this process, inorganic mercury is produced as a by-product and disposed of along with the tailings waste. Consequently, mercury-laden waste from the amalgamation process is discharged directly into the environment or nearby water bodies. This form of gold ore processing not only results in

The Seybold Report
ISSN 1533-9211

environmental pollution but also leads to bio magnification and bioaccumulation of mercury in living organisms. High levels of mercury have been detected in the hair of individuals residing in areas where ASGM occurs, posing a serious risk to their health. The neurotoxic effects of mercury are particularly concerning, as evidenced by an increased presence of Amyloid-beta (Aβ) 40 in the blood plasma of residents and the occurrence of cognitive impairment, such as dementia, even before the age of 60, as indicated by lower MoCA-Ina score.

It is crucial to recognize that this issue extends beyond local circumstances or solely Indonesia, demanding significant attention globally. The potential for similar or even greater issues exists in nearly all cities worldwide due to the prevalence of ASGM. Various countries, including Ghana, Ecuador, and Indonesia, engage in such activities. According to a survey conducted by the United States Geological Agency, it is estimated that approximately 16 million people are involved in small-scale gold mining or processing. The scale of this industry necessitates urgent action and awareness. It is imperative to address the hazards associated with mercury exposure, given its detrimental effects on the human nervous system. Cognitive disorders, including dementia, are among the consequences of mercury's toxic impact on the nervous system. The present study has provided evidence of elevated mercury levels in the hair of individuals residing in gold ore processing areas, indicating cognitive impairments consistent with dementia through clinical symptoms and screening assessments based on MoCA-Ina score and plasma amyloid beta values in blood.

Nomenclatures

Aβ	Amyloid-beta

Abbreviations

ASGM	Artisanal and Small-Scale Gold Mining
MoCA-Ina	Montreal Cognitive Assessments based on Indonesian version
WHO	World Health Organization
UNEP	United Nations Environment Programme
HRP	Horseradish Peroxidase
CIOMS	Council for International Organizations of Medical Sciences

Acknowledgements

The author would like to thank for funding through “Unggulan Profesi” by DIPA of Public Service Agency of Universitas Sriwijaya 2022. SP DIPA-023.17.2.677515/2022 on December 13, 2021. In accordance with the Rector’s Decree No. 0111/UN9.3.1/SK/2022, on April 28, 2022.

References

1) Goedert, M. (2015) Alzheimer’s and Parkinson’s diseases: The prion concept in relation to assembled Aβ, tau, and α-synuclein. *Science (80-.).*, **349** (6248).

2) Verlinden, V.J.A., Van Der Geest, J.N., De Bruijn, R.F.A.G., Hofman, A., Koudstaal, P.J., dan Ikram, M.A. (2016) Trajectories of decline in cognition and daily functioning in preclinical dementia. *Alzheimer’s Dement.*, **12** (2), 144–153.

3) Knopman, D.S., Amieva, H., Petersen, R.C., Chételat, G., Holtzman, D.M., Hyman, B.T., Nixon, R.A., dan Jones, D.T. (2021) Alzheimer disease. *Nat. Rev. Dis. Prim.*, **7** (1), 1–21.

The Seybold Report
ISSN 1533-9211

4) Gotz, J., Bodea, L.G., dan Goedert, M. (2018) Rodent models for Alzheimer disease. *Nat. Rev. Neurosci.*, **19** (10), 583–598.

5) Dye, L., Boyle, N.B., Champ, C., dan Lawton, C. (2017) The relationship between obesity and cognitive health and decline. *Proc. Nutr. Soc.*, **76** (4), 443–454.

6) Iadecola, C., Yaffe, K., Biller, J., Bratzke, L.C., Faraci, F.M., Gorelick, P.B., Gulati, M., Kamel, H., Knopman, D.S., Launer, L.J., Saczynski, J.S., Seshadri, S., dan Al Hazzouri, A.Z. (2016) Impact of Hypertension on Cognitive Function: A Scientific Statement from the American Heart Association. *Hypertension*, **68** (6), e67–e94.

7) Sanford, A.M. (2017) Mild Cognitive Impairment. *Clin. Geriatr. Med.*, **33** (3), 325–337.

8) Harrison, S.L., de Craen, A.J.M., Kerse, N., Teh, R., Granic, A., Davies, K., Wesnes, K.A., den Elzen, W.P.J., Gussekloo, J., Kirkwood, T.B.L., Robinson, L., Jagger, C., Siervo, M., dan Stephan, B.C.M. (2017) Predicting Risk of Cognitive Decline in Very Old Adults Using Three Models: The Framingham Stroke Risk Profile; the Cardiovascular Risk Factors, Aging, and Dementia Model; and Oxi-Inflammatory Biomarkers. *J. Am. Geriatr. Soc.*, **65** (2), 381–389.

9) Tublin, J.M., Adelstein, J.M., Del Monte, F., Combs, C.K., dan Wold, L.E. (2019) Getting to the Heart of Alzheimer Disease. *Circ. Res.*, **124** (1), 142–149.

10) Genchi, G., Sinicropi, M.S., Carocci, A., dan Lauria, G. (2017) Mercury Exposure and Heart Diseases. 1–13.

11) Yang, Y.W., Liou, S.H., Hsueh, Y.M., Lyu, W.S., Liu, C.S., Liu, H.J., Chung, M.C., Hung, P.H., dan Chung, C.J. (2018) *Risk of Alzheimer's disease with metal concentrations in whole blood and urine: A case–control study using propensity score matching*, Elsevier Inc.

12) Bakulski, K.M., Seo, Y.A., Hickman, R.C., Brandt, D., Vadari, H.S., Hu, H., dan Park, S.K. (2020) Heavy Metals Exposure and Alzheimer's Disease and Related Dementias. *J. Alzheimer's Dis.*, **76** (4), 1215–1242.

13) Kabir, M.T., Uddin, M.S., Zaman, S., Begum, Y., Ashraf, G.M., Bin-Jumah, M.N., Bungau, S.G., Mousa, S.A., dan Abdel-Daim, M.M. (2021) Molecular Mechanisms of Metal Toxicity in the Pathogenesis of Alzheimer's Disease. *Mol. Neurobiol.*, **58** (1).

14) Rosa-Silva, H.T. da, Panzenhagen, A.C., Schmidtt, V., Alves Teixeira, A., Espitia-Pérez, P., de Oliveira Franco, Á., Mingori, M., Torres-Ávila, J.F., Schnorr, C.E., Hermann, P.R.S., Moraes, D.P., Almeida, R.F., dan Moreira, J.C.F. (2020) Hepatic and neurobiological effects of foetal and breastfeeding and adulthood exposure to methylmercury in Wistar rats. *Chemosphere*, **244**, 125400.

15) Sundseth, K., Pacyna, J.M., Pacyna, E.G., Pirrone, N., dan Thorne, R.J. (2017) Global sources and pathways of mercury in the context of human health. *Int. J. Environ. Res. Public Health*, **14** (1).

16) Cropotova, J., dan Popel, S. (2012) Mercury-Contaminated Fish and Essential Fatty Acids : Problems and Solutions. **7** (1), 162–163.

17) Smith, N.M. (2019) "Our gold is dirty, but we want to improve": Challenges to addressing mercury use in artisanal and small-scale gold mining in Peru. *J. Clean. Prod.*, **222**, 646–654.

18) McGuirk, B., Theron, P., dan Maboeta, M. (2020) The Effects of Different Gold Mine Tailings on Growth, Reproduction and Avoidance-Behaviour of Earthworms. *African Zool.*, **55** (1), 35–42.

19) Marzela, F. (2018) Korelasi Antara Kadar Merkuri Krim Pemutih Dan Kadar Merkuri Urin Pengguna Krim Pemutih Wajah Di FKM UNAIR. *J. Kesehat. Lingkung.*, **10** (4), 424–433.

20) Manavi, P.N., dan Mazumder, A. (2018) Potential risk of mercury to human health in three species of fish from the southern Caspian Sea. *Mar. Pollut. Bull.*, **130** (December 2017), 1–5.

21) de Almeida Rodrigues, P., Ferrari, R.G., dos Santos, L.N., dan Conte Junior, C.A. (2019) Mercury in aquatic fauna contamination: A systematic review on its dynamics and potential health risks. *J. Environ. Sci. (China)*, **84**, 205–218.

The Seybold Report
ISSN 1533-9211

22) Leon-Canedo, J.A., Alarcon-Silvas, S.G., Fierro-Sanudo, J.F., Rodríguez-Montes de Oca, G.A., Partida-Ruvalcaba, L., Diaz-Valdes, T., dan Paez-Osuna, F. (2019) Mercury and other trace metals in lettuce (Lactuca sativa) grown with two low-salinity shrimp effluents: Accumulation and human health risk assessment. *Sci. Total Environ.*, **650**, 2535–2544.

23) Ha, E., Basu, N., Bose-O'Reilly, S., Dórea, J.G., McSorley, E., Sakamoto, M., dan Chan, H.M. (2017) Current progress on understanding the impact of mercury on human health. *Environ. Res.*, **152**, 419–433.

24) Wilczynska, K., dan Waszkiewicz, N. (2020) Diagnostic utility of selected serum dementia biomarkers: Amyloid β-40, amyloid β -42, tau protein, and YKL-40: A review. *J. Clin. Med.*, **9** (11), 1–26.

25) Vergallo, A., Megret, L., Lista, S., Cavedo, E., Zetterberg, H., Blennow, K., Vanmechelen, E., De Vos, A., Habert, M.O., Potier, M.C., Dubois, B., Neri, C., Hampel, H., Bakardjian, H., Benali, H., Bertin, H., Bonheur, J., Boukadida, L., Boukerrou, N., Chiesa, P., Colliot, O., Dubois, B., Dubois, M., Epelbaum, S., Gagliardi, G., Genthon, R., Habert, M.O., Houot, M., Kas, A., Lamari, F., Levy, M., Metzinger, C., Mochel, F., Nyasse, F., Poisson, C., Revillon, M., Santos, A., Andrade, K.S., Sole, M., Surtee, M., de Schotten M, T., Vergallo, A., Younsi, N., Aguilar, L.F., Babiloni, C., Baldacci, F., Benda, N., Black, K.L., Bokde, A.L.W., Bonuccelli, U., Broich, K., Cacciola, F., Castrillo, J., Ceravolo, R., Chiesa, P.A., Corvol, J.C., Cuello, A.C., Cummings, J.L., Depypere, H., Duggento, A., Escott-Price, V., Federoff, H., Ferretti, M.T., Fiandaca, M., Frank, R.A., Garaci, F., Geerts, H., Giorgi, F.S., Graziani, M., Haberkamp, M., Herholz, K., Karran, E., Kim, S.H., Koronyo, Y., Koronyo-Hamaoui, M., Lamari, F., Langevin, T., Lehéricy, S., Lorenceau, J., Mango, D., Mapstone, M., Nisticò, R., O'Bryant, S.E., Perry, G., Ritchie, C., Rossi, S., Saidi, A., Santarnecchi, E., Schneider, L.S., Sporns, O., Toschi, N., Verdooner, S.R., Villain, N., Welikovitch, L.A., Woodcock, J., dan Younesi, E. (2019) Plasma amyloid β 40/42 ratio predicts cerebral amyloidosis in cognitively normal individuals at risk for Alzheimer's disease. *Alzheimer's Dement.*, **15** (6), 764–775.

26) Fandos, N., Pérez-Grijalba, V., Pesini, P., Olmos, S., Bossa, M., Villemagne, V.L., Doecke, J., Fowler, C., Masters, C.L., dan Sarasa, M. (2017) Plasma amyloid β 42/40 ratios as biomarkers for amyloid β cerebral deposition in cognitively normal individuals. *Alzheimer's Dement. Diagnosis, Assess. Dis. Monit.*, **8**, 179–187.

27) Hanon, O., Vidal, J.S., Lehmann, S., Bombois, S., Allinquant, B., Tréluyer, J.M., Gelé, P., Delmaire, C., Blanc, F., Mangin, J.F., Buée, L., Touchon, J., Hugon, J., Vellas, B., Galbrun, E., Benetos, A., Berrut, G., Paillaud, E., Wallon, D., Castelnovo, G., Volpe-Gillot, L., Paccalin, M., Robert, P.H., Godefroy, O., Dantoine, T., Camus, V., Belmin, J., Vandel, P., Novella, J.L., Duron, E., Rigaud, A.S., Schraen-Maschke, S., Gabelle, A., Hanon, O., Blanc, F., Boudali, Y., Seux, M.L., Lenoir, H., Bayle, C., Bombois, S., Delbeuck, X., Moulin, F., Latour, F., Plichart, M., Pichierri, S., Orvoën, G., Labourée, F., Cassagnaud, P., Paquet, C., Lala, F., Dumurgier, J., Rigaud, A.S., Perret-Guillaume, C., Alonso, E., du Boisgueheneuc, F., Hugonot-Diener, L., Rollin-Sillaire, A., Martinaud, O., Boully, C., Spivac, Y., Devendeville, A., Robert, P.H., Caillard, L., Hannequin, D., Sastre, N., Haffen, S., Kearney-Schwartz, A., Novella, J.L., Deramecourt, V., Chauvire, V., Abitbol, G., Schwald, N., Hommet, C., Sellal, F., Cariot, M.A., Abdellaoui, M., Benisty, S., Gherabli, S., Anthony, P., Bloch, F., Charasz, N., Chauvelier, S., Gaubert, J.Y., Sacco, G., Guerin, O., Boddaert, J., Mackowiak, M.A., Rabus, M.T., Gissot, V., Picard, C., Guillemaud, C., Gervais, C., Hugon, J., Michel, J.M., David, J.P., Paulin, M., Ousset, P.J., Pariel, S., Chawakilian, A., Joffredo, L., Troussiere, A.C., Adam, C., Dupuy, D., Briault, H., Saulnier, I., Mondon, K., Picat, M.A., Laurent, M., Daheb, R., Libercier, S., Krabchi, D., Chupin, M., Chaussade, E., dan Schraen-Maschke, S. (2018) Plasma amyloid levels within the Alzheimer's process and correlations with central biomarkers. *Alzheimer's Dement.*, **14** (7), 858–868.

28) Mengel, D., Liu, W., Glynn, R.J., Selkoe, D.J., Strydom, A., Lai, F., Rosas, H.D., Torres, A., Patsiogiannis, V., Skotko, B., dan Walsh, D.M. (2020) Dynamics of plasma biomarkers in down syndrome: The relative levels of Aβ42 decrease with age, whereas NT1 tau and NfL increase. *Alzheimer's Res. Ther.*, **12** (1), 1–11.

29) Icp-ms, L.S. (2021) DIAGRAM ALIR (UNTUK EKSTERNAL).

The Seybold Report
ISSN 1533-9211

30) Lestari, S., Mistivani, I., Rumende, C.M., dan Kusumaningsih, W. (2017) Comparison between mini mental state examination (MMSE) and Montreal cognitive assessment Indonesian version (MoCA-Ina) as an early detection of cognitive impairments in post-stroke patients. *J. Phys. Conf. Ser.*, **884** (1), 0–8.

31) Rambe, A.S., Fitri, F.I., dan Utara, U.S. (2017) Correlation between the Montreal Cognitive Assessment-Indonesian Version (MoCA-Ina) and the Mini-Mental State Examination (MMSE) in Elderly. **5** (7), 915–919.

32) Untari, I., Subijanto, A.A., Mirawati, D.K., dan Sanusi, R. (2019) The Montreal Cognitive Assessment (MoCA-Ina) versus the Mini-Mental State Examination (MMSE-Ina) For Detecting Mild Cognitive Impairment among The Elderly. *Bangladesh J. Med. Sci.*, **20** (01), 164–169.

33) Hagen, E., Sømhovd, M., Hesse, M., Ajo, E., dan Erga, A.H. (2019) Journal of Substance Abuse Treatment Measuring cognitive impairment in young adults with polysubstance use disorder with MoCA or BRIEF-A – The signi fi cance of psychiatric symptoms. *J. Subst. Abuse Treat.*, **97** (August 2018), 21–27.

34) Sancesario, G.M., dan Bernardini, S. (2018) Diagnosis of neurodegenerative dementia : where do we stand , now ? **6** (17), 2–7.

35) Lee, N., Yang, S., Chieh, J., Huang, P., dan Chang, L. (2017) Blood Beta-Amyloid and Tau in Down Syndrome : A Comparison with Alzheimer ' s Disease. **8** (January), 1–8.

36) Gu, L., dan Guo, Z. (2013) Alzheimer's Aβ42 and Aβ40 peptides form interlaced amyloid fibrils. *J. Neurochem.*, **126** (3), 305–311.

37) Gabelle, A., Richard, F., Gutierrez, L.A., Schraen, S., Delva, F., Rouaud, O., Buée, L., Dartigues, J.F., Touchon, J., Lambert, J.C., dan Berr, C. (2013) Plasma amyloid-β levels and prognosis in incident dementia cases of the 3-city study. *J. Alzheimer's Dis.*, **33** (2), 381–391.

38) van Oijen, M., Hofman, A., Soares, H.D., Koudstaal, P.J., dan Breteler, M.M. (2006) Plasma Aβ1-40 and Aβ1-42 and the risk of dementia: a prospective case-cohort study. *Lancet Neurol.*, **5** (8), 655–660.

39) Kantarci, K., Lowe, V.J., Chen, Q., Przybelski, S.A., Lesnick, T.G., dan Xxx, P. (2020) β -Amyloid PET and neuropathology in dementia with Lewy bodies. **0**.

40) Cobb, W.J. (2018) The Potential Impact of Methyl Mercury Toxicity Within Alzheimer's Disease Progression, Considering the Tau Hypothesis, Neurovascular Hypothesis as Well as The Potential Role of Dietary and Botanical Mercury Chelators and that of Pharmacologically Develop. *Anat. Physiol. Biochem. Int. J.*, **5** (4).

41) Ajsuvakova, O.P., Tinkov, A.A., Aschner, M., Rocha, J.B.T., Michalke, B., Skalnaya, M.G., Skalny, A. V, Butnariu, M., Dadar, M., Sarac, I., Aaseth, J., dan Bjørklund, G. (2020) Sulfhydryl groups as targets of mercury toxicity. *Coord. Chem. Rev.*, **417**, 213343.

42) Azar, J., Yousef, M.H., El-fawal, H.A.N., dan Abdelnaser, A. (2021) Mercury and Alzheimer ' s disease : a look at the links and evidence. 361–374.

43) Mutter, J., Naumann, J., Schneider, R., Walach, H., dan Office, E. (2007) Quecksilber und Alzheimer-Erkrankung. 528–540.

44) Mining, S.G., dan Chalker, J.M. The Mercury Problem in Accepted Manuscript.

45) Mantey, J., Nyarko, K.B., Owusu-nimo, F., Awua, K.A., Bempah, C.K., Amankwah, R.K., Akatu, W.E., dan Appiah-effah, E. (2020) Heliyon Mercury contamination of soil and water media from different illegal artisanal small-scale gold mining operations (galamsey). *Heliyon*, **6** (June), e04312.

46) Green, C.S., Lewis, P.J., Wozniak, J.R., Drevnick, P.E., dan Thies, M.L. (2019) Science of the Total Environment A comparison of factors affecting the small-scale distribution of mercury from artisanal small-scale gold mining in a Zimbabwean stream system. *Sci. Total Environ.*, **647**, 400–410.