

BONE ALUMINUM AS A BIOLOGICAL MONITORING OF OCCUPATIONAL EXPOSURE TO ALUMINUM

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ABSTRACT

The current proposed biological monitoring of aluminum is based on the analysis of aluminum concentration in blood/serum or in urine, but both considered to be reflective of short-term exposure. Based on its toxic kinetics, aluminum has been demonstrated to be accumulated in the bone. The aim of this study is to find out whether by analyzing bone aluminum, we might have an overview of aluminum accumulation that might cause health problems in the future. This review was conducted through a method of search and selection of articles from Pubmed, Cochrane Library, and Google Scholar databases aimed to answer question rising from the problem statement of this study. The process of searching articles used the keywords “occupational aluminum” OR “bone aluminum” AND “biological monitoring” OR “biomonitoring”. The selection of articles was performed using the defined inclusion and exclusion criteria. Initially, 61 articles were obtained, but after the selection process and hand searching, four articles remained consisting of two case reports and two cross sectional studies. Based on the selected evidence-based resources, bone can be a promising potential biomarker of aluminum, especially for cumulative exposure assessment. The use of in vivo neutron activation analysis (IVNAA) or X-ray fluorescence (XRF) technology for the purpose of noninvasively quantifying aluminum concentration in the bone, is suitable enough to be performed in occupational settings.

Keywords: Bone aluminum, occupational exposure, IVNAA, XRF, biomonitoring, biological monitoring

INTRODUCTION

Aluminum (Al) is used in many industries to make millions of different products and for Indonesia, Al is one of the potential export commodities (Roesfitawati, 2017; Müller, 2020). Since in the global market, the demand of Al is predicted to keep growing until 2035, the Indonesian state-owned company specialized in aluminum smelting has set a long-term goal of tripling its production capacity by expanding the operations. The plan is also supported by the Nation's President and Ministry of Industry as the goal is to shift the country from an exporter of minerals into a major producer of processed metals (INALUM, 2019). By all means, more workers are needed to objectify the vision and more are prone to the health effects of aluminum.

Aluminum occurs naturally in soil, water, and air as one of the most common metal in the earth's crust. Despite of it is typical used in a huge variety of products, Al is considered unsafe to humans when the body burden achieved high levels. It is known to target the nervous system, bone, and affect respiratory function. Workers are usually exposed through breathing Al containing dusts or fumes (Agency for Toxic Substances and Disease Registry (ATSDR), 2008; Igbokwe, Igwenagu and Igbokwe, 2019). Unfortunately, the national occupational disease prevalence data related to Al exposure in Indonesia has not been well established. Only two studies were found, with both could barely describe effects other than respiratory symptoms (Suwanto, 2018; Hutapea, 2019). Urine and blood aluminum are being used as the biomarkers to determine the exposure of Al, but both considered to be reflective of short-term exposure. Based on the toxic kinetics,

Al has been demonstrated to be accumulated in the bone (ATSDR, 2008). The purpose of this review was to evaluate whether any method of bone aluminum measurement can be utilized as a biomonitoring to reflect the cumulative occupational exposure to aluminum.

METHOD

Following the search of articles used the keywords (Table 1), the selection was conducted based on the inclusion and exclusion criteria (Figure 1). The inclusion criteria were human studies, in occupational settings, and in English language. Articles that were irrelevant to the purpose of this review were excluded. The authors decided not to favor articles that were published only in the last few years, as the information regarding this topic was limited. Apart from the electronic database, hand searching was also performed. Four articles remained for appraisal, consisting of two case reports and two cross sectional studies.

The cross-sectional studies were critically appraised based on the Center of Evidence-Based Medicine, Oxford University {Formatting Citation}, while case report studies using the Joanna Briggs Institute's Checklist for Case Reports (Joanna Briggs Institute, 2017). The level of evidence was also determined based on the Center of Evidence-Based Medicine, Oxford University (CEBM, 2009). The results of the appraisal were presented in Tables 2, 3, 4, 5.

RESULT

The study by Elinder et al. (1991) found bone aluminum concentrations in two workers who had been exposed with aluminum for 20 years were 29 and 18 $\mu\text{g Al/g}$ dry weight, which were higher than previous studies in subjects without renal disorder (average 7.6 $\mu\text{g Al/g}$). The upper limits of normal Al content in bone are below 10 mg/g dry weight (Klein, 2019). The results suggest that the welders' bone

aluminum was about 10 times higher than normal but about 10 times lower than in patients with dialysis encephalopathy (ranged from 12 to 100 $\mu\text{g Al/g}$). Unfortunately, this study did not perform either bivariate or multivariate analysis between bone aluminum, urinary aluminum concentrations and years of exposure. The method was performed using invasive biopsy, which might limit further investigations due to ethical reasons and also likely be the reason why only two subjects were examined. This study was probably the initial study and the result was used to promote more studies on the evidence of aluminum accumulation in the bone (Elinder *et al.*, 1991).

Aslam et al. (2009) was first intended to describe the measurement of manganese accumulation in the human bone, but the authors expanded the research with technical improvements to the in vivo neutron activation analysis (IVNAA) and adjusting it for the purpose of bone aluminum detection. The population of this study comes from a group of manganese welders prior to their previous study. The occupational exposure to aluminum is only recorded in the crudest manner, namely "yes" or "no" without specific measurement, which might affect the precision of the analysis consequently. The result of this study indicated that there was a significant mean difference between the exposed and unexposed group ($14.1 \pm 6.7 \mu\text{g Al/gCa}$). Although this study did not provide a correlation between the bone aluminum level and exposure period, as it was a preliminary human study, it should be considered as an encouragement to proceed to further studies directed specifically at aluminum accumulation in human bone due to long-term occupational exposures. The non-invasive properties and minimal radiation dose of this bone aluminum detection method allowed us to take this method into account for conducting a routine biomonitoring analysis to workers who will be exposed to aluminum for some period of time. As this method was also

successfully conducted to determine manganese concentrations in the bone, it may be used for the purpose of differentiating the metal that majorly

responsible for developing metal-induced health effects in the case of multiple exposure (Aslam *et al.*, 2009).

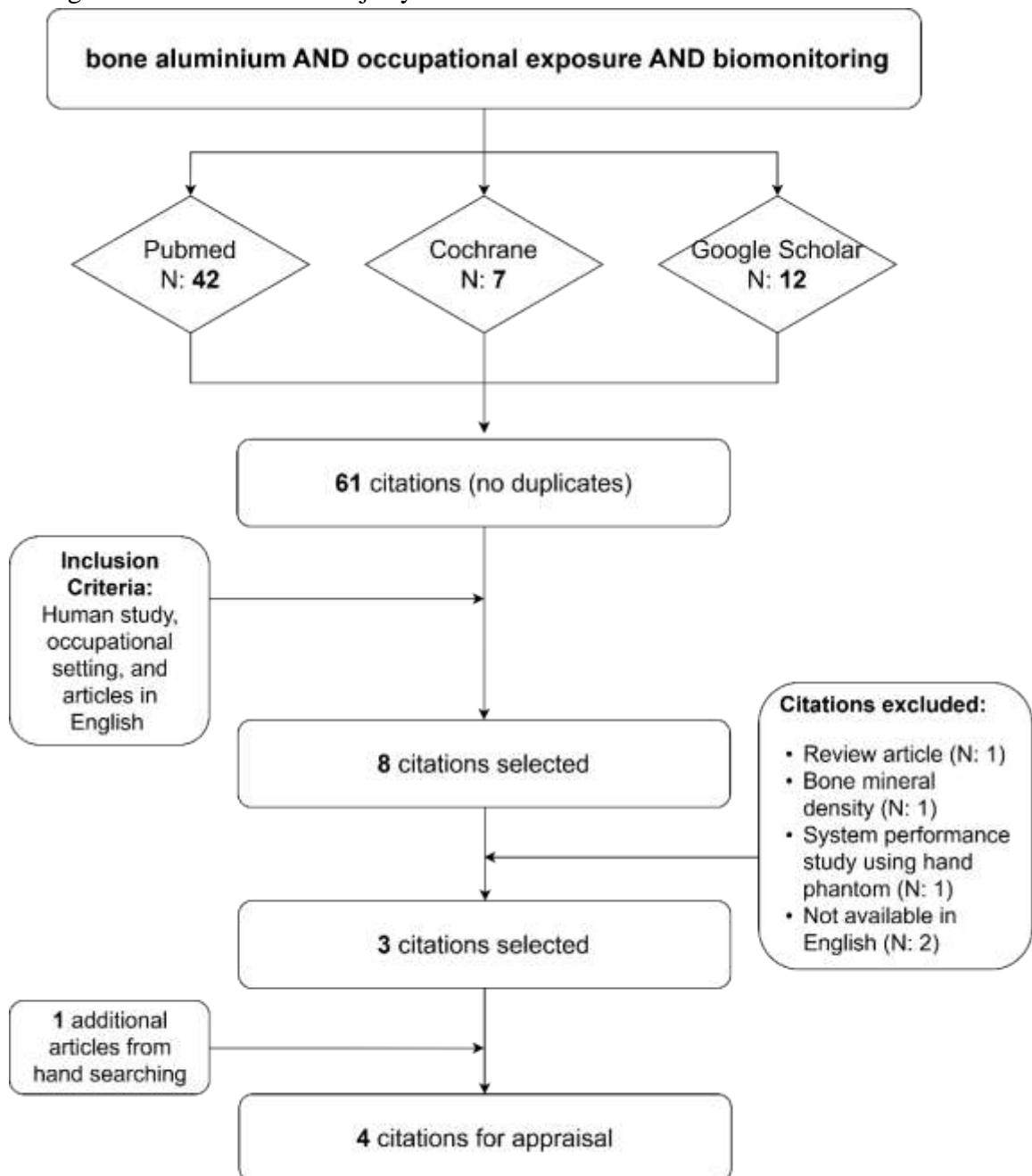


Figure 1. The Process of Article Selection

Hasan et al. (2020) performed the bone aluminum measurement on the right hand of the subject for 10 minutes and used deuterium-deuterium accelerator-based IVNAA system. The authors did not use the reference standard test (serum and urine aluminum analysis) probably based on the understanding that both of these tests only reflect short-term exposure. As a comparative indicator, they used fingernail aluminum and an environmental index (cumulative exposure indices, CEI). Fingernail was used because evidences suggested that the metal in nail presents the prior 2-12 months of exposure, hence it can be used in comparison to the years of metal

exposure that can be stored in the bone. The CEI was determined to ensure that the chronic exposure was cumulatively caused in the occupational setting. The limitations of this study were that the sample size was relatively small and the CEI was relied on work history, rather than specific measurement (such as air sampling evidence). But the authors claimed that the use of work history to compose the CEI was an established method which was sufficiently strong and précised enough to estimate the relative ranking of exposure within their study population over the working lifetime (Hasan *et al.*, 2020).

Table 1. Search Strategy Using Keywords

Database	Keyword	Found	Selected	Filter
PubMed	Search: ((occupational aluminum[MeSH Terms]) OR (occupational aluminum[Title/Abstract])) AND ((bone[Title/Abstract]) OR (bone[MeSH Terms]))	42	2	Title/ Abstract
Cochrane	#1 MeSH descriptor: [bone aluminum] explode all trees #2 MeSH descriptor: [biomarker OR biological monitoring OR biomonitoring] explode all trees #3 #1 AND #2	178 13491 7	0	Title/ Abstract
Google Scholar	"bone aluminum" AND "occupational exposure" AND "biomonitoring"	12	1	Title/ Abstract

Table 2. Critical Appraisal Checklist for Case Report (Article 1)

Article	Evidence of aluminum accumulation in aluminum welders
Author(s)	Elinder et al. (1991)
Level of Evidence	4
Were patient’s demographic characteristics clearly described?	Age, work history and duration of exposure were described, but medical history was not mentioned.

Article	Evidence of aluminum accumulation in aluminum welders
Was the patient's history clearly described and presented as a timeline?	Their work histories were mentioned, but nothing about their medical, family, and psychosocial history including relevant genetic information
Was the current clinical condition of the patient on presentation clearly described?	Inapplicable, because the subjects were considered healthy
Were diagnostic tests or assessment methods and the results clearly described?	Yes, the method of sampling and analysis for urine, blood, and bone biopsies were described in detail.
Was the intervention(s) or treatment procedure(s) clearly described?	Inapplicable, because no treatment applied on both of the subjects.
Was the post-intervention clinical condition clearly described?	Inapplicable
Were adverse events (harms) or unanticipated events identified and described?	Inapplicable
Did the case report provide takeaway lessons?	Yes, the report provided further evidence that long term exposure to aluminum by inhalation gives rise to accumulation of aluminum in the body of healthy persons, and that the elimination of aluminum was very slow

The result of Hasan et al. (2020) study suggested that there was a significant association between elevated bone Al with 15-year CEI ($p = 0,02$) and approaching significance for 20-year CEI ($p = 0,07$). Although a significant association between BnAl and lifetime CEI was not observed, it is considered that aluminum accumulation might not reflect multiple decades of

exposure even when the half-life is relatively long. The association between BnAl and FnAl could not be observed as well, but the result was consistent with evidence suggesting that nail and bone represent very different time periods with regards to exposure and metal accumulation in the body. (Hasan *et al.*, 2020).

Table 3. Critical Appraisal Checklist for Diagnostic Study (Article 2)

Title	Noninvasive measurement of aluminum in human bone: Preliminary human study and improved system performance
Author(s)	Aslam et al. (2009)
Level of Evidence	3b

Title	Noninvasive measurement of aluminum in human bone: Preliminary human study and improved system performance
Was the diagnostic test evaluated in a representative spectrum of patients (like those in whom it would be used in practice)?	Yes, this study involved 6 male subjects who self-reported some exposure to aluminum through welding, either presently or in the past. Therefore, this article was compatible with the main purpose of this scientific review in which to find out if bone aluminum could be used as a biomonitoring in occupational settings.
Was the reference standard applied regardless of the index test result?	No, other reference standard test such as serum or urine aluminum measurement was not performed, but the authors compared bone aluminum measurement between the exposed and unexposed group (general population).
Was there an independent, blind comparison between the index test and an appropriate reference ('gold') standard of diagnosis?	Unclear, this study did not explain whether the process of bone aluminum determination was done differently or blindly between the two groups.
Are test characteristics presented?	Although two types of results commonly reported in diagnostic test studies (accuracy and predictive values) were not presented in this study, the authors provided a comparison of estimated aluminum concentration between the two groups. A significant mean difference was established.
Were the methods for performing the test described in sufficient detail to permit replication?	Yes, the method of bone aluminum determination in this study was using the technique of in vivo neutron activation analysis. It is non-invasive and has an effective dose that is similar to a chest radiograph examination dose, thus might be applicable in occupational settings.

The case report by Assunção (2017) claimed to present an unprecedented case of multifocal osteonecrosis secondary to chronic occupational exposure to aluminum. The pathophysiology was because of the aluminum effect on inhibition of osteoid tissue calcification of the trabecular bone, thus resulting in osteomalacia that makes the bone tissue more fragile and susceptible to osteonecrosis from micro trauma. This proposed mechanism was proved in the patient as high concentration aluminum was related to the low concentration of calcium,

which in a healthy individual the levels were inverted. This disease has been described more commonly in patients with chronic renal failure or persons with regular intake of aluminum containing medicines. The author provided a sufficient information regarding patient's history of work, which can benefit us as the reader to draw a correlation between his occupational exposure and the disease. The diagnostic studies in the patient were completed thoroughly. Bone aluminum in this case report were determined using biopsy and x-ray fluorescence spectrometry.

Table 4. Critical Appraisal Checklist for Diagnostic Study (Article 3)

Title	Characterization of bone aluminum, a potential biomarker of cumulative exposure, within an occupational population from Zunyi, China
Author(s)	Hasan et al. (2020)
Level of Evidence	3b
Was the diagnostic test evaluated in a representative spectrum of patients (like those in whom it would be used in practice)?	Yes, this study was performed to adult (≥ 18 years) employed at manufacturing facility or a ferroalloy smelting factory in Zunyi, China, thus compatible with the main purpose of this scientific review in which to find out if bone aluminum could be used as a biomonitoring in occupational settings.
Was the reference standard applied regardless of the index test result?	No, the reference standard test (serum or urine aluminum measurement) was not performed, but instead the researchers used fingernail Al (FnAl) and a semi-quantitative methods namely cumulative exposure indices (CEIs), which incorporate a combination of air sampling and work history data to summarize the total inhaled concentration over time. CEI was based on distinct exposure group (ranking exposure) rather than specific measurement, while FnAl was measured using ICP-MS analysis.
Was there an independent, blind comparison between the index test and an appropriate reference ('gold') standard of diagnosis?	Unclear, the reference standard test (serum or urine aluminum measurement) was not performed. FnAl analysis was conducted at the Purdue Campus wide Mass Spectrometry Center without any information on who was performing the analysis. Determination of CEI was performed by constructing several CEIs over the prior 5, 10, 15, 20 years and lifetime exposure. The subjects were put into different group based on low, moderate, and high exposure that came with their job. Previously published Al exposure data for similar job titles in the literature were used to determine group assignment. It was not stated whether the CEI determination was blinded or conducted by someone other than the authors.
Are test characteristics presented?	Although two types of results commonly reported in diagnostic test studies (accuracy and predictive values) were not presented in this study, the association between BnAl with FnAl and CEI measures was determined using multiple linear regression models, to reflect the correlation of chronic Al exposure.
Were the methods for performing the test described in sufficient detail to permit replication?	Yes, the BnAl measurements were assessed with a compact deuterium-deuterium accelerator-based IVNAA system, which is non-invasive and posed minimal radiation risk. The research team has developed a transportable version of this technology and the procedure during the sampling was stated.

High aluminum level remained in the patient’s bone tissue, even after 3-years period of exposure cessation, about 2-fold compared to a healthy sample control. This result was suspected taking major part in causing symptoms of polyarthralgia related to osteonecrosis. Arthralgia was a usual

symptom complained middle age adults, and often underrated (Assunção *et al.*, 2017). Therefore, this case report has given us an insight that a proper history taking, including history of occupation must be assessed comprehensively.

Table 5. Critical Appraisal Checklist for Case Report (Article 4)

Title	Multifocal osteonecrosis secondary to occupational exposure to aluminum
Author(s)	Assunção et al. (2017)
Level of Evidence	4
Were patient’s demographic characteristics clearly described?	Yes, the patient was a black male, 39 years old, worked for eight years in a plant refining bauxite and producing aluminum.
Was the patient’s history clearly described and presented as a timeline?	Yes, it was stated that the symptoms started for years prior. A complete history of his work was also provided.
Was the current clinical condition of the patient on presentation clearly described?	Yes, his symptoms were presented.
Were diagnostic tests or assessment methods and the results clearly described?	Yes, the type of diagnostic tests, the location, and the result were well-defined.
Was the intervention(s) or treatment procedure(s) clearly described?	Yes, the patient was treated conservatively in this case report.
Was the post-intervention clinical condition clearly described?	Yes, within 6 years of follow-up, the pain improved partially and no collapse reported.
Were adverse events (harms) or unanticipated events identified and described?	No, the patient chose to take opioids regularly rather than having a surgery, but the adverse events relating to this were not elaborated.
Does the case report provide takeaway lessons?	Yes, this case reported provides a novel case of a patient with multifocal osteonecrosis associated with chronic occupational exposure to aluminum. No other reports found associating the occurrence of osteonecrosis with occupational exposure to aluminum.

DISCUSSION

The proposed mechanism is that aluminum can accumulate at the mineralization front of the bone surface and occupies the unmineralized type I collagen. Thus, aluminum act as a competitor to calcium, impairing calcification and resulting in osteomalacia. Aluminum also impair the secretion of parathyroid hormone which will result in a functional hypoparathyroidism with consequent hypercalciuria. It also inhibits renal enzyme 25 hydroxyvitamin D-1 alpha hydroxylase (25(OH)D-1-alpha hydroxylase), which converts 25(OH)D to 1 alpha, 25 dihydroxyvitamin D, resulting an alteration in calcium homeostasis, and bone cell differentiation (Klein, 2019).

During the past years, the only known method for bone aluminum measurement was performed with biopsy, which was implemented in the study of Elinder et al. (1991). Although the correlation between bone aluminum level and exposure time could not be determined by then, the result suggested more studies to prove more evidence. Both of Aslam et al. (2009) and Hasan et al. (2020) studies were using the technique of in vivo neutron activation analysis (IVNAA) for bone aluminum detection. This method was developed decades ago and had been used to measure certain elements in human body such as calcium, phosphorus, sodium, and chlorins (Shulyakova, Avtonomov and Kornienko, 2015). Both studies used hand bone as the site of detection, as it can be easily extended and not particularly sensitive to radiation-induced damage. Long half-times retention for aluminum were recognized for 29 years in cortical bone and 500 days in trabecular bone. The long half-time in bone is related to the slow rate of bone turnover, about 3% per year in cortical bone and 20% per year in trabecular bone. Human hand bone accounts for 1.5% of the skeleton and mainly consists of cortical bone, which makes it a suitable site of choice for irradiation (Riihimäki and

Aitio, 2012). Based on a systematic review of published articles between 1985 and 2016, only one cross-sectional study assessed the effect of aluminum exposure to the bone (Ferguson *et al.*, 2018). However, the study used bone mineral content and density rather than the concentration of aluminum, so it is considered irrelevant to the purpose of this review. This result suggest that the use of IVNAA for bone aluminum detection, probably other elements as well, has not been widely implemented in occupational practices. IVNAA is available in Indonesia under the supervision of National Nuclear Energy Agency of Indonesia (Badan Tenaga Nuklir Nasional, BATAN), but more commonly used for environmental sampling (Dwijananti *et al.*, 2018).

Out of the four journals appraised in this scientific review, unfortunately, none of them was a cohort study providing the exact relationship between aluminum accumulation in the bone and duration of exposure. This finding was expected as seen on a systematic review mentioned before, only 8 cohort studies were found with none of them analyzed bone aluminum concentrations (Ferguson *et al.*, 2018). Bone aluminum studies were more common to be assessed in populations with renal failure. Hasan et al. (2020) probably has the closest effort, as it compared BnAl with cumulative exposure indices (CEIs). However, the CEI as the potray of occupational exposure to aluminum, was only recorded in the crudest manner in this study, without specific measurement. This lack of available study is somehow understandable, as cohort studies might be time-consuming and not feasible. At the present, our information regarding the effectiveness of bone aluminum assessment as a biomonitoring for chronic exposure is still limited.

Nervous system has been known as the most sensitive target of aluminum exposure. Although the relation still controversial, aluminum has been associated with some neurodegenerative

disorders such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis. Aluminum may not be the only causative agent of the diseases, but it is possible that it may play a role in the disease progression (ATSDR, 2008; Inan-Eroglu and Ayaz, 2018). The chronic effects of aluminum are linked to the retention of aluminum in the depot (most probably in bone) from which it is slowly eliminated. The slow release and ongoing exposure can result in an increased aluminum body load (Klein, 2019). Assunção et al. (2017) provided us with a novel case of aluminum-induced bone toxicity, affirming us that the bone accumulation of aluminum may still pose a risk of health effect, even after the exposure had been stopped for years. The patient presented with arthralgia, which is a usual symptom complained middle age adults, and often underrated. Occupational specialists have to pay extra attention to any symptoms that may seemed common in regular setting.

Bone aluminum level in Assunção et al. (2017) study was determined using biopsy and x-ray fluorescence (XRF) spectrometry. Although biopsy may not be suitable, XRF is another method that may be feasible to be applied in occupational settings for routine monitoring. Like IVNAA, this XRF method is also available in Indonesia under the supervision of Indonesian Institute of Sciences (Lembaga Ilmu Pengetahuan Indonesia, LIPI) but it is currently used for environmental sampling.

CONCLUSION

In regard to around one-half of the total body burden of aluminum is stored in the bone (ATSDR, 2008), bone is a promising potential biomarker of aluminum, especially for cumulative exposure assessment. Using IVNAA or XRF technology to quantify aluminum concentration in the bone noninvasively, it is considered reliable enough to be performed in occupational settings. Although resulting in some radiation

exposure, the dose is minimal and may not posed health risks. IVNAA and XRF methods are both available in Indonesia but it's currently used for environmental sampling (Dwijananti *et al.*, 2018). There are wide opportunities in the future for the utilization of this method, especially in the occupational settings that we should look forward to.

Based on the knowledge from this scientific review, some recommendation can be applied for practices. Bone aluminum level should be assessed initially as a baseline, prior to a worker's employment or assignation to a high-risk occupational environment of aluminum. Whenever it is necessary, routine analysis can be implemented along with environmental monitoring and other supportive biomarkers, as a medical surveillance of aluminum-induced health effect. More evidence is still needed to compare bone aluminum measurement with other biomarkers and enviromental sampling in larger working populations. Performance study for optimization and improvement of IVNAA or XRF to be a routine monitoring of bone aluminum is also necessary. Further studies are also required regarding the correlatoin between bone aluminum accumulation and years of exposure, as well as the chronically emerging health effects long after the cessation of exposure. The workers should be encouraged to get the bone aluminum measurement because the data acquired may benefit the workers and their families who seek compensation after suffering aluminum health related problems that may develop long after the occupational exposure had been halted.

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