HOKKAIDO UNIVERSITY

Title	Assessment of toxicological effects regarding lead exposure and investigation of testing and treatment methods [an abstract of entire text]
Author(s)	中田, 北斗
Degree Grantor	北海道大学
Degree Name	博士(獣医学)
Dissertation Number	乙第7134号
Issue Date	2021-06-30
Doc URL	https://hdl.handle.net/2115/82655
Type	doctoral thesis
File Information	Hokuto_Nakata_summary.pdf

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Assessment of toxicological effects regarding lead exposure and investigation of testing and treatment methods
（鉛暴露による毒性影響の評価と検査・治療法の検証）

Hokuto NAKATA

Summary of the thesis

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Preface

There has been remarkable technological innovation and economic growth in human society while environmental pollution is a keyword that cannot be avoided when discussing the circumstances surrounding humanity in modern history. It is often said that industrial development and environmental pollution are trade-offs. This is true from a macroscopic perspective, but from a microscopic perspective, the reality differs greatly depending on the characteristics of each region and individual. While there are people who enjoy the benefits of development, there are also people who suffer only from the burdens of pollution. In other words, the trade-off is closely linked to social disparity and injustice, and is also a factor that contributes to them. Conversely, if the trade-off can be properly resolved, it should contribute to the correction of social disparity and injustice. It is important to realize this future through a multifaceted approach in today's world where the importance of sustainability is being emphasized, as represented by the Sustainable Development Goals (SDGs).

It is with this belief that I conducted my research on the subject of lead (Pb), which is one of the most serious pollutants. The Kabwe district of the Republic of Zambia was chosen as a model area for this study. The pollution in this area is mainly caused by mining development, which is a key industry in the national and regional economy. In Kabwe, where there is a typical trade-off between industry and environmental pollution, quantitative assessment of the actual health effect of the population is considered to be an important step towards solving the problem. In addition, an inexpensive and simple method of diagnosing and treating Pb poisoning is also important for continuous efforts to solve the problem with limited resources in developing countries.

I lived in Kabwe for approximately two years with my wife and daughters. Although our stay in Kabwe was short-lived, in these days, Pb contamination in Kabwe became not “a tragedy happening somewhere else in the world that we know through images and text” but "a personal matter concerning my own family, neighbors, and community”. The paradoxes and contradictions in the society mentioned above were again keenly felt. I have had many opportunities to come into contact with the thoughts and feelings of people who are raising their children in areas adjacent to mines that are heavily polluted. These experiences made me realize the need for an inexpensive and sustainable treatment method that local people can implement on their own.

Chapter 1

Narrative review of environmental lead contamination and implementable control measures in Kabwe, Republic of Zambia

Kabwe town, the capital of central province, Zambia has rapidly developed due to the discovery of Pb-zinc (Zn) deposits in 1902. The Pb-Zn mining activity began in 1904 and the operation was continued until its closure in 1994. However, industrial activities including the smelting of the mineral ores that were left in the mine dump or transported from other towns or countries have continued even now.

Extremely high Pb accumulation levels in various samples including soil, wild animals have been reported. In these reports, particularly high Pb concentrations were recorded near the mine, and both soil and animal-based monitoring suggest that Pb is spreading from the source of contamination, the mine, into the surrounding environment. Verification using Pb stable isotope ratio as an indicator similarly indicated that the mine is the dominant source of contamination. Moreover, some studies using animals from Kabwe have demonstrated the adverse health effects, suggesting the health effects even in the Kabwe population.

After careful screening for relevancy, 14 literatures were included into the review of Pb accumulation patterns and associated health effects in Kabwe population. Generally, areas near mine such as Chowa, Kasanda, and Makululu showed extremely high blood lead levels (BLLs) of approximately 20-50 μg/dL as arithmetic mean, geometric mean, or median in children. The BLLs in excess of 100 μg/dL have been reported in 4 literatures, indicating that even 20 years after the mine closure in 1994, extremely severe Pb contamination is still occurring. Compared to the literature on Pb accumulation status, there is a paucity of literature that has assessed health effects including hemato-, hepatic-, and renal-toxicity in Kabwe population.

For the remediation techniques, various approaches, in the two categories of 1) Physical shielding, fixation, or migration, and 2) Reduction of diffusion and uptake by organisms by conversion of chemical forms, were proposed. Other types of measures that can be taken by governments to prevent and manage environmental contamination were also described in this chapter.

Chapter 2

Clinical biochemical parameters associated with the exposure to multiple environmental metals in residents from Kabwe

Lead interferes with various bodily functions. Although high blood Pb levels in residents from Kabwe, Zambia have been reported, the accumulation pattern of other metals remains unknown. The study was designed to determine the BLL, blood cadmium level (BCdL), and blood zinc level (BZL) values within Kabwe, as well as the potential associated adverse health effects. After random selection, 504 representative samples were used for metal analysis, blood biochemical analysis, and δ-aminolevulinic acid dehydratase (ALAD) assay. The BLL level ranged from 0.79 to 154.75 μg/dL and generally increased in areas near the mine. A significant elevation of BCdL was also observed in two areas (0.37 ± 0.26 and 0.32 ± 0.30 μg/L) where the two highest mean BLL levels were recorded. By contrast, the BZL values did not differ greatly with respect to area. Some blood biochemical parameters relating to hepatic and renal function were out of the normal range in approximately 20 to 50% of studied adult participants. The ALAD activity was significantly inhibited in the two areas contaminated by Pb and cadmium (Cd). A significant negative relationship was observed between metal levels and clinical parameters, e.g., between BLL and ALAD for all the age categories and between BCdL and the estimated glomerular filtration rate for all the age categories except 0 to 4 years. The increase in BCdL in areas near the mine relative to the other areas suggested the potential adverse health effects of Cd and/or the interaction of Pb and Cd. A significant association of metal levels with clinical parameters also indicated the effects of metal exposure on hematopoietic, hepatic, and renal systems.

Chapter 3

The impact of elevated blood lead levels in children on the health-related quality of life in their mothers

Kabwe is a mining town in Zambia that has been ranked among “the ten most polluted places in the world” with previous findings of serious Pb pollution. In this study, we aim to examine the impact of childhood Pb poisoning on the health-related quality of life (HRQoL) of mothers in Kabwe. The HRQoL was assessed using the Short-Form 36 survey for 404 mothers coming from residences in 40 randomly selected standard enumeration areas (SEAs). The BLLs of the household members including the mothers themselves were measured. We found a significant positive correlation between the BLLs of the mothers and their children ($R = 0.6385$, $p < 0.0001$), while the BLLs of preschool-aged and school-aged children were significantly higher than those of their mothers and fathers. Using the data sets containing the BLLs of the household members, the age of the mothers, the household income, and the household SEA, we performed stepwise multiple linear regression analyses. The results showed significant negative associations between the representative BLL of household children and the BLL of preschool-aged children with the vitality and mental health scores of their mothers. Additionally, the BLL of school-aged children was only significantly associated with the mental health score of their mothers. By contrast, there was a significant negative association between the BLLs of the mothers with the social role functioning score. This suggests that elevated BLLs in children have a negative impact on the mental health conditions of their mothers regardless of the mothers’ BLL.

Chapter 4

Assessment of LeadCare® II analysis for testing of a wide range of blood lead levels in comparison with ICP–MS analysis

The LeadCare® testing system, which utilizes anodic stripping voltammetry (ASV) methodology, has been widely used worldwide for cost-effective BLL screening. However, some concerns have recently been issued regarding inaccurate results obtained using LeadCare®. Hence, we aimed to evaluate the accuracy of BLL measured by LeadCare® II (BLL_{LC}) by comparison with ICP-MS (BLL_{IM}) by the Passing–Bablok regression, Deming regression, and Bland–Altman analyses by using 994 venous blood samples. BLL_{LC} ranged from 3.3 to 162.3 μg/dL, while BLL_{IM} ranged from 0.8 to 154.8 μg/dL. Although BLL_{LC} and BLL_{IM} exhibited a strong and positive correlation, BLL_{LC} values were generally greater than BLL_{IM} values, indicative of the overestimation of the LeadCare® analysis. A large positive bias of 19.15 ± 8.26 μg/dL and 29.25 ± 14.04 μg/dL for BLL_{LC} compared with BLL_{IM} were recorded in the BLL_{LC} range of 45.0 to 64.9 μg/dL and for ≥65.0 μg/dL, respectively. In contrast, a bias of ≤0.3 μg/dL was observed at a BLL_{LC} of less than 10.0 μg/dL. Blood copper, cadmium, and iron levels did not exhibit an effect on the bias of BLL_{LC}, indicative of the minimal potential interferences of the metals; these interferences are a cause for concern with the ASV method. In conclusion, LeadCare® analysis is thought to be a good tool for screening purposes at a lower BLL around the reference level of 5 μg/dL in the initial stage; however, conversion or retesting using a laboratory analyzer is recommended at a higher BLL for appropriate clinical evaluation and research.

Chapter 5

Evaluation of the ameliorative effect of Spirulina (*Arthrospira platensis*) supplementation on parameters relating to lead poisoning and obesity in C57BL/6J mice

The current study aimed to validate the possible ameliorative effects of Spirulina (*Arthrospira platensis*) on lead poisoning and obesity using C57BL/6J mice. After a treatment period, we performed metal analyses, as well as hematocrit and plasma biochemical parameter measurements, and assayed oxidative stress markers and erythrocyte ALAD activity. Our results highlighted the effectiveness of Spirulina in improving anemia status with the normalization of hematocrit levels and ALAD activity ratios, even in mice that exhibited obesity in addition to lead poisoning. Spirulina treatment also decreased epididymal white adipose tissue weight and increased plasma high-density lipoprotein levels, which are normally reduced after lead exposure. However, most of the studied plasma biochemical parameters and oxidative stress markers did not show large changes after treatment, likely because of the short duration of treatment. Further studies with longer-term exposures are required to validate the usefulness of Spirulina suggested in the present study.

Chapter 6

Does *Moringa Oleifera* affect toxicokinetics and toxicity of lead in Sprague Dawley rat?

Moringa Oleifera (MO) has potential for nutritional and medical applications. We verified whether the administration of MO changed mineral accumulation patterns and mitigative effects of lead poisoning using Sprague–Dawley rats. MO leaves, aqueous leaf extracts, and seeds were administrated to rats in two different concentrations (100 and 600 mg/kg body weight/day) for 3 weeks. Element analysis, biochemical blood tests, oxidative-stress assessment, and blood ALAD activity assays were performed after euthanasia and dissection. Although apparent changes in element accumulation patterns and biochemical parameters for hepatic and renal function assessments were not observed, lead-induced oxidative stress was significantly mitigated by MO administration of leaves. The administration of high-dose MO leaves and seeds significantly recovered ALAD activity. Further investigations for potential mitigative effects of MO on lead toxicity and its mechanism are required.

Conclusion

As a typical example of contamination from industrial activities, Chapter 1 outlined the severe Pb contamination in the Kabwe mining area in the Republic of Zambia. Chapter 2 described the health effects assessment of metal exposure in the Kabwe population. Chapter 3 assessed the impact of Pb poisoning of children on the HRQoL of their mothers. Chapter 4 evaluated the reliability of LeadCare II, a simple BLL analysis instrument that can be used on-site. In Chapter 5 and Chapter 6, the potential of Moringa (*Moringa Oleifera)* and Spirulina (*Arthrospira platensis*), two locally available functional foods that are inexpensive and continuously available, to mitigate Pb poisoning was assessed *in vivo* experiments.

Environmental pollution caused by human industrial activities is widespread in all ages. On the other hand, there are many challenges in quantitative health impact assessment and continuous monitoring, and problem solving is usually prolonged. Balancing industrial and economic development with the reduction of environmental pollution is an essential proposition for building a sustainable society.