（様式５）Form 5

学位論文内容の要旨
Abstract of the dissertation

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学位論文題名
The title of the doctoral dissertation

Studies on toxicological effects of lead in animals for evaluation of worldwide environmental lead pollution
（環境中の鉛汚染評価のための生物における鉛の毒性影響に関する研究）

Lead (Pb) is a metal toxicant of global concern whose environmental presence in large quantities is directly related to human activities such as mining without “good-for-earth” practices in place. The objective of the present work was to investigate the toxicological impact of lead exposure on fish, animal and human health. Lead exposure in water at concentrations reported in Kabwe, Zambia in Africa (0.01-94 μg/L) to embryos and larval zebrafish (*Danio rerio*) under alternating dark and light illumination revealed negative toxicological effects on fish life. Lead exposure induced low survival rates, cardiovascular toxicity and neuromuscular toxicity (involuntary muscle twitching) at 50 μg/L concentration Pb and above in embryos. On the other hand, acute Pb exposure attenuated the larval zebrafish behaviour and induced hyperactivity under dark/light illumination. Lead induced oxidative stress system imbalance and caused the downregulation of catalase mRNA and upregulation of glutathione S-transferase mRNA in zebrafish embryos. Exposure further induced upregulation of the apoptosis regulator protein mRNA of B-cell lymphoma 2 gene in embryos. Acute exposure in larval zebrafish led to the upregulation uncoupling protein-2, cytochrome c oxidase subunit I and B-cell lymphoma 2 genes. The co- exposure of Pb together with zinc (Zn) like the Kabwe environment in Sprague-Dawley rats (*Rattus norvegicus*) revealed that Zn partially mitigated the toxic effects of lead at low and not at high exposure through reduced tissue Pb uptake in both the testes and muscles. A reduction in bone Pb uptake was also observed in the Zn and Pb co-exposed group. No mitigative Zn effects were seen in other tissues. Zinc co-administration prevented Pb inhibition of blood delta aminolaevulinic acid dehydratase enzyme activity at high level of exposure. Furthermore, Zn prevented the downregulation of the catalase, superoxide dismutase, glutathione peroxidase and other vital signalling genes in the liver, kidney and brain tissues. As sentinel marker of Pb exposure tool, the investigation of use of the crown incisor of the wild rat

(*Rattus rattus*) sampled from polluted areas of Kabwe, Zambia suggested that the accumulation of Pb in the "crown" incisor was reflective of the rat's habitat. In addition, the strong positive correlations between lead in blood and lead in teeth was observed suggesting that the "crown" incisor may be a useful tool in Pb exposure assessment. The investigation on the impact of chronic Pb exposure in adult male and female Kabwe residents on the levels of the plasma immunomodulatory protein cytokines revealed reduced levels of tumor necrosis factor alpha and interleukin-8 in female subjects only with blood lead levels above 10 μg/dL and a mean of 24 μg/dL. The increase in blood lead levels resulted in reduced concentration of plasma immunomodulatory protein cytokines in females.

Taken together, these findings suggest that the levels of lead in the Kabwe environment including the aquatic environment posed a negative impact on younger aquatic life, animals and humans. Further studies are required to ascertain the impact of chronic lead exposure in the presence of high levels of zinc especially in vulnerable groups such as expectant mothers, immunocompromised individuals and children living in lead polluted environment.