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| Author(s) | 本平, 航大; Motohira, Kodai |
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Abstract of the dissertation

博士の専攻分野の名称：博士（獣医学）　　氏名：Kodai Motohira
Name

学位論文題名
The title of the doctoral dissertation

# Evaluation and method establishment of biological and ecological effects of DDT: Imaging technique and molecular analysis approach

# (殺虫剤 DDT の生体・生態影響評価とその手法の確立：イメージングと分子解析アプローチ)


< abstract >

Dichlorodiphenyltrichloroethane (DDT) is a well-known organochlorine pesticide currently used for the vector control of malaria. However, DDT persists in the environment and in animals, raising concerns regarding its ecological and biological risks. Risk evaluation is crucial for the continued use of DDT. This thesis aimed to 1) evaluate the effects of DDT on wild rats in DDT-sprayed areas in South Africa, 2) develop new methods for evaluating chemical toxicities, and 3) apply the developed methods to an in vivo study of DDT. First, in 2014 and 2017, wild rats were collected from South Africa, and the DDT concentrations in organs and gene expression in the liver and plasma metabolome were evaluated. A sex-linked metabolic enzyme in rats was found to alter its expression pattern in highly DDT-polluted areas. Metabolomic analysis revealed a possible association between DDT and bile acids. As molecular analyses targeting wild rodents are rare, this study encourages further research to understand the ecological effects of DDT.

This thesis also discuss a new toxicity test utilizing computed tomography (CT) and multiomics analysis. Phenobarbital, a potent activator of the constitutive androstane receptor (CAR), is used as a model chemical for toxicity testing as it can induce hepatomegaly, and both DDT and phenobarbital are related to the CAR. In addition, new (multiomics) and classical (histopathology and quantitative PCR) methods were combined to identify plasma biomarkers of the molecular processes of hepatomegaly. This study demonstrated that micro-CT could be used to evaluate phenobarbital-induced hepatomegaly in live animals. Another finding was that plasma lipids, such as ceramides, are effective markers for interpreting biological reactions to phenobarbital. This new approach with combined micro-CT, multiomics, and classical methods can visualize toxic effects induced by chemicals and their molecular processes throughout an animal’s lifetime.

Finally, in vivo DDT exposure experiments were performed on rats from three generations. A low concentration of DDT and its metabolites were exposed through food. The expression of *Cyp2b1*, regulated by CAR, was markedly upregulated in DDT-exposed rats. Although hepatomegaly was observed in the female exposure group, histopathological changes and the significant toxic effects of DDT were not observed. CT did not adequately detect DDT-induced hepatomegaly, possible because the effects of DDT on the liver were lesser than those seen with phenobarbital. Thus, further improvements in the CT-based method and its application to the toxicity testing of other chemicals are necessary. The current analyses had some limitations, such as evaluating histopathology, clinical biomarkers, and CT analysis only. Thus, the results do not indicate that the whole toxicity of DDT in mammals. Further research is crucial to reveal the biological and ecological effects of low-dose DDT.

Overall, in vivo and field studies of DDT must coexist to assess the effects of DDT on the environment. This study describes the possible ecological and biological risks in DDT-sprayed areas and a new method for evaluating chemical toxicity. These findings will contribute to the re-evaluation of the effects of DDT, the comparison of its risks and benefits, and appropriate vector control.