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

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学位論文題名
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Exposure assessment and toxicological evaluations of neonicotinoid insecticides
(殺虫剤ネオニコチノイドへのばく露と毒性学的評価)

Currently, neonicotinoid insecticides (NNIs) are most the preferred class of insecticides used for extermination of various species of chewing, biting, and sucking insects across the world. Due to their high global application rates, residues of NNIs have become pervasive in various compartments of the ecosystem. However, current knowledge on exposure rates and potential human health risks of NNIs are highly limited in many parts of the world. Moreover, information on biological fates, bioaccumulation trends and the toxicological mechanisms of NNI associated metabolites in mammalian species are elusive. This thesis sought to (i) elucidate the potential toxicological effects of chronic low-dose exposures to NNIs, (ii) evaluate the exposure dynamics of NNIs in human populations, and (iii) to validate usage of organic dietary interventions as a countermeasure for NNI exposures in human populations. Specifically, I developed an LC-MS/MS-based method which was accurate (recoveries were ≥ 70% for most compounds), sensitive (LODs ≤ 0.47 ng/mL and LOQs ≤ 1.43 ng/mL were recorded for all detected compounds, $R^2 \geq 0.99$) and precise (RSDs ≤ 20%) for routine analysis of imidacloprid and seven of its metabolites in blood and various tissue specimens of mice. The method was applied to determine the biodistribution of imidacloprid and its metabolites in C57BL/6J male mice in a chronic low-dose exposure regimen. Following the analysis, imidacloprid-olefine occurred as the most recalcitrant imidacloprid metabolite in mice tissues. The desnitro-imidacloprid and desnitro-deshydro-imidacloprid metabolites of imidacloprid were found to show specific accumulation tendencies in liver, lung, kidney and testis of mice, under conditions of chronic low-dose exposures of imidacloprid in mice. In subsequent experimentations, the mechanistic role of the chronic low-dose exposures of imidacloprid in the prevalence of high fat diet (HFD)-induced liver steatosis was elucidated the C57BL/6J mice model. From the elucidations, chronic low-dose exposure of imidacloprid was found to potentiate HFD-induced body weight gain in mice. Also, imidacloprid increased the liver weights of mice, with complimentary reductions in mesenteric and gonadal white adipose tissue weights within the mice model. Imidacloprid potentiated high fat diet-induced hepatic steatosis; and subsequently upregulated hepatic transcription of fatty acid biosynthesis-related gene networks

in mice. In human biomonitoring studies, urinary levels of NNIs were quantified in Japanese subjects who consumed either organic diet only or conventional diet only, for 5-30 days. After the determination, 8 NNIs were detected in both organic and conventional diet groups. However, the levels and detection frequencies of NNIs were far lower in individuals who consumed organic diet only for 30-days. A regional exposure trends of NNIs were also determined in a population from Ghana. After the determination, 10 NNIs were detected; and most of subjects were exposed to multiple NNIs at the same time. Whereas the maximum EDIs of imidacloprid recorded in the Japanese population were found below imidacloprid RfD, the 100th percentile EDIs of imidacloprid recorded in the Ghanaian population were far higher than imidacloprid RfD estimated from animal studies. Ultimately, this thesis established a significant toxicological implication of imidacloprid in human populations with high exposure tendencies.