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学位論文内容の要旨

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学位論文題名

Exposure to Organophosphate Flame Retardants and its Associations with Allergies among School-aged Children

（学童期におけるリン系難燃剤曝露とアレルギーとの関連）

Exposure to organophosphate flame retardants and plasticizers (PFRs) has been reported to increase the risk of asthma and allergies. However, little is known about its association with type 2 inflammation (T2) biomarkers and oxidative stress biomarkers, which were associated with the development of allergies. The objective of this thesis was to identify the association between PFR exposure and allergic symptoms, T2 biomarkers, and oxidative stress biomarkers. The data and samples were collected between 2017 and 2020, including school children (n=427) aged 9–12 years living in Sapporo City, Japan, among the participants of "The Hokkaido Study on Environment and Children's Health." Thirteen urinary metabolites of five PFR were measured by LC-MS/MS. Allergic symptoms were assessed using the International Study of Asthma and Allergies in Childhood questionnaire. For T2 biomarkers, the peripheral blood eosinophil counts, fraction of exhaled nitric oxide level (FeNO), and serum total immunoglobulin E level were measured. For oxidative stress biomarkers, 4-hydroxynonenal (HNE), hexanoyl-lysine (HEL), and 8-hydroxy-2'-deoxyguanosine (8-OHdG), were measured in spot urine samples.

Chapter 1 investigated the biomonitoring of PFRs metabolites and the determinants of PFRs exposure in children aged 9-12 years old. The metabolites of bis(1,3-dichloro-2-propyl) phosphate (BDCIPP), 1-Hydroxy-2-propyl bis(1-chloro-2-propyl) phosphate (BCIPHIPP), and diphenyl phosphate (DPHP) were detectable for more than 60% of participants. The highest concentration of PFR was Σtris(1-chloro-isopropyl) phosphates (ΣTCIPP) (Median:1.20 nmol/L). Comparisons with study populations from other countries showed that urinary concentrations of PFRs were relatively lower. Determinants analysis found boys, higher BMI, higher annual household income, and experiencing environment tobacco smoking were associated with significantly higher levels of PFR metabolites. Higher age was associated with lower TPHP and higher EHDPHP.

Chapter 2 investigated associations among urinary PFR metabolite concentrations, allergic symptoms, and T2 biomarkers using both individual and mixture analyses. Multiple logistic regression analysis, quantile-based g-computation (qg-computation), and Bayesian kernel

machine regression (BKMR) were used to examine the associations between the health outcomes of the individual PFRs and the PFR mixtures. Tris(1,3-dichloro-2-propyl) phosphate (TDCIPP) was significantly associated with a high odds ratio (OR, 95% CI:1.36, 1.07 - 1.72) for wheeze. TDCIPP (1.19, 1.02 - 1.38), Σtriphenyl phosphate (ΣTPHP) (1.81, 1.40 - 2.37), and Σtris(2-butoxyethyl) phosphate (ΣTBOEP) (1.40, 1.13 - 1.74) were significantly associated with increased odds of FeNO (≥35 ppb). ΣTPHP (1.44, 1.15 - 1.83) was significantly associated with high eosinophil counts (≥300/μL). For the PFR mixtures, a one-quartile increase in all PFRs (1.48, 1.18 - 1.86) was significantly associated with high FeNO (≥35 ppb) in the qg-computation model. The PFR mixture was positively associated with high FeNO (≥35 ppb) and eosinophil counts (≥300/μL) in the BKMR models. These results may suggest that exposure to PFRs increases the probability of asthma, allergies, and T2 inflammation.

In Chapter 3, associations of individual and mixture of PFR with oxidative stress biomarkers in children were investigated, and the hypothesis of the mediation effect of oxidative stress on the associations between PFRs and T2 biomarkers are examined. The median for HNE, HEL, and 8-OHdG were 23.5 (μg/mL), 99.3 (nmol/L), and 9.2 (ng/mL), respectively. For the individual PFRs, a natural-log unit increase in TDCIPP (β, 95% CI: 0.12, 0.03 - 0.22), TPHP (0.52, 0.40 - 0.64), TBOEP (0.29, 0.16 - 0.41), and EHDPHP (0.16, 0.003 - 0.32) were significantly associated with higher HNE. Higher TDCIPP (0.04, 0.003 - 0.08), TPHP (0.10, 0.05 - 0.15), and TBOEP (0.07, 0.02 - 0.12) were associated with higher HEL. Higher TPHP (0.05, 0.03 - 0.08), and TBOEP (0.05, 0.03 - 0.08) were significantly associated with higher 8-OhdG. For the PFR mixtures, a one-quartile increase in all PFRs was associated with a significant increase in HNE (0.55, 0.36 - 0.73), HEL (0.08, 0.01 - 0.15), and 8-OHdG (0.07, 0.04 - 0.12) in the qg-computation model. The PFR mixture was positively associated with all three oxidative stress biomarkers in the BKMR models. No mediation effect of oxidative stress biomarkers among PFR exposure and levels of eosinophil and FeNO were found. PFR exposures were associated with oxidative stresses of DNA damage and lipid peroxidation among the general population of 9–12-year-old children. Future study including other environmental chemicals such as phthalates, bisphenols, and nonylphenol is needed to evaluate the mediation effect of oxidative stress for environmental chemicals exposure and asthma.

This thesis found that over half of school children are exposed to PFRs. The exposure concentrations were relatively low in Japan compared with other countries, and the estimated daily intake levels were well below the oral reference doses. The study results suggest that exposure to PFRs may increase the probability of asthma, allergies, T2 inflammation, and oxidative stress. Future studies focused on lifestyle and usage of daily necessities, as well as the source of PFRs, will be helpful in finding safe and effective ways to utilize the chemicals in daily life and finally reduce PFR exposure effectively.