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学位論文内容の要旨

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学位論文題名

Human biomonitoring of phthalates and their effect on respiratory and allergic symptoms in Japanese children

（フタル酸エステル類のヒトバイオモニタリングおよび呼吸器・アレルギー症状との関連）

Phthalates are ubiquitous environmental contaminants used in building materials as polyvinyl chloride materials, in food packing, toys, personal care products, etc. Previous studies have reported phthalates association with adverse health effects including respiratory and allergic symptoms. Moreover, children are more vulnerable than adults to phthalates exposure and health effect mainly due to children's still developing organs and age-related behaviors. Previous epidemiological studies focused on examining individual phthalates exposure effect on respiratory and allergic symptoms. However, this approach has limitations as humans are exposed to several phthalates in their daily lives.

Thus, in this thesis, study 1 investigated the secular trend of five parent phthalates is using their metabolites in children aged 7 years old. In the study 2, associations of individual and mixture of phthalate metabolites with wheeze, rhino-conjunctivitis, and eczema symptoms in children and the hypothesis of mediating effect of oxidative stress in the association between phthalates and symptoms are examined.

From the ongoing Hokkaido birth cohort study, 400 first-morning spot urine samples collected from 2012 to 2017 of 7 years old children were included in this study. The ISAAC questionnaire completed by parents or guardians of the children was used to investigate demographic and allergic symptoms (wheeze, rhino-conjunctivitis, and eczema). (i) Ten urinary phthalate metabolites: MiBP, MnBP, MBzP, MEHP, MEOHP, MEHHP, MECPP, MiNP, OH-MiNP, and cx-MiNP concentrations were measured by UPLC-MS/MS, (ii) the levels of three oxidative stress biomarkers, 8-OHdG, HEL, and HNE were measured, (iii) statistical analysis, study 1: multivariable regression model was performed to assess the secular trend of metabolites from 2012-2017 and the association between phthalate metabolites and building characteristics. Study 2: Weighted quantile sum (WQS) and Bayesian kernel machine regression (BKMR) models were used to investigate the association of individual and mixture effects of phthalate metabolites with health outcomes. Baron and Kenny's regression approach was used to investigate the possible mediating effect of oxidative stress biomarkers on the association between phthalate exposure and health outcomes.

Study 1 results and discussion

All phthalate metabolites were detected in more than 96% of the children's urine, indicating high detection frequency. High detection was observed in MECPP, MnBP and MEHHP with median concentrations of 37.4 ng/mL, 36.8 ng/mL and 25.8 ng/mL, respectively. Comparing phthalate metabolites levels in similar aged children with other countries, DEHP metabolites (MEHP, MEOHP, MEHHP, MECPP) were higher in Japanese children than children in the USA and Germany. On contrary, metabolites MiBP, MnBP, MBzP, MiNP, OH-MiNP and cx-MiNP were comparable or lower. A stable trend of phthalate metabolites was observed in children between 2012 and 2017. This stable or no change in phthalates exposure is despite the Japan's revised 2010 phthalates regulation which is only enforced to children and food products. Thus, the stable trend could be an indication of phthalates exposure from non-regulated products such as PVC floor/wall materials, and personal care products such as lotions, shampoo. Considering personal and building characteristics; elevated levels of ∑DINP in children from low-income households, MnBP from those living in old buildings, and MiBP, MnBP, and ∑DEHP from those with window opening habits of ≥1 h.

Study 2 results and discussion

The individual linear regression analysis showed MECPP (OR = 1.41, 95% CI: 1.02–1.97) and cx-MiNP (OR = 1.40, 95% CI: 1.07–1.86) were associated with wheeze. In the mixture analysis the WQS index had a significant association (OR = 1.43, 95% CI: 1.07–1.91) with wheeze and (OR = 1.37, 95% CI: 1.01–1.87) with eczema for which MiNP and OH-MiNP, respectively, were the most highly weighted metabolites. Considering BKMR, DINP metabolites showed the highest group posterior inclusion probability (PIP). Among DINP metabolites, cx-MiNP with wheeze and eczema as well as OH-MiNP with rhino-conjunctivitis showed the highest conditional PIPs. The overall effect of phthalate metabolites mixture showed increasing association with eczema. These findings showed the association of individual and phthalate metabolites mixture with wheeze and eczema. More importantly, metabolites of DINP followed by DEHP are the main contributors to the associations. No mediation of oxidative stress in the association between phthalates and symptoms was observed, this could be attributed to low oxidative stress. Yet, as this study's participants are only 7 years old the result may change when they get older.

In conclusion, this study revealed a stable trend of phthalate exposure from 2012 to 2017. The health assessment from different models emphasizes individual metabolites MECPP and cx-MiNP and mixture effect of DEHP and DINP metabolites are identified as the primary contributors to wheeze and eczema. In the future, trend biomonitoring of phthalates is important to surveil exposure level in different general population. More importantly, phthalates exposure may be associated with respiratory and allergic symptoms thus reduction of exposure level in children is warranted.