Systematic Development of Pharmacokinetic and Exposure Reconstruction Models for Chemicals of Personal Use

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[Abstract]

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In the large-scale birth cohort studies, the health effects of chemicals have been assessed by examining the association between the chemical levels in biospecimens, such as blood and urine, and health outcomes. It is, however, not possible to estimate the exposure from the levels in the biospecimen because the information on pharmacokinetics is available only for limited chemicals. In this regard, exposure reconstruction, which is to back calculate the exposure from the levels in biospecimen, is necessary for evidence-based policy making using data from the birth cohort studies. Pharmacokinetic parameters are often extrapolated from animal experiments, but it is difficult to obtain the reliable data due to species differences in absorption, metabolism, and excretion. In addition, administering chemicals to study subjects may raise ethical and risk issues, so it is not suitable for evaluating multiple chemicals. To investigate the pharmacokinetics of the chemicals in the daily use products, we conducted an intervention trial with controlled diet and use of personal care products. This approach allows us to obtain pharmacokinetic parameters without administering chemicals to the participants.

From 2020 to 2021, we recruited 100 Japanese general adult men and women, and asked them to use/consume prepared personal care products and meals during the intervention period for 5 consecutive days. Biological samples (urine, blood) and exposure media samples (personal care products, diet, beverages, house dust) were collected before, during and after the intervention period and subjected to chemical analysis. These intervention trials were approved by the institutional ethical review committees of the participating institutions and were conducted with written informed consent from all the participants. Parabens, bisphenols, triclosan, phthalates, neonicotinoids, and insect repellant (DEET) were analyzed to determine the pharmacokinetic parameters.

Decreasing trends were observed for some chemicals such as parabens, triclosan, neonicotinoids, during the study period. Based on the trends in urinary excretion rate, elimination half-lives were calculated using PBPK model software. Estimated elimination half-lives for parabens (methyl-, ethyl- and n-propyl-), neonicotinoids (thiamethoxam and clothianidin) and DEET, which were in the range of 10-20 hours, were consistent with the previous reports, indicating exposure was reduced during the intervention period. Exposure amount could be back-calculated with acceptable uncertainty from the urinary excretion amount using the fraction urinary excretion for some analytes. These results showed that information on pharmacokinetics can be obtained by the research method established in this study without administrating chemicals to the subjects.

[References]

1) Gwon H.R., Oh H.J., Chang K.H., Isobe T., Lee S.Y., Kim J.H., You S.J., Kim J.G., Kim J.W. (2021) Occurrence, distribution, and potential exposure risk of organophosphate flame retardants in house dust in South Korea. Science of the Total Environment, 770, 144571 (IF: 10.754)
2) Nishihama Y., Lai Y., Isobe T., Nakayama S.F. (2022) Optimal method for determining the intraclass correlation

coefficients of urinary biomarkers such as dialkylphosphates from imputed data. Environment International, 170, 107553 (IF: 13.352)

3) Ueyama J., Hayashi M., Hirayama M., Nishiwaki H., Ito M., Saito I., Tsuboi Y., Isobe T., Ohno K. (2023) Effects of Pesticide Intake on Gut Microbiota and Metabolites in Healthy Adults. International Journal of Environmental Research and Public Health, 20 (1), 213 (IF: 4.614)