Title of Research: 22-3-01

Prediction of internal concentrations of chemicals orally administered using data-driven pharmacokinetic modeling

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Summary of Research: To evaluate internal exposures in humans without any reference to experimental data, physiologically based pharmacokinetic (PBPK) modeling could be used. The input parameters for PBPK models (i.e., fraction absorbed x intestinal availability, absorption rate constants, volumes of the systemic circulation, and hepatic intrinsic clearances) were estimated for a panel of 355 chemicals using a light gradient boosting machine learning algorithms (LightGBM) based on between 11 and 29 *in silico*-calculated chemical descriptors. Parameters for human PBPK models for a diverse range of compounds could be successfully estimated using chemical descriptors. This approach to pharmacokinetic modeling has potential for application in computational toxicology and in the clinical setting for assessing the potential risk of general chemicals.

Timeline: From March 1, 2022 to February 28, 2023

Topics: The principal Investigator has been the recipient of Scientific Achievement Award from the International Society of Study of Xenobiotics (ISSX) for major contributions to the field of xenobiotics in the Asia Pacific Region (Bangalore, India, 2023).

Publications:

(1) Adachi, K., Shimizu, M., and Yamazaki, H. (2022) Updated *in Silico* Prediction Methods for Fractions Absorbed and Key Input Parameters of 355 Disparate Chemicals for Physiologically Based Pharmacokinetic Models for Time-Dependent Plasma Concentrations after Virtual Oral Doses in Humans. *Biol Pharm Bull 45*, 1812-1817.
(2) Kamiya, Y., Handa, K., Miura, T., Ohori, J., Kato, A., Shimizu, M., Kitajima, M., and Yamazaki, H. (2022) Machine Learning Prediction of the Three Main Input Parameters of a Simplified Physiologically Based Pharmacokinetic Model Subsequently Used to Generate Time-Dependent Plasma Concentration Data in Humans after Oral Doses of 212 Disparate Chemicals. *Biol Pharm Bull 45*, 124-128.
(3) Shimizu, M., Hayasaka, R., Kamiya, Y., and Yamazaki, H. (2022) Trivariate Linear Regression and Machine Learning Prediction of Possible Roles of Efflux Transporters in Estimated Intestinal Permeability Values of 301 Disparate Chemicals. *Biol Pharm Bull 45*, 1142-1157.
(4) Kamiya, Y., Handa, K., Miura, T., Ohori, J., Shimizu, M., Kitajima, M., Shono, F., Funatsu, K., and Yamazaki, H. (2022) Correction to "An Updated In Silico Prediction Method for Volumes of Systemic Circulation of 323 Disparate Chemicals for Use in Physiologically Based Pharmacokinetic Models to Estimate Plasma and Tissue Concentrations after Oral Doses in Rats". *Chem Res Toxicol 35*, 1433.
(5) Adachi, K., Shimizu, M., and Yamazaki, H. (2022) Updated in silico prediction methods for fractions absorbed and absorption rate constants of 372 disparate chemicals for use in physiologically based pharmacokinetic models for estimating internal concentrations in rats. *J Toxicol Sci 47*, 453-456.
(6) Miura, T., Uehara, S., Shimizu, M., Suemizu, H., and Yamazaki, H. (2022) Forward and reverse dosimetry for aniline and 2,6-dimethylaniline in humans extrapolated from humanized-liver mouse data using simplified physiologically based pharmacokinetic models. *J Toxicol Sci 47*, 531-538.