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: Physiologically based pharmacokinetic (PBPK) modelling can be used to evaluate internal exposure in humans without any reference to experimental data. The input parameters for PBPK models (i.e., fraction absorbed × intestinal availability, absorption rate constants, volumes of the systemic circulation, and hepatic intrinsic clearances) were estimated for a panel of ~350 chemicals using a light gradient boosting machine learning algorithm (LightGBM) based on within 30 *silico*-calculated chemical descriptors. The parameters for the human and rat PBPK models for a diverse range of compounds were successfully estimated using chemical descriptors. Significant inverse relationships between the hepatic/plasma concentrations of selected lipophilic food chemicals using forward dosimetry and reported rat hepatic lowest-observed-effect level (LOEL) values were observed. The output values from rat pharmacokinetic models based on *in silico* liver-to-plasma partition coefficient values derived from the primary Poulin and Theil model can be used to estimate toxicokinetics or internal exposure to substances. This approach to pharmacokinetic modeling has the potential for application in computational toxicology and in the clinical setting for assessing the potential risk of general chemicals.

Timeline: From March 1, 2023 to February 29, 2024

Publications:

1) Adachi K, Nakano H, Sato T, Shimizu M, Yamazaki H. Liver and Plasma Concentrations of Food Chemicals after Virtual Oral Doses Extrapolated Using in Silico Estimated Input Pharmacokinetic Parameters to Confirm Reported Liver Toxicity in Rats. *Biol Pharm Bull*, **46**, 1133-1140 (2023).
2) Adachi K, Ohyama K, Tanaka Y, Nakano H, Sato T, Murayama N, Shimizu M, Saito Y, Yamazaki H. Plasma and Hepatic Exposures of Celecoxib and Diclofenac Prescribed Alone in Patients with Cytochrome *P450 2C9*3* Modeled after Virtual Oral Administrations and Likely Associated with Adverse Drug Events Reported in a Japanese Database. *Biol Pharm Bull*, **46**, 856-863 (2023).
3) Adachi K, Utsumi M, Sato T, Nakano H, Shimizu M, Yamazaki H. Modeled Rat Hepatic and Plasma Concentrations of Chemicals after Virtual Administrations Using Two Sets of in Silico Liver-to-Plasma Partition Coefficients. *Biol Pharm Bull*, **46**, 1316-1323 (2023).
4) Adachi K, Ohyama K, Tanaka Y, Sato T, Murayama N, Shimizu M, Saito Y, Yamazaki H. High hepatic and plasma exposures of atorvastatin in subjects harboring impaired cytochrome *P450 3A4*16* modeled after virtual administrations and possibly associated with statin intolerance found in the Japanese adverse drug event report database. *Drug Metab Pharmacokinet*, **49**, 100486 (2023).
5) Shimizu M, Uehara S, Ohyama K, Nishimura H, Tanaka Y, Saito Y, Suemizu H, Yoshida S, Yamazaki H. Pharmacokinetic Models Scaled-up from Humanized-liver Mouse Data Can Account for Drug Monitoring Results of Atomoxetine and Its 4-Hydroxylated and N-Demethylated Metabolites in Pediatric Patients Genotyped for Cytochrome *P450 2D6*. *Drug Metab Dispos*, **52**, 35-43 (2024).