Title of Research:

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Human physiologically-based pharmacokinetic modeling of industrial chemicals with chimeric mice with humanized liver

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Summary of Research: A simplified physiologically based pharmacokinetic (PBPK) model was defined in humans based on metabolic parameters determined experimentally *in vitro* and/or *in vivo* and physiological parameters derived from the literature. In this study, the PBPK model basically consists of a chemical absorption compartment, a metabolizing compartment, and a central compartment for a wide of academic, regulatory, and industrial users. Test chemicals and primary metabolites, organophosphorus pesticides acephate and chlorpyrifos, herbicidal carbamate molinate, di(2-ethylhexyl)phthalate, and bisphenol A were evaluated in human bodies by the present PBPK modeling. Using humanized-liver mice, in which the liver has been repopulated with human hepatocytes is one of the challenge for evaluation of species differences. In order to overcome limitation of available human hepatocytes, the human hepatic cell line HepaRG were evaluated as promising donor cells for liver reconstitution in the TK-NOG mouse model. Taken together, the utility of this simplified PBPK model with humanized mice could be also expanded to the industry researchers and regulatory authorities to investigate a variety of chemicals.

Timeline: From November 1, 2013 to February 28, 2015

Topics: The principal Investigator was awarded by Japanese Society for the Study of Xenobiotics.

Publications:

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4. H. Suemizu, S. Sota, M. Kuronuma, M. Shimizu, and H. Yamazaki. Pharmacokinetics and effects on serum cholinesterase activities of organophosphorus pesticides acephate and chlorpyrifos in chimeric mice transplanted with human hepatocytes. *Regul.Toxicol.Pharmacol.* 70:468-473, 2014.
5. K. Adachi, H. Suemizu, N. Murayama, M. Shimizu, and H. Yamazaki. Human biofluid concentrations of mono(2-ethylhexyl)phthalate extrapolated from pharmacokinetics in chimeric mice with humanized liver administered with di(2-ethylhexyl)phthalate and physiologically based pharmacokinetic modeling. *Environ.Toxicol.Pharmacol.* in press (doi:10.1016/j.etap.2015.02.011)
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