Title of Research:

12_S01-02

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, melengestrol acetate (animal drug) and molinate (pesticide), were multi-dosed apparently accumulated 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.

Timeline: November 1, 2012 –

Topics:

An invited presentation in 2013 ICCA-LRI & NCATS Workshop, “What Is Normal? Implications for Chemical Safety Assessment”, Santa Fe, New Mexico, USA

Publications:

Y. Higuchi, K. Kawai, H. Yamazaki, M. Nakamura, F. Bree, C. Guillouzo, and H. Suemizu. The human hepatic cell line HepaRG cells, possible cell source for steady generation of humanized liver TK-NOG mice. *Xenobiotica,* in press (doi:10.3109/00498254.2013.836257)

A. Tsukada, H. Suemizu, N. Murayama, R. Takano, M. Shimizu, M. Nakamura, and H. Yamazaki. Plasma concentrations of melengestrol acetate in humans extrapolated from the pharmacokinetics established in in vivo experiments with rats and chimeric mice with humanized liver and physiologically based pharmacokinetic modeling. *Regul.Toxicol.Pharmacol.* 65:316-324, 2013.

H. Yamazaki, H. Suemizu, N. Murayama, M. Utoh, N. Shibata, M. Nakamura, and F. P. Guengerich. *In vivo* drug interactions of the teratogen thalidomide with midazolam: Heterotropic cooperativity of human cytochrome P450 in humanized TK-NOG mice. *Chem.Res.Toxicol.* 26:486-489, 2013.