

Supplementary Table 3. Publications on DMPK and liver toxicity using humanized mouse/cells

Category	No. of papers	Compound/ Drug	PXB-mouse	FRG mouse	TK-NOG mouse	uPA/SCID mouse (BE)*	PXB-cells	Publications
ADME	48	Butyrylfentanyl					O	Kanamori T, et al. Metabolism of Butyrylfentanyl in Fresh Human Hepatocytes: Chemical Synthesis of Authentic Metabolite Standards for Definitive Identification. <i>Biol Pharm Bull.</i> 2019;42(4):623-630.
		Dibutyl Phthalate			O			Miura T, et al. Steady-State Human Pharmacokinetics of Monobutyl Phthalate Predicted by Physiologically Based Pharmacokinetic Modeling Using Single-Dose Data from Humanized-Liver Mice Orally Administered with Dibutyl Phthalate. <i>Chem Res Toxicol.</i> 2019 Feb 18;32(2):333-340.
		diisononyl phthalate			O			Iwata H, et al. Predictability of human pharmacokinetics of diisononyl phthalate (DINP) using chimeric mice with humanized liver. <i>Xenobiotica.</i> 2019 Nov;49(11):1311-1322.
		Diclofenac, ketoprofen, nicardipine, pravastatin, salbutamol, warfarin, Acetaminophen, antipyrine, digitoxin, ibuprofen, itraconazole, naproxen, nifedipine, nitrendipine, phenytoin, zolpidem, Amiodarone and fexofenadine	O					Nakayama K, et al. Prediction of human pharmacokinetics of typical compounds by a physiologically based method using chimeric mice with humanized liver. <i>Xenobiotica.</i> 2019 Apr;49(4):404-414.
		amiodarone, aripiprazole, chlorthalidone, gavestinel, mefloquine, pazopanib, phenobarbital, probucol, pyrimethamine, tamoxifen, UCN-01, warfarin, compound A, compound B.	O					Miyamoto M, et al. Prediction of human pharmacokinetics of long half-life compounds using chimeric mice with humanised liver. <i>Xenobiotica.</i> 2019 Dec;49(12):1379-1387.
		fenclozic acid	O					Ekdahl A, et al. The metabolic fate of fenclozic acid in chimeric mice with a humanized liver. <i>Arch Toxicol.</i> 2018 Sep;92(9):2819-2828.
		fentanyl, acetylfentanyl					O	Kanamori T, et al. Use of hepatocytes isolated from a liver-humanized mouse for studies on the metabolism of drugs: application to the metabolism of fentanyl and acetylfentanyl. <i>Forensic Toxicol.</i> 2018;36(2):467-475.
		Benzylamine			O			Yamazaki-Nishioka M, et al. Human Plasma Metabolic Profiles of Benzydamine, a Flavin-containing Monooxygenase Probe Substrate, Simulated with Pharmacokinetic Data from Control and Humanized-liver Mice. <i>Xenobiotica.</i> 2018 Feb;48(2):117-123.
		organophosphate or carbamate			O			Suemizu H, et al. Chimeric Mice with Humanized Liver as a Model for Testing Organophosphate and Carbamate Pesticide Exposure. <i>Pest Manag Sci.</i> 2018 Jun;74(6):1424-1430.
		Diisononyl phthalate			O			Miura T, et al. Human urinary concentrations of monoisononyl phthalate estimated using physiologically based pharmacokinetic modeling and experimental pharmacokinetics in humanized-liver mice orally administered with diisononyl phthalate. <i>Xenobiotica.</i> 2018 May 18:1-8.

Diclofenac		O			Wilson CE, et al. The pharmacokinetics and metabolism of diclofenac in chimeric humanized and murinized FRG mice. Arch Toxicol. 2018 Jun;92(6):1953-1967.
O ⁶ -benzylguanine, and its AOX-derived metabolite, 8-oxo-O ⁶ -benzylguanine	O				Takaoka N, et al. Inhibitory effects of drugs on the metabolic activity of mouse and human aldehyde oxidases and influence on drug-drug interactions. Biochem Pharmacol. 2018 Aug;154:28-38.
YM543	O				Nakada N. Evaluation of the Utility of Chimeric Mice with Humanized Livers for the Characterization and Profiling of the Metabolites of a Selective Inhibitor (YM543) of the Sodium-Glucose Cotransporter 2. Pharm Res. 2017 Apr;34(4):874-886.
pomalidomide			O		Shimizu M, et al. Metabolic profiles of pomalidomide in human plasma simulated with pharmacokinetic data in control and humanized-liver mice. Xenobiotica. 2017 Oct;47(10):844-848.
PF-04937319			O		Kamimura H, et al. Simulation of human plasma concentration-time profiles of the partial glucokinase activator PF-04937319 and its disproportionate N-demethylated metabolite using humanized chimeric mice and semi-physiological pharmacokinetic modeling. Xenobiotica. 2017 May;47(5):382-393. .
Lumiracoxib		O			Dickie AP, et al. The pharmacokinetics and metabolism of lumiracoxib in chimeric humanized and murinized FRG mice. Biochem Pharmacol. 2017 Jul 1;135:139-150.
Albuterol, Antipyrine, Bazedoxifene, Benzydamine, BIBX1382, Carbazeran, Clonazepam, Dapsone, Diazepam, Diclofenaac, Dolasetron, Entacapone, Fasudil, Gemcitabine, Ibuprofen, Imipramine, Indomethacin, Ketanserin, Ketoprofen, Moxifloxacin, Mycophenolic acid, Naltrexone, O ⁶ -Benzylguanine, Pefloxacin, (S)-Naproxen, Sumatriptan, Telmisartan, XK-469, Zaleplon, Zoniporide	O				Miyamoto M, et al. Comparison of predictability for human pharmacokinetics parameters among monkeys, rats, and chimeric mice with humanised liver. Xenobiotica. 2017 Dec;47(12):1052-1063.
Lu AF09535	O				Jensen KG, et al. Lack of exposure in a first-in-man study due to aldehyde oxidase metabolism: Investigated by use of 14C-microdose, humanized mice, monkey pharmacokinetics and in vitro methods. Drug Metab Dispos. 2017 Jan;45(1):68-75.
Nefazodone	O				Nakada N, et al. Murine Cyp3a knockout chimeric mice with humanized liver: prediction of the metabolic profile of nefazodone in humans. Biopharm Drug Dispos. 2016 Jan;37(1):3-14.
dimethazine				O	Geldof L, et al. In-vitro and in-vivo metabolism studies of dimethazine. Biomed Chromatogr. 2016 Aug;30(8):1202-1209.
prostanazol				O	Geldof L, et al. Metabolic studies of prostanazol with the uPA-SCID chimeric mouse model and human liver microsomes. Steroids. 2016 Mar;107:139-148.

ASP015K	O				Nakada N, et al. Identification and characterization of metabolites of ASP015K, a novel oral Janus kinase inhibitor, in rats, chimeric mice with humanized liver, and humans. <i>Xenobiotica</i> . 2015;45(9):757-765.
Thalidomide			O		Nishiyama S, et al. Simulation of Human Plasma Concentrations of Thalidomide and Primary 5-Hydroxylated Metabolites Explored with Pharmacokinetic Data in Humanized TK-NOG Mice. <i>Chem Res Toxicol</i> . 2015 Nov 16;28(11):2088-2090.
Diclofenac			O		Kamimura H, et al. Formation of the Accumulative Human Metabolite and Human-Specific Glutathione Conjugate of Diclofenac in TK-NOG Chimeric Mice with Humanized Livers. <i>Drug Metab Dispos</i> . 2015 Mar;43(3):309-316.
Diazepam, midazolam, Quinidine, repaglinide, verapamil	O				Sanoh S, et al. Predictability of plasma concentration-time curves in humans using single-species allometric scaling of chimeric mice with humanized liver. <i>Xenobiotica</i> . 2015;45(7):605-14.
SUN13834	O				Igawa Y, et al. In vitro and in vivo metabolism of a novel chymase inhibitor, SUN13834, and the predictability of human metabolism using mice with humanized liver. <i>Xenobiotica</i> . 2014 Jan;44(2):154-163.
Diclofenac	O				Bateman T, et al. Application of Chimeric Mice with Humanized Liver for Study of Human-Specific Drug Metabolism. <i>Drug Metab Dispos</i> . 2014 Jun;42(6):1055-1065.
Troglitazone		O			Samuelsson K, et al. Troglitazone metabolism and transporter effects in chimeric mice: a comparison between chimeric humanized and chimeric murinized FRG mice. <i>Xenobiotica</i> . 2014 Jan;44(2):186-195.
methylstenbolone				O	Geldof L, et al. Metabolism of methylstenbolone studied with human liver microsomes and the uPA(+)/(+)-SCID chimeric mouse model. <i>Biomed Chromatogr</i> . 2014 Jul;28(7):974-985.
zaleplon	O				Tanoue C, et al. Prediction of human metabolism of the sedative-hypnotic zaleplon using chimeric mice transplanted with human hepatocytes. <i>Xenobiotica</i> . 2013 Nov;43(11):956-962.
Clemizole			O		Nishimura T, et al. Using chimeric mice with humanized livers to predict human drug metabolism and a drug-drug interaction. <i>J Pharmacol Exp Ther</i> . 2013 Feb;344(2):388-396.
FK3453	O				Sanoh S, et al. Prediction of human metabolism of FK3453 by aldehyde oxidase using chimeric mice transplanted with human or rat hepatocytes. <i>Drug Metab Dispos</i> . 2012 Dec;40(12):2267-2272.
Ibuprofen, (S)-naproxen	O				Sanoh S, et al. Predictability of metabolism of ibuprofen and naproxen using chimeric mice with human hepatocytes. <i>Drug Metab Dispos</i> . 2012 Jan;40(1):76-82.
Midazolam	O				Samuelsson K, et al. Pharmacokinetics and metabolism of midazolam in chimeric mice with humanised livers. <i>Xenobiotica</i> . 2012 Nov;42(11):1128-1137.
Troglitazone	O				Schulz-Utermoehl T, et al. Evaluation of the pharmacokinetics, biotransformation and hepatic transporter effects of troglitazone in mice with humanized livers. <i>Xenobiotica</i> . 2012 Jun;42(6):503-517.

6-Deoxypenciclovir, mirtazapine, Dapsone, lamotrigine, salbutamol, sulindac, Diclofenac, Fasudil, (S)-Naproxen, Ibuprofen, ketoprofen, and (S)-warfarin, Zaleplon, ibuprofen, (S)-Naproxen.	O					Sanoh S, et al. Prediction of in vivo hepatic clearance and half-life of drug candidates in human using chimeric mice with humanized liver. Drug Metab Dispos. 2012 Feb;40(2):322-328.
GDC-0834	O					Liu L, et al. Significant species difference in amide hydrolysis of GDC-0834, a novel potent and selective Bruton's tyrosine kinase inhibitor. Drug Metab Dispos. 2011 Oct;39(10):1840-9.
W695634, SB-406725, GW823093	O					De Serres M, et al. Evaluation of a chimeric (uPA ^{+/+})/SCID mouse model with a humanized liver for prediction of human metabolism. Xenobiotica. 2011 Jun;41(6):464-475.
promagnon, methylclostebol and methasterone				O		Lootens L, et al. Metabolic studies with promagnon, methylclostebol and methasterone in the uPA ^{+/+} -SCID chimeric mice. J Steroid Biochem Mol Biol. 2011 Nov;127(3-5):374-381.
stanozolol				O		Pozo OJ, et al. Detection and structural investigation of metabolites of stanozolol in human urine by liquid chromatography tandem mass spectrometry. Steroids. 2009 Oct;74(10-11):837-852.
methyltestosterone				O		Pozo OJ, et al. Detection and characterization of a new metabolite of 17alpha-methyltestosterone. Drug Metab Dispos. 2009 Nov;37(11):2153-2162.
Methandienone				O		Pozo OJ, et al. Combination of liquid-chromatography tandem mass spectrometry in different scan modes with human and chimeric mouse urine for the study of steroid metabolism. Drug Test Anal. 2009 Nov;1(11-12):554-567.
4-androstene-3,17-dione				O		Lootens L, et al. The uPA ^(+/+) -SCID mouse with humanized liver as a model for in vivo metabolism of 4-androstene-3,17-dione. Drug Metab Dispos. 2009 Dec;37(12):2367-2374.
19-Norandrost-4-ene-3,17-dione				O		Lootens L, et al. Steroid metabolism in chimeric mice with humanized liver. Drug Test Anal. 2009 Nov;1(11-12):531-537.
S-warfarin	O					Inoue T, et al. CYP2C9-catalyzed metabolism of S-warfarin to 7-hydroxywarfarin in vivo and in vitro in chimeric mice with humanized liver. Drug Metab Dispos. 2008 Dec;36(12):2429-2433.
N'-methylnicotinamide	O					Kitamura S, et al. Aldehyde oxidase-catalyzed metabolism of N1-methylnicotinamide in vivo and in vitro in chimeric mice with humanized liver. Drug Metab Dispos. 2008 Jul;36(7):1202-1205.
methandienone				O		Lootens L, et al. uPA ^{+/+} -SCID mouse with humanized liver as a model for in vivo metabolism of exogenous steroids: methandienone as a case study. Clin Chem. 2009 Oct;55(10):1783-1793.
Cefmetazole	O					Okumura H, et al. Humanization of excretory pathway in chimeric mice with humanized liver. Toxicol Sci. 2007 Jun;97(2):533-538.

Drug-drug interaction (DDI)	8	Rifampicin	O				Takehara I, et al. Effect of Rifampicin on the Plasma Concentrations of Bile Acid-O-Sulfates in Monkeys and Human Liver-Transplanted Chimeric Mice With or Without Bile Flow Diversion.. J Pharm Sci. 2019 Mar 21. pii: S0022-3549(19)30170-30174.
		VPA and meropenem			O		Suzuki E, et al. Observation of Clinically Relevant Drug Interaction in Chimeric Mice with Humanized Livers: The Case of Valproic Acid and Carbapenem Antibiotics.Eur J Drug Metab Pharmacokinet. 2017 Dec;42(6):965-972.
		3-methylcholanthrene, rifampicin	O				Kakuni M, et al. Chimeric mice with humanized livers: a unique tool for in vivo and in vitro enzyme induction studies.Int J Mol Sci. 2013 Dec 20;15(1):58-74.
		clemizole			O		Nishimura T, et al. Using chimeric mice with humanized livers to predict human drug metabolism and a drug-drug interaction.J Pharmacol Exp Ther. 2013 Feb;344(2):388-396.
		TCDD	O				Uno S, et al. CYP1A1 and CYP1A2 expression: comparing 'humanized' mouse lines and wild-type mice; comparing human and mouse hepatoma-derived cell lines.Toxicol Appl Pharmacol. 2009 May 15;237(1):119-126.
		dexamethasone	O				Emoto C, et al. Non-invasive method to detect induction of CYP3A4 in chimeric mice with a humanized liver. Xenobiotica. 2008 Mar;38(3):239-248.
		beta-naphthoflavone, rifampicin				O	Nishimura M, et al. Induction of human CYP1A2 and CYP3A4 in primary culture of hepatocytes from chimeric mice with humanized liver.Drug Metab Pharmacokinet. 2005 Apr;20(2):121-126.
		3-methylcholanthrene, rifampicin	O				Tateno C, et al. Near completely humanized liver in mice shows human-type metabolic responses to drugs.Am J Pathol. 2004 Sep;165(3):901-912.
Liver toxicity	24	ENU and aflatoxin B1	O				Tateno C, et al. Chimeric mice with human hepatocytes: A new system for genotoxicity studies. Mutat Res. 2019 Mar;839:9-12.
		antibody against TRAIL-receptor 2/death receptor 5	O				Nihira K, et al. Chimeric mice with humanized livers demonstrate human-specific hepatotoxicity caused by a therapeutic antibody against TRAIL-receptor 2/death receptor 5. Toxicol Sci. 2019 Jan 1;167(1):190-201. .
		styrene			O		Miura T, et al. Human plasma and liver concentrations of styrene estimated by combining a simple physiologically based pharmacokinetic model with rodent data. J Toxicol Sci. 2019;44(8):543-548.
		Ketoconazole or Rifampicin	O				Sanoh S, et al. Changes in Bile Acid Concentrations after Administration of Ketoconazole or Rifampicin to Chimeric Mice with Humanized Liver. Biol Pharm Bull. 2019;42(8):1366-1375.
		fungicide procymidone	O				Tomigahara Y, et al. Lack of human relevance for procymidone's developmental toxicity attributable to species difference in its kinetics and metabolism. J Pestic Sci. 2018 May 20;43(2):114-123.
		fenofibrate	O				de la Rosa Rodriguez MA, et al. The whole transcriptome effects of the PPARalpha agonist fenofibrate on livers of hepatocyte humanized mice. BMC Genomics. 2018 Jun 7;19(1):443.
		trimethylamine			O		Shimizu M,et al. Human plasma concentrations of trimethylamine N-oxide extrapolated using pharmacokinetic modeling based on metabolic profiles of deuterium-labeled trimethylamine in humanized-liver mice. J Toxicol Sci. 2018;43(6):387-393.

lenalidomide			O		Murayama N, et al. Association of pharmacokinetic profiles of lenalidomide in human plasma simulated using pharmacokinetic data in humanized-liver mice with liver toxicity detected by human serum albumin RNA. J Toxicol Sci. 2018;43(6):369-375.
miodarone	O				Sanoh S, et al. Assessment of amiodarone-induced phospholipidosis in chimeric mice with a humanized liver. J Toxicol Sci. 2017;42(5):589-596.
momfluorothrin, metofluthrin, Z-CMCA, NaPB	O				Okuda Y, et al. Evaluation of the human relevance of the constitutive androstane receptor-mediated mode of action for rat hepatocellular tumor formation by the synthetic pyrethroid momfluorothrin. J Toxicol Sci. 2017;42(6):773-788.
phenobarbital	O				Ohara A, et al. Candidate genes responsible for early key events of phenobarbital-promoted mouse hepatocellular tumorigenesis based on differentiation of regulating genes between wild type mice and humanized chimeric mice. Toxicol Res (Camb). 2017 Aug 24;6(6):795-813.
1,2-dichloropropane	O				Toyoda Y, et al. Halogenated hydrocarbon solvent-related cholangiocarcinoma risk: biliary excretion of glutathione conjugates of 1,2-dichloropropane evidenced by untargeted metabolomics analysis. Sci Rep. 2016 Apr 18;6:24586.
troglitazone and flutamide	O				Yamazaki H, et al. Zone analysis by two-dimensional electrophoresis with accelerator mass spectrometry of in vivo protein bindings of idiosyncratic hepatotoxicants troglitazone and flutamide bioactivated in chimeric mice with humanized liver. Toxicol. Res., 2015, 4:106–111
Fenofibrate	O				Tateno C, et al. Chimeric Mice with Hepatocyte-humanized Liver as an Appropriate Model to Study Human Peroxisome Proliferator-activated Receptor-alpha. Toxicol Pathol. 2015 Feb;43(2):233-248.
bosentan			O		Xu D, et al. Chimeric TK-NOG Mice: A Predictive Model for Cholestatic Human Liver Toxicity. J Pharmacol Exp Ther. 2015 Feb;352(2):274-280.
furosemide			O		Xu D, et al. Humanized TK-NOG mice can be used to identify drugs that cause animal-specific hepatotoxicity: a case study with furosemide. J Pharmacol Exp Ther. 2015 Jul;354(1):73-78.
Phenobarbital	O				Yamada T, et al. Human Hepatocytes Support the Hypertrophic but not the Hyperplastic Response to the Murine Nongenotoxic Hepatocarcinogen Sodium Phenobarbital in an In Vivo Study Using a Chimeric Mouse with Humanized Liver. Toxicol Sci. 2014 Nov;142(1):137-157.
troglitazone	O				Barnes AJ, et al. Endogenous and xenobiotic metabolite profiling of liver extracts from SCID and chimeric humanized mice following repeated oral administration of troglitazone. Xenobiotica. 2014 Jan;44(2):174-185.
troglitazone	O				Kakuni M, et al. Chimeric mice with a humanized liver as an animal model of troglitazone-induced liver injury. Toxicol Lett. 2012 Oct 2;214(1):9-18.
troglitazone	O				Foster JR, et al. Differential effect of troglitazone on the human bile acid transporters, MRP2 and BSEP, in the PXB hepatic chimeric mouse. Toxicol Pathol. 2012 Dec;40(8):1106-1116.
5-n-butyl-pyrazolo[1,5-a]pyrimidine	O				Yamazaki H, et al. Approach for in vivo protein binding of 5-n-butyl-pyrazolo[1,5-a]pyrimidine bioactivated in chimeric mice with humanized liver by two-dimensional electrophoresis with accelerator mass spectrometry. Chem Res Toxicol. 2010 Jan;23(1):152-158.
acetaminophen	O				Sato Y, et al. Human hepatocytes can repopulate mouse liver: histopathology of the liver in human hepatocyte-transplanted chimeric mice and toxicologic responses to acetaminophen. Toxicol Pathol. 2008 Jun;36(4):581-591.

		acetaminophen	O					Yamamoto T, et al. Evaluation of human hepatocyte chimeric mice as a model for toxicological investigation using panomic approaches--effect of acetaminophen on the expression profiles of proteins and endogenous metabolites in liver, plasma and urine. J Toxicol Sci. 2007 Aug;32(3):205-215.
		bezafibrate	O					Shoda J, et al. Bezafibrate induces multidrug-resistance P-Glycoprotein 3 expression in cultured human hepatocytes and humanized livers of chimeric mice. Hepatol Res. 2007 Jul;37(7):548-556.

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