Predictive performance of physiologically based kinetic (PBK) models based on *in silico*/*in vitro* to *in vivo* extrapolation (IS/IVIVE)

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PURPOSE

- The applicability of PBK modelling in next generation risk assessment (NGRA) hinges on accurate prediction of human plasma concentrations without reliance on animal *in vivo* kinetics data.
- IS/IVIVE approach illuminates the influence of various input strategies on PBK model prediction accuracy.
- Use the approach to estimate daily dose fold errors of these chemicals in humans.

OBJECTIVES

- PBK modelling of *in vitro* derived human data for 20 Toxcast [1,2] compounds (see Table 1) related to:
  - Intrinsic hepatic clearance (CL_{int})
  - Fraction unbound plasma (f_{up})
- Compare oral predicted plasma exposure against reported human exposure data

METHODS

- Use ADMET Predictor®[3] machine learning models to estimate physicochemical and biopharmaceutical properties.
- Implement human PBK models for oral dose in GastroPlus®[3] using reported f_{up} data[1,2].
- Evaluate 3 clearance parameters (**Figure 1**) to estimate *in vivo* chemical exposure:
  - *1: in silico* predicted human liver microsomal (HLM) clearance ($Cl_{in\ silico\ HLM}$)
  - 2: *in silico* predicted Hepatocyte (Hep) clearance ($Cl_{in\ silico\ Hepatocyte}$)
  - 3. *in vitro* hepatocyte Cl_{int} [1,2] ($Cl_{in\ vitro}$)

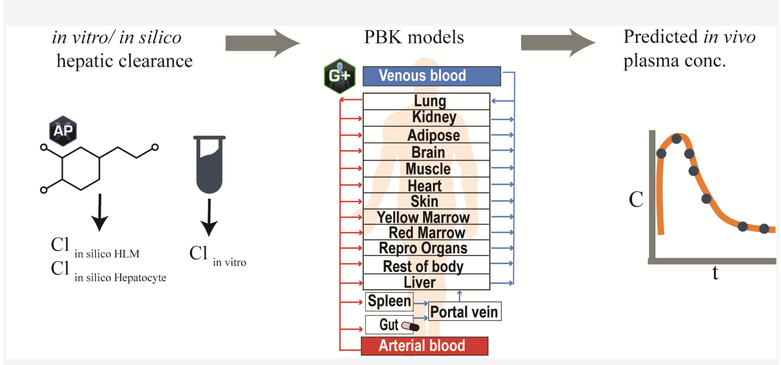

Figure 1: Graphical representation of the workflow

RESULTS

Table 1. Chemical-specific input data applied for PBK modelling of 20 chemicals using ADMET Predictor and GastroPlus are depicted. The Predicted/Observed ratios of systemic exposures (AUC [ug.h/ml]) and maximum concentration (C_{max} [ug/ml]) for all 20 chemicals using the three approaches are summarized in **Figure 2**.

Chemical	charge	Log P[a]	Fup[b]	$Cl_{in\ vitro}$ (ul/min/10^6)[c]	Oral dose Form	Dose (mg)	Human *in vivo* PK data Reference
Acetaminophen	Neutral	0.449	100.449	2.442	IR:Suspension	1400	Critchley et al., J Clin Pharm Ther, 30 (2005)
5,5 Diphenylhydantion	Neutral	2.157	16.241	2.33	IR:Capsule	400	Brien et al., Europ J Clin Pharmacol, 9 (1975)
6-PTU	Neutral	0.918	47.361	1.323	IR:Tablet	300	Kabanda et al., J Pharm Pharmcol, 48 (1996)
Candoxatril	Acid	3.926	26.586	9.898	IR:Solution	200	Kaye et al., Xenobiotica, 27 (1997)
Coumarin	Neutral	1.855	19.224	22.24	IR:Solution	10	Lamiable et al., J Chromatogr, 620 (1993)
Diphenhydramine hydrochloride	Base	3.347	41.31	0	IR:Capsule	50	Toothaker et al., Biopharm Drug Dispos, 21 (2000)
Flutamide	Neutral	2.881	3.758	30.38	IR:Tablet	250	Anjum et al., Br J Clin Pharmacol, 47 (1999)
Lovastatin	Neutral	4.501	1.429	21.9	IR:Tablet	40	Kothare et al., Int J Clin Pharm Th, 45 (2007)
Sulfasalazine	Acid	3.112	0.5	5.16	IR:Tablet	250	Gu et al., J Chromatogr B, 879 (2011)
Triamcinolone	Neutral	0.786	73.476	2.492	IR:Tablet	16	Hochhaus et al., Pharmaceut Res, 7 (1990)
Rifampicin	Neutral	2.104	13.037	6.09	IR:Tablet	450	Rafiq et al., Int J Agric Biol, 12 (2010)
Erythromycin	Base	2.304	56.534	4.04	IR:Tablet	500	Kroboth et al., Antimocrob Agents Ch, 21 (1982)
Oxytetracycline dihydrate	Zwitterion	-1.386	37.147	0.592	IR:Tablet	500	Green et al., Europ J Clin Pharmacol, 10 (1976)
Triclosan	Neutral	5.544	0.5	118.832	IR:Solution	4	Sandborgh-Englund et al., J Toxicol Environ Health A, 69 (2006)
Thiabendazole	Neutral	2.306	13.816	0	IR:Tablet	500	Bapiro et al., Eur J Clin Pharmacol, 61 (2005)
Picloram	Acid	2.091	0.5	3.109	IR:Tablet	35	Nolan et al., Toxicol Appl Pharm, 76 (1984)
Carbaryl	Neutral	2.517	69.225	27.274	IR:Solution	70	May et al., J Pharmacol Exp Ther, 262 (1992)
2,4,D	Acid	2.679	4.82	0	IR:Solution	350	Sauerhoff et al., Toxicology, 8 (1977)
Bisphenol A	Neutral	3.655	25.708	19.29	IR:Capsule	5	Voelkel et al., Chem. Res. Toxicol., 15(2002)
Propylparaben	Neutral	2.676	7.63	38	IR:Solution	43.5	Shin et al., Envir. International, 130 (2019)

Table 1: a) Predicted by ADMET Predictor. b) Determined using a rapid equilibrium dialysis approach applying different plasma concentrations [1,2] c) Cl_{int} obtained from the substrate depletion data, corrected for unspecific protein binding [1,2] for hepatocytes.

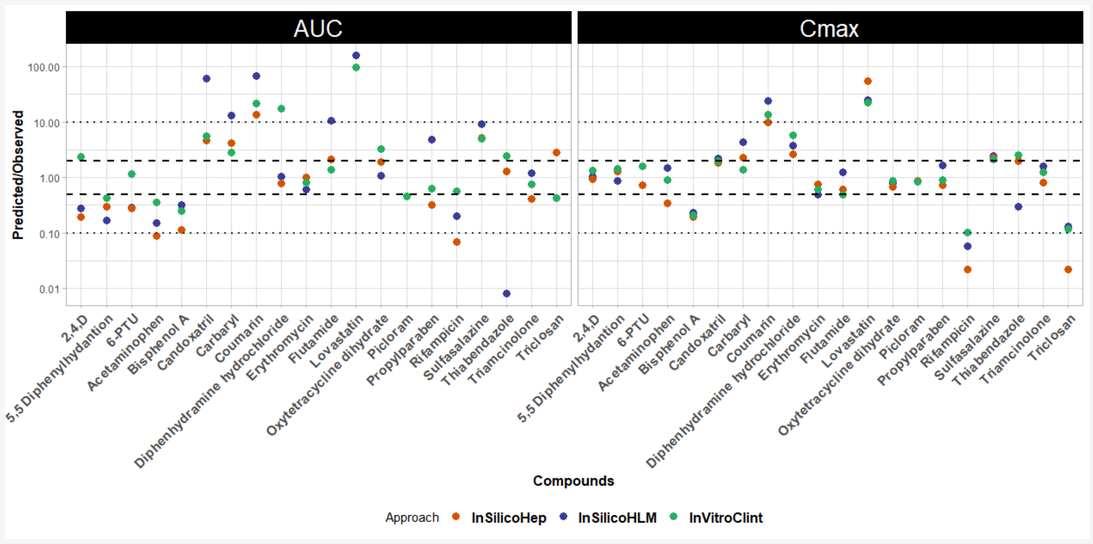

Figure 2: Predicted: observed ratios for 20 Toxcast compounds where dashed line depicts 2-fold range and dotted line represents 10-fold range for the different clearance sources

Figure 3 depicts the plasma concentrations predicted using the three different methods for selected subset of chemicals. Higher prediction errors were investigated, identifying non-hepatic clearances (e.g., active urine excretion for Picloram) and elimination via bile (e.g. Lovastatin) for the higher fold differences between predicted and measured AUC and C_{max}. Initially, picloram had a higher predicted error. The models were modified to include active urinary excretion potentially due to transport into the kidneys via OAT1.

Table 2 summarizes the number of chemicals with AUC and C_{max} predicted within 2-fold of the observed data for the 3 approaches.

Approach	AUC 2-fold	C_{max} 2-fold
1: *in silico* HLM	4	6
2: *in silico* Hep	4	11
3: *in vitro* Clint	6	11

Table 2: Number of chemicals predicted in a 2-fold range for AUC and C_{max} using the three approaches.

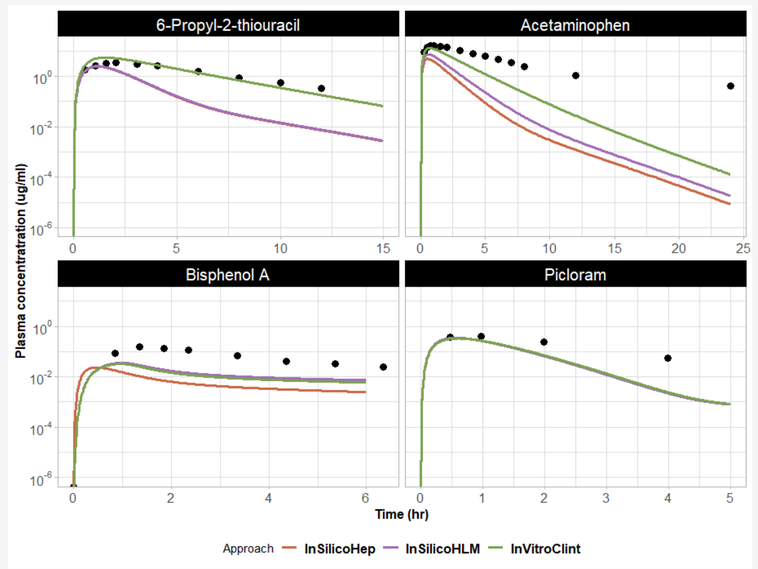

Figure 3:Predicted and observed plasma concentration time profiles for exemplary subset of chemicals.

MAIN FINDINGS AND FUTURE WORK

- Differences in internal exposure were predicted for 20 Toxcast chemicals.
- For chemicals, detailed analyses are warranted when extrapolating toxicity data. Kinetic processes related to either a reduced bioavailability or an increased volume of distribution need consideration. Some kinetics such as transporter effect and bile secretion, are not predicted from *in vitro* processes.
- Other strategies for scaling *in vitro* clearance to *in vivo* clearance will be explored
- Future work will estimate daily dose fold errors of these chemicals in rats and humans, using the lowest effective concentration (LEC) from in vitro tests to determine the in vivo dose range when feasible.

REFERENCES

1. US EPA, Wetmore et al. *Toxicol Sci*, 125(2012)
2. US EPA, Wetmore et al. *Toxicol Sci*, (2015)
3. Simulations Plus Inc., Lancaster, CA

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