Replication of PBTK Models for Bisphenol A with High-Throughput TK Models

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Concept

- High-throughput toxicokinetics can inform the regulation of thousands of untested chemicals currently in use as a new alternative method to animal testing.
- Several physiologically-based toxicokinetic (PBTK) models have been developed for Bisphenol A in human and rat.
- These models involve extra-hepatic metabolism and contain additional compartments and clearances relative to a basic TK model with parameters fit to *in vivo* data.
- In a high-throughput context, using minimal *in vitro* and *in silico* data, models such as these are not practical because of the inability to determine the necessary parameters for many chemicals.
- Here we evaluate the performance of various levels of model complexity in the prediction of BPA TK.

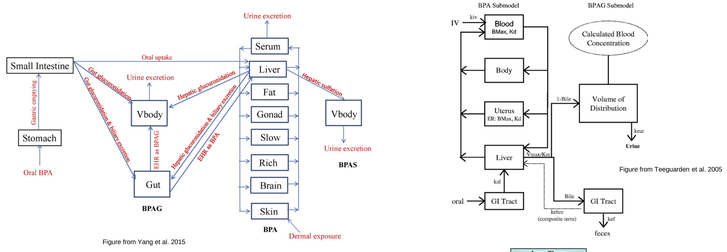
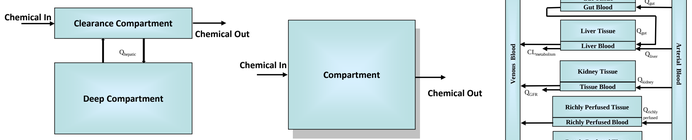


Figure from Yang et al. 2015

Figure from Teeguarden et al. 2005

EHR: enterohepatic recirculation

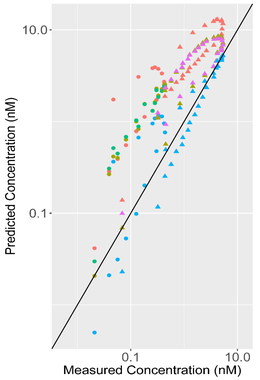


Methods

- Three models from the R package 'httk', a PBTK, 2 compartment, and 1 compartment model, were compared against 2 human and 3 rat models from the literature, all evaluated against *in vivo* data.
- Three of the rat studies used iv dosing, one simulating steady-state. The rest of the studies used oral dosing and single doses.
- Literature models were translated to code and simulated where possible.
- Root-mean-square-error (RMSE, the square root of the average squared difference in measured and predicted concentrations) and average fold error (AFE, the geometric mean of the quotient of the measured and predicted concentrations when the dividend is larger than the divisor) were used as metrics in the evaluation.
- Non-restrictive clearance was used, where the total rather than free concentration is subject to clearance.

Results

Human Evaluation

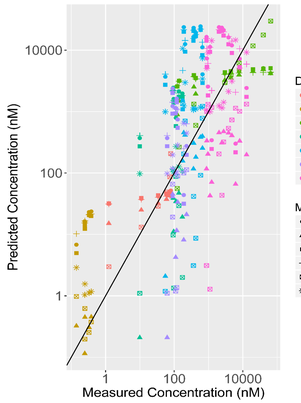


Teeguarden	1 comp.	2 comp.	pbtk	Yang 2015
AFE	6.2	5.9	8.5	2.5
RMSE (nM)	1.3	1.3	2.2	0.46
Thayer	**1 comp.**	**2 comp.**	**Pbtk**	**Yang 2015**
AFE	20	2.3	3.0	1.3
RMSE (nM)	43	2.9	5.1	0.33

- In the plot on the left, *in vivo* oral doses of 0.03 (Teeguarden) and 0.1 (Thayer) mg/kg were predicted. Parameters from the Yang et al. 2015 model were fit specifically to the higher dose.
- The measured data points in the plot below result from i.v. doses of 0.5 mg/kg given every 30 minutes. The literature model was approximated from the figure in the paper.
- In the bottom left plot, the Yang et al. 2013 and Teeguarden 2005 model fit parameters to the Doerge and Pottenger data, respectively. The pbtk model is included a second time with a clearance of Vmax/Km from Yang 2013, demonstrating the influence of clearance parameters.

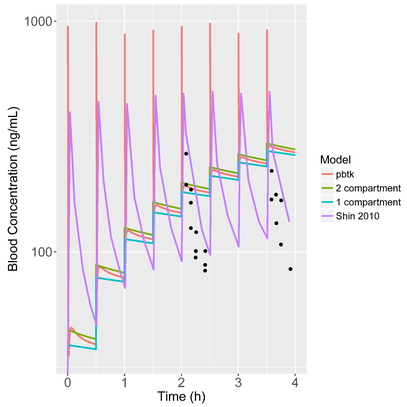
Shin Rat i.v.	1 comp.	2 comp.	pbtk	Shin
AFE	1.6	1.7	1.7	1.5
RMSE (ng/mL)	94	106	101	102

Rat Single Dose Evaluation



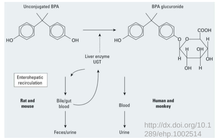
Upmeier p.o. 10 mg/kg	1 comp.	2 comp.	pbtk	Yang 2013	pbtk with Yang CL	Teeguarden
AFE	17	13	16	12	6.6	1.9
RMSE (nM)	1500	1400	1600	98	90.	79
Upmeier p.o. 100 mg/kg	**1 comp.**	**2 comp.**	**pbtk**	**Yang 2013**	**pbtk with Yang CL**	**Teeguarden**
AFE	41	27	34	7.8	2.5	6.9
RMSE (uM)	15	14	16	0.51	0.23	4.2

Rat Steady State Evaluation

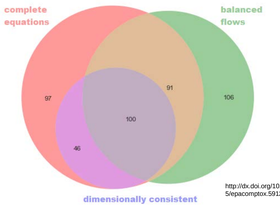


Upmeier i.v. 10 mg/kg	1 comp.	2 comp	pbtk	Yang 2013	pbtk with Yang CL
AFE	6.0	5.8	5.9	1.7	4.5
RMSE (uM)	23	22	23	13	23
Doerge i.v. 0.1 mg/kg	**1 comp.**	**2 comp**	**pbtk**	**Yang 2013**	**pbtk with Yang CL**
AFE	2.8	2.7	2.7	1.5	2.3
RMSE (nM)	27	24	24	53	22

Additional Sources of Error



- Enterohepatic recirculation is likely responsible for the changes in the effective elimination rate of the literature models, especially noticeable in rat. This requires additional modeling of the metabolites.



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- Models were not fully reproducible, due to lack of information or other problems. Many other BPA models could not be included in the analysis for this reason. Additionally, parameters were used in reproduced models not mentioned in the corresponding paper.

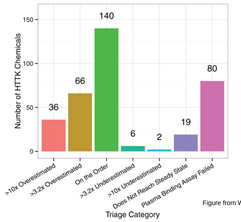

Figure from Wambaugh et al. 2015

- Wambaugh et al. 2015 predicted BPA steady state concentration to be 3.2x overpredicted using random forest, using transporters along with steady state and protein binding values as predictors.

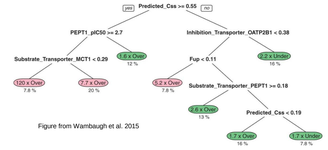

Figure from Wambaugh et al. 2015

- Compounds with very abnormal behavior such as PFOS and PFOA cannot be accurately predicted with high-throughput models.

Conclusion

- In the majority of cases, all 'httk' models predicted the *in vivo* data within an order of magnitude, with neither of the 2 compartment and pbtk models performing significantly better than the 1 compartment. Using the Yang et al. 2015 clearance value in rats, the pbtk model predicted the majority of data within a factor of 3.
- In rats, the pbtk model predicted as well as the model in Yang et al. 2013 when using the same flow-limited clearance, both having AFE of 5.1, although *in vivo* measurements sometimes differed by more than a factor of 10 at the same time point.
- A limited number of models were available for comparison due to poor reproducibility.
- Depending on the necessary level of accuracy, simpler TK models successfully make predictions using limited *in vitro* and *in silico* data, with the advantage of greater reproducibility and fewer sources for error.

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