Collaborative Evaluation of *In Silico* Predictions for High Throughput Toxicokinetics

Abstract 358

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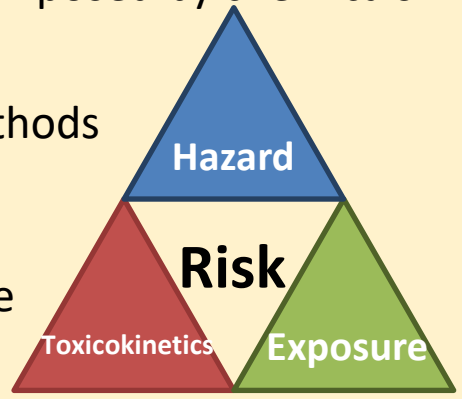
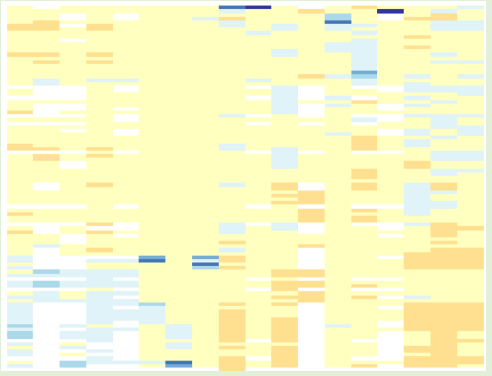
OBJECTIVES

- To understand toxicokinetics (chemical absorption, distribution, metabolism, and excretion by the body) in order to help assess public health risk posed by chemicals
- *In silico* predictions along with high throughput toxicokinetic (HTTK) methods are needed as *in vivo* and *in vitro* measurements are unavailable for thousands of chemicals in commerce and the environment



APPROACH

- This collaborative trial uses 101 chemicals with *in vivo* measured toxicokinetic (TK) data
- Six different sets of *in silico* (QSAR) tools for predicting TK were evaluated
- Predicted parameters and plasma concentrations (from generic PBTK model) were compared with empirical data



Phys-Chem and QSAR Predictions

MAIN RESULTS

- Models generally predicted consistently for *in vitro* measurements across chemicals; however, accuracies predicted for individual chemicals varied.
- When combined with a PBTK model (httk, https://cran.r-project.org/package=httk) to predict plasma concentration, the models performed similarly across all 101 chemicals (CvTdb, https://github.com/USEPA/CompTox-PK-CvTdb)

IMPACT

- Multiple QSARs exist that make comparably, and reasonably accurate predictions for *in vitro* TK parameters.
- This will allow risk-based prioritization of many thousands of chemicals without *in vitro* TK data
- **For more information, contact:**

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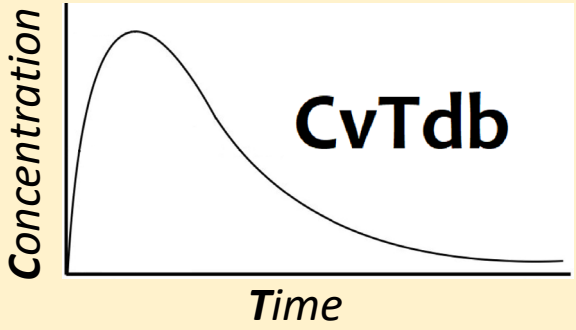
Collaborative Evaluation of *In Silico* Predictions for High Throughput Toxicokinetics

OBJECTIVES

- Four different modeling teams produced quantitative structure-activity relationship (QSAR) models for two key toxicokinetic parameters that can be measured *in vitro*: intrinsic hepatic clearance (Cl_{int} measured with hepatocyte incubations) and fraction unbound in plasma (f_{up})
- Models were evaluated for ability to reproduce the full concentration vs. time (Cvt) curve as well as summary statistics and parameters (such as half-life)
- Two additional models for chemical half-life were also evaluated



- *In vivo* plasma concentration vs. time data were available for 101 chemicals from the CvTdb (Sayre et al. 2020)
- *In vitro* measurements were available for 86 chemicals (httk v2.0.4)

Model	Team	Predictions	Mechanism	Reference
Simulations Plus ADMET Predictor®	Michael Lawless, Stephen Ferguson, Nisha Sipes, and John DiBella	Level 1 (*in vitro* parameters)	Sum of CYP-specific Artificial Neural Network (ANN)	Sipes et al. (2017)
Pradeep 2020	Prachi Pradeep, Grace Patlewicz, John Wambaugh, Richard Judson	Level 1	Random forest and support vectors method	Pradeep et al. (2020)
Dawson 2021	Daniel Dawson, John Wambaugh, Rogelio Tornero-Velez	Level 1	Random forest, clearance organized by categories	Dawson et al. (2021)
OPERA	Kamel Mansouri	Level 1	Nearest-neighbors	Mansouri et al. (2018, 2021)
IFS-QSAR	Jon Arnot, Trevor Brown, and Alessandro Sangion	Level 3 (Half-lives)	Fragment-based Multiple Linear Regressors (MRL)	Arnot et al. (2014
QSARINS-Chem	Ester Papa and Jon Arnot	Level 3	Ordinary Least Squares MLR	Papa et al. (2018)

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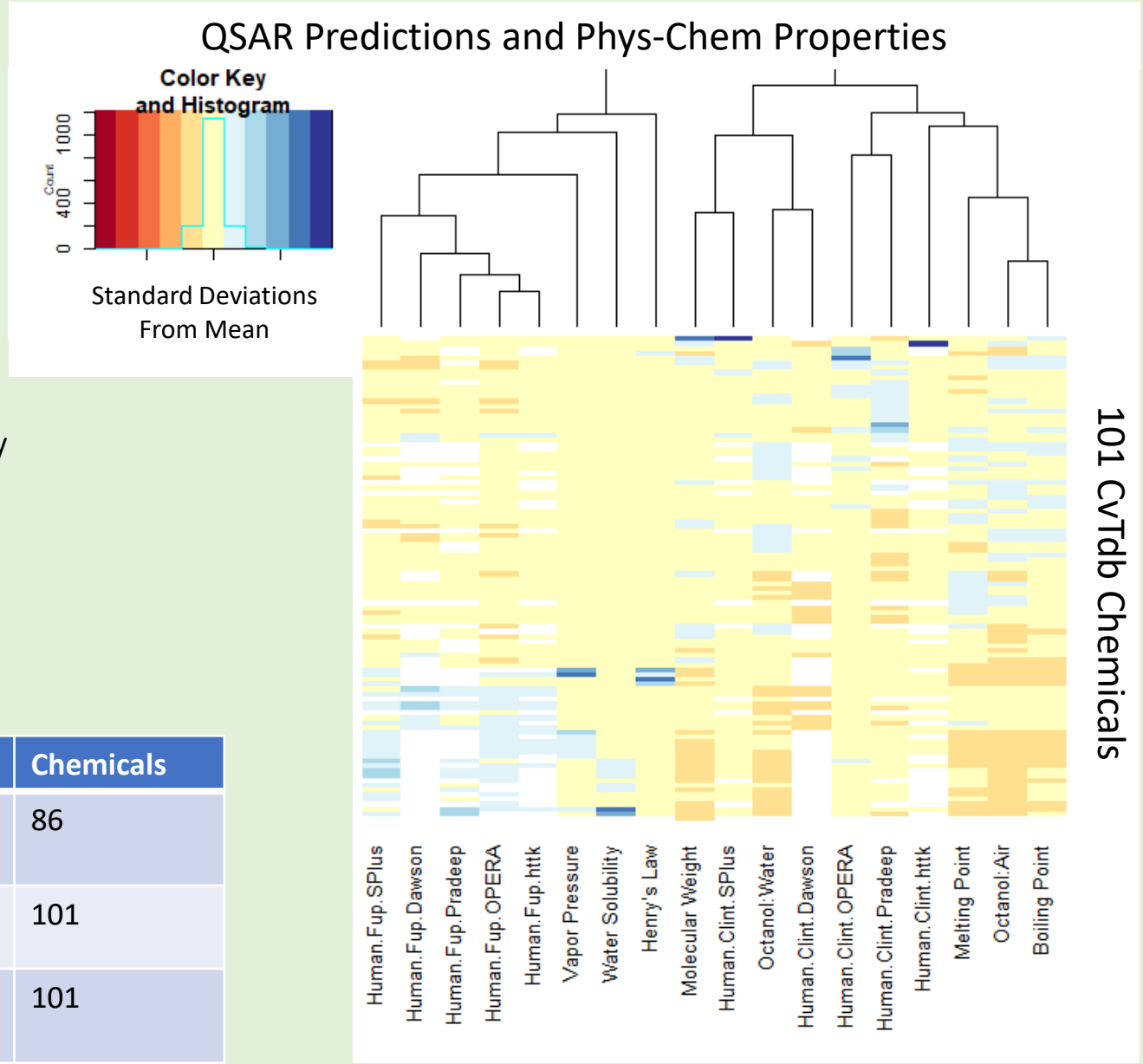
APPROACH

- R package "httk" (Pearce, 2017) can parameterize a physiologically-based toxicokinetic (PBTK) model based upon f_{up} and Cl_{int}
- For 86 of the test chemicals, *in vitro* measurements were also available for comparison
- There were 101 chemicals present in the CvTdb (Sayre, 2020) as of September 2019 that had plasma concentration data following either rat or human oral or intravenous doses
  - 57 from the Toxic Substances Control Act (TSCA) active inventory
  - 20 pharmaceuticals
  - 24 pesticides
  - 99 that are found in consumer products,
  - 7 per- and poly-fluorinated substances (PFAS)
  - 64 that are part of the ToxCast screening program
- Three levels of evaluation were performed:

Evaluation	TK Quantities	Chemicals
Level 1	*In Vitro* TK Measurements (f_{up}, Cl_{int})	86
Level 2	TK Concentration vs. Time (all points, C_{max}, time-integral/AUC)	101
Level 3	Summary Statistics (V_d, t_{half}, Cl_{tot})	101



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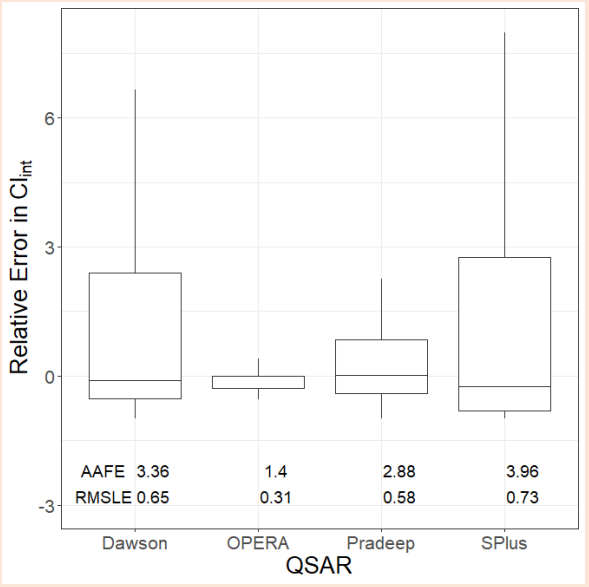
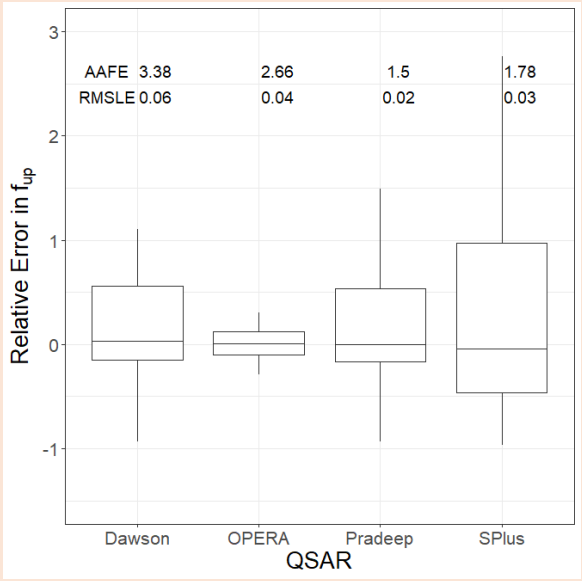
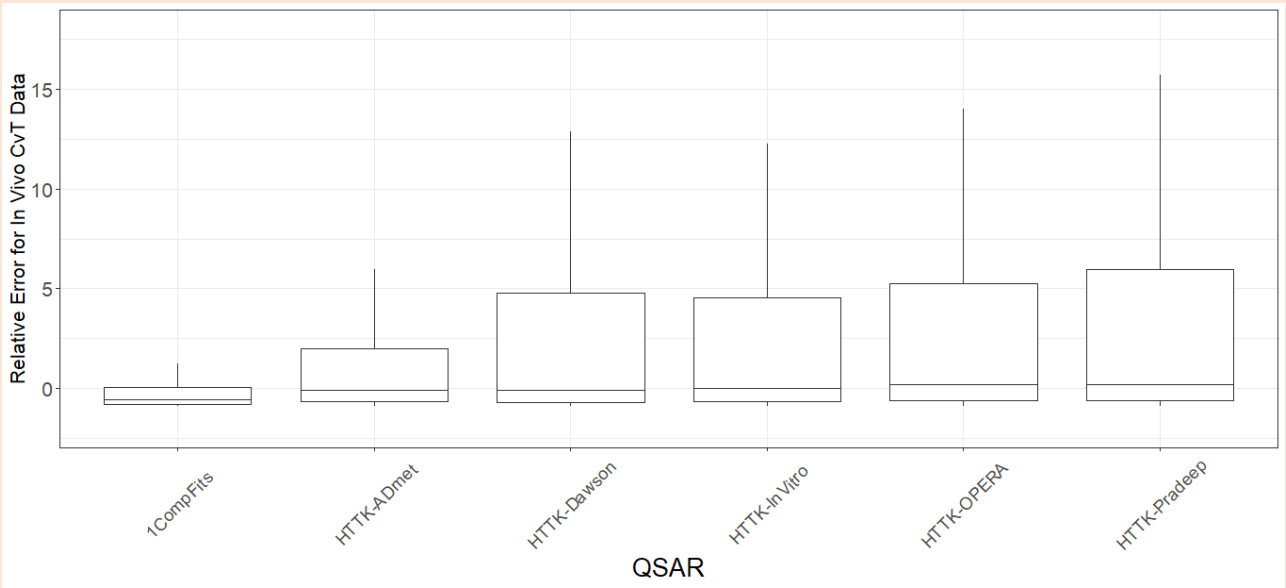
MAIN RESULTS







Models were evaluated against all chemicals based on Relative Predictive Error (RPE): $\frac{(pred-obs)}{obs}$

- Here we have evaluated all observed time points equally, neglecting phase (absorption/distribution/metabolism) and measurement accuracy. Other analyses focusing on key statistics (such as peak and time-integrated concentration) will be examined elsewhere
- Maximum likelihood 1 compartment model fits provide an estimate of ideal performance
- At left are box-and-whiskers plots showing the distribution of RPE at each observed time point across all 99 chemicals for which predictions were available (no model predicted Oxoacetic acid--water (1/1) or Nitrite)
- The upper and lower extent of the box for each model indicates the 25th to 75th quantiles, the mid-line indicates the median (50th quantile) and vertical line indicates 1.5x the range of the box.

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IMPACT/SIGNIFICANCE

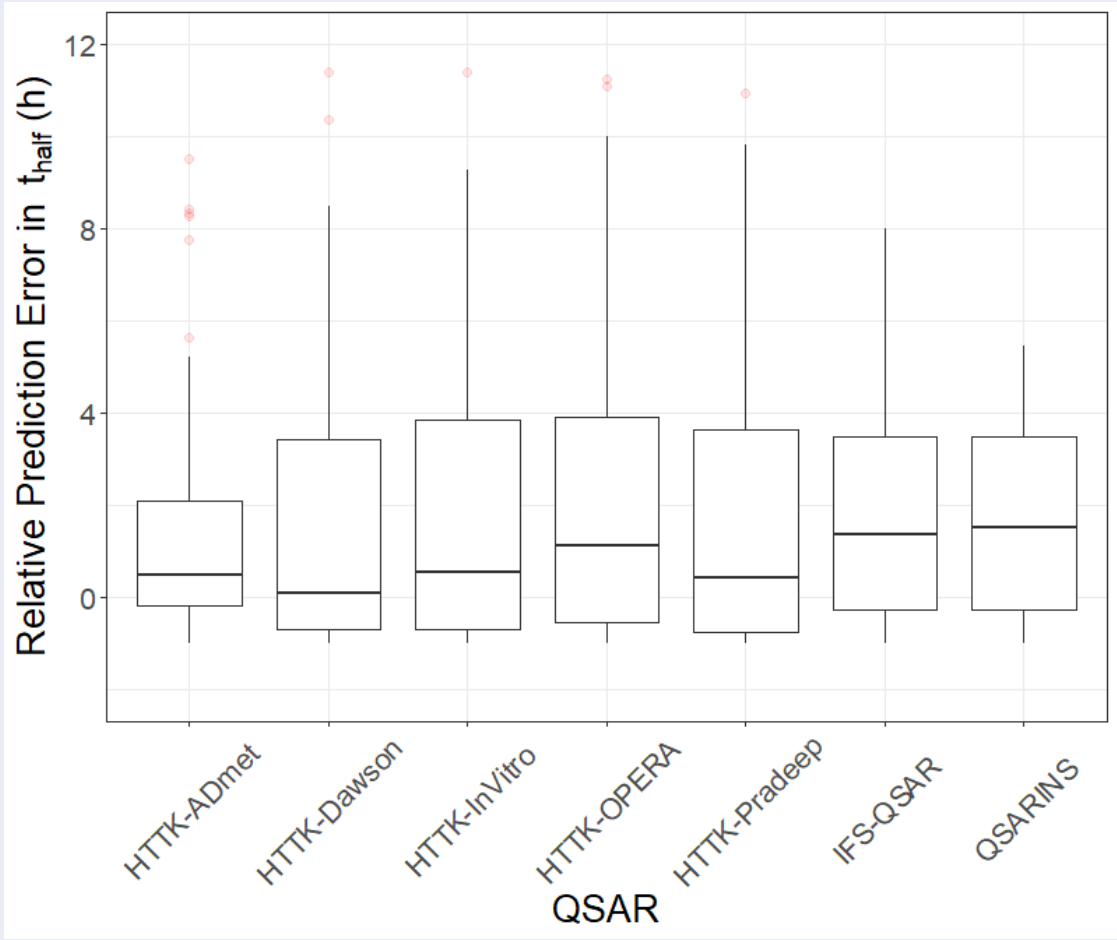
- TK information, such as elimination half-lives (t_{half}, plotted below), is critical for understanding chemical risk

- EPA is continuing to accumulate chemical-specific TK data, both:
  - *In vivo* (CvTdb, Sayre (2020))
  - *In vitro* (Wetmore (2012, 2015), Wambaugh (2019))

- However, several thousand chemicals remain in need of TK info. These QSARs provide options to fill this gap

- Overall, the HTTK PBTK model performed similarly when using TK QSARs for Cl_{int} and f_{up} as when the actual *in vitro* measured data were used ("HTTK-InVitro" in figure at right)

- These QSARs will enable public-health risk-based prioritization of chemicals in commerce and the environment



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