

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

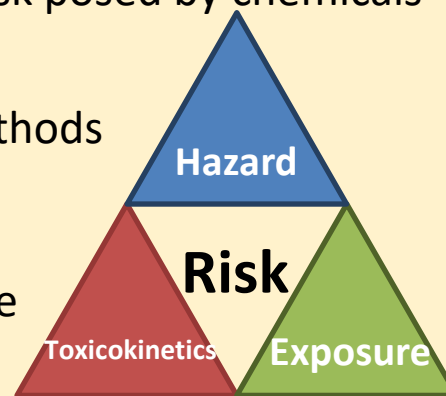
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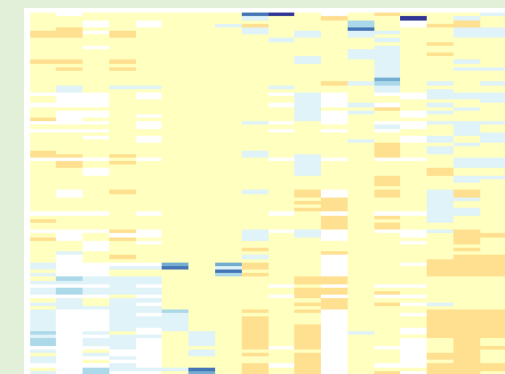
## OBJECTIVES

- We wish to understand toxicokinetics (chemical absorption, distribution, metabolism, and excretion by the body) 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 were compared with empirical data



Phys-Chem and QSAR Predictions

101 Chemicals

## MAIN RESULTS

- Model predictions for *in vitro* measurements were generally consistent across QSARs; however, accuracy varied by chemical
- 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

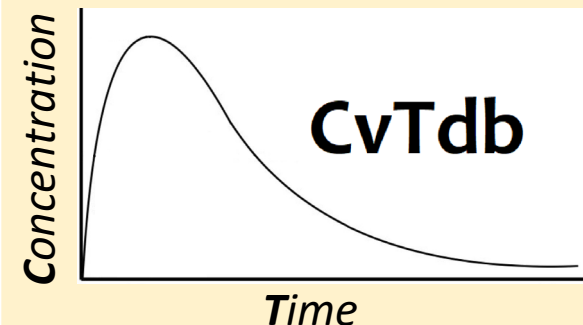
- Multiple QSARs exist that make reasonably accurate predictions for *in vitro* TK parameters
- This will provide key information for risk-based prioritization of many thousands of chemicals without either *in vivo* or *in vitro* TK data
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# Collaborative 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



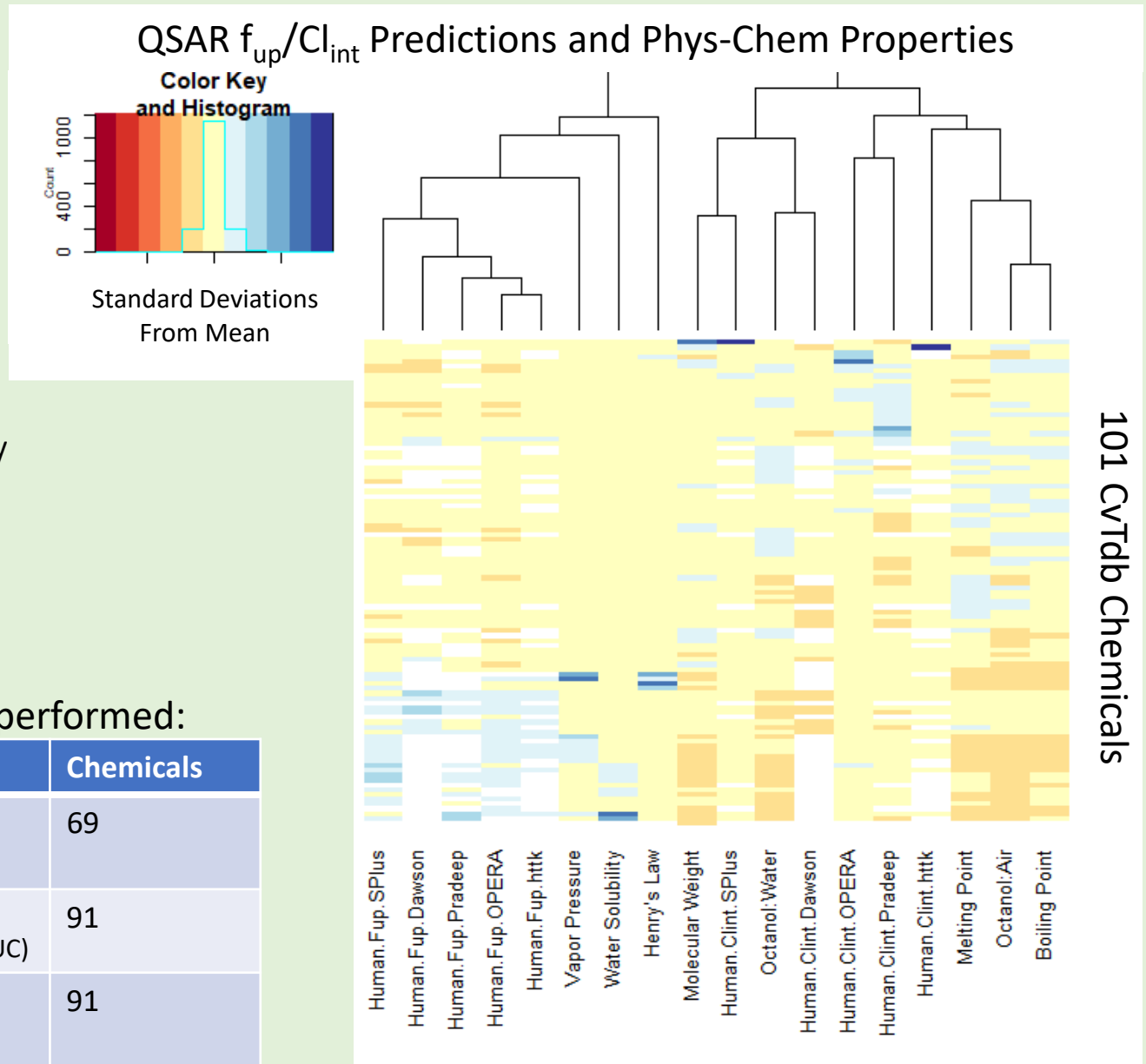
- *In vivo* plasma concentration vs. time data were available for 101 chemicals from the CvTdb (Sayre et al. 2020)
- *In vitro* measurements were available for 86 chemicals (httk v2.0.4)

Model	Team	Predictions	Mechanism	Reference
Simulations Plus ADMET Predictor®	Michael Lawless, Stephen Ferguson, Nisha Sipes, and John DiBella	Level 1 ( <i>in vitro</i> 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)

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

- R package “httk” (Pearce, 2017) can parameterize a physiologically-based toxicokinetic (PBTK) model based on chemical-specific values for  $f_{up}$  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

## APPROACH



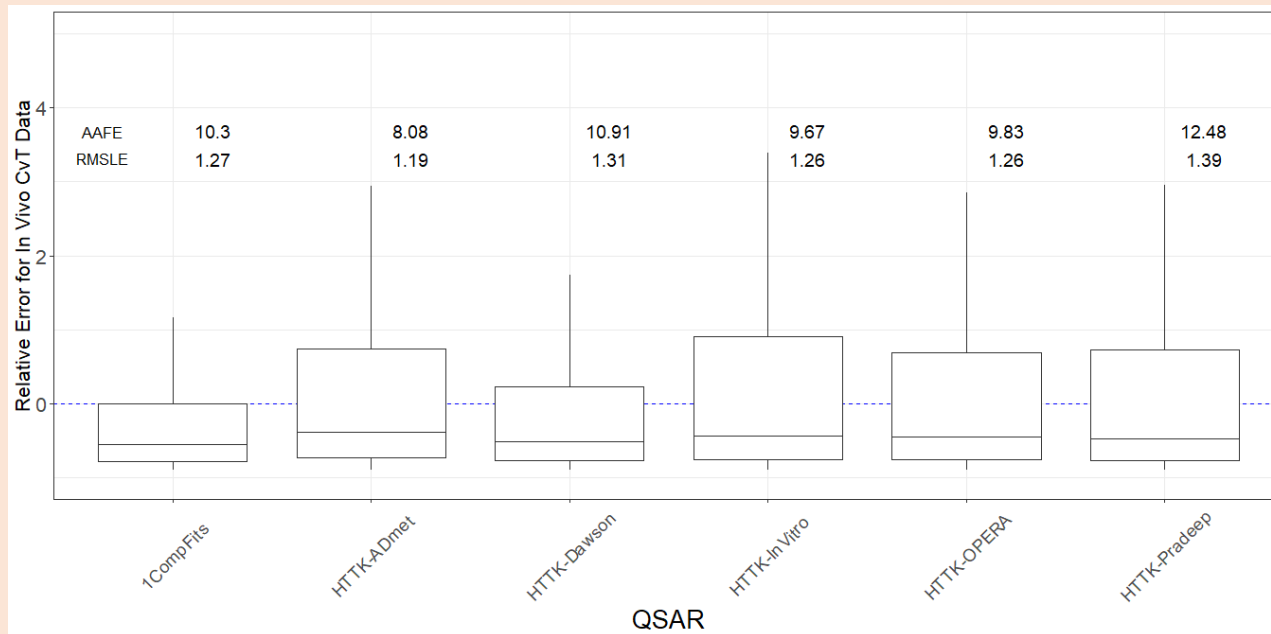
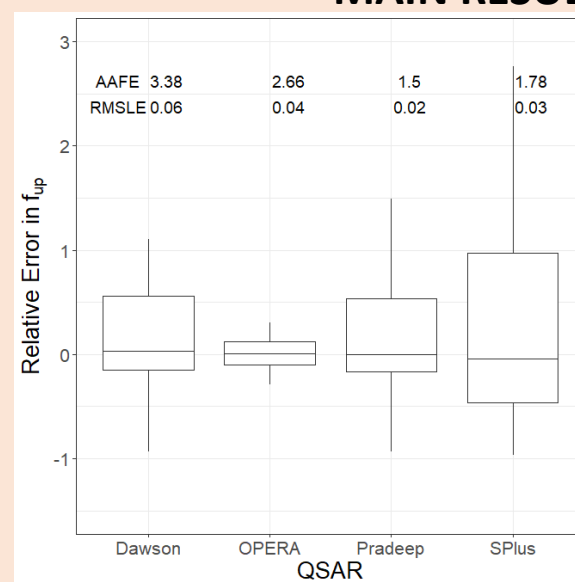
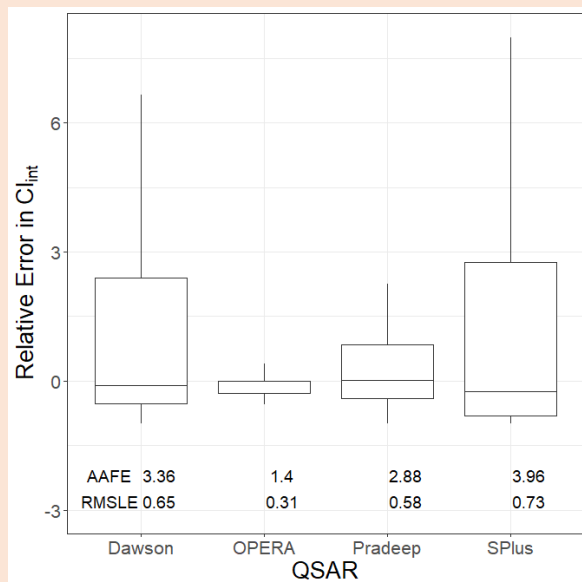
- 10 chemicals could not be predicted by most models

Three levels of evaluation were performed:

Evaluation	TK Quantities	Chemicals
Level 1	<i>In Vitro</i> TK Measurements ( $f_{up}$ , $Cl_{int}$ )	69
Level 2	TK Concentration vs. Time (all points, $C_{max}$ , time-integral/AUC)	91
Level 3	Summary Statistics ( $V_d$ , $t_{half}$ , $Cl_{tot}$ )	91

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

## MAIN RESULTS



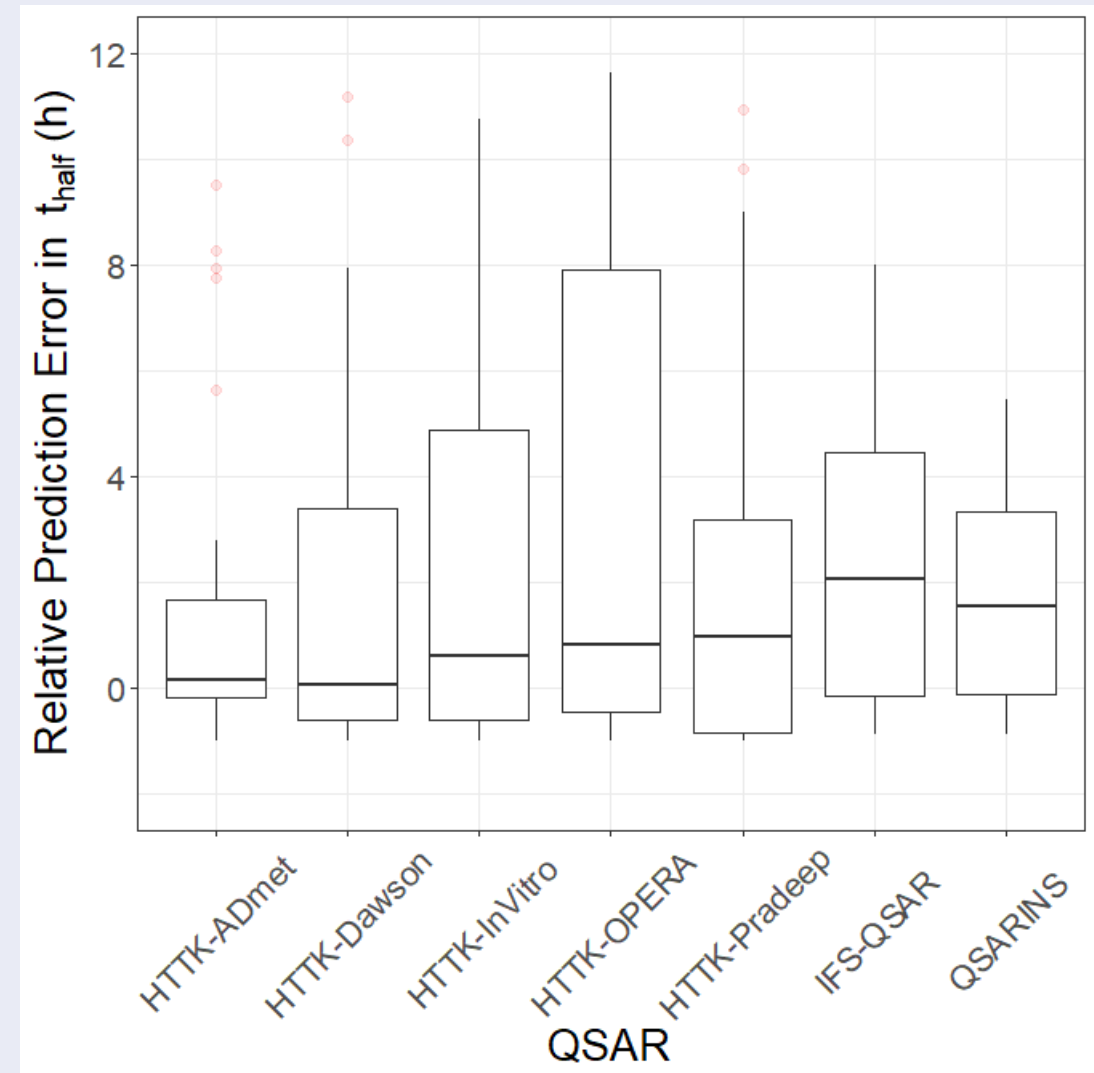
Models were evaluated against all chemicals based on Relative Predictive Error (RPE):  $\frac{pred-obs}{obs}$

- 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 empirical one-compartment model fits provide an estimate of ideal performance
- At left are box-and-whiskers plots showing the distribution of RPE 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 25<sup>th</sup> to 75<sup>th</sup> quantiles, the mid-line indicates the median (50<sup>th</sup> quantile) and vertical line indicates 1.5x the range of the box.

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

## IMPACT/SIGNIFICANCE

- TK information, such as elimination half-life ( $t_{\text{half}}$ , 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; the QSARs evaluated here provide options to fill this gap
- Overall, the HTTK PBTK model performed similarly when using TK QSARs for  $Cl_{\text{int}}$  and  $f_{\text{up}}$  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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