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

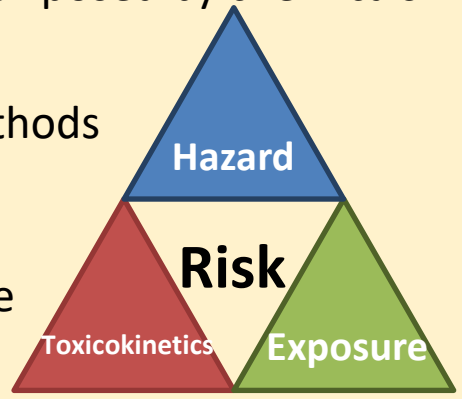
Abstract 358

John Wambaugh[1], Nisha Sipes[1], Jon Arnot[2], Trevor Brown[2], Daniel Dawson[1], Sarah Davidson[1], Michael Devito[1], John DiBella[4], Stephen Ferguson[3], Rocky Goldsmith[1], Chris Grulke[1], Richard Judson[1], Michael Lawless[4], Kamel Mansouri[5], Grace Patlewicz[1], Ester Papa[6], Prachi Pradeep[1,7], Alessandro Sangion[2], Risa Sayre[1], Rogelio Tornero-Velez[1], Barbara Wetmore[1]

1. Center for Computational Toxicology and Exposure, U.S. Environmental Protection Agency (EPA), 2. ARC Arnot Research and Consulting Inc., 3. Division of the National Toxicology Program (NTP), National Institute of Environmental Health Sciences, 4. Simulations Plus, Inc., 5. NTP Interagency Center for the Evaluation of Alternative Toxicological Methods, National Institute of Environmental Health Sciences., 6. Department of Theoretical and Applied Sciences, University of Insubria, Varese, 7. German Federal Institute for Risk Assessment (BfR)

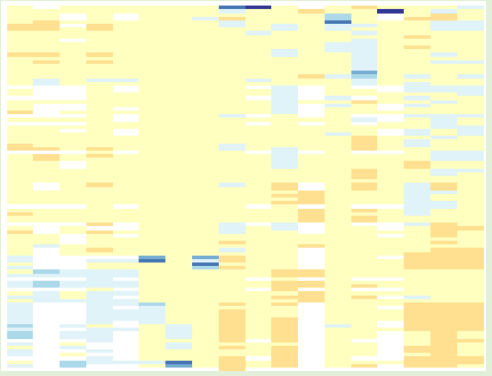
OBJECTIVES

- 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

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
- **For more information, contact:**

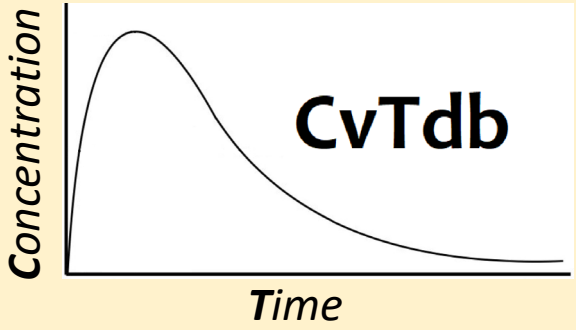
John Wambaugh (wambaugh.john@epa.gov)

http://orcid.org/0000-0002-4024-534X

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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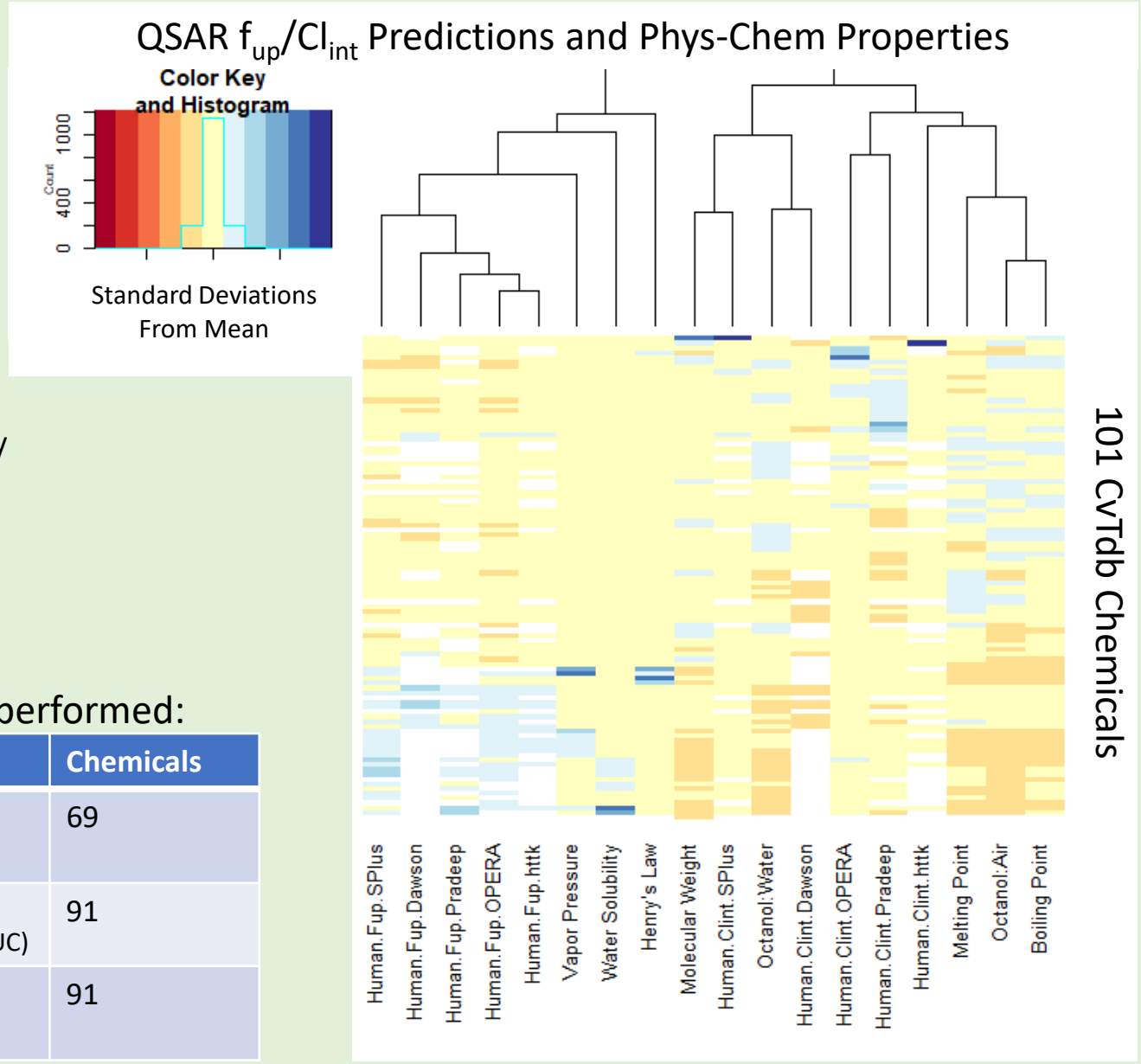
APPROACH

- R package "httk" (Pearce, 2017) can parameterize a physiologically-based toxicokinetic (PBTK) model based 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
- 10 chemicals could not be predicted by most models



Three levels of evaluation were performed:

Evaluation	TK Quantities	Chemicals
Level 1	*In Vitro* 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

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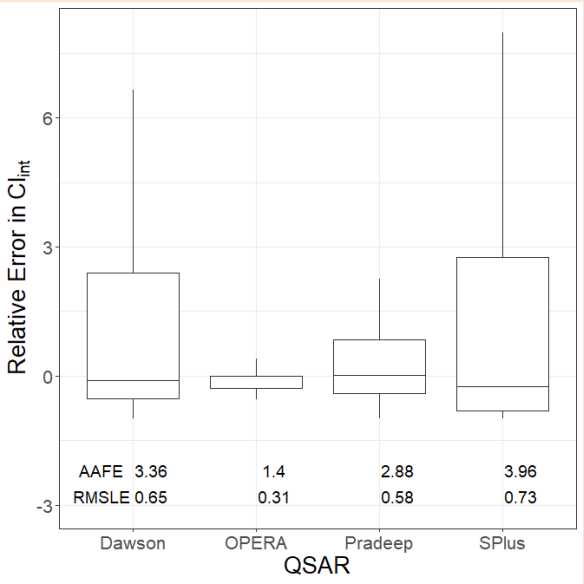
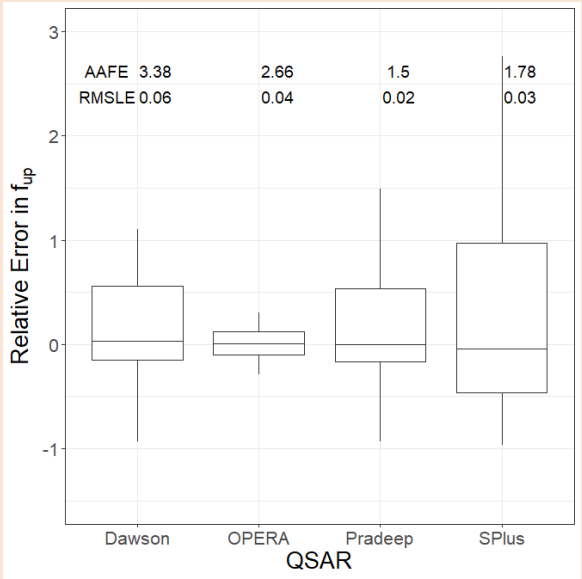
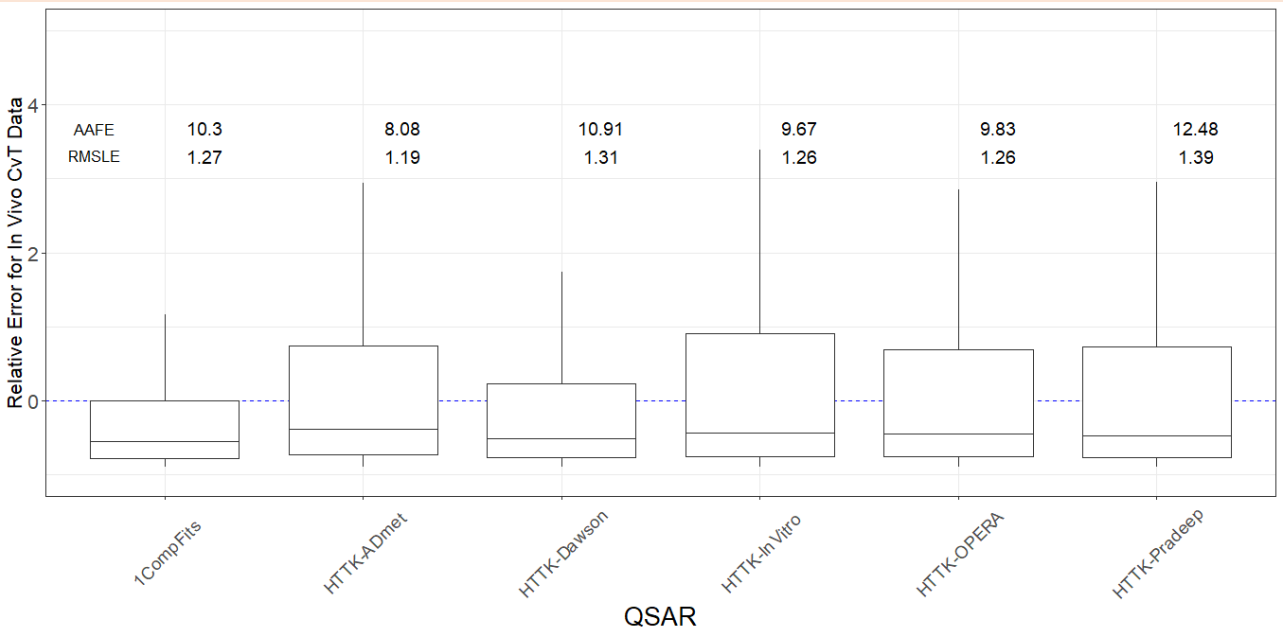
MAIN RESULTS







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 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 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

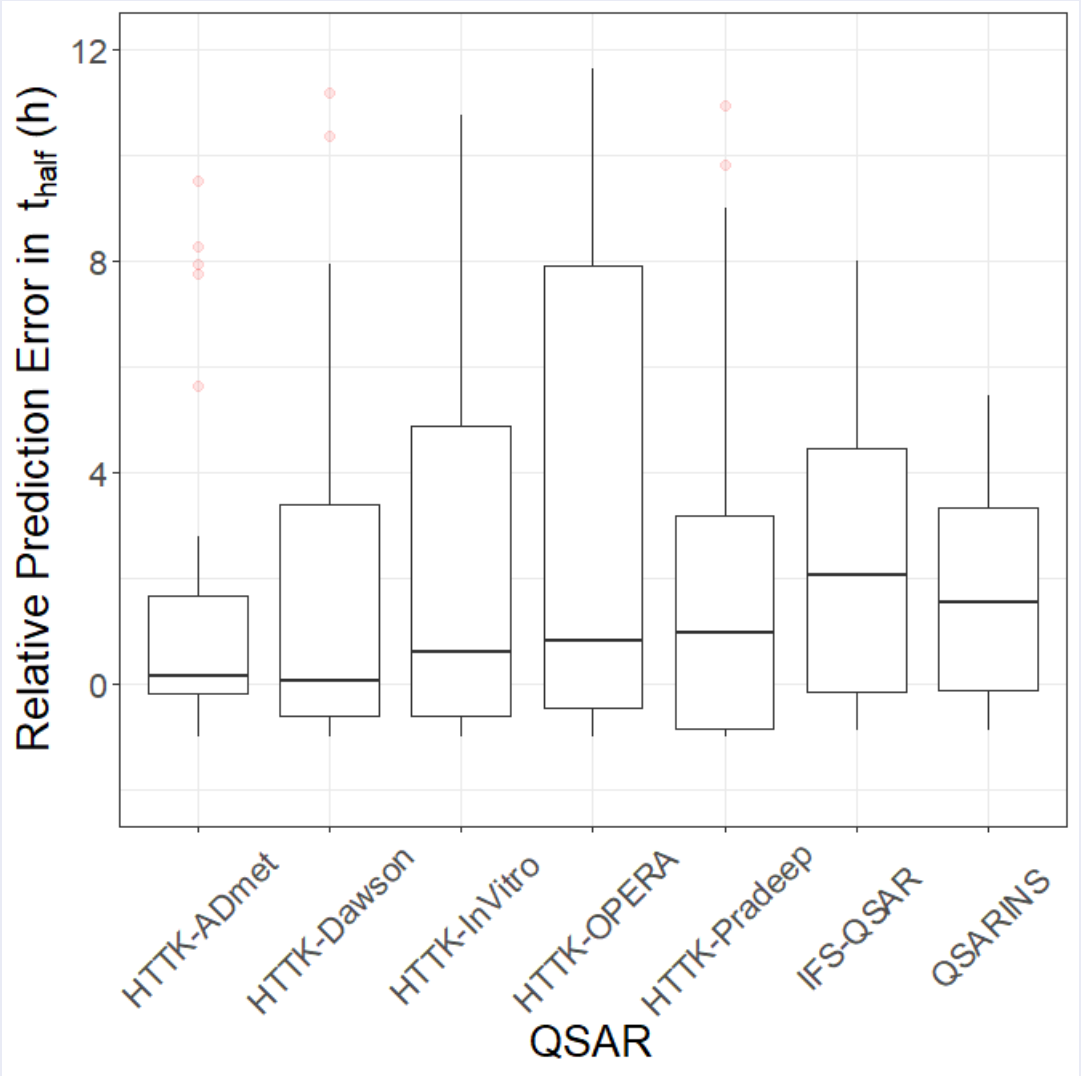
- TK information, such as elimination half-life (t_{half}, plotted below), is critical for understanding chemical risk

- 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; the QSARs evaluated here 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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