Evidence Based Toxicokinetics

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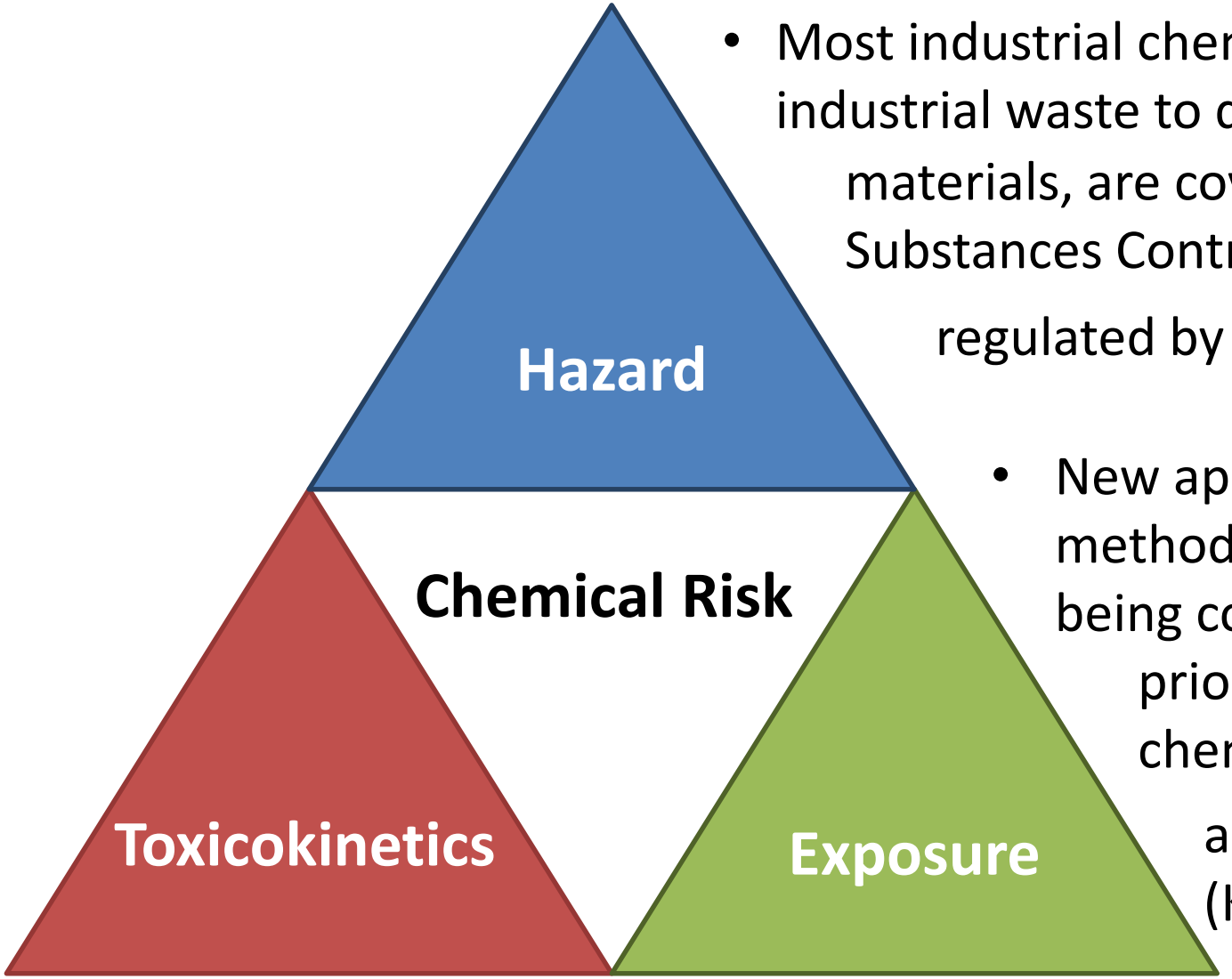
Conflict of Interest Statement

I have no conflicts of interest to disclose

The views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the U.S. EPA

New Approach Methodologies: High Throughput Toxicokinetics (HTTK)



Three Components for Chemical Risk (NRC, 1983)

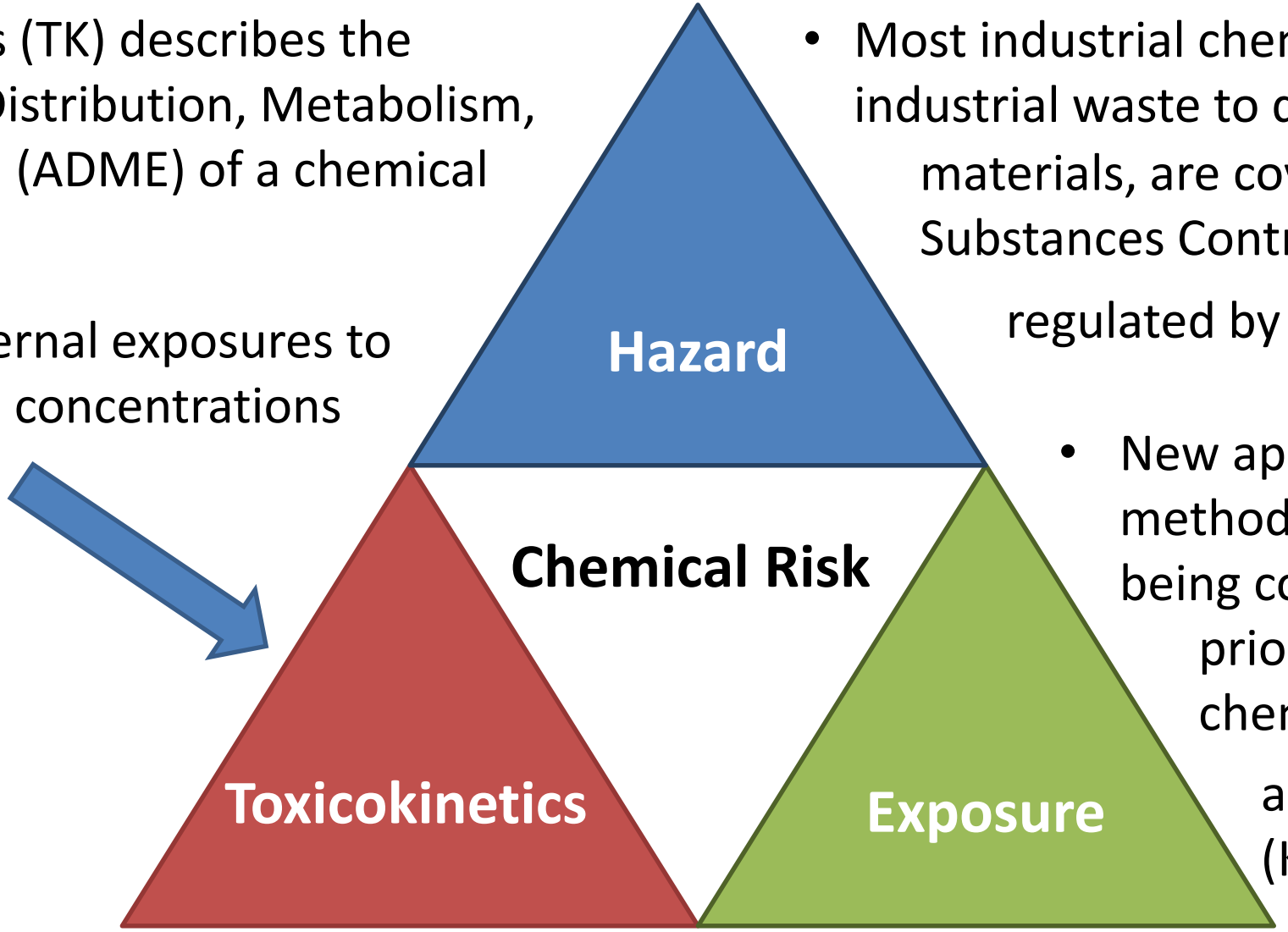
- Most industrial chemicals, ranging from industrial waste to dyes to packing materials, are covered by the Toxic Substances Control Act (TSCA) and regulated by EPA

- New approach methodologies (NAMs) are being considered to inform prioritization of chemicals for testing and evaluation (Kavlock et al., 2018)

New Approach Methodologies: High Throughput Toxicokinetics (HTTK)

Toxicokinetics (TK) describes the Absorption, Distribution, Metabolism, and Excretion (ADME) of a chemical by the body

TK relates external exposures to internal tissue concentrations of chemical



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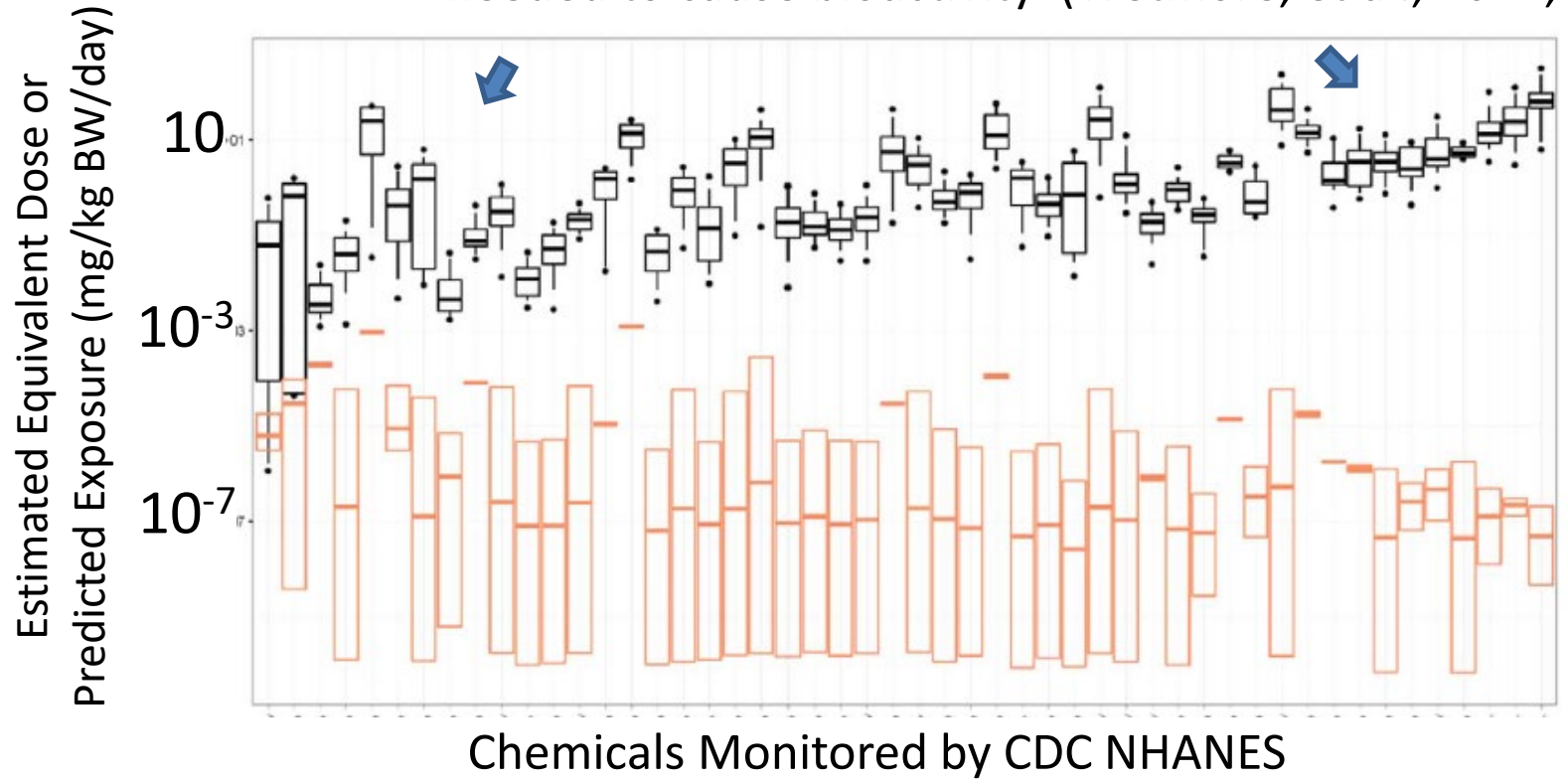
Three Components for Chemical Risk (NRC, 1983)

Selecting Chemical Priorities

High Throughput Screening + HTTK can estimate doses needed to cause bioactivity (Wetmore, et al., 2012, 2015)



Exposure intake rates can be inferred from biomarkers (Wambaugh et al., 2014)

National Health and Nutrition Examination Survey (NHANES) is an ongoing survey that covers ~10,000 people every two years

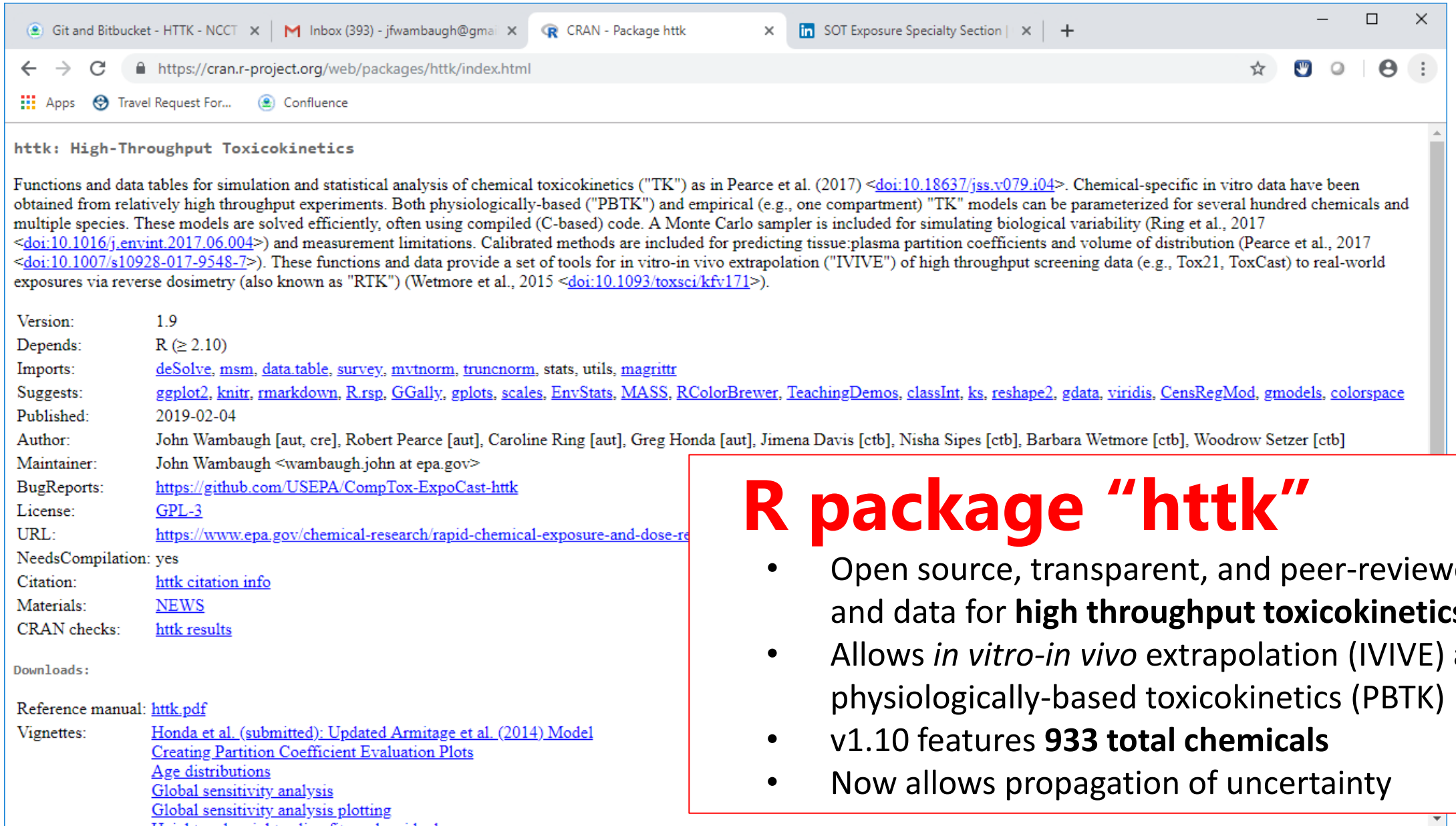
Most NHANES chemicals do not have traditional PK models (Strope et al., 2018)

Ring *et al.* (2017)

New Version 1.10 of HTTK Coming Soon

Wambaugh et al. (in clearance)

https://CRAN.R-project.org/package=httk



R package "httk"

- Open source, transparent, and peer-reviewed tools and data for **high throughput toxicokinetics (httk)**
- Allows *in vitro-in vivo* extrapolation (IVIVE) and physiologically-based toxicokinetics (PBTK)
- v1.10 features **933 total chemicals**
- Now allows propagation of uncertainty

In Silico HTTK Predictions

Predicting Metabolic Clearance Rates for Drug Leads and Environmental Chemical Risk Assessment

8 am, Tuesday – Room CC309

Daniel Mucs: “Implementation and Evaluation of State-of-the Art In Silico Models for In Vitro and In Vivo Endpoint Predictions”

Michael Lawless: “Applying in silico-in vitro-in vivo extrapolation (IS-IVIVE) techniques to predict exposure and guide risk assessment”

Christopher Kirman: “Quantitative Property–Property Relationship for Screening-Level Prediction of Intrinsic Metabolic Clearance”

Brandall Ingle: “Designing QSARs for metabolic clearance and plasma protein binding in diverse chemical space using pharmaceutical data”

Prachi Pradeep: “Using Chemical Structure Information to Develop Predictive Models for In Vitro Toxicokinetic Parameters to Inform High-Throughput Risk Assessment”

httk v1.10 includes uncertainty propagation

Evidence Based Toxicokinetics

- **Most chemicals do not have TK data (Wetmore et al., 2015; Bell et al., 2017)**
  - In order to address greater numbers of chemicals we collect *in vitro*, high throughput toxicokinetic (HTTK) data (Rotroff et al., 2010; Wetmore et al., 2012, 2015)
  - HTTK methods have been used by the pharmaceutical industry to determine range of efficacious doses and to prospectively evaluate success of planned clinical trials (Jamei *et al.*, 2009)
  - To use these methods for non-pharmaceuticals we must quantify the confidence

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  - To use these methods for non-pharmaceuticals we must quantify the confidence
- **We recognize that what we can do now is a product of the moment:**
  - We are not the first to ask (Yoon et al., 2014), rather more public tools now exist to answer the questions
  - Further, we accept that pharma has already pursued these approaches (Wang et al., 2010)

CompTox Specialty Section Paper of the Year

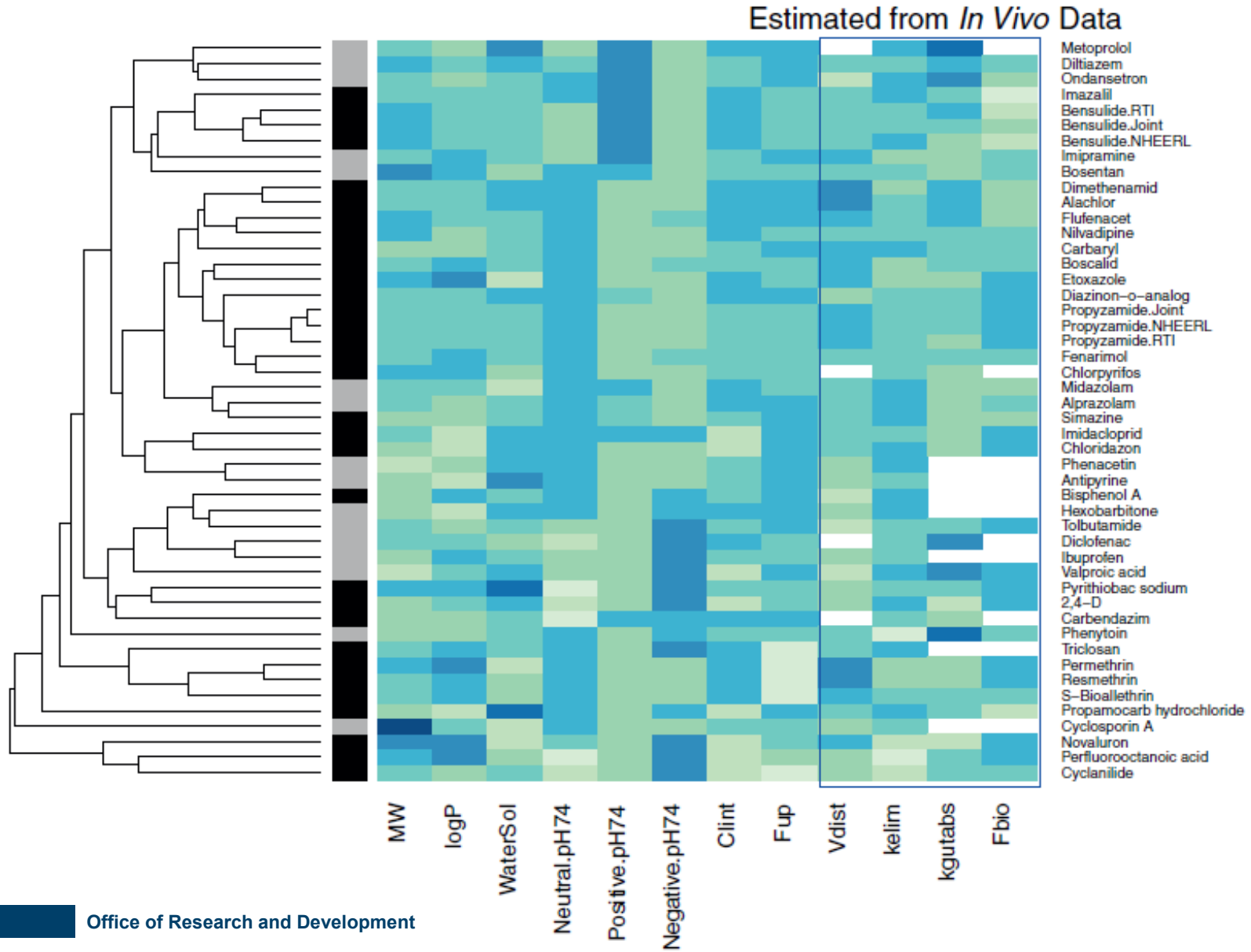
TOXICOLOGICAL SCIENCES, 2018, 1–18

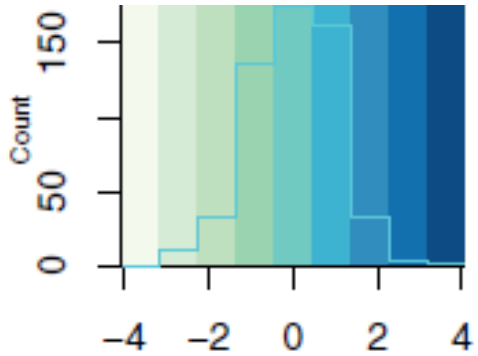
doi: 10.1093/toxsci/kfy020
Advance Access Publication Date: January 27, 2018
Research Article

Evaluating *In Vitro-In Vivo* Extrapolation of Toxicokinetics

John F. Wambaugh,[*,1] Michael F. Hughes,[†] Caroline L. Ring,[*,‡,2] Denise K. MacMillan,[†] Jermaine Ford,[†] Timothy R. Fennell,[§] Sherry R. Black,[§] Rodney W. Snyder,[§] Nisha S. Sipes,[¶] Barbara A. Wetmore,[‖] Joost Westerhout,[|||] R. Woodrow Setzer,[*] Robert G. Pearce,[*,‡] Jane Ellen Simmons,[†] and Russell S. Thomas[*]

New Data for Evaluating IVIVE



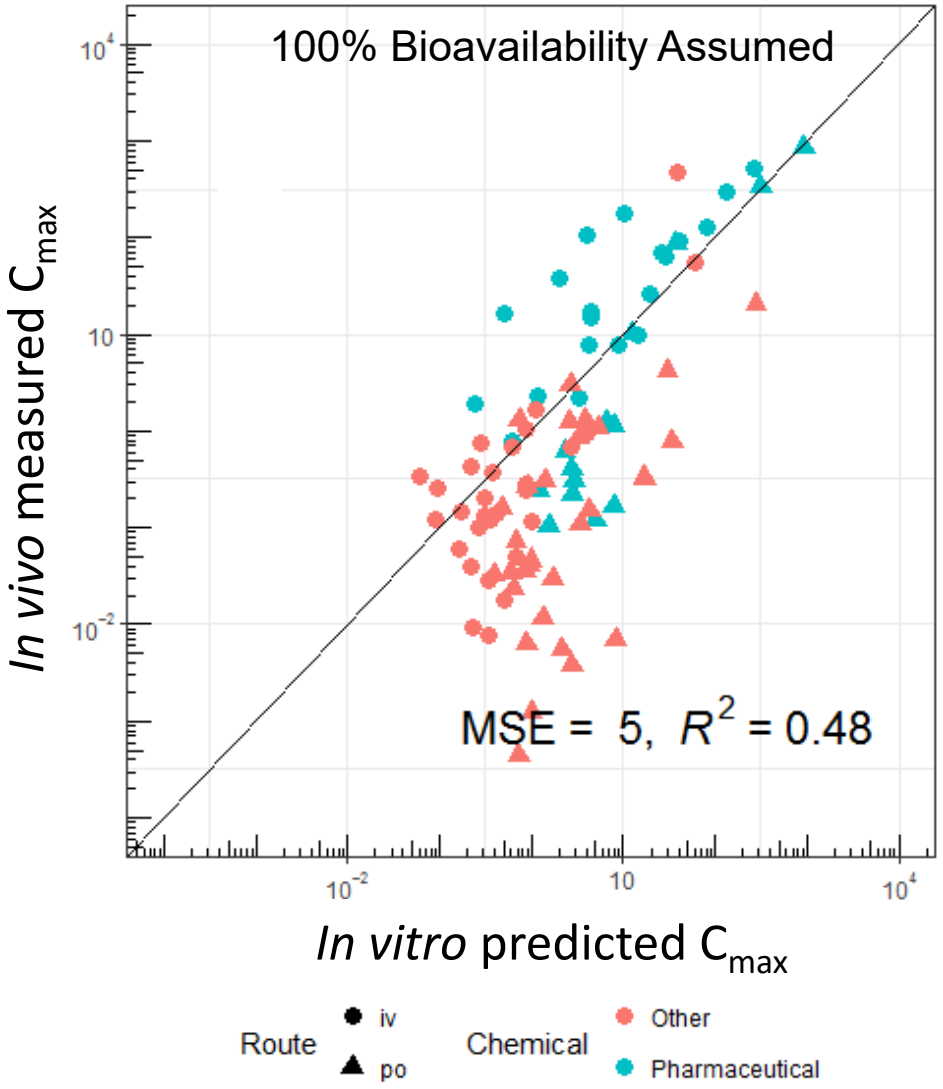


Number of Standard Deviations Above/Below Mean

- Physico-chemical properties, *in vitro* TK parameters (Wetmore et al., 2013), and TK parameters estimated from *in vivo* plasma concentration.

Wambaugh et al. (2018)

Impact of Oral Bioavailability



We evaluate HTTK by comparing predictions with observations for as many chemicals as possible

Wambaugh et al. (2018)

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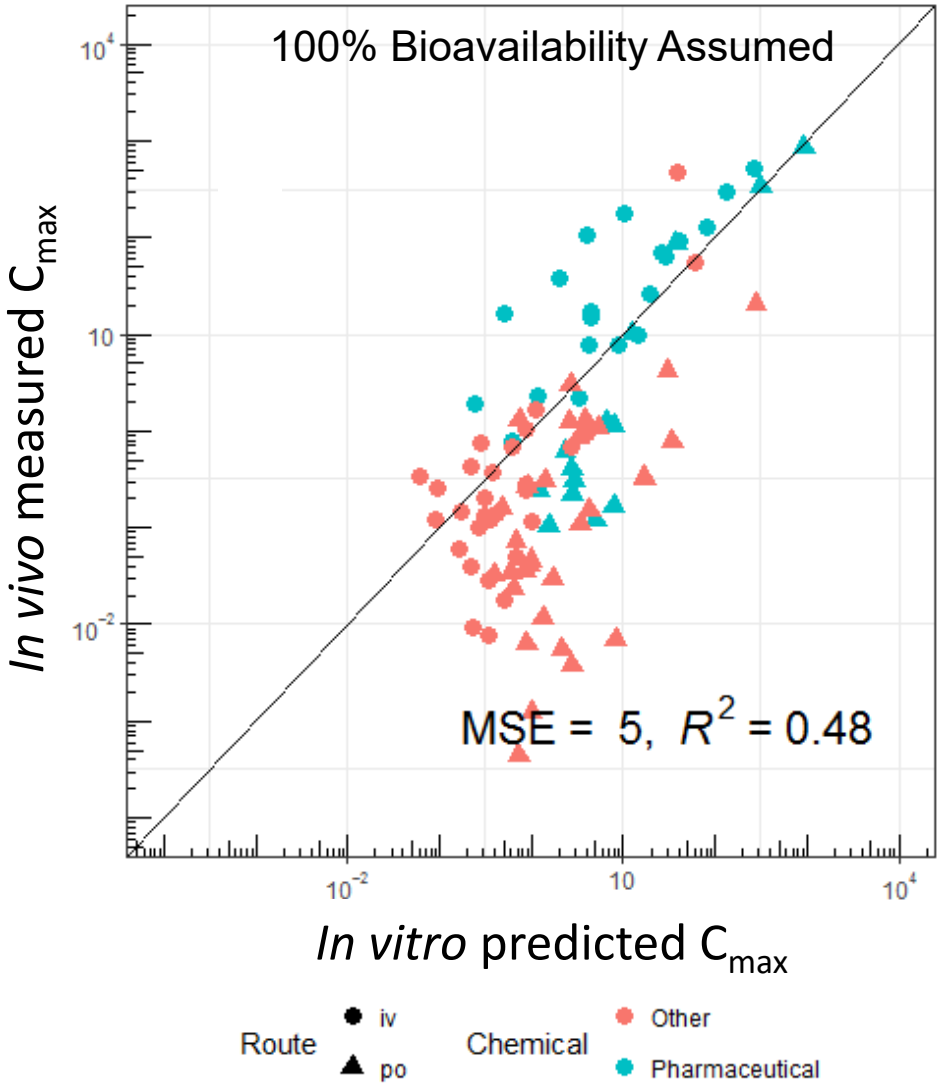
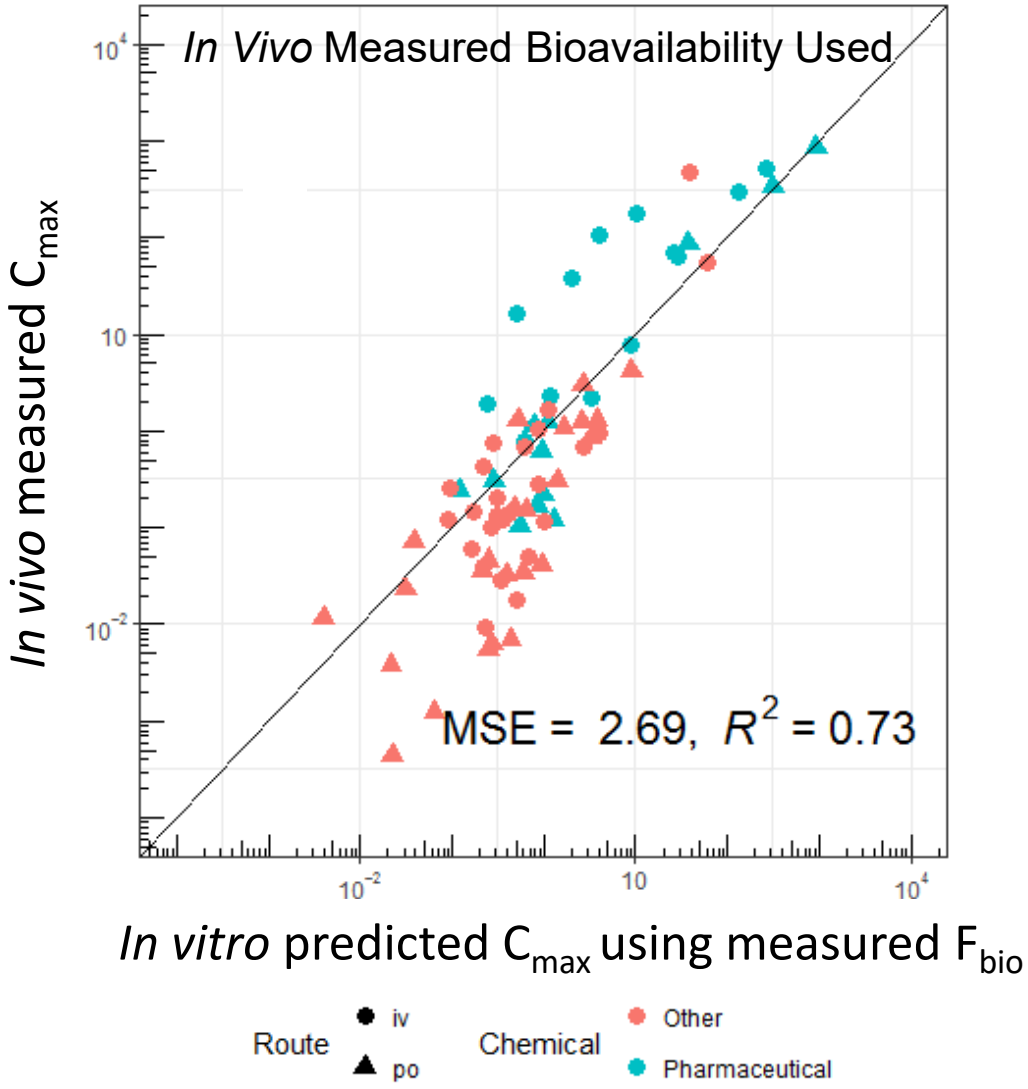




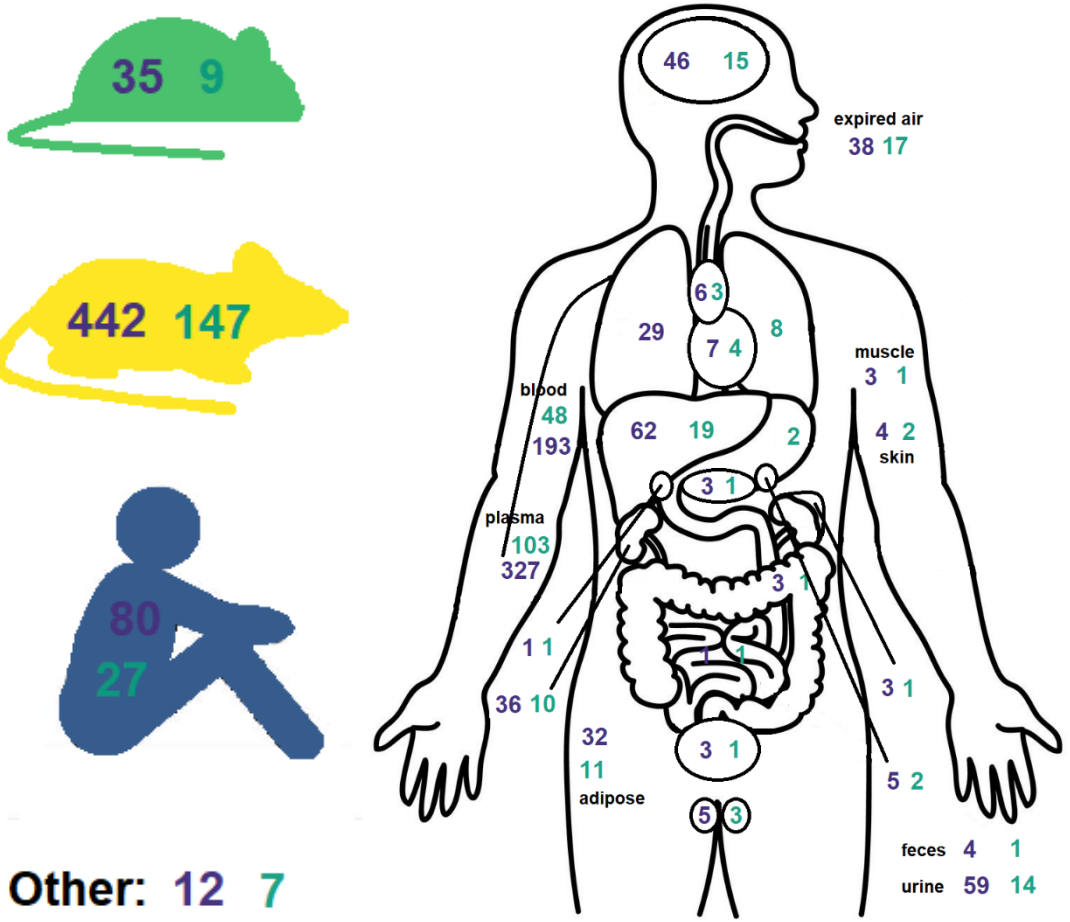
See Honda et al., Wednesday Afternoon, 3137/P711

Wambaugh et al. (2018)

In Vivo TK Database

- EPA is developing a public database of concentration vs. time data for building, calibrating, and evaluating TK models

- Curation and development ongoing, but to date includes:
  - 198 analytes (EPA, National Toxicology Program, literature)
  - Routes: Intravenous, dermal, oral, sub-cutaneous, and inhalation exposure
- Database will be made available through web interface and through the “httk” R package



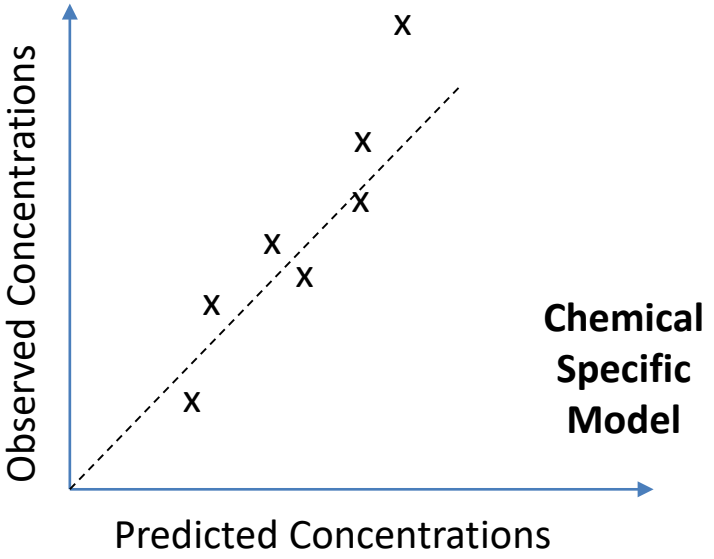
- Standardized, open source curve fitting software invivoPKfit used to calibrate models to all data: https://github.com/USEPA/CompTox-ExpoCast-invivoPKfit

See Sayre et al Tuesday Morning, 1766/P142

Sayre et al. (in preparation)

Building Confidence in TK Models

- In order to evaluate a **chemical-specific TK model** for "chemical x" you can compare the predictions to *in vivo* measured data
  - Can estimate bias
  - Can estimate uncertainty
  - Can consider using model to extrapolate to other situations (dose, route, physiology) where you don't have data



Cohen Hubal et al. (2018)

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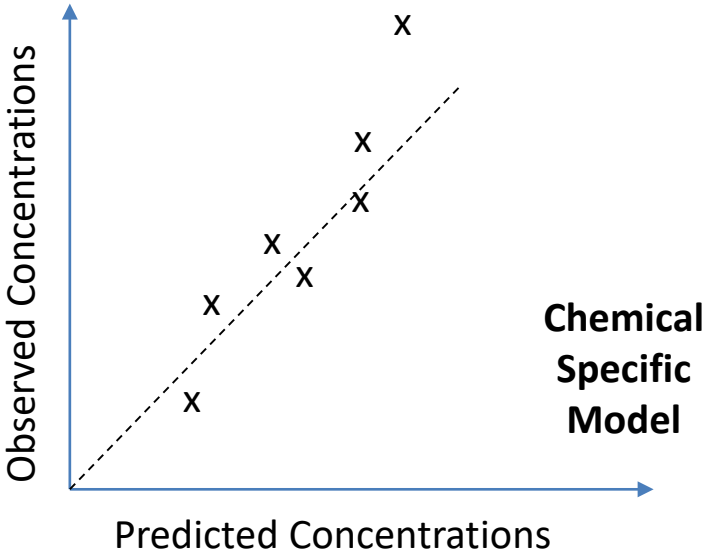

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- We can parameterize a **generic TK model**, and evaluate that model for as many chemicals as we do have data
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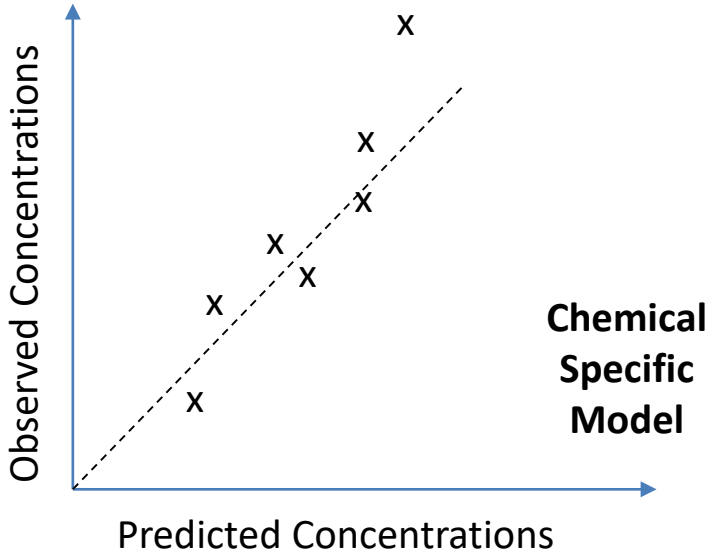
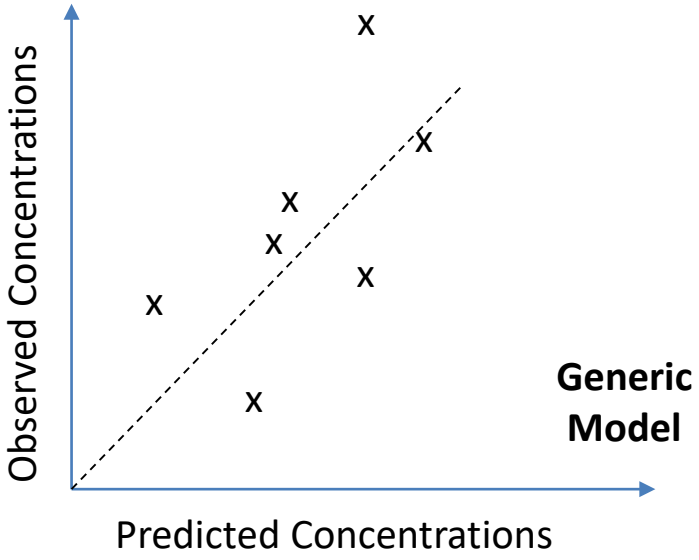
  - Estimate bias and uncertainty, and try to correlate with chemical-specific properties





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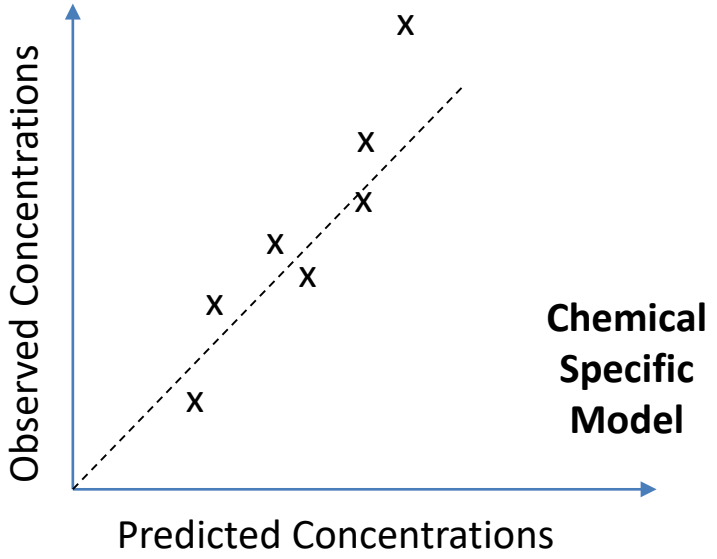

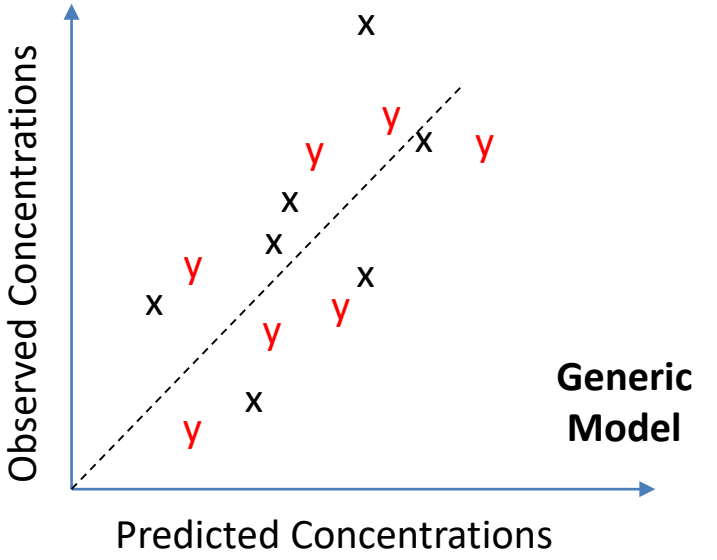

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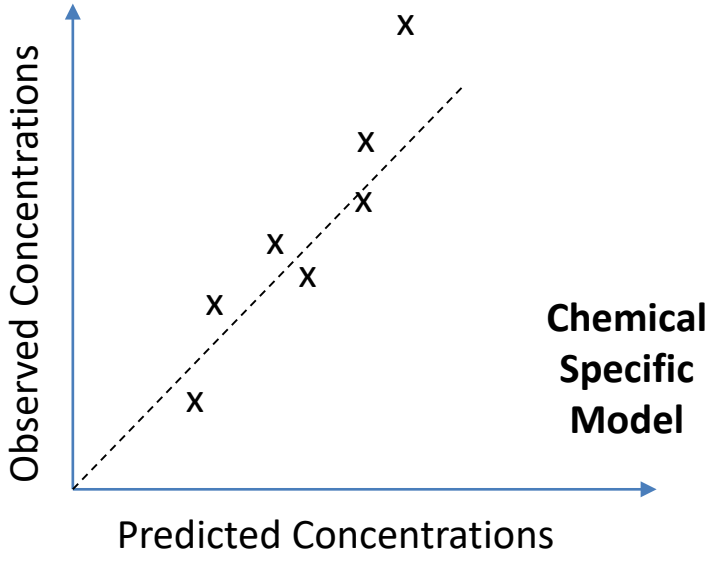
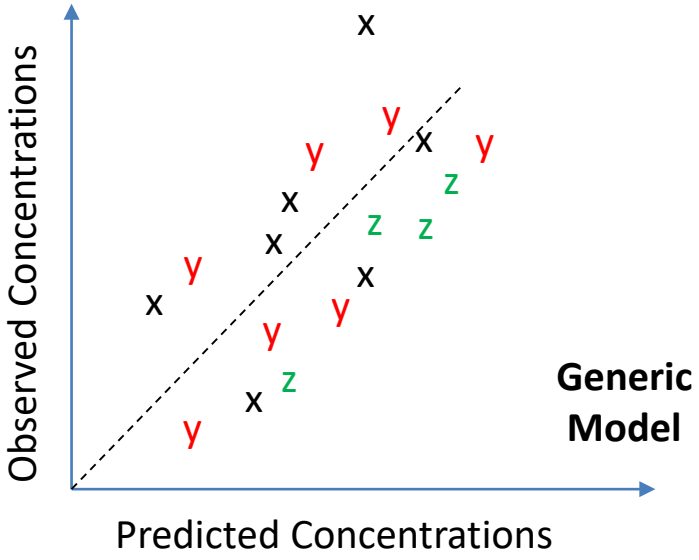
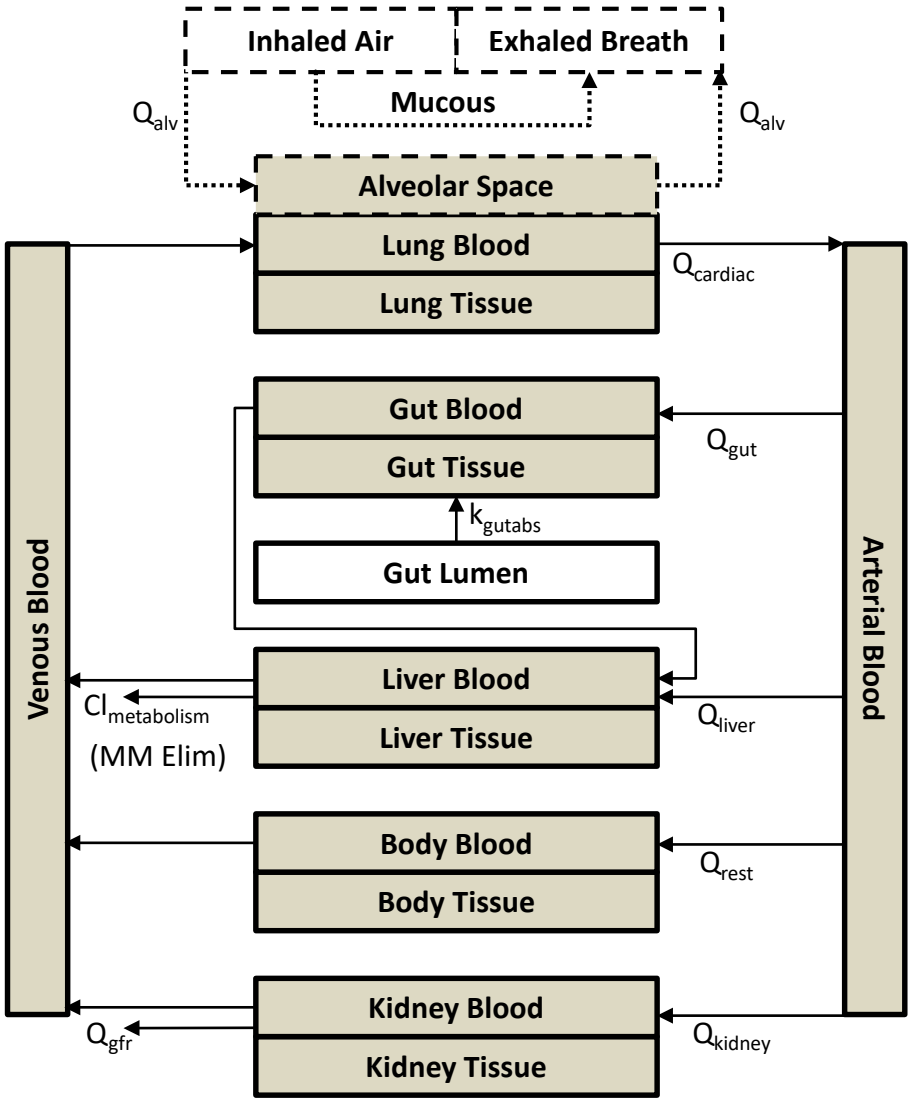


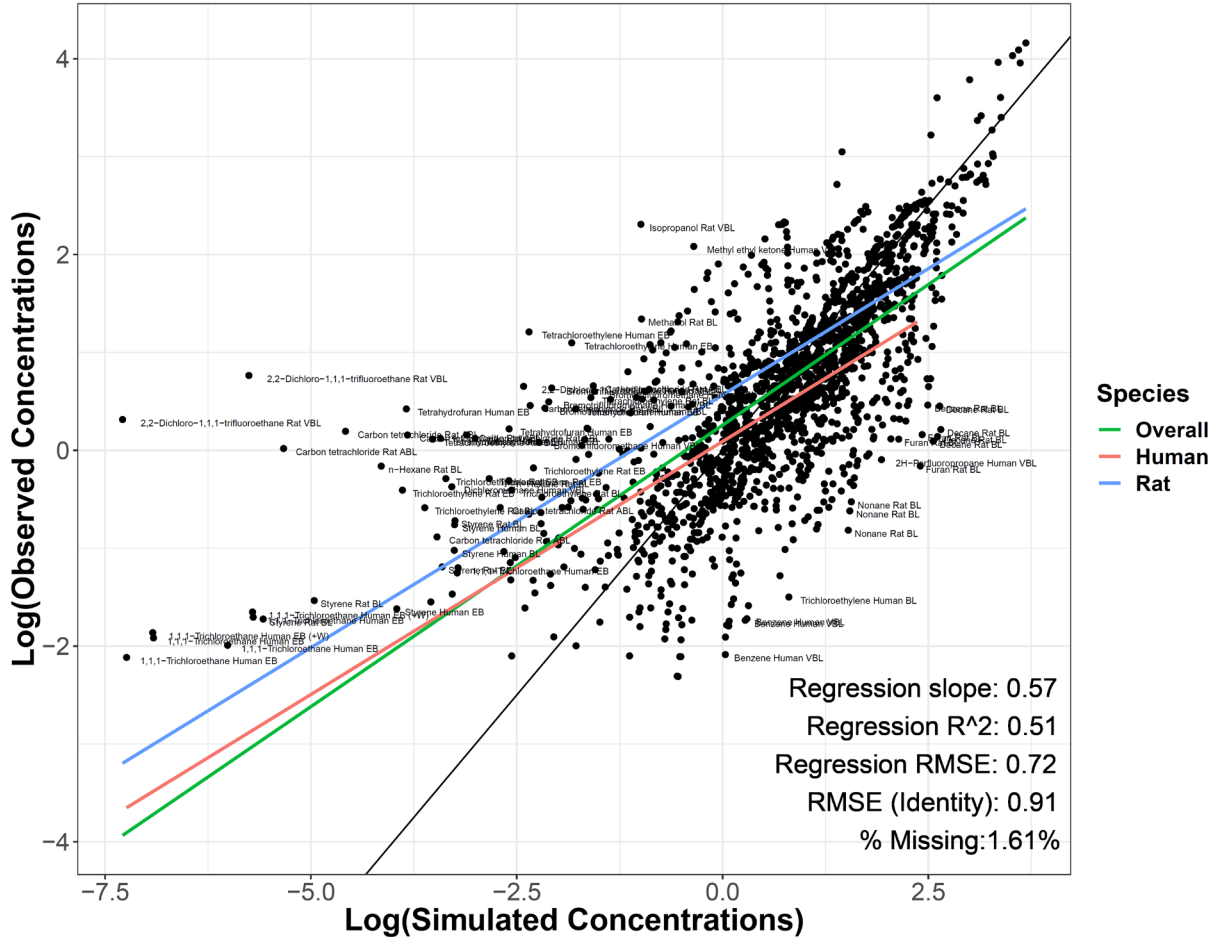


Cohen Hubal et al. (2018)

Generic Gas Inhalation Model



In Vivo TK database allowed rapid development and evaluation

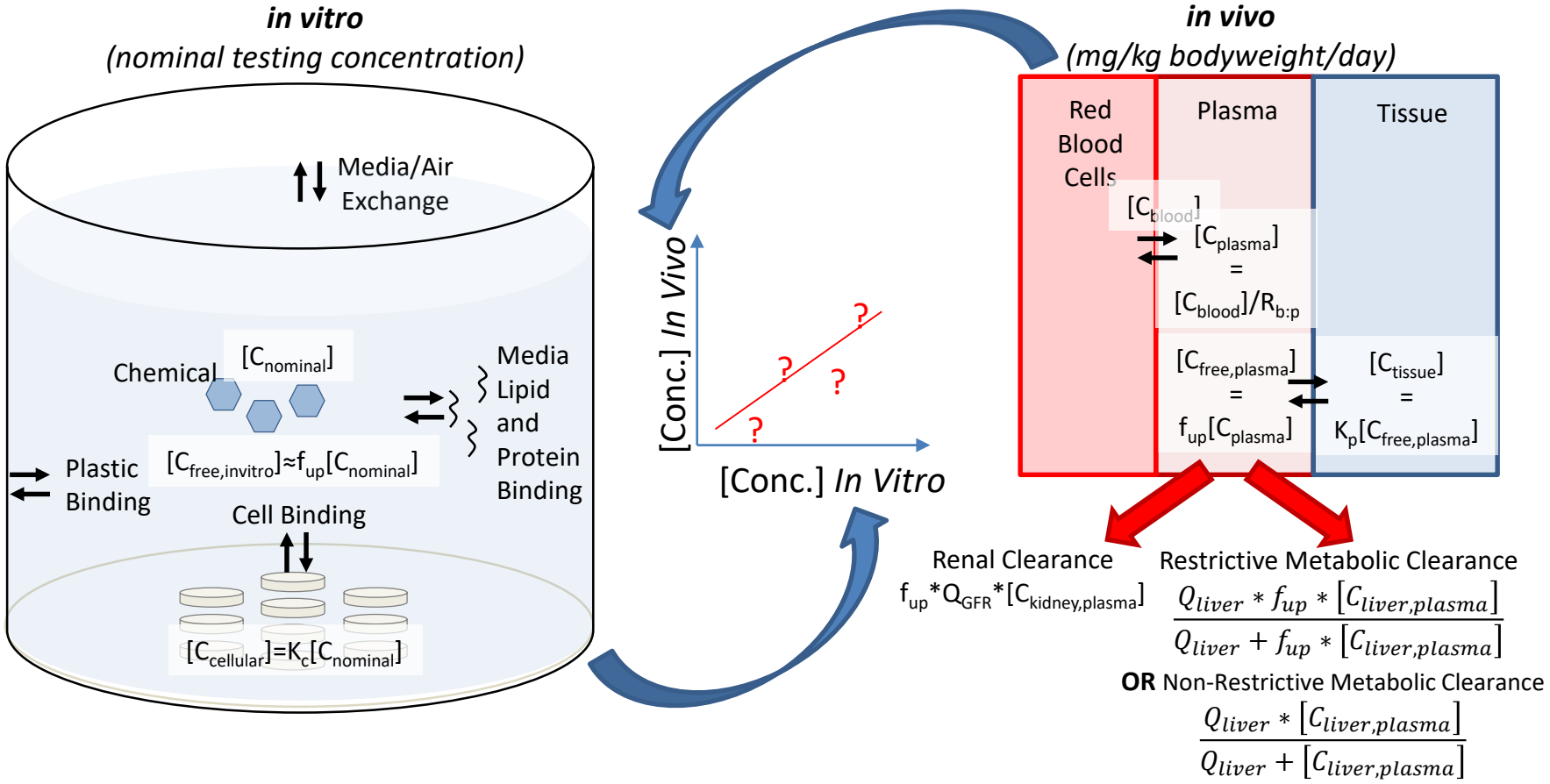


See Linakis et al., Tuesday Morning, 1791/P167

Linakis et al. (in preparation)

High-Throughput Toxicokinetics (HTTK) for *In Vitro-In Vivo* Extrapolation (IVIVE)

Using the generic HTTK PBTK model to inform IVIVE…



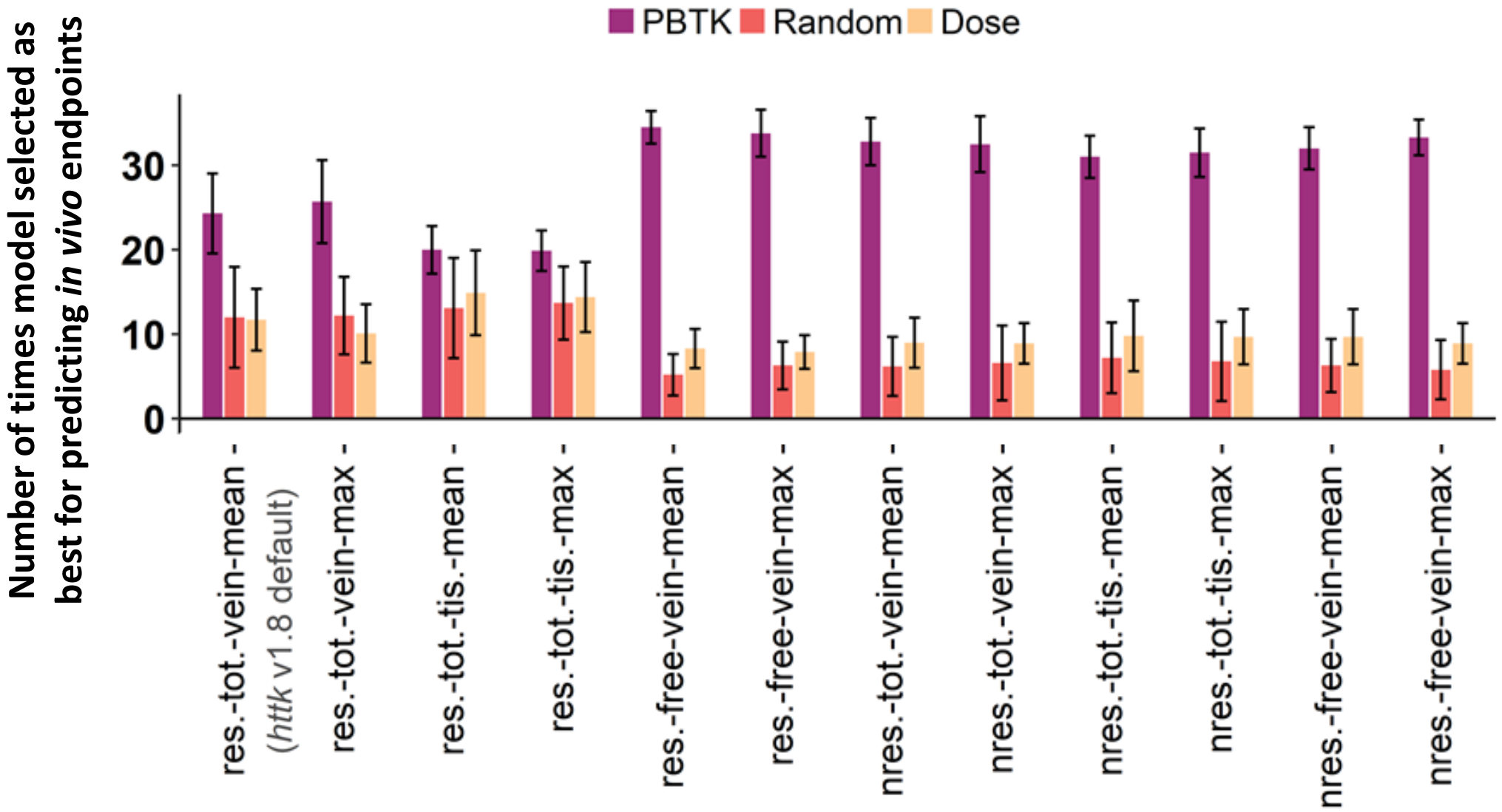
$$\frac{Q_{liver} * f_{up} * [C_{liver,plasma}]}{Q_{liver} + f_{up} * [C_{liver,plasma}]}$$

$$\frac{Q_{liver} * [C_{liver,plasma}]}{Q_{liver} + [C_{liver,plasma}]}$$

Selecting the appropriate *in vitro* and *in vivo* concentrations for extrapolation

Honda et al. (submitted)

Optimizing HTTK-based IVIVE



Honda et al. (submitted)

EPA United States Environmental Protection Agency

Final Thought

"Scientists should resist the demand to describe any model, no matter how good, as validated. Rather than talking about strategies for validation, we should be talking about means of evaluation."

Naomi Oreskes

ExpoCast Project (Exposure Forecasting)

United States Environmental Protection Agency

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EPA United States Environmental Protection Agency

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