EPA
United States
Environmental Protection
Agency

High Throughput Toxicokinetics Enables Risk-based Prioritization

John Wambaugh

Center for Computational Toxicology and Exposure

Office of Research and Development

U.S. Environmental Protection Agency

Society of Toxicology Annual Meeting
Virtual Event

March, 2021

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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

US EPA Office of Research and Development

- The Office of Research and Development (ORD) is the scientific research arm of EPA
  - 543 peer-reviewed journal articles in 2019
- Research is conducted by ORD's four national centers, and three offices organized to address:
  - Public health and env. assessment; comp. tox. and exposure; env. measurement and modeling; and env. solutions and emergency response.
- 13 facilities across the United States
- Research conducted by a combination of Federal scientists (including uniformed members of the **Public Health Service**); contract researchers; and postdoctoral, graduate student, and post-baccalaureate trainees

ORD Facility in Research Triangle Park, NC

US EPA's ExpoCast Project:
New Approach Methodologies for Exposure Forecasting

*"**Investment in 21st century exposure science is now required** to fully realize the potential of the NRC vision for toxicity testing."*
Cohen Hubal (2009)

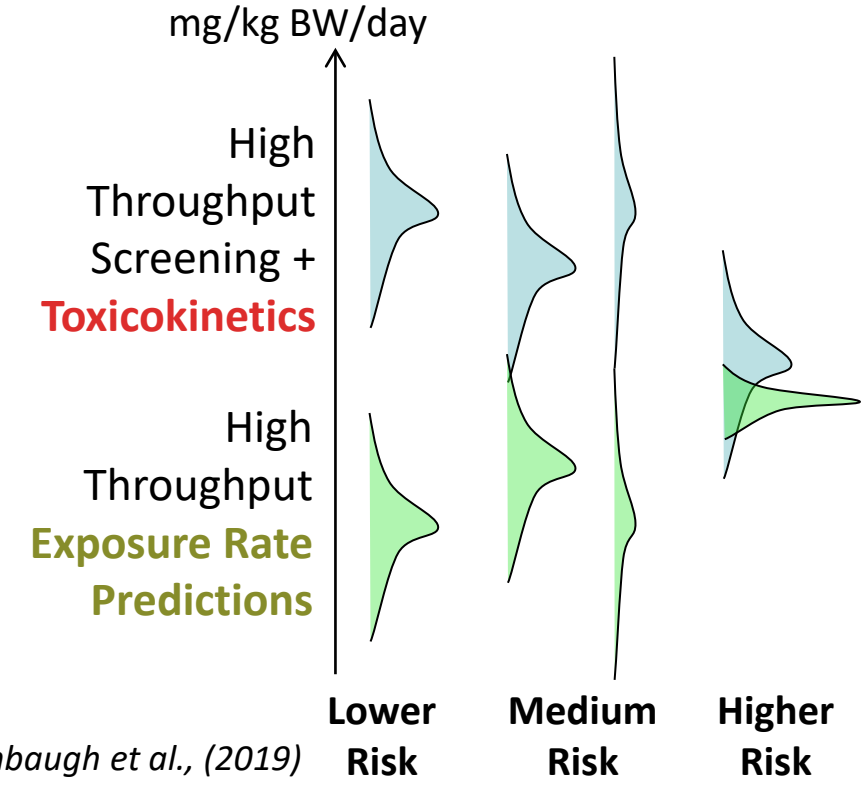
"Obama's FY10 Budget Includes Increased Toxicology":

- Funding allows for complementary exposure predictions from ExpoCast, which is slated to be **launched in FY10**
- Predict the impact of chemicals on the human body using data from ToxCast

Thomas et al. (2019)

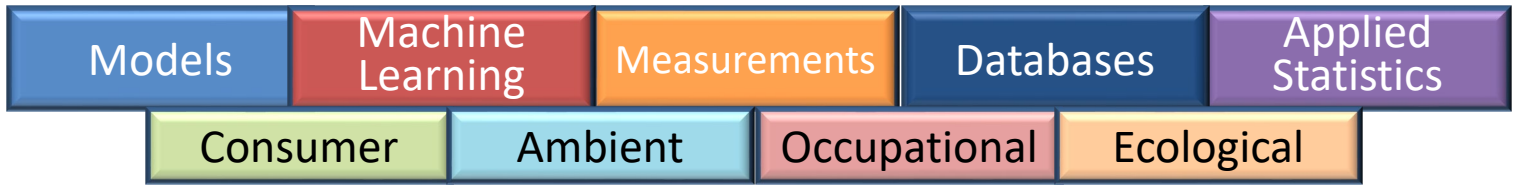
Since 2010:

- 45 peer-reviewed publications
- 5 STAR grants awarded
- 3 Federal research contracts (SWRI and Battelle)



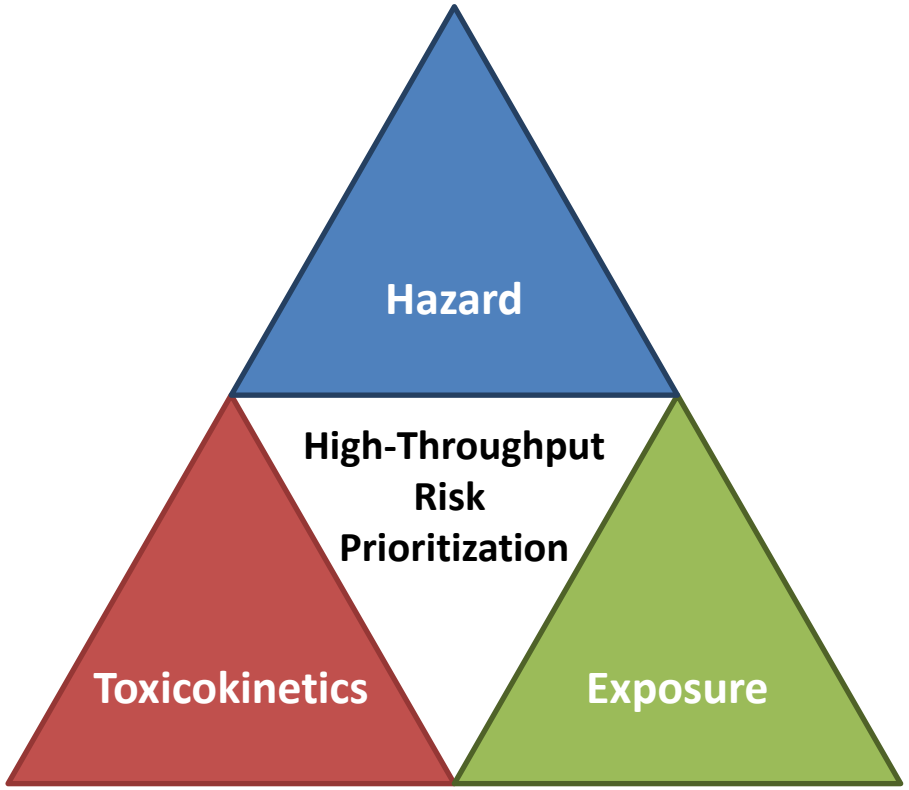
Wambaugh et al., (2019)

ExpoCast is



Calculating Chemical Risk

- High throughput risk prioritization based upon *in vitro* screening requires comparison to exposure (for example, NRC, 1983)
- Information must be relevant to the scenario, for example, consumer, ambient, or occupational exposure.
- Data obtained *in vitro* must be placed in an *in vivo* context: *in vitro-in vivo* extrapolation (IVIVE)



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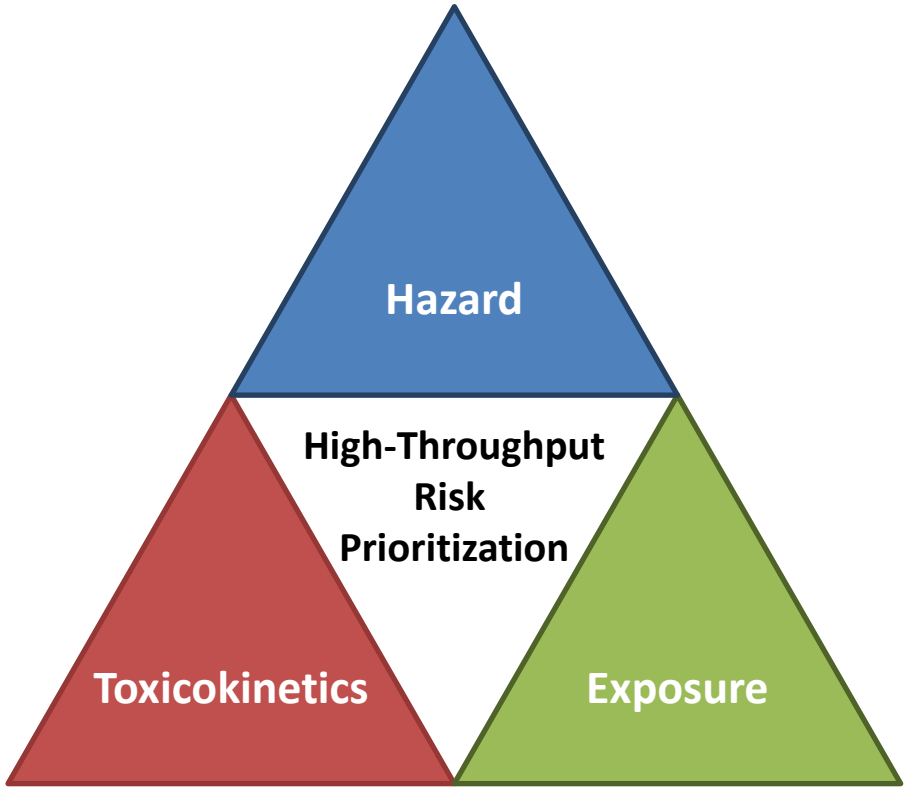
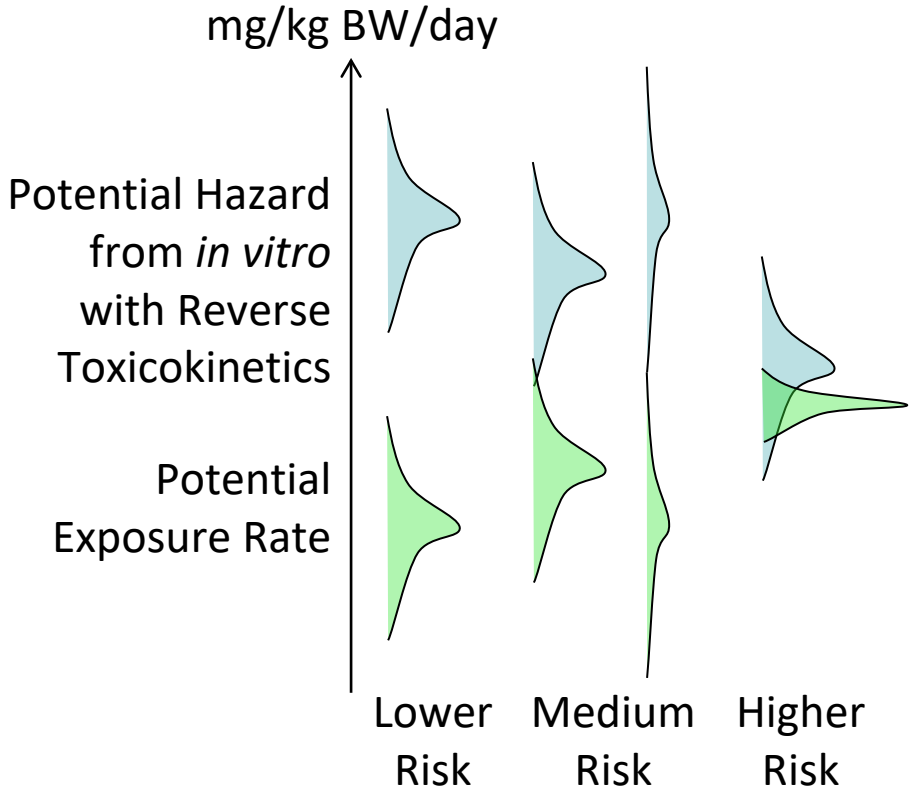




Most Chemicals lack Toxicokinetic Data

- Toxicokinetics (TK) describes adsorption, distribution, metabolism, and excretion (ADME) by the body
- Most non-pharmaceutical chemicals – for example, flame retardants, plasticizers, pesticides, solvents – do not have human *in vivo* TK data.
- Non-pesticidal chemicals are unlikely to have any *in vivo* TK data, even from animals

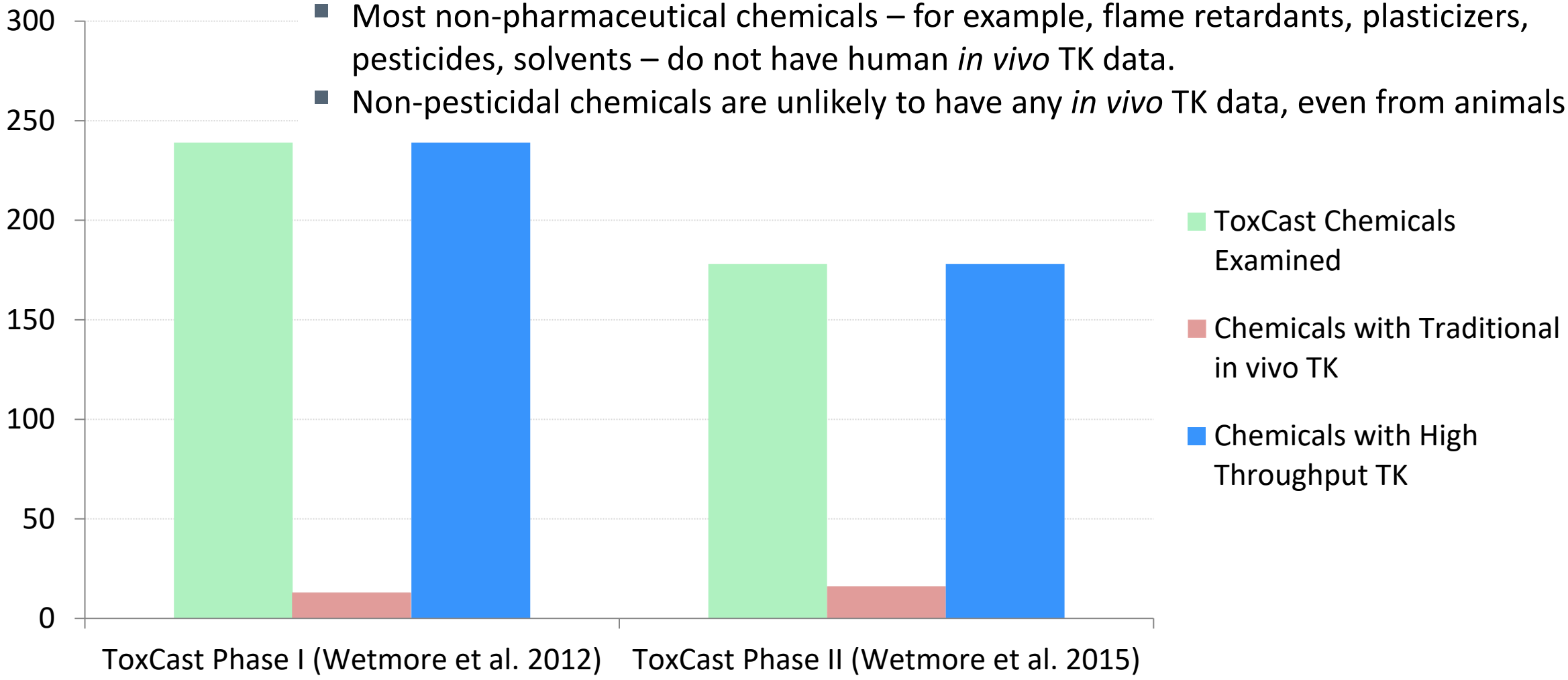


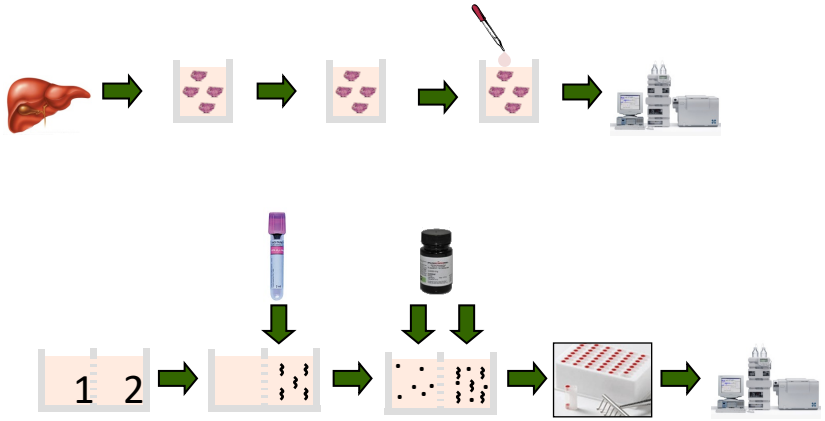
Figure from Bell et al. (2018)

HTTK: A NAM for Exposure

- To provide toxicokinetic data for larger numbers of chemicals collect *in vitro*, high throughput toxicokinetic (HTTK) data (for example, 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; Wang, 2010)
- The **primary goal** of HTTK is to provide a human dose context for bioactive *in vitro* concentrations from HTS (that is*, in vitro-in vivo* extrapolation, or **IVIVE**) (for example, Wetmore et al., 2015)
- A **secondary goal** is to provide **open source data and models** for evaluation and use by the broader scientific community (Pearce et al, 2017a)

High Throughput Toxicokinetics (HTTK)

In vitro toxicokinetic data



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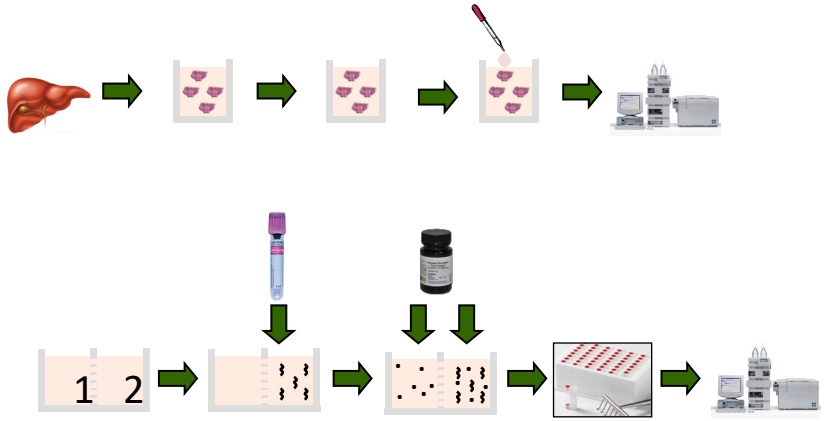

Rotroff et al. (2010)
Wetmore et al. (2012)
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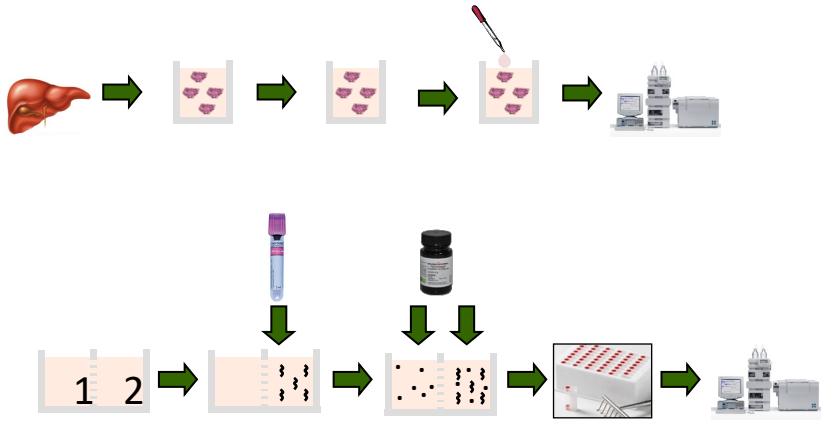
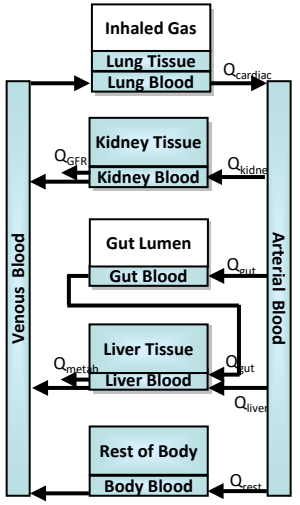
High Throughput Toxicokinetics (HTTK)

In vitro toxicokinetic data + generic toxicokinetic model





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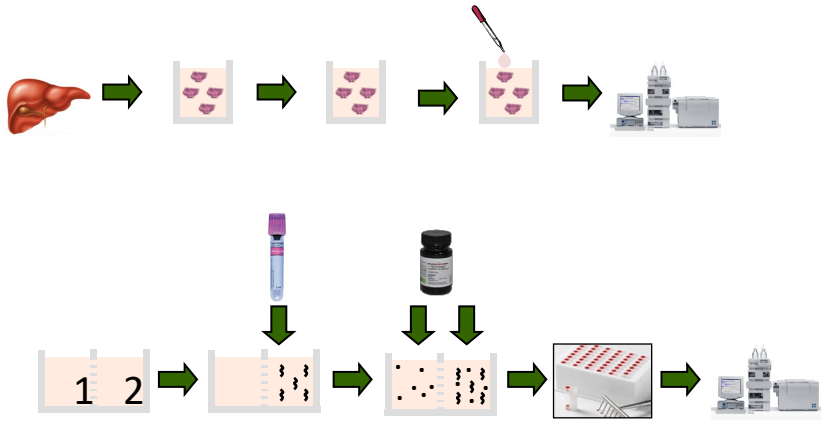

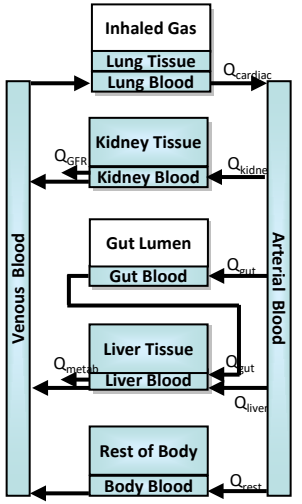

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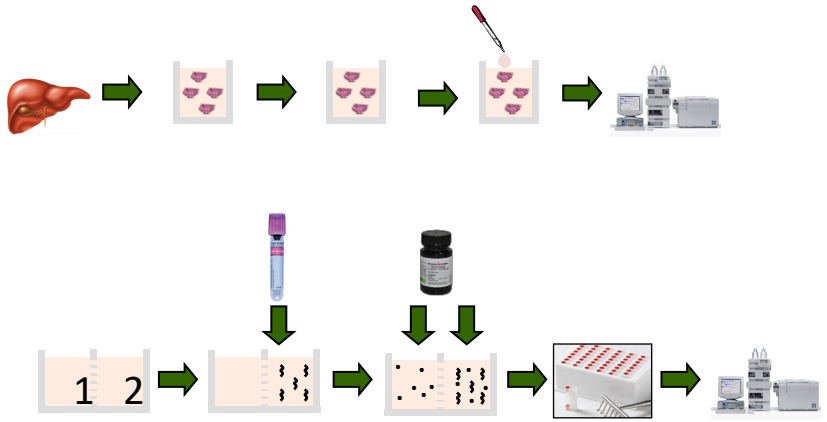
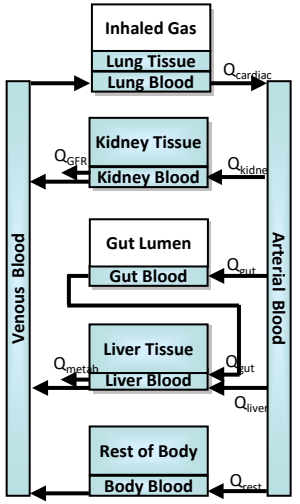
High Throughput Toxicokinetics (HTTK)

In vitro toxicokinetic data + generic toxicokinetic model

= high(er) throughput toxicokinetics





Rotroff et al. (2010)
Wetmore et al. (2012)
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Wambaugh et al. (2019)

= *httk*

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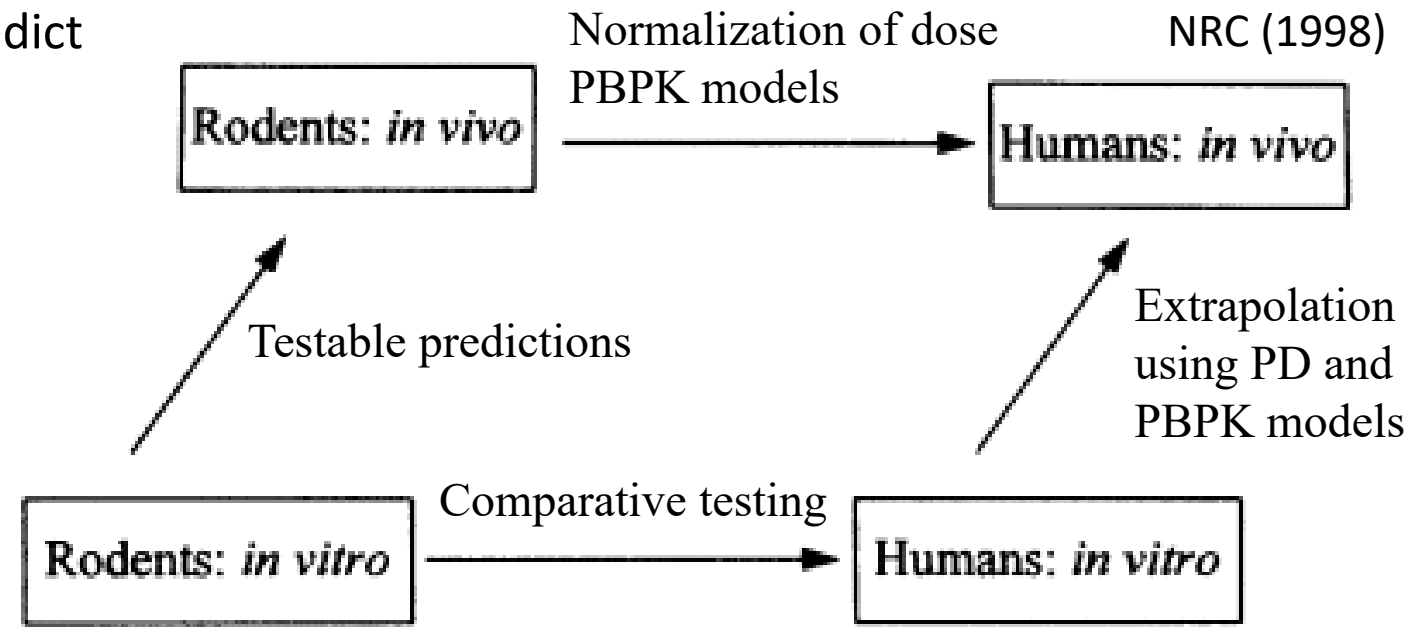
In Vitro - In Vivo Extrapolation (IVIVE)

- HTTK allows *in vitro-in vivo* extrapolation (IVIVE) – the use of *in vitro* experimental data to predict phenomena *in vivo*.



"The Parallelogram Approach" (Sobels, 1982)

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  - IVIVE-PK/TK (**Pharmacokinetics/Toxicokinetics**):
    - Fate of molecules/chemicals in body
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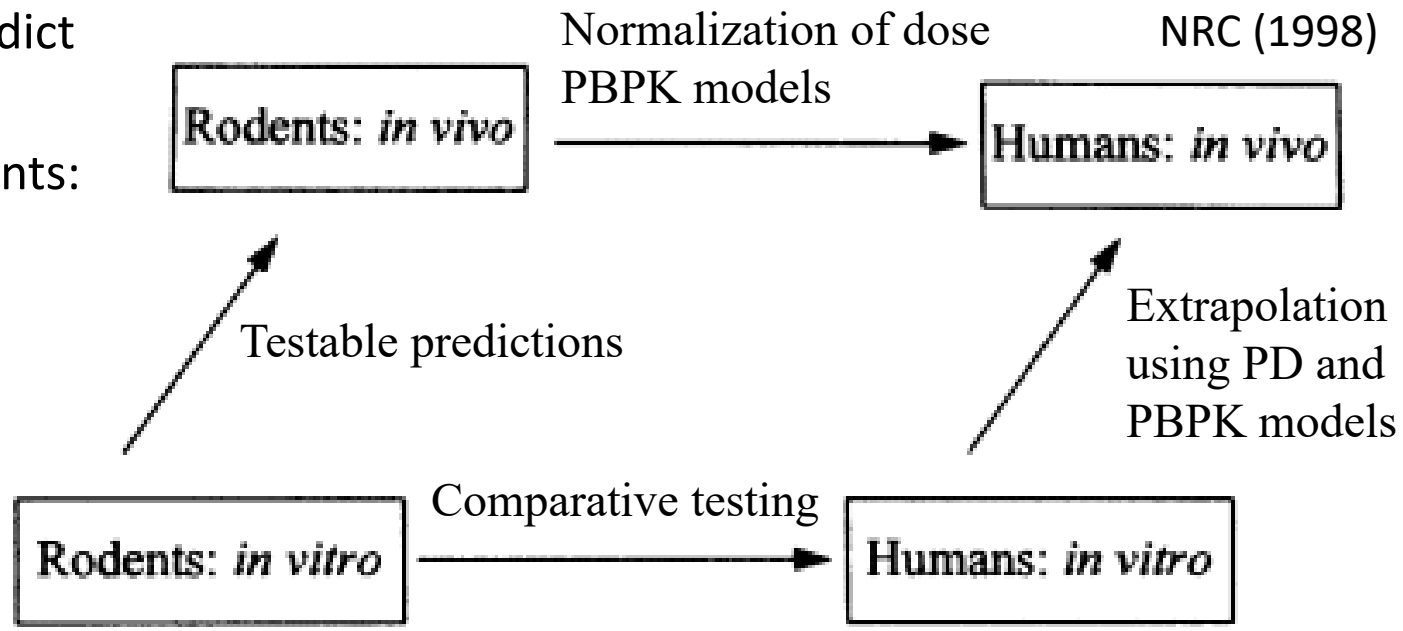
    - Can use empirical PK or physiologically-based (PBPK)



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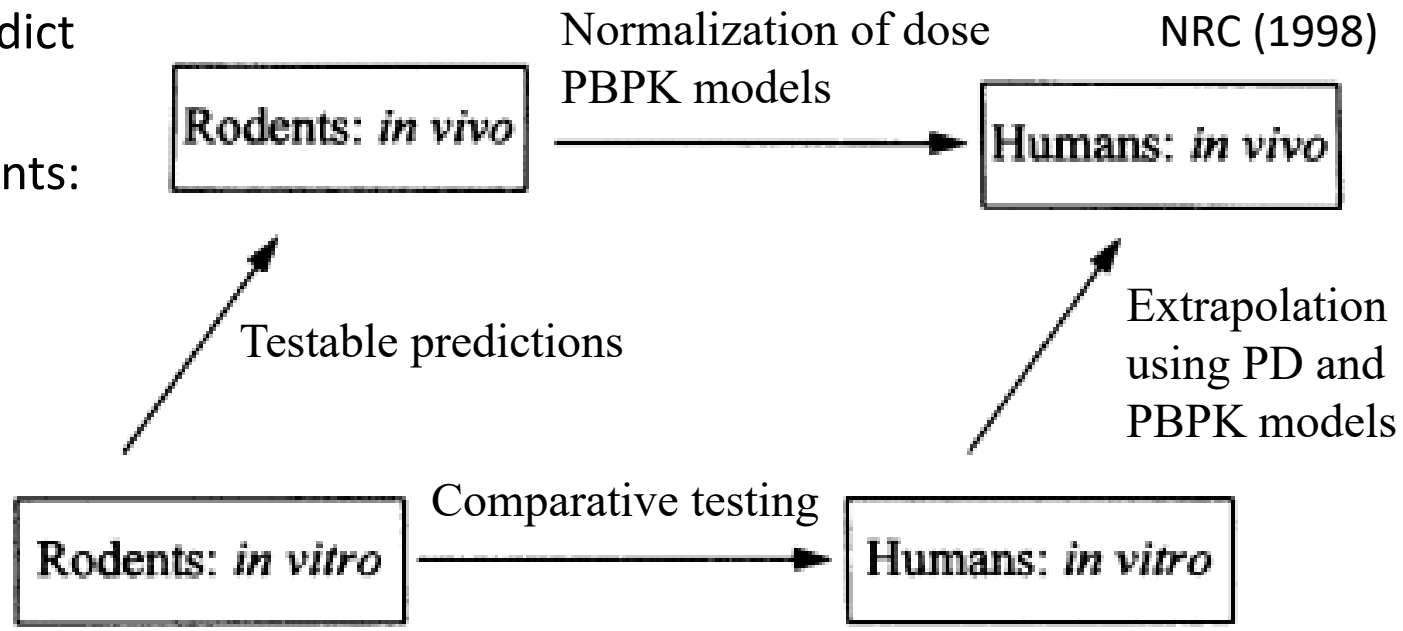
  - IVIVE-PD/TD (**Pharmacodynamics/Toxicodynamics**):
    - Effect of molecules/chemicals at biological target *in vivo*
    - Perturbation as adverse/therapeutic effect, reversible/ irreversible effects



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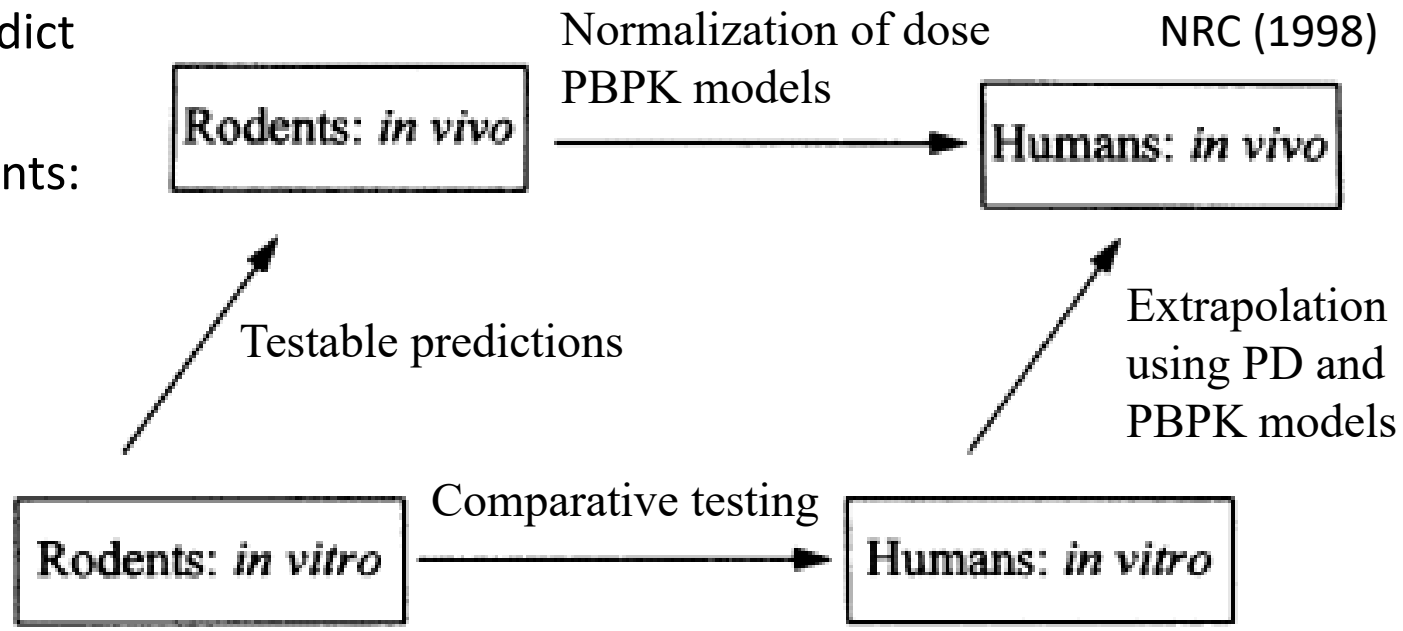
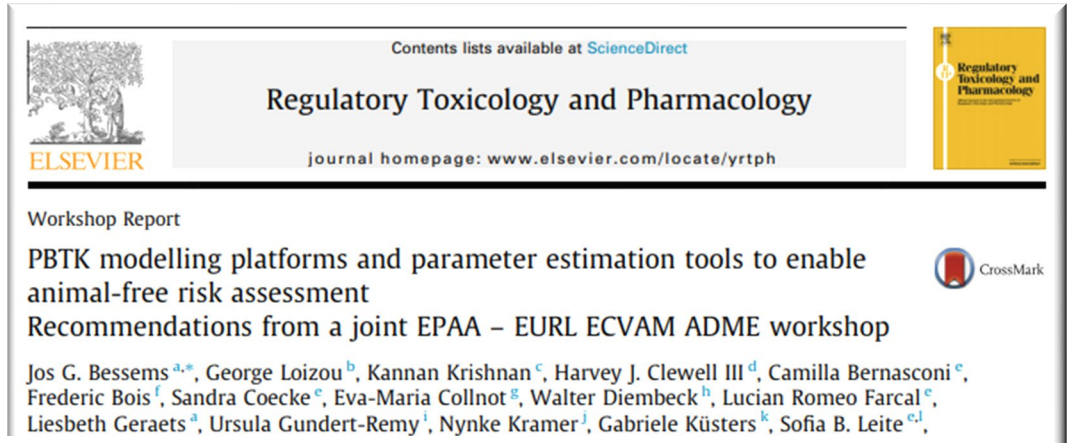


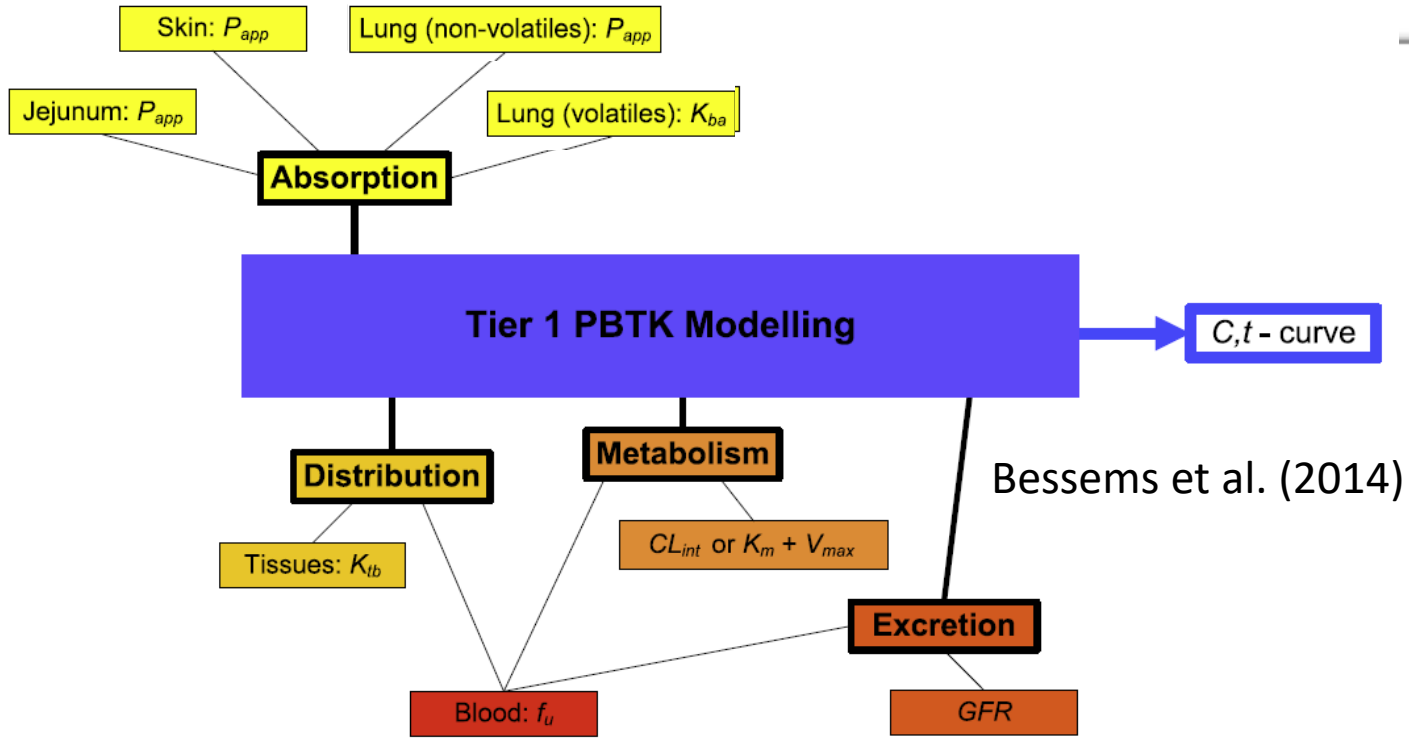
"The Parallelogram Approach" (Sobels, 1982)

HTTK only covers toxicokinetic extrapolation

Fit for Purpose IVIVE

- Make the complexity of the model and the number of physiological processes appropriate to decision context
- Bessems et al. (2014): We need "a first, relatively quick ('Tier 1'), estimate" of concentration vs. time in blood, plasma, or cell
- They suggested that we neglect active metabolism – thanks to *in vitro* measurements we can now do better
- We still neglect transport and other protein-specific phenomena





Bessems et al. (2014)

IVIVE by Scaling Factor

- We make various assumptions that allow simple conversion of an *in vitro* concentration $[\boldsymbol{X}]$ (µM) into an **administered equivalent dose** (AED) with units of mg/kg body weight/day:

$$\mathbf{AED} = \boldsymbol{F_{IVIVE}} \times [\boldsymbol{X}]$$

- **AED** is the **external dose rate** that would be needed to **cause a given steady-state plasma concentration**
- F_{IVIVE} is a scaling factor that varies by chemical

IVIVE by Scaling Factor

- For a given chemical, $F_{IVIVE} = 1 / C_{ss,95}$
- $C_{ss,95}$ is the steady-state plasma concentration as the result of a 1 mg/kg/day exposure

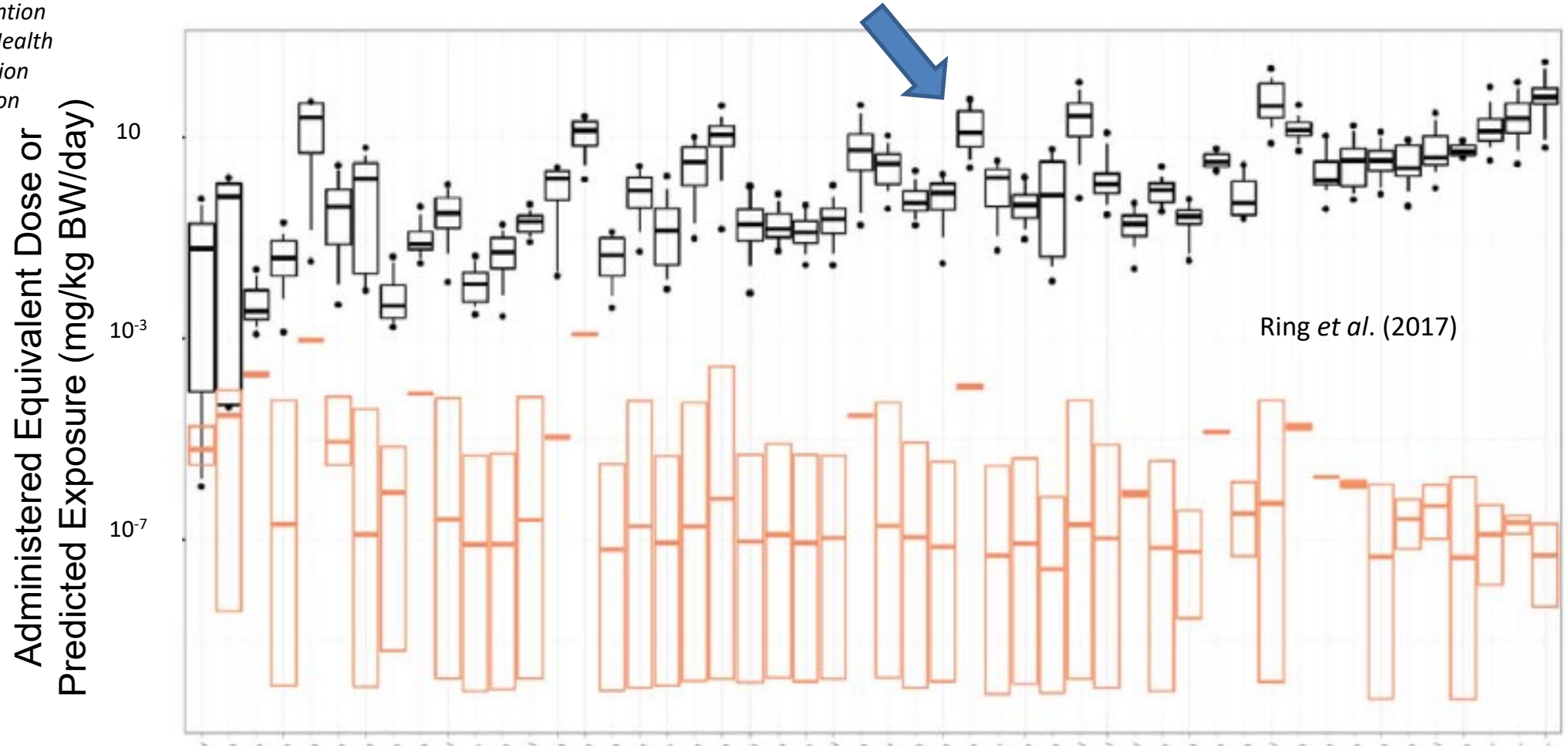
$$\mathbf{AED_{95}} = \frac{[\boldsymbol{X}]}{\boldsymbol{C_{ss,95}}}$$

- The "95" refers to the upper 95th percentile – due to human variability and measurement uncertainty there are a range of possible C_{ss} values
- All of this assumes that the individuals have enough time to come to "steady-state" with respect to their daily exposures

IVIVE Allows Chemical Prioritization

CDC NHANES: U.S. Centers for Disease Control and Prevention National Health and Nutrition Examination Survey

In Vitro Screening + IVIVE can estimate doses needed to cause bioactivity (Wetmore et al., 2015)



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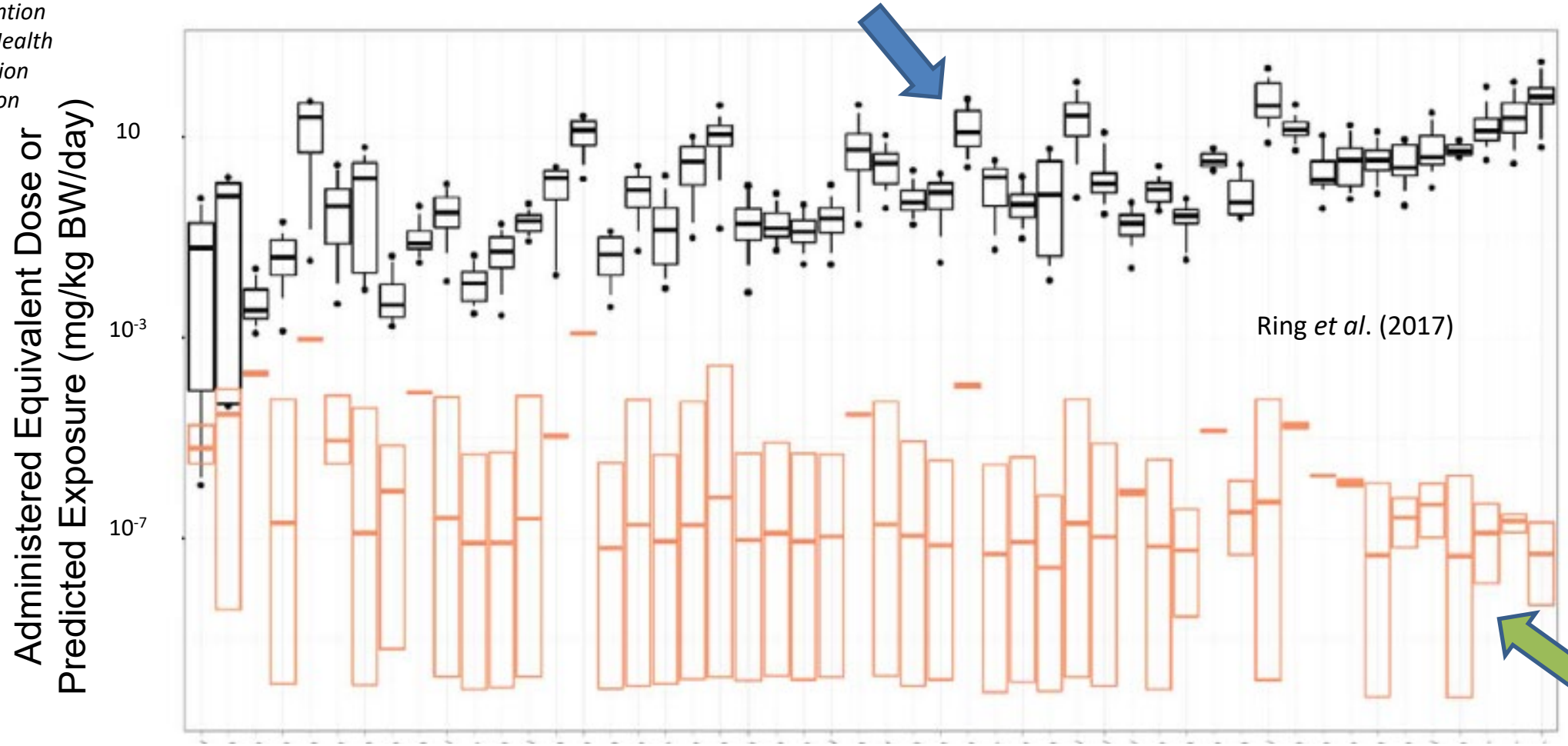

Exposure intake rates can be inferred from biomarkers (Wambaugh et al., 2014)

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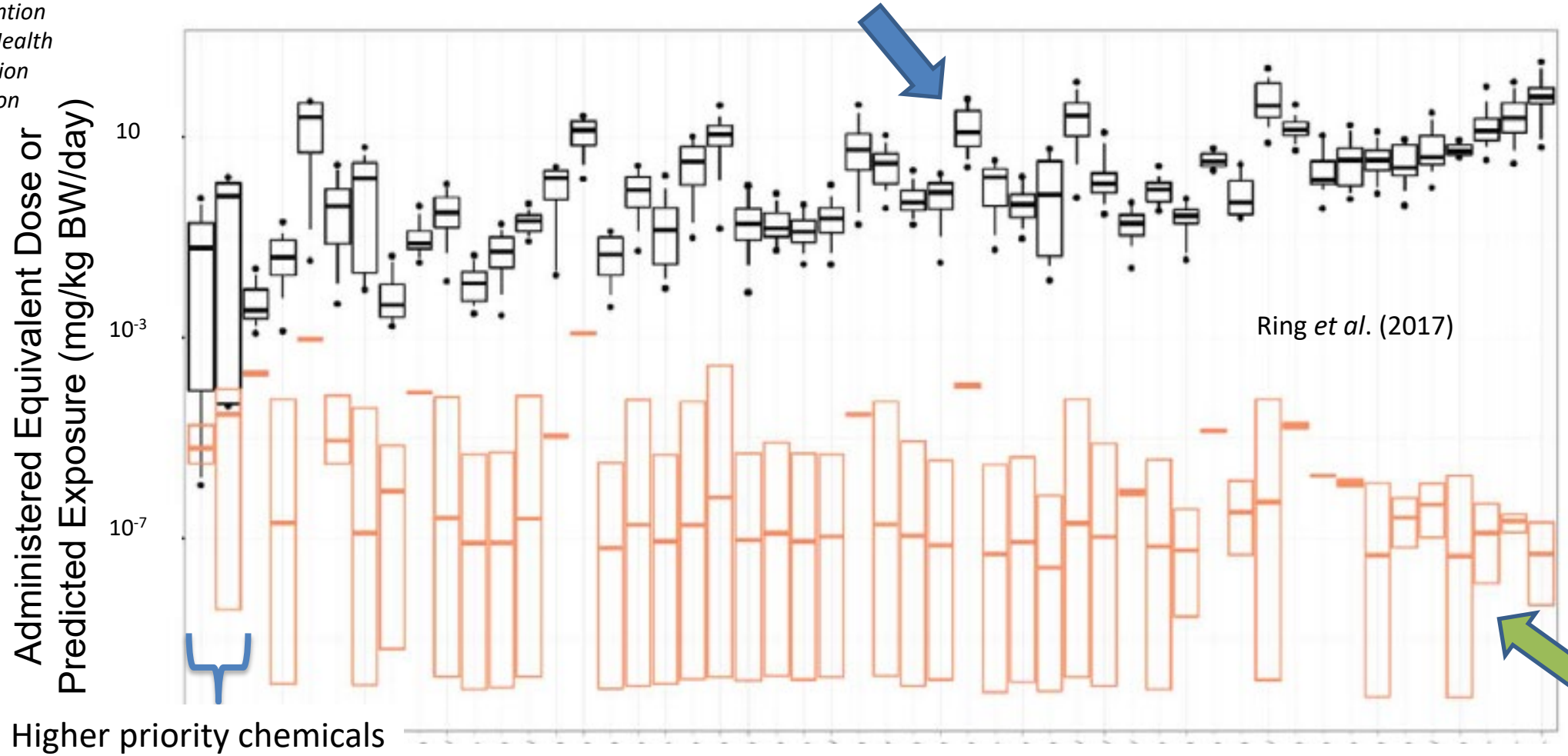

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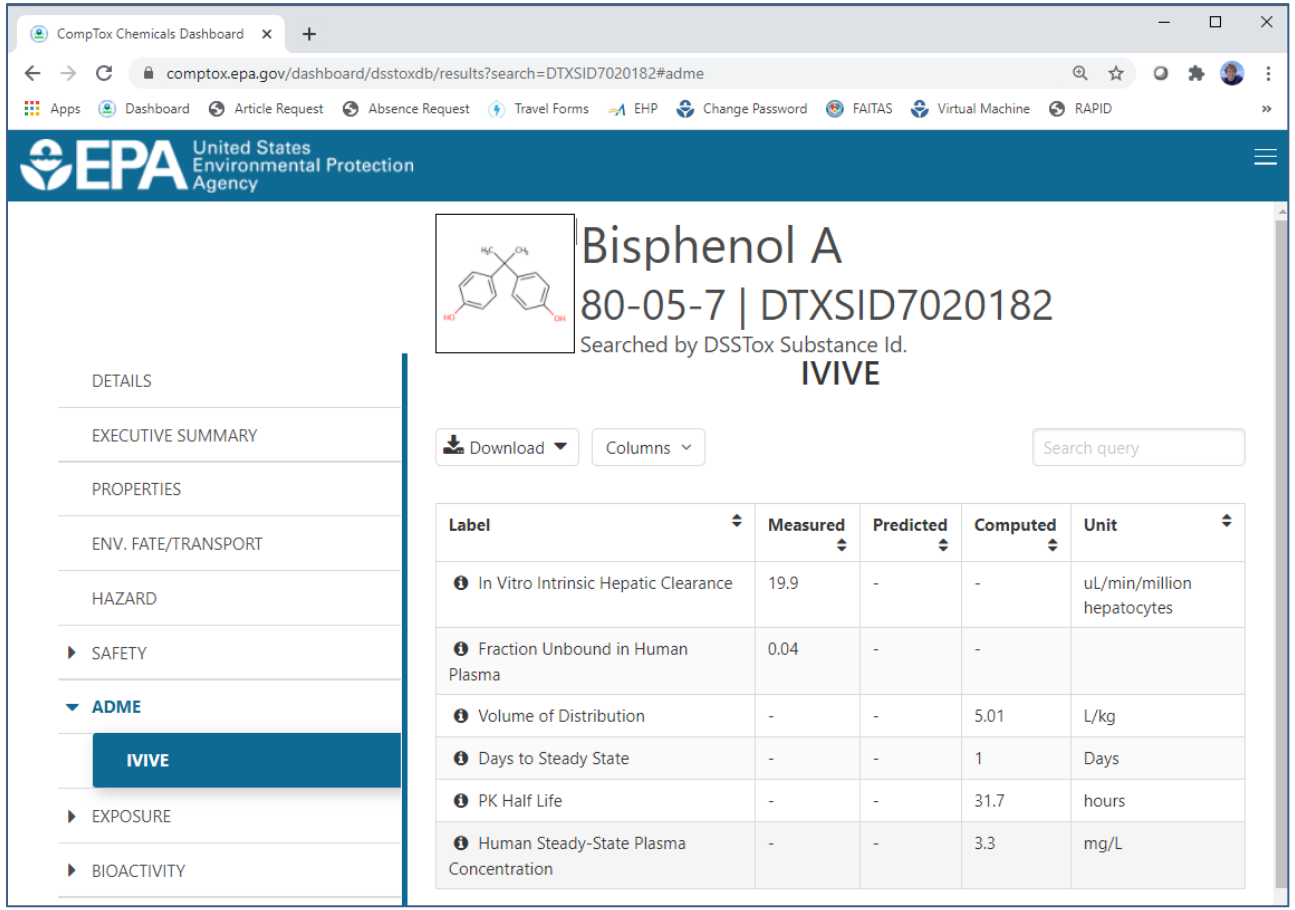
HTTK on the CompTox Chemicals Dashboard

- The CompTox Chemicals Dashboard provides $C_{ss,95}$ values for >1000 chemicals

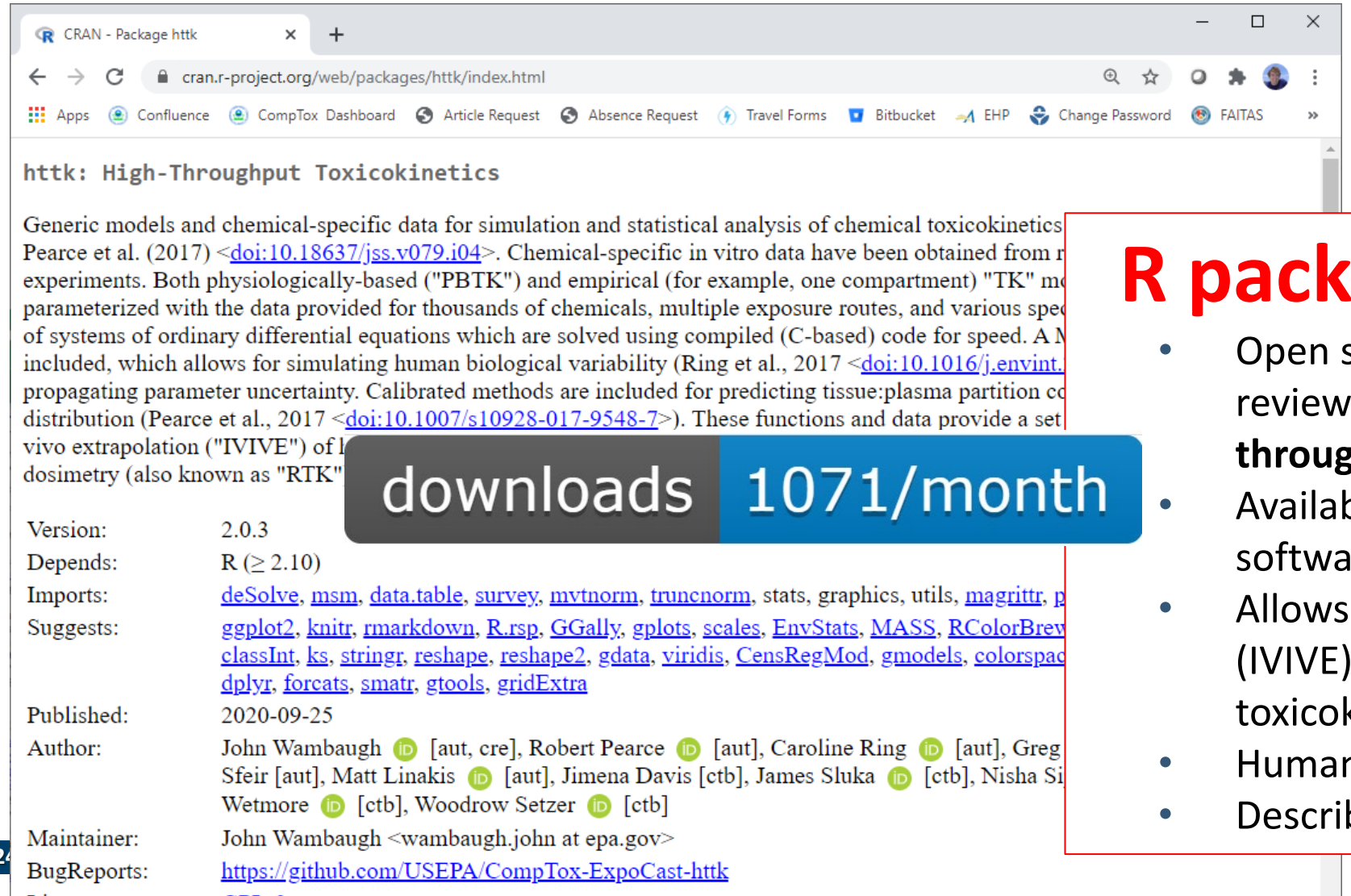
https://comptox.epa.gov/dashboard/

- We use EPA's R package "httk" to provide IVIVE predictions
- The value reported is calculated assuming a 1 mg/kg/day dose rate
- We give the upper 95th percentile of the calculated values based on a Monte Carlo simulation of human variability and uncertainty



Open Source Tools and Data for HTTK

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

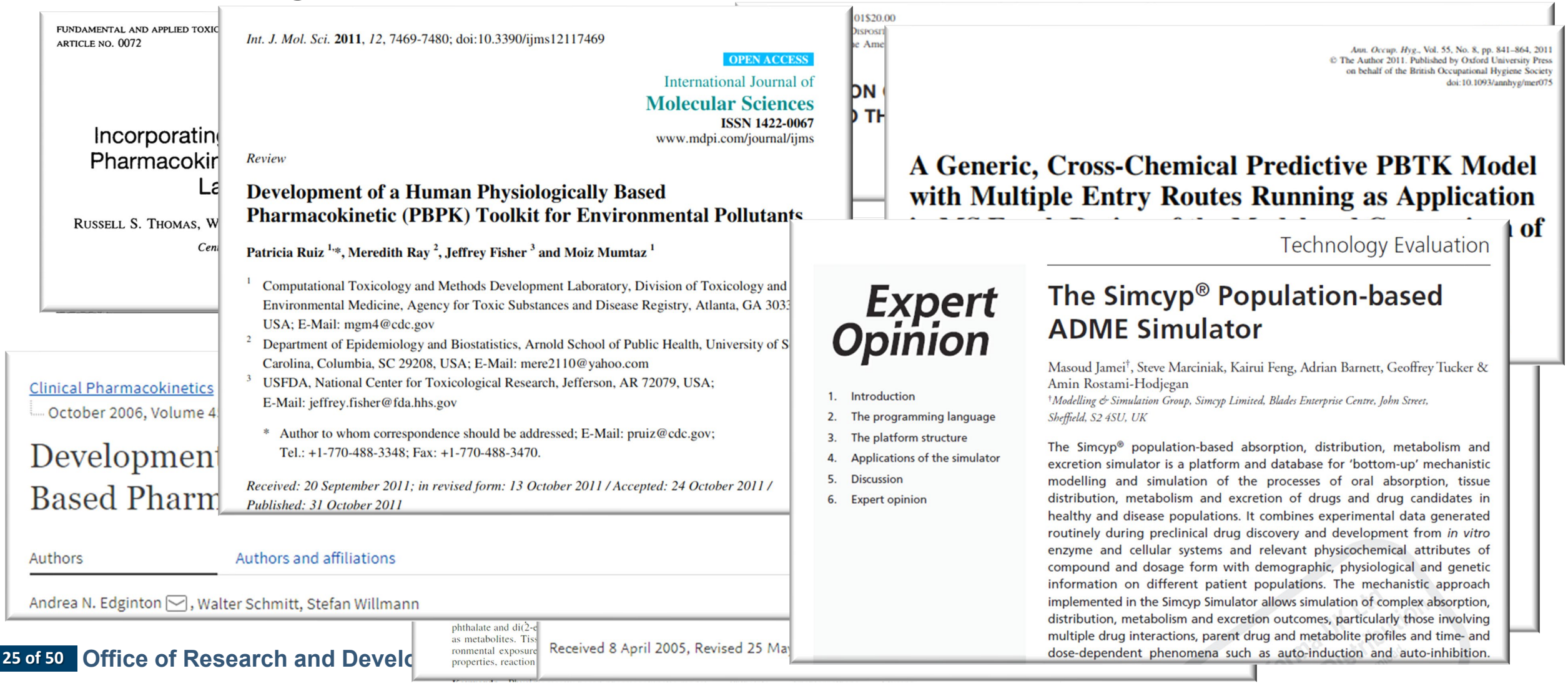


R package "httk"

- Open source, transparent, and peer-reviewed tools and data for **high throughput toxicokinetics (httk)**
- Available publicly for free statistical software R
- Allows *in vitro-in vivo* extrapolation (IVIVE) and physiologically-based toxicokinetics (PBTK)
- Human-specific data for 987 chemicals
- Described in Pearce et al. (2017a)

Generic PBTK Models

The idea of generic PBTK has been out there for a while…



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Int. J. Mol. Sci. **2011**, *12*, 7469-7480; doi:10.3390/ijms12117469

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International Journal of
Molecular Sciences
ISSN 1422-0067
www.mdpi.com/journal/ijms

Review

Development of a Human Physiologically Based Pharmacokinetic (PBPK) Toolkit for Environmental Pollutants

Patricia Ruiz [1,*], Meredith Ray [2], Jeffrey Fisher [3] and Moiz Mumtaz [1]

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[3] USFDA, National Center for Toxicological Research, Jefferson, AR 72079, USA; E-Mail: jeffrey.fisher@fda.hhs.gov

* Author to whom correspondence should be addressed; E-Mail: pruiz@cdc.gov; Tel.: +1-770-488-3348; Fax: +1-770-488-3470.

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Ann. Occup. Hyg., Vol. 55, No. 8, pp. 841–864, 2011
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doi:10.1093/annhyg/mer075

A Generic, Cross-Chemical Predictive PBTK Model with Multiple Entry Routes Running as Application

Clinical Pharmacokinetics
October 2006, Volume 4

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Authors | Authors and affiliations

Andrea N. Edginton, Walter Schmitt, Stefan Willmann

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properties, reaction

Received 8 April 2005, Revised 25 May

Technology Evaluation

Expert Opinion

1. Introduction
2. The programming language
3. The platform structure
4. Applications of the simulator
5. Discussion
6. Expert opinion

The Simcyp® Population-based ADME Simulator

Masoud Jamei†, Steve Marciniak, Kairui Feng, Adrian Barnett, Geoffrey Tucker & Amin Rostami-Hodjegan

†*Modelling & Simulation Group, Simcyp Limited, Blades Enterprise Centre, John Street, Sheffield, S2 4SU, UK*

The Simcyp® population-based absorption, distribution, metabolism and excretion simulator is a platform and database for 'bottom-up' mechanistic modelling and simulation of the processes of oral absorption, tissue distribution, metabolism and excretion of drugs and drug candidates in healthy and disease populations. It combines experimental data generated routinely during preclinical drug discovery and development from *in vitro* enzyme and cellular systems and relevant physicochemical attributes of compound and dosage form with demographic, physiological and genetic information on different patient populations. The mechanistic approach implemented in the Simcyp Simulator allows simulation of complex absorption, distribution, metabolism and excretion outcomes, particularly those involving multiple drug interactions, parent drug and metabolite profiles and time- and dose-dependent phenomena such as auto-induction and auto-inhibition.

Why Build Another Generic PBTK Tool?

	SimCYP	ADMET Predictor / GastroPlus	PK-Sim	IndusChemFate	httk
Maker	SimCYP Consortium / Certara	Simulations Plus	Open Systems Pharmacology	Cefic LRI	US EPA
Reference	Jamei et al. (2009)	Lukacova et al., (2009)	Eissing et al., (2011)	Jongeneelen et al., (2013)	Pearce et al. (2017a)
Availability	License, but inexpensive for research	License, but inexpensive for research	**Free:** http://www.open-systems-pharmacology.org/	**Free:** http://cefic-lri.org/lri_toolbox/induschemfate/	**Free:** https://CRAN.R-project.org/package=httk
Open Source	No	No	**GitHub**	No	**CRAN and GitHub**
Default PBPK Structure	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Population Variability	**Yes**	**Yes**	**Yes**	No	**Yes**
Batch Mode	**Yes**	**Yes**	**Yes**	No	**Yes**
Graphical User Interface	**Yes**	**Yes**	**Yes**	Excel	No*
Built-in Chemical-Specific Library	Many Clinical Drugs	No	Many pharmaceutical-specific models available	15 Environmental Compounds	980 Pharmaceutical and ToxCast Compounds
Ionizable Compounds	**Yes**	**Yes**	**Yes**	No	**Yes**
Export Function	No	No	Matlab and R	No	SBML and Jarnac
R Integration	No	No	**Yes** (2017)	No	**Yes**
Easy Reverse Dosimetry	**Yes**	**Yes**	**Yes**	No	**Yes**

*Both **PLETHEM** (Pendse et al., 2020) and **Web-ICE** (Bell et al., 2020) provide GUI's to HTTK and other models

Pre-computed HTTK results are also available at https://comptox.epa.gov/dashboard

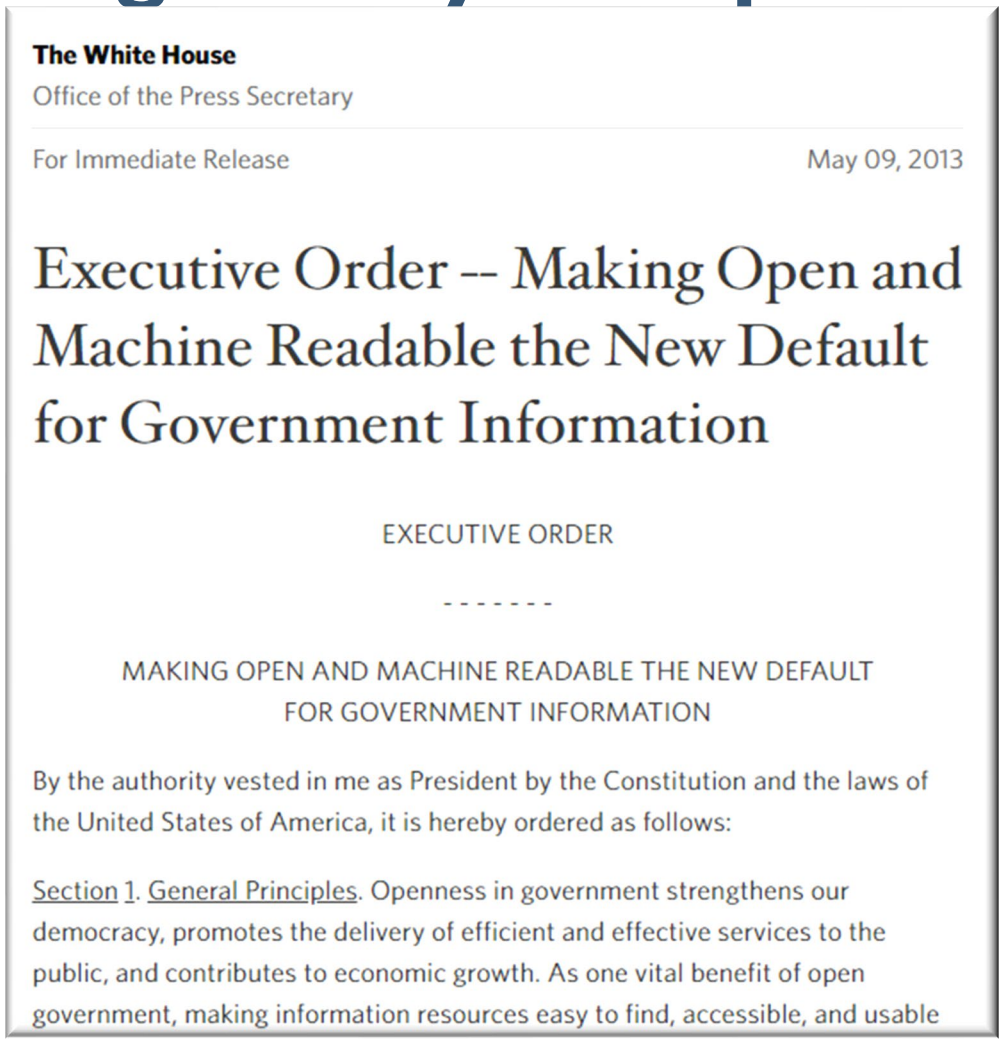
Obstacles to Regulatory Acceptance

TOXICOLOGICAL SCIENCES 126(1), 5–15 (2012)
doi:10.1093/toxsci/kfr295
Advance Access publication November 1, 2011

Physiologically Based Pharmacokinetic Model Use in Risk Assessment—Why Being Published Is Not Enough

Eva D. McLanahan,*[,1] Hisham A. El-Masri,† Lisa M. Sweeney,‡ Leonid Y. Kopylev,|| Harvey J. Clewell,§ John F. Wambaugh,¶ and P. M. Schlosser||

"Although publication of a PBPK model in a peer-reviewed journal is a mark of good science, subsequent evaluation of published models and the supporting computer code is necessary for their consideration for use in [Human Health Risk Assessments]"



The White House
Office of the Press Secretary

For Immediate Release May 09, 2013

Executive Order -- Making Open and Machine Readable the New Default for Government Information

EXECUTIVE ORDER

- - - - - - -

MAKING OPEN AND MACHINE READABLE THE NEW DEFAULT FOR GOVERNMENT INFORMATION

By the authority vested in me as President by the Constitution and the laws of the United States of America, it is hereby ordered as follows:

Section 1. General Principles. Openness in government strengthens our democracy, promotes the delivery of efficient and effective services to the public, and contributes to economic growth. As one vital benefit of open government, making information resources easy to find, accessible, and usable

"…the default state of new and modernized Government information resources shall be open and machine readable."

Why Build Another Generic PBTK Tool?

	SimCYP	ADMET Predictor / GastroPlus	PK-Sim	IndusChemFate	httk
Maker	SimCYP Consortium / Certara	Simulations Plus	Open Systems Pharmacology	Cefic LRI	US EPA
Reference	Jamei et al. (2009)	Lukacova et al., (2009)	Eissing et al., (2011)	Jongeneelen et al., (2013)	Pearce et al. (2017a)
Availability	License, but inexpensive for research	License, but inexpensive for research	**Free:** http://www.open-systems-pharmacology.org/	**Free:** http://cefic-lri.org/lri_toolbox/induschemfate/	**Free:** https://CRAN.R-project.org/package=httk
Open Source	No	No	**GitHub**	No	**CRAN and GitHub**
Default PBPK Structure	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Population Variability	**Yes**	**Yes**	**Yes**	No	**Yes**
Batch Mode	**Yes**	**Yes**	**Yes**	No	**Yes**
Graphical User Interface	**Yes**	**Yes**	**Yes**	Excel	No*
Built-in Chemical-Specific Library	Many Clinical Drugs	No	Many pharmaceutical-specific models available	15 Environmental Compounds	980 Pharmaceutical and ToxCast Compounds
Ionizable Compounds	**Yes**	**Yes**	**Yes**	No	**Yes**
Export Function	No	No	Matlab and R	No	SBML and Jarnac
R Integration	No	No	**Yes** (2017)	No	**Yes**
Easy Reverse Dosimetry	**Yes**	**Yes**	**Yes**	No	**Yes**

*Both **PLETHEM** (Pendse et al., 2020) and **Web-ICE** (Bell et al., 2020) provide GUI's to HTTK and other models

Pre-computed HTTK results are also available at https://comptox.epa.gov/dashboard

Verifying PBTK Models

Process for the Evaluation of PBPK Models

1. Assessment of Model Purpose
2. Assessment of Model Structure and Biological Characterizations
3. Assessment of Mathematical Descriptions
4. Assessment of Computer Implementation
5. Parameter Analysis and Assessment of Model Fitness
6. Assessment of any Specialized Analyses

Clark et al. (2004)

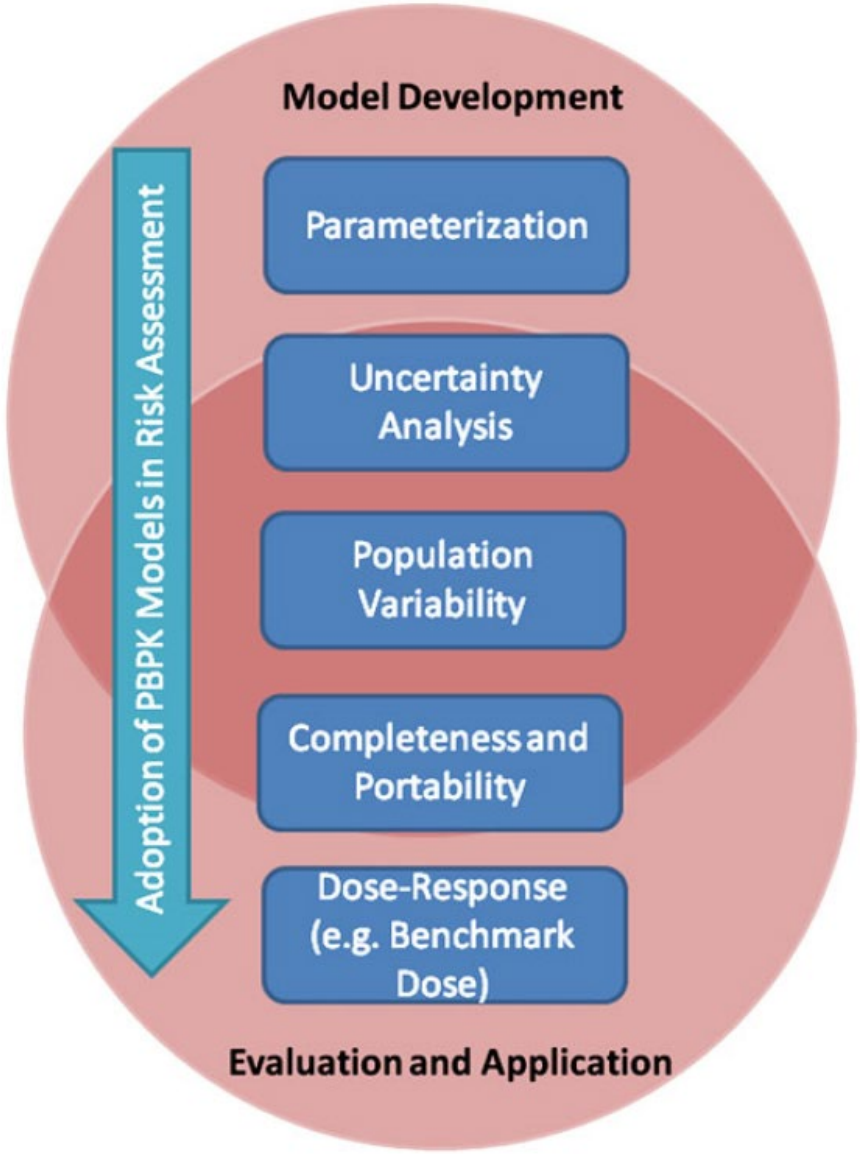
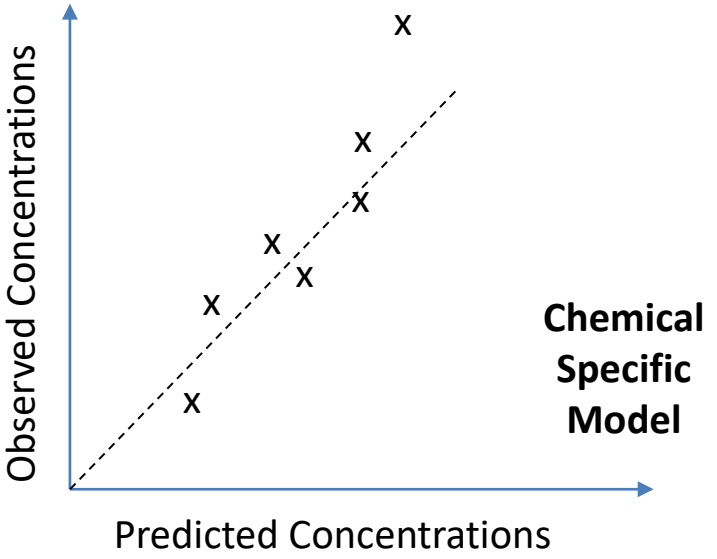


FIG. 1. This figure shows examples of key considerations during model development, evaluation, and application that are necessary before a PBPK model may be adopted for use in a HHRA.

McLanahan et al. (2012)

Building Confidence in TK Models

- 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 have no data



Cohen Hubal et al. (2018)

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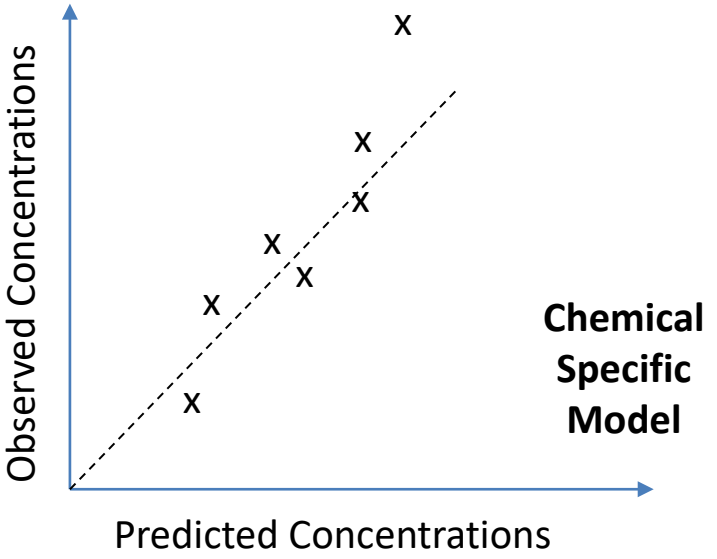
- However, we do not typically have TK data



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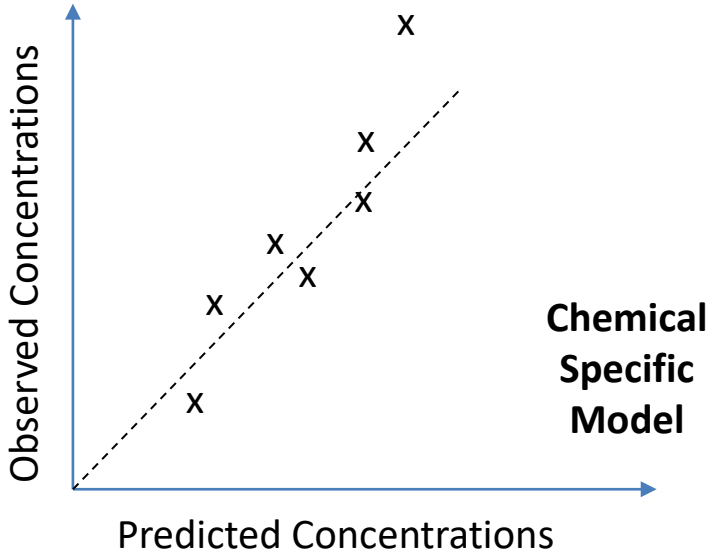
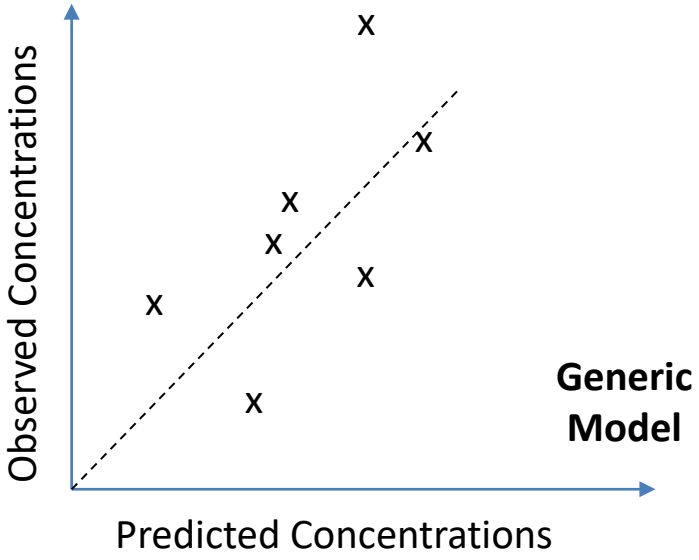
- We can parameterize a **generic TK model**, and evaluate that model for as many chemicals as we do have data
  - We do expect larger uncertainty, but also greater confidence in model implementation
  - Estimate bias and uncertainty, and try to correlate with chemical-specific properties





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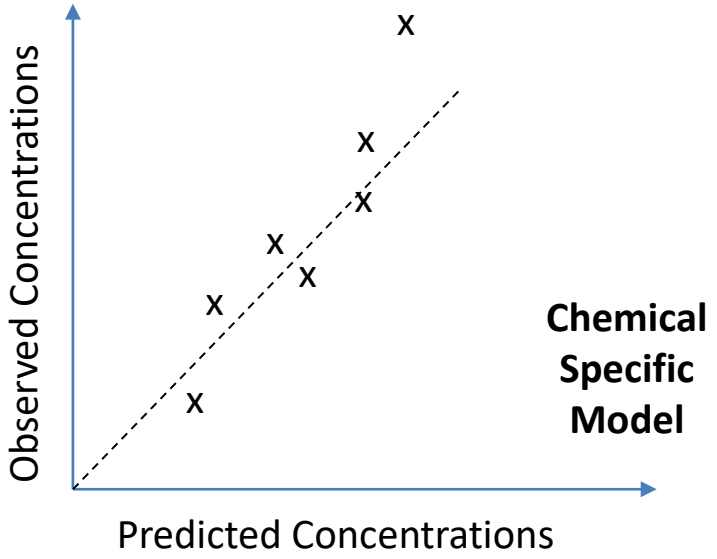

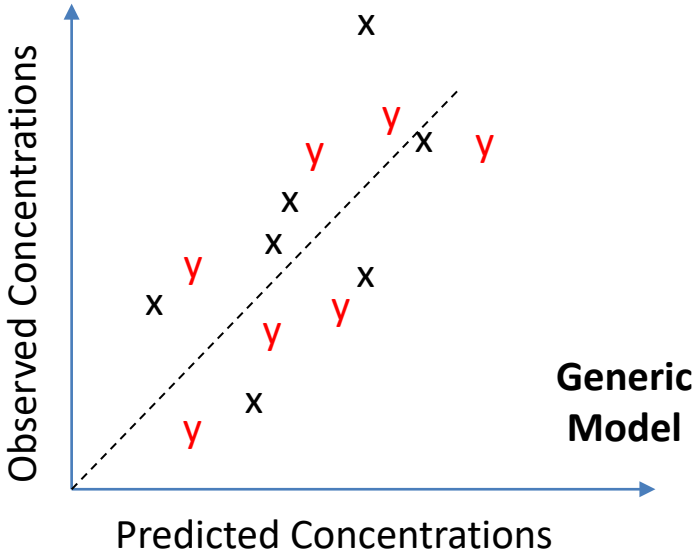

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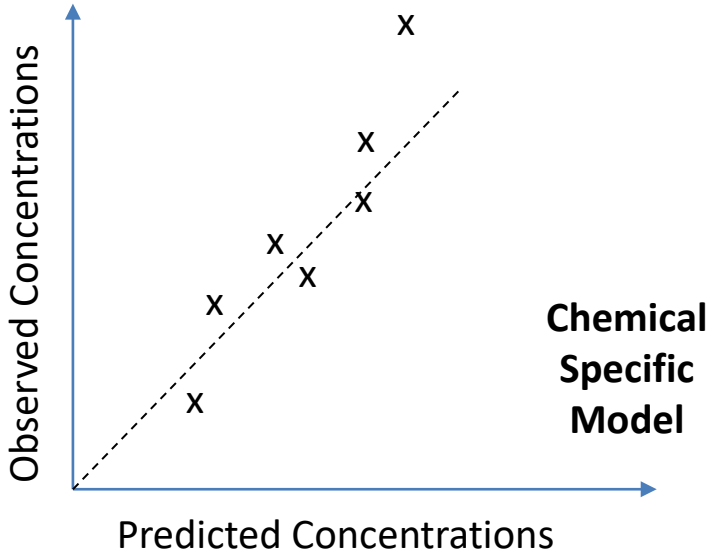
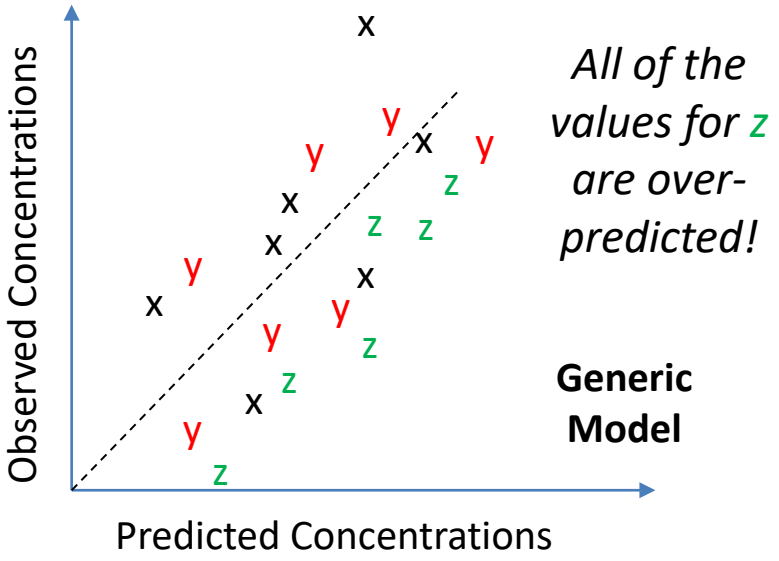




Cohen Hubal et al. (2018)

In Vivo TK Database

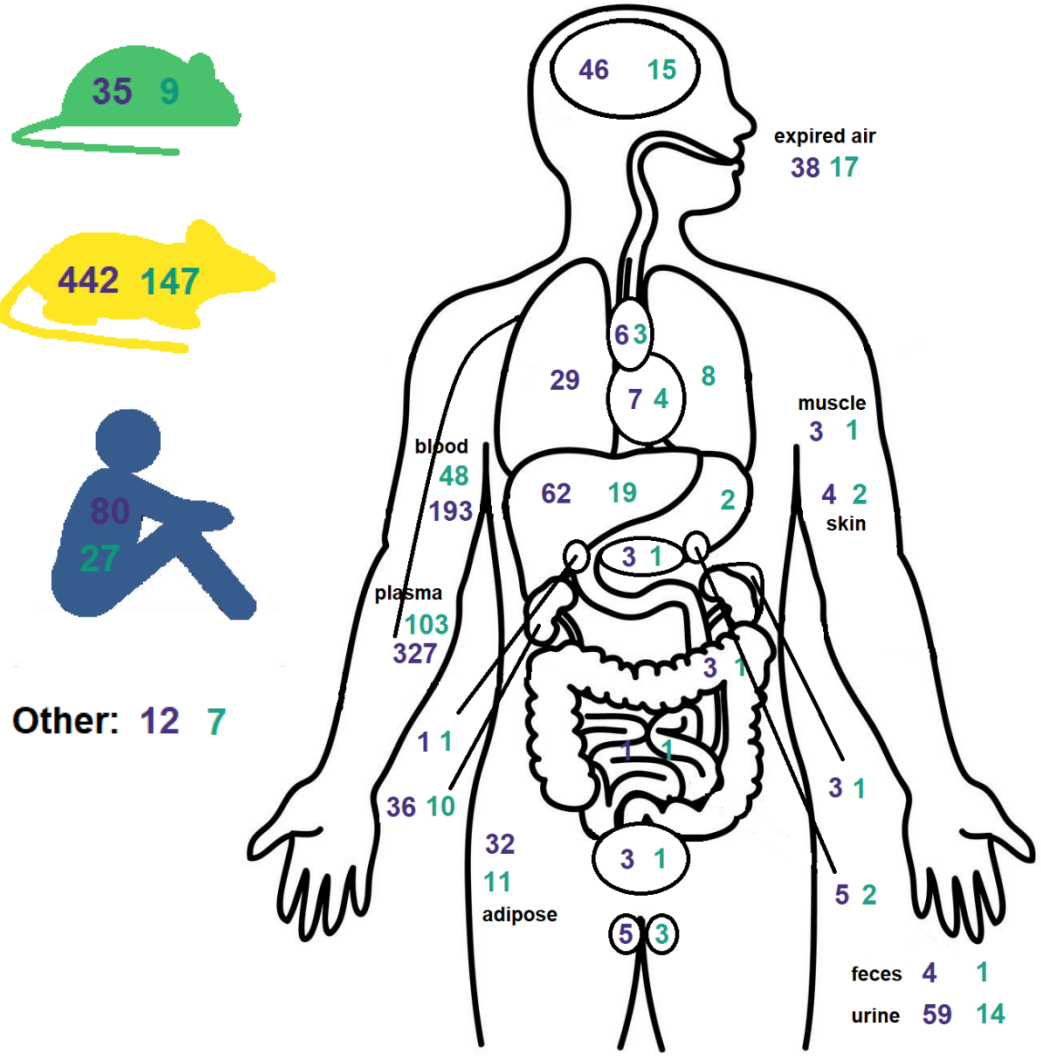
https://github.com/USEPA/CompTox-PK-CvTdb

- EPA has developed a **public database** of **concentration vs. time data** for building, calibrating, and evaluating TK models

- Curation and development is ongoing, but to date includes:
  - 198 analytes (EPA, National Toxicology Program, literature)
  - Routes: Intravenous, dermal, oral, sub-cutaneous, and inhalation exposure

- Standardized, open-source curve fitting software invivoPKfit used to calibrate models to all data:

  https://github.com/USEPA/CompTox-ExpoCast-invivoPKfit



Sayre et al. (2020)

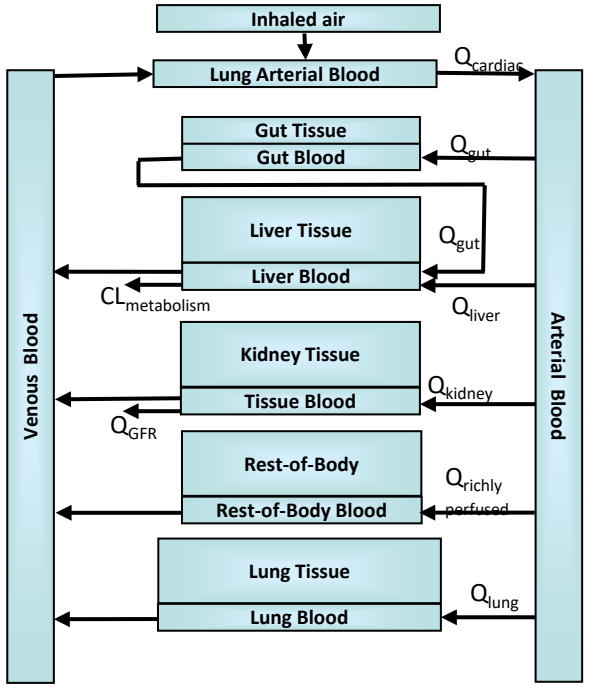
Modules within R Package "httk"

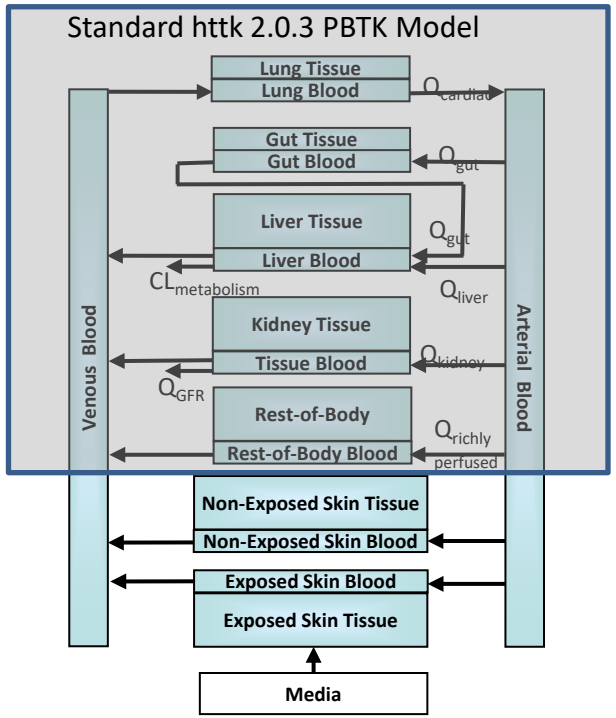
Feature	Description	Reference
Chemical Specific *In Vitro* Measurements	Metabolism and protein binding for ~1000 chemicals in human and ~200 in rat	Wetmore et al. (2012, 2013, 2015), plus others
Chemical-Specific *In Silico* Predictions	Metabolism and protein binding for ~8000 Tox21 chemicals	Sipes et al. (2017)
Generic toxicokinetic models	One compartment, three compartment, physiologically-based oral, intravenous, and inhalation (PBTK)	Pearce et al. (2017a), Linakis et al. (2020)
Tissue partition coefficient predictors	Modified Schmitt (2008) method	Pearce et al. (2017b)
Variability Simulator	Based on NHANES biometrics	Ring et al. (2017)
In Vitro Disposition	Armitage et al. (2014) model	Honda et al. (2019)
Uncertainty Propagation	Model parameters can be described by distributions reflecting uncertainty	Wambaugh et al. (2019)

New HT-PBTK Models

Gas Inhalation Exposure Route

Linakis et al. (2020)



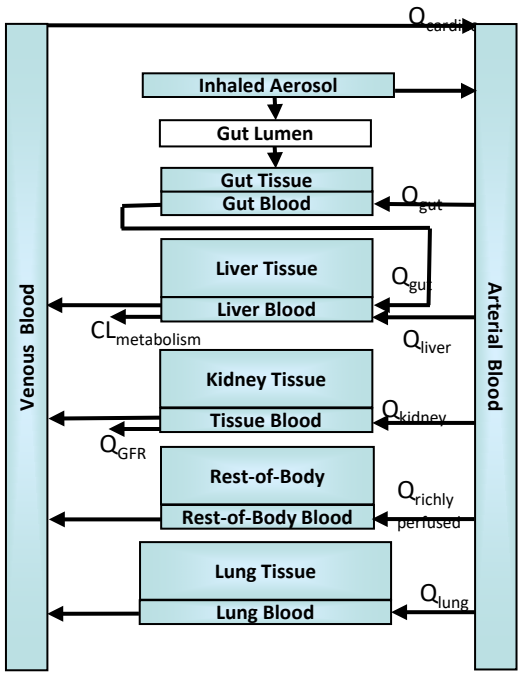


Dermal Exposure Route

EPA, Unilever

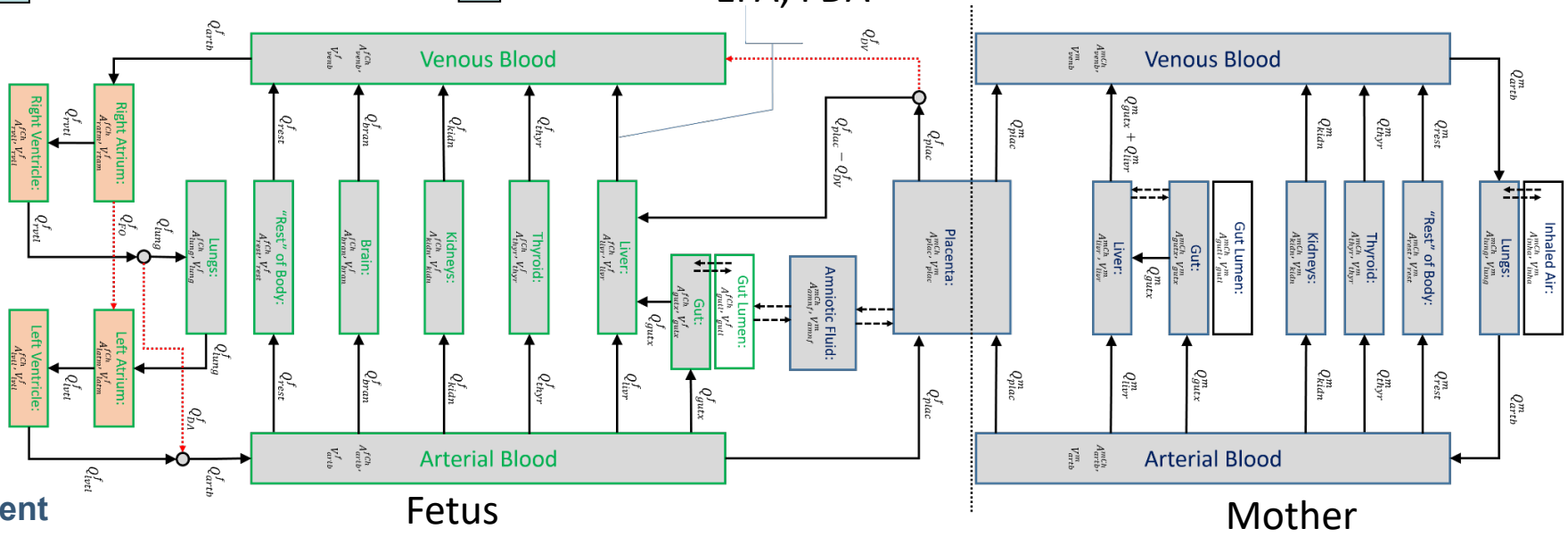
Aerosol Inhalation Exposure Route (including APEX model)

EPA, USAF



Human Gestational Model

EPA, FDA

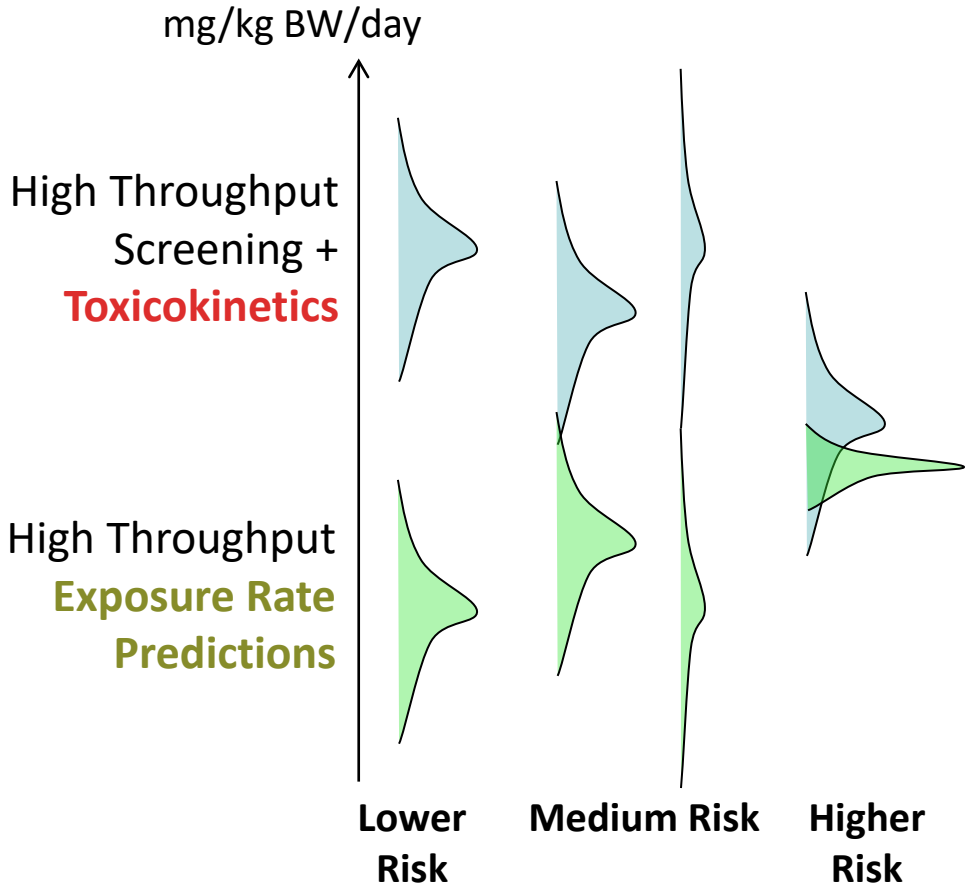


HTTK Limitations: "Domain of Applicability"

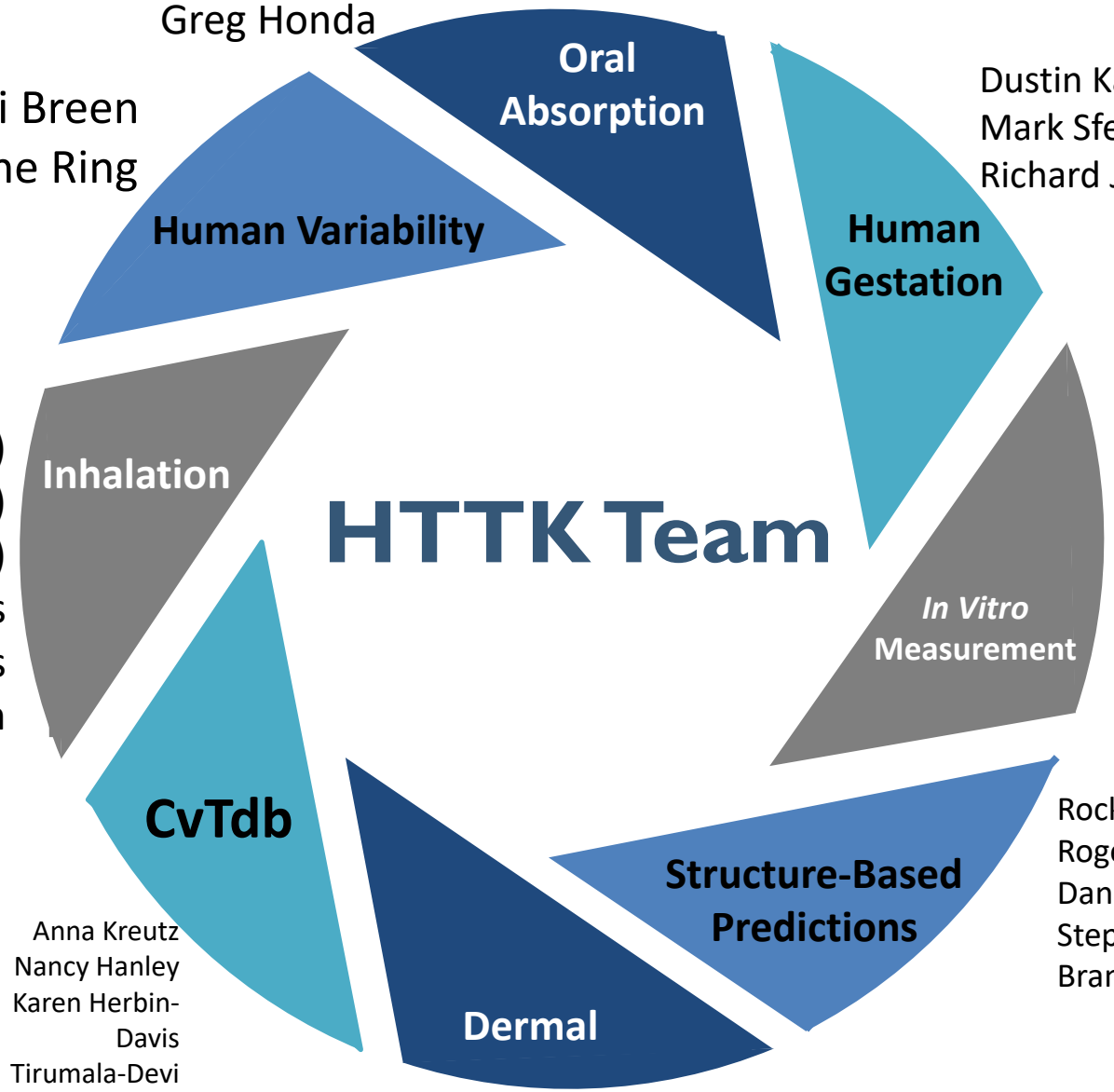
- Oral absorption
  - 100% assumed, but may be very different
  - *In silico* models not necessarily appropriate for environmental chemicals
  - Honda et al. (in preparation) developing QSAR using new *in vitro* data for ToxCast Chemicals
- Hepatic Clearance (CL_{int})
  - Not isozyme-specific (Isozyme-specific metabolism assays not HT)
  - Ten donor pool in suspension for 2-4 h misses variability and low turnover compounds
  - Isozyme abundances and activity: varies with age, ethnicity (at least) (Yasuda et al. 2008, Howgate et al. 2006, Johnson et al. 2006)
  - Parent chemical depletion only
  - *In silico* predictions of isozyme-specific metabolism? Not easy!
    - Though ADMET Predictor can do this for some isozymes, training data is mostly for pharmaceuticals
- Plasma binding assay (F_{up})
  - Plasma protein concentration variability (Johnson et al. 2006, Israili et al. 2001)
  - Albumin or AAG binding? (Routledge 1986)
- Analytical chemistry
  - Must be able to develop method for each compound
  - Working to develop QSARs for other compounds

Conclusions

- HTTK allows dosimetric adjustment of high-throughput screening (HTS) data
  - Thousands of chemicals
  - Open source, free, and evaluated software
- Generic PBTK models allow for verification of model implementation
- Comparing model predictions for chemicals with *in vivo* data allows estimation of model bias and uncertainty
- Establishes the confidence in predictions for chemicals without *in vivo* data



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



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