United States Environmental Protection Agency

ExpoCast
*exposure forecasting*

# High-Throughput Toxicokinetic Models and *In Vitro-In Vivo* Extrapolation (IVIVE)

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US EPA CSS-HERA Board of Scientific Counselors
Chemical Safety Subcommittee Meeting



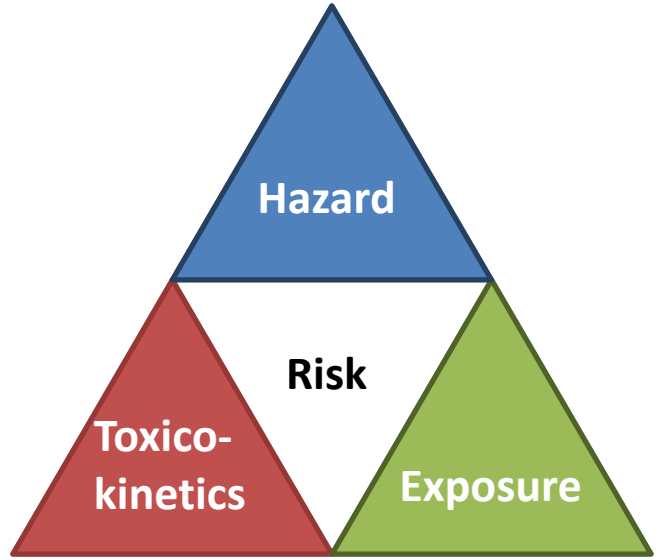
*February 2, 2021*

# NAMs for Exposure *Toxicokinetics*

*Acceptance and use of* in vitro *data for hazard identification is limited by uncertainties associated with exposure characterization and metabolism*

**Many *in vitro* systems:**

- lack consideration of biotransformation capabilities
  - Overestimation of hazard for chemicals rapidly cleared *in vivo*
  - Underestimation of hazard for chemicals bioactivated *in vivo*
- lack consideration of exposure route
- lack consideration of susceptible populations / life stages
- *In vitro* potency estimates are often not adjusted for chemical availability in the *in vitro* system (ie, *in vitro* disposition)



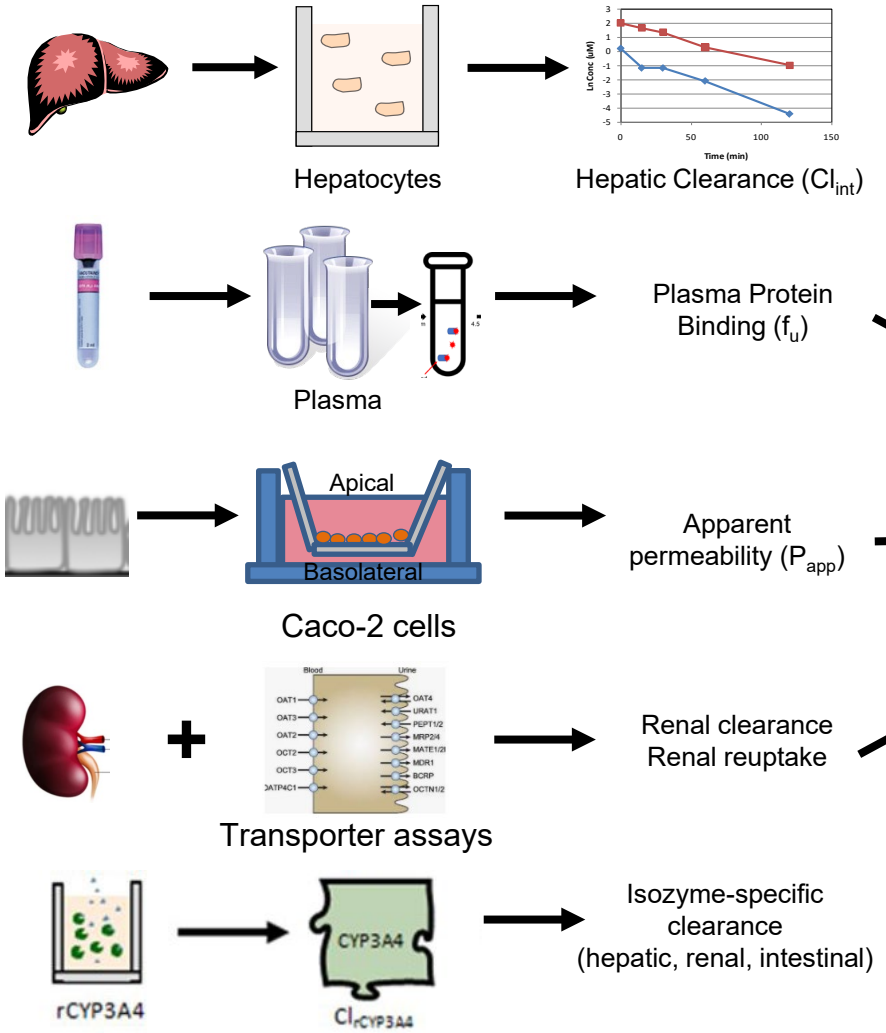

*Recent Agency Case Study Finding:*

***→ TK data availability rate limiting factor in TSCA screening for chemical prioritization***

*"A Proof-of-Concept Case Study Integrating Publicly Available Information to Screen Candidates for Chemical Prioritization under TSCA"

# *In Vitro-In Vivo* Extrapolation (IVIVE)

## I. *In Vitro* Toxicokinetic Assays




IVIVE originally used and vetted in pharma applications
HT-IVIVE approach uses
- hepatic clearance
- plasma protein binding
- conservative assumptions

Predictions consistently protective of human health

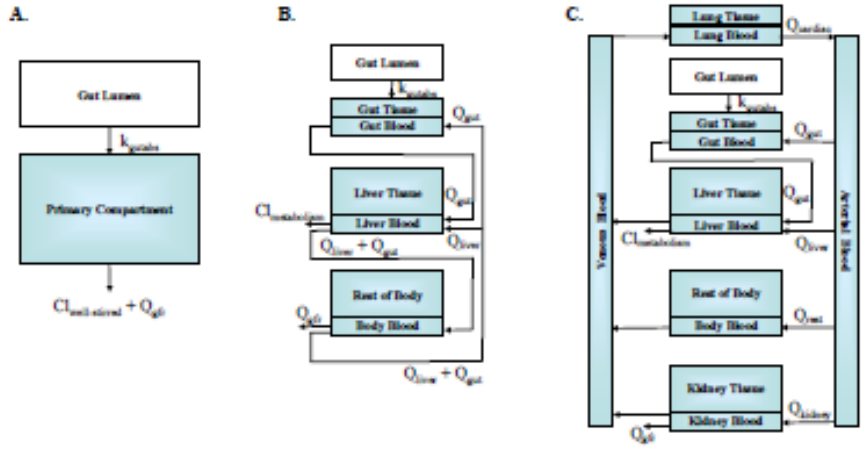
**IVIVE**

**Internal Concentration Predictions Given a Set Administered Dose**

**Ongoing efforts will:**
- Incorporate additional TK inputs for better predictivity
- Assess impact of transporter involvement
- Evaluate extent of population variability
- Employ experimental measures to develop predictive tools


Rotroff *et al., Tox Sci.*, 2010
Wetmore *et al., Tox Sci.,* 2012
Wetmore *et al.*, Tox Sci., 2014
Wetmore *et al., Tox Sci.,* 2015
Wambaugh *et al.*,*Tox Sci.,* 2015
Honda *et al.,* 2019
Wambaugh *et al.*, 2019
Smeltz *et al.*, in preparation
Kreutz *et al.*, in preparation

# *In Vitro-In Vivo* Extrapolation
# II. Physiologically-based Toxicokinetic Modeling




**Evolving Capabilities**

- Augmentation of PBTK models based on need
- Expanding to incorporate additional TK data (intestinal, renal compartments)
- Incorporating additional exposure routes
- Incorporating additional pathways (gestational)
- Incorporating demographic info to expand population-based info (variability)

## "httk": Open-source modeling package

**Modeling Platform** incorporates:

- **chemical-specific** inputs (TK data, physico-chemical)
- **physiologic** inputs (blood flow rates, tissue size)

into ***Simulations*** set up for:

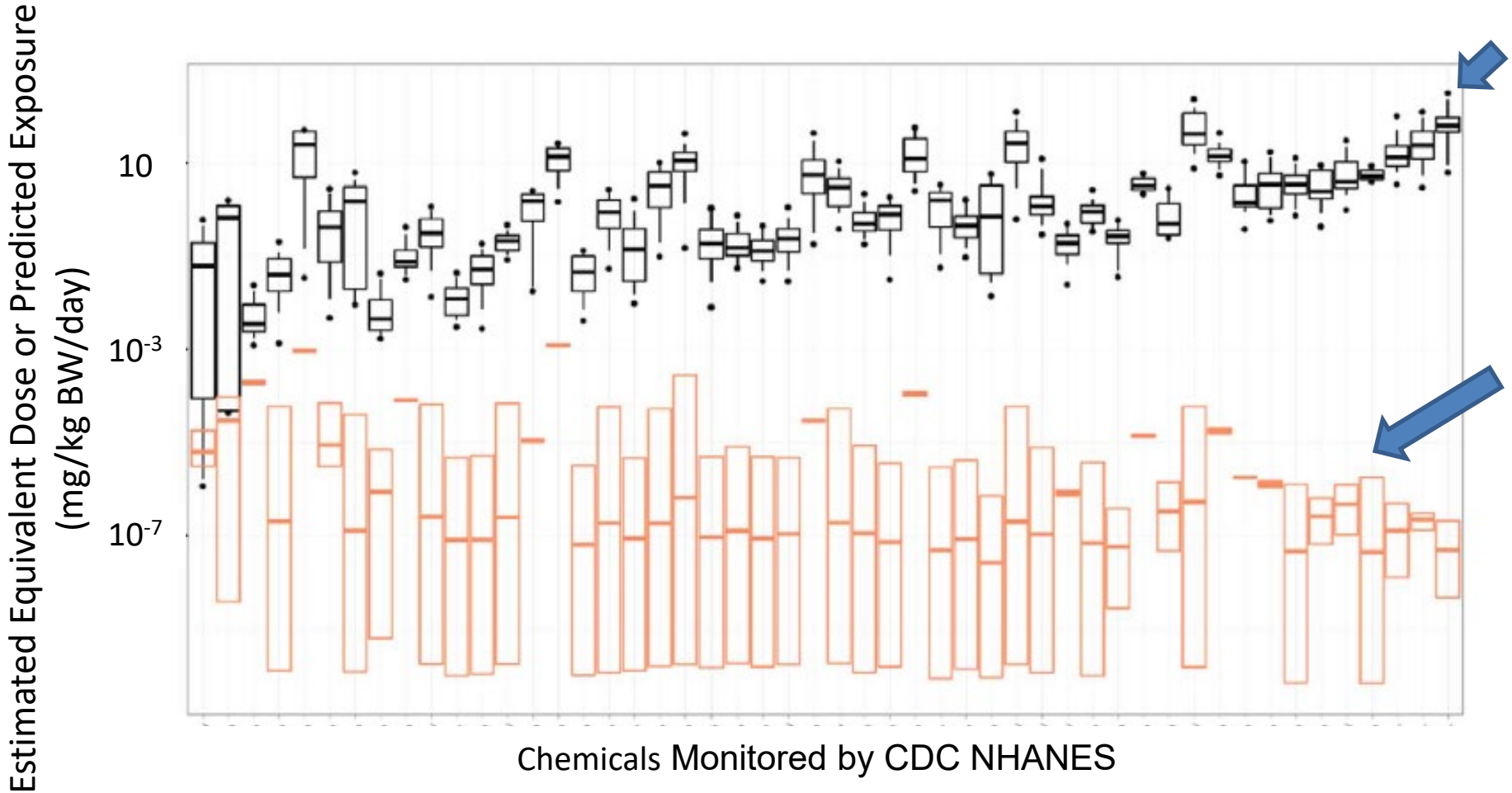
- **populations** of interest
- **exposures** of interest
  - Capturing **variability** (within or across populations)

Based on variations in the physiologic inputs (Monte Carlo)

Pearce *et al.*, 2017, *J Statistical Software*

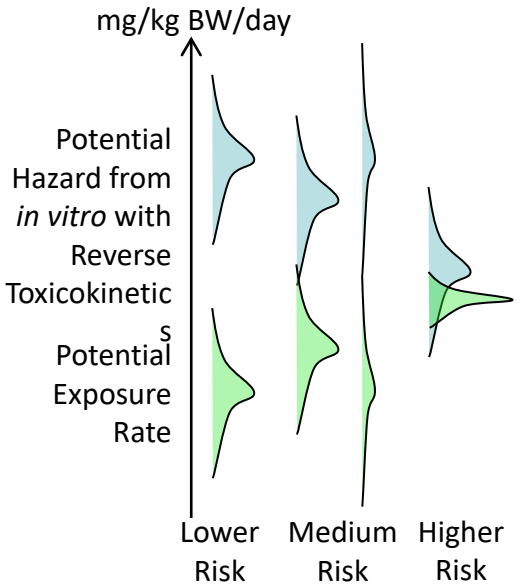
# NAMs for Prioritization

## *Integrating Hazard, TK, and Exposure*




High throughput *in vitro* screening can be used to estimate doses needed to cause bioactivity

Exposure intake rates can be inferred from biomarkers




Wambaugh *et al.*, 2014
Wetmore *et al.*, 2015
Ring *et al.* (2017)
*And others…*

# Toxicokinetics and IVIVE – Stakeholder Needs

## Ongoing Development of Toxicokinetic and IVIVE Tools for use in NAMs

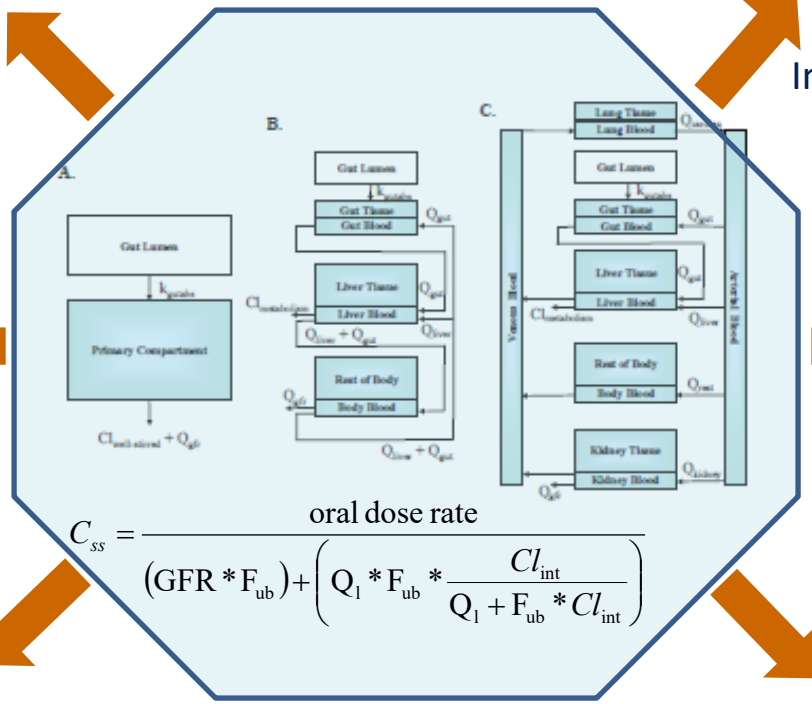
- Primary goal: to provide a human exposure-dose context for bioactive *in vitro* concentrations from NAMs for hazard testing
  - TK Methods across TSCA landscape – including *challenging chemistries*, *emerging contaminants*
  - Incorporating more exposure routes and pathways
  - Tools to characterize exposures to sensitive populations and life stages
  - Characterize *in vitro* disposition across TSCA landscape
  - Tools to identify, quantitate and/or reduce sources of uncertainty
- Secondary goal: to provide **open-source data and models** for evaluation and use by the broader scientific community
  - Concomitant incorporation of above tools and data in HTTK package
  - Databases with *in vitro*, *in vivo* data for use in IVIVE evaluations, *in silico* tool development

# Rapid Exposure Modeling and Dosimetry

**HTTK: Open-Source Platform**

**Predictive Tools**
Plasma protein binding
Hepatic clearance
Transporter Involvement
Isozyme Involvement

**Model Expansion**
Multi-compartment; PBTK
Exposure routes
Gestational pathway
Incorporating new TK data streams




$$C_{ss} = \frac{\text{oral dose rate}}{(\text{GFR} * \text{F}_{ub}) + \left(\text{Q}_l * \text{F}_{ub} * \frac{Cl_{int}}{\text{Q}_l + \text{F}_{ub} * Cl_{int}}\right)}$$

**Databases**
*in vitro* TK data
In vivo TK data (CvTdb)

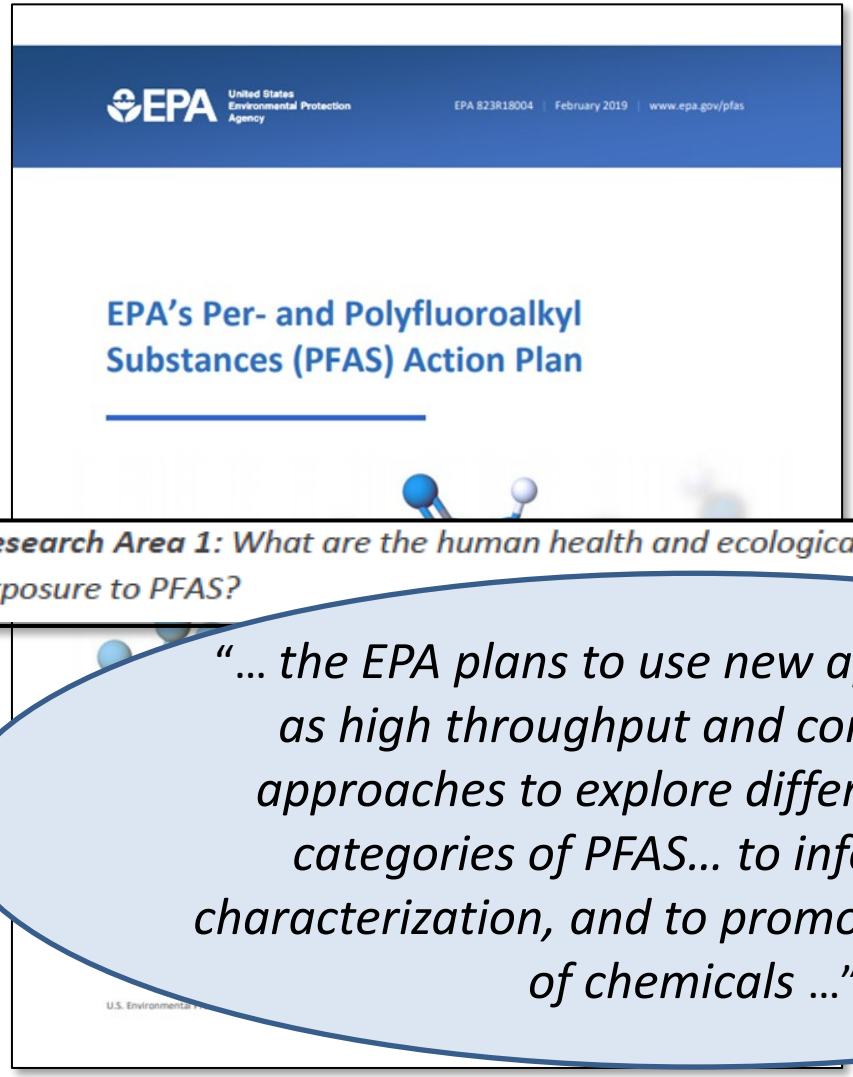
**Refinement**
IVIVE / IVIVC efforts
*In Vitro* Disposition
Best Practices

**TK Data Generation**
***in vitro:***
More chemicals, chemistries
Species expansion (rat, human)
TK assay expansion (intestinal, renal)
***in vivo:***
Rat (cross-species extrapolation)

**Population Variability**
NHANES; physiology
Toxicokinetic variability

**Uncertainty / Variability Assessments**
Bayesian approaches
Experimental uncertainty
Biologic variability

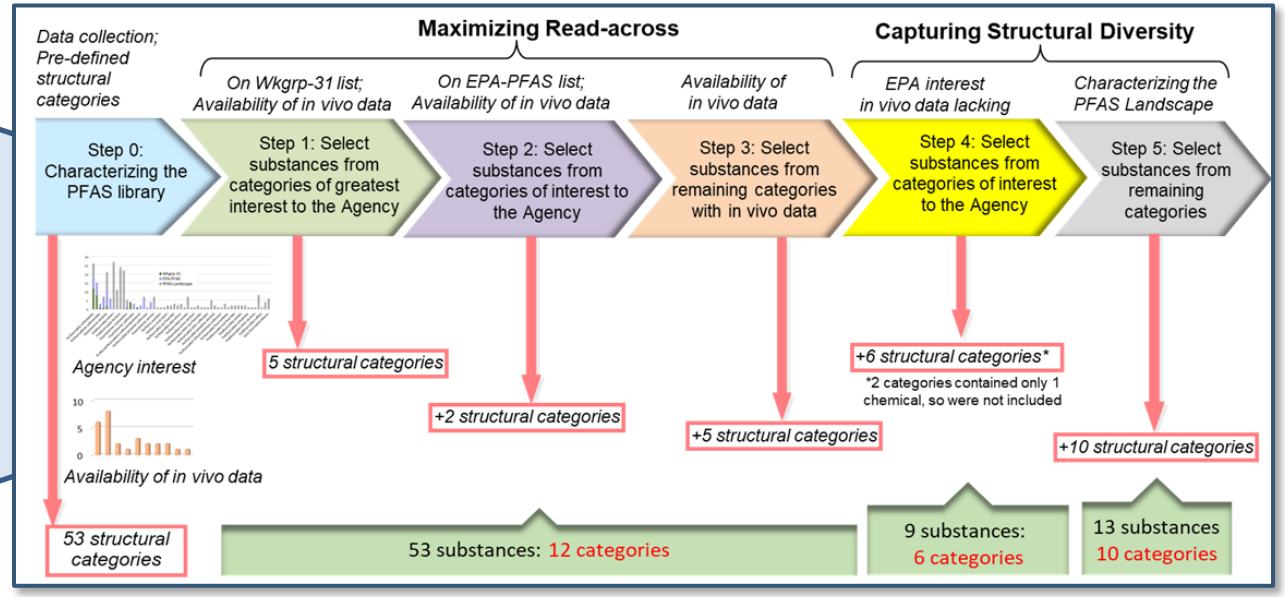
# - *In Vitro* Toxicokinetic Data Generation -
# PFAS: Using NAMs to Fill Information Gaps




Goals:

- Generate data to support development and refinement of categories and read-across evaluation
- Incorporate substances of interest to Agency
- Characterize mechanistic and toxicokinetic properties of the broader PFAS landscape

*"… the EPA plans to use new approaches such as high throughput and computational approaches to explore different chemical categories of PFAS… to inform hazard characterization, and to promote prioritization of chemicals …"*

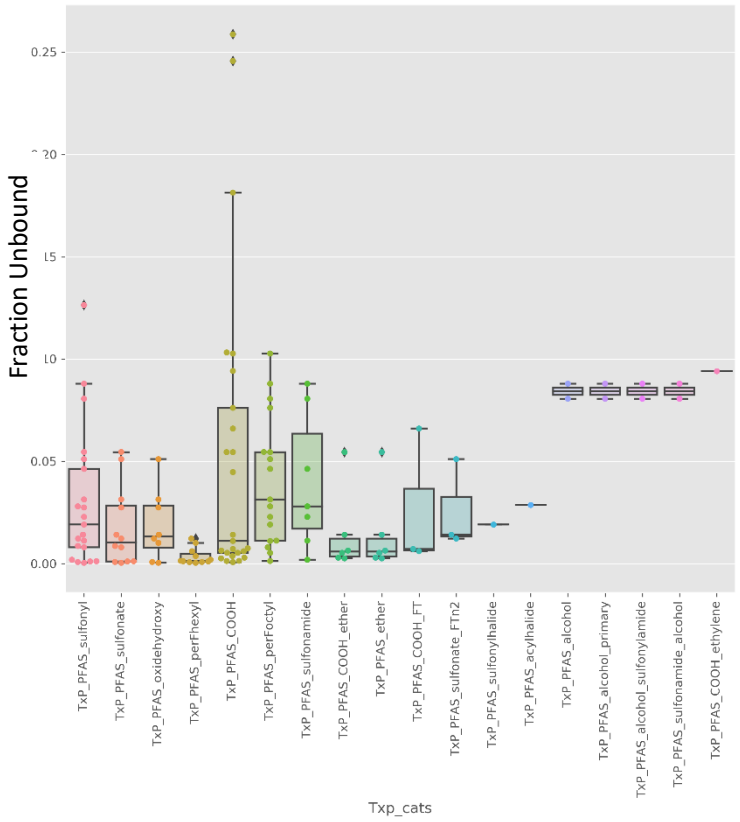


# - *In Vitro* Toxicokinetic Data Generation -
## Category-Based Analyses of Toxicokinetic Data

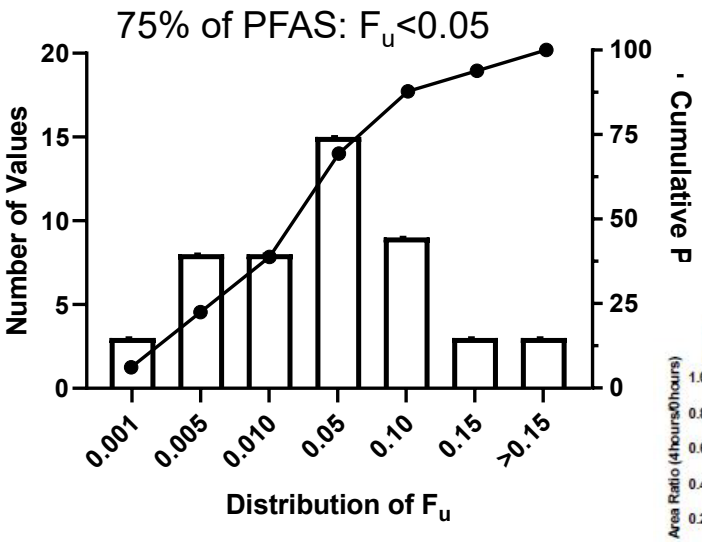
**PFAS TK data: ~150 PFAS**
- Hepatic clearance
- Plasma protein binding
- Renal transporter activity

→ IVIVE, modeling, TK NAMs

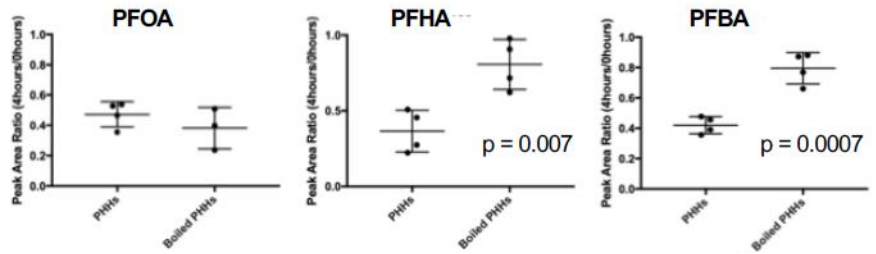
**Category-Based Analysis of Plasma Protein Binding Data**

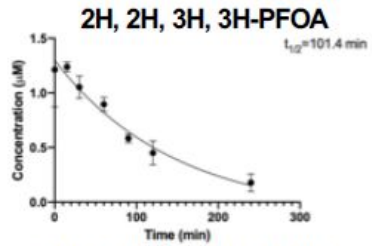



**Preliminary set: Plasma protein binding data across 50+ PFAS**

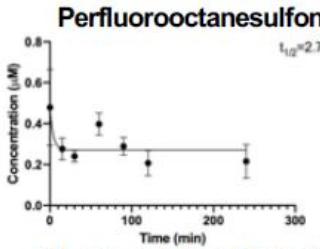



**Hepatic Clearance Data**



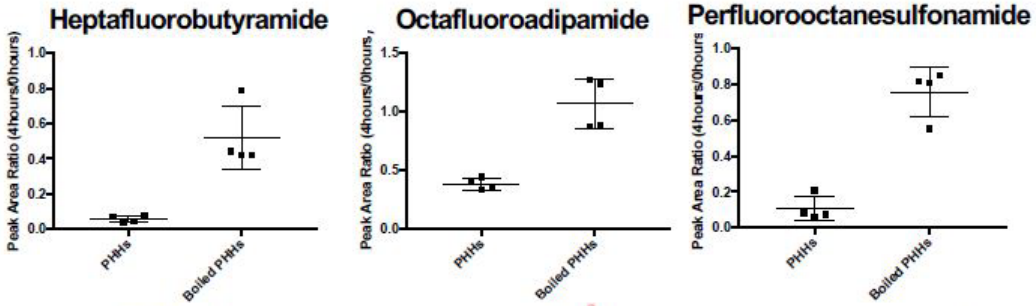




CLint = 0.9 mL/min/kg




CLint = 33.5 mL/min/kg

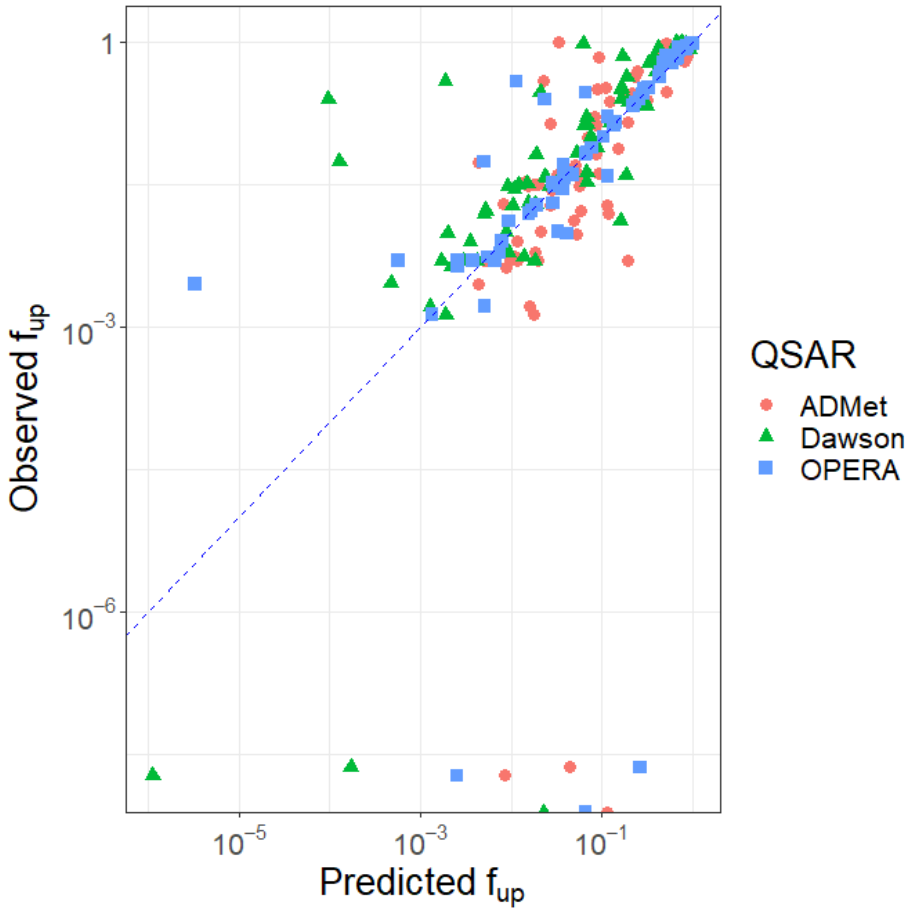
**PFAS - Amides**

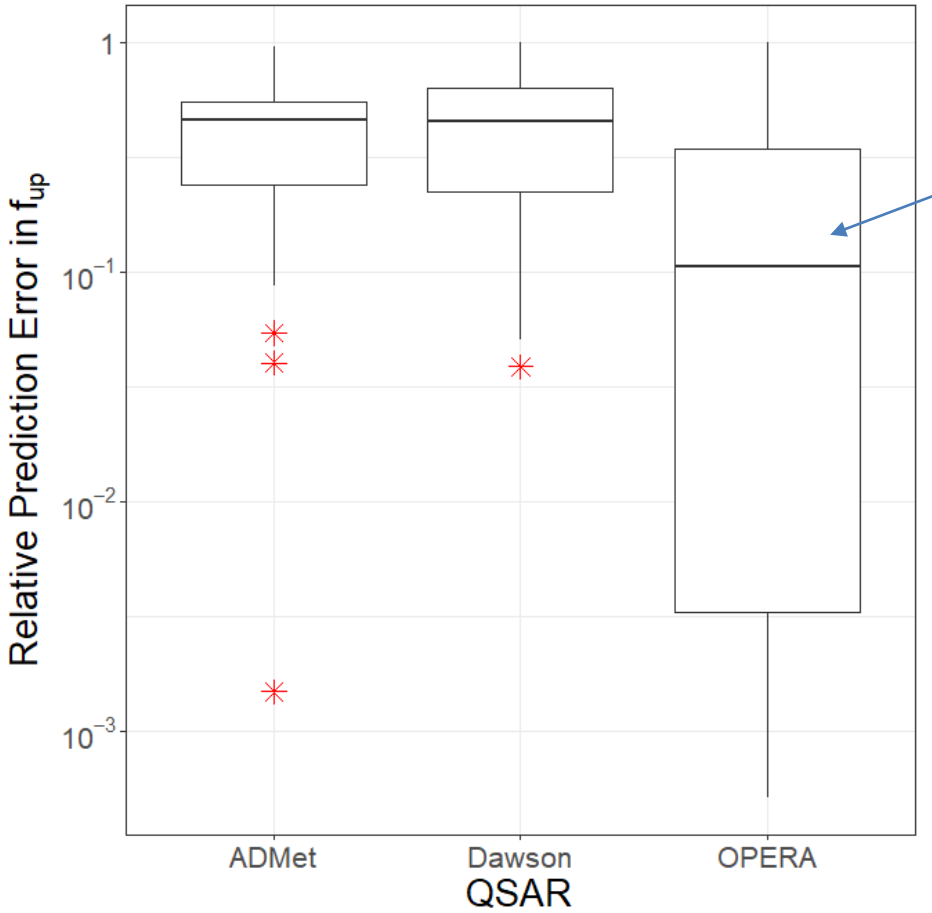


# - Predictive Tool Development -

- *In vitro* TK measurements are being employed in model development and evaluation.
  - Plasma protein binding ($f_u$); hepatic clearance ($Cl_{int}$) underway; others to follow.

*In silico* predictions for $f_u$ (plasma protein binding)




This method uses nearest neighbors, and many evaluation chemicals are in training set

Dawson *et al.* submitted
Pradeep *et al.*, 2020
Tornero-Velez *et al.*, underway
Sipes *et al.*, 2017

# - Model Expansion - Gestational Pathway

RESEARCH ARTICLE

## Empirical models for anatomical and physiological changes in a human mother and fetus during pregnancy and gestation

**Dustin F. Kapraun[1]*, John F. Wambaugh[2], R. Woodrow Setzer[2], Richard S. Judson[2]**

**1** National Center for Environmental Assessment, US Environmental Protection Agency, Research Triangle Park, North Carolina, United States of America, **2** National Center for Computational Toxicology, US Environmental Protection Agency, Research Triangle Park, North Carolina, United States of America

* kapraun.dustin@epa.gov

**Table 1. Itemized comparison of selected publications that contain one or more formulae related to human gestation and pregnancy.**

| Manuscript | [27] | [15] | [25] | [28] | [29] | [31] | [3] | [32] |
|---|---|---|---|---|---|---|---|---|
| Presents original data* | N | N | N | N | N | N | N | N |
| Presents original compiled data* set(s) | Y | N | N | Y | N | N | Y | Y |
| Presents original models† based on compiled data sets of Abduljalil et al. [28] | N | N | N | Y | Y | N | N | N |
| Presents original models† based on compiled data sets of Abduljalil et al. [33] | N | N | N | N | N | N | N | N |
| (+) Employs and thoroughly describes rigorous statistical methods for parameter‡ estimation | Y | N | Y | N | N | N | Y | N |
| (+) Employs and thoroughly describes rigorous statistical methods for model† selection | N | N | N | N | N | N | Y | N |
| (+) Presents original models† for multiple maternal compartments | N | Y | N | Y | Y | Y | Y | N |
| (+) Presents original models† for multiple fetal compartments | N | Y | Y | N | N | Y | N | Y |
| (+) Presents models that reflect a biologically accurate depiction of the fetal circulatory system§ | N | N | N | N | N | Y | N | N¶ |
| (+) Presents explicit models† for "rest of body" compartments that yield feasible (e.g., non-negative) values for all relevant time points | N | N | N | N | N | N | N | Y |
| (+) Systematically compares original models† with previously published models† | N | N | N | N | N | N | N | N | N | Y |
| (-) Presents models that contain errors or inconsistencies identified in the current manuscript | N | Y | N | N | Y | N | Y | Y | Y | N |

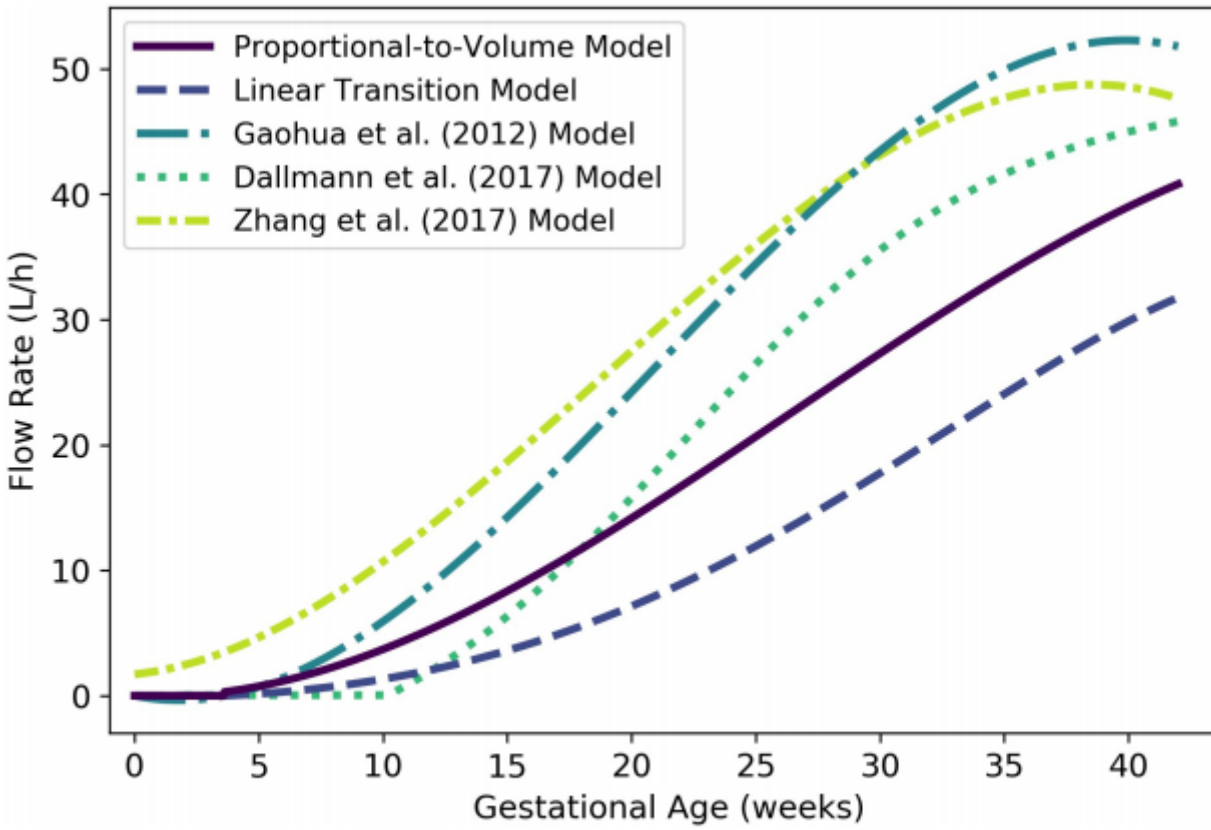
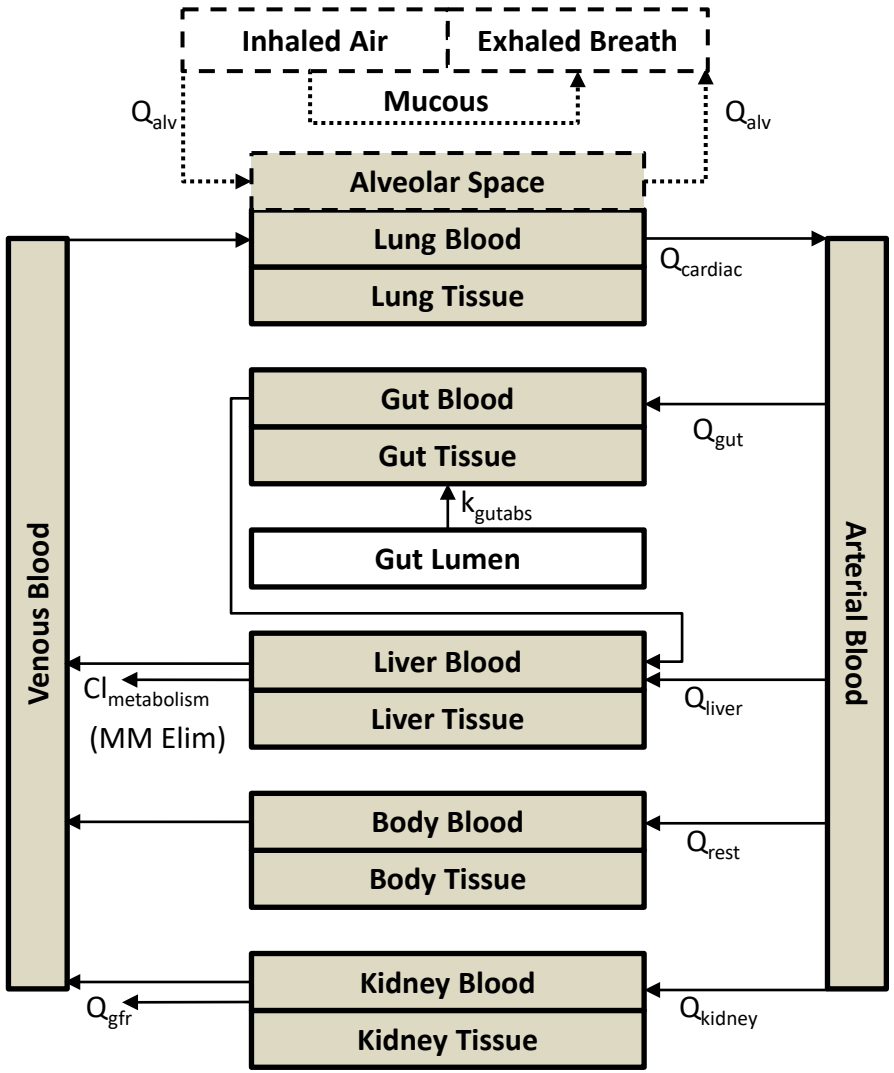



**Fig 11. Maternal blood flow to the placenta vs. gestational age.** The proportional-to-volume model (solid line) given by Eq 22, the linear transition model given by Eq 21, and two published models [3, 29, 32] are shown.

Kapraun *et al.*, 2019 PLOS One

# - Model Expansion - Generic Gas Inhalation Model



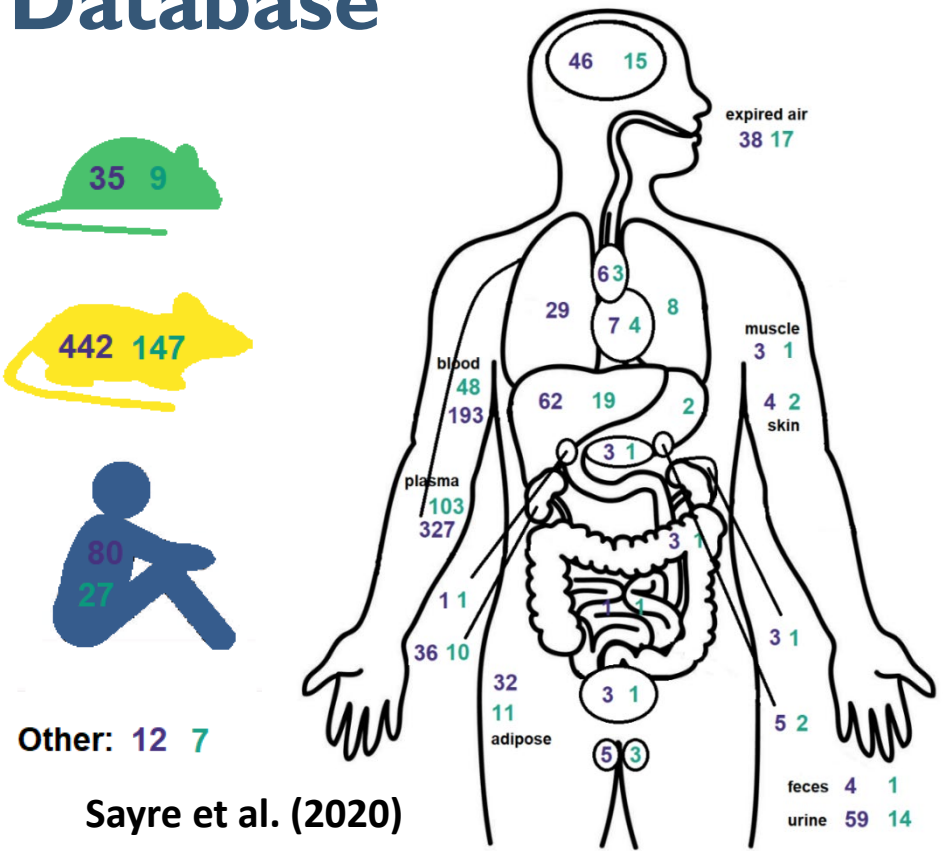

- "**Development and Evaluation of a High Throughput Inhalation Model for Organic Chemicals**" by **Linakis *et al.***, 2020 (Journal of Exposure Science and Environmental Epidemiology) – *Collaboration with Air Force Research Laboratories*
- The structure of the inhalation model was developed from two previously published physiologically-based models from Jongeneelen *et al.* (2011) and Clewell *et al*. (2001)
- The model can be parameterized with chemical-specific *in vitro* data from the HTTK package for 917 chemicals in human and 181 chemicals in rat
- Model was made publicly available with the release of httk v2.0.0 in February 2020

# - Database Development -
# CvTdb: An *In Vivo* TK Database

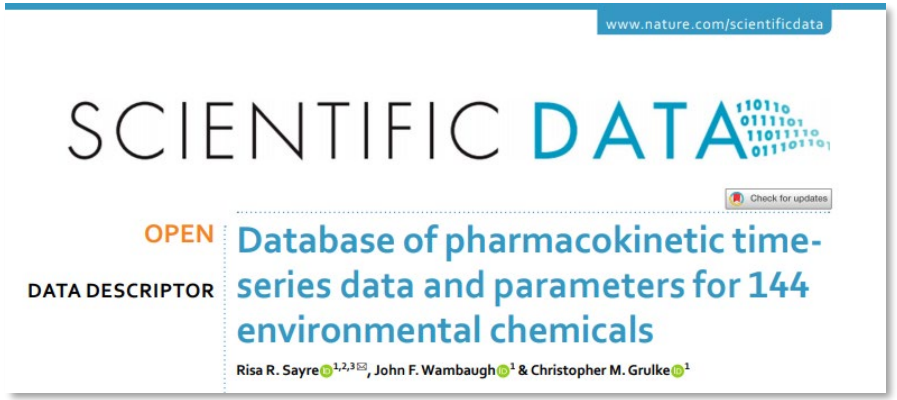
- EPA has developed a **public database** of **concentration vs. time data** across several species for building, calibrating, and evaluating TK models
- Effort ongoing, but to date includes:
  - 198 analytes (EPA, National Toxicology Program, literature)
  - Routes: Intravenous, dermal, oral, sub-cutaneous, and inhalation exposure
- Standardized, open-source curve fitting software invivoPKfit used to calibrate models to all data

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

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

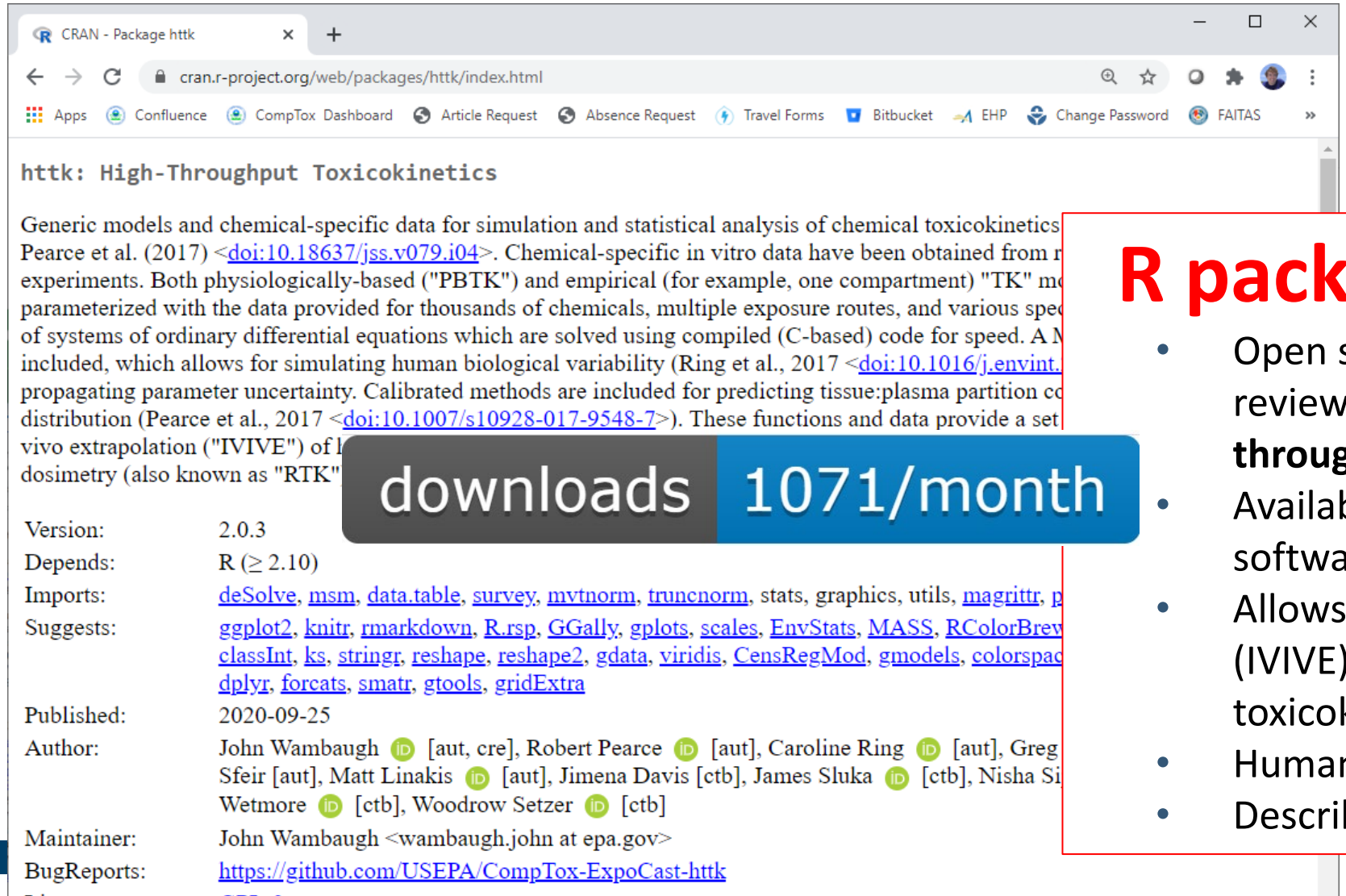



Sayre et al. (2020)



# - HTTK Platform -
# 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)

EPA United States Environmental Protection Agency

# - HTTK Platform - 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) |

# - *In Vitro* Disposition –
# A Tox21 Cross Partner Project (EPA, NTP, FDA)

**An Experimental Evaluation of Mass Balance Models**
describing *in vitro* partitioning and disposition

- Pilot study completed
- 20 chemical case study underway
- Chemical levels quantitated across 5 *in vitro* compartments

Armitage et al. 2014 PMID 25014875

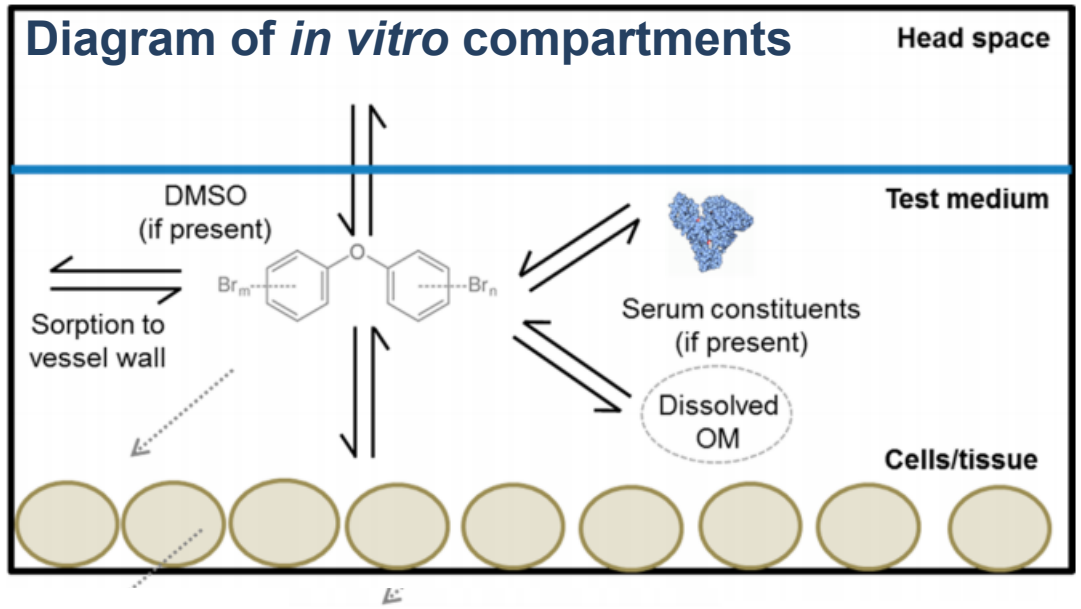
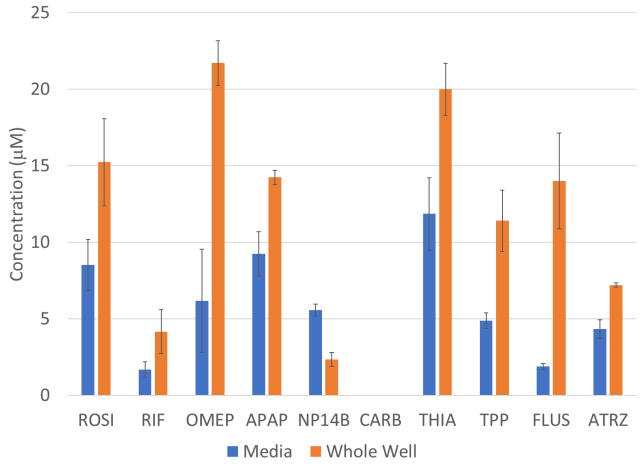



**Figure 1.** Conceptual representation of an in vitro test system.

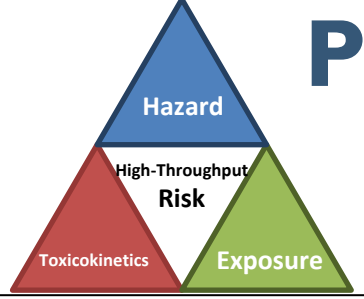
*Preliminary Design and Data*

**Table 2. Plate Matrix**

| Test Plate | Test Plate Barcode | Plating Condition | Exposure Duration (hr) | Measured Compartment |
|---|---|---|---|---|
| A | TC00000013 | Medium - cells | 1 | Medium |
| | | Medium - cells | 1 | Plastic |
| B | TC00000014 | Medium + cells | 1 | Medium |
| | | Medium + cells | 1 | Plastic + Cells |
| C | TC00000015 | Medium + cells | 1 | Whole Well Crash |
| D | TC00000016 | Medium - cells | 6 | Medium |
| | | Medium - cells | 6 | Plastic |
| E | TC00000017 | Medium + cells | 6 | Medium |
| | | Medium + cells | 6 | Plastic + Cells |
| F | TC00000018 | Medium + cells | 6 | Whole Well Crash |
| G | TC00000019 | Medium - cells | 24 | Medium |
| | | Medium - cells | 24 | Plastic |
| H | TC00000020 | Medium + cells | 24 | Medium |
| | | Medium + cells | 24 | Plastic + Cells |
| I | TC00000021 | Medium + cells | 24 | Whole Well Crash |



# Providing the Pieces for Prioritization



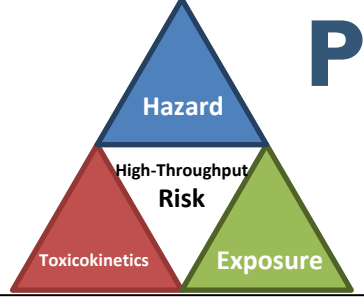

**Informing TSCA**

**Target Population**

| | Consumers | General Population |
|---|---|---|
| | ToxCast | ToxCast |
| | HTTK Oral Route | HTTK Oral Route |
| | Dermal Route Needed | Aerosol Route Needed |
| | Evaluation Data: NHANES | Evaluation Data: NHANES |
| | **Human** ExpoCast/SEEM | **Human** ExpoCast/SEEM |
| | Many Exposure Predictors | Many Exposure Predictors |
| **Pathways Covered** | **Consumer** | **Ambient** |

# Providing the Pieces for Prioritization

United States Environmental Protection Agency

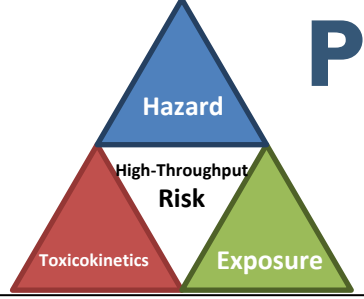



**Informing TSCA**

*Highly Exposed and Sensitive Populations*

| **Target Population** | **Consumers** | **General Population** | **Workers** | **Gestational** |
|---|---|---|---|---|
| | ToxCast | ToxCast | ToxCast | ToxCast |
| | HTTK Oral Route; Dermal Route Needed | HTTK Oral Route; Aerosol Route Needed | Aerosol Route Needed | Gestational Model Needed |
| | Evaluation Data: NHANES | Evaluation Data: NHANES | Evaluation Data: OSHA | Evaluation Data: NHANES |
| | **Human** ExpoCast/SEEM | **Human** ExpoCast/SEEM | **Occupational** ExpoCast/SEEM | **Demographic Human** ExpoCast / SEEM |
| | Many Exposure Predictors | Many Exposure Predictors | HT ChemSTEER, others | Many Exposure Predictors |
| **Pathways Covered** | **Consumer** | **Ambient** | **Occupational** | **Multiple** |

# Providing the Pieces for Prioritization



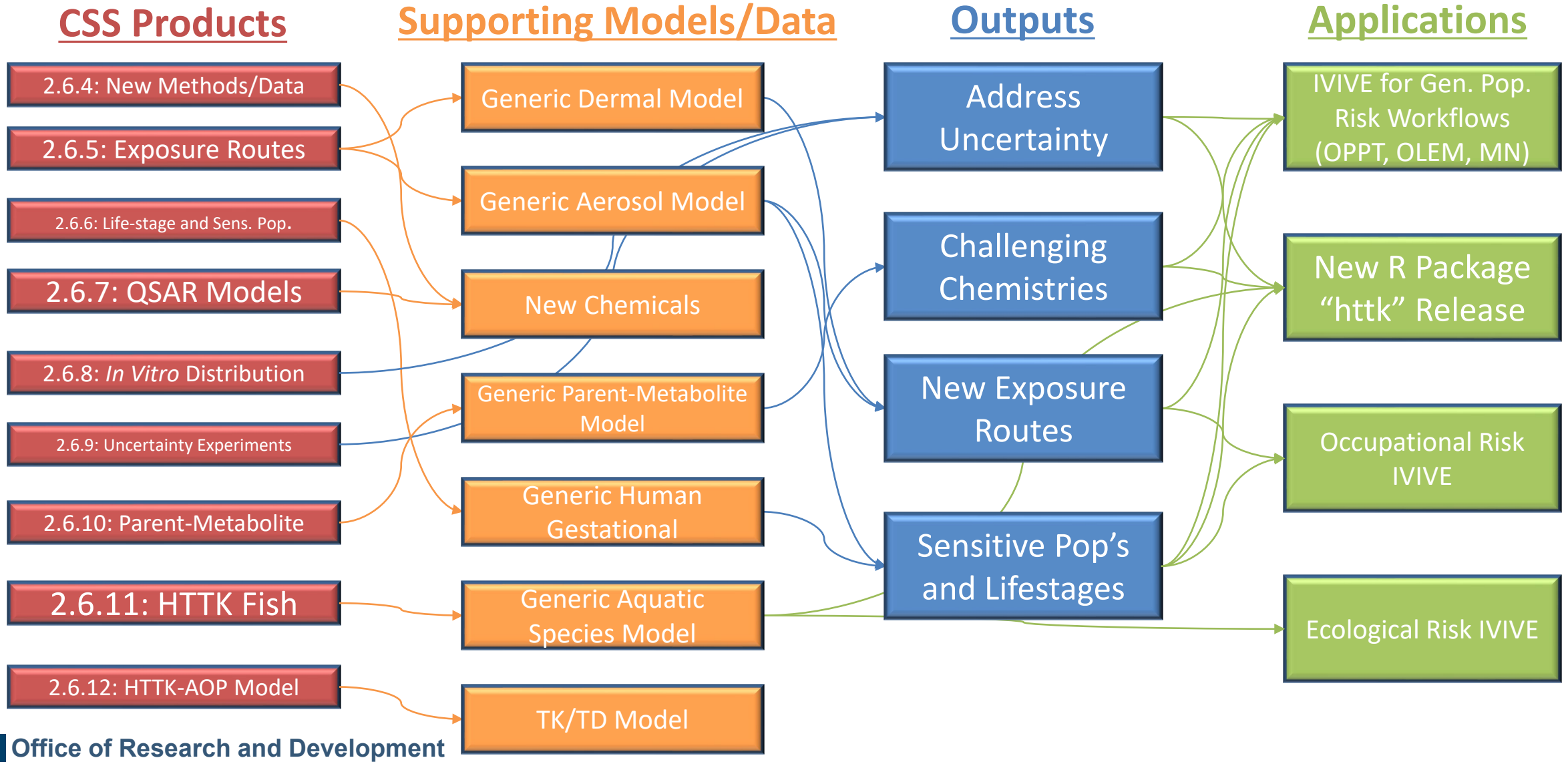

Informing TSCA

*Highly Exposed and Sensitive Populations*

Informing EDSP

| Target Population | Consumers | General Population | Workers | Gestational | Ecological (Fish) |
|---|---|---|---|---|---|
| | ToxCast | ToxCast | ToxCast | ToxCast | ToxCast + SeqaPass / LC50 Models |
| | HTTK Oral Route; Dermal Route Needed | HTTK Oral Route; Aerosol Route Needed | Aerosol Route Needed | Gestational Model Needed | EPI Suite BCF*; HTTK Fish Needed |
| | Evaluation Data: NHANES; **Human** ExpoCast/SEEM; Many Exposure Predictors | Evaluation Data: NHANES; **Human** ExpoCast/SEEM; Many Exposure Predictors | Evaluation Data: OSHA; **Occupational** ExpoCast/SEEM; HT ChemSTEER, others | | Evaluation Data: USGS Surface Water; **Ecological** ExpoCast/SEEM; 3 HT Models |
| **Pathways Covered** | **Consumer** | **Ambient** | **Occupational** | **Multiple** | **Ambient** |

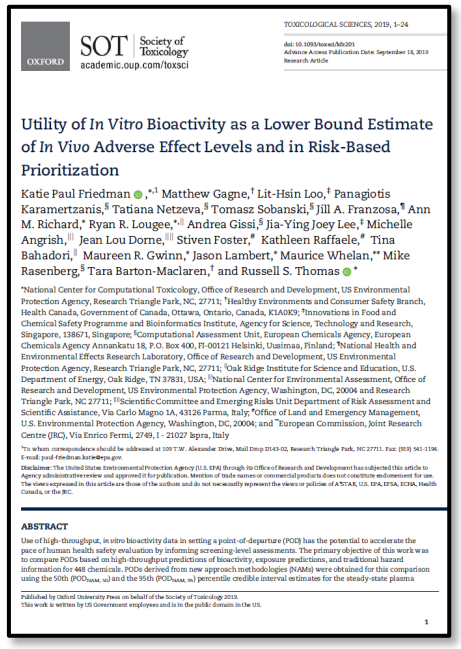
# TK and IVIVE Projects and Relationships



# International Collaborations

## - Accelerating the Pace of Chemical Risk Assessment (APCRA) -

## *In Vitro* Bioactivity, HTTK, and *In Vivo* Toxic Doses



TOXICOLOGICAL SCIENCES, 2019, 1–24

doi: 10.1093/toxsci/kfz201
Advance Access Publication Date: September 18, 2019
Research Article

OXFORD SOT Society of Toxicology
academic.oup.com/toxsci

**Utility of *In Vitro* Bioactivity as a Lower Bound Estimate of *In Vivo* Adverse Effect Levels and in Risk-Based Prioritization**

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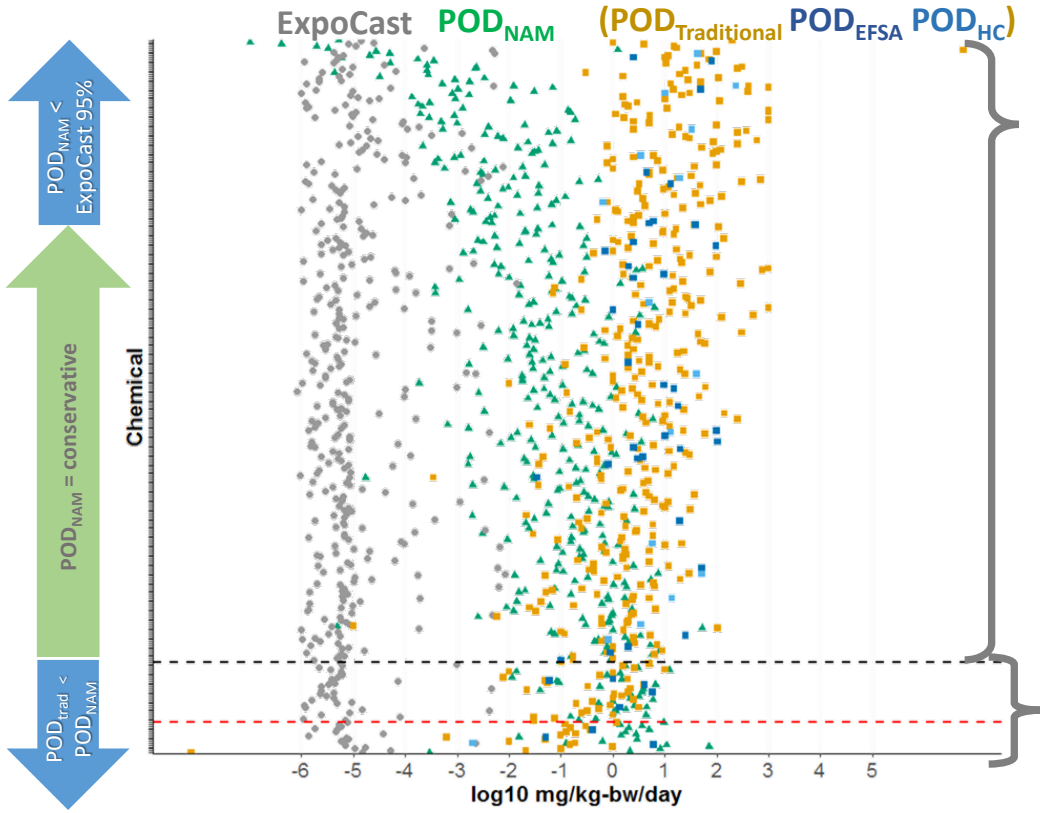
**ABSTRACT**

Use of high-throughput, *in vitro* bioactivity data in setting a point-of-departure (POD) has the potential to accelerate the pace of human health safety evaluation by informing screening-level assessments. The primary objective of this work was to compare PODs based on high-throughput predictions of bioactivity, exposure predictions, and traditional hazard information for 448 chemicals. PODs derived from new approach methodologies (NAMs) were obtained for this comparison using the 50th ($POD_{NAM,\ 50}$) and the 95th ($POD_{NAM,\ 95}$) percentile credible interval estimates for the steady-state plasma

Published by Oxford University Press on behalf of the Society of Toxicology 2019.




International case study with EPA, ASTAR, ECHA, Health Canada, and EFSA




*For ~89% of the chemicals, $POD_{NAM}$ was conservative.*

*(~100-fold on average), but less conservative than a TTC*

*Chemicals where $POD_{NAM}$ was not conservative enriched in OPs/carbamates*

Paul-Friedman *et al.* 2020

# Additional Efforts and Outreach

## Additional Efforts

- ***In vitro* TK data generation:** Ongoing, internal (>400 TSCA, incl. 150 PFAS) and external (>215); as needed on program office-initiated efforts (Office of Chemical Safety and Pollution Prevention, Office of Water)
- ***In vivo* TK:** rat *in vivo* studies for comparative assessments and IVIVE evaluation (Hughes *et al.,* underway)
- **Dermal Route:** permeability/partitioning models completed (Evans *et al*.), integration with HTTK begun
- **Bioavailability:** incorporation of Caco-2 data in IVIVE (Honda *et al.,* 2019; Honda *et al*., in preparation)
- **Transporters:** TK renal transporter data generation for PFAS IVIVE modeling (Smeltz *et al*., underway)
- **Sensitive Populations/Variability:** Isozyme-specific chemical evaluations to evaluate TK variability and supply *in silico* predictive efforts (Kreutz *et al.,* underway*)*; Correlated Monte Carlo approach to incorporate physiologic variability (Ring *et al.*, 2017)
- **Parent-Metabolite HTTK:** NTA data for metabolism of ToxCast chemicals generated by contractor and being analyzed (Boyce *et al.* underway)

## Stakeholder Outreach and Collaborations

- CompTox Chemicals Dashboard: Contains ADME data for >1000 chemicals.
- 2020 SOT: “New Data and Tools for Understanding Chemical Distribution *In Vitro*” - Nynke Kramer and John Wambaugh
- FIFRA SAP “The use of new approach methodologies (NAMs) to derive extrapolation factors and evaluate developmental neurotoxicity for human health risk assessment” - Incorporation of *in vitro* TK / HTTK
- Integration of high throughput hazard, exposure, and TK NAMs into proposed TSCA workflows (white paper, peer review)
- APCRA Collaborations – HTTK case study (underway) and NAM prospective case study (underway)
- Ongoing collaborations with Health Canada, US Geological Survey, and MN Department of Health

# References


- Armitage J.M. *et al. "*Application of mass balance models and the chemical activity concept to facilitate the use of *in vitro* toxicity data for risk assessment.“ *Environmental Science & Technology* (2014) 48, 9770-9779.
- Bell, S.M., *et al.* "In vitro to in vivo extrapolation for high throughput prioritization and decision making." *Toxicology* In Vitro (2018) 47: 213-227.
- Honda, G.S., *et al.* "Using the concordance of *in vitro* and *in vivo* data to evaluate extrapolation assumptions." *PloS One* (2019) 14(5): e0217564.
- Jamei, M., *et al*. "The Simcyp® population-based ADME simulator." *Expert Opinion on Drug Metabolism & Toxicology* (2009) 5(2):211-223.
- Kapraun, D., *et al.* “Empirical Models for anatomical and physiological changes in a human mother and fetus during pregnancy and gestation.” *PloS One* (2019). 14(5):e0215906.
- Linakis, M. *et al*. “Development and Evaluation of a high throughput inhalation model for organic chemicals.” *Journal of Exposure Science & Environmental Epidemiology* (2020) 30:866-877.
- Lukacova, V. *et al.* "Prediction of modified release pharmacokinetics and pharmacodynamics from in vitro, immediate release, and intravenous data." *The AAPS journal* (2009) 11(2): 323-334.
- Mansouri, K., *et al.* “OPERA models for predicting physicochemical properties and environmental fate endpoints.” *Journal of Cheminformatics* (2018). 10(1): 10.
- National Research Council. Risk Assessment in the Federal Government: Managing the Process Working Papers. (1983). National Academies Press.
- National Research Council. Issues in Potable Reuse: The viability of augmenting drinking water supplies with reclaimed water. (1998). National Academies Press.
- Paul-Friedman, K. *et al. "*Utility of *In Vitro* Bioactivity as a Lower Bound Estimate of In Vivo Adverse Effect Levels and in Risk-Based Prioritization.” *Toxicological Sciences* (2020) 173(1):202-225.
- Pearce, R.G,, *et al.* “httk: R Package for High-Throughput Toxicokinetics.” *Journal of Statistical Software*, (2017a) 79(4):1-26.
- Pearce, R.G., *et al.* "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." Journal of Pharmacokinetics and Pharmacodynamics 44.6 (2017b): 549-565.
- Pradeep, P., *et al.* “Using chemical structure information to develop predictive models for *in vitro* toxicokinetic parameters to inform high-throughput risk assessment.” *Computational Toxicology* (2020) Epub.
- Ring, C.L., *et al.* "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International* 106 (2017): 105-118.
- Rotroff, D.M., *et al.* "Incorporating human dosimetry and exposure into high-throughput *in vitro* toxicity screening." *Toxicological Sciences* (2010) 117(2): 348-358.
- Sayre, R. *et al*., “Database of pharmacokinetic time-series data and parameters for 144 environmental chemicals”, *Scientific Data* (2020) 7(1): 1-10.
- Schmitt, W. "General approach for the calculation of tissue to plasma partition coefficients." Toxicology *in Vitro* (2008) 22(2): 457-467.
- Shibata, Y., *et al.* Prediction of hepatic clearance and availability by cryopreserved human hepatocytes: an application of serum incubation method. *Drug Metabolism and Disposition* (2002), 30(8), 892-896
- Sipes, N.S., *et al.* "An intuitive approach for predicting potential human health risk with the Tox21 10k library." *Environmental Science & Technology* (2017) 51(18): 10786-10796.
- Sobels, F. H. “The parallelogram; an indirect approach for the assessment of genetic risks from chemical mutagens.” In: Progress in Mutation Research, Vol. 3. 1982. (K. C. Bora, G. R. Douglas, and E. R. Nestman, Eds.), Elsevier, Amsterdam, pp. 233-327.
- Tan, Y.-M., *et al*. "Reverse dosimetry: interpreting trihalomethanes biomonitoring data using physiologically based pharmacokinetic modeling." *Journal of Exposure Science & Environmental Epidemiology* (2007) 17(7):591-603.
- Thomas, Russell S., *et al.* "Incorporating Monte Carlo simulation into physiologically based pharmacokinetic models using advanced continuous simulation language (ACSL): a computational method." *Toxicological Sciences* (1996) 31(1):19-28.
- Wambaugh, J.F., *et al.* "Evaluating *In Vitro-In Vivo* Extrapolation of Toxicokinetics." *Toxicological Sciences (*2018) 163(1): 152-169.
- Wambaugh, J.F., *et al.* “Assessing Toxicokinetic Uncertainty and Variability in Risk Prioritization” *Toxicological Sciences*, 172(2), 235-251.
- Wang, Y.-H. "Confidence assessment of the Simcyp time-based approach and a static mathematical model in predicting clinical drug-drug interactions for mechanism-based CYP3A inhibitors." *Drug Metabolism and Disposition* (2010) 38(7):1094-1104.
- Wetmore, B.A., *et al*. "Integration of dosimetry, exposure and high-throughput screening data in chemical toxicity assessment." *Toxicological Sciences* (2012) 125(1):157-174.
- Wetmore, B.A., *et al.* "Relative impact of incorporating pharmacokinetics on predicting in vivo hazard and mode of action from high-throughput in vitro toxicity assays." *Toxicological Sciences* (2013) 132(2) 327-346.
- Wetmore, B.A., *et al*. "Incorporating high-throughput exposure predictions with dosimetry-adjusted in vitro bioactivity to inform chemical toxicity testing." *Toxicological Sciences* (2015) 148(1): 121-136.

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