EPA
United States
Environmental Protection
Agency

High throughput toxicokinetic (HTTK) modeling of inhalation exposures

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50 EPA at
Progress for a Stronger Future

ACS Virtual Meeting
Fall 2020

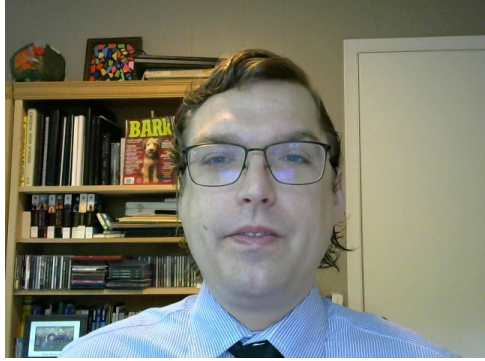
http://orcid.org/0000-0002-4024-534X

US EPA Office of Research and Development

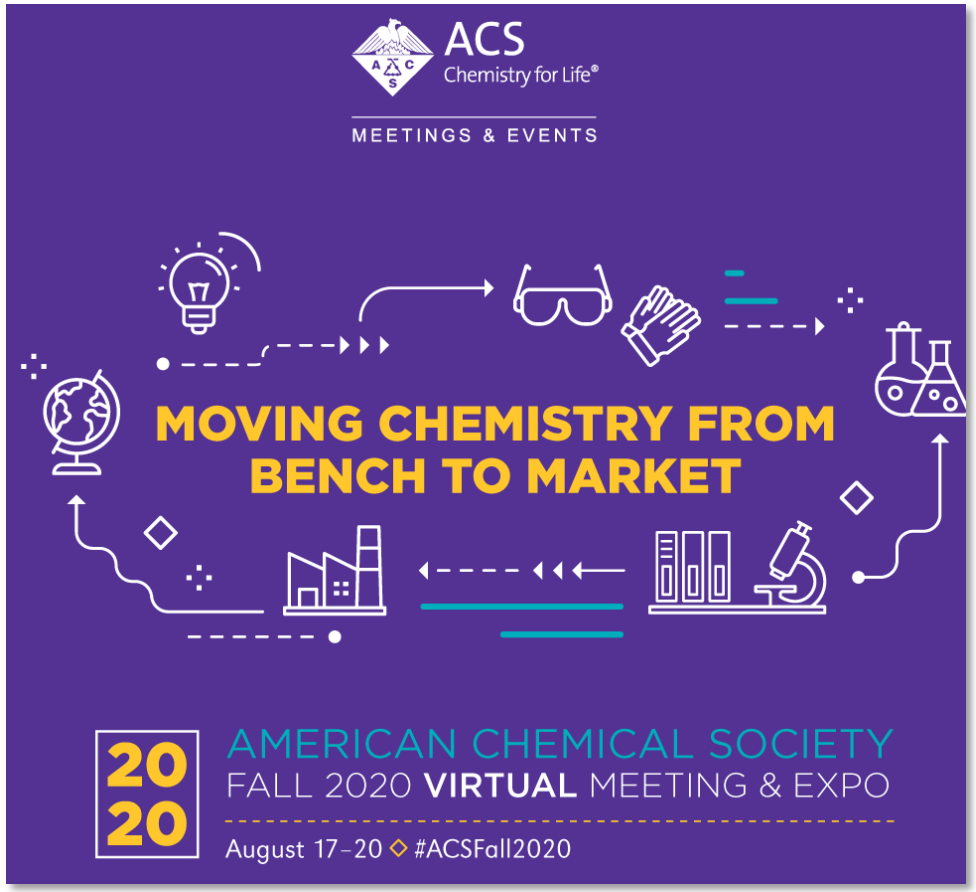
- The Office of Research and Development is the scientific research arm of EPA
  - 530 peer-reviewed journal articles in 2019
- Research is conducted by Office of Research and Development 's four national centers:
  - Computational toxicology and exposure, public health and environmental assessment; environmental measurement and modeling; and environmental solutions and emergency response
- 13 facilities across the United States
- Research is 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

Trivia Time!



- **Q:** This year the ACS Fall meeting is being held virtually. Where was the meeting originally planned to be held?



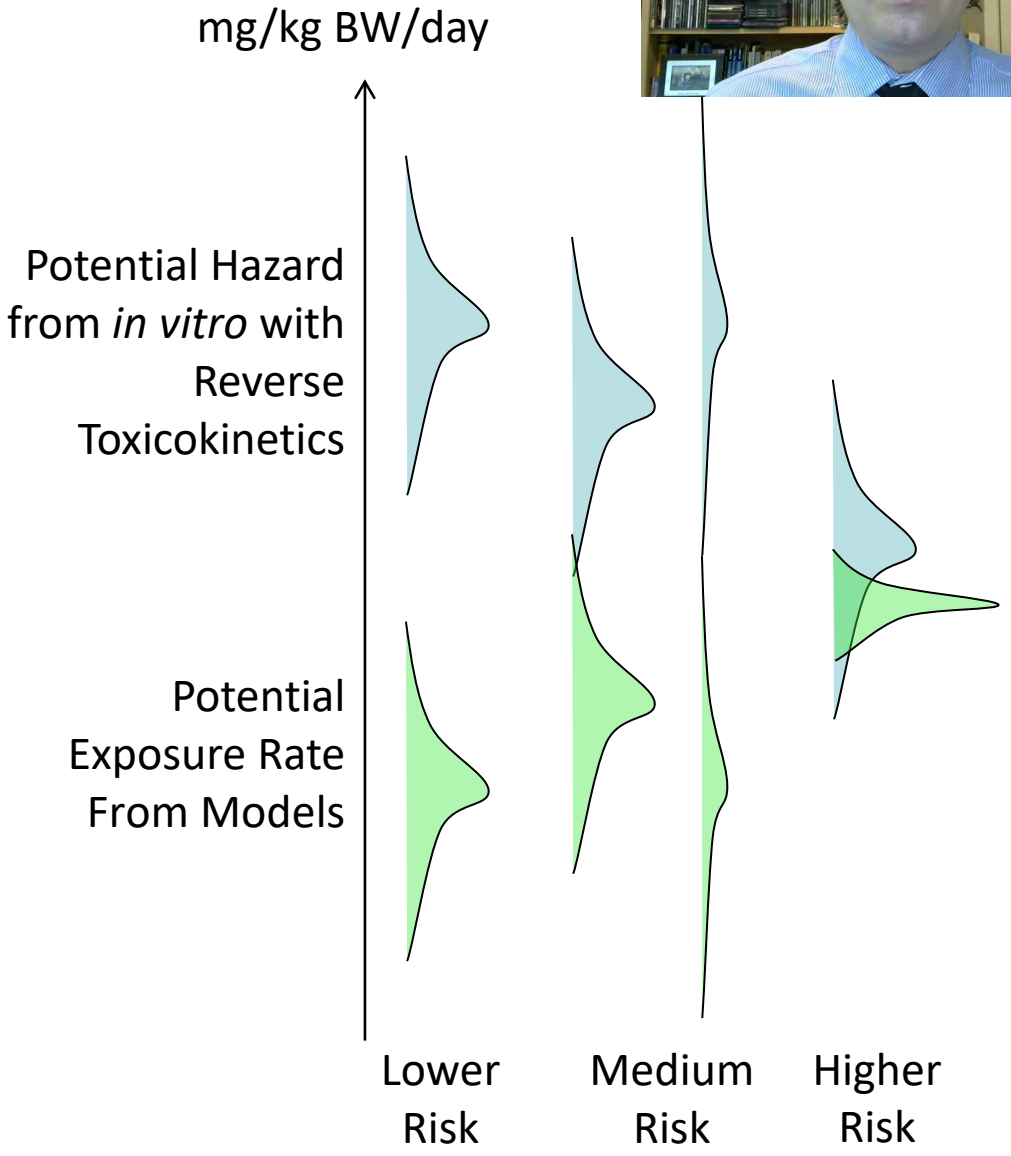
Chemical Regulation in the United States

- Park *et al.* (2012): At least 3221 chemical signatures in pooled human blood samples, many appear to be exogenous
- A tapestry of laws covers the chemicals people are exposed to in the United States (Breyer, 2009)
- Chemical safety testing is primarily for food additives, pharmaceuticals, and pesticide active ingredients (NRC, 2007)
  - Level of testing (human, rodent, *in vitro, in silico*) depends on how chemical is used

November 29, 2014

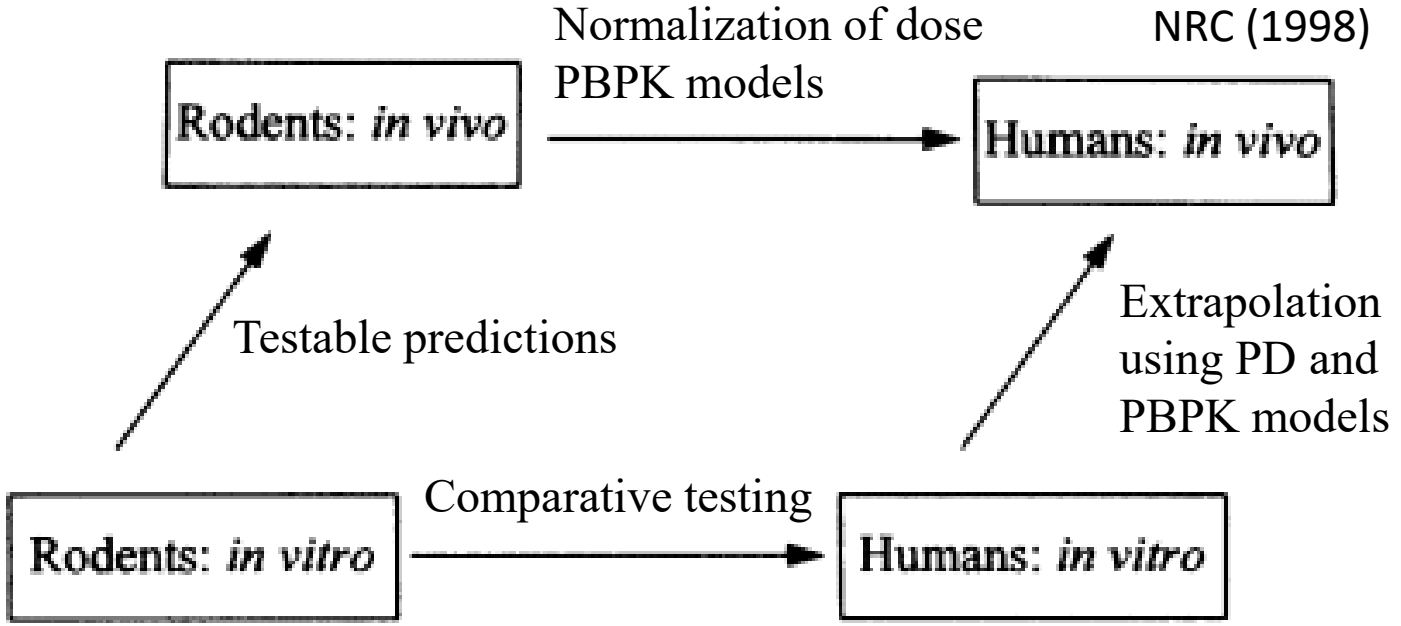
New Approach Methodologies for Chemical Risk Identification

- There are at least 10,000 chemicals produced, used in commerce, and potentially present in the environment
  - Traditional methods are too resource-intensive to address all of these
- New Approach Methodologies (NAMs, Kavlock et al. 2018) include:
  - High throughput screening (ToxCast)
  - High throughput exposure estimates (ExpoCast)
  - High throughput toxicokinetics (HTTK)



In Vitro - In Vivo Extrapolation (IVIVE)

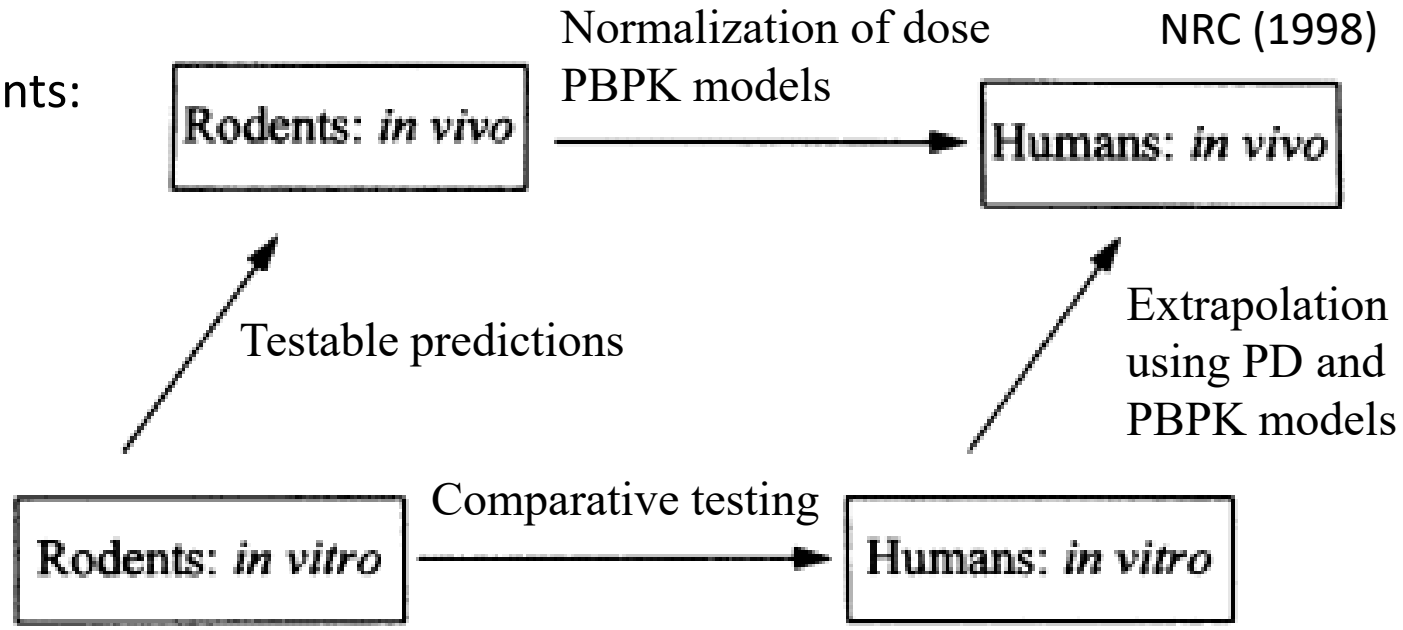
- IVIVE is the use of *in vitro* data to predict phenomena *in vivo*



"The Parallelogram Approach" (Sobels, 1982)

In Vitro – In Vivo Extrapolation (IVIVE)

- IVIVE is the use of *in vitro* data to predict phenomena *in vivo*
- IVIVE can be broken down into two components:
  - IVIVE-PK/TK (**Pharmacokinetics/Toxicokinetics**):
    - Fate of molecules/chemicals in body
    - Considers absorption, distribution, metabolism, excretion (ADME)
    - Can use empirical PK or physiologically-based (PBPK)



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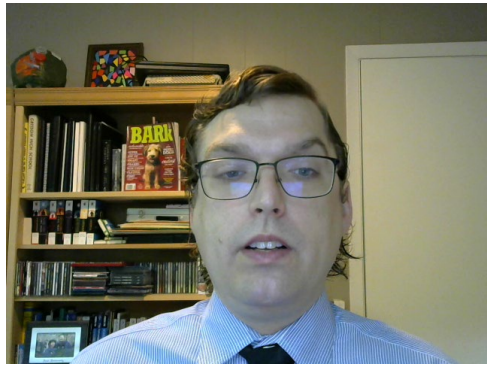

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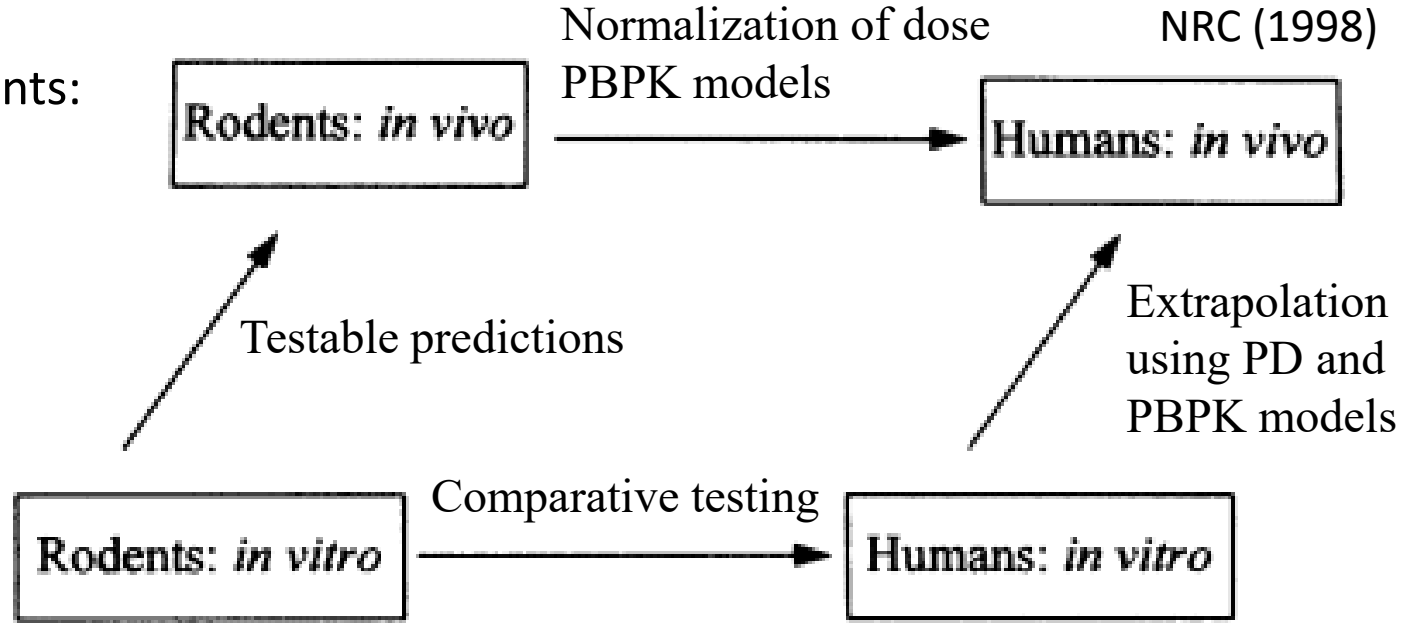


"The Parallelogram Approach" (Sobels, 1982)

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

Trivia Time!

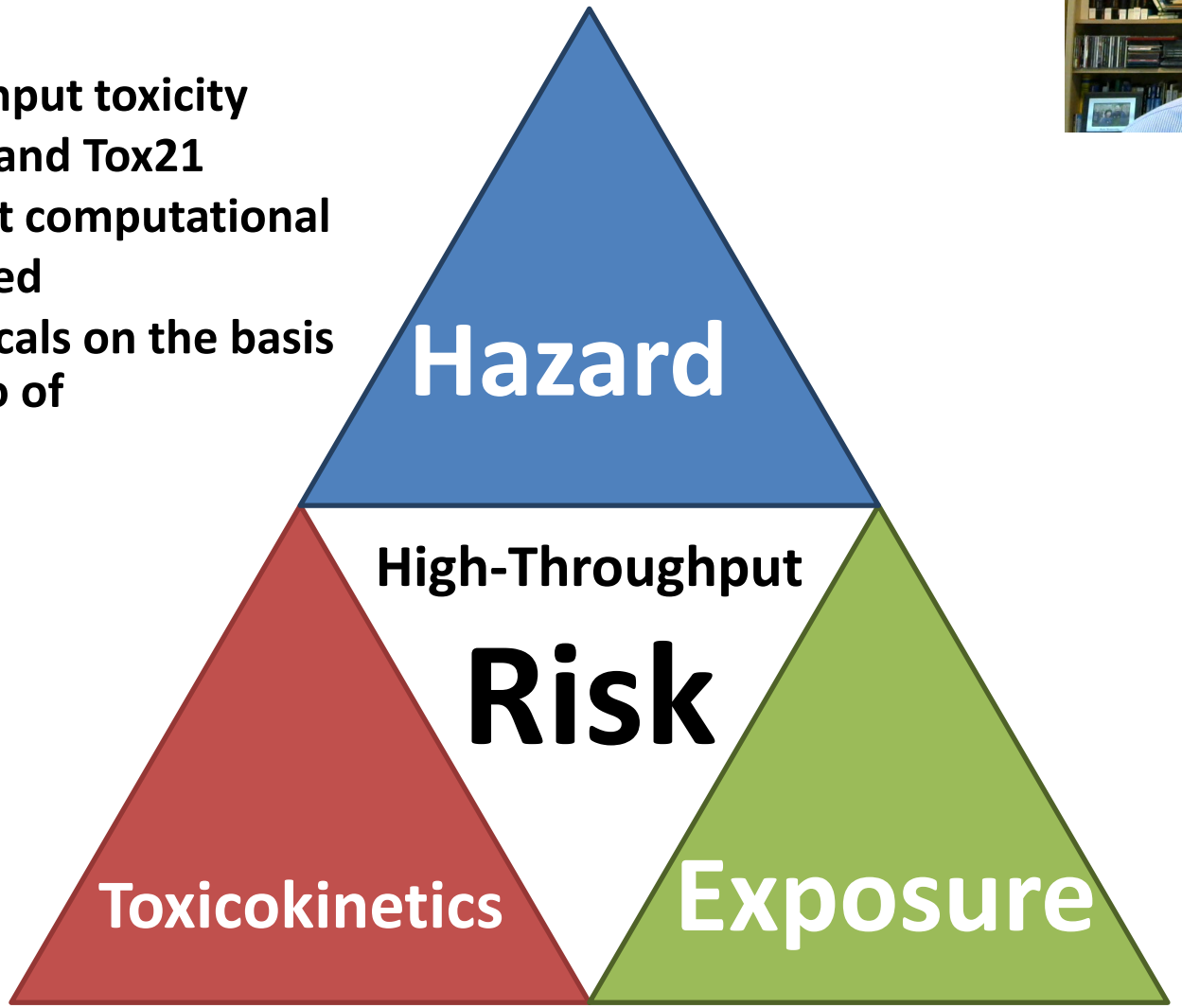
- **Q:** This year the ACS Fall meeting is being held virtually. Where was the meeting originally planned to be held?
- **A:** San Francisco

- **Q:** The 1968 hit “"(Sittin' On) The Dock of the Bay“ was composed in Sausalito adjacent to the San Francisco bay. Who co-wrote and sang it?

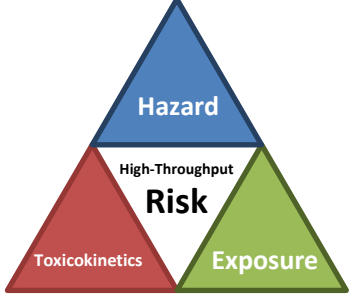
Providing the Pieces for Prioritization

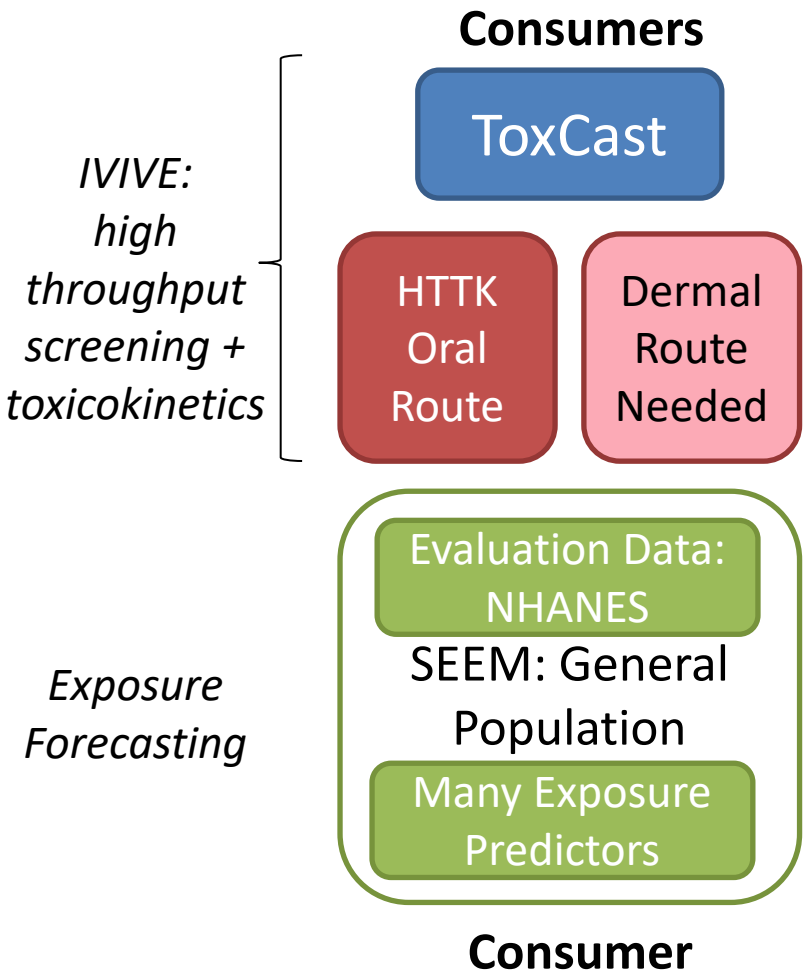
"Recent advances in high-throughput toxicity assessment, notably the ToxCast and Tox21 programs, and in high-throughput computational exposure assessment have enabled first-tier based rankings of chemicals on the basis of margins of exposure—the ratio of exposures that cause effects (or bioactivity) to measured or estimated human exposures"

U.S. National Academies of Science, Engineering, and Medicine (2017)



Providing the Pieces for Prioritization

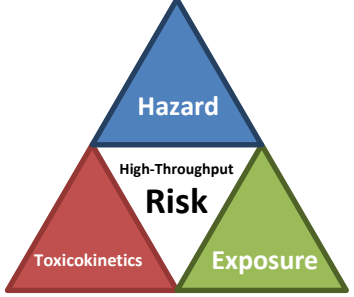




ToxCast: EPA's Toxicity Forecast high throughput *in vitro* screening battery
HTTK: High Throughput Toxicokinetics
NHANES: CDC's National Health and Nutrition Examination Survey
SEEM: EPA's Systematic Empirical Evaluation of Models (consensus model)

Providing the Pieces for Prioritization

EPA United States Environmental Protection Agency



Consumers

ToxCast

HTTK Oral Route

Dermal Route Needed

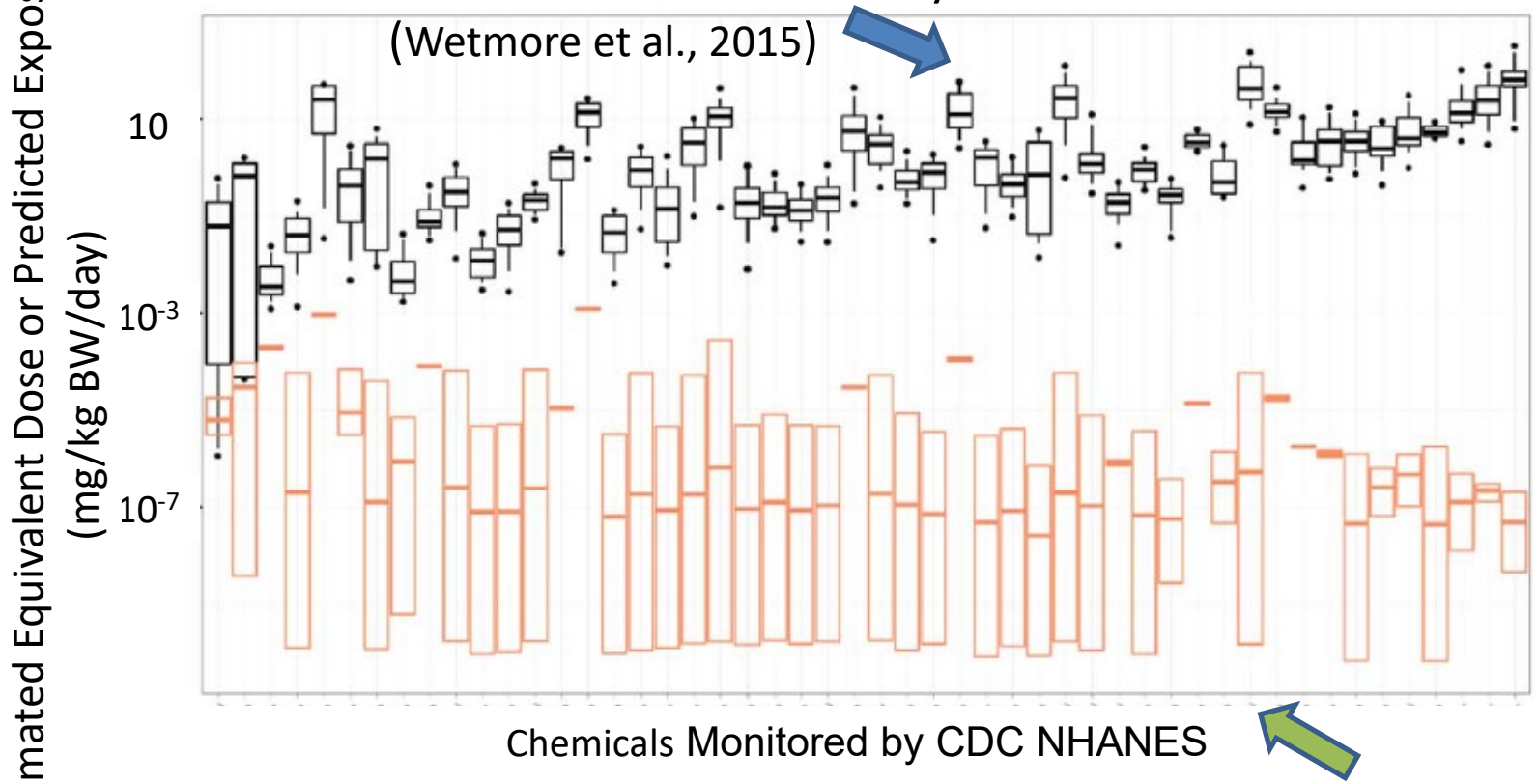
Evaluation Data: NHANES

SEEM: General Population

Many Exposure Predictors

Consumer

ToxCast + HTTK can estimate doses needed to cause bioactivity (Wetmore et al., 2015)

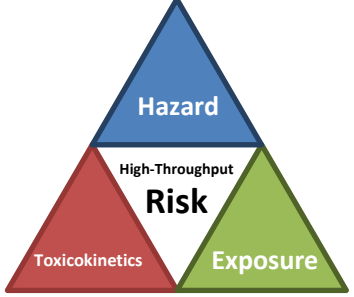


Exposure intake rates can be inferred from biomarkers (Wambaugh et al., 2014)

Figure from Ring *et al*. (2017)

Providing the Pieces for Prioritization

United States Environmental Protection Agency



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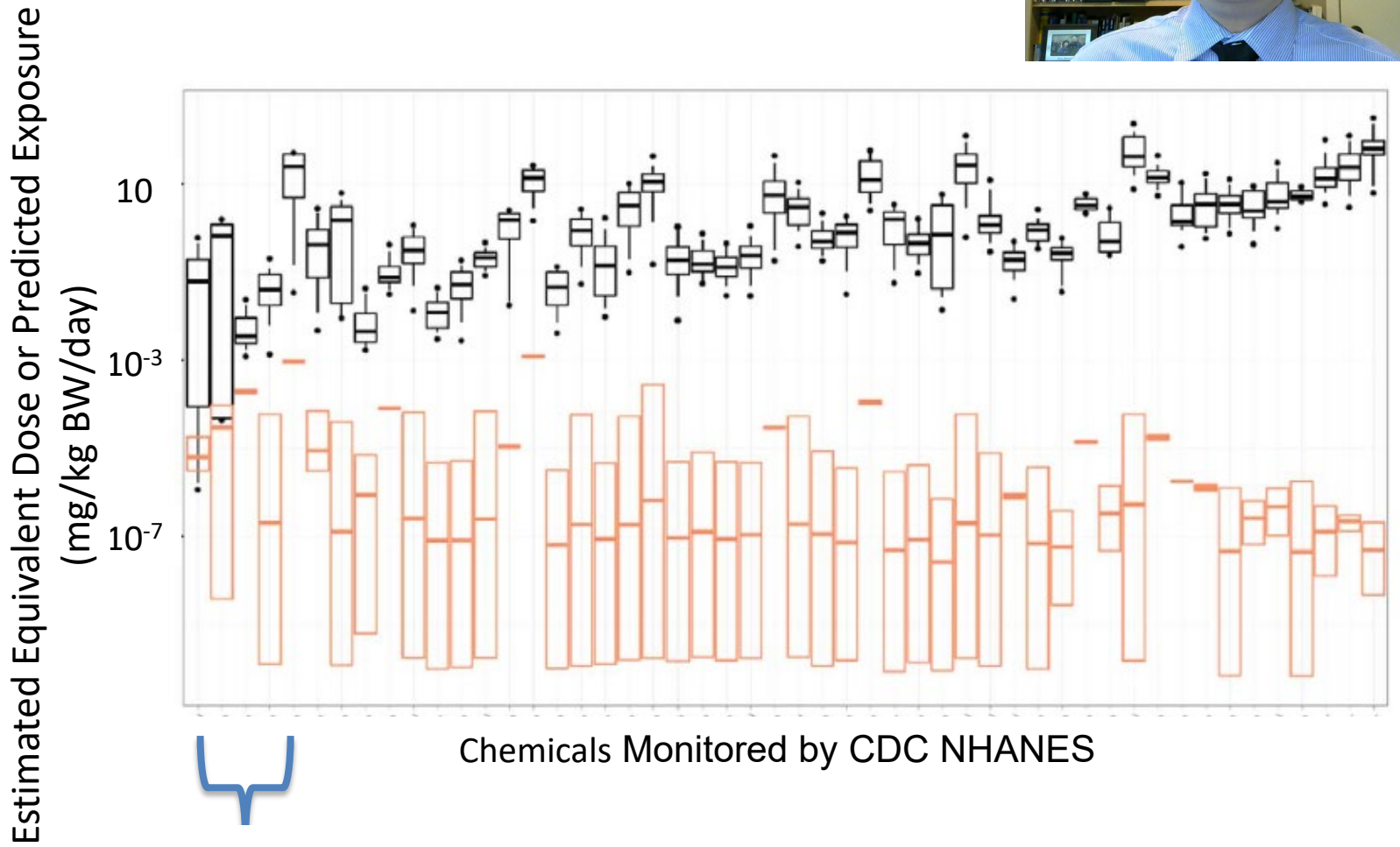
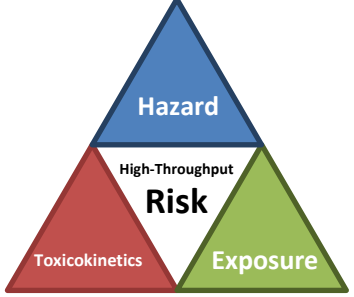


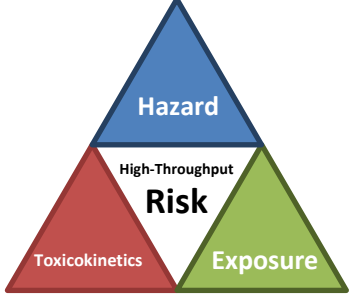
Figure from Ring *et al*. (2017)

Providing the Pieces for Prioritization



Target Population	Consumers	General Population
	ToxCast	ToxCast
	HTTK Oral Route; Dermal Route Needed	HTTK Oral Route; Gas / Aerosol Route Needed
Pathways Covered	Evaluation Data: NHANES; SEEM: General Population; Many Exposure Predictors	Evaluation Data: NHANES; SEEM: General Population; Many Exposure Predictors
	Consumer	Ambient

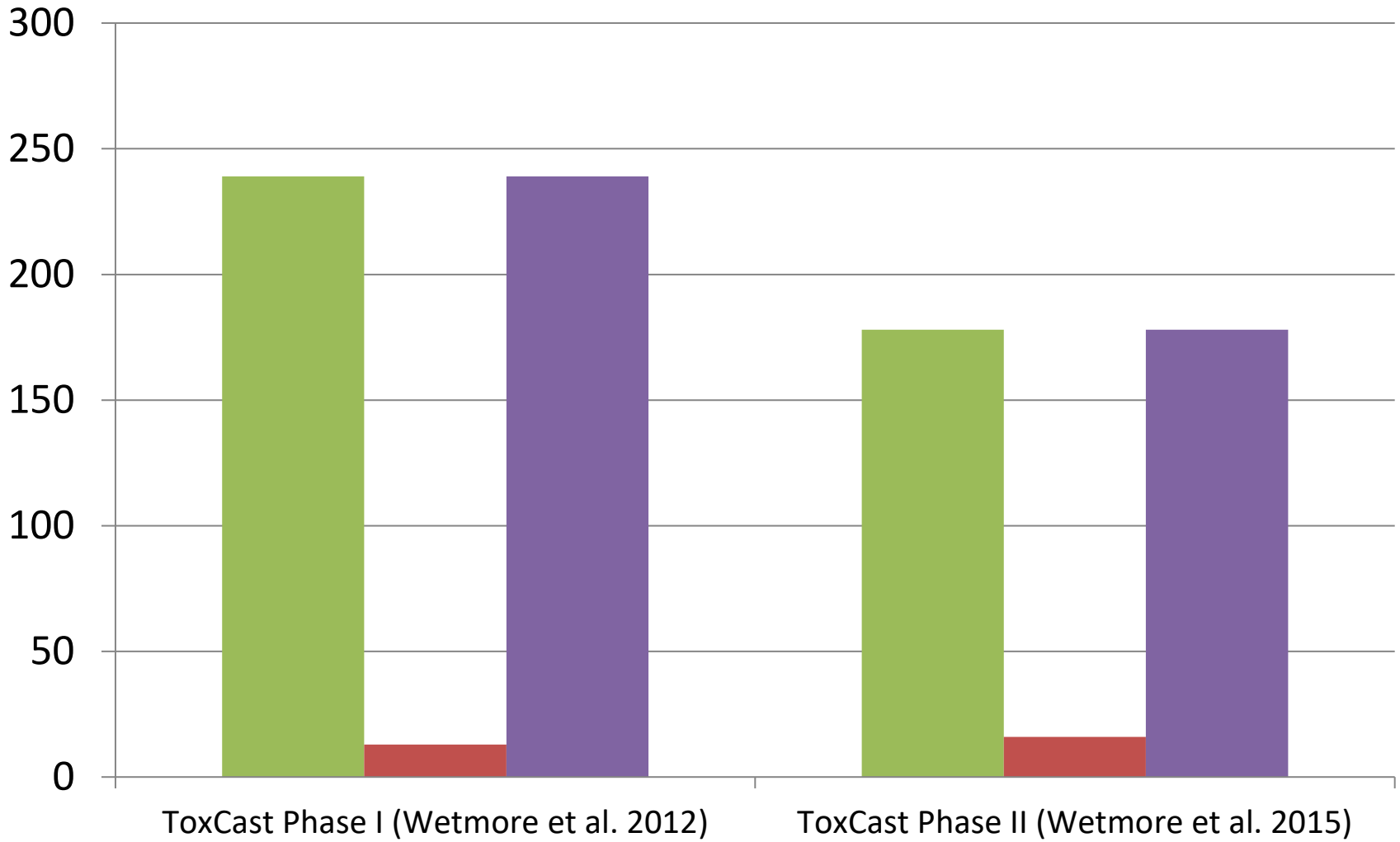
Providing the Pieces for Prioritization



Target Population	Consumers	General Population	Workers
	ToxCast	ToxCast	ToxCast
	HTTK Oral Route; Dermal Route Needed	HTTK Oral Route; Gas / Aerosol Route Needed	Dermal Route Needed; Gas / Aerosol Route Needed
	Evaluation Data: NHANES; SEEM: General Population; Many Exposure Predictors	Evaluation Data: NHANES; SEEM: General Population; Many Exposure Predictors	Evaluation Data: OSHA; SEEM: Occupational; HT ChemSTEER, others
Pathways Covered	Consumer	Ambient	Occupational

Highly Exposed and Sensitive Populations

Most chemicals do not have TK Data



Bell et al. (2018)

EPA United States Environmental Protection Agency

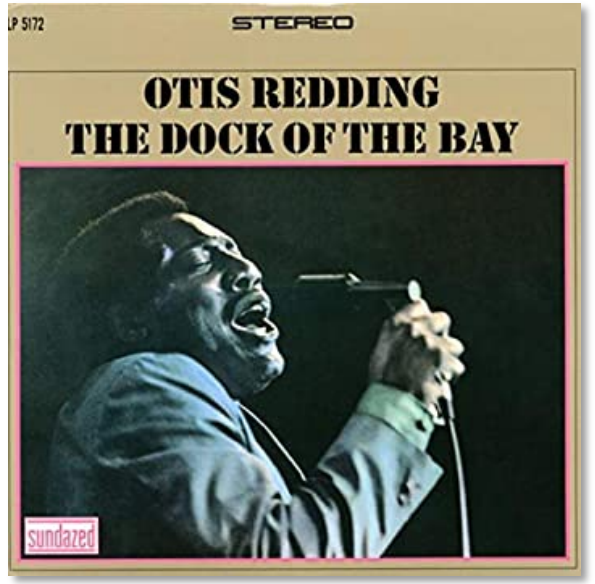
NAMs for Toxicokinetics

- 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, 2017)

Trivia Time!

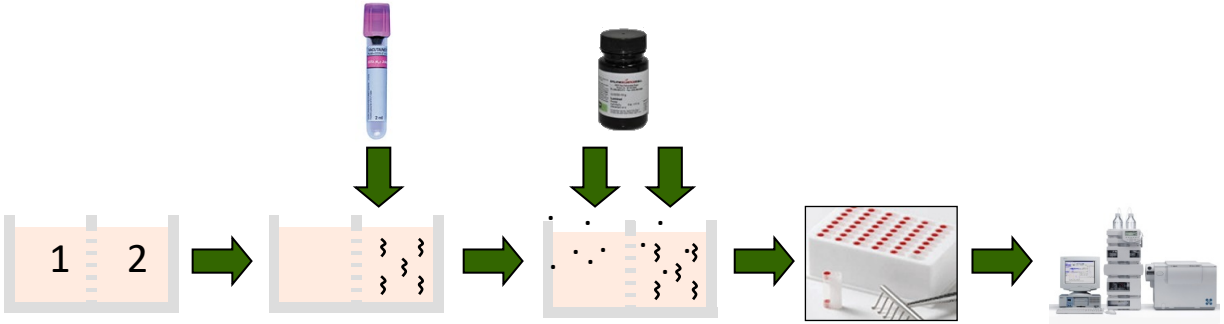
- **Q:** What device did Stanford professor Patrick Brown help invent in the 1990's?

- **Q:** The 1968 hit "(Sittin' On) The Dock of the Bay" was composed in Sausalito adjacent to the San Francisco bay. Who co-wrote and sang that song?
- **A:** Otis Redding



High Throughput Toxicokinetics (HTTK)

In vitro toxicokinetic data



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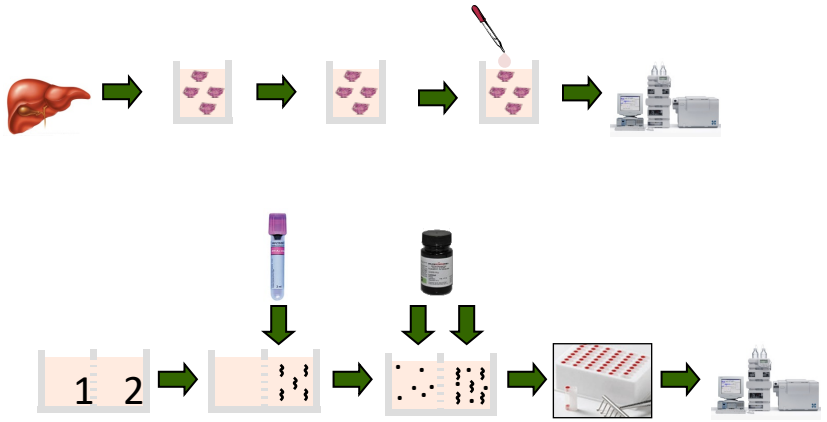
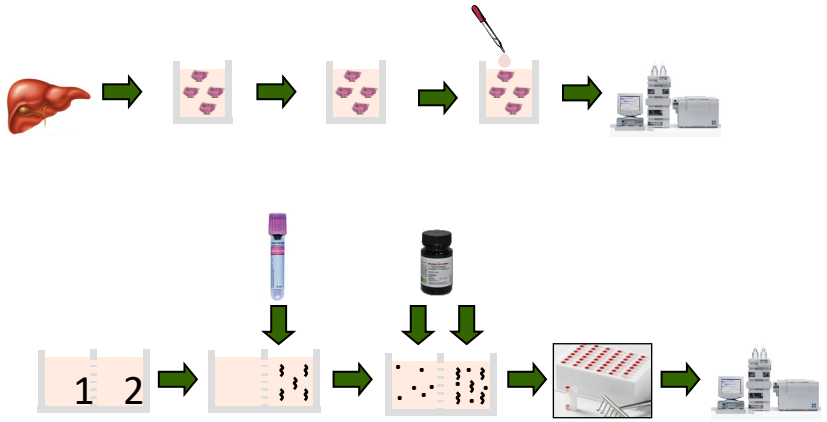
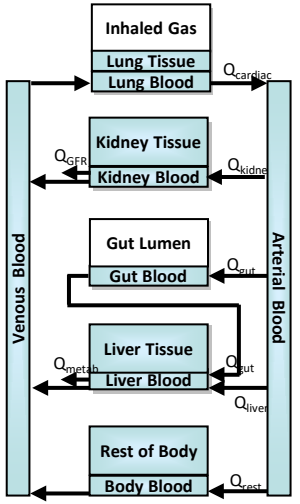


Rotroff et al. (2010)
Wetmore et al. (2012)
Wetmore et al. (2015)
Wambaugh et al. (2019)

High Throughput Toxicokinetics (HTTK)

In vitro toxicokinetic data + generic toxicokinetic model





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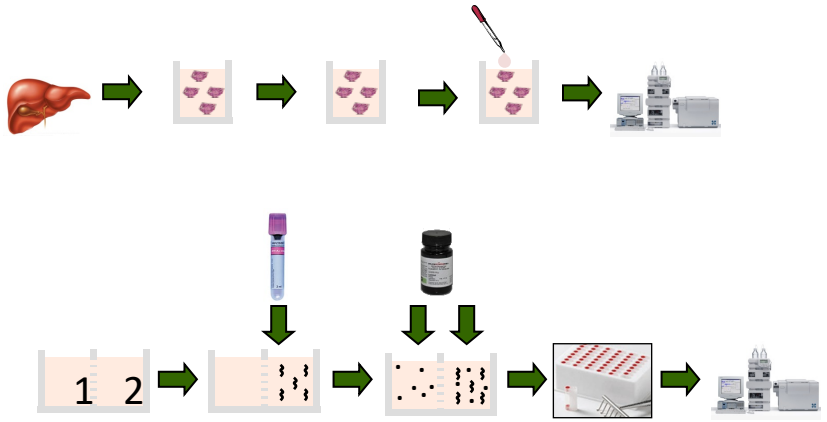
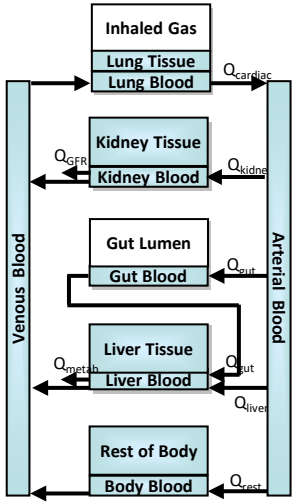
High Throughput Toxicokinetics (HTTK)

In vitro toxicokinetic data + generic toxicokinetic model





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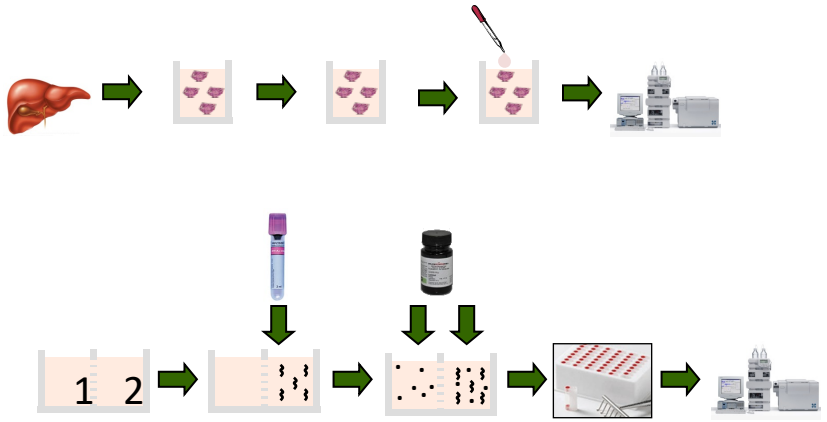
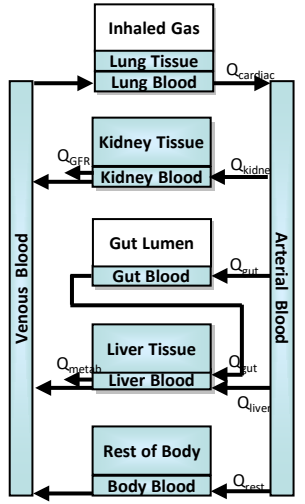
Pearce et al. (2017)
Ring et al. (2017)
Linakis et al. (2020)

High Throughput Toxicokinetics (HTTK)

In vitro **toxicokinetic data + generic toxicokinetic model**

= high(er) throughput toxicokinetics





= ***httk***

Rotroff et al. (2010)
Wetmore et al. (2012)
Wetmore et al. (2015)
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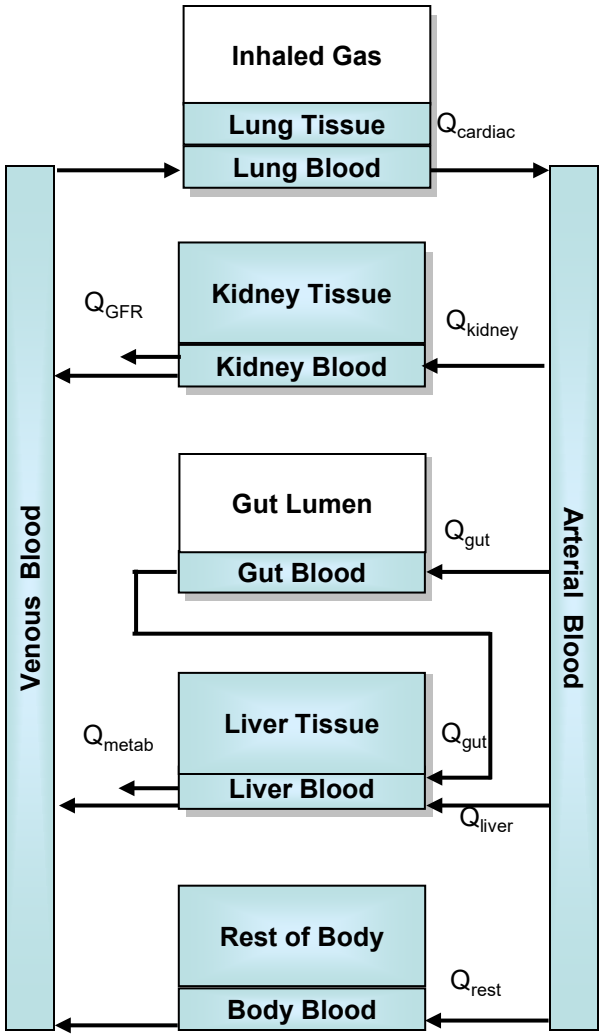
Pearce et al. (2017)
Ring et al. (2017)
Linakis et al. (2020)

The "httk" General Physiologically-based Toxicokinetic (PBTK) Model



- Tissues are modeled by compartments:
  - Some tissues (for example, arterial blood) are simple compartments
  - Others (for example, kidney) are compound compartments consisting of separate blood and tissue sections with constant partitioning (that is, tissue specific tissue:plasma partition coefficients)
  - Remaining tissues (for example, fat, brain, bones) are lumped into the "Rest of Body" compartment
- Clearance from the body depends on two processes:
  - Metabolism in the liver (estimated from *in vitro* clearance and binding)
  - Excretion by glomerular filtration in the kidney (estimated from *in vitro* binding)
- Model parameters are either:
  - **Physiological:** determined by species and potentially varied via Monte Carlo (including HTTK-pop, Ring et al. 2017)
  - **Chemical-specific**: physico-chemical properties (Mansouri et al., 2018) and equilibrium partition coefficients plus plasma binding and metabolism rates that are determined from *in vitro* measurements or potentially predicted from structure

Open Source Tools and Data for HTTK

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

CRAN - Package httk

cran.r-project.org/web/packages/httk/index.html

Apps | Absence Request | Travel Request For... | REMD-HTTK | Confluence | Bitbucket | CompTox Dashboard | EHP | Change Password

httk: High-Throughput Toxicokinetics

Functions and data tables for simulation and statistical analysis of chemical toxicokinetics ("TK") as in Pearce et al. (2017) <doi:10.18637/jss.v079.i04>. Chemical-specific in vitro data have been obtained from relatively high throughput experiments. Both physiologically-based ("PBTK") and empirical (e.g., one compartment) "TK" models can be parameterized for several hundred chemicals and multiple species. These models are solved efficiently, often using compiled (C-based) code. A Monte Carlo sampler is included for simulating biological variability (Ring et al., 2017 <doi:10.1016/j.envint.2017.06.004>) and measurement limitations. Calibrated methods are included for predicting tissue:plasma partition coefficients and volume of distribution (Pearce et al., 2017 <doi:10.1007/s10928-017-9548-7>). These functions and data provide a set of tools for in vitro-in vivo extrapolation ("IVIVE") of high throughput screening data (e.g., Tox21, ToxCast) to real-world exposures via reverse dosimetry (also known as "RTK") (Wetmore et al. 2015 <doi:10.1093/toxsci/kfv171>).

Version:	2.0.1
Depends:	R (≥ 2.10)
Imports:	deSolve, msm, data.table, survey, mvtnorm, truncnorm, stats, graphics, utils, r
Suggests:	ggplot2, knitr, rmarkdown, R.rsp, GGally, gplots, scales, EnvStats, MASS, RC ggrepel, dplyr, forcats, smatr, gtools, gridExtra
Published:	2020-03-02
Author:	John Wambaugh [aut, cre], Robert Pearce [aut], Caroline Ring [a [ctb], Barbara Wetmore [ctb], Woodrow Setzer [ctb]
Maintainer:	John Wambaugh <wambaugh.john at epa.gov>
BugReports:	https://github.com/USEPA/CompTox-ExpoCast-httk
License:	GPL-3
URL:	https://www.epa.gov/chemical-research/rapid-chemical-exposure-and-dose-re
NeedsCompilation:	yes
Citation:	httk citation info
Materials:	NEWS
CRAN checks:	httk results

Downloads:

downloads 806/month

Reference manual:	httk.pdf
Vignettes:	Frank et al. (2018): Creating IVIVE Figure (Fig. 6)
	Honda et al. (2019): Updated Armitage et al. (2014) Model
	Linakis et al. (Submitted): Analysis and Figure Generation
	Pearce et al. (2017): Creating Partition Coefficient Evaluation Plots

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. (2017)

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)

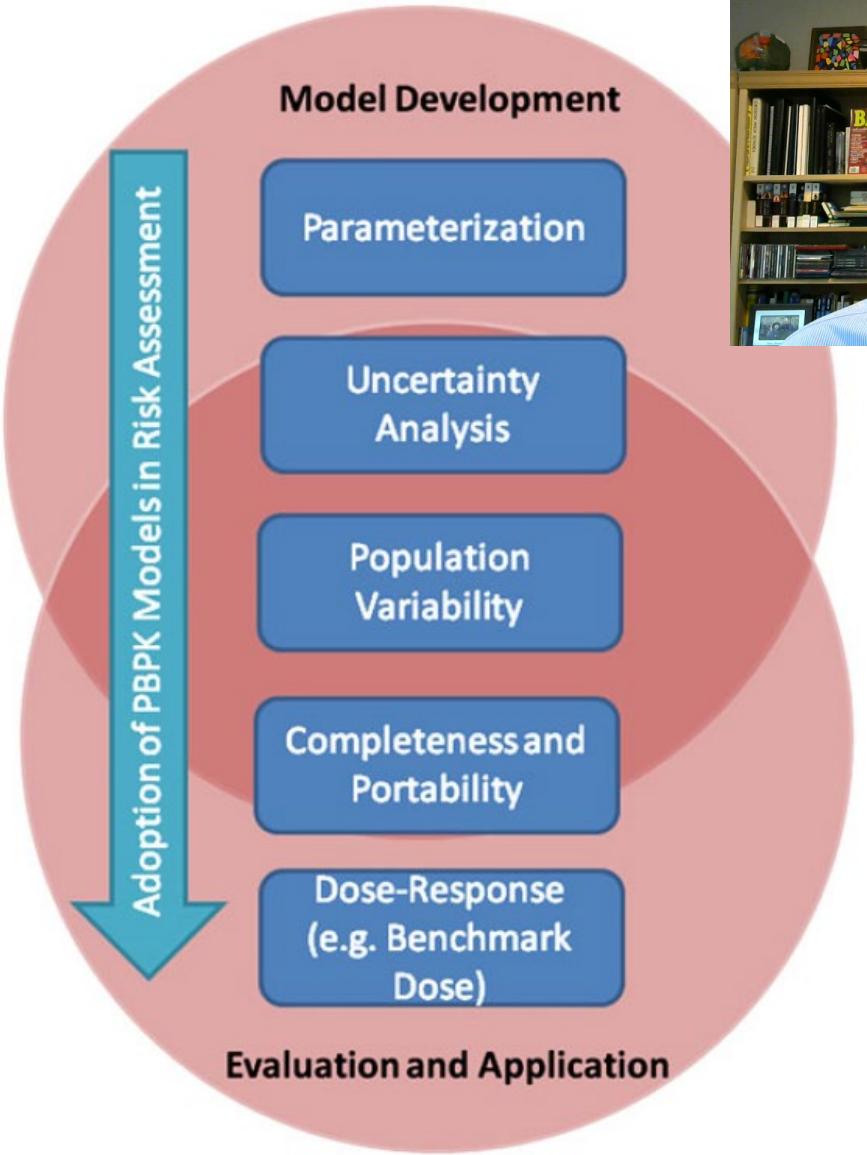


FIG. 1. This figure shows examples of key considerations during model development, evaluation, and application that are necessary before a PBPK model may be adopted for use in a HHRA.

McLanahan et al. (2012)

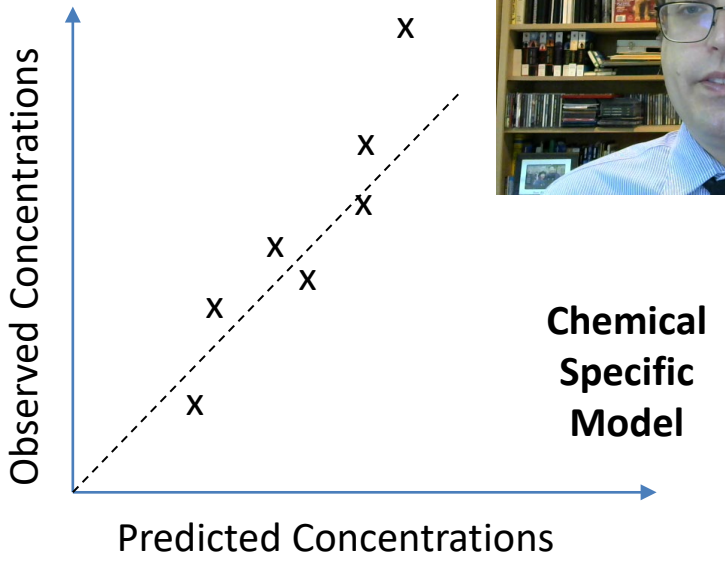
Trivia Time!

- **Q:** What device did Stanford professor Patrick Brown help invent in the 1990's?
- **A:** The DNA microarray (also PLoS and Impossible Foods!)

- **Q:** What standard was established in 2001 for the reporting of microarray data?

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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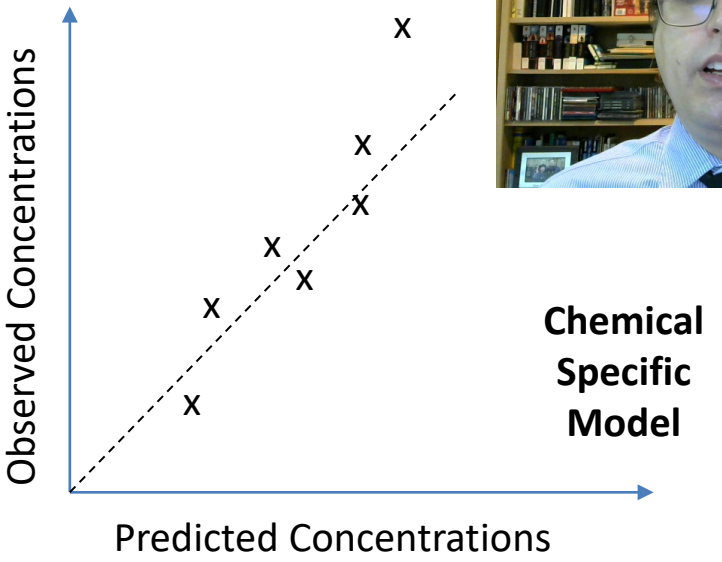
- However, we do not typically have TK data



Cohen Hubal et al. (2018)

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  - Can estimate bias
  - Can estimate uncertainty
  - Can consider using model to extrapolate to other situations (dose, route, physiology) where you have no data

- However, we do not typically have TK data

- 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
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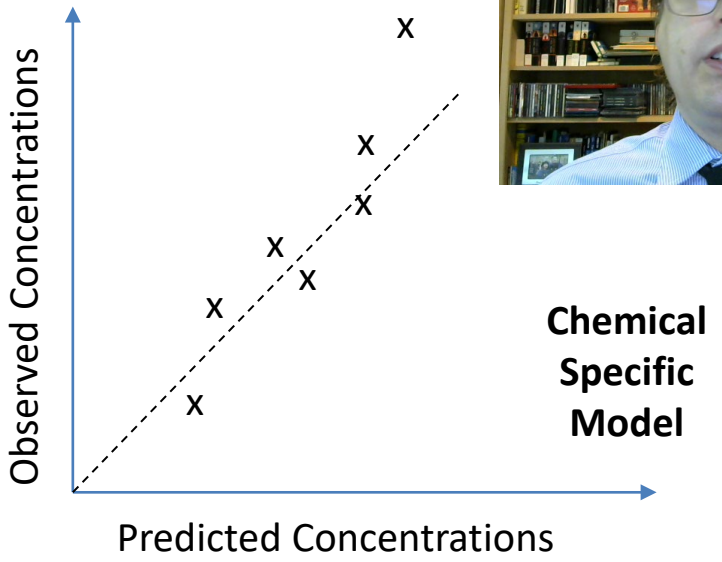

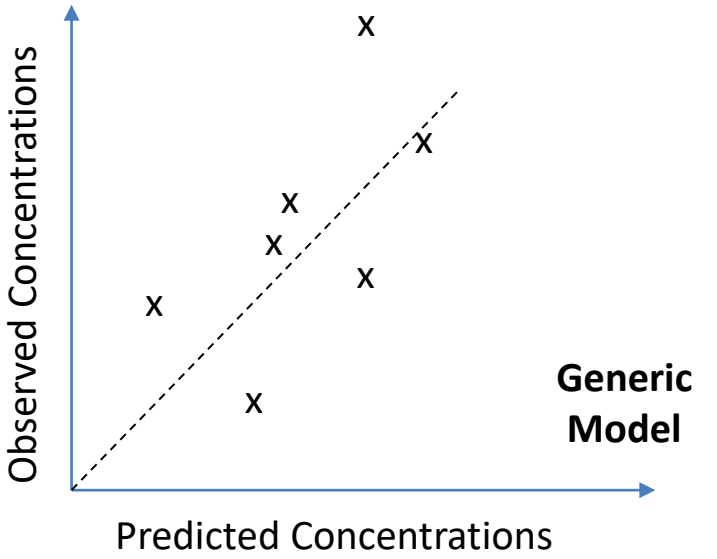

Cohen Hubal et al. (2018)

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
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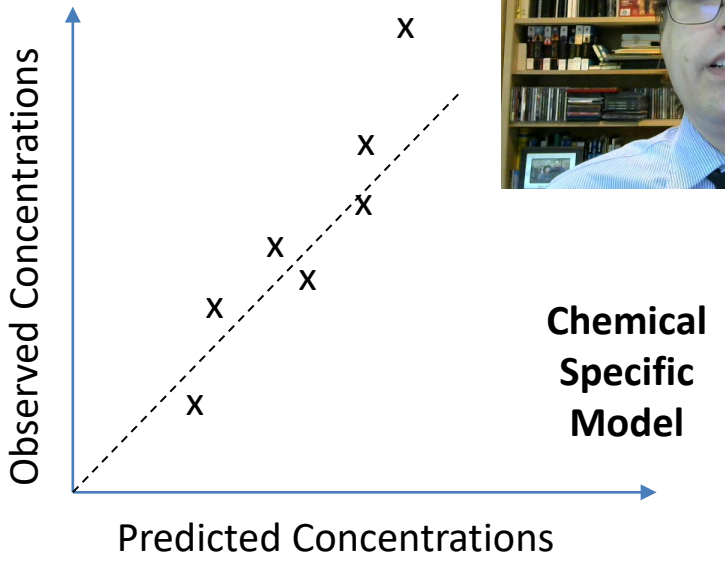

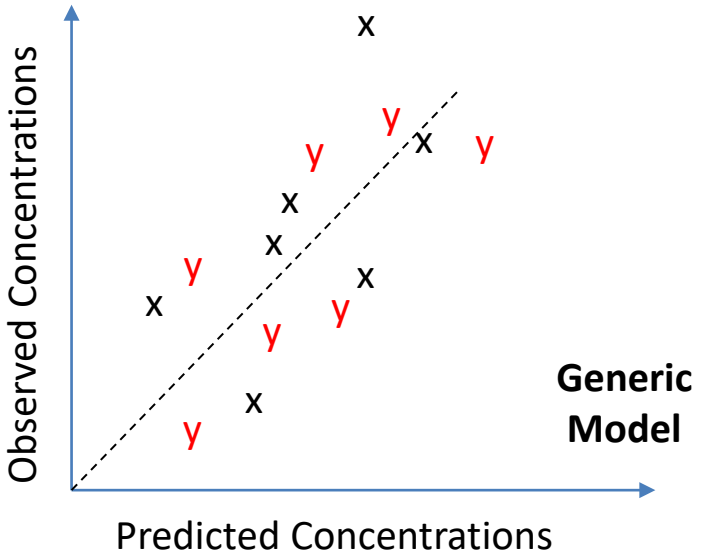

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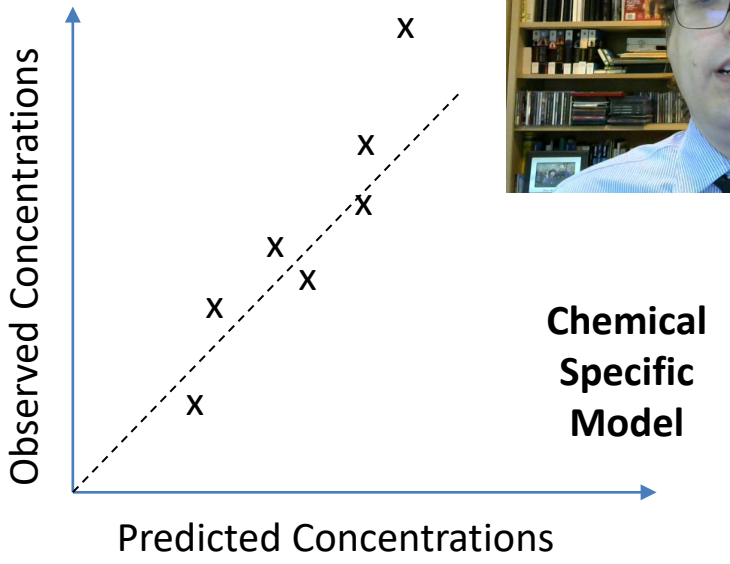
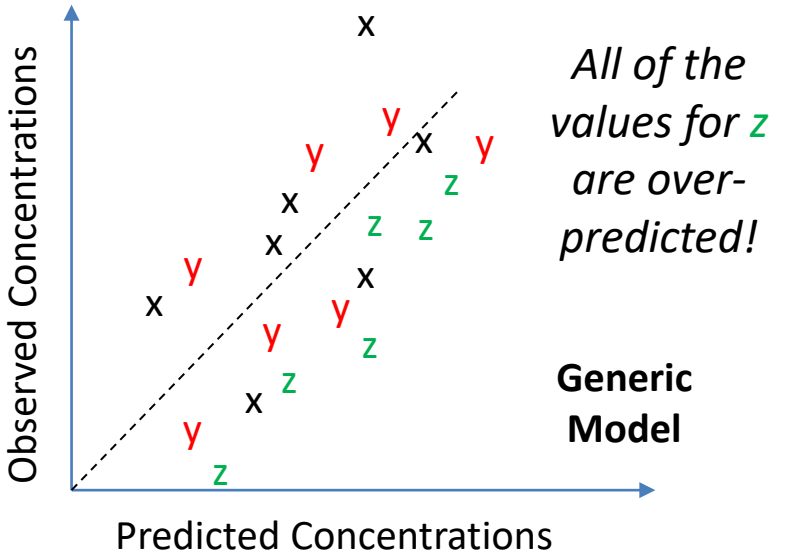
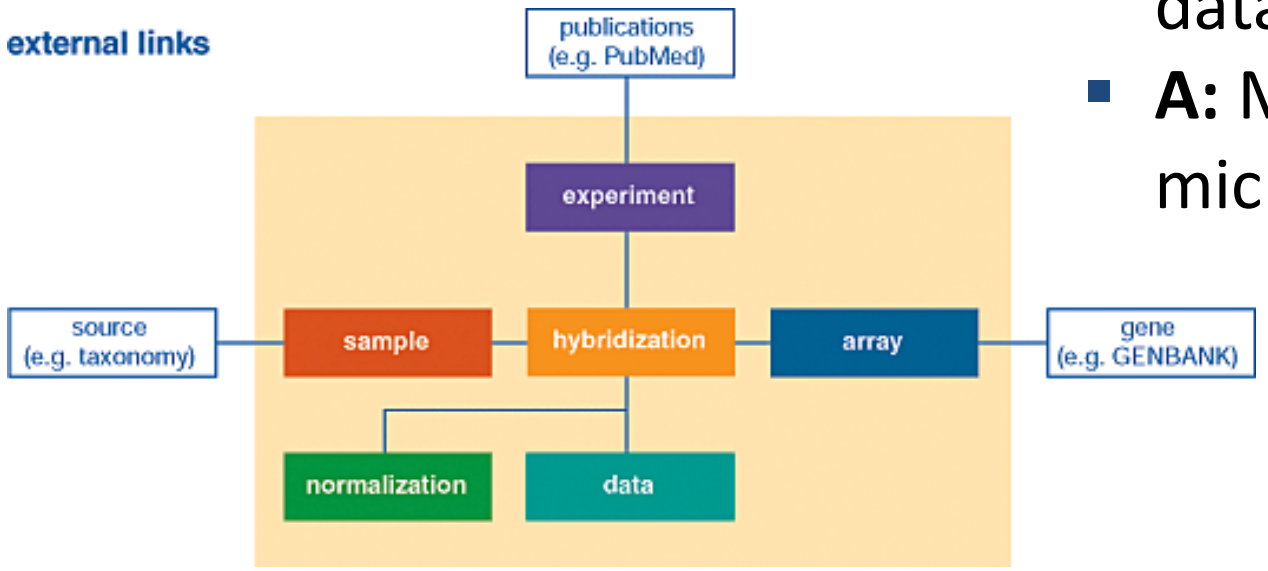




Cohen Hubal et al. (2018)

Trivia Time!



- **Q:** What standard was established in 2001 for the reporting of microarray data?
- **A:** Minimum information about a microarray experiment (MIAME)

In Vivo TK Database

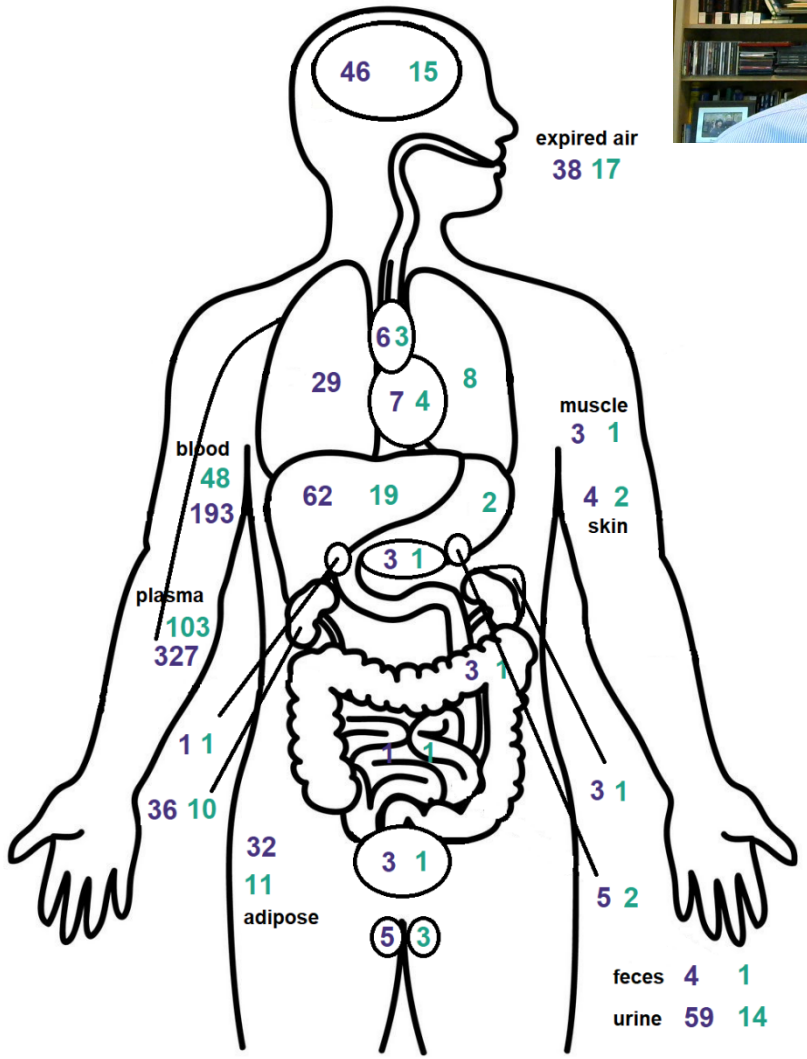
https://github.com/USEPA/CompTox-PK-CvTdb

- 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



Other: 12 7

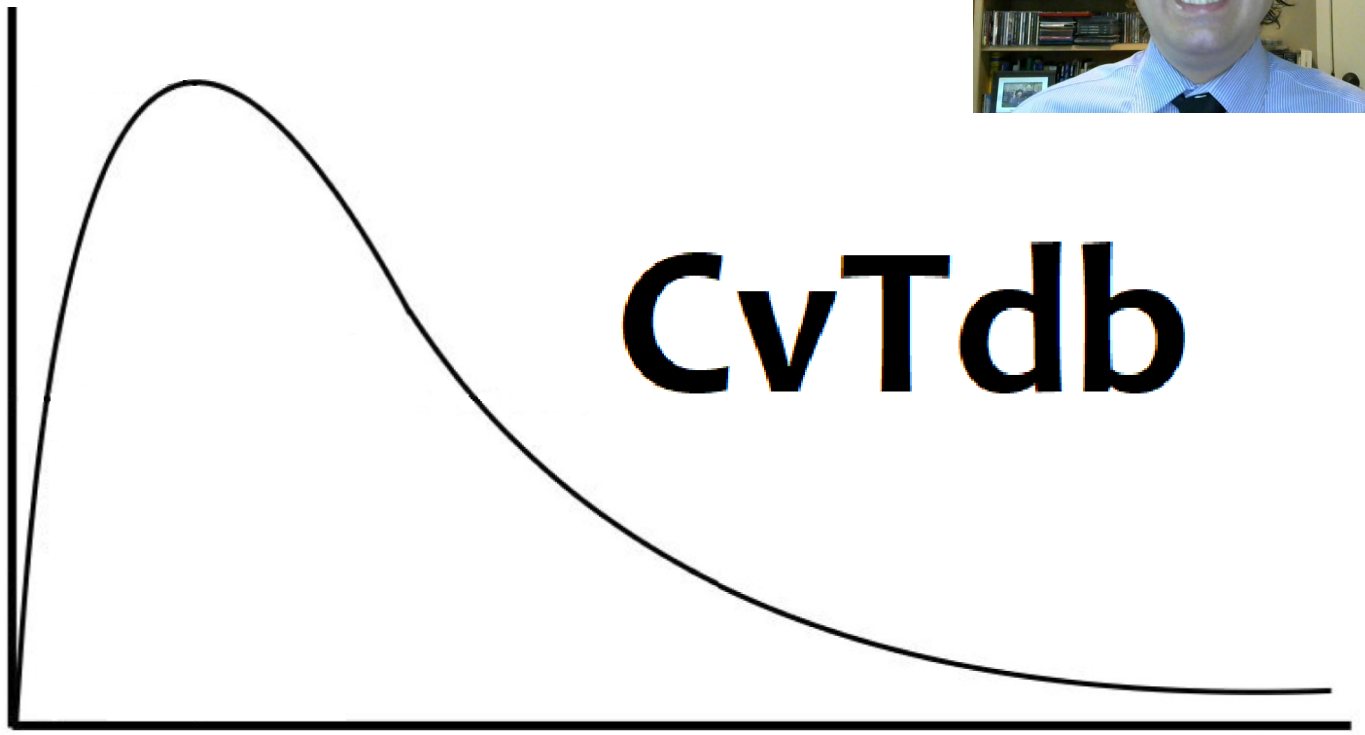
Sayre et al. (2020)

CvTdb Team

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

- Started by Risa Sayre and Chris Grulke
- Ongoing curation of journal articles by:
  - Mike Hughes
  - Anna Kreutz
  - Nancy Hanley
  - Karen Herbin-Davis
  - Tirumala-Devi Kodavanti
  - Evgenia Korol-Bexell
  - Mark Sfeir
  - Lucas Albrecht

  and others

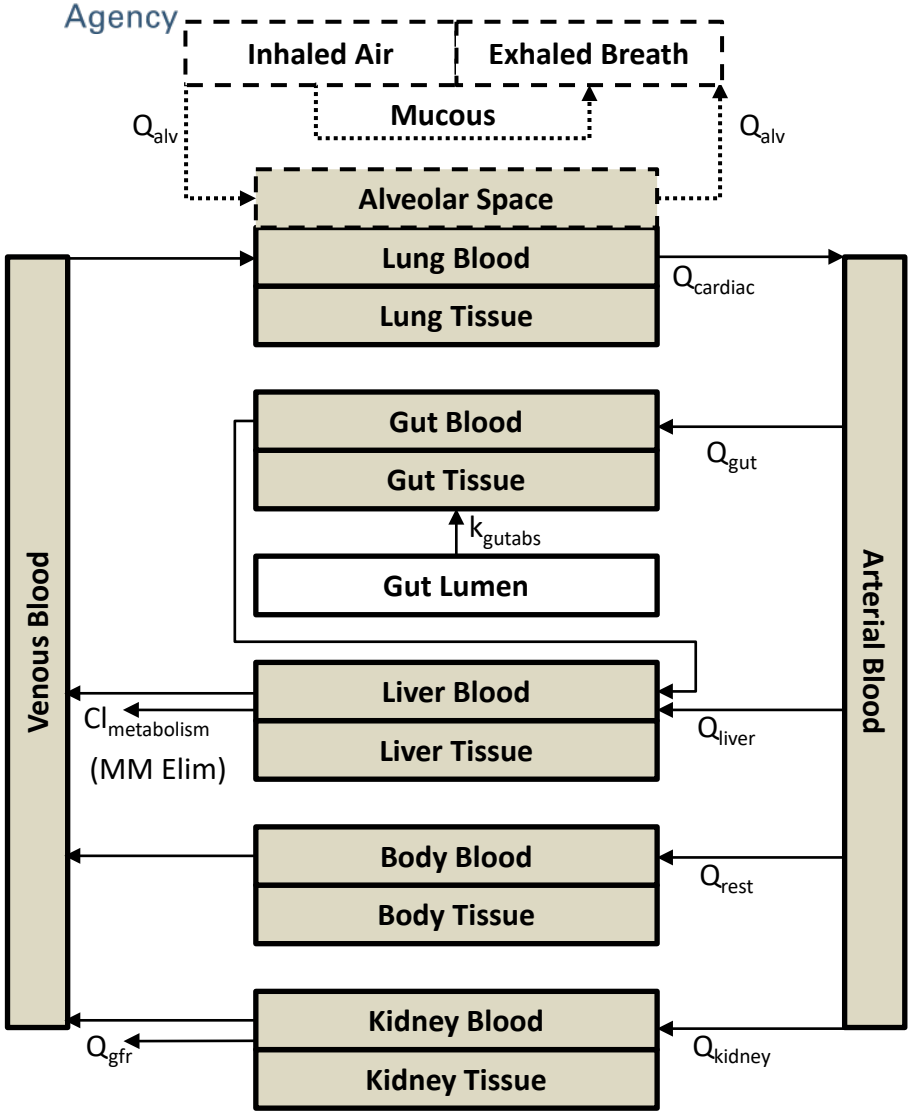


- Currently advertising a master-level position to manage curation and development of CvTdb. See advertisement EPA-ORD-CCTE-CCED-2020-02 for "**EPA Toxicokinetic Database Engineering Internship**" on Zintellect:

https://www.zintellect.com/Opportunity/Details/EPA-ORD-CCTE-CCED-2020-02

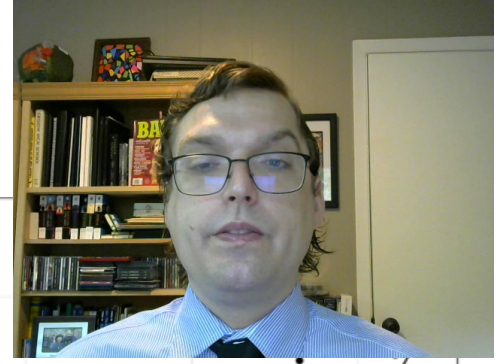
Sayre et al. (2020)

Generic Gas Inhalation Model

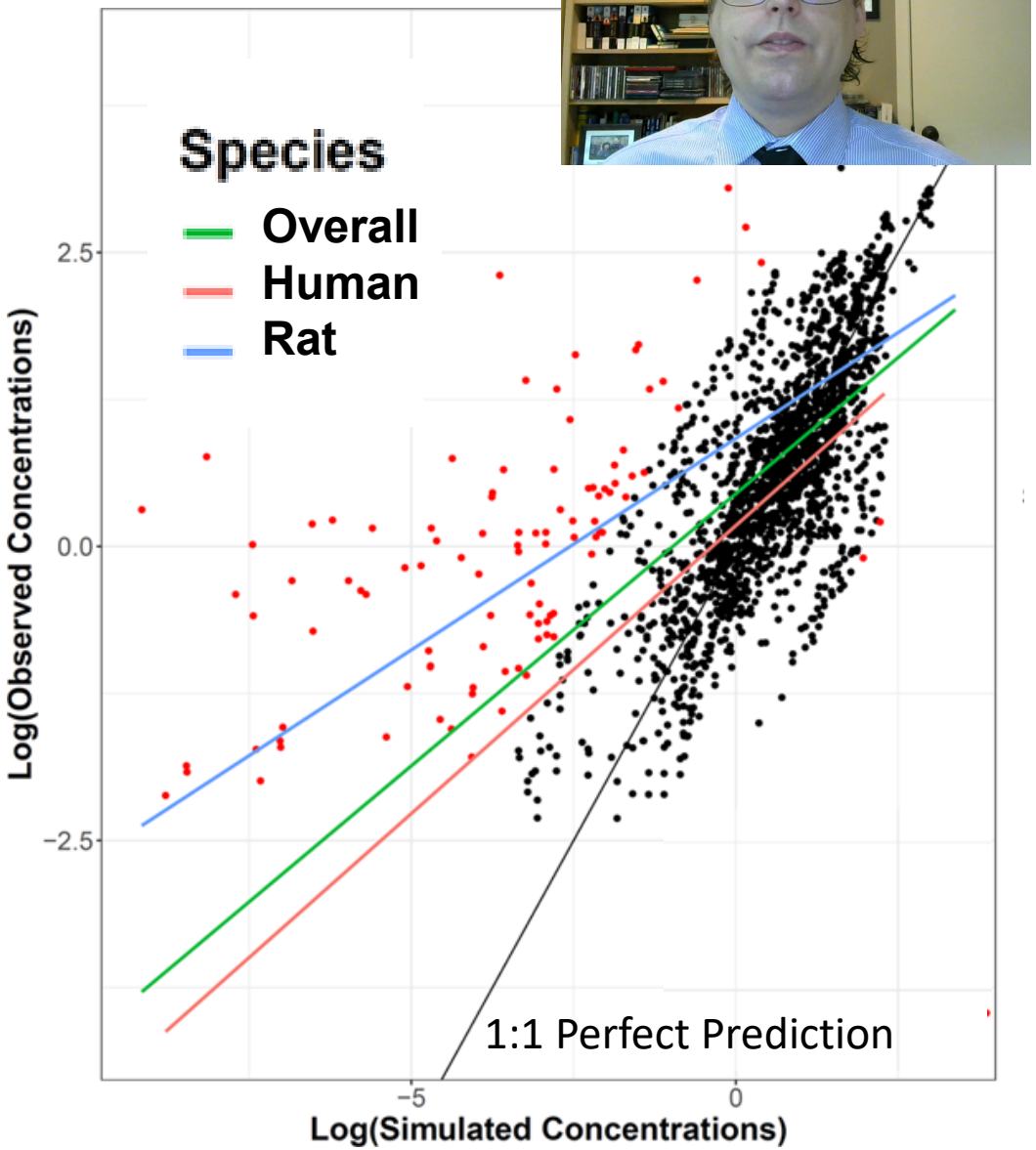


- Inhalation is an important route of exposure, particularly for occupational settings
- "**Development and Evaluation of a High Throughput Inhalation Model for Organic Chemicals**" by **Linakis et al.** was just published at Journal of Exposure Science and Environmental Epidemiology
- The structure 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

Developing Models with the CvT Database



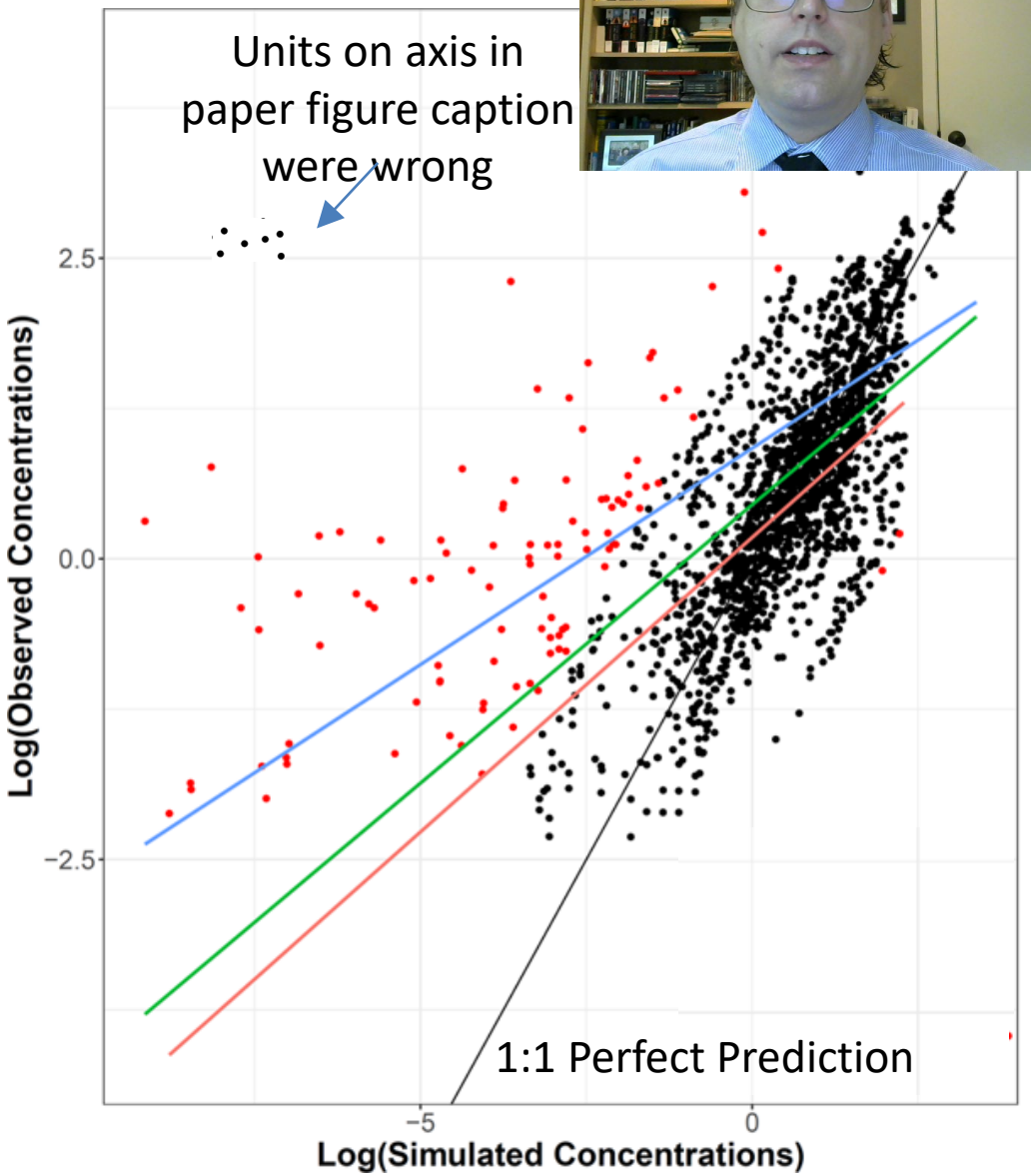
- Access to *in vivo* concentration vs. time data made it easier to identify coding and other modeling errors
- 142 exposure scenarios across 41 volatile organic chemicals were modeled and compared to published *in vivo* data for humans and rat



Linakis et al. (2020)

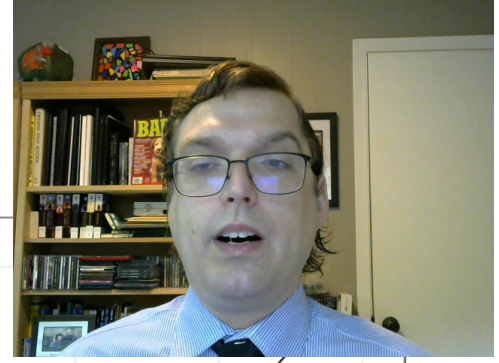
Developing Models with the CvT Database

- Access to *in vivo* concentration vs. time data made it easier to identify coding and other modeling errors
- **Access to *in vivo* concentration vs. time data also made it easier to find fault with specific data sets**

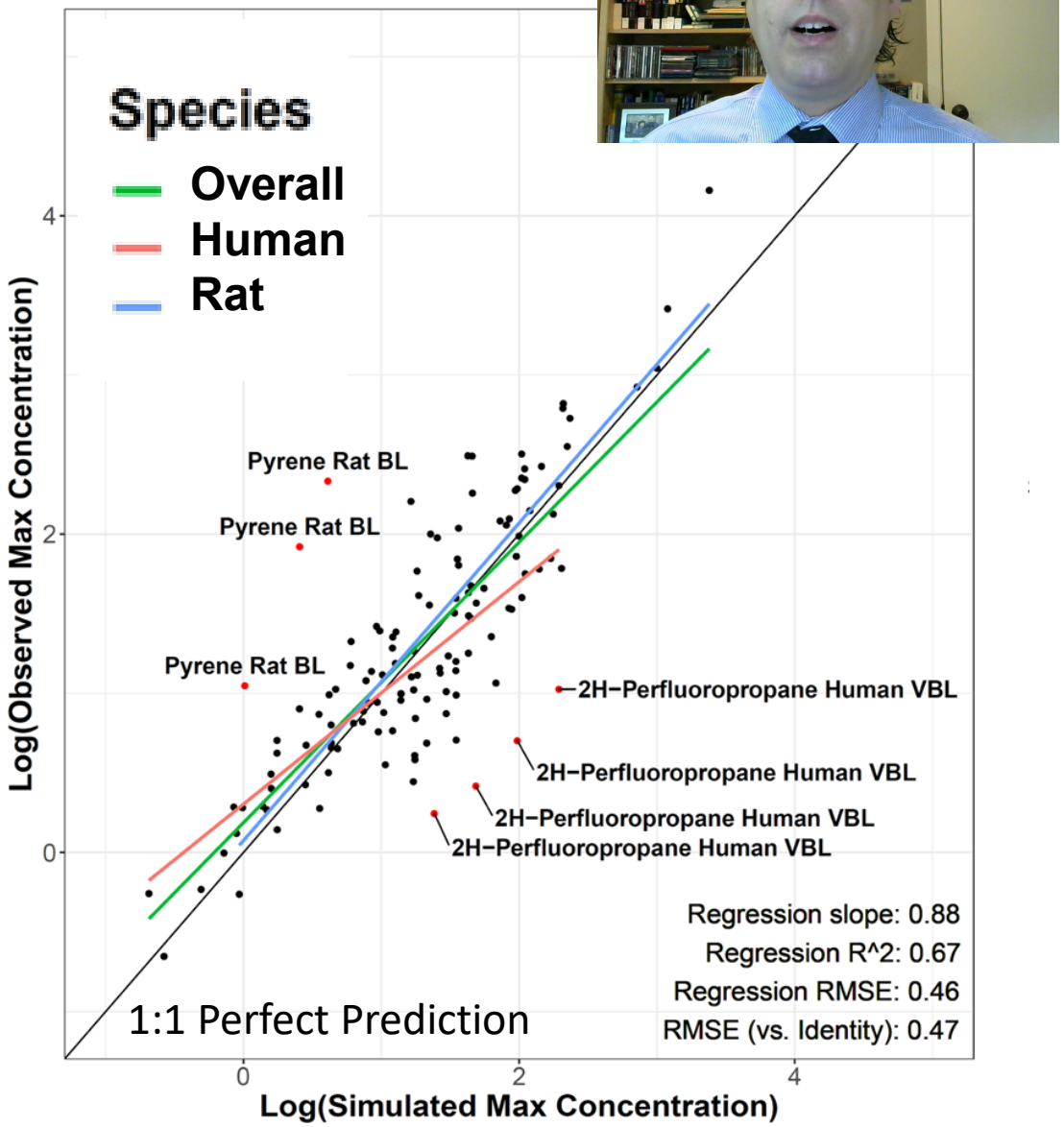


Linakis et al. (2020)

Developing Models with the CvT Database

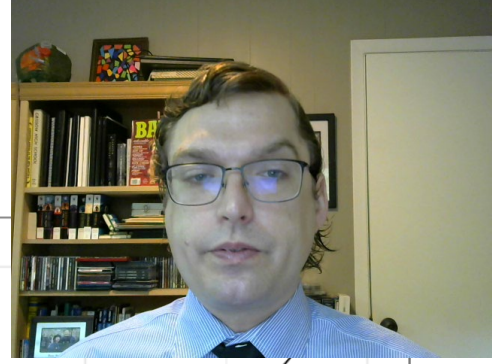


- Access to *in vivo* concentration vs. time data made it easier to identify coding and other modeling errors
- Overall RMSE was 0.69 and R^2 was 0.54 for full concentration time-course across all chemicals and both species
- R^2 was 0.67 for predicting peak concentration



Linakis et al. (2020)

Developing Models with the CvT Database



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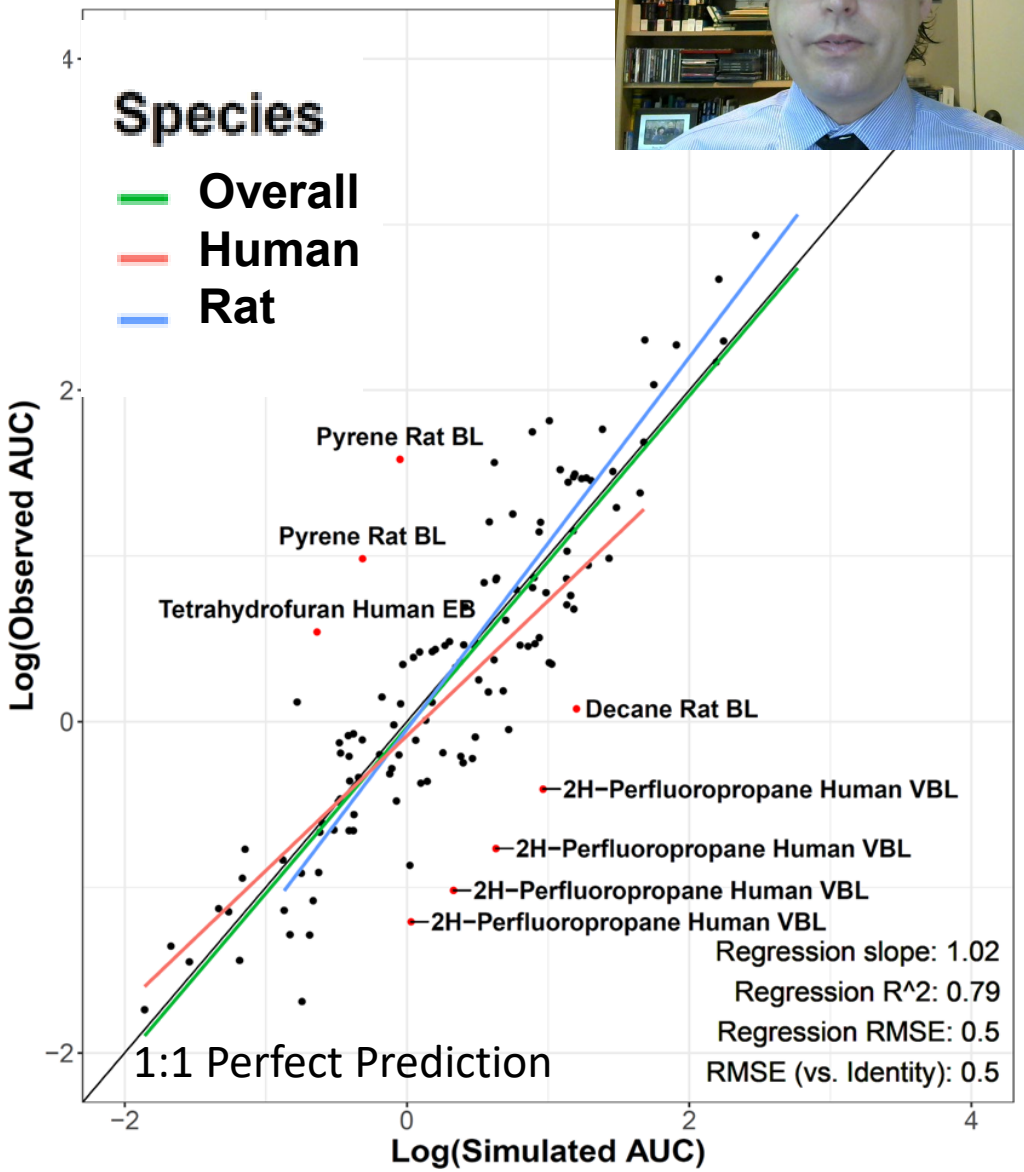
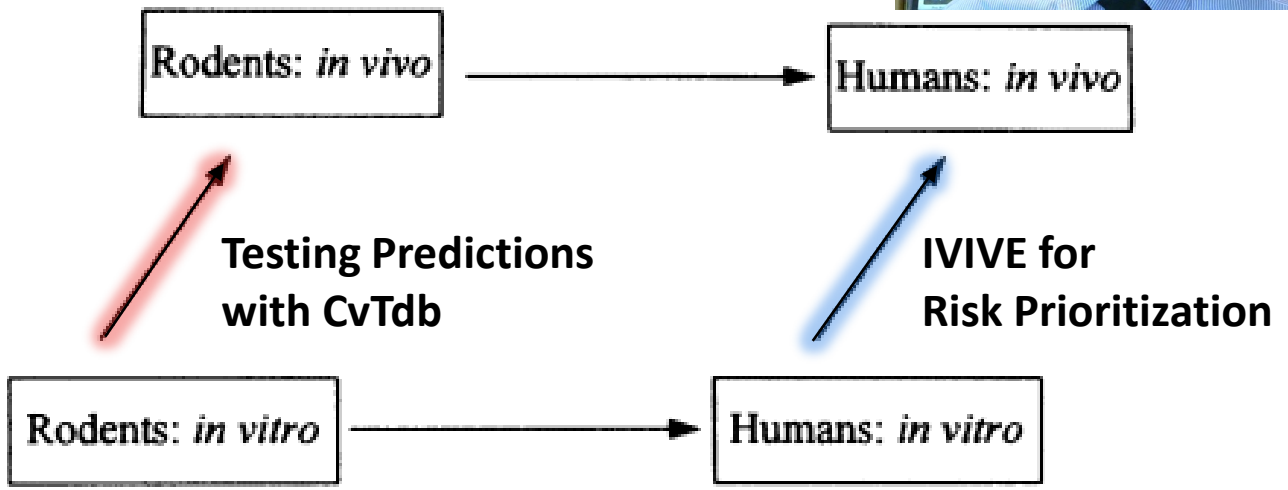
- Overall RMSE was 0.69 and R^2 was 0.54 for full concentration time-course across all chemicals and both species
- R^2 was 0.67 for predicting peak concentration
- R^2 was 0.79 for predicting time integrated plasma concentration (Area Under the Curve, AUC)



Linakis et al. (2020)

Conclusions

- The inhalation route is important for both occupational and general population chemical exposures.
- HTTK combines relatively rapid *in vitro* measurements of toxicokinetics with generic mathematical models that make use of the *in vitro* data and physico-chemical properties.



- The inhalation models have been statistically evaluated using EPA's Concentration vs. Time toxicokinetics database (CvTdb).
- HTTK inhalation models allow for *in vitro-in vivo* extrapolation of volatile compounds, enabling comparison of estimates of bioactive *in vivo* doses with estimates of chemical exposures.
- These approaches have the potential to integrate *in vitro* toxicity data for air pollutants into chemical risk evaluations.

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

EPA United States Environmental Protection Agency

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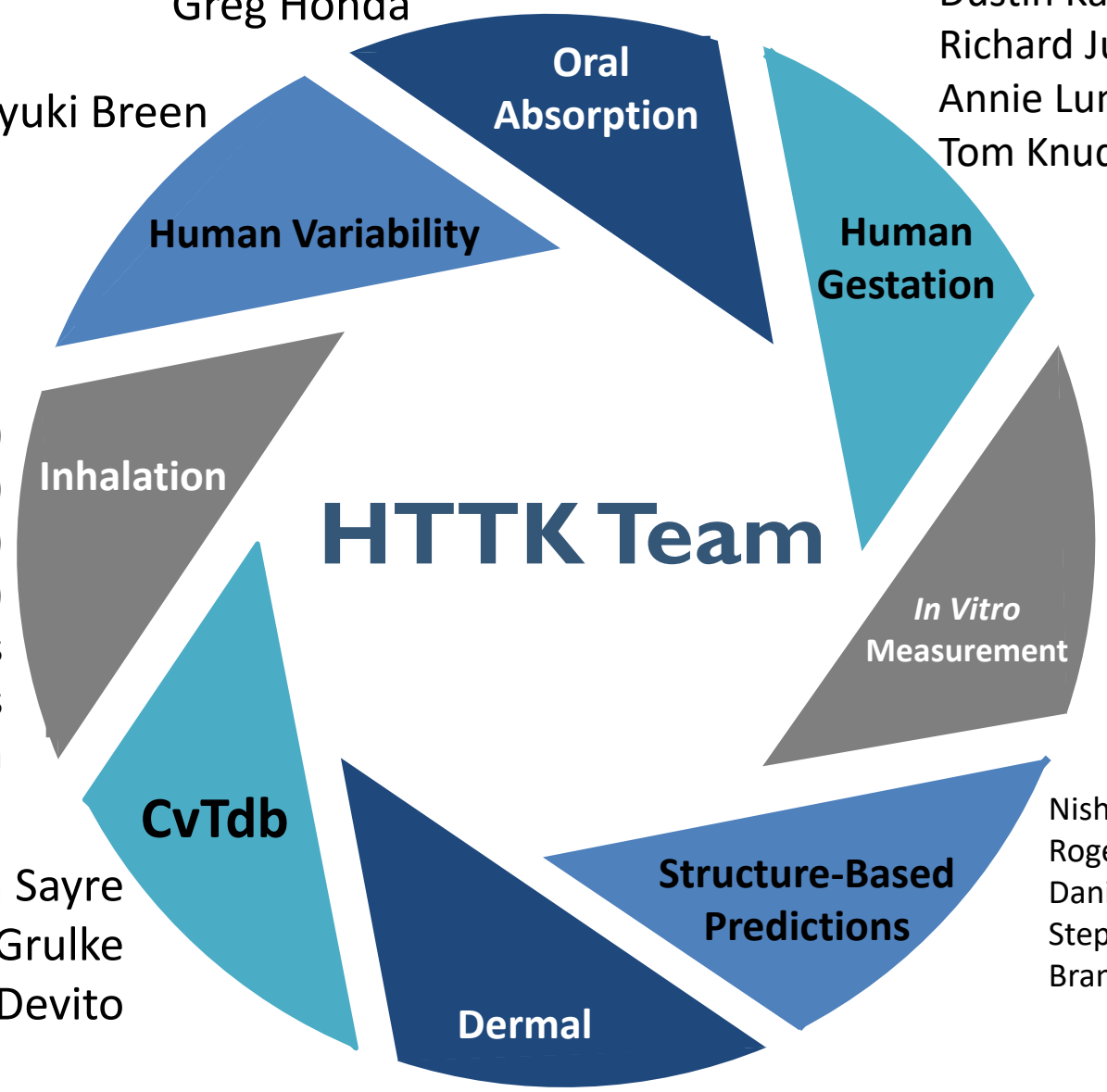

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