High Throughput Inhalation Toxicokinetics with the HTTK R Package

John Wambaugh

Center for Computational Toxicology and Exposure

Office of Research and Development

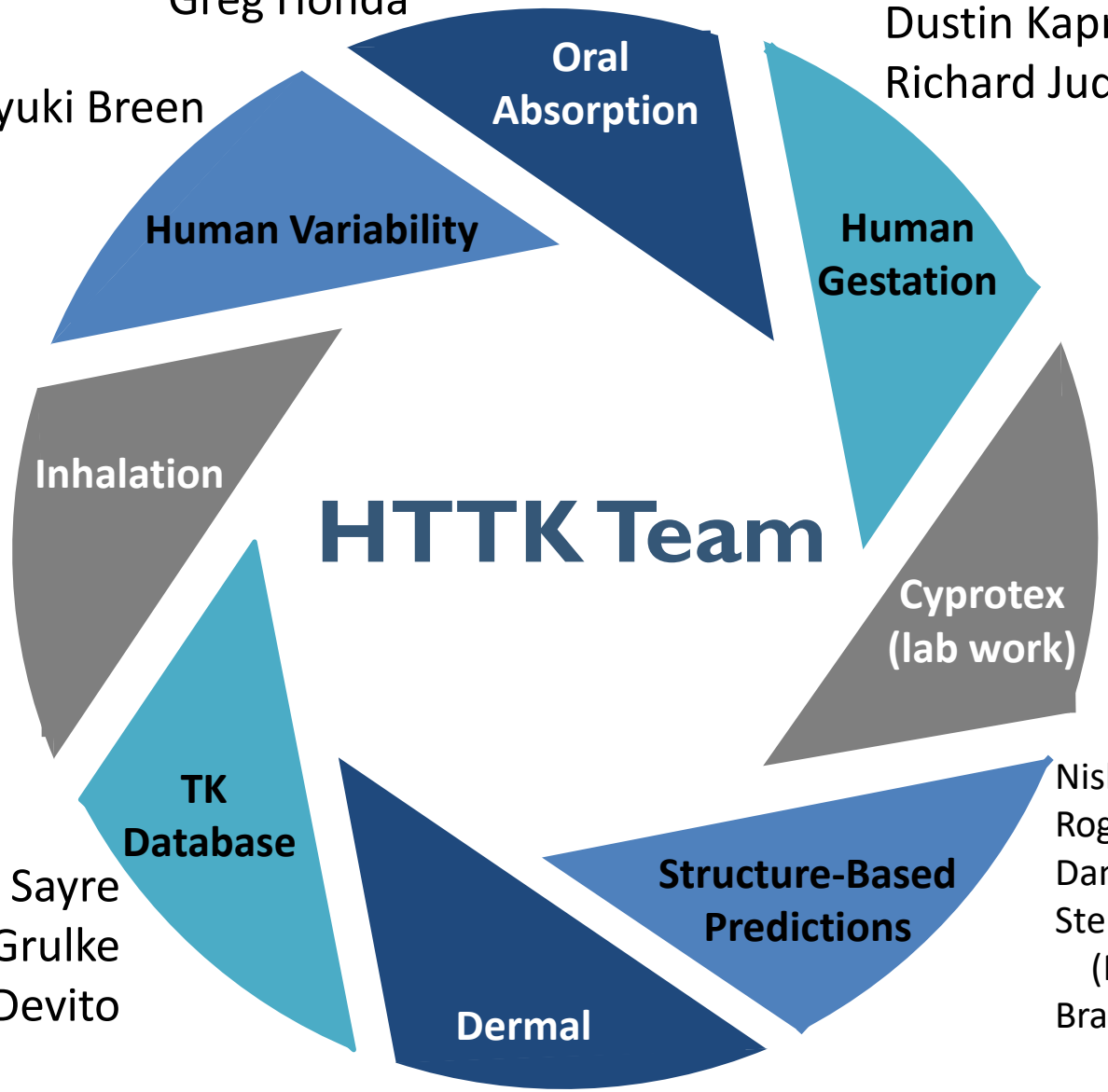
U.S. Environmental Protection Agency

Computational Toxicology Community of Practice Webinar

March 26, 2020

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

HTTK Team



Greg Honda

Miyuki Breen

Dustin Kapraun
Richard Judson

Tom Knudsen
Annie Lumen
(FDA)

Mark Sfeir
Software Engineer

cyprotex
AN EVOTEC COMPANY

Derek Angus
Maria Bacolod
Akshay Badrinarayanan
Adam Brockman
Roger Dinallo
Briana Franz
Jon Gilbert
Teresa Sierra
Bradley Snodgrass
Chris Strock

Matt Linakis (AFRL)
Heather Pangburn (AFRL)
Jeffery Gearhart (AFRL)
Nisha Sipes (NTP)
Kristin Isaacs
Marina Evans
Miyuki Breen

Nisha Sipes (NTP)
Rogelio Tornero-Velez
Daniel Dawson
Stephen Ferguson (NTP)
Brandall Ingle (ICF)
Richard Judson
Jon Arnot (ARC)
Kamel Mansouri (ILS
Michael Lawless (Simulations Plus)
Prachi Pradeep

Russell Thomas
Barbara Wetmore
Mike Devito
David Murphy
Katherine Coutros
Ann Richard

Risa Sayre
Chris Grulke
Mike Devito

Marina Evans
Tom Moxon (Unilever)
Beate Nicol (Unilever)

Alumni

Robert Pearce
Woody Setzer
Caroline Ring
Greg Honda Cory Strope
Jimena Davis
Chantel Nicolas

Funded by EPA's Office of Research and Development and Office of Science Coordination and Policy

US EPA Office of Research and Development

- The Office of Research and Development (ORD) is the scientific research arm of EPA
  - 562 peer-reviewed journal articles in 2018
- 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

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)
  - Different levels depending on category

November 29, 2014

Toxic Substances Control Act (TSCA)

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

- TSCA was updated in June, 2016 to allow more rapid evaluation of chemicals (Frank R. Lautenberg Chemical Safety for the 21st Century Act)

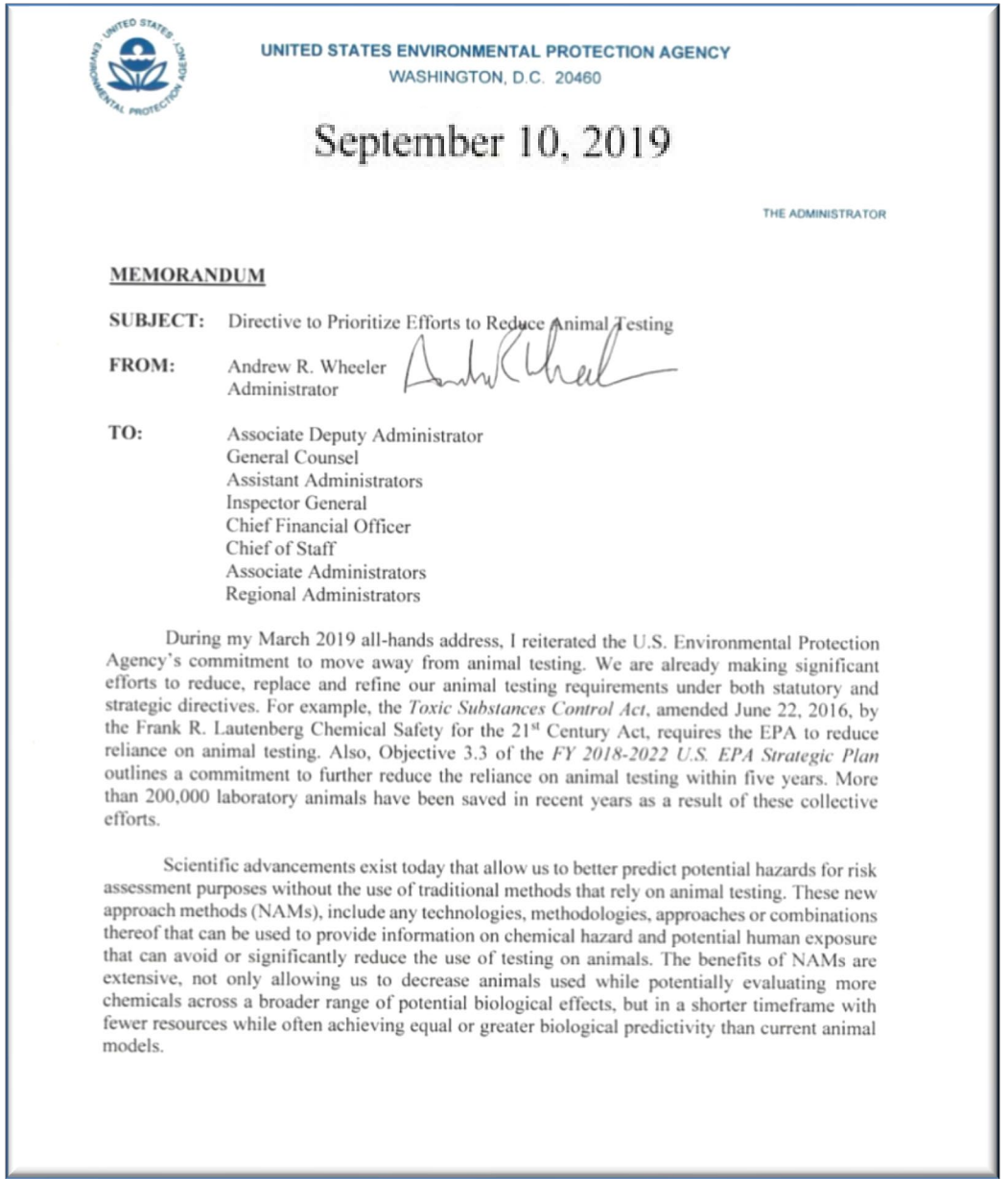
"Tens of thousands of chemicals are listed with the Environmental Protection Agency (EPA) for commercial use in the United States, with an average of 600 new chemicals listed each year."
U.S. Government Accountability Office

Schmidt, C. W. (2016)

Replacing Animal Testing with NAMs

- Administrator of the EPA: "I am directing leadership and staff in the Office of Chemical Safety and Pollution Prevention and the Office of Research and Development to prioritize … the reduction of animal testing while ensuring protection of human health and the environment."

- "These new approach methods (NAMs), include any technologies, methodologies, approaches or combinations thereof that can be used to provide information on chemical hazard and potential human exposure that can avoid or significantly reduce the use of testing on animals"



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

September 10, 2019

THE ADMINISTRATOR

MEMORANDUM

SUBJECT: Directive to Prioritize Efforts to Reduce Animal Testing

FROM: Andrew R. Wheeler
Administrator

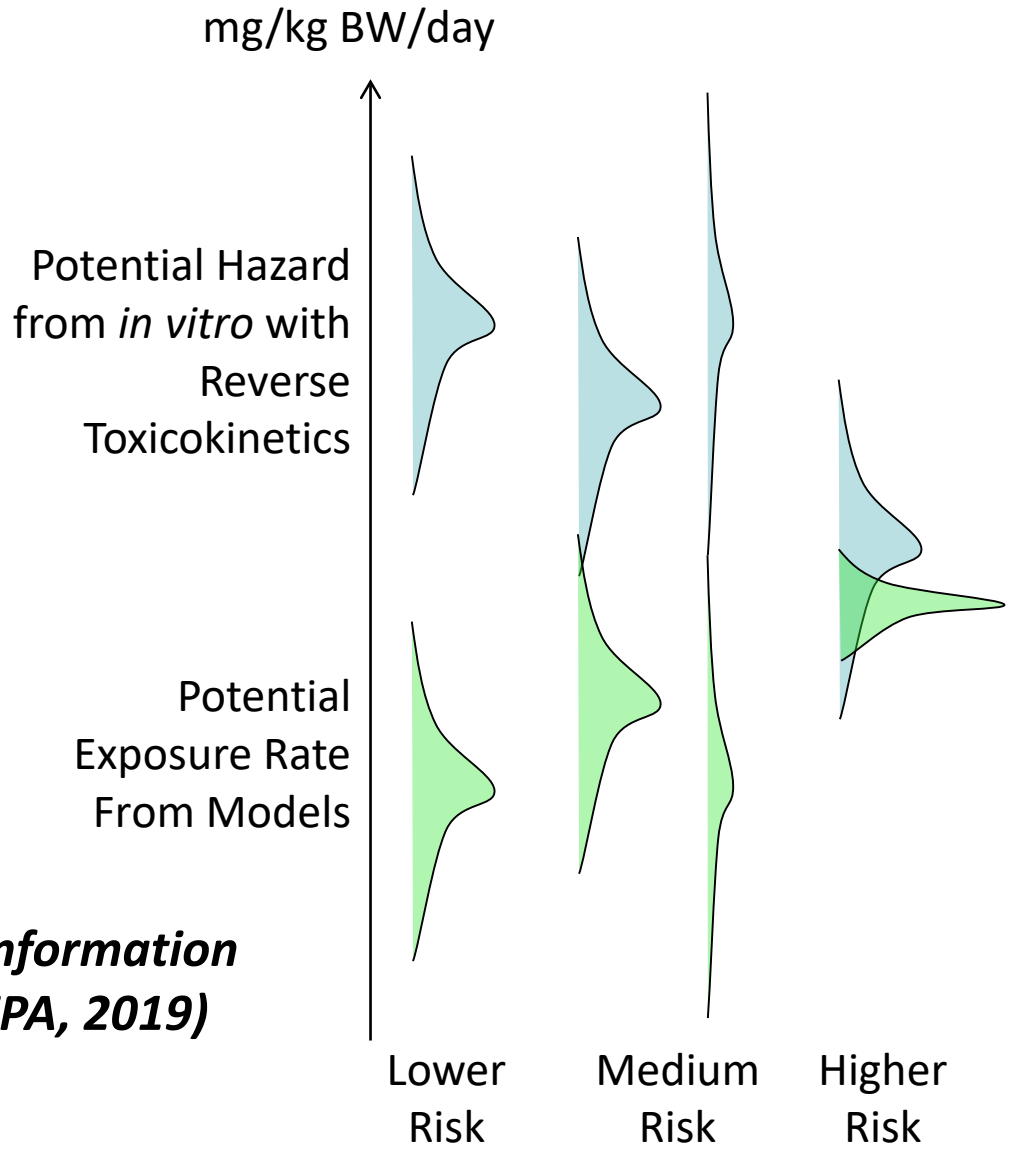
TO: Associate Deputy Administrator
General Counsel
Assistant Administrators
Inspector General
Chief Financial Officer
Chief of Staff
Associate Administrators
Regional Administrators

During my March 2019 all-hands address, I reiterated the U.S. Environmental Protection Agency's commitment to move away from animal testing. We are already making significant efforts to reduce, replace and refine our animal testing requirements under both statutory and strategic directives. For example, the *Toxic Substances Control Act*, amended June 22, 2016, by the Frank R. Lautenberg Chemical Safety for the 21st Century Act, requires the EPA to reduce reliance on animal testing. Also, Objective 3.3 of the *FY 2018-2022 U.S. EPA Strategic Plan* outlines a commitment to further reduce the reliance on animal testing within five years. More than 200,000 laboratory animals have been saved in recent years as a result of these collective efforts.

Scientific advancements exist today that allow us to better predict potential hazards for risk assessment purposes without the use of traditional methods that rely on animal testing. These new approach methods (NAMs), include any technologies, methodologies, approaches or combinations thereof that can be used to provide information on chemical hazard and potential human exposure that can avoid or significantly reduce the use of testing on animals. The benefits of NAMs are extensive, not only allowing us to decrease animals used while potentially evaluating more chemicals across a broader range of potential biological effects, but in a shorter timeframe with fewer resources while often achieving equal or greater biological predictivity than current animal models.

New Approach Methodologies (NAMs)

- There are roughly 10,000 TSCA-relevant chemicals in commerce
  - Traditional methods are too resource-intensive to address all of these
- NAMs include:
  - High throughput screening (ToxCast)
  - High throughput exposure estimates (ExpoCast)
  - High throughput toxicokinetics (HTTK)
- TSCA Proof of concept: Examine ~200 chemicals with ToxCast, ExpoCast and HTTK
  - HTTK was rate limiter on number of chemicals



"A Proof-of-Concept Case Study Integrating Publicly Available Information to Screen Candidates for Chemical Prioritization under TSCA" (EPA, 2019)

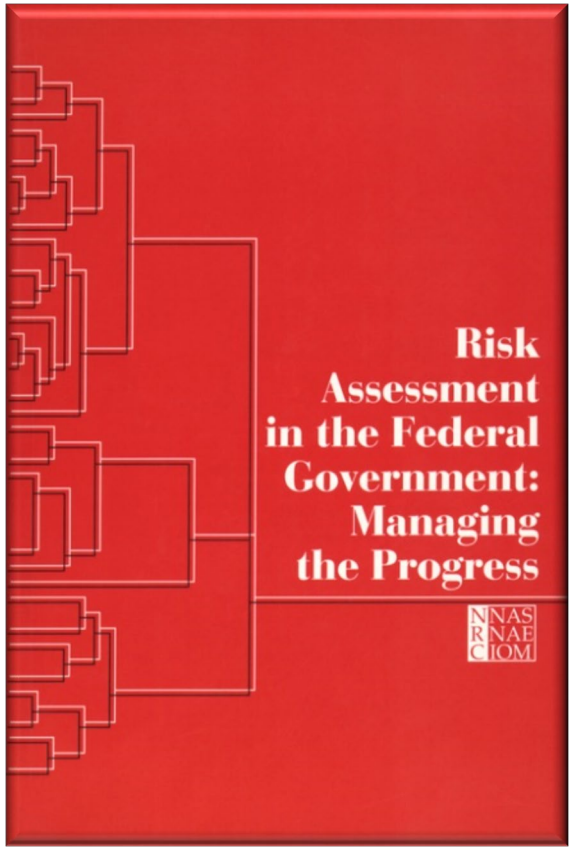
For the Kids at Home

Home Safari

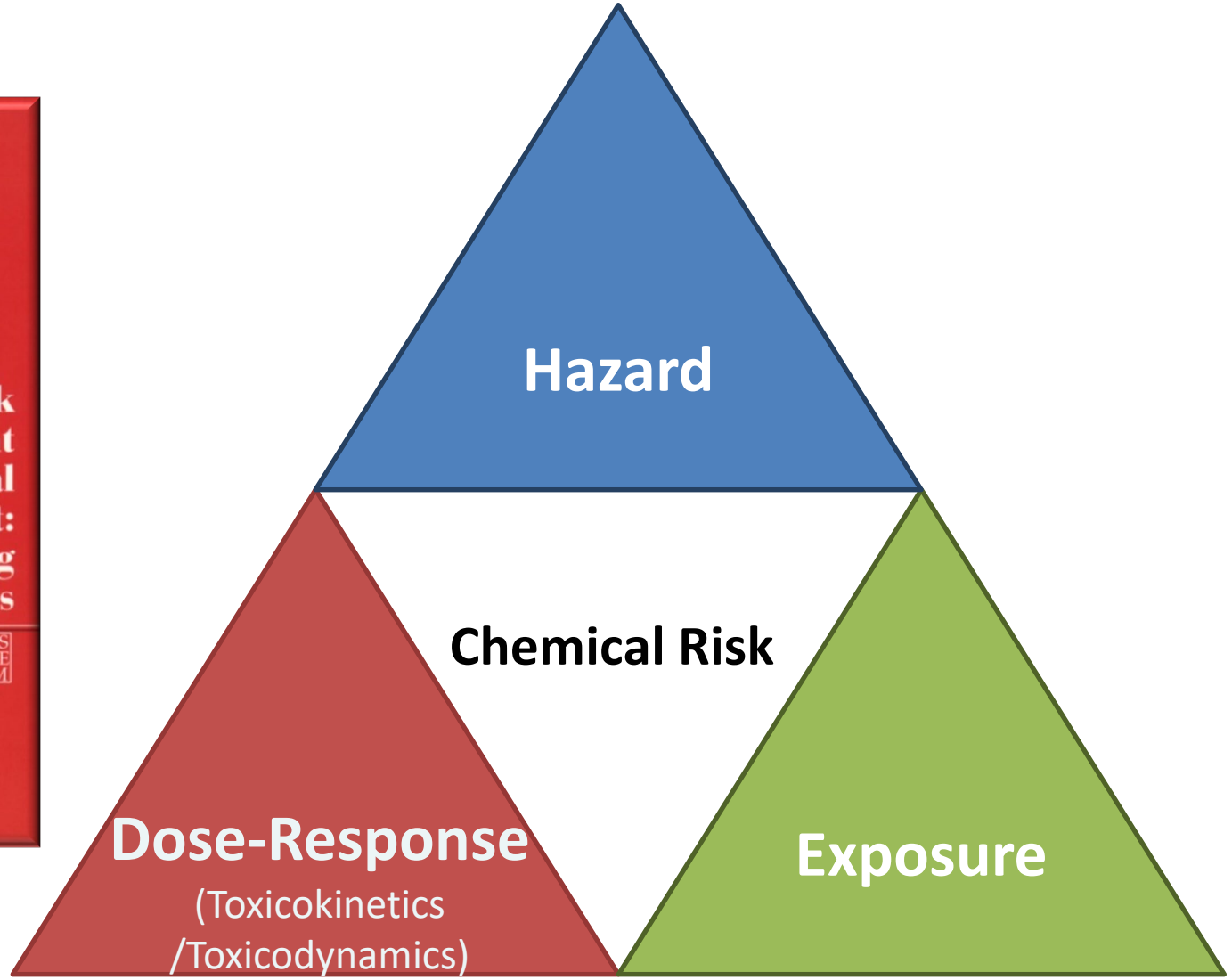
While the Cincinnati Zoo is closed and kids are home from school, let us help make your children's hiatus from school fun and educational.

Join us for a Home Safari Facebook Live each day at 3pm EDT where we will highlight one of our amazing animals and include an activity you can do from home

Three Components for Chemical Risk

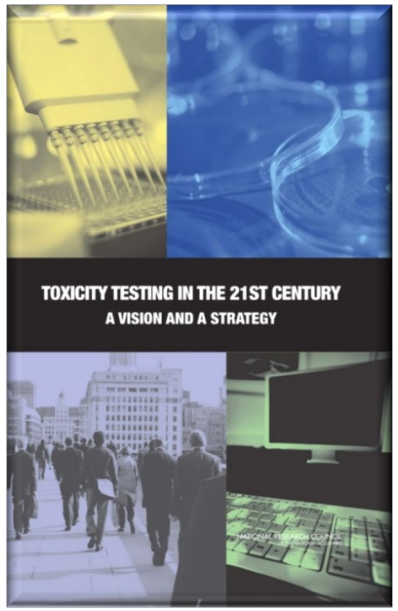


NRC (1983)



The National Academy of Sciences, Engineering and Medicine (1983) outlined three components for determining chemical risk.

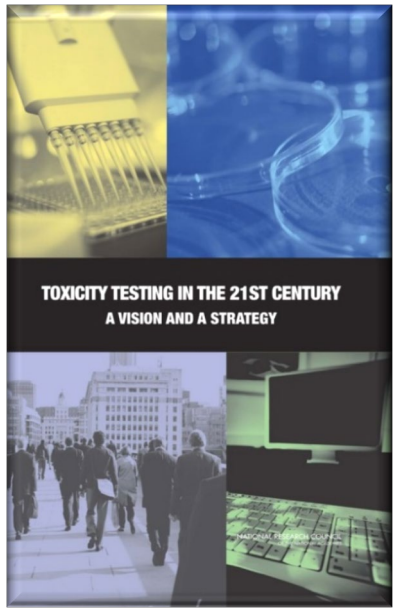
High-Throughput Risk Prioritization



NRC (2007)

High throughput screening (HTS) for *in vitro* bioactivity potentially allows characterization of thousands of chemicals for which no other testing has occurred

High-Throughput Risk Prioritization



NRC (2007)

"Translation of high-throughput data into risk-based rankings is an important application of exposure data for chemical priority-setting. Recent advances in high-throughput toxicity assessment, notably the ToxCast and Tox21 programs… and in **high-throughput computational exposure assessment** [ExpoCast] have enabled first-tier risk-based rankings of chemicals on the basis of margins of exposure"

National Academies of Sciences, Engineering, and Medicine (NASEM), 2017

In Vitro - In Vivo Extrapolation (IVIVE)

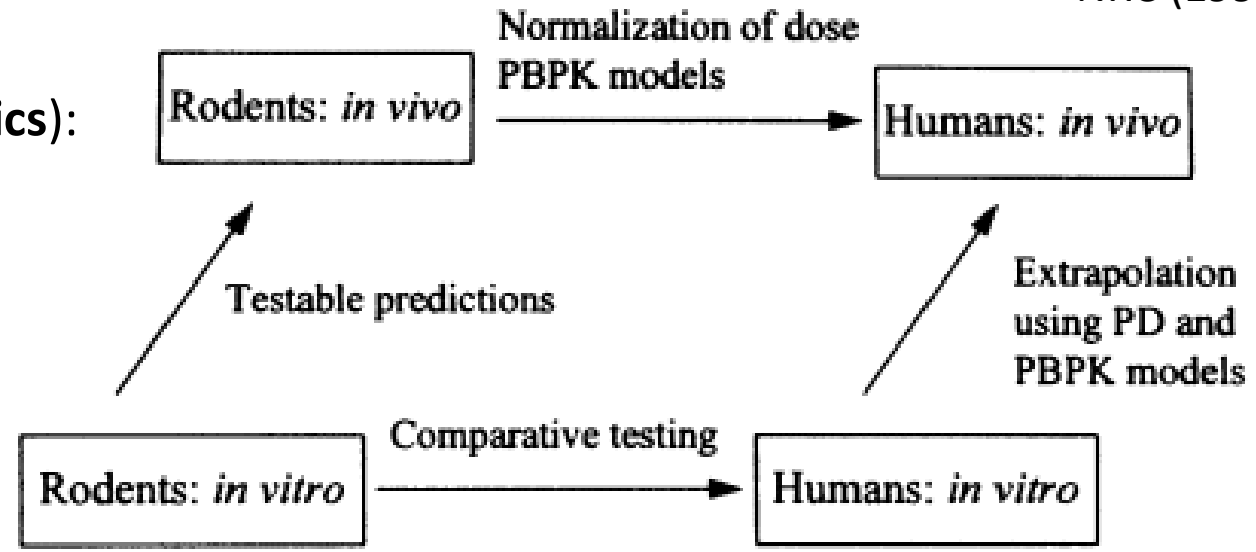
- IVIVE is the use of *in vitro* data to predict phenomena *in vivo*

  *T*his can be broken down into two components:

- IVIVE-PK/TK (**Pharmacokinetics/Toxicokinetics**):
  - Fate of molecules/chemicals in body
  - Considers absorption, distribution, metabolism, excretion (ADME)
  - Uses empirical PK and physiologically-based (PBPK) modeling

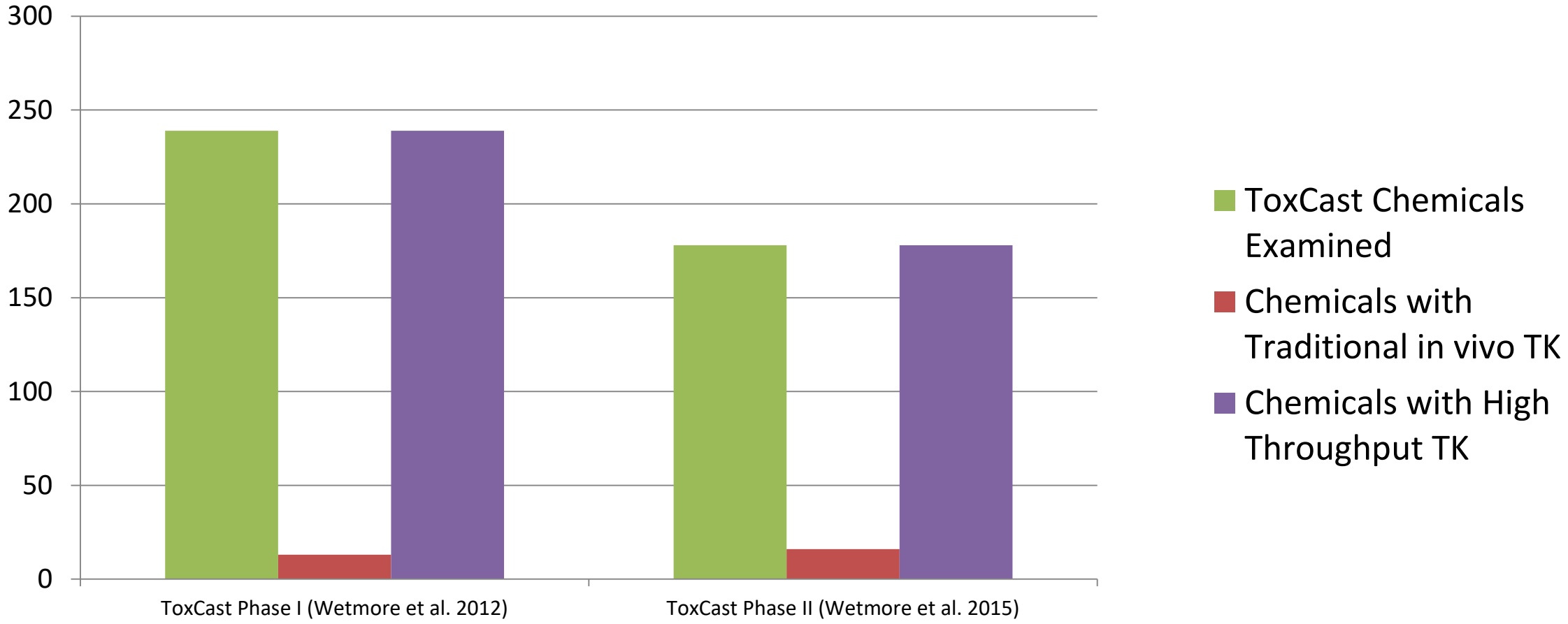
- IVIVE-PD/TD (**Pharmacodynamics/Toxicodynamics**):
  - Effect of molecules/chemicals at biological target *in vivo*
  - Assay design/selection important
  - Perturbation as adverse/therapeutic effect, reversible/ irreversible effeccts

NRC (1998)



The Need for Toxicokinetics NAMs

Most chemicals do not have TK data (Wetmore et al., 2015)



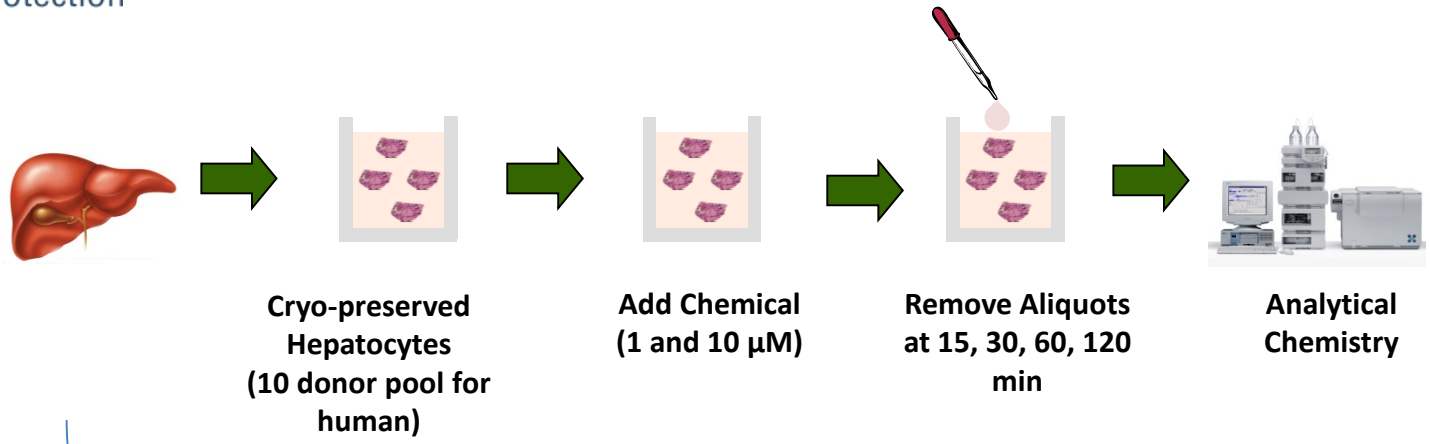
Bell et al. (2018)

NAMs for Toxicokinetics

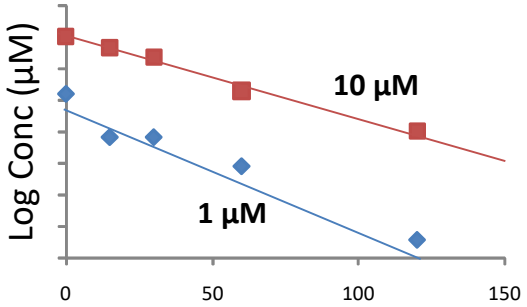
- In order to address greater numbers of chemicals we collect *in vitro*, high throughput toxicokinetic (HTTK) data (for example, Rotroff et al., 2010, Wetmore et al., 2012, 2015)
- HTTK methods have been used by the pharmaceutical industry to determine range of efficacious doses and to prospectively 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)

In Vitro Data for HTTK

Cryo-preserved hepatocyte suspension Shibata *et al.* (2002)



The rate of disappearance of parent compound (slope of line) is the **hepatic clearance** (µL/min/10^6 hepatocytes)



We perform the assay at 1 and 10 µM to check for saturation of metabolizing enzymes.

- **Most chemicals do not have TK data** – we use *in vitro* HTTK methods adapted from pharma to fill gaps
- In drug development, HTTK methods allow IVIVE to estimate therapeutic doses for clinical studies – predicted concentrations are typically on the order of values measured in clinical trials (Wang, 2010)

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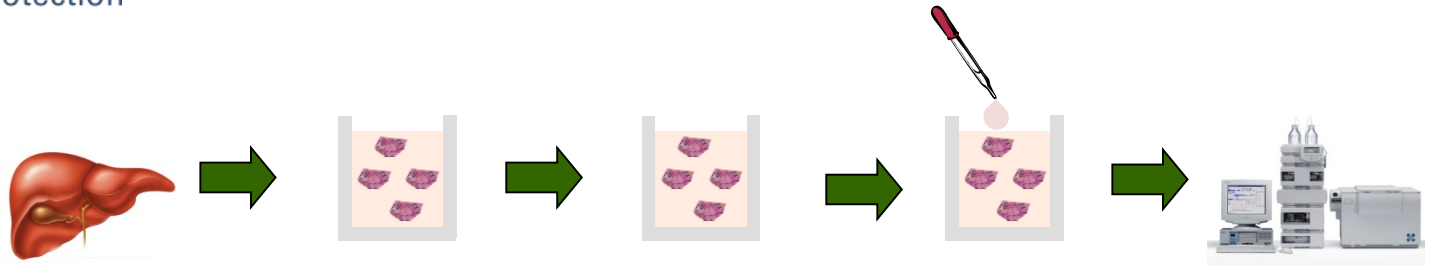
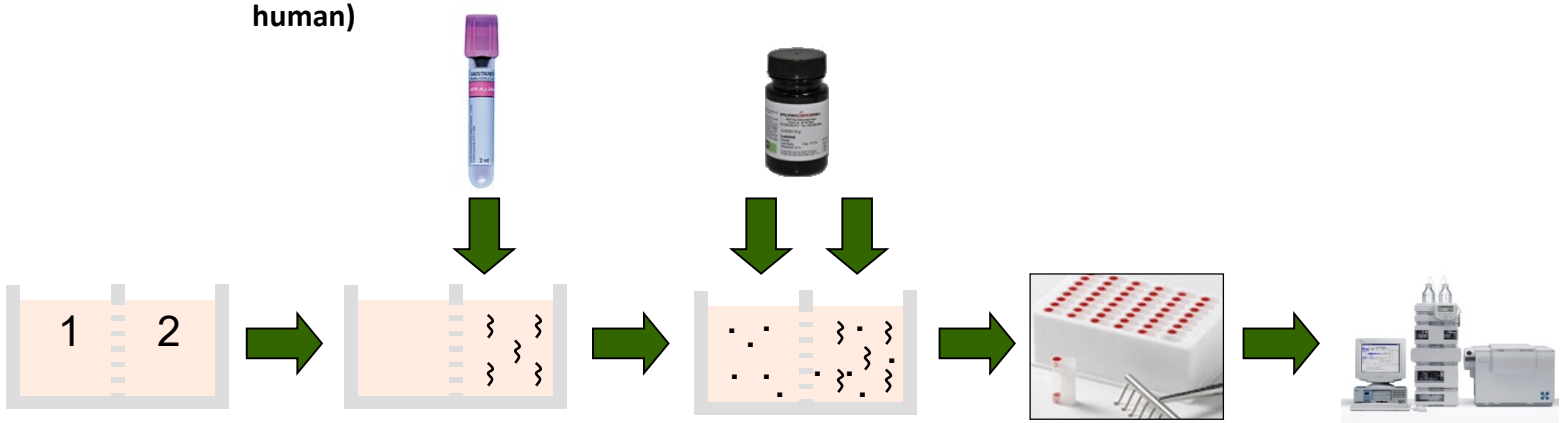


Rapid Equilibrium Dialysis (RED)
Waters *et al.* (2008)



$$F_{ub,p} = \frac{C_{well1}}{C_{well2}}$$

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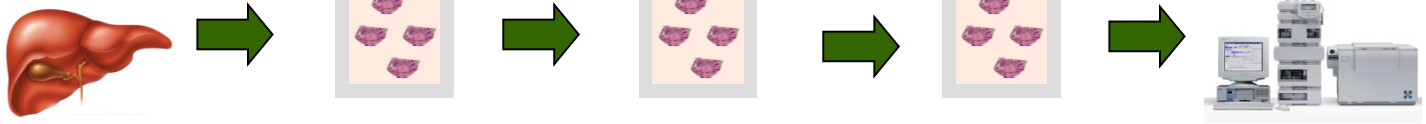


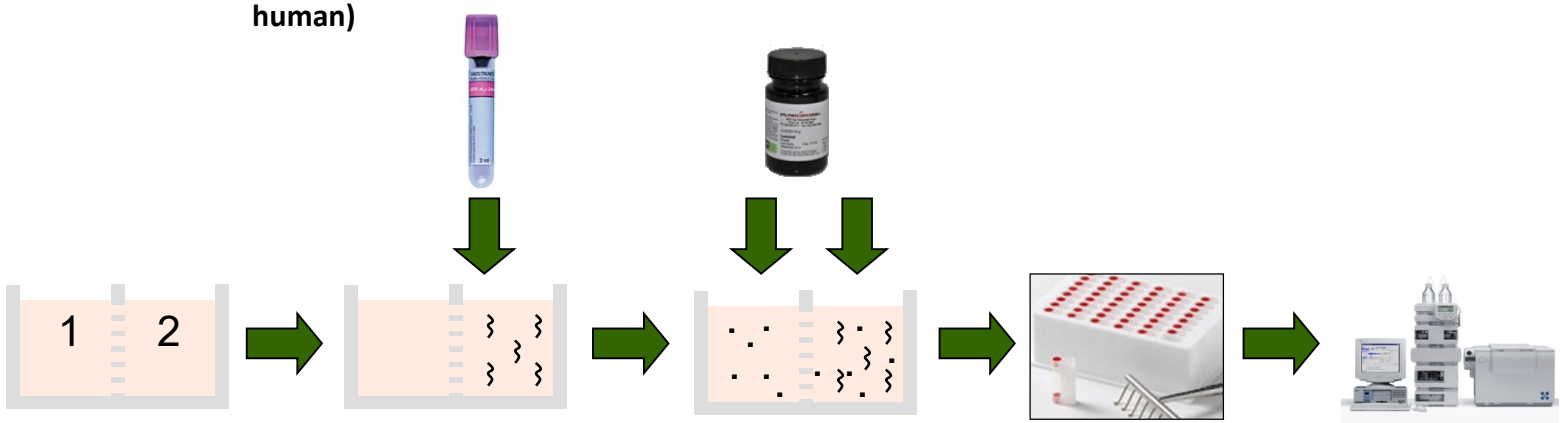
Cryo-preserved Hepatocytes (10 donor pool for human)

Add Chemical (1 and 10 µM)

Remove Aliquots at 15, 30, 60, 120 min

Analytical Chemistry

Rapid Equilibrium Dialysis (RED)
Waters *et al.* (2008)



Double-wells connected by semi-permeable membrane on a Rapid Equilibrium Dialysis (RED) Plate

Add plasma (6 donor pool for human) to one well

Add chemical

Incubate plates to allow wells with and without protein to come to equilibrium

Determine concentration in both wells (analytical chemistry)

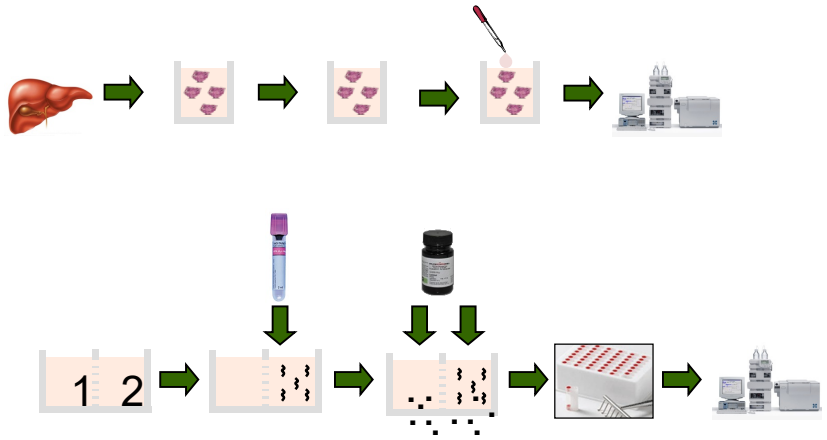
$$F_{ub,p} = \frac{C_{well1}}{C_{well2}}$$

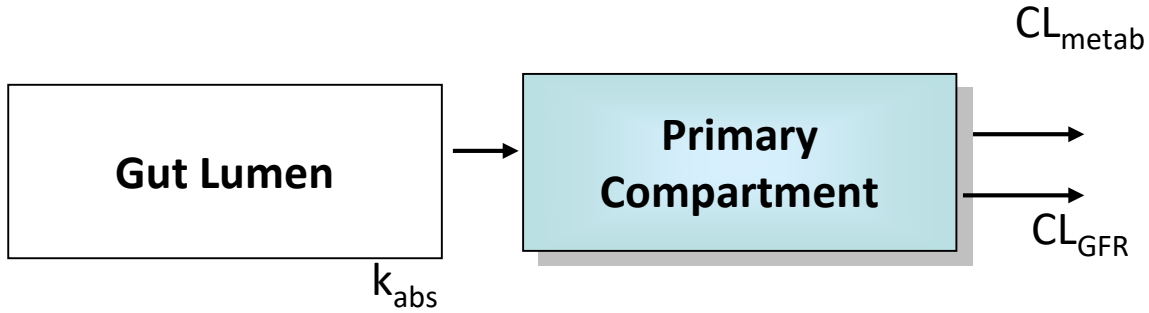
- **Most chemicals do not have TK data** – we use *in vitro* HTTK methods adapted from pharma to fill gaps
- Environmental chemicals:
  - Rotroff et al. (2010) **35** chemicals
  - Wetmore et al. (2012) **+204** chemicals
  - Wetmore et al. (2015) **+163** chemicals
  - Wambaugh et al. (2019) **+389** chemicals

High Throughput Toxicokinetics (HTTK)

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

= high(er) throughput toxicokinetics

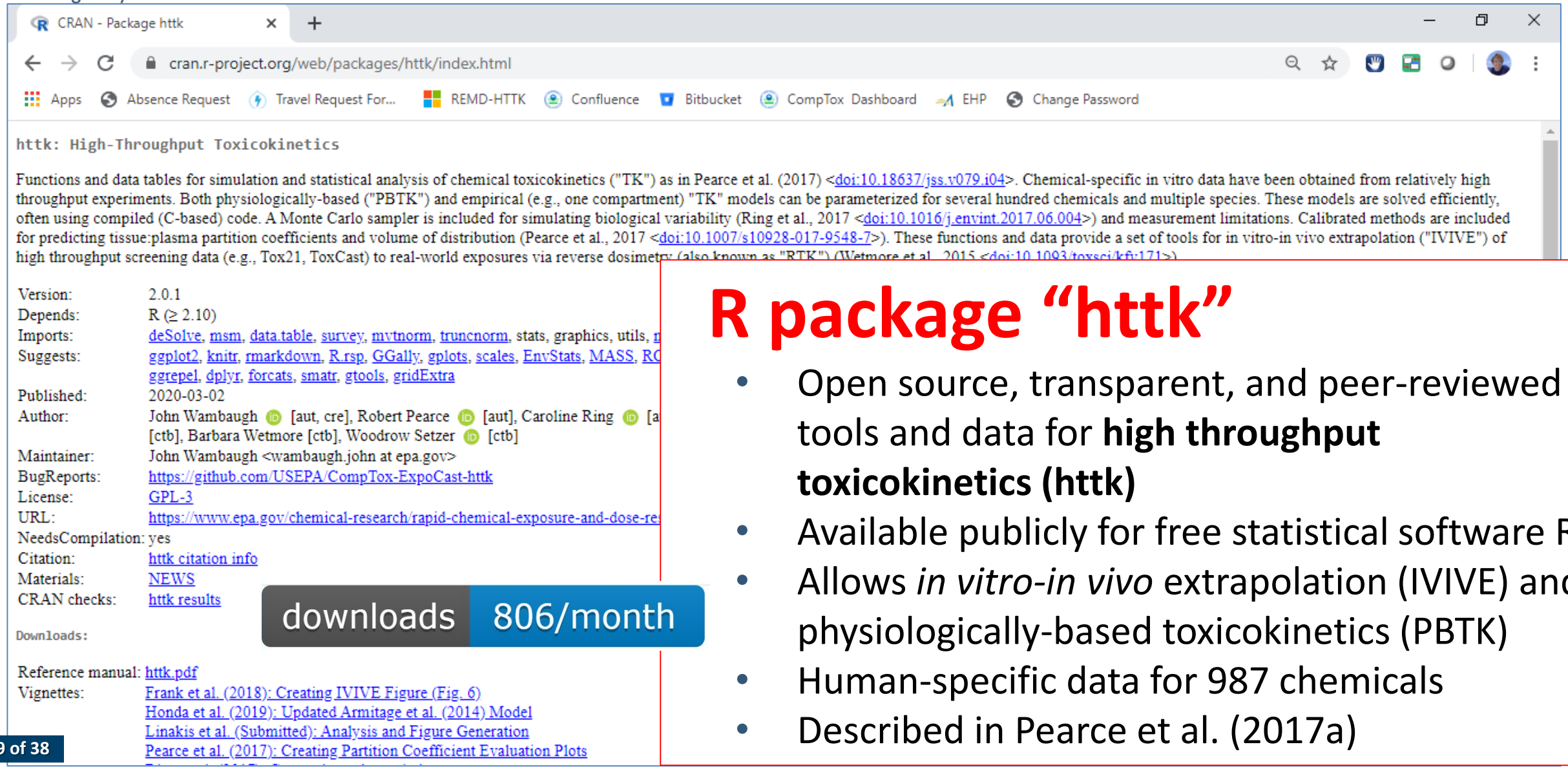




httk

Open Source Tools and Data for HTTK

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



R package "httk"

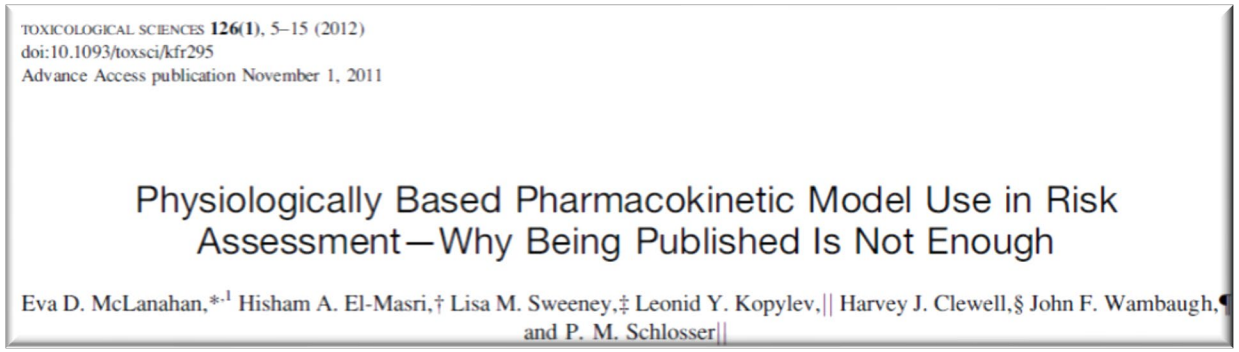
- Open source, transparent, and peer-reviewed tools and data for **high throughput toxicokinetics (httk)**
- Available publicly for free statistical software R
- Allows *in vitro-in vivo* extrapolation (IVIVE) and physiologically-based toxicokinetics (PBTK)
- Human-specific data for 987 chemicals
- Described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

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** (Scitovation) and **Web-ICE** (NICEATM) provide GUI's to HTTK and other models
Pre-computed HTTK results are also available at https://comptox.epa.gov/dashboard

Open Source, Verifiable, Reproducible



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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]"

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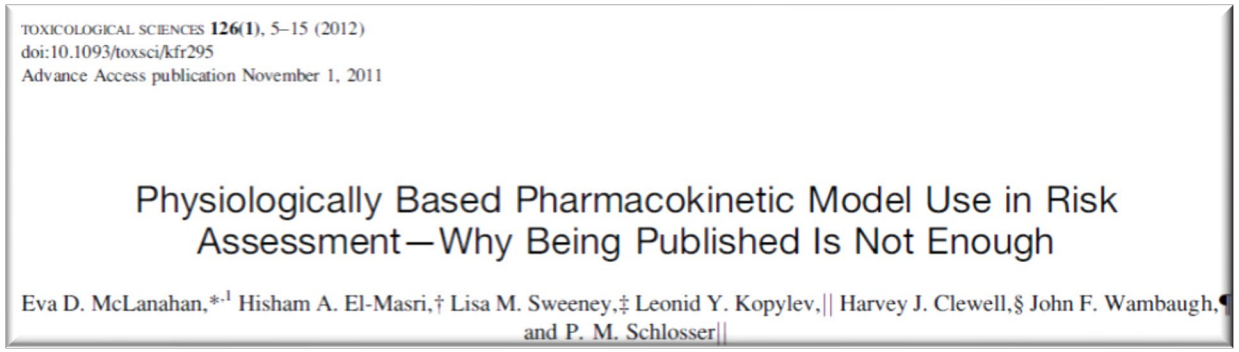

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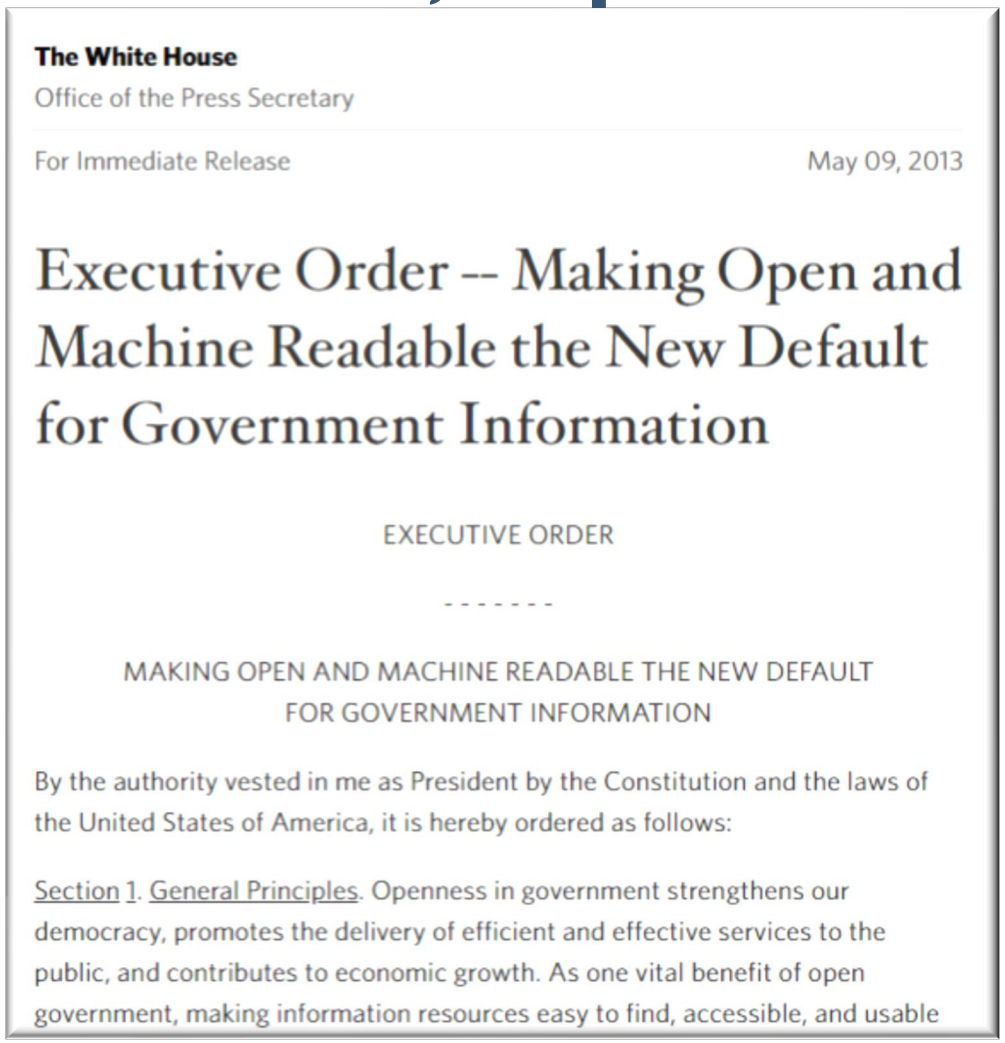


The White House
Office of the Press Secretary

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."

Doing Statistical Analysis with HTTK

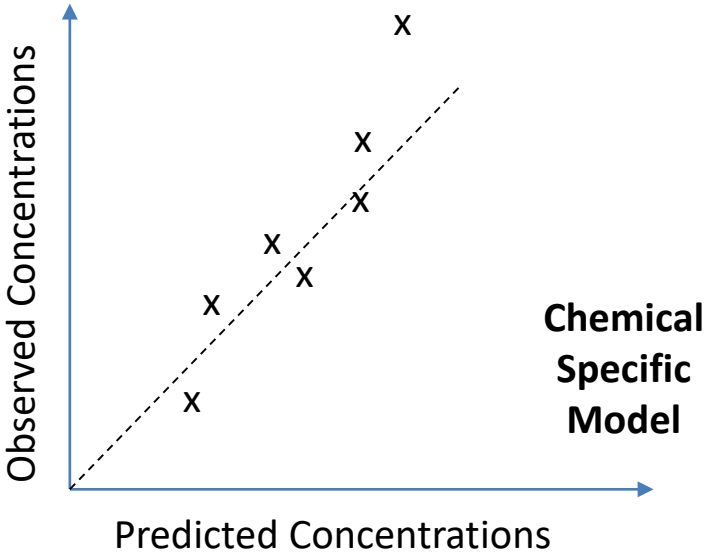
- If we are to use HTTK, we need confidence in predictive ability

- In drug development, HTTK methods estimate therapeutic doses for clinical studies – predicted concentrations are typically on the order of values measured in clinical trials (Wang, 2010)
  - For most compounds in the environment there will be no clinical trials

- Uncertainty must be well characterized
  - We compare to *in vivo* data to get **empirical estimates of HTTK uncertainty**
  - Any approximations, omissions, or mistakes should work to increase the estimated uncertainty when evaluated systematically across chemicals

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 don't have data



Cohen Hubal et al. (2018)

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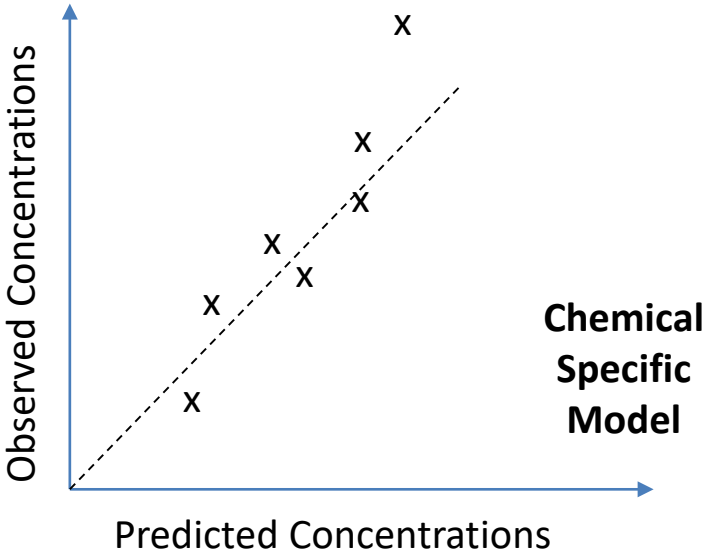

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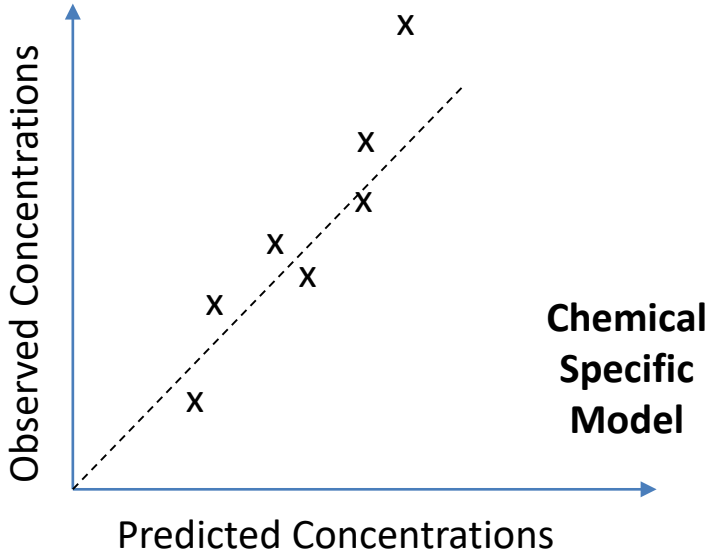
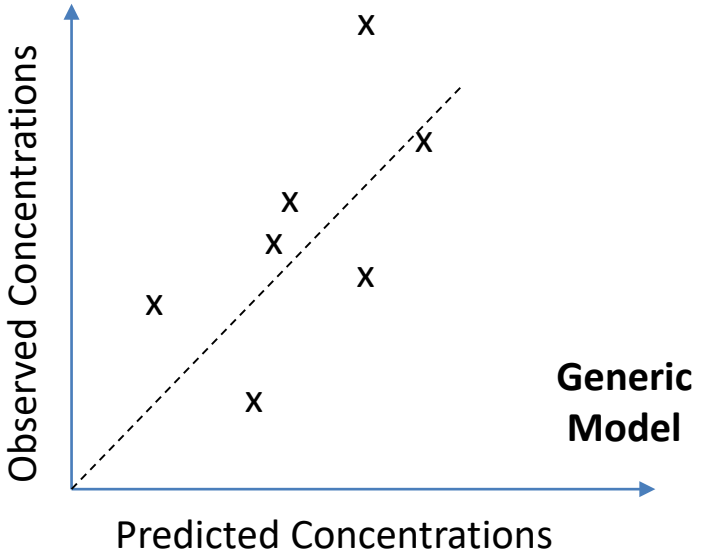
- We can parameterize a **generic TK model**, and evaluate that model for as many chemicals as we do have data
  - We do expect larger uncertainty, but also greater confidence in model implementation
  - Estimate bias and uncertainty, and try to correlate with chemical-specific properties





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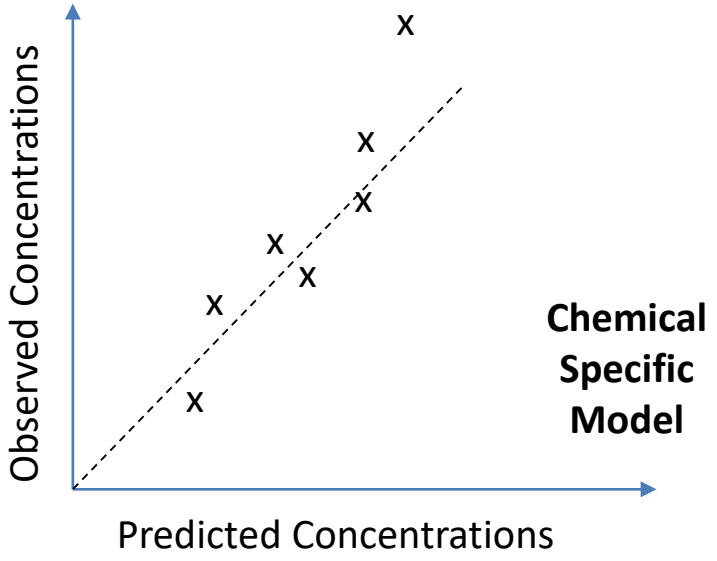
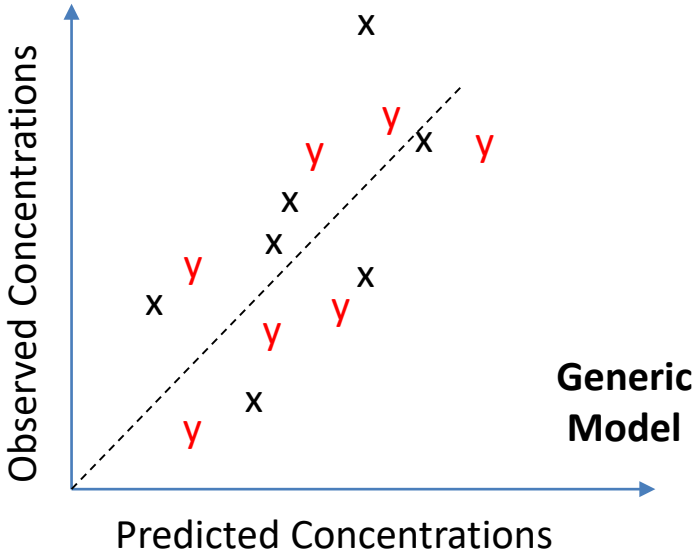
  - Estimate bias and uncertainty, and try to correlate with chemical-specific properties
  - Can consider using model to extrapolate to other situations (chemicals without *in vivo* data)





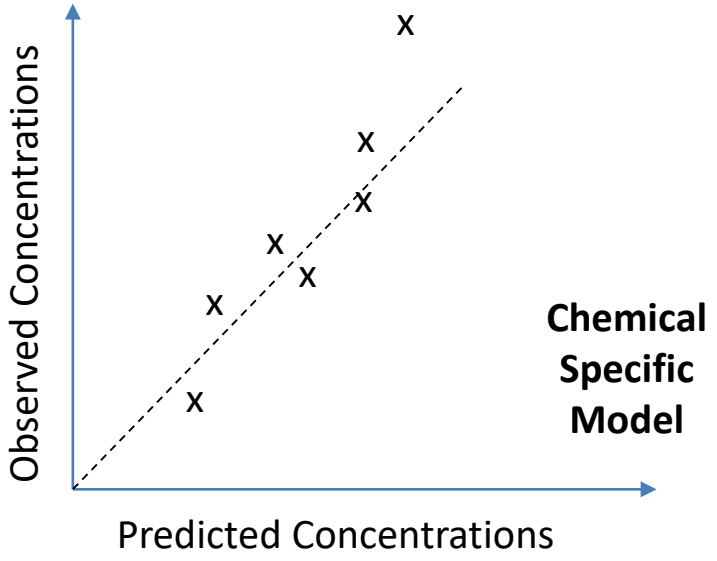
Cohen Hubal et al. (2018)

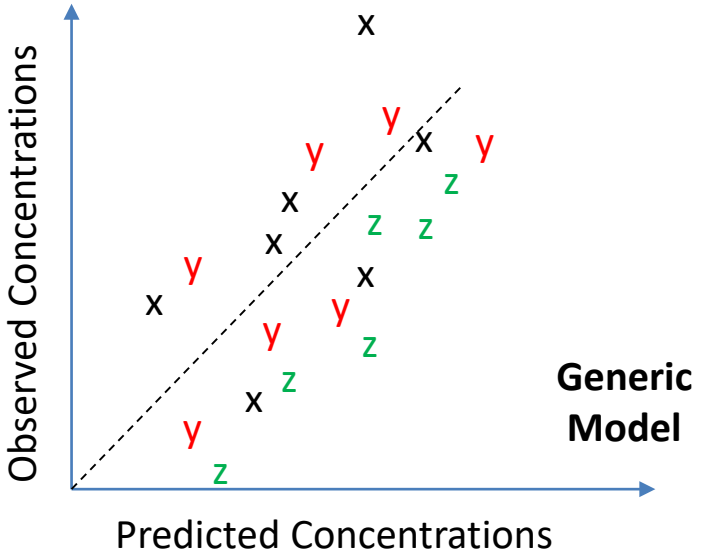
Building Confidence in TK Models

- To evaluate a **chemical-specific TK model** for "chemical x" you can compare the predictions to *in vivo* measured data
  - Can estimate bias
  - Can estimate uncertainty
  - Can consider using model to extrapolate to other situations (dose, route, physiology) where you don't have 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
  - Estimate bias and uncertainty, and try to correlate with chemical-specific properties
  - Can consider using model to extrapolate to other situations (chemicals without *in vivo* data)





Cohen Hubal et al. (2018)

In Vivo TK Database

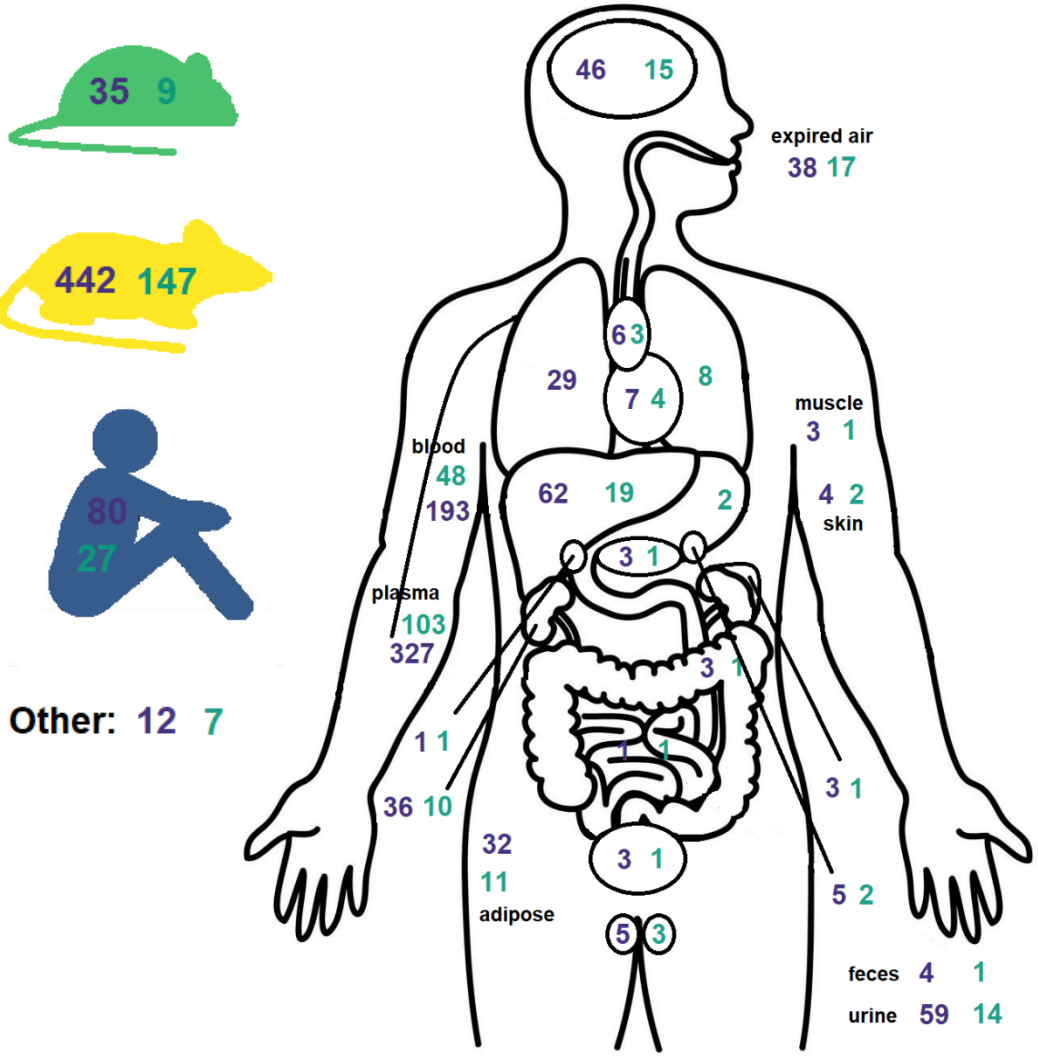
https://github.com/USEPA/CompTox-PK-CvTdb

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

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

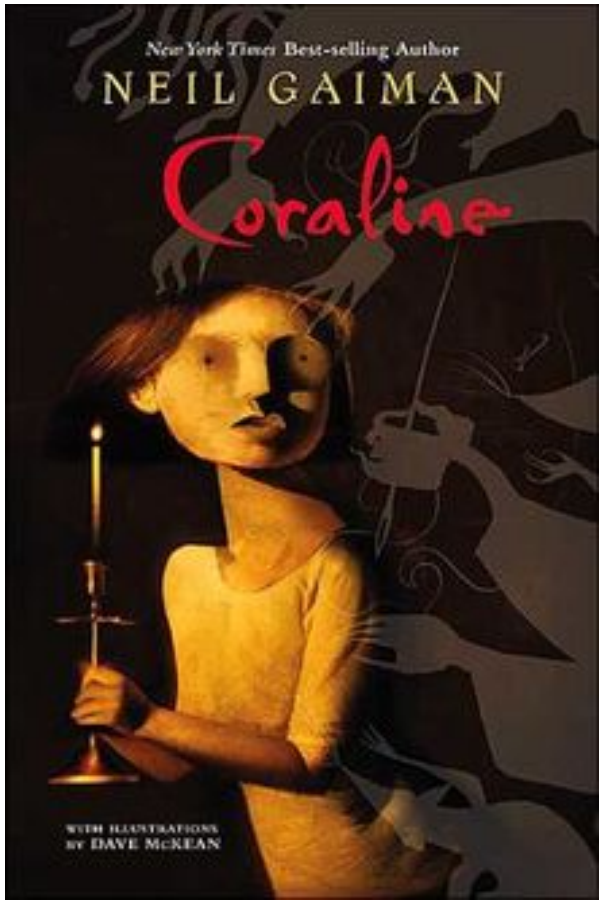
- Standardized, open source curve fitting software invivoPKfit used to calibrate models to all data:

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



Sayre et al. (accepted at Scientific Data)

For the Kids at Home

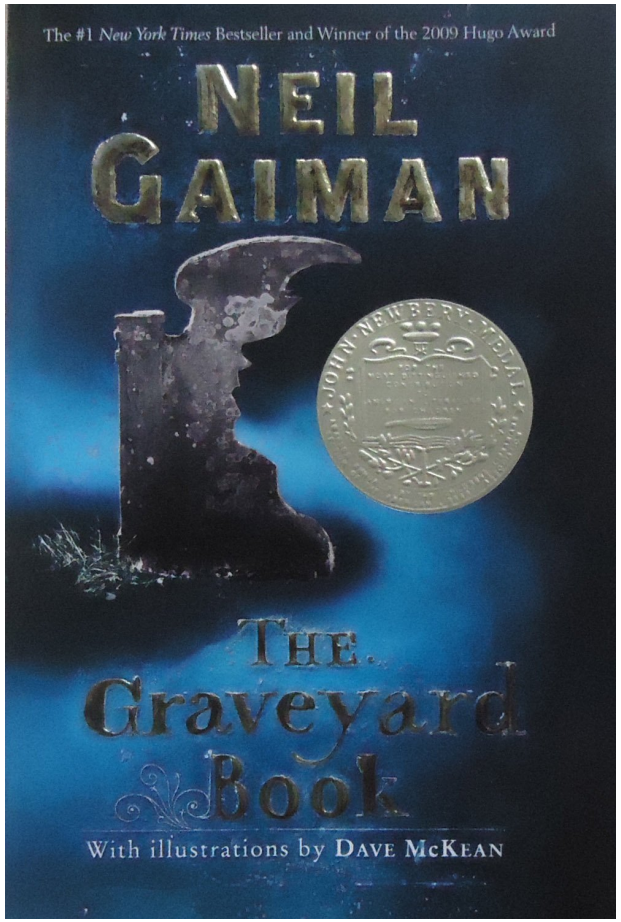


Mouse Circus

THE OFFICIAL NEIL GAIMAN WEBSITE FOR YOUNGER READERS

http://www.mousecircus.com/

Go to the videos section for the author reading the entirety of The Graveyard Book and Coraline. Creepy but great for the right kid!

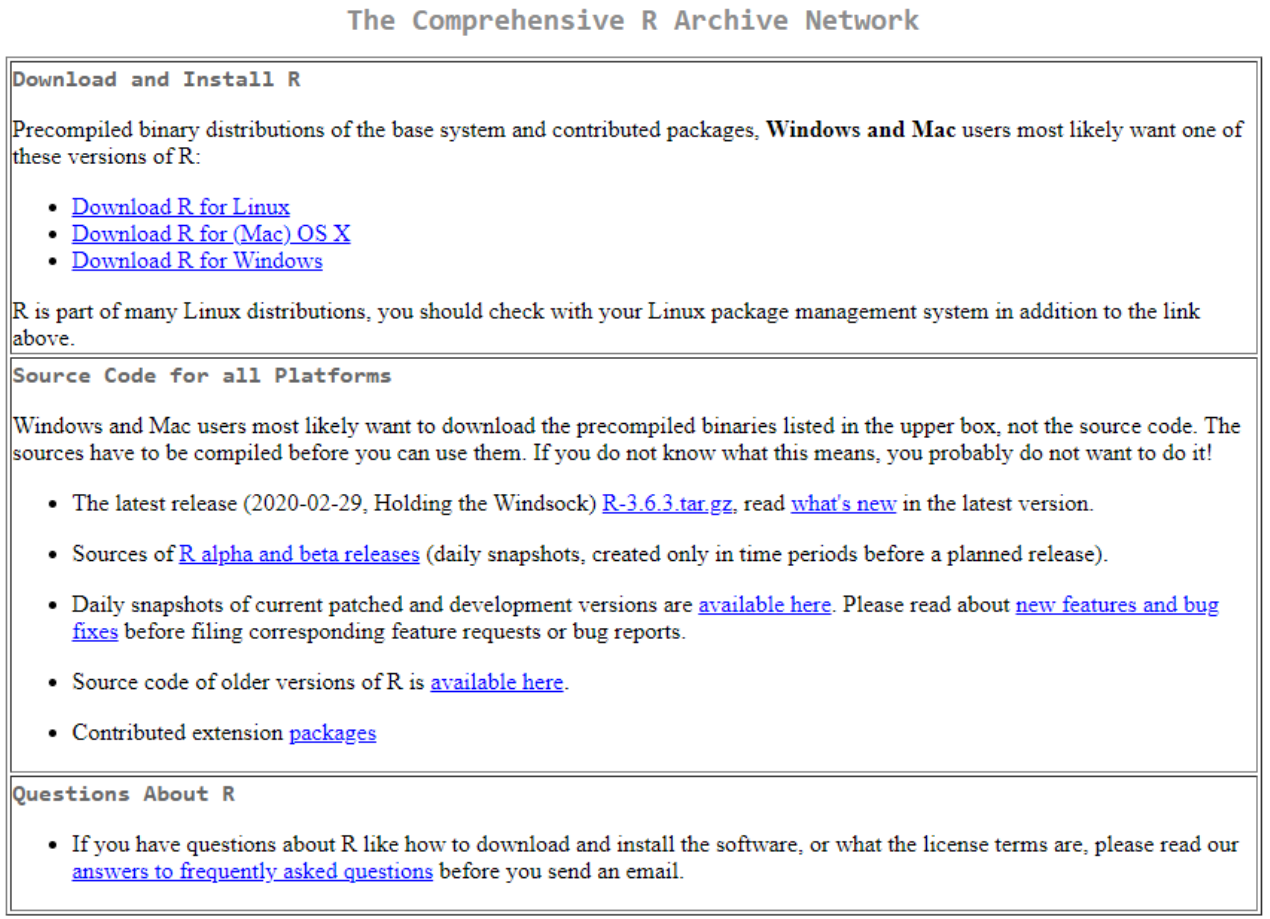


EXAMPLE: Where Do I Get R?

- R is freely available from the Comprehensive R Archive Network (CRAN):
  https://cloud.r-project.org/

- It is often helpful to set an environmental variable that points to a personal library of R packages, for me, on Windows, I have the "user variable" R_LIBS_USER set to "c:/users/jwambaug/Rpackages"

- Many people like to use a graphical user interface (GUI) such as RStudio, which also may be freely available to you:
  https://rstudio.com/



The Comprehensive R Archive Network

Download and Install R

Precompiled binary distributions of the base system and contributed packages, **Windows and Mac** users most likely want one of these versions of R:

- Download R for Linux
- Download R for (Mac) OS X
- Download R for Windows

R is part of many Linux distributions, you should check with your Linux package management system in addition to the link above.

Source Code for all Platforms

Windows and Mac users most likely want to download the precompiled binaries listed in the upper box, not the source code. The sources have to be compiled before you can use them. If you do not know what this means, you probably do not want to do it!

- The latest release (2020-02-29, Holding the Windsock) R-3.6.3.tar.gz, read what's new in the latest version.
- Sources of R alpha and beta releases (daily snapshots, created only in time periods before a planned release).
- Daily snapshots of current patched and development versions are available here. Please read about new features and bug fixes before filing corresponding feature requests or bug reports.
- Source code of older versions of R is available here.
- Contributed extension packages

Questions About R

- If you have questions about R like how to download and install the software, or what the license terms are, please read our answers to frequently asked questions before you send an email.

EXAMPLE: Getting Started with HTTK

Install HTTK from the command line
(GUI's like RStudio also provide menus for this)

```
> install.packages("httk")
Installing package into 'c:/Users/jwambaug/Rpackages'
(as 'lib' is unspecified)
--- Please select a CRAN mirror for use in this session ---
trying URL 'https://cloud.r-project.org/bin/windows/contrib/3.6/httk_2.0.1.zip'
Content type 'application/zip' length 10127063 bytes (9.7 MB)
downloaded 9.7 MB

package 'httk' successfully unpacked and MD5 sums checked

The downloaded binary packages are in
        C:\Users\jwambaug\AppData\Local\Temp\Rtmp4STebz\downloaded_packages
> library(httk)
Warning message:
package 'httk' was built under R version 3.6.3
> packageVersion("httk")
[1] '2.0.1'
```

Load the HTTK data, models, and functions

Check what version you are using

EPA United States Environmental Protection Agency

What you can do with R Package "httk"?

- Allows prediction of internal tissue concentrations from dose regimen (oral and intravenous)
- Allows conversion of *in vitro* concentration to *in vivo* doses
- A peer-reviewed paper in the Journal of Statistical software provides a how-to guide (Pearce et al., 2017a)
- You can use the built in chemical library or add more chemical information (examples provided in JSS paper)
- You can use specific demographics in the population simulator (Ring et al., 2017)
- You can control the built in random number generator to reproduce the same random sequence (function set.seed())

EXAMPLE: Does My Chemical Have HTTK Data?

```
> library(httk)
```

List all CAS numbers for all chemicals with sufficient data

```
> get_cheminfo()
  [1] "2971-36-0"   "94-75-7"     "94-82-6"     "90-43-7"     "1007-28-9"
  [6] "71751-41-2"  "30560-19-1"  "135410-20-7" "34256-82-1"  "50594-66-6"
 [11] "15972-60-8"  "116-06-3"    "834-12-8"    "33089-61-1"  "101-05-3"
 [16] "1912-24-9"   "86-50-0"     "131860-33-8" "22781-23-3"  "1861-40-1" …
```

Is a chemical available?

```
> "80-05-7" %in% get_cheminfo()
[1] TRUE
```

All data on chemicals A, B, C

```
subset(get_cheminfo(info="all"),Compound%in%c("A","B","C"))
```

```
> get_cheminfo(info="all")
```

List all information

Compound	CAS	logP	pKa Accept	pKa Donor	MW	Human Clint	Human Clint pValue	Human Funbound plasma	DSSTox Substance Id	Formula	Substance Type
2,4-d	94-75-7	2.81	<NA>	2.81	221.03	0	0.149	0.04	DTXSID0020442	C8H6Cl2O3	Single Compound
2,4-db	94-82-6	3.53	<NA>	4.5	249.09	0	0.104	0.01	DTXSID7024035	C10H10Cl2O3	Single Compound
2-phenylphenol	90-43-7	3.09	<NA>	10.6	170.211	2.08	0.164	0.04	DTXSID2021151	C12H10O	Single Compound
6-desisopropylatrazine	1007-28-9	1.15	1.59	<NA>	173.6	0	0.539	0.46	DTXSID0037495	C5H8ClN5	Single Compound

EXAMPLE: IVIVE Oral Equivalent Dose

```
#State-state oral equivalent dose (mg/kg BW/day) to produce 0.1 uM serum concentration for human, 0.95
quantile, for Acetochlor (calculated value):
> calc_mc_oral_equiv(0.1,chem.cas="34256-82-1")
uM concentration converted to mgpkgpday dose for 0.95 quantile.
      95%
0.04530

#State-state oral equivalent dose (mg/kg BW/day) to produce 0.1 uM serum concentration for rat, 0.95
quantile, for Acetochlor (calculated value):
> calc_mc_oral_equiv(0.1,chem.cas="34256-82-1",species="Rat")
uM concentration converted to mgpkgpday dose for 0.95 quantile.
     95%
0.1376

#State-state oral equivalent dose (mg/kg BW/day) to produce 0.1 uM serum concentration for human, 0.95
quantile, for Acetochlor (published value):
> get_lit_oral_equiv(0.1,chem.cas="34256-82-1")
Human uM concentration converted to mg /kg bw/day dose.
[1] 0.6750
```

IVIVE with HTTK: Frank et al. (2018)

Toxicology and Applied Pharmacology 354 (2018) 81–93

Contents lists available at ScienceDirect

Toxicology and Applied Pharmacology

journal homepage: www.elsevier.com/locate/taap

Defining toxicological tipping points in neuronal network development☆

Christopher L. Frank[a,1], Jasmine P. Brown[a,2], Kathleen Wallace[a], John F. Wambaugh[b], Imran Shah[b], Timothy J. Shafer[a,*]

[a] Integrated Systems Toxicology Division, National Health and Environmental Effects Research Laboratory, EPA, Research Triangle Park, NC, USA
[b] National Center for Computational Toxicology, EPA, Research Triangle Park, NC, USA

IVIVE with HTTK: Frank et al. (2018)

Toxicology and Applied Pharmacology 354 (2018) 81–93

Contents lists available at ScienceDirect

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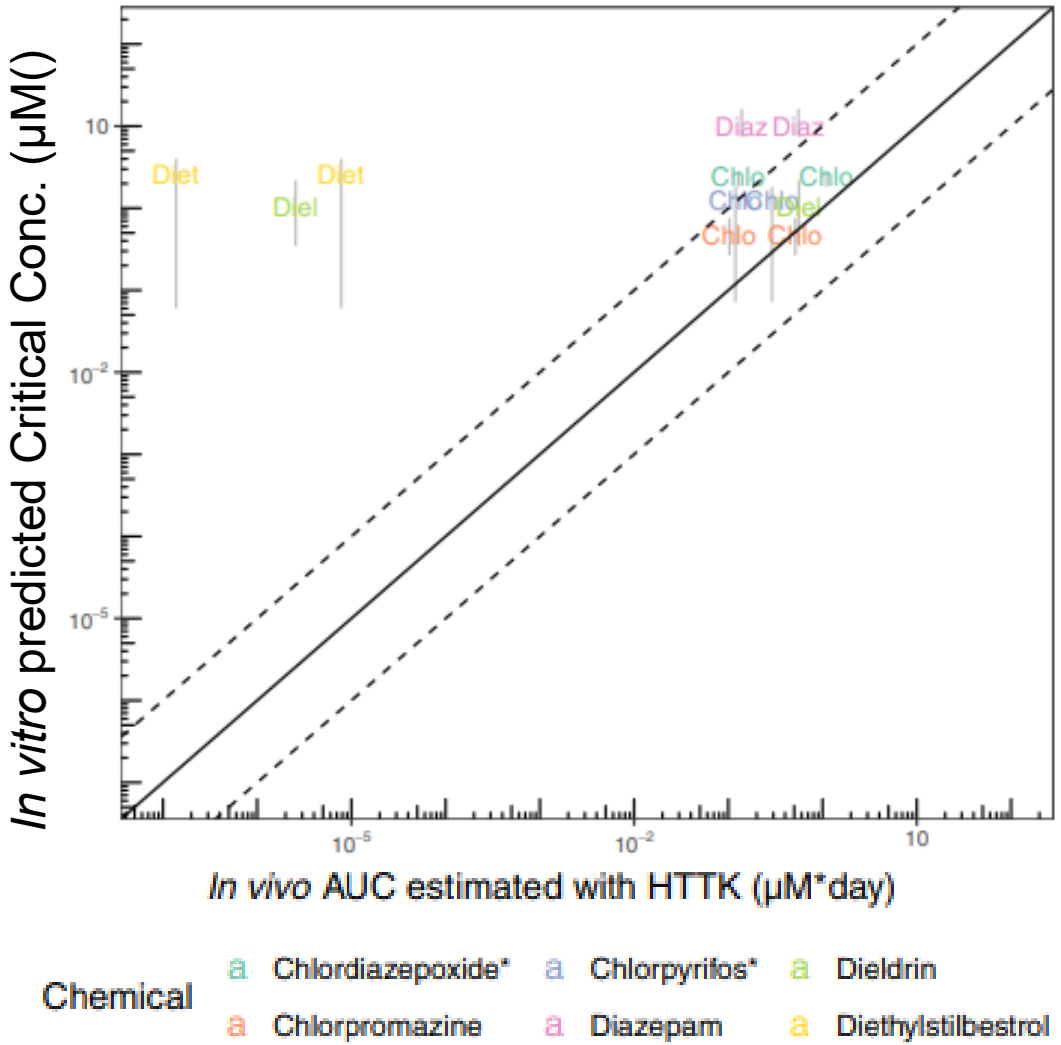
Defining t

Christopher
Imran Shah[b]

[a] Integrated Systems T
[b] National Center for

Fig. 6. Comparison between predicted plasma levels for critical concentrations and *in vivo* estimates from the httk model. For those chemicals with 1) *in vitro* predicted critical concentrations, 2) *in vivo* studies indicating neurological effect, and 3) available toxicokinetic data the time-integrated plasma concentration (area under the curve or AUC) was predicted for the LOEL associated with each chemical-specific study. The chemical-specific prediction is indicated by the first four letters of each chemicals name. There were two available studies for each chemical. The identity ("perfect predictor") line is indicated by a solid black line, while the dashed lines indicate ten-fold above and below perfect prediction. Because all *in vitro* treatments were exposed for the same amount of time, the relationship between nominal *in vitro* concentration and time-integrated concentration is a constant.



EXAMPLE: Vignettes in R

A vignette is R terminology for an example or walk-through that provides the code and outputs for doing a task in R.

```
> vignette(package="httk")
```

List all vignettes for a specific package

```
Frank2018                                  Frank et al. (2018): Creating IVIVE Figure (Fig. 6) (source, html)
Honda2019                                  Honda et al. (2019): Updated Armitage et al. (2014) Model (source, html)
LinakisSubmitted                           Linakis et al. (Submitted): Analysis and Figure Generation (source, html)
Pearce2017                                 Pearce et al. (2017): Creating Partition Coefficient Evaluation Plots (source, html)
Ring_2017_vignette06_aerplotting           Ring et al. (2017): AER plotting (source, html)
Ring_2017_vignette02_evalmodelsubpop       Ring et al. (2017): Evaluating HTTK models for subpopulations (source, html)
Ring_2017_vignette03_paper_fig2            Ring et al. (2017): Generating Figure 2 (source, html)
Ring_2017_vignette04_paper_fig3            Ring et al. (2017): Generating Figure 3 (source, html)
Ring_2017_vignette01_subpopulations        Ring et al. (2017): Generating subpopulations (source, html)
Ring_2017_vignette05b_plothowgatejohnson   Ring et al. (2017): Plotting Howgate/Johnson data (source, html)
Ring_2017_vignette_05a_virtualstudypops    Ring et al. (2017): Virtual study populations (source, html)
Wambaugh2018                               Wambaugh et al. (2018): Creating All Figures (source, html)
Wambaugh2019                               Wambaugh et al. (2019): Creating Figures for the Manuscript (source, html)
```

EXAMPLE: Vignettes in R

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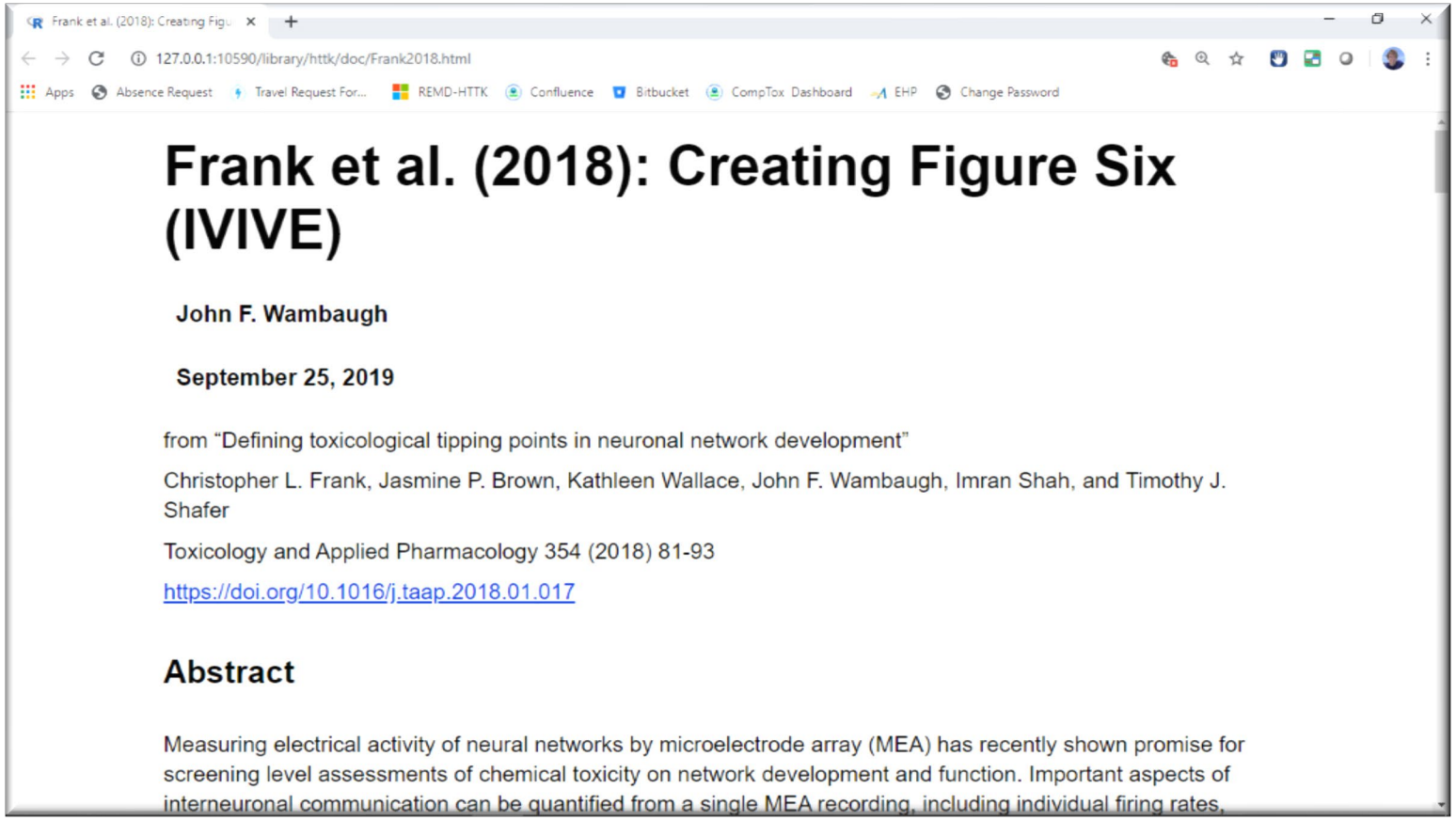
```
> vignette("Frank2018")
```



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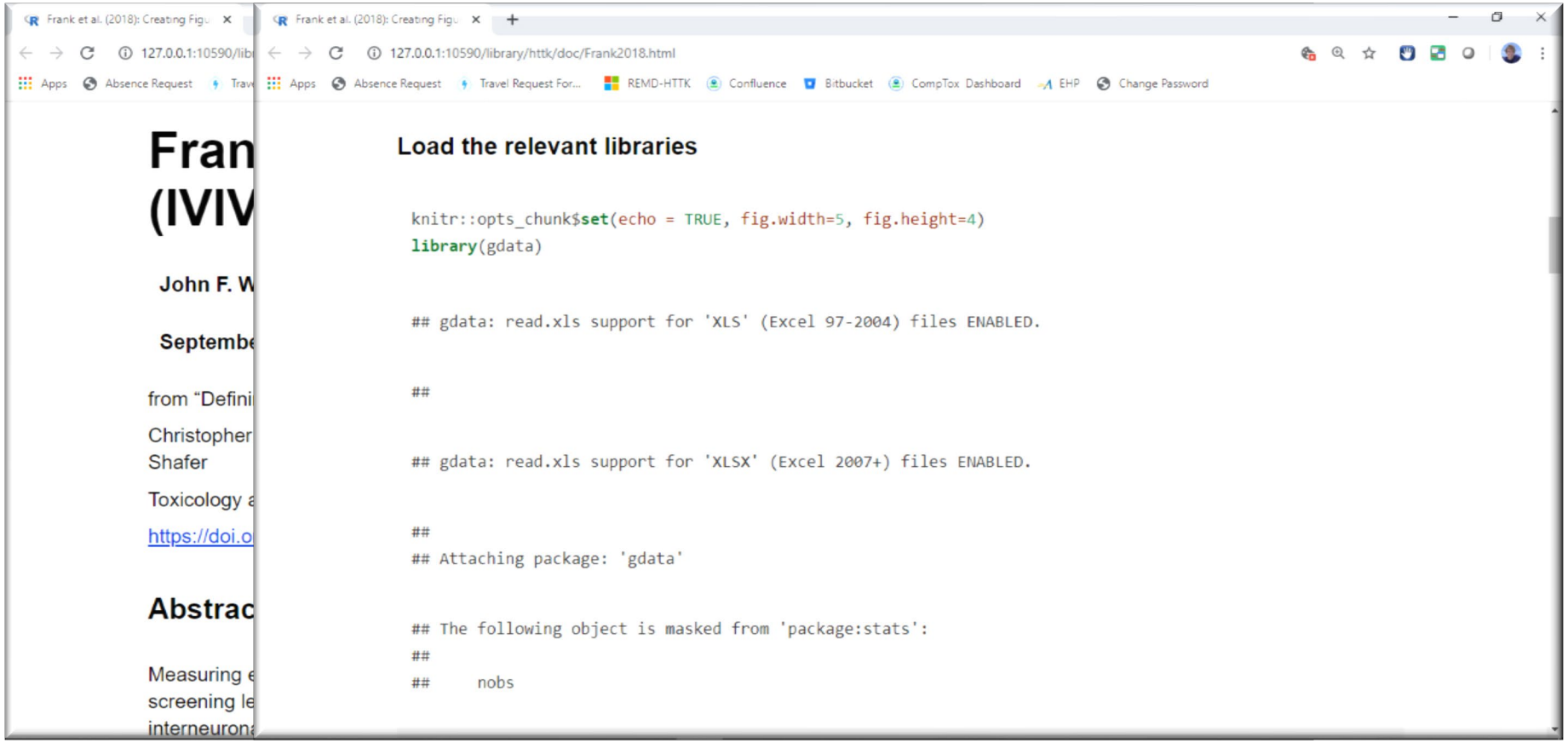

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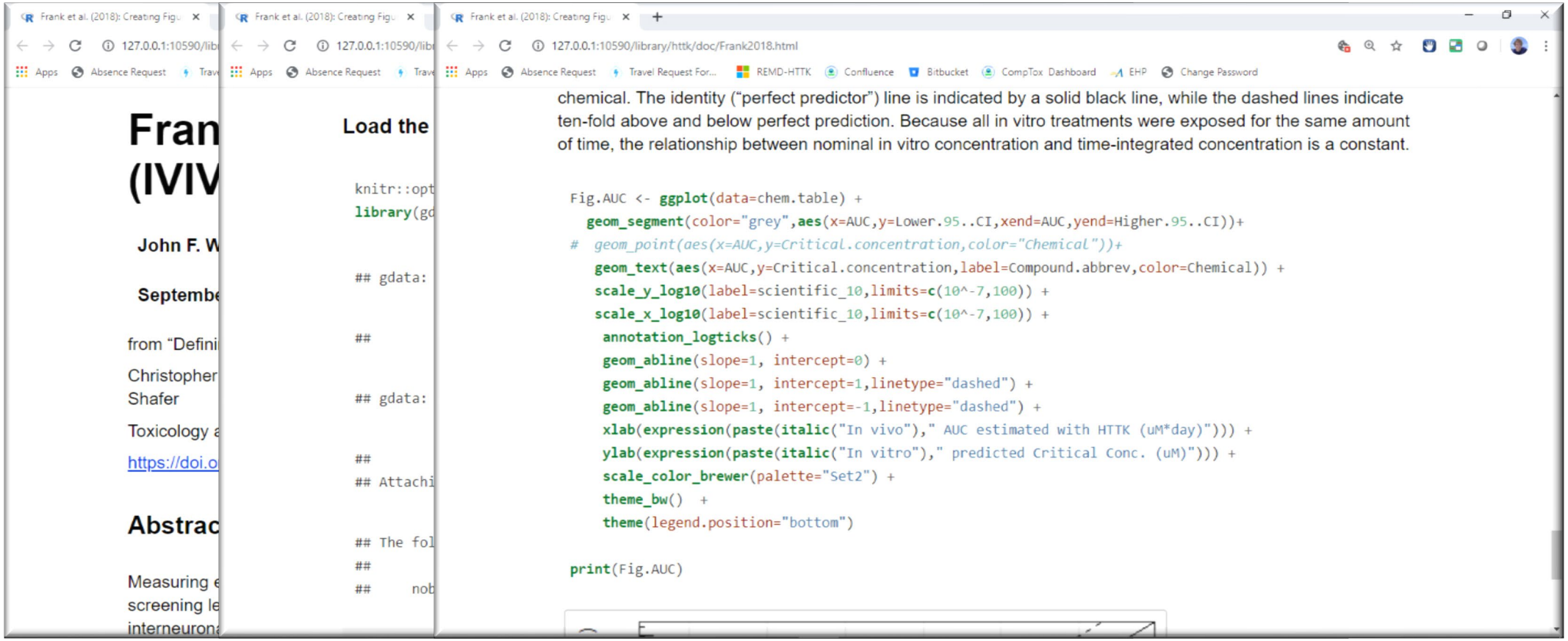

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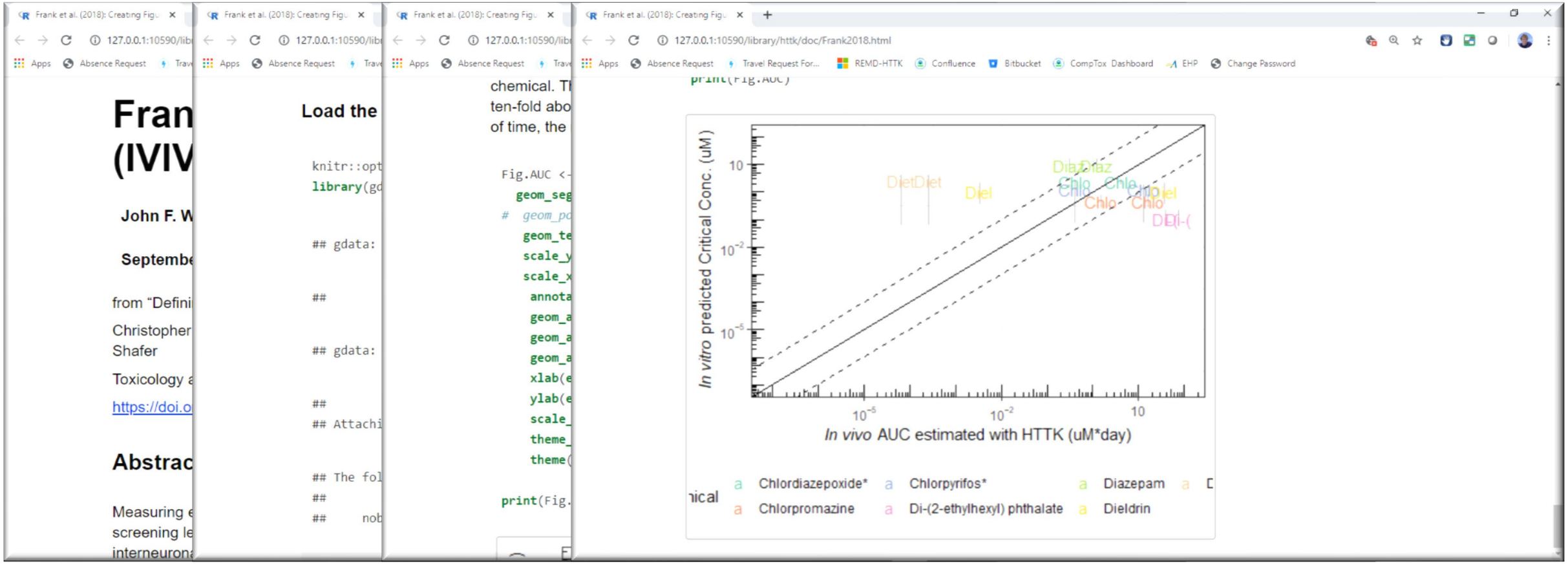
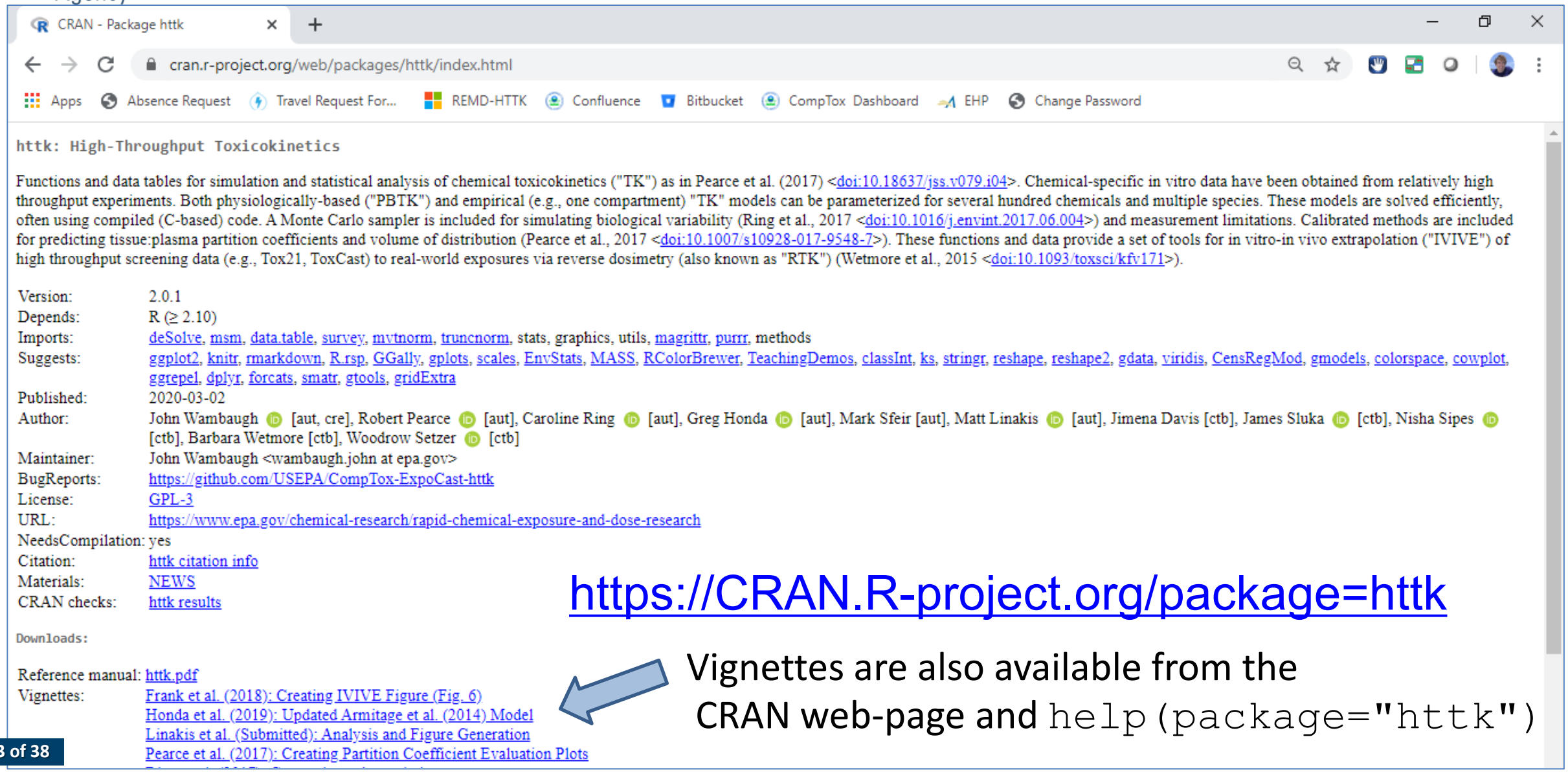
```



EXAMPLE: Vignettes in R



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, magrittr, purrr, methods
Suggests:	ggplot2, knitr, rmarkdown, R.rsp, GGally, gplots, scales, EnvStats, MASS, RColorBrewer, TeachingDemos, classInt, ks, stringr, reshape, reshape2, gdata, viridis, CensRegMod, gmodels, colorspace, cowplot, ggrepel, dplyr, forcats, smatr, gtools, gridExtra
Published:	2020-03-02
Author:	John Wambaugh [aut, cre], Robert Pearce [aut], Caroline Ring [aut], Greg Honda [aut], Mark Sfeir [aut], Matt Linakis [aut], Jimena Davis [ctb], James Sluka [ctb], Nisha Sipes [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-research
NeedsCompilation:	yes
Citation:	httk citation info
Materials:	NEWS
CRAN checks:	httk results

Downloads:

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

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

Vignettes are also available from the CRAN web-page and `help(package="httk")`

For the Kids at Home

Exhibition: The Advent of the Artist'.
For its fifth season, the Louvre's Petite Galerie—a space dedicated to art and cultural education— is holding an exhibition titled 'The Advent of the Artist'. Discover artworks from Delacroix, Rembrandt or Tintoretto.

Remains of the Louvre's Moat
The Louvre was originally a fortress built by the French king Philippe Auguste. It was intended to reinforce the defenses that the king had ordered to be built in 1190 to protect Paris from attack via the Seine. Today, visitors can walk around the original perimeter moat and view the piers that supported the drawbridge.

https://www.louvre.fr/en/visites-en-ligne
Virtual Tours of the Louvre

Egyptian Antiquities
Collections from the Pharaonic period are displayed on the east side of the Sully wing, on the ground floor and 1st floor.

Galerie d'Apollon
The Galerie d'Apollon, situated above the Petite Galerie, was destroyed by fire in 1661 and rebuilt by Le Vau. The ceiling, begun by Le Brun, is a homage to the Sun King, Louis XIV. The central panel, *Apollo Slaying the Serpent Python*, is by Delacroix (1851). The gallery was recently restored.

EXAMPLE: TK Statistics

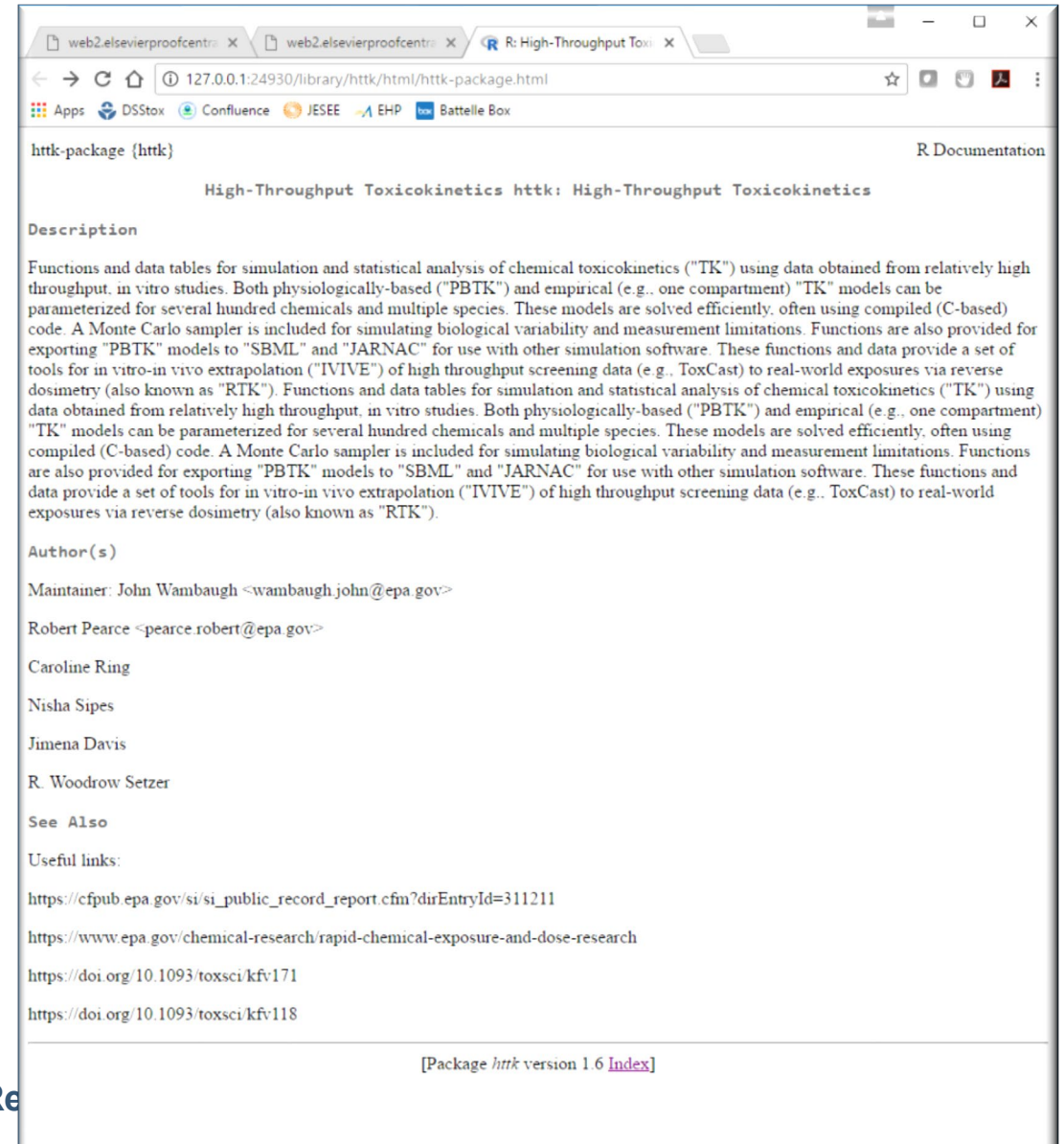
Calculate the mean, AUC, and peak concentrations for a 28 day study (default)

```
> calc_stats(chem.cas="34256-82-1")
Human plasma concentrations returned in uM units.
AUC is area under plasma concentration curve in uM * days units with Rblood2plasma =
$AUC
[1] 3.541
$peak
[1] 0.8966
$mean
[1] 0.1265

#Oops, I meant to do a rat, not a human study:
> calc_stats(chem.cas="34256-82-1", species="rat")
Rat plasma concentrations returned in uM units.
AUC is area under plasma concentration curve in uM * days units with Rblood2plasma = .
$AUC
[1] 1.287
$peak
[1] 0.4182
$mean
[1] 0.04596
```

EXAMPLE: Getting Help:

Within R: type "help(httk)"



web2.elsevierproofcentr | web2.elsevierproofcentr | R: High-Throughput Toxi

127.0.0.1:24930/library/httk/html/httk-package.html

Apps DSStox Confluence JESEE EHP Battelle Box

httk-package {httk} R Documentation

High-Throughput Toxicokinetics httk: High-Throughput Toxicokinetics

Description

Functions and data tables for simulation and statistical analysis of chemical toxicokinetics ("TK") using data obtained from relatively high throughput, in vitro studies. 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 and measurement limitations. Functions are also provided for exporting "PBTK" models to "SBML" and "JARNAC" for use with other simulation software. These functions and data provide a set of tools for in vitro-in vivo extrapolation ("IVIVE") of high throughput screening data (e.g., ToxCast) to real-world exposures via reverse dosimetry (also known as "RTK"). Functions and data tables for simulation and statistical analysis of chemical toxicokinetics ("TK") using data obtained from relatively high throughput, in vitro studies. 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 and measurement limitations. Functions are also provided for exporting "PBTK" models to "SBML" and "JARNAC" for use with other simulation software. These functions and data provide a set of tools for in vitro-in vivo extrapolation ("IVIVE") of high throughput screening data (e.g., ToxCast) to real-world exposures via reverse dosimetry (also known as "RTK").

Author(s)

Maintainer: John Wambaugh <wambaugh.john@epa.gov>

Robert Pearce <pearce.robert@epa.gov>

Caroline Ring

Nisha Sipes

Jimena Davis

R. Woodrow Setzer

See Also

Useful links:

https://cfpub.epa.gov/si/si_public_record_report.cfm?dirEntryId=311211

https://www.epa.gov/chemical-research/rapid-chemical-exposure-and-dose-research

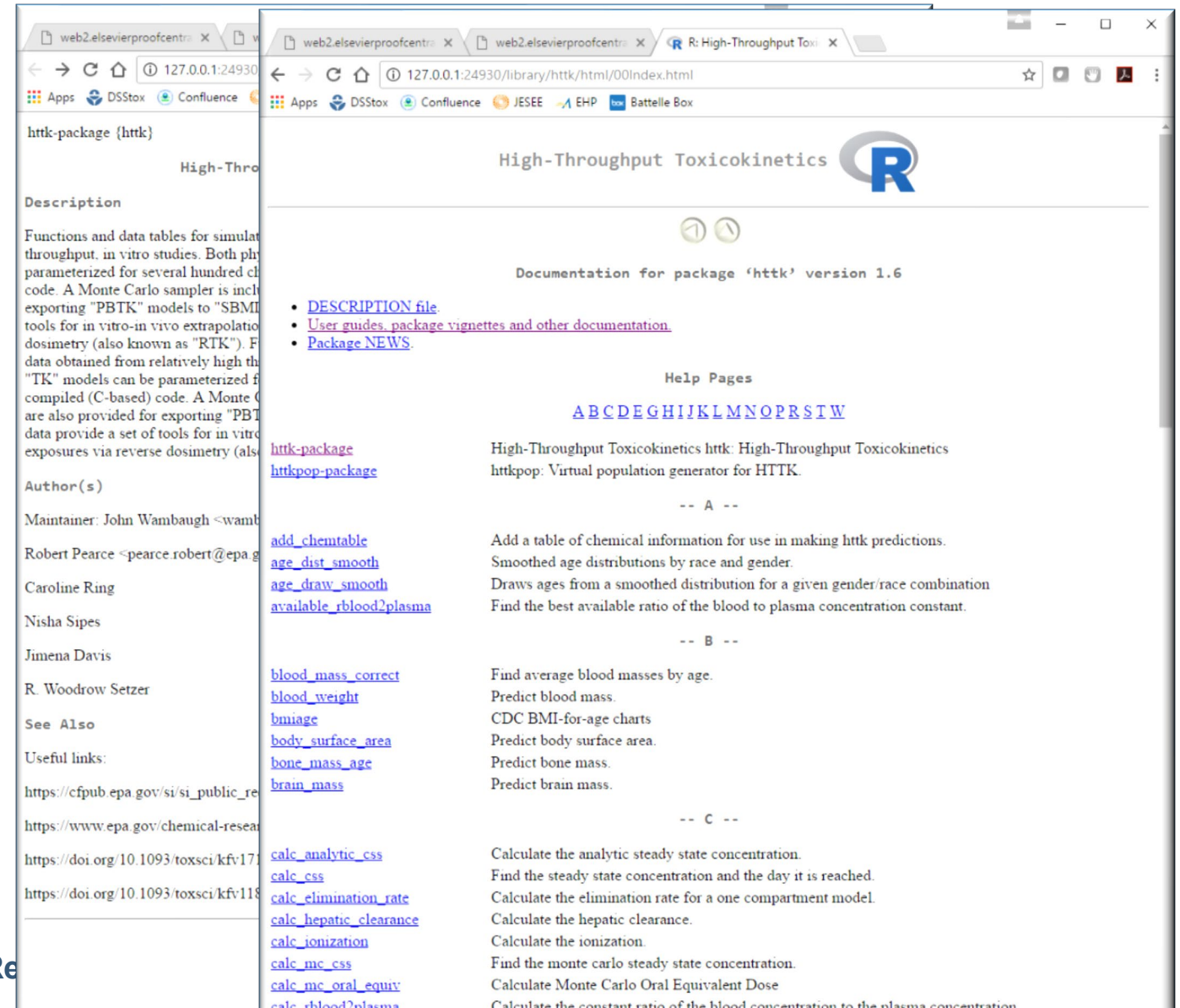
https://doi.org/10.1093/toxsci/kfv171

https://doi.org/10.1093/toxsci/kfv118

[Package *httk* version 1.6 Index]

EXAMPLE: Getting Help:

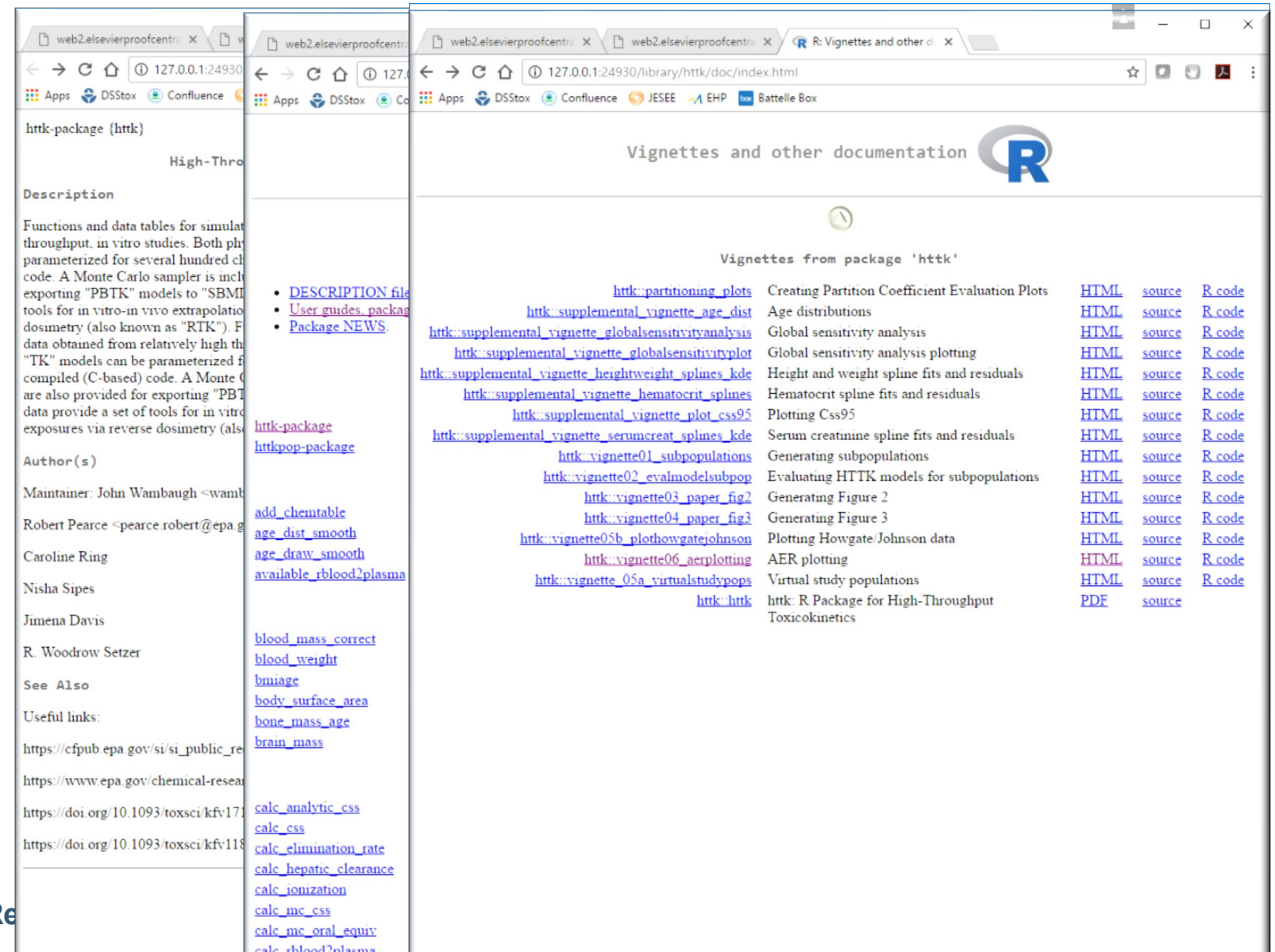
Within R: type "help(httk)"



You can go straight to the index with `help(package="httk")`

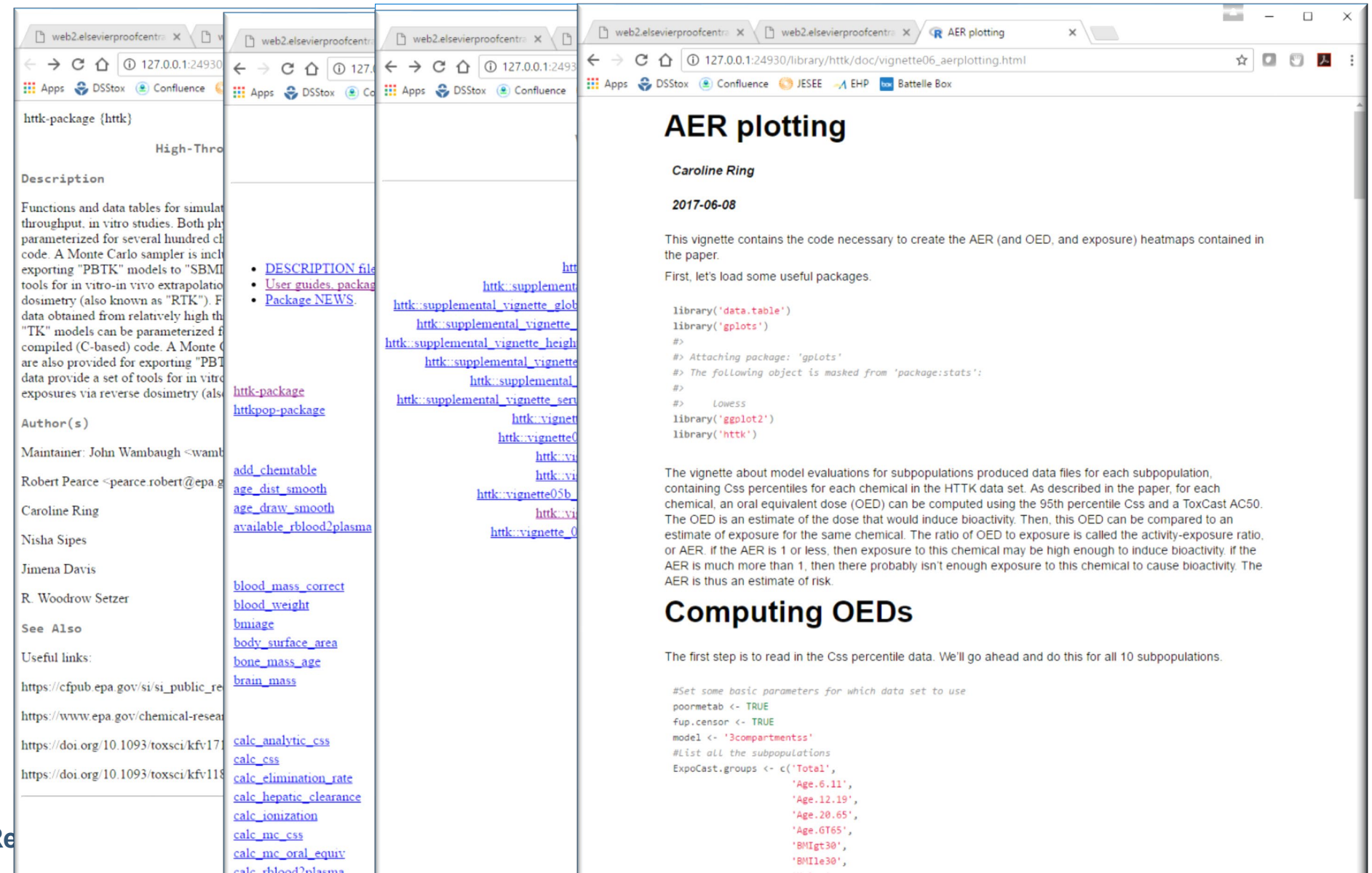
EXAMPLE: Getting Help:

Within R: type "help(httk)"



EXAMPLE: Getting Help:

Within R: type "help(httk)"

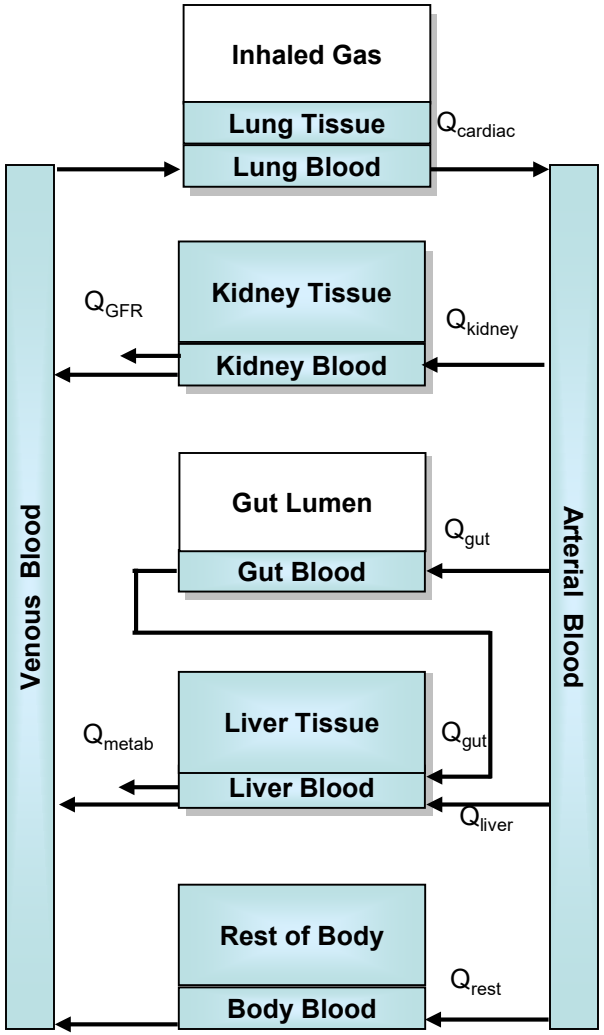


EXAMPLE: Getting Help:

Within R: type "help(httk)"

Please also feel free to email me at wambaugh.john@epa.gov

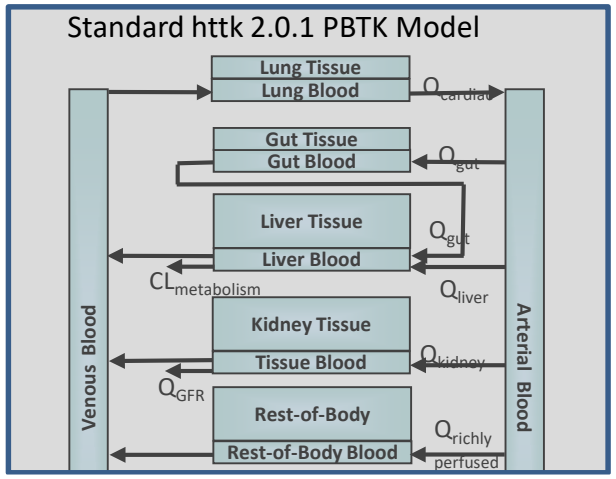
A General Physiologically-based Toxicokinetic (PBTK) Model



- "httk" includes a generic PBTK model
- Some tissues (for example, arterial blood) are simple compartments, while others (for example, kidney) are compound compartments consisting of separate blood and tissue sections with constant partitioning (that is, tissue specific partition coefficients)
- Some specific tissues (lung, kidney, gut, and liver) are modeled explicitly, others (for example, fat, brain, bones) are lumped into the "Rest of Body" compartment.
- The only ways chemicals "leave" the body are through metabolism (change into a metabolite) in the liver or excretion by glomerular filtration into the proximal tubules of the kidney (which filter into the lumen of the kidney).

New HT-PBTK Models

- We are working to augment the basic HT-PBPTK model with new PBTK models
  - For example, inhalation PBTK will allow for calculation of "inhalation equivalent doses" instead of oral equivalents

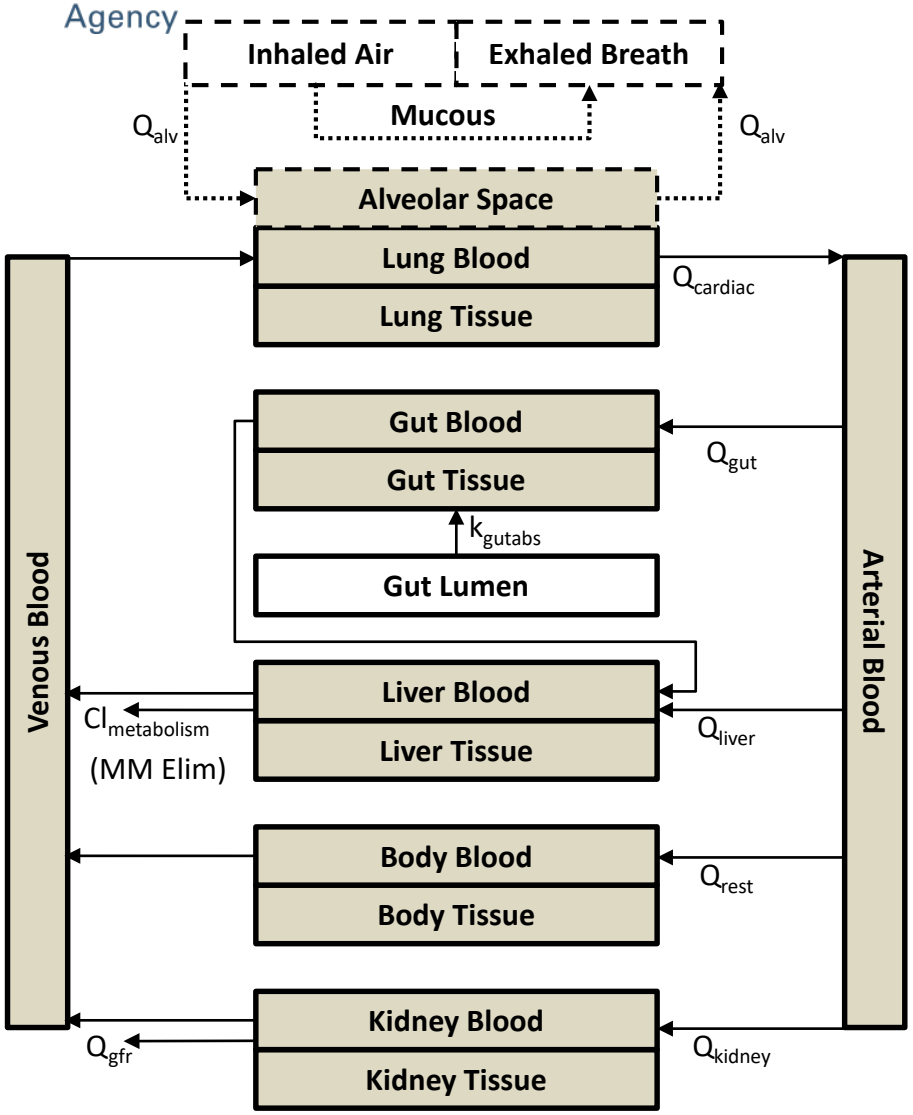


- Each model will be released publicly upon peer-reviewed publication

- Pre-publication models can be shared under a material transfer agreement (MTA)

- We assume there will be coding errors and over-simplifications, so each publication involves curation of evaluation data from the scientific literature and through statistical analysis

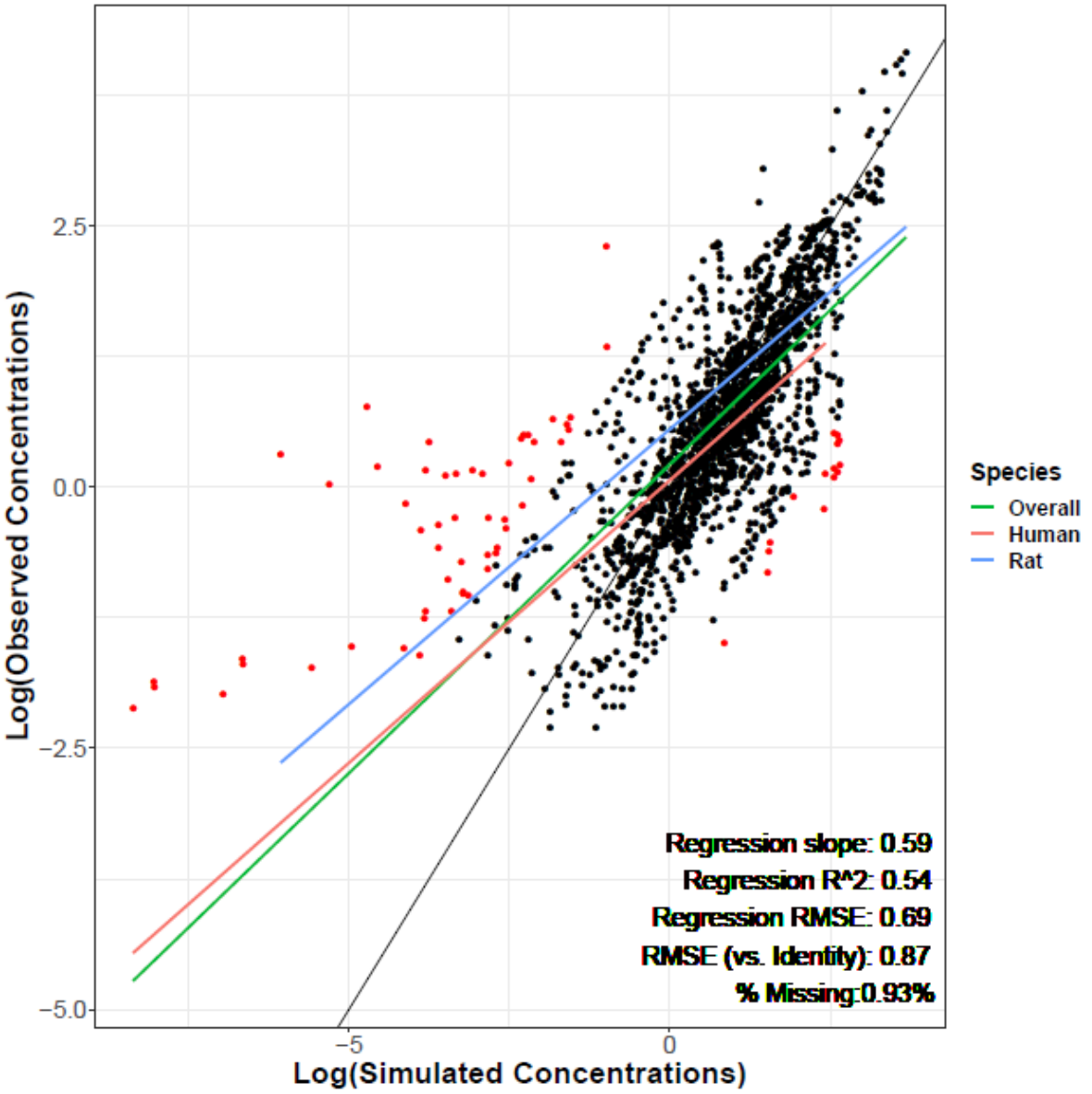
Generic Gas Inhalation Model



- 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 accepted 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
- Overall RMSE was 0.69, R^2 was 0.54 for full concentration time-course across all chemicals and both species



Linakis et al. (accepted)

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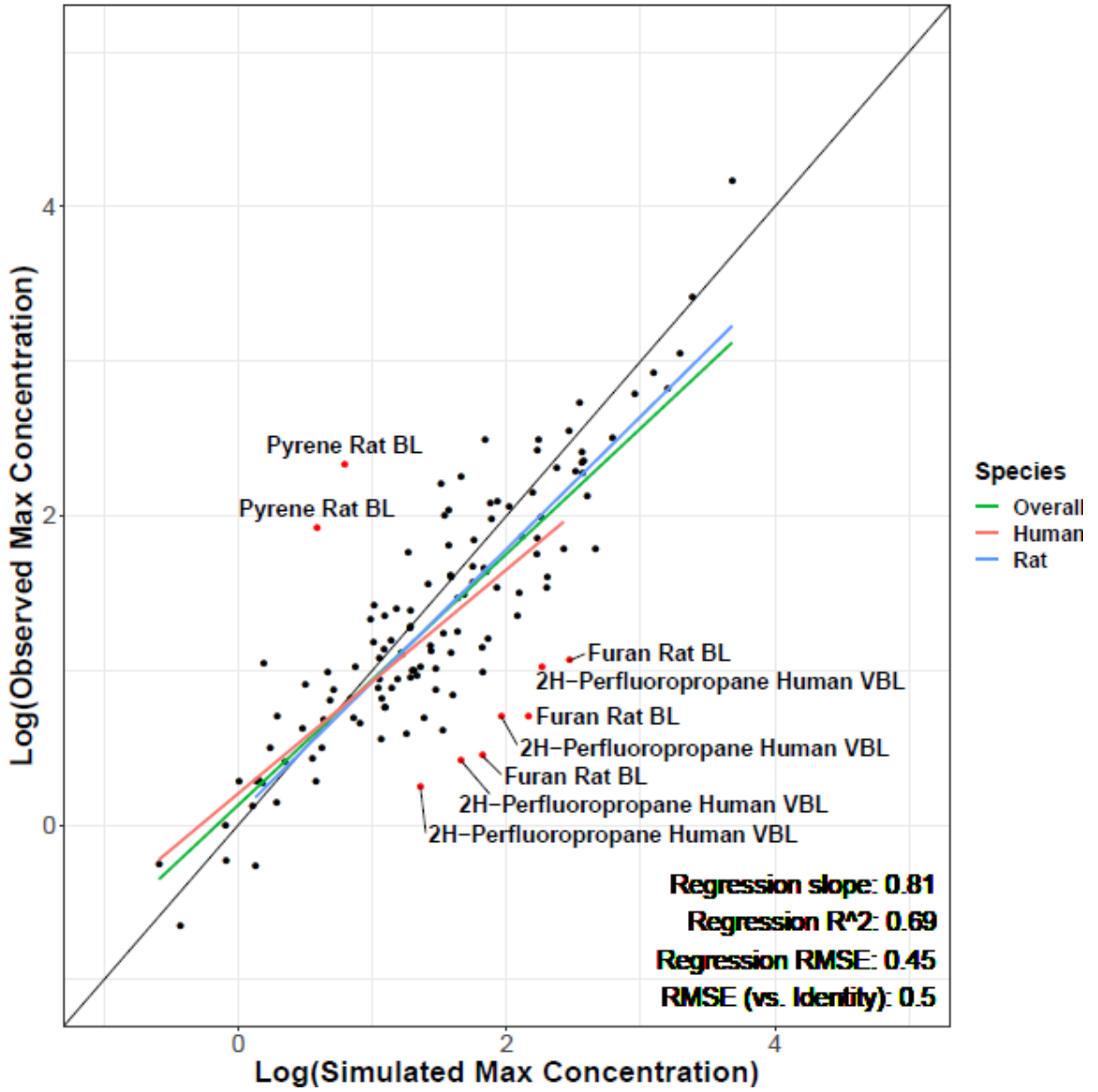
- R^2 was 0.69 for predicting peak concentration



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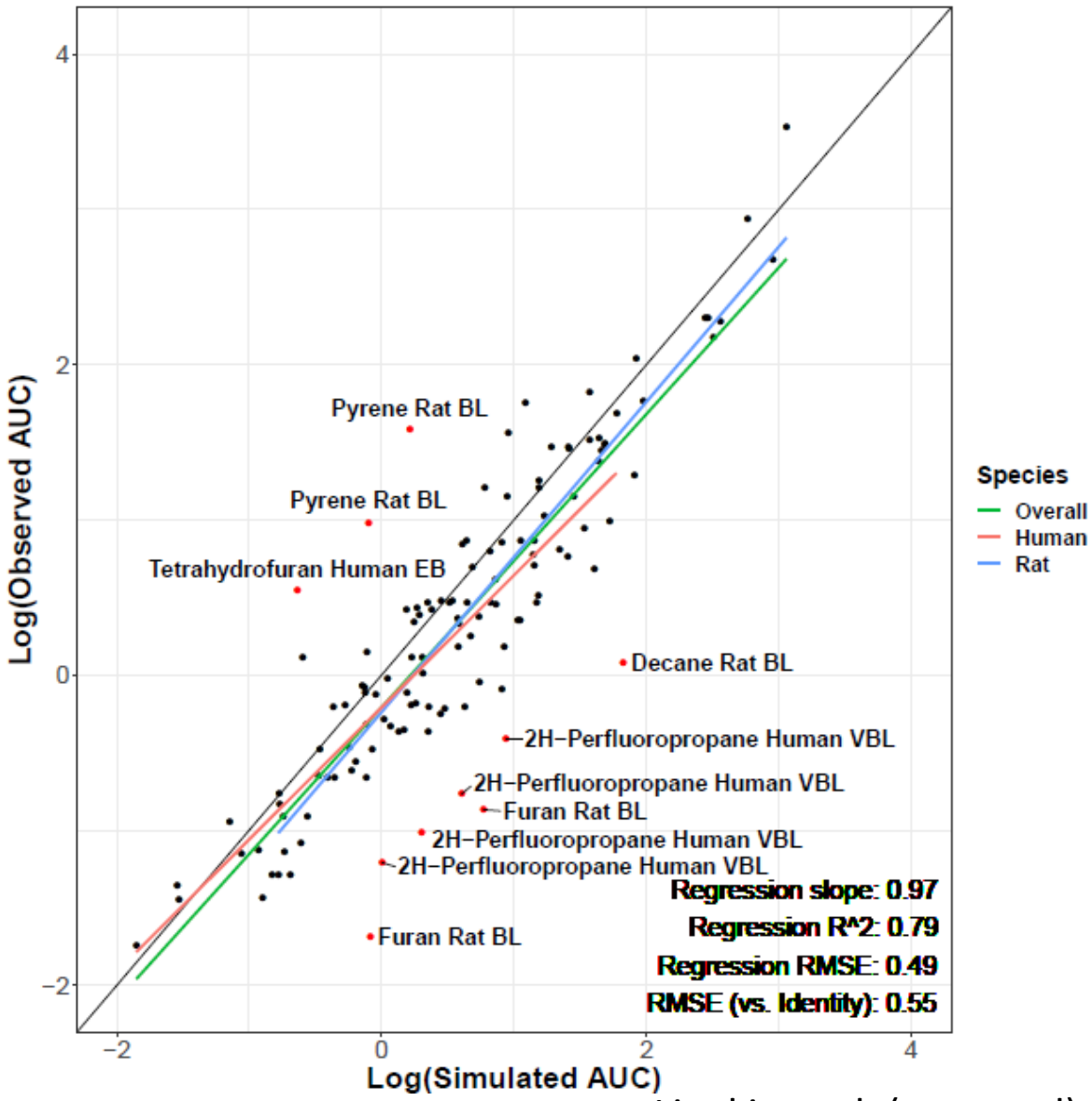
- R^2 was 0.69 for predicting peak concentration
- R^2 was 0.79 for predicting time integrated plasma concentration (Area Under the Curve, AUC)



Linakis et al. (accepted)

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**

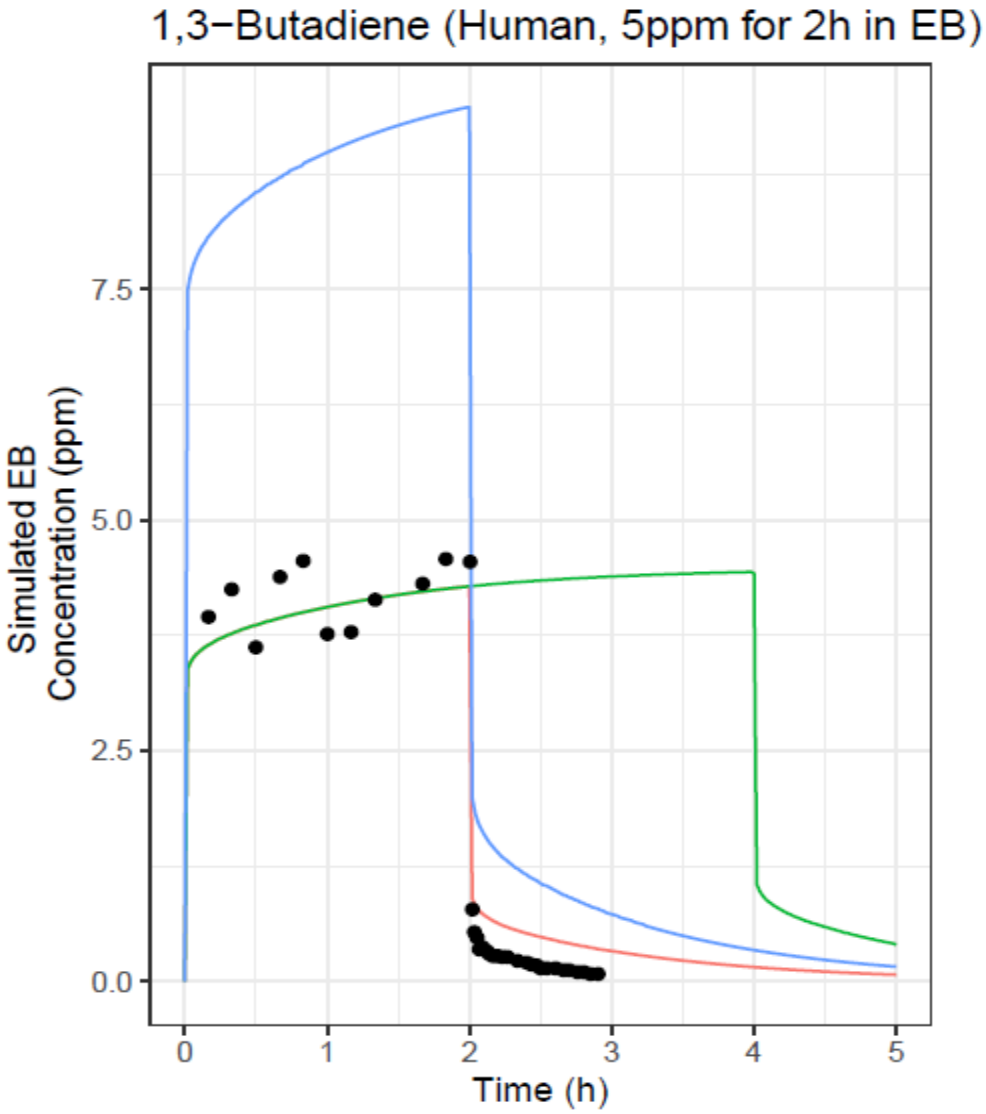


Figure from Matt Linakis (AFRL)

Developing Models with the CvT Database

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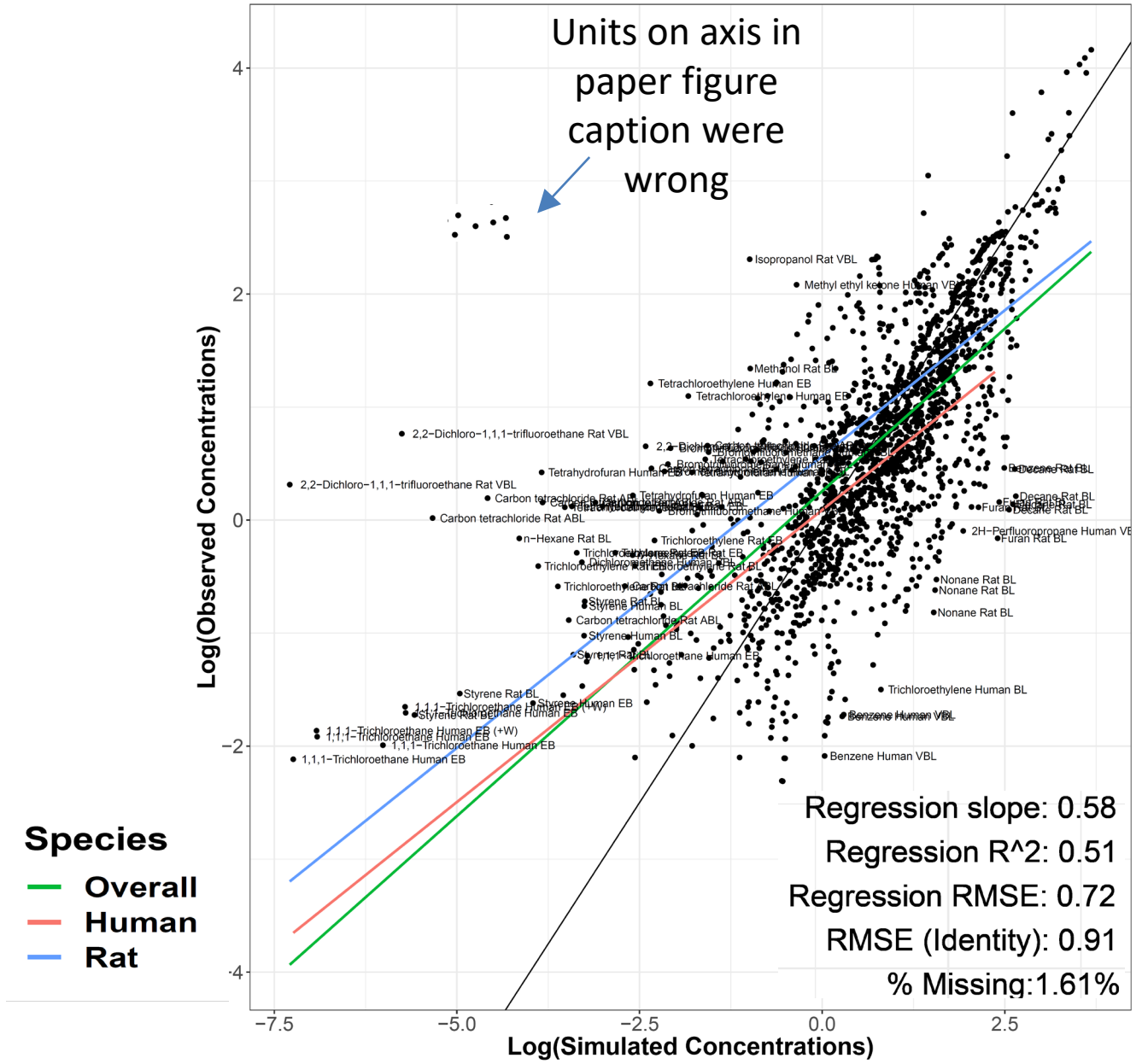
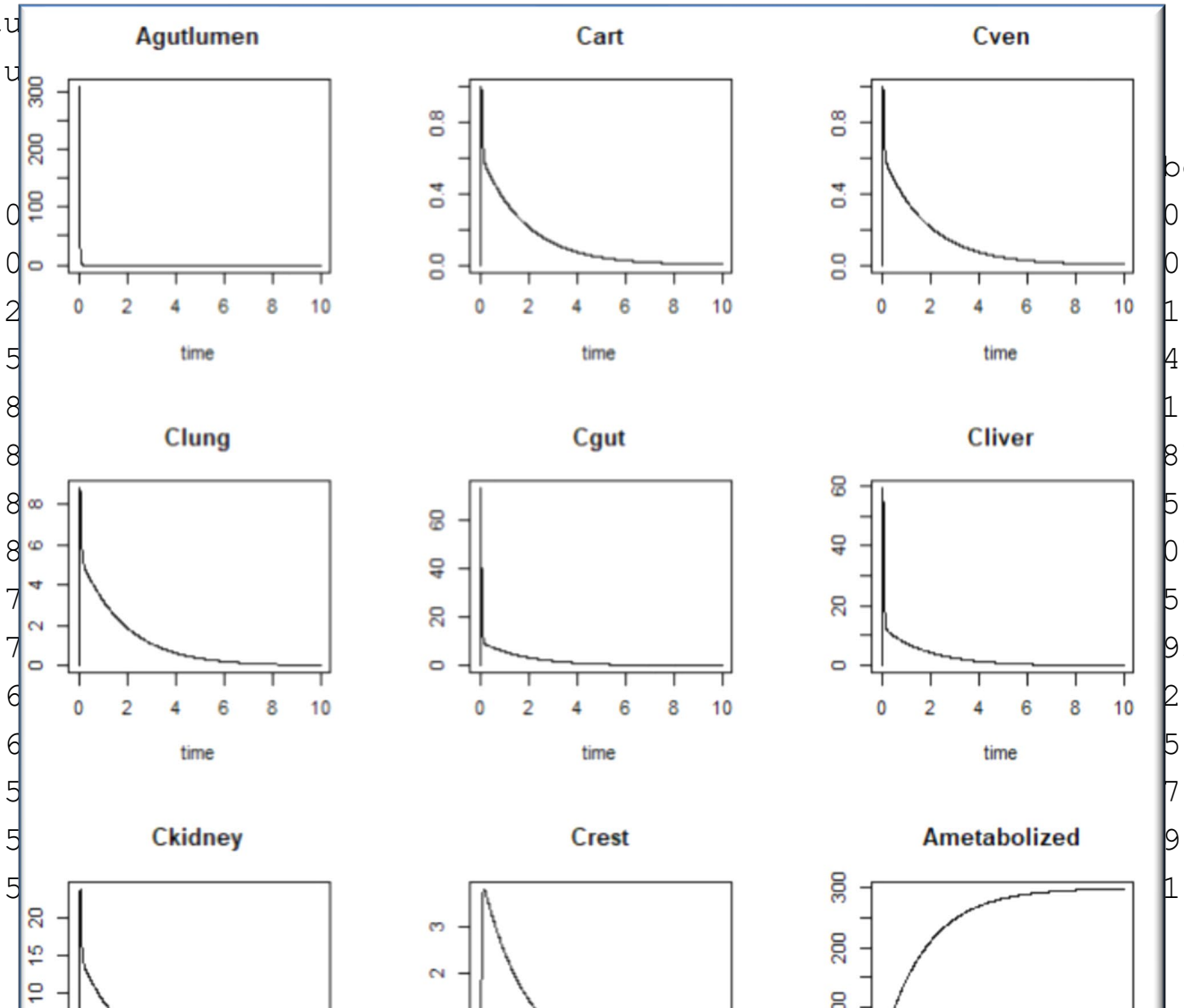


EXAMPLE: Using the PBPK Solver

```
> solve_pbtk(chem.name="bisphenol a", plots=TRUE)
Human amounts returned in umol and concentration retu
AUC is area under plasma concentration in uM * days u
Rblood2plasma = 0.79.
        time Agutlumen     Cgut    Cliver      Cven
1    0.00000 3.066e+02  0.00000 0.000e+00 0.000e+00 0
2    0.00001 3.065e+02  0.14490 4.420e-05 5.000e-09 0
3    0.01042 1.778e+02 71.93000 2.389e+01 2.896e-01 2
4    0.02083 1.031e+02 72.91000 4.930e+01 6.929e-01 5
5    0.03125 5.978e+01 59.22000 5.922e+01 9.241e-01 8
6    0.04167 3.466e+01 45.55000 5.813e+01 9.967e-01 8
7    0.05208 2.010e+01 34.87000 5.188e+01 9.783e-01 8
8    0.06250 1.165e+01 27.10000 4.416e+01 9.207e-01 8
9    0.07292 6.757e+00 21.62000 3.683e+01 8.536e-01 7
10   0.08333 3.918e+00 17.79000 3.061e+01 7.910e-01 7
11   0.09375 2.272e+00 15.12000 2.566e+01 7.380e-01 6
12   0.10420 1.317e+00 13.28000 2.186e+01 6.955e-01 6
13   0.11460 7.638e-01 11.99000 1.903e+01 6.625e-01 5
14   0.12500 4.429e-01 11.10000 1.694e+01 6.372e-01 5
15   0.13540 2.568e-01 10.47000 1.543e+01 6.179e-01 5
1
```



EXAMPLE: Multiple Ways to Use Functions

By chemical name:

```
> calc_analytic_css(chem.name="bisphenol a", model="pbtk")
Plasma concentration returned in uM units.
[1] 1.173
```

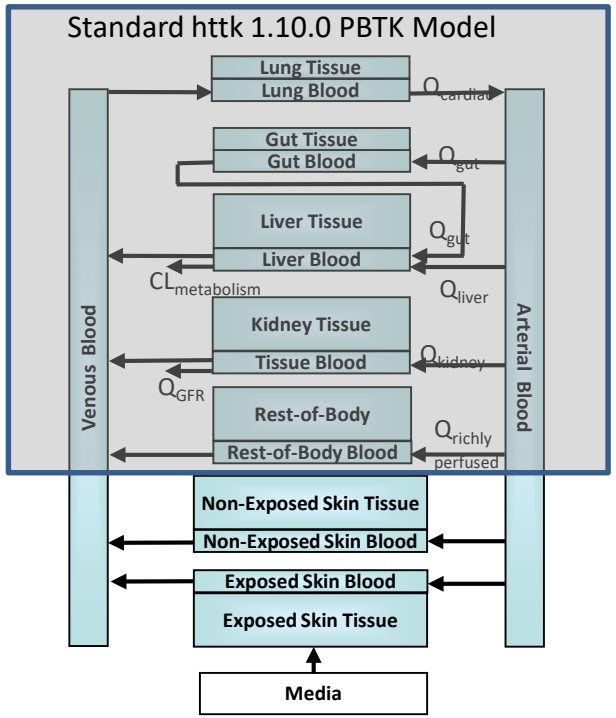
By CAS number:

```
> calc_analytic_css(chem.cas="80-05-7", model="pbtk")
Plasma concentration returned in uM units.
[1] 1.173
```

You can change the parameters (for example, compromised renal filtration):

```
> p <- parameterize_pbtk(chem.cas="80-05-7")
> p$Qgfrc <- p$Qgfrc/10
> calc_analytic_css(parameters=p, model="pbtk")
Plasma concentration returned in uM units.
[1] 1.197
```

New HT-PBTK Models

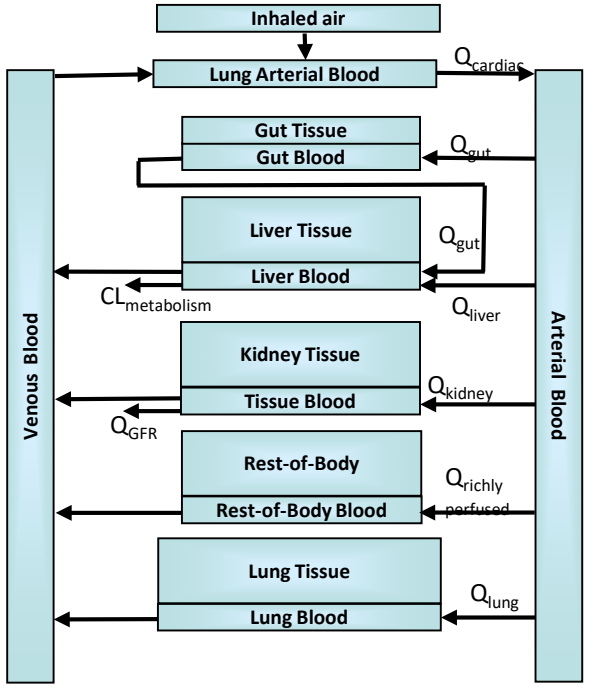


Dermal Exposure Route

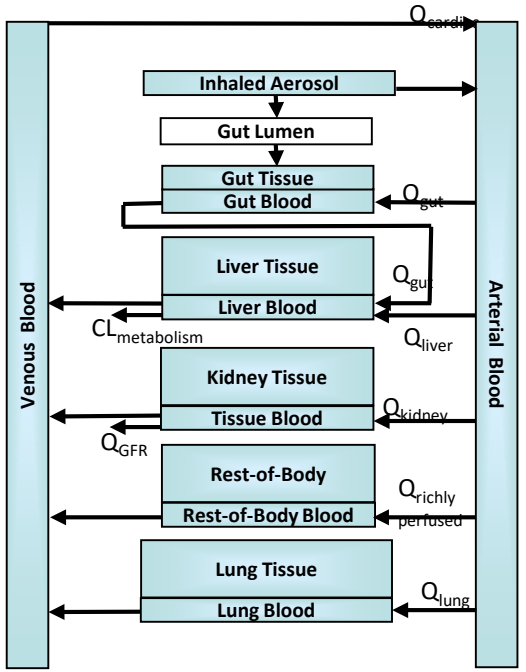
EPA, Unilever

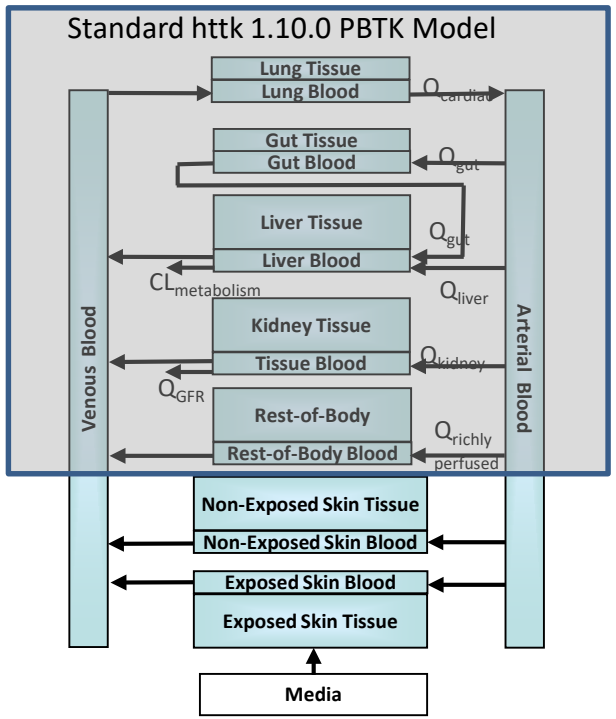
New HT-PBTK Models

Gas Inhalation Exposure Route
(Linakis et al., 2020)



Aerosol Inhalation Exposure Route (with APEX model)
EPA, AFRL





Dermal Exposure Route
EPA, Unilever

New HT-PBTK Models

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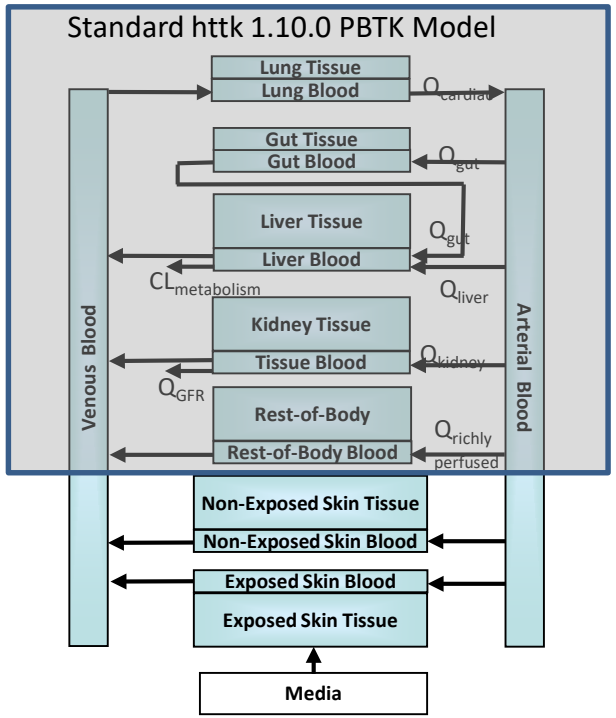
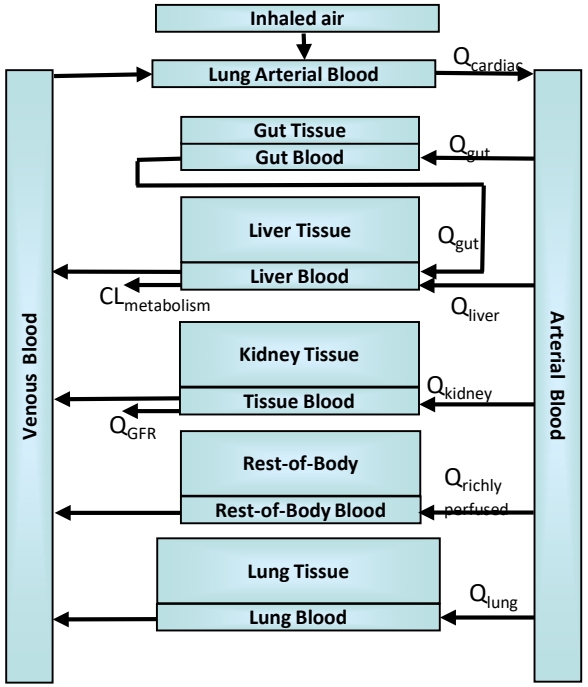
(Linakis et al., 2020)



Dermal Exposure Route
EPA, Unilever



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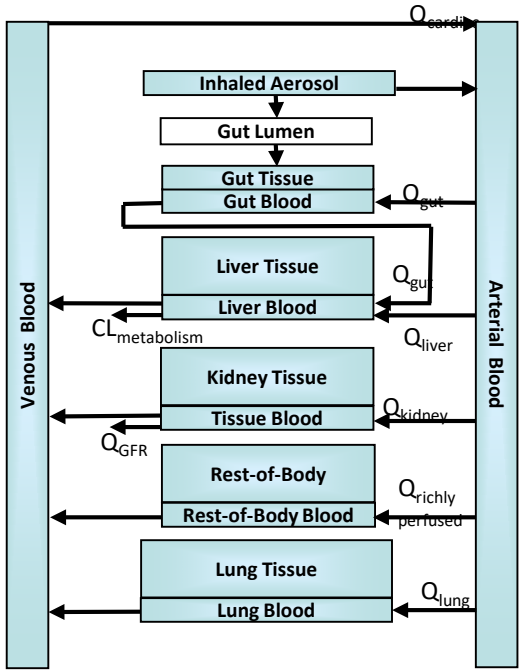
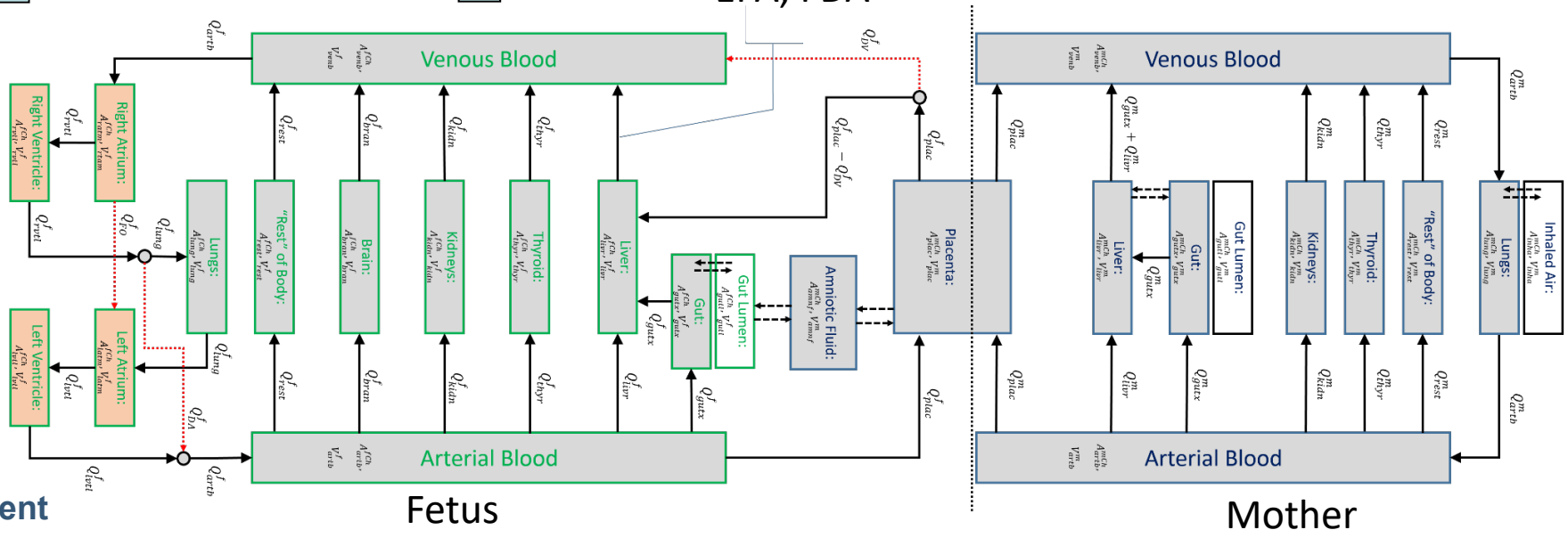
EPA, AFRL



Human Gestational Model
EPA, FDA



HTTK Limitations

- 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

HTTK Limitations

- Oral absorption
- 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

HTTK Limitations

- Oral absorption
- Hepatic Clearance (CL_{int})
- Plasma binding assay (F_{up})
  - Plasma protein concentration variability (Johnson et al. 2006, Israili et al. 2001)
  - Albumin or AAG binding? (Routledge 1986)

HTTK Limitations

- Oral absorption
- Hepatic Clearance (CL_{int})
- Plasma binding assay (F_{up})
- Analytical chemistry
  - Must be able to develop method for each compound
  - Working to develop QSARs for other compounds

HTTK Limitations

- Oral absorption
- Hepatic Clearance (CL_{int})
- Plasma binding assay (F_{up})
- Analytical chemistry
- Relatively slow throughput (1000 chemicals in last decade)
  - Quantitative Structure-Property Relationship (QSPR) models are being developed and evaluated as part of a collaborative study

HTTK Limitations

- Oral absorption
- Hepatic Clearance (CL_{int})
- Plasma binding assay (F_{up})
- Analytical chemistry
- Relatively slow throughput (1000 chemicals in last decade)
- *In vitro* methods are less than ideal for volatile chemicals
    - Generic inhalation TK IVIVE model has been developed (Linakis et al., submitted)
    - QSPR models can be evaluated for volatile chemicals with measured data

HTTK Limitations

- Oral absorption
- Hepatic Clearance (CL_{int})
- Plasma binding assay (F_{up})
- Analytical chemistry
- Relatively slow throughput (1000 chemicals in last decade)
- *In vitro* methods are less than ideal for volatile chemicals

HTTK QSPR Evaluation Team:

SimulationsPlus
SCIENCE + SOFTWARE = SUCCESS

Arnot Research & Consulting

National Toxicology Program
U.S. Department of Health and Human Services

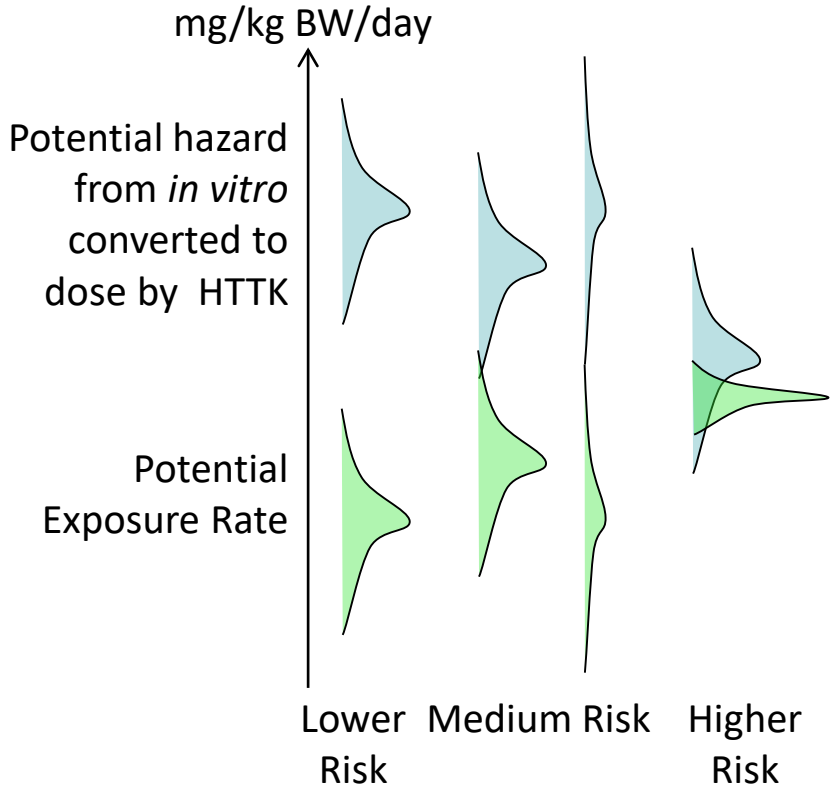
ILS
Advancing Science, Improving Lives

Conclusions

- HTTK allows dosimetric adjustment of high-throughput screening (HTS) data across thousands of chemicals with open source, free, and evaluated software

- Comparison predicted concentrations and *in vivo* data is a valuable approach for evaluation and establishing confidence
  - A new database of *in vivo* concentration vs. time data has being developed (Sayre et al., *in press*)
  - Can characterize model bias and uncertainty

- Guided in part by "CvT" database, a generic inhalation model has been developed (Linakis et al., in press)



ExpoCast Project (Exposure Forecasting)

Center for Computational Toxicology and Exposure

Linda Adams
Miyuki Breen*
Alex Chao*
Daniel Dawson*
Mike Devito
Kathie Dionisio
Christopher Eklund
Peter Egeghy
Marina Evans
Chris Grulke
Hongtai Huang*
Mike Hughes
Kristin Isaacs
Ashley Jackson*
Richard Judson
Jen Korol-Bexell*
Anna Kreutz*
Charles Lowe*
Katherine Phillips
Ann Richard
Risa Sayre*
Mark Sfeir*
Jane Ellen Simmons
Marci Smeltz*
Jon Sobus
Mike Tornero-Velez
Rusty Thomas
Elin Ulrich
Dan Vallero
Barbara Wetmore
John Wambaugh
Antony Williams

Center for Environmental Measurement and Modeling

Hongwan Li
Xiaoyu Liu
Seth Newton
Mark Strynar

*Trainees

Collaborators

Arnot Research and Consulting
Jon Arnot
Johnny Westgate
Integrated Laboratory Systems
Kamel Mansouri
Xiaoqing Chang
National Toxicology Program
Steve Ferguson
Nisha Sipes
Ramboll
Harvey Clewell
Silent Spring Institute
Robin Dodson
Simulations Plus
Michael Lawless
Southwest Research Institute
Alice Yau
Kristin Favela
Summit Toxicology
Lesa Aylward
Technical University of Denmark
Peter Fantke
ToxStrategies
Caroline Ring
Unilever
Beate Nicol
Cecilie Rendal
Ian Sorrell
United States Air Force
Heather Pangburn
Matt Linakis
University of California, Davis
Deborah Bennett
University of Michigan
Olivier Jolliet
University of Texas, Arlington
Hyeong-Moo Shin

United States Environmental Protection Agency

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