Using the U.S. EPA's ToxCast, HTTK, and ExpoCast tools for chemical risk prioritization: *in vitro-in vivo* extrapolation and reverse dosimetry

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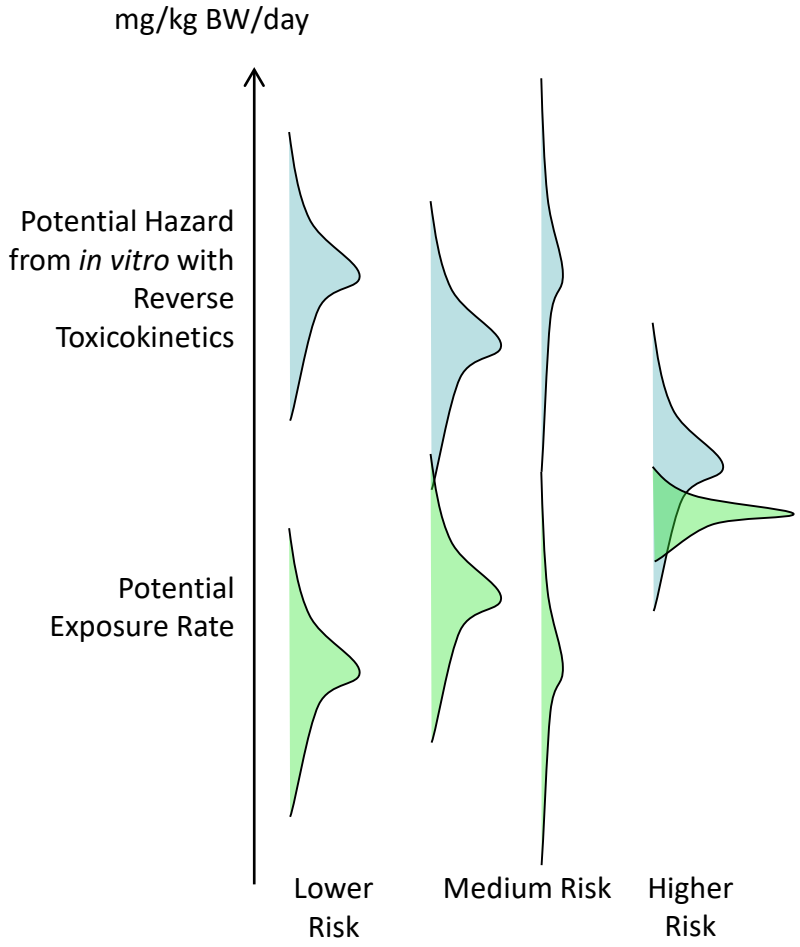
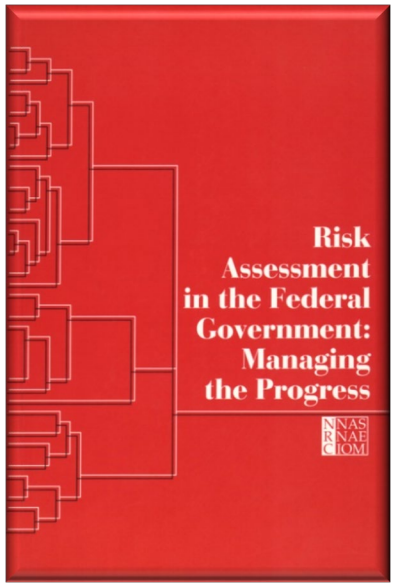
High Throughput Toxicokinetics (HTTK)

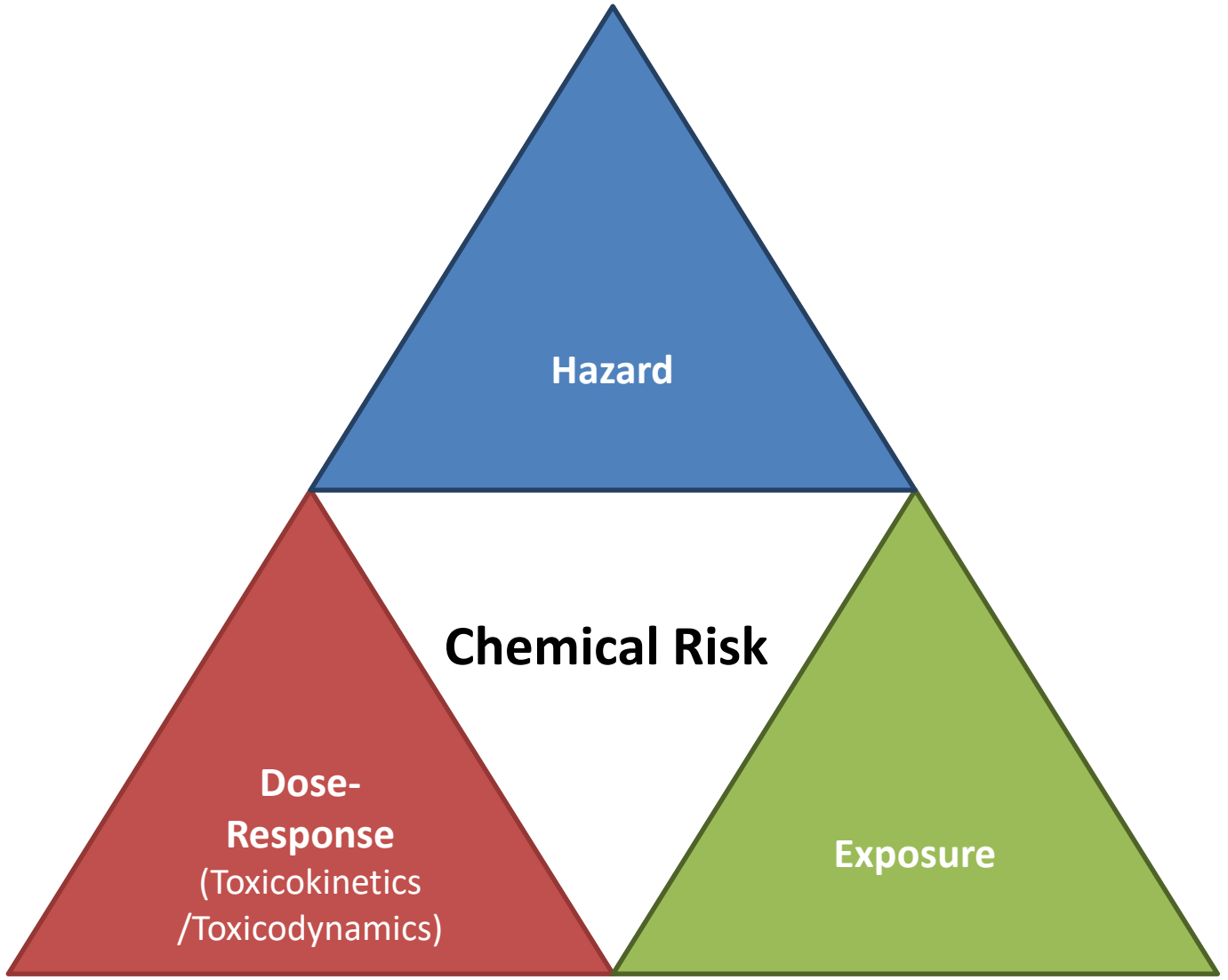
- **Most chemicals do not have TK data**
- In order to address greater numbers of chemicals we collect *in vitro*, high throughput toxicokinetic (HTTK) data (Rotroff et al., 2010, Wetmore et al., 2012, 2015)
- HTTK methods have been used by the pharmaceutical industry to determine range of efficacious doses and to prospectively evaluate success of planned clinical trials (Jamei, *et al.*, 2009; Wang, 2010)
- The **primary goal** of HTTK is to provide a human dose context for bioactive *in vitro* concentrations from HTS (*i.e., in vitro-in vivo* extrapolation, or **IVIVE**) (e.g., Wetmore et al., 2015)
- **Secondary goal** is to provide **open source data and models** for evaluation and use by the broader scientific community (Pearce et al, 2017a)



Three Components for Chemical Risk

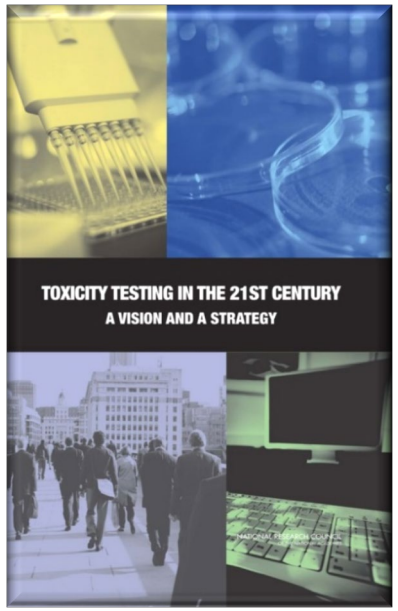


NRC (1983)



High-Throughput Risk Prioritization

United States Environmental Protection Agency



NRC (2007)

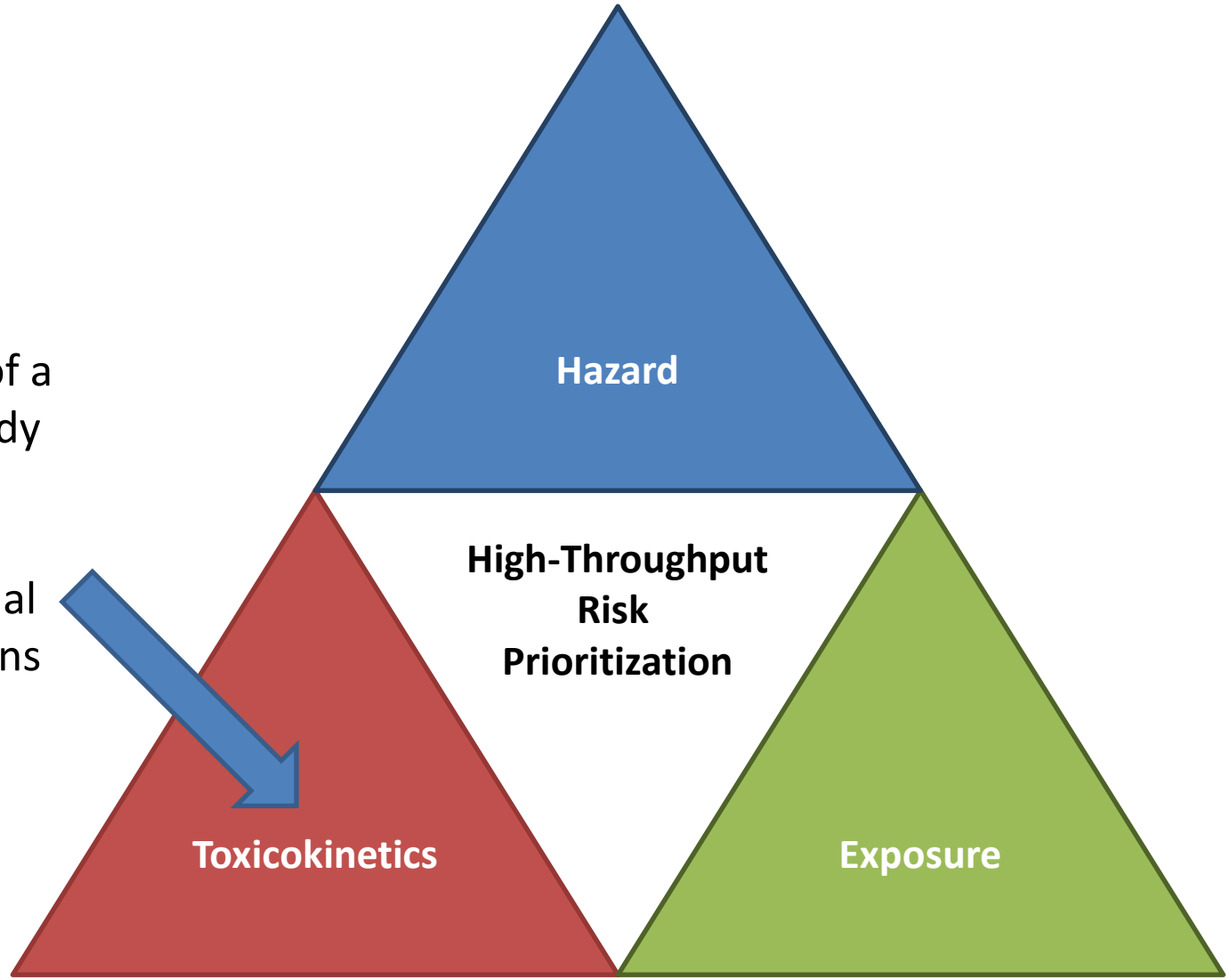
High throughput screening (HTS) for *in vitro* bioactivity potentially allows characterization of thousands of chemicals for which no other testing has occurred

High Throughput Toxicokinetics (HTTK)

United States Environmental Protection Agency

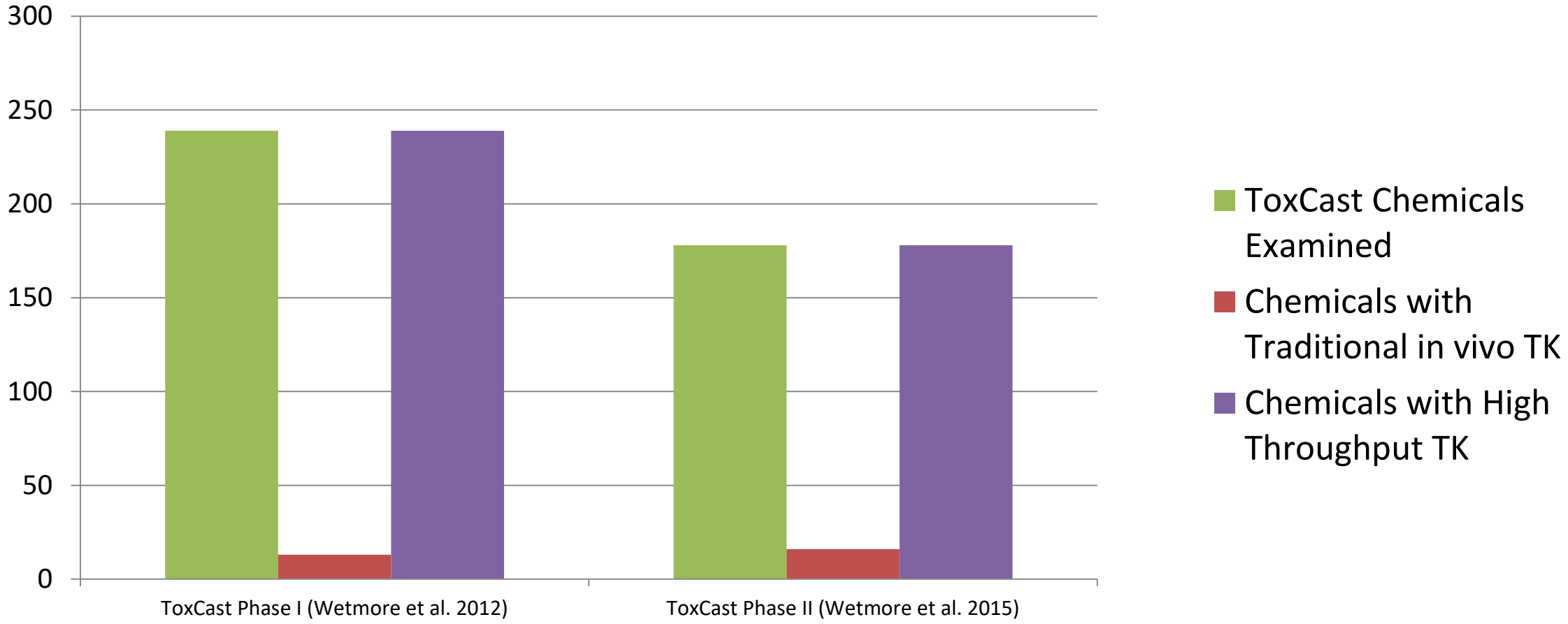
Toxicokinetics (TK) describes the Absorption, Distribution, Metabolism, and Excretion (ADME) of a chemical by the body

TK relates external exposures to internal tissue concentrations of chemical



The Need for *In Vitro* Toxicokinetics

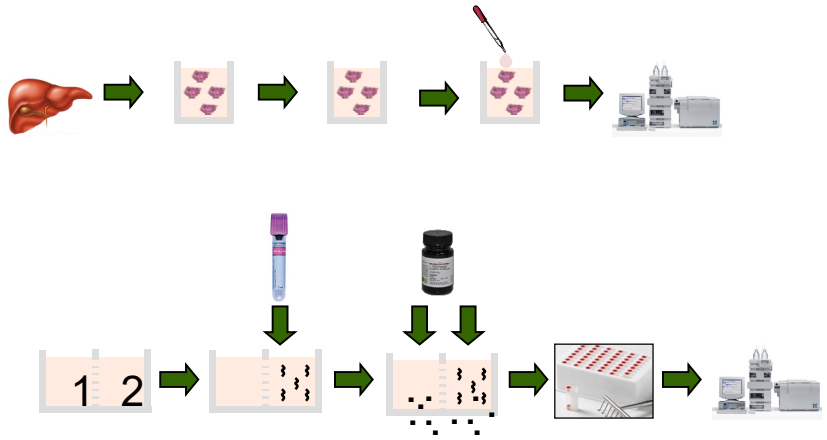
Most chemicals do not have TK data – Wetmore et al. (2012…) use *in vitro* methods adapted from pharma to fill gaps

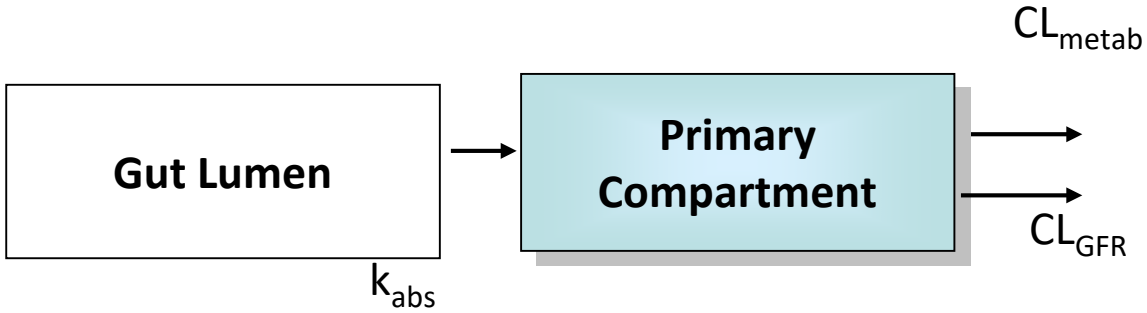


High Throughput Toxicokinetics (HTTK)

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

= high(er) throughput toxicokinetics





httk

HTTK for Public Health Risk Assessment

- In order to address greater numbers of chemicals we collect *in vitro* toxicokinetic data (Rotroff et al., 2010, Wetmore et al., 2012, 2015)
- *In vitro* TK 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)
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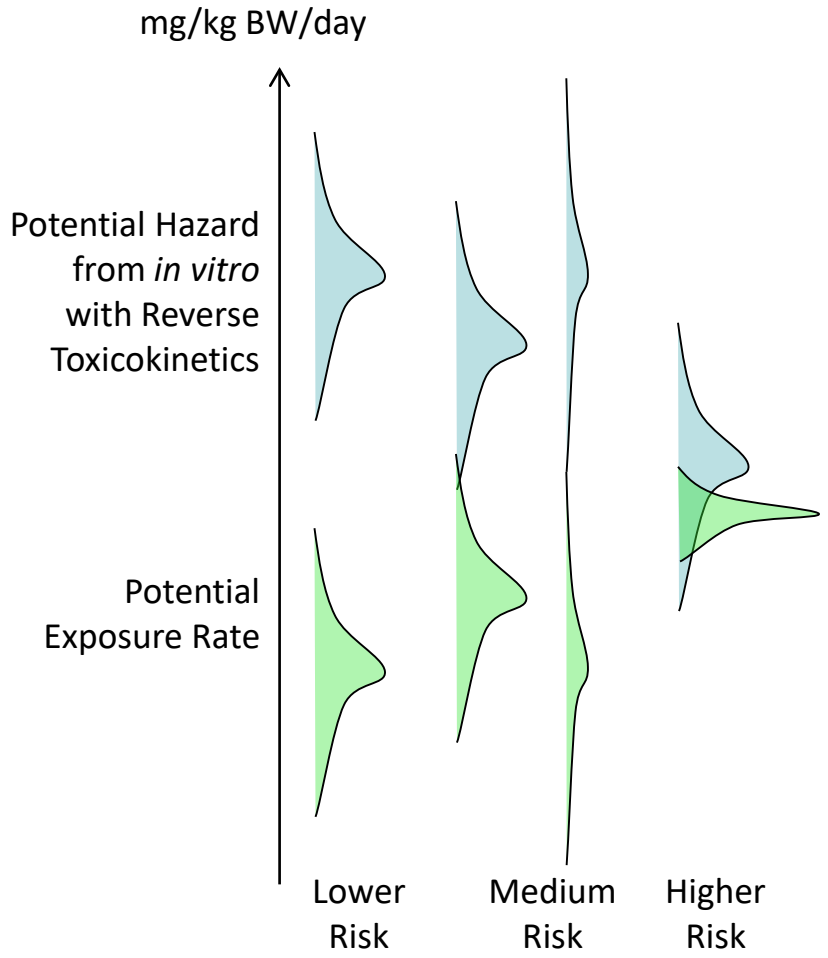


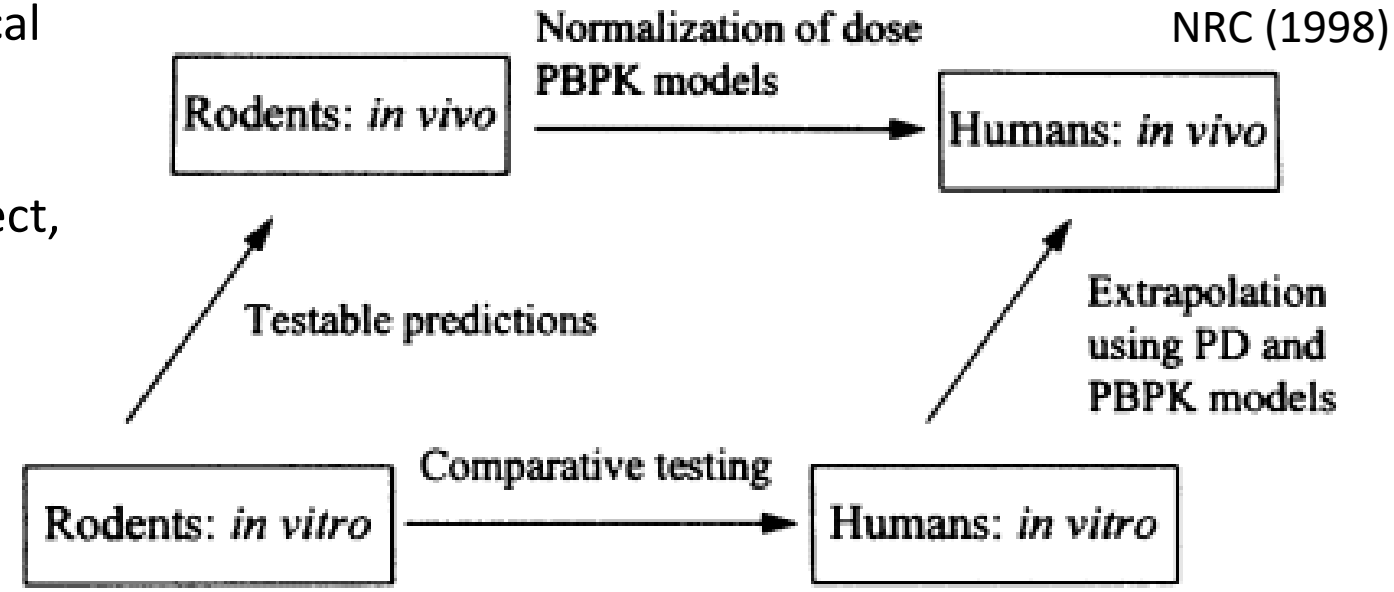
In Vitro - In Vivo Extrapolation (IVIVE)

Utilization of *in vitro* experimental data to predict phenomena *in vivo*

- 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

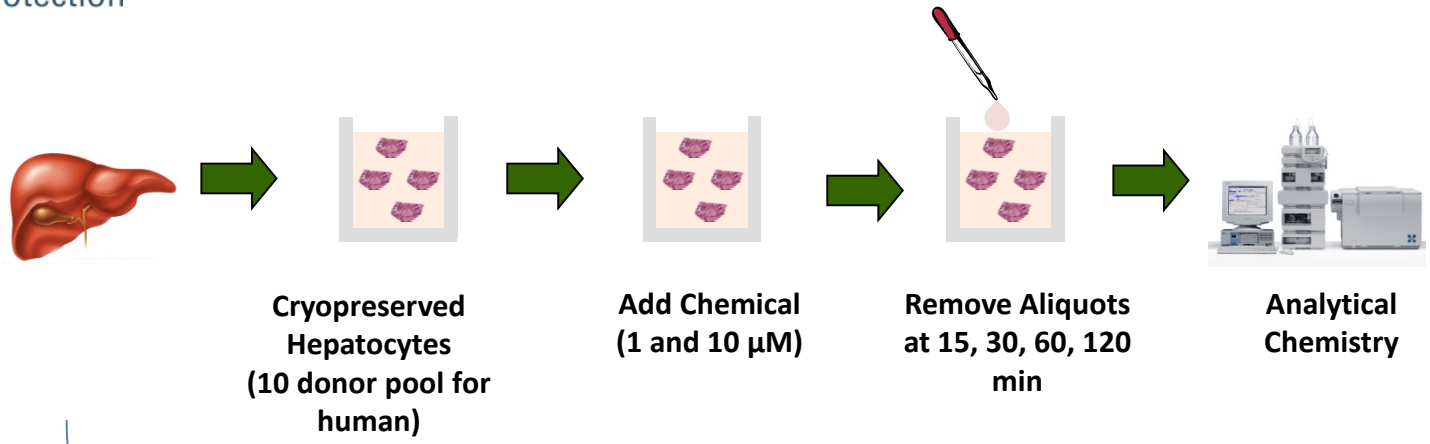
- Both contribute to *in vivo* effect prediction



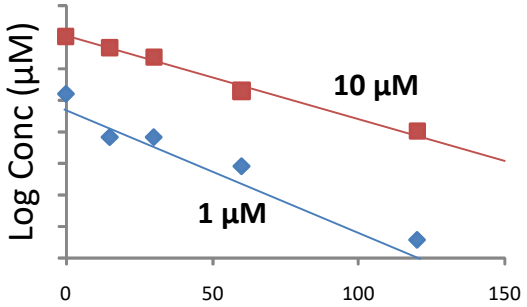
NRC (1998)

In Vitro Data for HTTK

Cryopreserved 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)

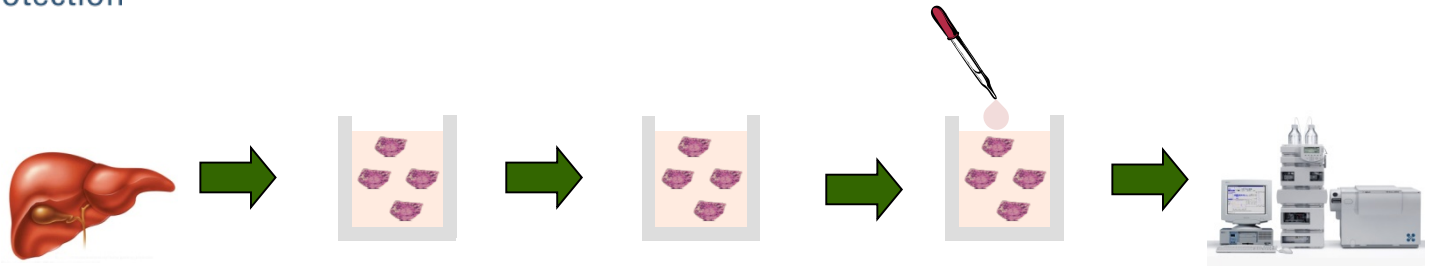


We perform the assay at 1 and 10 µM to check for saturation of metabolizing enzymes.

- **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)

In Vitro Data for HTTK

Cryopreserved hepatocyte suspension
Shibata *et al.* (2002)



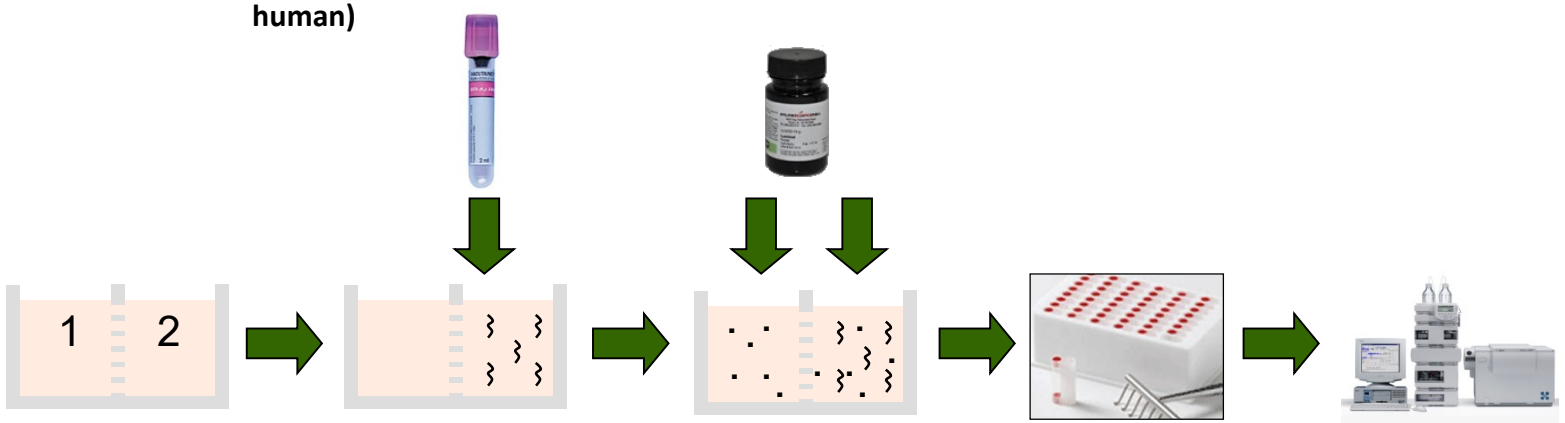
Cryopreserved Hepatocytes (10 donor pool for human)

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)

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

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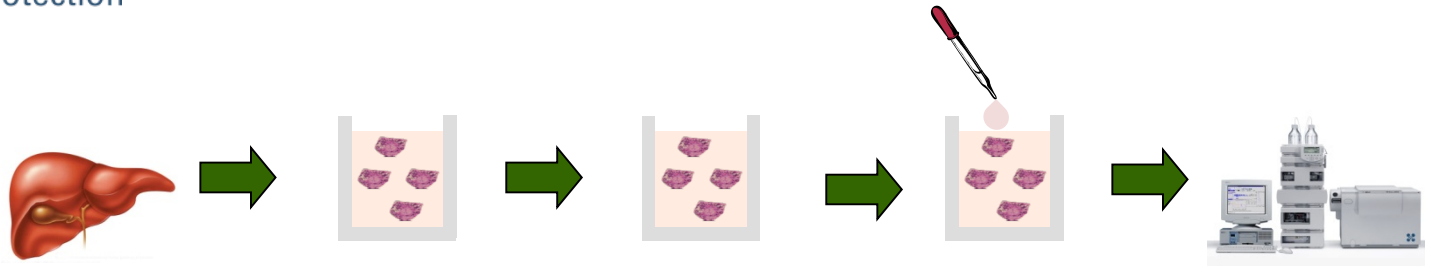

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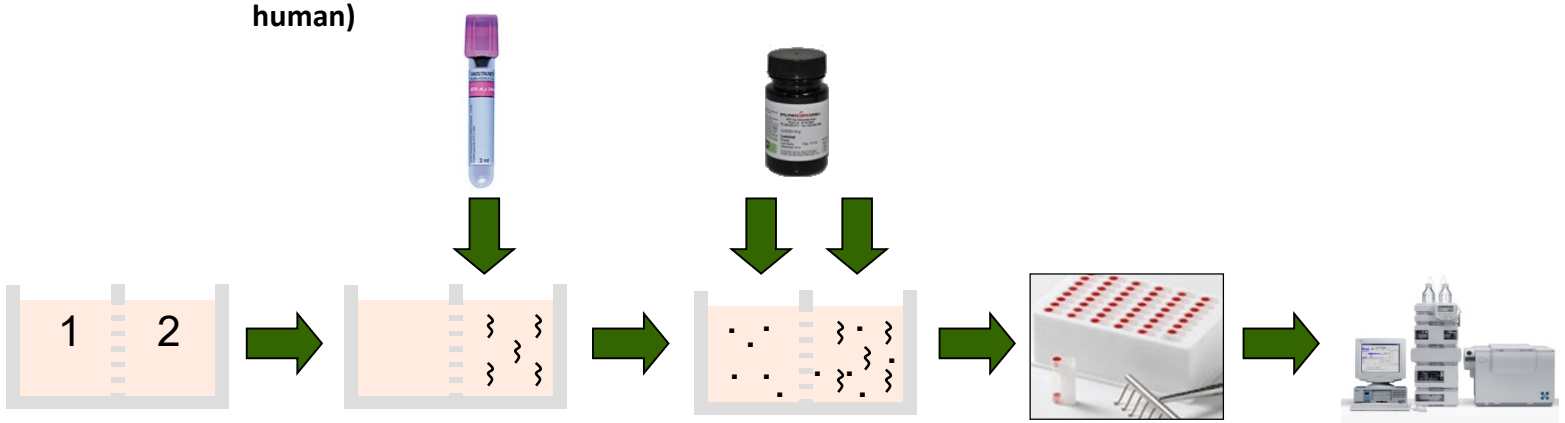

$$F_{ub,p} = \frac{C_{well1}}{C_{well2}}$$

- **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. (submitted) **+389** chemicals

Simple Model for Steady-State Plasma Concentration (C_{ss})

$$C_{ss} = \frac{oral\ dose\ rate}{\left(GFR * f_{up}\right) + \left(Q_l * f_{up} * \frac{Cl_{int}}{Q_l + f_{up} * Cl_{int}}\right)}$$

Wilkinson and Shand (1975)

Passive Renal Clearance
(GFR: Glomerular filtration rate
f_{up}: fraction unbound in plasma)

Hepatic Metabolism
(Cl_{int}: Scaled hepatic clearance
Q_l: Blood flow to liver)

Assume that Steady-State is Linear with Dose

$$C_{ss} = \frac{oral\ dose\ rate}{(GFR * f_{up}) + \left(Q_l * f_{up} * \frac{Cl_{int}}{Q_l + f_{up} * Cl_{int}}\right)}$$

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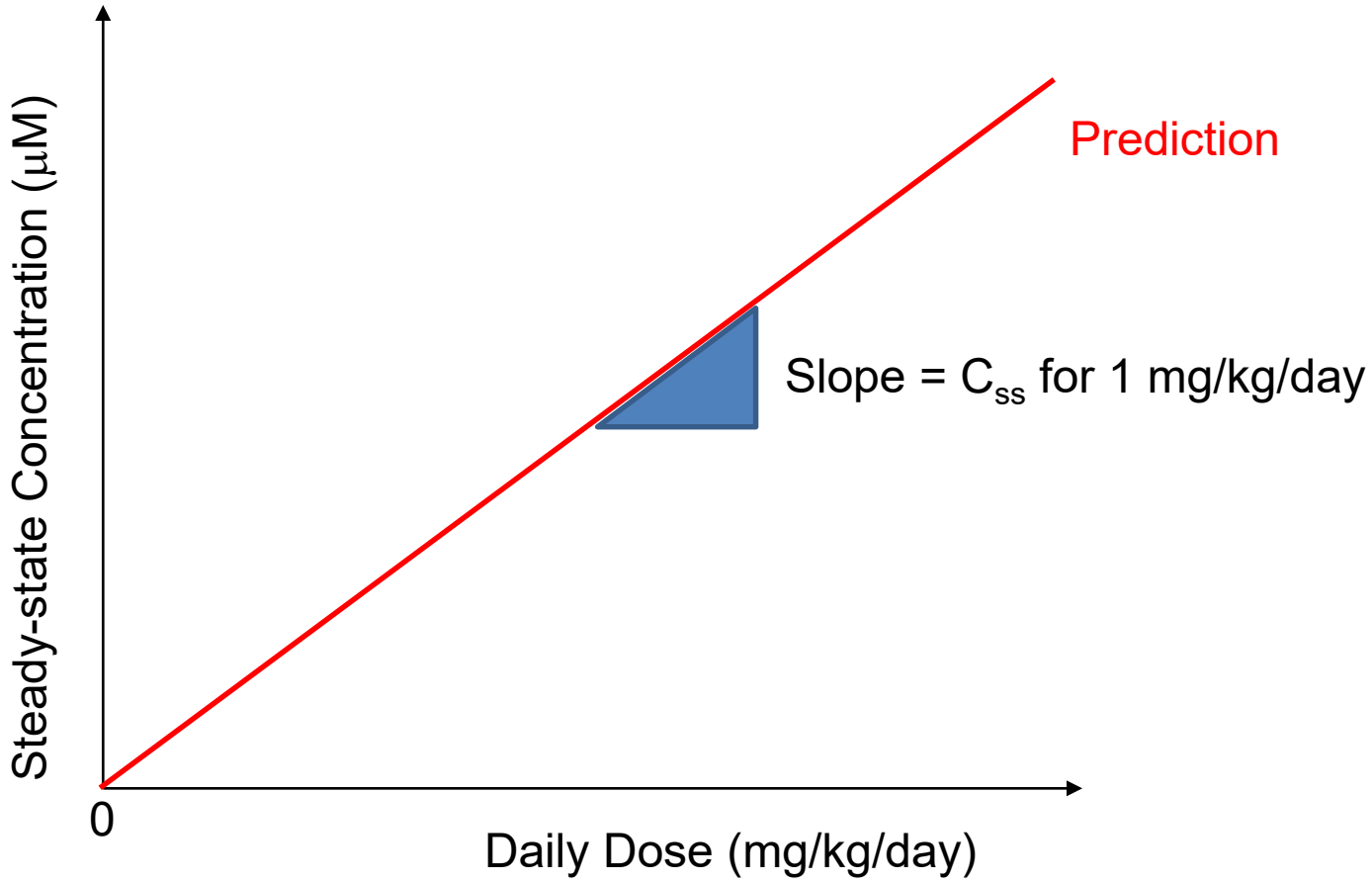
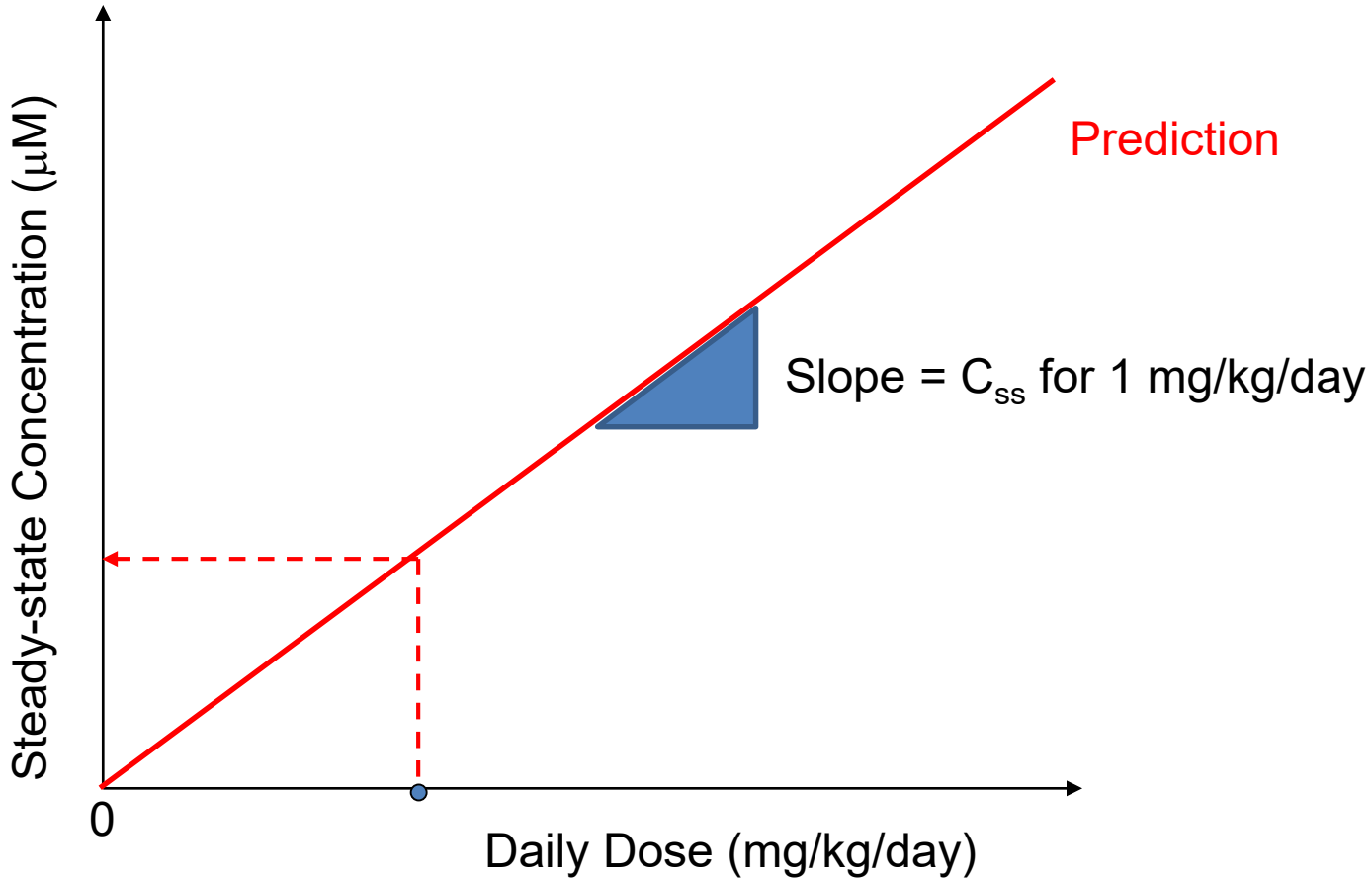


- Can calculate predicted steady-state concentration (C_{ss}) for a 1 mg/kg/day dose and multiply to get concentrations for other doses

Wetmore *et al*. (2012)

Assume that Steady-State is Linear with Dose

$$C_{ss} = \frac{oral\ dose\ rate}{(GFR * f_{up}) + \left(Q_l * f_{up} * \frac{Cl_{int}}{Q_l + f_{up} * Cl_{int}}\right)}$$



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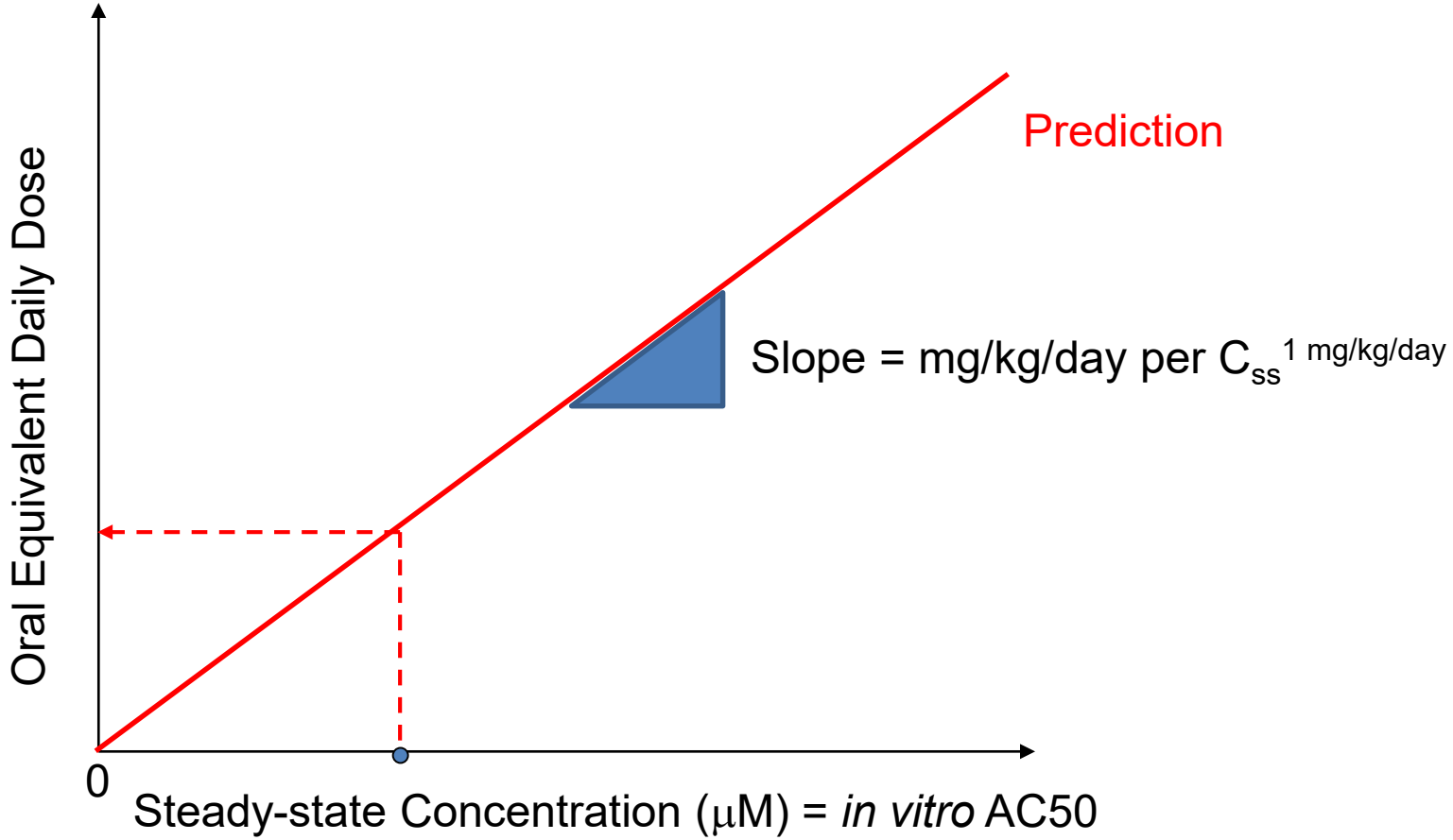
HTTK Allows Steady-State *In Vitro-In Vivo* Extrapolation (IVIVE)

$$C_{ss} = \frac{oral\ dose\ rate}{(GFR * f_{up}) + \left(Q_l * f_{up} * \frac{Cl_{int}}{Q_l + f_{up} * Cl_{int}}\right)}$$

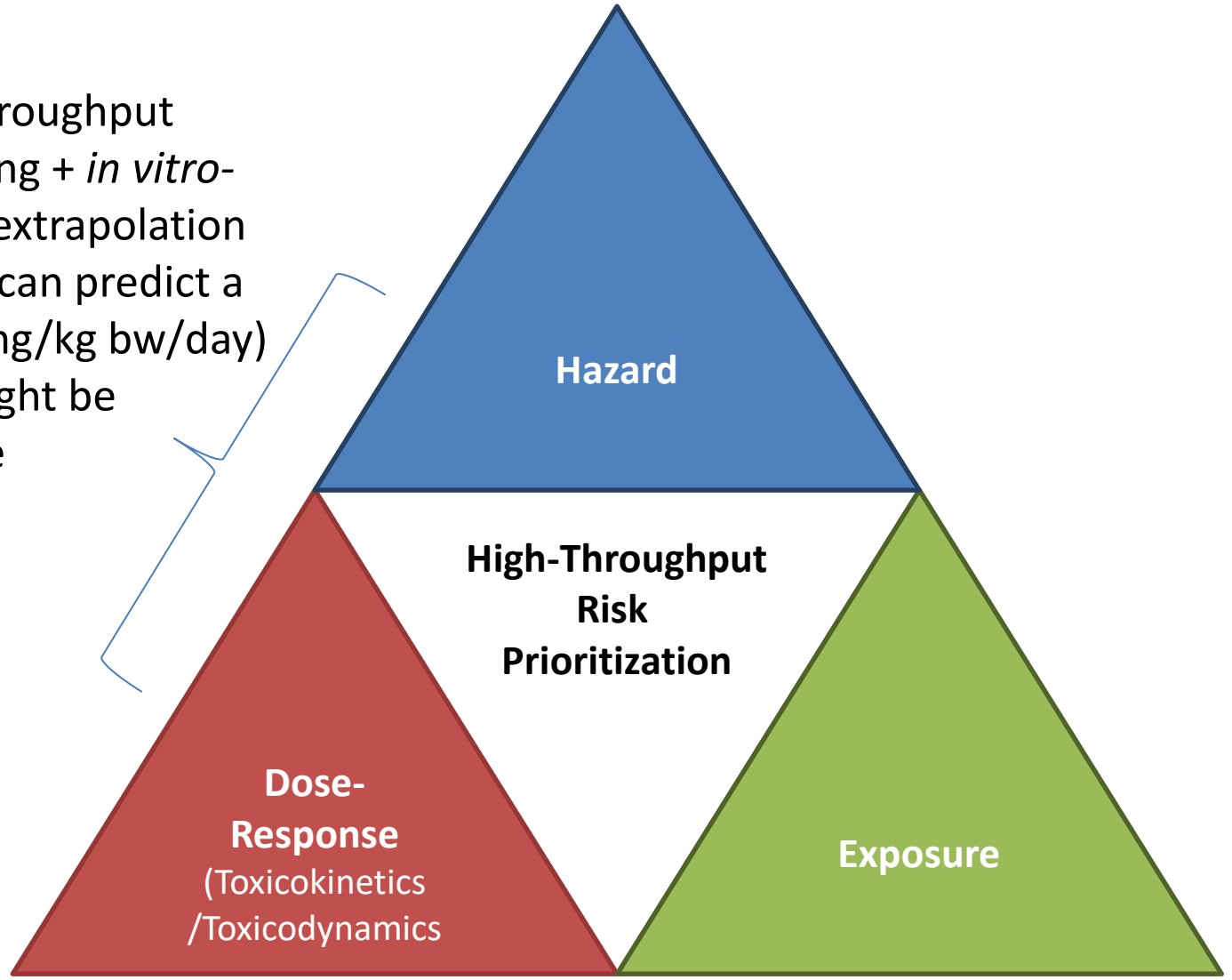


- Can calculate predicted steady-state concentration (C_{ss}) for a 1 mg/kg/day dose and multiply to get concentrations for other doses

Wetmore *et al*. (2012)

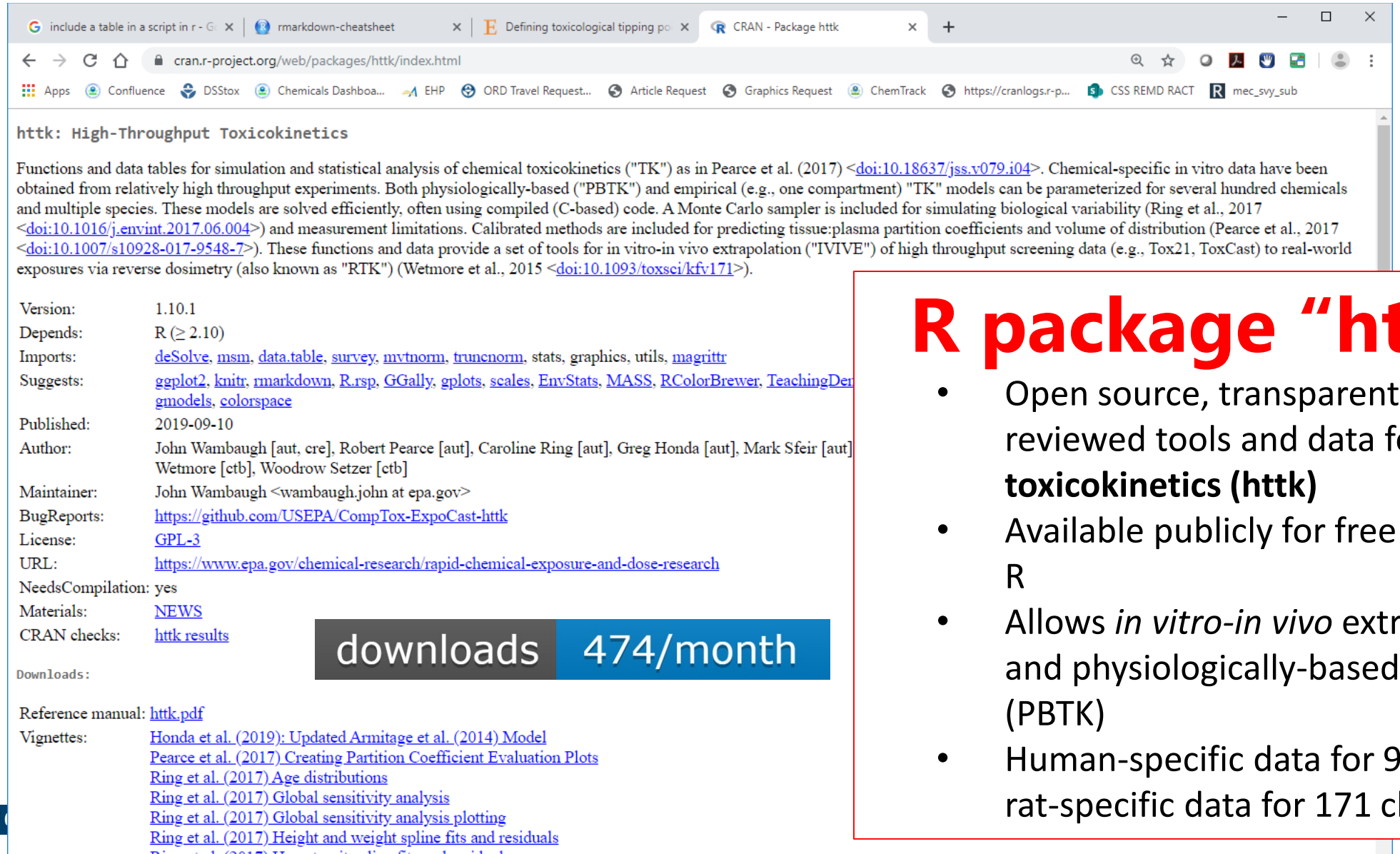
New Exposure Data and Models

High throughput screening + *in vitro-in vivo* extrapolation (IVIVE) can predict a dose (mg/kg bw/day) that might be adverse



Open Source Tools and Data for HTTK

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



include a table in a script in r - G | rmarkdown-cheatsheet | Defining toxicological tipping po | CRAN - Package httk

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

Apps | Confluence | DSStox | Chemicals Dashboa... | EHP | ORD Travel Request... | Article Request | Graphics Request | ChemTrack | https://cranlogs.r-p... | CSS REMD RACT | mec_svy_sub

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:	1.10.1
Depends:	R (≥ 2.10)
Imports:	deSolve, msm, data.table, survey, mvtnorm, truncnorm, stats, graphics, utils, magrittr
Suggests:	ggplot2, knitr, rmarkdown, R.rsp, GGally, gplots, scales, EnvStats, MASS, RColorBrewer, TeachingDem gmodels, colorspace
Published:	2019-09-10
Author:	John Wambaugh [aut, cre], Robert Pearce [aut], Caroline Ring [aut], Greg Honda [aut], Mark Sfeir [aut] 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
Materials:	NEWS
CRAN checks:	httk results

Downloads:

downloads 474/month

Reference manual: httk.pdf

Vignettes:
- Honda et al. (2019): Updated Armitage et al. (2014) Model
- Pearce et al. (2017) Creating Partition Coefficient Evaluation Plots
- Ring et al. (2017) Age distributions
- Ring et al. (2017) Global sensitivity analysis
- Ring et al. (2017) Global sensitivity analysis plotting
- Ring et al. (2017) Height and weight spline fits and residuals

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 944 chemicals and rat-specific data for 171 chemicals

Open Source Tools and Data for HTTK

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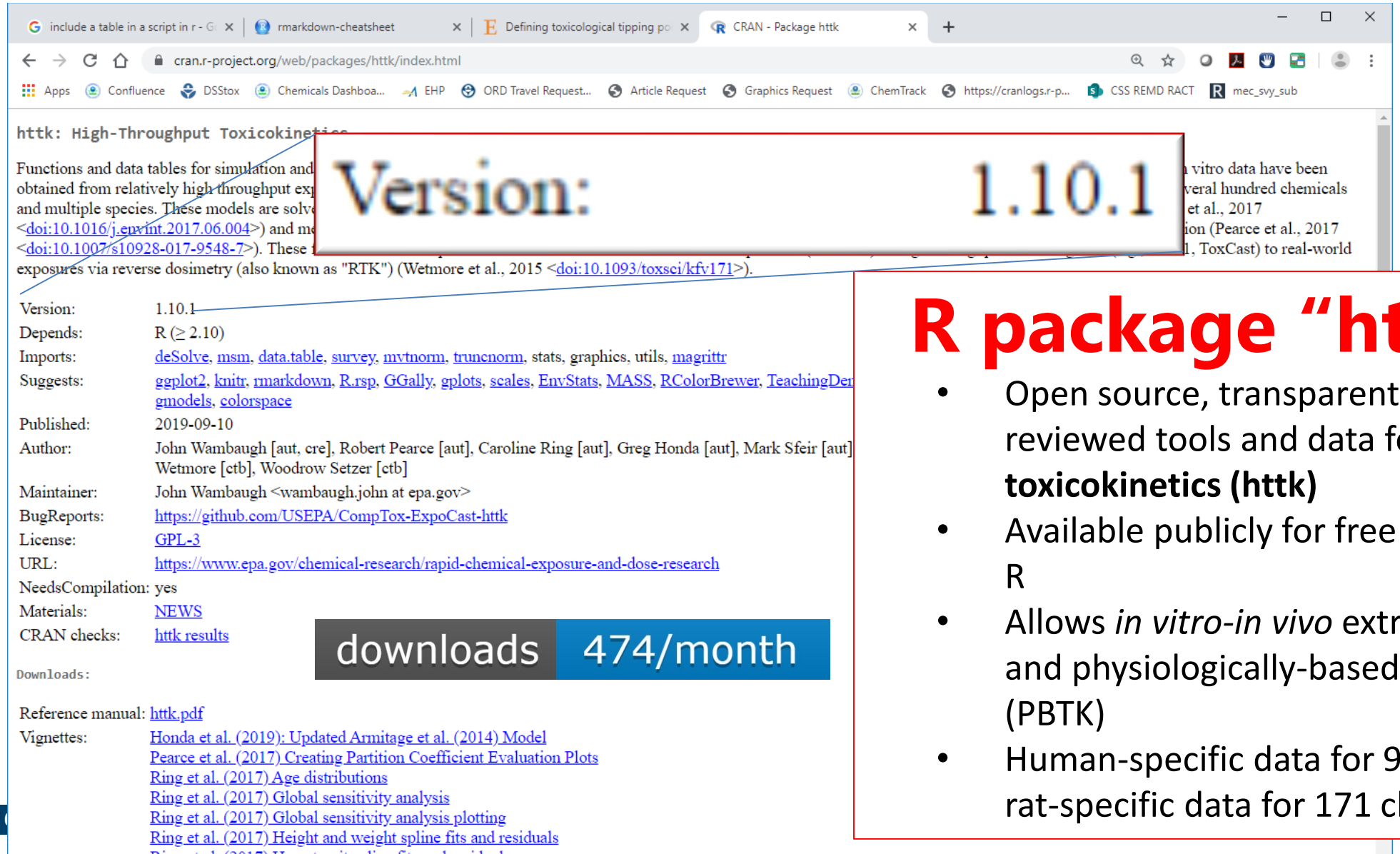

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EPA United States Environmental Protection Agency

What you can do with R Package "httk"?

- Predict internal tissue concentrations from dose regimen (oral and intravenous)
- Convert *in vitro* concentration to *in vivo* doses (reverse dosimetry)
- Use the built in chemical library or add more chemical information (examples provided in JSS paper)
- Load specific (older) versions of the package
- Use specific demographics in the population simulator (v1.5 and later – Ring et al., 2017)
  - Gender, age, weight, ethnicity, renal function
- Control the built in random number generator to reproduce the same random sequence (function set.seed())

Does My Chemical Have HTTK Data?

Is a chemical available?

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

All data on chemicals A, B,

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

```
> library(httk)
> 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" …
> get_cheminfo(info="all")
```

Compound	CAS	logP	pKa_Accept	pKa_Donor	MW	Human.Clint	Human.Clint.pValue	Human.Funbound.plasma	DSSTox_Substance_Id	Structure_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

Oral Equivalent Dose Examples

```
#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_wetmore_oral_equiv(0.1,chem.cas="34256-82-1")

#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")

#State-state oral equivalent dose (mg/kg BW/day) to produce 0.1 uM serum concentration for human, 0.05, 0.5, and 0.95 quantile, for Acetochlor (published values):
get_wetmore_oral_equiv(0.1,chem.cas="34256-82-1",which.quantile=c(0.05,0.5,0.95))

#State-state oral equivalent dose (mg/kg BW/day) to produce 0.1 uM serum concentration for human, 0.05, 0.5, and 0.95 quantiles, for Acetochlor (calculated value):
calc_mc_oral_equiv(0.1,chem.cas="34256-82-1",which.quantile=c(0.05,0.5,0.95))

#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")
```

Interspecies Extrapolation Examples

```
#Steady-state concentration (uM) for 1 mg/kg/day for 0.95 quantile for human for Acetochlor (calculated value):
calc_mc_css(chem.cas="34256-82-1")

#Steady-state concentration (uM) for 1 mg/kg/day for 0.95 quantile for rat for Acetochlor (should produce errors since
there is no published value, 0.5 quantile only):
get_wetmore_css(chem.cas="34256-82-1",species="Rat")

#Steady-state concentration (uM) for 1 mg/kg/day for 0.95 quantile for rat for Acetochlor (calculated value):
calc_mc_css(chem.cas="34256-82-1",species="Rat")

#Steady-state concentration (uM) for 1 mg/kg/day for 0.5 quantile for rat for Acetochlor (published value):
get_wetmore_css(chem.cas="34256-82-1",species="Rat",which.quantile=0.5)

#Steady-state concentration (uM) for 1 mg/kg/day for 0.5 quantile for rat for Acetochlor (calculated value):
calc_mc_css(chem.cas="34256-82-1",species="Rat",which.quantile=0.5)

#Steady-state concentration (uM) for 1 mg/kg/day for 0.95 quantile for mouse for Acetochlor (should produce error since
there is no published value, human and rat only):
get_wetmore_css(chem.cas="34256-82-1",species="Mouse")

#Steady-state concentration (uM) for 1 mg/kg/day for 0.95 quantile for  mouse for Acetochlor (calculated value):
calc_mc_css(chem.cas="34256-82-1",species ="Mouse")
calc_mc_css(chem.cas="34256-82-1",species ="Mouse",default.to.human=T)
```

Doing Statistical Analysis with HTTK

- If we are to use HTTK, then we need confidence in its 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**
  - ORD has both compiled existing (literature) TK data (Wambaugh *et al*., 2015) and conducted new experiments in rats on chemicals with HTTK *in vitro* data (Wambaugh *et al*., 2018)
  - Any approximations, omissions, or mistakes should work to increase the estimated uncertainty when evaluated systematically across chemicals

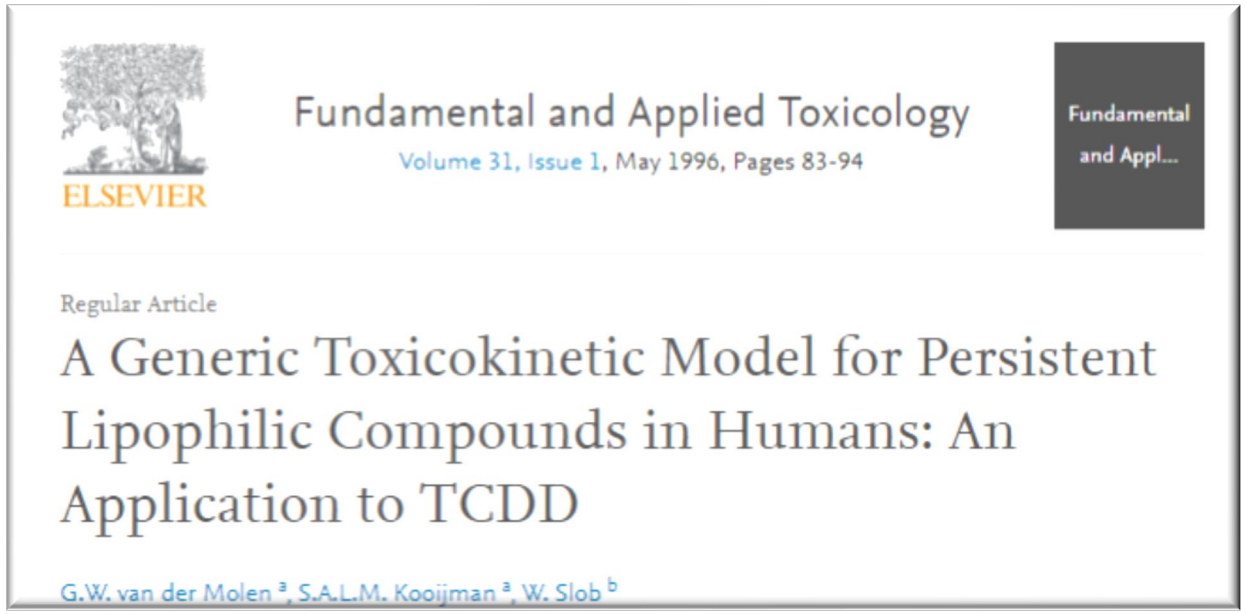
Why Build Another Generic PBTK Tool?

	SimCYP	ADMET Predictor / GastroPlus	MEGen	IndusChemFate	httk
Maker	SimCYP Consortium / Certara	Simulations Plus	UK Health and Safety Laboratory	Cefic LRI	US EPA
Reference	Jamei et al. (2009)	Lukacova et al., (2009)	Loizou et al. (2011)	Jongeneelen et al., (2013)	Pearce et al. (2017a)
Availability	License, but inexpensive for research	License, but inexpensive for research	Free: http://xnet.hsl.gov.uk/megen	Free: http://cefic-lri.org/lri_toolbox/induschemfate/	Free: https://CRAN.R-project.org/package=httk
Open Source	No	No	**Yes**	No	**Yes**
Default PBPK Structure	**Yes**	**Yes**	No	**Yes**	**Yes**
Expandable PBPK Structure	No	No	**Yes**	No	No
Population Variability	**Yes**	No	No	No	**Yes**
Batch Mode	**Yes**	**Yes**	No	No	**Yes**
Graphical User Interface	**Yes**	**Yes**	**Yes**	Excel	No
Physiological Data	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Chemical-Specific Data Library	Many Clinical Drugs	No	No	15 Environmental Compounds	543 Pharmaceutical and ToxCast Compounds
Ionizable Compounds	**Yes**	**Yes**	Potentially	No	**Yes**
Export Function	No	No	Matlab and AcslX	No	SBML and Jarnac
R Integration	No	No	No	No	**Yes**
Easy Reverse Dosimetry	**Yes**	**Yes**	No	No	**Yes**
Future Proof XML	No	No	**Yes**	No	No

We want to do a statistical analysis (using R) for as many chemicals as possible

Generic PBTK Models

There is nothing new about the idea of generic PBTK models…



ELSEVIER

Fundamental and Applied Toxicology

Volume 31, Issue 1, May 1996, Pages 83-94

Fundamental and Appl...

Regular Article

A Generic Toxicokinetic Model for Persistent Lipophilic Compounds in Humans: An Application to TCDD

G.W. van der Molen [a], S.A.L.M. Kooijman [a], W. Slob [b]

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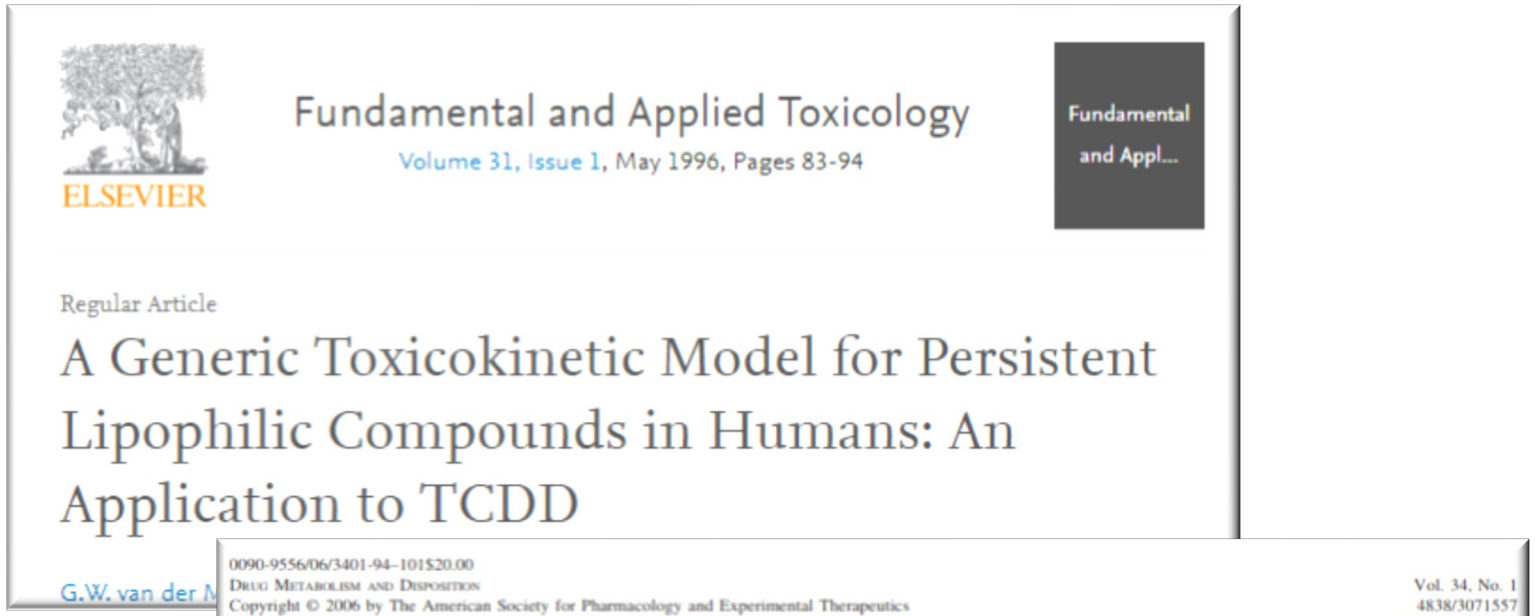

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0090-9556/06/3401-94–101$20.00
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DMD 34:94–101, 2006

Vol. 34, No. 1
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APPLICATION OF A GENERIC PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL TO THE ESTIMATION OF XENOBIOTIC LEVELS IN HUMAN PLASMA[S]

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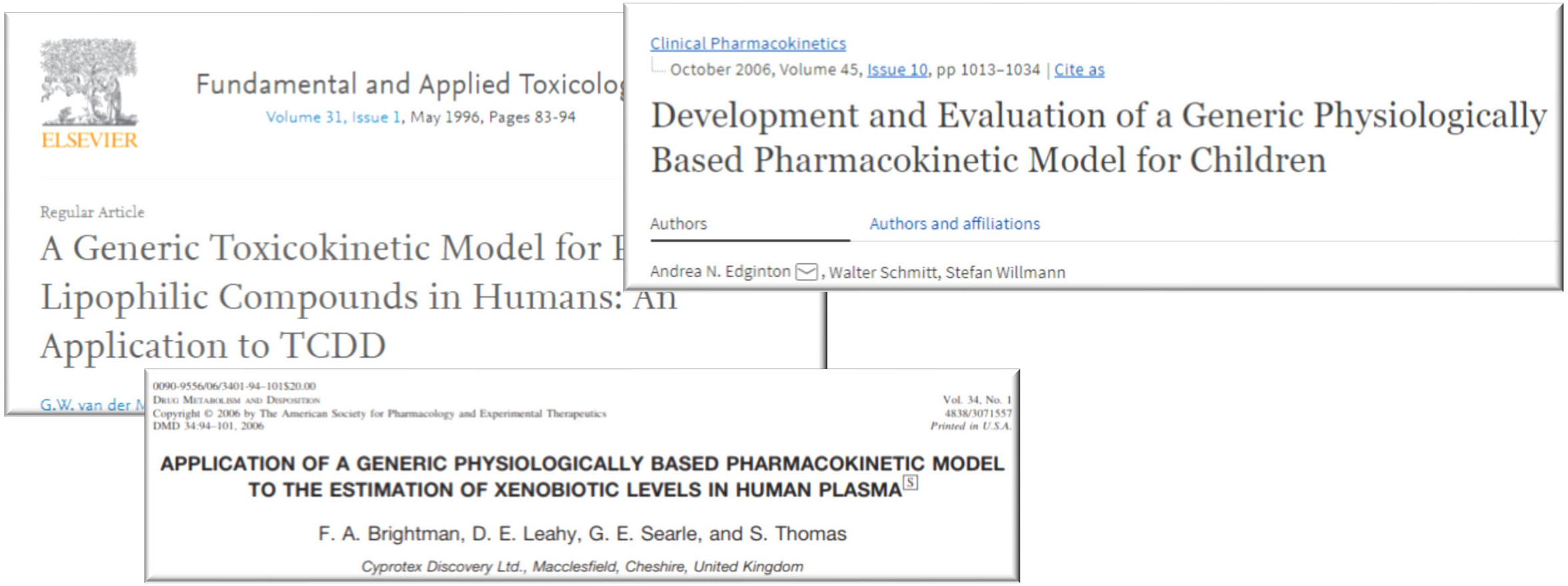

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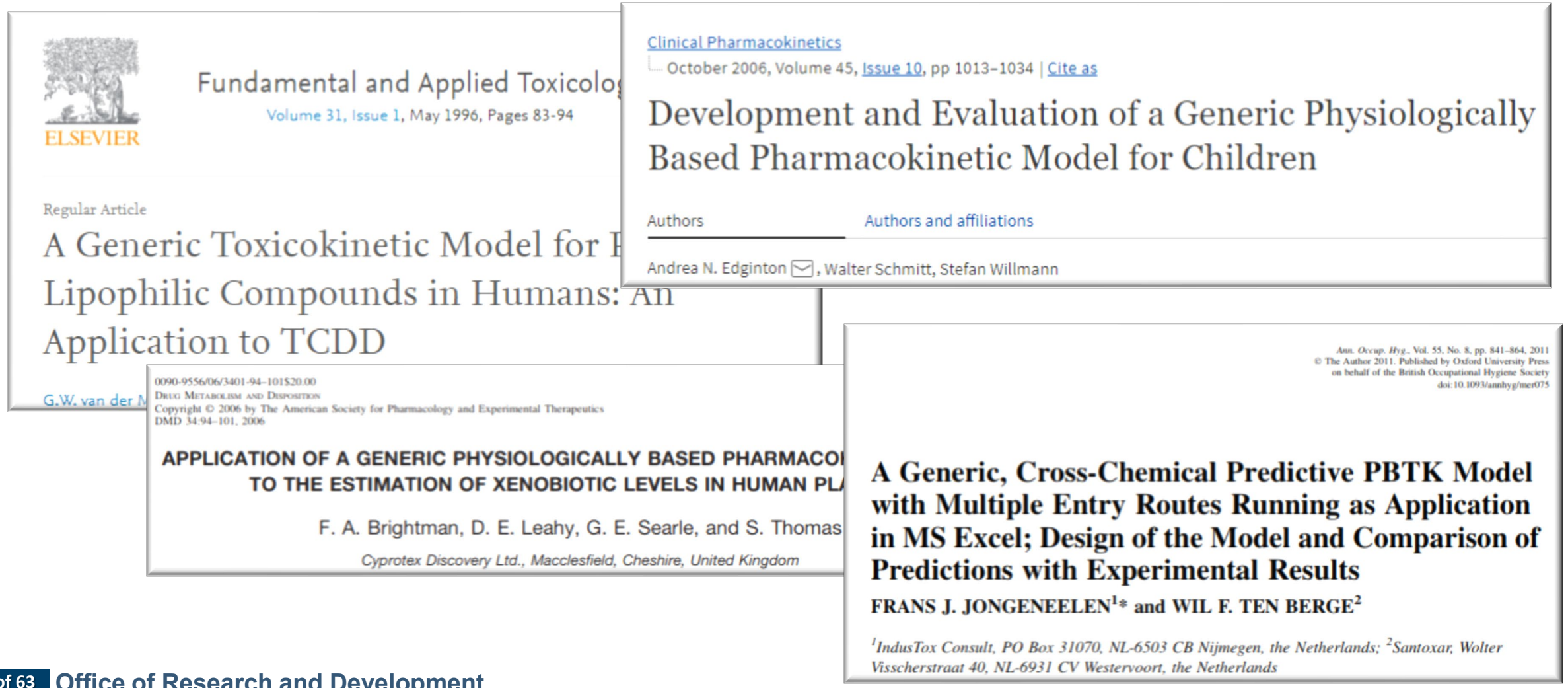

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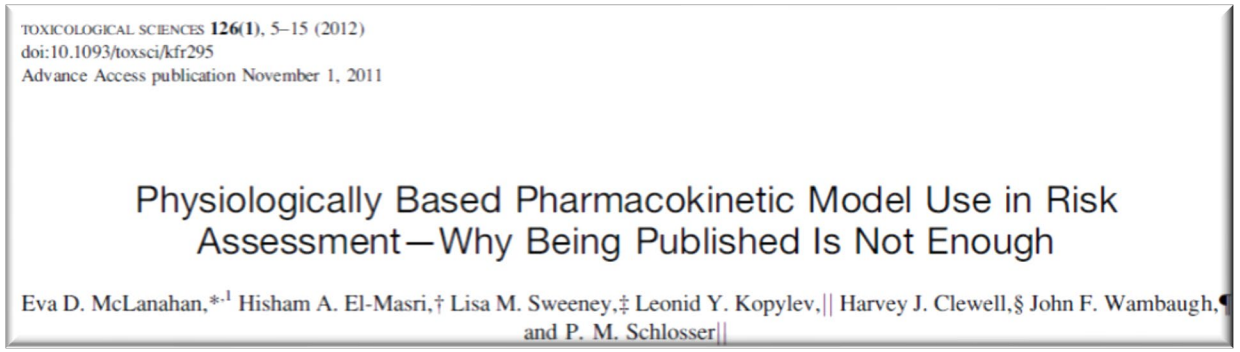
Ann. Occup. Hyg., Vol. 55, No. 8, pp. 841–864, 2011
© The Author 2011. Published by Oxford University Press on behalf of the British Occupational Hygiene Society
doi:10.1093/annhyg/mer075

A Generic, Cross-Chemical Predictive PBTK Model with Multiple Entry Routes Running as Application in MS Excel; Design of the Model and Comparison of Predictions with Experimental Results

FRANS J. JONGENEELEN[1]* and WIL F. TEN BERGE[2]

[1]IndusTox Consult, PO Box 31070, NL-6503 CB Nijmegen, the Netherlands; [2]Santoxar, Wolter Visscherstraat 40, NL-6931 CV Westervoort, the Netherlands

Open Source, Verifiable, Reproducible

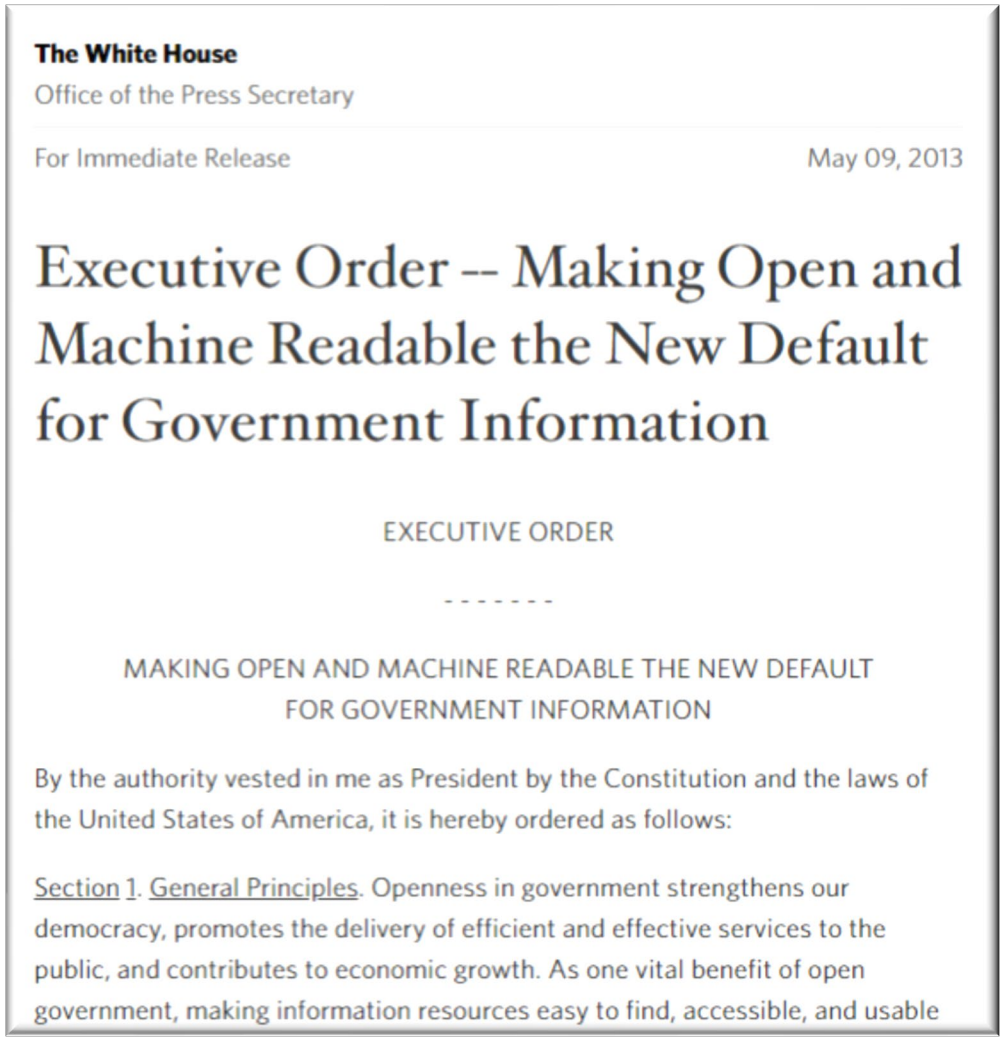


TOXICOLOGICAL SCIENCES 126(1), 5–15 (2012)
doi:10.1093/toxsci/kfr295
Advance Access publication November 1, 2011

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

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

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



The White House

Office of the Press Secretary

For Immediate Release May 09, 2013

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

EXECUTIVE ORDER

- - - - - - -

MAKING OPEN AND MACHINE READABLE THE NEW DEFAULT FOR GOVERNMENT INFORMATION

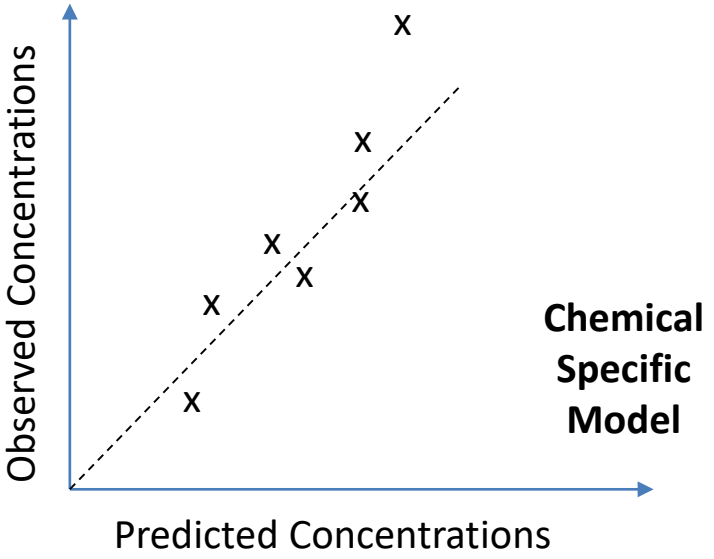
By the authority vested in me as President by the Constitution and the laws of the United States of America, it is hereby ordered as follows:

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

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

Building Confidence in TK Models

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



Cohen Hubal et al. (2018)

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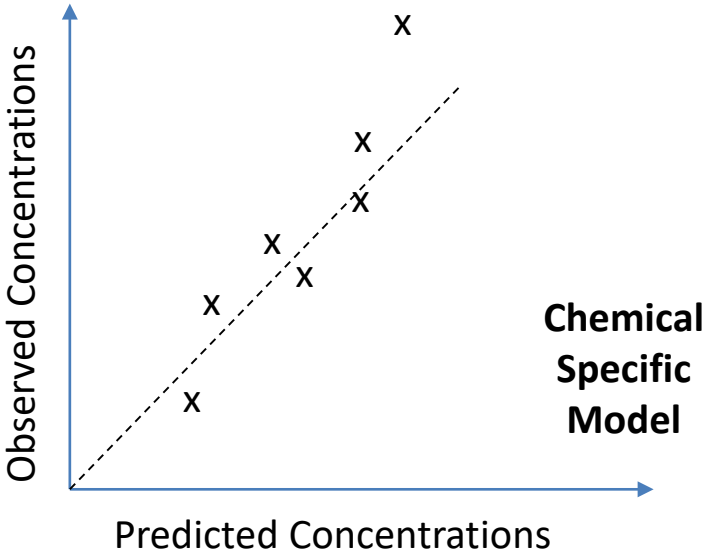
- However, we do not typically have TK data



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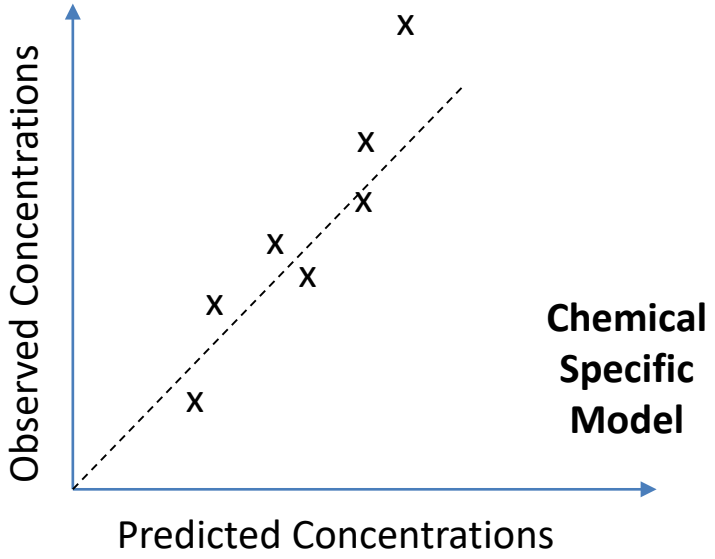

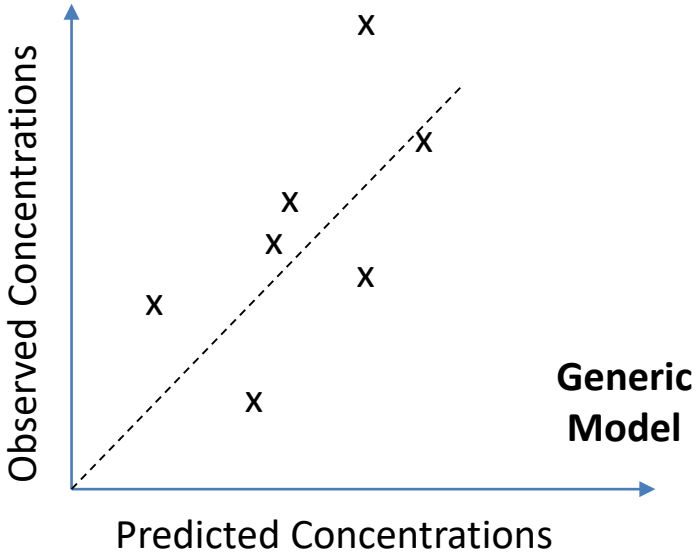

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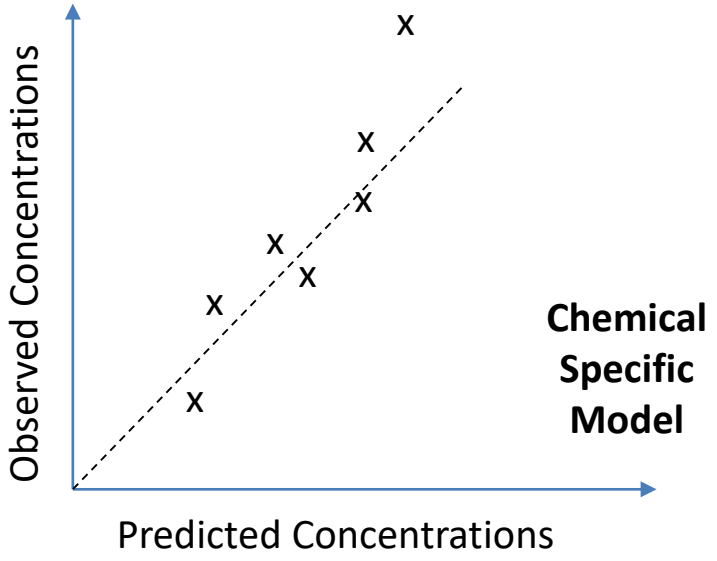

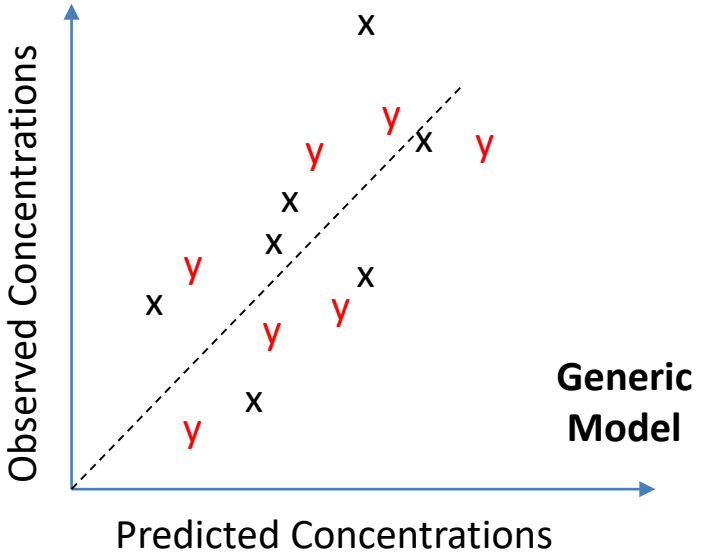

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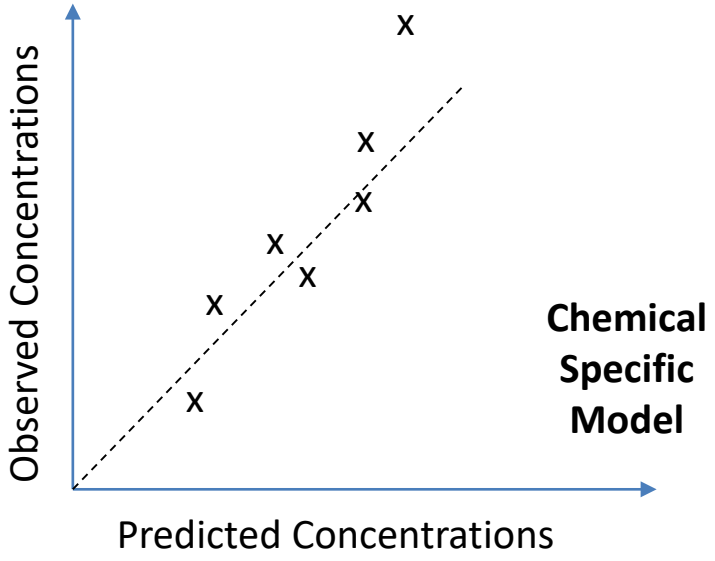
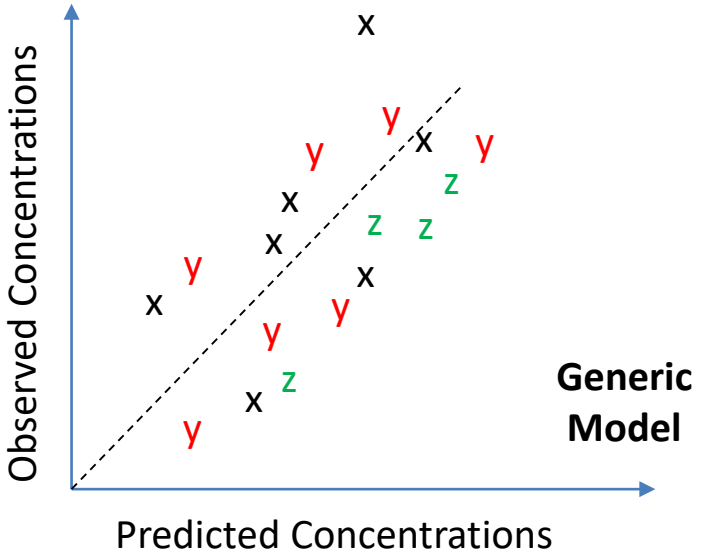


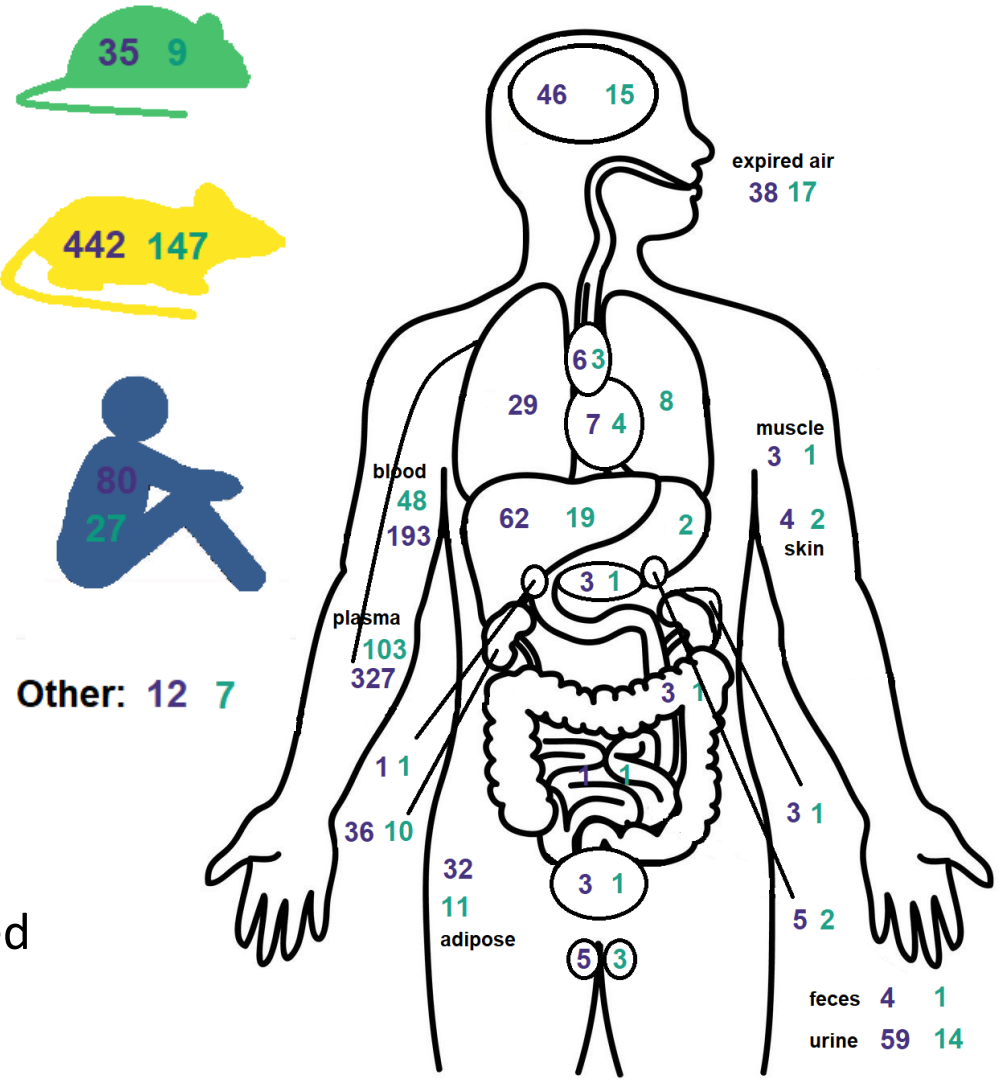


Cohen Hubal et al. (2018)

In Vivo TK Database

- EPA is developing a **public database** of **concentration vs. time data** for building, calibrating, and evaluating TK models
- Curation and development ongoing, but to date includes:
  - 198 analytes (EPA, National Toxicology Program, literature)
  - Routes: Intravenous, dermal, oral, sub-cutaneous, and inhalation exposure
- Database will be made available through web interface and through the “httk” R package
- Standardized, open source curve fitting software invivoPKfit used to calibrate models to all data:

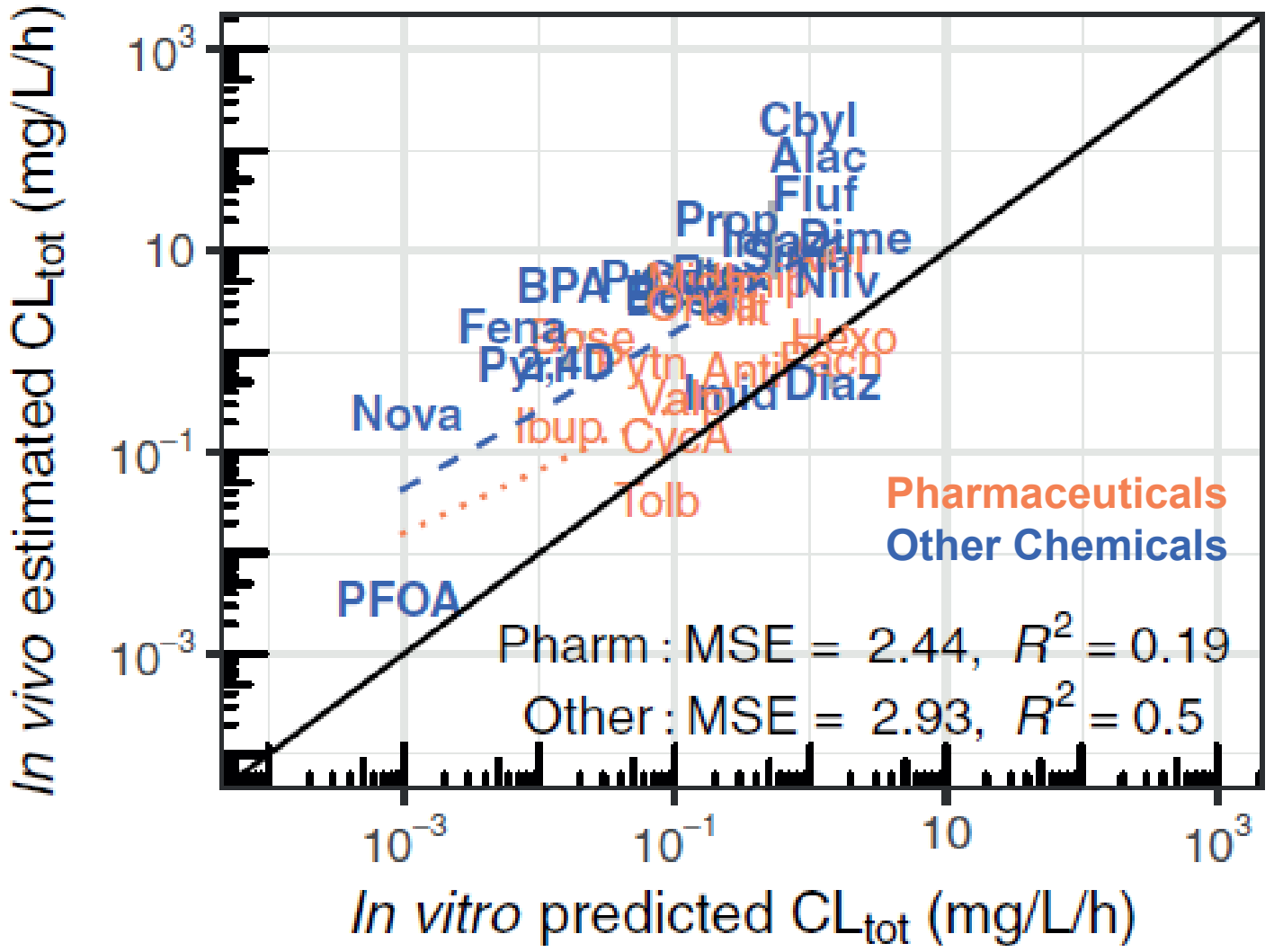
  https://github.com/USEPA/CompTox-ExpoCast-invivoPKfit



Sayre et al. (in clearance)

Observed Total Clearance

- We estimate clearance from two processes – hepatic metabolism (liver) and passive glomerular filtration (kidney)
- This appears to work better for pharmaceuticals than other chemicals:
  - ToxCast chemicals are overestimated
- Non-pharmaceuticals may be subject to extrahepatic metabolism and/or active transport



Wambaugh et al. (2018)

Uncertainty

Until I open the box, I don't know what colors I have...

...especially if my six-year-old has been around.

Variability

Different crayons have different colors…

Variability

Different crayons have different colors, and none of them are the "average" color

Population simulator for HTTK

Correlated Monte Carlo sampling of physiological model parameters built into R “httk” package (Pearce et al., 2017):

Sample NHANES biometrics for actual individuals:

- Sex
- Race/ethnicity
- Age
- Height
- Weight
- Serum creatinine

Slide from Caroline Ring (ToxStrategies)

Ring *et al.* (2017)

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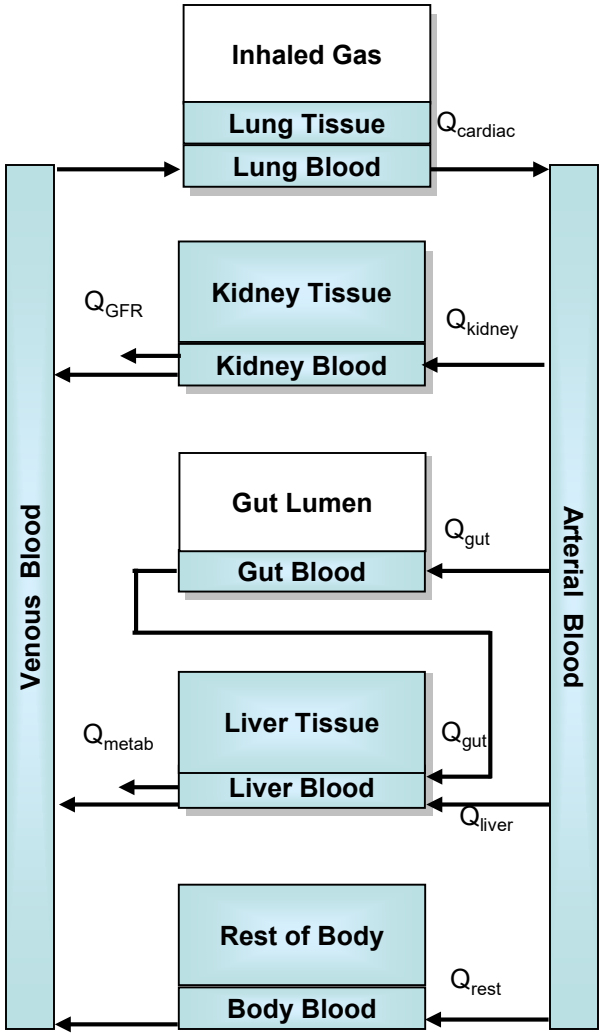
Predict physiological quantities

Tissue masses
Tissue blood flows
GFR (kidney function)
Hepatocellularity

Slide from Caroline Ring (ToxStrategies)

Ring *et al.* (2017)

A General Physiologically-based Toxicokinetic (PBTK) Model



- "httk" includes a generic PBTK model
- Some tissues (e.g. arterial blood) are simple compartments, while others (e.g. kidney) are compound compartments consisting of separate blood and tissue sections with constant partitioning (i.e., tissue specific partition coefficients)
- Exposures are absorbed from reservoirs (gut lumen)
- Some specific tissues (lung, kidney, gut, and liver) are modeled explicitly, others (e.g. 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).

Using the PBPK Solver Directly

➢ `solve_pbtk(chem.name="bisphenol a")`

```
Human values returned in uM units.
AUC is area under plasma concentration curve in uM * days units with Rblood2plasma = 0.79 .
```

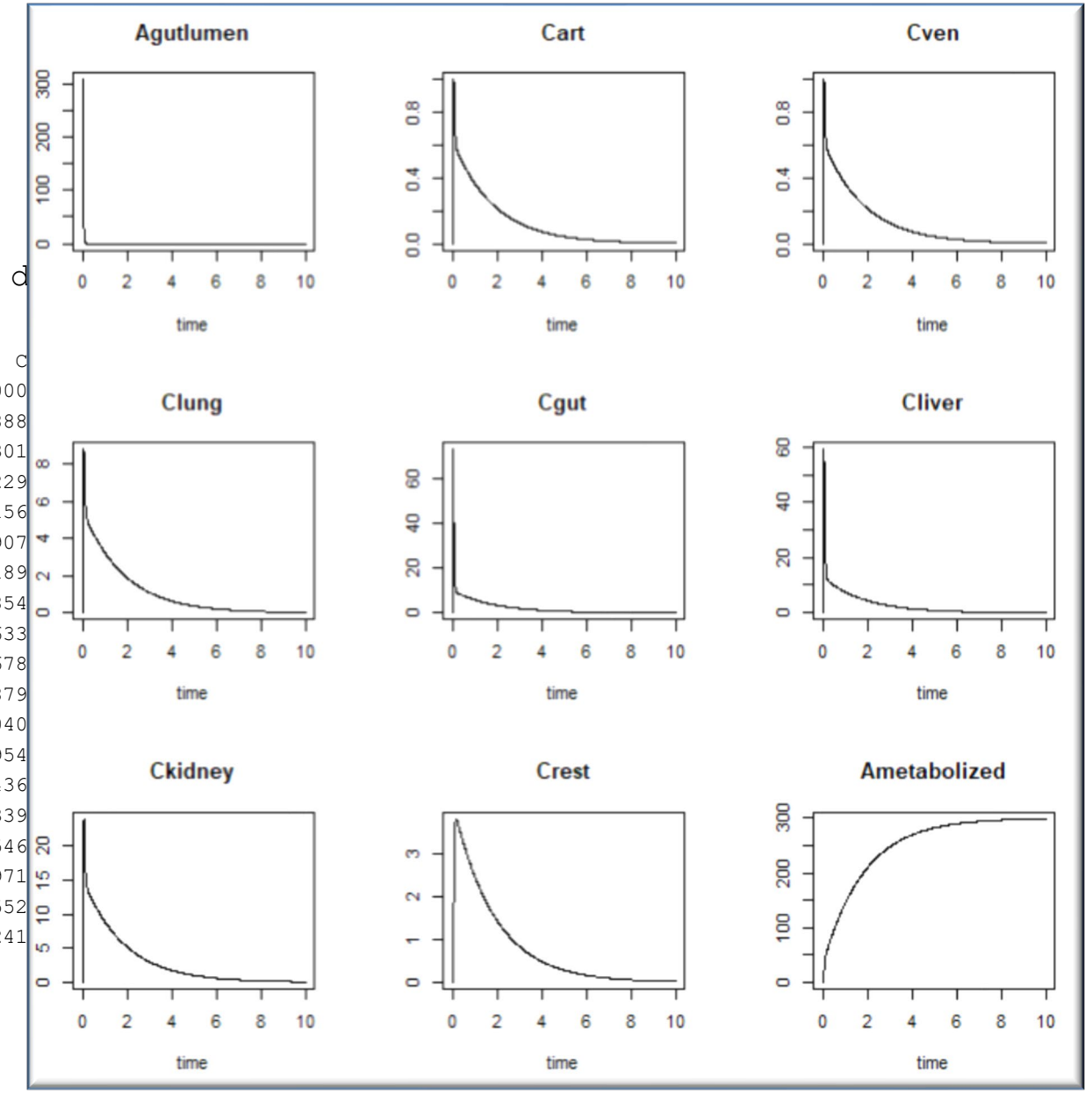
	time	Agutlumen	Cart	Cven	Clung	Cgut	Cliver	Ckidney	Crest	Ametabolized	Atubules	Cplasma	AUC
1	0.00000000	3.066262e+02	0.000000000	0.000000000	0.00000000	0.00000000	0.00000000	0.00000000	0.00000000	0.000000	0.000000000	0.000000000	0.000000000
2	0.01041667	1.777946e+02	0.252404604	0.289357401	2.34961222	71.95247714	23.88887805	3.17239051	0.06633834	1.103540	0.001965999	0.366275191	0.001415222
3	0.02083333	1.030928e+02	0.663546801	0.692443919	5.95361948	72.94086101	49.30121077	12.53395472	0.41370538	5.477242	0.019805484	0.876511290	0.008020654
4	0.03125000	5.977750e+01	0.910686939	0.923595117	8.08203766	59.24553284	59.22914959	20.03511570	0.97336122	11.891203	0.058155028	1.169107743	0.018881627
5	0.04166667	3.466149e+01	0.994369826	0.996290830	8.78392675	45.57617061	58.15644856	23.47916048	1.58728598	18.754595	0.109072218	1.261127633	0.031675711
6	0.05208333	2.009818e+01	0.981524867	0.977956640	8.65208184	34.88429585	51.90784716	23.99286252	2.15118704	25.147879	0.164256077	1.237919798	0.044758176
7	0.06250000	1.165377e+01	0.926013496	0.920482876	8.15543311	27.11616810	44.18962567	23.00423256	2.62028642	30.707988	0.218657261	1.165168198	0.057297100
8	0.07291667	6.757339e+00	0.859093229	0.853432034	7.56423243	21.62793934	36.85482136	21.46883885	2.98678435	35.386289	0.270011356	1.080293714	0.068992681
9	0.08333333	3.918189e+00	0.795826455	0.790823076	7.00793962	17.79524147	30.63396494	19.89308327	3.26066390	39.277132	0.317711616	1.001041868	0.079823984
10	0.09375000	2.271930e+00	0.741984727	0.737874203	6.53564219	15.13140336	25.67820521	18.49771463	3.45816558	42.521813	0.361960026	0.934017979	0.089890783
11	0.10416667	1.317360e+00	0.698658233	0.695416151	6.15609013	13.28227465	21.87980008	17.34966522	3.59596179	45.261901	0.403270191	0.880273609	0.099329065
12	0.11458333	7.638604e-01	0.664880689	0.662381169	5.86041120	11.99714143	19.04089773	16.44307537	3.68868577	47.620183	0.442214748	0.838457176	0.108271310
13	0.12500000	4.429182e-01	0.638989326	0.637082881	5.63384704	11.10081093	16.95420599	15.74336009	3.74820158	49.695527	0.479313885	0.806434026	0.116830921
14	0.13541667	2.568224e-01	0.619267632	0.617815518	5.46128059	10.47174511	15.43657309	15.20907954	3.78368216	51.564032	0.514997202	0.782044959	0.125098496
15	0.14583333	1.489164e-01	0.604208820	0.603095237	5.32948738	10.02601172	14.33906095	14.80163868	3.80200220	53.282565	0.549600846	0.763411692	0.133143464
16	0.15625000	8.634796e-02	0.592592053	0.591725876	5.22777312	9.70583761	13.54631982	14.48876481	3.80820273	54.892746	0.583379000	0.749020097	0.141017591
17	0.16666667	5.006815e-02	0.583474067	0.582786199	5.14788498	9.47155766	12.97181396	14.24503448	3.80592168	56.424569	0.616519237	0.737704050	0.148758699
18	0.17708333	2.903162e-02	0.576148301	0.575587653	5.08364620	9.29599319	12.55204217	14.05115505	3.79775308	57.899409	0.649157738	0.728591965	0.156394049
19	0.18750000	1.683374e-02	0.570096828	0.569626301	5.03053172	9.16055179	12.24115055	13.89285375	3.78552942	59.332367	0.681392276	0.721045950	0.163943113

Using the PBPK Solver Directly

➢ `solve_pbtk(chem.name="bisphenol a", plots=TRUE)`

```
Human values returned in uM units.
AUC is area under plasma concentration curve in uM * d
```

	time	Agutlumen	Cart	Cven	Clung	Cgut	C
1	0.00000000	3.066262e+02	0.000000000	0.000000000	0.00000000	0.00000000	0.000
2	0.01041667	1.777946e+02	0.252404604	0.289357401	2.34961222	71.95247714	23.888
3	0.02083333	1.030928e+02	0.663546801	0.692443919	5.95361948	72.94086101	49.301
4	0.03125000	5.977750e+01	0.910686939	0.923595117	8.08203766	59.24553284	59.229
5	0.04166667	3.466149e+01	0.994369826	0.996290830	8.78392675	45.57617061	58.156
6	0.05208333	2.009818e+01	0.981524867	0.977956640	8.65208184	34.88429585	51.907
7	0.06250000	1.165377e+01	0.926013496	0.920482876	8.15543311	27.11616810	44.189
8	0.07291667	6.757339e+00	0.859093229	0.853432034	7.56423243	21.62793934	36.854
9	0.08333333	3.918189e+00	0.795826455	0.790823076	7.00793962	17.79524147	30.633
10	0.09375000	2.271930e+00	0.741984727	0.737874203	6.53564219	15.13140336	25.678
11	0.10416667	1.317360e+00	0.698658233	0.695416151	6.15609013	13.28227465	21.879
12	0.11458333	7.638604e-01	0.664880689	0.662381169	5.86041120	11.99714143	19.040
13	0.12500000	4.429182e-01	0.638989326	0.637082881	5.63384704	11.10081093	16.954
14	0.13541667	2.568224e-01	0.619267632	0.617815518	5.46128059	10.47174511	15.436
15	0.14583333	1.489164e-01	0.604208820	0.603095237	5.32948738	10.02601172	14.339
16	0.15625000	8.634796e-02	0.592592053	0.591725876	5.22777312	9.70583761	13.546
17	0.16666667	5.006815e-02	0.583474067	0.582786199	5.14788498	9.47155766	12.971
18	0.17708333	2.903162e-02	0.576148301	0.575587653	5.08364620	9.29599319	12.552
19	0.18750000	1.683374e-02	0.570096828	0.569626301	5.03053172	9.16055179	12.241



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Multiple Ways to Use Functions

By chemical name:

```
calc_analytic_css(chem.name="bisphenol a",model="pbtk")
```

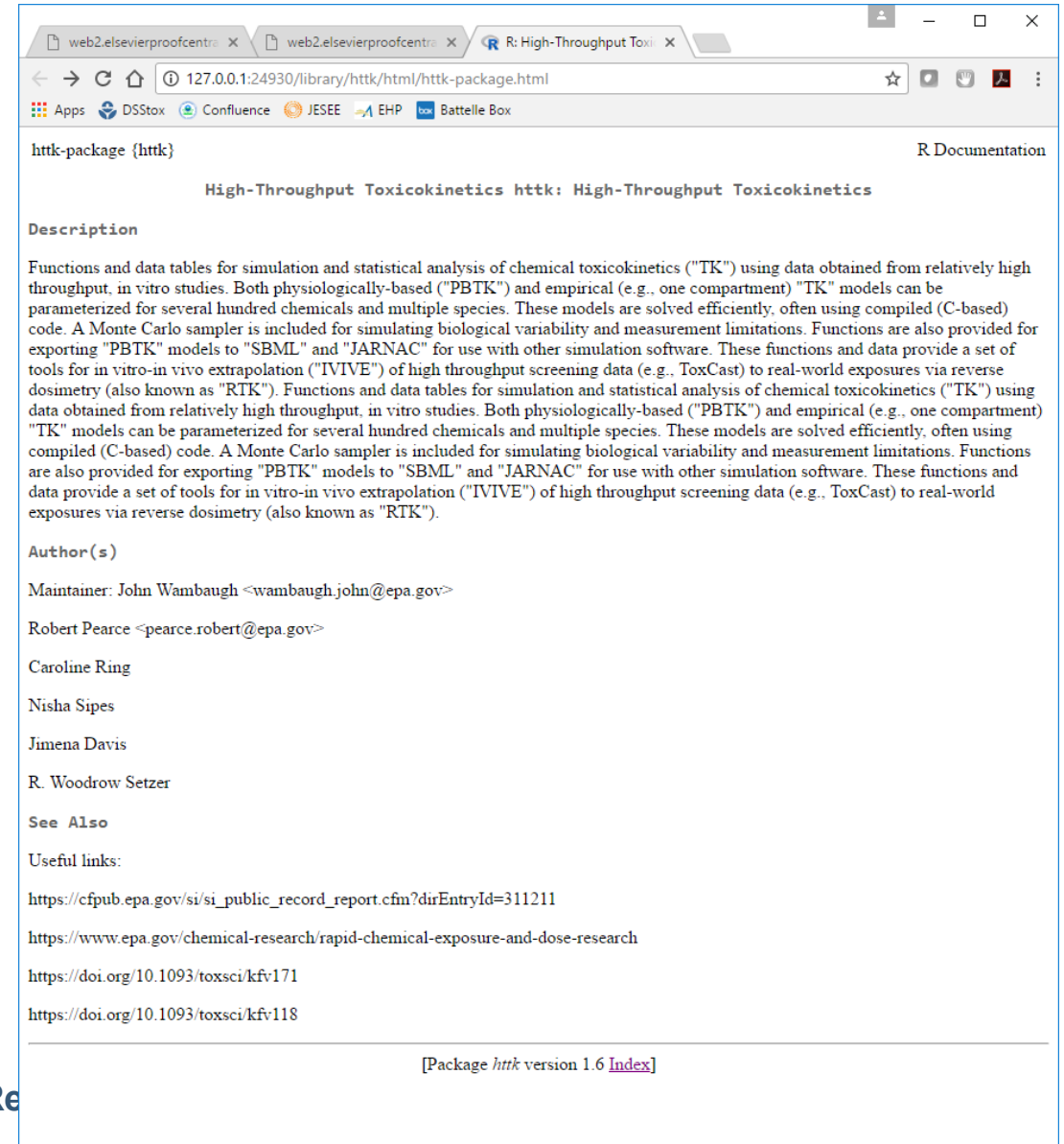
By chemical CAS:

```
calc_analytic_css(chem.cas="80-05-7",model="pbtk")
```

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")
```

Getting Help:
Within R: type "help(httk)"



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").

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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

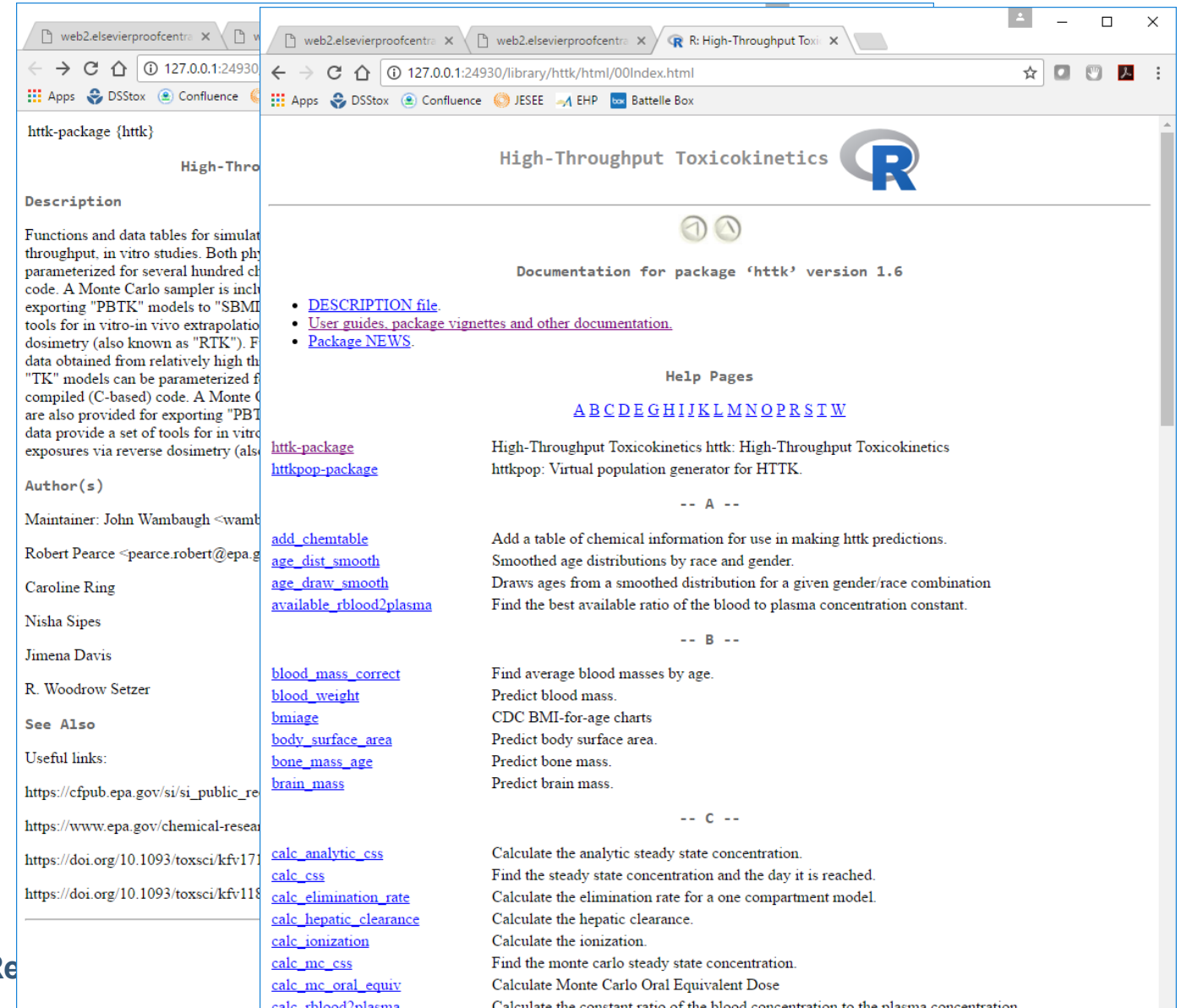
https://www.epa.gov/chemical-research/rapid-chemical-exposure-and-dose-research

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

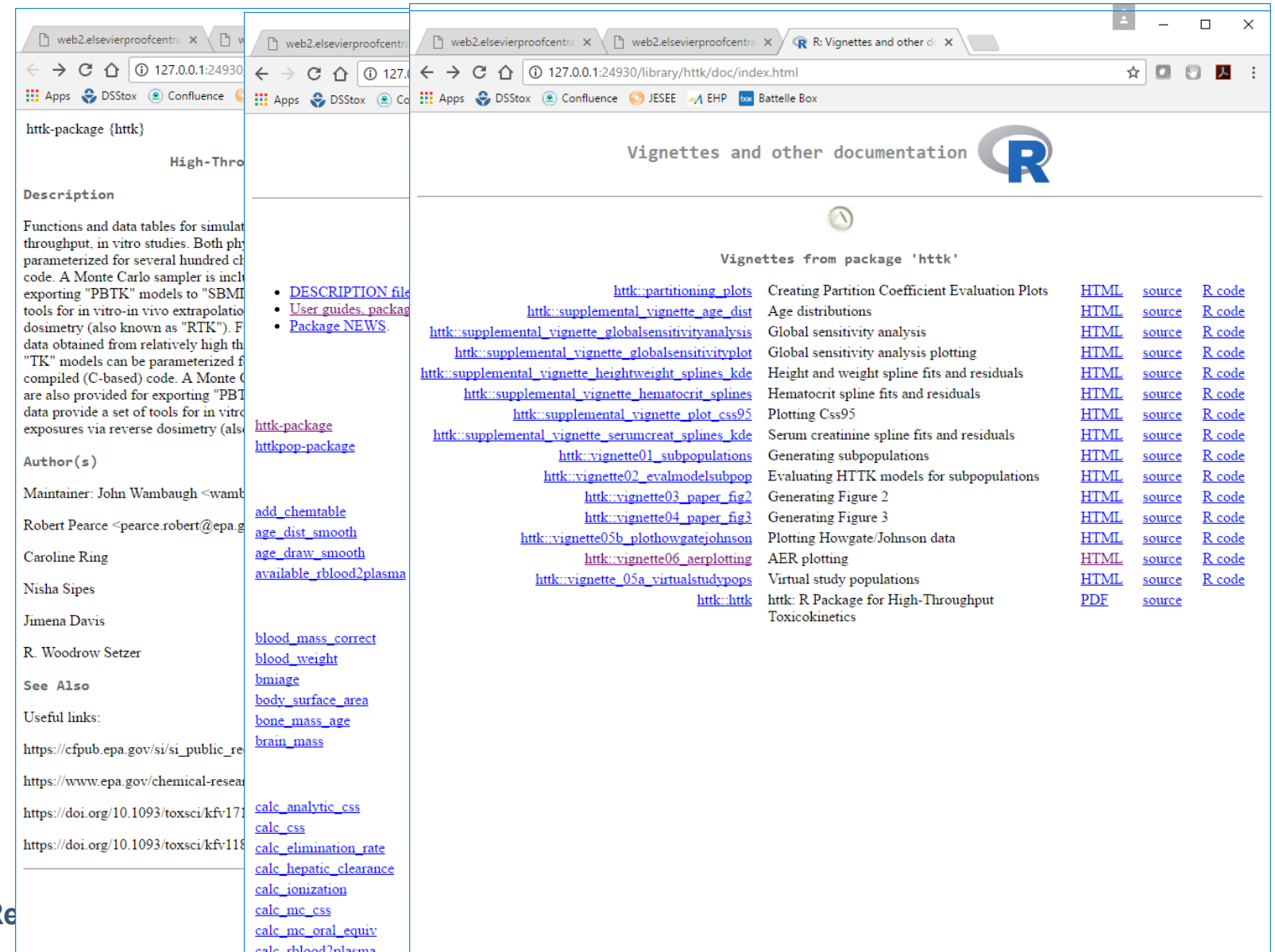
https://doi.org/10.1093/toxsci/kfv118

[Package *httk* version 1.6 Index]

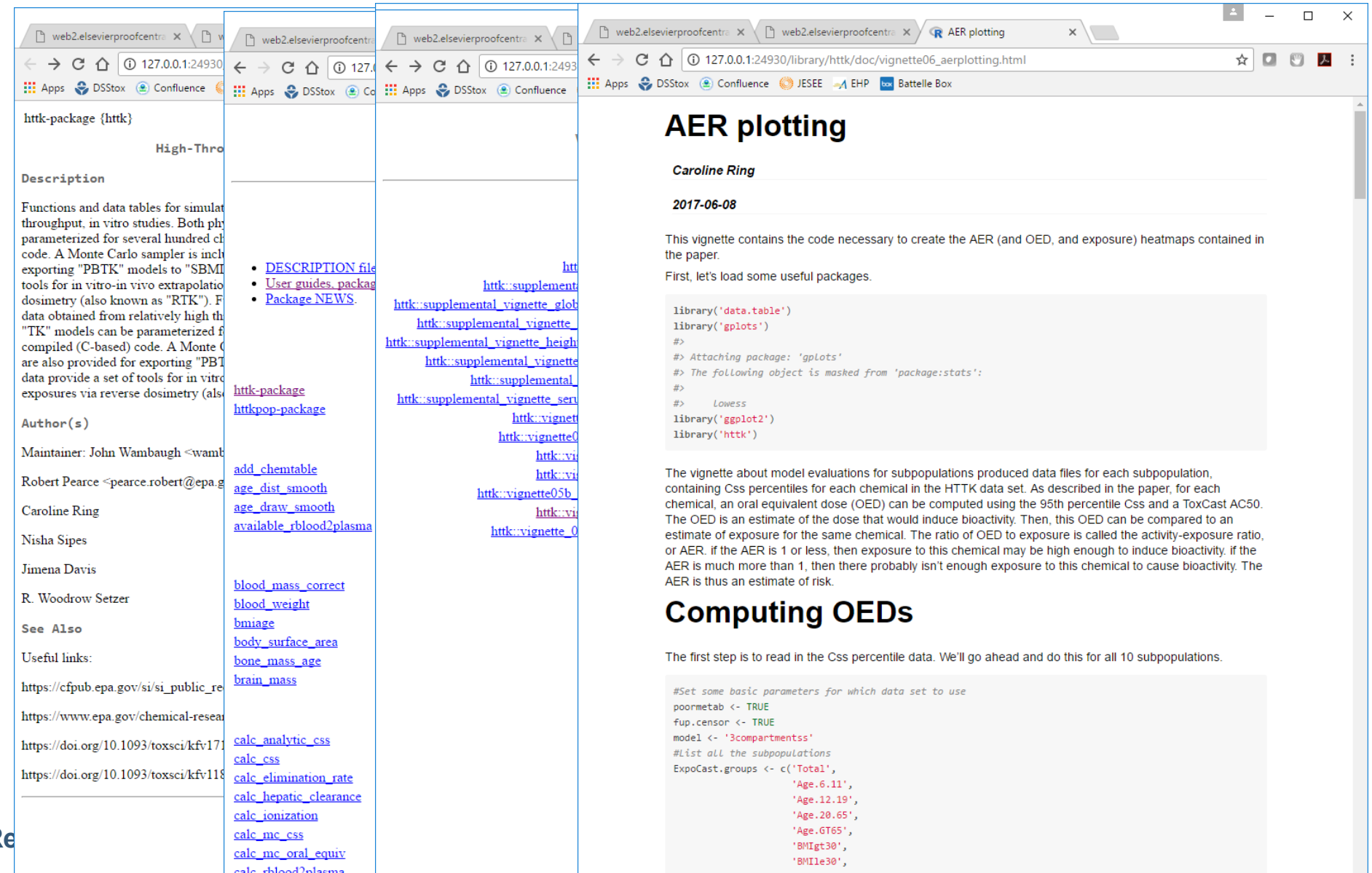
Getting Help:
Within R: type "help(httk)"



Getting Help:
Within R: type "help(httk)"



Getting Help:
Within R: type "help(httk)"



Getting Help:

Within R: type "help(httk)"

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

Vignettes

- R packages can include vignettes which give examp on how to use the package
- "httk" includes step-by-step walkthroughs allowing you recreate figures from paper that used HTTK

Reference manual: httk.pdf

Vignettes:

- Honda et al. (2019): Updated Armitage et al. (2014) Model
- Pearce et al. (2017) Creating Partition Coefficient Evaluation Plots
- Ring et al. (2017) Age distributions
- Ring et al. (2017) Global sensitivity analysis
- Ring et al. (2017) Global sensitivity analysis plotting
- Ring et al. (2017) Height and weight spline fits and residuals
- Ring et al. (2017) Hematocrit spline fits and residuals
- Ring et al. (2017) Plotting Css95
- Ring et al. (2017) Serum creatinine spline fits and residuals
- Ring et al. (2017) Generating subpopulations
- Ring et al. (2017) Evaluating HTTK models for subpopulations
- Ring et al. (2017) Generating Figure 2
- Ring et al. (2017) Generating Figure 3
- Ring et al. (2017) Plotting Howgate/Johnson data
- Ring et al. (2017) AER plotting
- Ring et al. (2017) Virtual study populations
- Wambaugh et al. (2018): Creating All Figures
- Wambaugh et al. (submitted): Creating Figures for the Manuscript

See also Pearce et al. (2017): https://10.18637/jss.v079.i04

IVIVE with HTTK: Franke 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
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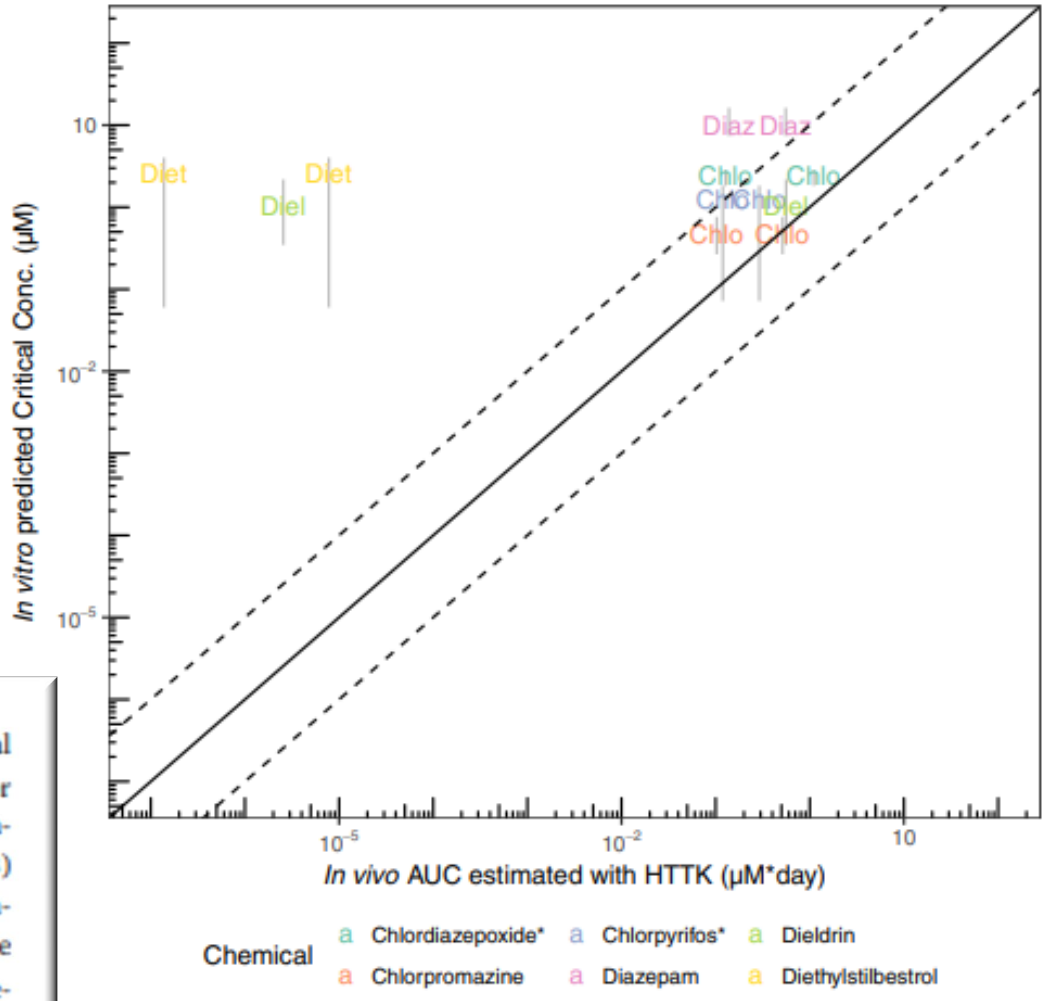
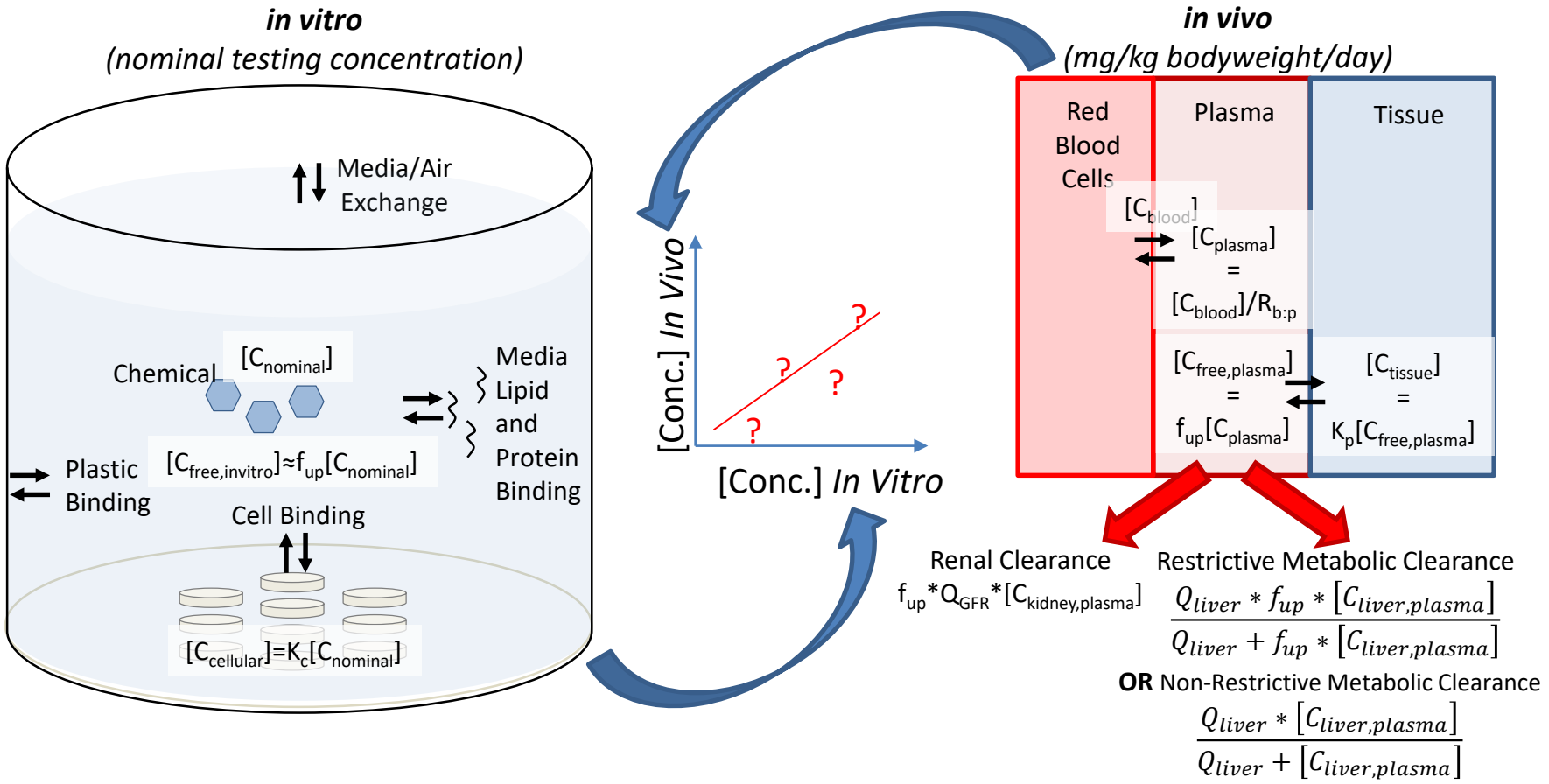


Fig. 6. Comparison between predicted plasma levels for critical concentrations and *in vivo* estimates from the httk model. For those chemicals with 1) *in vitro* predicted critical concentrations, 2) *in vivo* studies indicating neurological effect, and 3) available toxicokinetic data the time-integrated 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.

There Are Many Considerations When Doing IVIVE

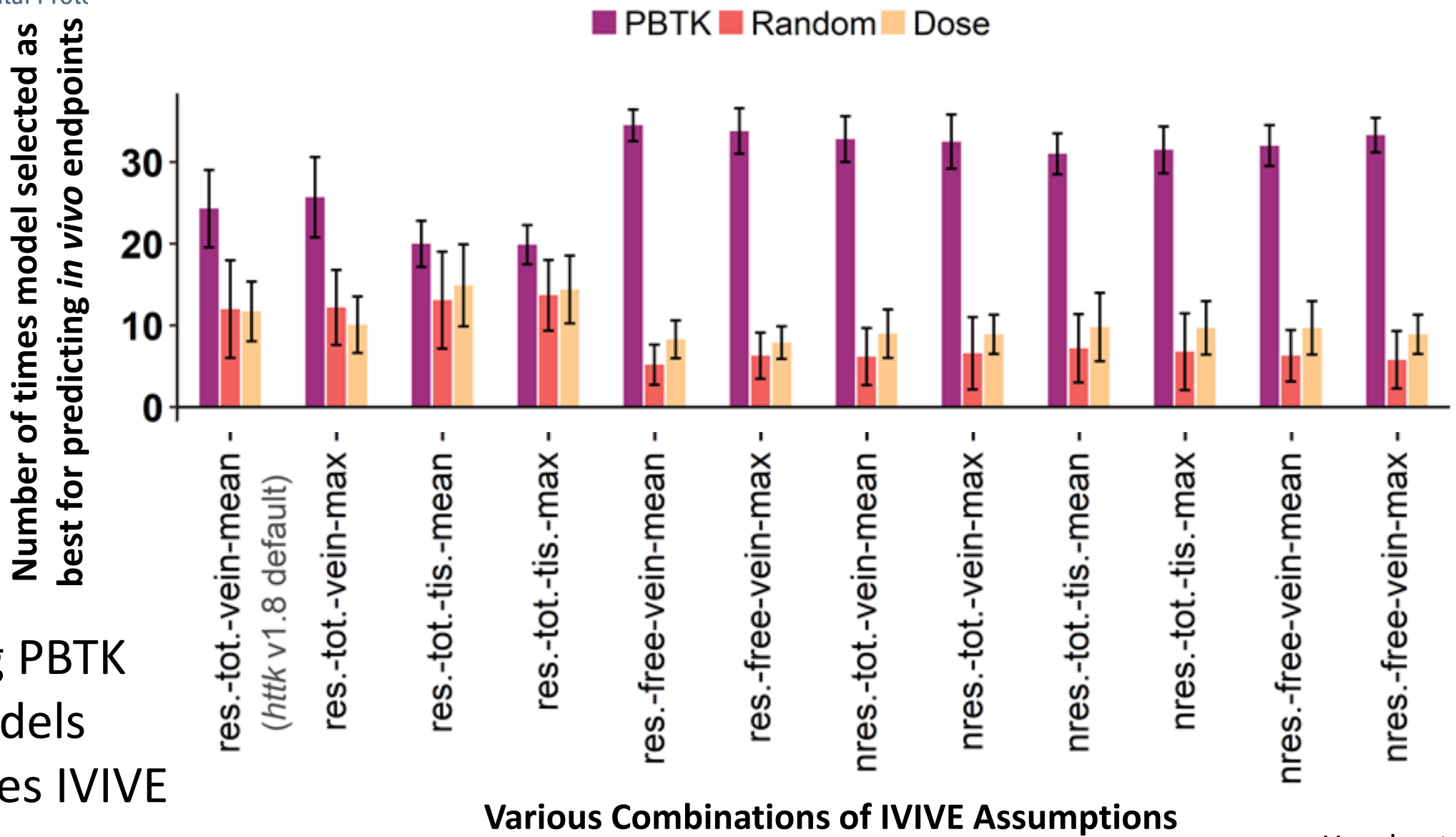
Using the generic HTTK physiologically based toxicokinetics model to inform IVIVE…



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

Honda et al. (2019)

Optimizing HTTK-based IVIVE



Using PBTK Models Improves IVIVE

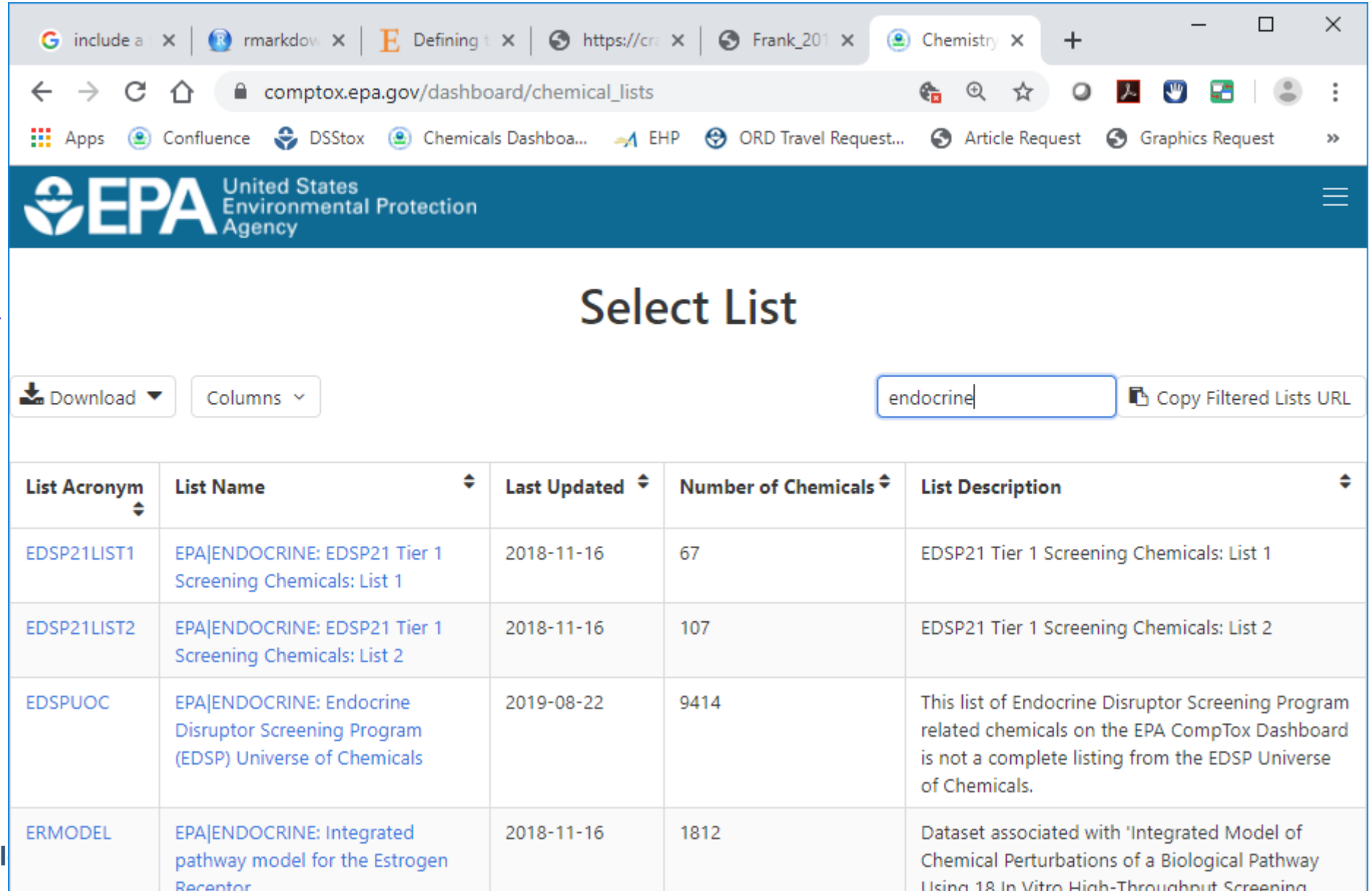
Honda et al. (2019)

"IVIVE-Example.R": Using IVIVE to Prioritize

STEP ONE:

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

Select the "EDSP21LIST1"



List Acronym	List Name	Last Updated	Number of Chemicals	List Description
EDSP21LIST1	EPA|ENDOCRINE: EDSP21 Tier 1 Screening Chemicals: List 1	2018-11-16	67	EDSP21 Tier 1 Screening Chemicals: List 1
EDSP21LIST2	EPA|ENDOCRINE: EDSP21 Tier 1 Screening Chemicals: List 2	2018-11-16	107	EDSP21 Tier 1 Screening Chemicals: List 2
EDSPUOC	EPA|ENDOCRINE: Endocrine Disruptor Screening Program (EDSP) Universe of Chemicals	2019-08-22	9414	This list of Endocrine Disruptor Screening Program related chemicals on the EPA CompTox Dashboard is not a complete listing from the EDSP Universe of Chemicals.
ERMODEL	EPA|ENDOCRINE: Integrated pathway model for the Estrogen Receptor	2018-11-16	1812	Dataset associated with 'Integrated Model of Chemical Perturbations of a Biological Pathway Using 18 In Vitro High-Throughput Screening

"IVIVE-Example.R": Using IVIVE to Prioritize

STEP ONE:

Load the ToxCast, then add in the CAS numbers so we can match chemicals:

```
toxcast <-
read.csv("ac50_Matrix_190708.csv",stringsAsFactors=F)

toxcast$CAS <- sapply(toxcast$X,function(x) paste(
  substr(x,2,nchar(x)-3),
  substr(x,nchar(x)-2,nchar(x)-1),
  substr(x,nchar(x),nchar(x)),
  sep="-"))

toxcast[regexpr("NOCAS",toxcast$CAS)!=-1,"CAS"] <-
  gsub("-","",toxcast[regexpr("NOCAS",toxcast$CAS)!=-1,"CAS"])
```

"IVIVE-Example.R": Using IVIVE to Prioritize

STEP ONE:

Load your chemicals of interest:

```
library(gdata)
#install.packages("gdata") if you don't have it

mychems <- read.xls("mychems.xls",stringsAsFactors=F)

head(mychems)

my.tox <- subset(toxcast,CAS%in%mychems$CASRN)

dim(my.tox)
dim(mychems)
```

"IVIVE-Example.R": Using IVIVE to Prioritize

STEP ONE: **Calculate the tenth percentile of the ToxCast AC50's:**

```
toxcast.start <- 2
toxcast.end <- 1474

my.tox$tenth <- apply(my.tox[,toxcast.start:toxcast.end],
                      1,
                      function(x) quantile(x,0.1,na.rm=T))

my.tox <- subset(my.tox,tenth<1e6)
my.tox <- my.tox[,c("CAS","tenth")]
my.tox <- merge(my.tox,mychems,by.x="CAS",by.y="CASRN")
```

"IVIVE-Example.R": Using IVIVE to Prioritize

STEP TWO:

Add the HTTK plasma steady-state concentration where available:

```
library(httk)
for (this.cas in my.tox$CAS)
{
  if (this.cas %in% get_cheminfo())
  {
    set.seed(12345)
    my.tox[my.tox$CAS==this.cas,"Css"] <-
      calc_mc_css(chem.cas=this.cas,output.units="uM")
    my.tox[my.tox$CAS==this.cas,"Css.Type"] <- "in vitro"
  }
}
my.tox[,c("PREFERRED_NAME","tenth","Css","Css.Type")]
```

"IVIVE-Example.R": Using IVIVE to Prioritize

STEP THREE: **Use the Sipes et al. (2017) QSAR numbers to fill in the rest:**

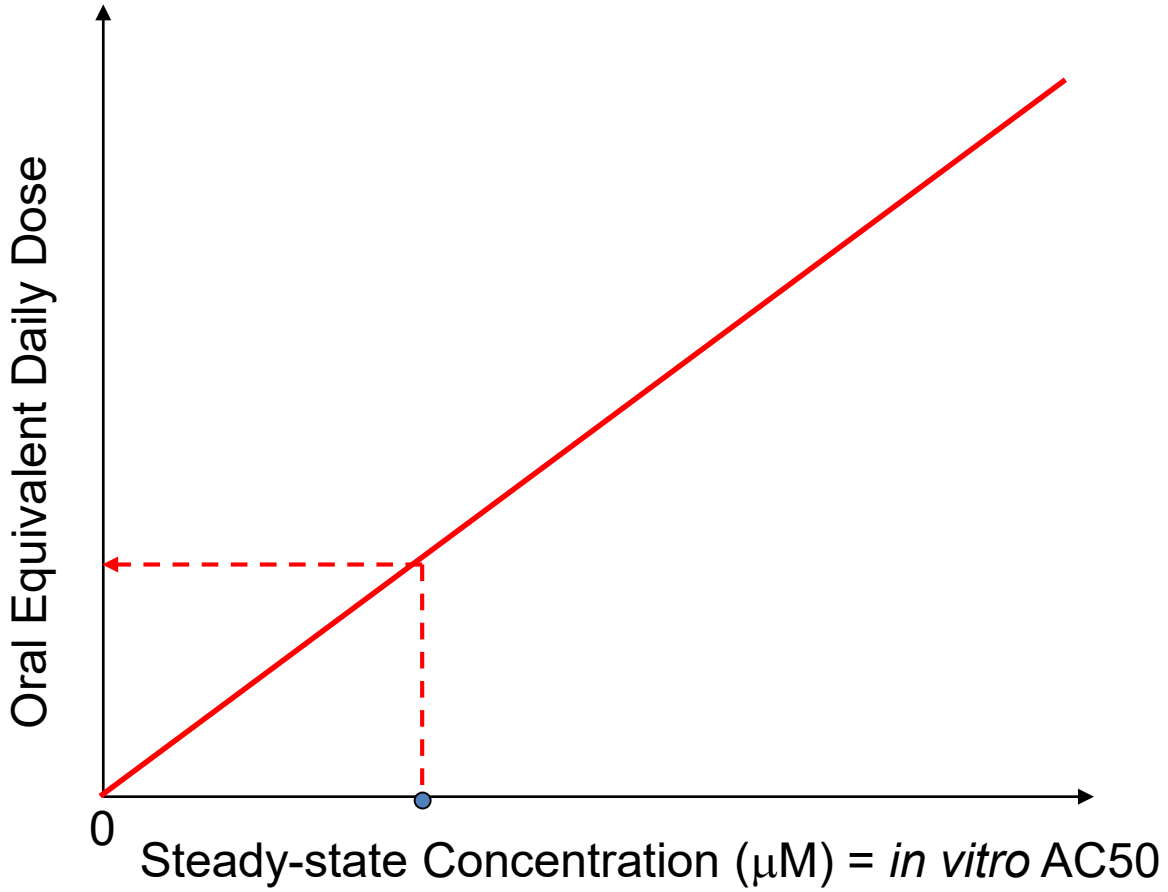
```
load_sipes2017()
for (this.cas in my.tox$CAS)
{
  if (this.cas %in% get_cheminfo() &
    is.na(my.tox[my.tox$CAS==this.cas,"Css"]))
  {
    set.seed(12345)
  my.tox[my.tox$CAS==this.cas,"Css"] <-
      calc_mc_css(chem.cas=this.cas,output.units="uM")
    my.tox[my.tox$CAS==this.cas,"Css.Type"] <- "in silico"
  }
}
my.tox[,c("PREFERRED_NAME","tenth","Css","Css.Type")]
```

"IVIVE-Example.R": Using IVIVE to Prioritize

STEP FOUR: **Calculate the equivalent steady-state dose (mg / kg bodyweight / day) to produce a plasma concentration equal to tenth percentile ToxCast AC50:**

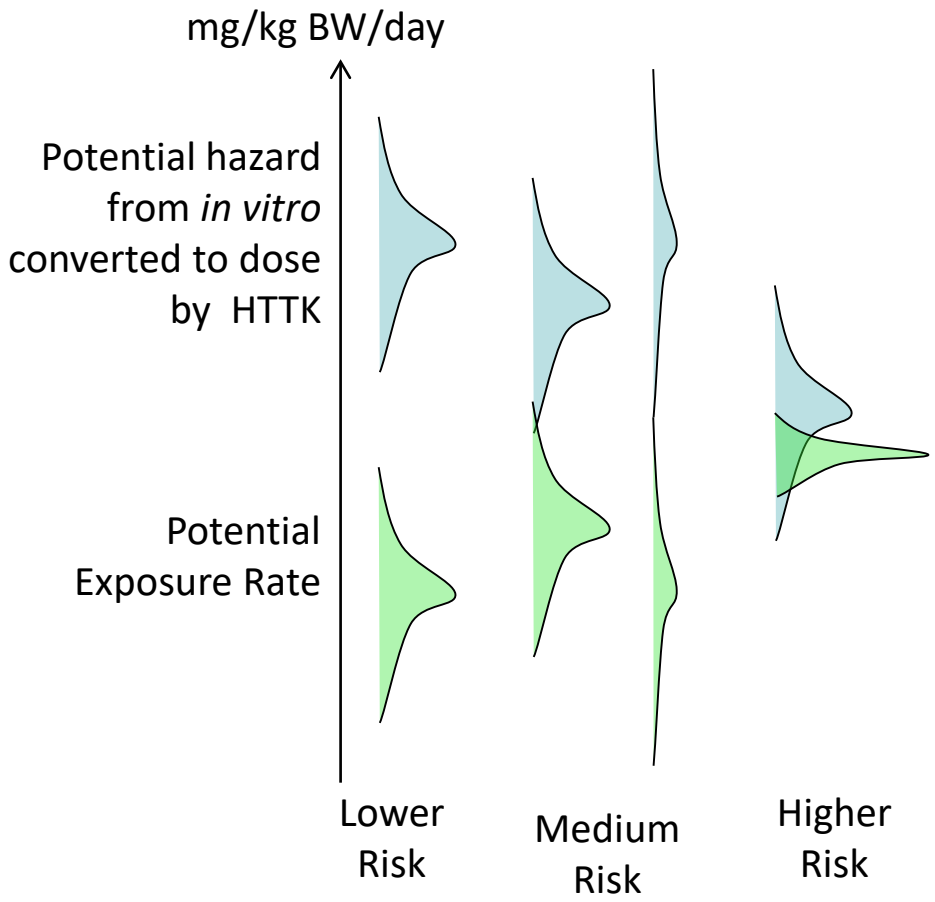
```
my.tox$EquivDose <-
my.tox$tenth / my.tox$Css

my.tox[,c("PREFERRED_NAME",
"tenth","EquivDose")]
```



Summary

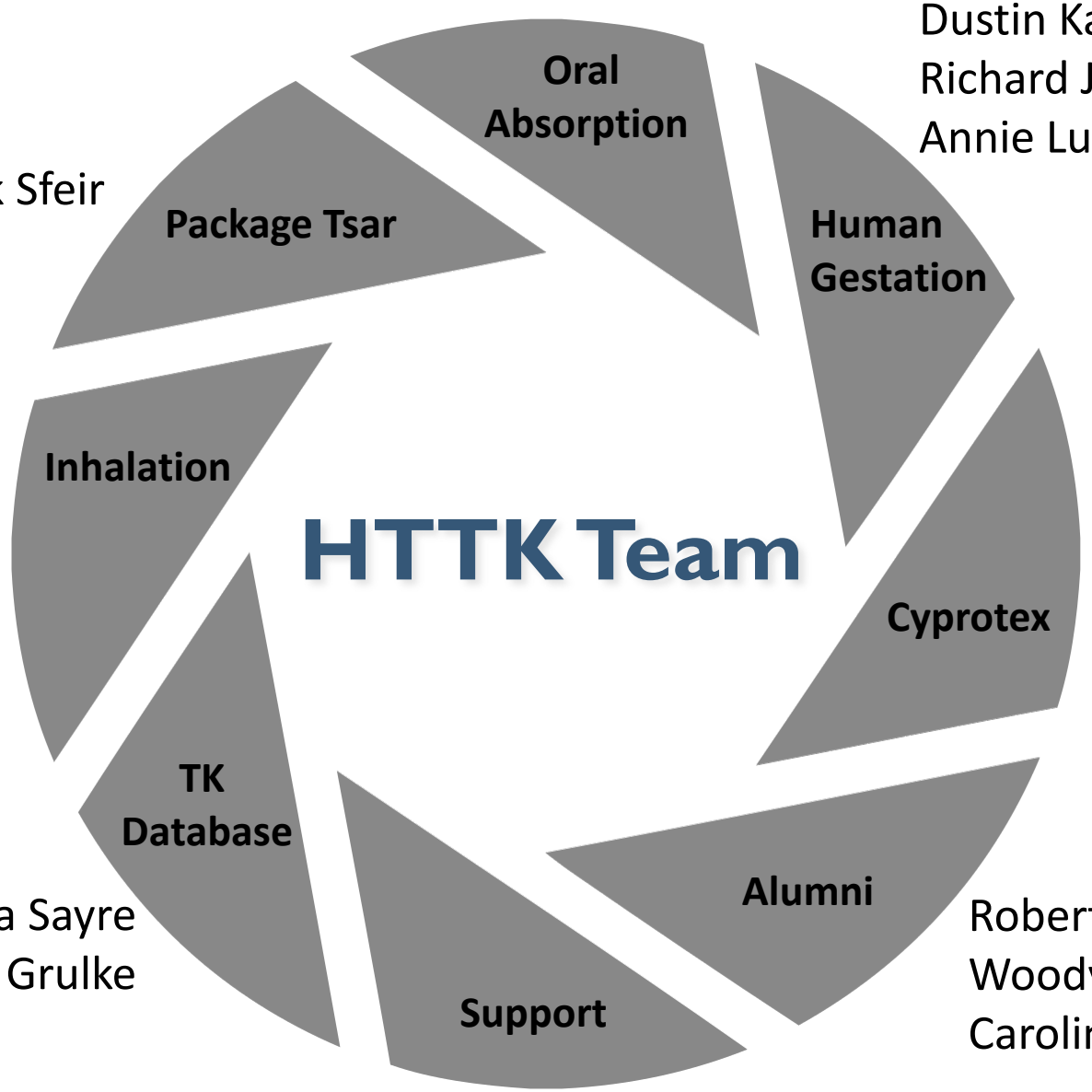
- We would like to know more about the risk posed by thousands of chemicals in the environment – which ones should we start with?
- We need data on absorption, distribution, metabolism and excretion -- HTTK (high throughput toxicokinetics) provides a generic model that can be developed with *in vitro* data
- HTTK new approach methodologies (NAMs) are being evaluated through comparison between *in vitro* predictions and *in vivo* measurements of both plasma concentrations and doses associated with the onset of effects



- NAMs for TK allow risk-based prioritization of large numbers of chemicals. 1

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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United States Environmental Protection Agency

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