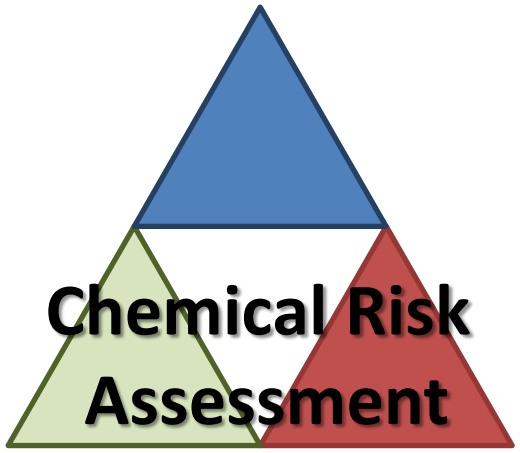
Bioactivity:Exposure Ratio Example
Comparing NAM-based PODs to Estimates of Human Daily Intake

NAMs Training Workshop

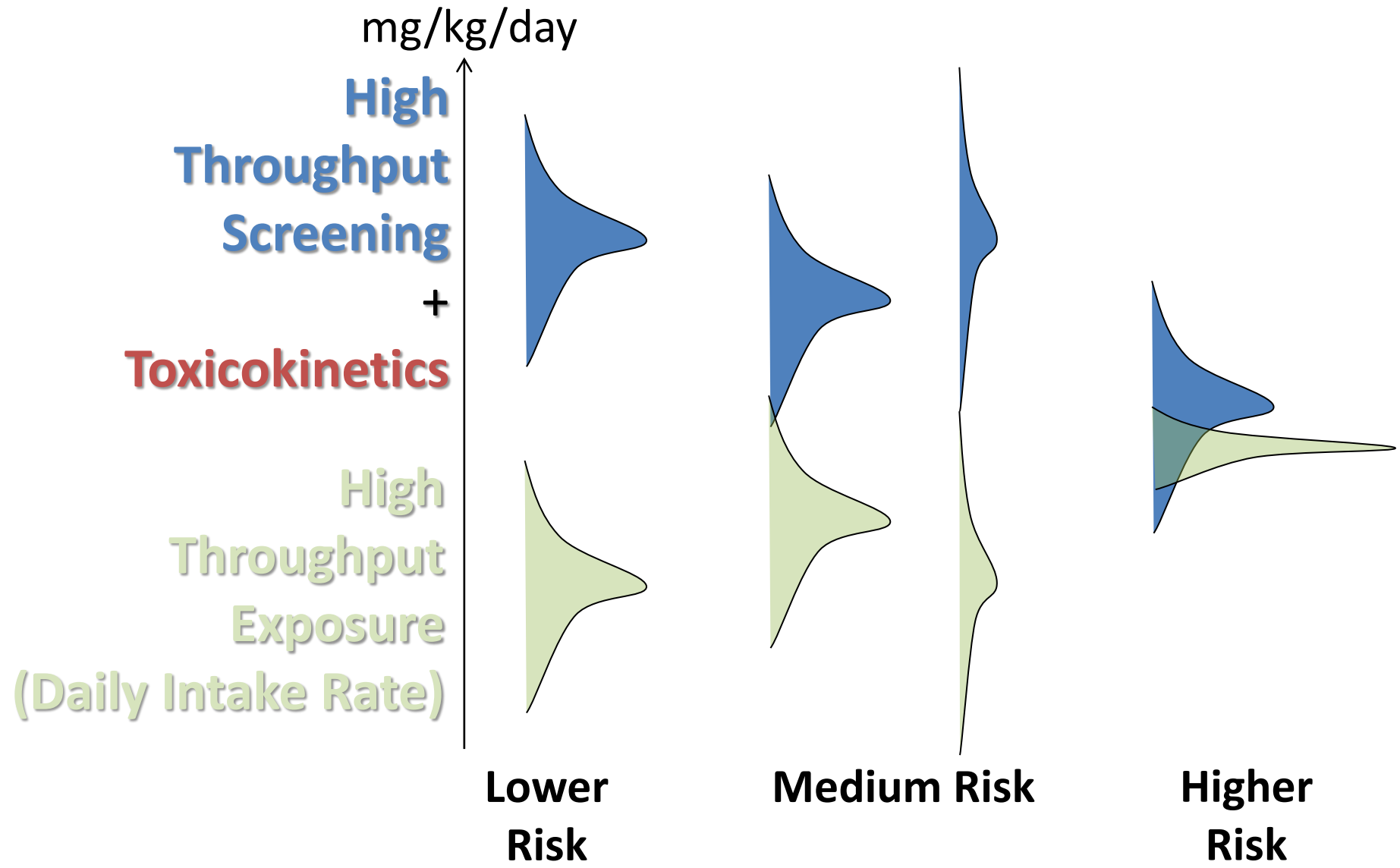
April 24th – 25th, 2024

John Wambaugh

Bioactivity : Exposure Ratios (BERs)

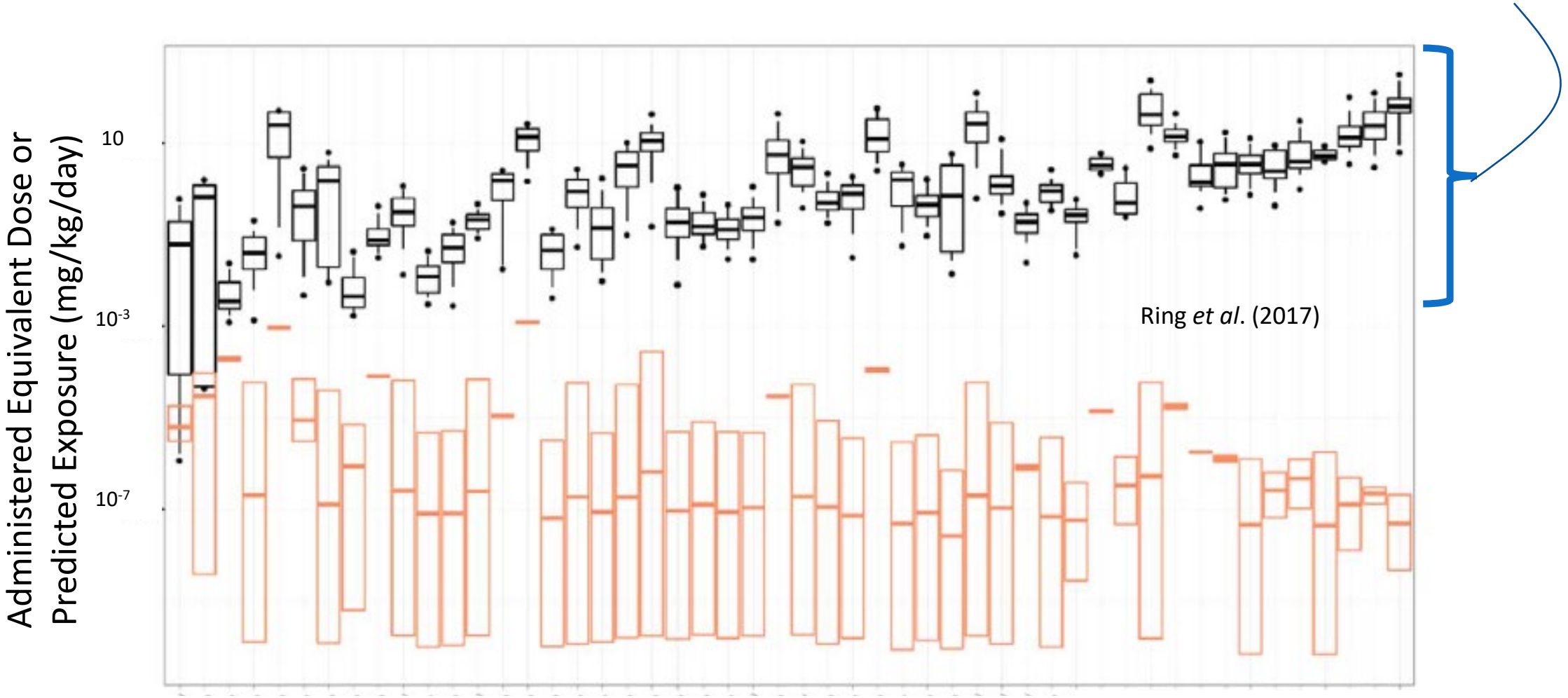


NRC, 1983



BERs Allow Chemical Prioritization

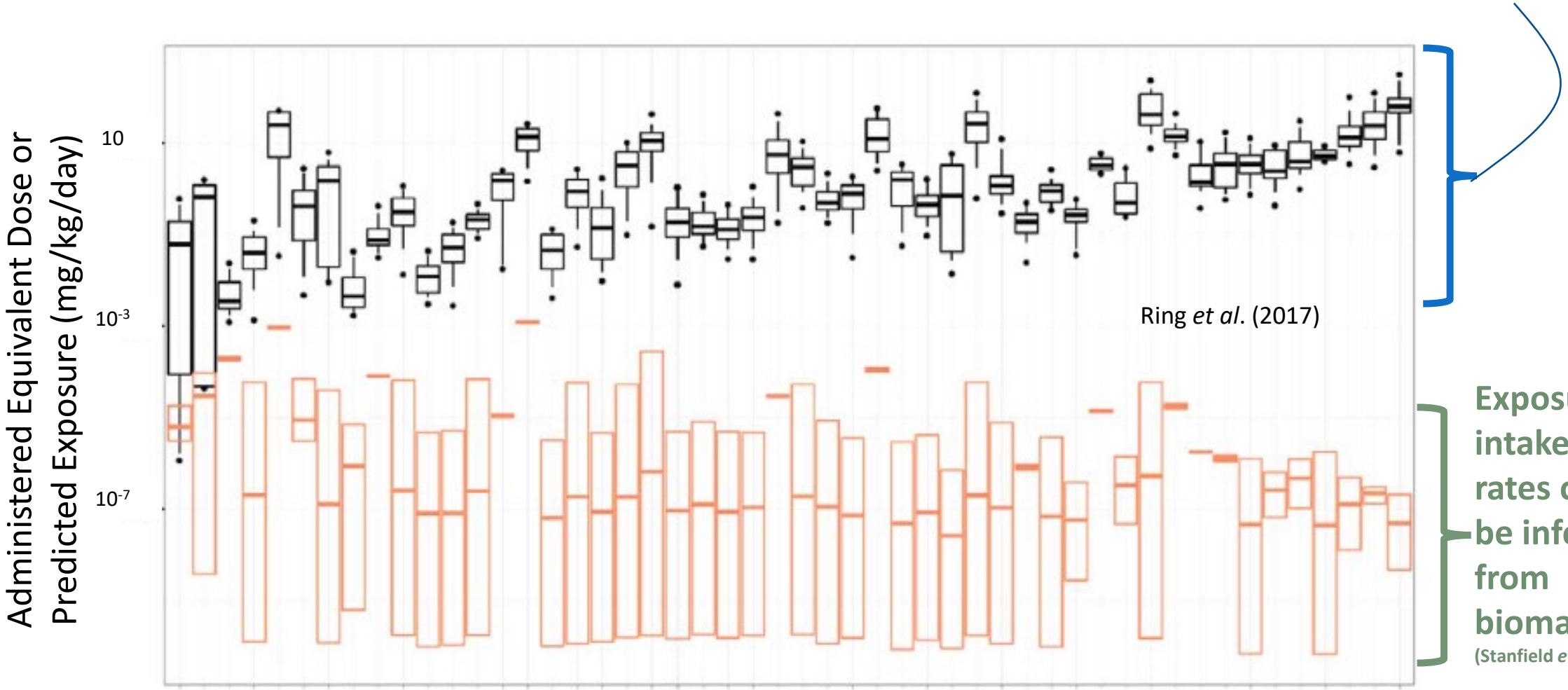
***In Vitro* Screening + IVIVE can estimate doses needed to cause bioactivity (Wetmore *et al.*, 2015b)**



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

BERs Allow Chemical Prioritization

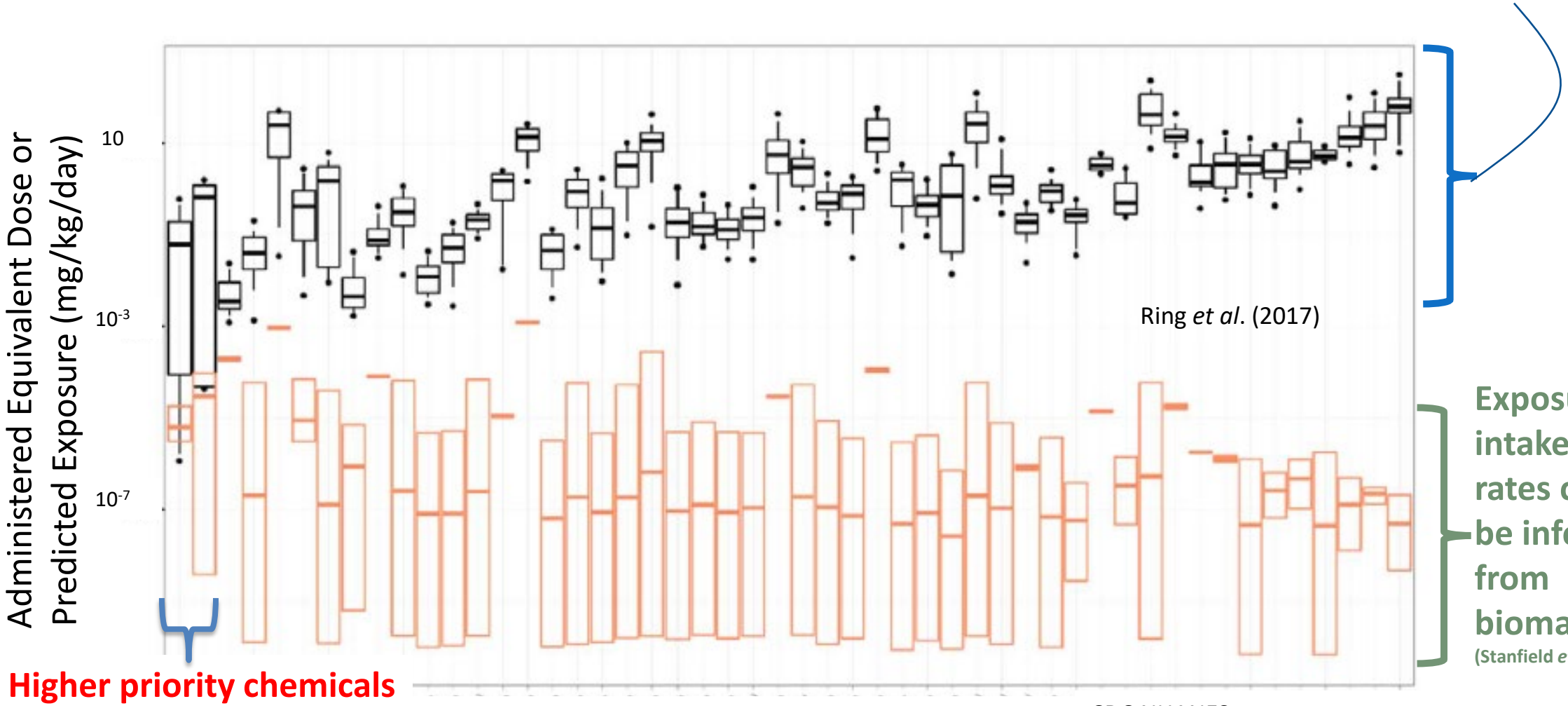
***In Vitro* Screening + IVIVE can estimate doses needed to cause bioactivity (Wetmore *et al.*, 2015b)**



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

BERs Allow Chemical Prioritization

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



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

Most Chemicals Do Not Have TK Data

- We need chemical-specific toxicokinetics (TK) for *in vitro-in vivo* extrapolation (IVIVE) (Rotroff et al., 2010), **but:**
  - Most non-pharmaceutical chemicals – for example, flame retardants, plasticizers, pesticides, solvents – do not have human *in vivo* TK data
  - Non-pesticidal chemicals are unlikely to have any *in vivo* TK data, even from animals

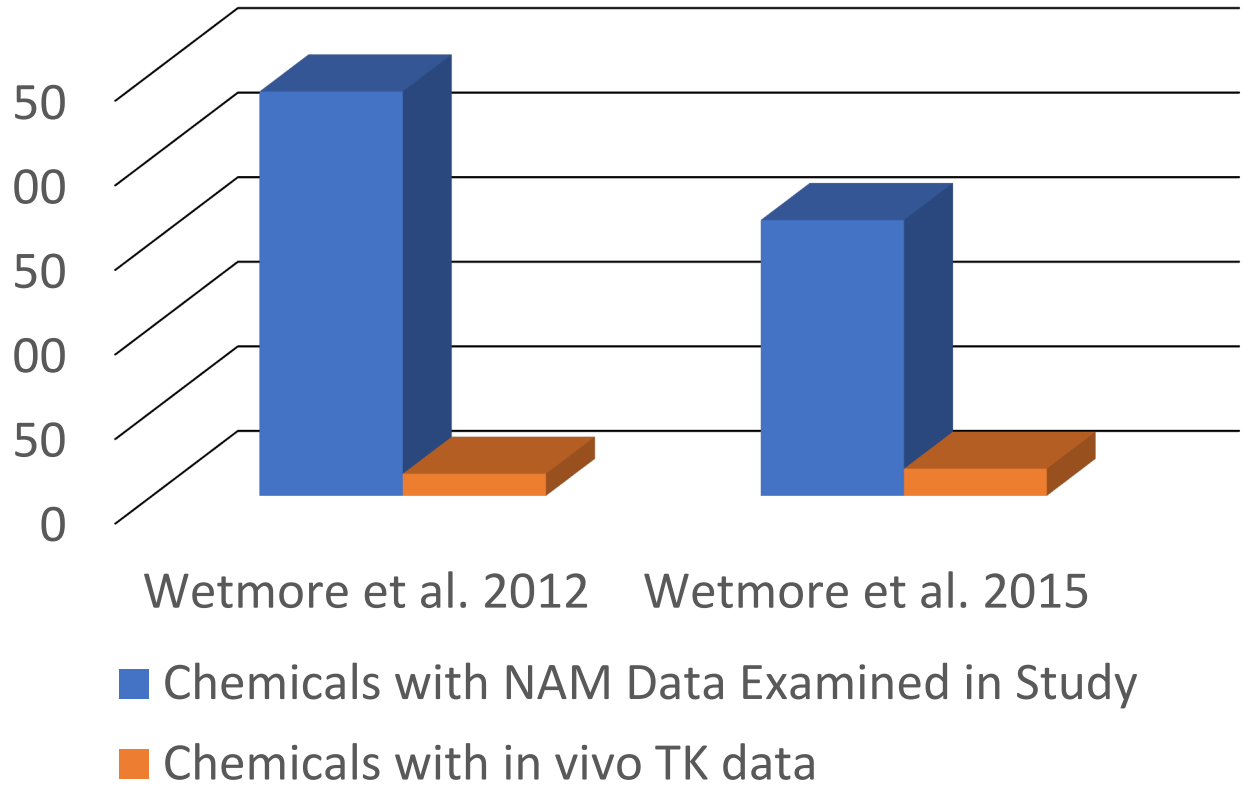
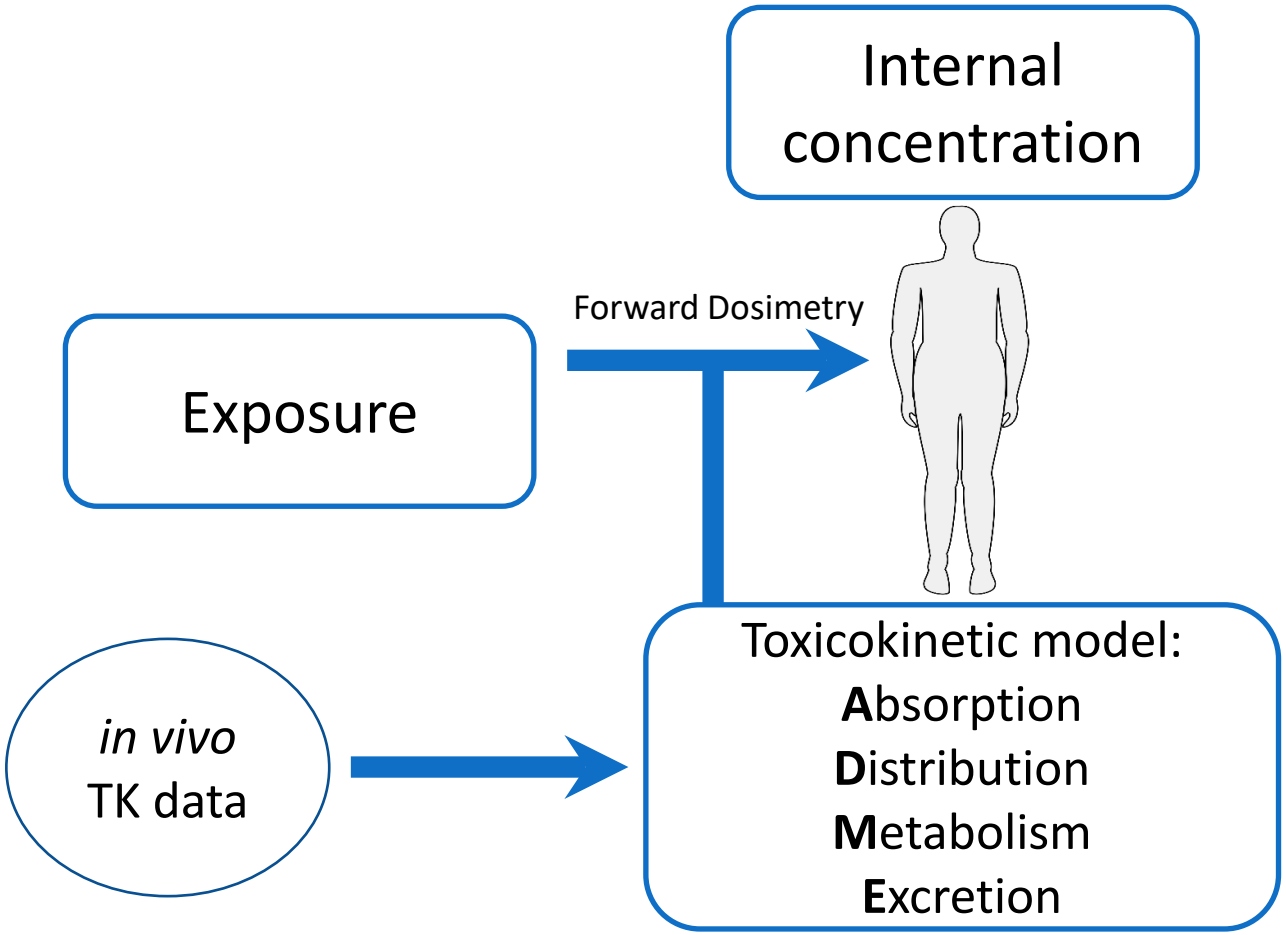


Figure modified from Bell et al. (2018)

Toxicokinetics

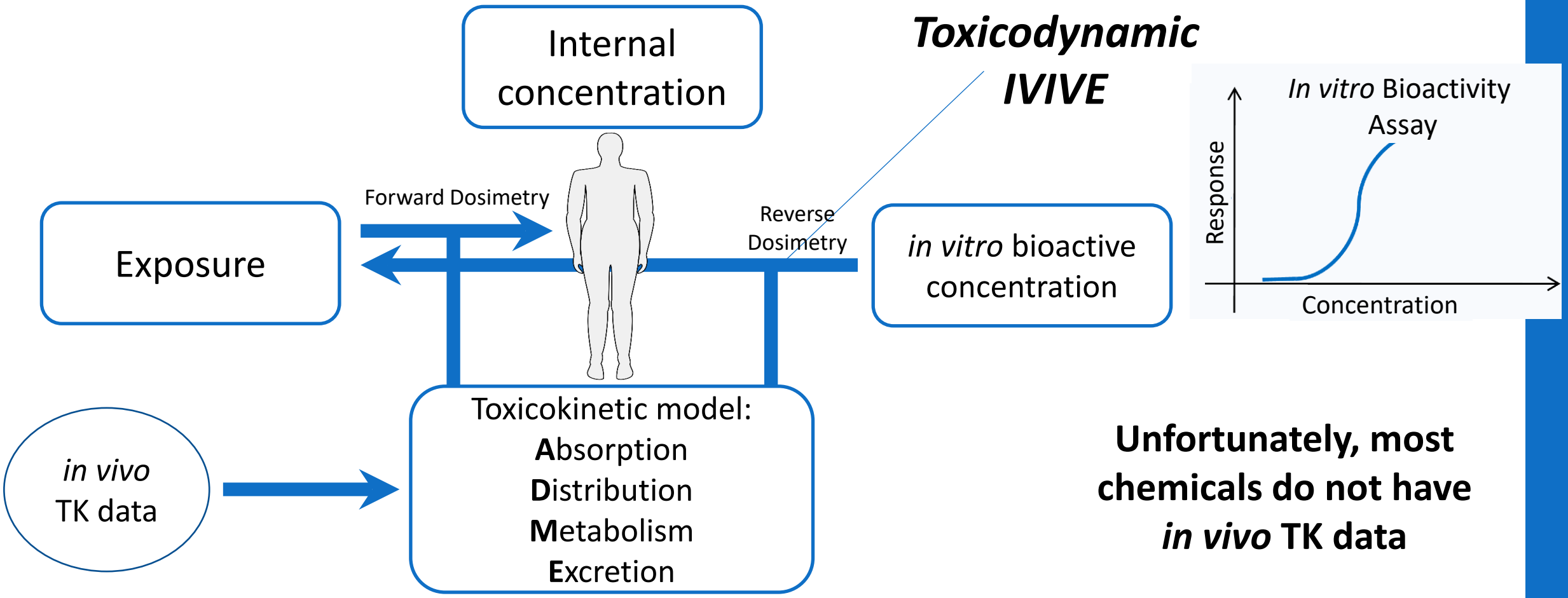


Breen et al. (2021)

- Toxicokinetics describes the absorption, distribution, metabolism, and excretion of a chemical by the body:
  - Chemical-specific
  - Links exposure with internal concentrations

In Vitro-In Vivo Extrapolation (IVIVE)

- Translation of *in vitro* high throughput screening requires chemical-specific toxicokinetic models
  - Needed for anywhere from dozens to thousands of chemicals

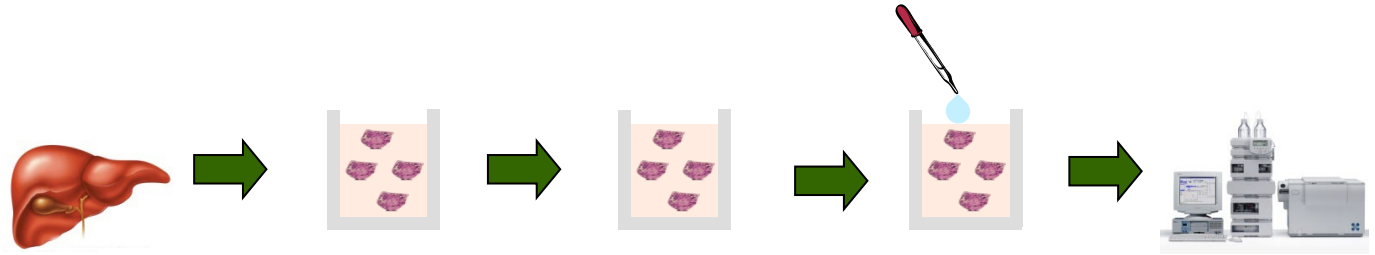


Unfortunately, most chemicals do not have *in vivo* TK data

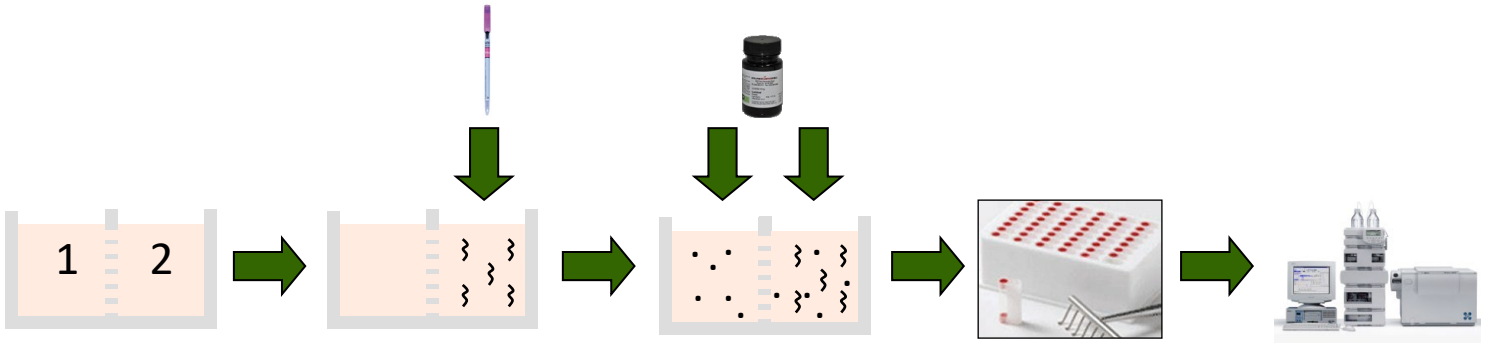
Breen et al. (2021)

High Throughput Toxicokinetics (HTTK) for IVIVE

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



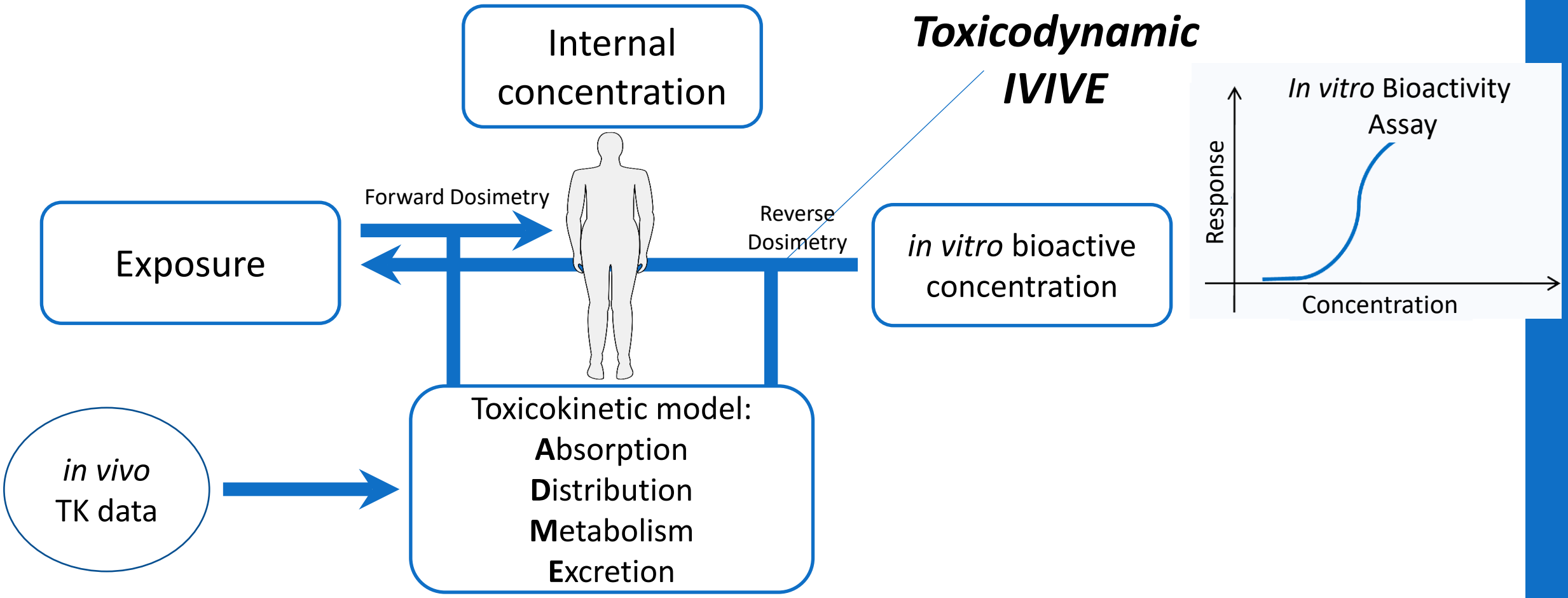
Rapid Equilibrium Dialysis (RED) Waters *et al.* (2008)



- **Most chemicals do not have TK data** – we use *in vitro* HTTK methods adapted from pharma to fill gaps
- In drug development, predicted concentrations are typically on the order of values measured in clinical trials (Wang, 2010)
- Chemical-specific data are steadily being generated by ORD laboratories (Barbara Wetmore), EPA contractors, and collaborators

In Vitro-In Vivo Extrapolation (IVIVE)

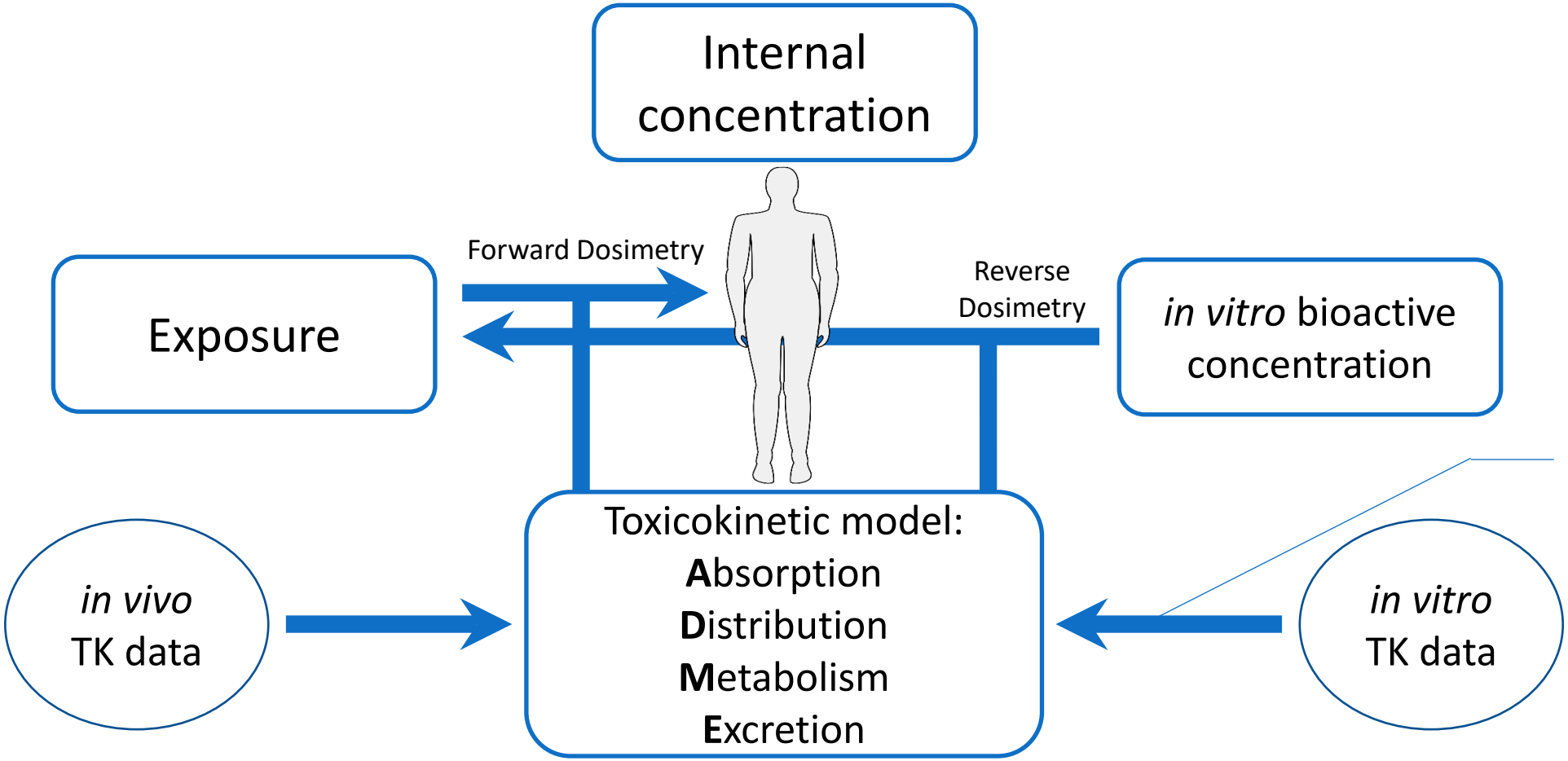
- Translation of *in vitro* high throughput screening requires chemical-specific toxicokinetic models
  - Needed for anywhere from dozens to thousands of chemicals



Breen et al. (2021)

In Vitro-In Vivo Extrapolation (IVIVE)

- Translation of *in vitro* high throughput screening requires chemical-specific toxicokinetic models
  - Needed for anywhere from dozens to thousands of chemicals



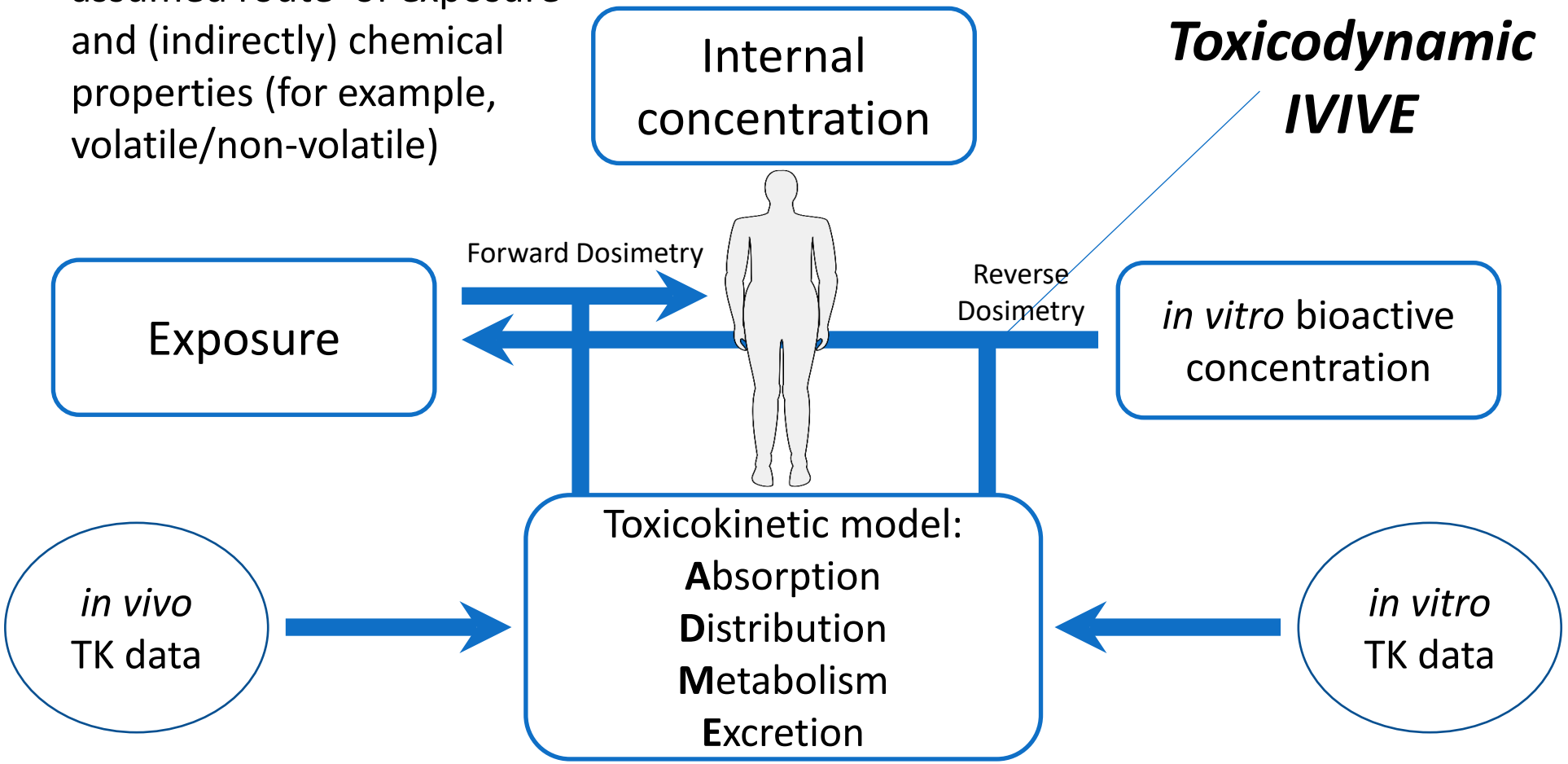
Breen et al. (2021)

Toxicokinetic IVIVE

Chemical-specific data are steadily being generated by ORD laboratories (Barbara Wetmore), EPA contractors and collaborators.

In Vitro-In Vivo Extrapolation (IVIVE)

- IVIVE estimates equivalent doses that depend on the assumed route of exposure and (indirectly) chemical properties (for example, volatile/non-volatile)



Breen et al. (2021)

IVIVE by Scaling Factor

- There are many approaches to IVIVE, but we choose a relatively simple one:
- We make various assumptions that allow conversion of an *in vitro* concentration $[\boldsymbol{X}]$ (μM) into an **administered equivalent dose** (AED) with units of mg/kg body weight/day:

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

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

HTTK can predict F_{IVIVE}

IVIVE by Scaling Factor

- For a given chemical, $\mathbf{F_{IVIVE} = 1 / C_{ss,95}}$
- $C_{ss,95}$ is the steady-state plasma concentration resulting from a 1 mg/kg/day exposure
- HTTK can predict $C_{ss,95}$ using "reverse dosimetry" IVIVE (Tan et al., 2007)

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

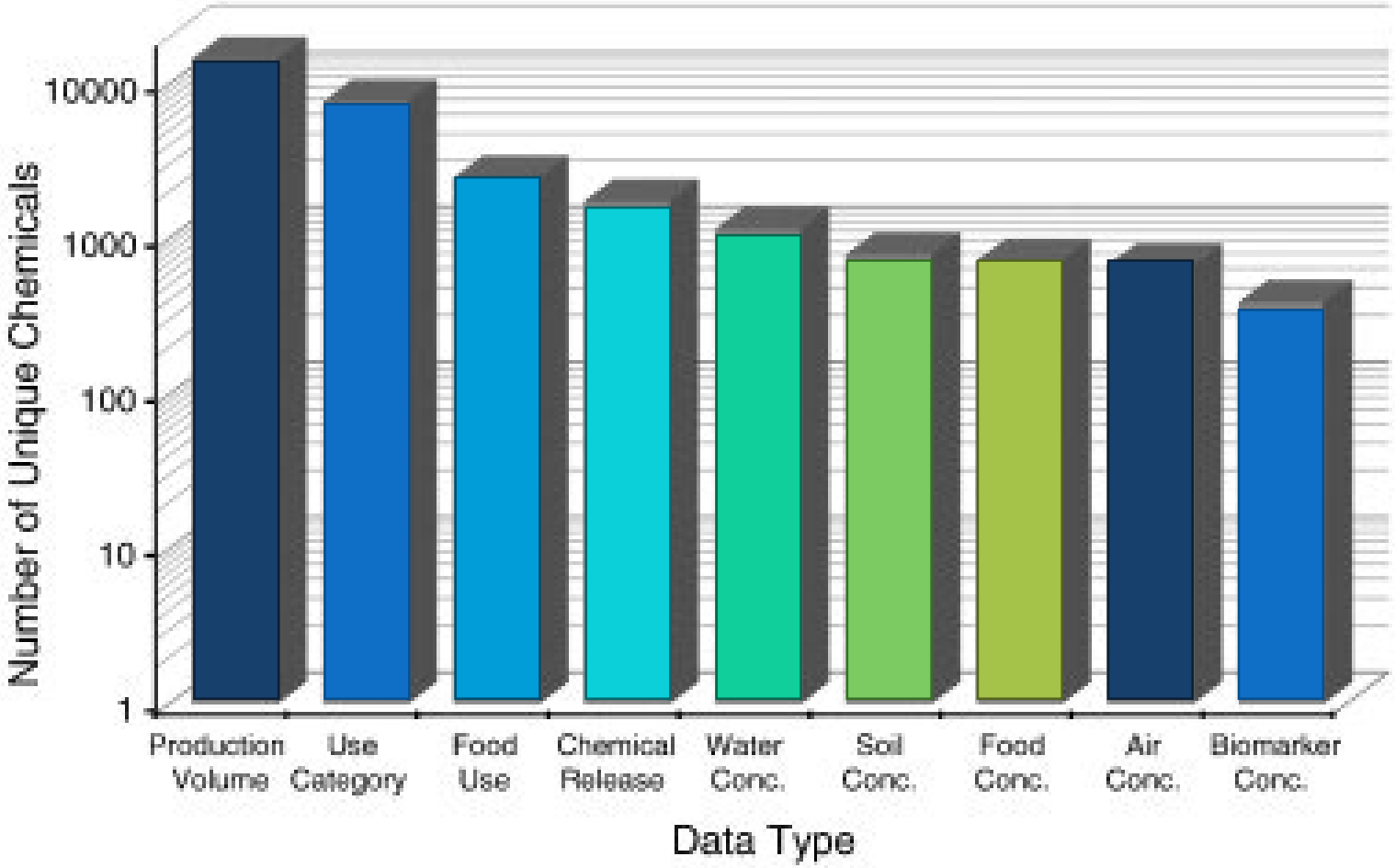
- The "95" refers to the upper 95th percentile – due to human variability and measurement uncertainty there are a range of possible C_{ss} values
- All of this assumes that the individuals have enough time to come to "steady-state" with respect to their daily exposures

Don't forget:

$$\mu\boldsymbol{M} = \mathbf{1000}\frac{\mathbf{1}}{\boldsymbol{MW}}\frac{\boldsymbol{mg}}{\boldsymbol{L}}$$

Limited Available Data for Exposure Estimation

Most chemicals lack public exposure-related data beyond production volume (Egeghy et al., 2012)



New approach methods for exposure address these gaps

Fit-for-Purpose Exposure Modeling Frameworks

- All models vary in complexity and data needed to describe chemical exposure
- High throughput exposure (HTE) models can handle many chemicals with minimal descriptive information
- HTE models can provide rough but quantitative estimates of exposure

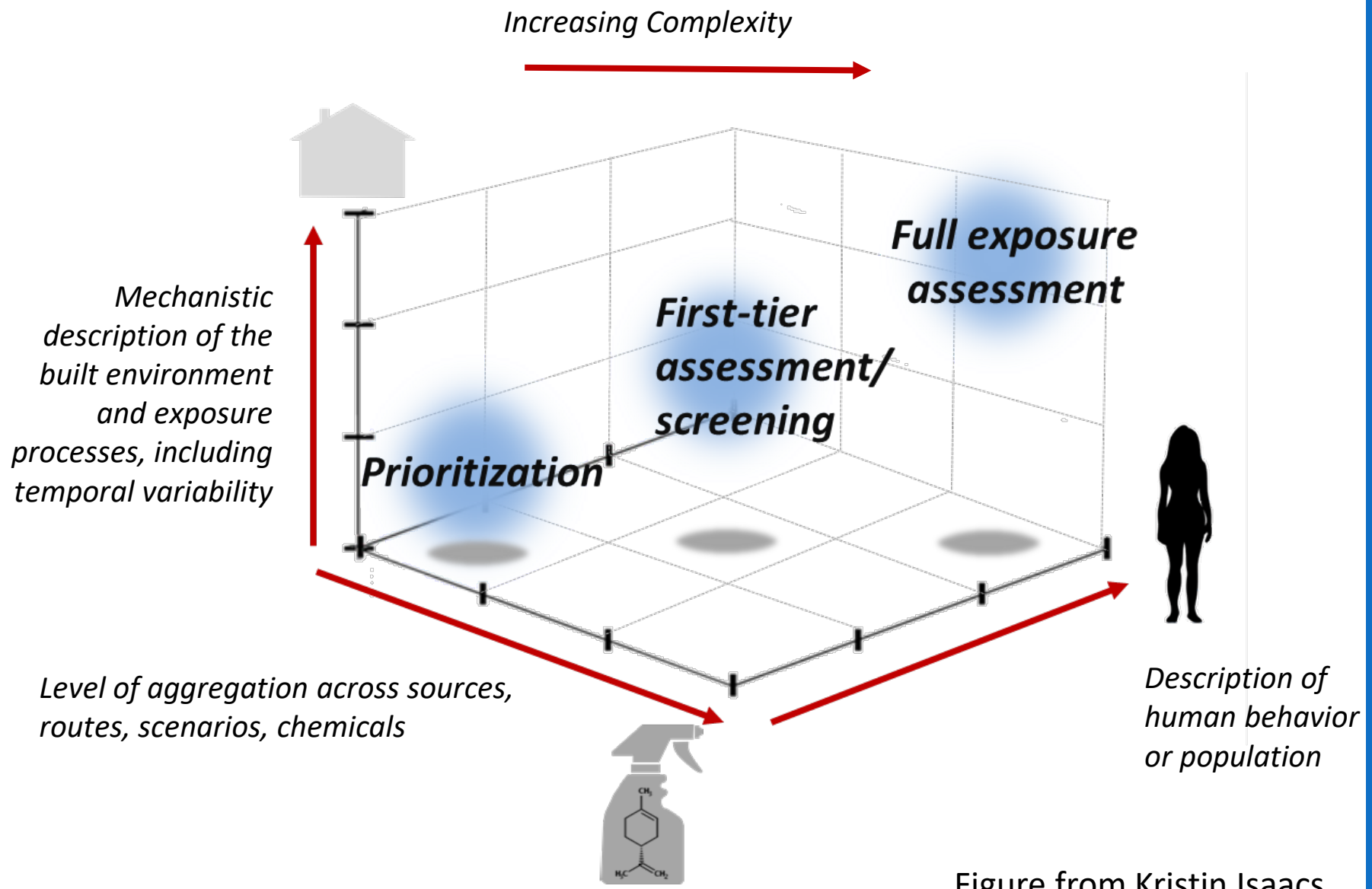
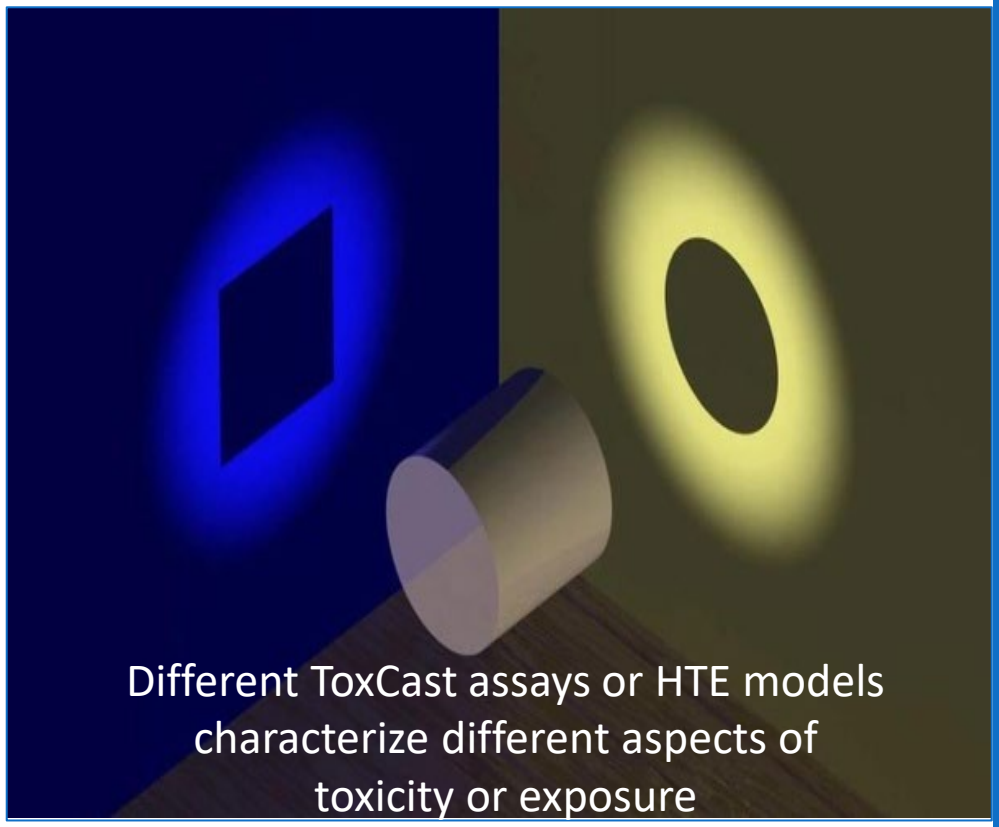


Figure from Kristin Isaacs

High Throughput Exposure: Analogy to *In Vitro* Screening

- EPA's Toxicity Forecasting (ToxCast) high throughput testing project:
  - >3000 chemicals tested to date
  - Each ToxCast assay-endpoint has the potential to capture *an aspect* of chemical biology – more than 1000 to date
  - No one assay gives the whole picture
  - Reference chemicals covering diverse mechanisms to establish what different types hazard "look like"
- ExpoCast (Exposure Forecasting):
  - Various HTE models provide the "assays" for different aspects (pathways, chemistries, assumptions) of exposure
  - Monitoring data provides our "reference" exposures
  - We build a probabilistic, consensus prediction using multiple HTE models and other predictors



Different ToxCast assays or HTE models characterize different aspects of toxicity or exposure

Individual Model Predictions Available on CompTox Dashboard

SEEM3 Collaboration

Jon Arnot, Deborah H. Bennett, Peter P. Egeghy, Peter Fantke, Lei Huang, Kristin K. Isaacs, Olivier Jolliet, Hyeong-Moo Shin, Katherine A. Phillips, Caroline Ring, R. Woodrow Setzer, John F. Wambaugh, Johnny Westgate

Predictor	Reference(s)	Chemicals Predicted	Pathway(s)
EPA Inventory Update Reporting and Chemical Data Reporting (CDR) (2015)	US EPA (2018)	7856	All
Stockholm Convention of Banned Persistent Organic Pollutants (2017)	Lallas (2001)	248	far field Industrial and Pesticide
EPA Pesticide Reregistration Eligibility Documents (REDs) Exposure Assessments (Through 2015)	Wetmore et al. (2012, 2015)	239	far field Pesticide
United Nations Environment Program and Society for Environmental Toxicology and Chemistry toxicity model (USEtox) Industrial Scenario (2.0)	Rosenbaum et al. (2008)	8167	far field Industrial
USEtox Pesticide Scenario (2.0)	Fantke et al. (2011, 2012, 2016)	940	far field Pesticide
Risk Assessment IDentification And Ranking (RAIDAR) far field (2.02)	Arnot et al. (2008)	8167	far field Pesticide
EPA Stochastic Human Exposure Dose Simulator High Throughput (SHEDS-HT) near field Direct (2017)	Isaacs (2017)	7511	far field Industrial and Pesticide
SHEDS-HT near field Indirect (2017)	Isaacs (2017)	1119	Residential
Fugacity-based INdoor Exposure (FINE) (2017)	Bennett et al. (2004), Shin et al. (2012)	645	Residential
RAIDAR-ICE near field (0.803)	Arnot et al., (2014), Zhang et al. (2014)	1221	Residential
USEtox Residential Scenario (2.0)	Jolliet et al. (2015), Huang et al. (2016,2017)	615	Residential
USEtox Dietary Scenario (2.0)	Jolliet et al. (2015), Huang et al. (2016), Ernstoff et al. (2017)	8167	Dietary

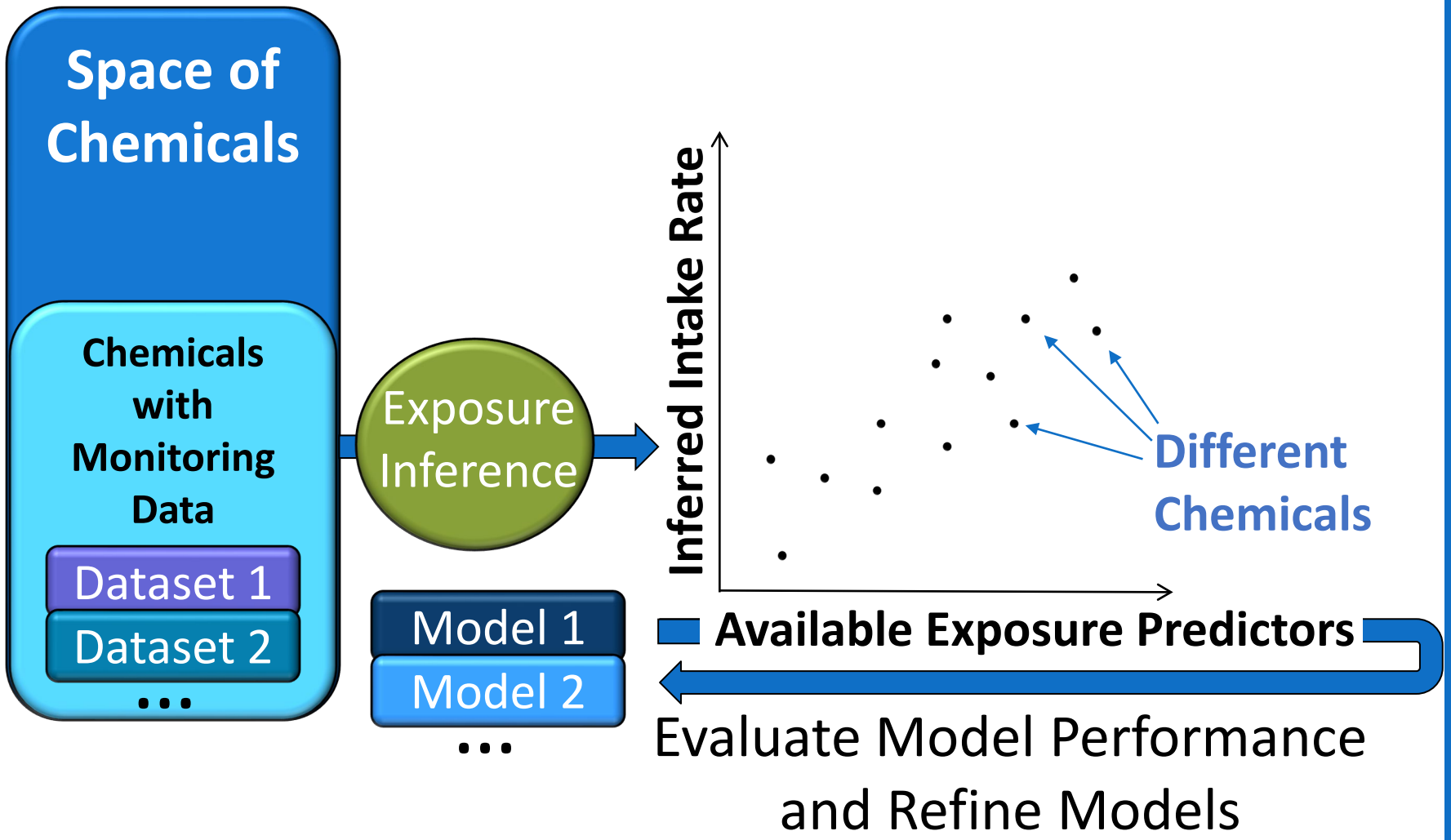
Individual Model Predictions Available on CompTox Dashboard

Ring et al., 2018

Evaluating Exposure Models with the SEEM Framework

We use Bayesian methods to incorporate multiple models into consensus predictions for 1000s of chemicals within the **Systematic Empirical Evaluation of Models (SEEM)**

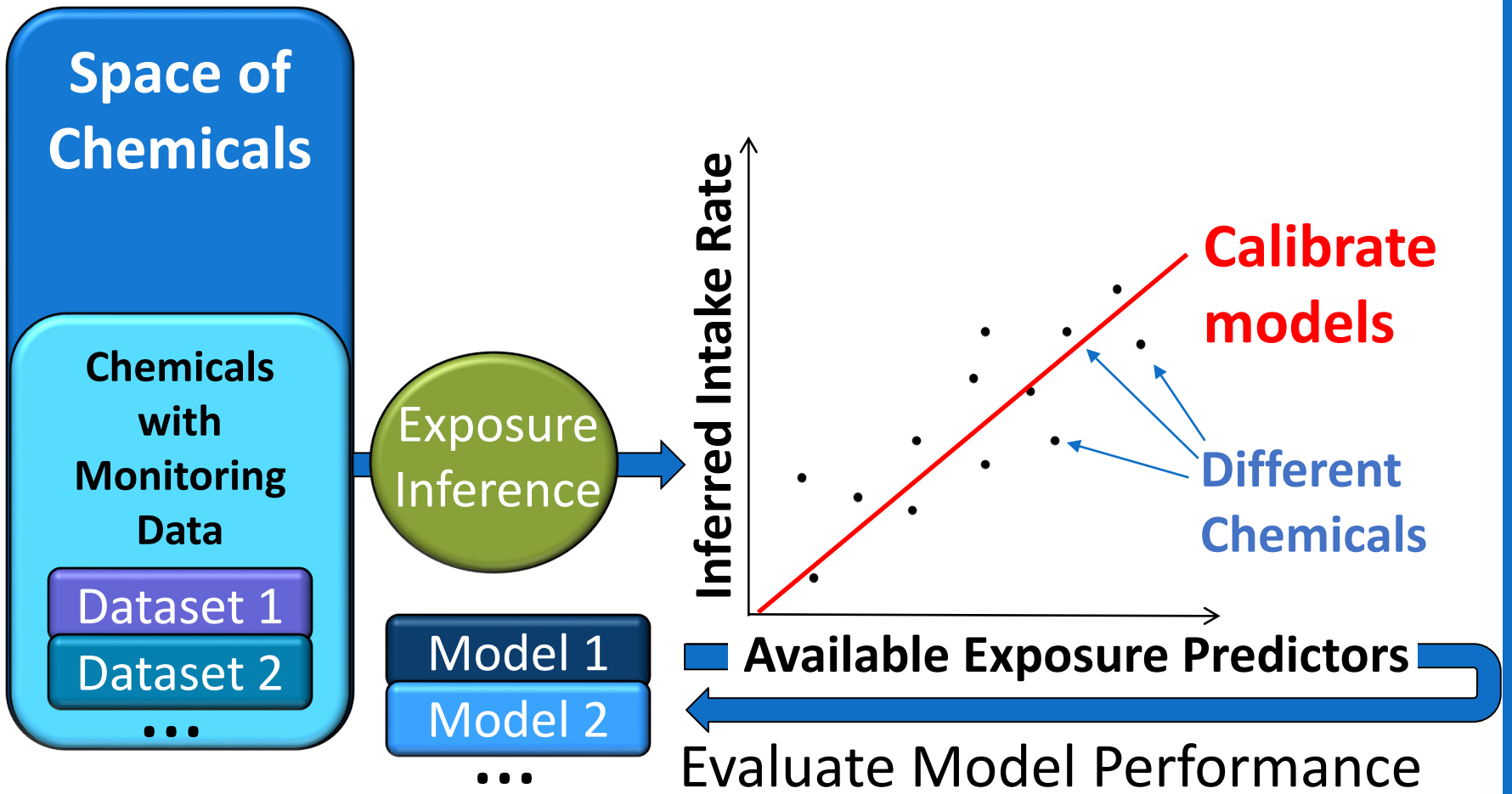
(Wambaugh et al., 2013, 2014; Ring et al., 2018)



Wambaugh et al., 2019

Evaluating Exposure Models with the SEEM Framework

We use Bayesian methods to incorporate multiple models into consensus predictions for 1000s of chemicals within the **Systematic Empirical Evaluation of Models (SEEM)**
(Wambaugh et al., 2013, 2014; Ring et al., 2018)

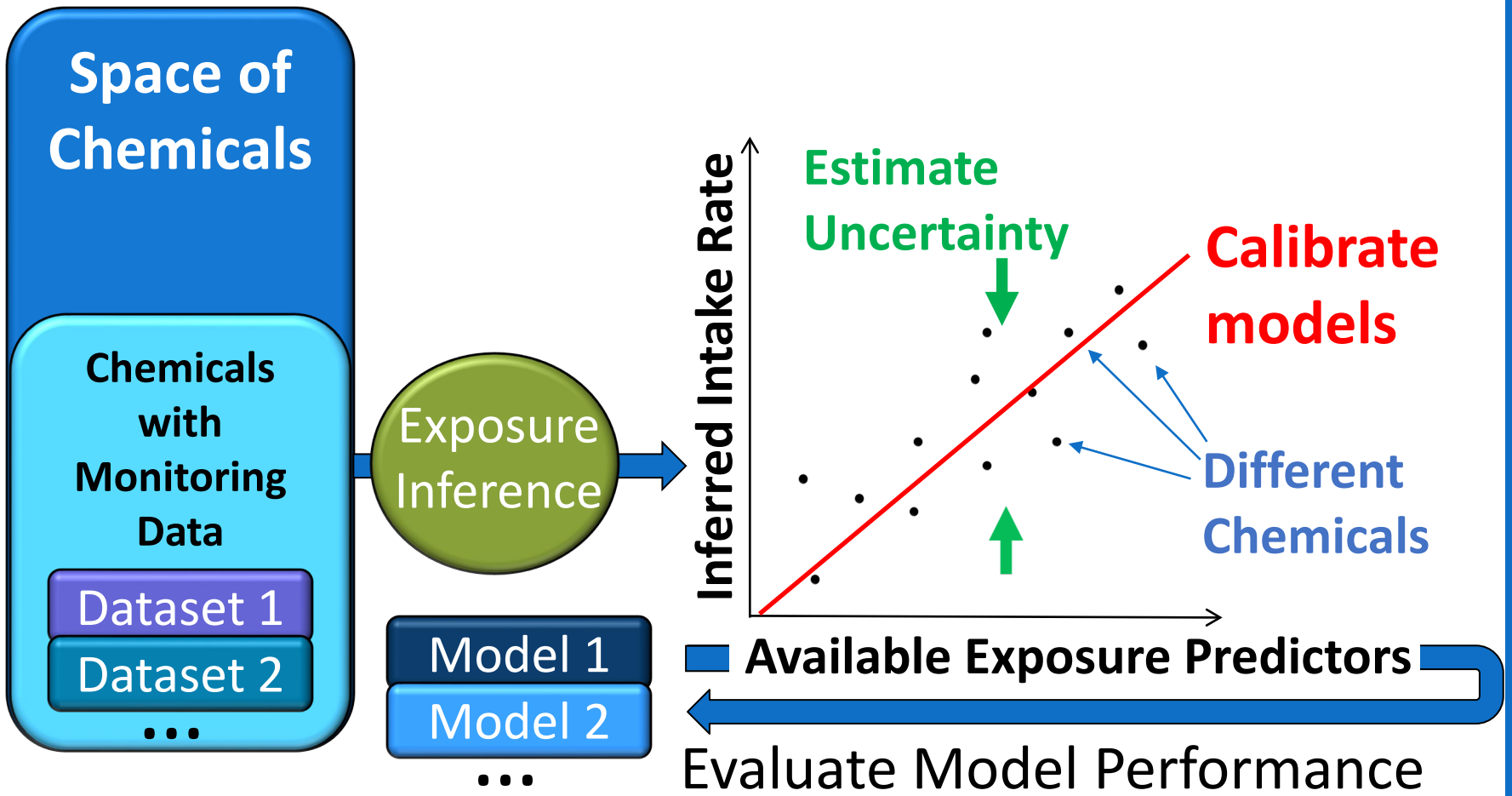


Wambaugh et al., 2019

Evaluating Exposure Models with the SEEM Framework

We use Bayesian methods to incorporate multiple models into consensus predictions for 1000s of chemicals within the **Systematic Empirical Evaluation of Models (SEEM)**

(Wambaugh et al., 2013, 2014; Ring et al., 2018)

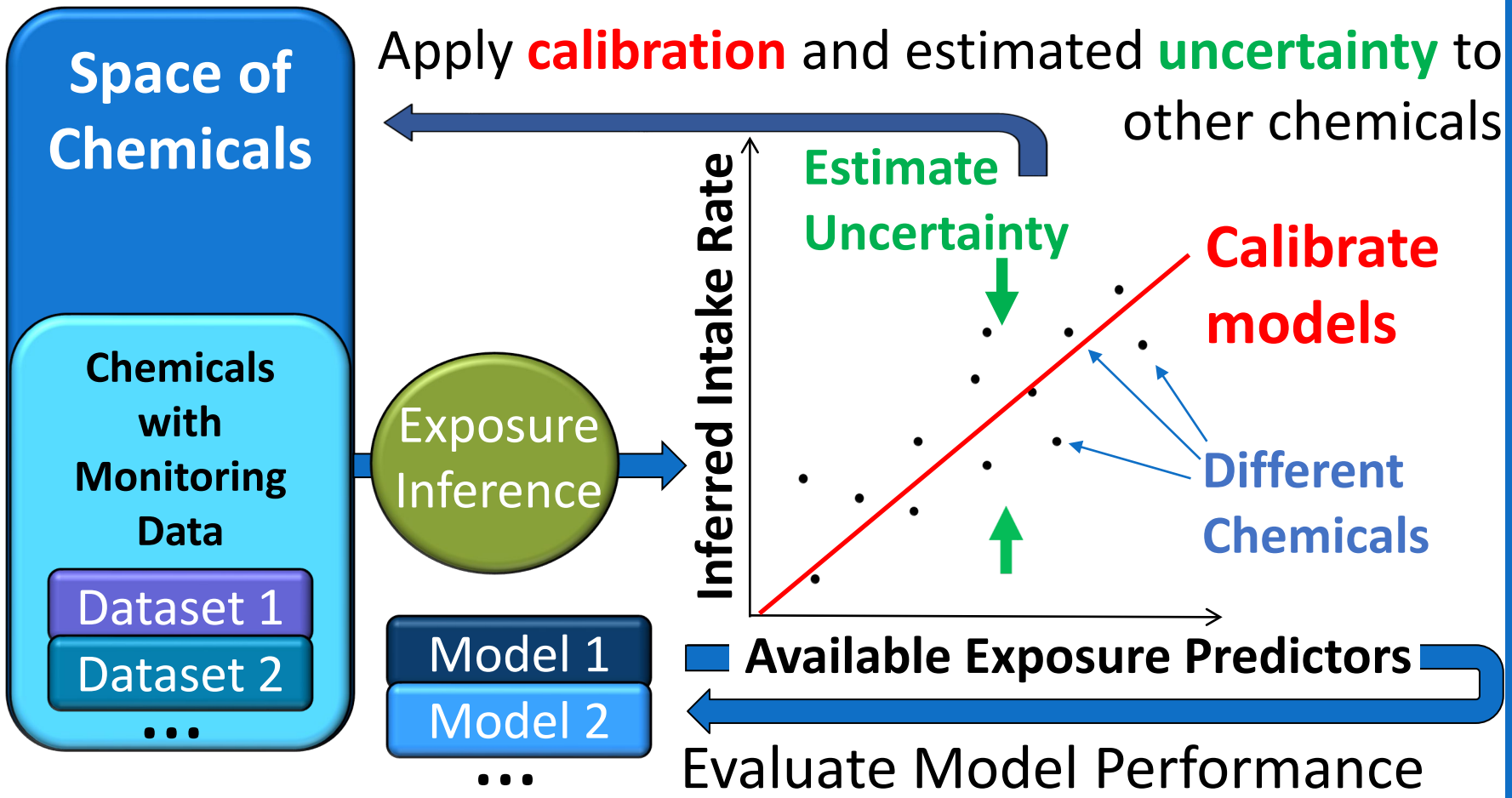


Wambaugh et al., 2019

Evaluating Exposure Models with the SEEM Framework

We use Bayesian methods to incorporate multiple models into consensus predictions for 1000s of chemicals within the **Systematic Empirical Evaluation of Models (SEEM)**

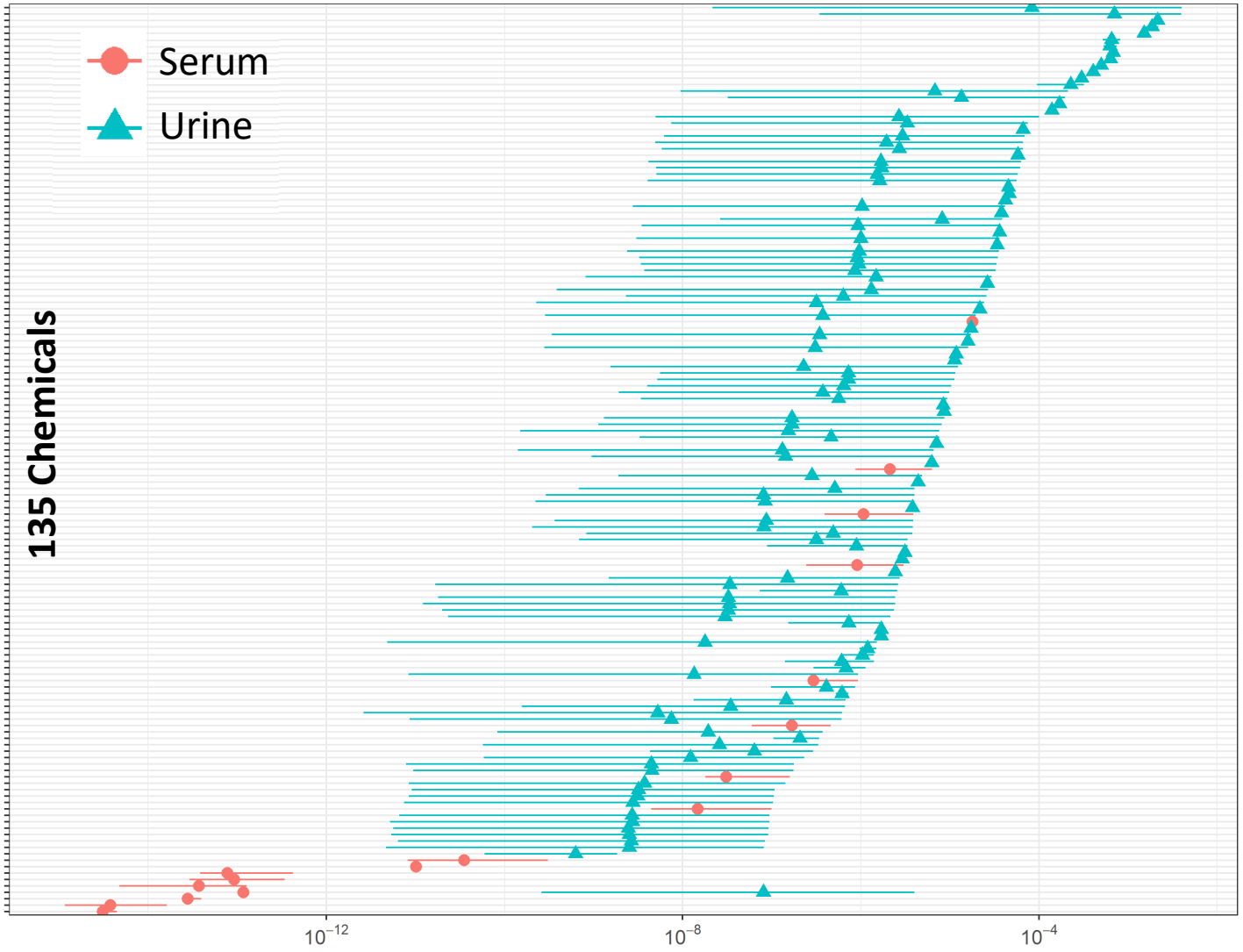
(Wambaugh et al., 2013, 2014; Ring et al., 2018)



Wambaugh et al., 2019

Inferred Exposure Rates from CDC NHANES

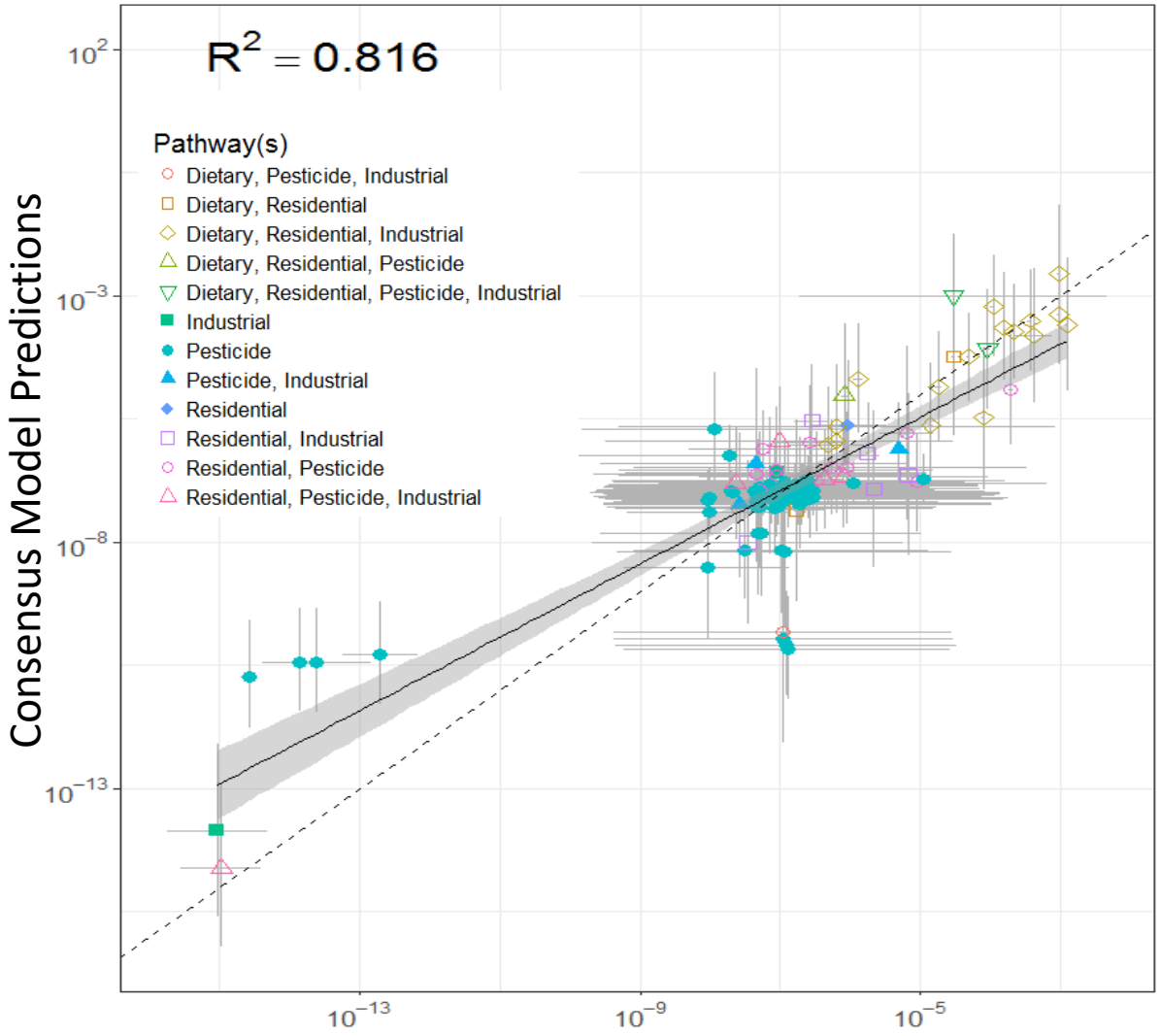
- Monitoring data provides our “reference” exposures for SEEM
- We infer exposure from CDC NHANES biomarker data
- We propagate uncertainty in inferences
  - Considering multiple parent chemicals for a given analyte
  - Limit of detection issues
- These exposure inferences are made available on CCD



work with Miyuki Breen and Zach Stanfield

National Health and Nutrition Examination Survey

SEEM3: Pathway-Based Consensus Modeling

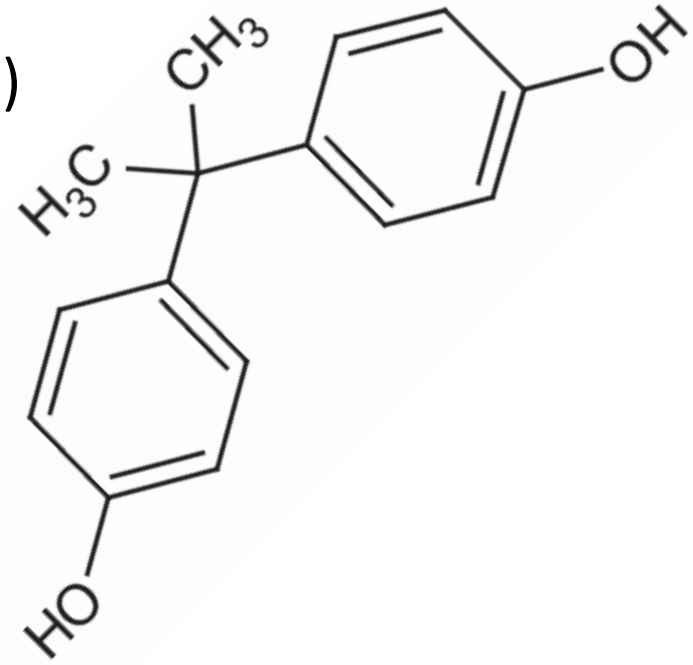


- SEEM3 consensus model provides estimates of human median intake rate (mg/kg/day) for nearly 500,000 chemicals via the CompTox Chemicals Dashboard (http://comptox.epa.gov/dashboard)
- SEEM3 first predicts relevant exposure pathways from chemical structure – model predictions are then weighted according to the models' abilities to explain NHANES data
- We rely on pathway determinations from CPDat
- We rely on NHANES biomonitoring data
  - 2014 FIFRA Scientific Advisory Panel identified need for broader sets of evaluation data

Ring et al., 2018

Computational Toxicology and Exposure

- Given a structure we can estimate bioactivity, distribution, and exposure
  - Quantitative structure-property relationships (QSPRs)



- If we have a sample, we can test it *in vitro:*
  - High throughput screening and toxicokinetics
  - HTTK QSPRs allow predictions from structure

- If we have monitoring data, can estimate daily intake
  - High throughput exposure tools provide forecasts from structure

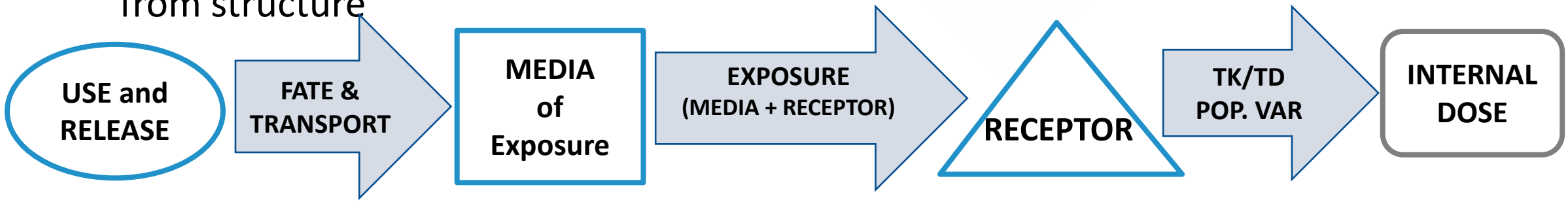
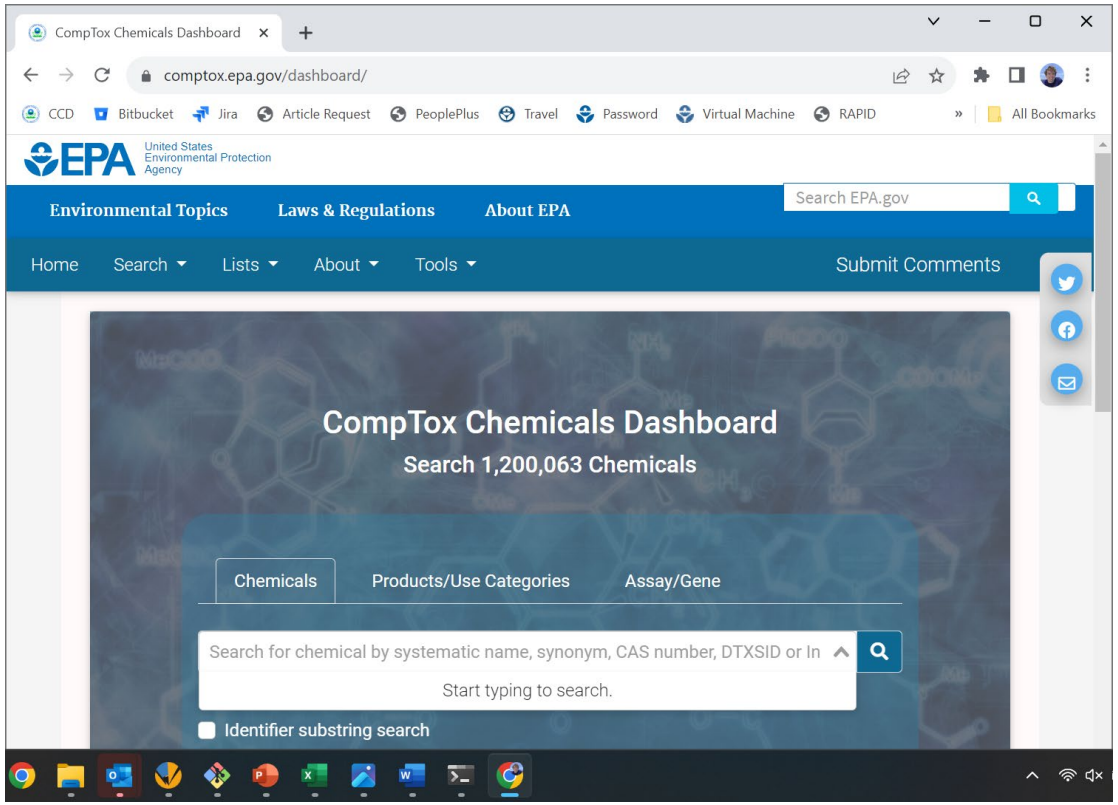


Figure from Caroline Ring

Standardized NAM Data and Tools

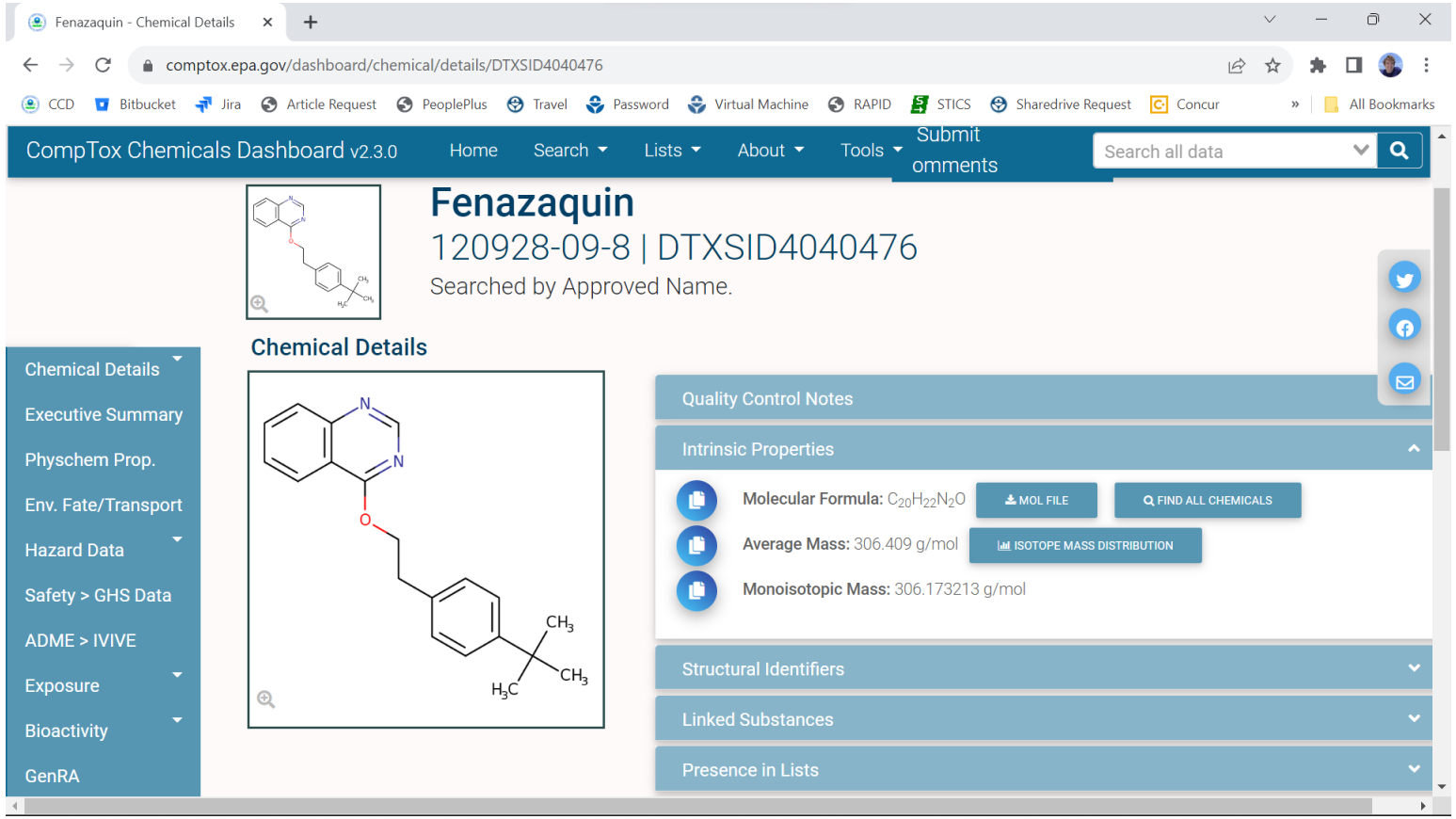
- **Hazard:** There are nearly 10,000 chemicals with *in vitro* bioactivity data
- **Exposure:** There are more than 400,000 chemicals with “exposure forecasts” (ExpoCast)
- **Dose-Response:** There are currently 7,569 chemicals with httk data/predictions (including C_{ss}, V_d, t_{half}) available on the CompTox Chemicals Dashboard:

https://comptox.epa.gov/dashboard



Openly Available TK Information

- EPA's data and tools for HTTK are made available through R package "httk"
- The "httk" tool has been used to calculate key TK information that is available on the CompTox Chemicals Dashboard and elsewhere

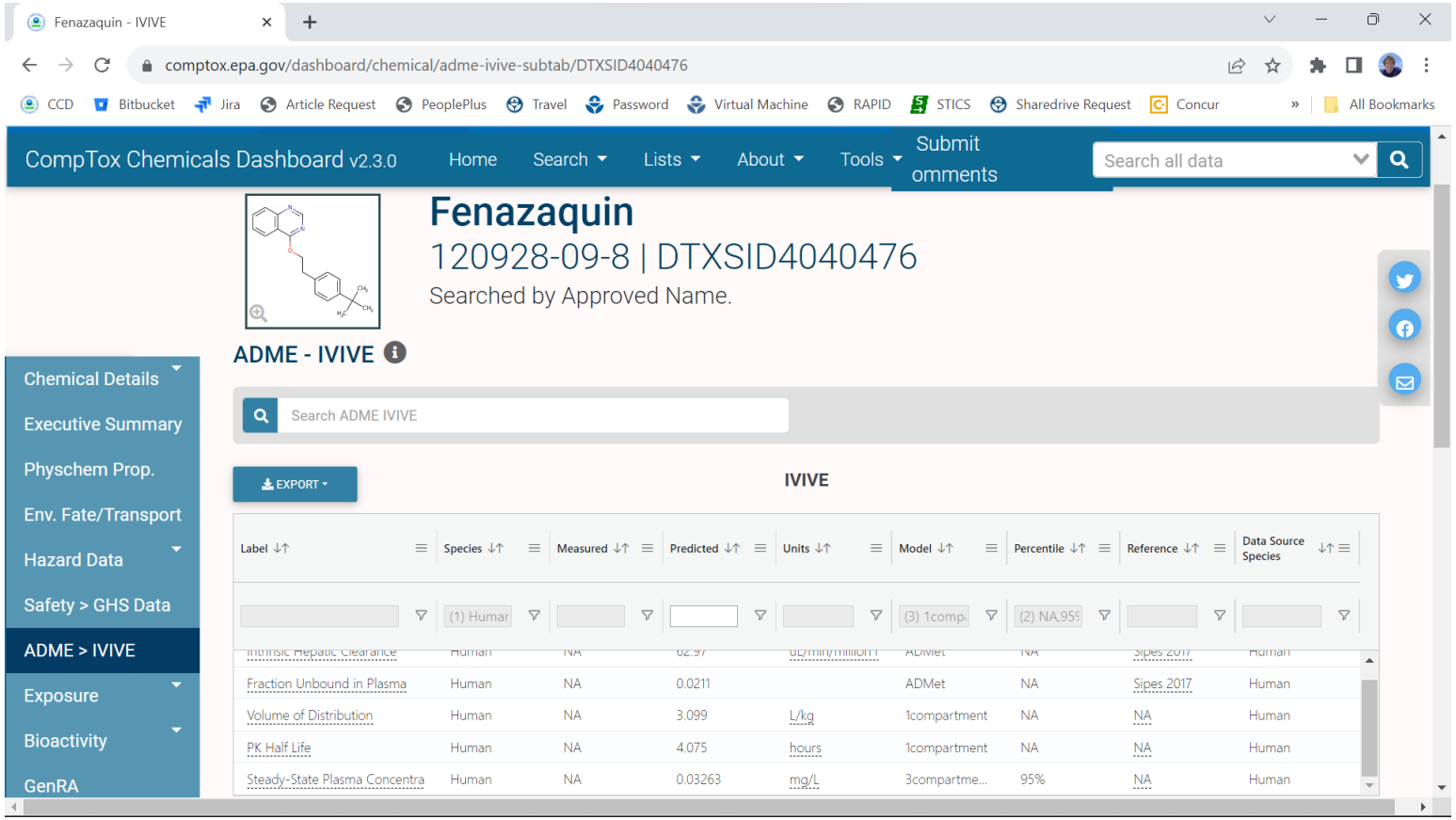


https://comptox.epa.gov/dashboard

The current HTTK data in CCD is HTTK v2.2.1. Please see the Data Sources table in the Release Notes for more information

Openly Available TK Information

- EPA's data and tools for HTTK are made available through R package "httk"
- The "httk" tool has been used to calculate key TK information that is available on the CompTox Chemicals Dashboard and elsewhere

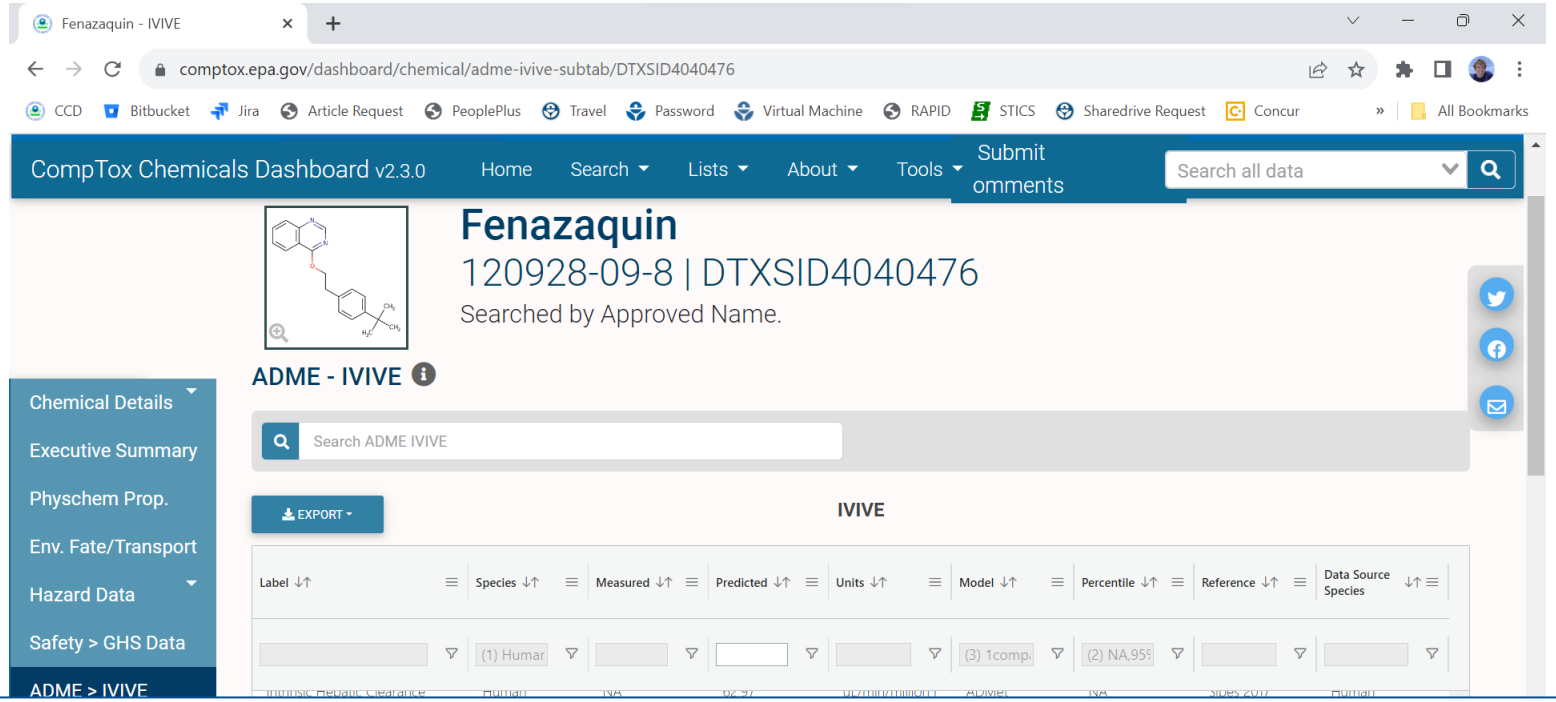


https://comptox.epa.gov/dashboard

The current HTTK data in CCD is HTTK v2.2.1. Please see the Data Sources table in the Release Notes for more information

Openly Available TK Information

- EPA's data and tools for HTTK are made available through R package "httk"
- The "httk" tool has been used to calculate key TK information that is available on the CompTox Chemicals Dashboard and elsewhere

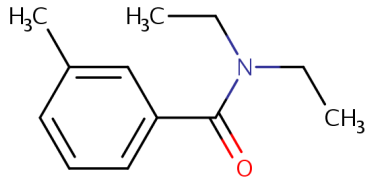


V_d	Volume of Distribution	Human	NA	3.099	L/kg	1compartment	NA	NA	Human
t_{half}	PK Half Life	Human	NA	4.075	hours	1compartment	NA	NA	Human
C_{ss}	Steady-State Plasma Concentra	Human	NA	0.03263	mg/L	3compartme...	95%	NA	Human

https://comptox.epa.gov/dashboard

The current HTTK data in CCD is HTTK v2.2.1. Please see the Data Sources table in the Release Notes for more information

Calculation 1: Reverse Dosimetry, Steady-State Exposure



DEET (CASRN 134-62-3, DTXSID2021995):
$C_{ss,95}$ = 1.37 mg/L per 1 mg/kg/day

In vitro estimated point of departure ($POD_{in\ vitro}$) (in µM units)

✖

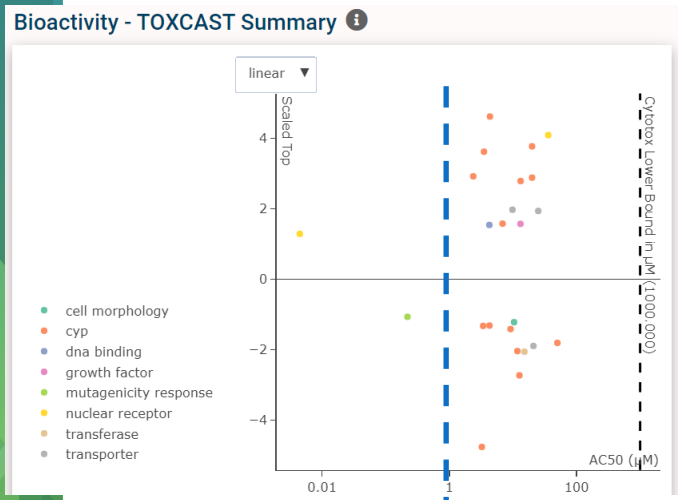
Perform chemical-specific unit conversion from µM to mg/L

➗

Divide by chemical-specific TK C_{ss} (mg/L for 1 mg/kg/day intake rate)

=

Estimated steady-state intake rate needed to cause plasma concentration = $POD_{in\ vitro}$



1 µM seems protective

1 µM = 1 µmol / L
x *Molecular Weight (191.2 g/mol)*
x 1 mg / 1000 ug
= 0.191 mg / L

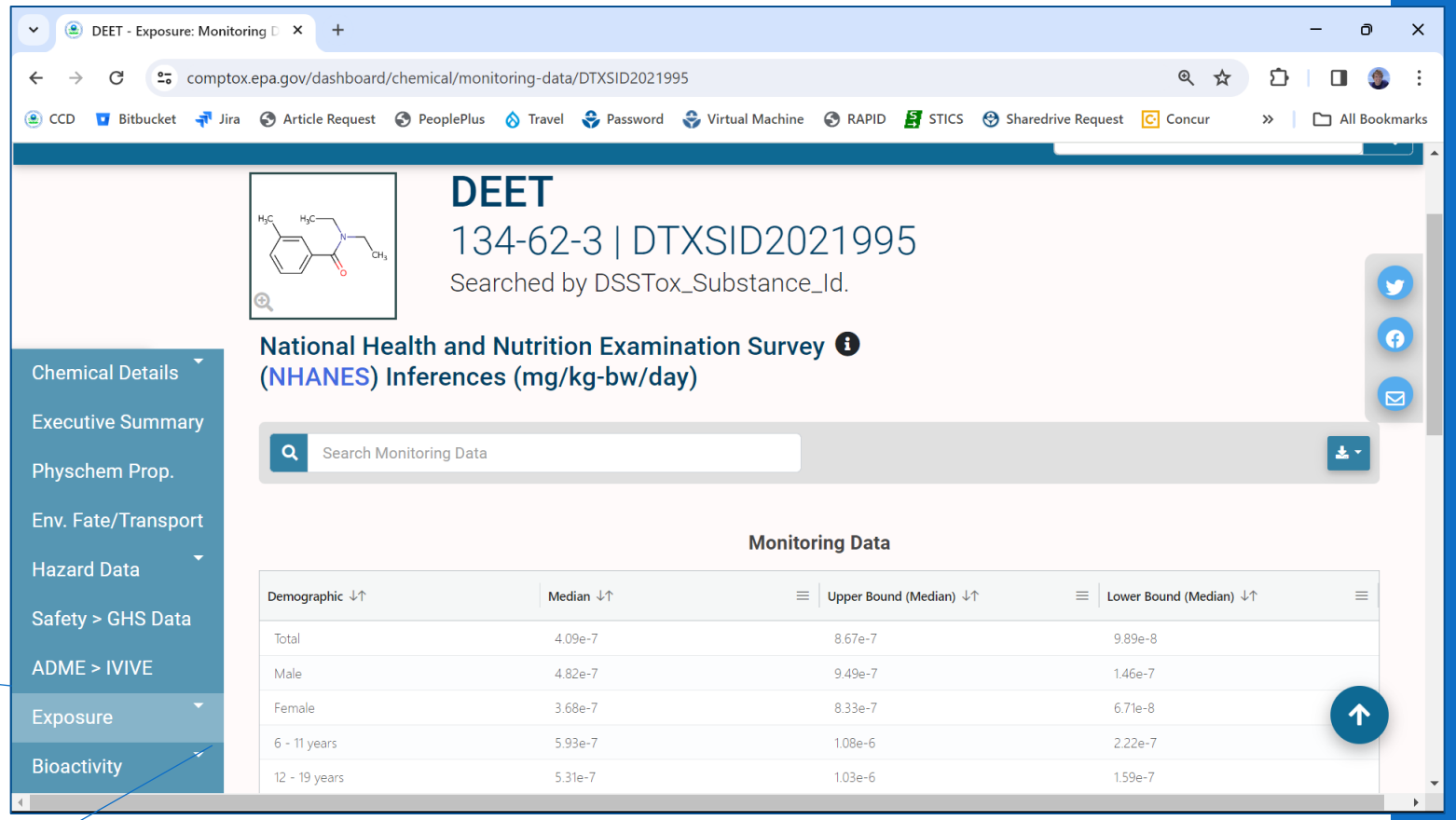
0.191 mg / L
/ 1.37 mg / L
per 1 mg/kg/day

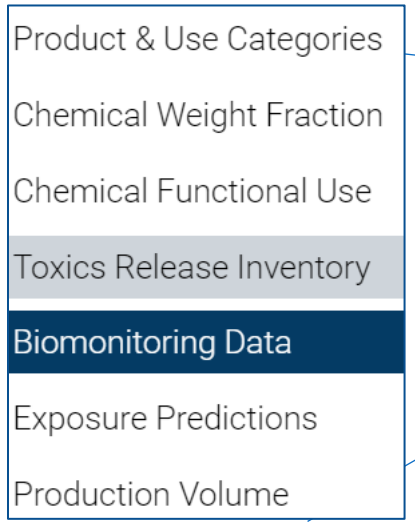
0.14 mg/kg/day exposure will produce 0.191 mg/L plasma concentration at steady-state

Openly Available Exposure Information

https://comptox.epa.gov/dashboard

- For chemicals monitored by the Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination Survey (NHANES) we have inferred daily intake rates (mg/kg/day) for the median U.S. population (Only ~100 chemicals)

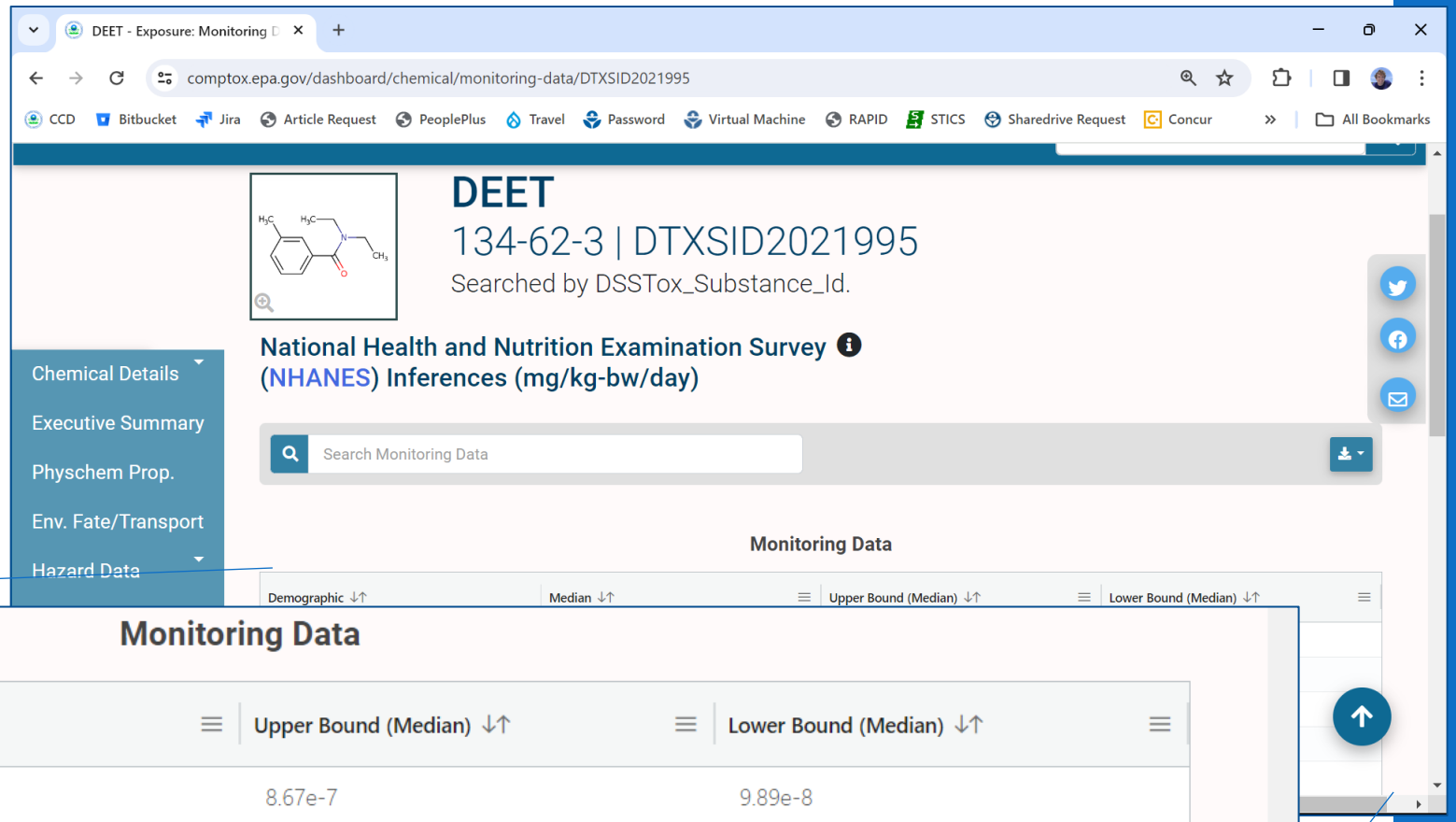


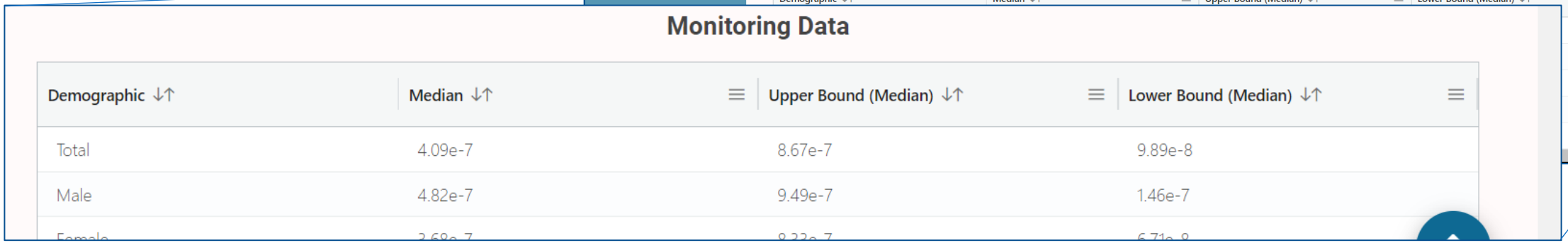


Openly Available Exposure Information

https://comptox.epa.gov/dashboard

- The 95th percentile refers to the uncertainty about the median value, **it does not reflect variability**
- We typically use the upper 95th limit on the uncertainty to be conservative – but this is still only for the population median



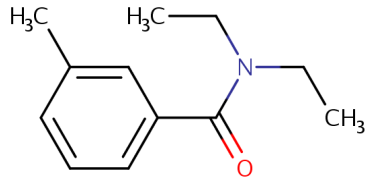


Monitoring Data

Demographic	Median	Upper Bound (Median)	Lower Bound (Median)
Total	4.09e-7	8.67e-7	9.89e-8
Male	4.82e-7	9.49e-7	1.46e-7

Inferences from Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination Survey (NHANES) made using R package bayesMarker (Stanfield et al., 2022 & 2024)

Calculation 2: NHANES Bioactivity:Exposure Ratio



DEET (CASRN 134-62-3, DTXSID2021995):
NHANES Total Population Daily Intake Rate
Upper 95th: 8.67 x 10^{-7} mg/kg/day

Estimated steady-state intake rate needed to cause plasma concentration = $POD_{in\ vitro}$	÷	Divide by Inferred Exposure for Median U.S. Population	=	Bioactivity Exposure Ratio (BER)

0.14 mg/kg/day exposure will produce 0.191 mg/L plasma concentration at steady-state

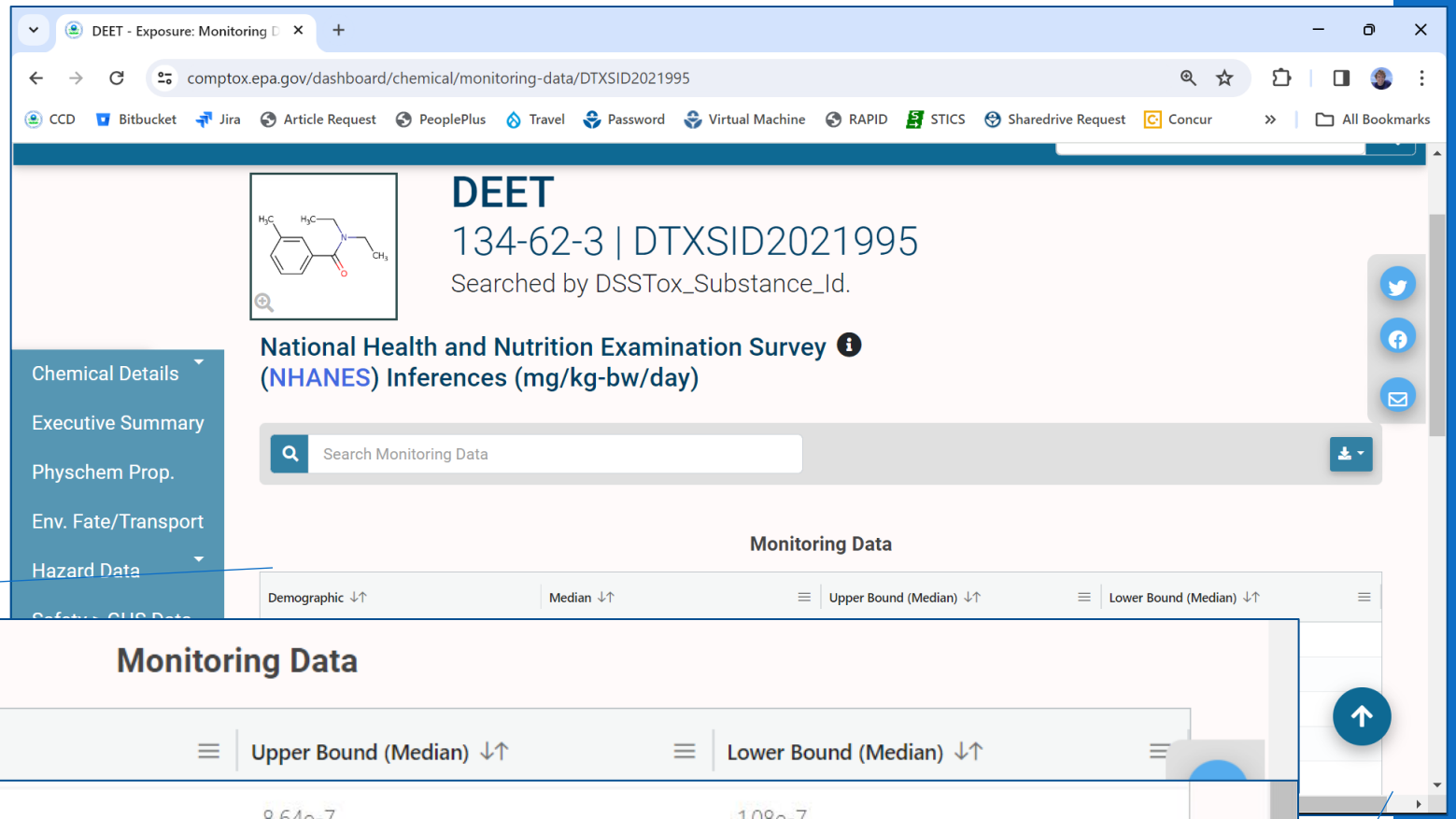
0.14 mg/kg/day / 0.000000867 mg/kg/day

Bioactive Dose is **162,000 times higher** than dose inferred from CDC biomonitoring data → Low general population risk

Openly Available Exposure Information

https://comptox.epa.gov/dashboard

- Demographic-specific inferences from NHANES are available for certain demographic groups
- Again, only for median
- Again, we have only ~100 chemicals

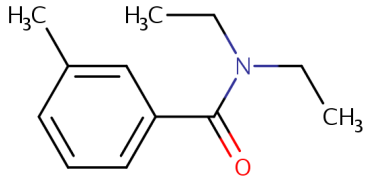


Monitoring Data

Demographic	Median	Upper Bound (Median)	Lower Bound (Median)
66 years and older	4.35e-7	8.64e-7	1.08e-7
ReproAgeFemale	3.82e-7	8.89e-7	7.74e-8
BMI <= 30	4.42e-7	9.18e-7	1.07e-7

trition Examination Survey (NHANES) made using R package bayesMarker (Stanfield et al., 2022 & 2024)

Calculation 3: NHANES Demographic Bioactivity:Exposure Ratio



DEET (CASRN 134-62-3, DTXSID2021995):
NHANES Total Population Daily Intake Rate
Upper 95th: 8.89 x 10^{-7} mg/kg/day

Estimated steady-state intake rate needed to cause plasma concentration = $POD_{in\ vitro}$	÷	Divide by Inferred Exposure for Median U.S. Population	=	Bioactivity Exposure Ratio (BER)

0.14 mg/kg/day exposure will produce 0.191 mg/L plasma concentration at steady-state

0.14 mg/kg/day / 0.000000889 mg/kg/day

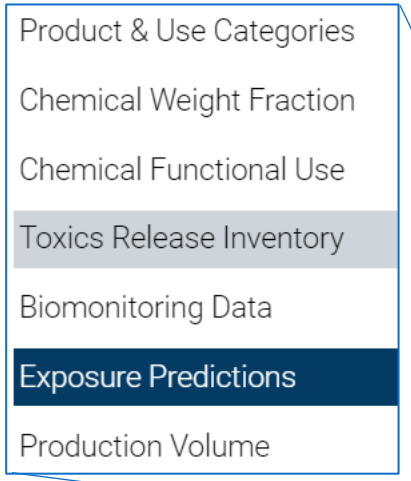
Bioactive Dose is **157,000 times higher** than dose inferred from CDC biomonitoring data

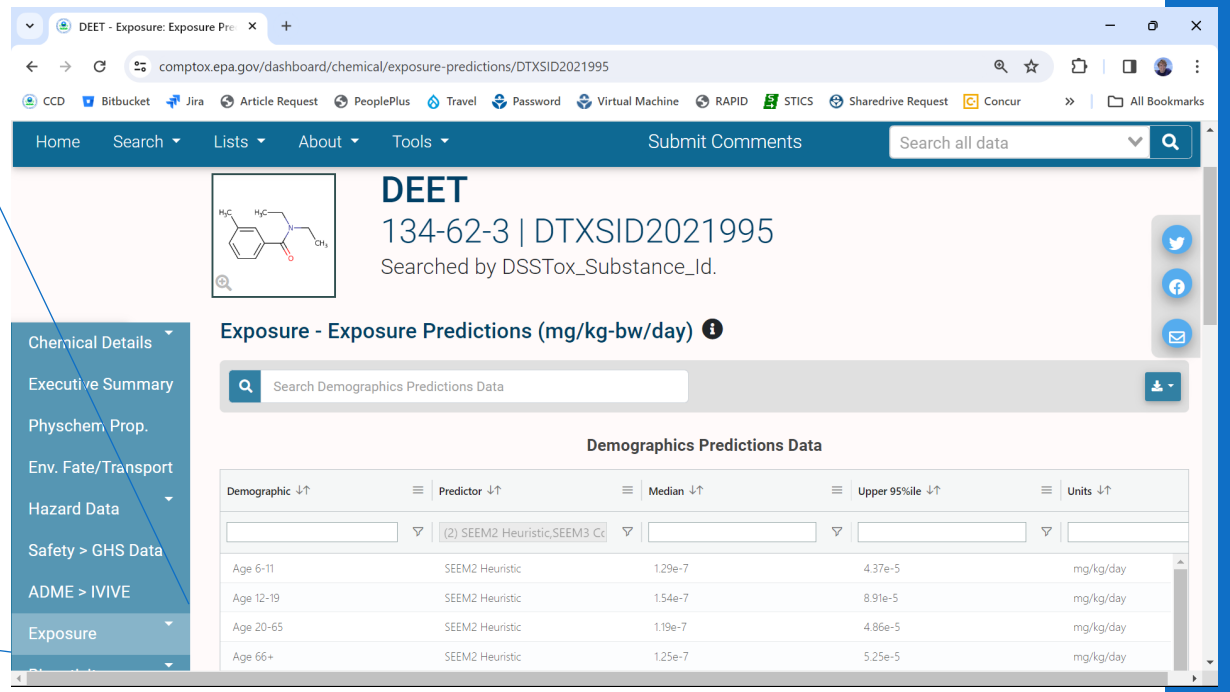
Low risk for median woman of reproductive age

Openly Available Exposure Information

https://comptox.epa.gov/dashboard

- For most chemicals we do not have intake rates from NHANES
- However, systematic empirical evaluation of models (SEEM) gives estimated intake rates for hundreds of thousands of chemicals



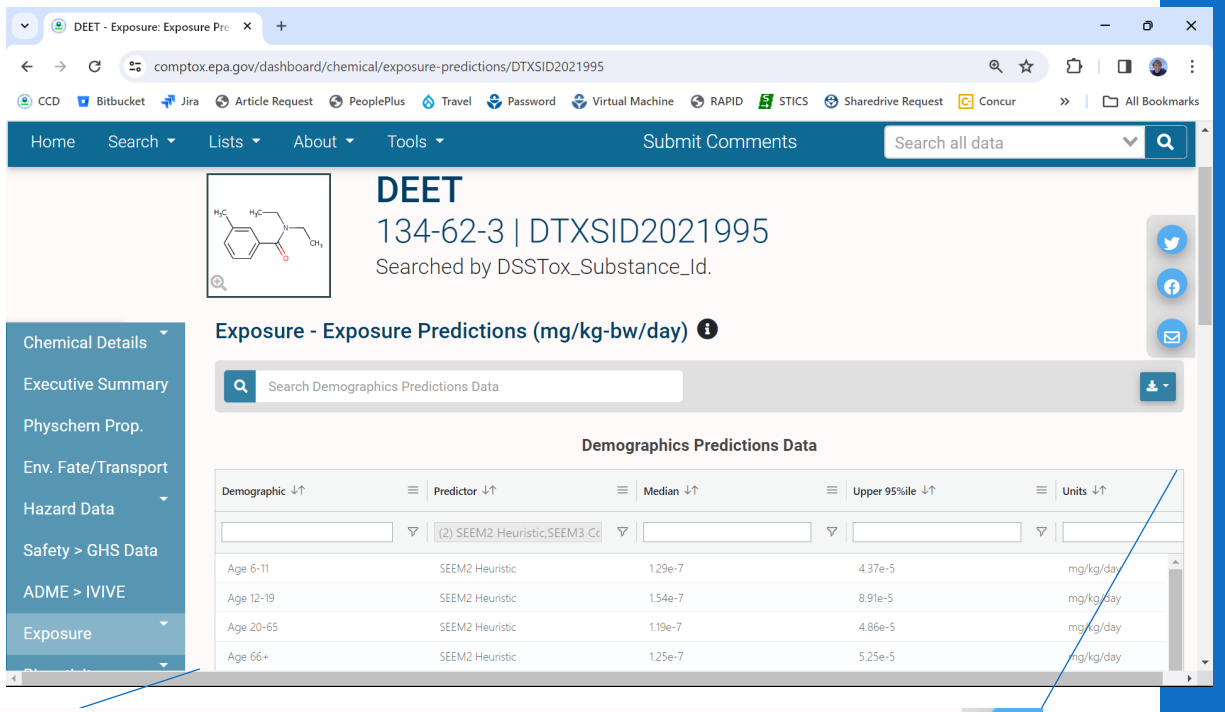


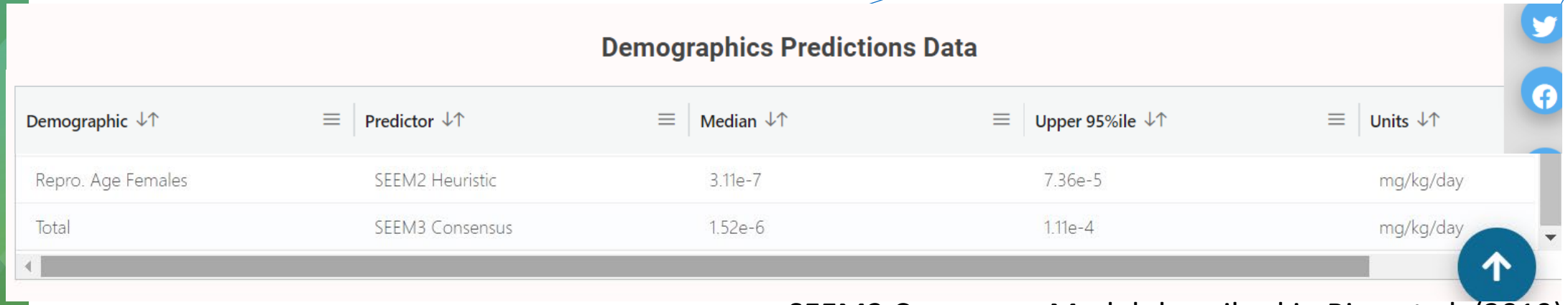
SEEM3 Consensus Model described in Ring et al. (2019)

Openly Available Exposure Information

https://comptox.epa.gov/dashboard

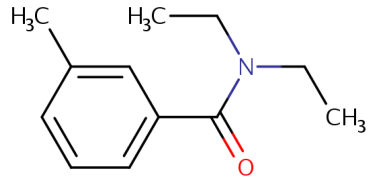
- SEEM forecasts are much more uncertain than NHANES measurements
- For sake of conservatism, we use upper 95th limit on estimated median intake
- **This does not reflect population variability**





SEEM3 Consensus Model described in Ring et al. (2019)

Calculation 4: SEEM Bioactivity:Exposure Ratio



DEET (CASRN 134-62-3, DTXSID2021995):
SEEM Total Population Daily Intake Rate
Upper 95th: 1.11 x 10^{-4} mg/kg/day

Estimated steady-state intake rate needed to cause plasma concentration = $POD_{in\ vitro}$	÷	Divide by Inferred Exposure for Median U.S. Demographic Group	=	Bioactivity Exposure Ratio (BER)

0.14 mg/kg/day exposure will produce 0.191 mg/L plasma concentration at steady-state

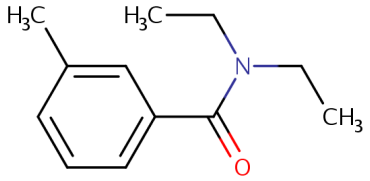
0.14 mg/kg/day / 0.000111 mg/kg/day

Bioactive Dose is **1,260 times higher** than intake rate forecast by SEEM

→ Low general population risk

Note that this BER is less than for NHANES because of greater uncertainty

Calculation 5: Forward Dosimetry, Single Exposure

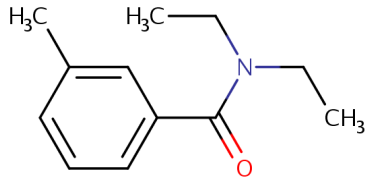


DEET (CASRN 134-62-3, DTXSID2021995):
V_d = 1.7 L/kg, t_{half} = 6.5 h

Single exposure (mg/kg)	×	If oral dose multiply by fraction bioavailable (F_{bio})	÷	Divide by volume of distribution (V_d) (units of L/kg)	=	Peak concentration (C_{max})	95% of dose gone after three half-lives (3 x t_{half})
15% in sun lotion, use 60 g lotion, Body weight 70 kg: 60 * 1000 * 0.15 / 70 = 129 mg/kg		100% absorption in lieu of data to contrary		129 mg/kg / 1.737 L/kg		**74 mg/L**	3 x 6.5 = 19.5 h

Note that if we use a mathematical simulation tool (such as R package httk) we could do more elaborate, tissue specific predictions (httk:solve_pbtk) as well as simulate other exposure routes (inhalation – httk::solve_gas_pbtk(), gestational – httk::solve_fetal_pbtk())

Calculation 6: Forward Dosimetry, Steady-State Exposure



DEET (CASRN 134-62-3, DTXSID2021995):
$C_{ss,95}$ = 1.37 mg/L per 1 mg/kg/day = 1.37 kg-day/L

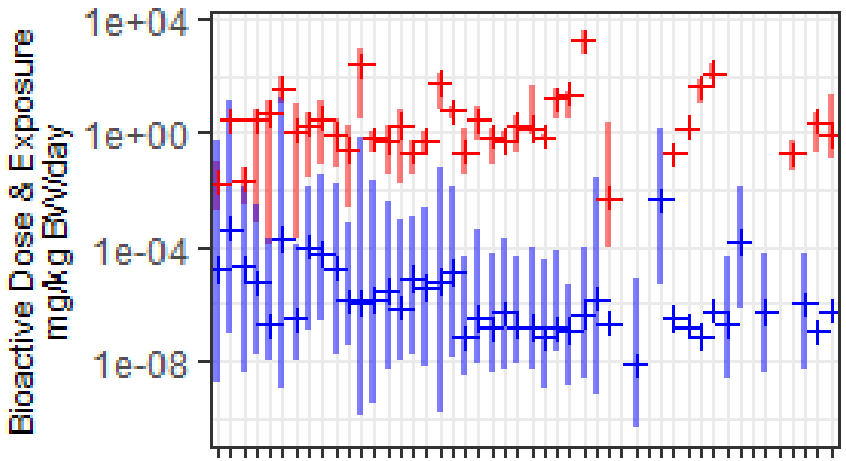
ppm in drinking water	×	Perform unit conversion from ppm to mg/L	×	37 mL/kg/day water intake	÷	Divide by chemical-specific TK clearance (L/kg/dau)	=	Steady-state mg/L in plasma
Scenario, chemical spill causes 1 ppm in drinking water:		1 ppm = 1 µg / g / 1 mL/g (water density) x 1 mg / 1000 µg = 0.001 mg / mL		0.001 mg / mL X 37 mL/kg/day = 0.037 mg/kg/day		0.037 mg/kg/day / CL (L/kg/day)= 0.037 * 1.37 **Convenient TK fact: Clearance (Cl) = 1/C_{ss}**		**0.051 mg/L**

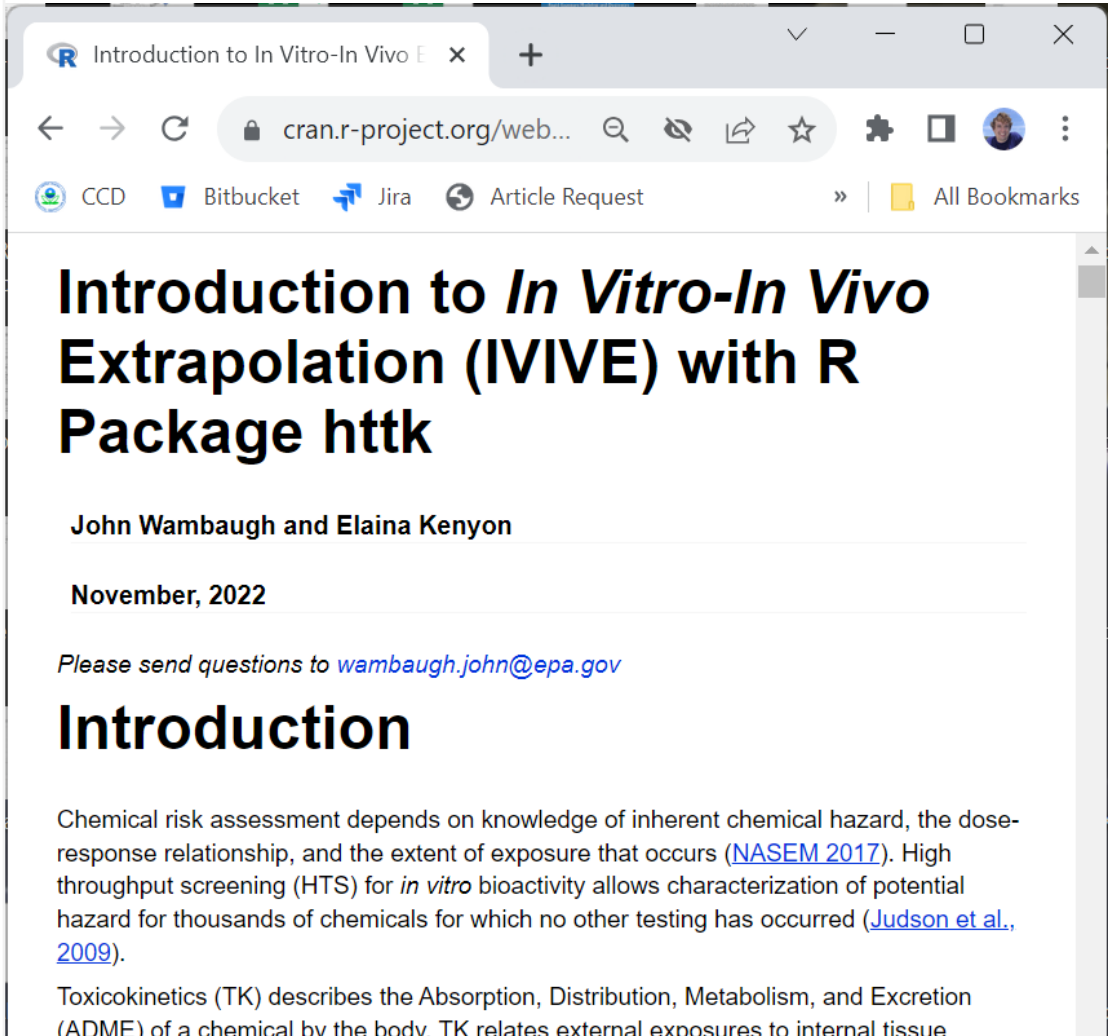
37 mL/kg/day water intake Is from
the EPA Exposure Factors Handbook Table 3-1 for all ages, 95th Percentile

Online Tutorial on Bioactivity : Exposure Ratios

https://cran.r-project.org/web/packages/httk/vignettes/V2_IntrotoIVIVE.html

- An online R tutorial walks you through the steps needed to calculate Bioactivity:Exposure Ratios. It covers:
  - Loading *in vitro* screening data into R
  - HTTK-based IVIVE
  - Applying relevant QSPRs
  - Comparing with Exposure predictions
  - Making a BER Plot

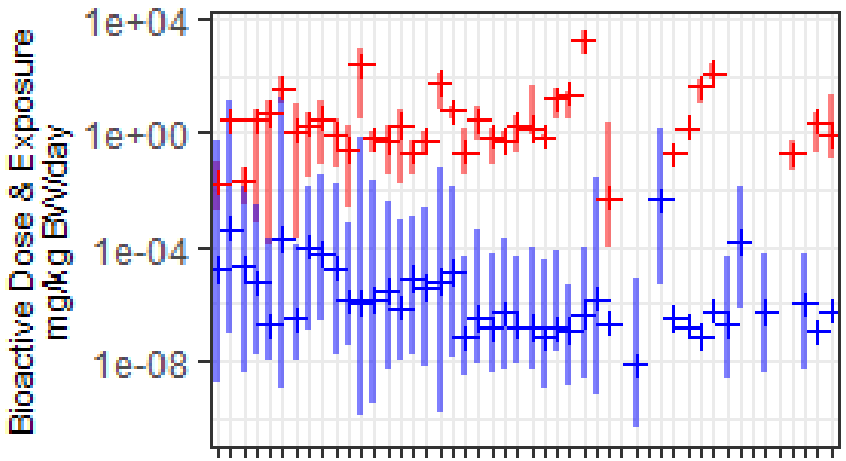


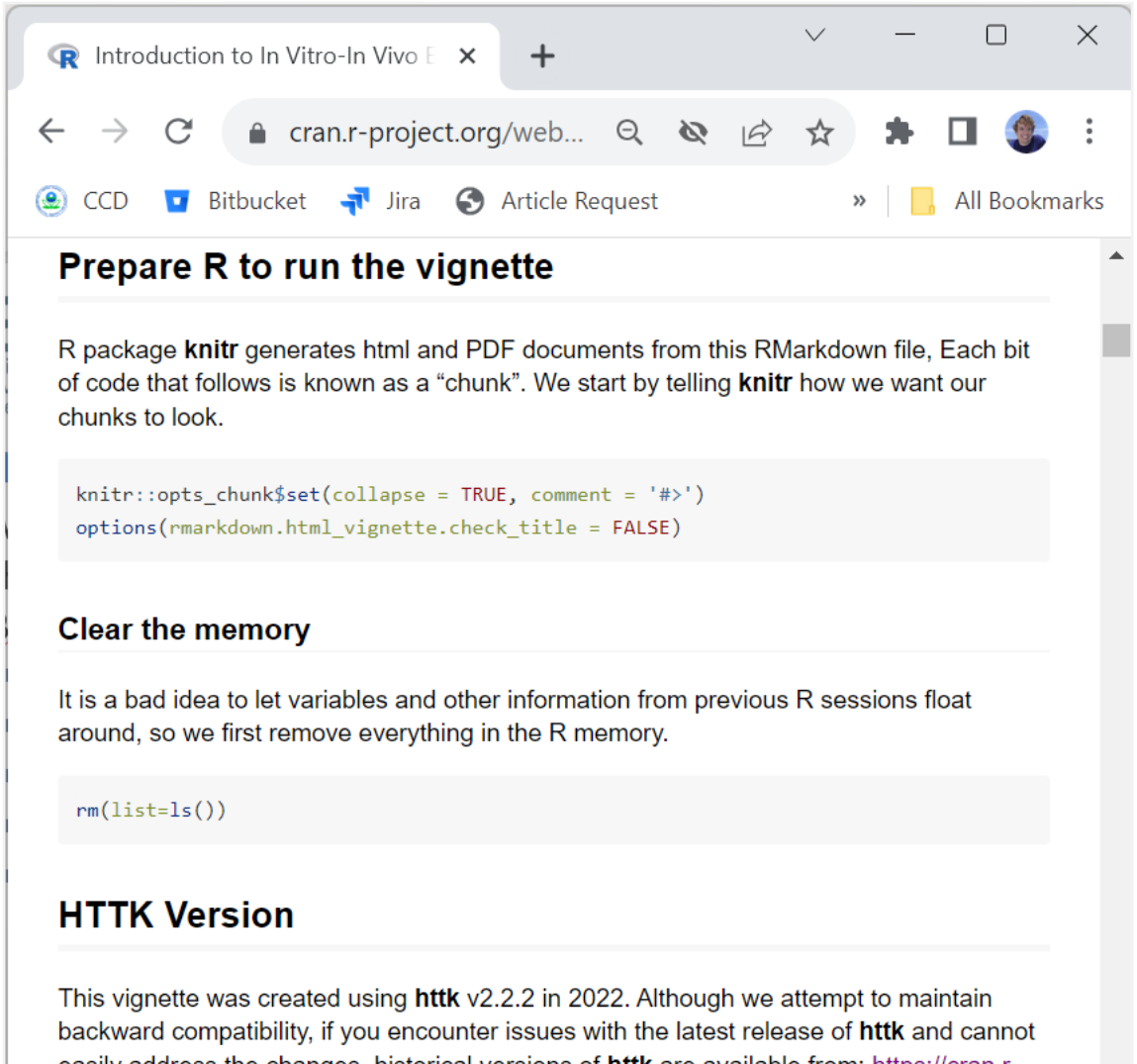


Online Tutorial on Bioactivity : Exposure Ratios

https://cran.r-project.org/web/packages/httk/vignettes/V2_IntrotoIVIVE.html

- An online R tutorial walks you through the steps needed to calculate Bioactivity:Exposure Ratios. It covers:
  - Loading *in vitro* screening data into R
  - HTTK-based IVIVE
  - Applying relevant QSPRs
  - Comparing with Exposure predictions
  - Making a BER Plot

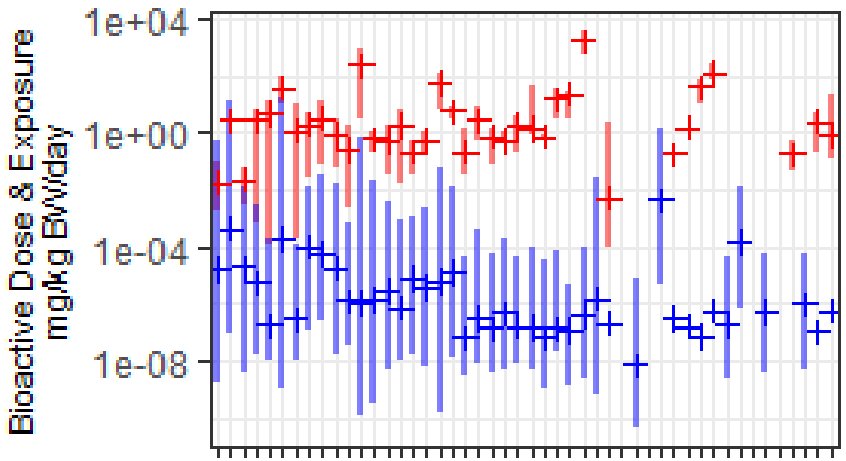


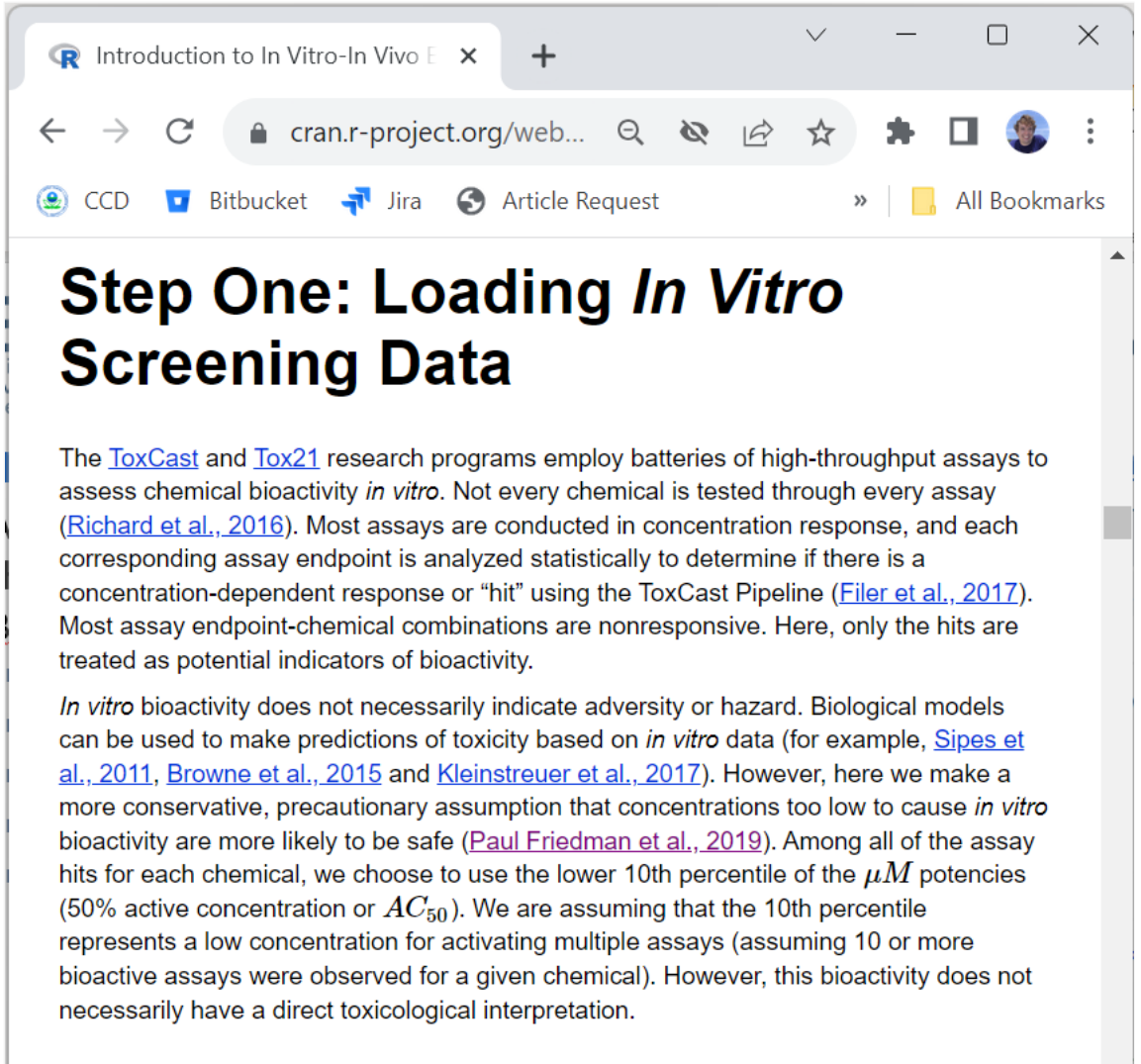


Online Tutorial on Bioactivity : Exposure Ratios

https://cran.r-project.org/web/packages/httk/vignettes/V2_IntrotoIVIVE.html

- An online R tutorial walks you through the steps needed to calculate Bioactivity:Exposure Ratios. It covers:
  - Loading *in vitro* screening data into R
  - HTTK-based IVIVE
  - Applying relevant QSPRs
  - Comparing with Exposure predictions
  - Making a BER Plot

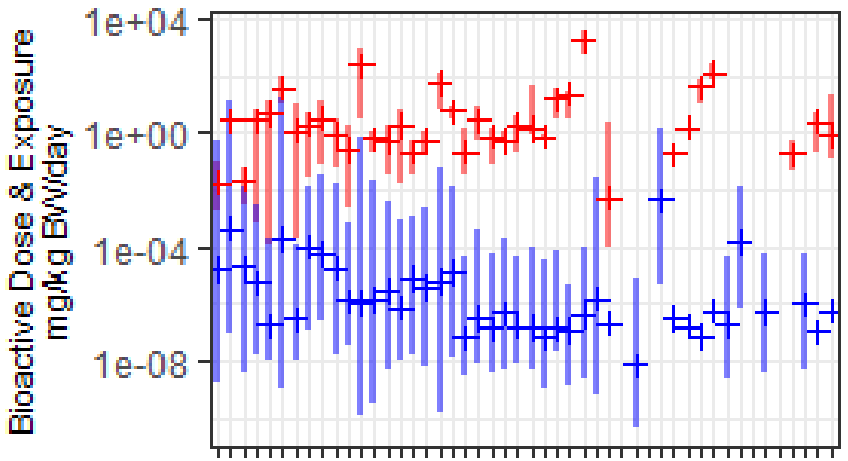


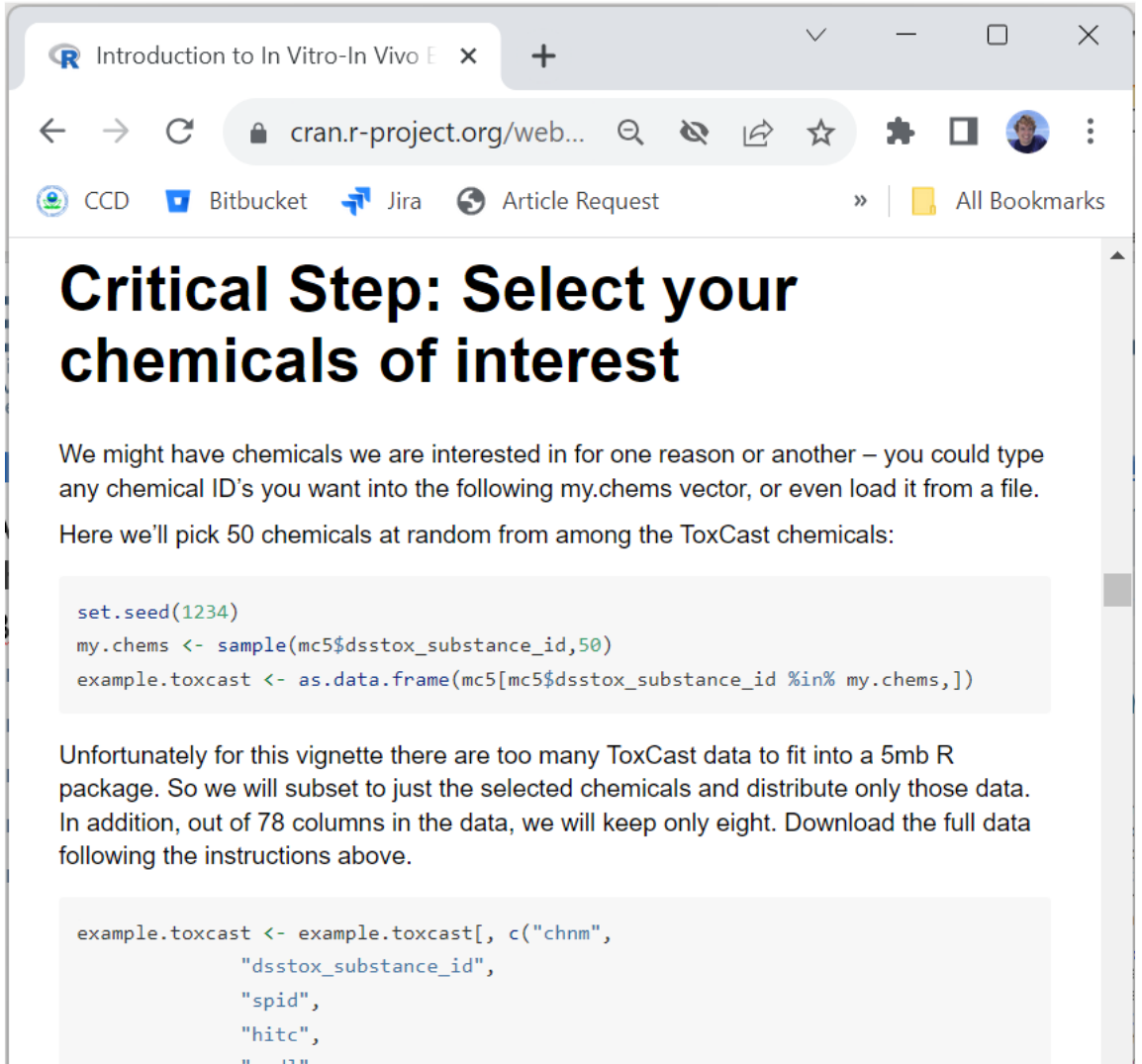


Online Tutorial on Bioactivity : Exposure Ratios

https://cran.r-project.org/web/packages/httk/vignettes/V2_IntrotoIVIVE.html

- An online R tutorial walks you through the steps needed to calculate Bioactivity:Exposure Ratios. It covers:
  - Loading *in vitro* screening data into R
  - HTTK-based IVIVE
  - Applying relevant QSPRs
  - Comparing with Exposure predictions
  - Making a BER Plot

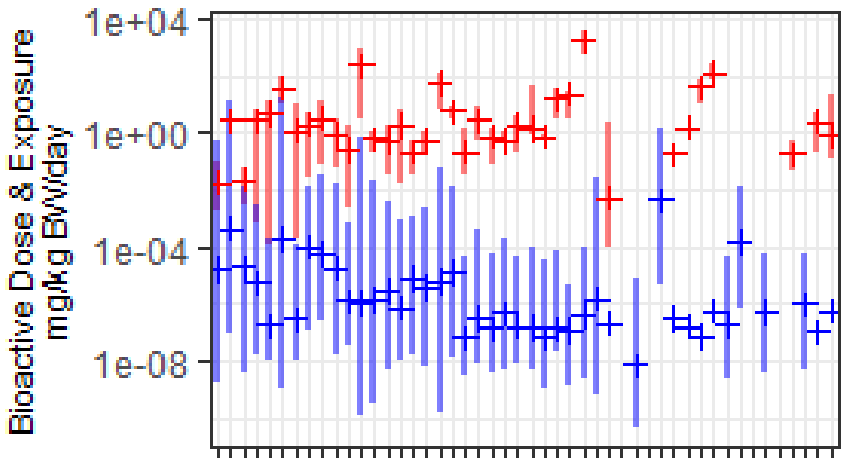


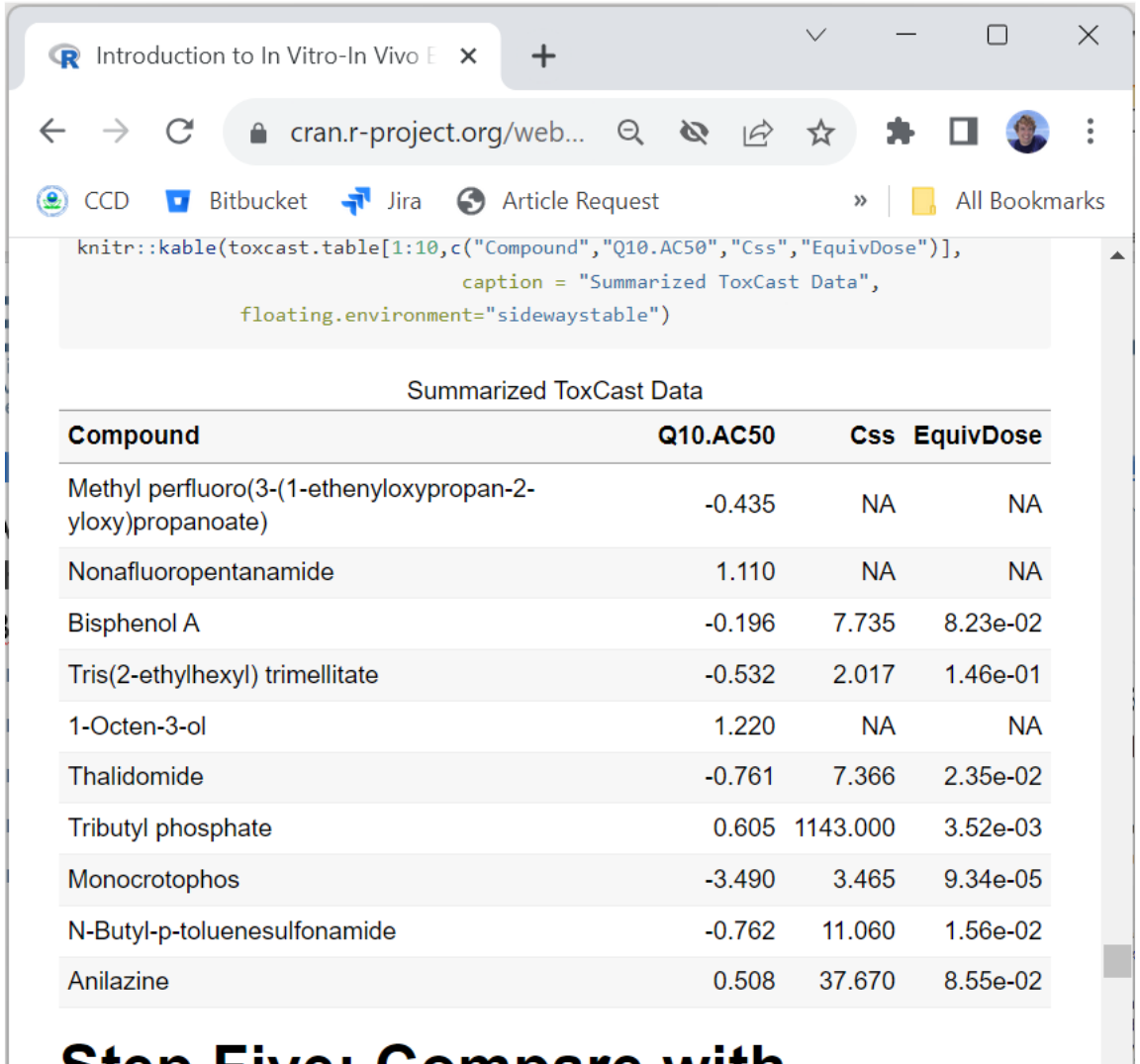


Online Tutorial on Bioactivity : Exposure Ratios

https://cran.r-project.org/web/packages/httk/vignettes/V2_IntrotoIVIVE.html

- An online R tutorial walks you through the steps needed to calculate Bioactivity:Exposure Ratios. It covers:
  - Loading *in vitro* screening data into R
  - HTTK-based IVIVE
  - Applying relevant QSPRs
  - Comparing with Exposure predictions
  - Making a BER Plot





Summarized ToxCast Data

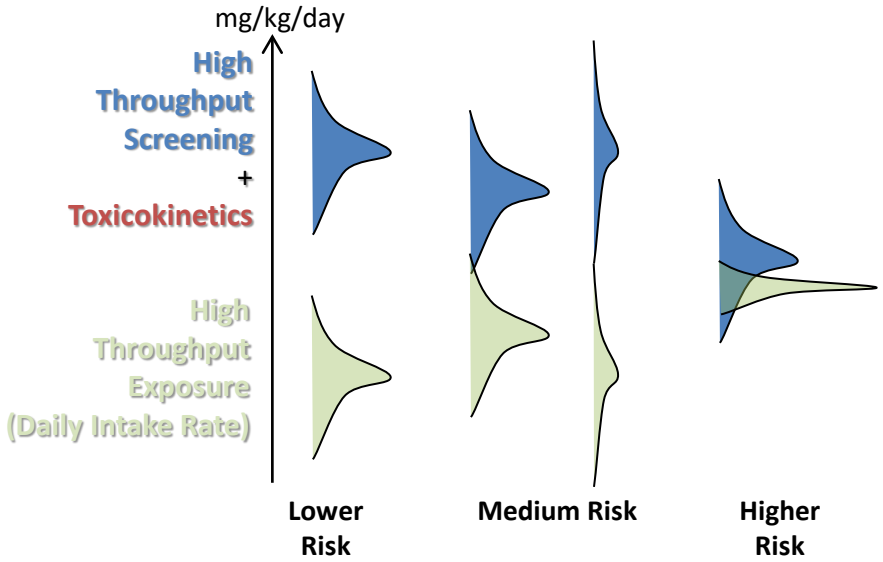
Compound	Q10.AC50	Css	EquivDose
Methyl perfluoro(3-(1-ethenyloxypropan-2-yloxy)propanoate)	-0.435	NA	NA
Nonafluoropentanamide	1.110	NA	NA
Bisphenol A	-0.196	7.735	8.23e-02
Tris(2-ethylhexyl) trimellitate	-0.532	2.017	1.46e-01
1-Octen-3-ol	1.220	NA	NA
Thalidomide	-0.761	7.366	2.35e-02
Tributyl phosphate	0.605	1143.000	3.52e-03
Monocrotophos	-3.490	3.465	9.34e-05
N-Butyl-p-toluenesulfonamide	-0.762	11.060	1.56e-02
Anilazine	0.508	37.670	8.55e-02

Step Five: Compare with

Conclusions

Please send any questions to:
wambaugh.john@epa.gov

- High throughput toxicokinetics (HTTK) are available to convert from bioactive *in vitro* concentrations to putative dose rates that might cause those concentrations (**new approach method-based points of departure or POD_{NAM}**)
- We calculate the **Bioactivity:Exposure Ratio (BER)** by comparing POD_{NAM} to a daily intake rate



- For a small subset of chemicals daily intake rates are monitored by the U.S. CDC
- The **systematic empirical evaluation of models (SEEM)** tool provides estimated intake rates for most chemicals
  The 95% interval on SEEM intake rates reflects uncertainty on median population value and does not reflect population variability

References

Please send any questions to:
wambaugh.john@epa.gov

- Bell, Shannon M., et al. "In vitro to in vivo extrapolation for high throughput prioritization and decision making." Toxicology in vitro 47 (2018): 213-227.
- Bell, Shannon, et al. "An integrated chemical environment with tools for chemical safety testing." *Toxicology in Vitro* 67 (2020): 104916.
- Breen, Miyuki, et al. "High-throughput PBTK models for in vitro to in vivo extrapolation." Expert opinion on drug metabolism & toxicology 17.8 (2021): 903-921.
- Coecke, Sandra, et al. "Toxicokinetics as a key to the integrated toxicity risk assessment based primarily on non-animal approaches." Toxicology in vitro 27.5 (2013): 1570-1577.
- Dorne, Jean-Lou, et al. "Reconnecting exposure, toxicokinetics and toxicity in food safety: OpenFoodTox and TKplate for human health, animal health and ecological risk assessment." *54. Congress of the European Societies of Toxicology (EUROTOX 2018)*. Vol. 295. No. Suppl. 1. 2018.
- Kapraun, Dustin F., et al. "Evaluation of a rapid, generic human gestational dose model." Reproductive Toxicology 113 (2022): 172-188.
- Khalidi, Hiba, et al. "SimRFlow: An R-based workflow for automated high-throughput PBPK simulation with the Simcyp® simulator." *Frontiers in Pharmacology* 13 (2022).
- Linakis, Matthew W., et al. "Development and evaluation of a high throughput inhalation model for organic chemicals." Journal of exposure science & environmental epidemiology 30.5 (2020): 866-877.
- National Research Council. "Risk assessment in the federal government: managing the process." (1983).
- Paul Friedman, Katie, et al. "Utility of in vitro bioactivity as a lower bound estimate of in vivo adverse effect levels and in risk-based prioritization." Toxicological Sciences 173.1 (2020): 202-225.
- Pearce, Robert G., et al. "Httk: R package for high-throughput toxicokinetics." *Journal of Statistical Software* 79.4 (2017a): 1.
- Pearce, Robert G., et al. "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." Journal of pharmacokinetics and pharmacodynamics 44 (2017b): 549-565.
- Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118.
- Sayre, Risa R., John F. Wambaugh, and Christopher M. Grulke. "Database of pharmacokinetic time-series data and parameters for 144 environmental chemicals." Scientific data 7.1 (2020): 122.
- Sobels, F. H. (1982) "The parallelogram; an indirect approach for the assessment of genetic risks from chemical mutagens." In: Progress in Mutation Research, Vol. 3 (K. C. Bora, G. R. Douglas, and E. R. Nestman, Eds.), Elsevier, Amsterdam, pp. 233-327.
- Stanfield, Zachary, et al. "Bayesian inference of chemical exposures from NHANES urine biomonitoring data." Journal of Exposure Science & Environmental Epidemiology 32.6 (2022): 833-846.
- Stanfield, Zachary, et al. "Characterizing Chemical Exposure Trends from NHANES Urinary Biomonitoring Data." Environmental Health Perspectives 132.1 (2024): 017009.
- Tan, Yu-Mei, Kai H. Liao, and Harvey J. Clewell. "Reverse dosimetry: interpreting trihalomethanes biomonitoring data using physiologically based pharmacokinetic modeling." Journal of exposure science & environmental epidemiology 17.7 (2007): 591-603.
- Wambaugh, John F., et al. "Evaluating in vitro-in vivo extrapolation of toxicokinetics." Toxicological Sciences 163.1 (2018): 152-169.
- Wang, Ying-Hong. "Confidence assessment of the Simcyp time-based approach and a static mathematical model in predicting clinical drug-drug interactions for mechanism-based CYP3A inhibitors." Drug Metabolism and Disposition 38.7 (2010): 1094-1104.
- Wetmore, Barbara A., et al. "Integration of dosimetry, exposure, and high-throughput screening data in chemical toxicity assessment." Toxicological Sciences 125.1 (2012): 157-174.
- Wetmore, Barbara A. "Quantitative in vitro-to-in vivo extrapolation in a high-throughput environment." Toxicology 332 (2015a): 94-101.
- Wetmore, Barbara A., et al. "Incorporating high-throughput exposure predictions with dosimetry-adjusted in vitro bioactivity to inform chemical toxicity testing." Toxicological Sciences 148.1 (2015b): 121-136.
- Williams, Antony J., et al. "The CompTox Chemistry Dashboard: a community data resource for environmental chemistry." *Journal of cheminformatics* 9 (2017): 1-27.

The views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the author's institution