EPA United States Environmental Protection Agency

ExpoCast
*exposure forecasting*

# The Exposome and the Public: Toxicity and Exposure Models


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**American Society for Mass Spectrometry**

Unravelling the Exposome

**January 23 - 26, 2020**
**Captiva Island, FL**

**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**

# US EPA Office of Research and Development

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

- Research is conducted by ORD's four national centers, and three offices organized to address:
  - Public health and env. assessment; comp. tox. and exposure; env. measurement and modeling; and env. solutions and emergency response.

- 13 facilities across the United States

- Research conducted by a combination of Federal scientists (including uniformed members of the **Public Health Service**); contract researchers; and postdoctoral, graduate student, and post-baccalaureate trainees


ORD Facility in
Research Triangle Park, NC

# Chemical Regulation in the United States

- Park *et al.* (2012): At least 3221 chemical signatures in pooled human blood samples, many appear to be exogenous

- A tapestry of laws covers the chemicals people are exposed to in the United States (Breyer, 2009)

- Chemical safety testing is primarily for food additives, pharmaceuticals, and pesticide active ingredients (NRC, 2007)

    - Different levels of testing depending on chemical category


November 29, 2014

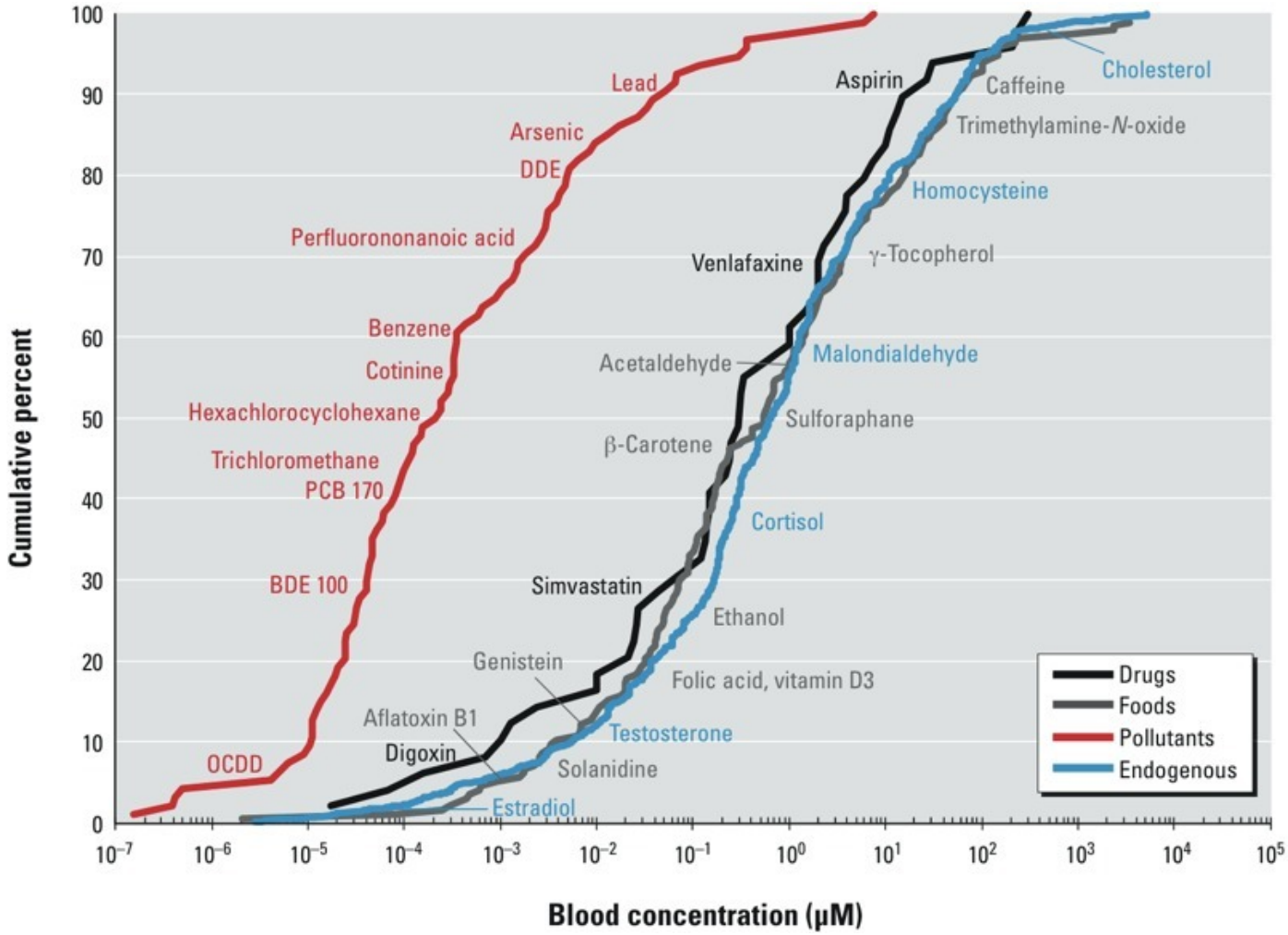
# Chemical Regulation in the United States

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

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

- Thousands of chemicals on the market were "grandfathered" in without assessment
Judson et al. (2009), Egeghy et al. (2012), Wetmore et al. (2015)

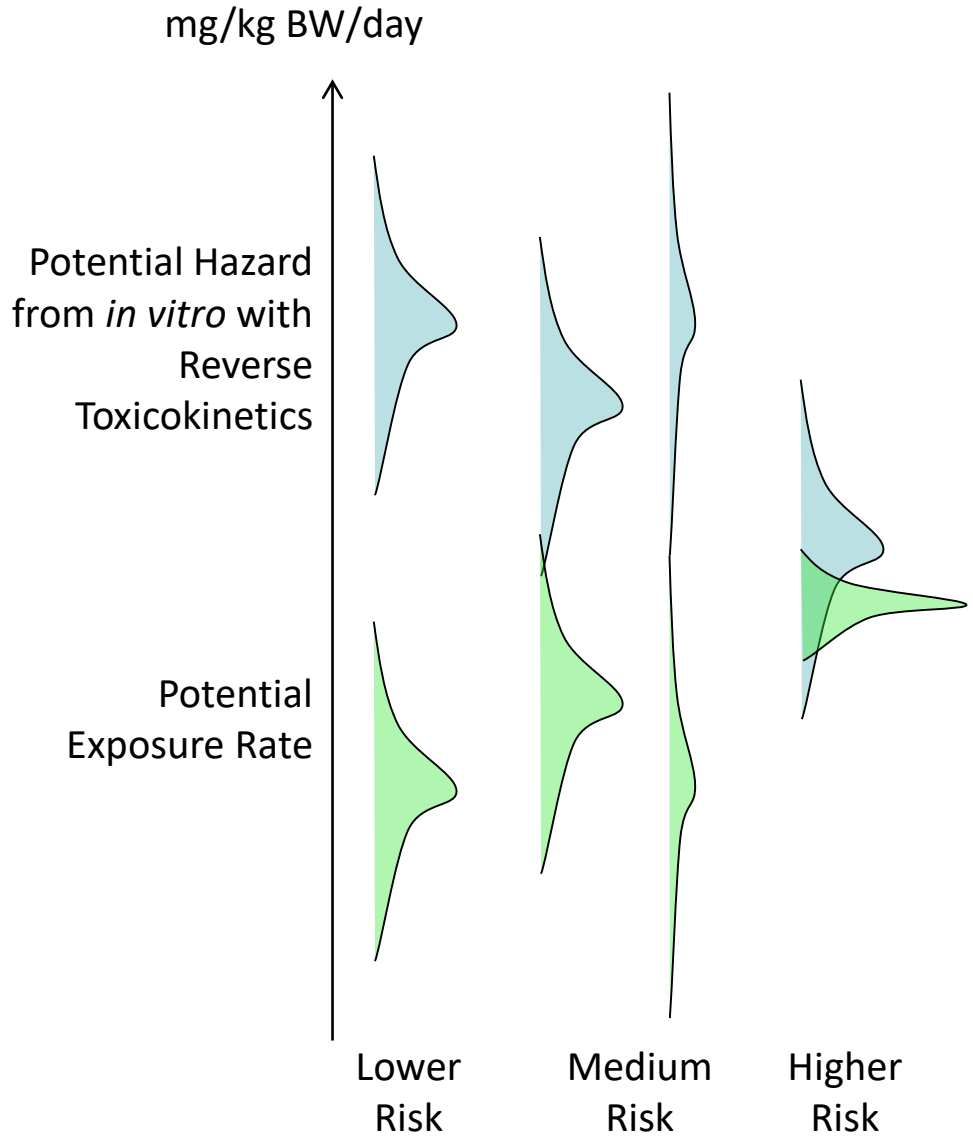
*We need risk assessment to establish what is a "low level"*




Rappaport et al. (2014)

# Chemical Risk = Hazard x Exposure

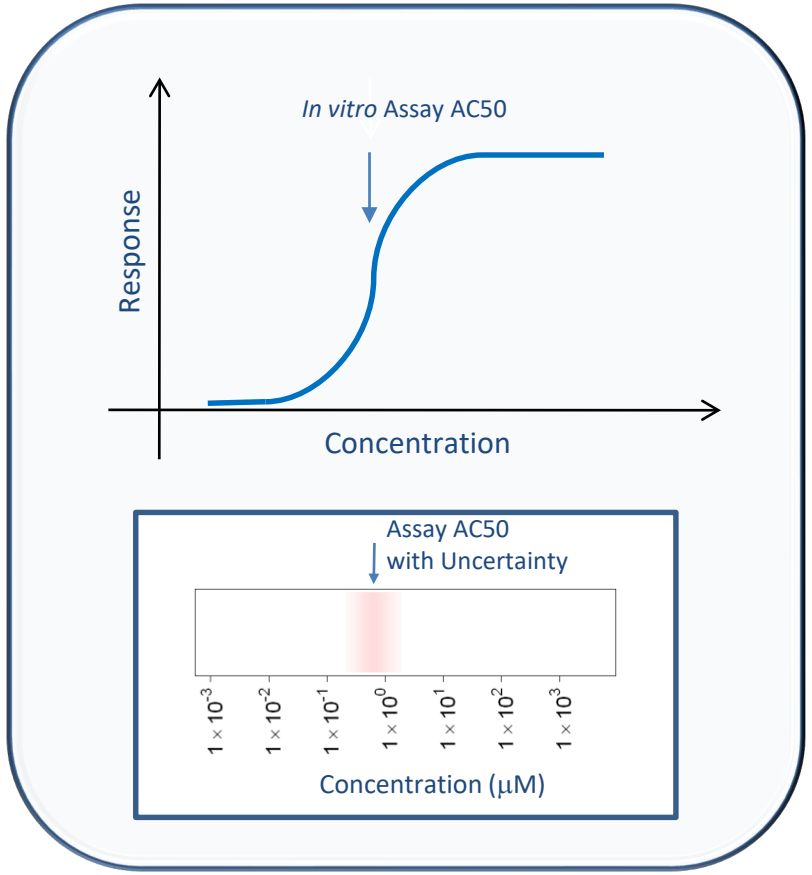
- The U.S. National Research Council (1983) identified chemical risk as a function of both inherent **hazard** and **exposure**
- Addressing thousands of chemicals requires "**new approach methodologies**" (**NAMs***):
  1. High throughput hazard characterization (Dix et al., 2007, Collins et al., 2008)
  2. High throughput exposure forecasts (Wambaugh et al., 2013, 2014)
  3. High throughput toxicokinetics (i.e., dose-response relationship) linking hazard and exposure (Wetmore et al., 2012, 2015)




*Kavlock et al. (2018)

# High-Throughput Bioactivity Screening Projects

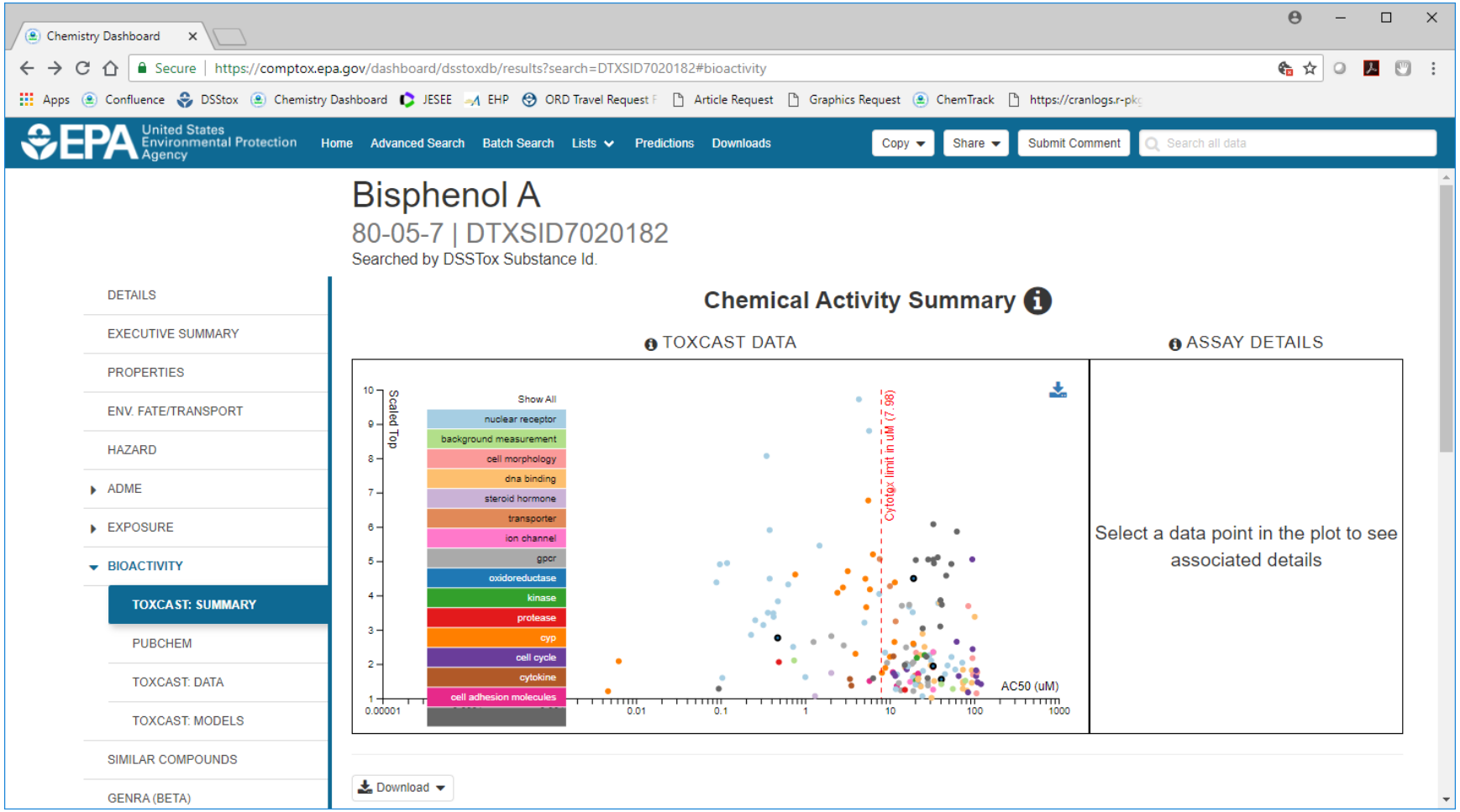
- With high throughput "toxicity" screening we attempt to estimate points of departure *in vitro* using high throughput screening (HTS)
- **Tox21**: Examining >8,000 chemicals using ~50 assays intended to identify interactions with biological pathways (Schmidt, 2009)
- **ToxCast** (Toxicity Forecast): For a subset (>3000) of Tox21 chemicals EPA has measured >1100 additional assays-endpoints (Kavlock *et al.*, 2012)
- Most assays conducted in dose-response format (identify 50% activity concentration – $AC_{50}$ – and efficacy if data described by a Hill function, Filer *et al.*, 2016)
- All data are public: http://comptox.epa.gov/dashboard/



# Chemical Bioactivity Data

- Data from the ToxCast and Tox21 projects are available through the dashboard

**https://comptox.epa.gov/dashboard/**



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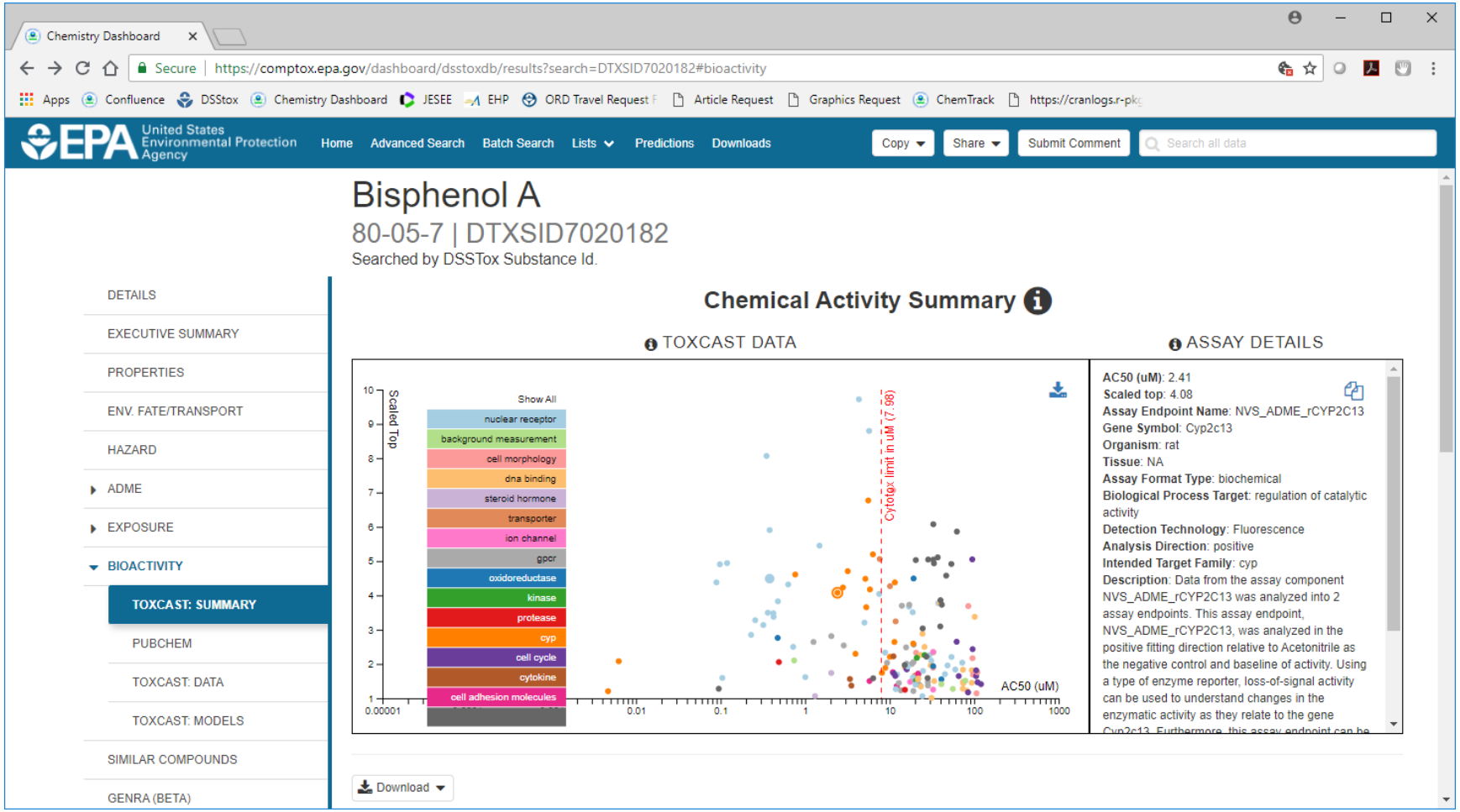


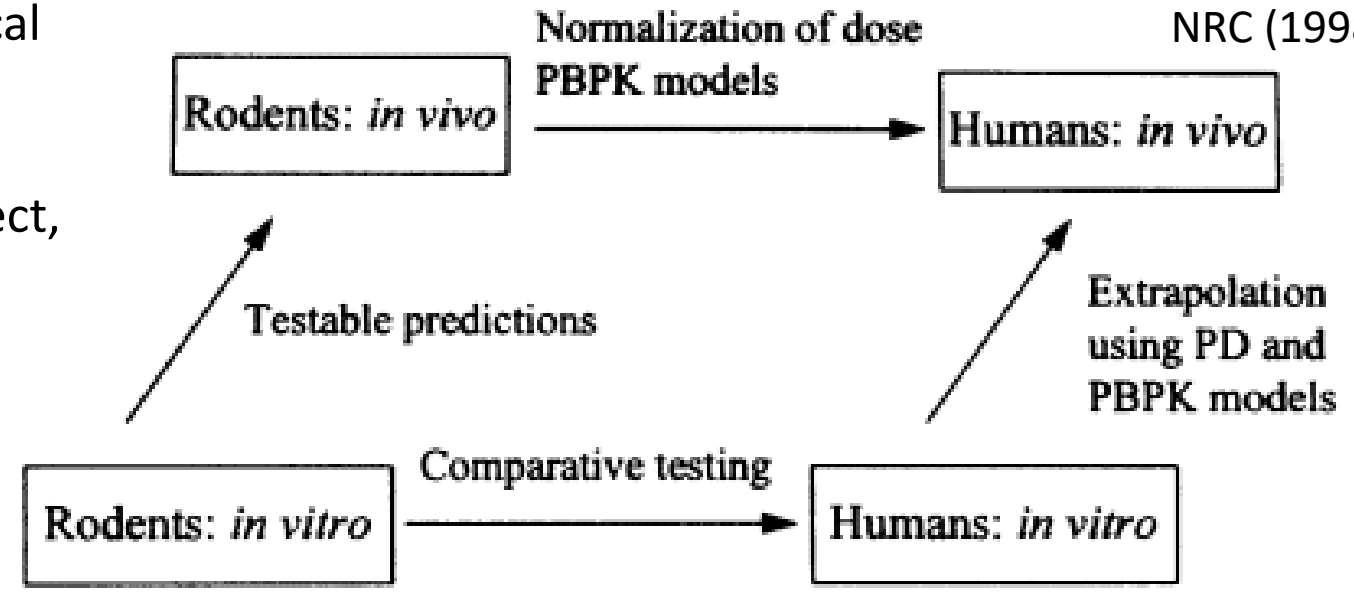
# *In Vitro - In Vivo* Extrapolation (IVIVE)

IVIVE is the use 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

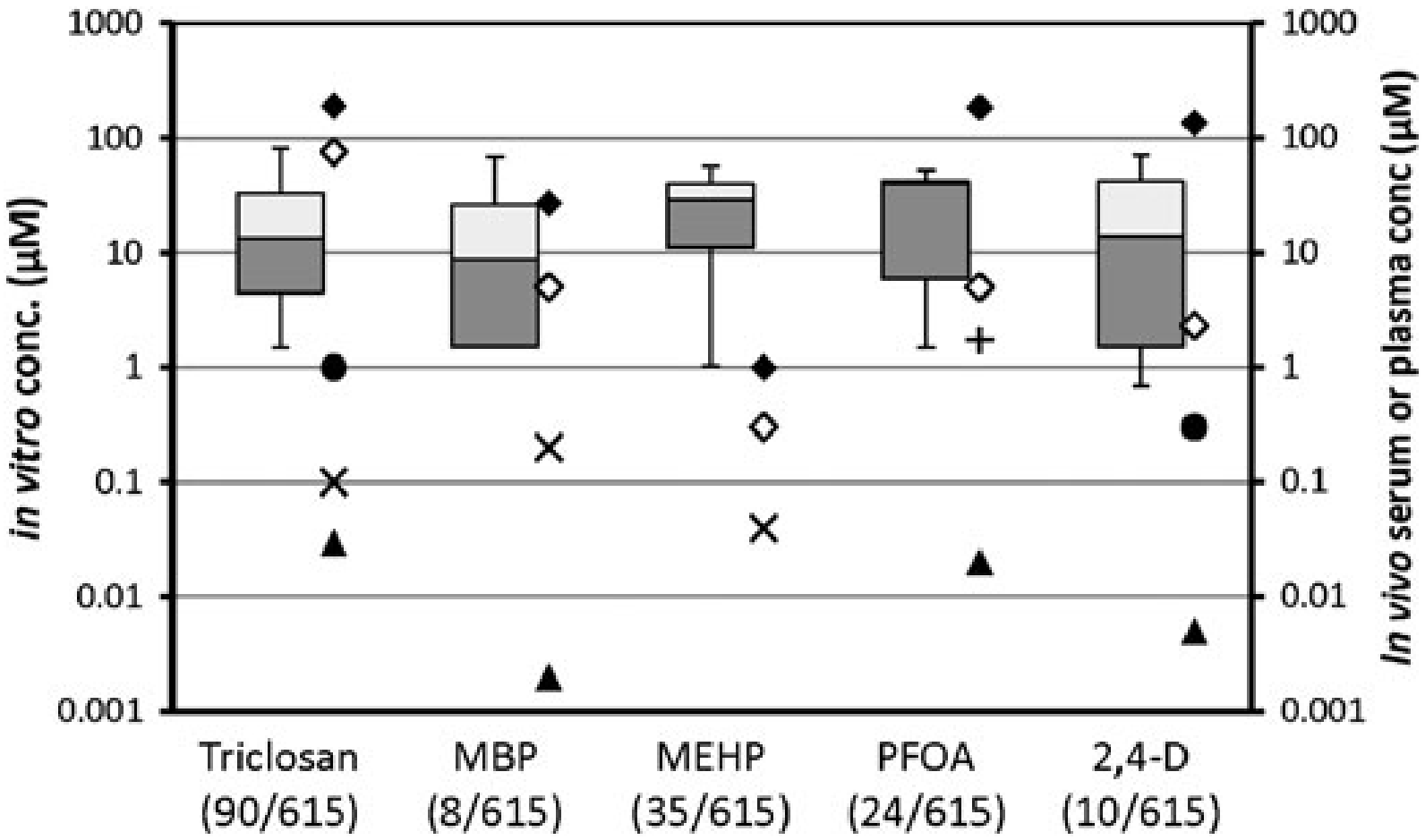
- IVIVE-PD/TD (**Pharmacodynamics/Toxicodynamics**):
  - Effect of molecules/chemicals at biological target *in vivo*
  - Assay design/selection important
  - Perturbation as adverse/therapeutic effect, reversible/ irreversible effeccts

- Both contribute to *in vivo* effect prediction




NRC (1998)

# The Margin Between Exposure and Hazard




- ◆ estimated or measured average concentrations associated with the LOAEL in animal studies
- ◇ NOAEL in animal studies
- ● Humans with chronic exposure reference values (solid circles)
- x Volunteers using products containing the chemical
- \+ Biomonitored occupational populations
- ▲ General populations

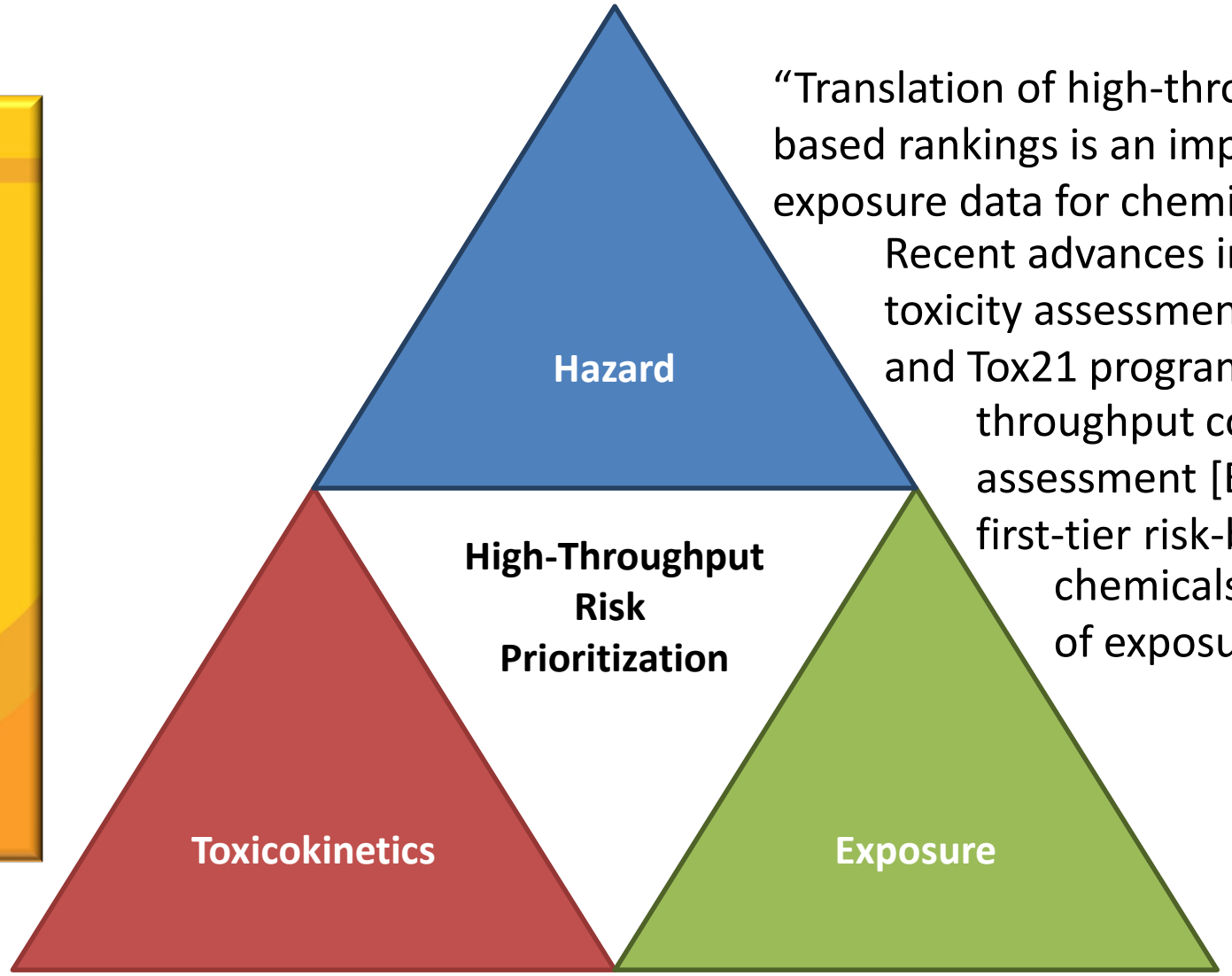
The five chemicals (as of 2011) with plasma biomonitoring AND ToxCast data… what do we do about the other 1000's?

Aylward and Hays (2011)

# Most Chemicals Lack Data on Exposure and Toxicokinetics

United States Environmental Protection Agency


NASEM (2017)




"Translation of high-throughput data into risk-based rankings is an important application of exposure data for chemical priority-setting.

Recent advances in high-throughput toxicity assessment, notably the ToxCast and Tox21 programs… and in high-throughput computational exposure assessment [ExpoCast] have enabled first-tier risk-based rankings of chemicals on the basis of margins of exposure" - National Academies of Sciences, Engineering, and Medicine (NASEM)

# NAMs for Exposure Science

| Exposure NAM Class | Description | Traditional Approach | Makes Use of: Measurement | Toxicokinetics | Models | Descriptors | Evaluation | Machine Learning |
|---|---|---|---|---|---|---|---|---|
| Measurements | New techniques including screening analyses capable of detecting hundreds of chemicals present in a sample | Targeted (chemical-specific) analyses | - | ● | ● | ● | | ● |
| Toxicokinetics | High throughput methods using in vitro data to generate chemical-specific models | Analyses based on in vivo animal studies | ● | - | | ● | | ● |
| HTE Models | Models capable of making predictions for thousands of chemicals | Models requiring detailed, chemical- and scenario-specific information | ● | ● | - | ● | | |
| Chemical Descriptors | Informatic approaches for organizing chemical information in a machine-readable format | Tools targeted at single chemical analyses by humans | | | | - | | ● |
| Evaluation | Statistical approaches that use the data from many chemicals to estimate the uncertainty in a prediction for a new chemical | Comparison of model predictions to data on a per chemical basis | ● | ● | ● | ● | - | ● |
| Machine Learning | Computer algorithms to identify patterns | Manual Inspection of the data | ● | ● | | ● | | - |
| Prioritization | Integration of exposure and other NAMs to identify chemicals for follow-up study | Expert decision making | ● | ● | ● | ● | ● | ● |



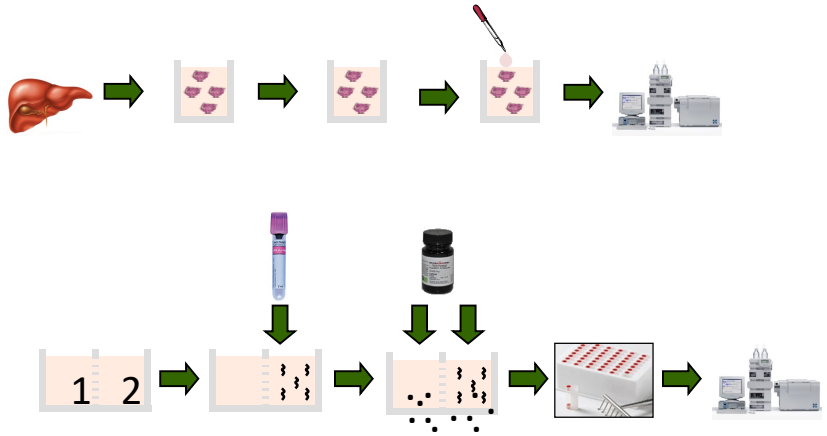
Wambaugh et al., (2019)

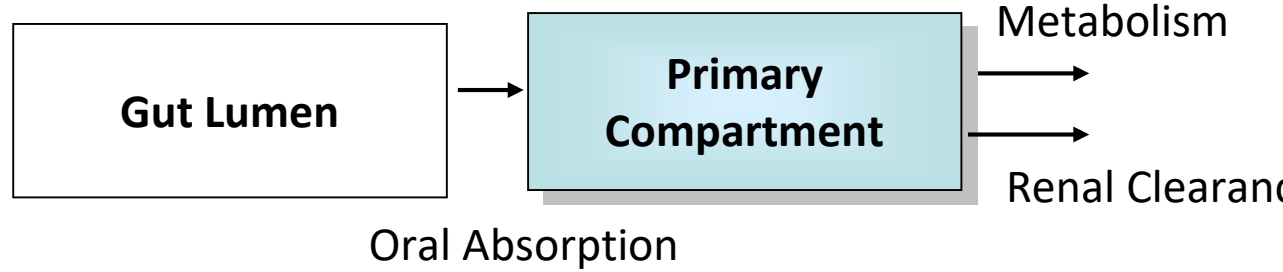
# High Throughput Toxicokinetics (HTTK)

Most chemicals lack public toxicokinetic-related data (Wetmore et al., 2012):

**_In vitro_ toxicokinetic data + generic toxicokinetic model**

**= high(er) throughput toxicokinetics**

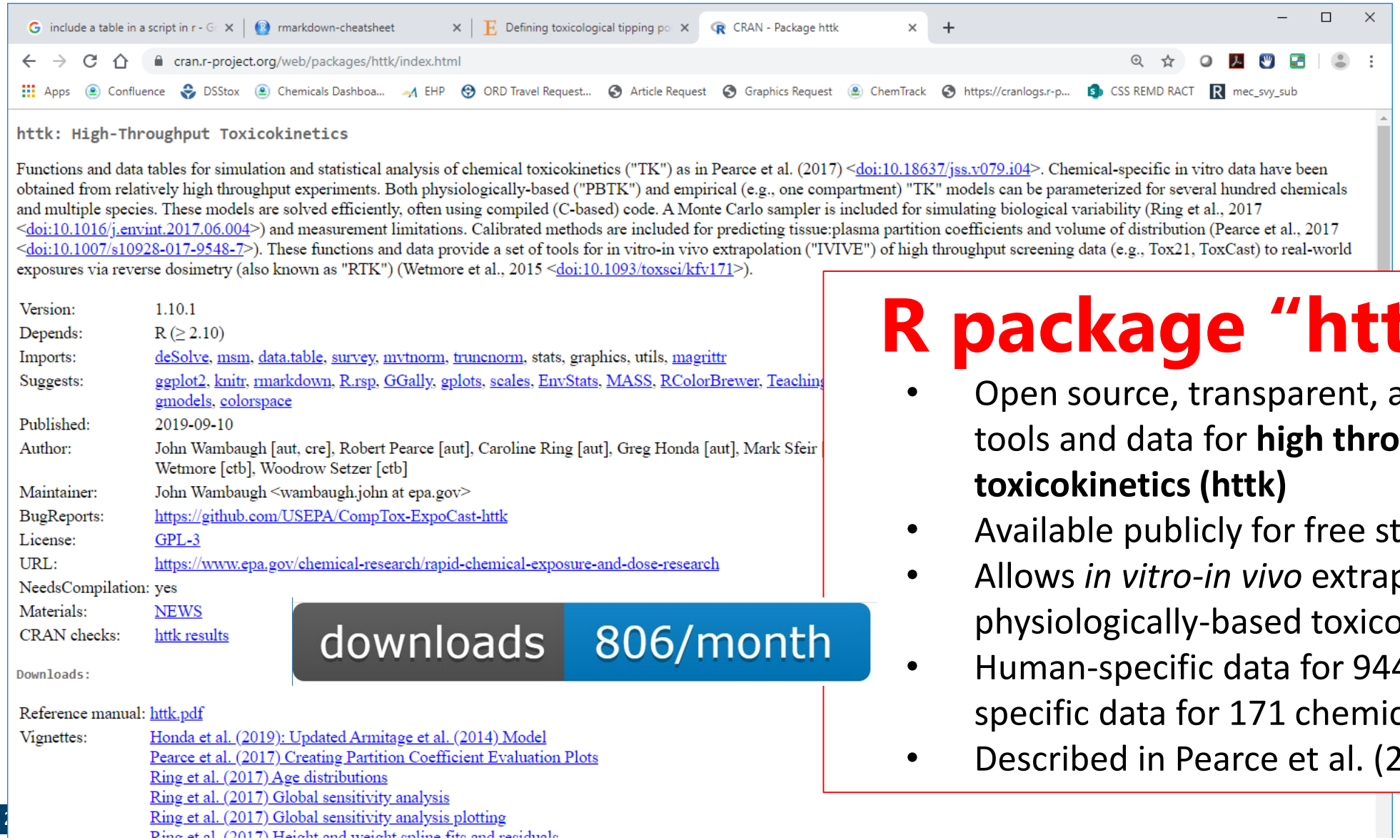



= *httk*

# Open Source Tools and Data for HTTK

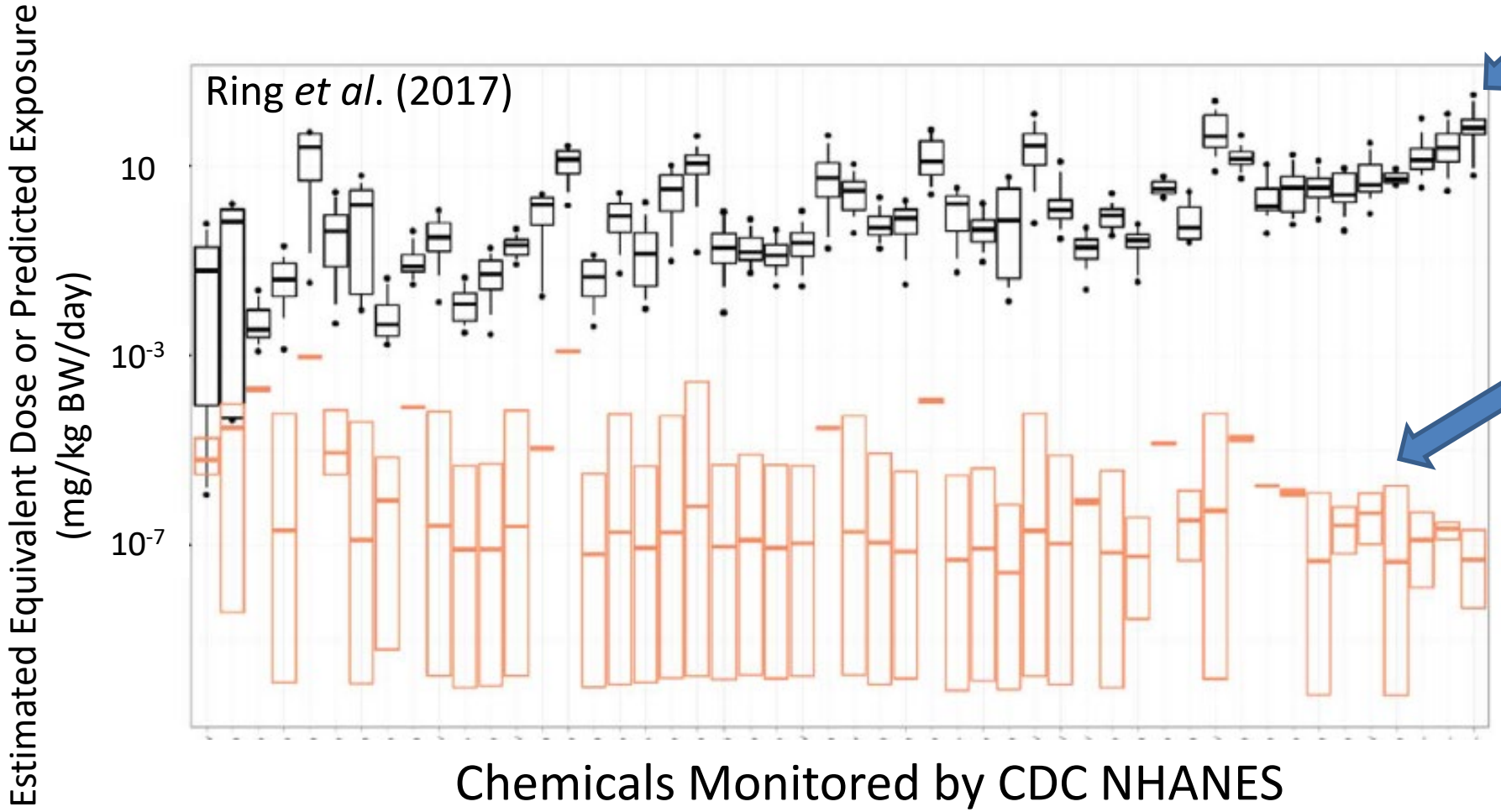
https://CRAN.R-project.org/package=httk




## R package "httk"

- Open source, transparent, and peer-reviewed tools and data for **high throughput toxicokinetics (httk)**
- Available publicly for free statistical software R
- Allows *in vitro-in vivo* extrapolation (IVIVE) and physiologically-based toxicokinetics (PBTK)
- Human-specific data for 944 chemicals and rat-specific data for 171 chemicals
- Described in Pearce et al. (2017)

# Chemical Prioritization NAMs

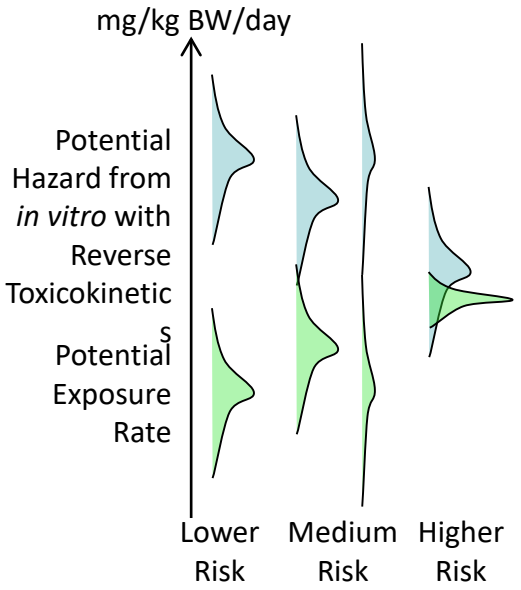



Chemicals Monitored by CDC NHANES

(Most chemicals do not have monitoring data – Egeghy et al. 2012)

High throughput *in vitro* screening can estimate doses needed to cause bioactivity (e.g., Wetmore et al., 2015)

Exposure intake rates can be inferred from biomarkers (e.g., Ring et al., 2018)



# What Do We Know About Exposure? Biomonitoring Data

- Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination Survey (NHANES) provides an important tool for monitoring public health
- Large, ongoing CDC survey of US population: demographic, body measures, medical exam, biomonitoring (health and exposure), …
- Designed to be representative of US population according to census data
- Data sets publicly available (http://www.cdc.gov/nchs/nhanes.htm)
- Includes measurements of:
    - Body weight
    - Height
    - **Chemical analysis of blood and urine**

# What Do We Know About Exposure? Exposure Models

- Human chemical exposures can be coarsely grouped into "**near field**" sources that are close to the exposed individual (consumer or occupational exposures) '**far-field**' scenarios wherein individuals are exposed to chemicals that were released or used far away (ambient exposure) (Arnot *et al.*, 2006).

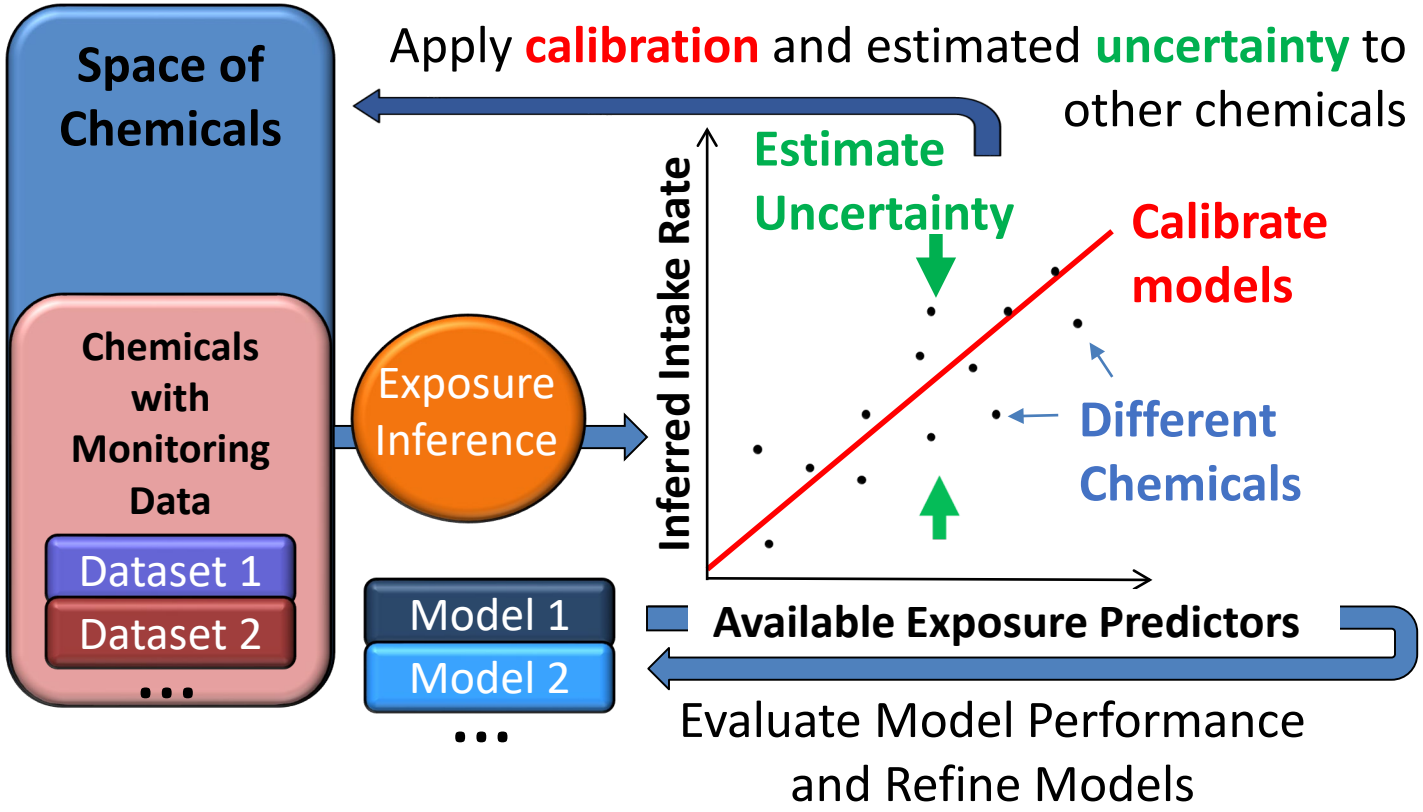
- A model captures knowledge and a hypothesis of how the world works (MacLeod *et al.*, 2010)

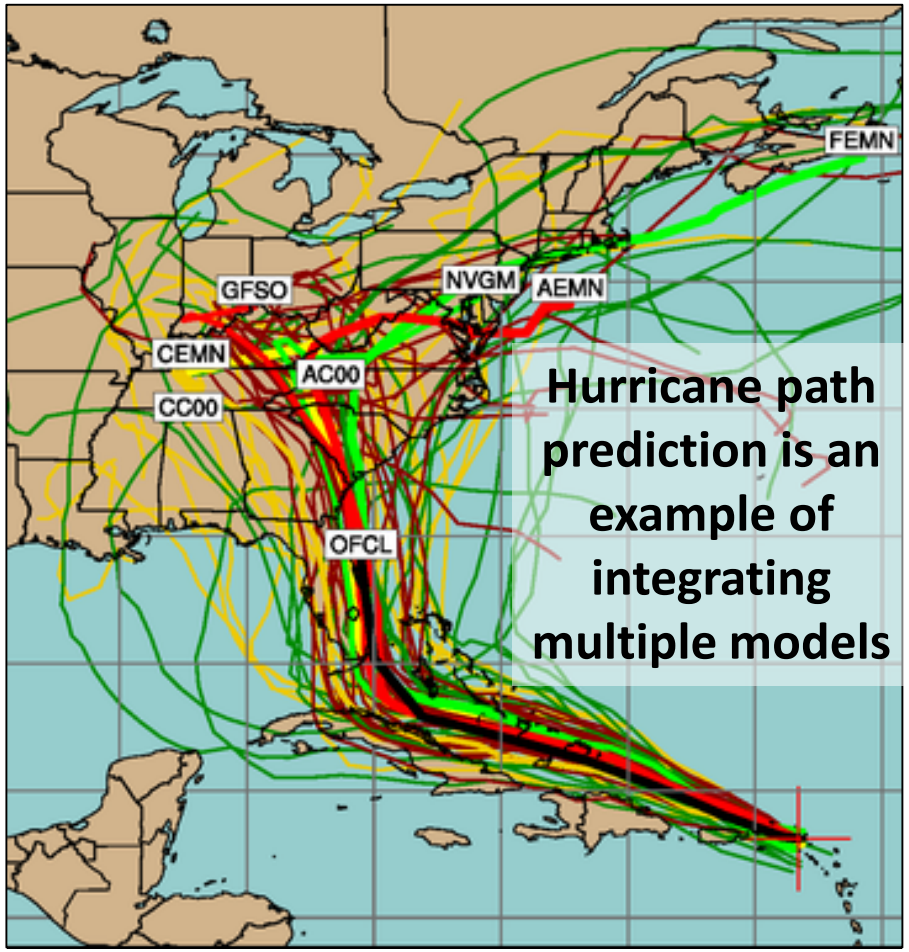
- EPA's EXPOsure toolBOX (EPA ExpoBox) is a toolbox created to assist individuals from within government, industry, academia, and the general public with assessing exposure
  - Includes many, many models (https://www.epa.gov/expobox)

**"Now it would be very remarkable if any system existing in the real world could be exactly represented by any simple model. However, cunningly chosen parsimonious models often do provide remarkably useful approximations… The only question of interest is 'Is the model illuminating and useful?'"**
**- George Box**

# EPA's ExpoCast (Exposure Forecast) Project and 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)



*Ring et al., 2018*

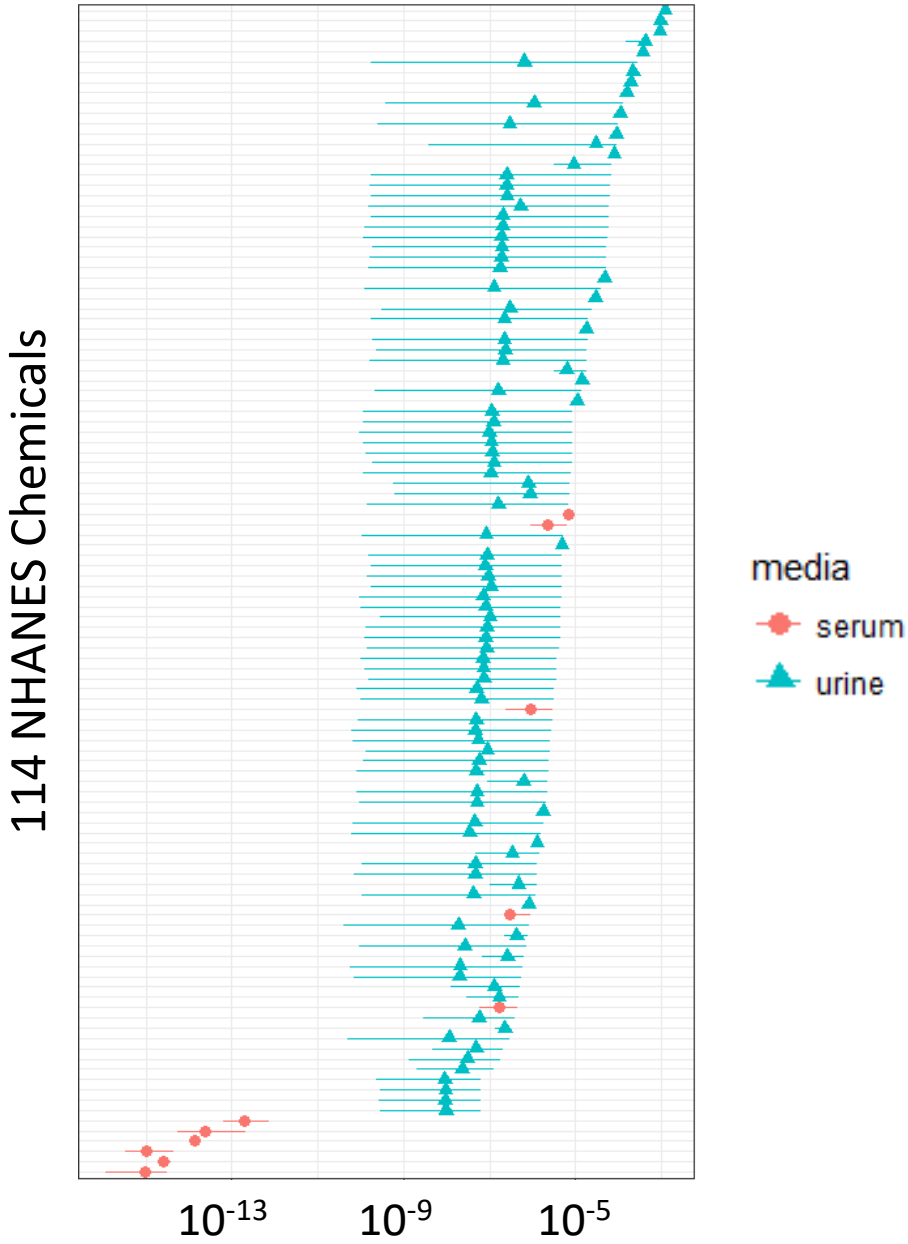
# Collaboration on High Throughput Exposure Predictions

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 | Pathways |
|---|---|---|---|
| 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 |

# Reverse Dosimetry (Tan et al., 2006)

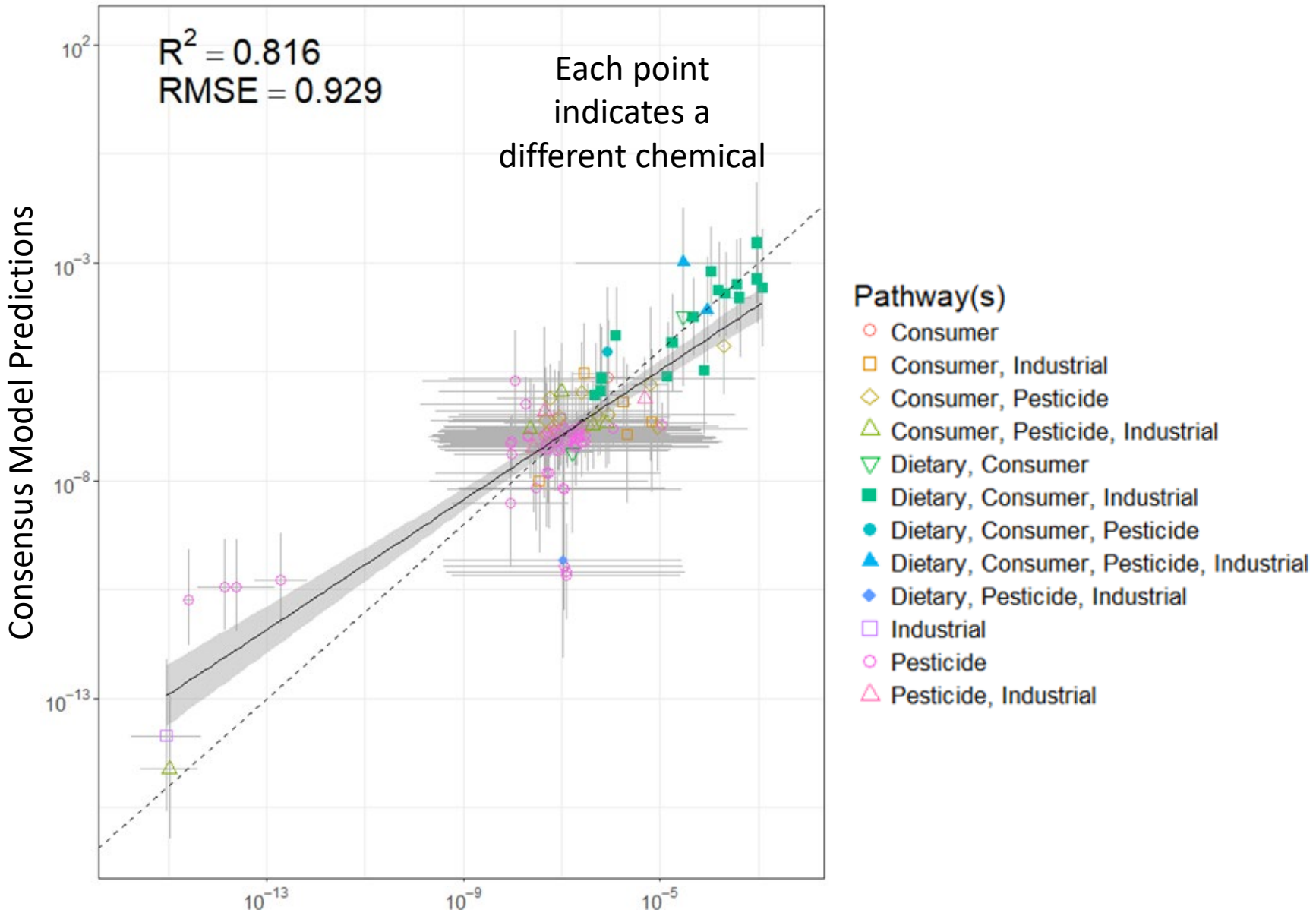
- Median chemical intake rates (mg / kg body weight /day) were inferred from:
  - NHANES urine (Wambaugh et al, 2014, Ring et al. 2017)
  - NHANES serum/blood either using HTTK clearance (Pearce et al., 2017)
    - Literature clearance estimates were used for methodologically challenging chemicals not suited to HTTK




Ring et al. (2018)

# Pathway-Based Consensus Modeling of NHANES

- Machine learning models were built for each of four exposure pathways
- Pathway predictions can be used for large chemical libraries
- Use prediction (and accuracy of prediction) as a prior for Bayesian analysis
- Each chemical may have exposure by multiple pathways

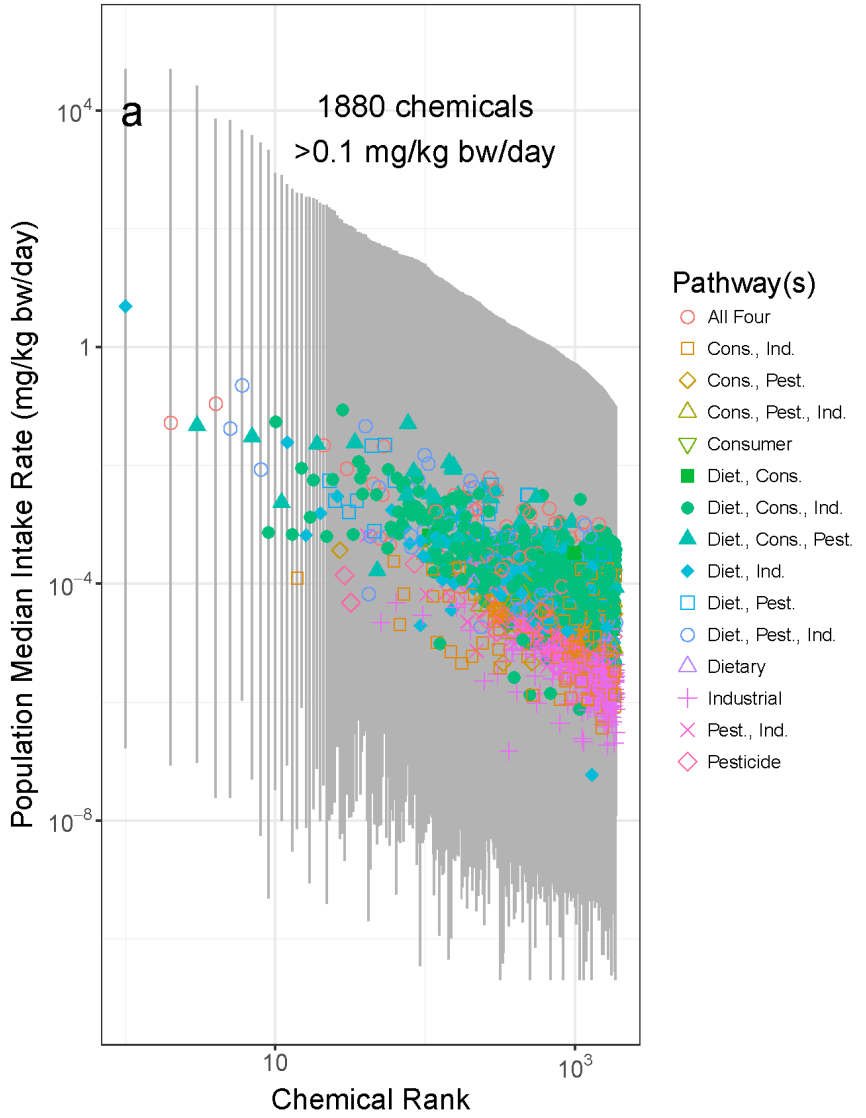



*Ring et al., 2018*

# Consensus Modeling of Median Chemical Intake

- We predict relevant pathway(s), median intake rate, and credible interval for each of 479,926 chemicals

- Of 687,359 chemicals evaluated, 30% have low probability for exposure via any of the four pathways
  - They are considered outside the "domain of applicability"






*Ring et al., 2018*

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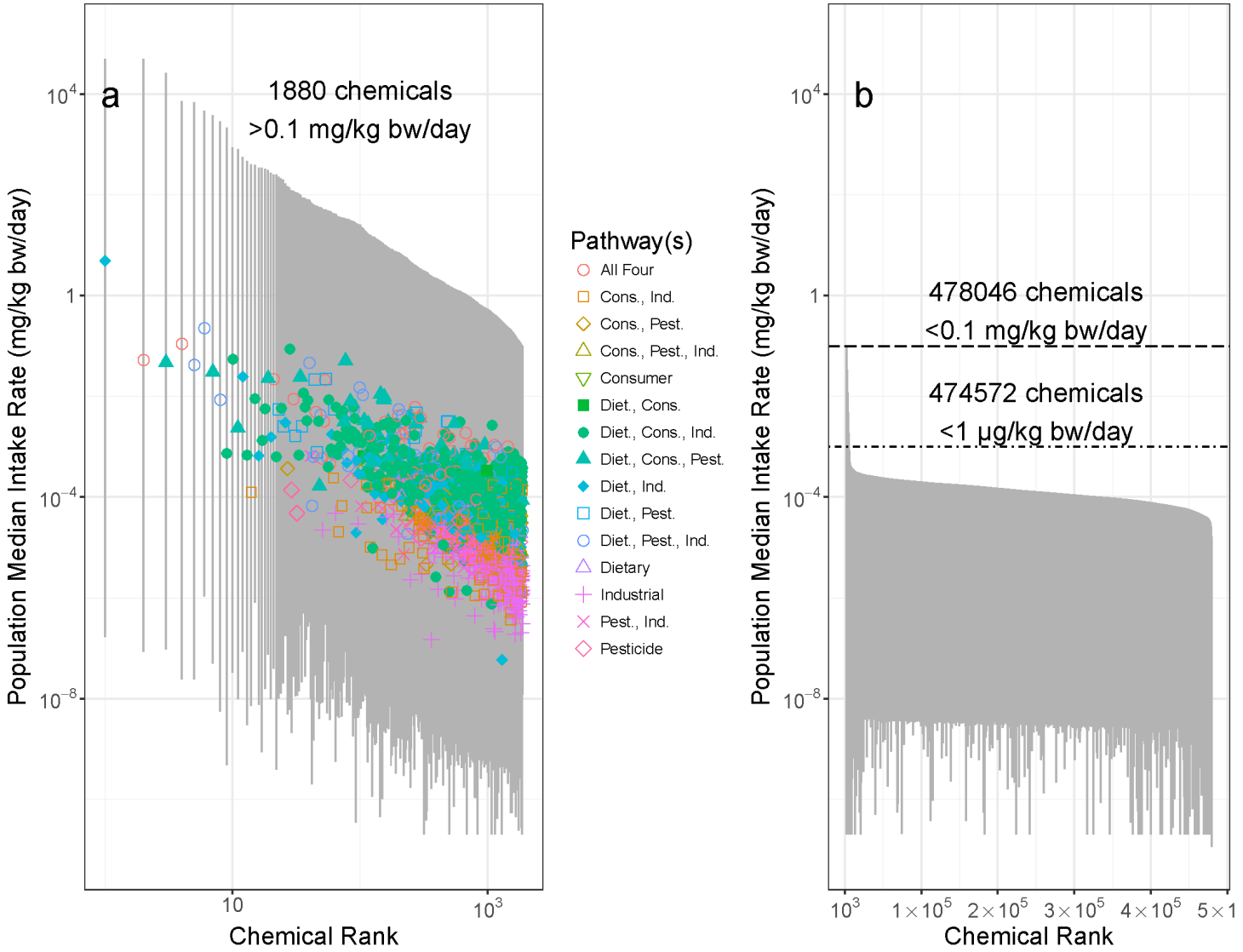
- We predict relevant pathway(s), median intake rate, and credible interval for each of 479,926 chemicals

- Of 687,359 chemicals evaluated, 30% have low probability for exposure via any of the four pathways
  - They are considered outside the "domain of applicability"

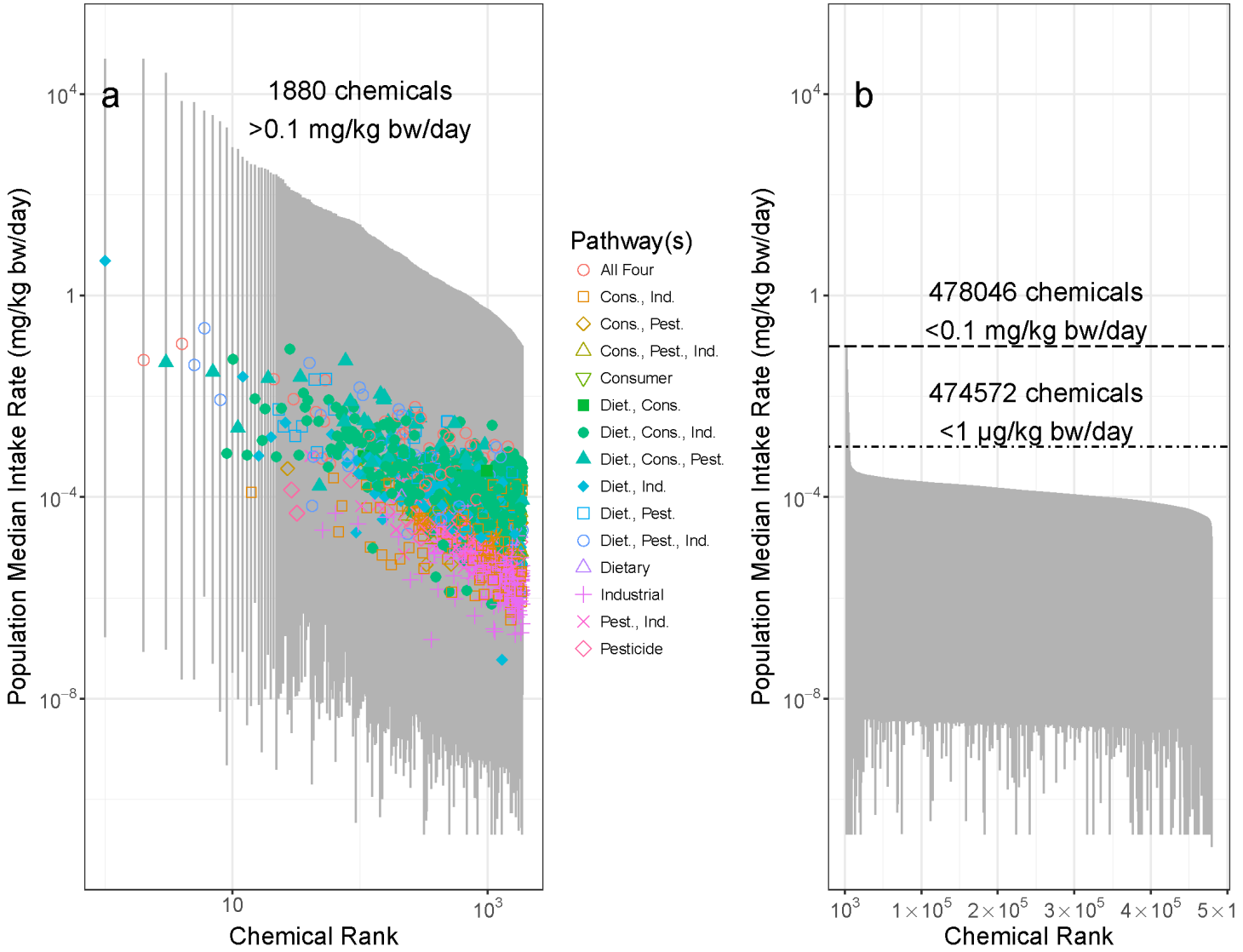
- There is 95% confidence that the median intake rate is below 1 µg/kg BW/day for 474,572 compounds.
  - This 95% interval reflects confidence in the median estimate – not the most highly exposed individuals




*Ring et al., 2018*

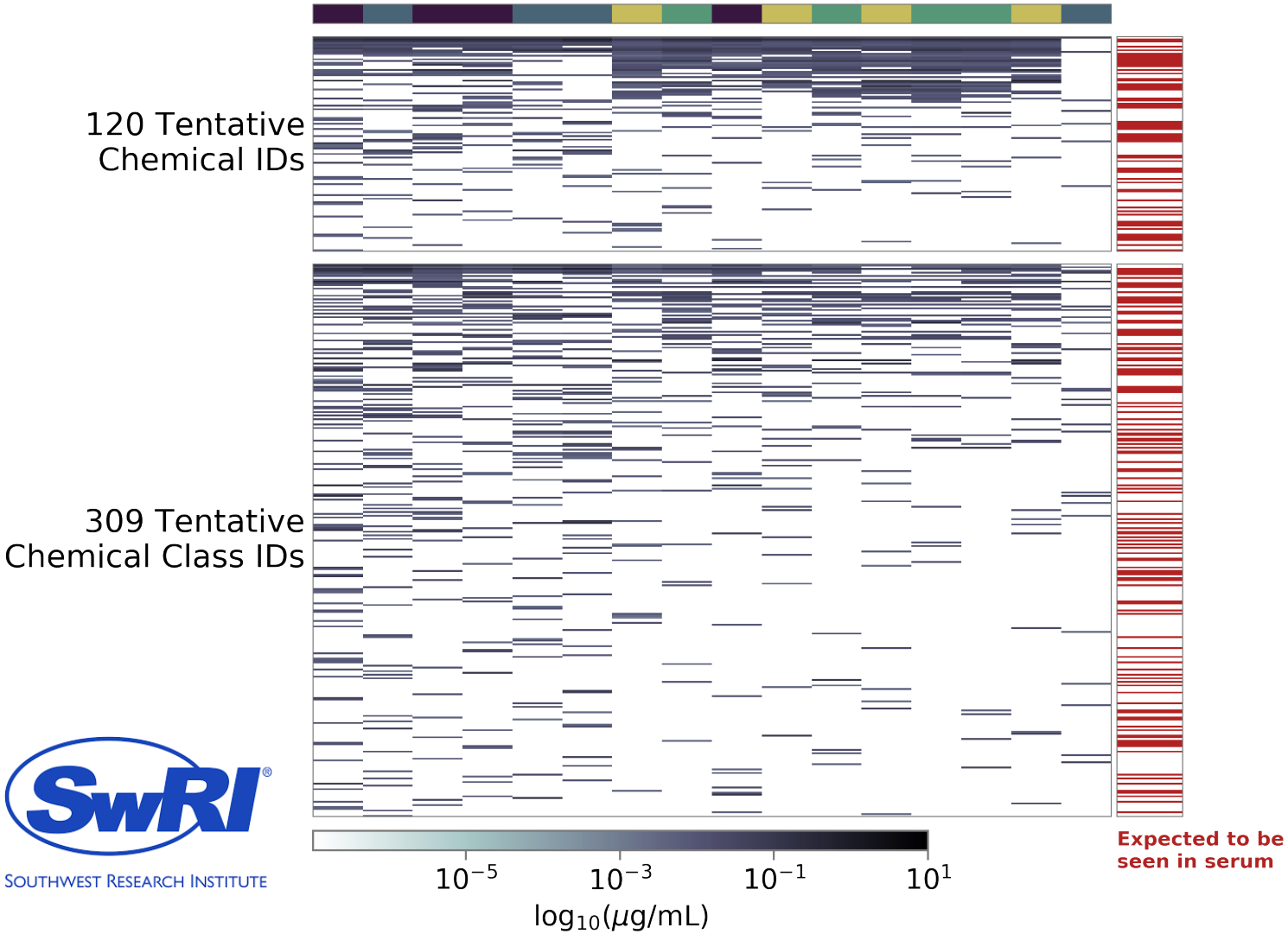
# Consensus Modeling of Median Chemical Intake

- We predict relevant pathway(s), median intake rate, and credible interval for each of 479,926 chemicals
- Potentially helpful for identifying chemicals when suspect screening
- Need to broaden the monitoring data – **this is based on only 114 chemicals!**
- Likewise, broader data can better inform chemical pathway domain of applicability




*Ring et al., 2018*

# Reducing Model Uncertainty with Expanded Biomonitoring




Suspect screening analysis of pooled samples of human blood

Analytical chemistry work by Kristin Favela and Alice Yau of Southwest Research Institute (SWRI)

Informatics team (EPA) led by Katherine Phillips includes Alex Chao, Barbara Wetmore, Risa Sayre, Jon Sobus, Kristin Isaacs

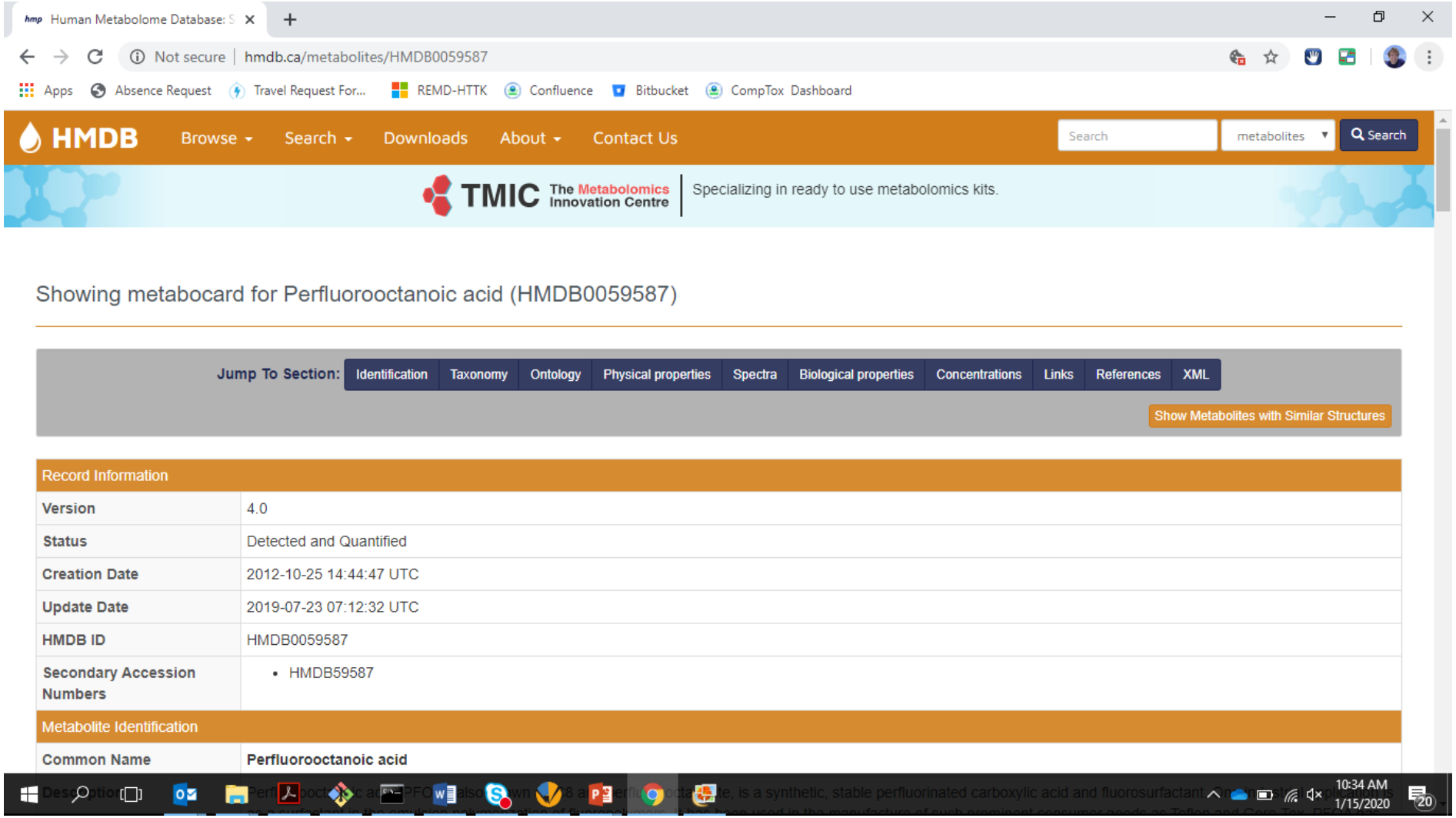
**Strata**
- Female > 45
- Female ≤ 45
- Male ≤ 45
- Male > 45

Study design by Lesa Aylward and John Wambaugh

# Removing the "Background" from Blood

We aren't especially interested in cholesterol, or glucose, or even aspirin

However, without categorization the ubiquitous "metabolome" contains things like PFOA (at right)



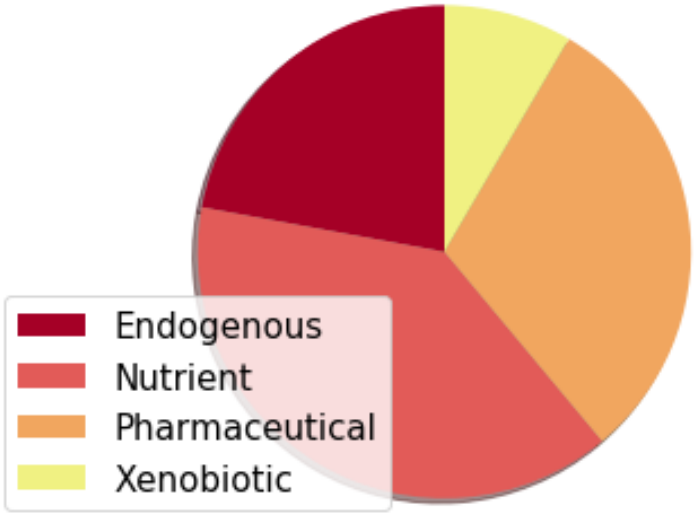
# Coarsely Categorizing the Metabolome

- A categorize metabolome database is under development by Risa Sayre, Chris Grulke, Antony Williams, Jon Sobus, and Alex Chao

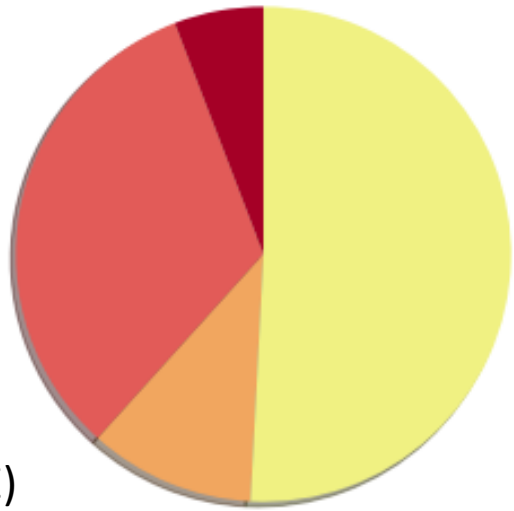
- We have identified five categories of chemical origin (based on Rappaport *et al. (*2014) of small molecules found in human blood biomonitoring samples:

  1) **endogenous metabolome**
  2a) **exogenous nutrients**
  2b) **markers of exposure to exogenous nutrients**
  3a) **xenobiotics** (pharmaceuticals, pesticides, and others)
  3b) **markers of exposure to xenobiotics**

Liquid Chromatography (n=95)




Gas Chromatography (n=120)





Work led by Risa Sayre (EPA/UNC/ORISE)

# Inferring Exposure from the Exposome

- SEEM analyses rely upon exposure inferences from NHANES urine and blood biomonitoring
  - Kristin Isaacs and team are developing publicly available tools to automate that inference

- Working with Robin Dodson and the Silent Spring Institute to generalize methods to correlate chemical concentrations in dust with urine and exposure

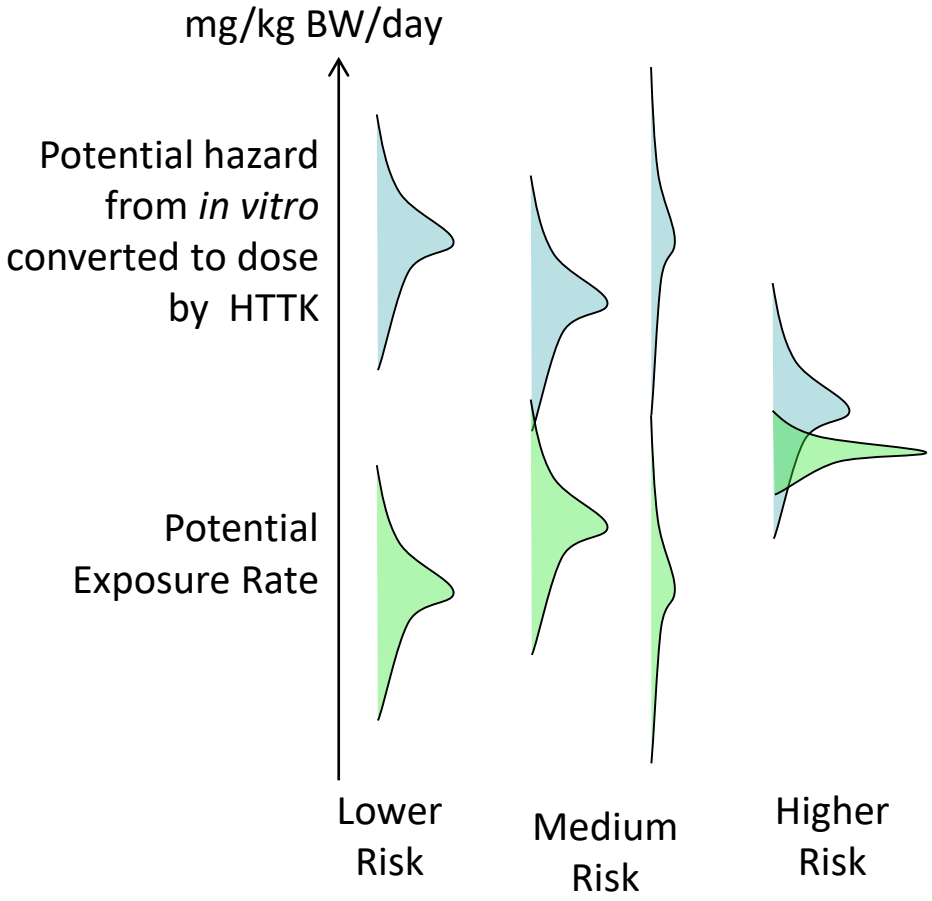
- For exposure inference from blood we need to know the clearance, volume of distribution
  - *We can do this with HTTK!*

- However, toxicokinetic (TK) IVIVE has limitations:
  - Relatively slow throughput (1000 chemicals in last decade)
    - Quantitative Structure-Property Relationship (QSPR) models are being developed and evaluated as part of a collaborative study led by Nisha Sipes (NTP)

  - *In vitro* methods are less than ideal for volatile chemicals
    - Generic inhalation TK IVIVE model has been developed (Linakis et al., submitted)
    - QSPR models can be evaluated specifically for volatile chemicals with measured data

# Summary

- A tapestry of laws covers the chemicals people are exposed to in the United States (Breyer, 2009)
- Many chemicals, ranging from industrial waste to dyes to packing materials, are covered by the recently updated Toxic Substances Control Act (TSCA) and administered by the EPA
- New approach methodologies (NAMs) are being developed to prioritize these existing and new chemicals for testing
- **Calibrated high throughput exposure predictions are available, but rely heavily on the NHANES sampling library – reducing uncertainty and model evaluation depends on better understanding the whole exposome**

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# ExpoCast Project (Exposure Forecasting)

## Center for Computational Toxicology and Exposure

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