EPA United States Environmental Protection Agency

RISK HUNT3R

Physical Kickoff Meeting
5-8 July, 2022
Egmond aan Zee, NL

A Vision for Next Generation Risk Assessment at the U.S. Environmental Protection Agency

John Wambaugh, *Katie Paul Friedman, Alison Harrill, Kristin Isaacs, Timothy Buckley, John Cowden, Chad Deisenroth, Michael Devito, Peter Egeghy, Josh Harrill, Sid Hunter, Richard Judson, Ann Richard, Caroline Ring, Risa Sayre, Amar Singh, Jon Sobus, Elin Ulrich, Barbara Wetmore, Antony Williams, Russell Thomas*

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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
- 539 peer-reviewed journal articles in 2021
- Research is conducted by ORD's four national centers, and three offices organized to address:
  - Public health and environmental assessment
  - Computational toxicology and exposure
  - Environmental measurement and modeling
  - Environmental 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 to which people are exposed in the United States (Breyer, 2009)
- Chemical safety testing is primarily for food additives, pharmaceuticals, and pesticide active ingredients (NRC, 2007)
- Most other chemicals, ranging from industrial waste to dyes to packing materials, are covered by the Toxic Substances Control Act (TSCA)
  - *Limited or no data for these chemicals!*

Schmidt, C. W. (2016). TSCA 2.0: A new era in chemical risk management", Environmental Health Perspectives, A182-A186.

Next Generation Risk Assessment at the U.S. Environmental Protection Agency Office of Research and Development

- *Where has ORD led efforts for NAM based assessments?*
- *Do bioactivity NAMs fill critical biological data gaps (if not POD gaps)?*
- *Does in vitro bioactivity + HTTK inform useful and/or conservative points of departure?*
- *What is the role of QSAR and/or chemical categories as a substitute or partner for in vitro bioactivity and/or HTTK?*
- *Exposure NAMs: Which exposure pathways and/or contexts has ORD been working on to inform key decisions?*

Slide from Katie Paul Friedman

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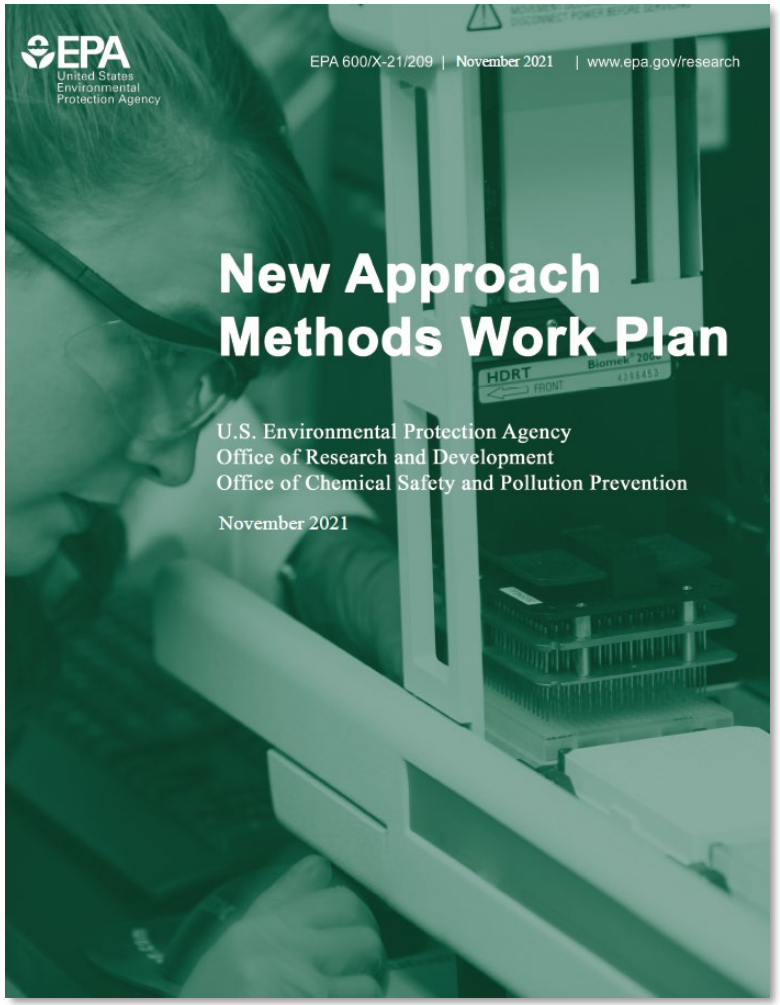
Slide from Katie Paul Friedman

The release of the EPA NAM Work Plan provided clear objectives, strategies and deliverables



- Five objectives for achieving the reduction goals while ensuring that Agency decisions remain fully protective of human health and the environment
  - Evaluate regulatory flexibility
  - Develop baselines and metrics
  - Establish scientific confidence and demonstrate application
  - Develop NAMs to address information gaps
  - Engage and communicate with stakeholders
- Changes in 2021 updated work plan:
  - Modified timelines & deliverables through 2024; two case studies
  - Covered species now includes all vertebrate animals, consistent with TSCA
  - Pilot study to develop NAMs training courses for a broad range of stakeholders

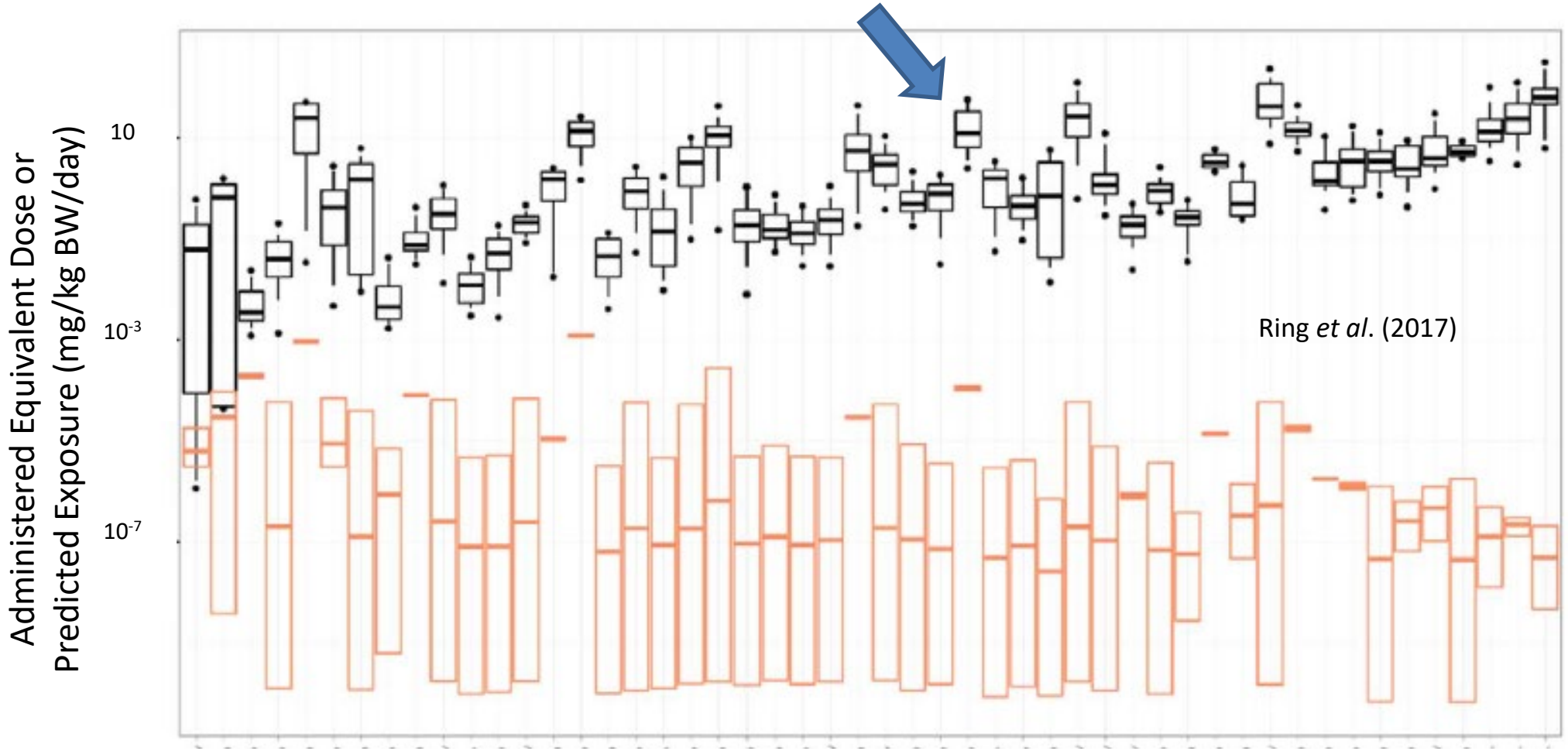
https://www.epa.gov/chemical-research/epa-new-approach-methods-work-plan-reducing-use-vertebrate-animals-chemical

Slide from Alison Harrill

Chemical Prioritization NAMs

U.S. EPA Endocrine Disruptor Screening Program

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



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

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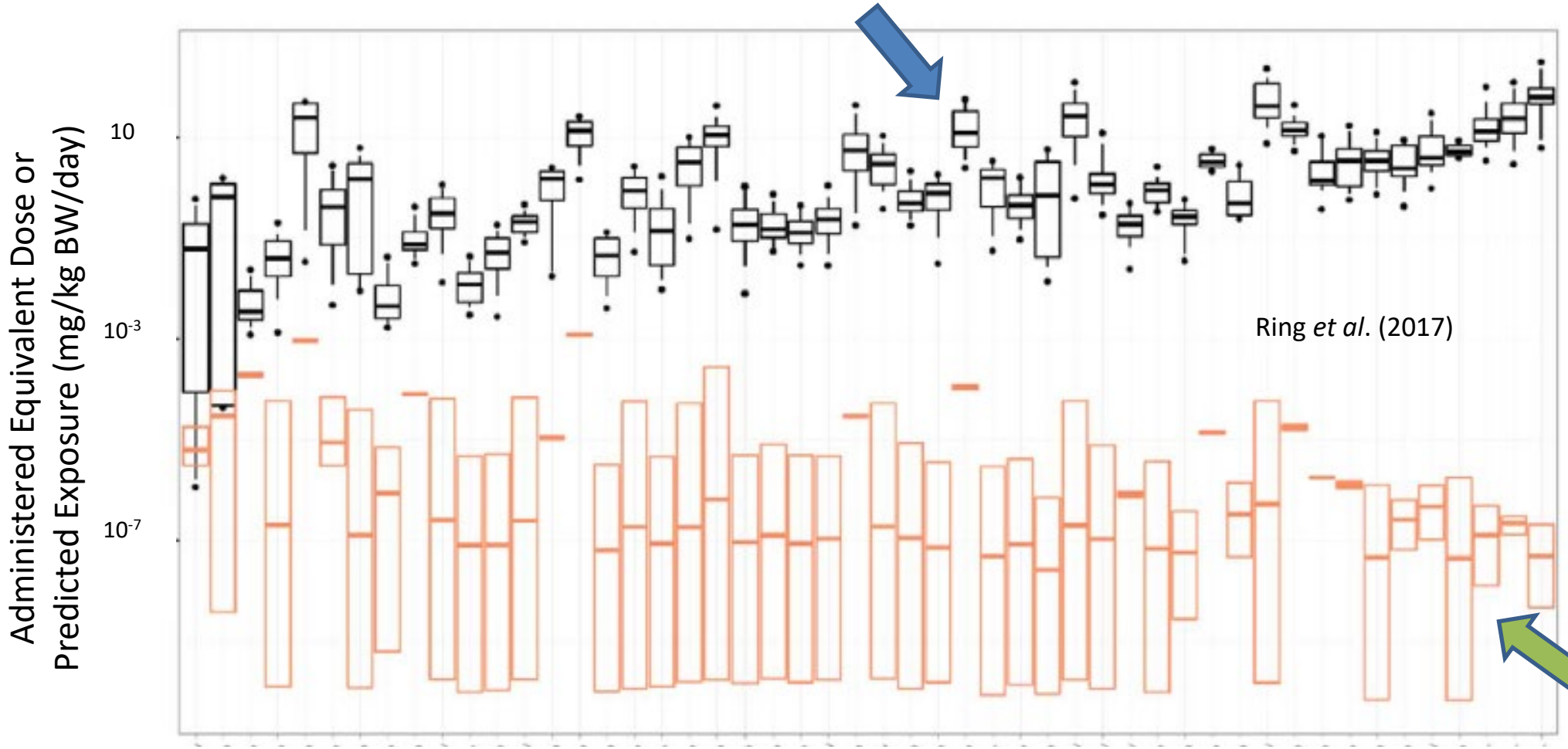

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Exposure intake rates can be inferred from biomarkers (Wambaugh et al., 2014)

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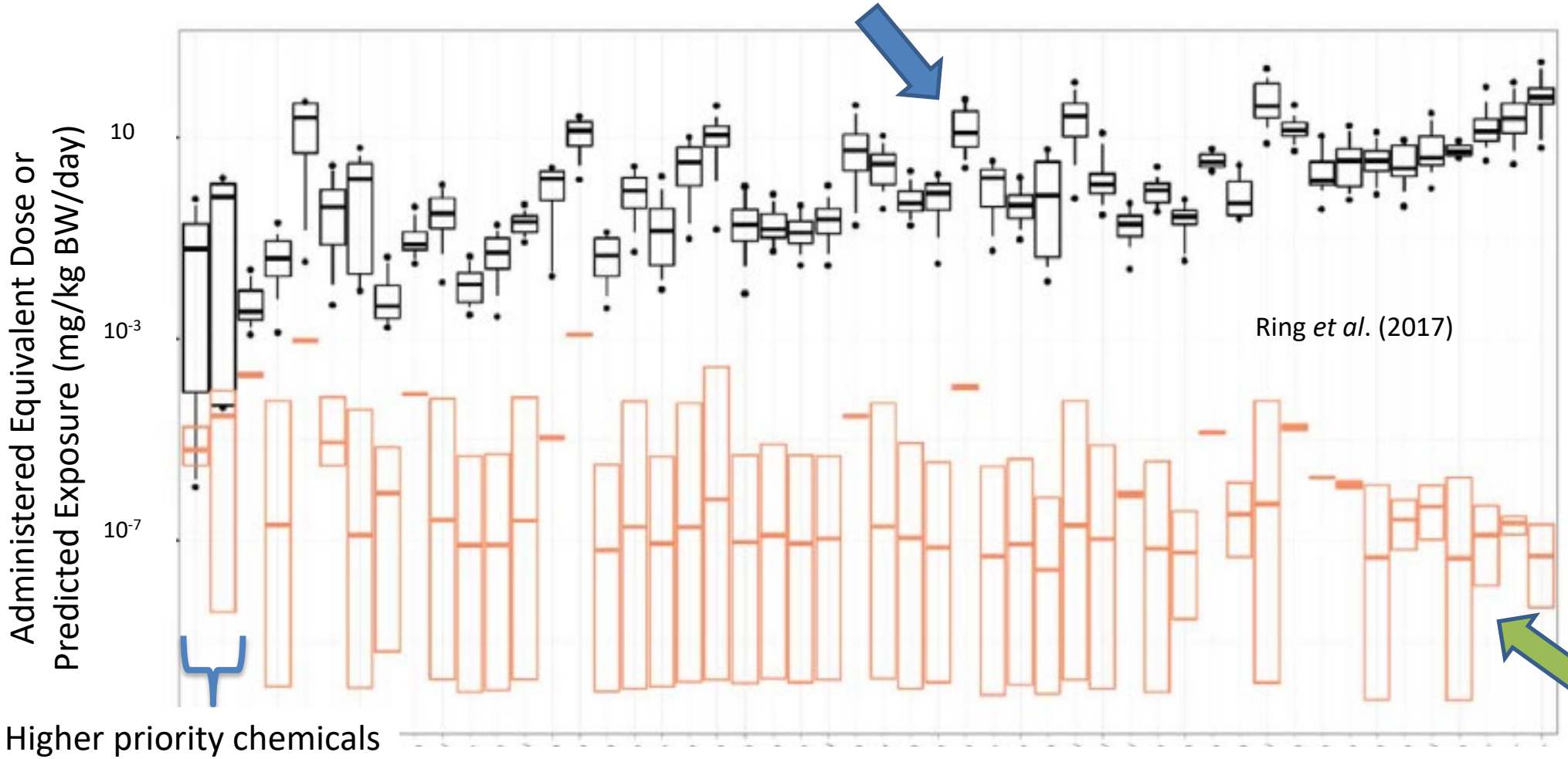

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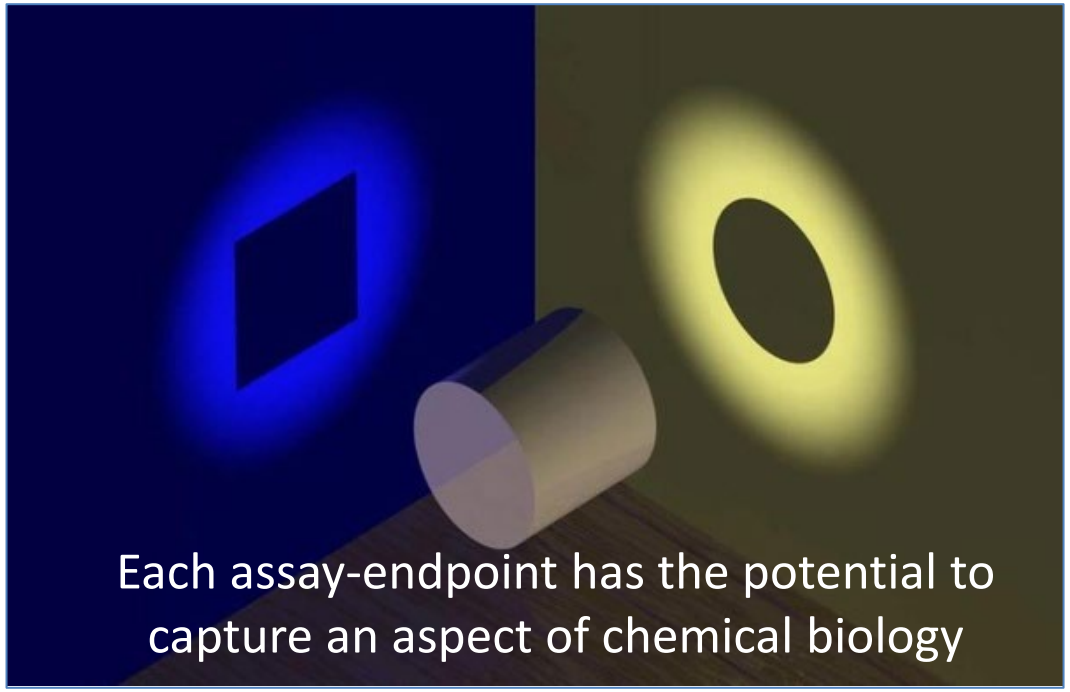
Slide from Katie Paul Friedman

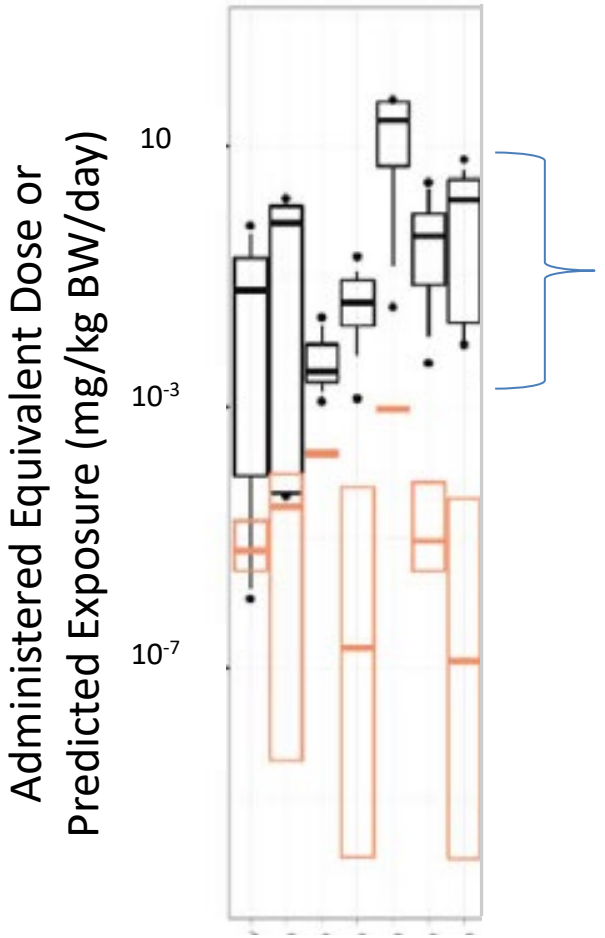
High-Throughput Bioactivity Screening Projects

- We attempt to estimate points of departure *in vitro* using high throughput screening (HTS) for bioactivity as a surrogate for hazard data
- **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 (determine potency and efficacy via Hill function, Filer *et al*., 2016)

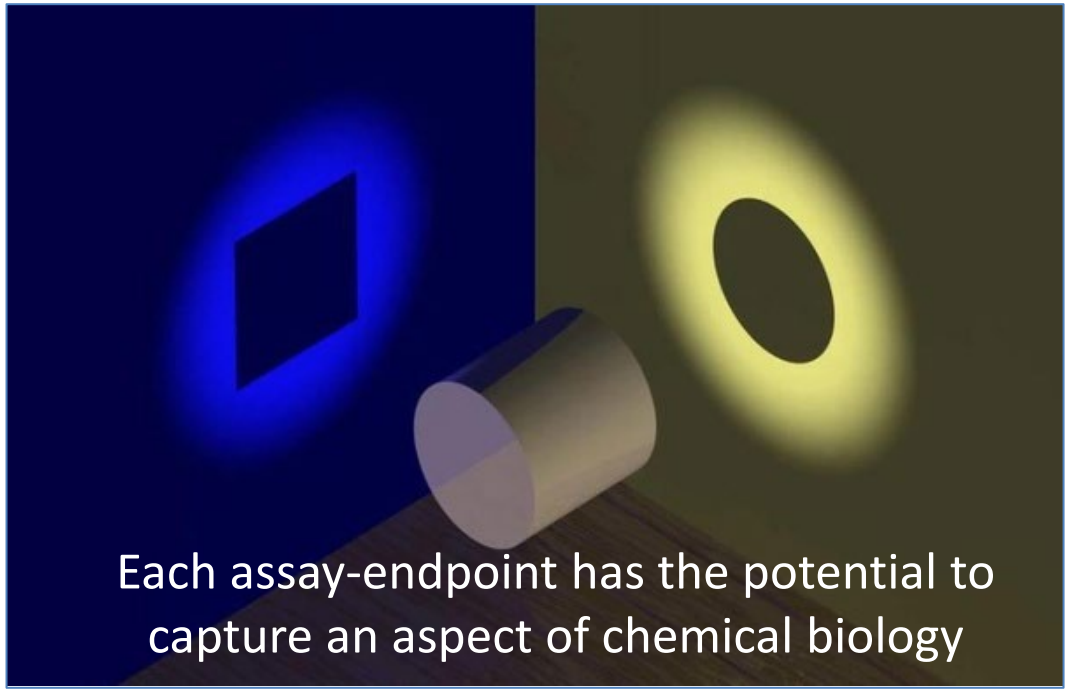


All data are public: http://comptox.epa.gov/dashboard/

What Are We Missing?

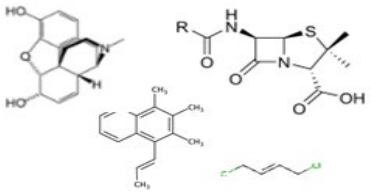


ToxCast Assay Endpoints currently cover ~300 human genes and have limited metabolism (HepaRG, zebrafish)

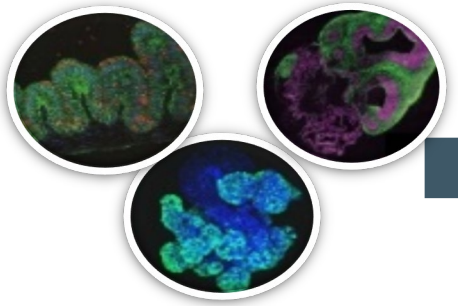


Chemicals Monitored by CDC NHANES

Incorporating High-Content Technologies to Increase Biological Coverage

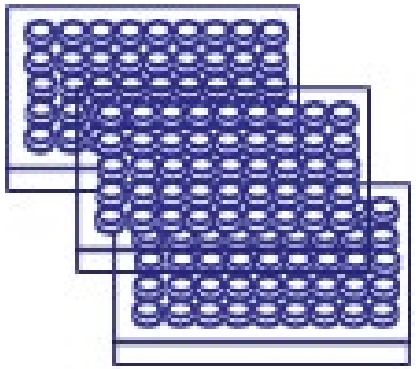


Thousands of Chemicals

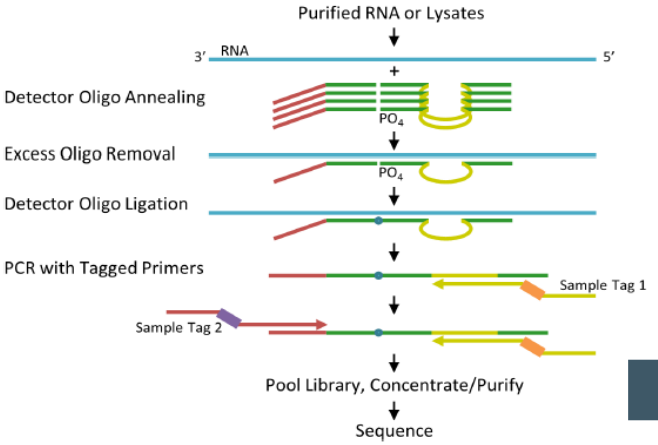


Multiple Cell Types

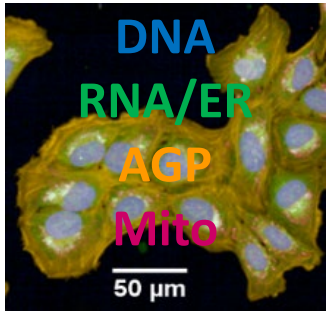
Concentration Response Screening



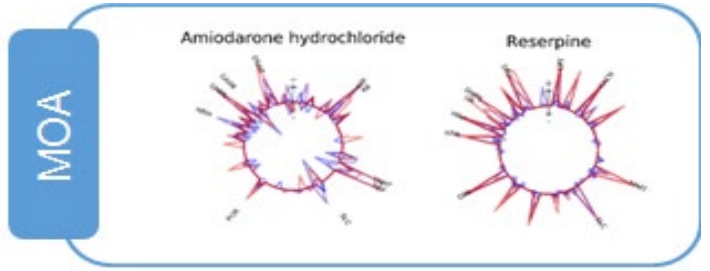
Whole Genome Transcriptomics



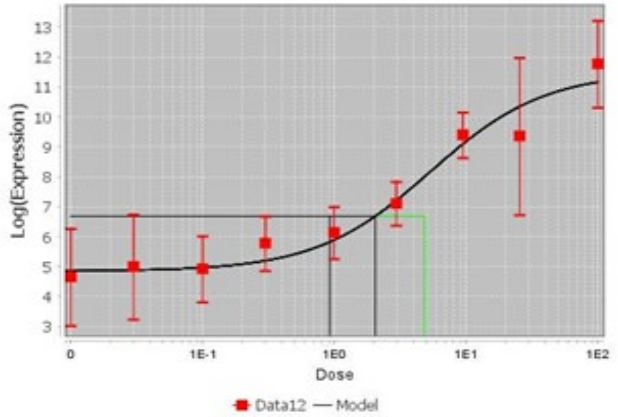
Multi-Parameter Cellular Phenotypic Profiling



Mode-of-Action Identification



Concentration Response Modeling

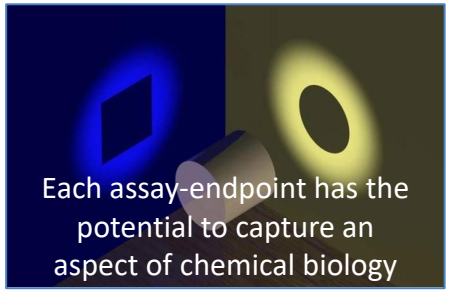


- 384-well, laboratory automation compatible
- Relatively inexpensive ($2.50 - $1,500 per chemical)
- Broad complementary coverage of molecular and phenotypic responses

Slide from Maureen Guinn

Nyffeler et al. SLAS Discov. 2021 Feb;26(2):292-308. doi: 10.1177/2472555220950245
Harrill et al. Toxicol Sci. 2021 Feb 4;kfab009. doi: 10.1093/toxsci/kfab009

EPA continues to innovate and address limitations in NAMs



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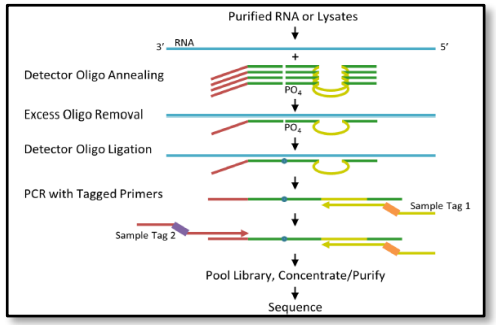
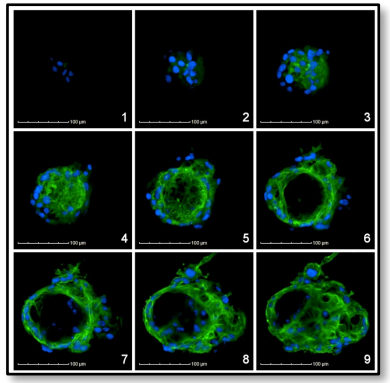
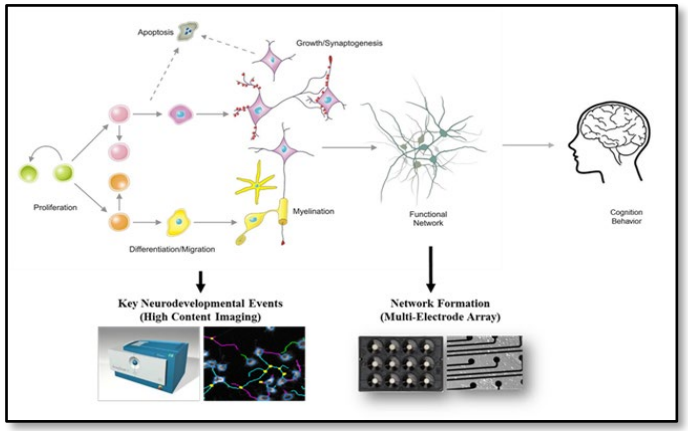


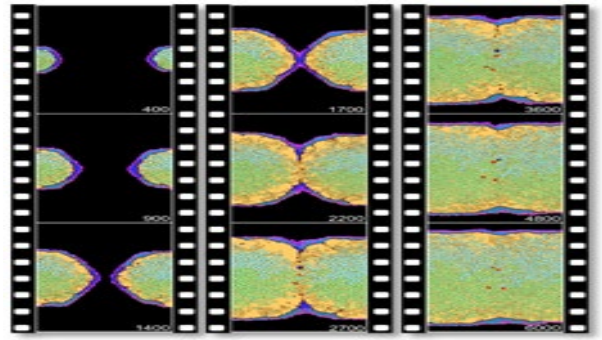
Organotypic Culture Models



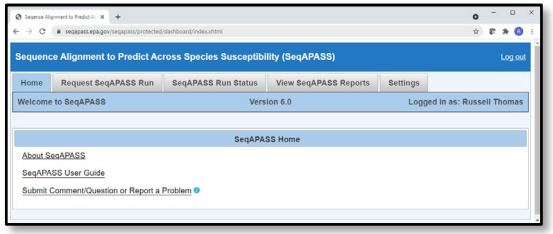
Integrated Testing and Assessment for Developmental Neurotoxicity



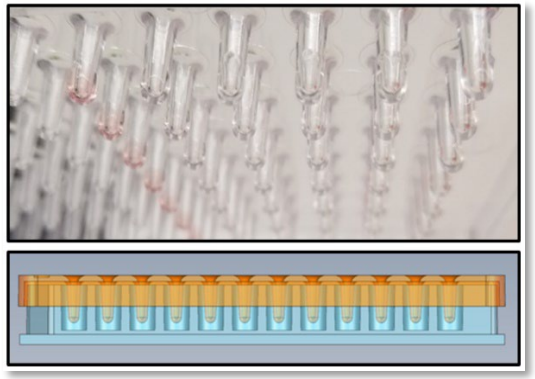
Virtual Tissue Models



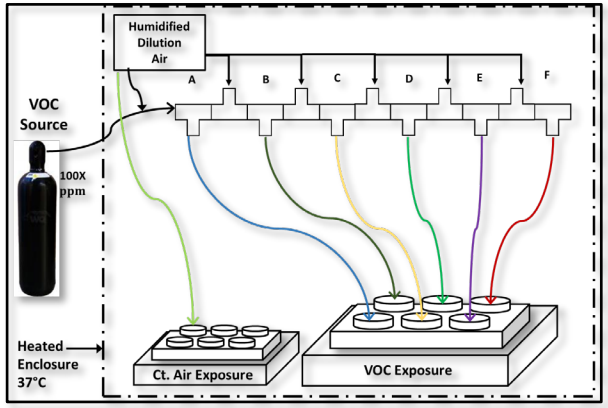
Sequence Alignment to Predict Across Species Susceptibility



Metabolic Retrofitting



Volatile/Aerosol *In Vitro* Exposure Systems



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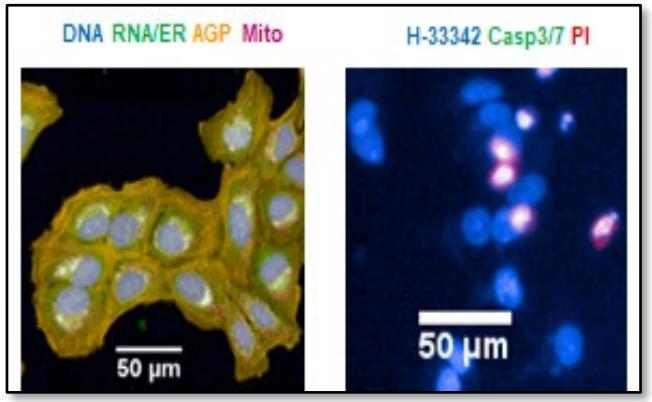
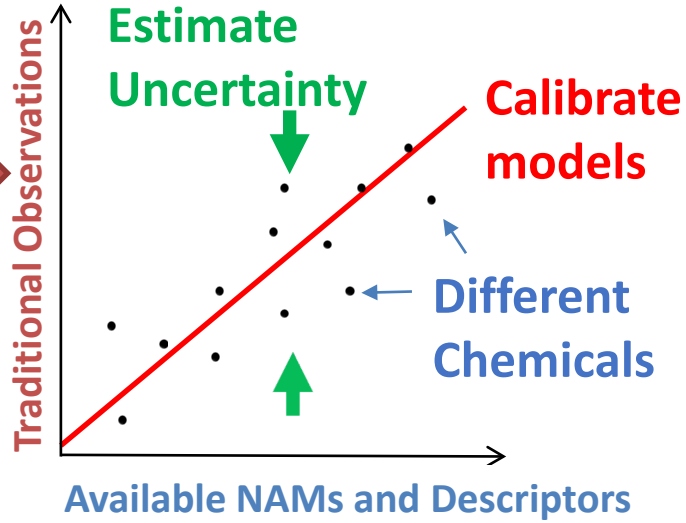


Slide from Alison Harrill

Evaluating High Throughput Screening

Evaluate Model Performance and Refine Models

ToxRefDB
5000+ *in vivo* tox studies
Watford et al. (2019)



Apply **calibration** and estimated **uncertainty** to other chemicals

Mechanistic / Statistical / Machine Learning Models for Prediction

R Package tcpl
Filer et al. (2017)

invitroDB:
ToxCast and Tox21 *in vitro* high throughput screening assays

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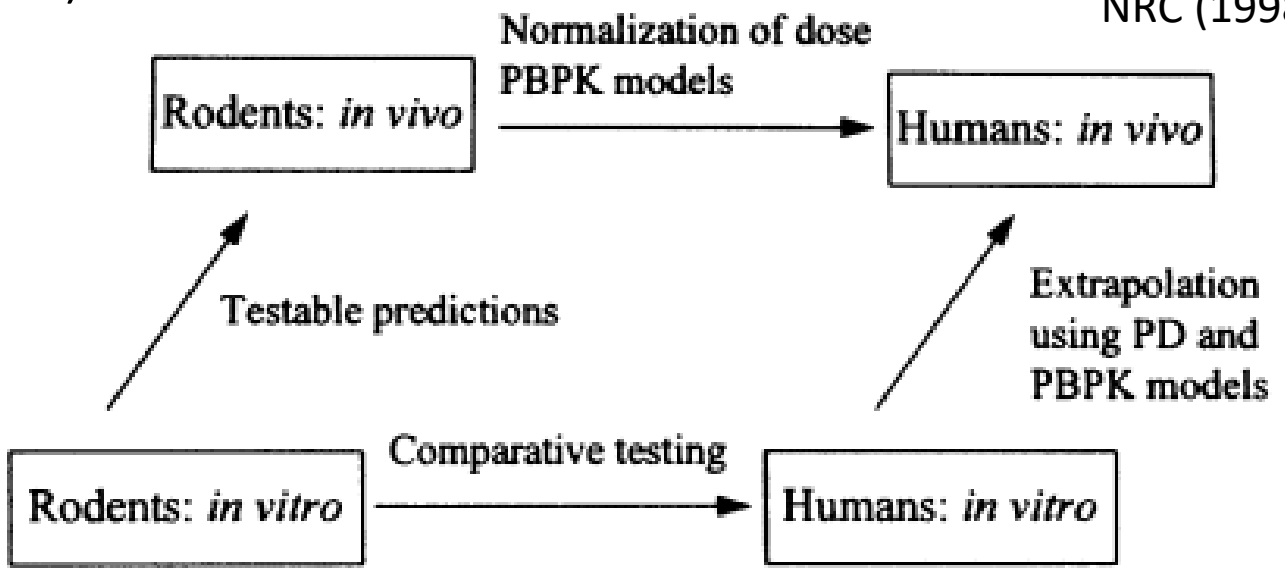
Slide from Katie Paul Friedman

In Vitro - In Vivo Extrapolation (IVIVE)

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

- *In Vitro* Disposition:
  - Difference between nominal and effective concentration of chemical
  - Partitioning to plate wall, nutrients, volatilization
- IVIVE-PK/TK (**Pharmacokinetics/Toxicokinetics**):
  - Fate of molecules/chemicals in body
  - Considers absorption, distribution, metabolism, excretion (ADME)
- 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 effects

NRC (1998)

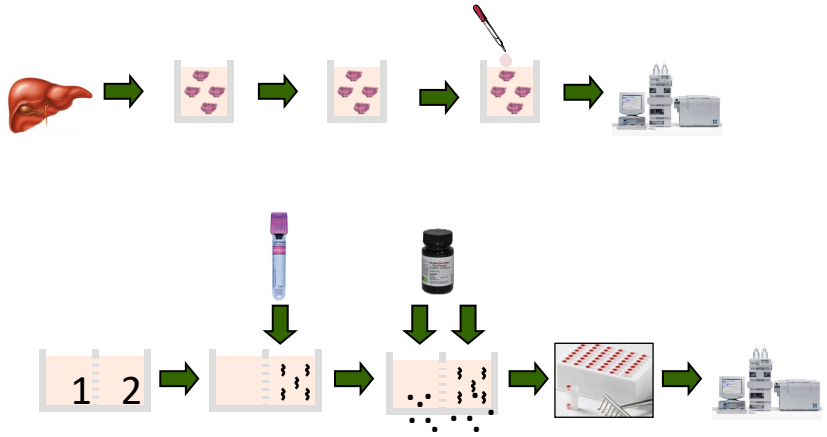


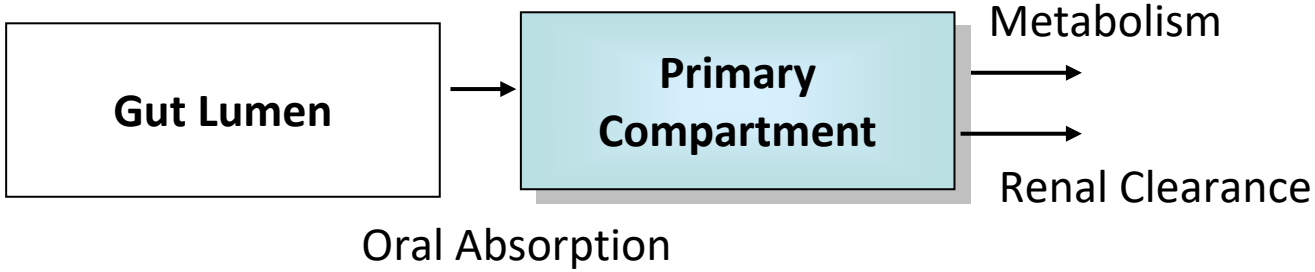
High Throughput Toxicokinetics (HTTK)

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

In vitro toxicokinetic data + generic toxicokinetic model

= high(er) throughput toxicokinetics

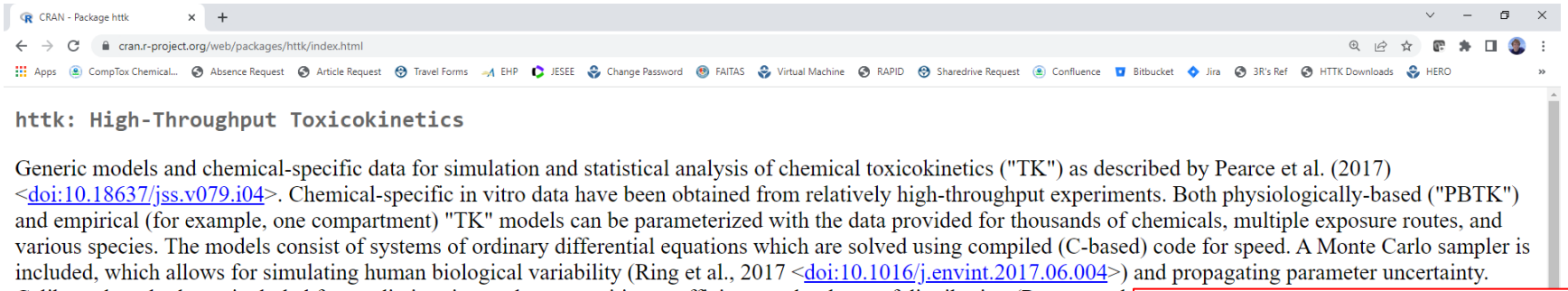




httk

Open-Source Tools and Data for HTTK

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


CRAN - Package httk

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

Apps CompTox Chemical... Absence Request Article Request Travel Forms EHP JESEE Change Password FAITAS Virtual Machine RAPID Sharedrive Request Confluence Bitbucket Jira 3R's Ref HTTK Downloads HERO

httk: High-Throughput Toxicokinetics

Generic models and chemical-specific data for simulation and statistical analysis of chemical toxicokinetics ("TK") as described by 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 (for example, one compartment) "TK" models can be parameterized with the data provided for thousands of chemicals, multiple exposure routes, and various species. The models consist of systems of ordinary differential equations which are solved using compiled (C-based) code for speed. A Monte Carlo sampler is included, which allows for simulating human biological variability (Ring et al., 2017 <doi:10.1016/j.envint.2017.06.004>) and propagating parameter uncertainty. Calibrated methods are included for predicting tissue:plasma partition coefficients and volume of distribution (Pearce et al. These functions and data provide a set of tools for in vitro-in vivo extrapolation ("IVIVE") of high-throughput screening da world exposures via reverse dosimetry (also known as "RTK") (Wetmore et al., 2015 <doi:10.1093/toxsci/kfv171>).

Version:	2.1.0
Depends:	R (≥ 2.10)
Imports:	deSolve, msm, data.table, survey, mvtnorm, truncnorm, stats, graphics, utils, magrittr, purrr, methods,
Suggests:	ggplot2, knitr, rmarkdown, R.rsp, GGally, gplots, scales, EnvStats, MASS, RColorBrewer, TeachingDe reshape2, viridis, CensRegMod, gmodels, colorspace, cowplot, ggrepel, dplyr, forcats, smatr, gridExtra
Published:	2022-03-26
Author:	John Wambaugh [aut, cre], Sarah Davidson [aut], Robert Pearce [aut], Caroline Ring [aut], Matt Linakis [aut], Dustin Kapraun [aut], Miyuki Breen [ctb], Shannon Bell [ct Antonijevic [ctb], Jimena Davis [ctb], James Sluka [ctb], Nisha Sipes [ctb], Barbara Wetn
Maintainer:	John Wambaugh <wambaugh.john at epa.gov>
BugReports:	https://github.com/USEPA/CompTox-ExpoCast-httk
License:	GPL-3
Copyright:	This package is primarily developed by employees of the U.S. Federal government as part of their offi
URL:	https://www.epa.gov/chemical-research/rapid-chemical-exposure-and-dose-research
NeedsCompilation:	yes
Citation:	httk citation info

R package "httk"

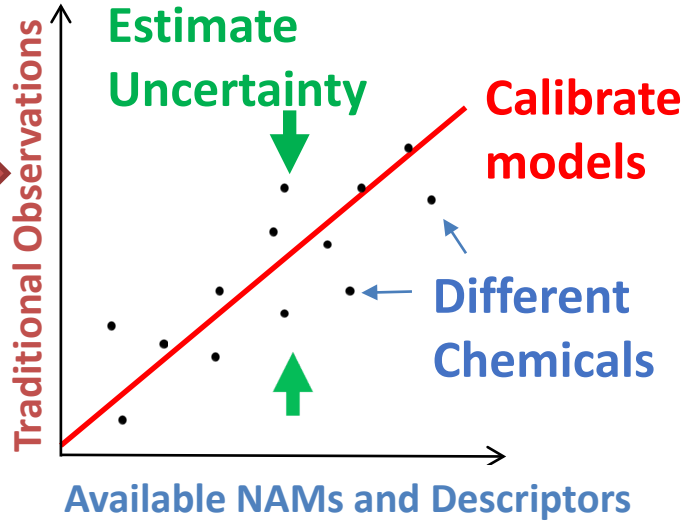
- Open source, transparent, and peer-reviewed tools and data for **HTTK**
- Available publicly for free statistical software R
- Allows *in vitro-in vivo* extrapolation (IVIVE) and physiologically-based toxicokinetics (PBTK)
- Human-specific data for 987 chemicals
- Human population variability (Ring et al., 2017)
- Includes *in vitro* disposition (Armitage et al., 2014)
- Described in Pearce et al. (2017)

Evaluating HTTK

Evaluate Model Performance and Refine Models

CvTdb
Toxicokinetic concentration vs. time data for ~300 analytics
Sayre et al. (2020)

R Package invivoPKfit
Wambaugh et al. (2018)



Apply **calibration** and estimated **uncertainty** to other chemicals

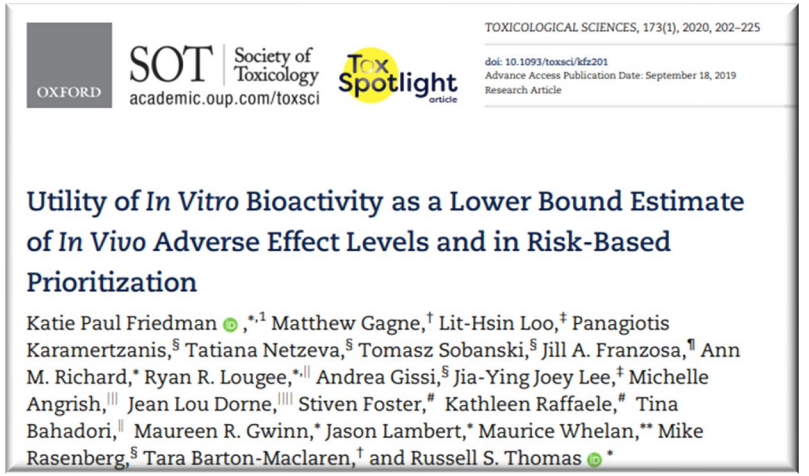
R Package httk
Pearce et al. (2017)

R Package invitroTKstats

HTTK *in vitro* assays
Wetmore et al. (2012,2015)
Wambaugh et al. (2019)

Evaluating High Throughput Screening

APCRA Consortium Case Study


TOXICOLOGICAL SCIENCES, 173(1), 2020, 202–225
doi: 10.1093/toxsci/kfz201
Advance Access Publication Date: September 18, 2019
Research Article

Utility of *In Vitro* Bioactivity as a Lower Bound Estimate of *In Vivo* Adverse Effect Levels and in Risk-Based Prioritization

Katie Paul Friedman,*,1 Matthew Gagne,† Lit-Hsin Loo,‡ Panagiotis Karamertzanis,§ Tatiana Netzeva,§ Tomasz Sobanski,§ Jill A. Franzosa,¶ Ann M. Richard,* Ryan R. Lougee,*,|| Andrea Gissi,§ Jia-Ying Joey Lee,‡ Michelle Angrish,|| Jean Lou Dorne,|| Stiven Foster,# Kathleen Raffaele,# Tina Bahadori,# Maureen R. Gwinn,* Jason Lambert,* Maurice Whelan,** Mike Rasenberg,§ Tara Barton-Maclaren,† and Russell S. Thomas*

ToxRefDB
5000+ *in vivo* tox studies
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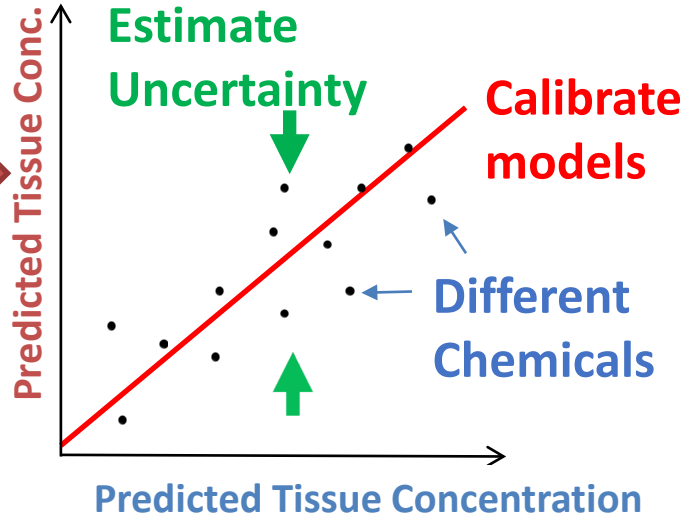
Evaluate Model Performance and Refine Models



Apply **calibration** and estimated **uncertainty** to other chemicals

Honda et al. (2019) showed that HT-PBPK modeling improved correlation between *in vitro* and *in vivo* PODs

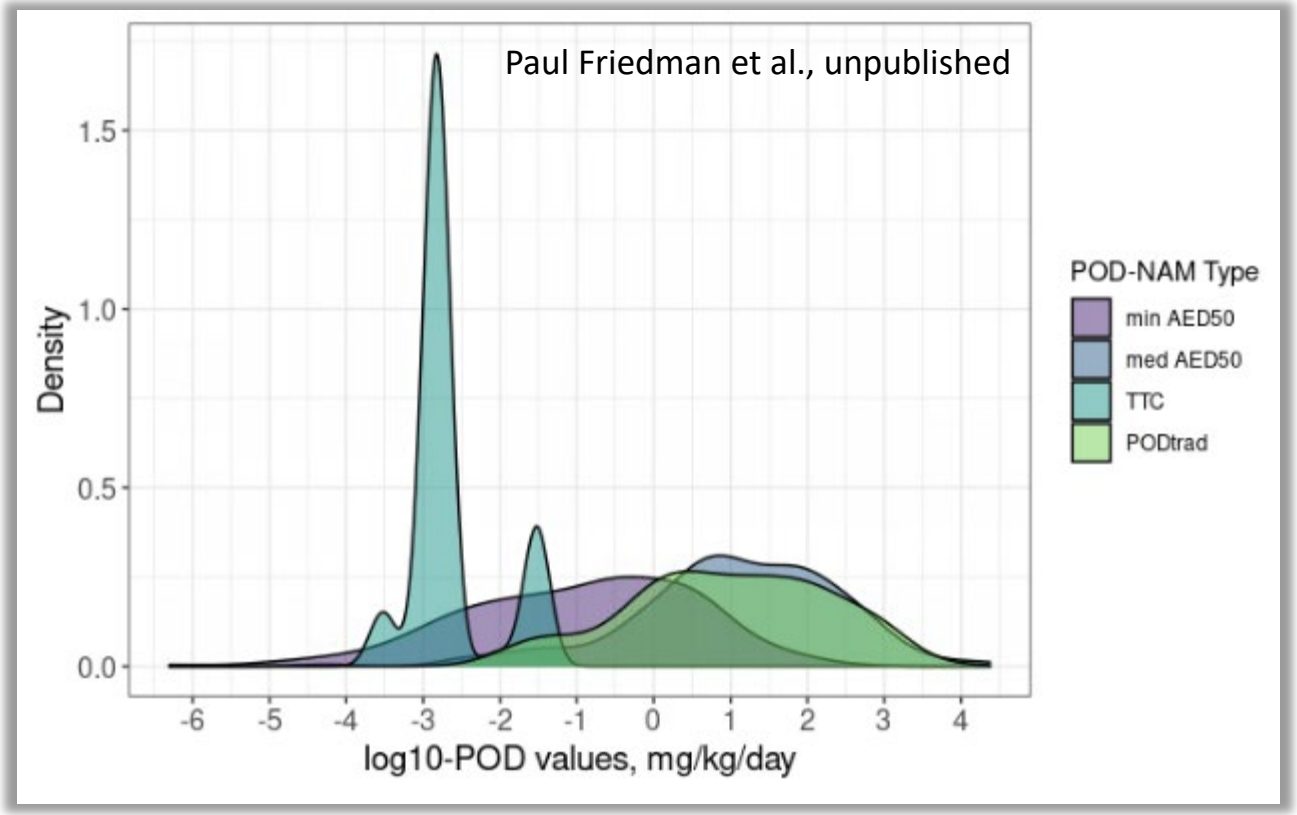
Mechanistic / Statistical / Machine Learning Models for Prediction

R Package tcpl
Filer et al. (2017)

invitroDB:
ToxCast and Tox21 *in vitro* high throughput screening assays

Building confidence in NAMs:

In silico POD_{SAR} and *in vitro* POD_{AED50}



- A POD_{AED50} (point of departure) based on the median of minimum AED50s by assay technology is an empirical and less conservative estimate of POD than TTC (threshold of toxicological concern) that overlaps with the distribution of $POD_{traditional}$
- Min AED50 is more conservative/overlapping with TTC
- TTC may appear more conservative because safety/uncertainty factors are built into the approach

TTC values were based on Cramer classes, including a specific class for organophosphates and carbamates.

No TTC values for genotoxic carcinogens were used.

Slide from Katie Paul Friedman

Next Generation Risk Assessment at the U.S. Environmental Protection Agency Office of Research and Development

- *Where has ORD led efforts for NAM based assessments?*
- *Do bioactivity NAMs fill critical biological data gaps (if not POD gaps)?*
- *Does in vitro bioactivity + HTTK inform useful and/or conservative points of departure?*
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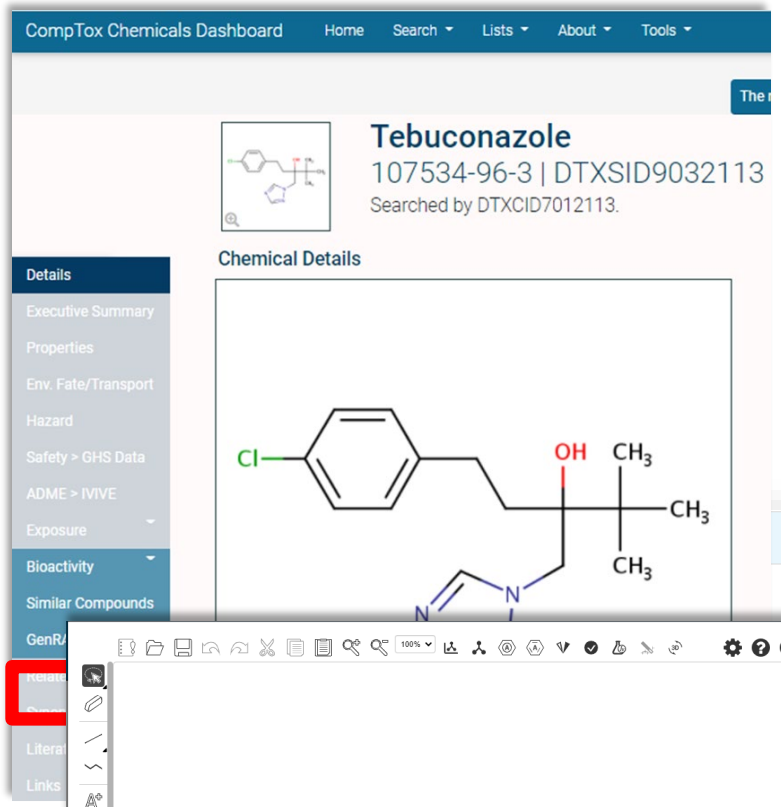
- *Exposure NAMs: Which exposure pathways and/or contexts has ORD been working on to inform key decisions?*

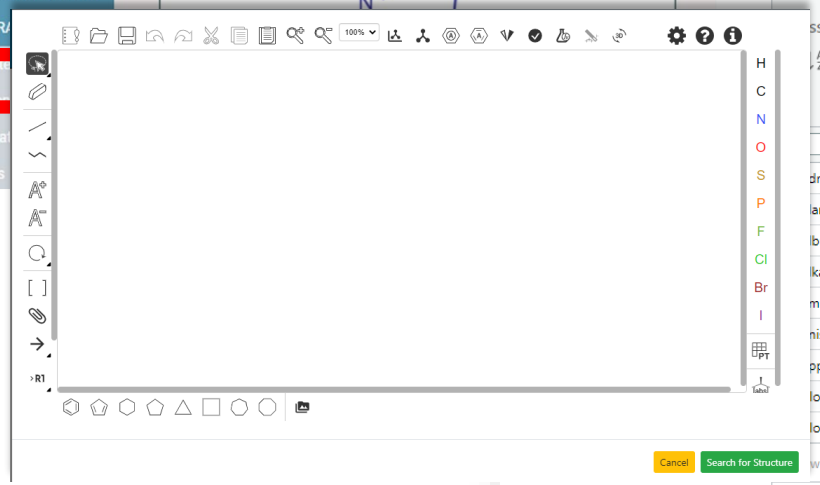
Slide from Katie Paul Friedman

Public tools for systematic read-across

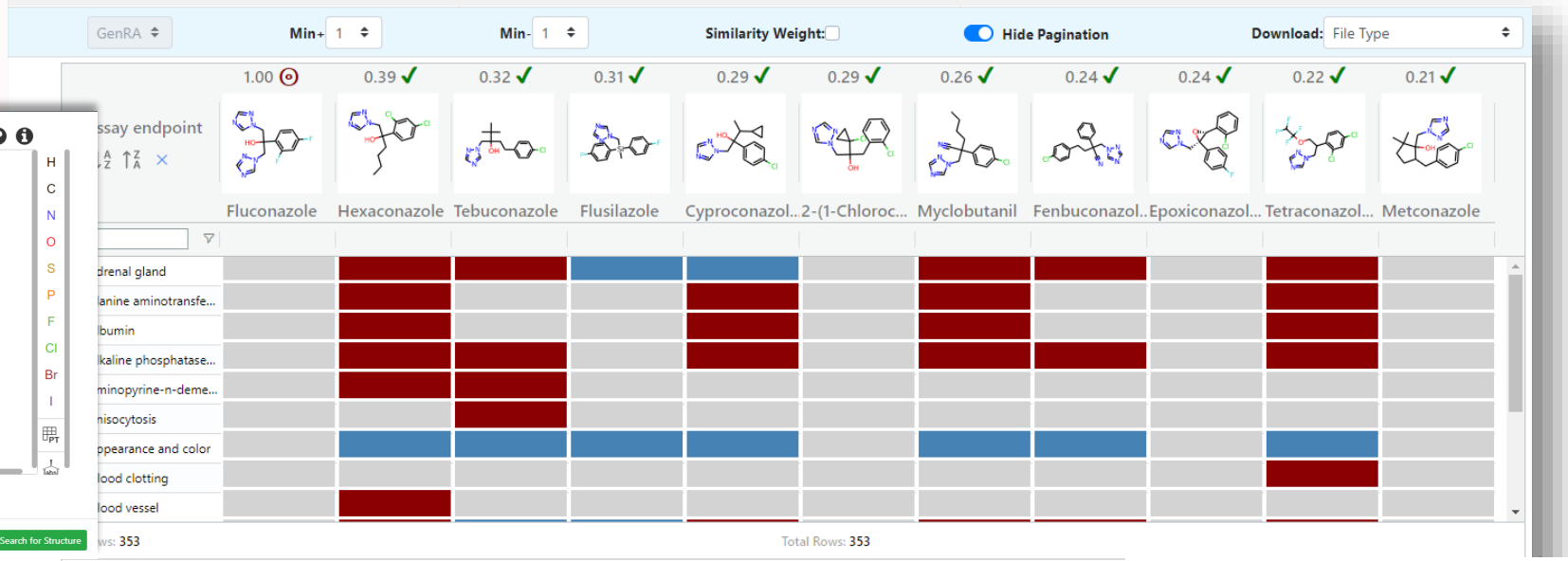
United States Environmental Protection Agency

www.comptox.epa.gov/dashboard





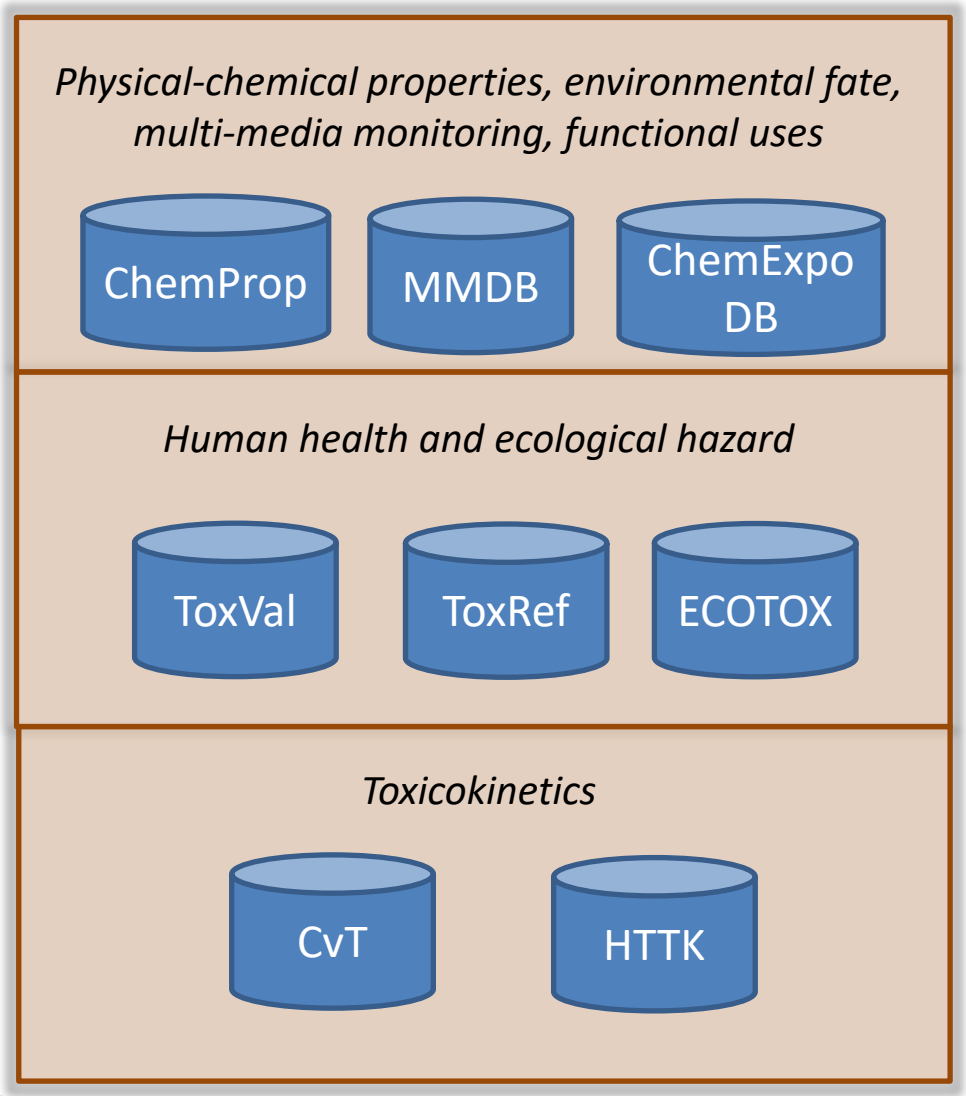
- Work by Patlewicz, Shah, and colleagues for objective read-across (now GenRA v3)
- Quantitative evaluation of similarity and confidence in predictions
- Interactive workflow: CompTox Chemicals Dashboard and Python package (genra-py)

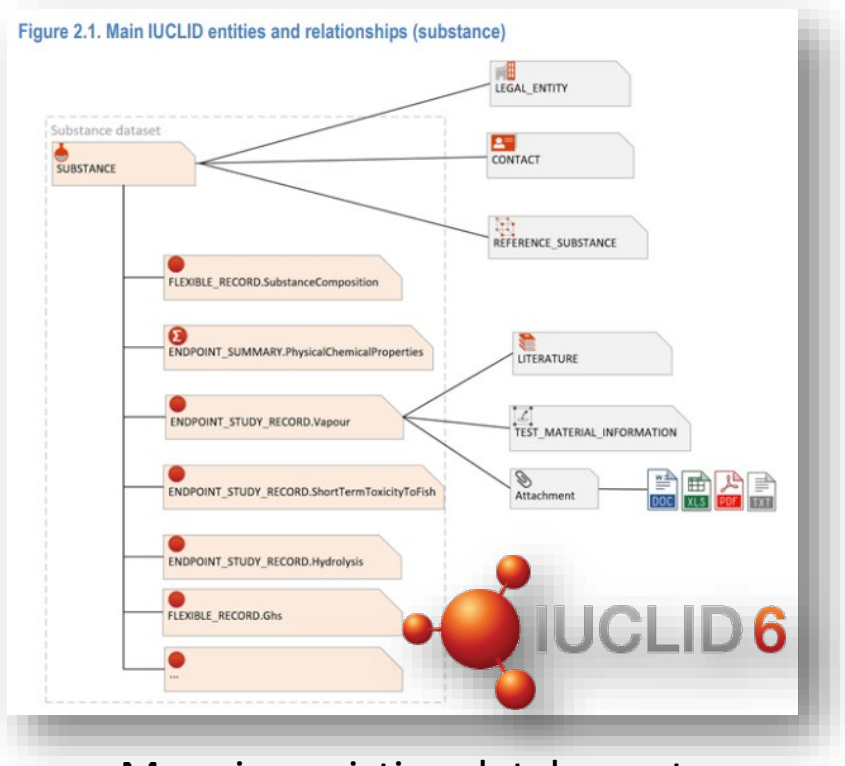


Slide from Katie Paul Friedman

Curating existing data into computationally accessible resources is ongoing in preparation for operational use

Curating data into computationally accessible formats supports efforts to establish confidence in NAMs, characterize uncertainty and variability, and develop software and tools to inform chemical safety.





Mapping existing databases to IUCLID formats enables international collaboration and data sharing.

Slide from Katie Paul Friedman

Fill Database Gaps with Non-Targeted Analysis

United States Environmental Protection Agency

Source and Release

Pilot: 20 Consumer Product Categories

Phillips *et al.*, *Env. Sci. Tech*. 2018

Recycled Consumer Materials

Lowe *et al.*, *2021*

Consumer Product Emissions from Different Substrates

Fate and Transport

Residential Air

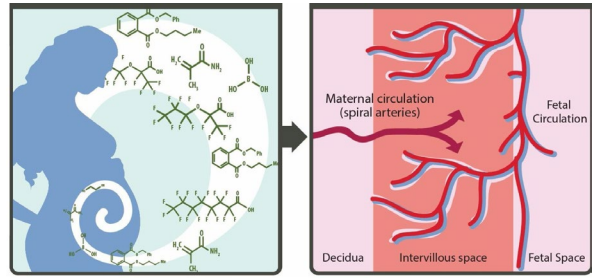
Residential Dust

Rager *et al.*, *Env. Int.*, 2016

Exposure

Pooled Human Blood

Human Placenta



Rager *et al.*, *Repro. Tox.* , 2020

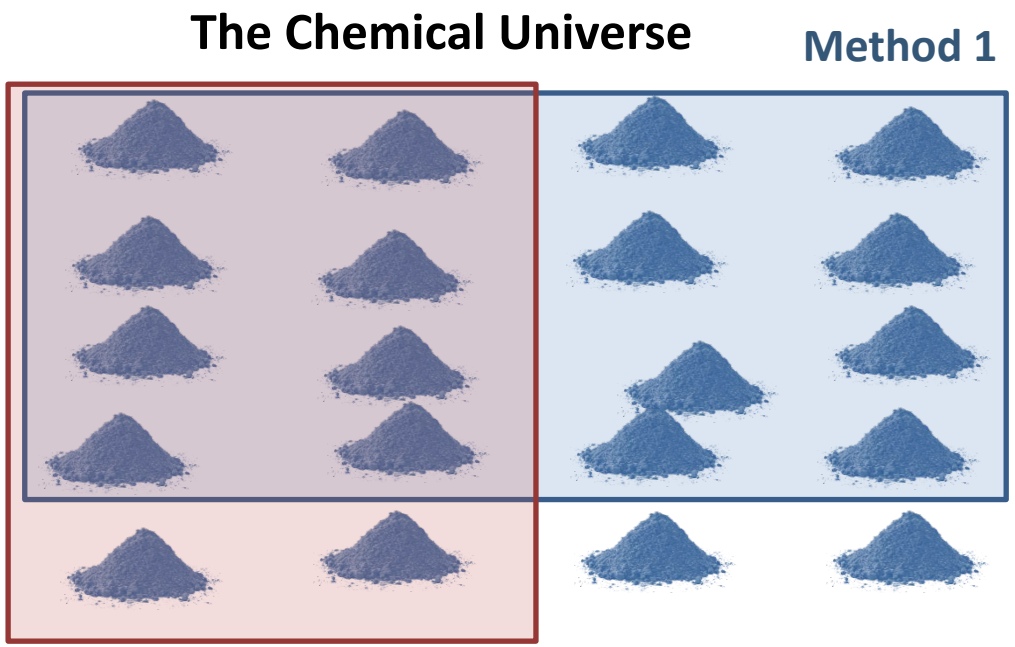
Emerging Science: How can we **quantify** concentrations of chemicals in media using NTA?

Slide from Kristin Isaacs

EPA's Non-Targeted Analysis Collaborative Trial (ENTACT)

- Suspect screening / Non-targeted analyses (SSA/NTA) present opportunities for new exposure data

- What NTA methods are available? What is the coverage of chemical universe and matrices? How do methods differ in their coverage?



Led by Jon Sobus,
Seth Newton and Elin Ulrich

- Phase 1:
  - Collaborators provided 10 mixtures of 100-400 ToxCast chemicals each
  - Mass spectrometry equipment vendors provided with individual chemical standards

- Phase 2: Fortified reference house dust, human serum, and silicone wristbands

Ulrich et al. (2019)
Sobus et al. (2019)

Fill Database Gaps with Machine Learning

United States Environmental Protection Agency

Chemical Functional Use Database (FUSE)

Positive Examples | Negative Examples

Machine Learning:
Use training data (examples) to identify patterns that allow classification of new data

Slide from Kristin Isaacs

Phillips *et al.* (2017)

Fill Database Gaps with Machine Learning

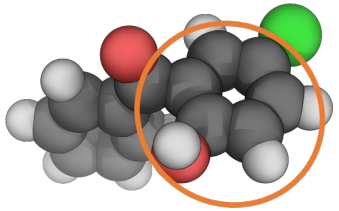
United States Environmental Protection Agency

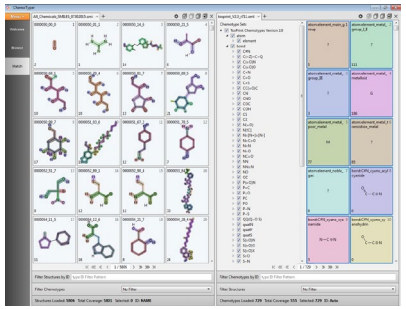
Chemical Functional Use Database (FUSE)

Positive Examples

Negative Examples

Chemical Structure and Property Descriptors (ToxPrint, OPERA)





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Slide from Kristin Isaacs

Phillips *et al.* (2017)

Fill Database Gaps with Machine Learning

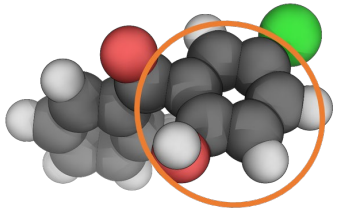
United States Environmental Protection Agency

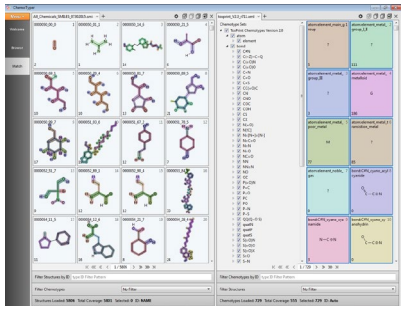
Chemical Functional Use Database (FUSE)

Positive Examples | Negative Examples

Random Forest Classification Models (Breiman, 2001) with five-fold cross validation

Chemical Structure and Property Descriptors (ToxPrint, OPERA)





Successful Model

Failed Model

Probabilistic Predictions of Potential Chemical Uses

Slide from Kristin Isaacs

Phillips *et al.* (2017)

Next Generation Risk Assessment at the U.S. Environmental Protection Agency Office of Research and Development

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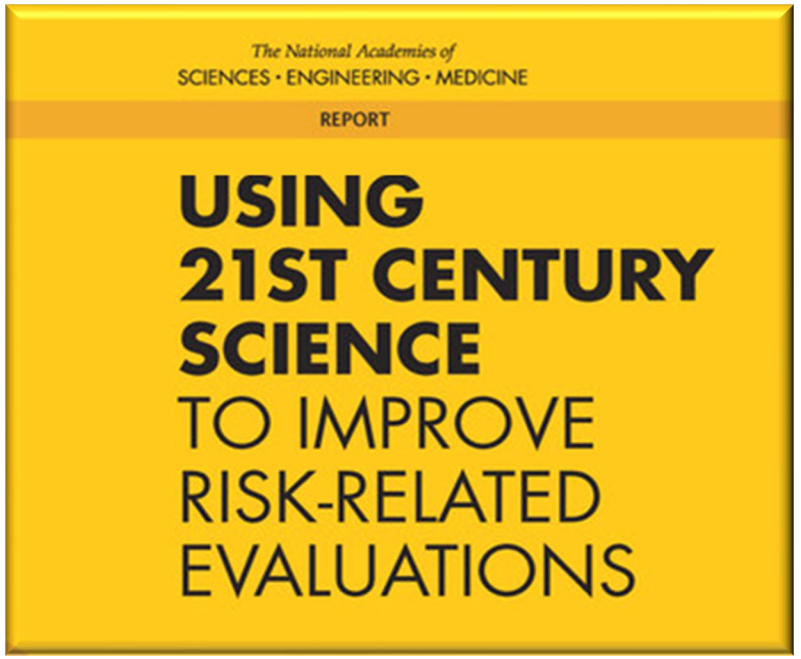
Slide from Katie Paul Friedman

New Approach Methodologies and Exposure

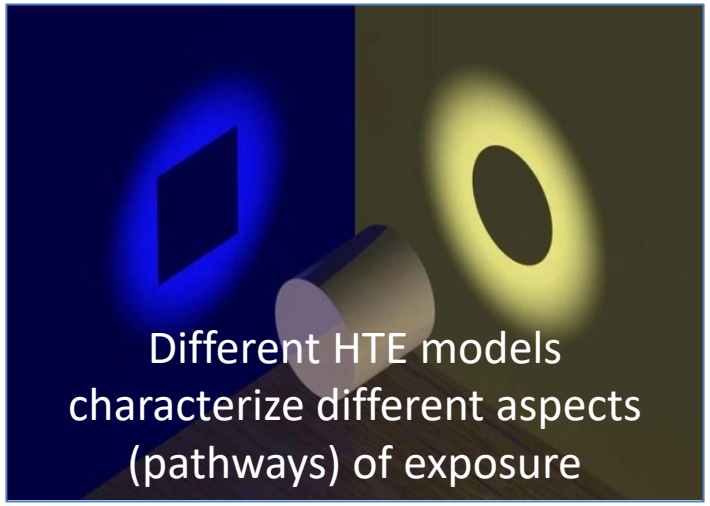
*"NAMs were taken in a broad context to **include in silico approaches**, in chemico and in vitro assays, as **well as the inclusion of information from the exposure of chemicals** in the context of hazard assessment"*



*"…the committee sees the potential for the application of **computational exposure science** to be highly valuable and credible for comparison and priority-setting among chemicals in a risk-based context."*

High Throughput Exposure (HTE) Models

- Monitoring data provides our “reference” exposures
- We build a probabilistic, consensus prediction using multiple HTE models and other predictors
- Various HTE models provide the “assays” for different aspects (pathways, chemistries, assumptions) of exposure



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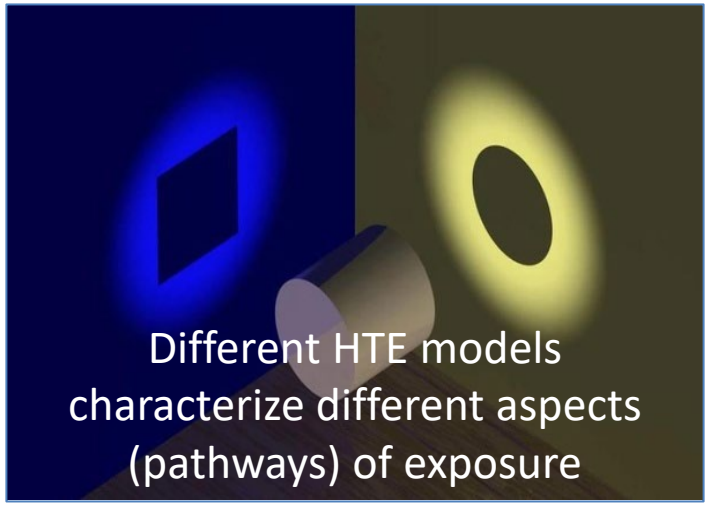

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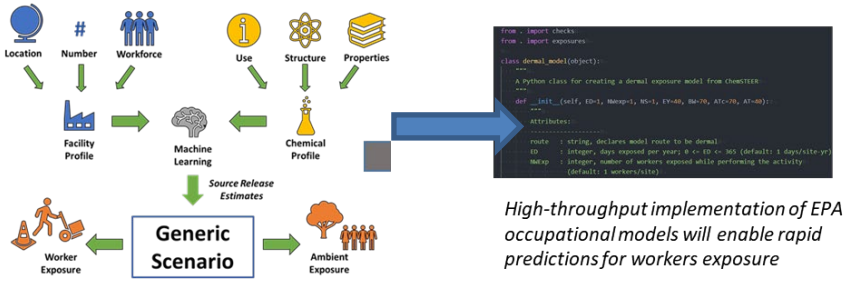
Occupational

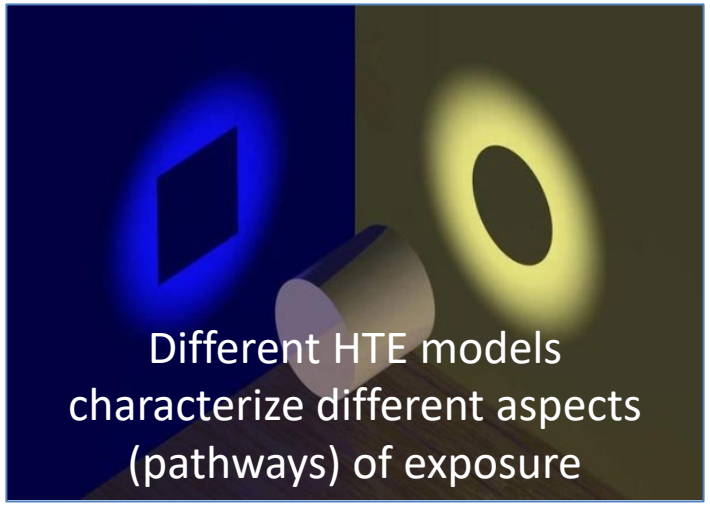
ChemSteer



Meyer et al. (2018)

High-throughput implementation of EPA occupational models will enable rapid predictions for workers exposure

High Throughput Exposure (HTE) Models



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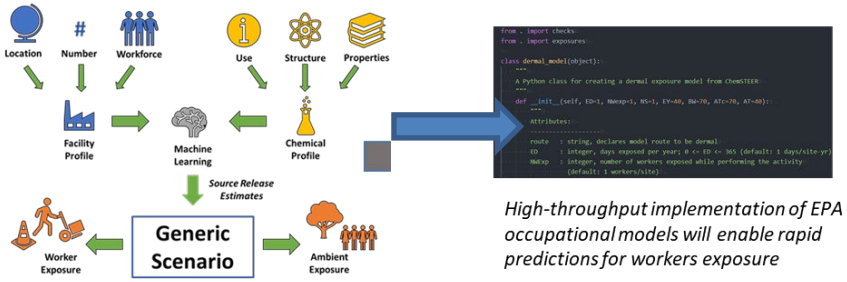

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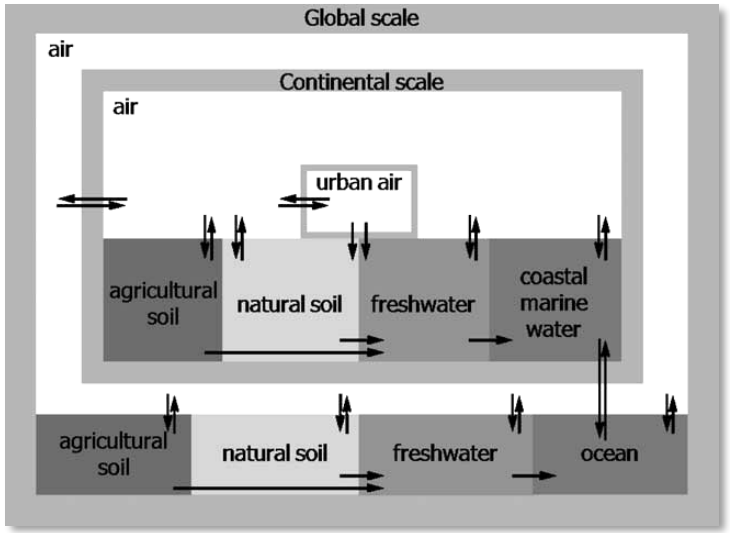
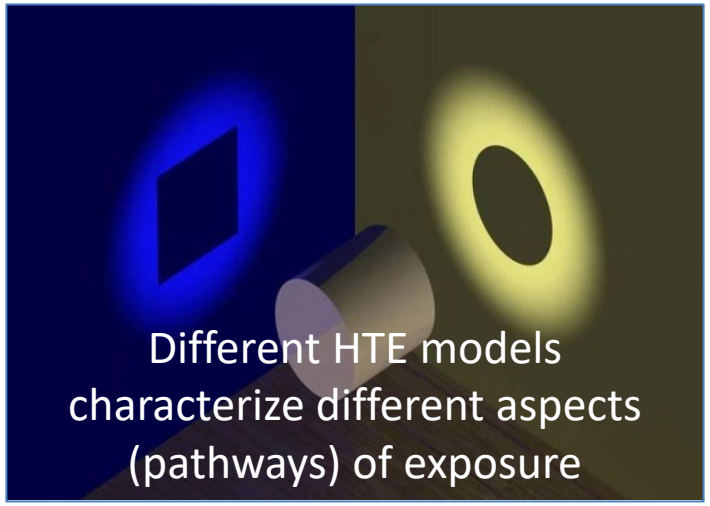
Ambient

USEtox

Rosenbaum *et al.* (2008)



High Throughput Exposure (HTE) Models



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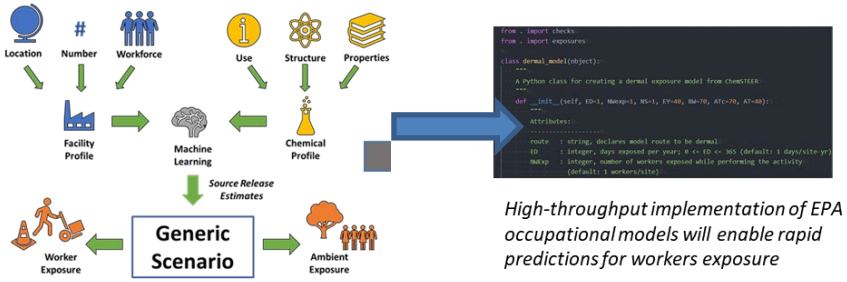

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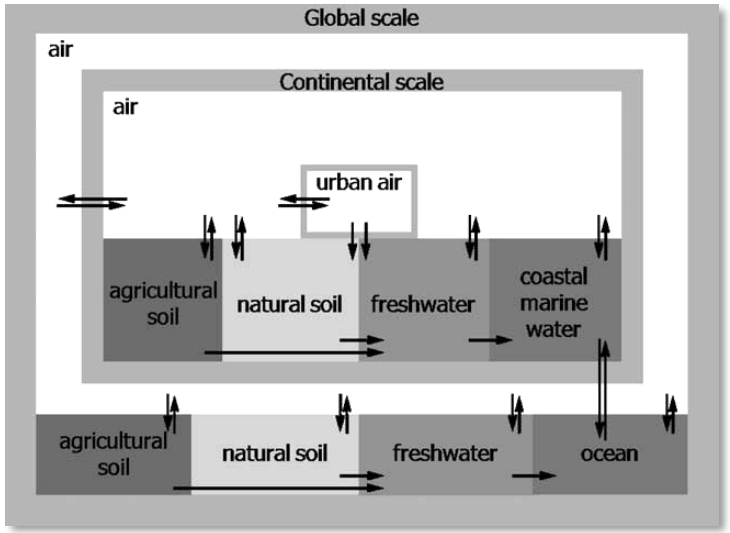
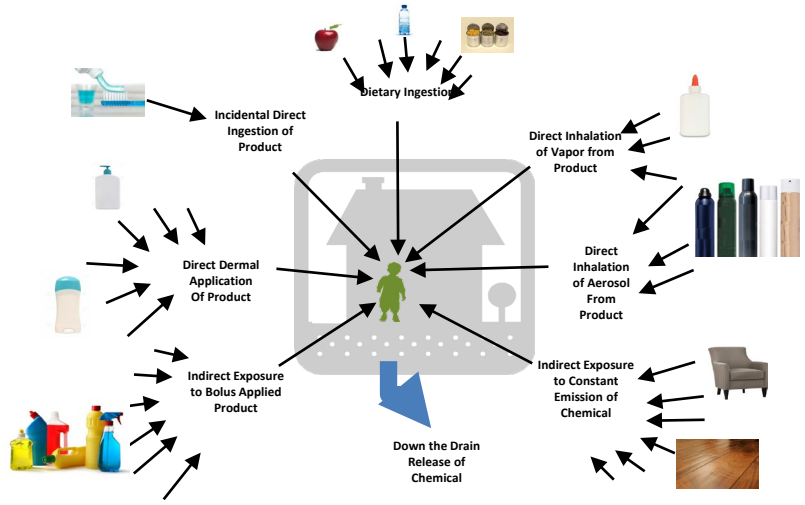


Consumer

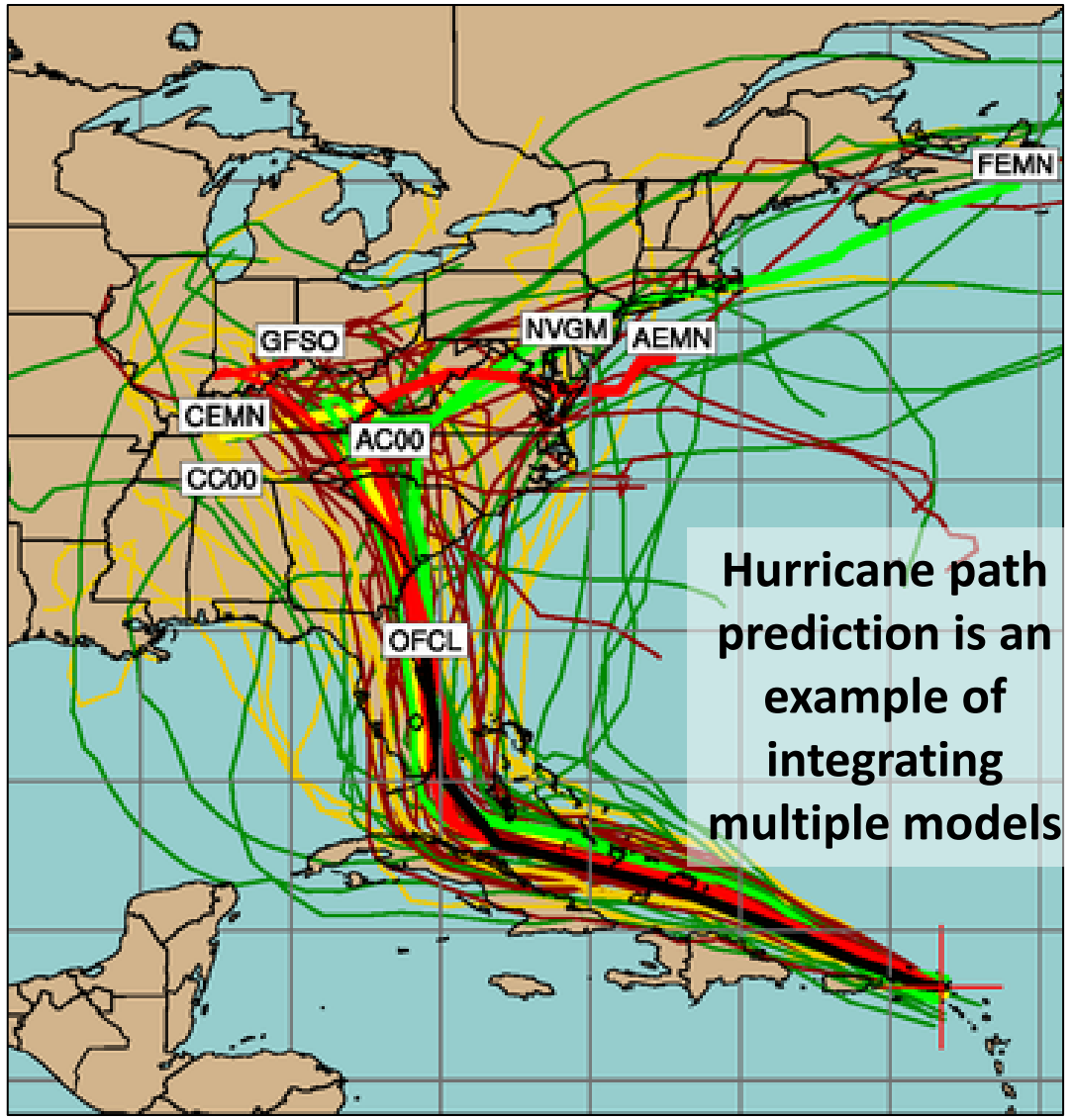
SHEDS-HT

Isaacs *et al.* (2014)



Exposure NAMs: The SEEM Framework

- We build a probabilistic, consensus prediction using multiple HTE models and other predictors
- Various HTE models provide the “assays” for different aspects (pathways, chemistries, assumptions) of exposure
- We use Bayesian methods to incorporate multiple models into consensus predictions for 1000s of chemicals within the **Systematic Empirical Evaluation of Models (SEEM)** framework (Wambaugh et al., 2013, 2014; Ring et al., 2018)

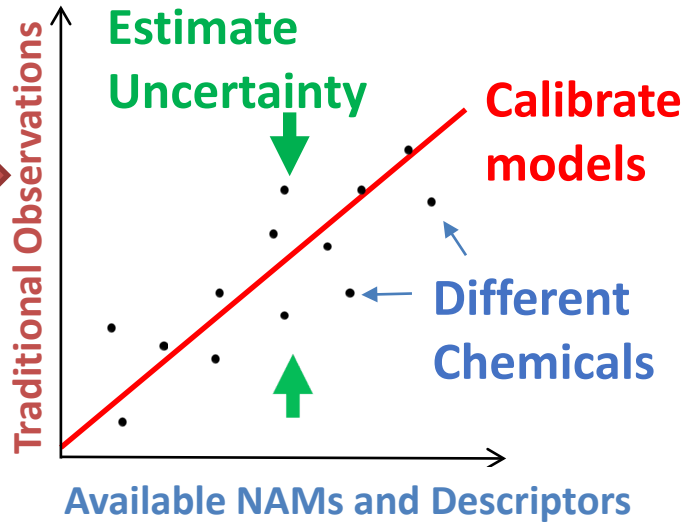


Evaluating High Throughput Exposure Models

CDC NHANES Blood and Urine Biomonitoring

R Package Bayesmarker Stanfield et al. (2022)

Evaluate Model Performance and Refine Models



Apply **calibration** and estimated **uncertainty** to other chemicals

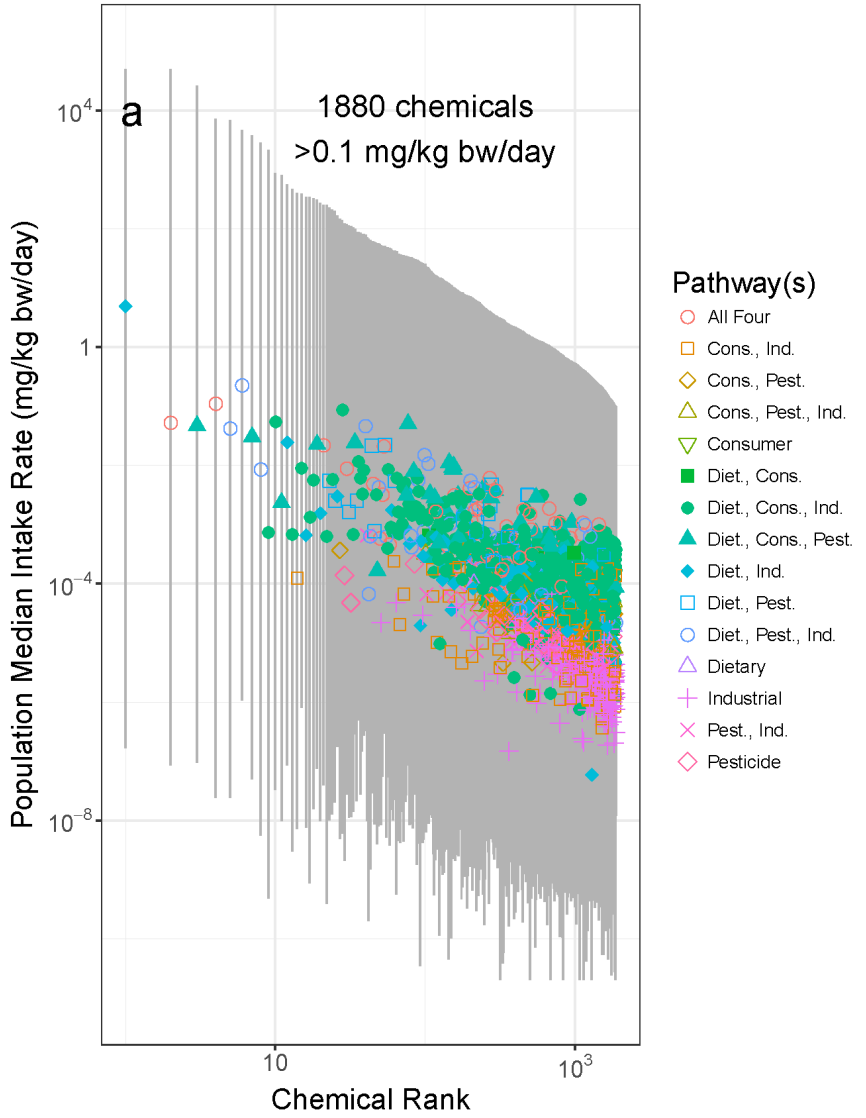
Systematic Empirical Evaluation of Models

High Throughput Exposure Models and Exposure Descriptors

SEEM Consensus Model of Median Chemical Intake

- We predict relevant pathway(s), median intake rate, and credible interval for each of 687,359 chemicals with structures available from the CompTox Chemicals Dashboard

- Of these chemicals, 30% have low probability for exposure via any of the four pathways
  - These are considered outside the “domain of applicability”



Ring et al., 2018

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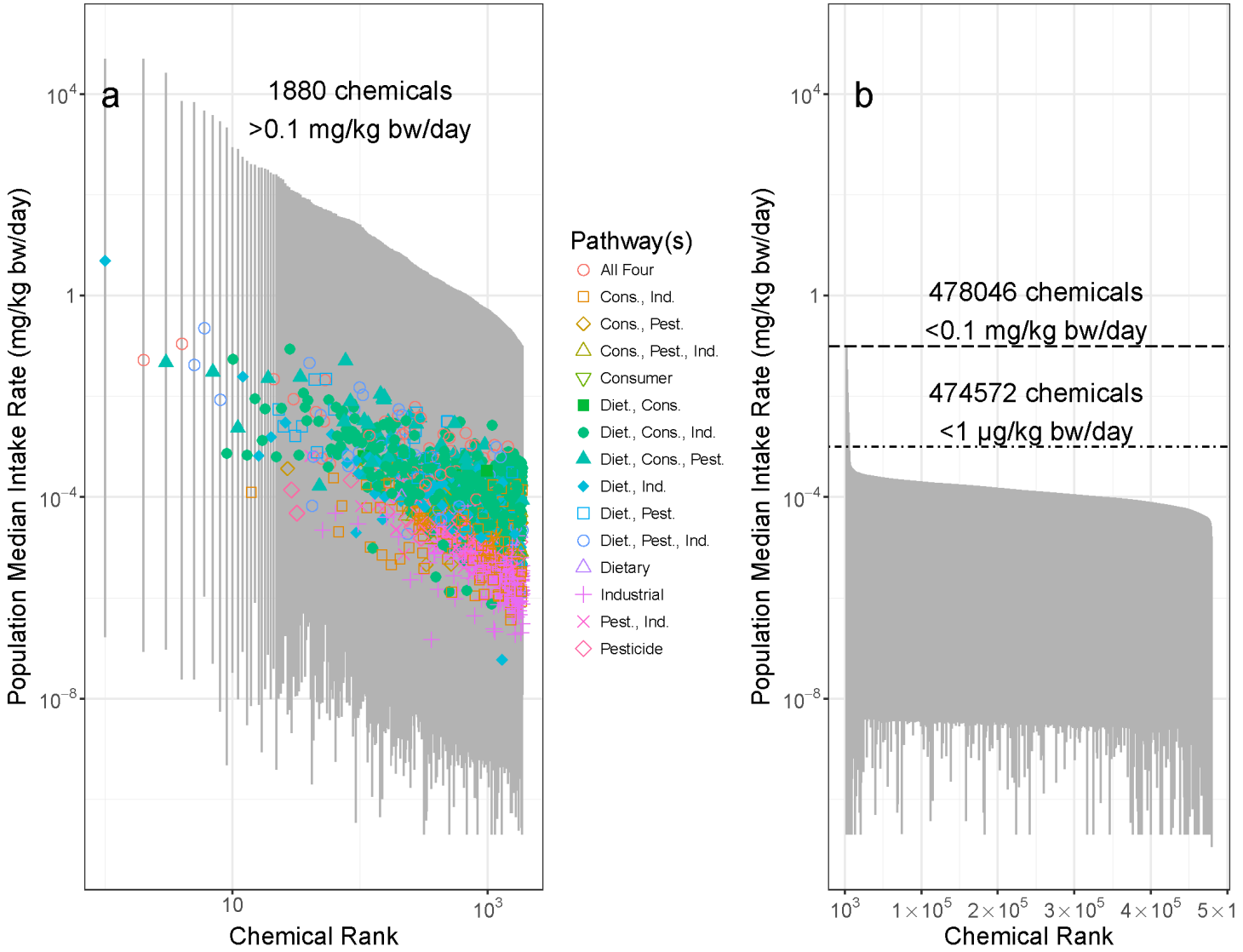
- There is 95% confidence that the median intake rate is below 1 µg/kg BW/day for 474,572 compounds.
  - We have not said anything about the 95th percentile highest exposed individuals!



Ring et al., 2018

United States Environmental Protection Agency

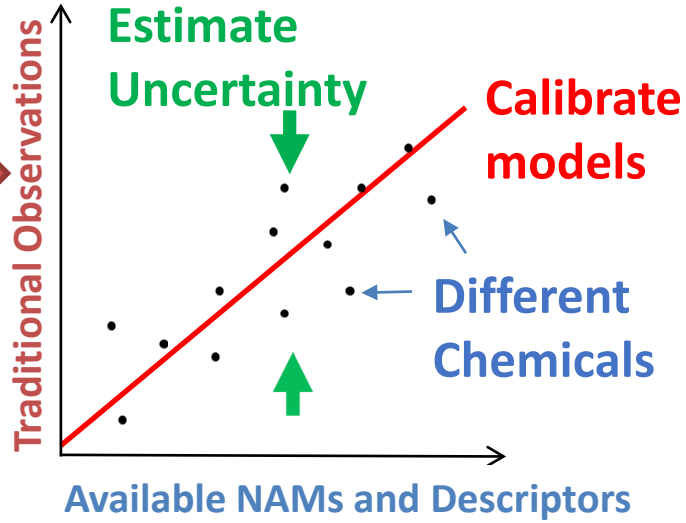
Final Thoughts

Evaluating NAMs for Risk Assessment

Standardized Database of Traditional Observations Across All Available Chemicals

Open-Source Analysis Toolkit

Evaluate Model Performance and Refine Models



Apply **calibration** and estimated **uncertainty** to other chemicals

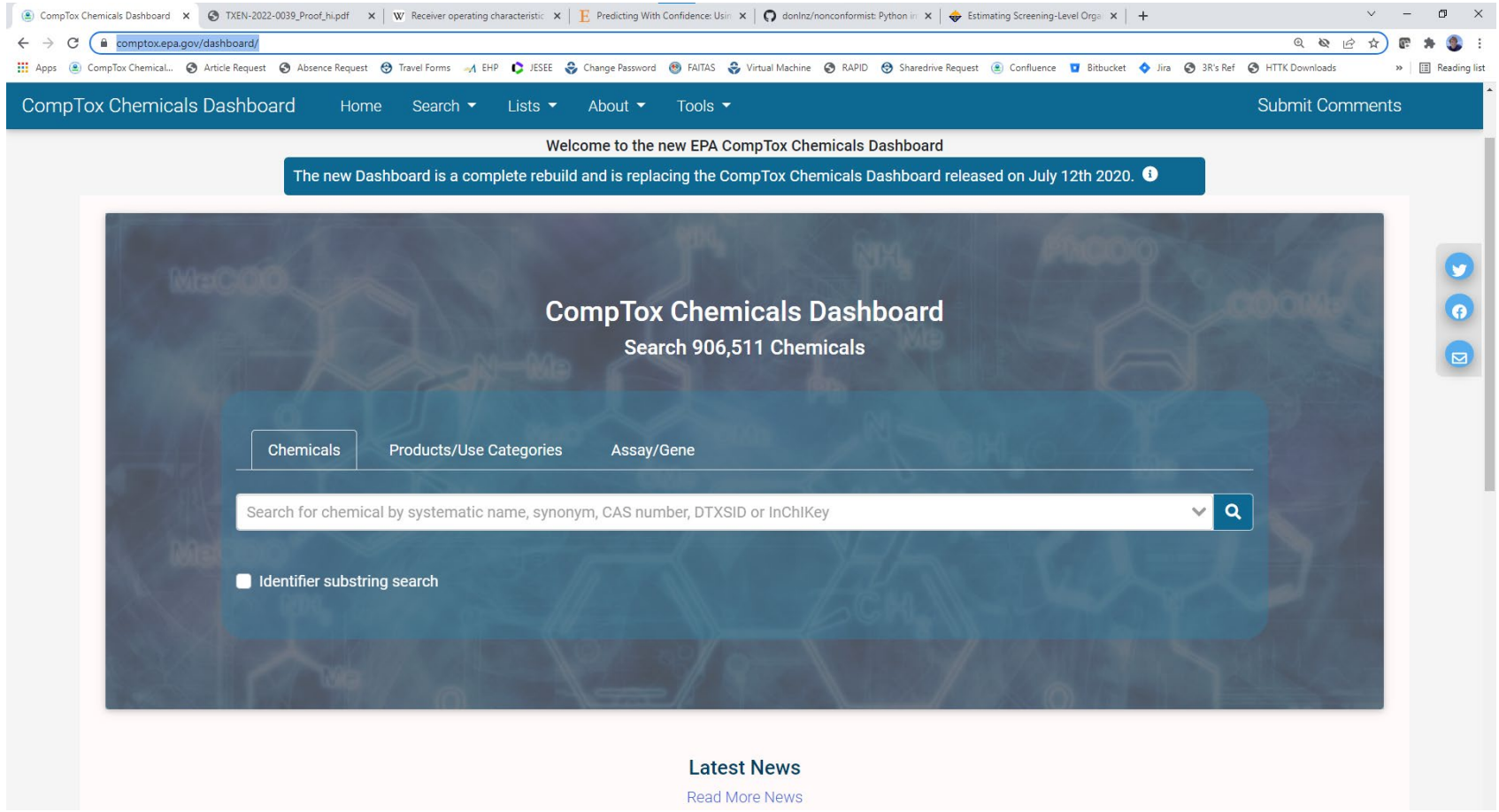
Mechanistic / Statistical / Machine Learning Models for Prediction

Open-Source Analysis Toolkit

New Approach Methodologies and Chemical Structure-Derived Descriptors

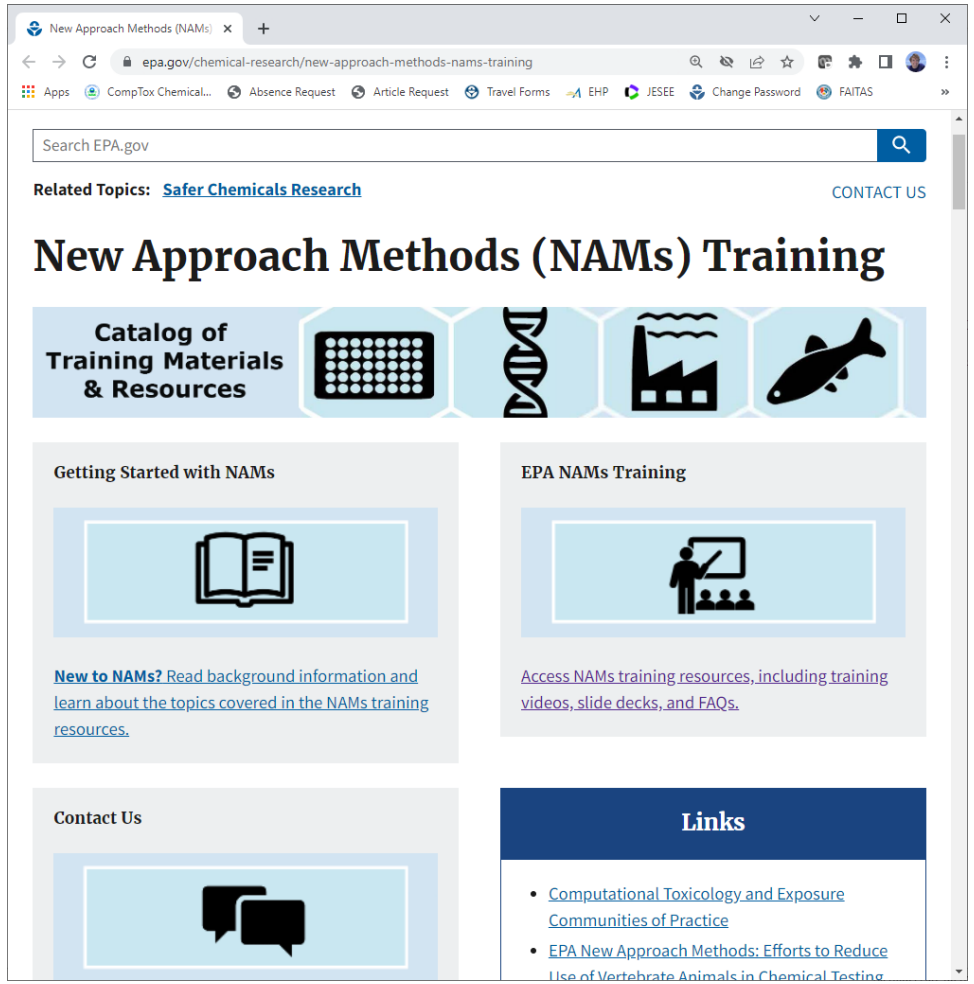
CompTox Chemicals Dashboard

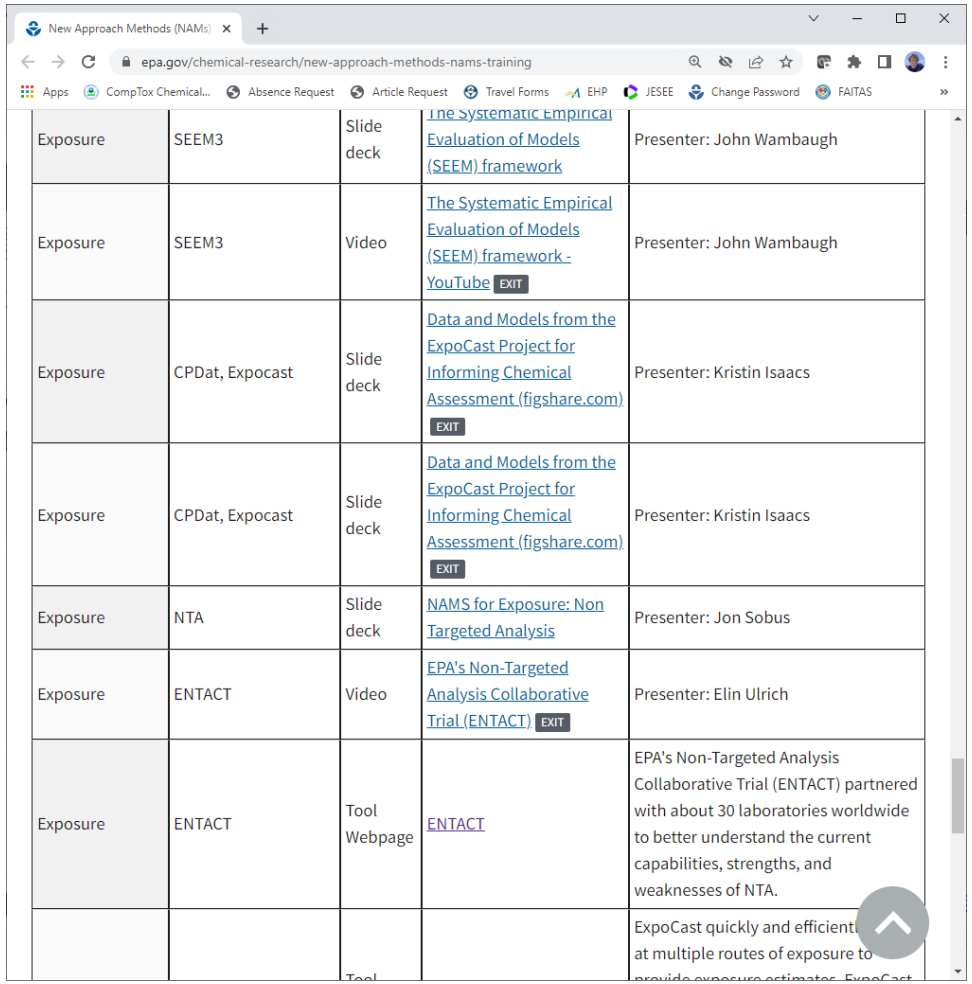
Chemicals are curated, assigned unique identifiers, and linked to a wide variety of databases: https://comptox.epa.gov/dashboard/



EPA NAMs Training Material

- Dozens of presentations and other resources for EPA NAMs are available online





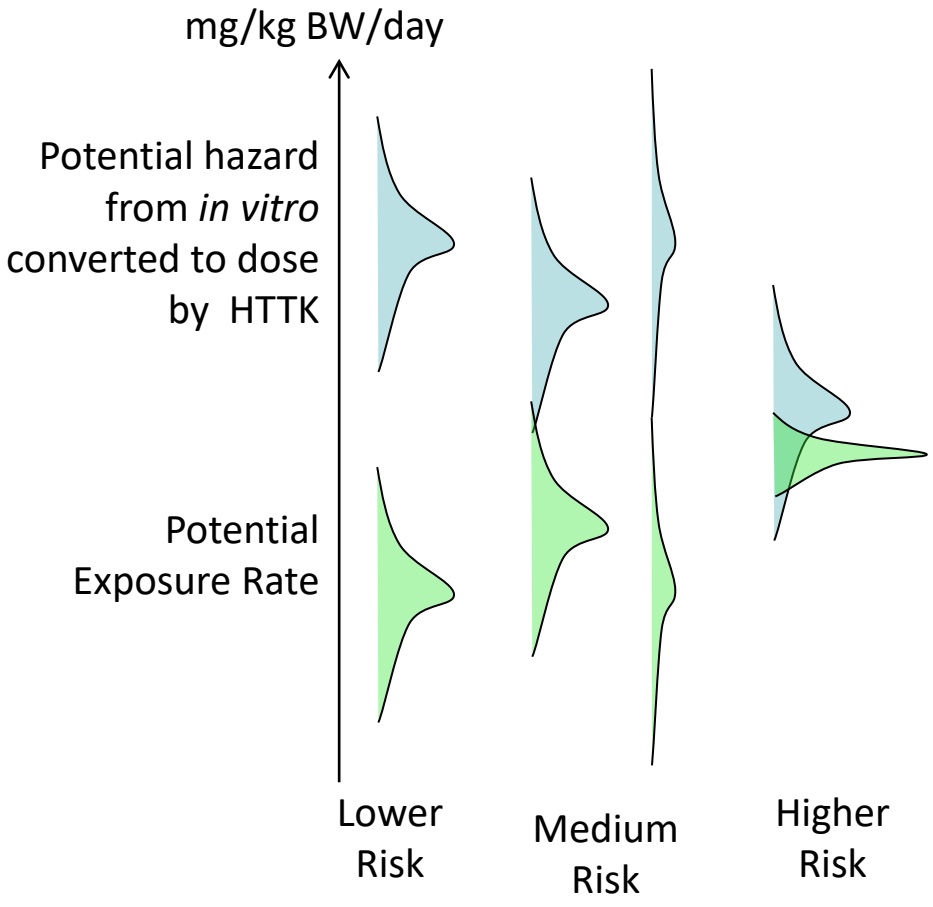
https://www.epa.gov/chemical-research/new-approach-methods-nams-training

Summary

- New approach methodologies (NAMs) are being applied to prioritize existing and new chemicals for testing and new NAMs are being developed to expand biological and chemical coverage

- Quantitative statistical evaluation of NAMs requires:
  - 1) careful construction of a database of traditional data,
  - 2) tools for summarizing these data,
  - 3) development of sufficient NAM data, AND
  - 4) standardized tools for analysis of NAM data

- All EPA data are being made public:
  - The CompTox Chemicals Dashboard (A search engine for chemicals) http://comptox.epa.gov/
  - R and Python packages



Acknowledgements

Center for Computational Toxicology and Exposure (CCTE)

EPA Colleagues:
- CPHEA
- CEMM
- OCSPP
- OLEM
- Regions

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- NTP
- FDA
- NCATS
- Health Canada
- ECHA
- JRC
- EFSA
- A*STAR

Research Triangle Park, NC

Duluth, MN

Washington, DC

Gulf Breeze, FL

Cincinnati, OH

Athens, GA

Slide from Alison Harrill

EPA United States Environmental Protection Agency

References