Australian College of Toxicology & Risk Assessment (ACTRA)

US EPA's ExpoCast program: New approach methodologies for exposure

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United States Environmental Protection Agency

The views expressed in this presentation are those of the author(s) and do not necessarily reflect the views or policies of the U.S. EPA.

ANNUAL SCIENTIFIC MEETING

MELBOURNE | 24 - 25 AUGUST 2022

EPA's ExpoCast project: developing methods to generate rapid exposure predictions for next-generation risk assessment

ExpoCast = "Exposure Forecasting"

ELSEVIER

Current Opinion in Toxicology

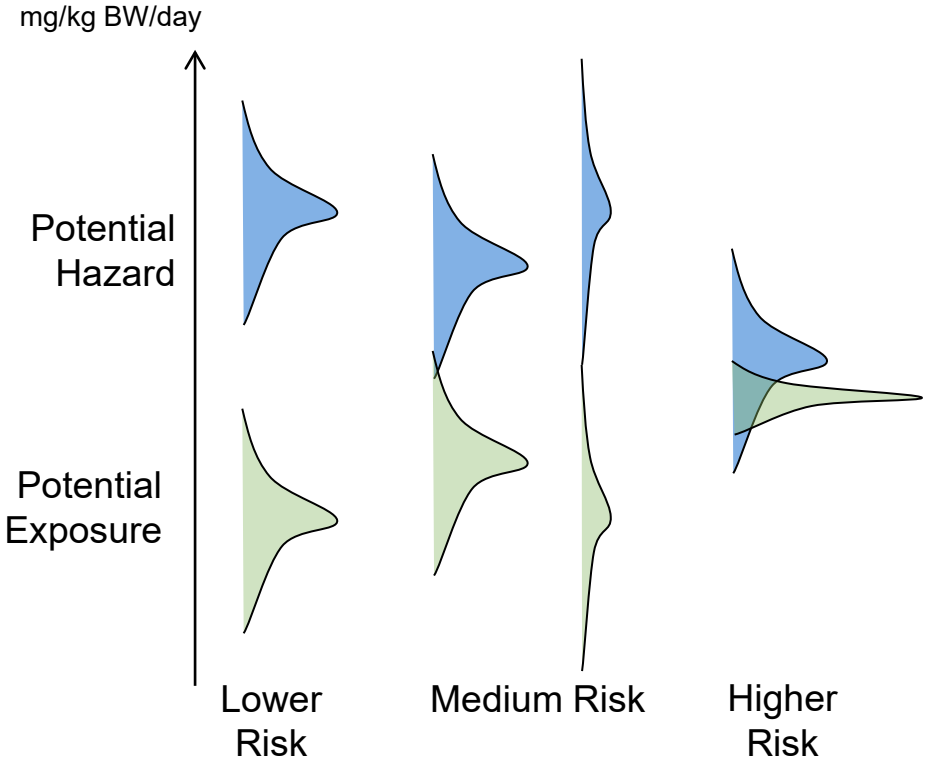
Available online 31 July 2019

In Press, Journal Pre-proof

New Approach Methodologies for Exposure Science

John F. Wambaugh [1], Jane C. Bare [2], Courtney C. Carignan [3], Kathie L. Dionisio [4], Robin E. Dodson [5, 6], Olivier Jolliet [7], Xiaoyu Liu [8], David E. Meyer [2], Seth R. Newton [4], Katherine A. Phillips [4], Paul S. Price [4], Caroline L. Ring [9], Hyeong-Moo Shin [10], Jon R. Sobus [4], Tamara Tal [11], Elin M. Ulrich [4], Daniel A. Vallero [4], Barbara A. Wetmore [4], Kristin K. Isaacs [4]

Risk is a function of both hazard and exposure



Wambaugh et al. (2019)

Problem: Too many chemicals

41,953 chemicals listed with "active" commercial use in the US (per Toxic Substances Control Act [TSCA] inventory)

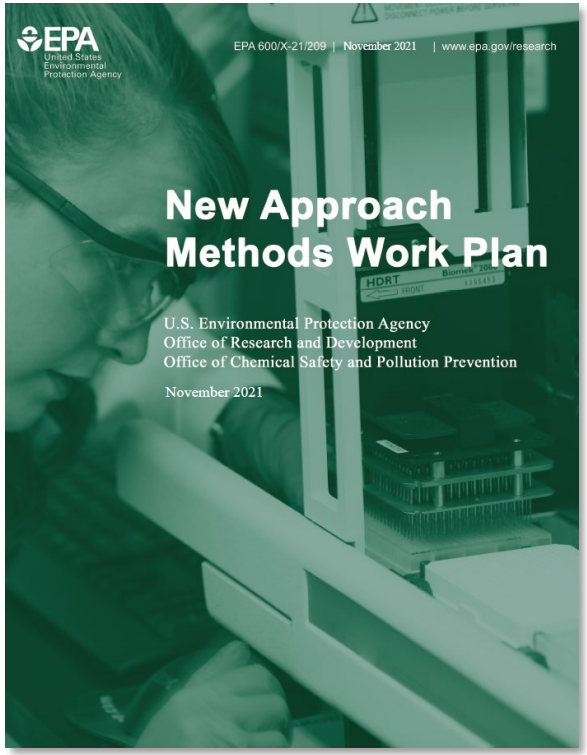
+ hundreds added each year

(**Not counting** food, drugs, cosmetics, pesticides, tobacco, nuclear materials, munitions, and other chemicals not regulated under TSCA!)

Most of these chemicals have **limited or no data** on hazard & exposure!

Schmidt, C. W. (2016)

EPA New Approach Methods Work Plan: Clear Objectives, Strategies and Deliverables



Five objectives for reducing animal testing while ensuring that Agency decisions remain fully protective of human health and the environment

- Evaluate regulatory flexibility to apply NAMs
- Develop baselines and metrics to assess progress
- **Establish scientific confidence and demonstrate applications of NAMs**
- **Develop NAMs to address information gaps**
- Engage and communicate with stakeholders

2021 update to 2020 work plan:

- 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 via John Wambaugh

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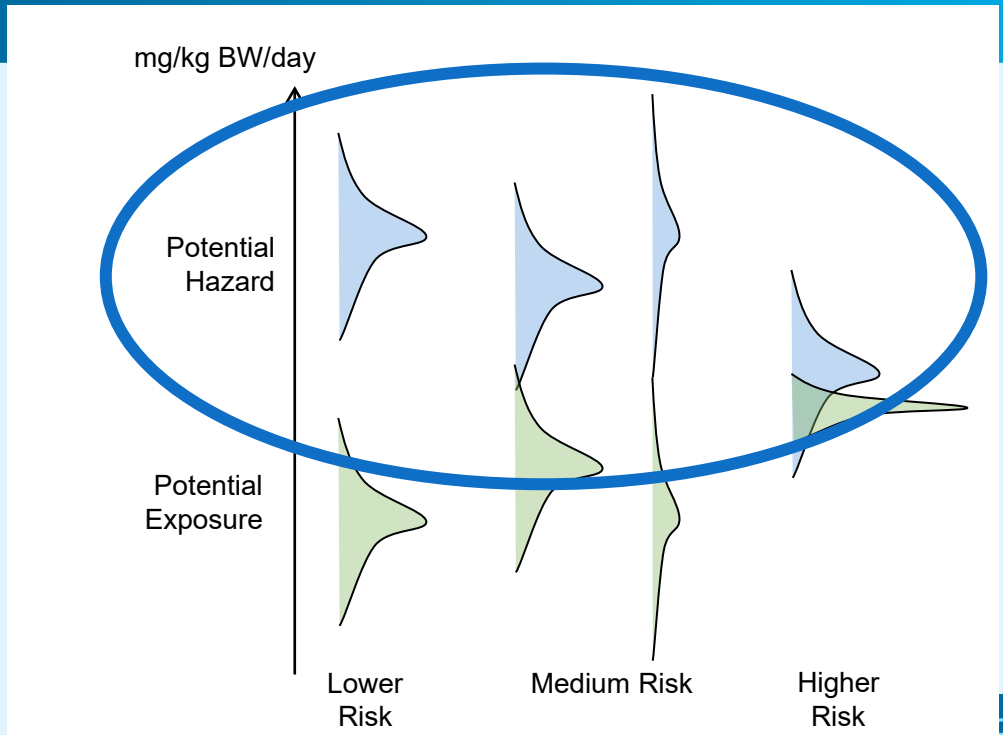
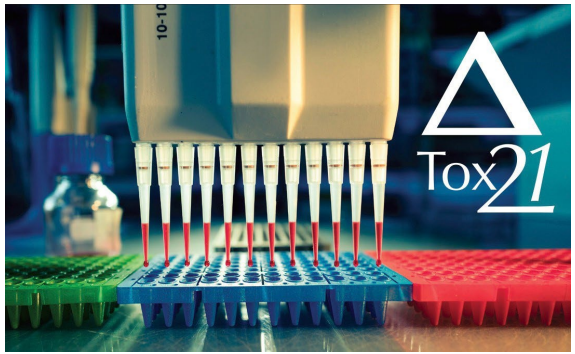
NAMs for hazard



Potential chemical hazard can be rapidly screened using *in vitro* high-throughput screening (HTS) assays, *e.g.* ToxCast/Tox21

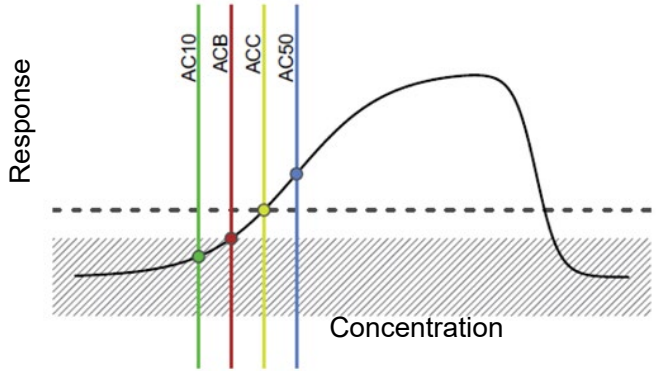


- Thousands of chemicals
- Dozens/hundreds of *in vitro* assays
  - various kinds of bioactivity (binding, signaling, viability…)
- Concentration-response screening

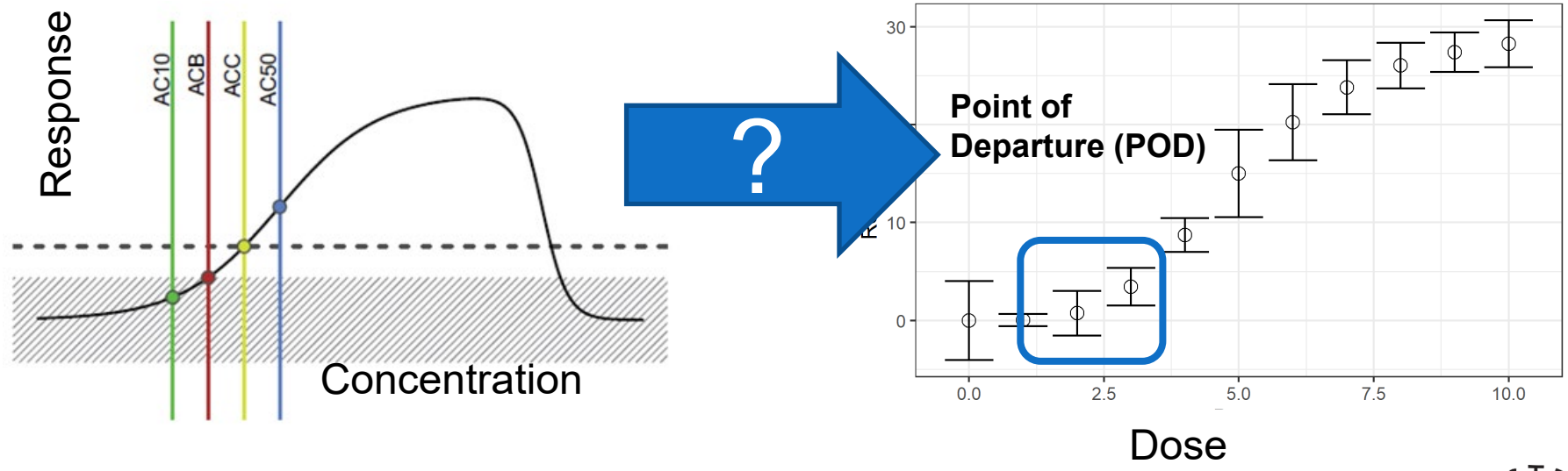
Data: **Bioactive *in vitro* concentration by chemical/assay**

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

[Schmidt 2009; Dix et al. 2007; Kavlock et al. 2018; Filer et al. 2016]

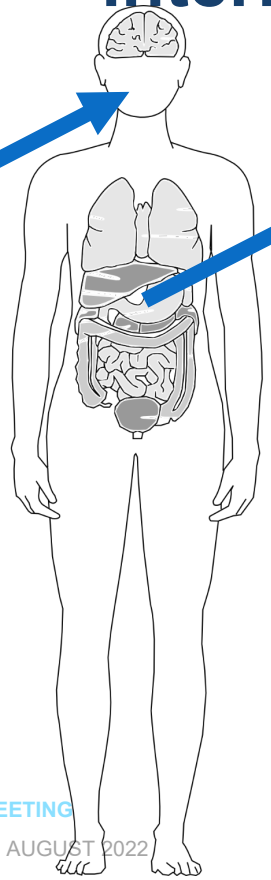


How to convert *in vitro* bioactive concentration to equivalent *in vivo* POD dose?



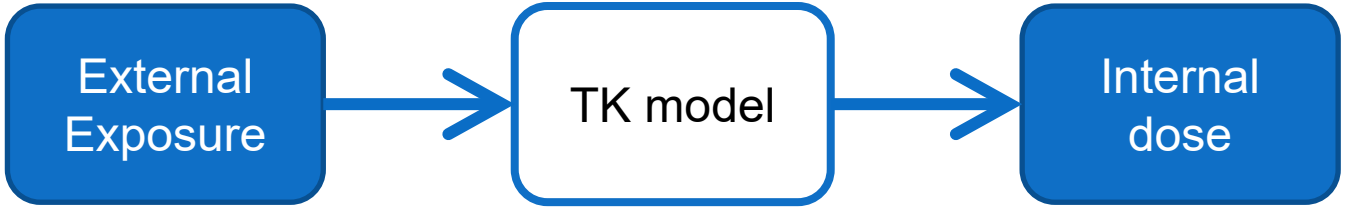
High-throughput toxicokinetics

Toxicokinetics links external exposures to internal doses by describing ADME



External exposure

Internal dose = Concentration of chemical or drug in one or more body tissues of interest

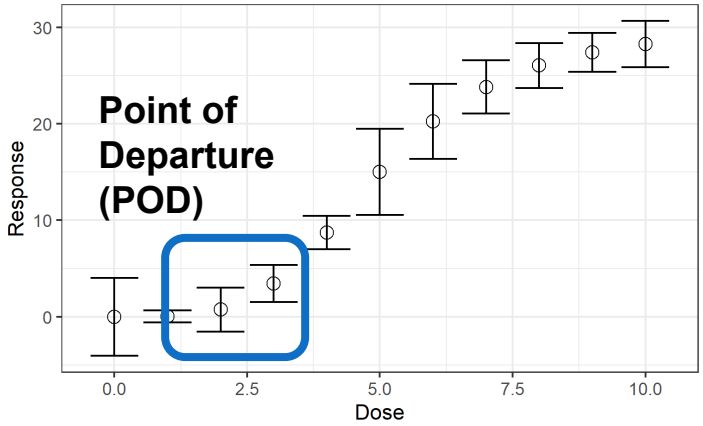


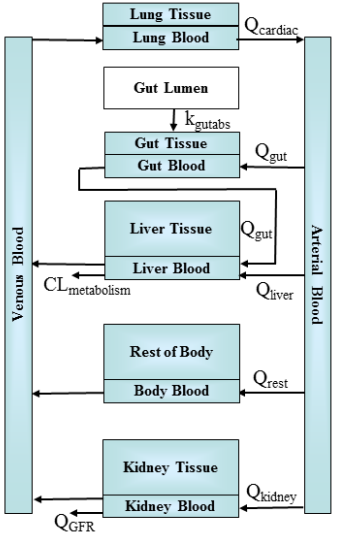
ADME

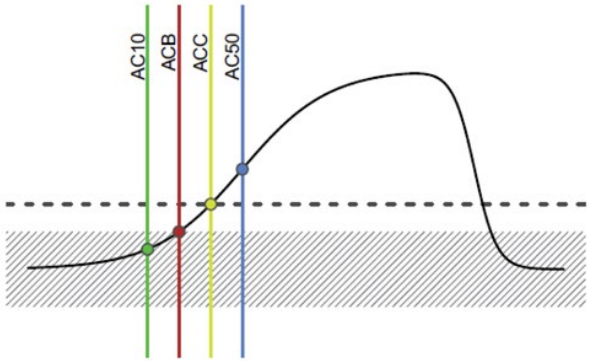
- **Absorption**: How does the chemical get absorbed into the body tissues?
- **Distribution**: Where does the chemical go inside the body?
- **Metabolism**: How do enzymes in the body break apart the chemical molecules?
- **Excretion**: How does the chemical leave the body?

Reverse toxicokinetics or reverse dosimetry: *In vitro-in vivo* extrapolation

External Exposure ← TK model ← Internal dose = HTS bioactive conc.





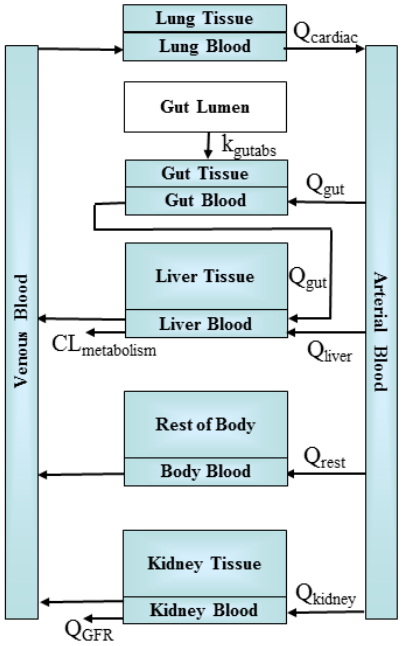


Tan et al. (2007)

High-throughput TK (HTTK)

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

Generic physiologically-based TK (PBTK) model



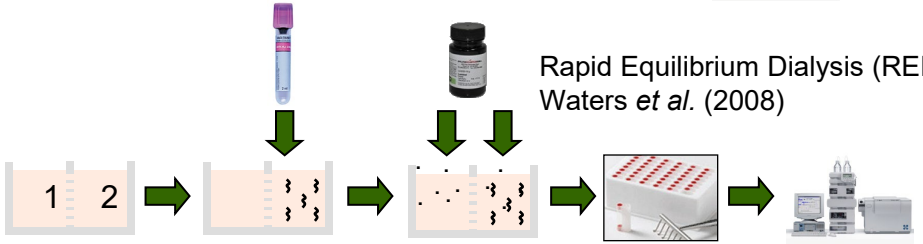
Wambaugh et al. (2015)
Pearce et al. (2017b)
Ring et al. (2017)
Linakis et al. (2020)

+

Chemical-specific TK model parameters:
in vitro or *in silico*

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

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



Use of *in vitro* TK parameters:
Rotroff et al. (2010)
Wetmore et al. (2012)
Wetmore et al. (2015)
Wambaugh et al. (2019)

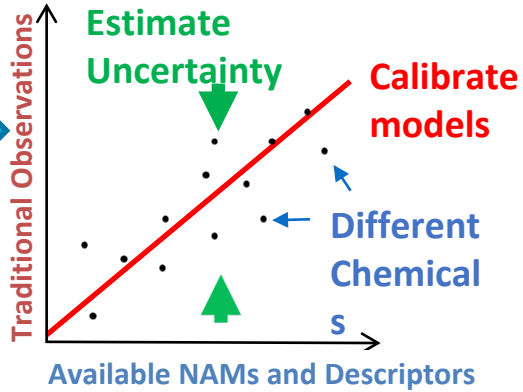
In silico TK parameters:
Pearce et al. (2017a)
Sipes et al. (2017)
Pradeep et al. (2020)
Dawson et al. (2021)

Evaluation of 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 chemicals without traditional data


OXFORD SOT Society of Toxicology www.toxsci.oxfordjournals.org ToxSci 20 Years

TOXICOLOGICAL SCIENCES, 2018, 1–18
doi: 10.1093/toxsci/kfy020
Advance Access Publication Date: January 27, 2018
Research Article

Evaluating *In Vitro-In Vivo* Extrapolation of Toxicokinetics

John F. Wambaugh,*,[1] Michael F. Hughes,[†] Caroline L. Ring,*,[‡,2] Denise K. MacMillan,[†] Jermaine Ford,[†] Timothy R. Fennell,[§] Sherry R. Black,[§] Rodney W. Snyder,[§] Nisha S. Sipes,[¶] Barbara A. Wetmore,[‖] Joost Westerhout,[‖] R. Woodrow Setzer,* Robert G. Pearce,*,[‡] Jane Ellen Simmons,[†] and Russell S. Thomas*

R Package httk
Pearce et al. (2017)

R Package invitroTKstats

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

Slide from Dr. John Wambaugh

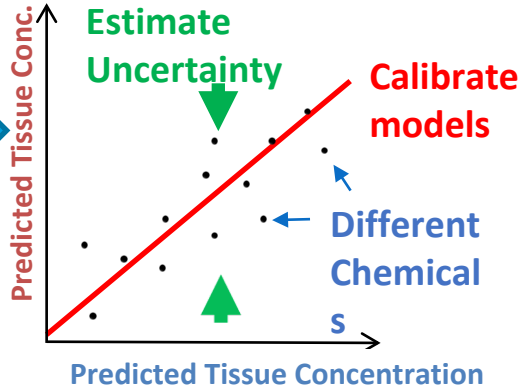
Using HTTK to evaluate HTS NAMs for hazard

Slide from Dr. John Wambaugh

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

R Package httk
Pearce et al. (2017)

Evaluate Model Performance and Refine Models



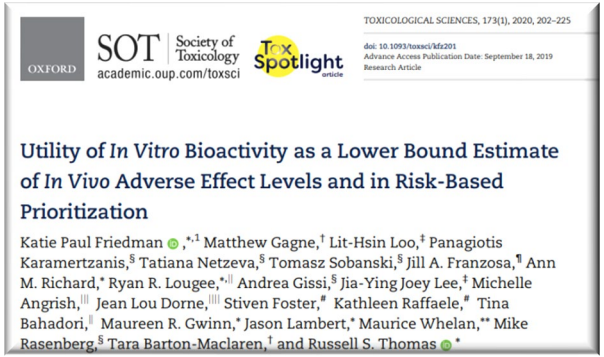
Honda et al. (2019) showed that HTTK modeling improved correlation between *in vitro* and *in vivo* PODs

Mechanistic / Statistical / Machine Learning Models for Prediction

R Package tcpl Filer et al. (2017)

invitroDB:
ToxCast and Tox21
in vitro high throughput screening assays

APCRA Consortium Case Study (Friedman et al. 2020)


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

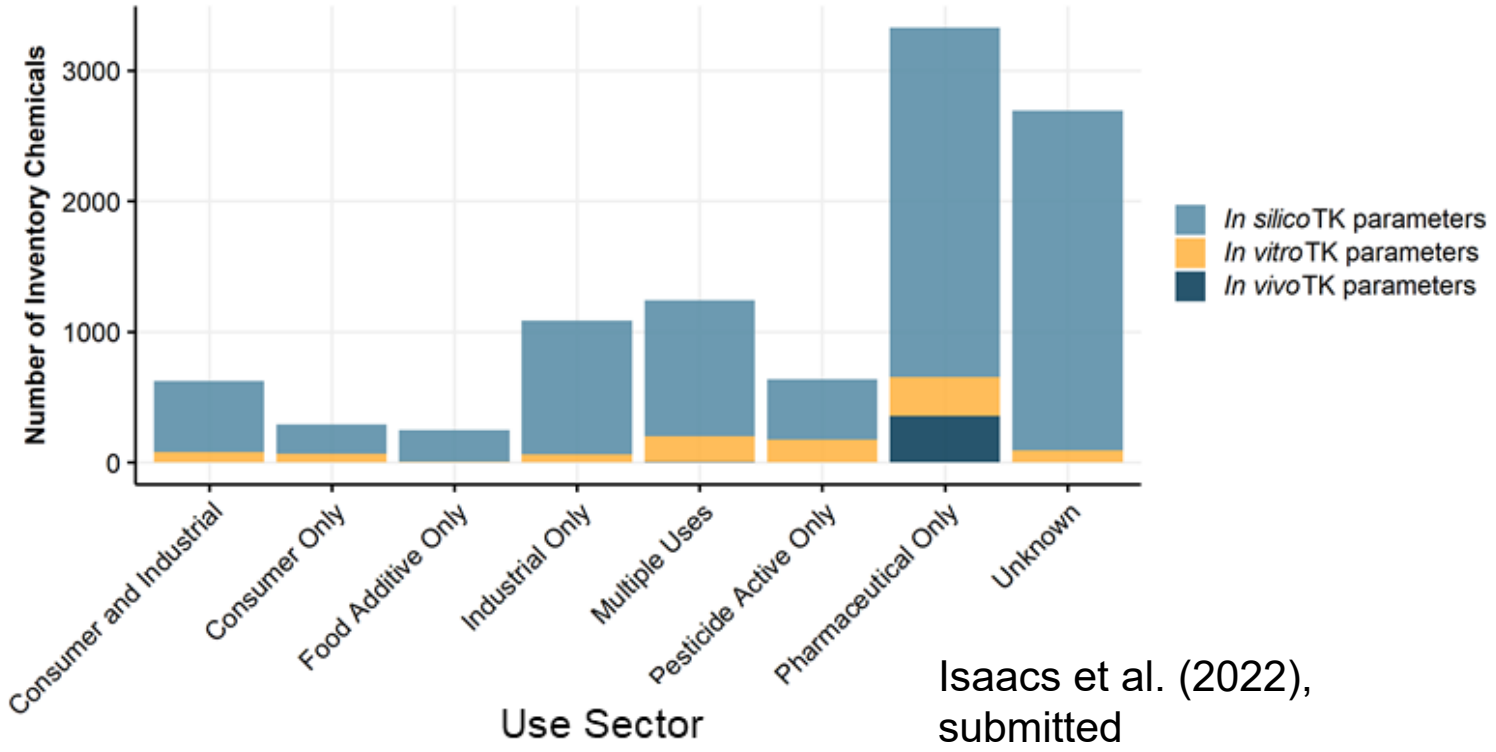
OXFORD SOT Society of Toxicology academic.oup.com/toxsci Tox Spotlight article

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 *

ExpoCast HTTK efforts have already filled TK data gaps for thousands of chemicals

A



Isaacs et al. (2022), submitted

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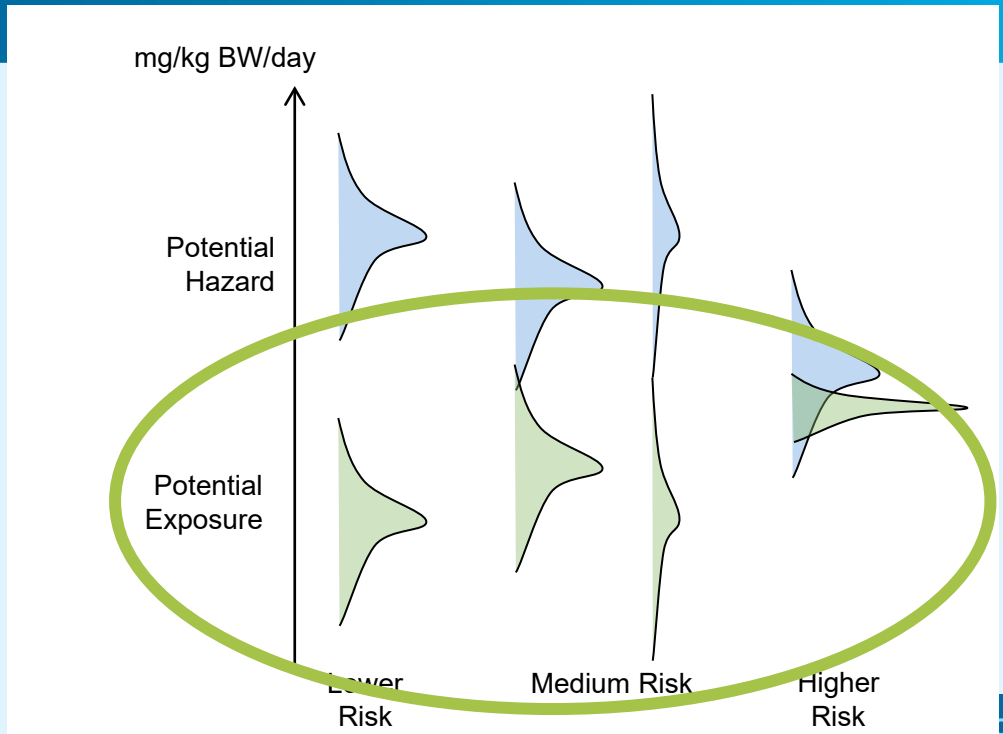
NAMs for exposure



ExpoCast exposure NAMs can be organized by considering a generic conceptual model of exposure, from source to dose

ExpoCast aims to inform every part of this conceptual model, in ways that:

- can be applied **rapidly**, to large numbers of chemicals
- **leverage existing information** to make **predictions** for **data-poor** chemicals
- quantify **uncertainty** in predictions
- can be used to **prioritize** chemicals by potential risk

Source/use and release information

Informatics: organize & combine data streams for consumer product use/release

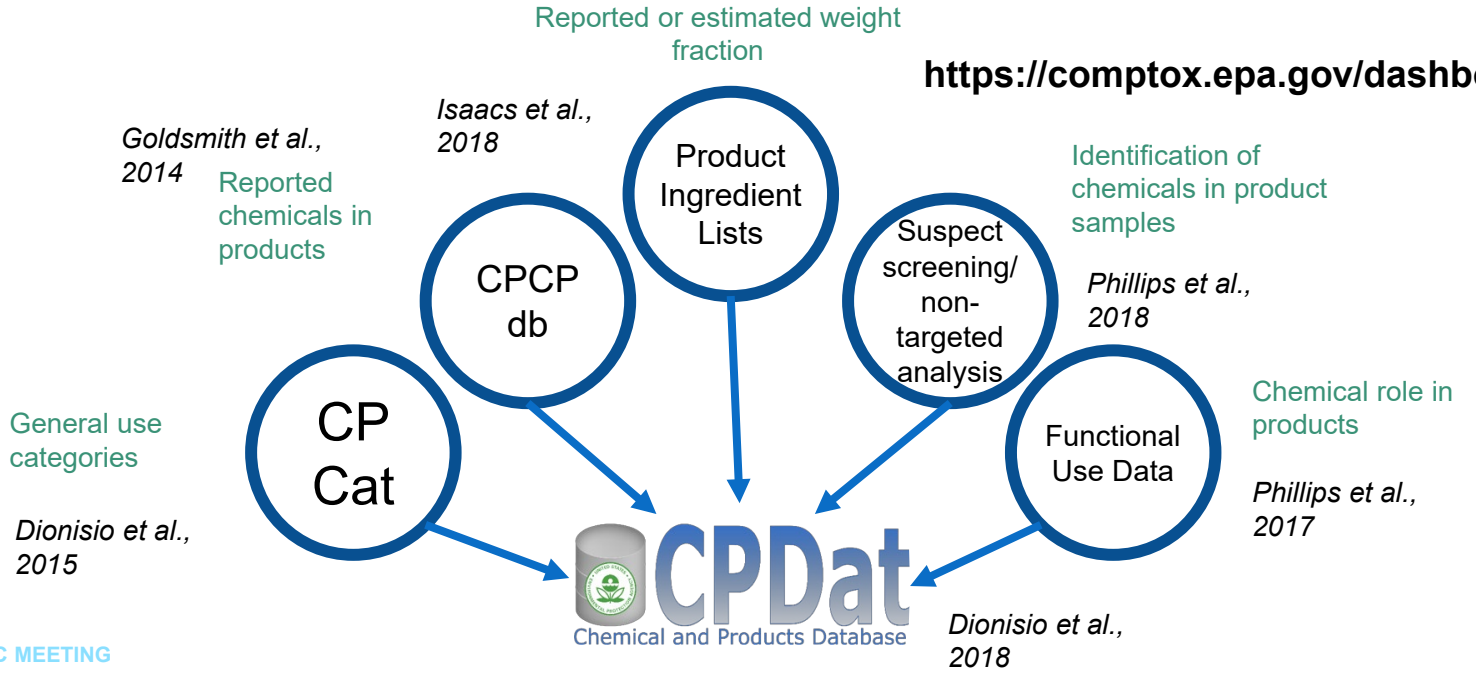
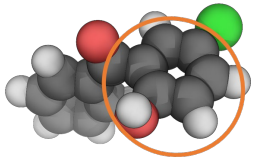
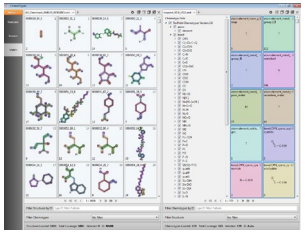


Figure from Dr. Kristin Isaacs

Fill data gaps: Predict unknown functional uses with machine learning

Phillips *et al.* (2017)





Chemical Functional Use Database (FUSE)

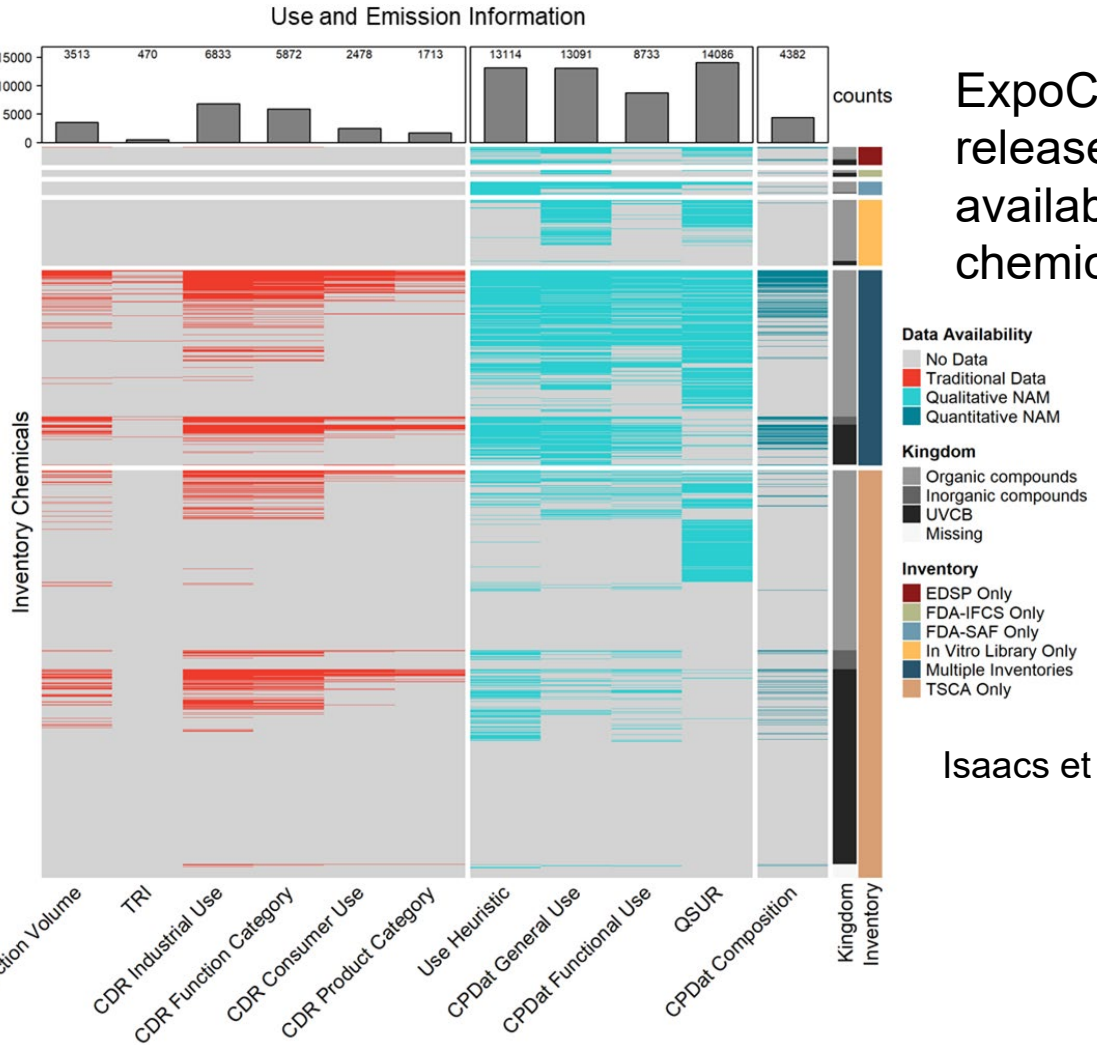
Positive Examples | Negative Examples

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

Successful Model

Failed Model

Probabilistic Predictions of Potential Chemical Uses



ExpoCast expands use & release information availability across chemicals

Isaacs et al. (2022), submitted

Monitoring information

What's in products, environmental media, biological media?

Multimedia Monitoring Database (MMDB) [Isaacs et al. 2022]: Informatics approach to organizing media monitoring data

Raw data sources: Various monitoring programs
United States Geological Service
US Food & Drug Administration
US EPA Ambient Monitoring Archive (air)
US EPA UCMR (drinking water)
[…many others…]

Harmonize
Chemical identifiers
Media identifiers (air, water, soil, serum, etc.…)
Other metadata
[…]

Result		
Chemical	Medium	Monitored value
DTXSID1…	Air	#
DTXSD1…	Water	#
DTXSID2…	Soil	#
DTXSID2…	Biosolids	#
[…]	[…]	[…]

Non-Targeted Analysis:

Detecting unknown chemicals without knowing *a priori* what to look for

Source/Use and Release

Pilot: 20 Consumer Product Categories

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

Recycled Consumer Materials

Lowe *et al.*, *2018*

Consumer Product Emissions from Different Substrates

Fate and Transport/Media

Residential Air

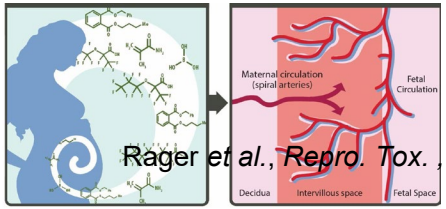
Residential Dust

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

Internal Dose

Pooled Human Blood

Human Placenta



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

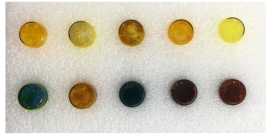
Slide adapted from Dr. Kristin Isaacs

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

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

Round-robin collaborative trial

Part 1. Ten ToxCast mixtures



Part 2. Three standardized exposure relevant extracts

Unaltered

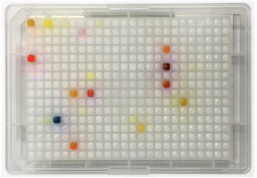
Fortified

NIST SRM 1957- Organic Contaminants in Non-fortified Human Serum

Oregon State University- Outdoor air exposed silicone bands

NIST SRM 2585- Organic Contaminants in House Dust

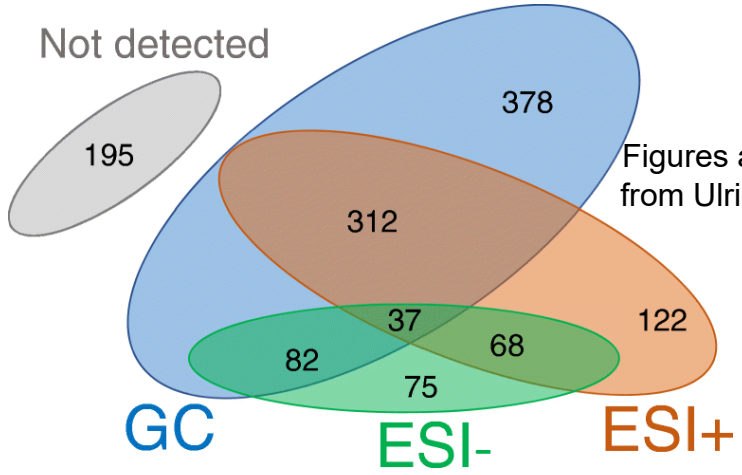
Part 3. Individual ToxCast standards



Part 1. Blinded analysis of ten mixtures of 1269 total ToxCast substances

Part 2. Blinded analysis of ToxCast mixtures spiked into environmentally relevant media (human serum, silicone wristbands, house dust)

Part 3. Develop reference spectra from individual ToxCast standards



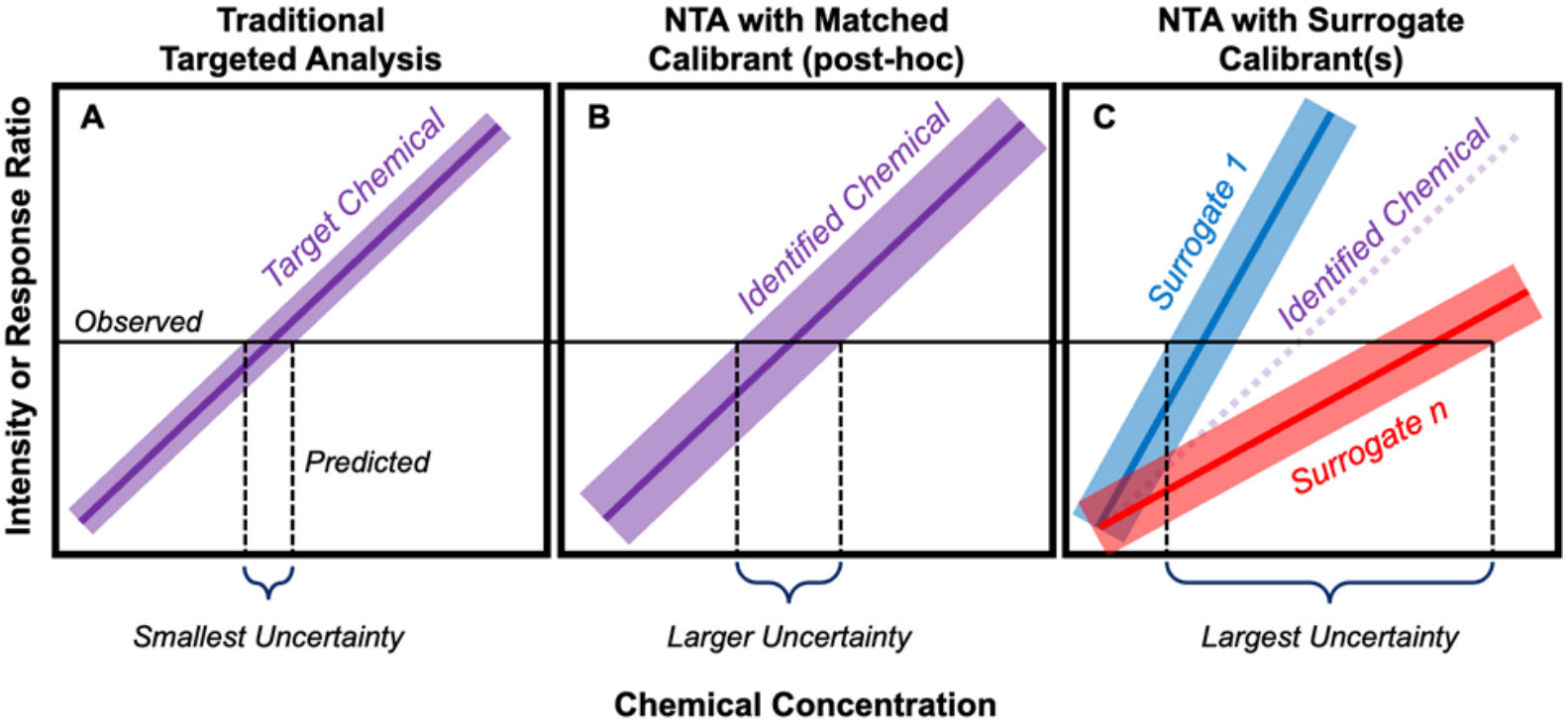
Figures adapted from Ulrich et al. (2019)

Results from Part 1: Number of ToxCast substances correctly detected by three different NTA methods

Quantitative NTA (qNTA): not just *what's there*, but *how much*?

Figure: Fisher et al. (2022)

also see Groff et al. (2022)

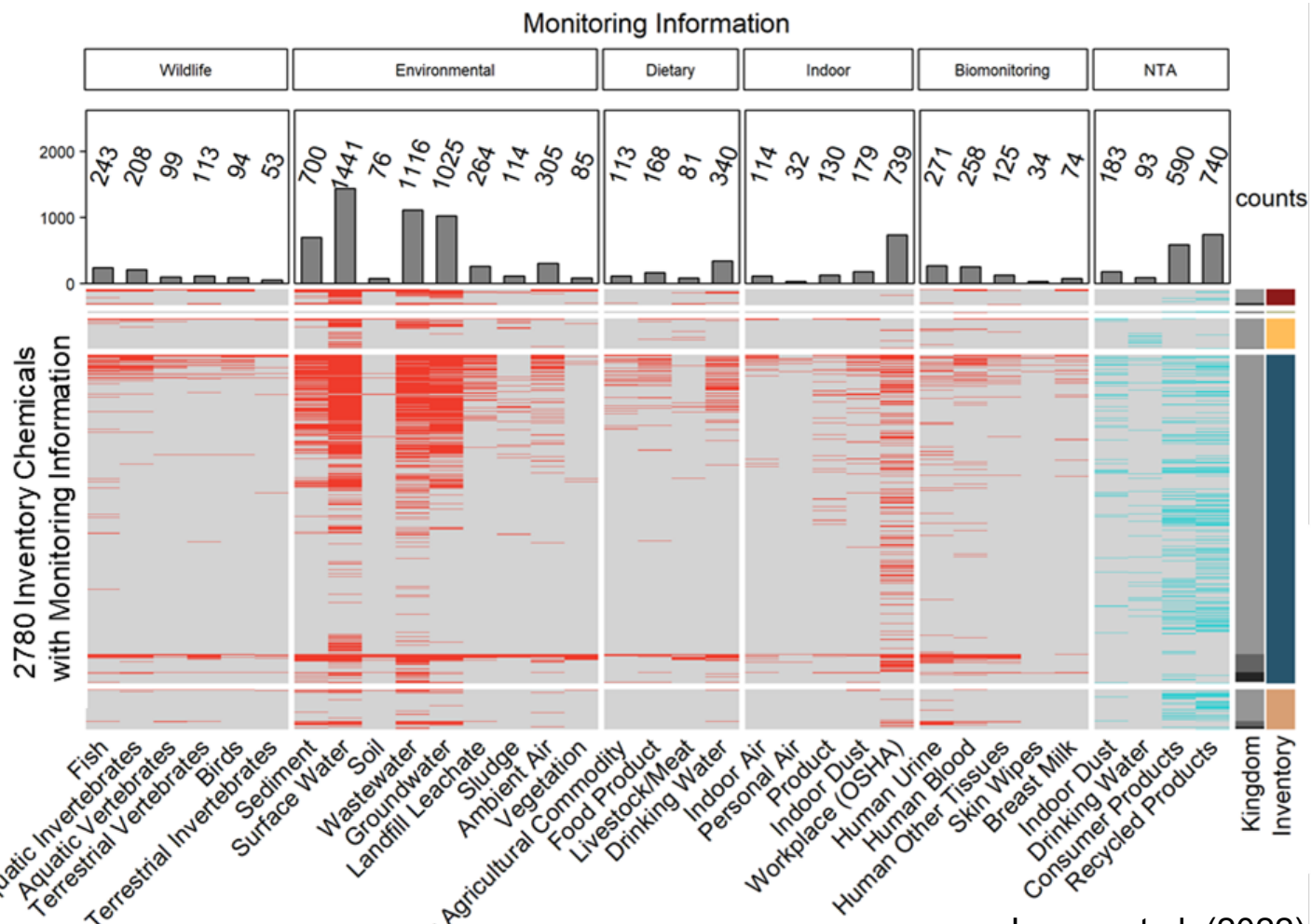


Filling monitoring data gaps (works in progress)

Machine-learning models to predict chemical occurrence in various media, based on:

- Structure
- Functional use categories
- Phys-chem properties
- Other source/use-release information
- Predictions of existing fate & transport models
- etc…..

Eddy et al. (2022 poster)
Sayre et al. (2022), in review
Kruse & Ring (2021 poster)



Isaacs et al. (2022), submitted

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Exposure factors

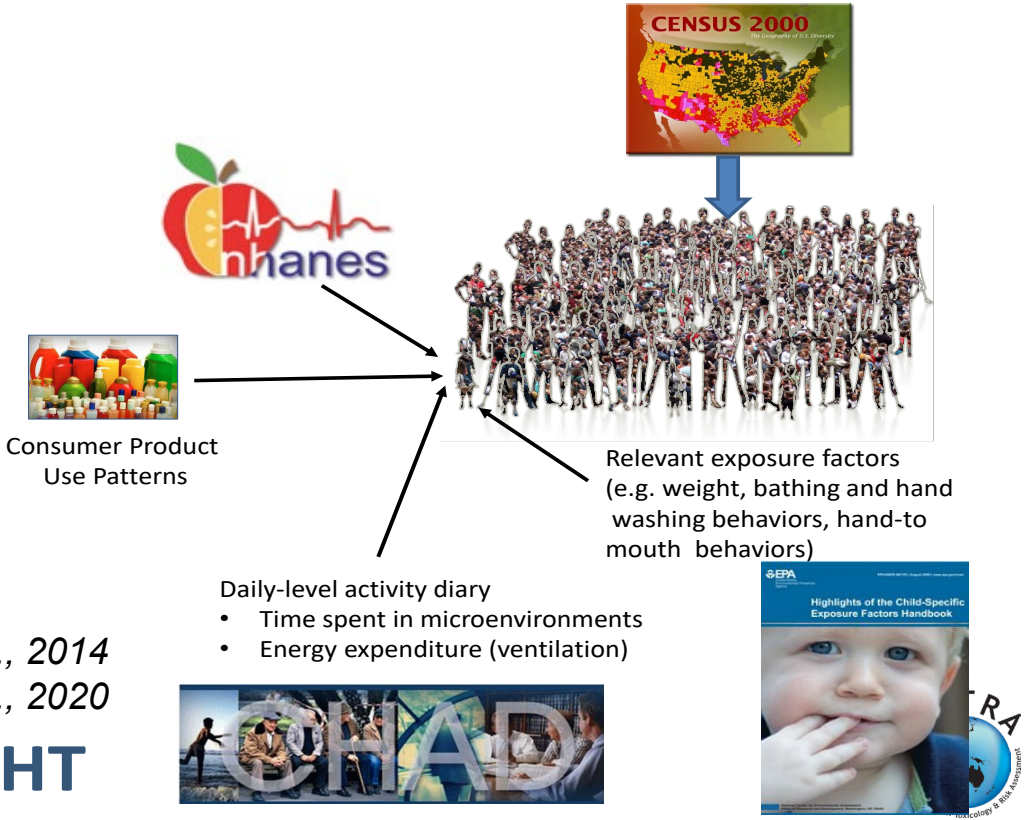
Informatics approach to organizing information about human receptors

Consumer habits & practices

Residential activity diaries

Demographics & physiology

Other exposure factors



Isaacs et al., 2014
Isaacs et al., 2020

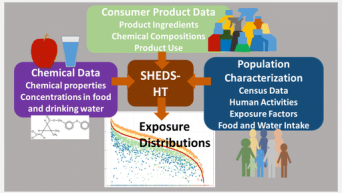
SHEDS-HT

High-throughput exposure models

High Throughput Exposure (HTE) Models for Key Pathways

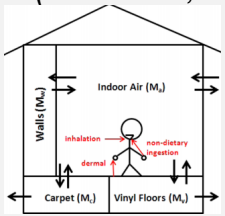
Consumer (Near-Field) Pathways ***Ambient (Far-Field) Pathways*** ***Dietary Pathways***

SHEDS-HT *(Isaacs et al., 2014)*

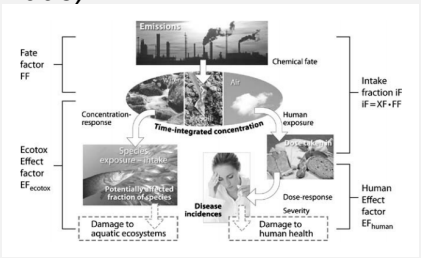


RAIDAR-ICE *(Li et al., 2018)*

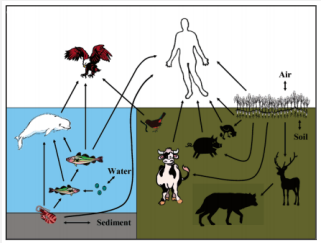
FINE *(Shin et al., 2015)*



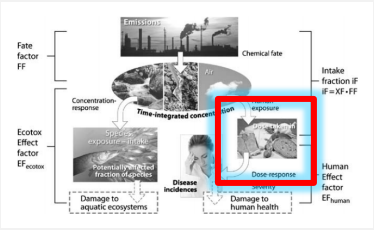
UseTox *(Rosenbaum et al., 2008)*



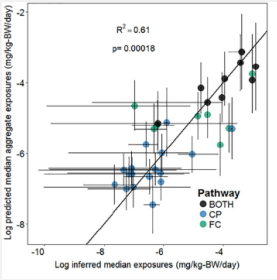
RAIDAR *(Arnot et al., 2006, 2008)*



UseTox *(Rosenbaum et al. (2008)*



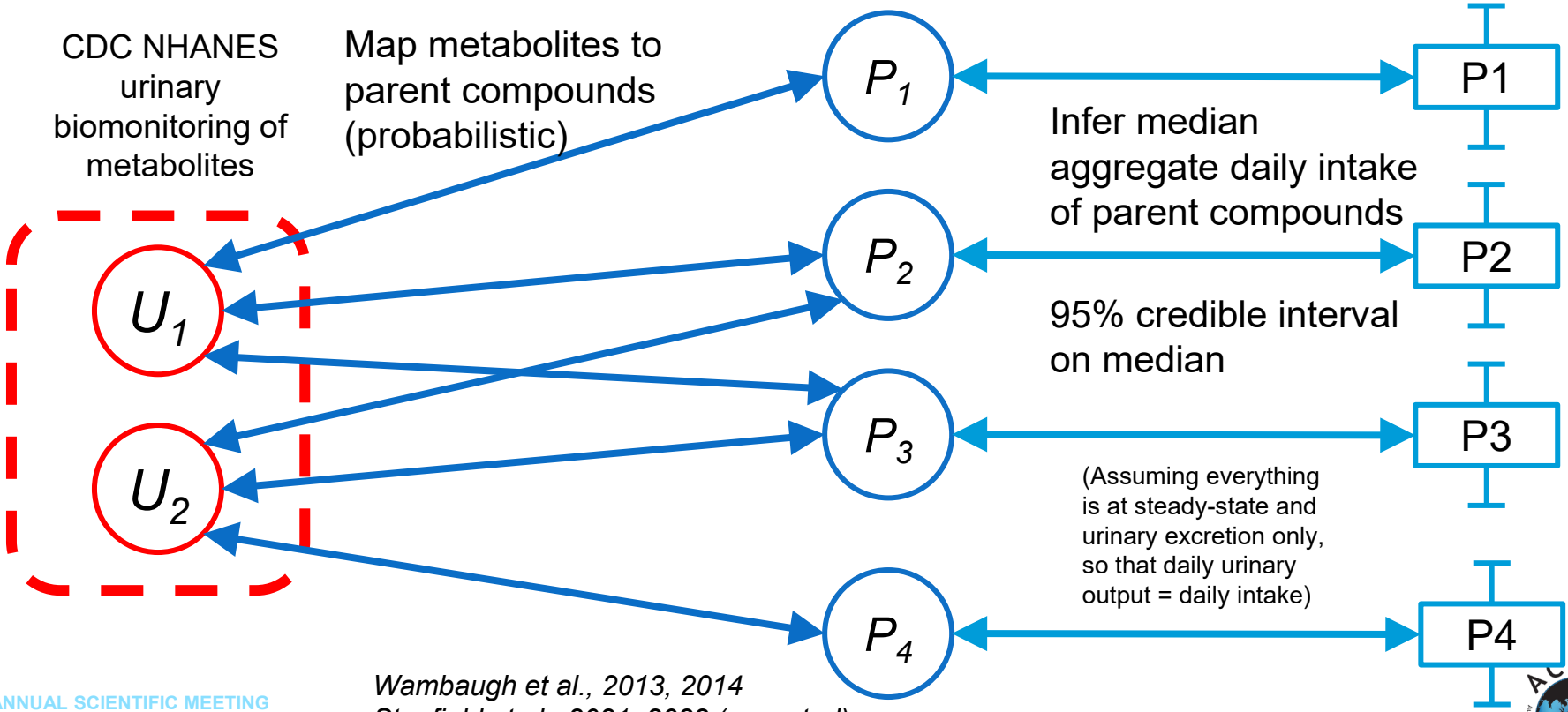
SHEDS-HT *(Biryol et al., 2017)*



Slide from Kristin Isaacs

High-throughput exposure inferences

Bayesian inference of external exposures from biomonitoring data

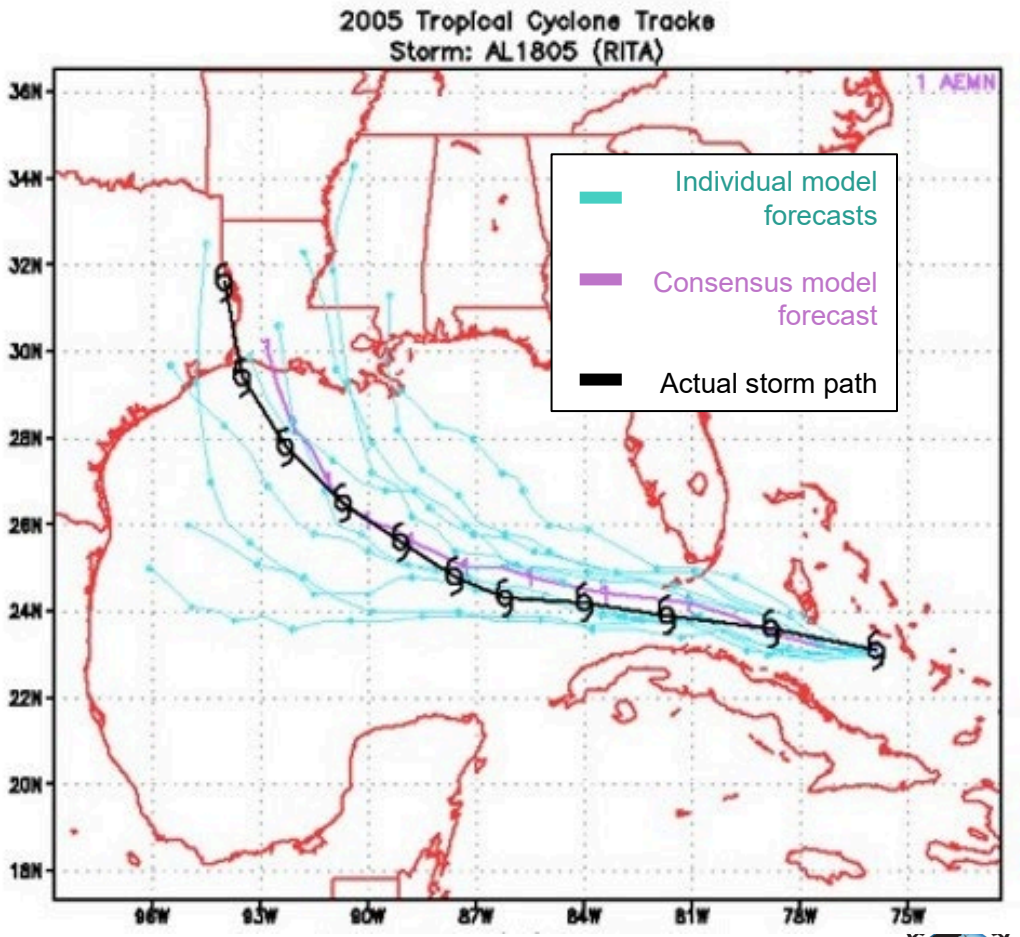


Wambaugh et al., 2013, 2014
Stanfield et al., 2021, 2022 (accepted)

High-throughput exposure model evaluation & consensus model

Consensus model example: Hurricane tracking

- Average together individual models
- Weight individual models to adjust for biases
  - Calibrate weighting using known hurricane tracks
  - Also a way to *evaluate* models –
    heavier weight = stronger predictor



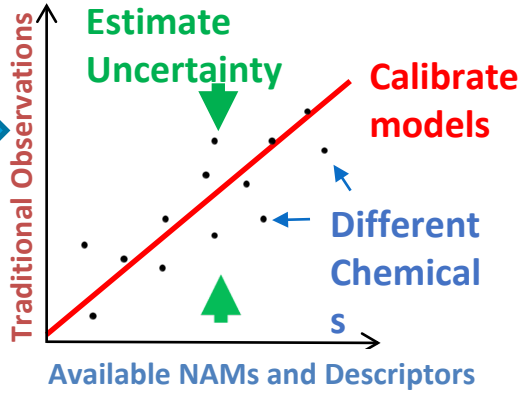
Source:
http://www.hurricanescience.org/science/forecast/models/modeltypes/ensemble/.
Image credit: Timothy Marchok, NOAA/GFDL.

Evaluating High Throughput Exposure Models by Building a Consensus Exposure Model

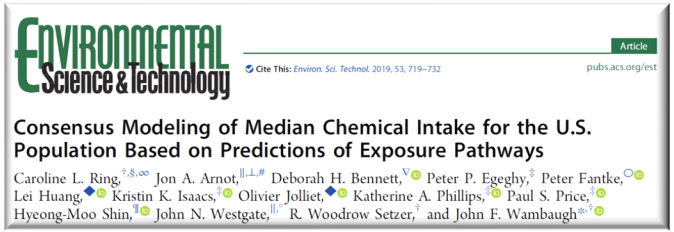
Evaluate Model Performance and Refine Models

CDC NHANES Blood and Urine Biomonitoring

R Package Bayesmarker Stanfield et al. (2022)



Apply **calibration** and estimated **uncertainty** to chemicals without traditional data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Article

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Consensus Modeling of Median Chemical Intake for the U.S. Population Based on Predictions of Exposure Pathways

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

Systematic Empirical Evaluation of Models

High Throughput Exposure Models and Exposure Descriptors

Slide from Dr. John Wambaugh

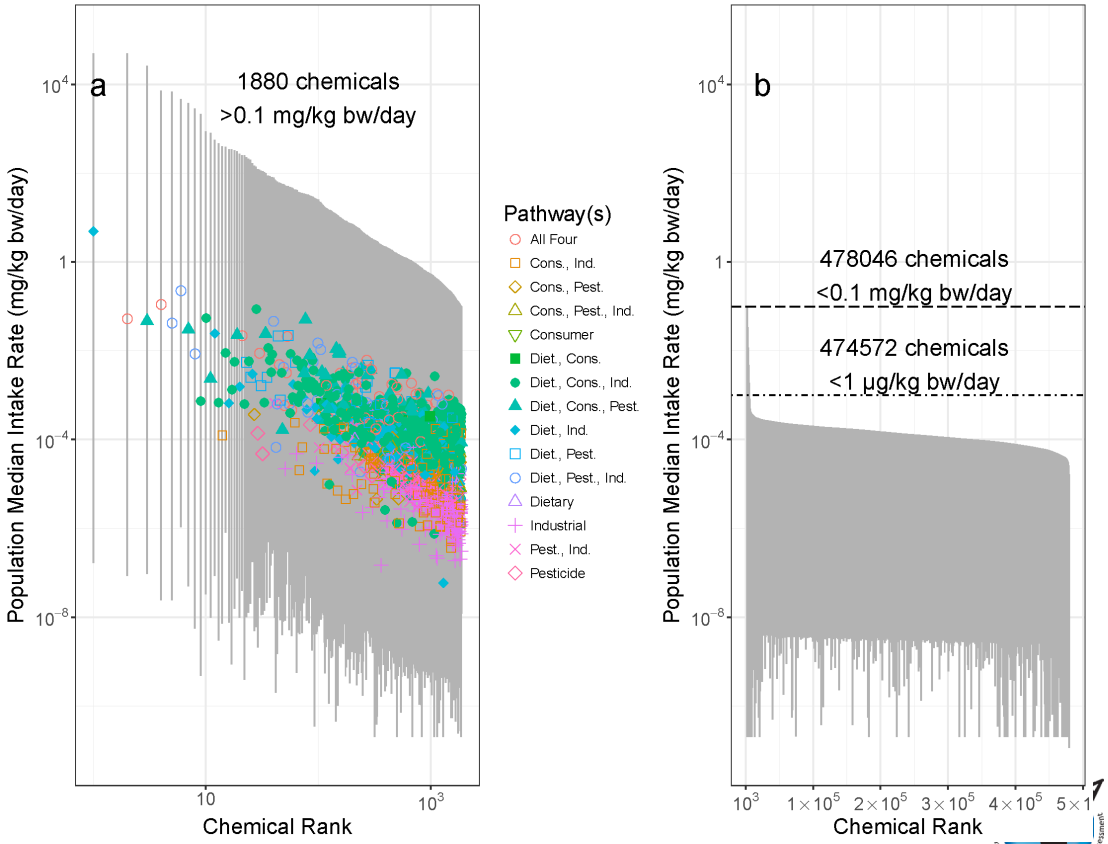
SEEM Consensus Model of Median Chemical Intake

- 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”

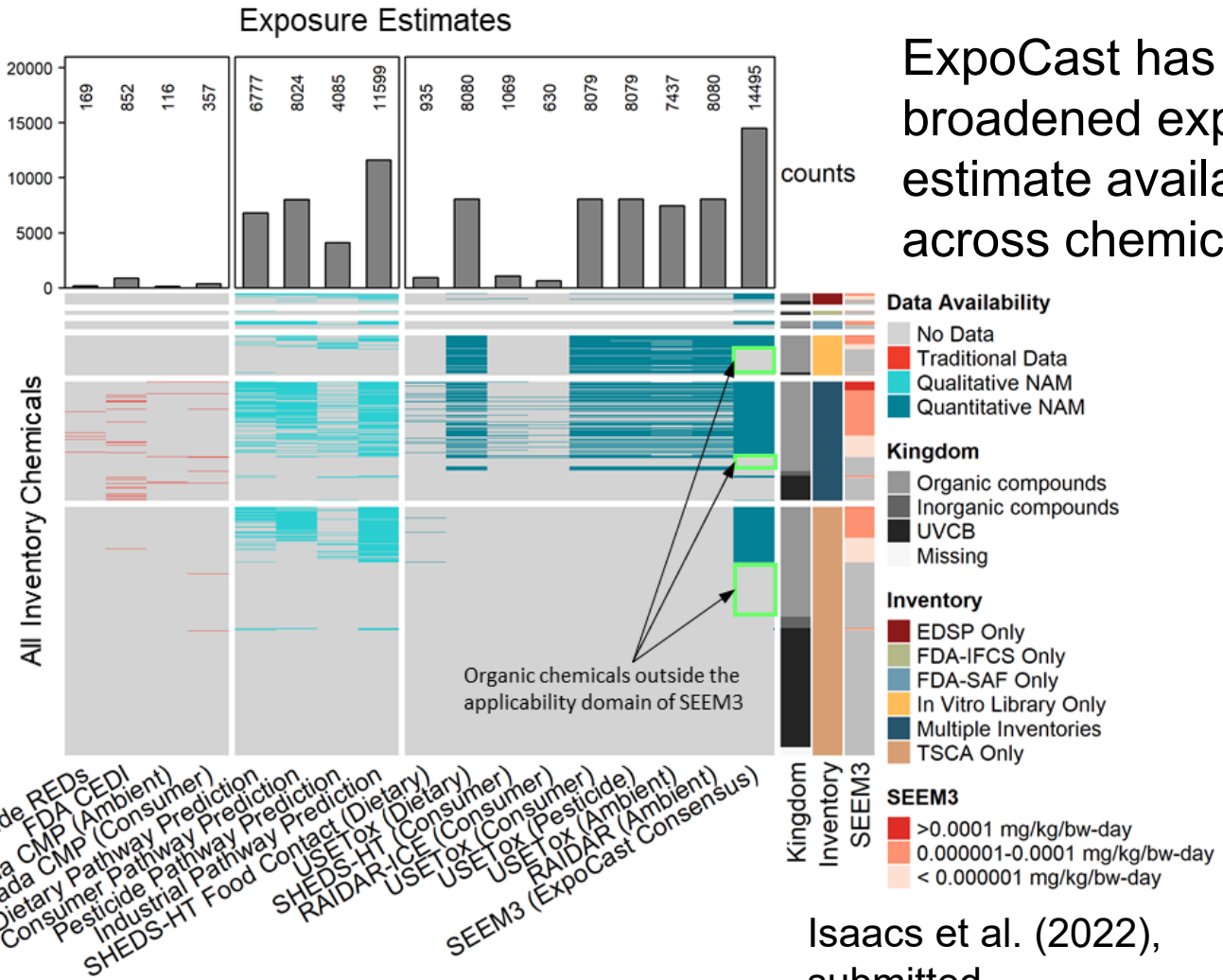
- There is 95% confidence that the median intake rate is below 1 µg/kg BW/day for 474,572 compounds.
  - We have not said anything about the 95th percentile highest exposed individuals!

Ring et al., 2018



Slide from Dr. John Wambaugh

A

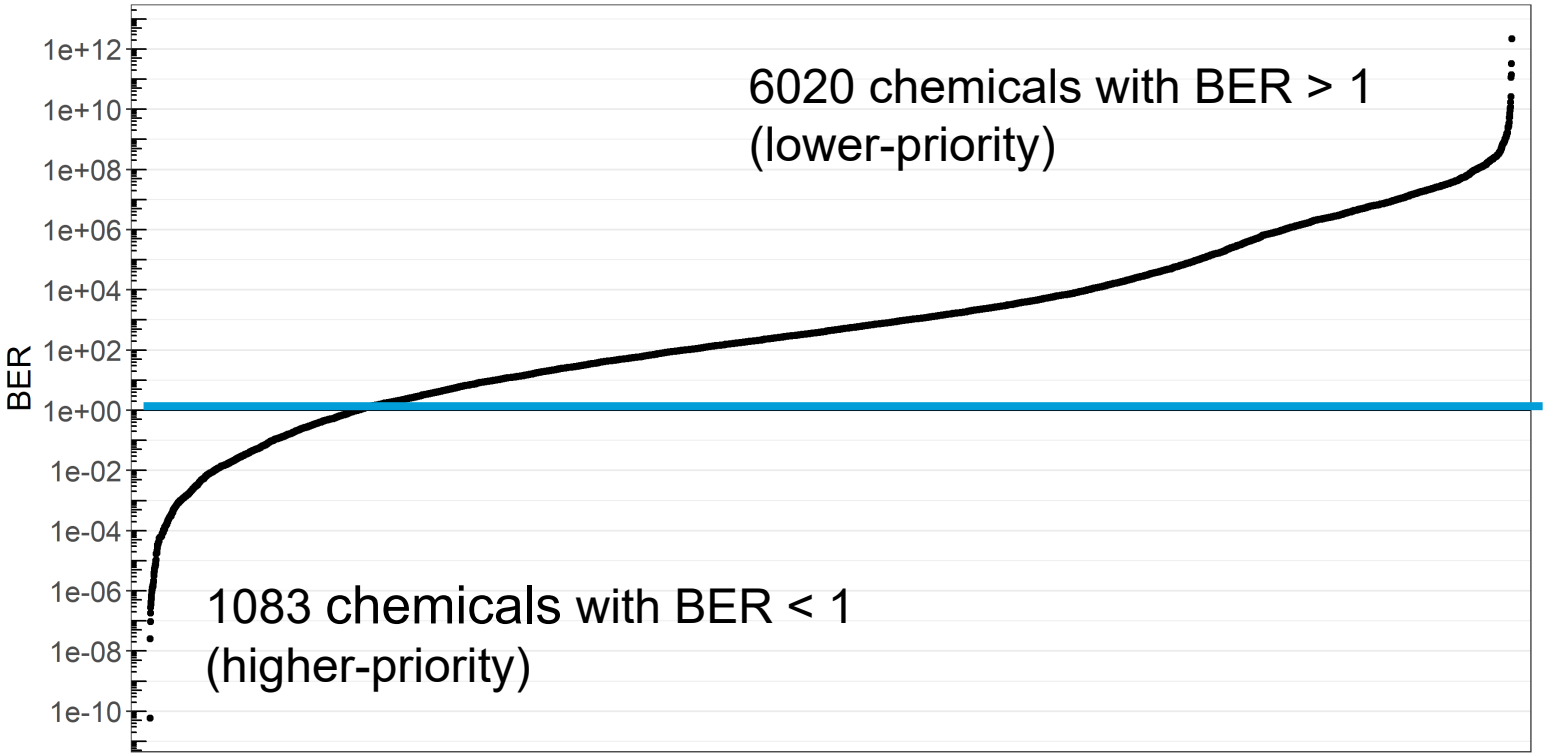


ExpoCast has broadened exposure estimate availability across chemicals

Isaacs et al. (2022), submitted

Chemical prioritization using bioactivity-exposure ratio (BER)

An even-more high-throughput application: BER prioritization of 7104 chemicals



Closing thoughts: ExpoCast has expanded the exposure information landscape

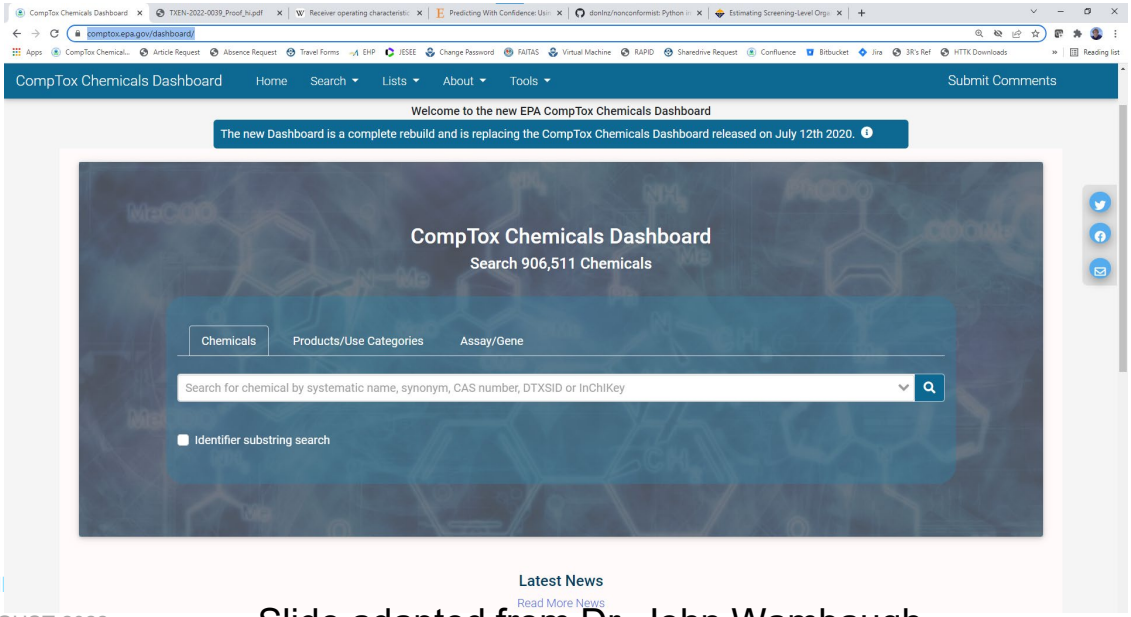
… but there is still more work to be done!

ExpoCast has some running themes…

- **Informatics**: Gather & organize available measured data in a harmonized, machine-readable databas, using reproducible workflows.
- **Filling data gaps**: Where *in vivo* chemical-specific measurements don't exist, use *in vitro* and *in silico* methods & models to make predictions.
- **Evaluation:** Use available measured data to train and test *in vitro* and *in silico* methods & models.
- **Transparency, Reproducibility, Accessibility:** Free & public data, models, algorithms (e.g. R packages)

Data & NAMs are available on the CompTox Chemicals Dashboard

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



Williams et al. (2017)

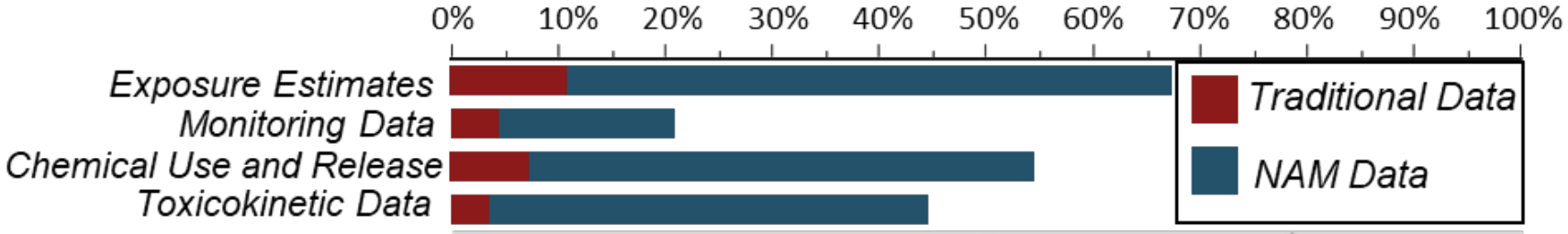
- Details
- Executive Summary
- Properties
- Env. Fate/Transport
- Hazard
- Safety > GHS Data
- ADME > IVIVE
- Exposure
- Bioactivity
- Similar Compounds
- GenRA
- Related Substances
- Synonyms
- Literature
- Links
- Comments

Slide adapted from Dr. John Wambaugh

More work to be done….

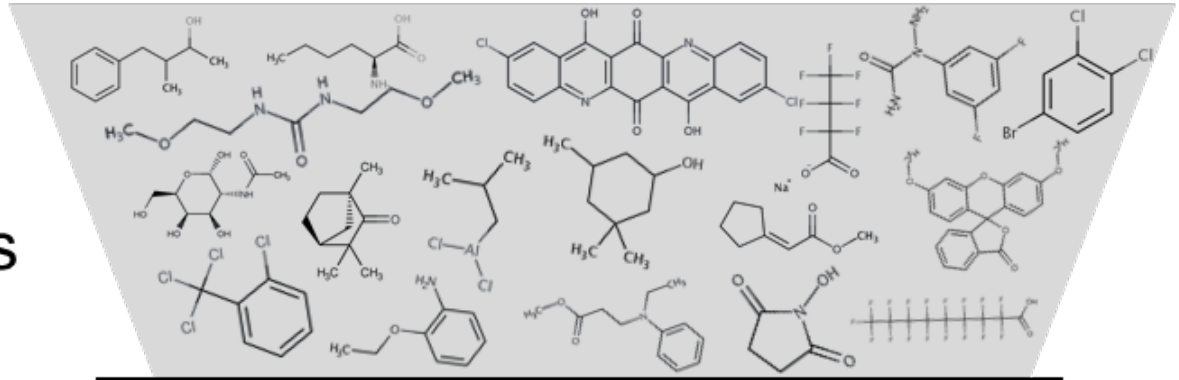
- Occupational/worker exposures
- Demographic-specific exposures
- Route-specific exposures
  - e.g. inhalation, dermal
- Pathway-specific exposures
  - e.g. biosolids
- Mixture/UVCB exposures
- …..

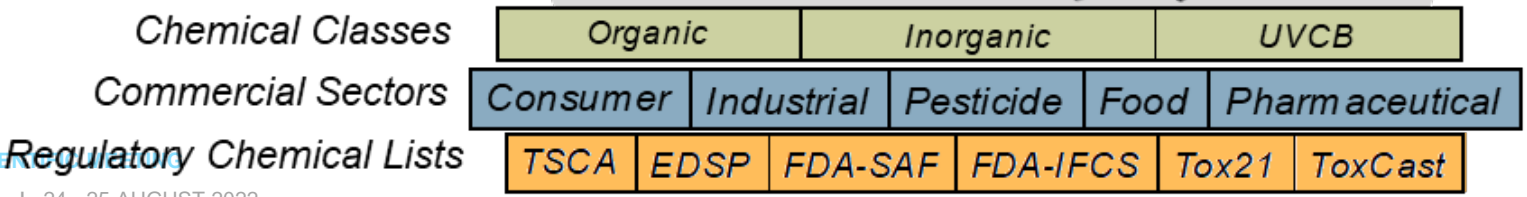
… but ExpoCast is opening up the landscape of exposure information!



37,746 Substances

Isaacs et al. (2022), submitted





Thank you!

Questions?

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