November 7, 2019

Rapid Chemical Exposure and Dose Research

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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
  - 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)
- Different testing requirements exist for food additives, pharmaceuticals, and pesticide active ingredients (NRC, 2007)

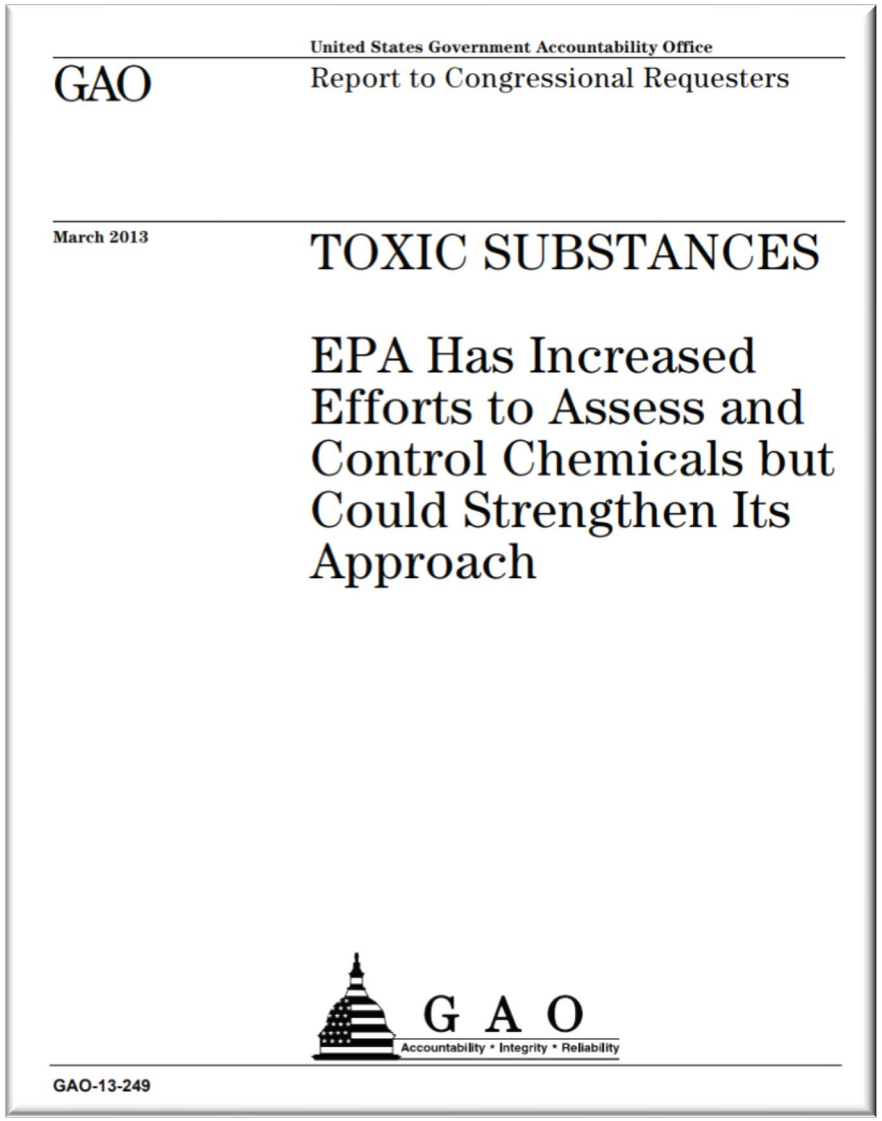
November 29, 2014

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)

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

"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


United States Government Accountability Office
GAO
Report to Congressional Requesters

March 2013

TOXIC SUBSTANCES

EPA Has Increased Efforts to Assess and Control Chemicals but Could Strengthen Its Approach

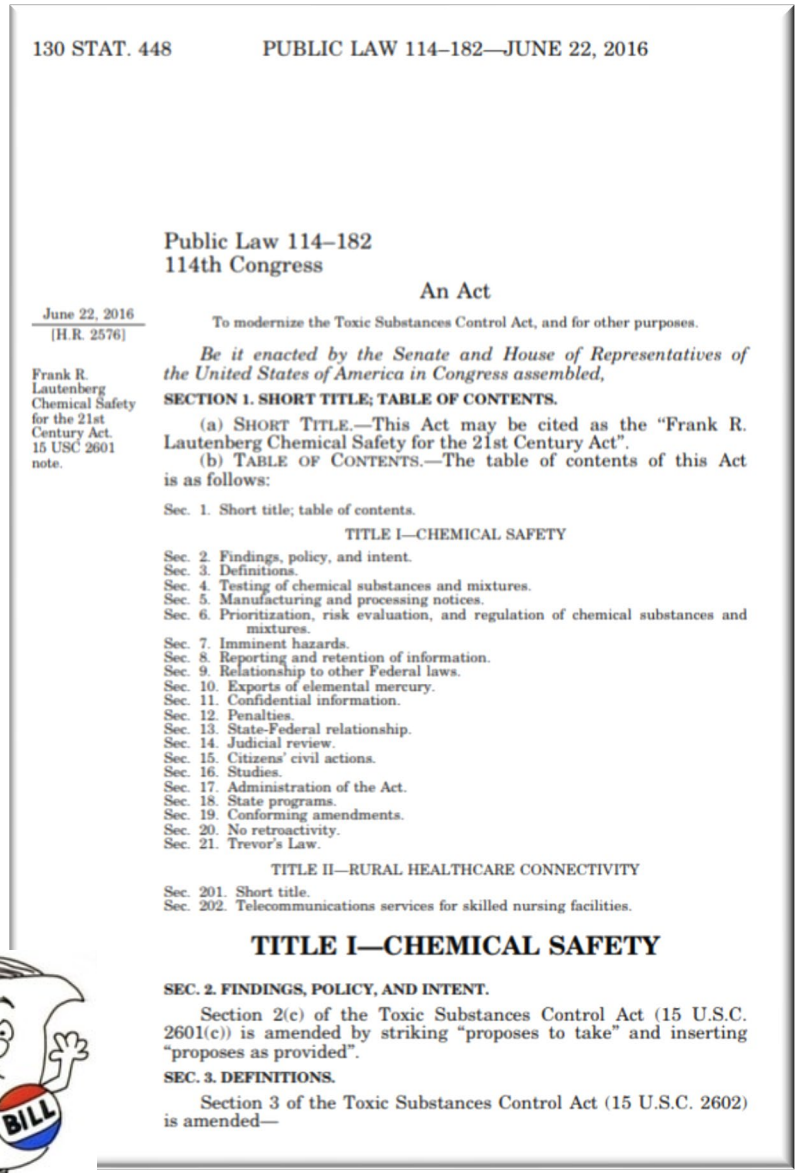
G A O
Accountability • Integrity • Reliability

GAO-13-249

March, 2013

Chemical Regulation in the United States

- TSCA was updated in June, 2016 to allow more rapid evaluation of chemicals (Frank R. Lautenberg Chemical Safety for the 21st Century Act)
- New approach methodologies (NAMs) are being considered to inform prioritization of chemicals for testing and evaluation (Kavlock et al., 2018)
- EPA has released a "A Working Approach for Identifying Potential Candidate Chemicals for Prioritization" (September, 2018)



130 STAT. 448 PUBLIC LAW 114–182—JUNE 22, 2016

Public Law 114–182
114th Congress

An Act

To modernize the Toxic Substances Control Act, and for other purposes.

June 22, 2016
[H.R. 2576]

Frank R. Lautenberg Chemical Safety for the 21st Century Act.
15 USC 2601 note.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE; TABLE OF CONTENTS.

(a) SHORT TITLE.—This Act may be cited as the "Frank R. Lautenberg Chemical Safety for the 21st Century Act".

(b) TABLE OF CONTENTS.—The table of contents of this Act is as follows:

Sec. 1. Short title; table of contents.

TITLE I—CHEMICAL SAFETY

Sec. 2. Findings, policy, and intent.
Sec. 3. Definitions.
Sec. 4. Testing of chemical substances and mixtures.
Sec. 5. Manufacturing and processing notices.
Sec. 6. Prioritization, risk evaluation, and regulation of chemical substances and mixtures.
Sec. 7. Imminent hazards.
Sec. 8. Reporting and retention of information.
Sec. 9. Relationship to other Federal laws.
Sec. 10. Exports of elemental mercury.
Sec. 11. Confidential information.
Sec. 12. Penalties.
Sec. 13. State-Federal relationship.
Sec. 14. Judicial review.
Sec. 15. Citizens' civil actions.
Sec. 16. Studies.
Sec. 17. Administration of the Act.
Sec. 18. State programs.
Sec. 19. Conforming amendments.
Sec. 20. No retroactivity.
Sec. 21. Trevor's Law.

TITLE II—RURAL HEALTHCARE CONNECTIVITY

Sec. 201. Short title.
Sec. 202. Telecommunications services for skilled nursing facilities.

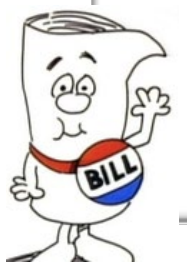
TITLE I—CHEMICAL SAFETY

SEC. 2. FINDINGS, POLICY, AND INTENT.

Section 2(c) of the Toxic Substances Control Act (15 U.S.C. 2601(c)) is amended by striking "proposes to take" and inserting "proposes as provided".

SEC. 3. DEFINITIONS.

Section 3 of the Toxic Substances Control Act (15 U.S.C. 2602) is amended—



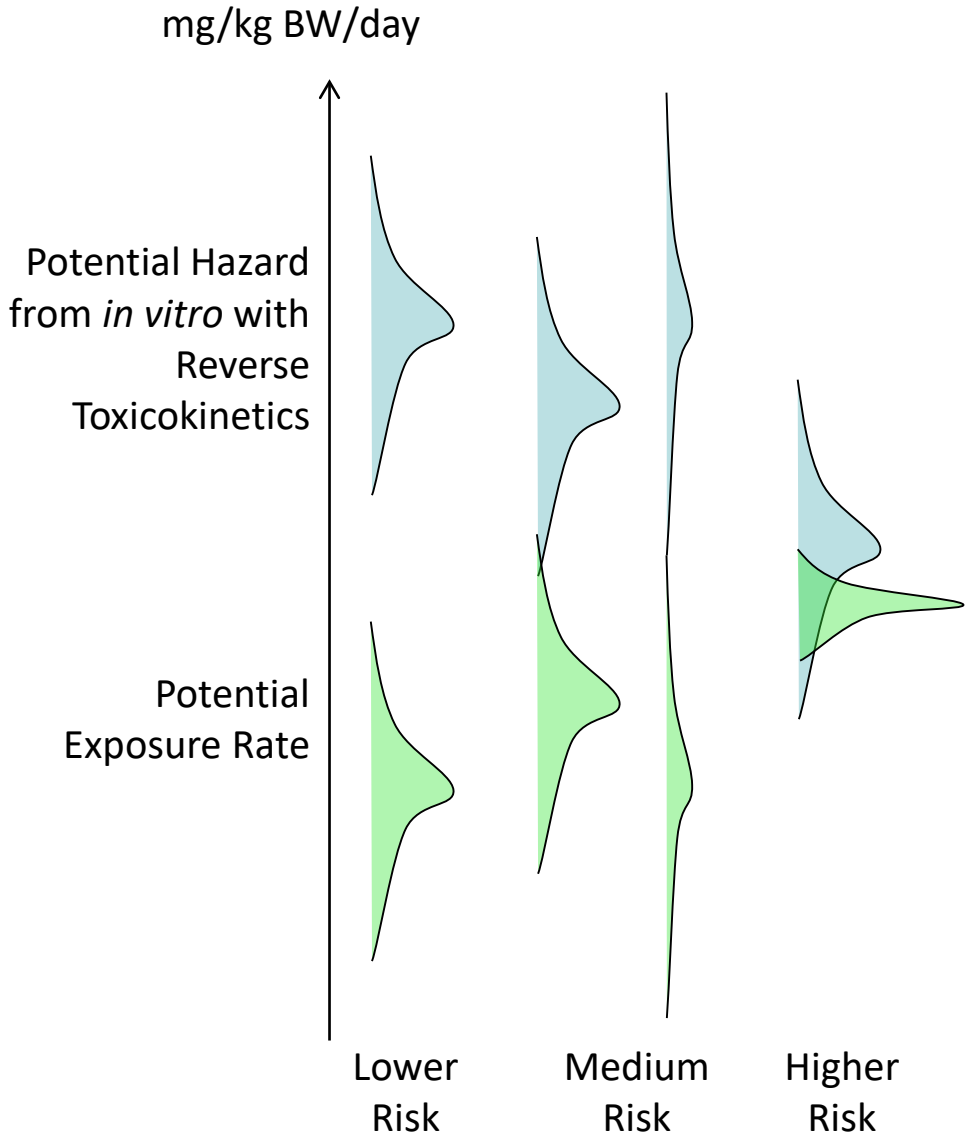
June 22, 2016

Chemical Risk = Hazard x Exposure

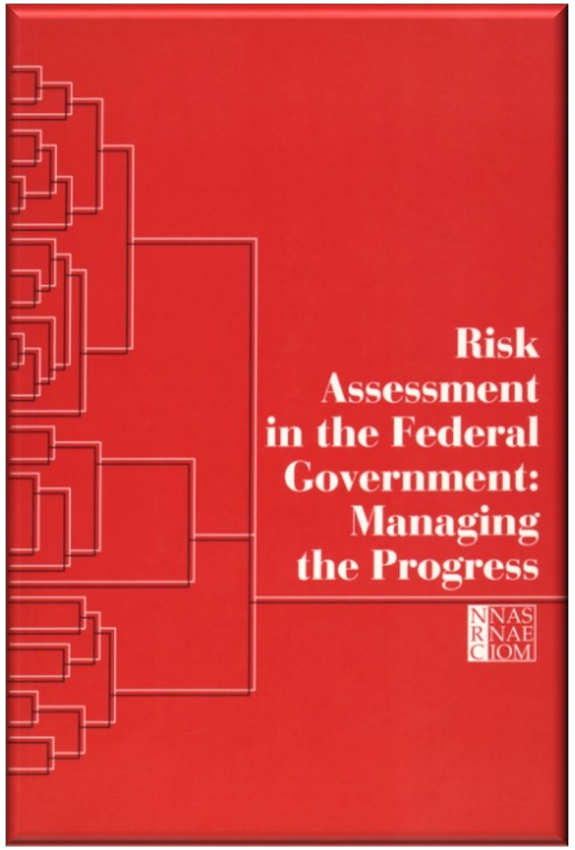
- The U.S. National Research Council (1983) identified chemical risk as a function of both inherent hazard and exposure

- To address thousands of chemicals, we need NAMs that can inform prioritization of chemicals most worthy of additional study

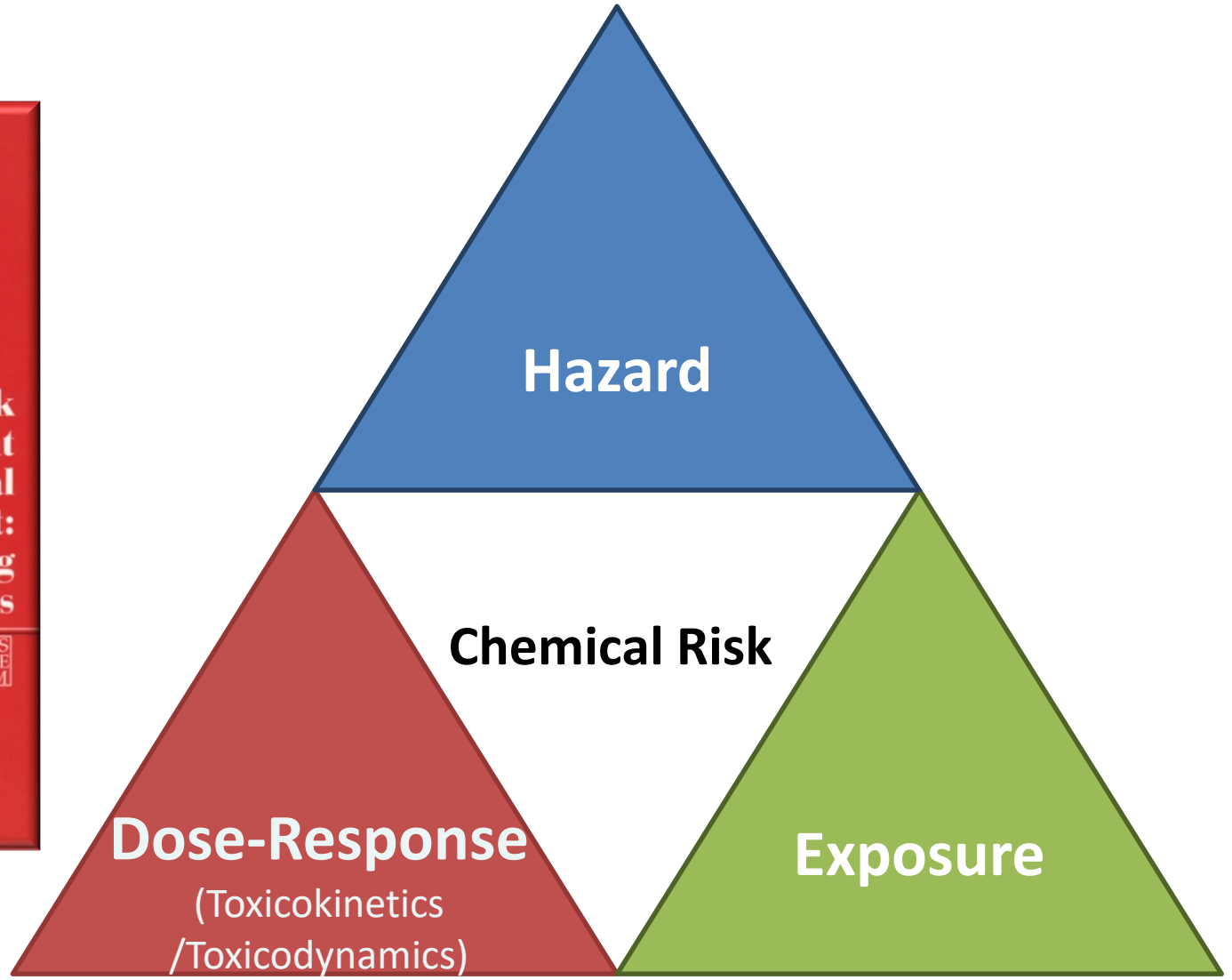
- High throughput risk prioritization needs:
  1. High throughput hazard characterization (Dix et al., 2007, Collins et al., 2008)
  2. High throughput exposure forecasts (Wambaugh et al., 2013, 2014)
  3. High throughput toxicokinetics (i.e., dose-response relationship) linking hazard and exposure (Wetmore et al., 2012, 2015)



Three Components for Chemical Risk

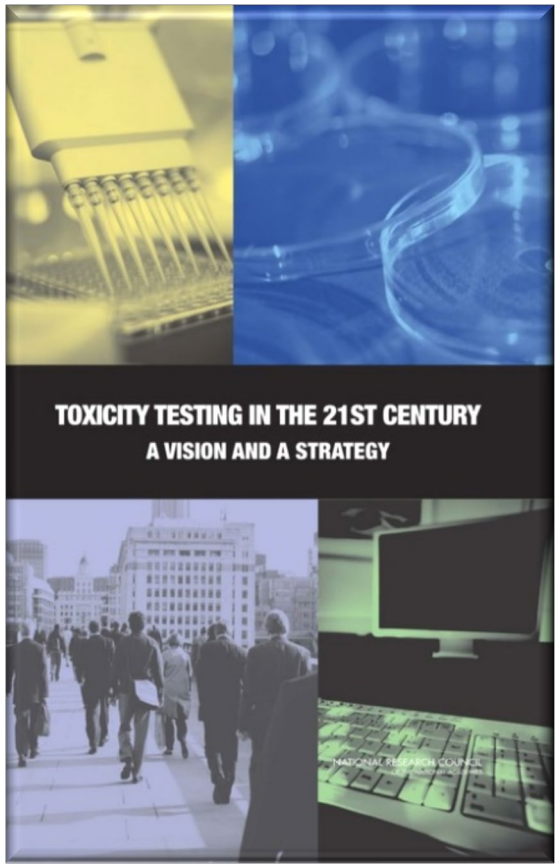


NRC (1983)

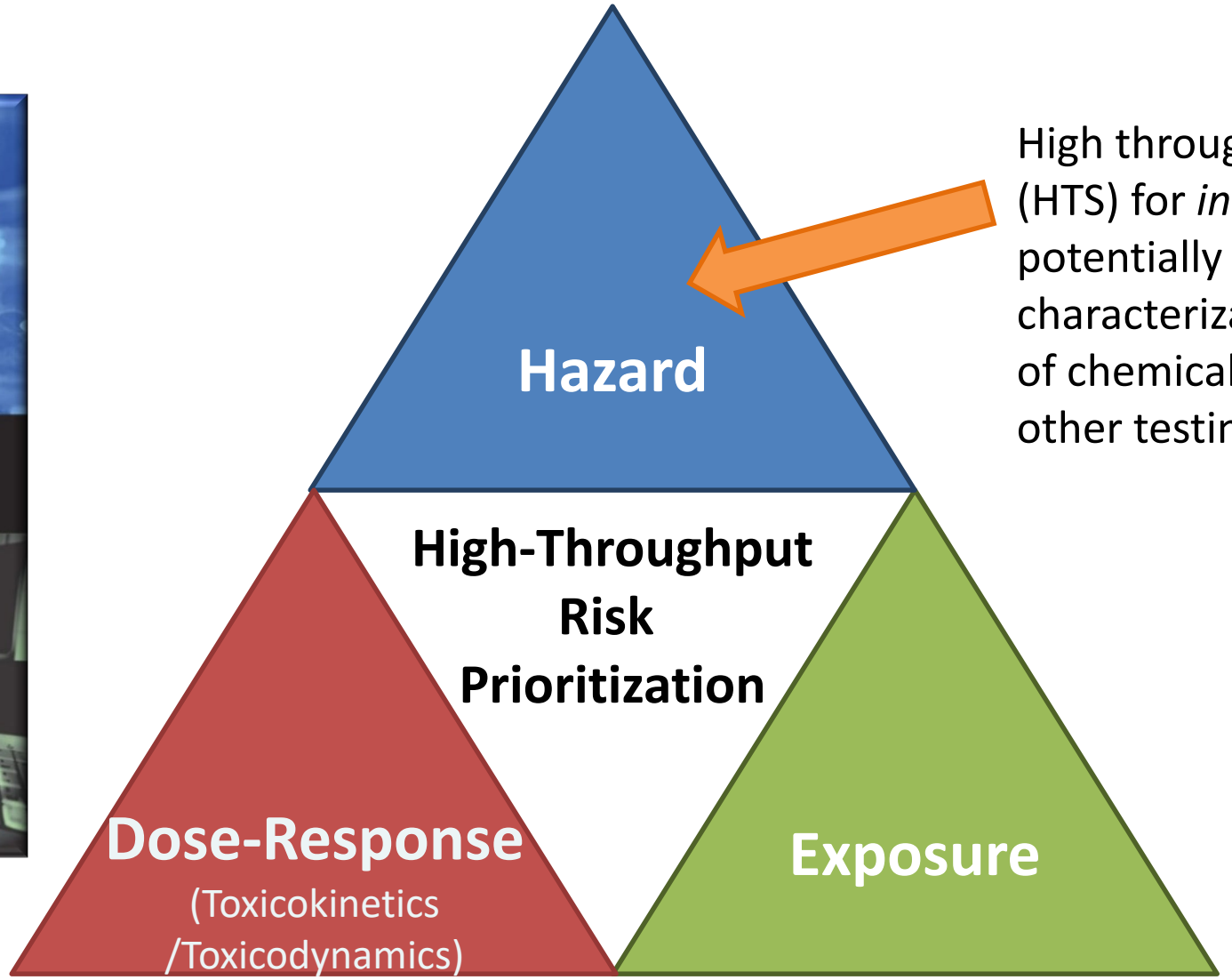


The National Academy of Sciences, Engineering and Medicine (1983) outlined three components for determining chemical risk.

High-Throughput Risk Prioritization



NRC (2007)



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

To perform high throughput risk prioritization, we need all three components

High-throughput Screening

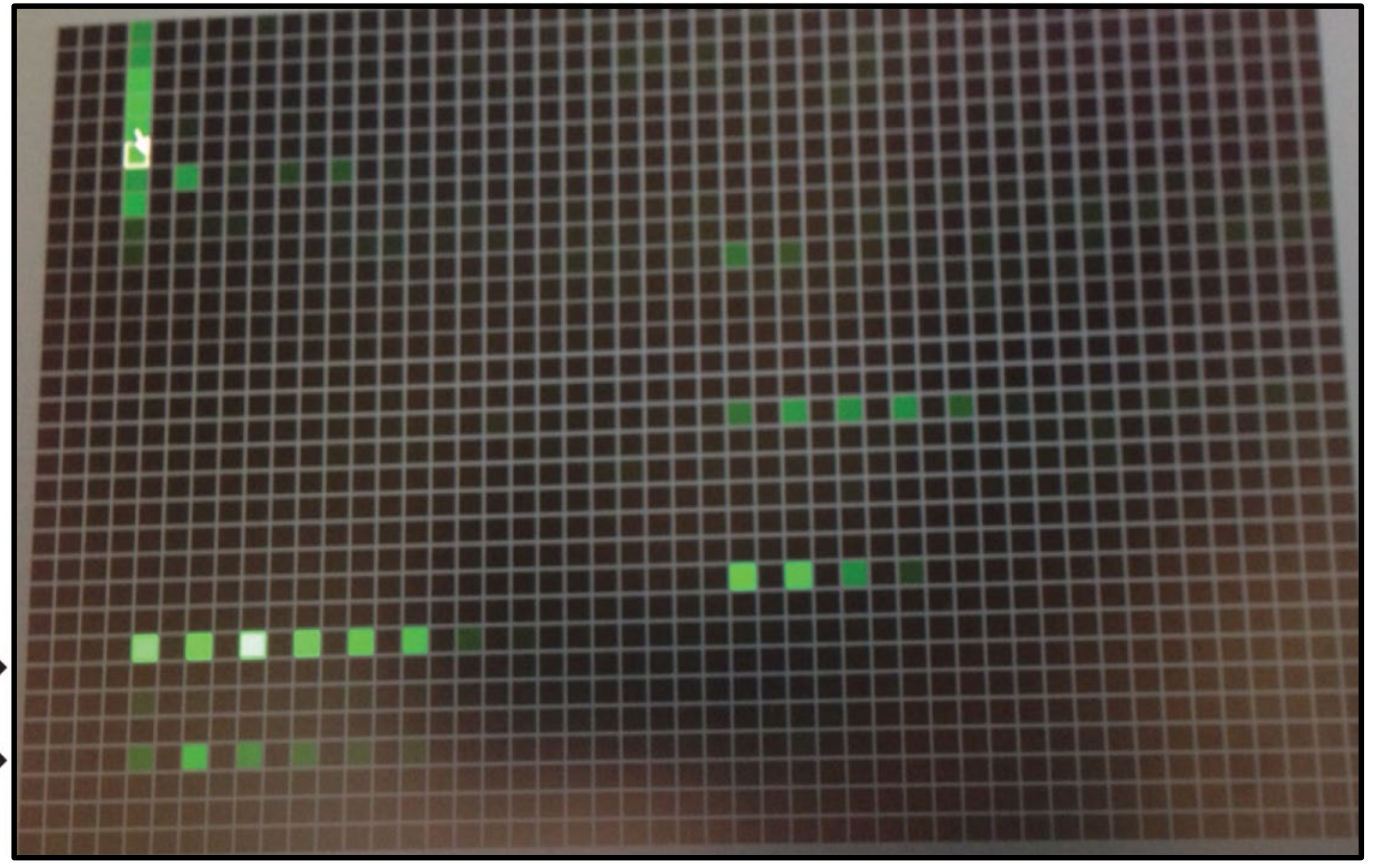
Hertzberg and Pope (2000):

- "New technologies in high-throughput screening have significantly increased throughput and reduced assay volumes…"

- "…new fluorescence methods, detection platforms and liquid-handling technologies."

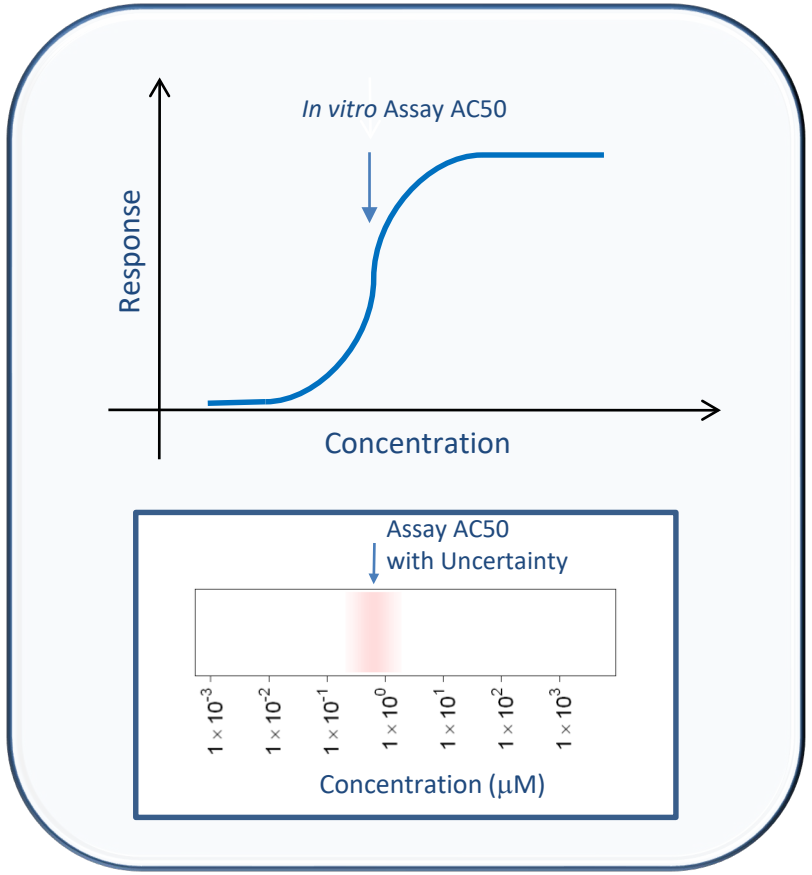
- Typically assess many chemicals with a signal readout (e.g., green fluorescent protein).

Kaewkhaw et al. (2016)

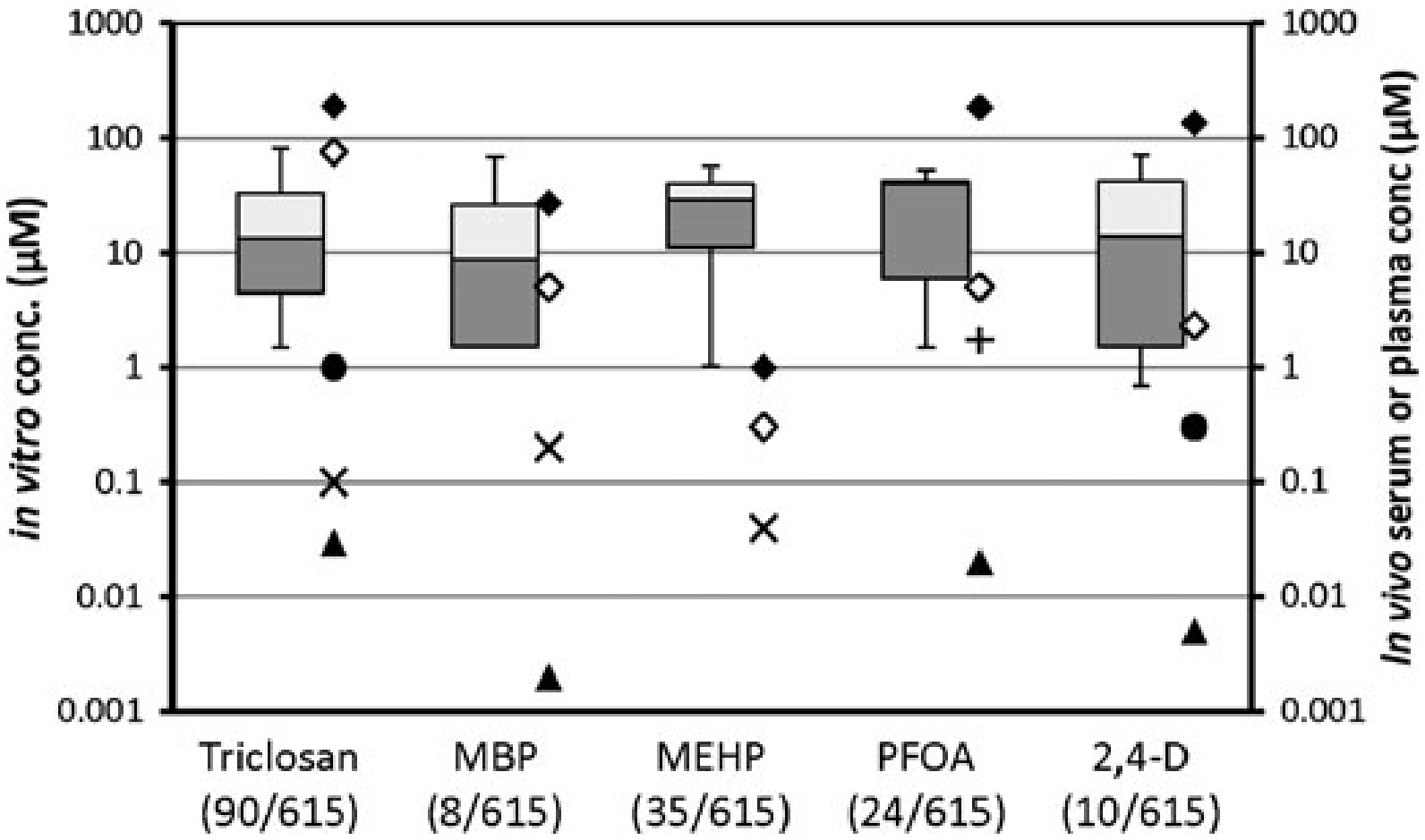


High-Throughput Bioactivity Screening Projects

- 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**: For a subset (>2000) of Tox21 chemicals ran >1100 additional assays (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/



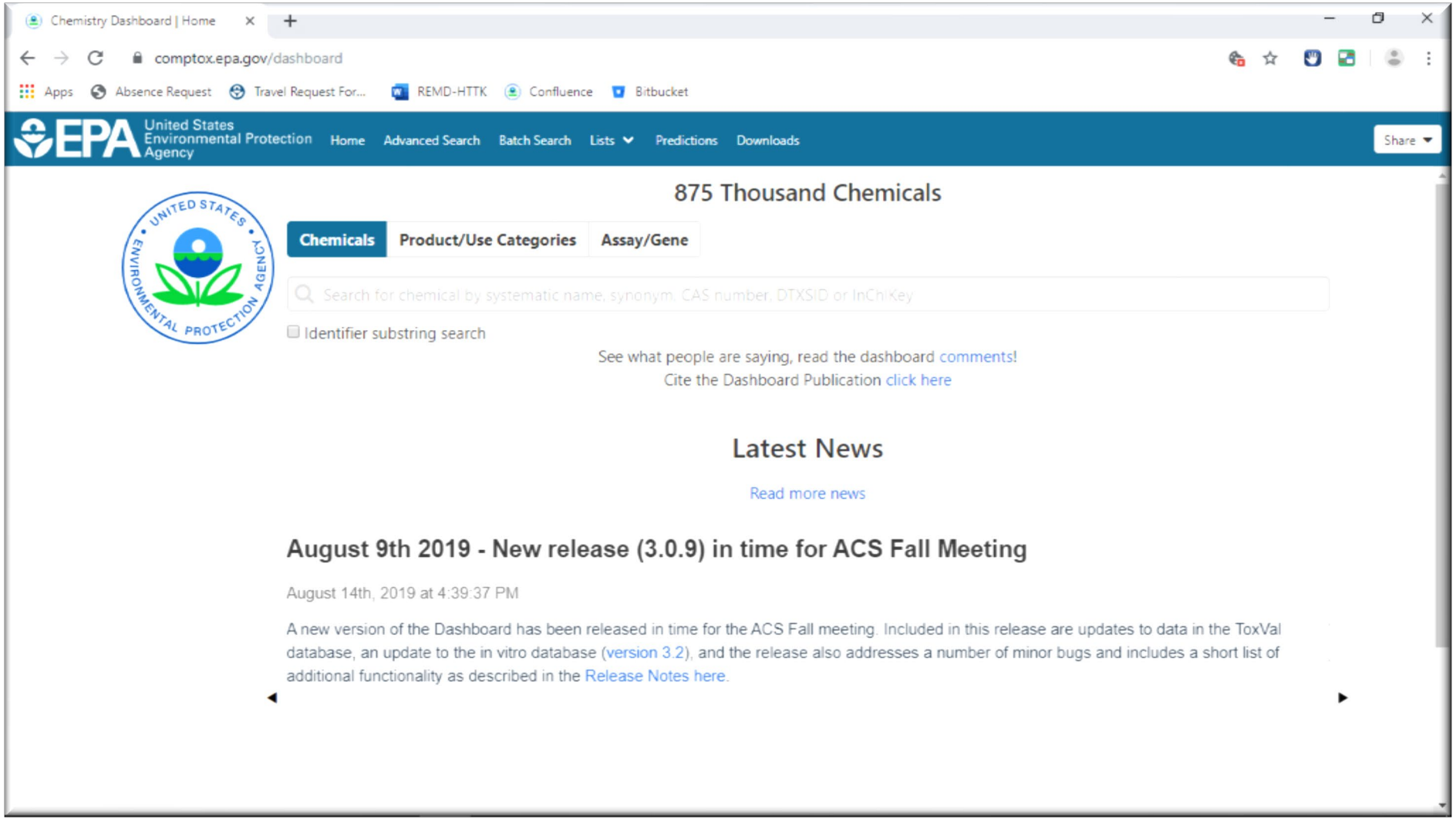
The Margin Between Exposure and Hazard



- ◆ 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

Aylward and Hays (2011)
Journal of Applied Toxicology **31** 741-751

The CompTox Chemicals Dashboard

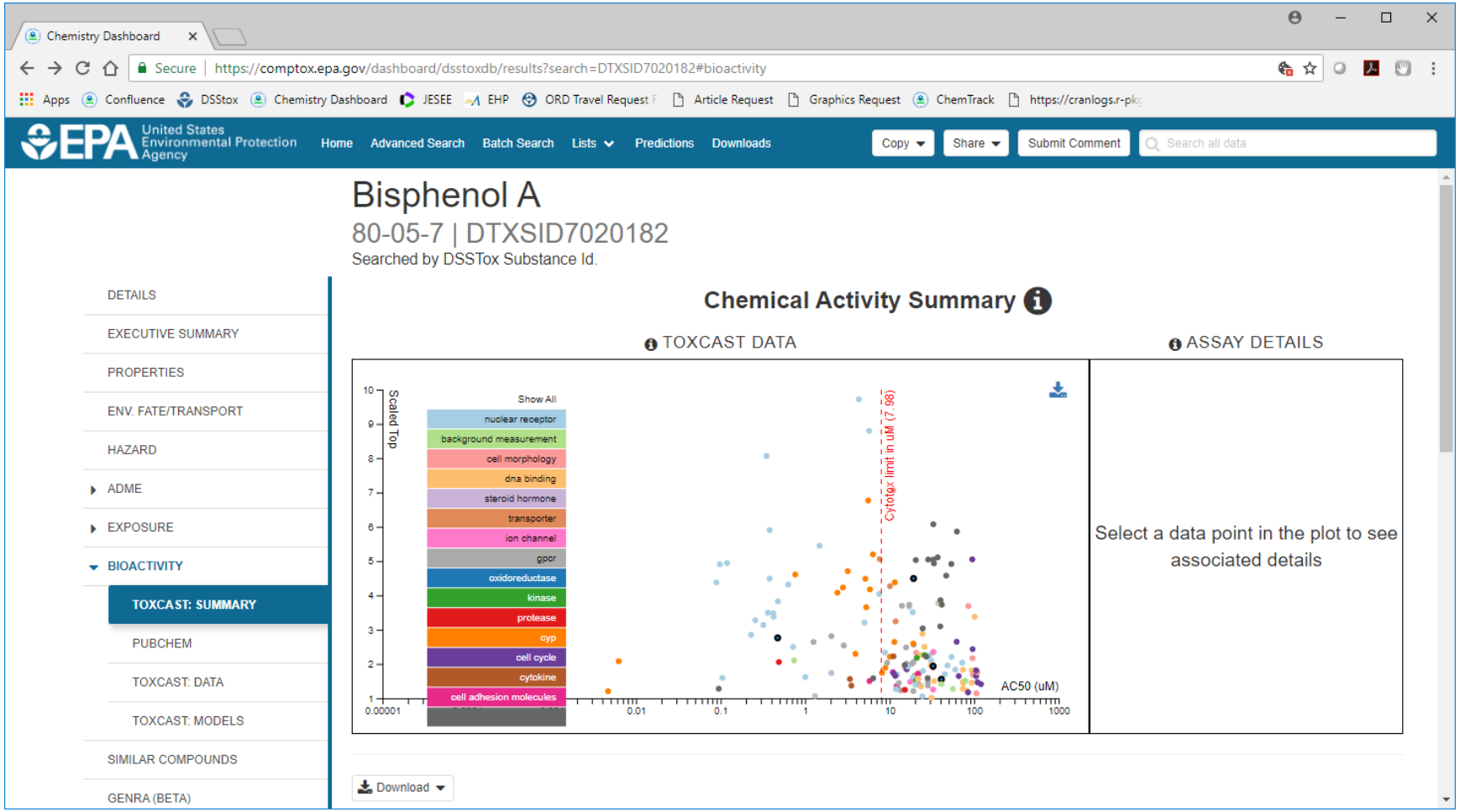


https://comptox.epa.gov/dashboard

Chemical Bioactivity Data

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

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



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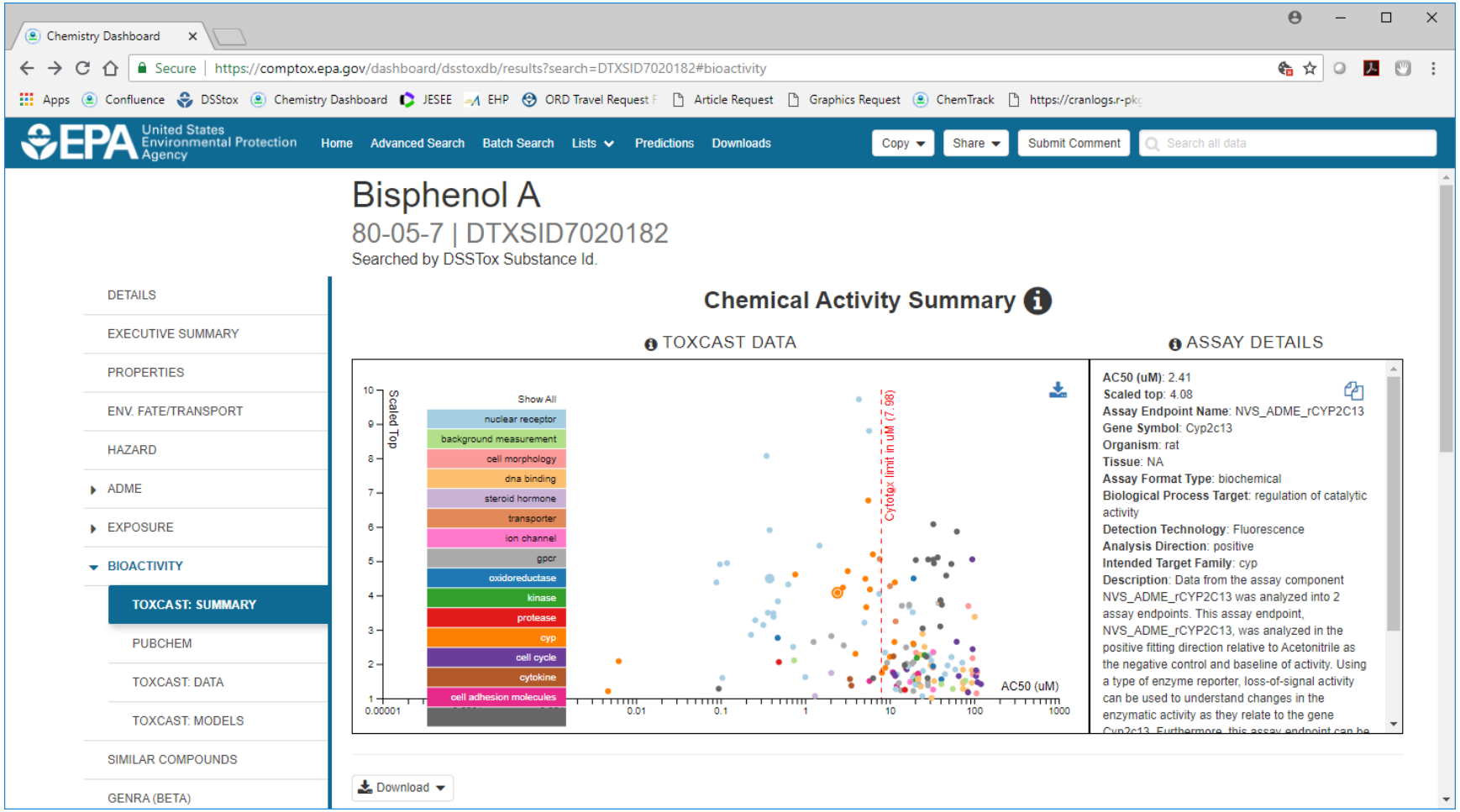

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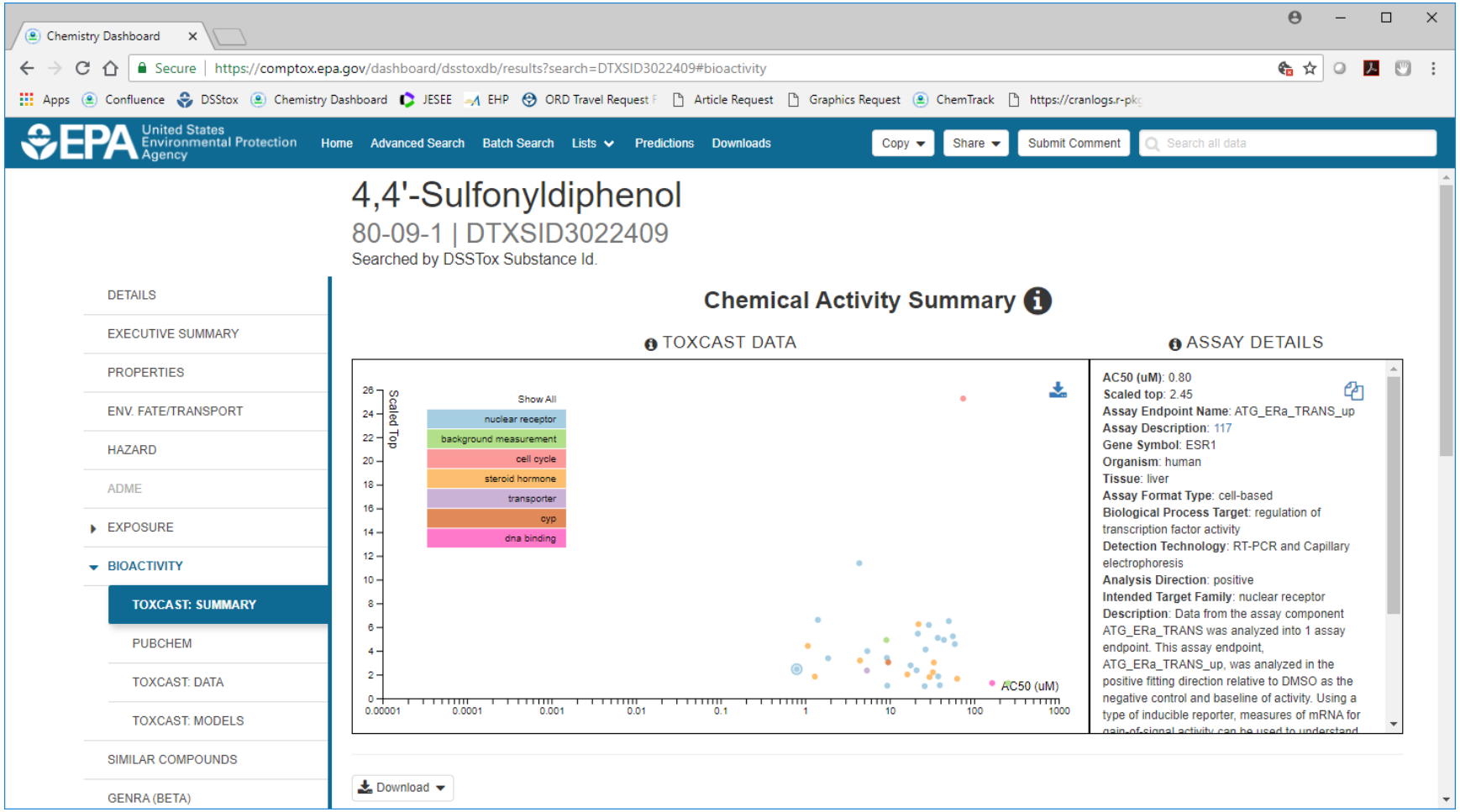
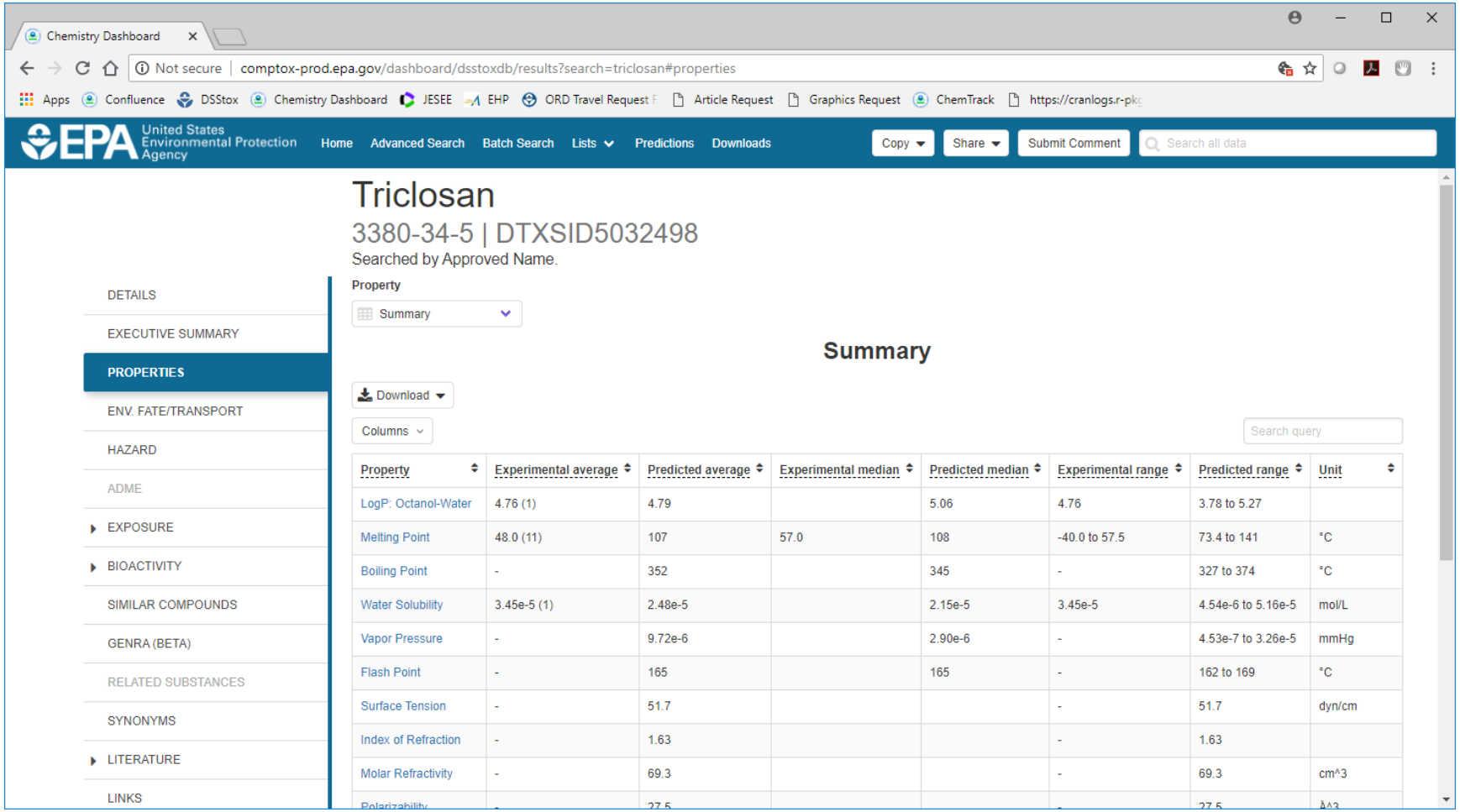


Physicochemical Properties

- Measured and predicted physicochemical properties are available
  - OPEn structure–activity/property Relationship App (OPERA) by Mansouri, et al. (2018)

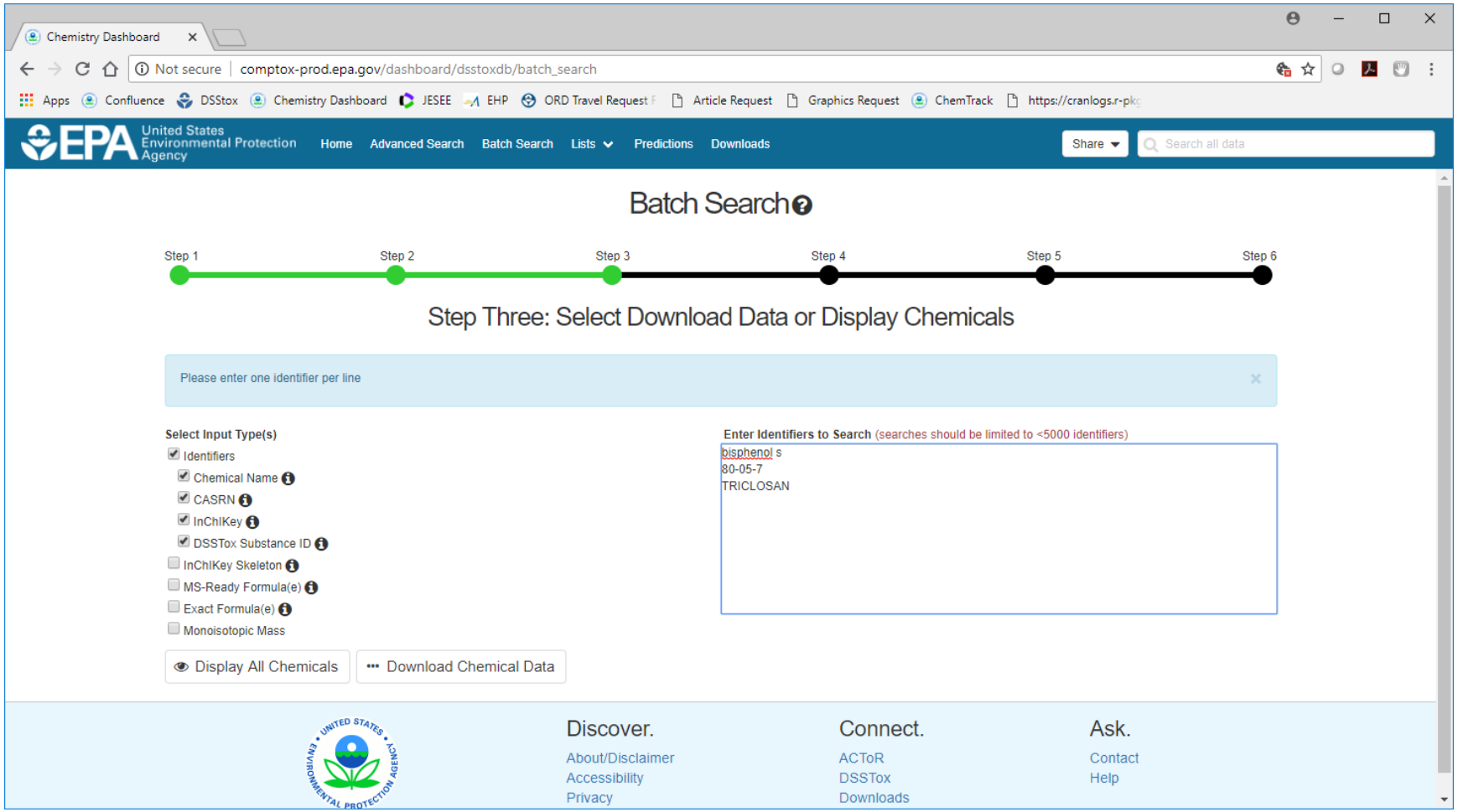
https://comptox.epa.gov/dashboard/



Bulk Download of Data

- Can download databases and spreadsheets of data using Batch Search

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



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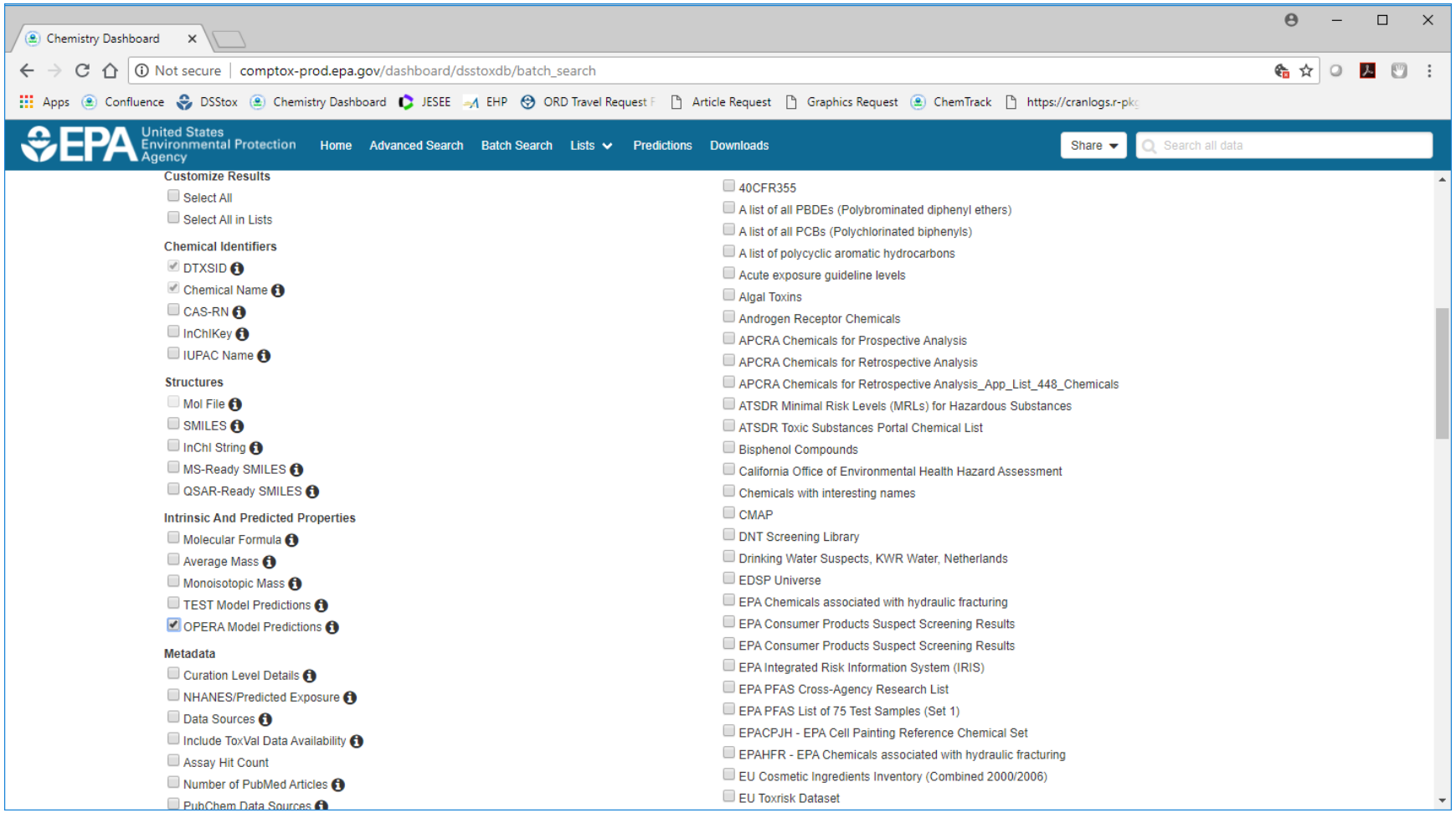


TSCA

- The updated Toxic Substances Control Act (TSCA) has been considering the inclusion of new approach methodologies (NAMs). These NAMs include:
  - High throughput screening (ToxCast)
  - High throughput exposure estimates (ExpoCast)
  - High throughput toxicokinetics (HTTK)

- ~10,000 TSCA-relevant chemicals in commerce

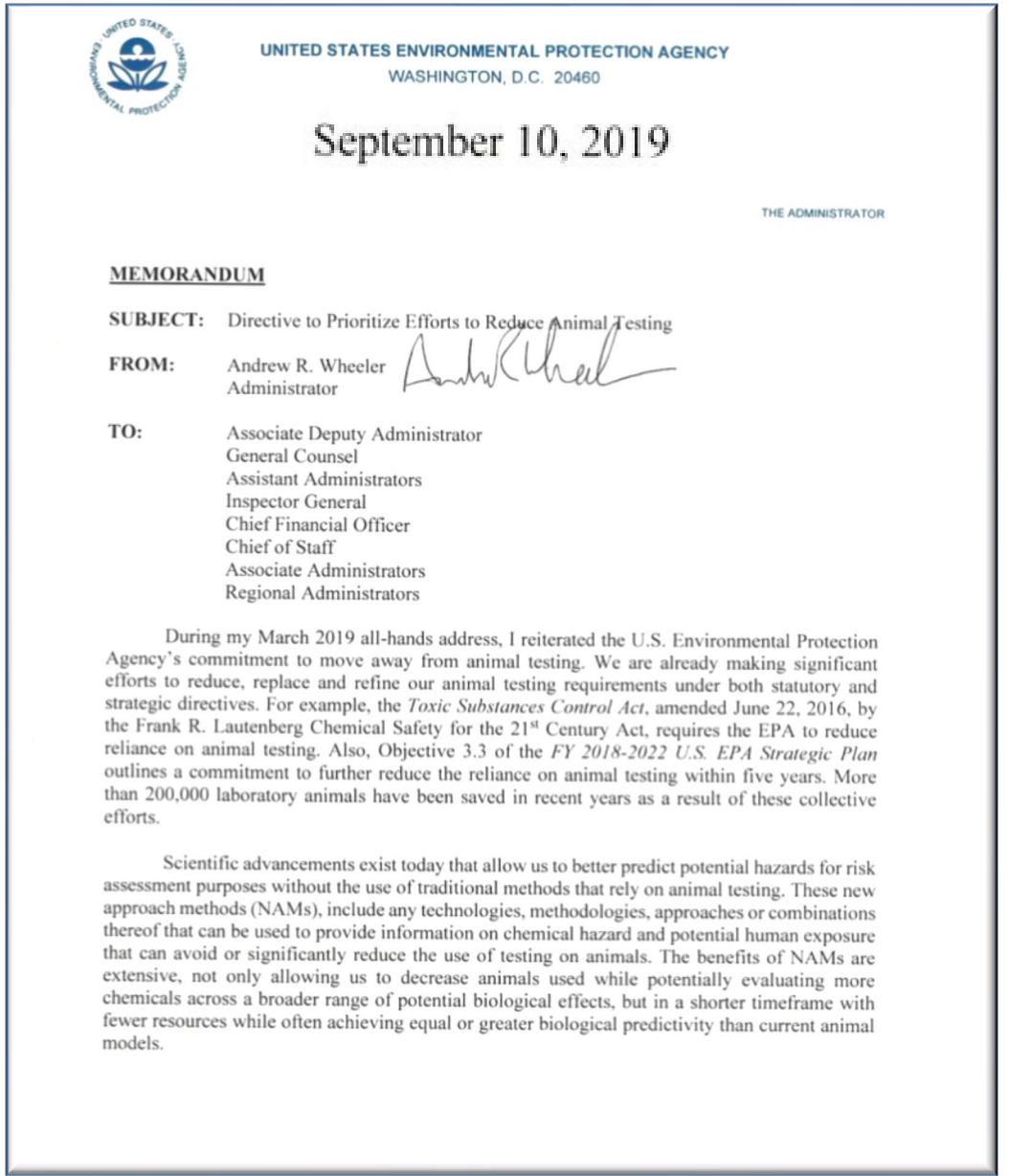
- Proof of concept: ~200 chemicals with ToxCast, ExpoCast and HTTK
  - HTTK was rate limiter on number of chemicals
  - *"A Proof-of-Concept Case Study Integrating Publicly Available Information to Screen Candidates for Chemical Prioritization under TSCA"*

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

Replacing Animal Testing with NAMs

- "To aggressively pursue a reduction in animal testing, I am directing leadership and staff in the Office of Chemical Safety and Pollution Prevention and the Office of Research and Development [ORD] to prioritize … the reduction of animal testing while ensuring protection of human health and the environment."

- "These new approach methods (NAMs), include any technologies, methodologies, approaches or combinations thereof that can be used to provide information on chemical hazard and potential human exposure that can avoid or significantly reduce the use of testing on animals"
  - NAMs for filling information gaps for decision-making
  - integrating data steams into chemical risk assessment
  - making the information publicly available



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

September 10, 2019

THE ADMINISTRATOR

MEMORANDUM

SUBJECT: Directive to Prioritize Efforts to Reduce Animal Testing

FROM: Andrew R. Wheeler
Administrator

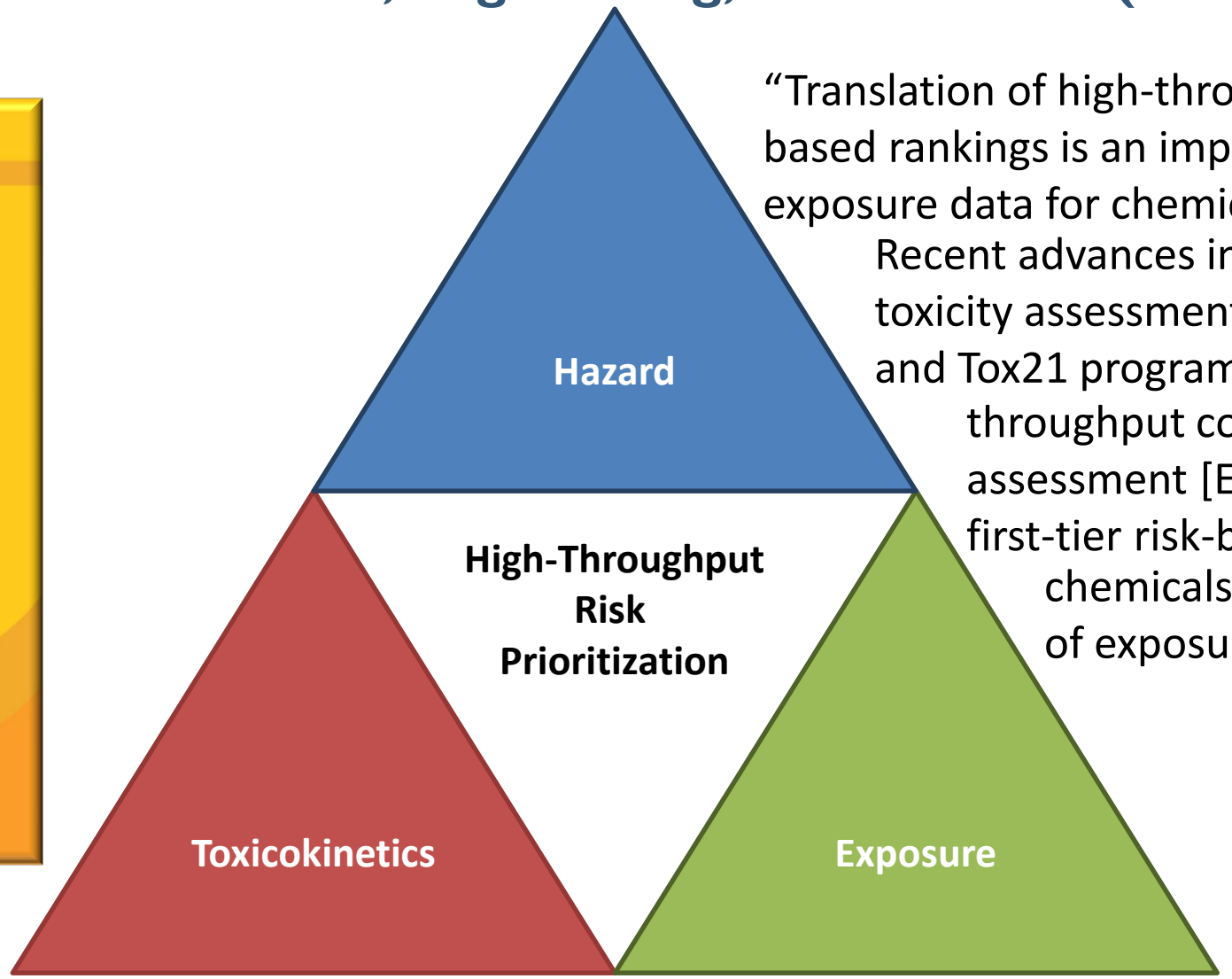
TO: Associate Deputy Administrator
General Counsel
Assistant Administrators
Inspector General
Chief Financial Officer
Chief of Staff
Associate Administrators
Regional Administrators

During my March 2019 all-hands address, I reiterated the U.S. Environmental Protection Agency's commitment to move away from animal testing. We are already making significant efforts to reduce, replace and refine our animal testing requirements under both statutory and strategic directives. For example, the *Toxic Substances Control Act*, amended June 22, 2016, by the Frank R. Lautenberg Chemical Safety for the 21st Century Act, requires the EPA to reduce reliance on animal testing. Also, Objective 3.3 of the *FY 2018-2022 U.S. EPA Strategic Plan* outlines a commitment to further reduce the reliance on animal testing within five years. More than 200,000 laboratory animals have been saved in recent years as a result of these collective efforts.

Scientific advancements exist today that allow us to better predict potential hazards for risk assessment purposes without the use of traditional methods that rely on animal testing. These new approach methods (NAMs), include any technologies, methodologies, approaches or combinations thereof that can be used to provide information on chemical hazard and potential human exposure that can avoid or significantly reduce the use of testing on animals. The benefits of NAMs are extensive, not only allowing us to decrease animals used while potentially evaluating more chemicals across a broader range of potential biological effects, but in a shorter timeframe with fewer resources while often achieving equal or greater biological predictivity than current animal models.

Risk-Related Evaluations Report from National Academies of Sciences, Engineering, and Medicine (NASEM)

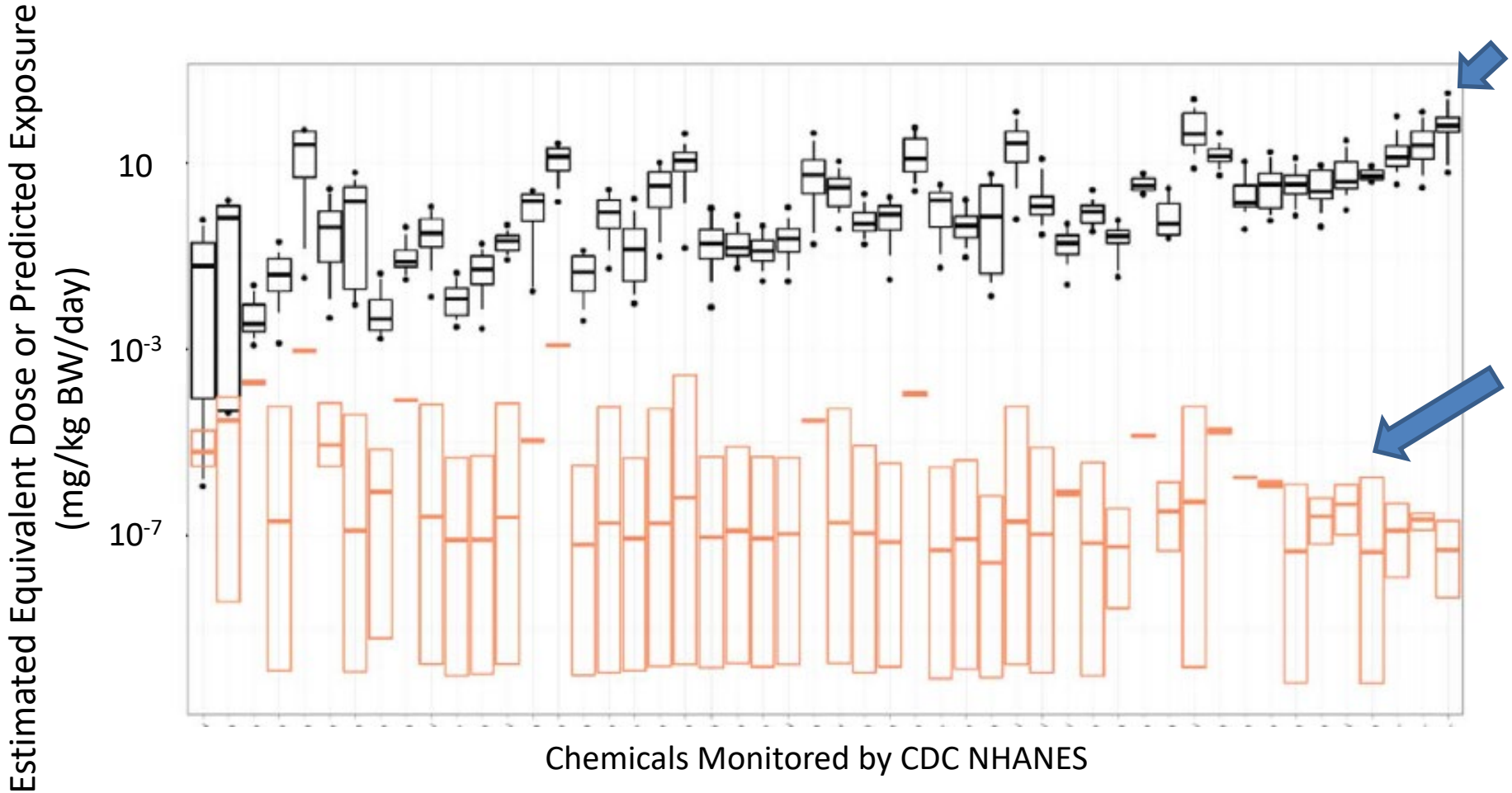
NASEM (2017)



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

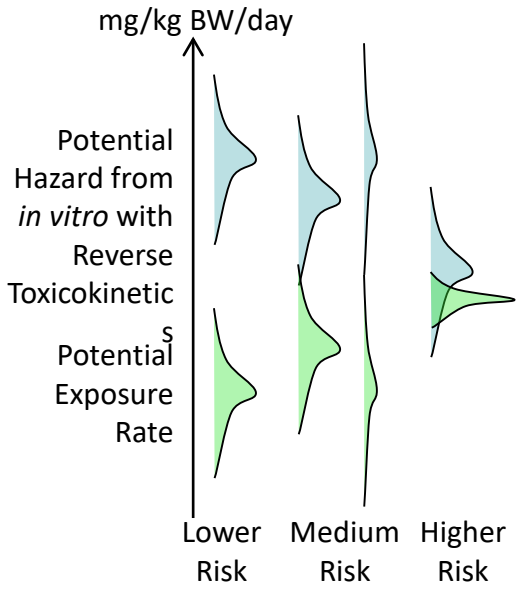
Recent advances in high-throughput toxicity assessment, notably the ToxCast and Tox21 programs… and in high-throughput computational exposure assessment [ExpoCast] have enabled first-tier risk-based rankings of chemicals on the basis of margins of exposure"

Chemical Prioritization NAMs



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)



Ring *et al*. (2017)

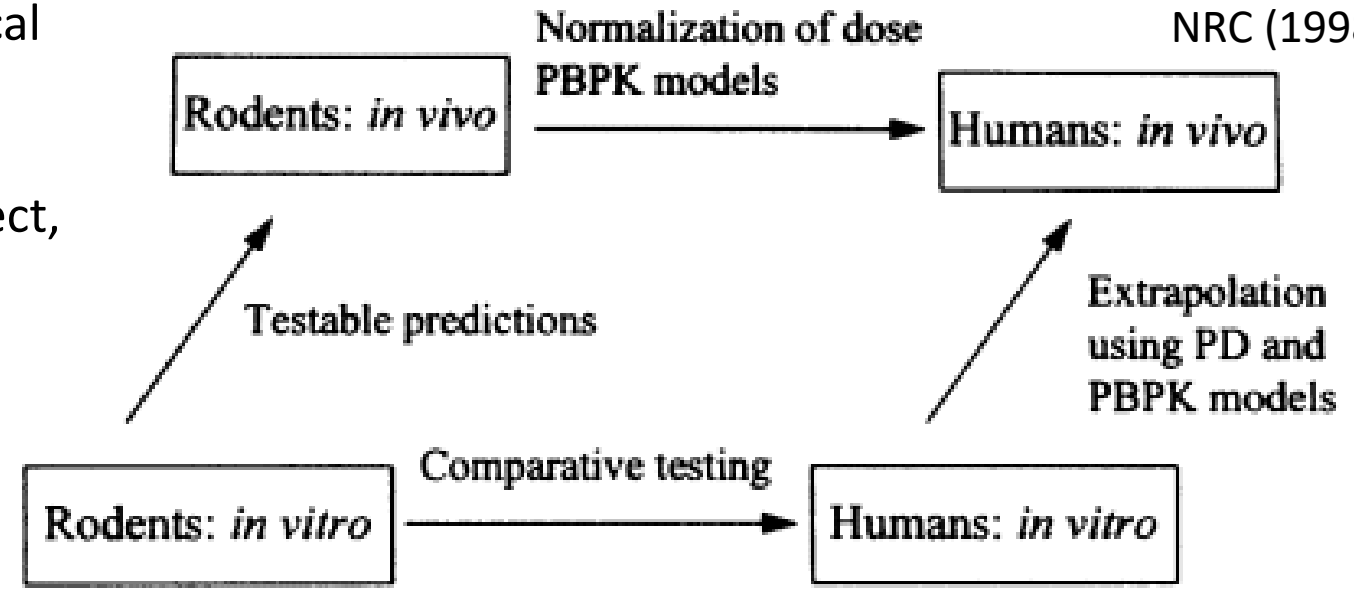
In Vitro - In Vivo Extrapolation (IVIVE)

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

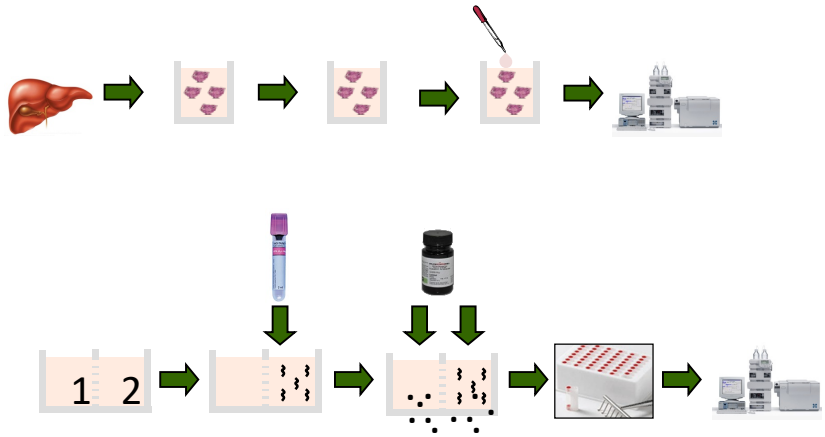


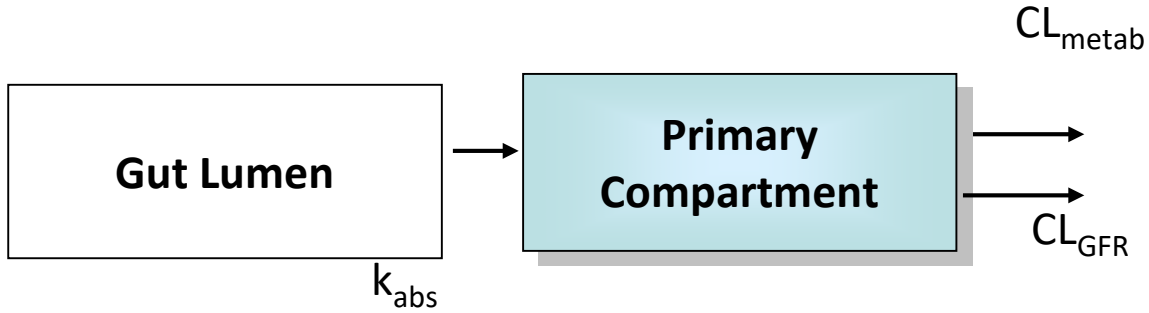
NRC (1998)

High Throughput Toxicokinetics (HTTK)

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

= high(er) throughput toxicokinetics



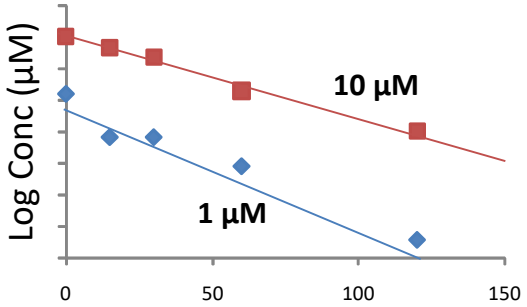


httk

In Vitro Data for HTTK

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

The rate of disappearance of parent compound (slope of line) is the **hepatic clearance** (µL/min/10^6 hepatocytes)



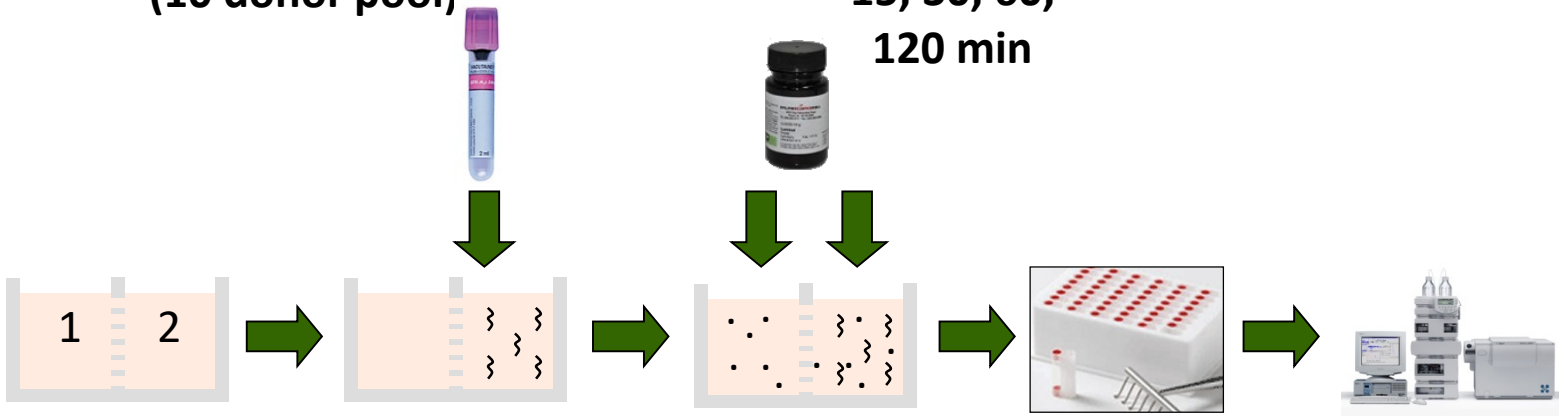
We perform the assay at 1 and 10 µM to check for saturation of metabolizing enzymes.

- **Most chemicals do not have TK data** – we use *in vitro* HTTK methods adapted from pharma to fill gaps
- In drug development, HTTK methods allow IVIVE to estimate therapeutic doses for clinical studies – predicted concentrations are typically on the order of values measured in clinical trials (Wang, 2010)

In Vitro Data for HTTK

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

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



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

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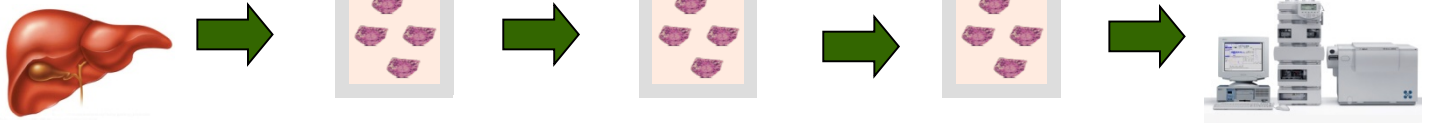
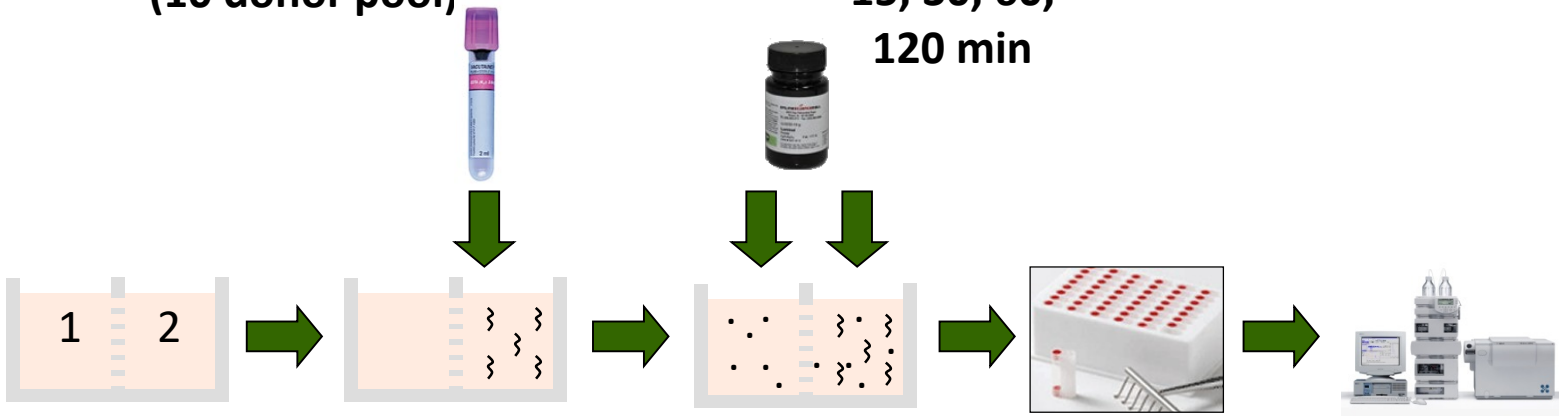


Rapid Equilibrium Dialysis (RED) Waters *et al.* (2008)

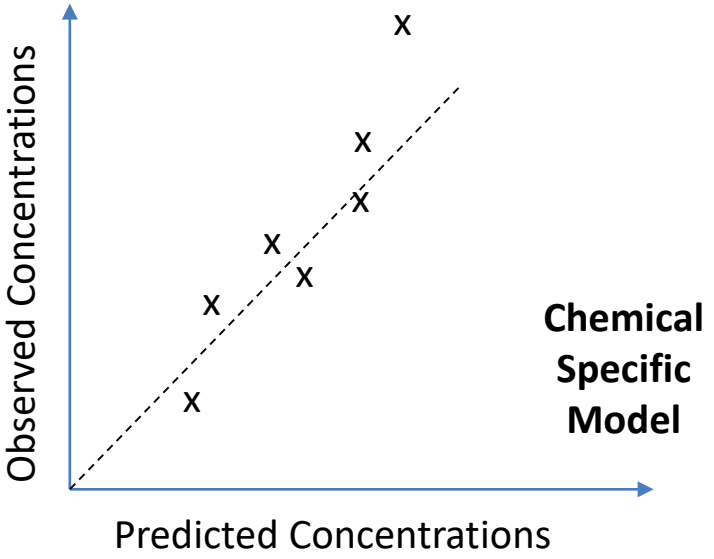


$$F_{ub,p} = \frac{C_{well1}}{C_{well2}}$$

- **Most chemicals do not have TK data** – we use *in vitro* HTTK methods adapted from pharma to fill gaps
- Environmental chemicals:
  - Rotroff et al. (2010) **35** chemicals
  - Wetmore et al. (2012) **+204** chemicals
  - Wetmore et al. (2015) **+163** chemicals
  - Wambaugh et al. (2019) **+389** chemicals

Building Confidence in TK Models

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



Cohen Hubal et al. (2018)

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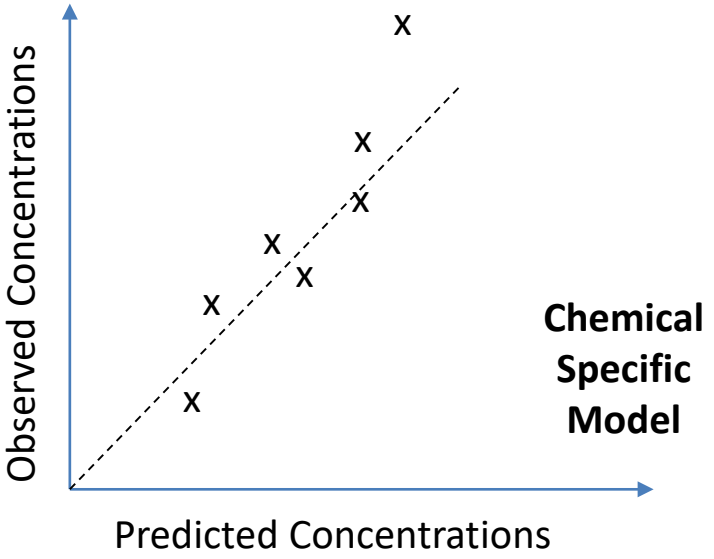
- However, we do not typically have TK data



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- However, we do not typically have TK data

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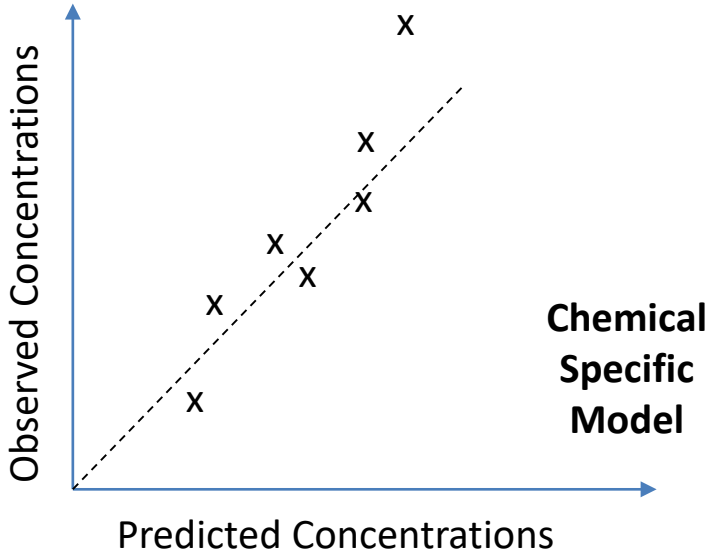

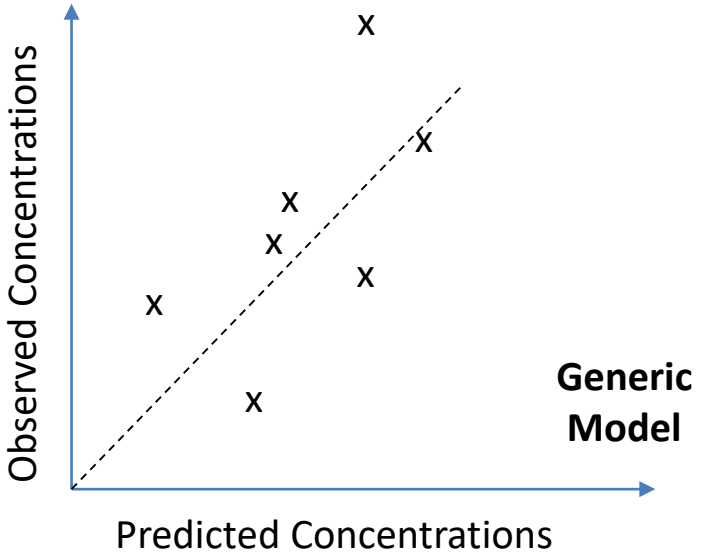

Cohen Hubal et al. (2018)

Building Confidence in TK Models

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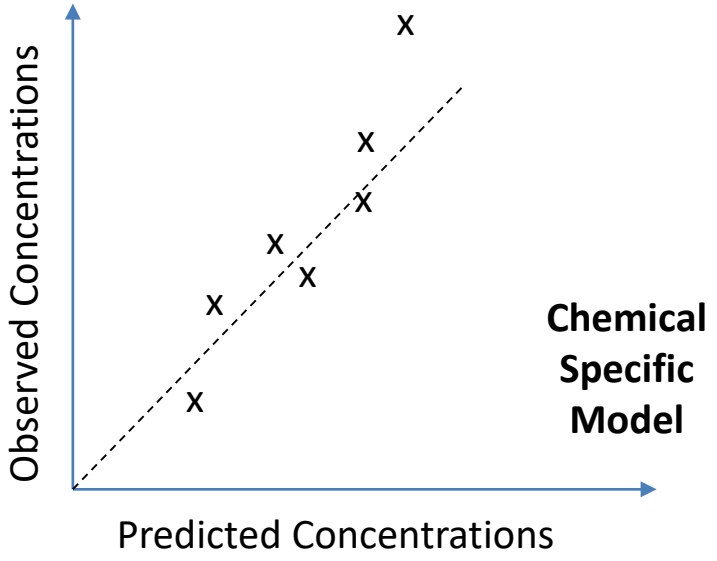

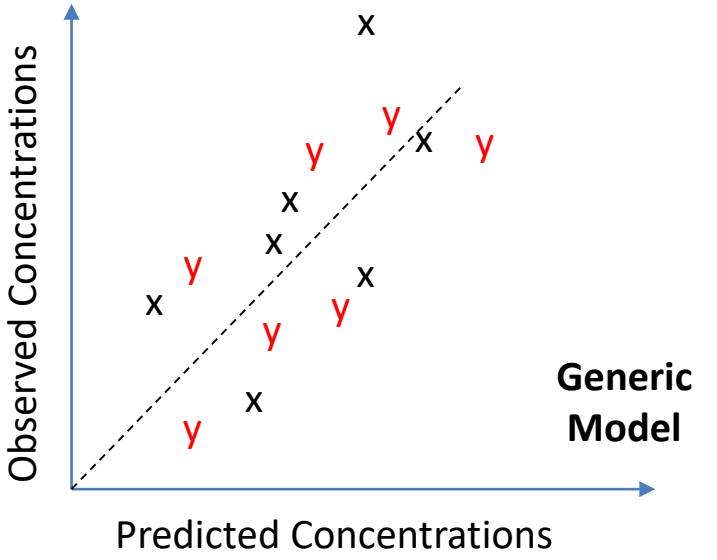

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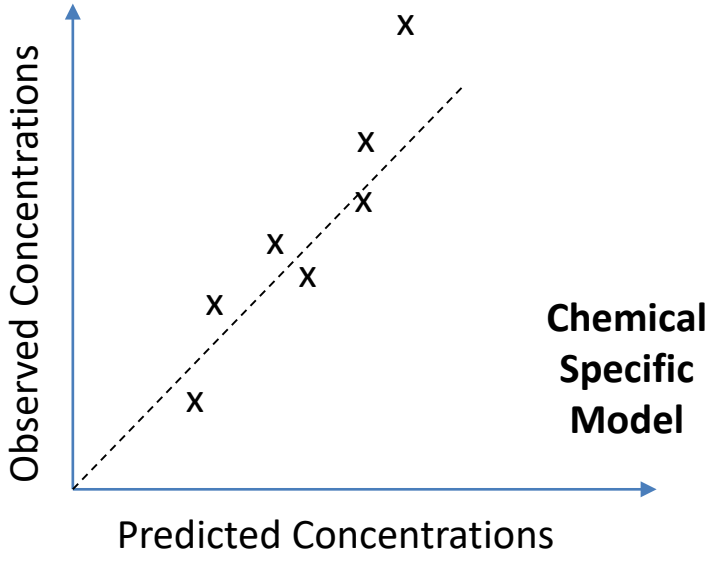
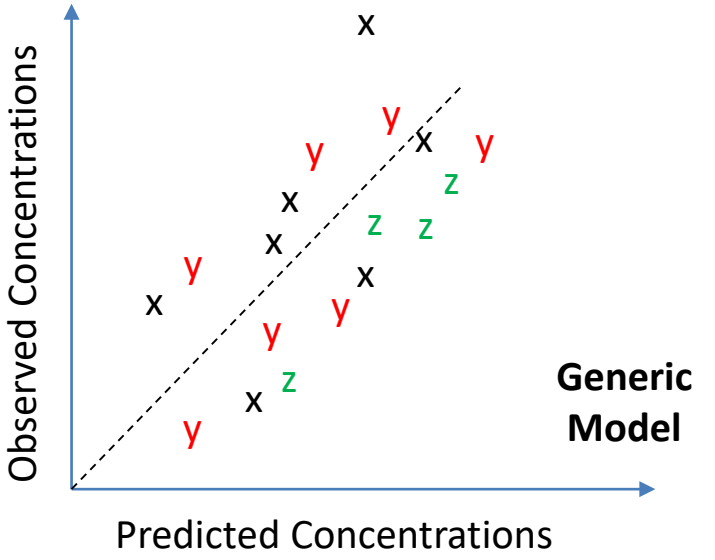
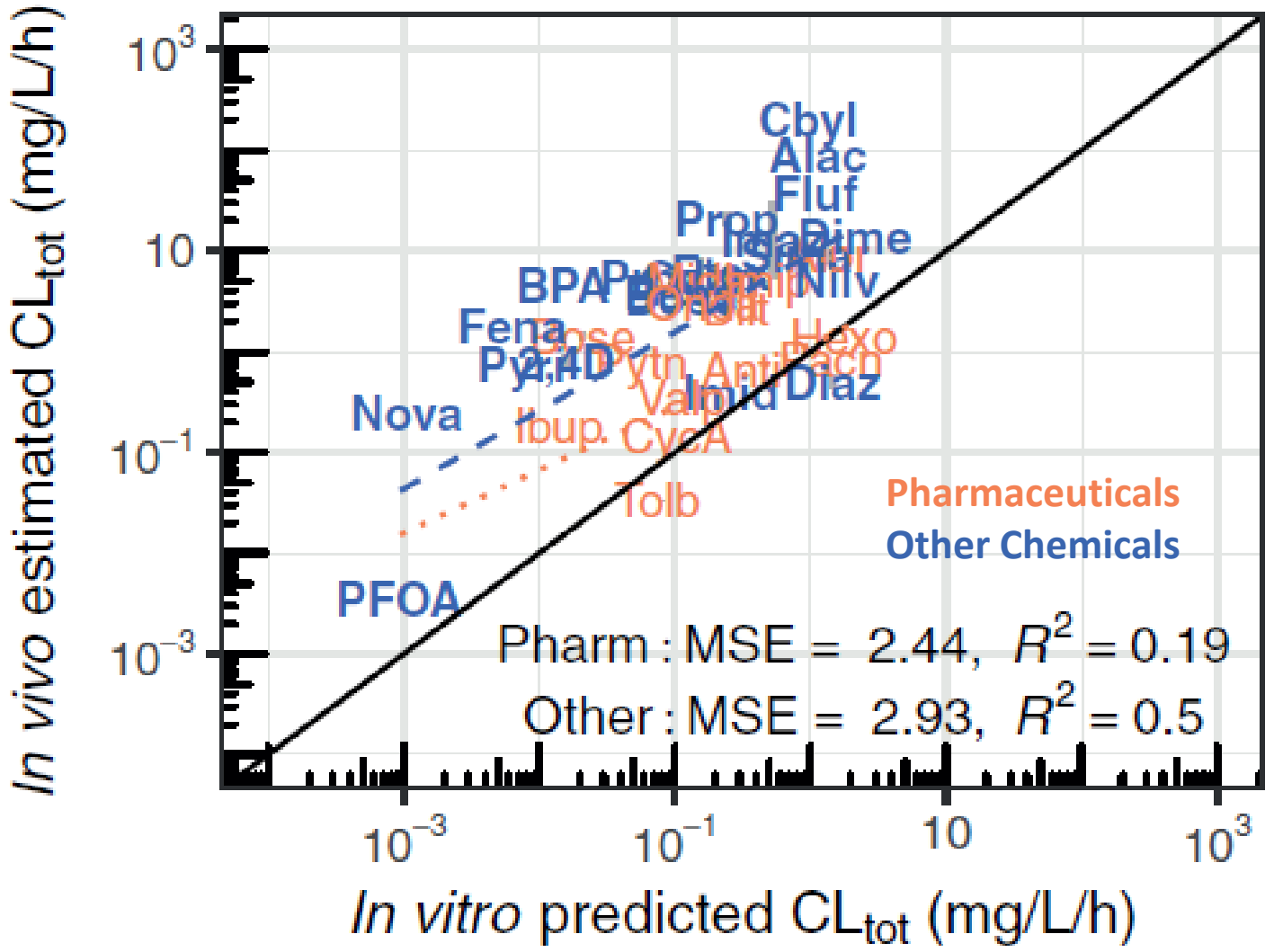




Cohen Hubal et al. (2018)

Evaluation Example

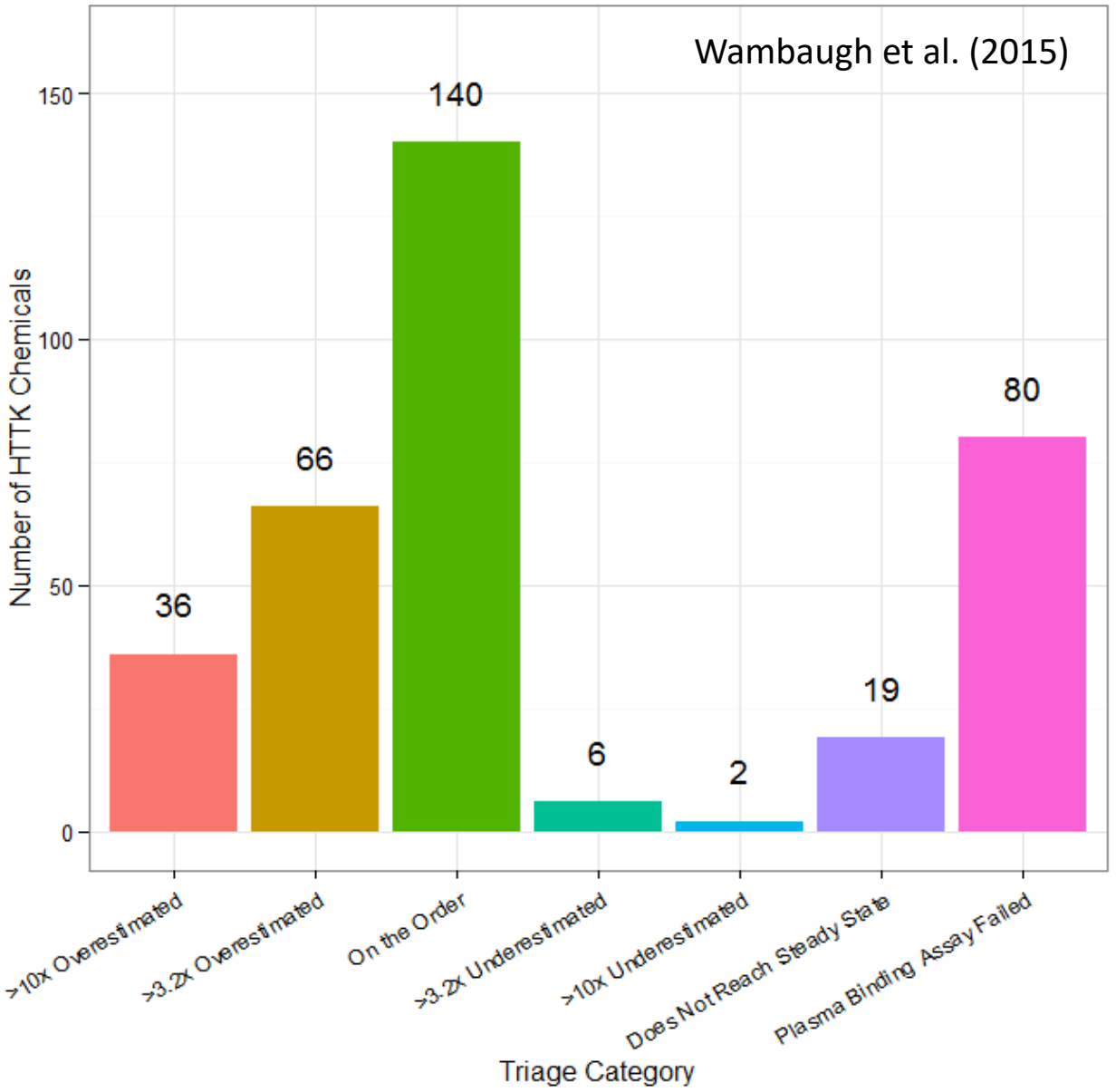
- We estimate clearance from two processes – hepatic metabolism (liver) and passive glomerular filtration (kidney)
- This appears to work better for pharmaceuticals than other chemicals:
  - ToxCast chemicals are overestimated
- Non-pharmaceuticals may be subject to extrahepatic metabolism and/or active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



Wambaugh et al. (2018)

Toxicokinetic Triage: When Does TK IVIVE

- Through comparison to *in vivo* data, a cross-validated (random forest) predictor of success or failure of HTTK has been constructed
- All chemicals can be placed into one of seven confidence categories
  - Added categories for chemicals that do not reach steady-state or for which plasma binding assay fails
- Plurality of chemicals end up in the "on the order" bin (within a factor of 3.2x) which is consistent with Wang (2010)



Uncertainty

Different crayons have different colors…

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

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

Variability

Different crayons have different colors…

The “average” color may not even be in the box!

Variability

Different crayons have different colors…

The “average” color may not even be in the box!

Population simulator for HTTK

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

Sample NHANES biometrics for actual individuals:

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

Slide from Caroline Ring (ToxStrategies)

Ring *et al.* (2017)

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Regression equations from literature
(McNally *et al.*, 2014)
(+ residual marginal variability)

(Similar approach used in SimCYP [Jamei et al. 2009], GastroPlus, PopGen [McNally et al. 2014], P3M [Price et al. 2003], physB [Bosgra et al. 2012], etc.)

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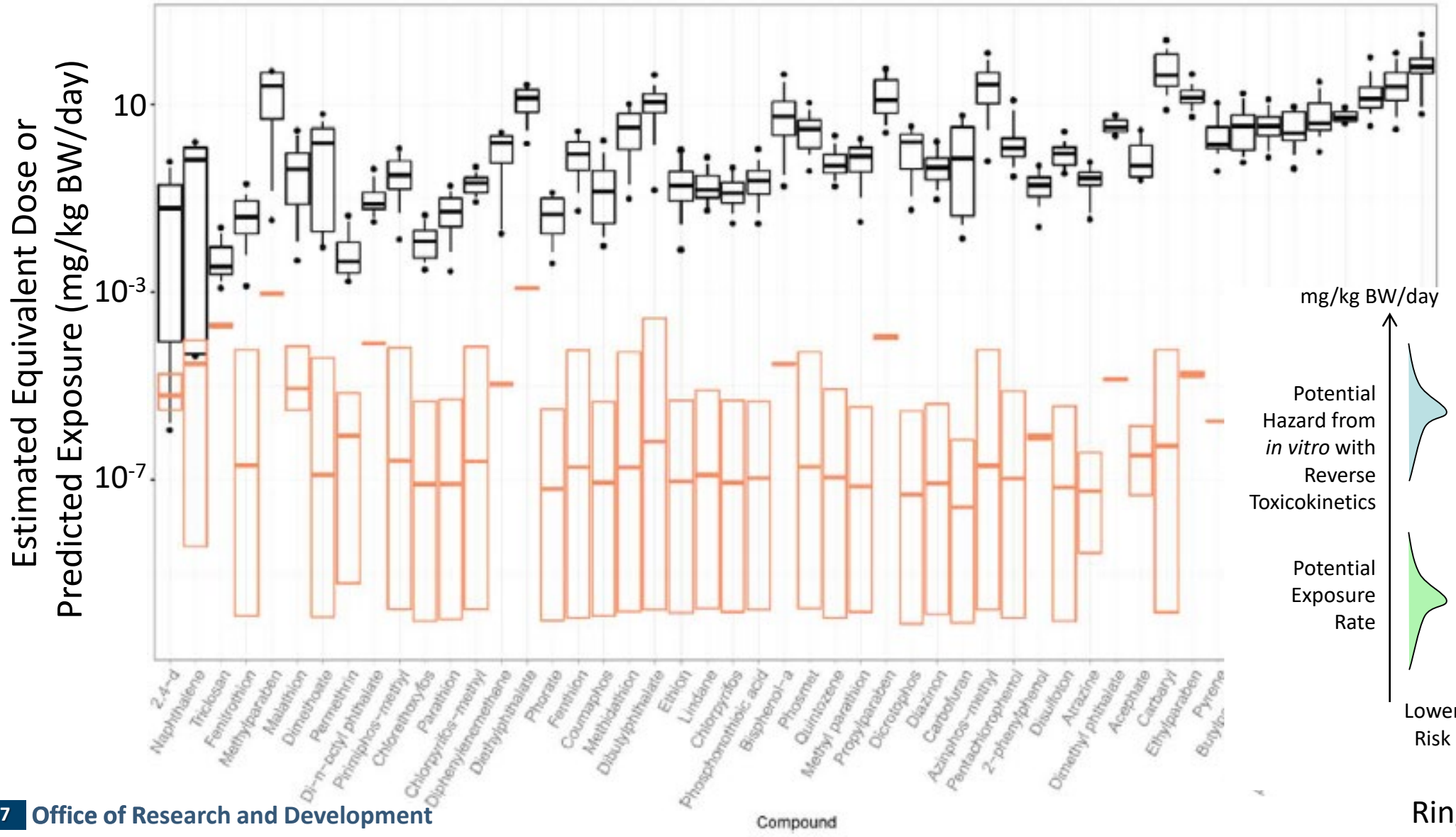
Predict physiological quantities

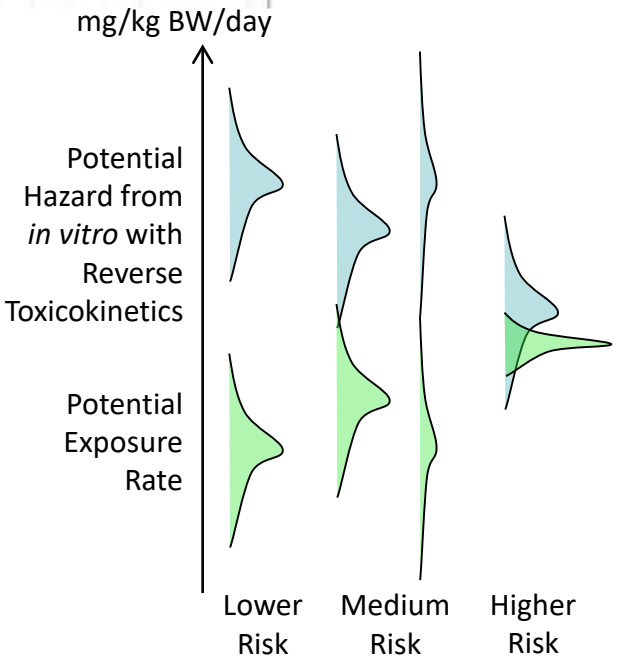
Tissue masses
Tissue blood flows
GFR (kidney function)
Hepatocellularity

Slide from Caroline Ring (ToxStrategies)

Ring *et al.* (2017)

Risk-Based Ranking for Total NHANES Population

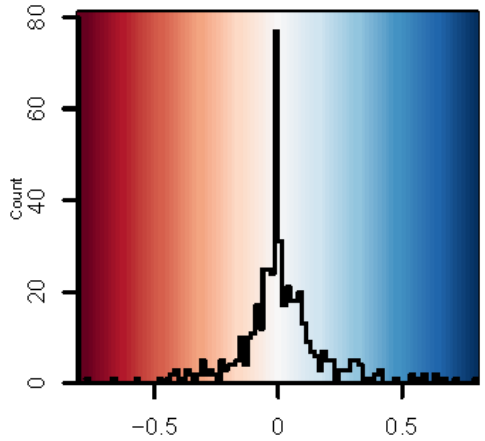




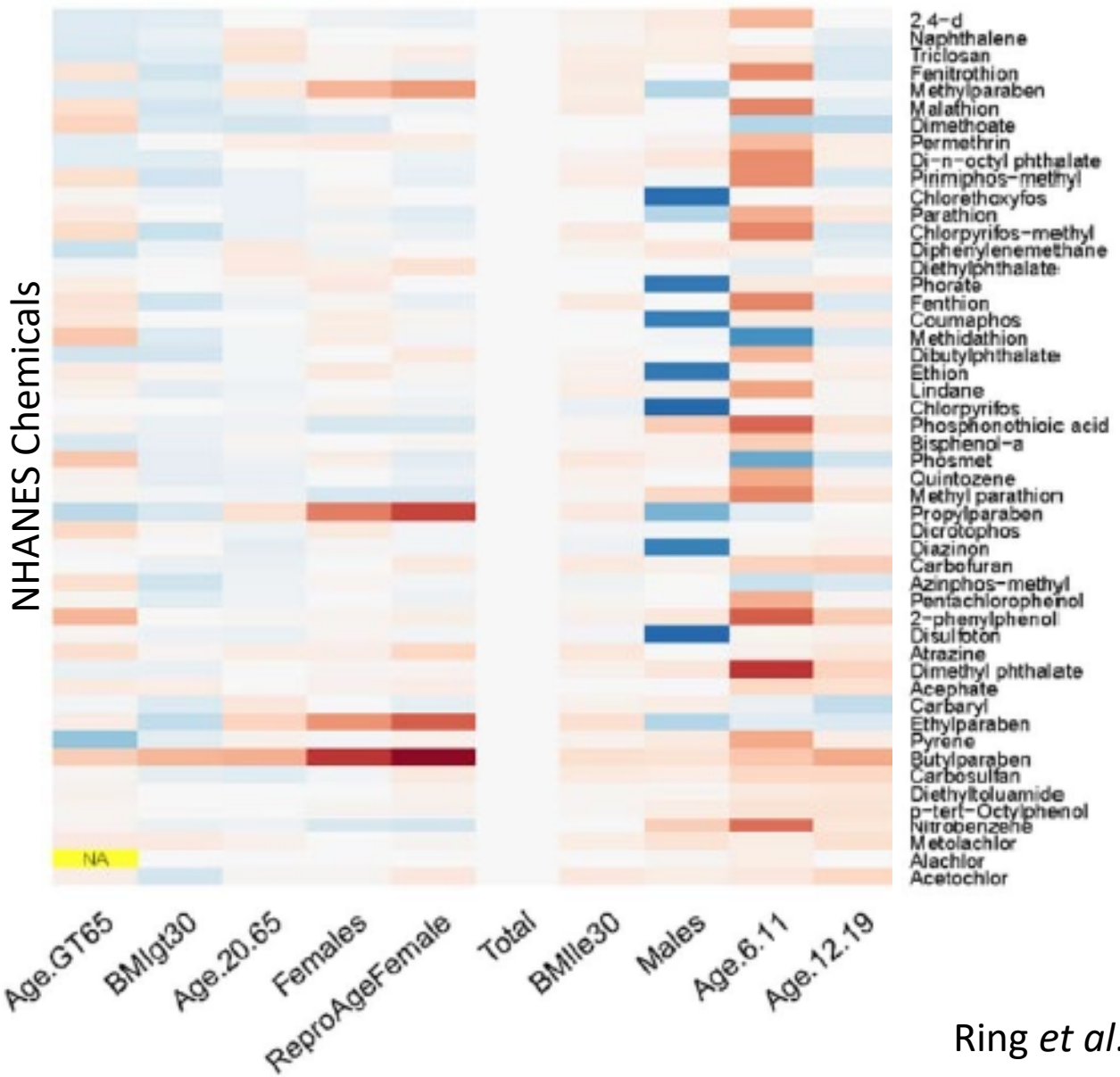
Ring *et al*. (2017)

Life-stage and Demographic Variation in Exposure

- Wambaugh *et al.* (2014) made steady-state inferences of exposure rate (mg/kg/day) from NHANES data for various demographic groups



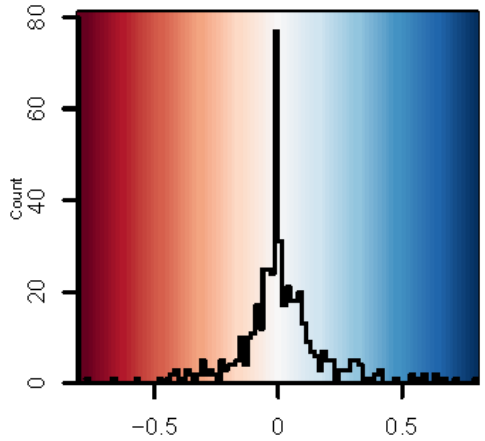
Change in Exposure Relative to Total Population



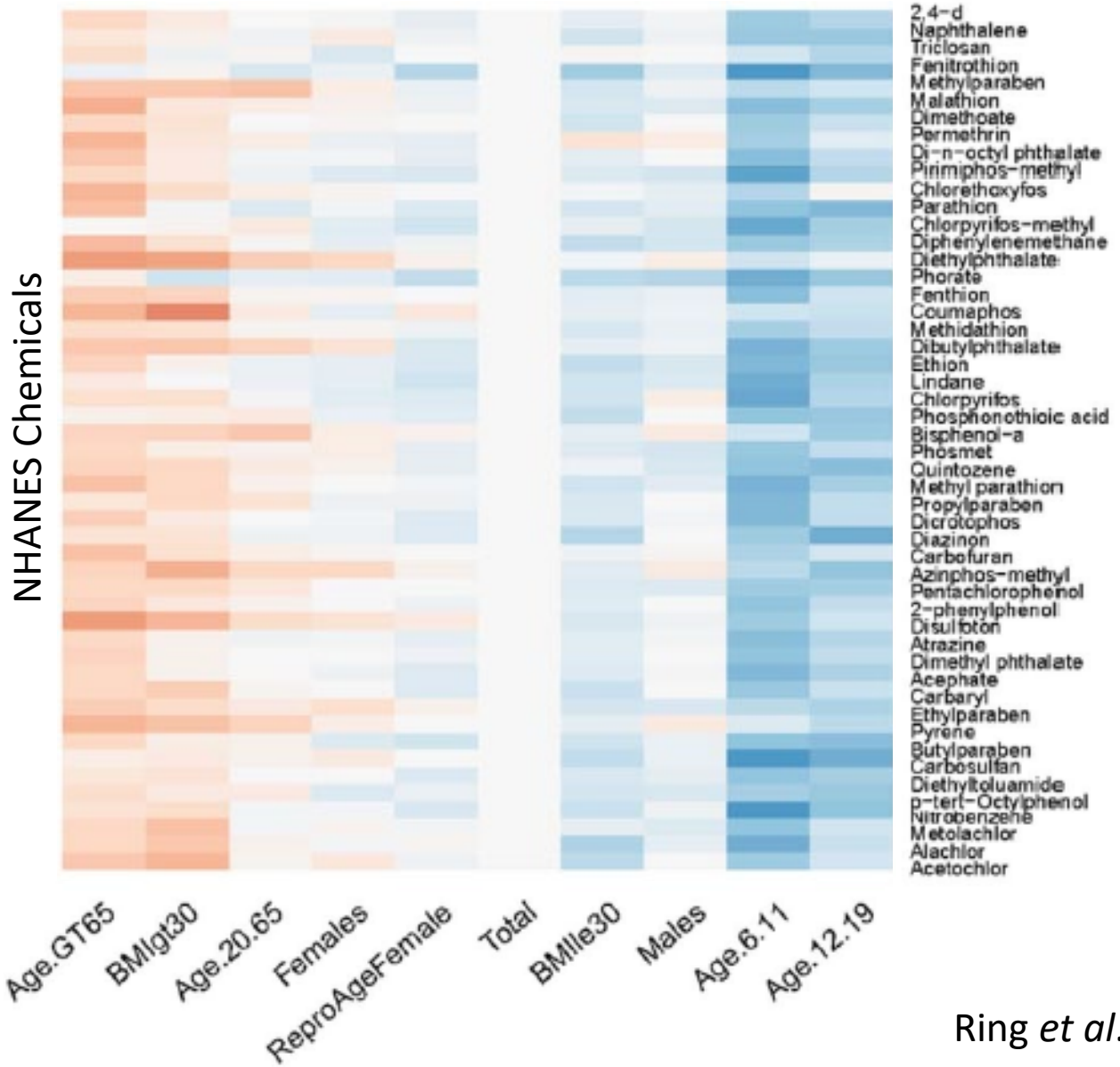
Ring *et al.* (2017)

Life-stage and Demographic Variation in TK

- Ring *et al.* (2017) made demographic-specific predictions of change in plasma concentrations for a 1 mg/kg bw/day exposure



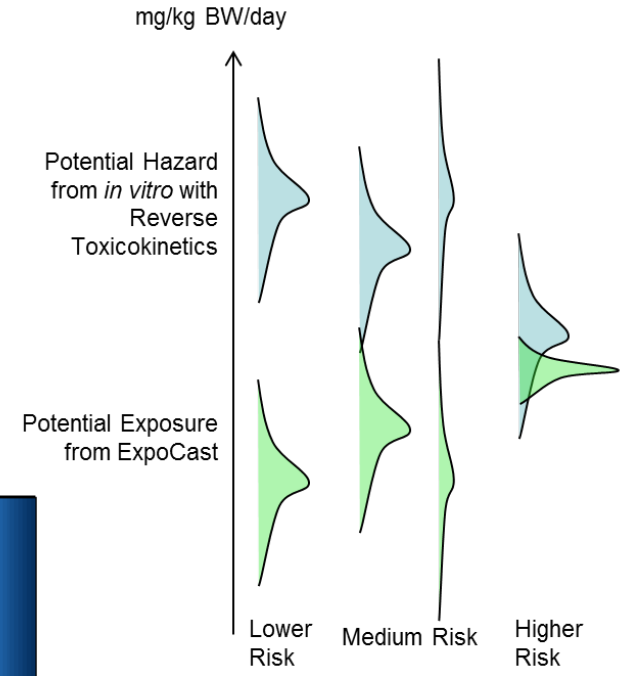
Change in Toxicokinetics Relative to Total Population

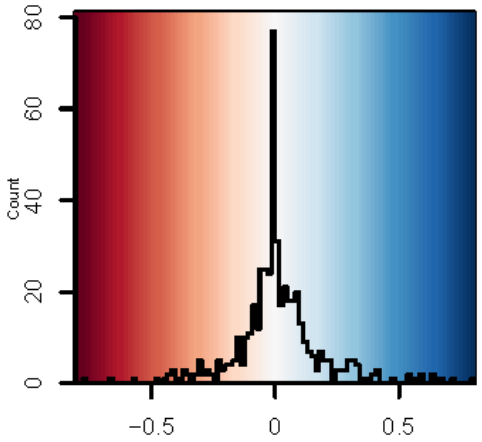


Ring *et al.* (2017)

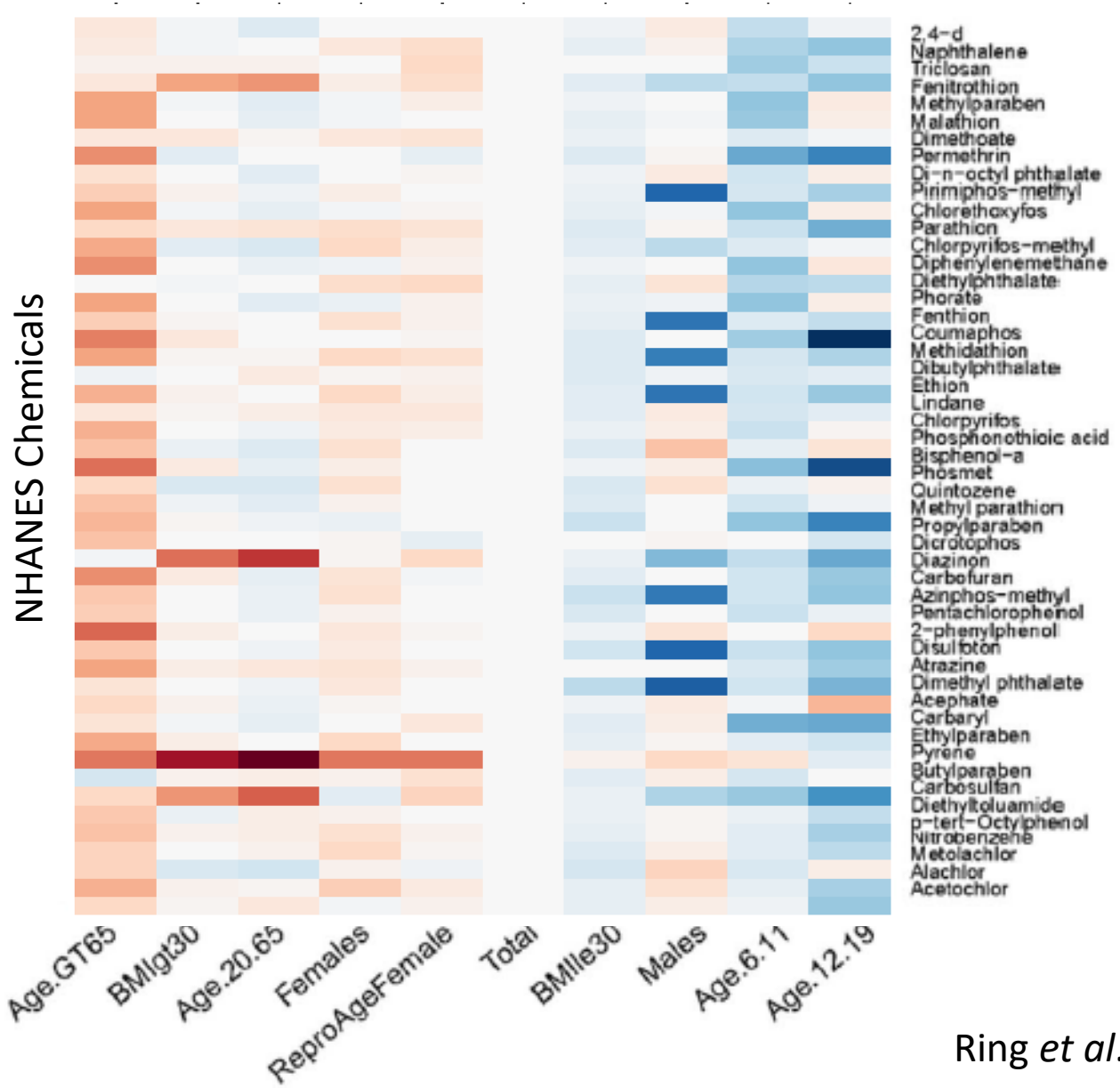
Life-stage and Demographic Variation in Risk Priority

- Can calculate margin between bioactivity and exposure for specific populations





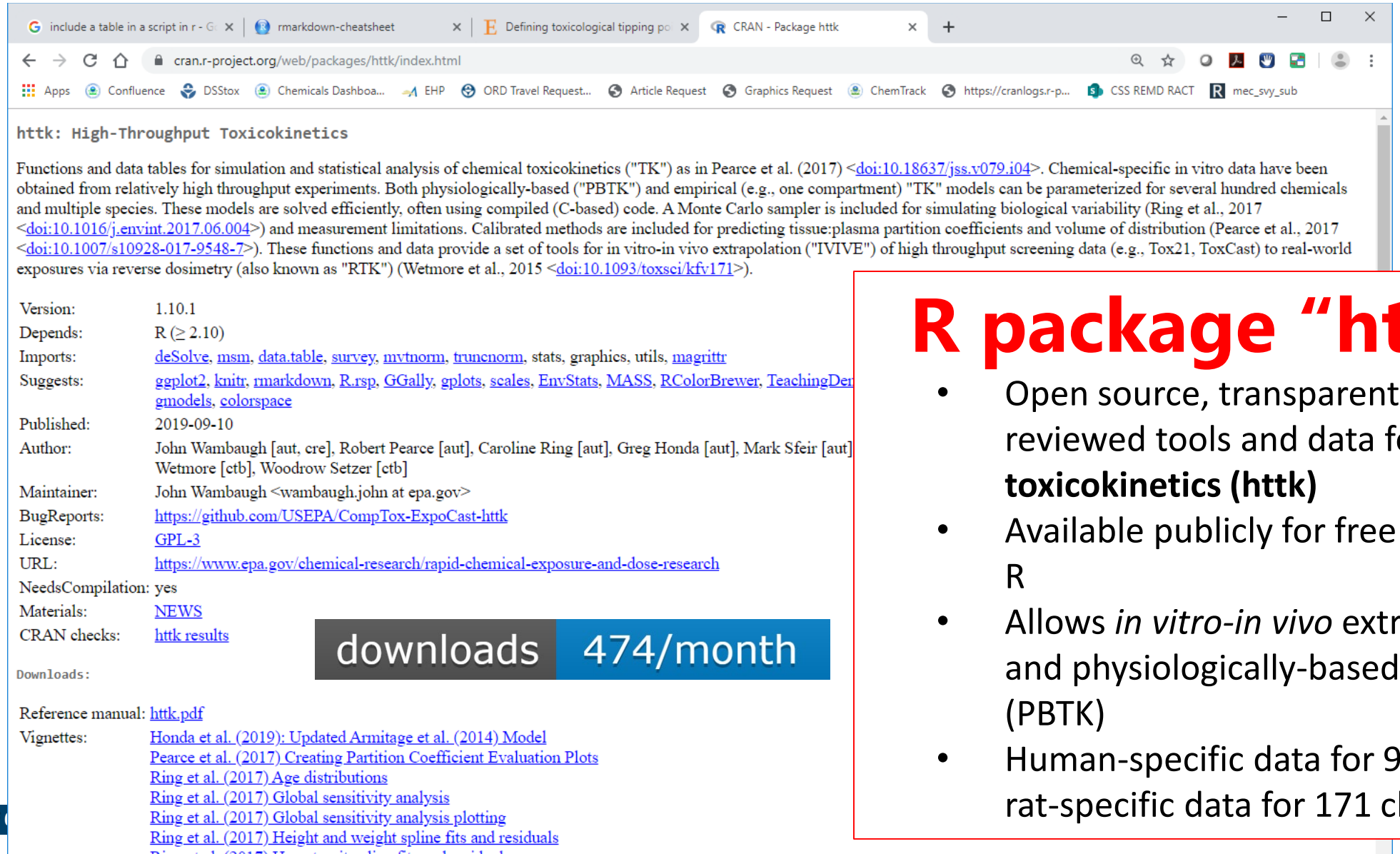
Change in Risk Relative to Total Population



Ring *et al.* (2017)

Open Source Tools and Data for HTTK

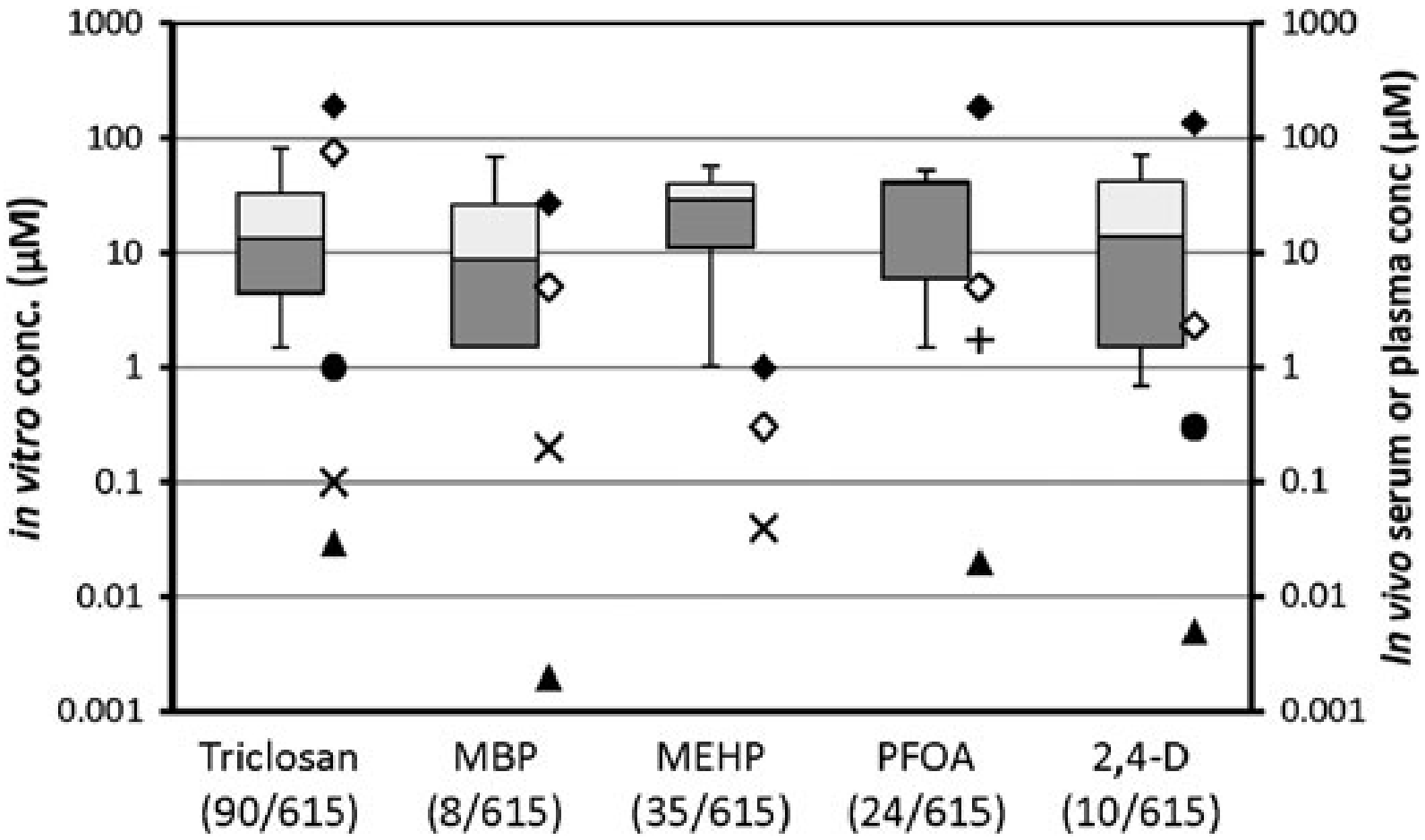
https://CRAN.R-project.org/package=httk



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

What Can We Do When We Don't Have TK?

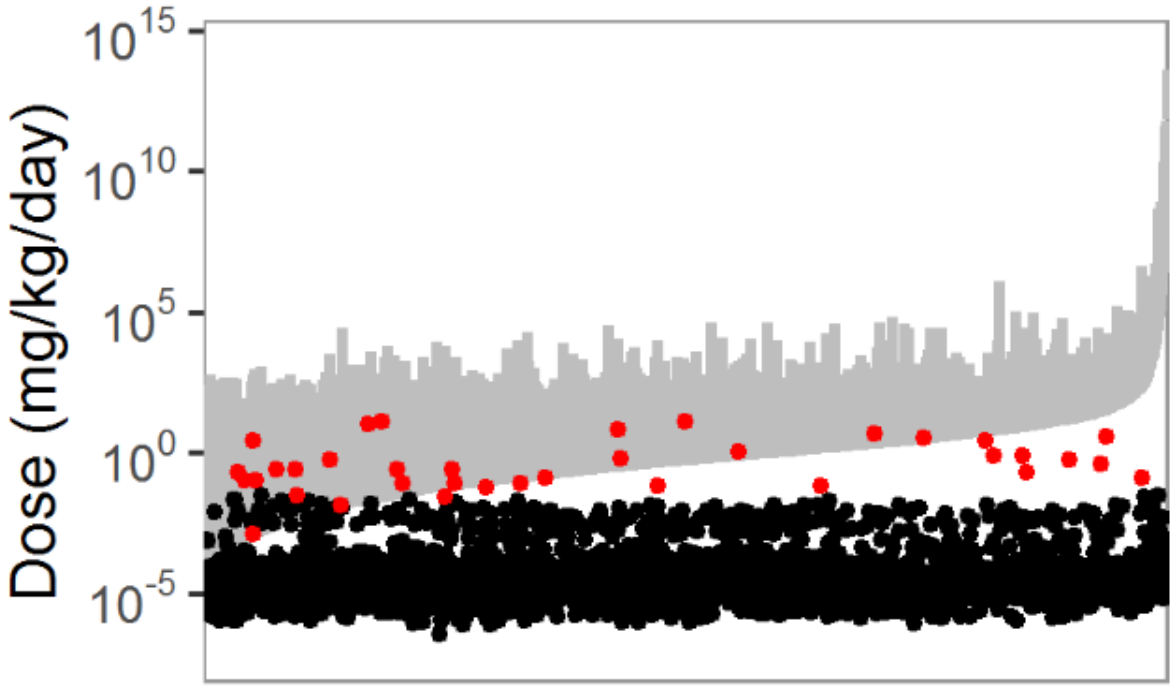


- ◆ estimated or measured average concentrations associated with the LOAEL in animal studies
- ◇ NOAEL in animal studies
- ● Humans with chronic exposure reference values (solid circles)
- x Volunteers using products containing the chemical
- \+ Biomonitored occupational populations
- ▲ General populations

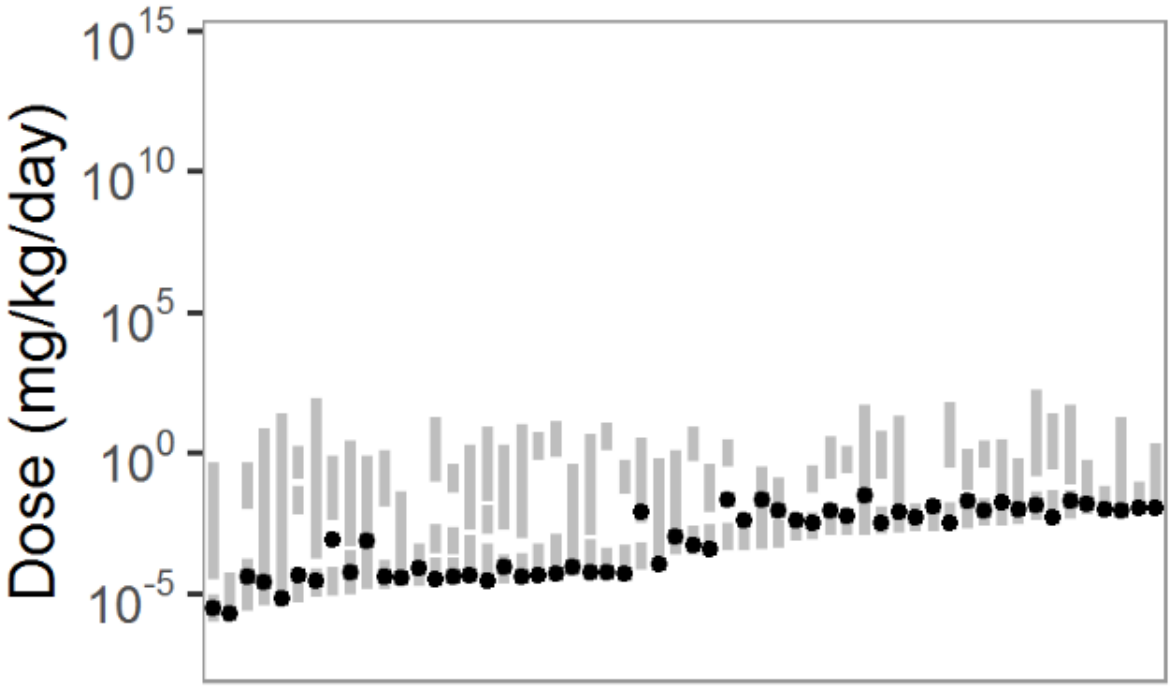
Aylward and Hays (2011)
Journal of Applied Toxicology **31** 741-751

Using Predicted HTTK for Risk Prioritization

Sipes et al., (2017) used Simulations Plus ADMET Predictor to make *in silico* predictions of metabolism and protein binding:



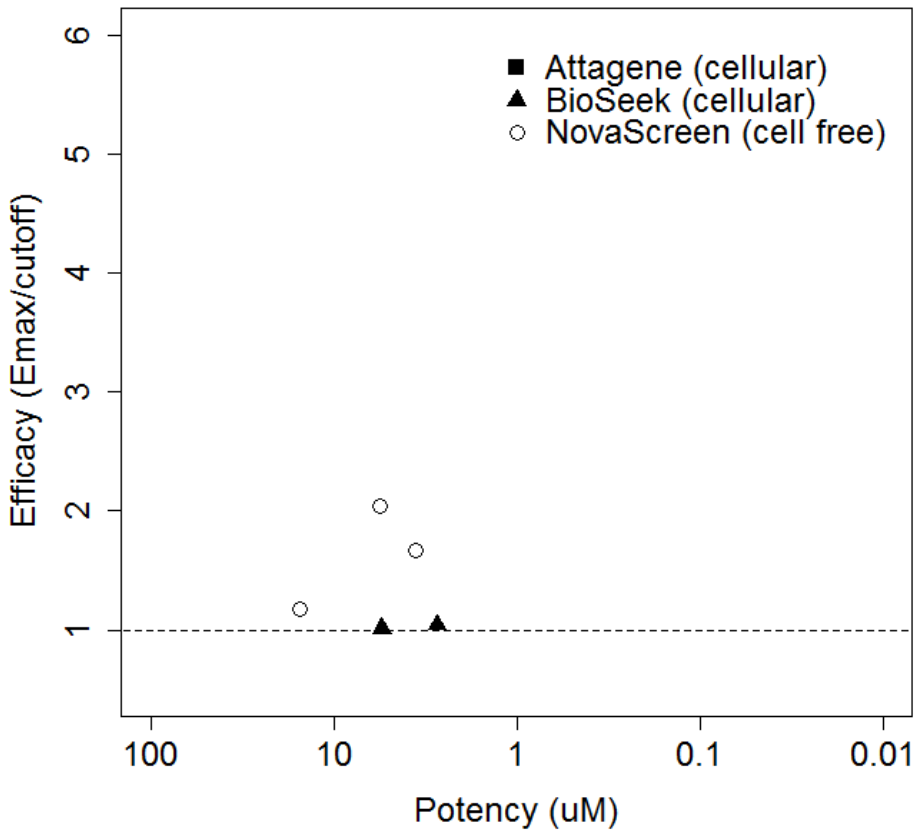
Doses ranges for all 3925 Tox21 compounds eliciting a 'possible'-to-'likely' human *in vivo* interaction alongside estimated daily exposure



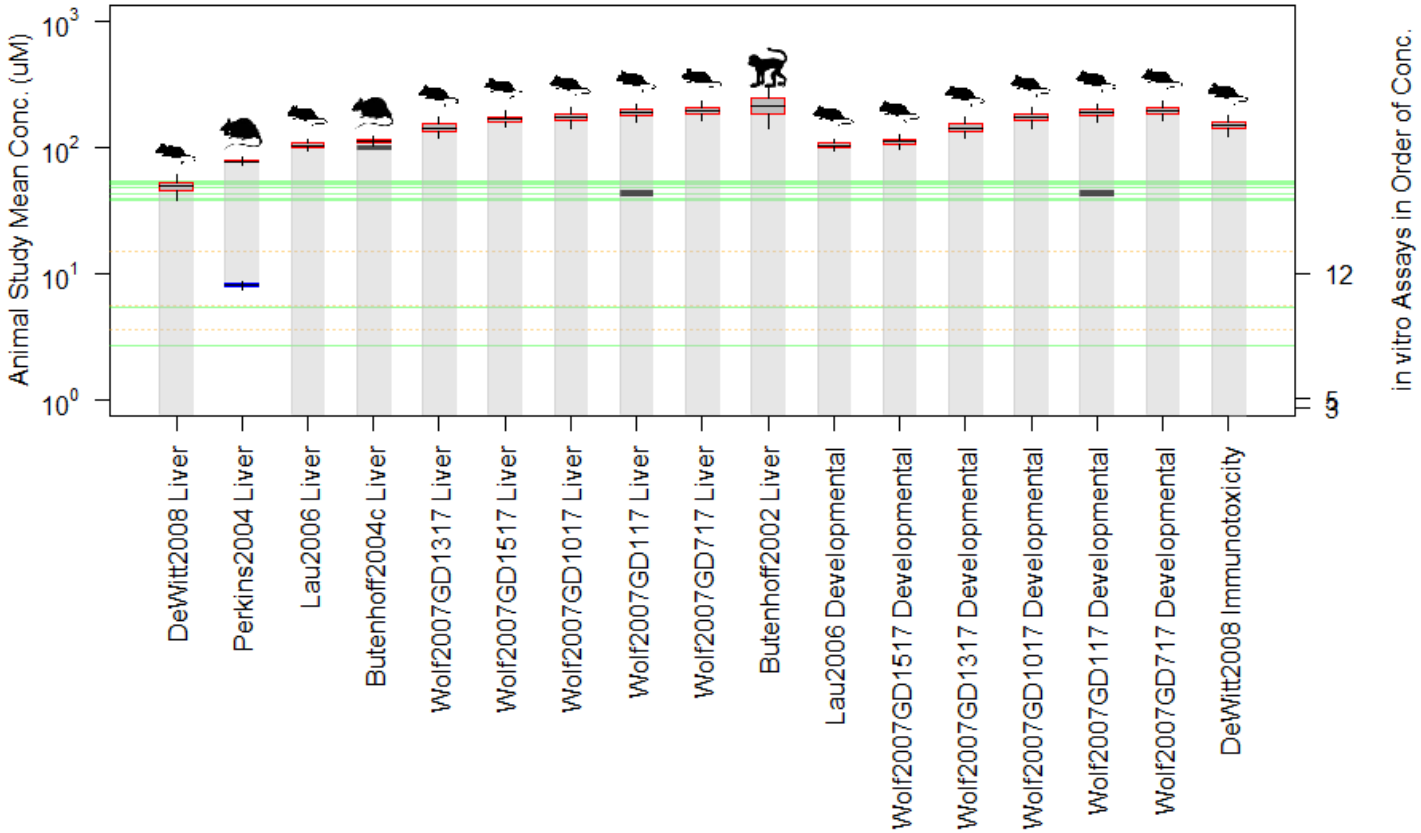
56 compounds with potential *in vivo* biological interaction at or above estimated environmental exposures

What Can We Do When We Don't Have TK?

ToxCast



in vivo toxicity studies



Wambaugh et al., (2013)

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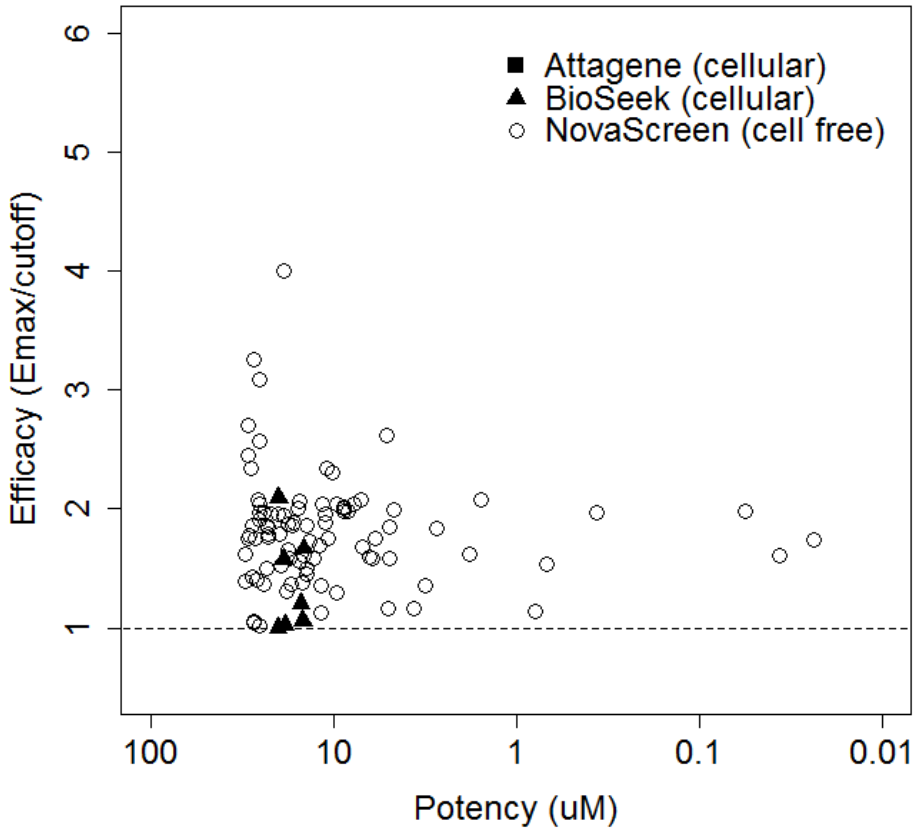

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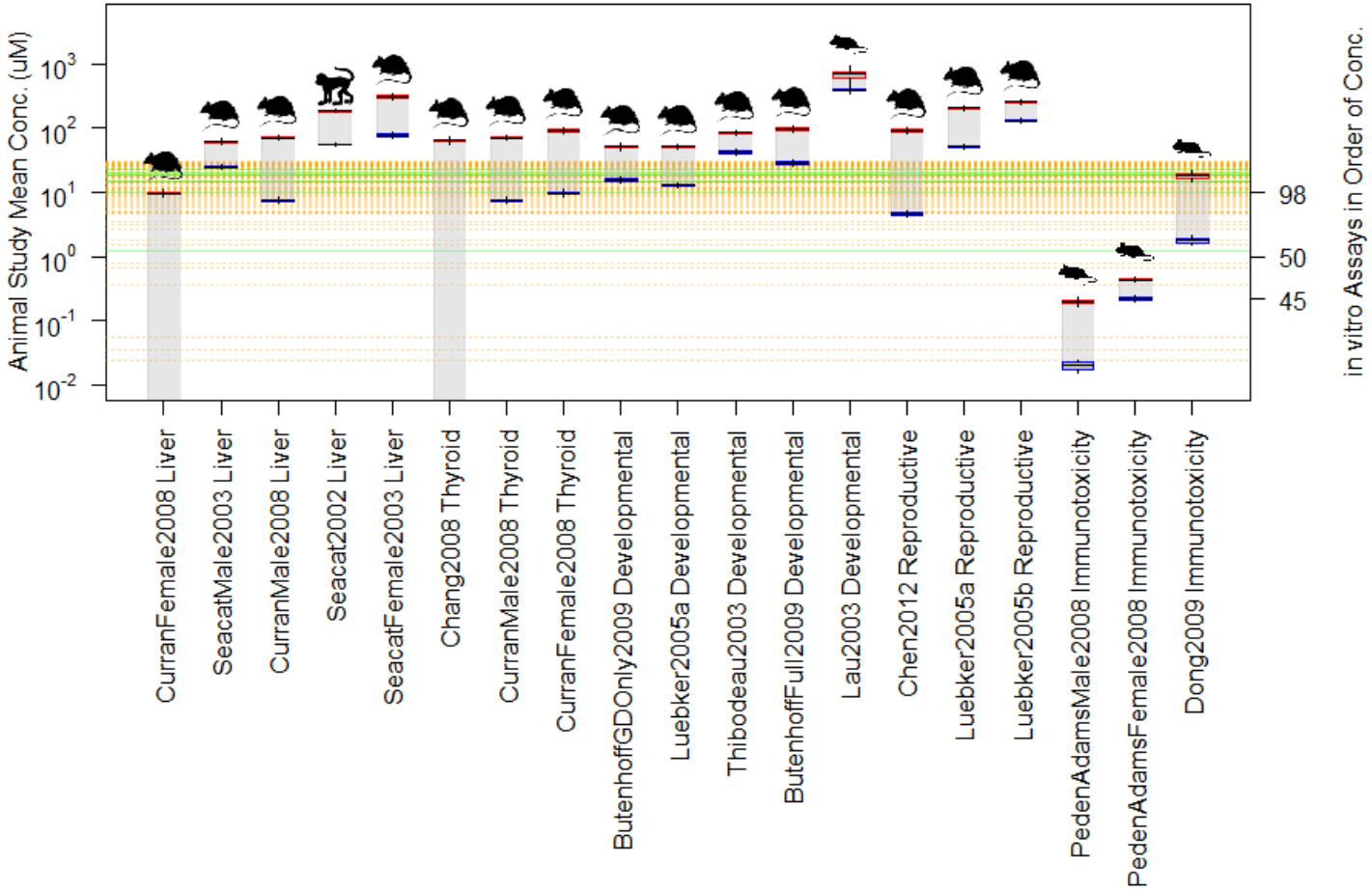
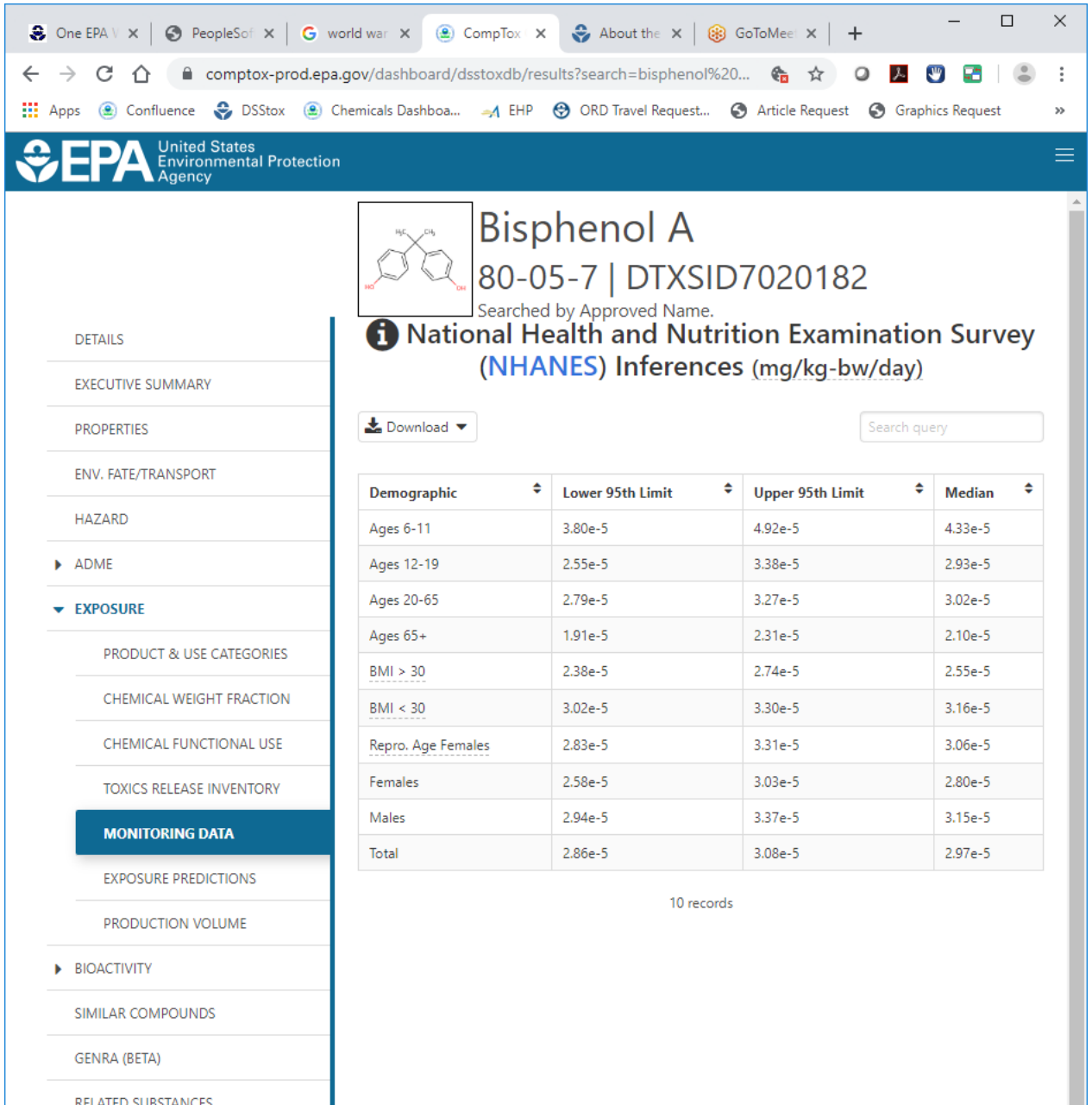


Wambaugh et al., (2013)

NHANES Gives Blood/Serum Levels of Chemicals

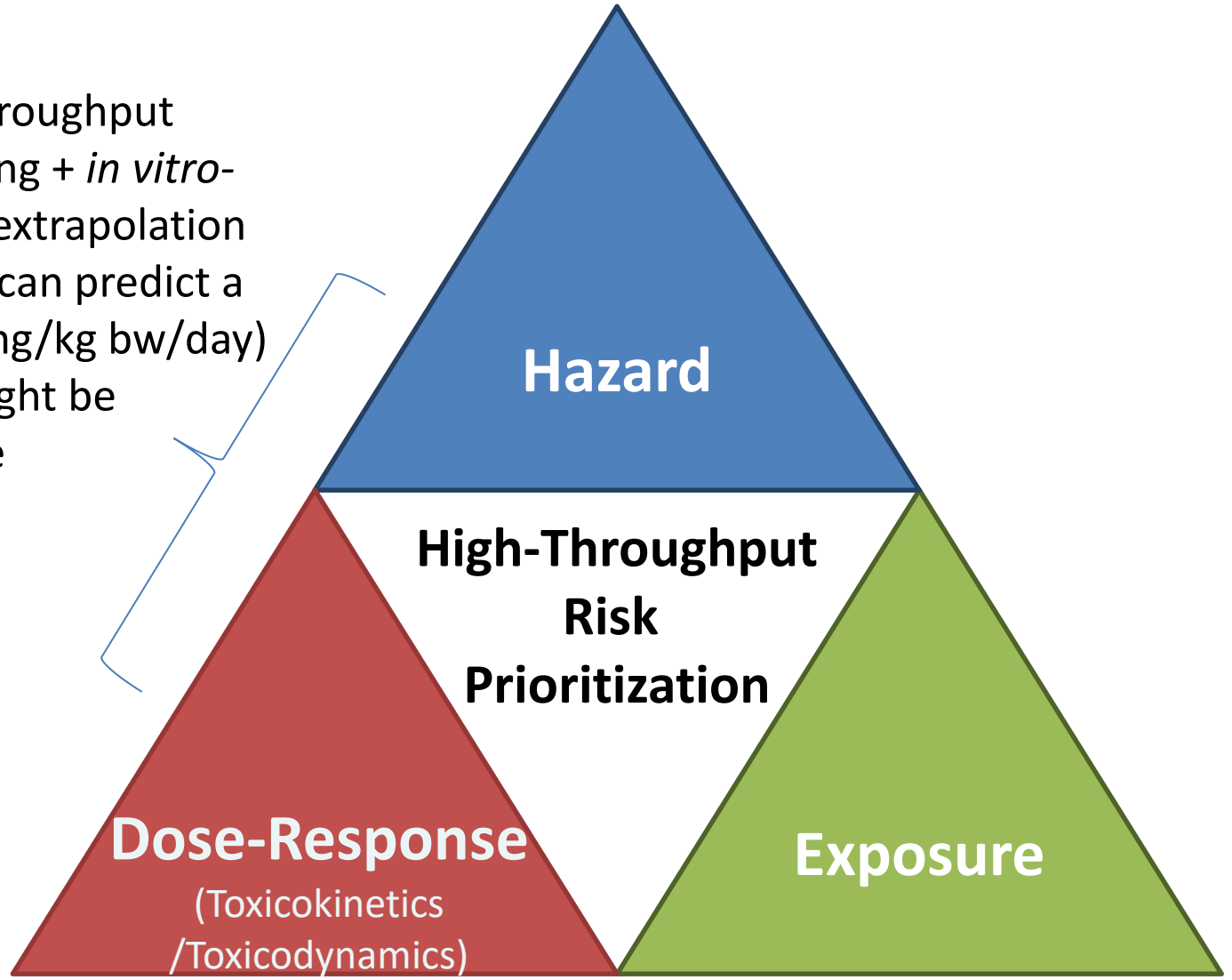
- Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination Survey (NHANES) provides an important tool for monitoring public health
- Currently only have NHANES values from Wambaugh et al. (2014) on dashboard
- Working to include all NHANES chemicals in future dashboard release
- CDC NHANES data can be obtained from:

https://www.cdc.gov/exposurereport/index.html



New Exposure Data and Models

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



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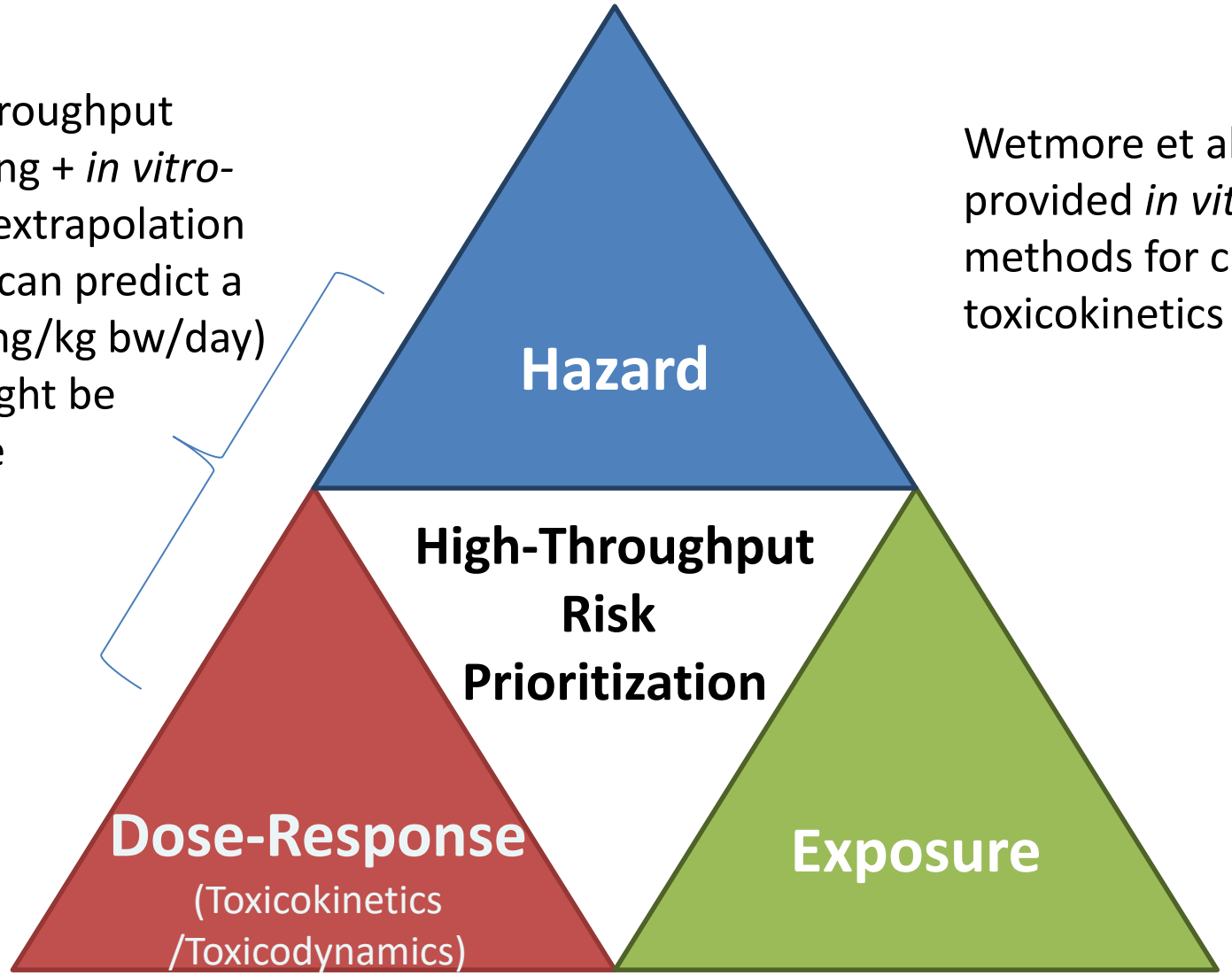
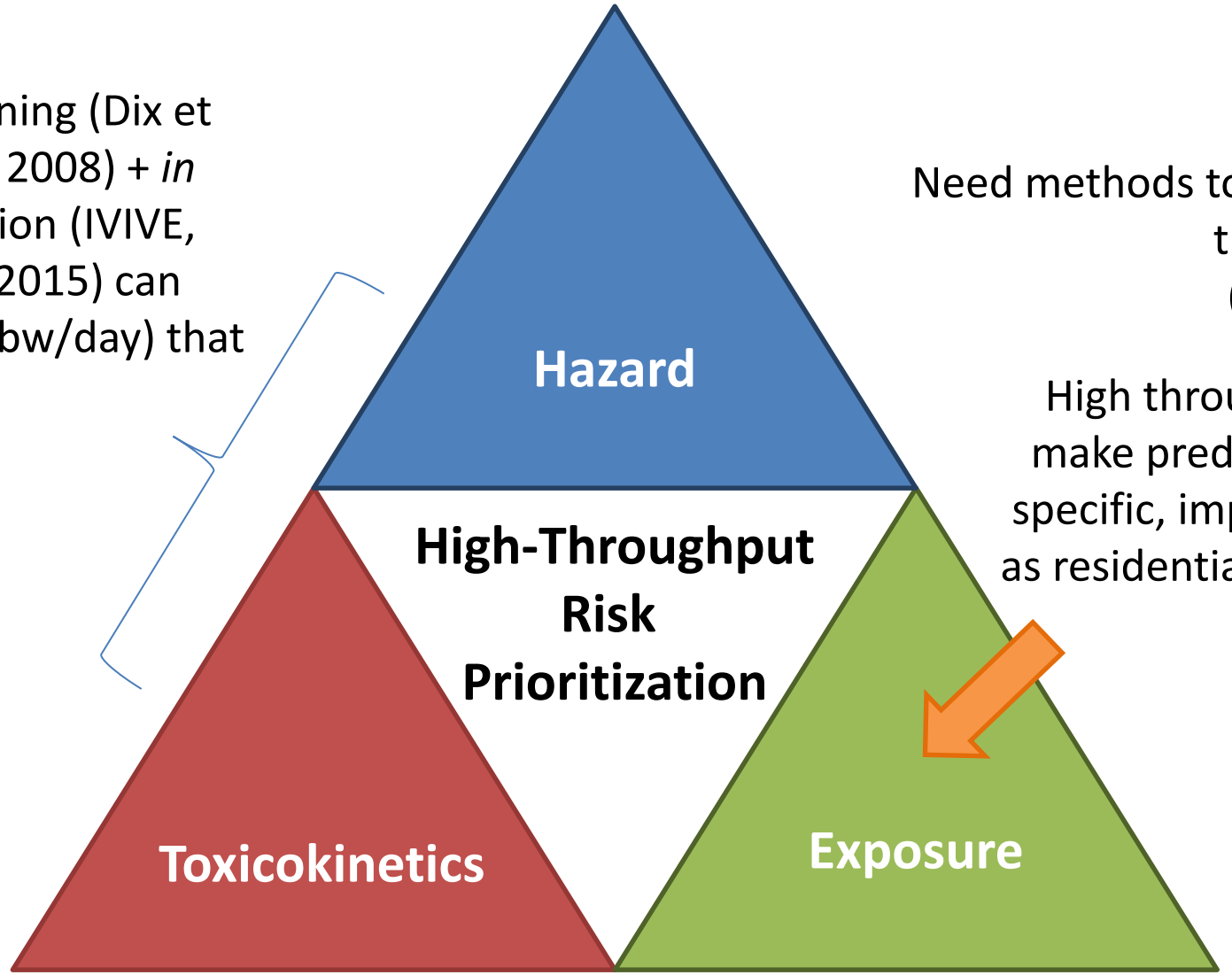


Wetmore et al. (2012, 2015) have provided *in vitro* and simulation methods for characterizing toxicokinetics

Risk = Hazard x Exposure

High throughput screening (Dix et al., 2006, Collins et al., 2008) + *in vitro-in vivo* extrapolation (IVIVE, Wetmore et al., 2012, 2015) can predict a dose (mg/kg bw/day) that might be adverse



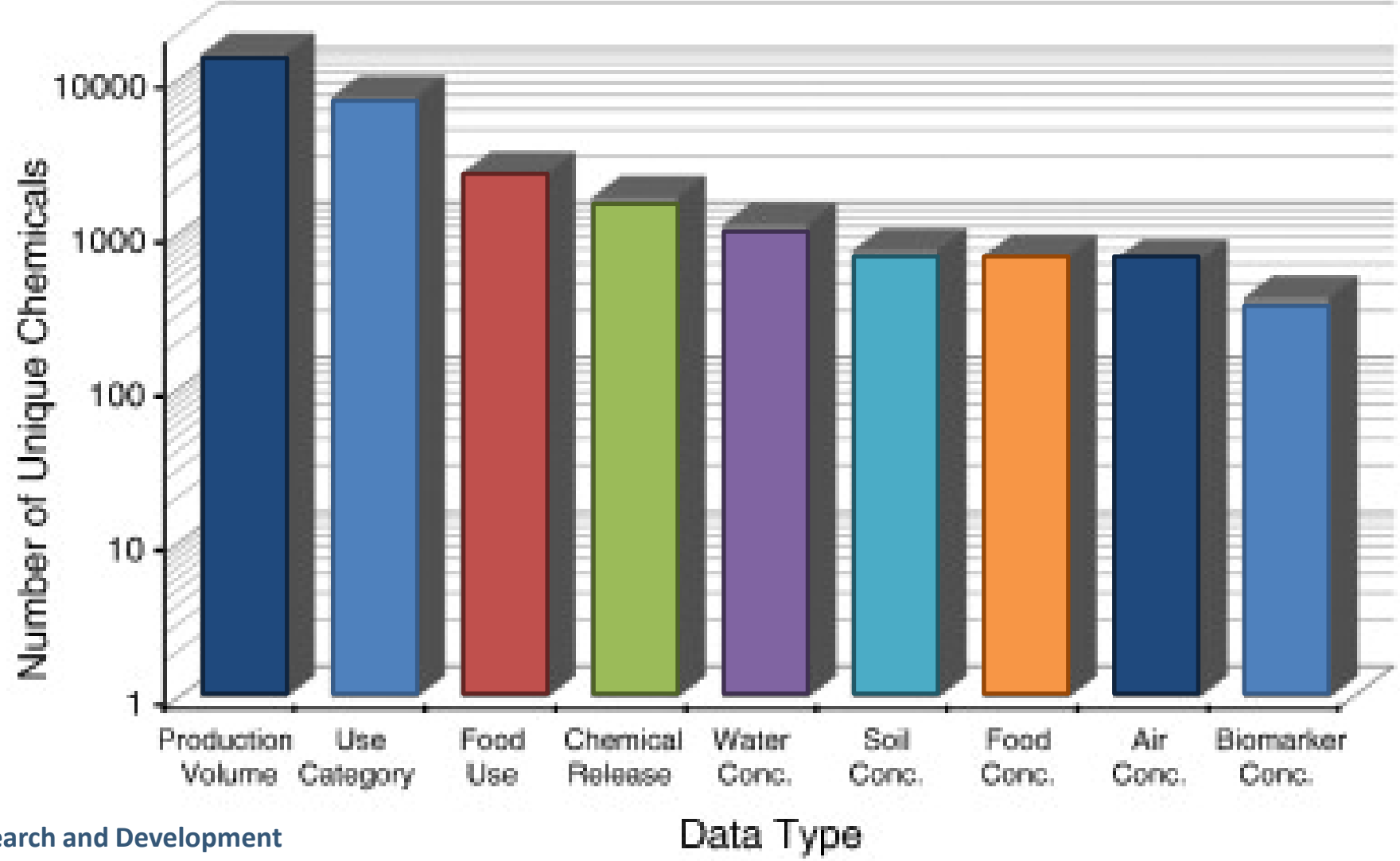
Need methods to forecast exposure for thousands of chemicals (Wetmore et al., 2015)

High throughput models exist to make predictions of exposure via specific, important pathways such as residential product use and diet

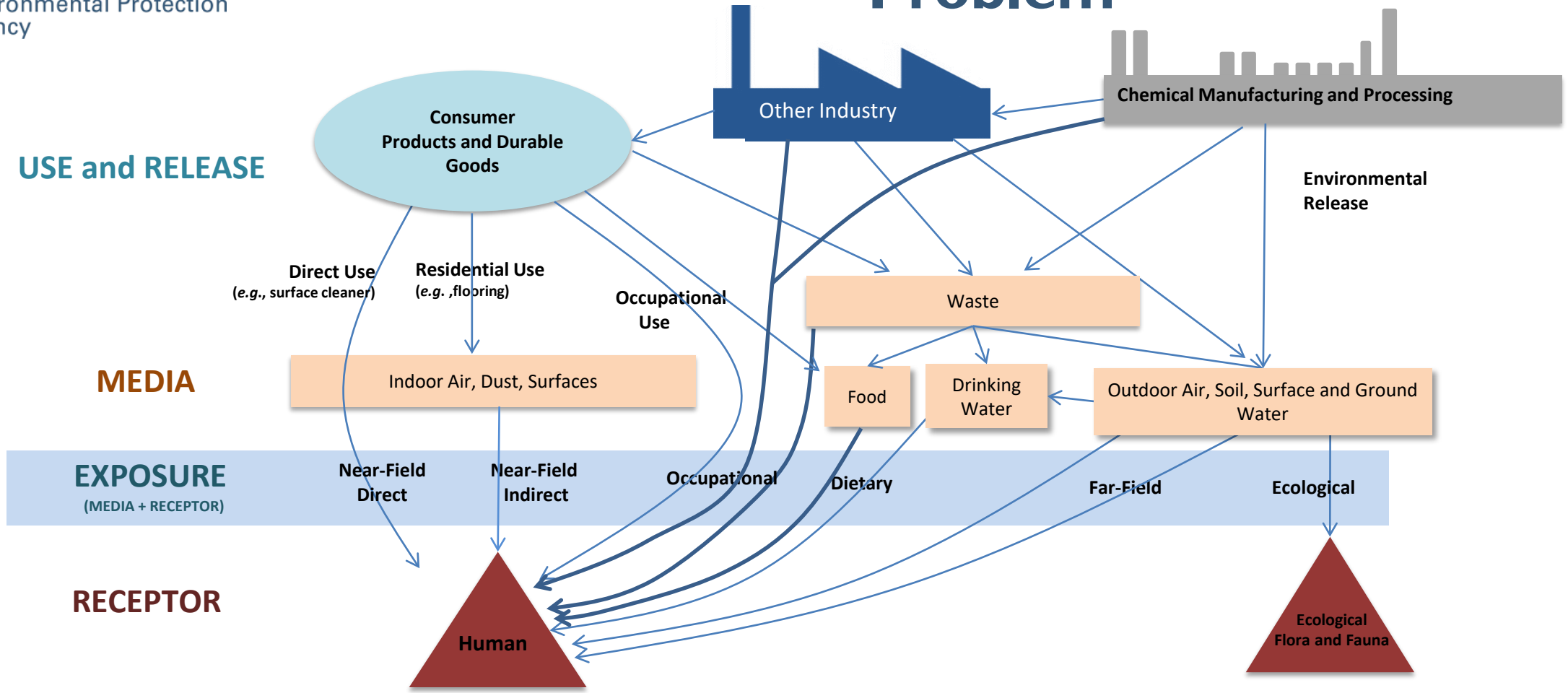
NRC (1983)

Limited Available Data for Exposure Estimation

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



Understanding Exposure is a Systems Problem



- **Exposure event unobservable:** Can try to predict exposure by characterizing pathway
- Some pathways have much higher average exposures: In home "Near field" sources significant (Wallace, *et al.,* 1987)

New Approach Methodologies 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)

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)

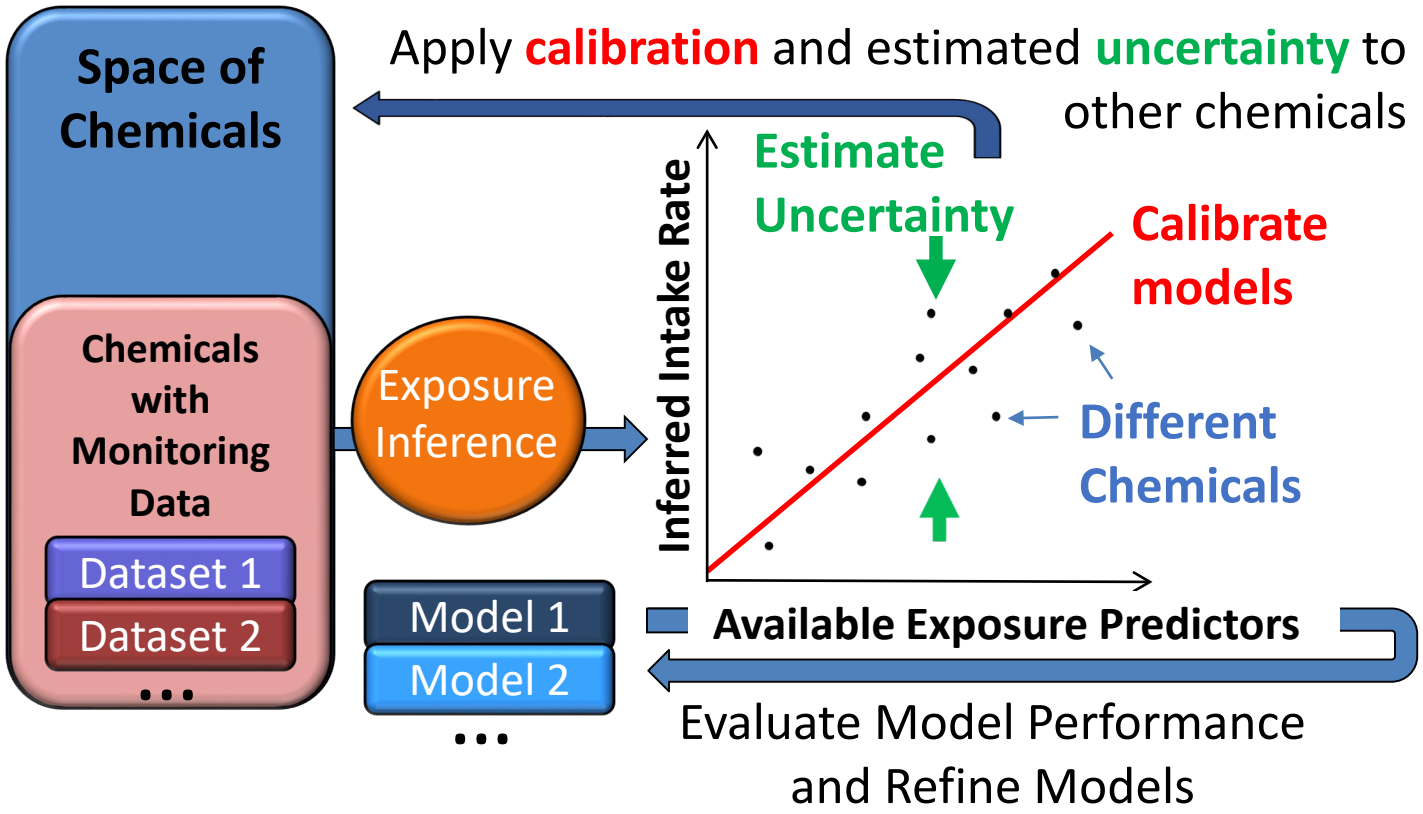
- EPA's EXPOsure toolBOX (EPA ExpoBox) is a toolbox created to assist individuals from within government, industry, academia, and the general public with assessing exposure
  - Includes many, many models

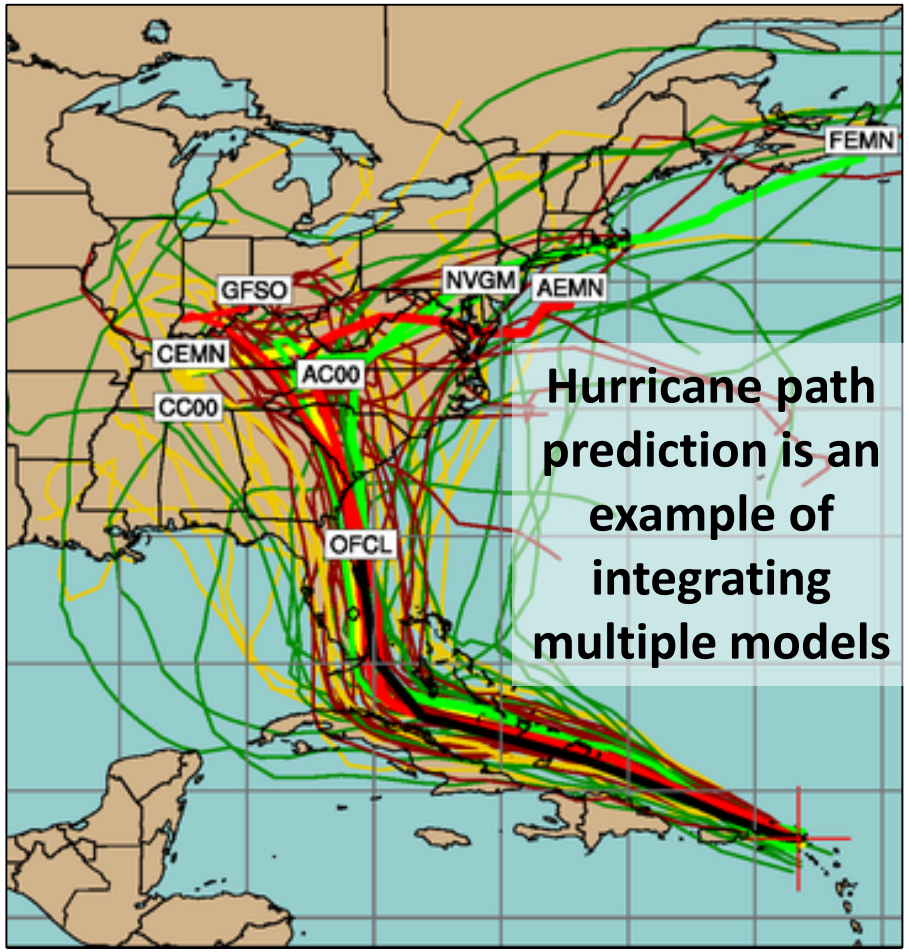
  https://www.epa.gov/expobox

"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

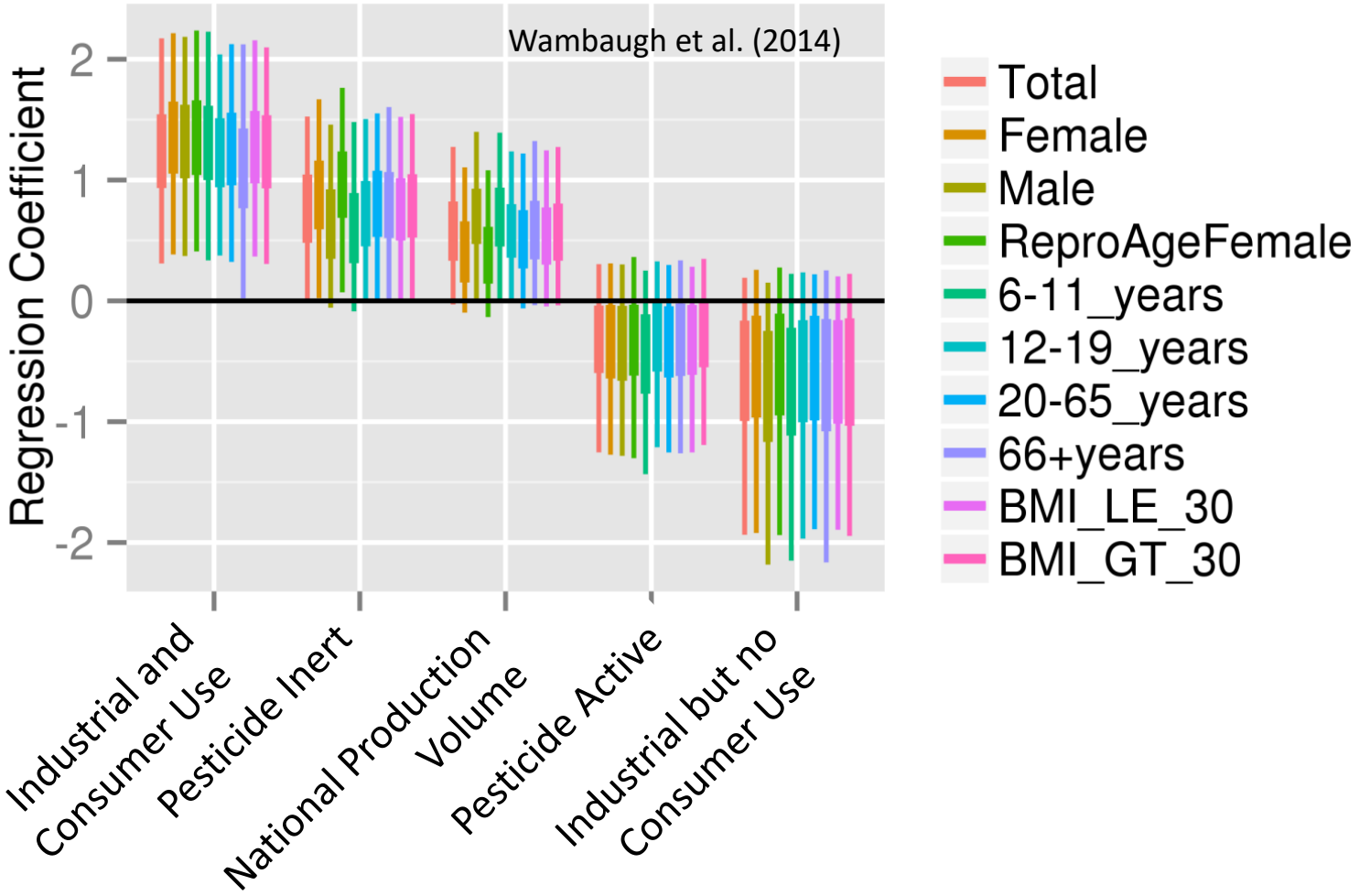
Evaluation NAMs: The SEEM Framework

- 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)





Heuristics of Exposure



$R^2 \approx 0.5$ indicates that we can predict 50% of the chemical to chemical variability in median NHANES exposure rates

Same five predictors work for all NHANES demographic groups analyzed – stratified by age, sex, and body-mass index:

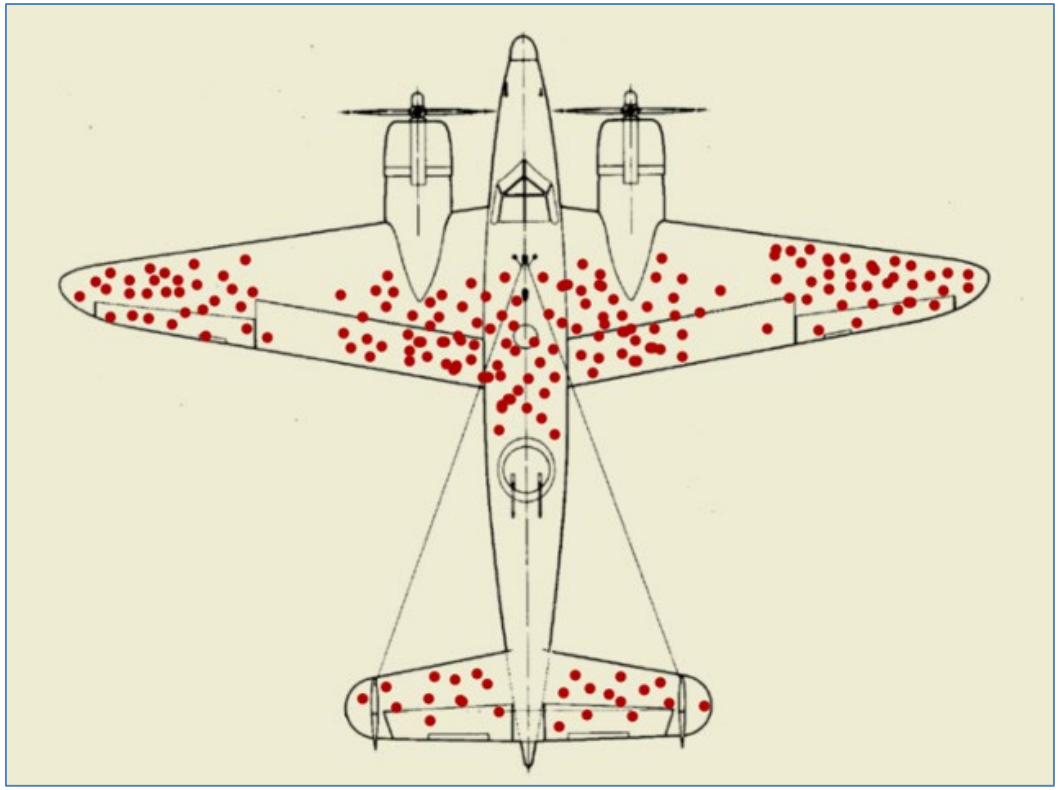
- Industrial and Consumer use
- Pesticide Inert
- Pesticide Active
- Industrial but no Consumer use
- Production Volume

Correlation is Not Causation

- Wambaugh et al. (2014) found that “pesticide inerts” had higher than average levels in biomonitoring data, while “pesticide actives” had lower than average

- In World War II, there Royal Air Force (UK) wanted to armor planes against anti-aircraft fire
  - Initial proposal was to place armor wherever bullet holes were most common
  - Mathematician Abraham Wald pointed out that they were looking at the planes that had returned
  - *See Drum, Kevin (2010) “The Counterintuitive World”*

- Pesticide inerts have many other uses, but there are more stringent reporting requirements for pesticides
  - **Exposure is occuring by other pathways**

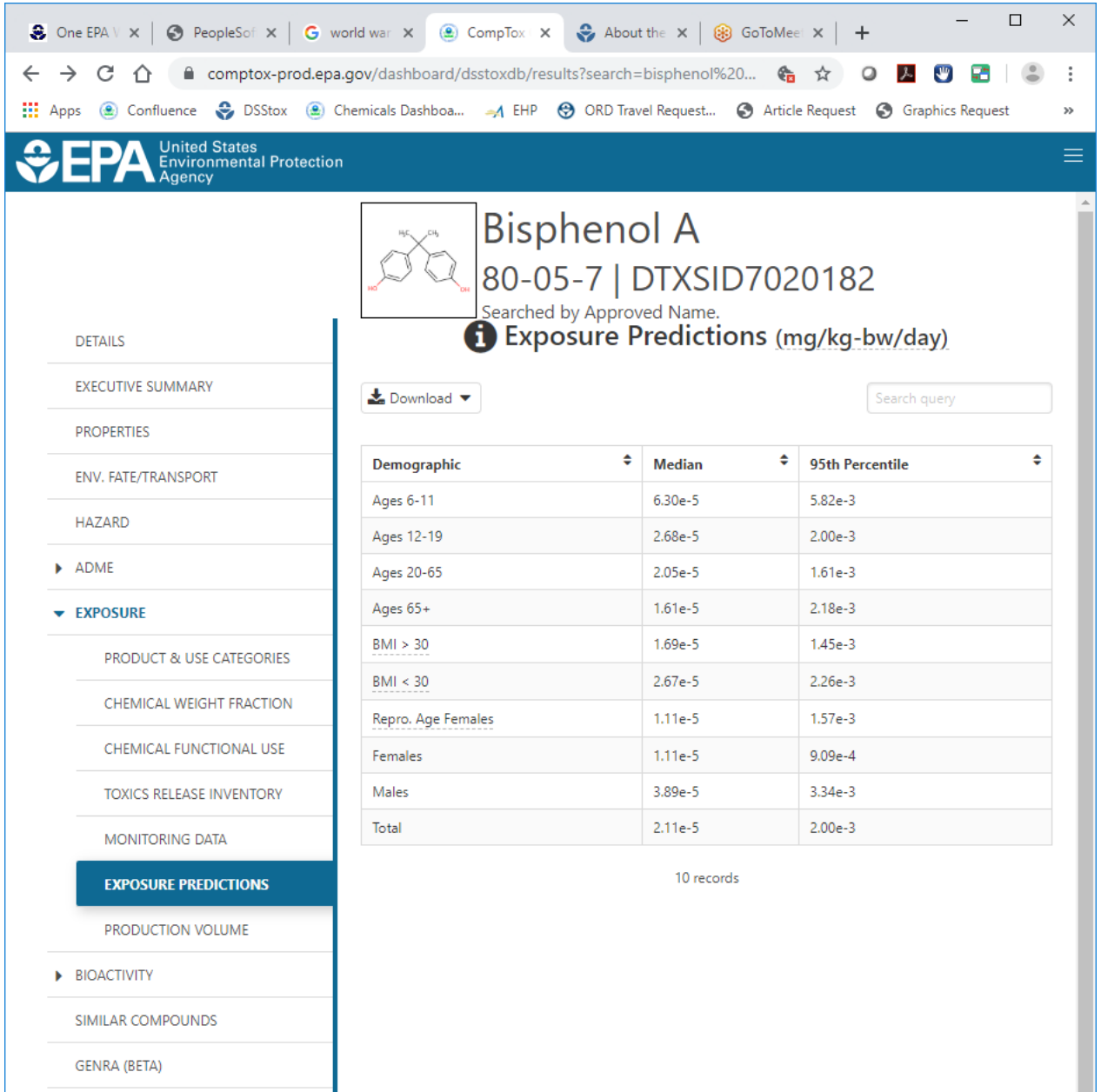


Chemical Dashboard Provides SEEM Predictions

United States Environmental Protection Agency

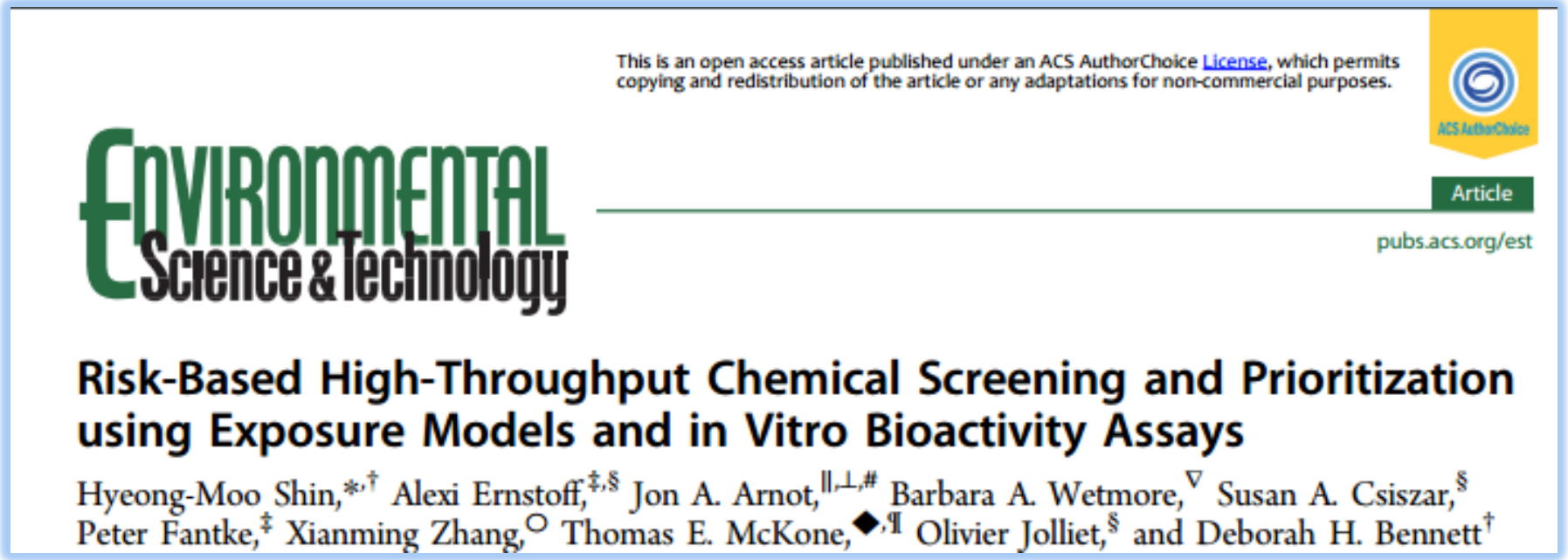
- Currently only have SEEM2 exposure predictions from Wambaugh et al. (2014) on dashboard
- Working to include SEEM3 in future dashboard release
- SEEM3 Predictions can be obtained from Ring et al. (2018) Supporting Information:

https://pubs.acs.org/doi/10.1021/acs.est.8b04056



Knowledge of Exposure Pathways Limits High Throughput Exposure Models

"In particular, the assumption that 100% of [quantity emitted, applied, or ingested] is being applied to each individual use scenario is a very conservative assumption for many compound / use scenario pairs."



Environmental Science & Technology

Article

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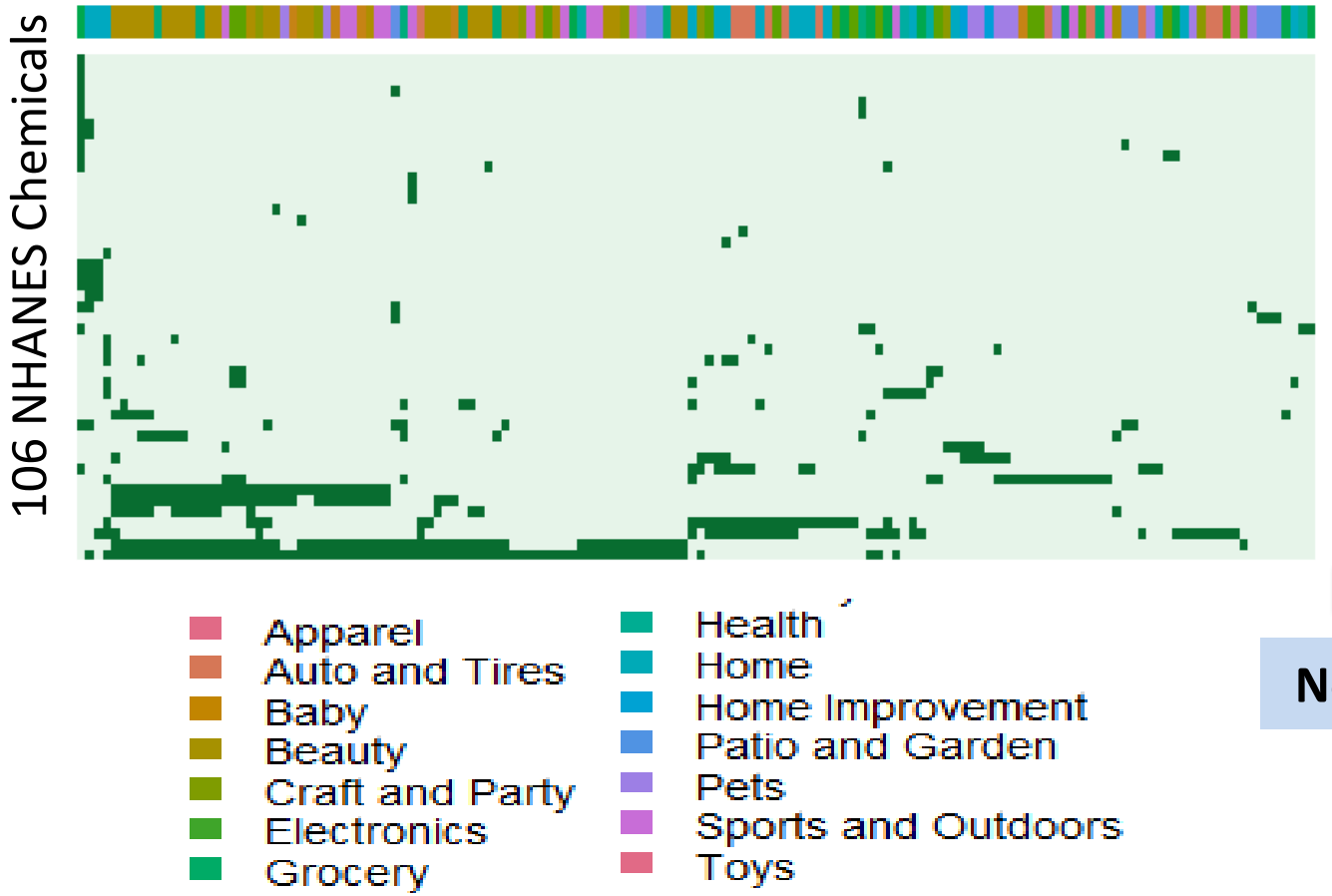
Risk-Based High-Throughput Chemical Screening and Prioritization using Exposure Models and in Vitro Bioactivity Assays

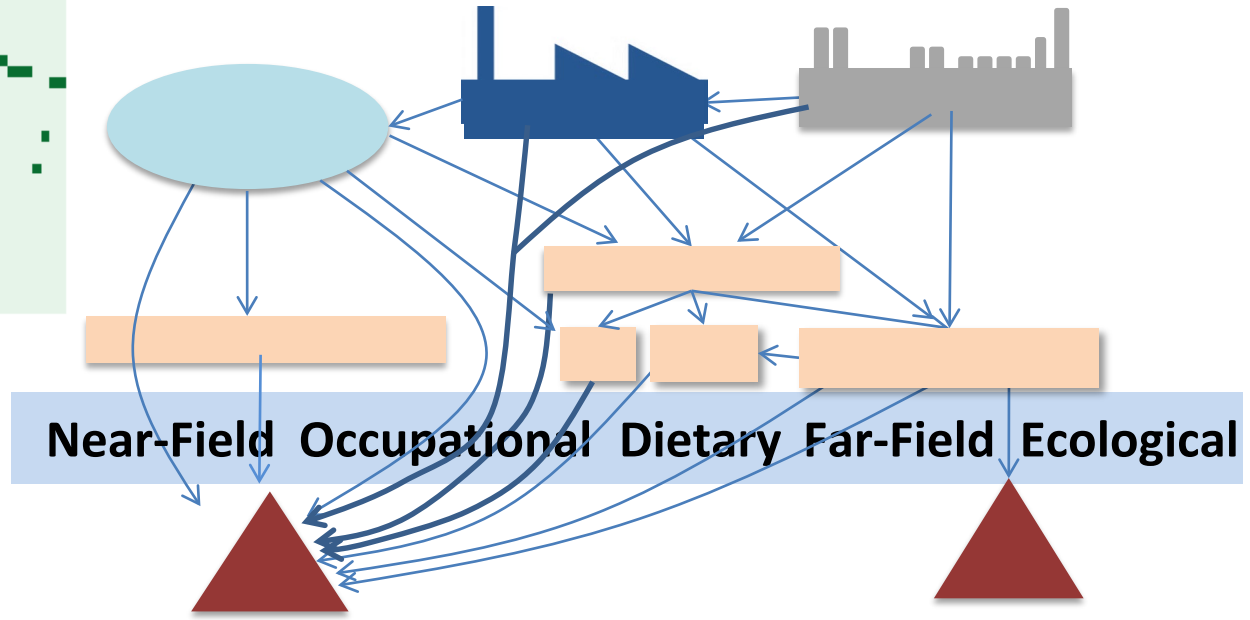
Hyeong-Moo Shin,[*,†] Alexi Ernstoff,[‡,§] Jon A. Arnot,[∥,⊥,#] Barbara A. Wetmore,[▽] Susan A. Csiszar,[§] Peter Fantke,[‡] Xianming Zhang,[○] Thomas E. McKone,[◆,¶] Olivier Jolliet,[§] and Deborah H. Bennett[†]

Chemical Use Identifies Relevant Pathways

>2000 chemicals with Material Safety Data Sheets (MSDS) in CPCPdb (Goldsmith *et al.*, 2014)



Some pathways have much higher average exposures!



Near field sources have been known to be important at least since 1987 – see Wallace, *et al.*

Chemical Property NAMs

United States Environmental Protection Agency


Contents lists available at ScienceDirect

Food and Chemical Toxicology

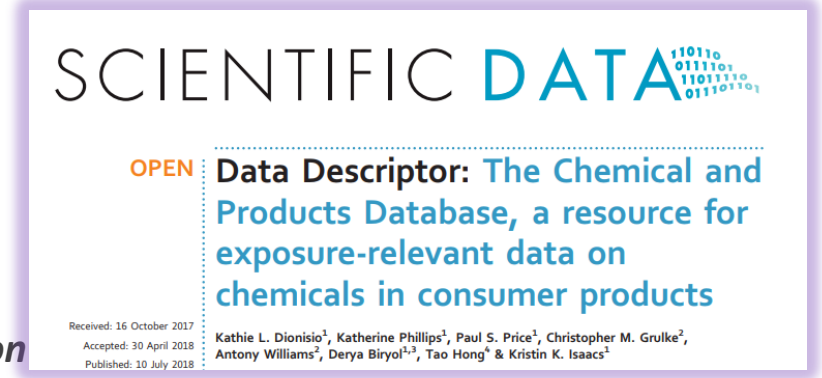
journal homepage: www.elsevier.com/locate/foodchemtox

Development of a consumer product ingredient database for chemical exposure screening and prioritization

M.-R. Goldsmith[a,*], C.M. Grulke[a], R.D. Brooks[b], T.R. Transue[c], Y.M. Tan[a], A. Frame[a,e], P.P. Egeghy[a], R. Edwards[d], D.T. Chang[a], R. Tornero-Velez[a], K. Isaacs[a], A. Wang[a,e], J. Johnson[a], K. Holm[a], M. Reich[f], J. Mitchell[g], D.A. Vallero[a], L. Phillips[a], M. Phillips[a], J.F. Wambaugh[a], R.S. Judson[a], T.J. Buckley[a], C.C. Dary[a]

MSDS Data

Occurrence and quantitative chemical composition


SCIENTIFIC DATA

OPEN

Data Descriptor: The Chemical and Products Database, a resource for exposure-relevant data on chemicals in consumer products

Received: 16 October 2017
Accepted: 30 April 2018
Published: 10 July 2018

Kathie L. Dionisio[1], Katherine Phillips[1], Paul S. Price[1], Christopher M. Grulke[2], Antony Williams[2], Derya Biryol[1,3], Tao Hong[4] & Kristin K. Isaacs[1]

Broad "index" of chemical uses


Contents lists available at ScienceDirect

Toxicology Reports

journal homepage: www.elsevier.com/locate/toxrep

Exploring consumer exposure pathways and patterns of use for chemicals in the environment

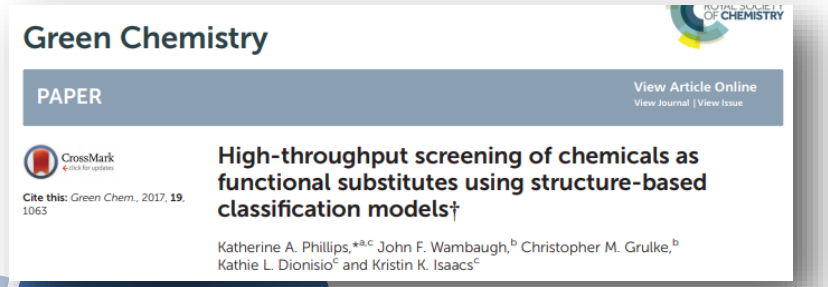
Kathie L. Dionisio[a], Alicia M. Frame[b,1], Michael-Rock Goldsmith[a,2], John F. Wambaugh[b], Alan Liddell[c,3], Tommy Cathey[d], Doris Smith[b], James Vail[b], Alexi S. Ernstoff[e], Peter Fantke[e], Olivier Jolliet[f],

CPCat

CPDat

EPA United States Environmental Protection Agency

Chemistry Dashboard


Green Chemistry

PAPER

View Article Online

High-throughput screening of chemicals as functional substitutes using structure-based classification models†

Cite this: Green Chem., 2017, 19, 1063

Katherine A. Phillips,*[a,c] John F. Wambaugh,[b] Christopher M. Grulke,[b] Kathie L. Dionisio[c] and Kristin K. Isaacs[c]

Functional Use Data

The roles that chemicals serve in products

Ingredient Lists


Journal of Exposure Science and Environmental Epidemiology (2018) 28, 216–222

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www.nature.com/jes

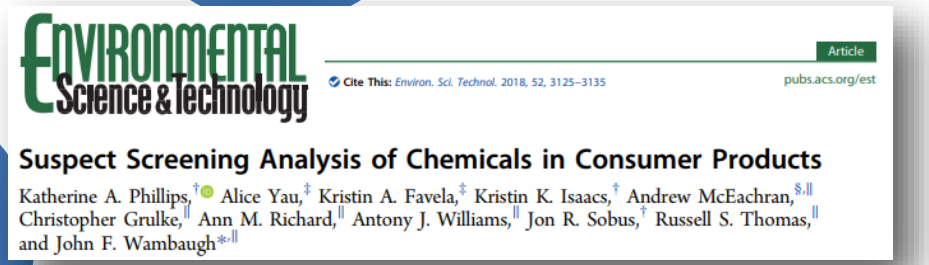
ORIGINAL ARTICLE

Consumer product chemical weight fractions from ingredient lists

Kristin K. Isaacs[1], Katherine A. Phillips[1], Derya Biryol[1,2], Kathie L. Dionisio[1] and Paul S. Price[1]

Occurrence data

Measured Data


Environmental Science & Technology

Article

Cite This: Environ. Sci. Technol. 2018, 52, 3125–3135

pubs.acs.org/est

Suspect Screening Analysis of Chemicals in Consumer Products

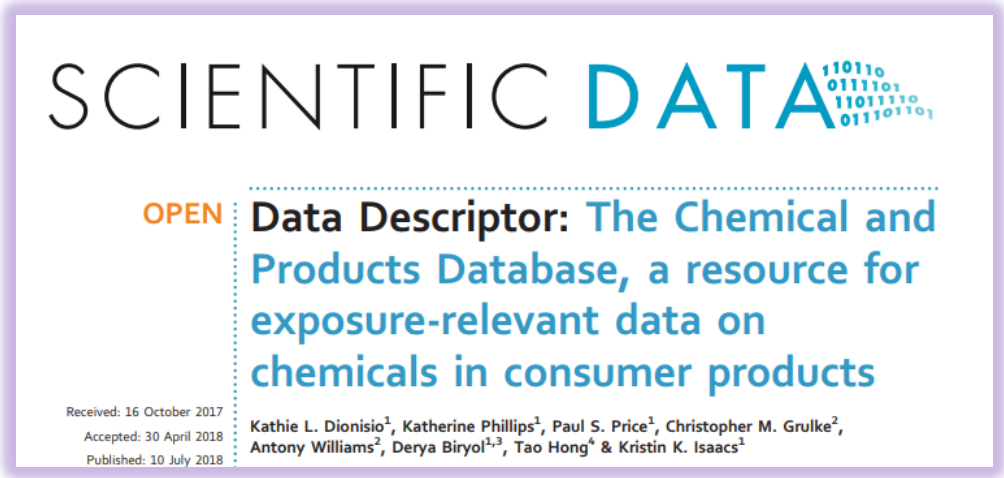
Katherine A. Phillips,[†] Alice Yau,[‡] Kristin A. Favela,[‡] Kristin K. Isaacs,[†] Andrew McEachran,[§,∥] Christopher Grulke,[∥] Ann M. Richard,[∥] Antony J. Williams,[∥] Jon R. Sobus,[†] Russell S. Thomas,[∥] and John F. Wambaugh*[,∥]

Measurement of chemicals in consumer products

https://comptox.epa.gov/dashboard

Chemical Dashboard Provides Use Information

- CPdat: The Chemical and Products Database (Dionisio, et al. 2018)
- Curated information on the occurrence of chemicals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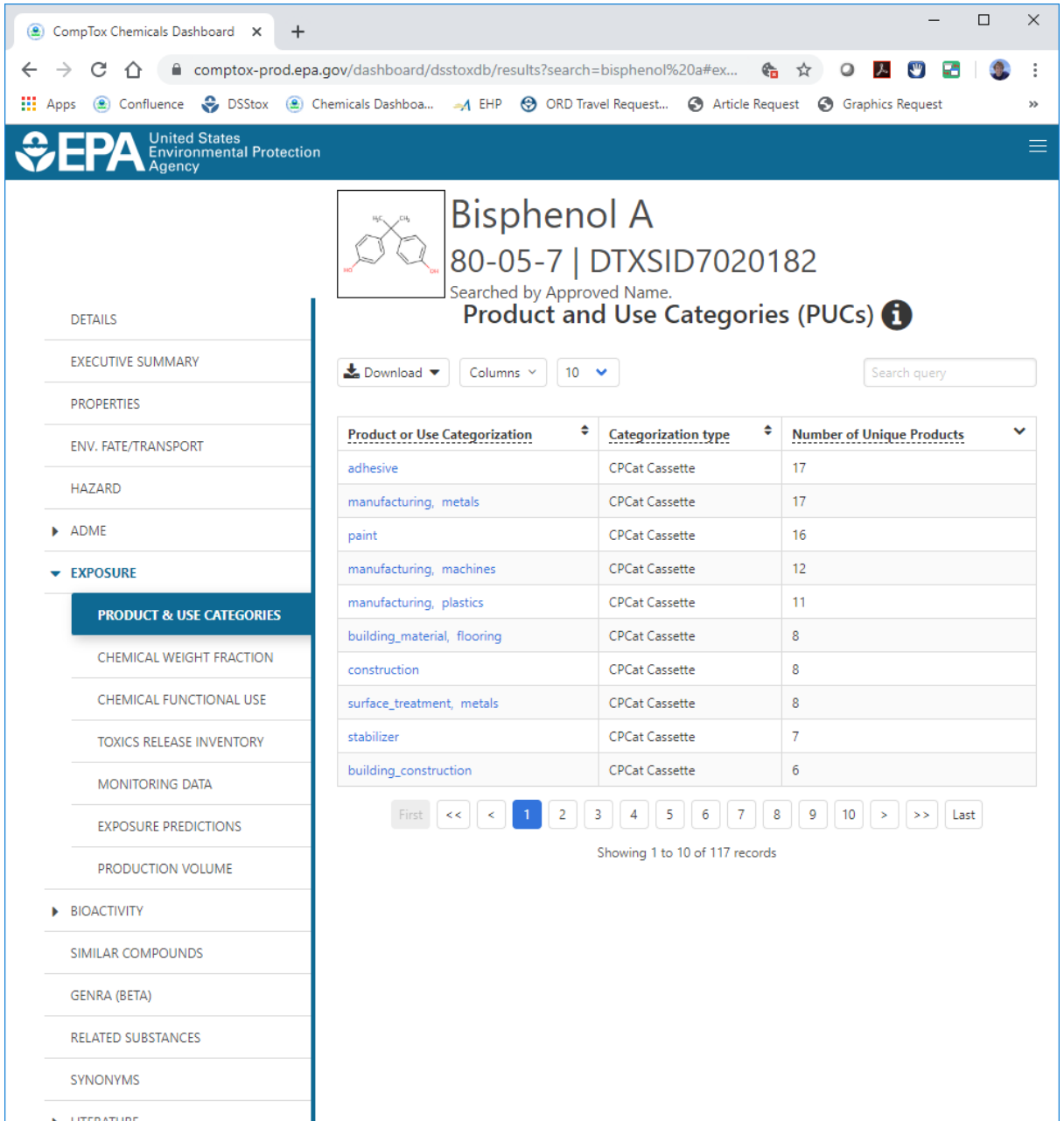
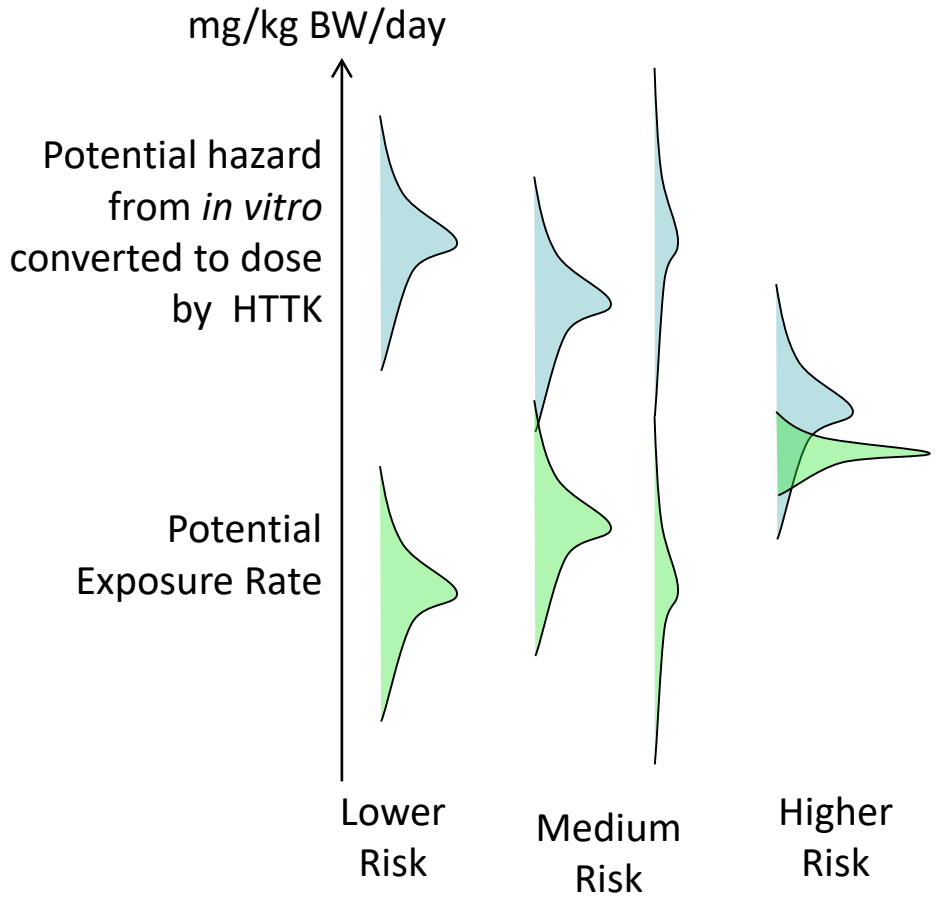


Summary

- A tapestry of laws covers the chemicals people are exposed to in the United States (Breyer, 2009)
- Most other 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
- All data are being made public:
  - The CompTox Chemicals Dashboard (A search engine for chemicals) http://comptox.epa.gov/
  - R package "httk": https://CRAN.R-project.org/package=httk



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

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References

- Cohen Hubal, EA, et al. "Advancing internal exposure and physiologically-based toxicokinetic modeling for 21st-century risk assessments." Journal of exposure science & environmental epidemiology (2018).
- Eissing, Thomas, et al. "A computational systems biology software platform for multiscale modeling and simulation: integrating whole-body physiology, disease biology, and molecular reaction networks." Frontiers in physiology 2 (2011): 4.
- Frank, Christopher L., et al. "Defining toxicological tipping points in neuronal network development." Toxicology and applied pharmacology 354 (2018): 81-93.
- Honda, Gregory S., et al. "Using the concordance of in vitro and in vivo data to evaluate extrapolation assumptions." PloS one 14.5 (2019): e0217564.
- Jamei, et al. “The Simcyp® population-based ADME simulator.” Expert opinion on drug metabolism & toxicology 2009b;5:211-223
- Jongeneelen, Frans J., and Wil F. Ten Berge. "A generic, cross-chemical predictive PBTK model with multiple entry routes running as application in MS Excel; design of the model and comparison of predictions with experimental results." Annals of occupational hygiene 55.8 (2011): 841-864.
- Lukacova, Viera, Walter S. Woltosz, and Michael B. Bolger.
- Breyer, Stephen. Breaking the vicious circle: Toward effective risk regulation. Harvard University Press, 2009
- Collins FS, Gray GM, Bucher JR. Transforming environmental health protection. Science. 2008;319:906–907. [PMC free article] [PubMed]
- Dix David, et al. “The ToxCast program for prioritizing toxicity testing of environmental chemicals.” Toxicol Sci. 2007;95:5–12
- Egeghy, P. P., et al. (2012). The exposure data landscape for manufactured chemicals. Science of the Total Environment, 414, 159-166.
- Judson, Richard S., et al. "In vitro screening of environmental chemicals for targeted testing prioritization: the ToxCast project." Environmental health perspectives 118.4 (2009): 485-492.
- Kavlock, R. J., et al. (2018). Accelerating the pace of chemical risk assessment. Chemical research in toxicology, 31(5), 287-290.
- Mansouri, Kamel, et al. "OPERA models for predicting physicochemical properties and environmental fate endpoints." Journal of cheminformatics 10.1 (2018): 10.
- McLanahan, Eva D., et al. "Physiologically based pharmacokinetic model use in risk assessment—why being published is not enough." Toxicological Sciences 126.1 (2011): 5-15.
- Breyer, Stephen. Breaking the vicious circle: Toward effective risk regulation. Harvard University Press, 2009
- Egeghy, P. P., et al. (2012). The exposure data landscape for manufactured chemicals. Science of the Total Environment, 414, 159-166.
- Filer, Dayne L.. "The ToxCast analysis pipeline: An R package for processing and modeling chemical screening data." US Environmental Protection Agency: http://www. epa. gov/ncct/toxcast/files/MySQL% 20Database/Pipeline_Overview. pdf (2014)
- Hertzberg, R. P., & Pope, A. J. (2000). High-throughput screening: new technology for the 21st century. Current opinion in chemical biology, 4(4), 445-451.
- Ingle, Brandall L., et al. "Informing the Human Plasma Protein Binding of Environmental Chemicals by Machine Learning in the Pharmaceutical Space: Applicability Domain and Limits of Predictability." Journal of Chemical Information and Modeling 56.11 (2016): 2243-2252.
- Jamei, et al. “The Simcyp® population-based ADME simulator.” Expert opinion on drug metabolism & toxicology 2009;5:211-223
- Kaewkhaw, R., et al. (2016). Treatment paradigms for retinal and macular diseases using 3-D retina cultures derived from human reporter pluripotent stem cell linestreatment design using PSC-Derived 3-D retina cultures. Investigative ophthalmology & visual science, 57(5), ORSFl1-ORSFl11.
- Kavlock, Robert, et al. "Update on EPA’s ToxCast program: providing high throughput decision support tools for chemical risk management." Chemical research in