

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



Credit: the Research Triangle Foundation

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)

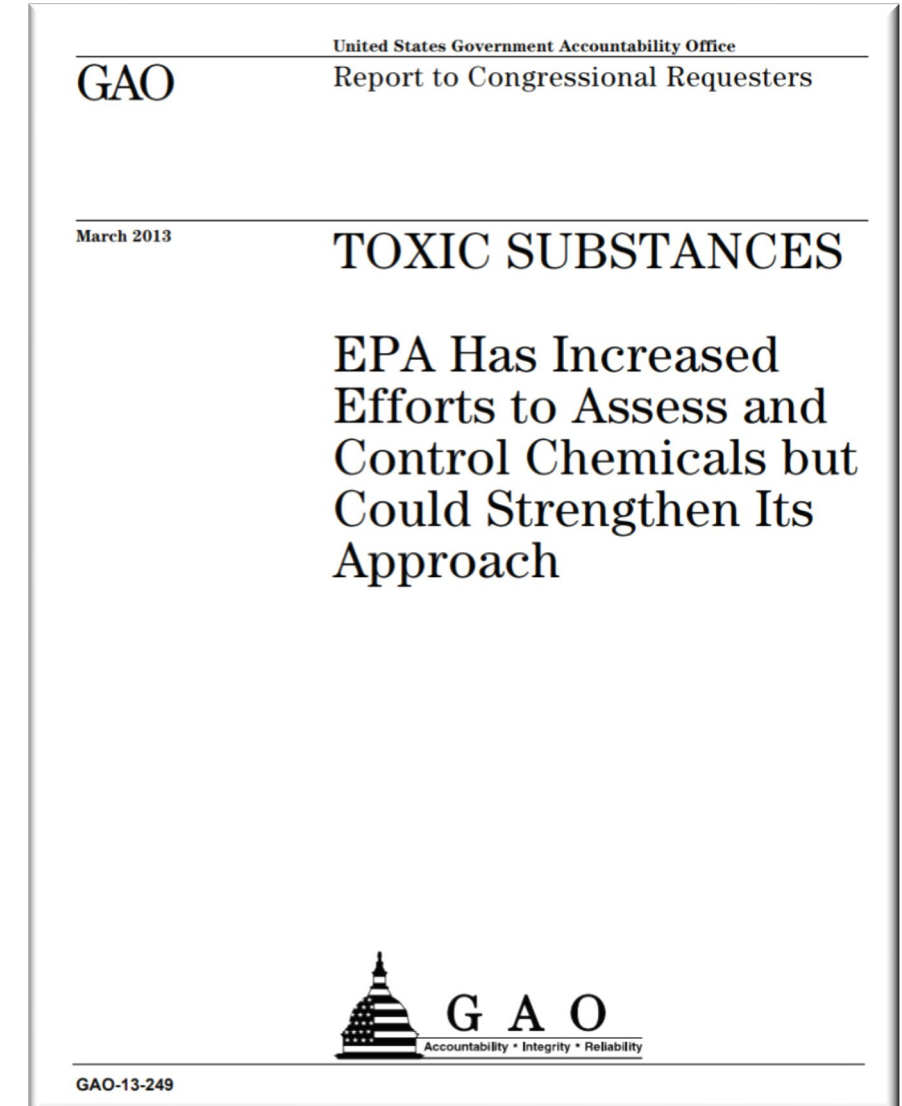


Chemical Regulation in the United States

- 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.”

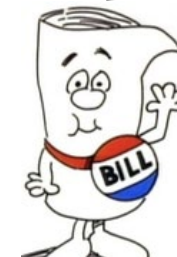
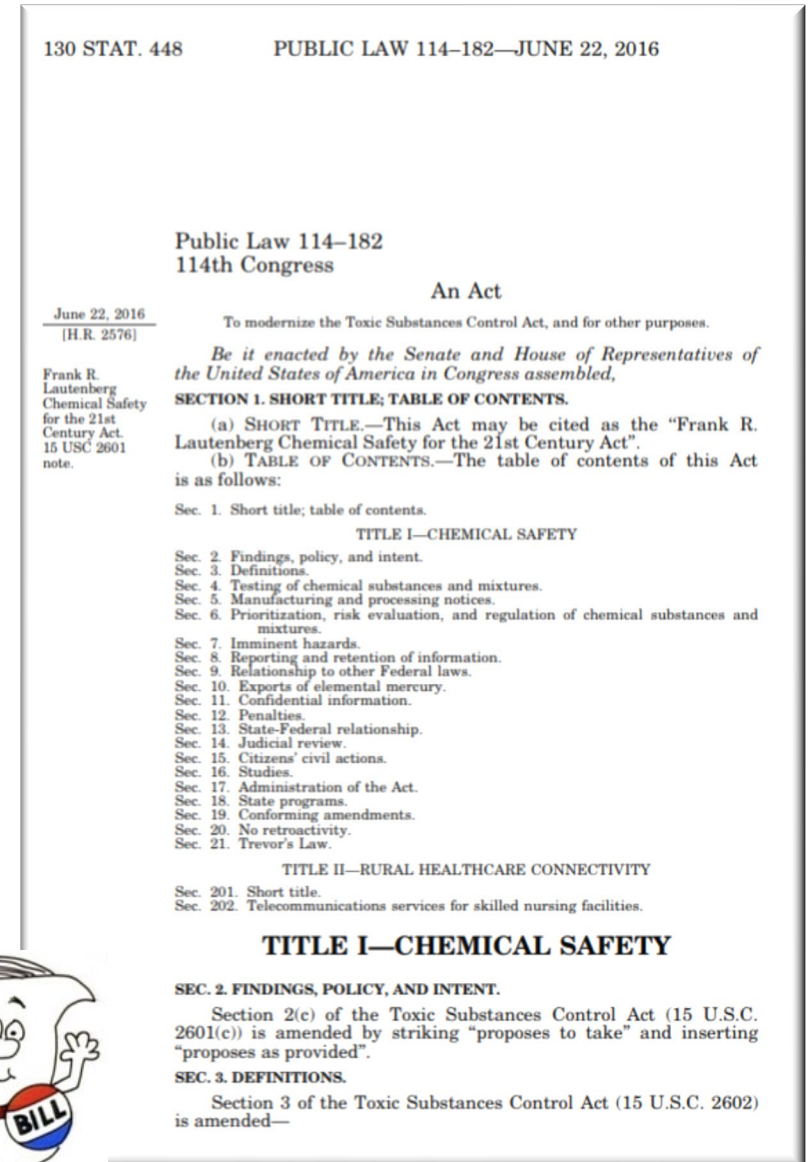
U.S. Government Accountability Office



March, 2013

Chemical Regulation in the United States

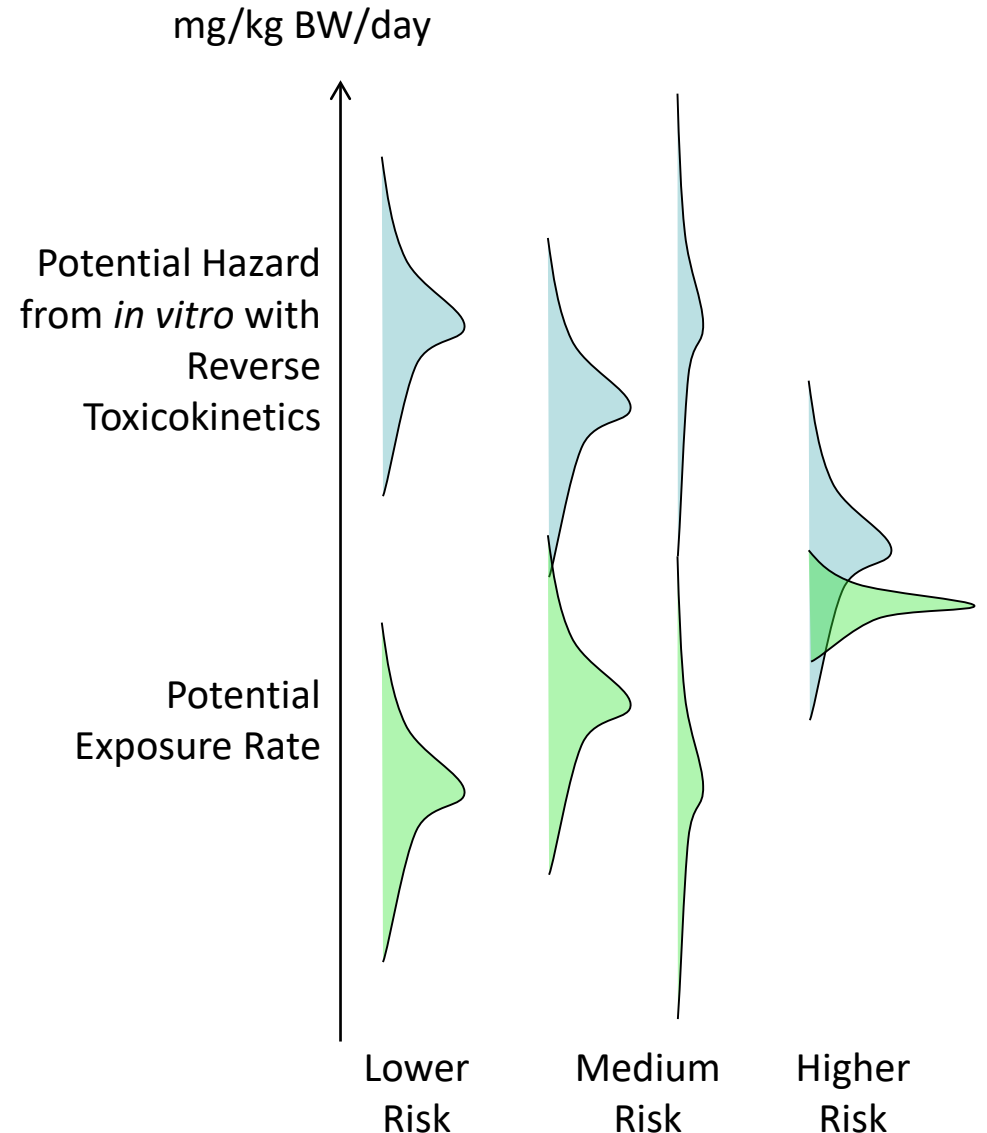
- TSCA was updated in June, 2016 to allow more rapid evaluation of chemicals (Frank R. Lautenberg Chemical Safety for the 21st Century Act)
- New approach methodologies (NAMs) are being considered to inform prioritization of chemicals for testing and evaluation (Kavlock et al., 2018)
- EPA has released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



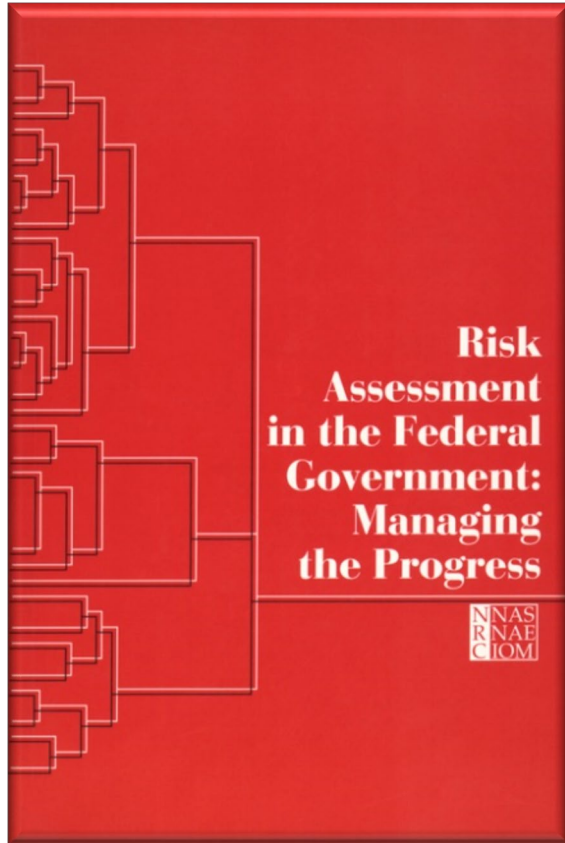
June 22, 2016

Chemical Risk = Hazard x Exposure

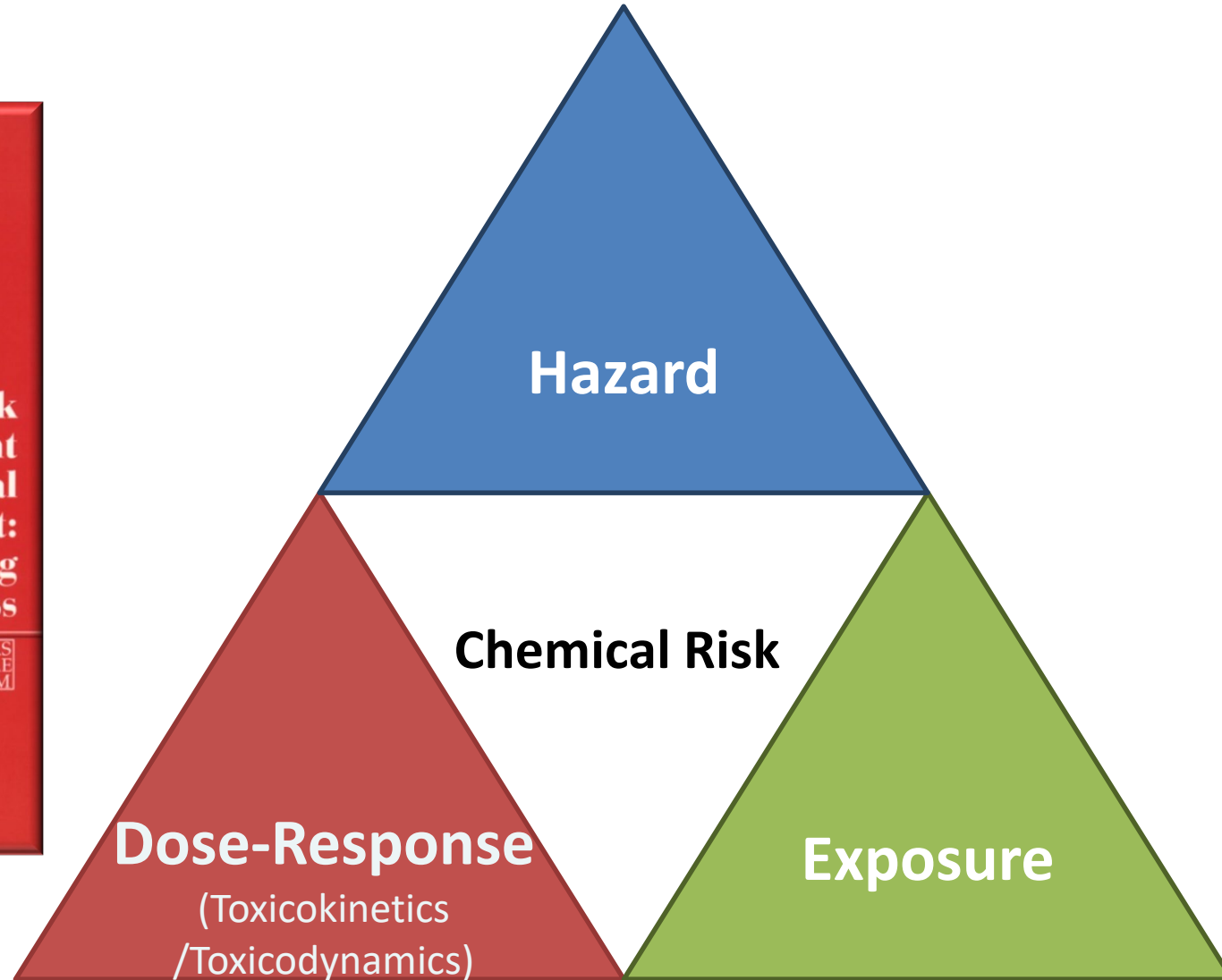
- The U.S. National Research Council (1983) identified chemical risk as a function of both inherent hazard and exposure
- To address thousands of chemicals, we need NAMs that can inform prioritization of chemicals most worthy of additional study
- High throughput risk prioritization needs:
 1. High throughput 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

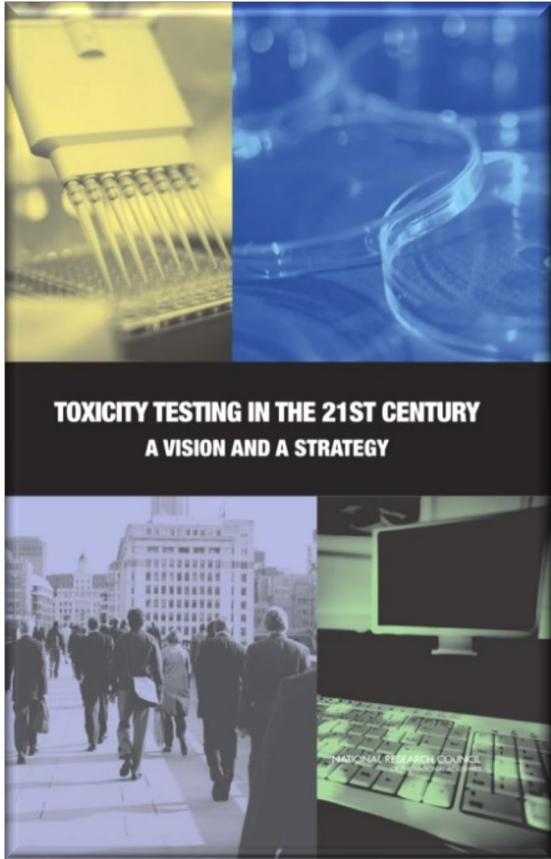


NRC (1983)

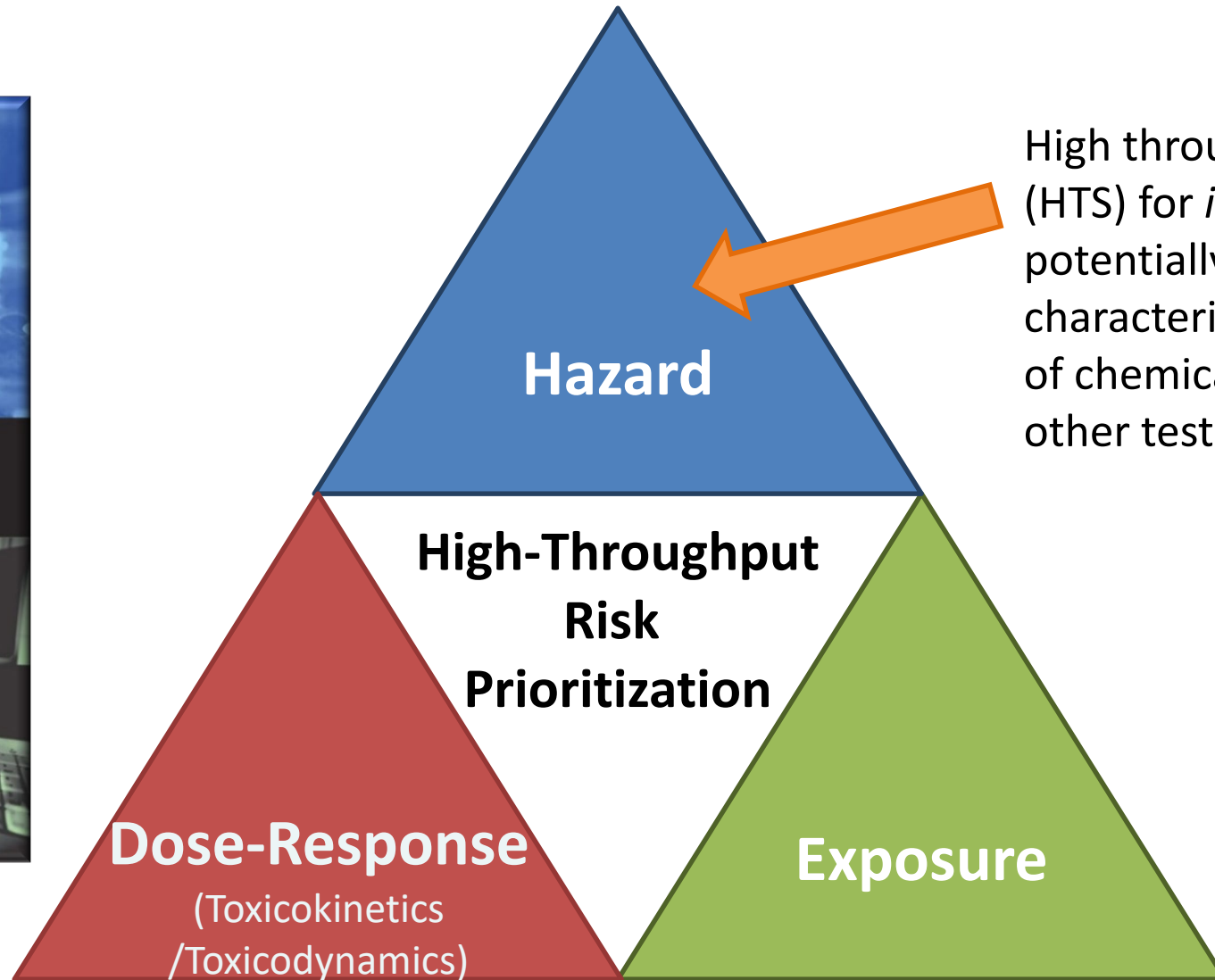


The National Academy of Sciences, Engineering and Medicine (1983) outlined three components for determining chemical risk.

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

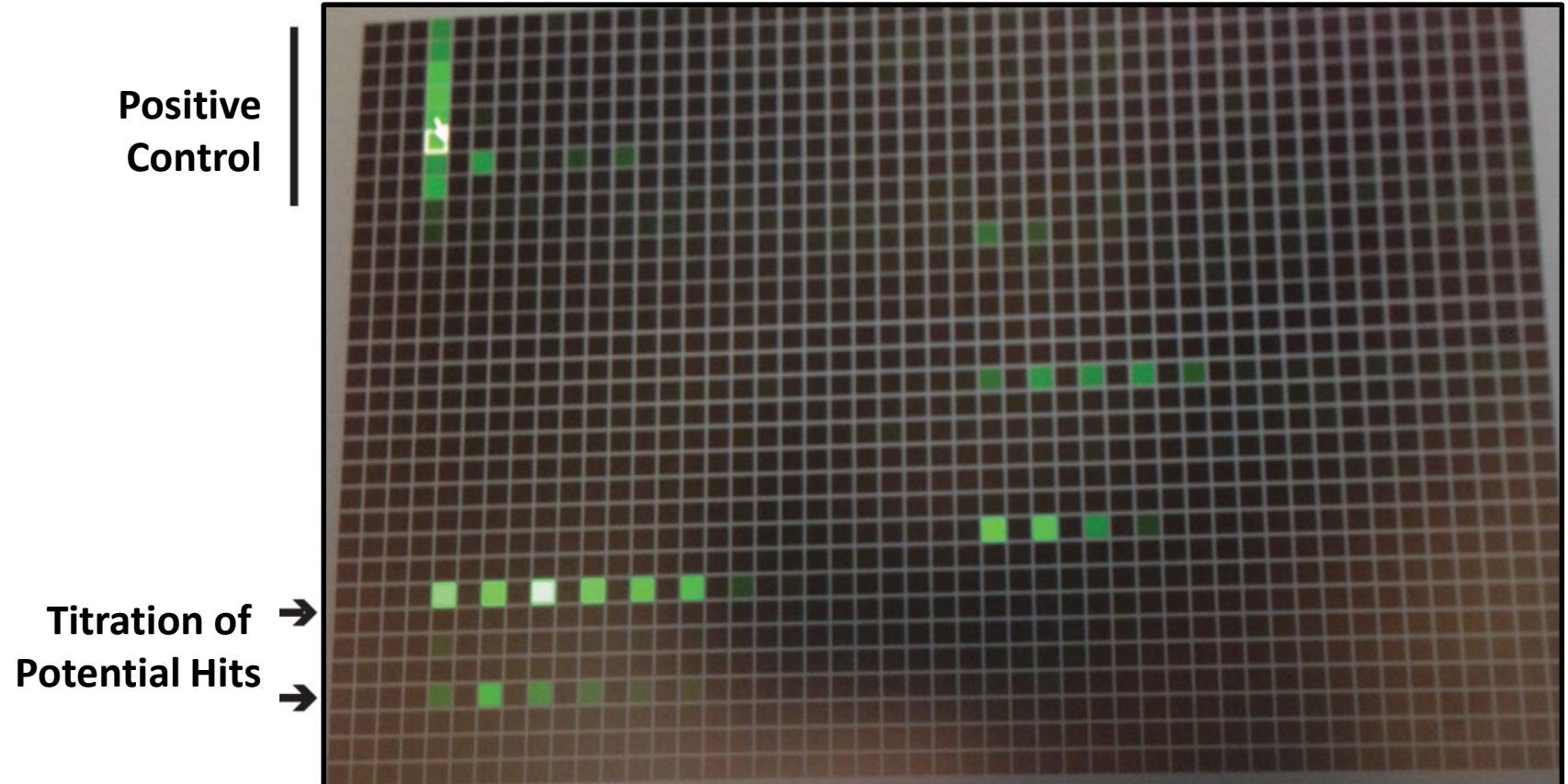
To perform high throughput risk prioritization, we need all three components

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).

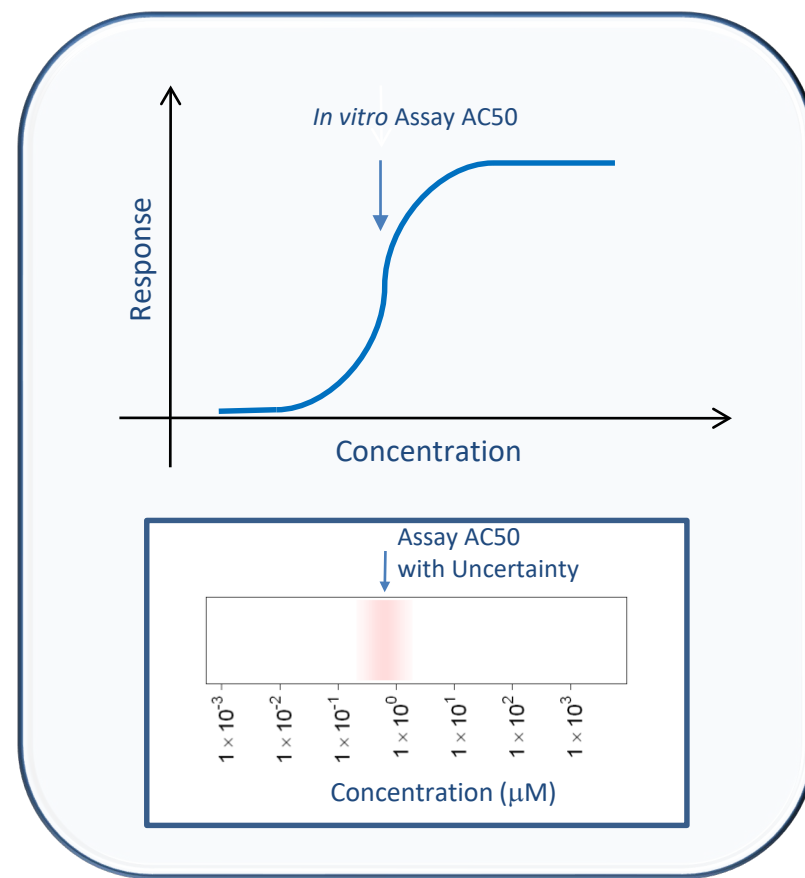
Kaewkhaw et al. (2016)



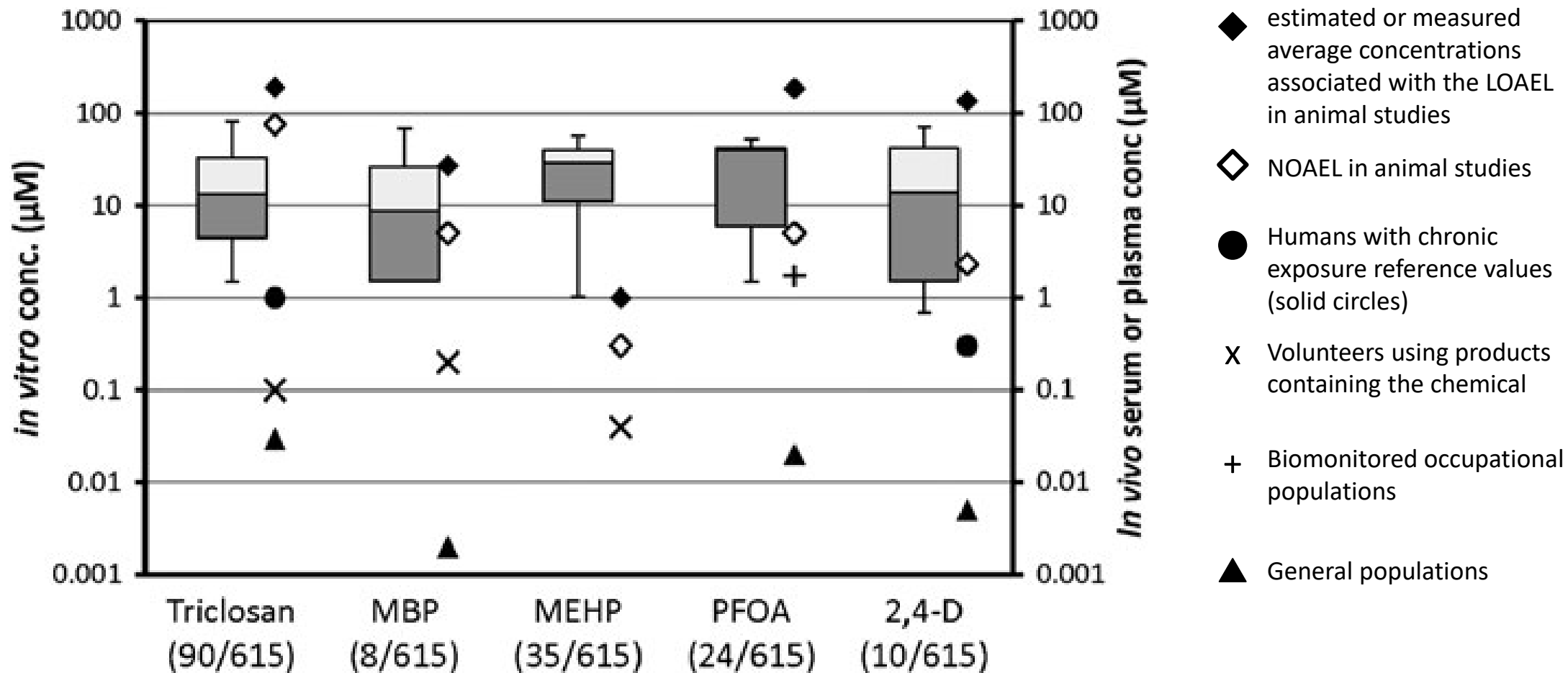
High-Throughput Bioactivity Screening Projects



- 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/>



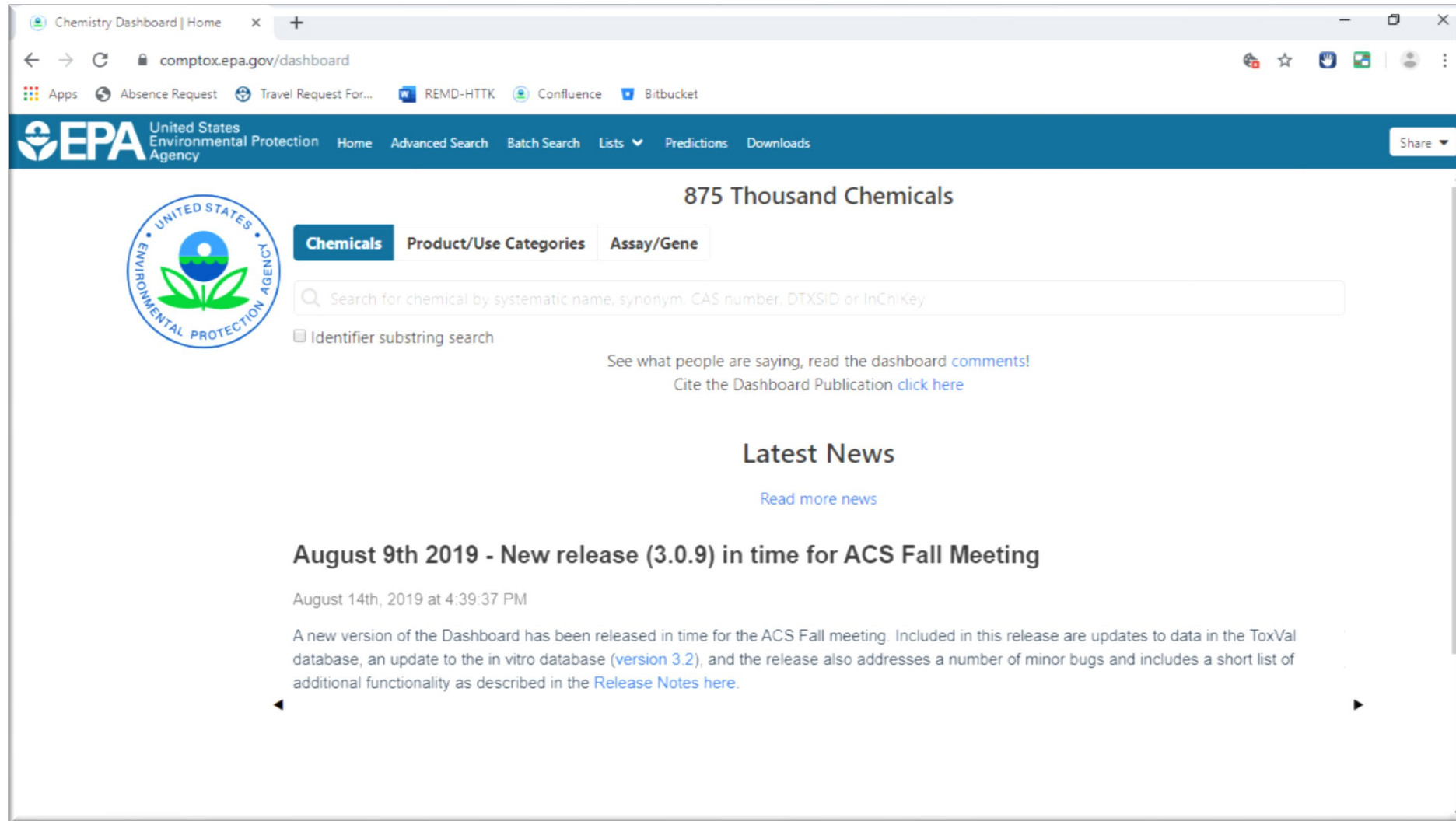
The Margin Between Exposure and Hazard



Aylward and Hays (2011)

Journal of Applied Toxicology **31** 741-751

The CompTox Chemicals Dashboard



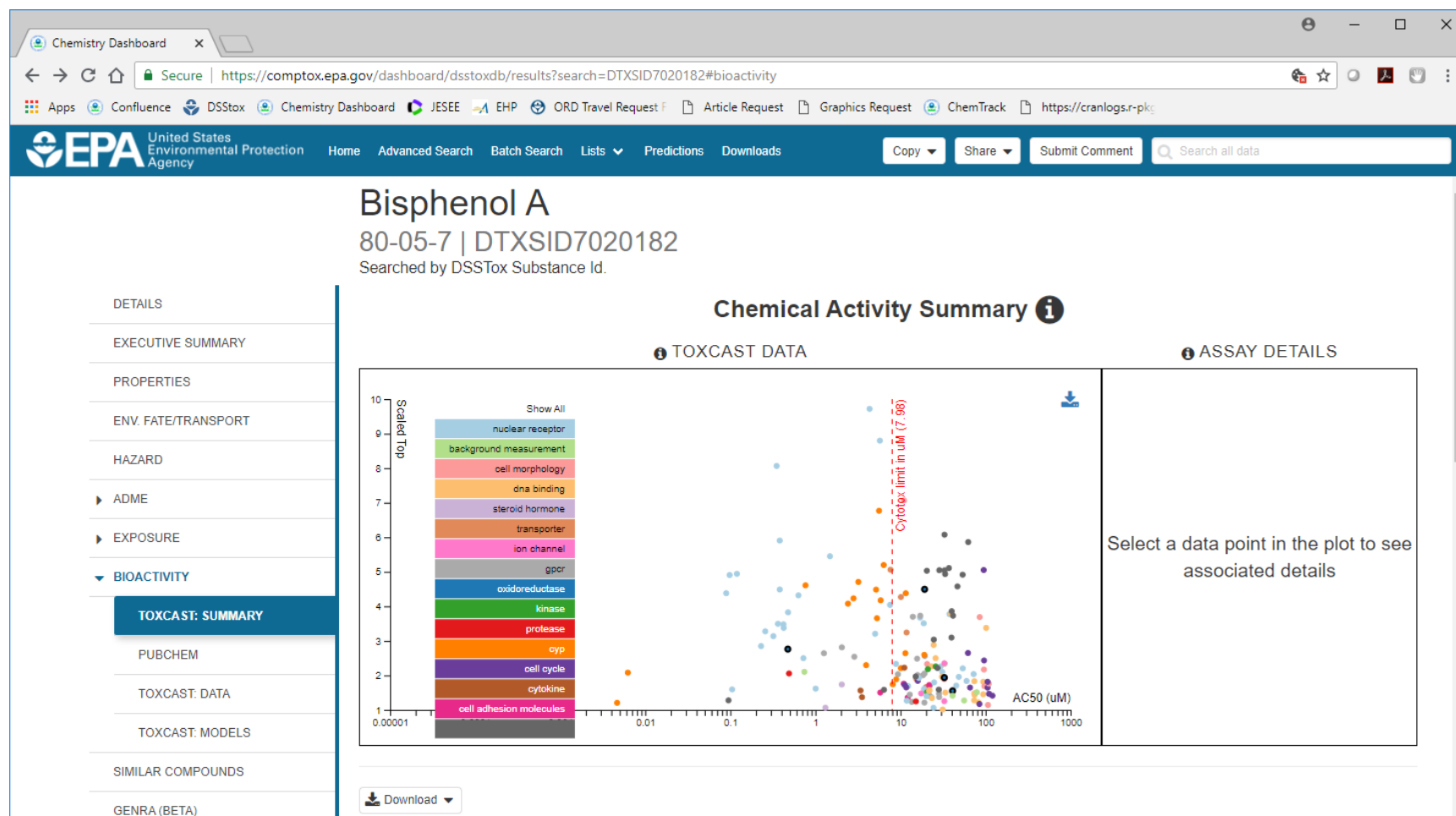
The screenshot shows a web browser window with the URL comptox.epa.gov/dashboard. The page features the EPA logo and a navigation bar with links to Home, Advanced Search, Batch Search, Lists, Predictions, and Downloads. The main content area displays "875 Thousand Chemicals" and includes tabs for "Chemicals", "Product/Use Categories", and "Assay/Gene". A search bar is present with the placeholder text "Search for chemical by systematic name, synonym, CAS number, DTXSID or InChIKey". Below the search bar, there is a checkbox for "Identifier substring search" and links to "See what people are saying, read the dashboard comments!" and "Cite the Dashboard Publication click here". The "Latest News" section features a headline "August 9th 2019 - New release (3.0.9) in time for ACS Fall Meeting" dated "August 14th, 2019 at 4:39:37 PM". The news text states: "A new version of the Dashboard has been released in time for the ACS Fall meeting. Included in this release are updates to data in the ToxVal database, an update to the in vitro database (version 3.2), and the release also addresses a number of minor bugs and includes a short list of additional functionality as described in the Release Notes here."

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

Chemical Bioactivity Data

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

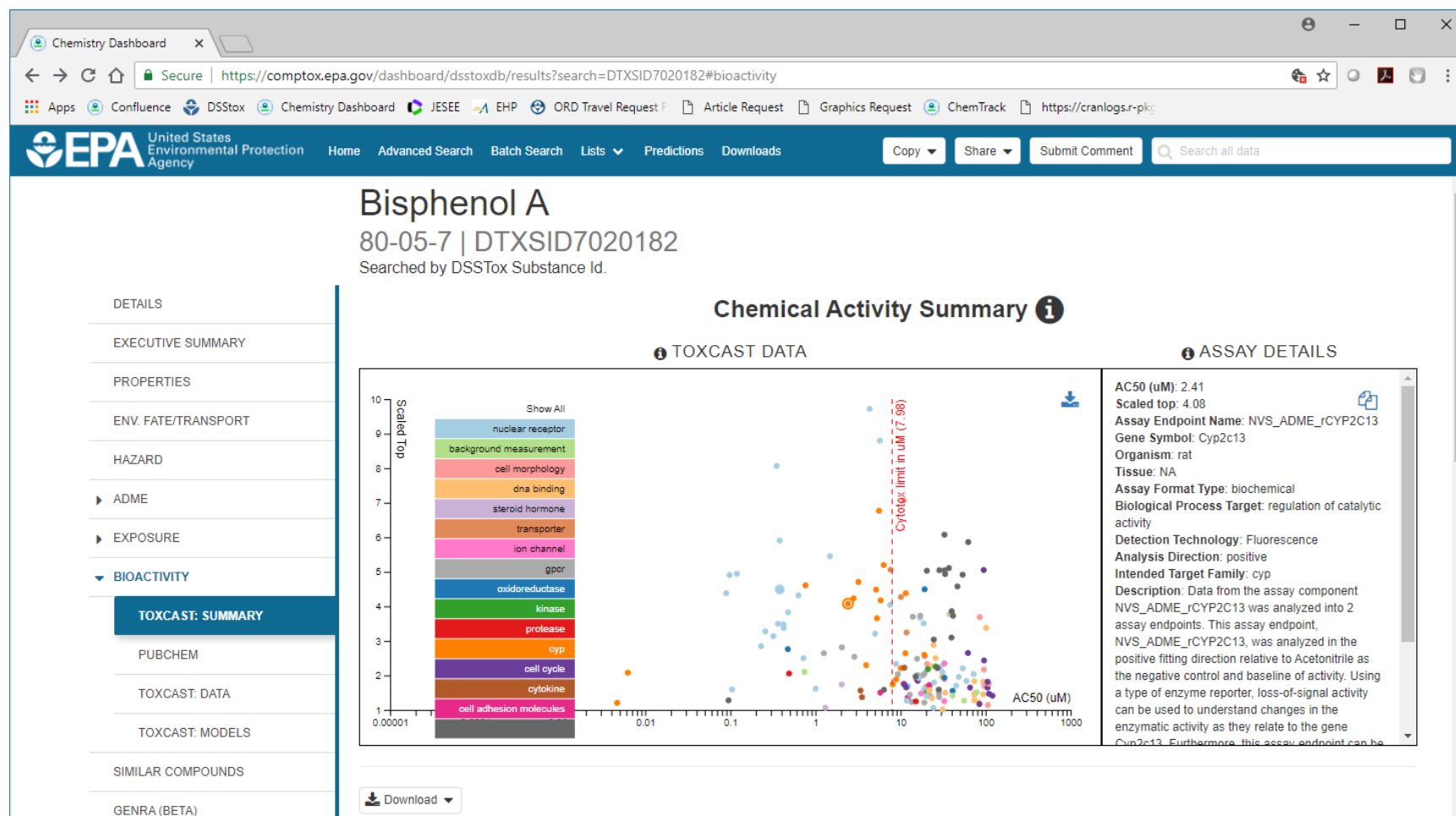
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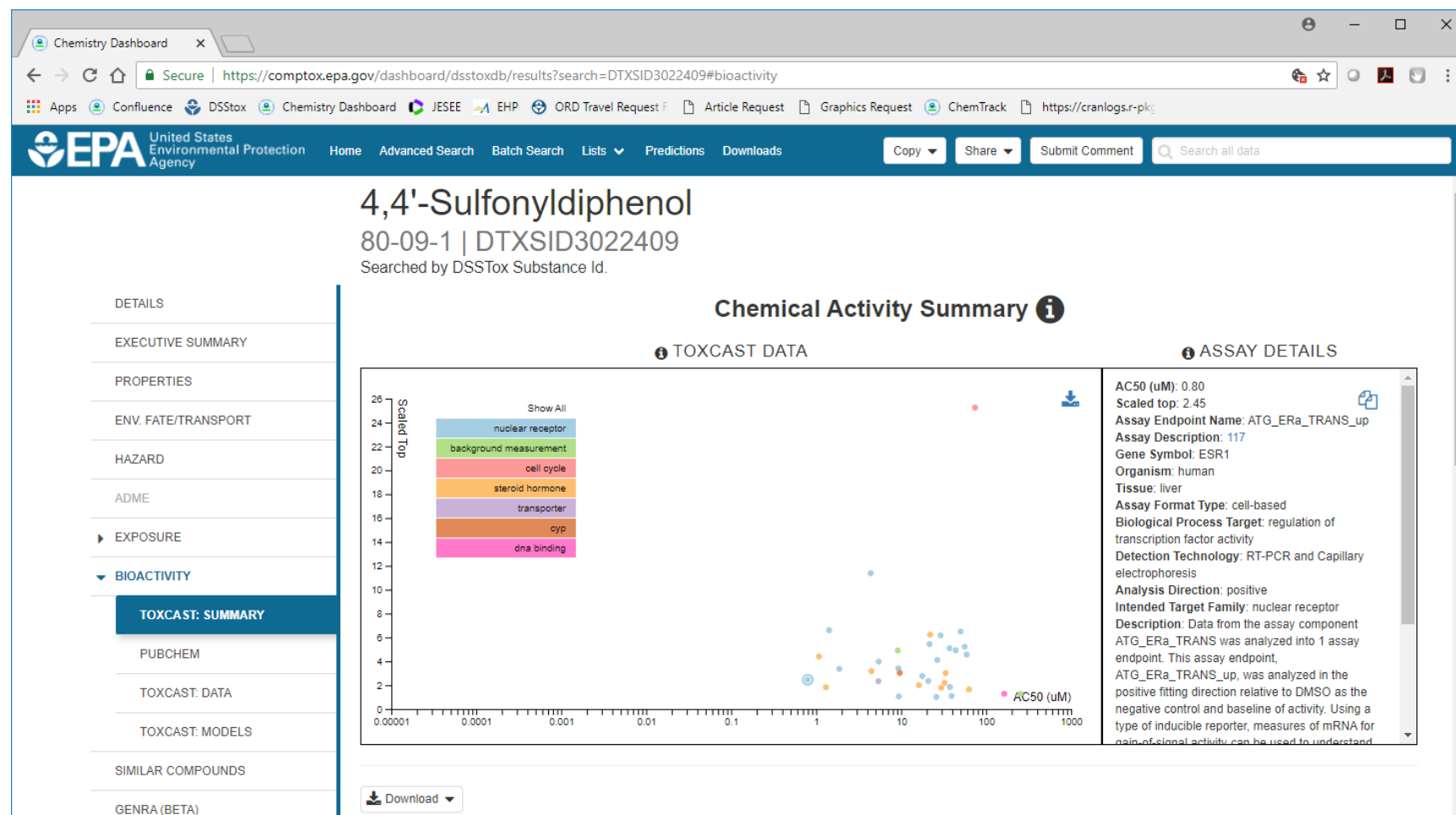
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Chemical Bioactivity Data

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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)

Chemistry Dashboard

Not secure | comptox-prod.epa.gov/dashboard/dsstoxdb/results?search=triclosan#properties

Apps Confluence DSStox Chemistry Dashboard JESEE EHP ORD Travel Request Article Request Graphics Request ChemTrack https://cranlogs.r-pkg

EPA United States Environmental Protection Agency Home Advanced Search Batch Search Lists Predictions Downloads Copy Share Submit Comment Search all data

Triclosan

3380-34-5 | DTXSID5032498

Searched by Approved Name.

Property

Summary

Download

Columns

Search query

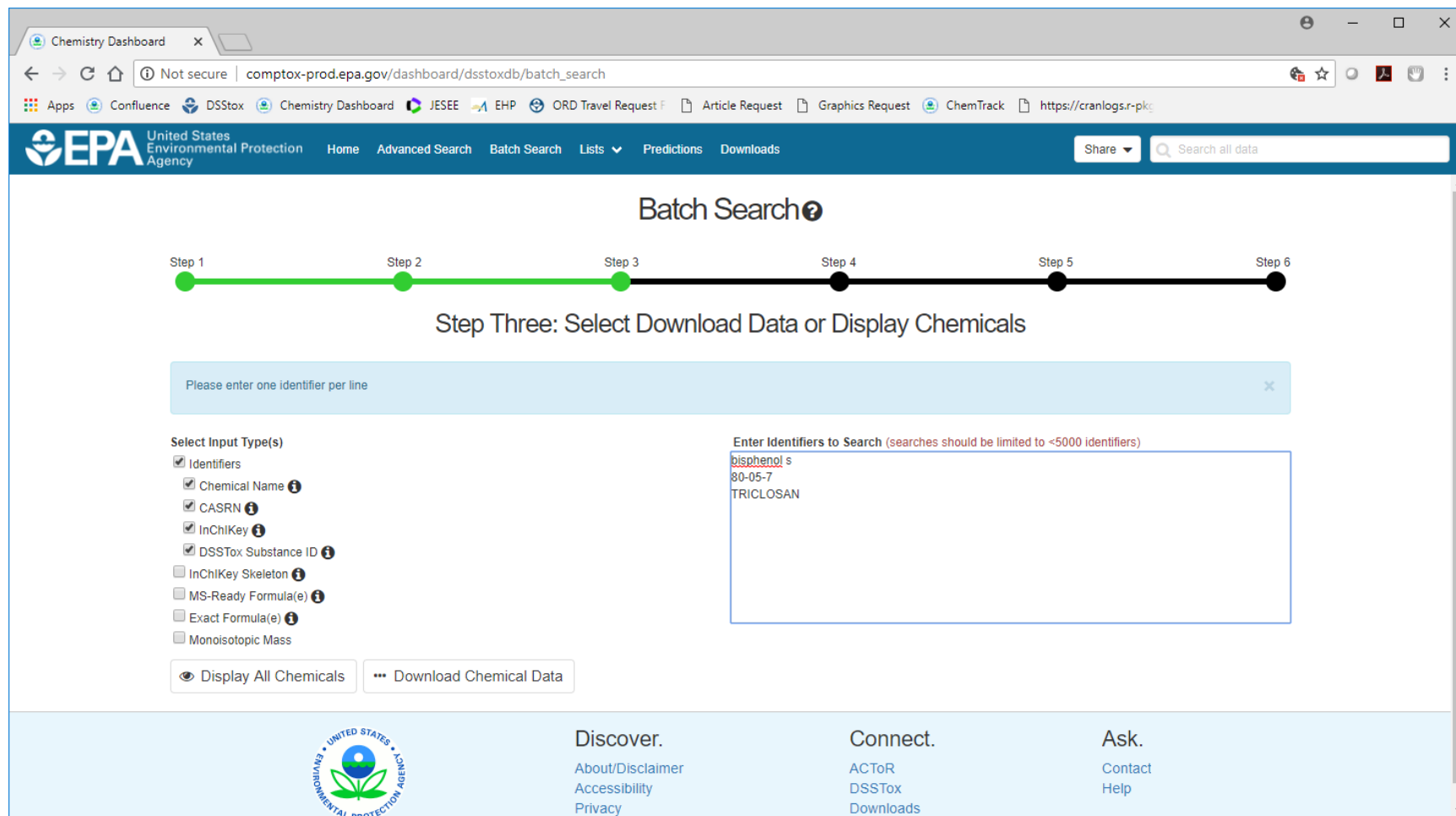
Property	Experimental average	Predicted average	Experimental median	Predicted median	Experimental range	Predicted range	Unit
LogP: Octanol-Water	4.76 (1)	4.79		5.06	4.76	3.78 to 5.27	
Melting Point	48.0 (11)	107	57.0	108	-40.0 to 57.5	73.4 to 141	°C
Boiling Point	-	352		345	-	327 to 374	°C
Water Solubility	3.45e-5 (1)	2.48e-5		2.15e-5	3.45e-5	4.54e-6 to 5.16e-5	mol/L
Vapor Pressure	-	9.72e-6		2.90e-6	-	4.53e-7 to 3.26e-5	mmHg
Flash Point	-	165		165	-	162 to 169	°C
Surface Tension	-	51.7		-	-	51.7	dyn/cm
Index of Refraction	-	1.63		-	-	1.63	
Molar Refractivity	-	69.3		-	-	69.3	cm³
Polarizability	-	27.5		-	-	27.5	Å³

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

Bulk Download of Data

- Can download databases and spreadsheets of data using Batch Search

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

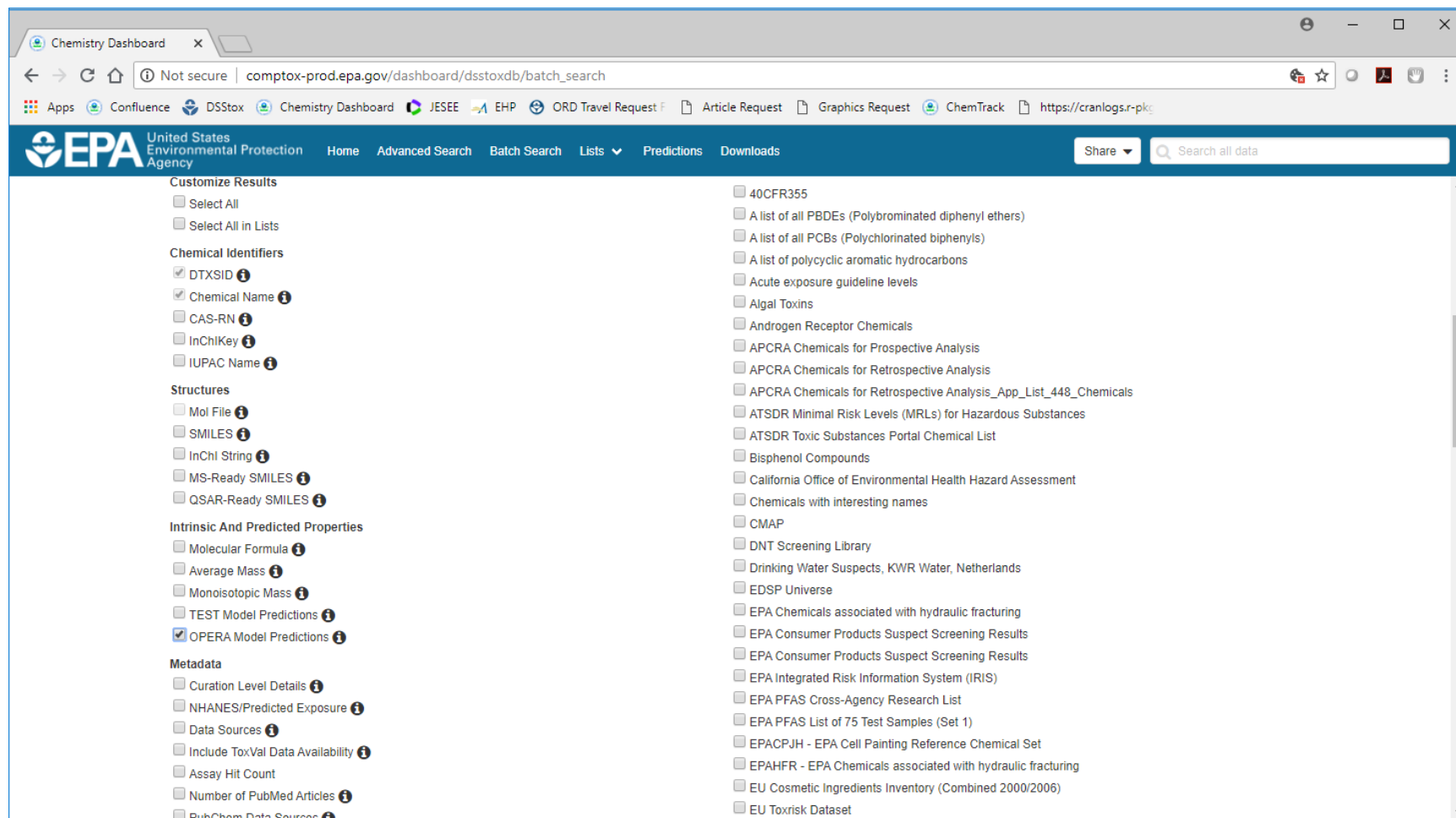


The screenshot shows the EPA Chemistry Dashboard's Batch Search interface. The browser address bar displays `comptox-prod.epa.gov/dashboard/dsstoxdb/batch_search`. The page features a progress bar with six steps, where Step 3, "Select Download Data or Display Chemicals", is the current active step. Below the progress bar, a light blue box prompts the user to "Please enter one identifier per line". To the left, under "Select Input Type(s)", several options are checked: Identifiers, Chemical Name, CASRN, InChIKey, and DSSTox Substance ID. To the right, a text area titled "Enter Identifiers to Search" contains the text "bisphenol s", "80-05-7", and "TRICLOSAN". At the bottom of the interface, there are two buttons: "Display All Chemicals" and "Download Chemical Data". The footer includes the EPA logo and navigation links for "Discover.", "Connect.", and "Ask.".

Bulk Download of Data

- Can download databases and spreadsheets of data using Batch Search

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



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Customize Results

- ☐ Select All
- ☐ Select All in Lists

Chemical Identifiers

- ☒ DTXSID
- ☒ Chemical Name
- ☐ CAS-RN
- ☐ InChIKey
- ☐ IUPAC Name

Structures

- ☐ Mol File
- ☐ SMILES
- ☐ InChI String
- ☐ MS-Ready SMILES
- ☐ QSAR-Ready SMILES

Intrinsic And Predicted Properties

- ☐ Molecular Formula
- ☐ Average Mass
- ☐ Monoisotopic Mass
- ☐ TEST Model Predictions
- ☒ OPERA Model Predictions

Metadata

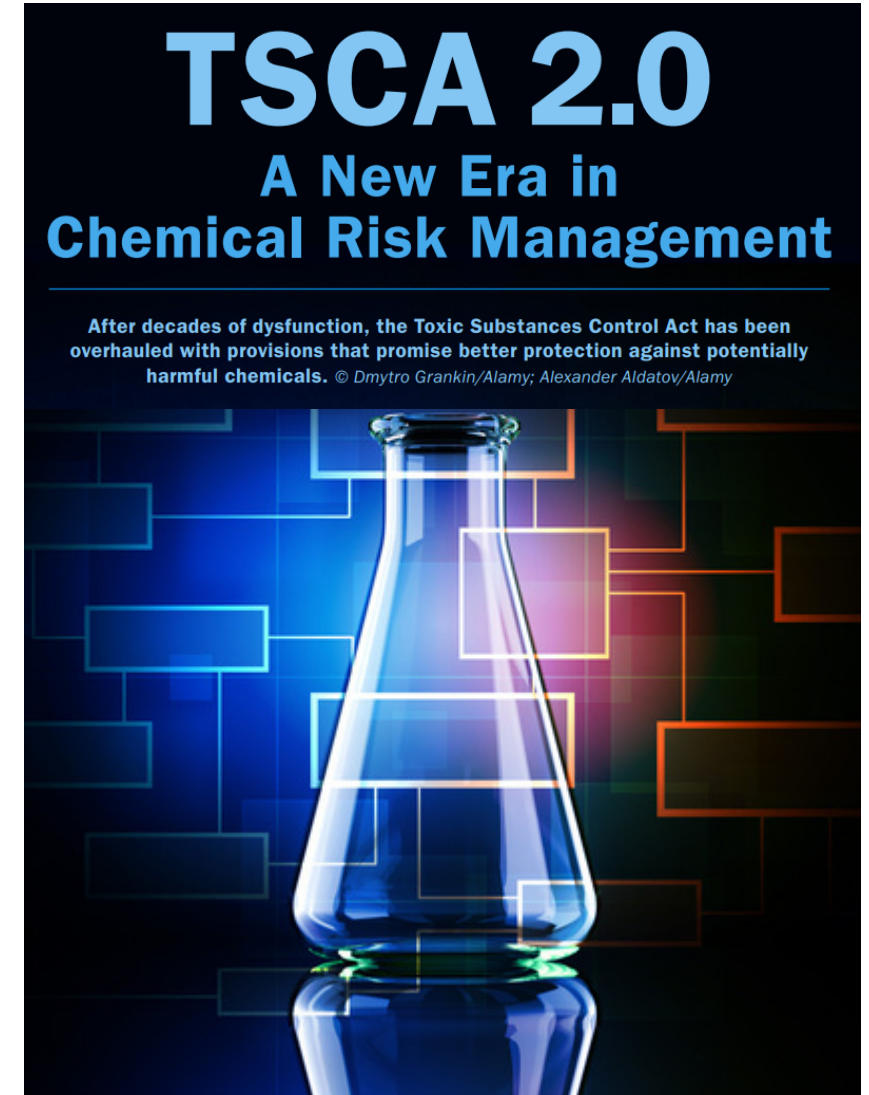
- ☐ Curation Level Details
- ☐ NHANES/Predicted Exposure
- ☐ Data Sources
- ☐ Include ToxVal Data Availability
- ☐ Assay Hit Count
- ☐ Number of PubMed Articles
- ☐ PubChem Data Sources

40CFR355

- ☐ A list of all PBDEs (Polybrominated diphenyl ethers)
- ☐ A list of all PCBs (Polychlorinated biphenyls)
- ☐ A list of polycyclic aromatic hydrocarbons
- ☐ Acute exposure guideline levels
- ☐ Algal Toxins
- ☐ Androgen Receptor Chemicals
- ☐ APCRA Chemicals for Prospective Analysis
- ☐ APCRA Chemicals for Retrospective Analysis
- ☐ APCRA Chemicals for Retrospective Analysis_App_List_448_Chemicals
- ☐ ATSDR Minimal Risk Levels (MRLs) for Hazardous Substances
- ☐ ATSDR Toxic Substances Portal Chemical List
- ☐ Bisphenol Compounds
- ☐ California Office of Environmental Health Hazard Assessment
- ☐ Chemicals with interesting names
- ☐ CMAP
- ☐ DNT Screening Library
- ☐ Drinking Water Suspects, KWR Water, Netherlands
- ☐ EDSP Universe
- ☐ EPA Chemicals associated with hydraulic fracturing
- ☐ EPA Consumer Products Suspect Screening Results
- ☐ EPA Consumer Products Suspect Screening Results
- ☐ EPA Integrated Risk Information System (IRIS)
- ☐ EPA PFAS Cross-Agency Research List
- ☐ EPA PFAS List of 75 Test Samples (Set 1)
- ☐ EPACPJH - EPA Cell Painting Reference Chemical Set
- ☐ EPAHFR - EPA Chemicals associated with hydraulic fracturing
- ☐ EU Cosmetic Ingredients Inventory (Combined 2000/2006)
- ☐ EU Toxrisk Dataset

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 streams into chemical risk assessment
 - making the information publicly available



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

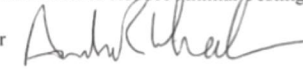
September 10, 2019

THE ADMINISTRATOR

MEMORANDUM

SUBJECT: Directive to Prioritize Efforts to Reduce Animal Testing

FROM: Andrew R. Wheeler
Administrator

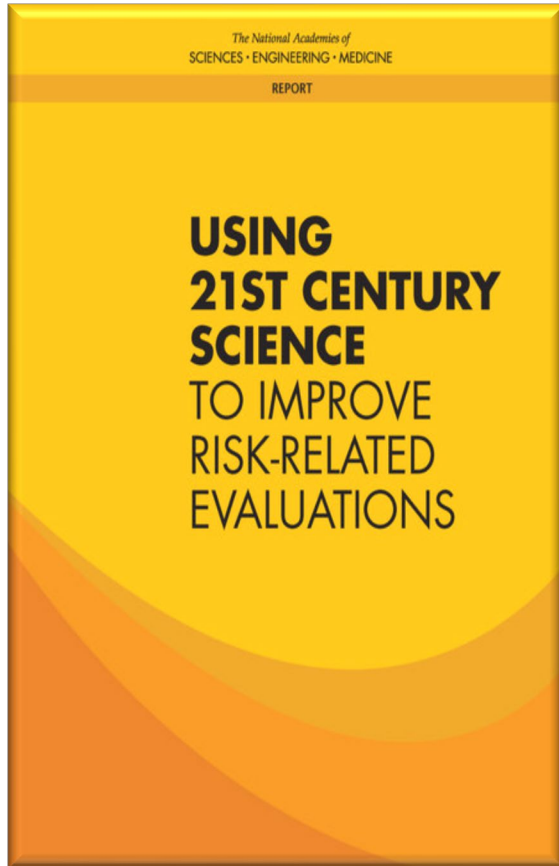


TO: Associate Deputy Administrator
General Counsel
Assistant Administrators
Inspector General
Chief Financial Officer
Chief of Staff
Associate Administrators
Regional Administrators

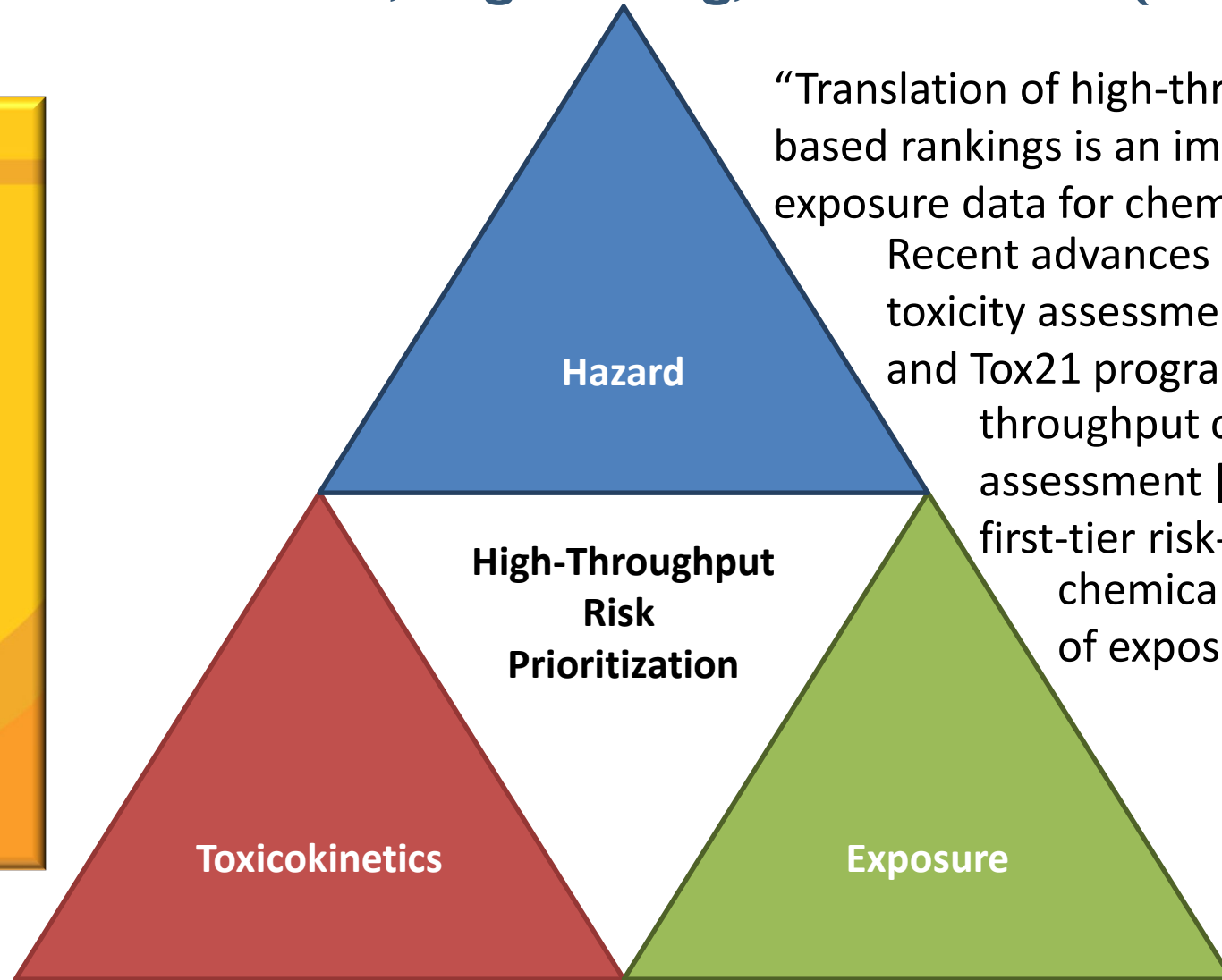
During my March 2019 all-hands address, I reiterated the U.S. Environmental Protection Agency's commitment to move away from animal testing. We are already making significant efforts to reduce, replace and refine our animal testing requirements under both statutory and strategic directives. For example, 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)



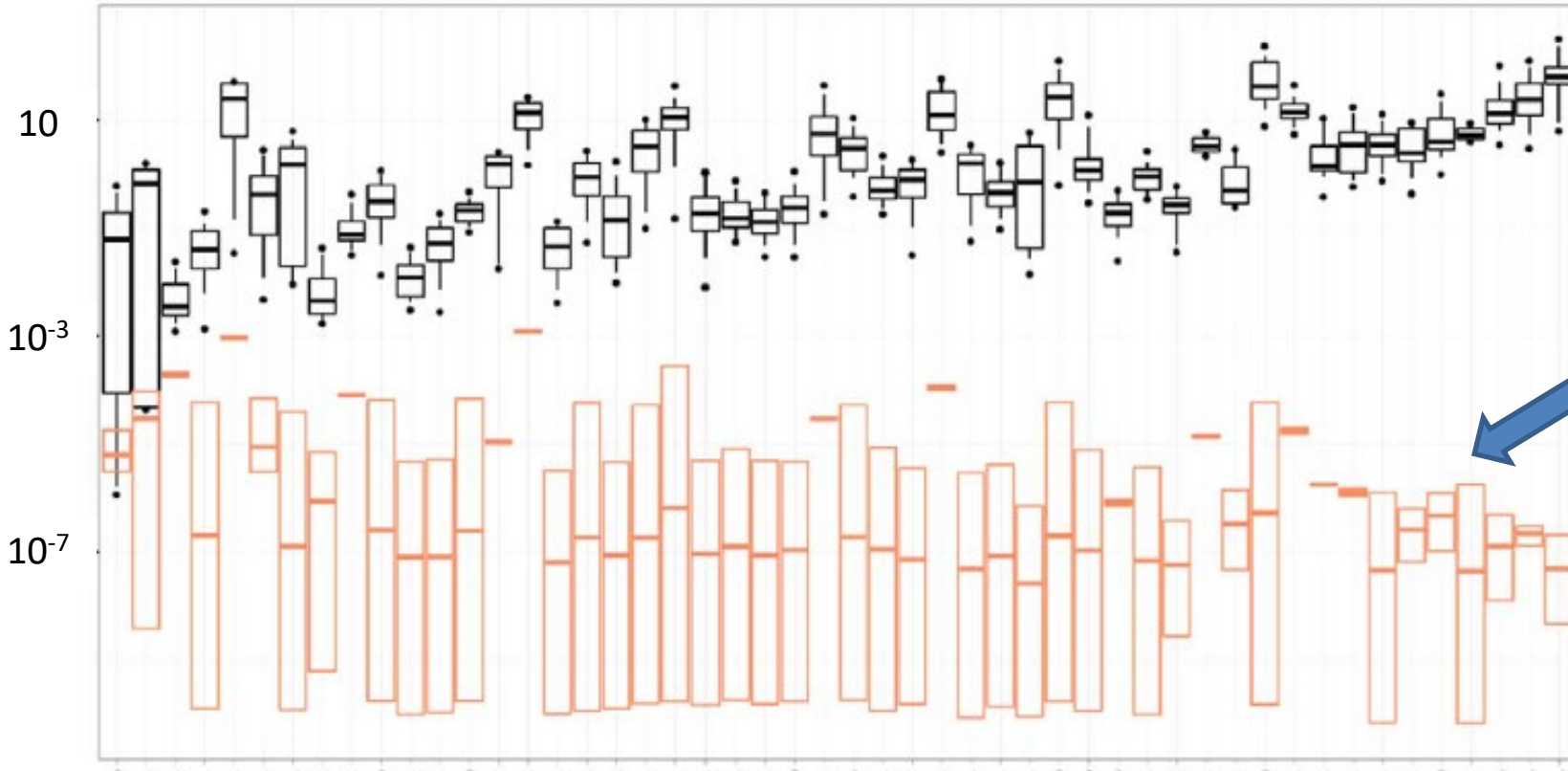
“Translation of high-throughput data into risk-based rankings is an important application of exposure data for chemical priority-setting. Recent advances in high-throughput toxicity assessment, notably the ToxCast and Tox21 programs... and in high-throughput computational exposure assessment [ExpoCast] have enabled first-tier risk-based rankings of chemicals on the basis of margins of exposure”

Chemical Prioritization NAMs

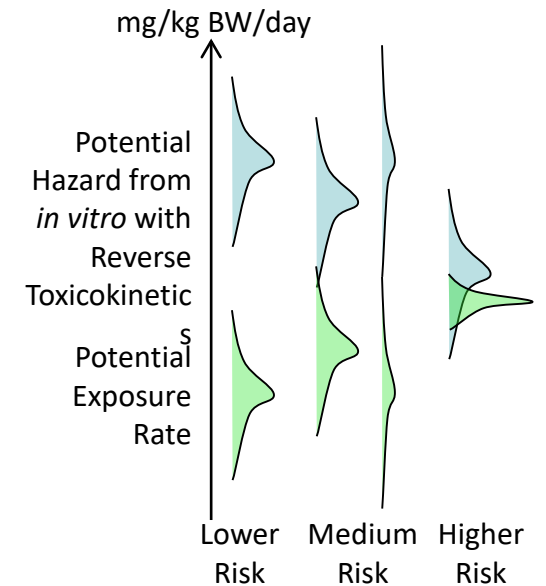
High throughput *in vitro* screening can estimate doses needed to cause bioactivity (e.g., Wetmore et al., 2015)

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

Estimated Equivalent Dose or Predicted Exposure
(mg/kg BW/day)



Chemicals Monitored by CDC NHANES



Ring et al. (2017)

In Vitro - *In Vivo* Extrapolation (IVIVE)

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

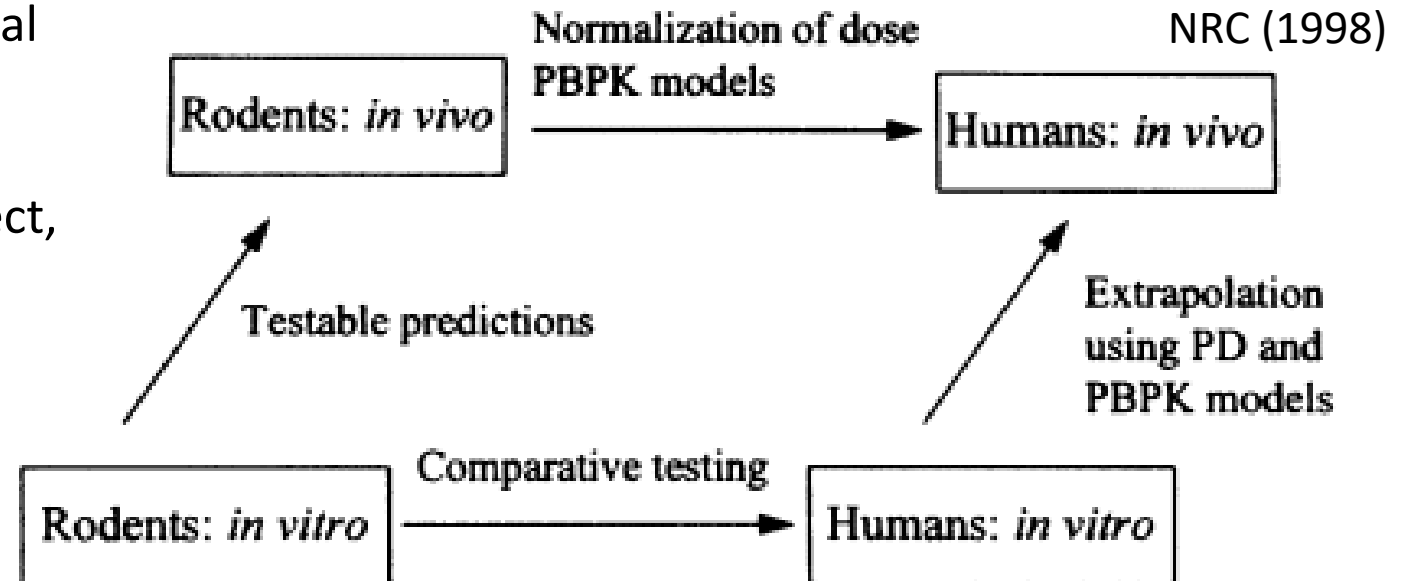
- IVIVE-PK/TK (**Pharmacokinetics/Toxicokinetics**):

- 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**):

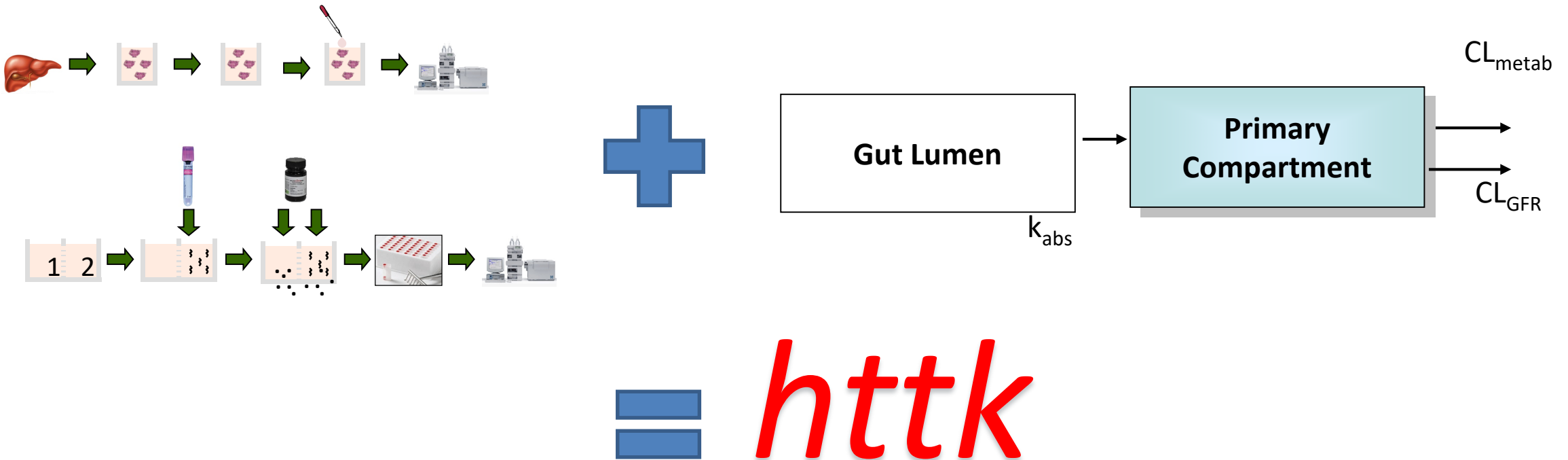
- Effect of molecules/chemicals at biological target *in vivo*
- Assay design/selection important
- Perturbation as adverse/therapeutic effect, reversible/ irreversible effects

- Both contribute to *in vivo* effect prediction



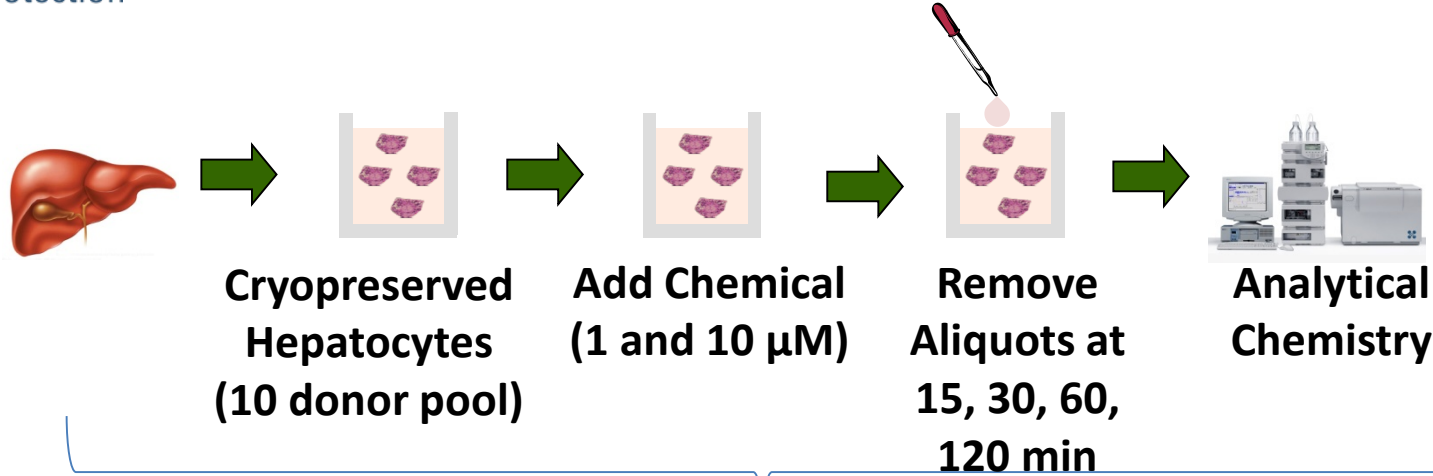
High Throughput Toxicokinetics (HTTK)

***In vitro* toxicokinetic data + generic toxicokinetic model
= high(er) throughput toxicokinetics**

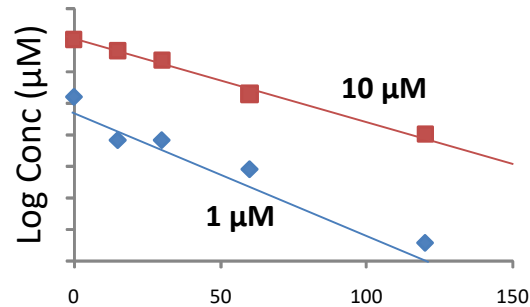


In Vitro Data for HTTK

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



The rate of disappearance of parent compound (slope of line) is the **hepatic clearance** ($\mu\text{L}/\text{min}/10^6$ hepatocytes)

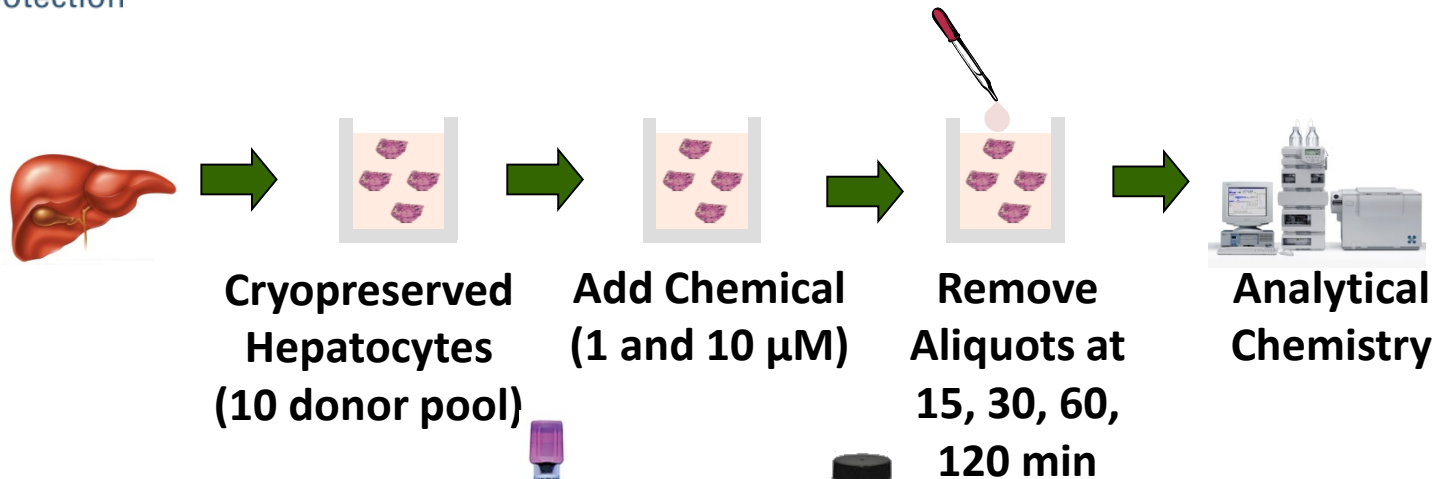


We perform the assay at 1 and 10 μM to check for saturation of metabolizing enzymes.

- **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)

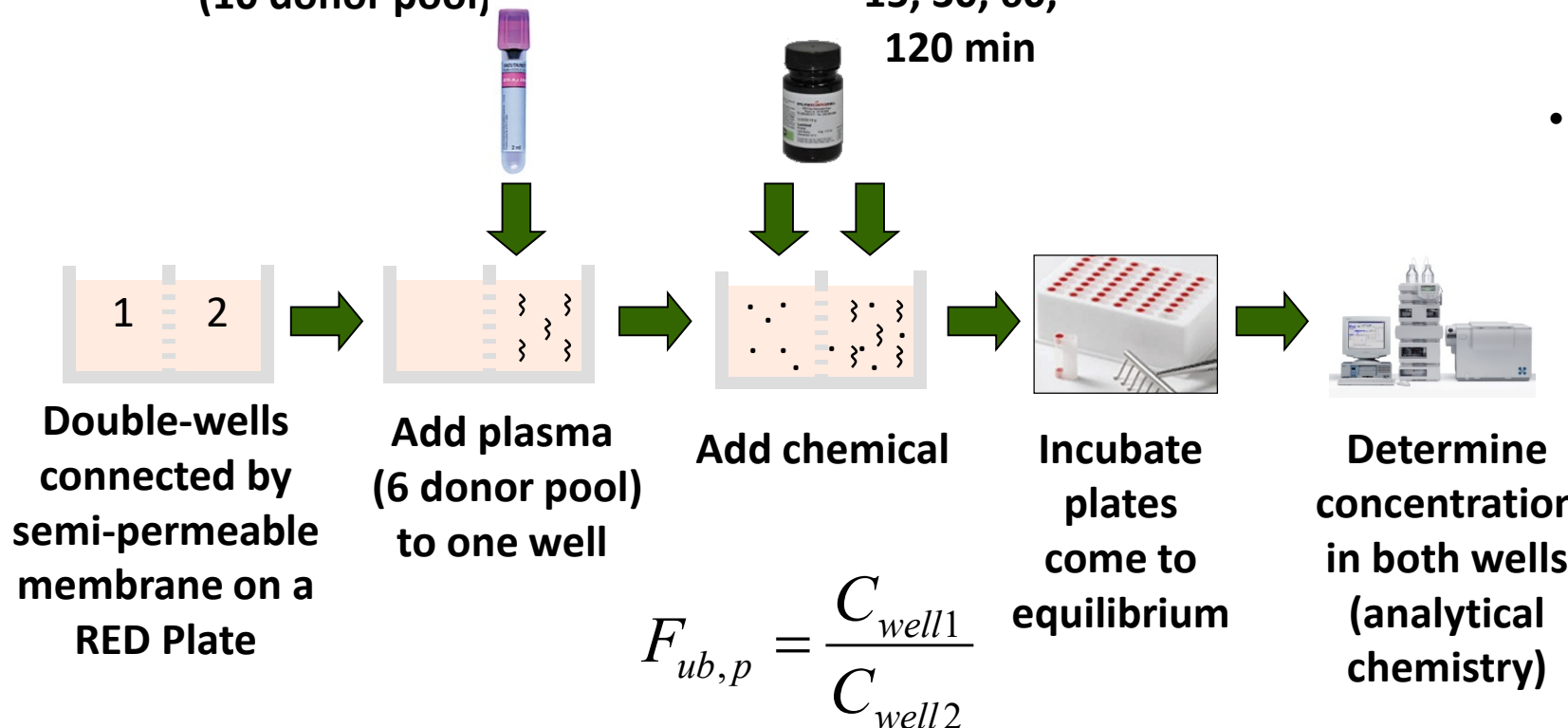
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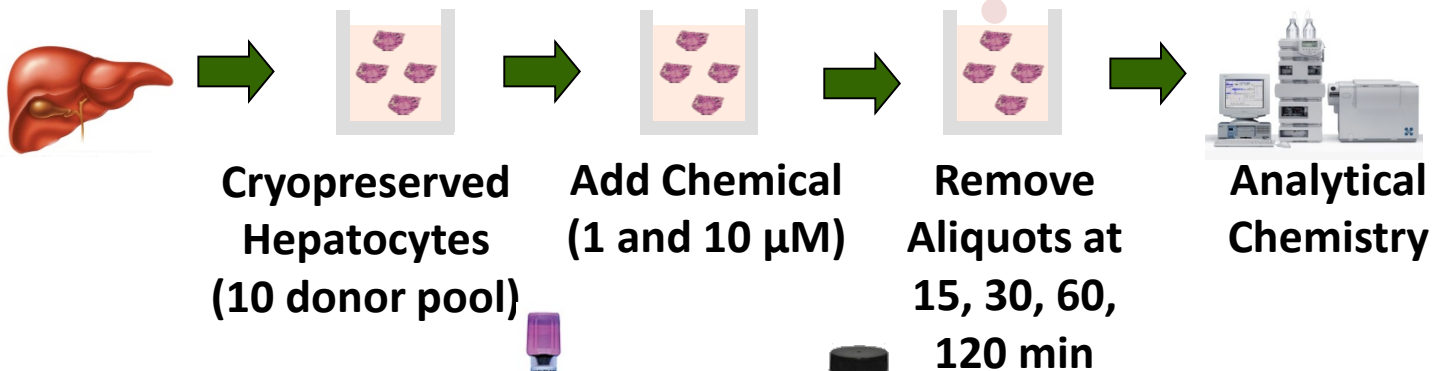
Rapid
Equilibrium
Dialysis (RED)
Waters *et al.*
(2008)



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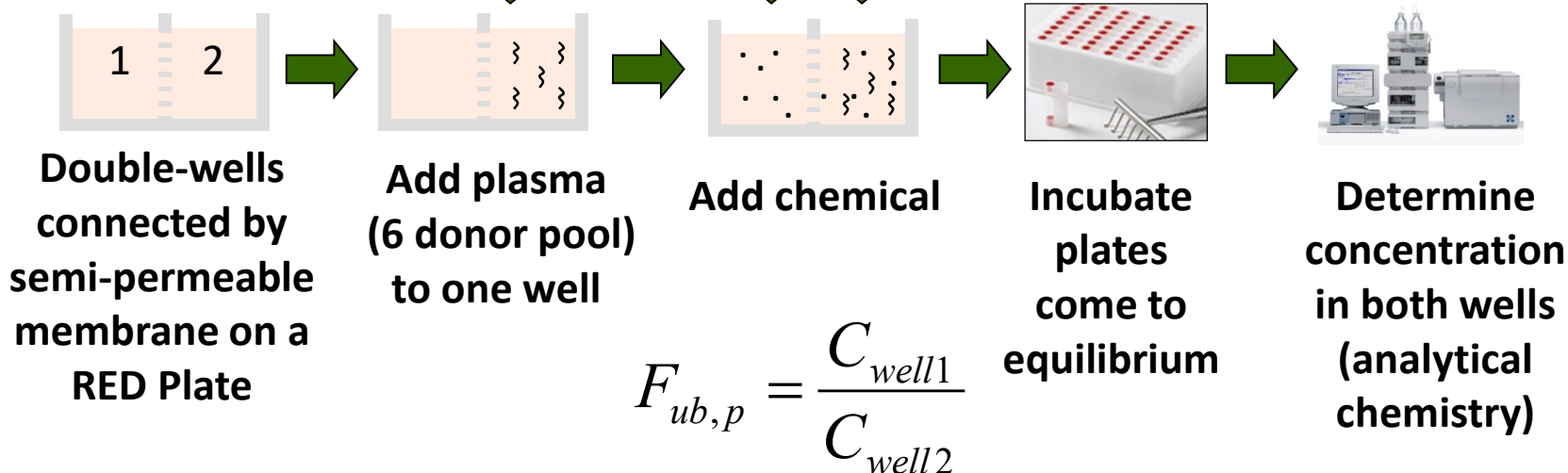
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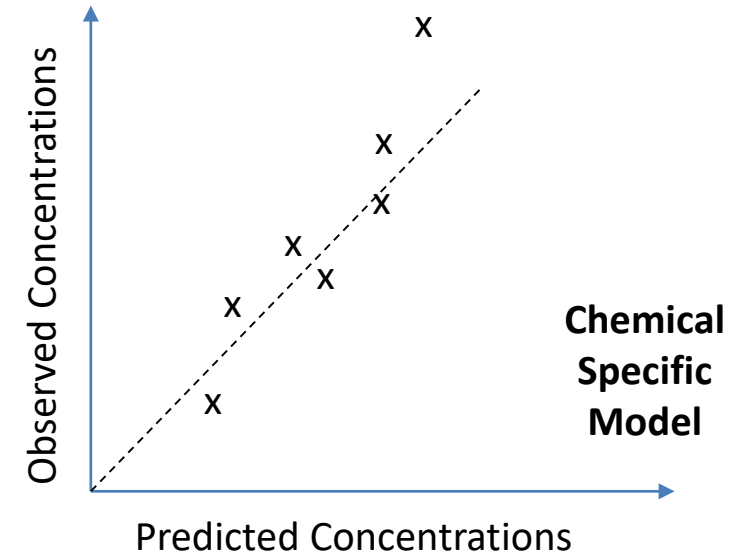
Rapid
Equilibrium
Dialysis (RED)
Waters *et al.*
(2008)



- Environmental chemicals:
 Retroff *et al.* (2010) **35** chemicals
 Wetmore *et al.* (2012) **+204** chemicals
 Wetmore *et al.* (2015) **+163** chemicals
 Wambaugh *et al.* (2019) **+389** chemicals

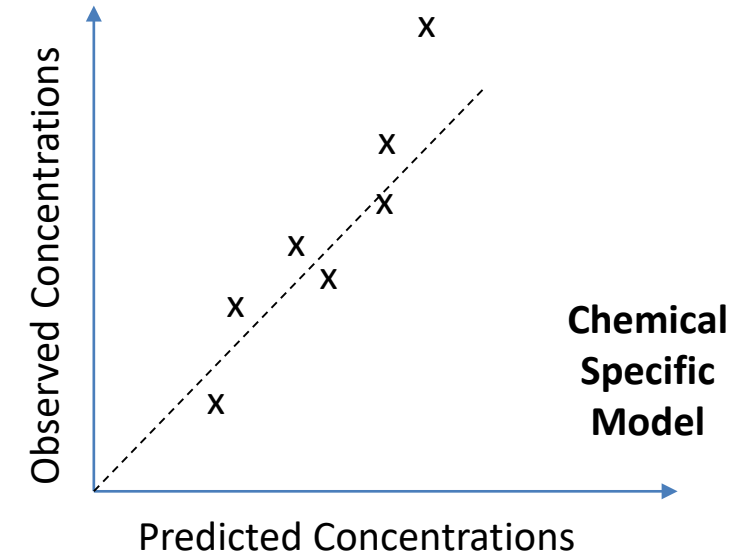
Building Confidence in TK Models

- 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



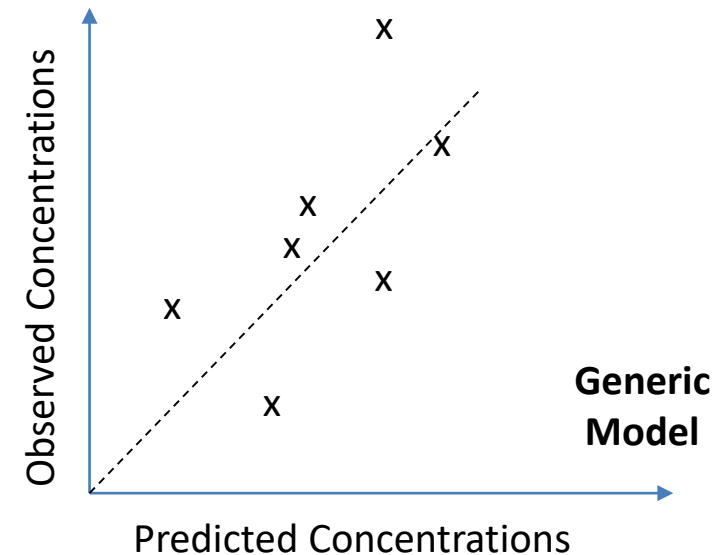
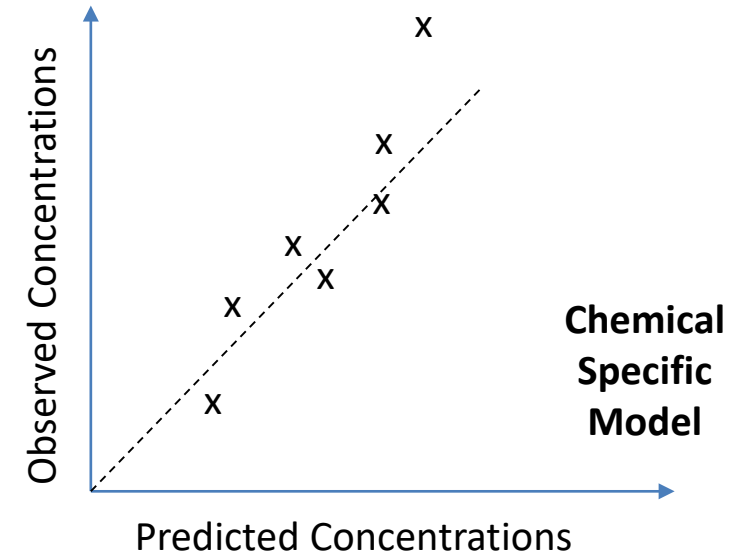
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- However, we do not typically have TK data



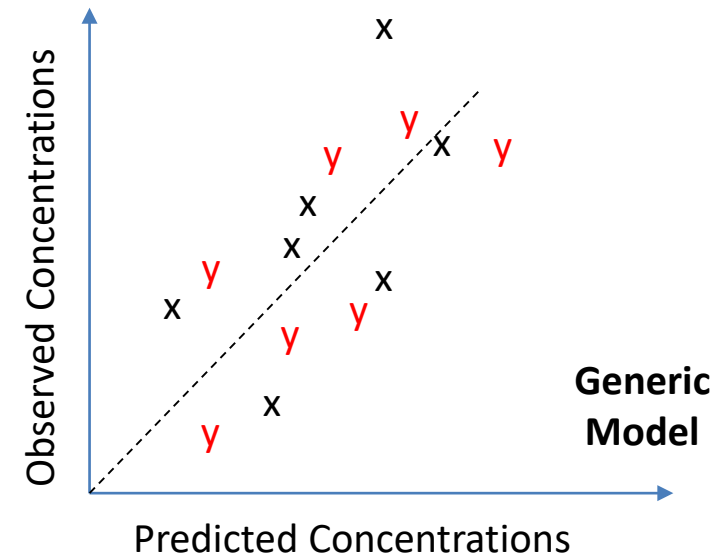
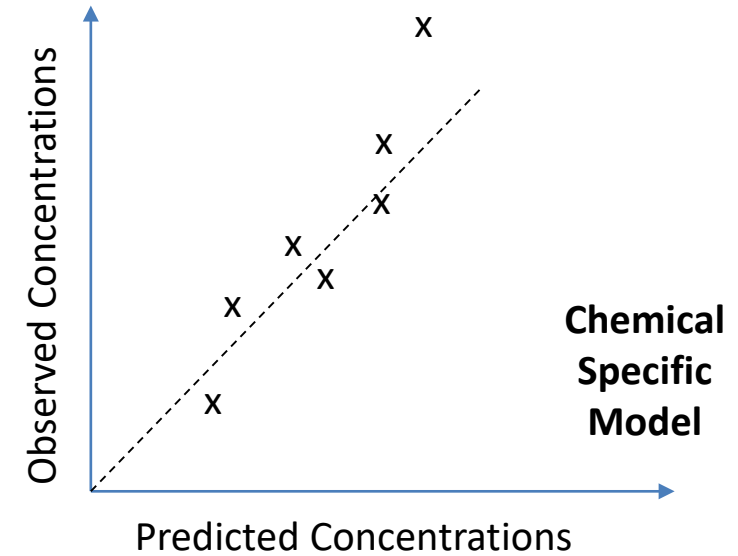
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- We can parameterize a **generic TK model**, and evaluate that model for as many chemicals as we do have data
 - We do expect larger uncertainty, but also greater confidence in model implementation
 - Estimate bias and uncertainty, and try to correlate with chemical-specific properties



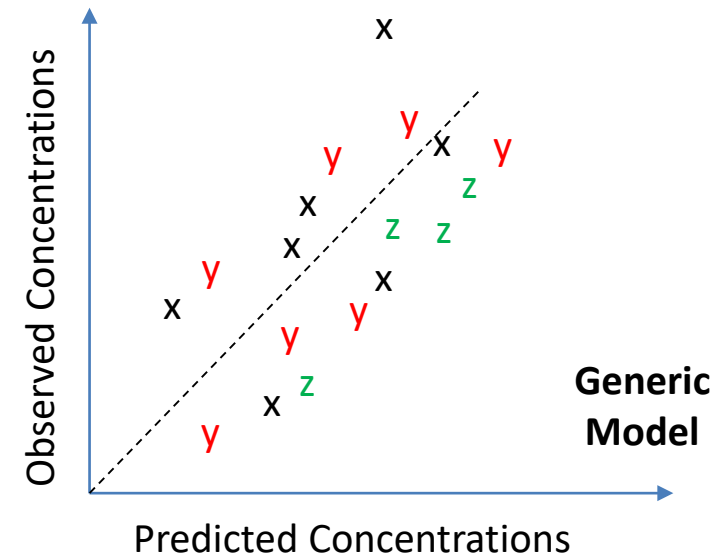
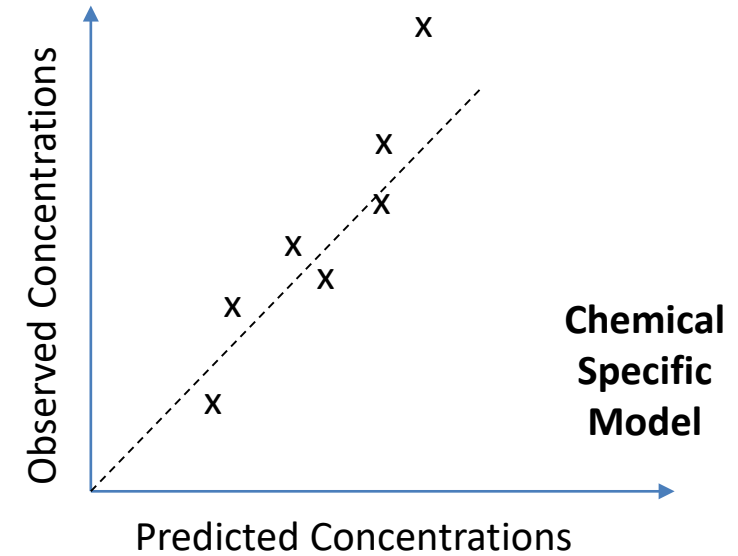
Building Confidence in TK Models

- 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
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 - Can consider using model to extrapolate to other situations (chemicals without *in vivo* data)



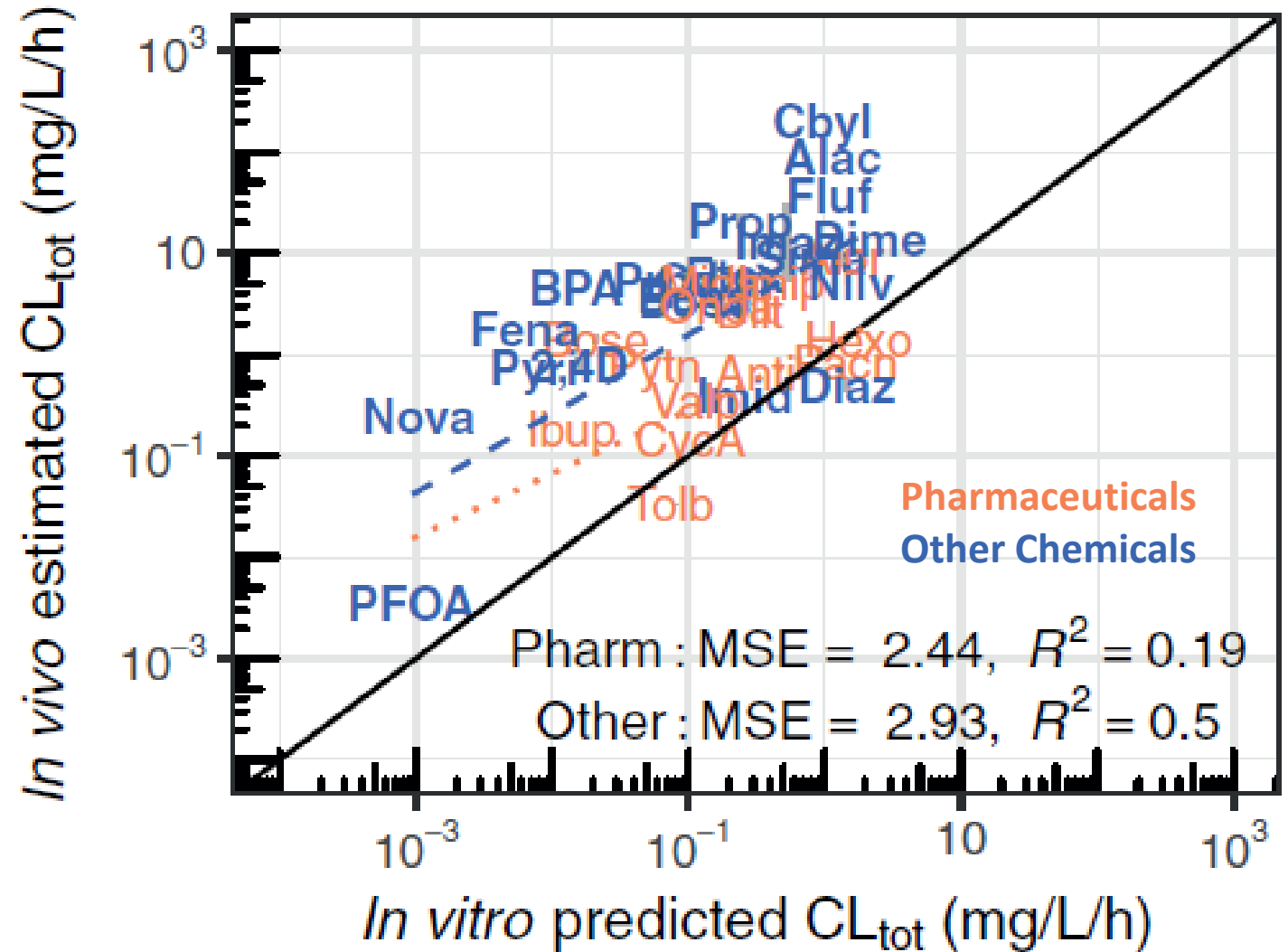
Building Confidence in TK Models

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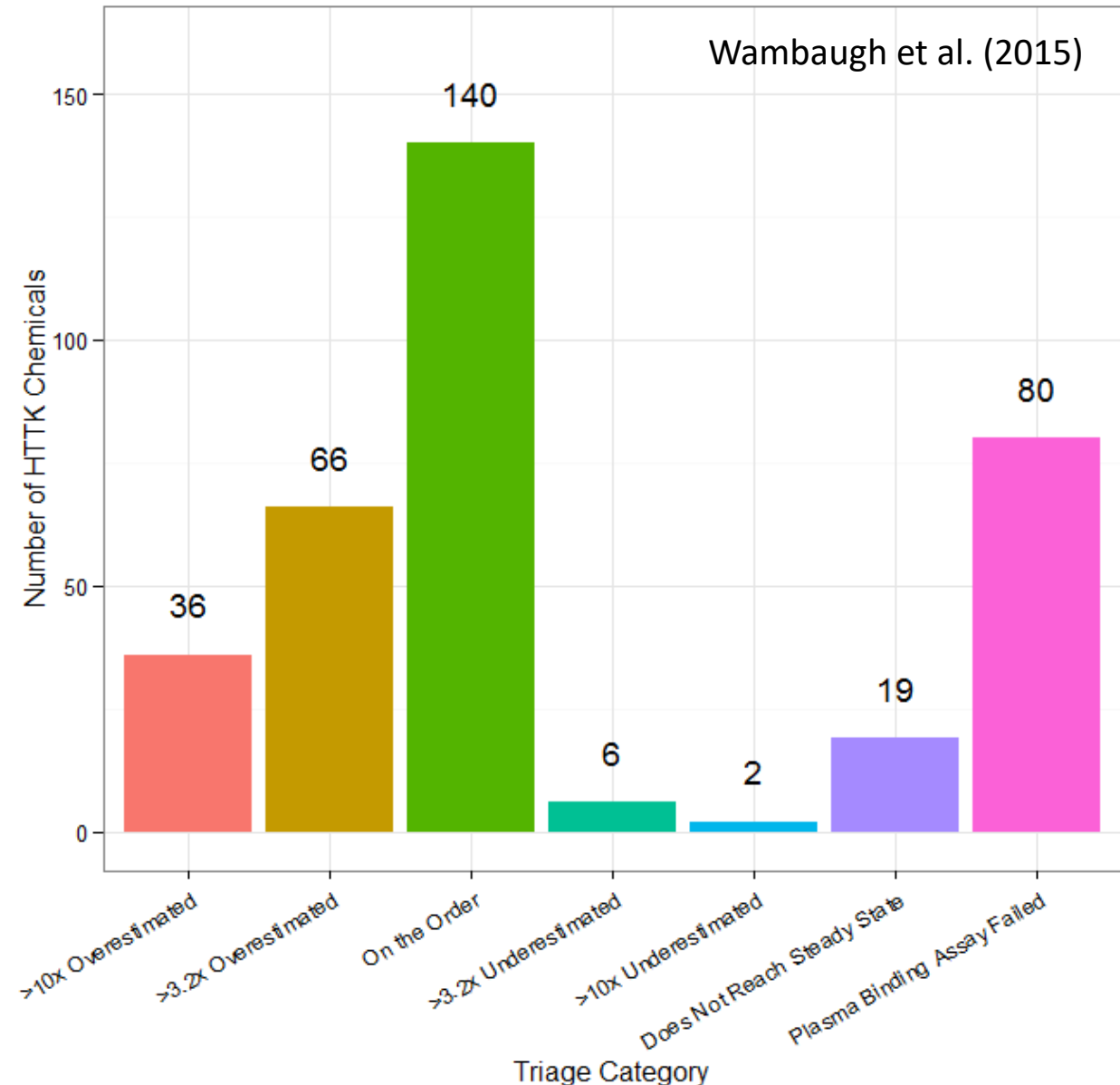
- We estimate clearance from two processes – hepatic metabolism (liver) and passive glomerular filtration (kidney)
- This appears to work better for pharmaceuticals than other chemicals:
 - ToxCast chemicals are overestimated
- Non-pharmaceuticals may be subject to extrahepatic metabolism and/or active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

Evaluation Example



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
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The “average”
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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



Population simulator for HTTK

Correlated Monte Carlo
sampling of physiological
model parameters built
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(Pearce et al., 2017):

Sample NHANES
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actual individuals:

Sex
Race/ethnicity
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Height
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Serum creatinine



Population simulator for HTTK



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.)

Slide from Caroline Ring (ToxStrategies)

Ring *et al.* (2017)

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

Sample NHANES
biometrics for
actual individuals:

Sex
Race/ethnicity
Age
Height
Weight
Serum creatinine



Population simulator for HTTK

Predict physiological
quantities

Tissue masses
Tissue blood flows
GFR (kidney function)
Hepatocellularity

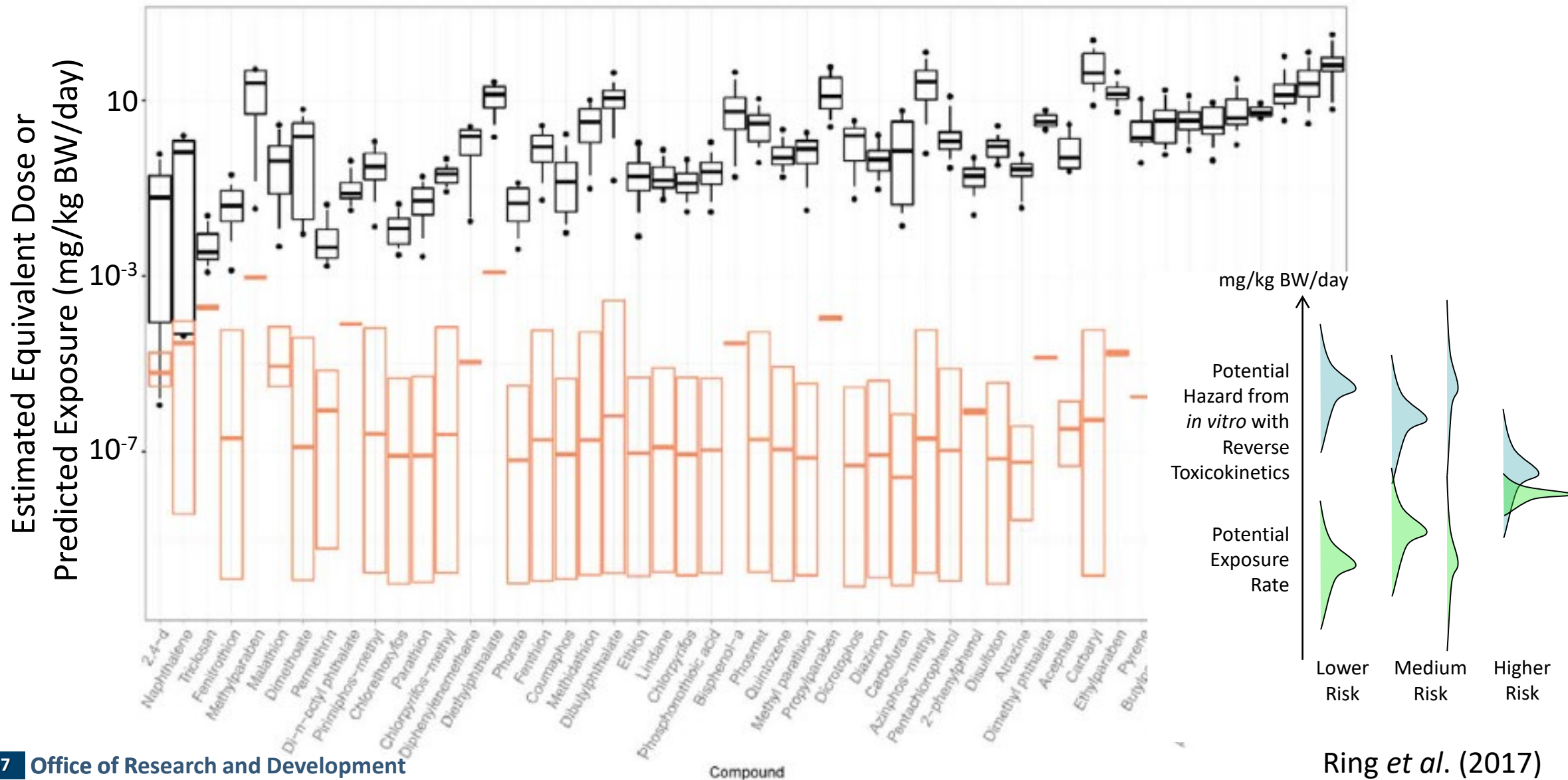
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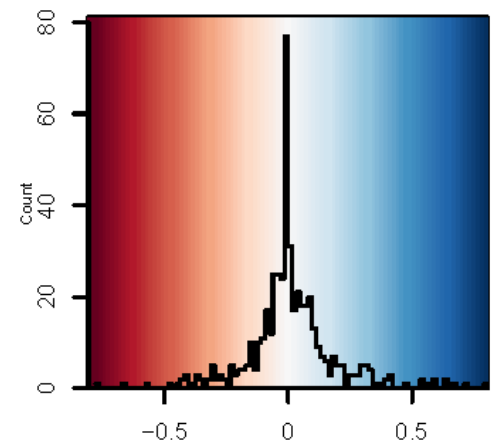
Ring *et al.* (2017)

Risk-Based Ranking for Total NHANES Population

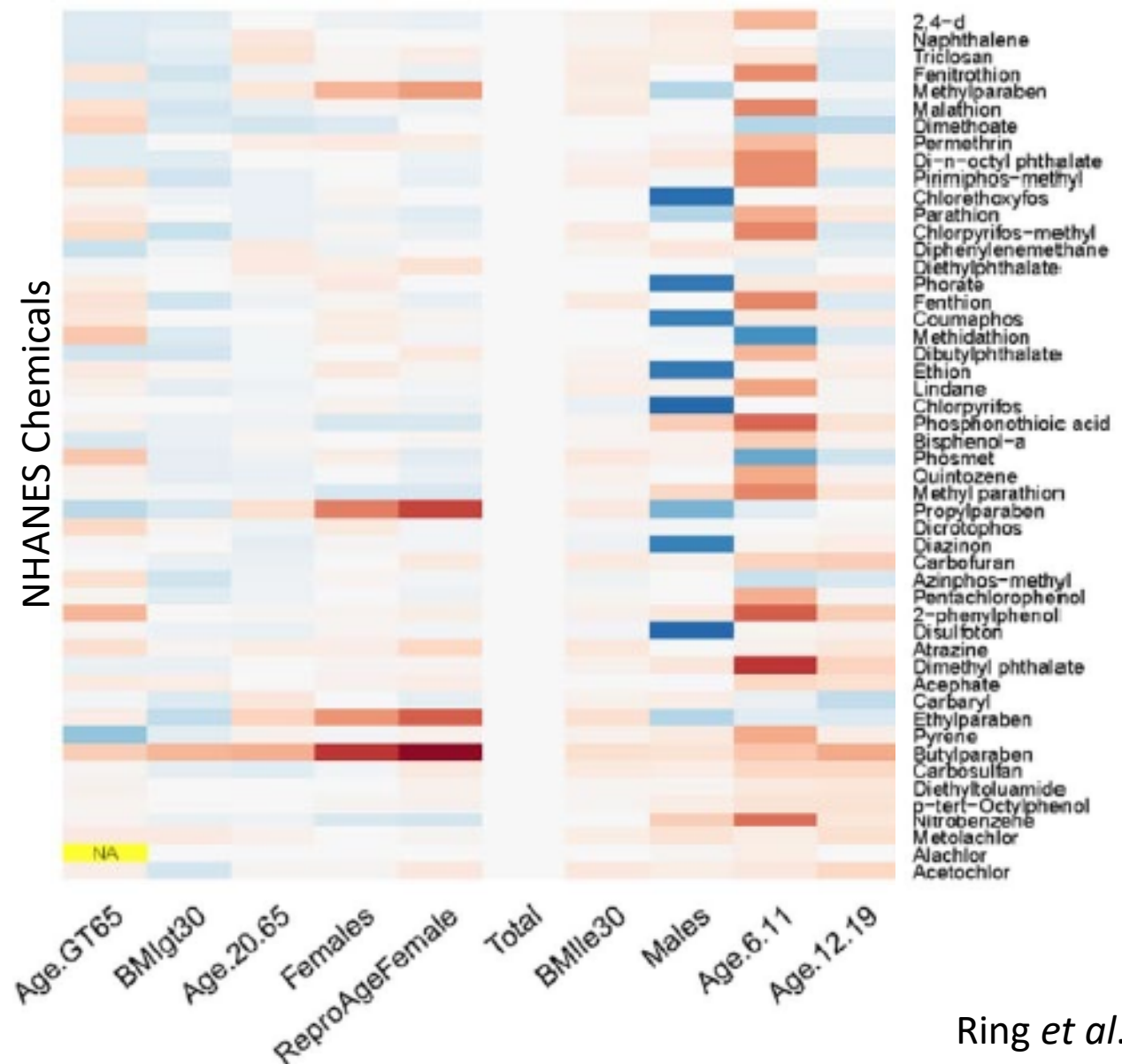


Life-stage and Demographic Variation in Exposure

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

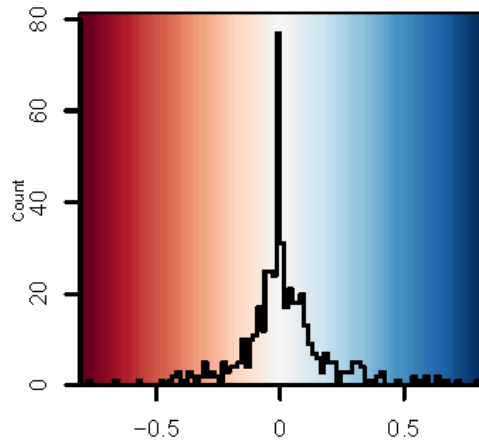


Change in Exposure
Relative to Total Population

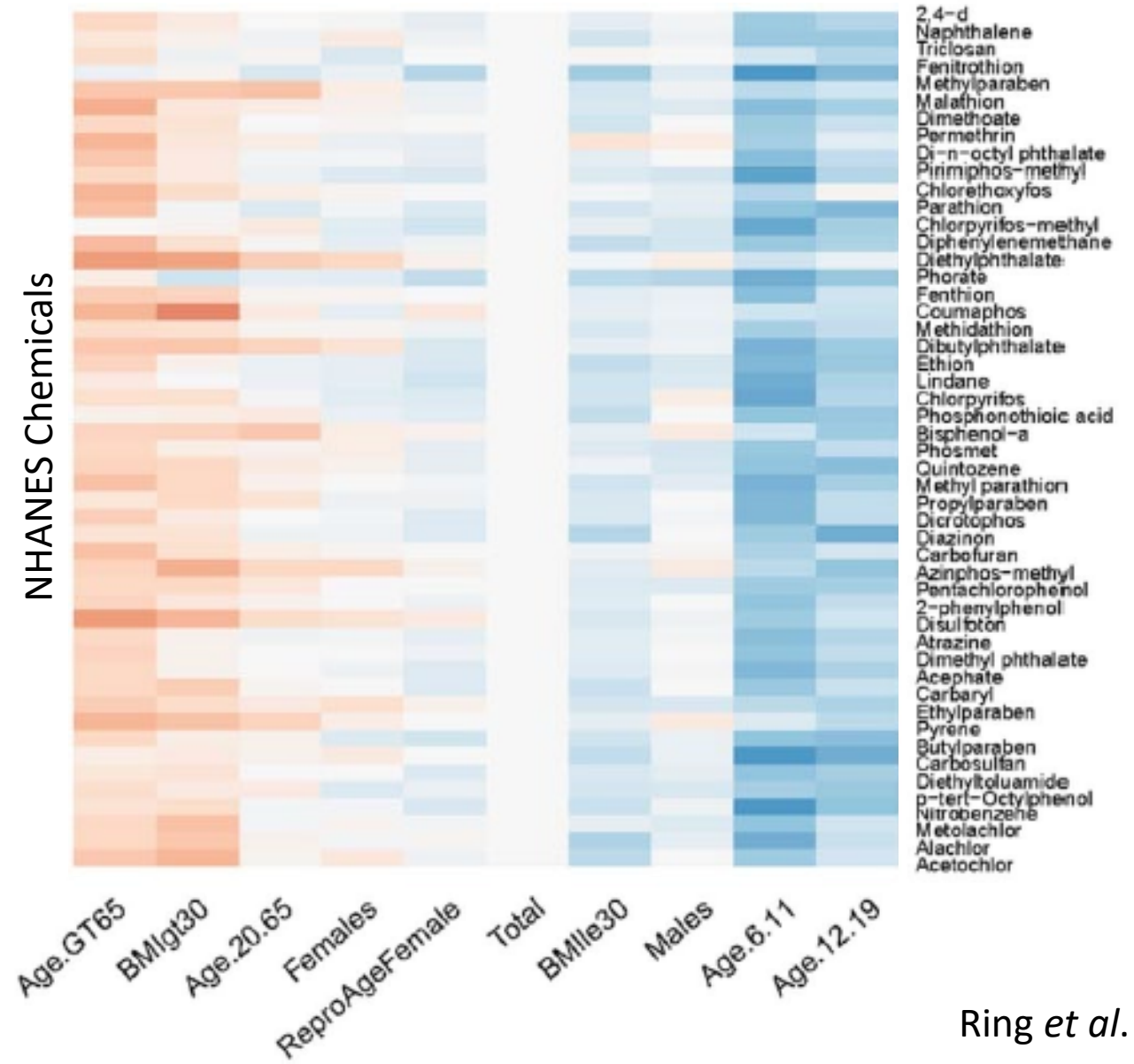


Life-stage and Demographic Variation in TK

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

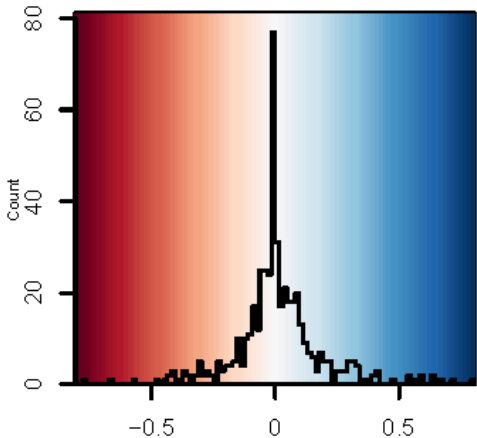


Change in Toxicokinetics
Relative to Total Population

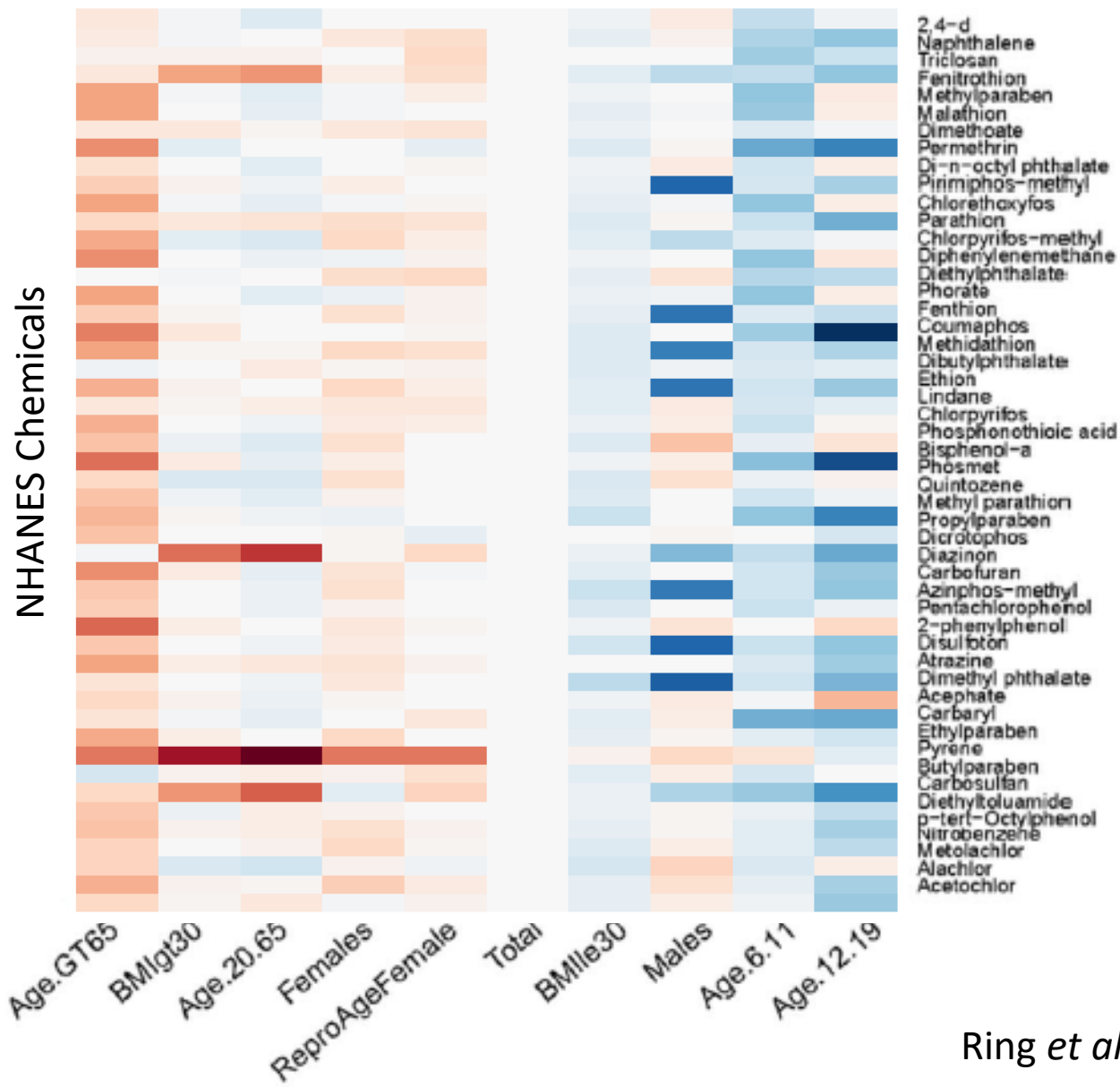
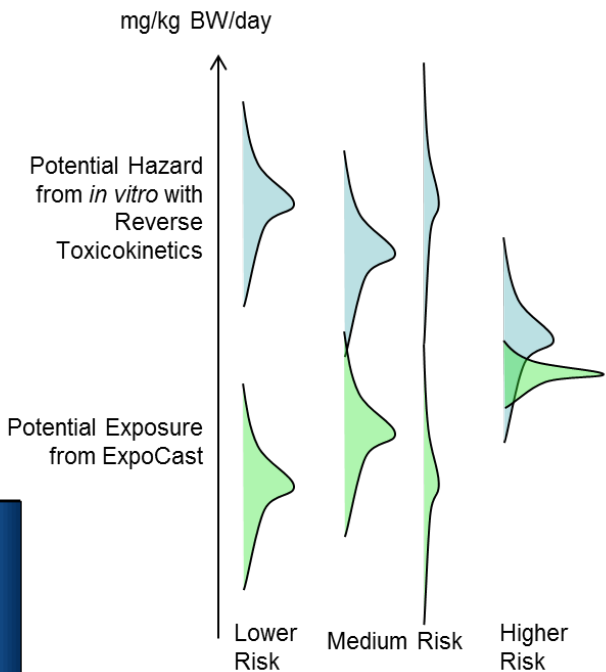


Life-stage and Demographic Variation in Risk Priority

- Can calculate margin between bioactivity and exposure for specific populations



Change in Risk Relative to
Total Population



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

include a table in a script in R - G... | rmarkdown-cheatsheet | Defining toxicological tipping po... | CRAN - Package httk

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

Apps Confluence DSStox Chemicals Dashboa... EHP ORD Travel Request... Article Request Graphics Request ChemTrack https://cranlogs.r-p... CSS REMD RACT mec_svy_sub

httk: High-Throughput Toxicokinetics

Functions and data tables for simulation and statistical analysis of chemical toxicokinetics ("TK") as in Pearce et al. (2017) <[doi:10.18637/jss.v079.i04](https://doi.org/10.18637/jss.v079.i04)>. Chemical-specific in vitro data have been obtained from relatively high throughput experiments. Both physiologically-based ("PBTK") and empirical (e.g., one compartment) "TK" models can be parameterized for several hundred chemicals and multiple species. These models are solved efficiently, often using compiled (C-based) code. A Monte Carlo sampler is included for simulating biological variability (Ring et al., 2017 <[doi:10.1016/j.envint.2017.06.004](https://doi.org/10.1016/j.envint.2017.06.004)>) and measurement limitations. Calibrated methods are included for predicting tissue:plasma partition coefficients and volume of distribution (Pearce et al., 2017 <[doi:10.1007/s10928-017-9548-7](https://doi.org/10.1007/s10928-017-9548-7)>). These functions and data provide a set of tools for in vitro-in vivo extrapolation ("IVIVE") of high throughput screening data (e.g., Tox21, ToxCast) to real-world exposures via reverse dosimetry (also known as "RTK") (Wetmore et al., 2015 <[doi:10.1093/toxsci/kfv171](https://doi.org/10.1093/toxsci/kfv171)>).

Version: 1.10.1
Depends: R (≥ 2.10)
Imports: [deSolve](#), [msm](#), [data.table](#), [survey](#), [mvtnorm](#), [truncnorm](#), stats, graphics, utils, [magrittr](#)
Suggests: [ggplot2](#), [knitr](#), [rmarkdown](#), [R.rsp](#), [GGally](#), [gplots](#), [scales](#), [EnvStats](#), [MASS](#), [RColorBrewer](#), [TeachingDemos](#), [gmodels](#), [colorspace](#)
Published: 2019-09-10
Author: John Wambaugh [aut, cre], Robert Pearce [aut], Caroline Ring [aut], Greg Honda [aut], Mark Sfeir [aut], Wetmore [ctb], Woodrow Setzer [ctb]
Maintainer: John Wambaugh <wambaugh.john@epa.gov>
BugReports: <https://github.com/USEPA/CompTox-ExpoCast-httk>
License: [GPL-3](#)
URL: <https://www.epa.gov/chemical-research/rapid-chemical-exposure-and-dose-research>
NeedsCompilation: yes
Materials: [NEWS](#)
CRAN checks: [httk results](#)

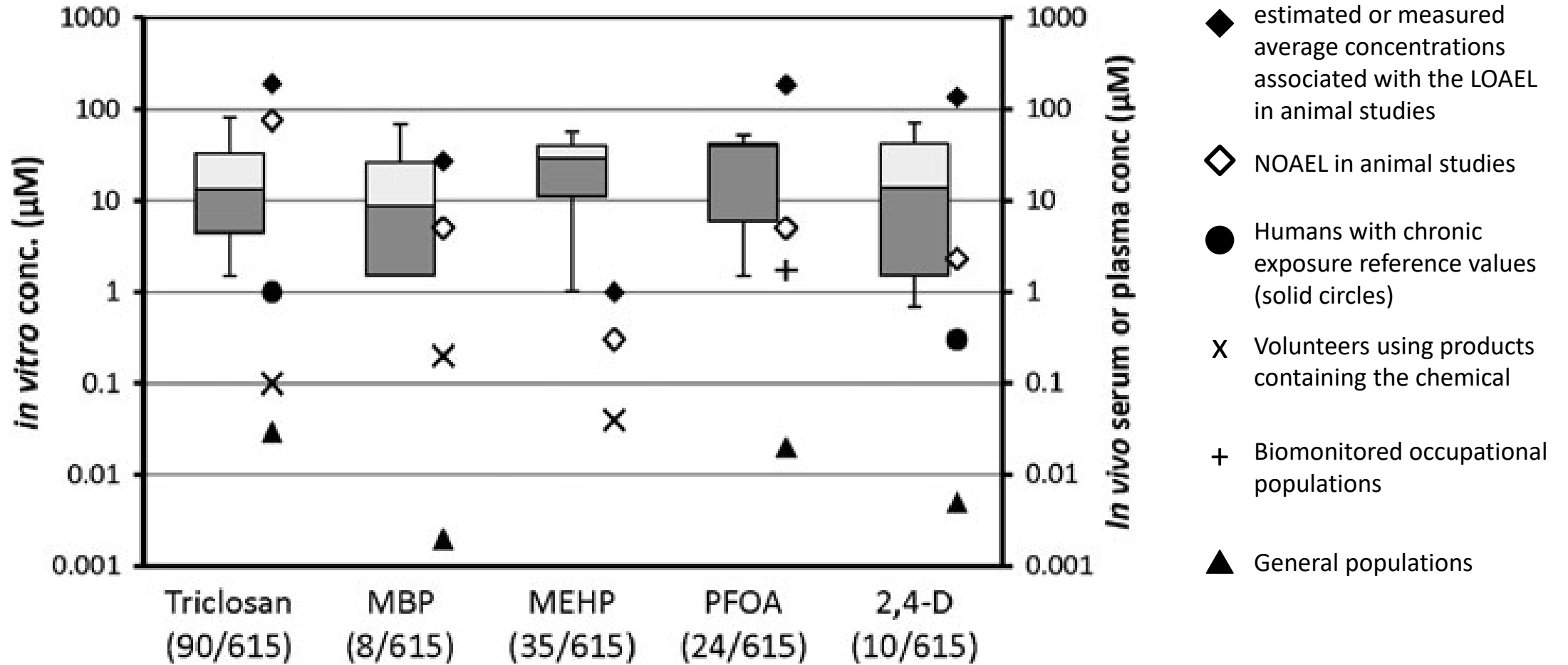
Downloads: **downloads 474/month**

Reference manual: [httk.pdf](#)
Vignettes: [Honda et al. \(2019\): Updated Armitage et al. \(2014\) Model](#), [Pearce et al. \(2017\): Creating Partition Coefficient Evaluation Plots](#), [Ring et al. \(2017\) Age distributions](#), [Ring et al. \(2017\) Global sensitivity analysis](#), [Ring et al. \(2017\) Global sensitivity analysis plotting](#), [Ring et al. \(2017\) Height and weight spline fits and residuals](#), [Ring et al. \(2017\) Human-specific data for 944 chemicals](#)

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?



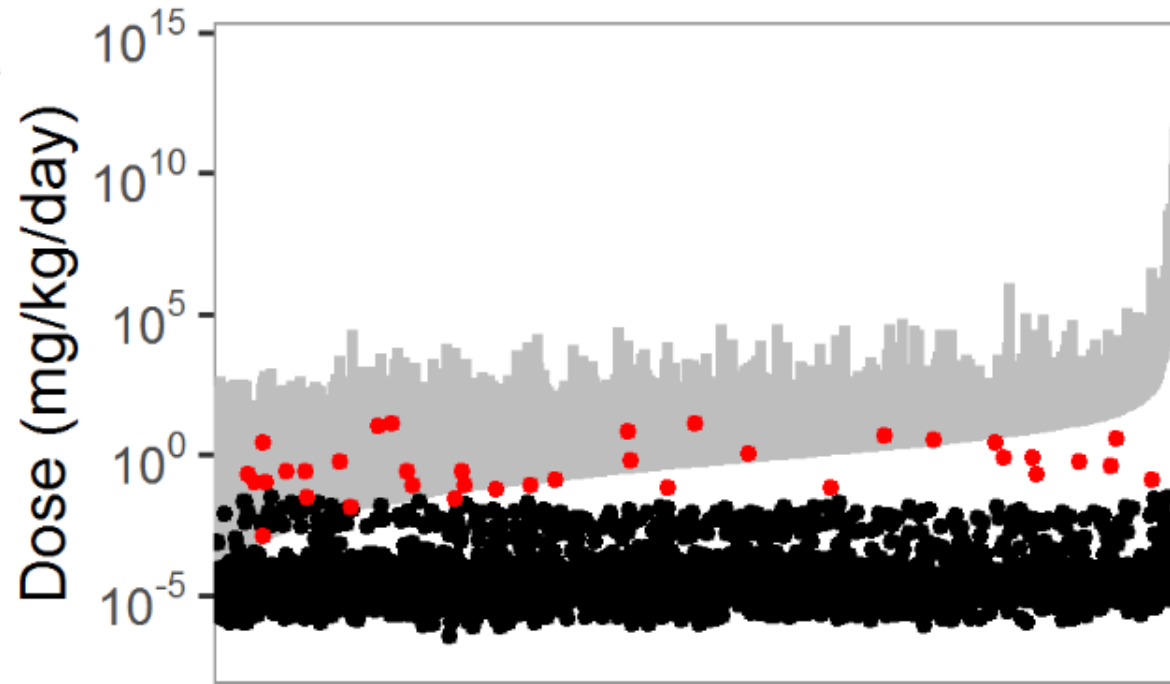
Aylward and Hays (2011)

Journal of Applied Toxicology **31** 741-751

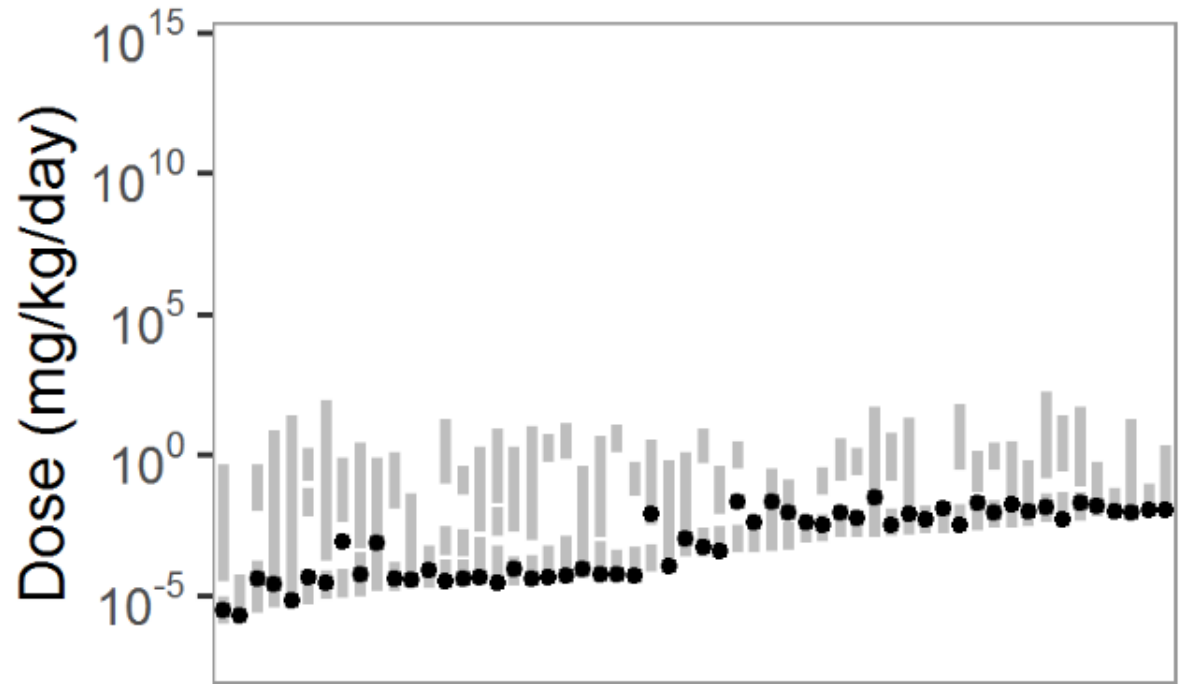
Using Predicted HTTK for Risk Prioritization



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

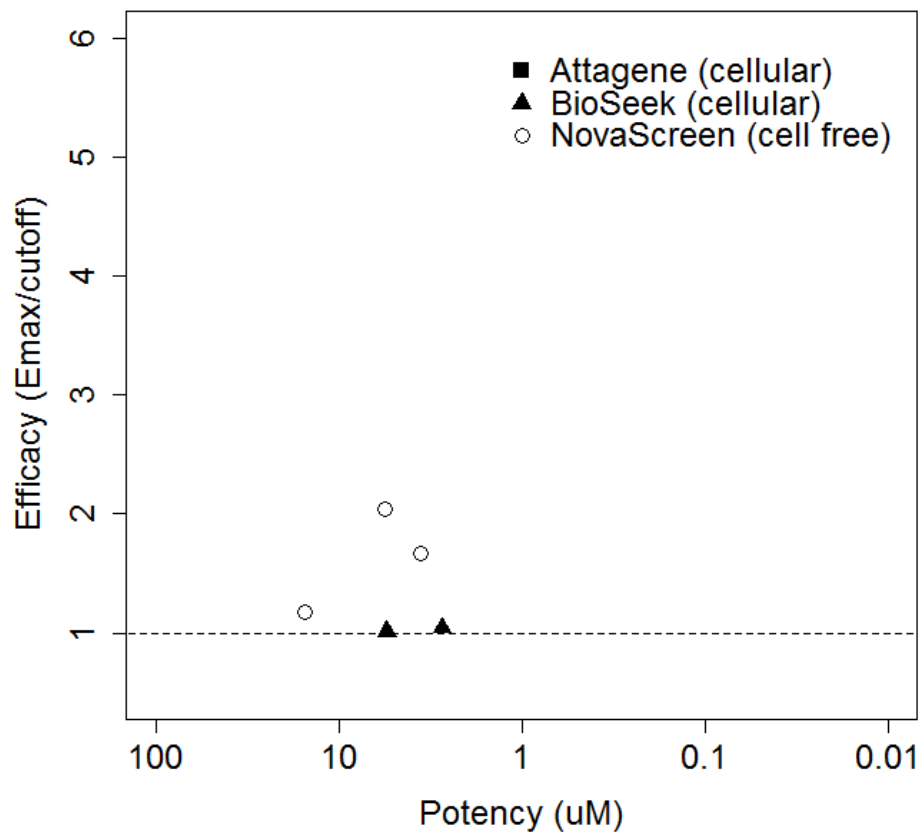


56 compounds with potential *in vivo* biological interaction at or above estimated environmental exposures

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

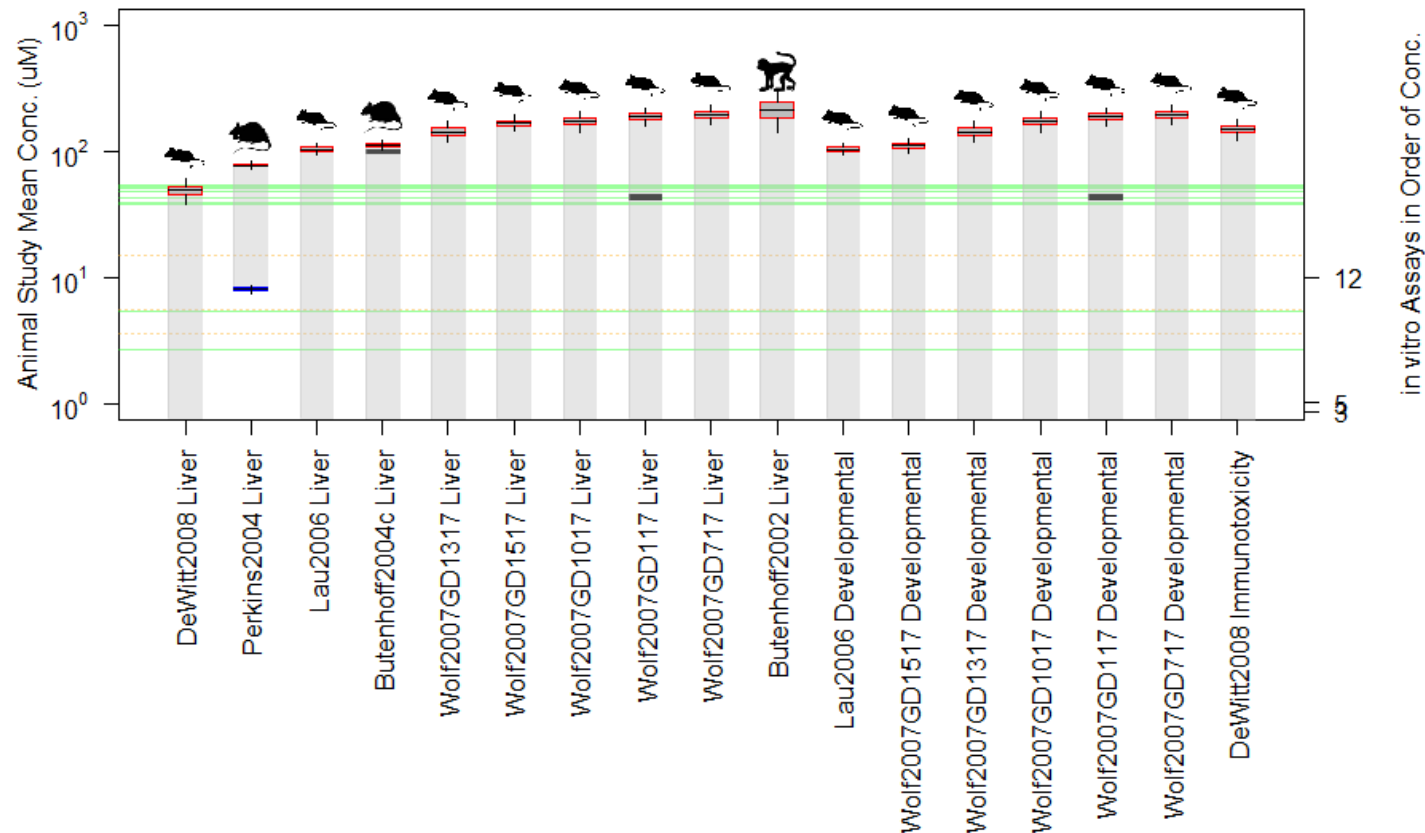
ToxCast

Perfluorooctanoic acid



Average Serum PFOA Concentration

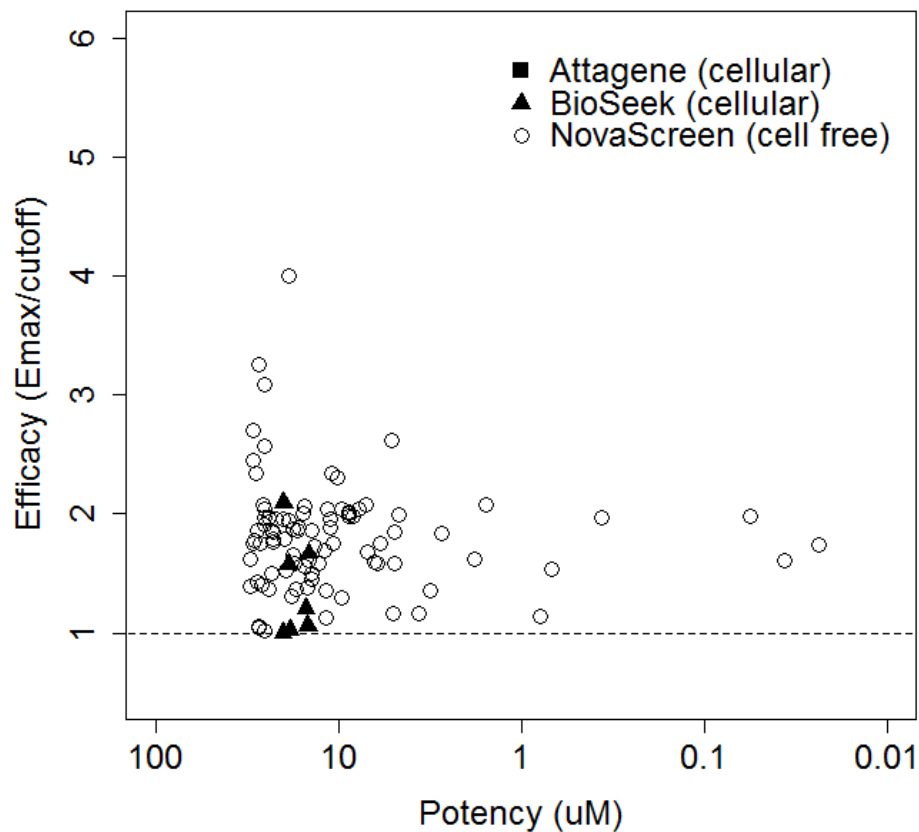
in vivo
toxicity studies



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

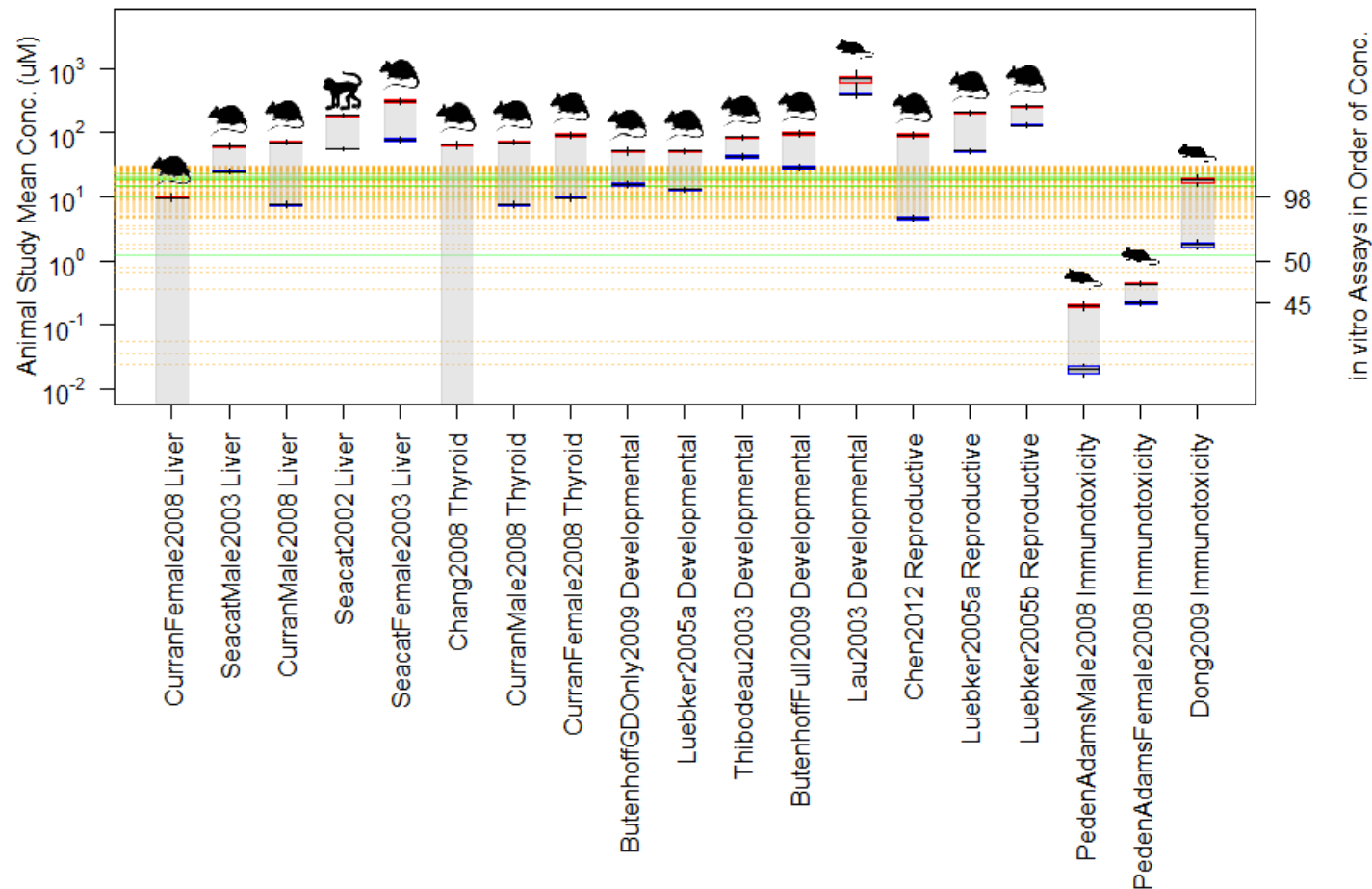
ToxCast

Perfluorooctane sulfonic acid



Average Serum PFOS Concentration

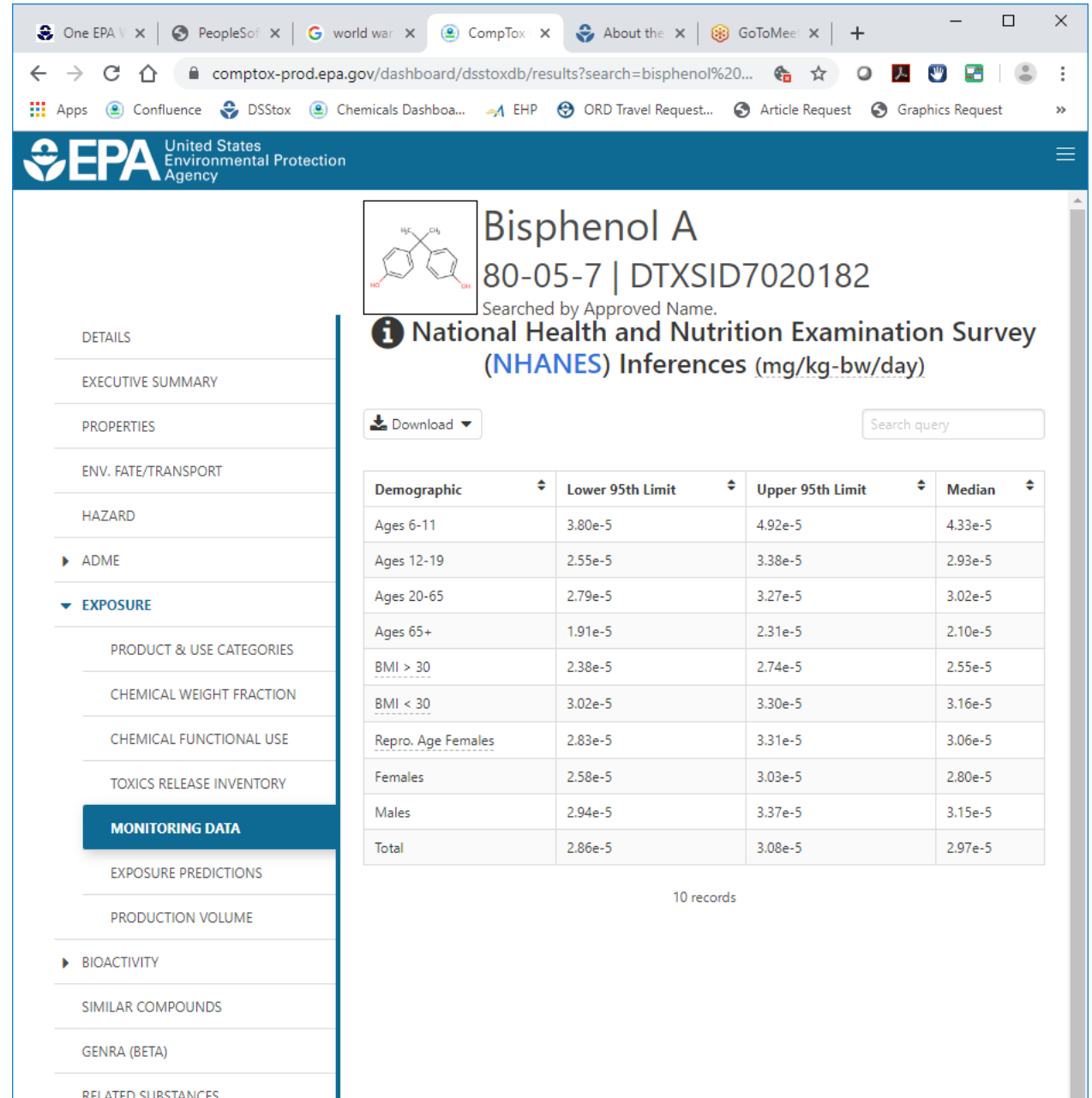
in vivo
toxicity studies



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>



The screenshot shows the EPA Comptox dashboard for Bisphenol A. The dashboard includes a sidebar with navigation options: DETAILS, EXECUTIVE SUMMARY, PROPERTIES, ENV. FATE/TRANSPORT, HAZARD, ADME, EXPOSURE (selected), PRODUCT & USE CATEGORIES, CHEMICAL WEIGHT FRACTION, CHEMICAL FUNCTIONAL USE, TOXICS RELEASE INVENTORY, MONITORING DATA (highlighted), EXPOSURE PREDICTIONS, PRODUCTION VOLUME, BIOACTIVITY, SIMILAR COMPOUNDS, GENRA (BETA), and RELATED SUBSTANCES.

The main content area displays the chemical structure of Bisphenol A, its name, and its DTXSID (80-05-7 | DTXSID7020182). It also indicates the search method (Searched by Approved Name) and the data source (National Health and Nutrition Examination Survey (NHANES) Inferences (mg/kg-bw/day)).

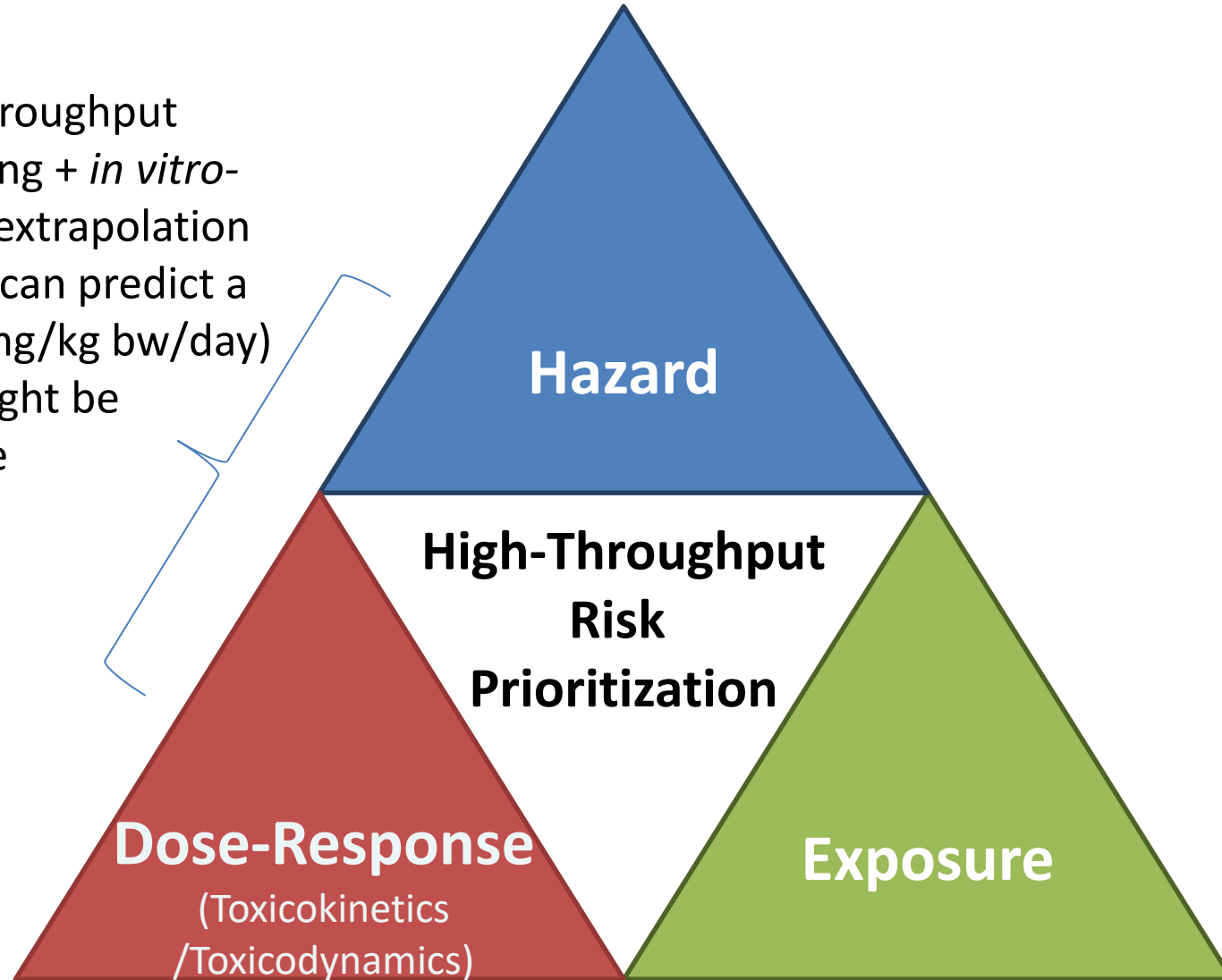
A table provides exposure data for various demographic groups:

Demographic	Lower 95th Limit	Upper 95th Limit	Median
Ages 6-11	3.80e-5	4.92e-5	4.33e-5
Ages 12-19	2.55e-5	3.38e-5	2.93e-5
Ages 20-65	2.79e-5	3.27e-5	3.02e-5
Ages 65+	1.91e-5	2.31e-5	2.10e-5
BMI > 30	2.38e-5	2.74e-5	2.55e-5
BMI < 30	3.02e-5	3.30e-5	3.16e-5
Repro. Age Females	2.83e-5	3.31e-5	3.06e-5
Females	2.58e-5	3.03e-5	2.80e-5
Males	2.94e-5	3.37e-5	3.15e-5
Total	2.86e-5	3.08e-5	2.97e-5

10 records

New Exposure Data and Models

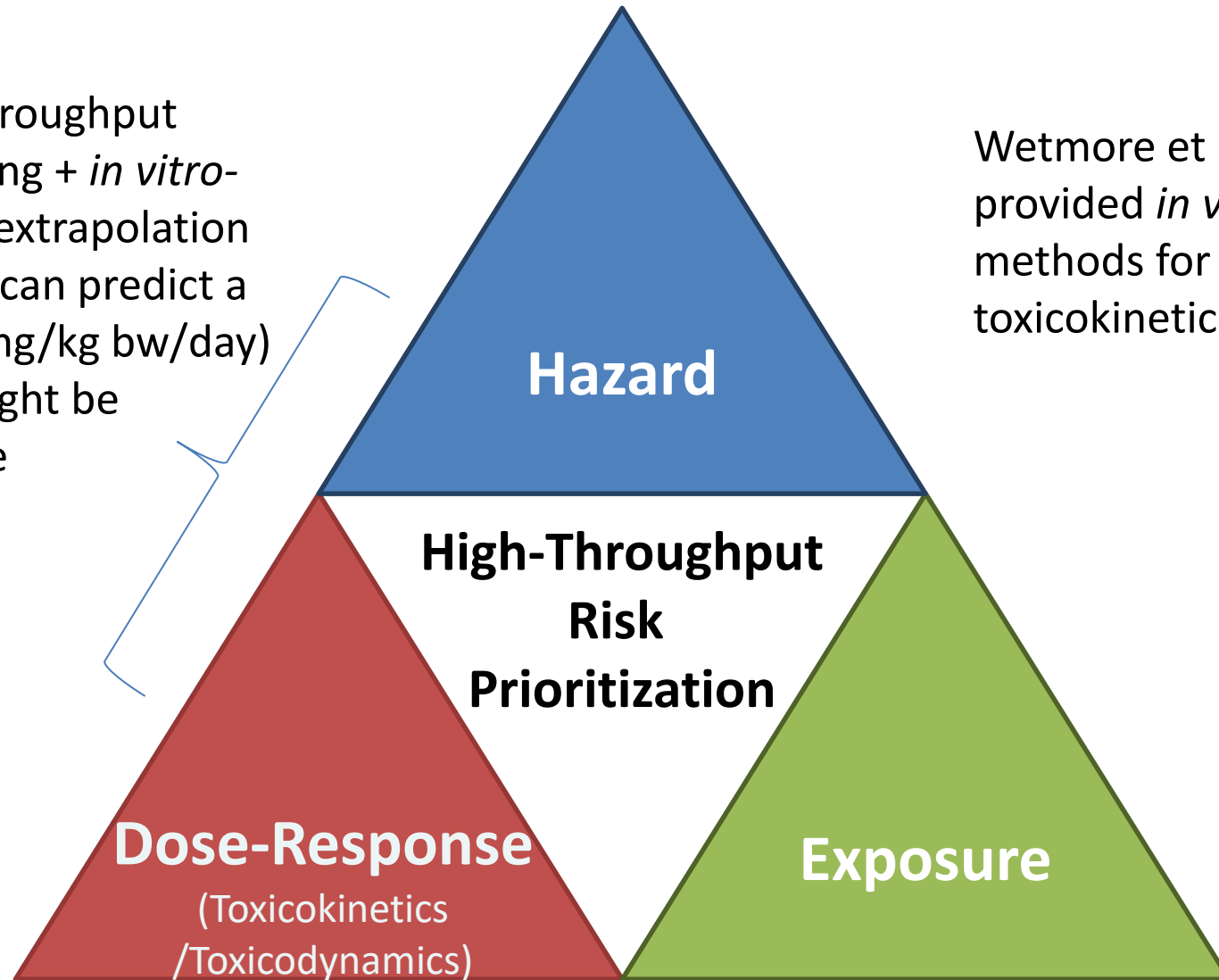
High throughput
screening + *in vitro*-
in vivo extrapolation
(IVIVE) can predict a
dose (mg/kg bw/day)
that might be
adverse



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

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

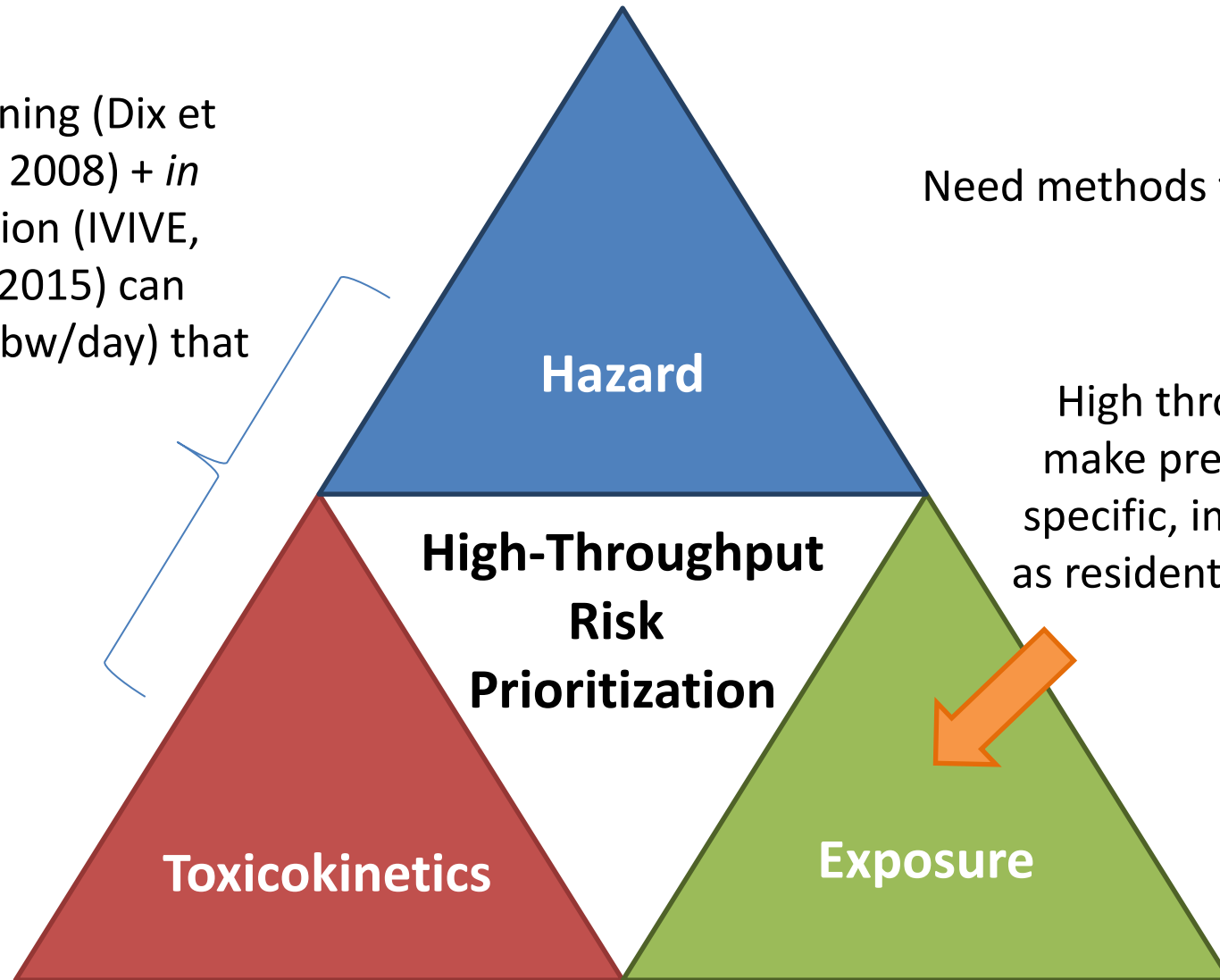


Risk = Hazard x Exposure

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)

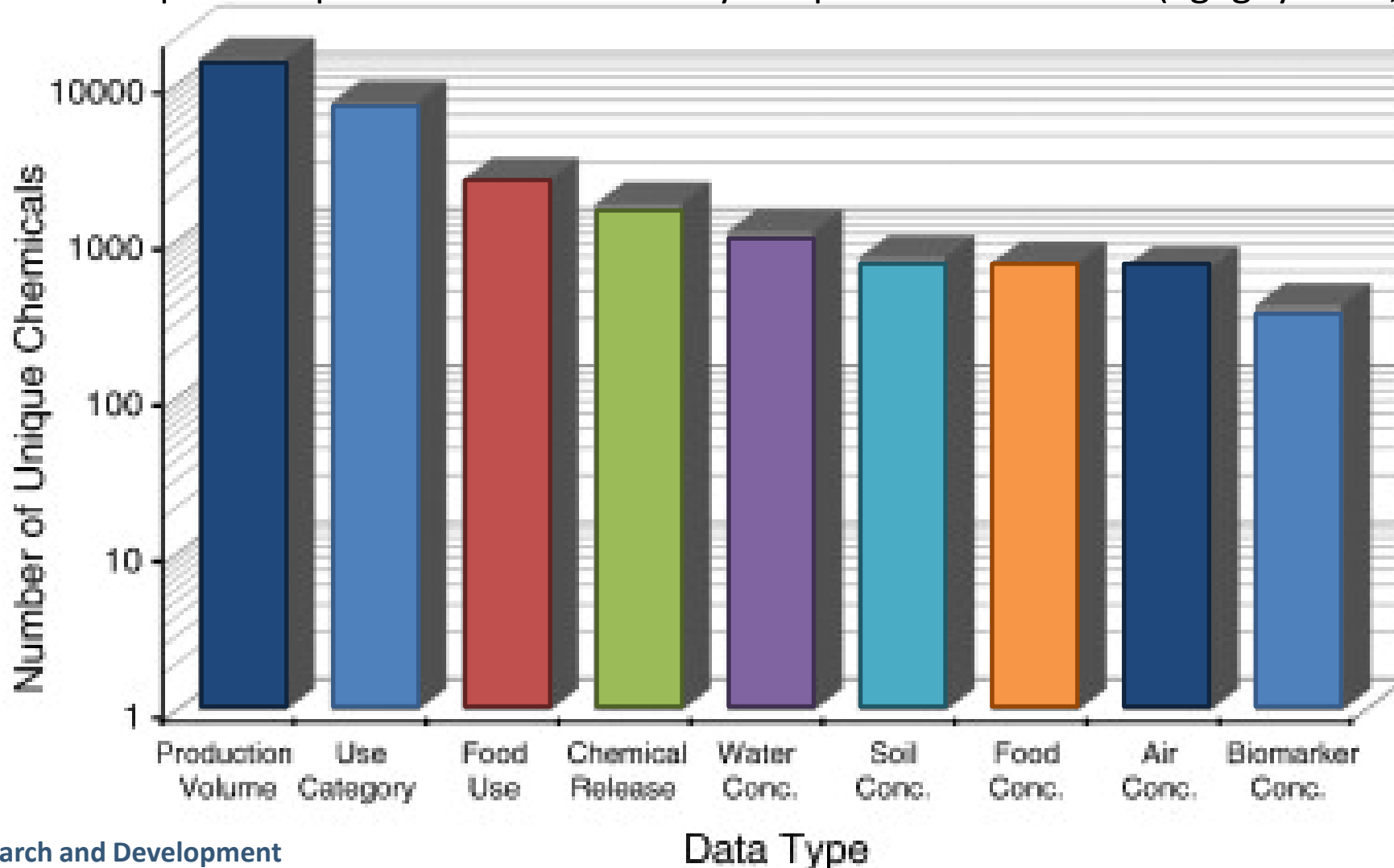
High throughput models exist to make predictions of exposure via specific, important pathways such as residential product use and diet



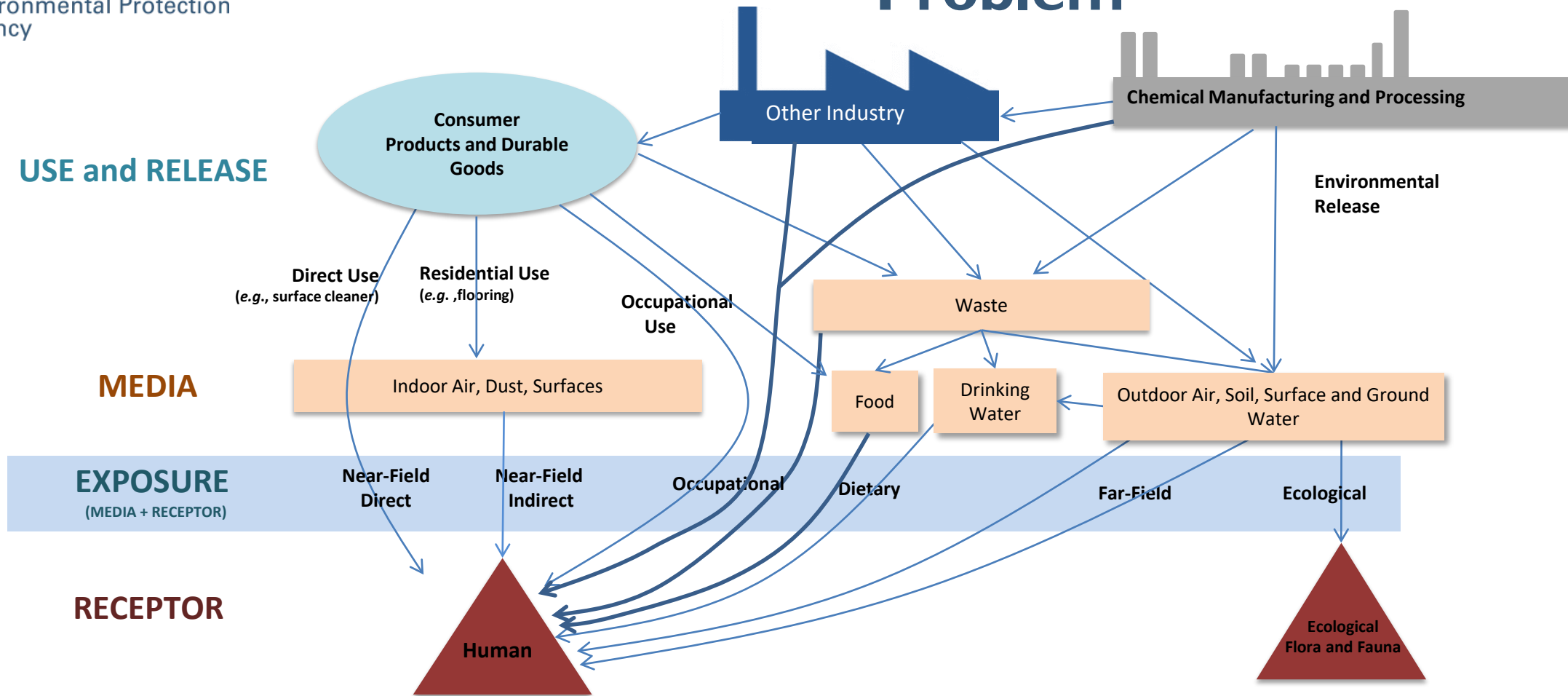
NRC (1983)

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	●	●	●	●	●	●

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**



National Health and Nutrition Examination Survey

What Do We Know About Exposure?

Exposure Models

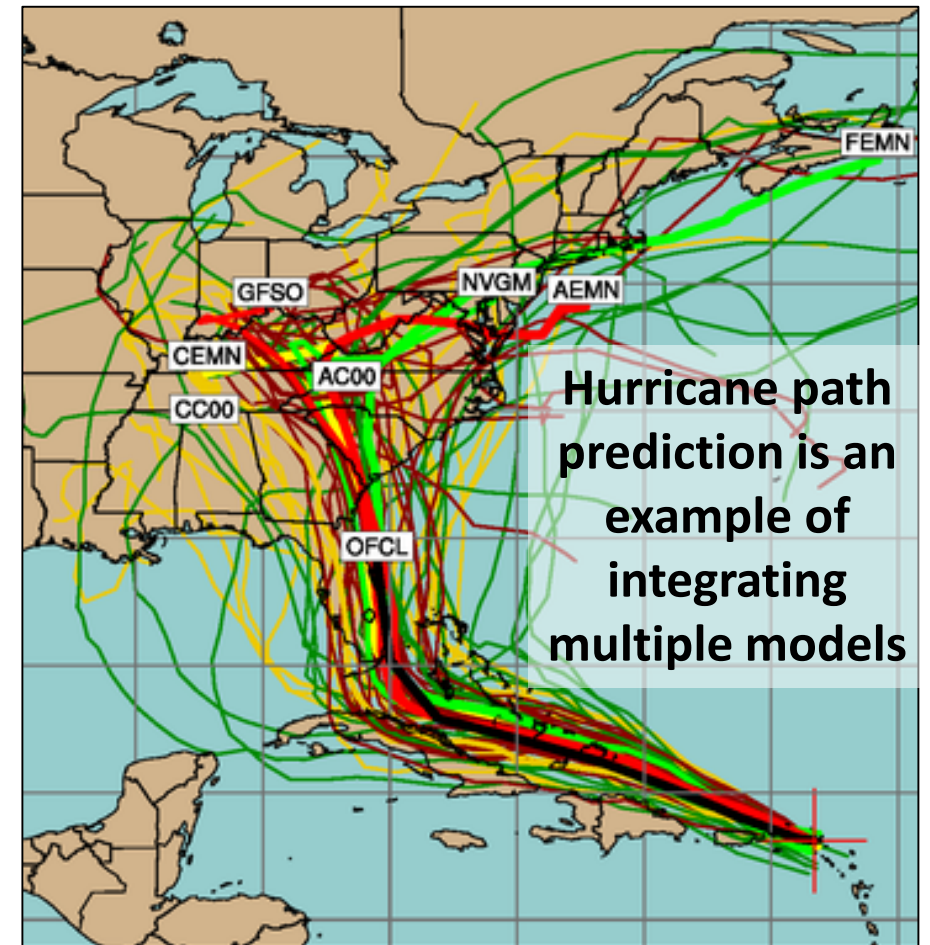
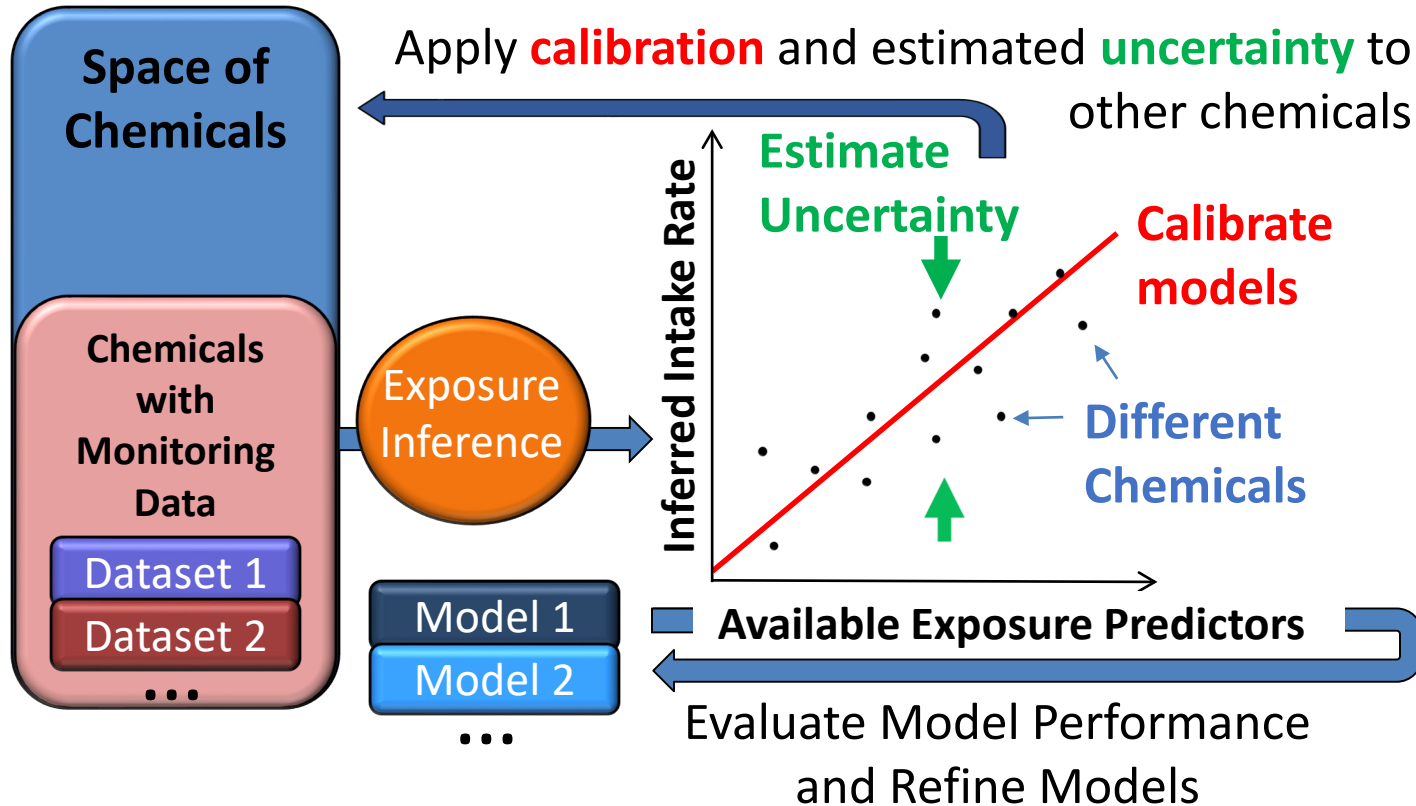
- Human chemical exposures can be coarsely grouped into “**near field**” sources that are close to the exposed individual (consumer or occupational exposures) ‘**far-field**’ scenarios wherein individuals are exposed to chemicals that were released or used far away (ambient exposure) (Arnot *et al.*,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

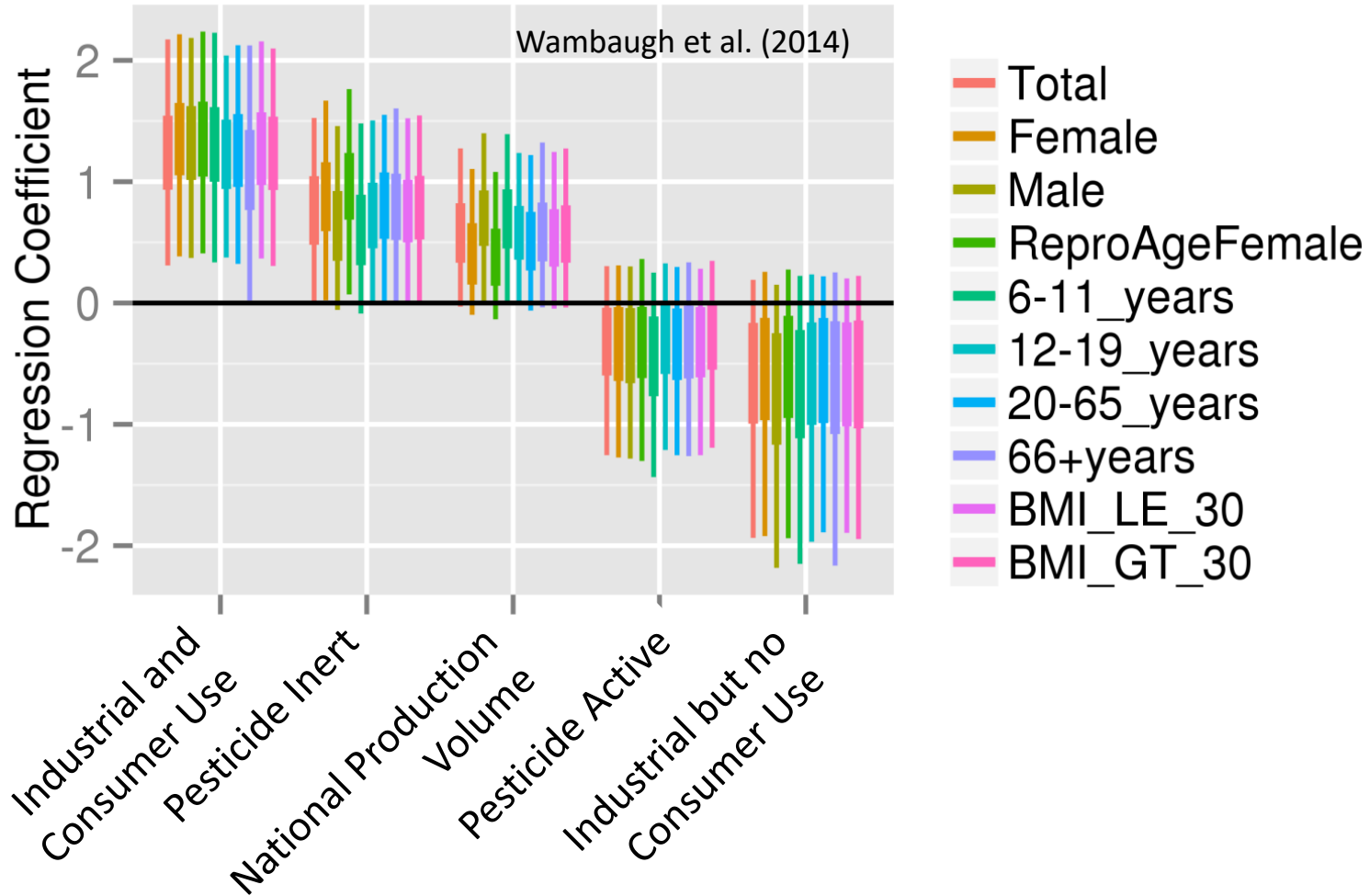
“Now it would be very remarkable if any system existing in the real world could be exactly represented by any simple model. However, cunningly chosen parsimonious models often do provide remarkably useful approximations... The only question of interest is ‘Is the model illuminating and useful?’” George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



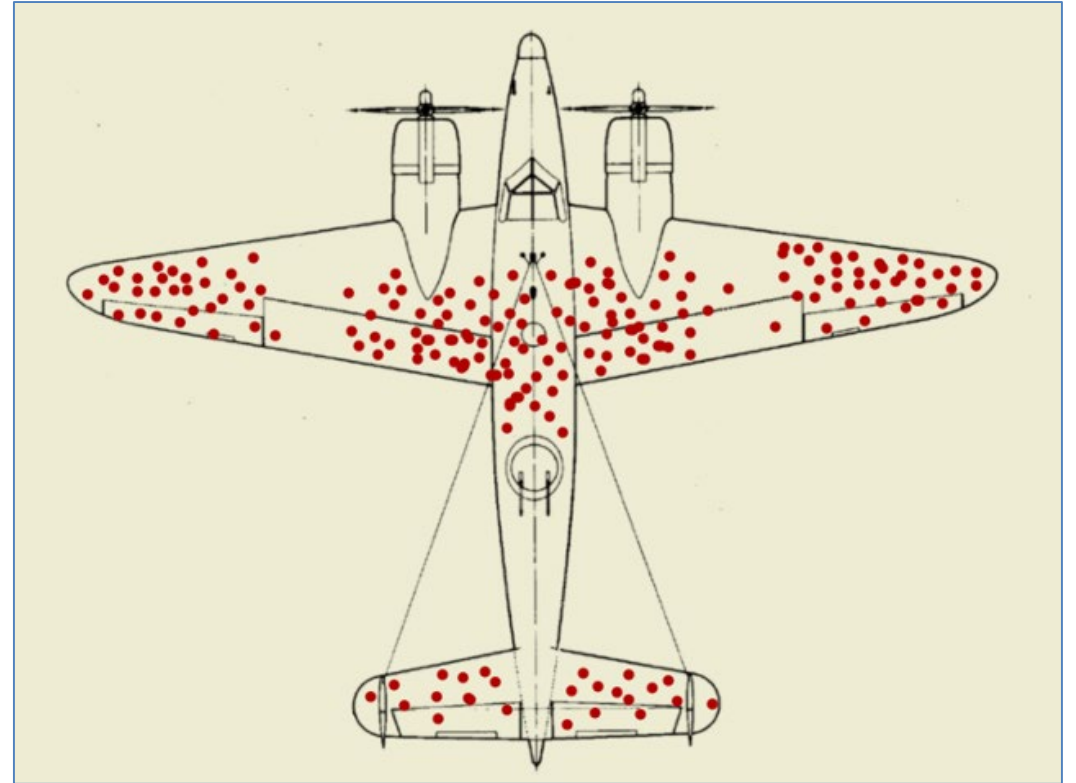
$R^2 \approx 0.5$ indicates that we can predict 50% of the chemical to chemical variability in median NHANES exposure rates

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, the 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 occurring by other pathways**

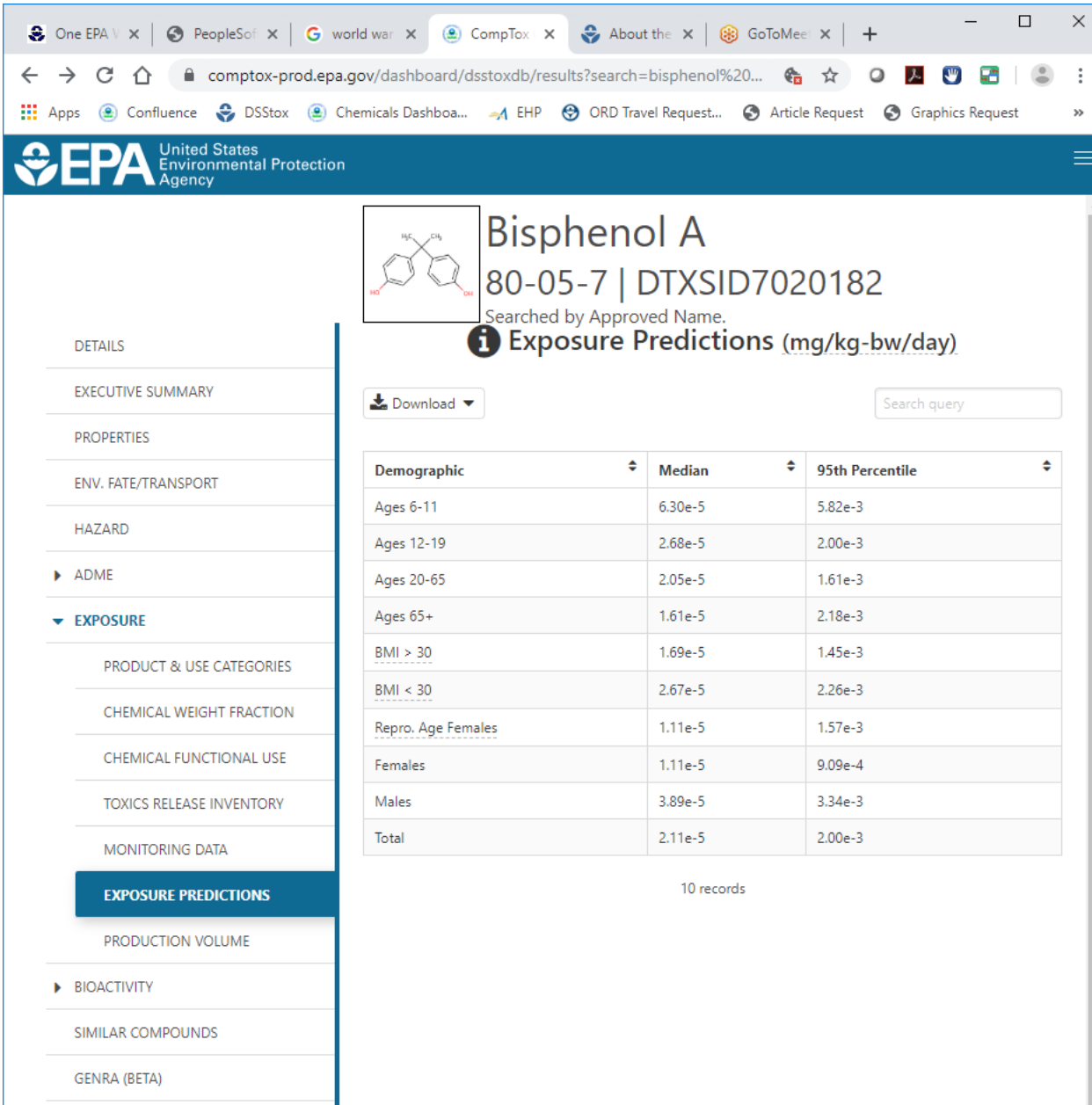


EPA Chemical Dashboard Provides SEEM Predictions

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>




The screenshot shows the EPA Chemical Dashboard interface. The top navigation bar includes the EPA logo and the text "United States Environmental Protection Agency". The main header displays the chemical name "Bisphenol A" and its identifier "80-05-7 | DTXSID7020182". Below this, it states "Searched by Approved Name." and "Exposure Predictions (mg/kg-bw/day)". A "Download" button and a "Search query" input field are visible. The main content area features a table with exposure predictions for various demographic groups. The table has three columns: "Demographic", "Median", and "95th Percentile". The rows include age groups (Ages 6-11, 12-19, 20-65, 65+), BMI categories (BMI > 30, BMI < 30), and gender (Repro. Age Females, Females, Males, Total). The "EXPOSURE PREDICTIONS" section is highlighted in the left sidebar. The bottom of the page shows "10 records" and a list of other sections like "PRODUCT & USE CATEGORIES", "CHEMICAL WEIGHT FRACTION", "CHEMICAL FUNCTIONAL USE", "TOXICS RELEASE INVENTORY", "MONITORING DATA", "PRODUCTION VOLUME", "BIOACTIVITY", "SIMILAR COMPOUNDS", and "GENRA (BETA)".

Demographic	Median	95th Percentile
Ages 6-11	6.30e-5	5.82e-3
Ages 12-19	2.68e-5	2.00e-3
Ages 20-65	2.05e-5	1.61e-3
Ages 65+	1.61e-5	2.18e-3
BMI > 30	1.69e-5	1.45e-3
BMI < 30	2.67e-5	2.26e-3
Repro. Age Females	1.11e-5	1.57e-3
Females	1.11e-5	9.09e-4
Males	3.89e-5	3.34e-3
Total	2.11e-5	2.00e-3

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.”

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Article

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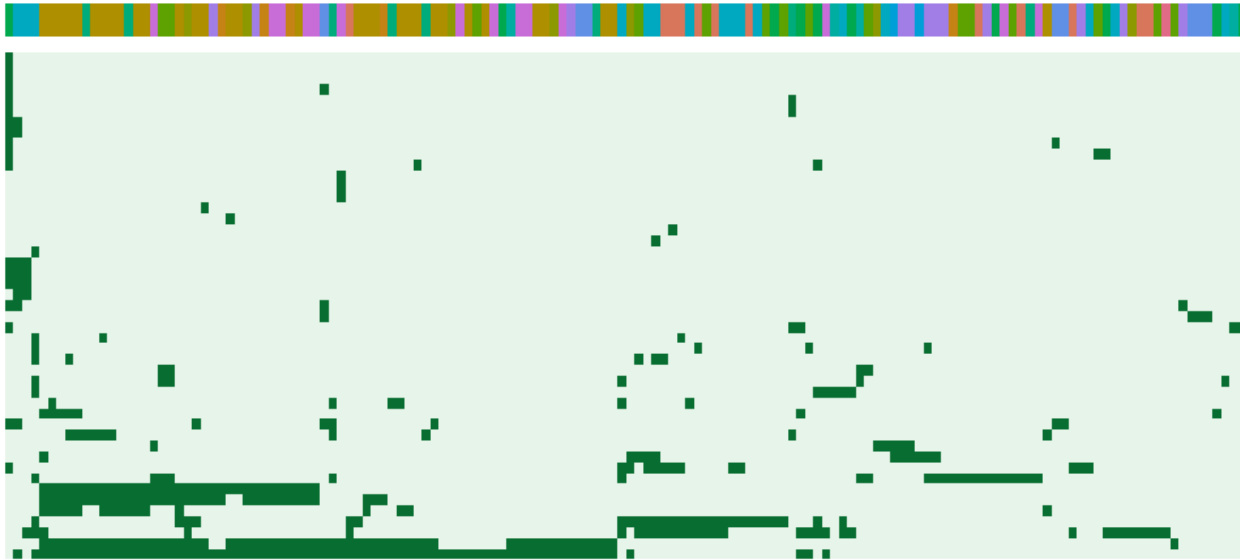
Risk-Based High-Throughput Chemical Screening and Prioritization using Exposure Models and in Vitro Bioactivity Assays

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

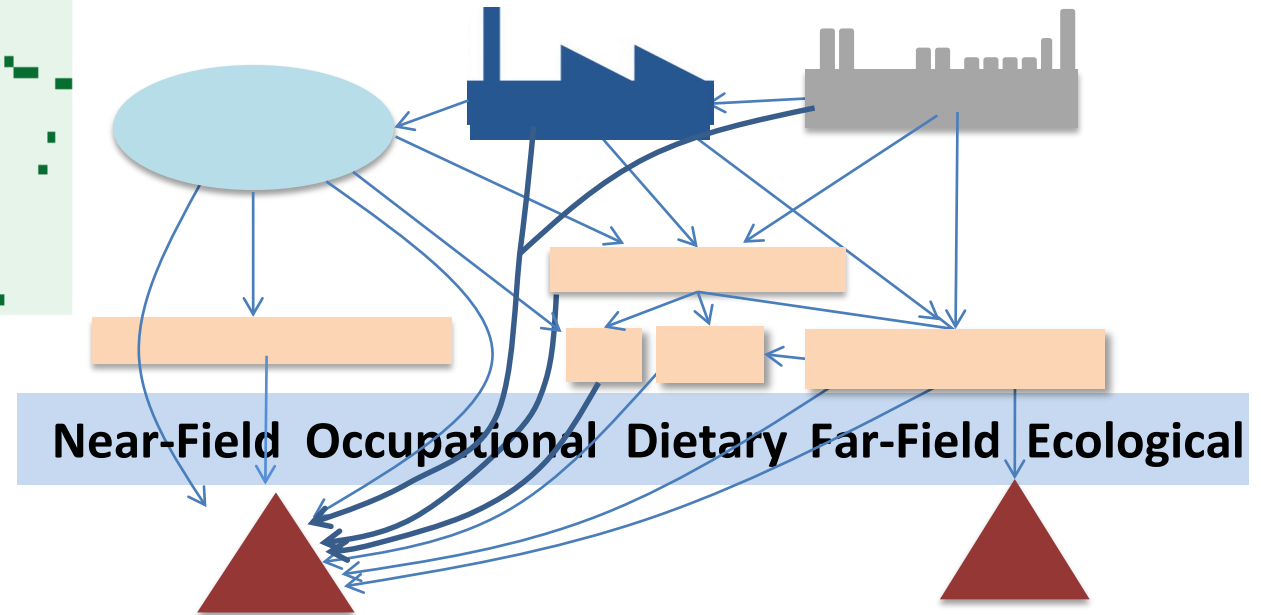
>2000 chemicals with Material Safety Data Sheets
(MSDS) in CPCPdb (Goldsmith *et al.*, 2014)

106 NHANES Chemicals



- | | |
|-----------------|---------------------|
| Apparel | Health |
| Auto and Tires | Home |
| Baby | Home Improvement |
| Beauty | Patio and Garden |
| Craft and Party | Pets |
| Electronics | Sports and Outdoors |
| Grocery | Toys |

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

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
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Kathie L. Dionisio¹, Katherine Phillips¹, Paul S. Price¹, Christopher M. Grulke², Anthony Williams², Derya Biryol^{1,2}, Tao Hong³ & Kristin K. Isaacs¹

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,c}, P.P. Egeghy^a, R. Edwards^d, D.T. Chang^a, R. Tornero-Velez^a, K. Isaacs^a, A. Wang^{a,c}, 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

Green Chemistry

PAPER

View Article Online
View Journal | View Issue

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

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

Environmental Science & Technology

Article

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

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^{*,||}

Measured
Data

Measurement of chemicals in
consumer products

Ingredient
Lists

Occurrence
data

CPCat

CPDat



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

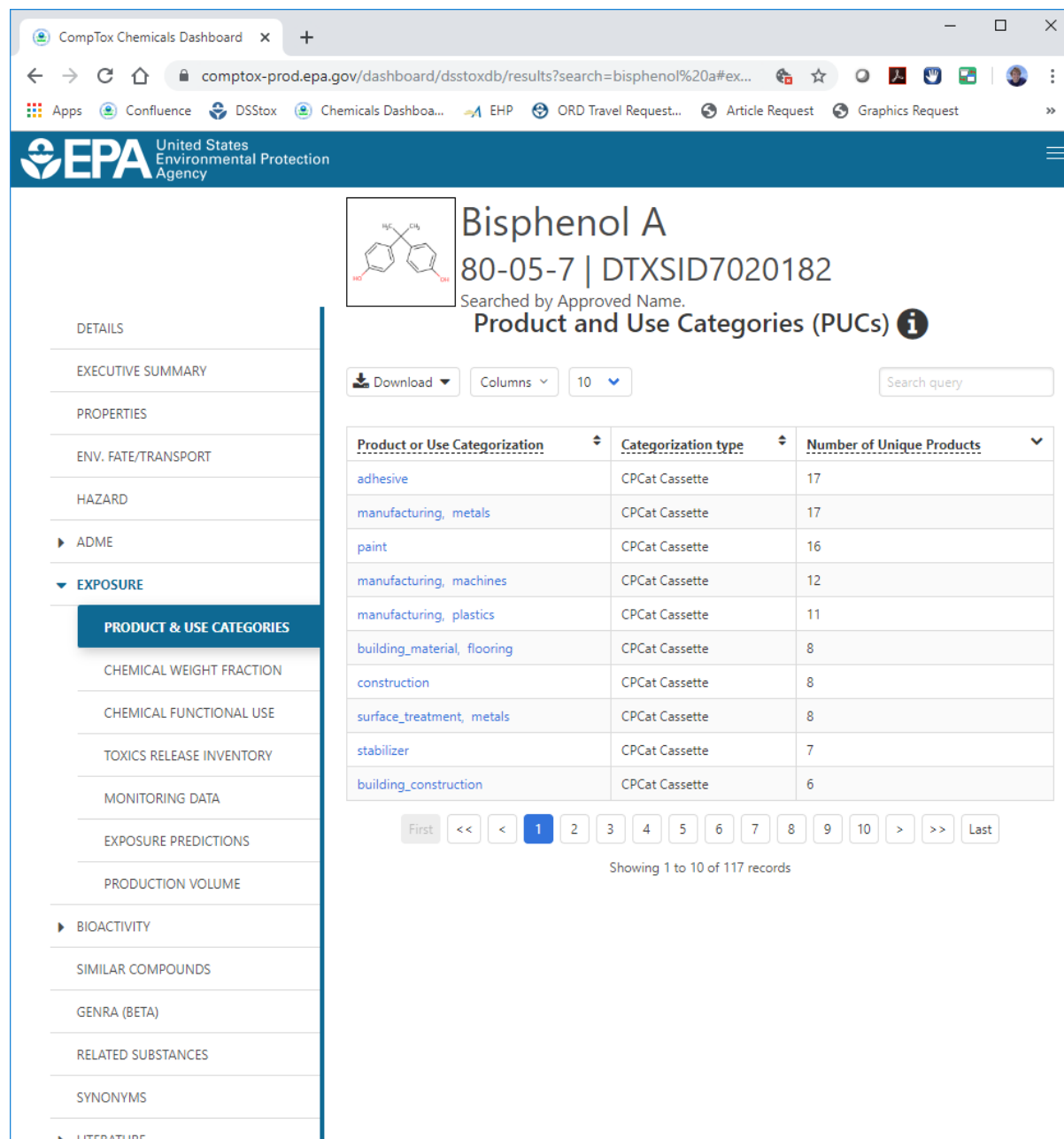
Journal of Exposure Science and Environmental Epidemiology (2018) 28, 216–222
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www.nature.com/jes

ORIGINAL ARTICLE

Consumer product chemical weight fractions from ingredient lists

Kristin K. Isaacs¹, Katherine A. Phillips¹, Derya Biryol^{1,2}, Kathie L. Dionisio¹ and Paul S. Price¹

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



The screenshot shows the EPA Chemical Dashboard interface for Bisphenol A. The left sidebar contains a navigation menu with options like DETAILS, EXECUTIVE SUMMARY, PROPERTIES, ENV. FATE/TRANSPORT, HAZARD, ADME, EXPOSURE (selected), PRODUCT & USE CATEGORIES, CHEMICAL WEIGHT FRACTION, CHEMICAL FUNCTIONAL USE, TOXICS RELEASE INVENTORY, MONITORING DATA, EXPOSURE PREDICTIONS, PRODUCTION VOLUME, BIOACTIVITY, SIMILAR COMPOUNDS, GENRA (BETA), RELATED SUBSTANCES, SYNONYMS, and LITERATURE. The main content area displays the chemical structure of Bisphenol A, its CAS number (80-05-7), and DTSID (DTXSID7020182). Below this, there is a table titled 'Product and Use Categories (PUCs)' showing various product categories and the number of unique products for each. The table has three columns: Product or Use Categorization, Categorization type, and Number of Unique Products. The categories listed include adhesive, manufacturing, metals, paint, manufacturing, machines, manufacturing, plastics, building material, flooring, construction, surface treatment, metals, stabilizer, and building construction. The table shows 10 records, with a total of 117 records available.

Product or Use Categorization	Categorization type	Number of Unique Products
adhesive	CPCat Cassette	17
manufacturing, metals	CPCat Cassette	17
paint	CPCat Cassette	16
manufacturing, machines	CPCat Cassette	12
manufacturing, plastics	CPCat Cassette	11
building material, flooring	CPCat Cassette	8
construction	CPCat Cassette	8
surface treatment, metals	CPCat Cassette	8
stabilizer	CPCat Cassette	7
building construction	CPCat Cassette	6

SCIENTIFIC DATA

OPEN

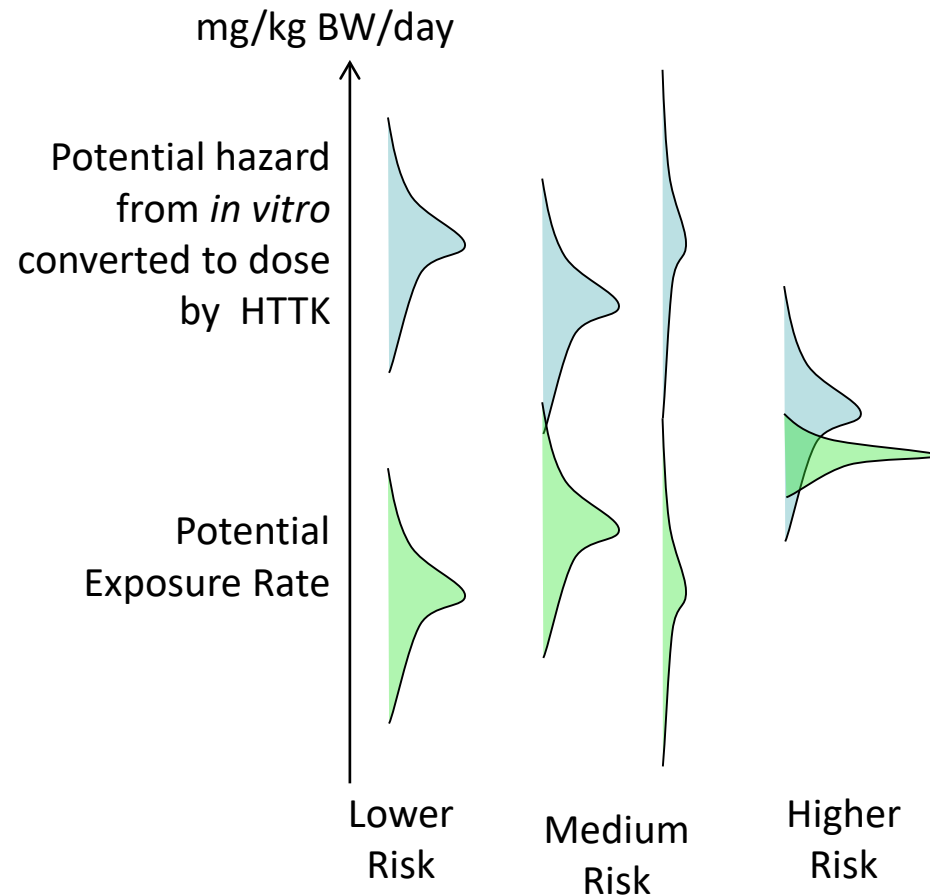
Data Descriptor: The Chemical and Products Database, a resource for exposure-relevant data on chemicals in consumer products

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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



ExpoCast Project (Exposure Forecasting)

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