EPA's Rapid Exposure and Dosimetry Project

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EPA United States Environmental Protection Agency

Chemical Safety for Sustainability (CSS) Rapid Exposure and Dosimetry (RED) Project

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Introduction

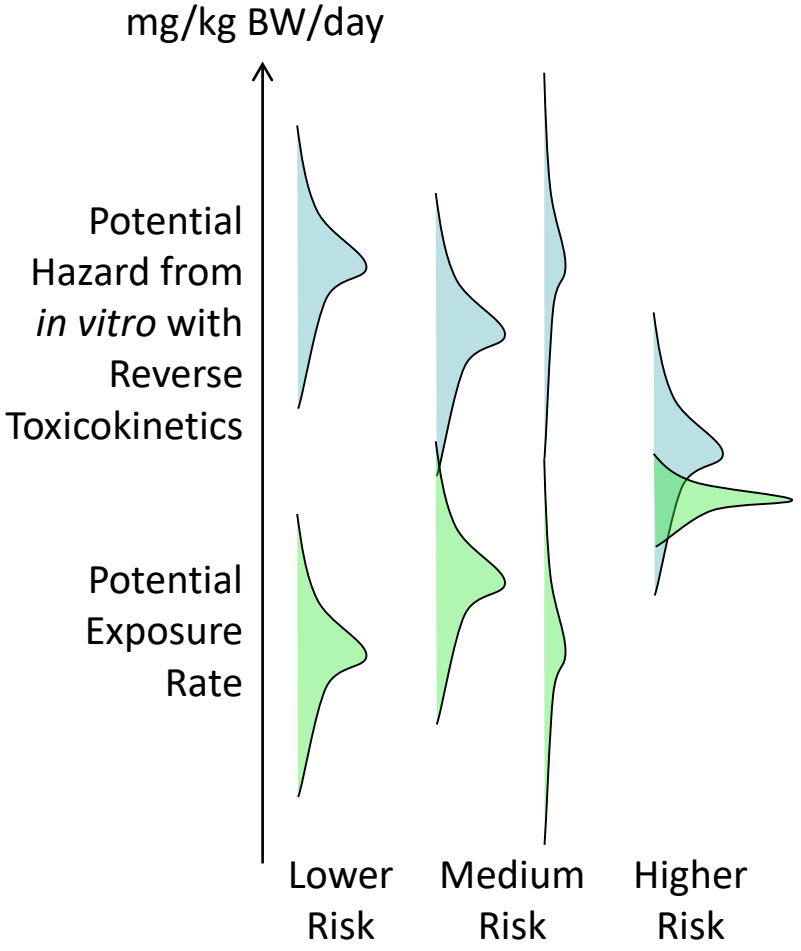
The timely characterization of the human and ecological risk posed by thousands of existing and emerging commercial chemicals is a critical challenge facing EPA in its mission to protect public health and the environment

- Park *et al*. (2012): At least 3221 chemicals in humans, many appear to be exogenous

November 29, 2014

High Throughput Risk Prioritization

- **High throughput risk prioritization** needs:
  1. high throughput **hazard** characterization (from HTT project)
  2. high throughput **exposure** forecasts
  3. high throughput **toxicokinetics** (*i.e.*, dosimetry)



High-Throughput Bioactivity

- **Tox21**: Examining >10,000 chemicals using ~50 assays intended to identify interactions with biological pathways (Schmidt, 2009)

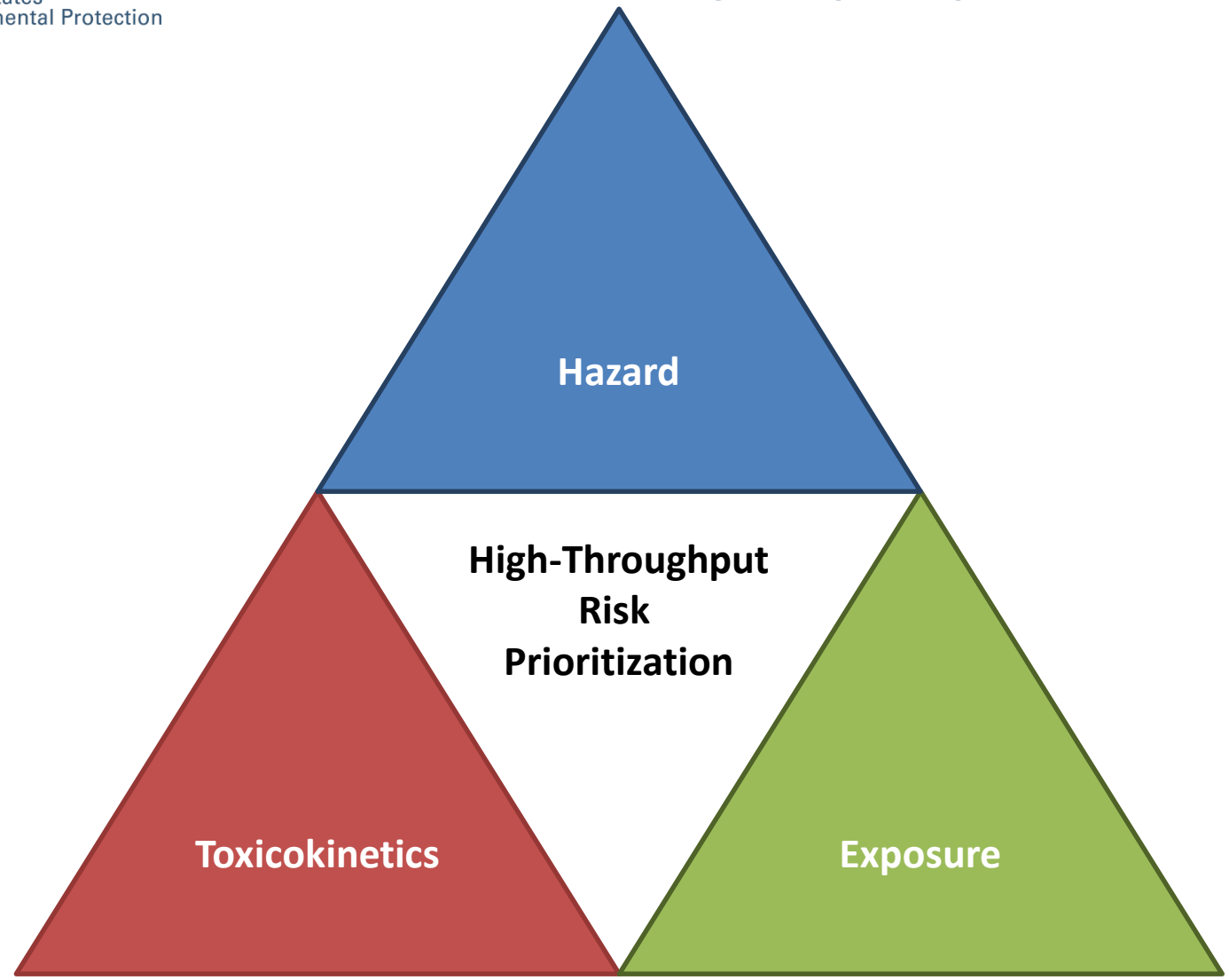
- **EPA Toxicity Forecaster (ToxCast)**:

  For a subset (>3000) of Tox21 chemicals run >1000 additional assay endpoints (Judson et al., 2010)

  Most assays conducted in dose-response format (identify 50% activity concentration – AC50 – and efficacy if data described by a Hill function)

http://actor.epa.gov/dashboard/

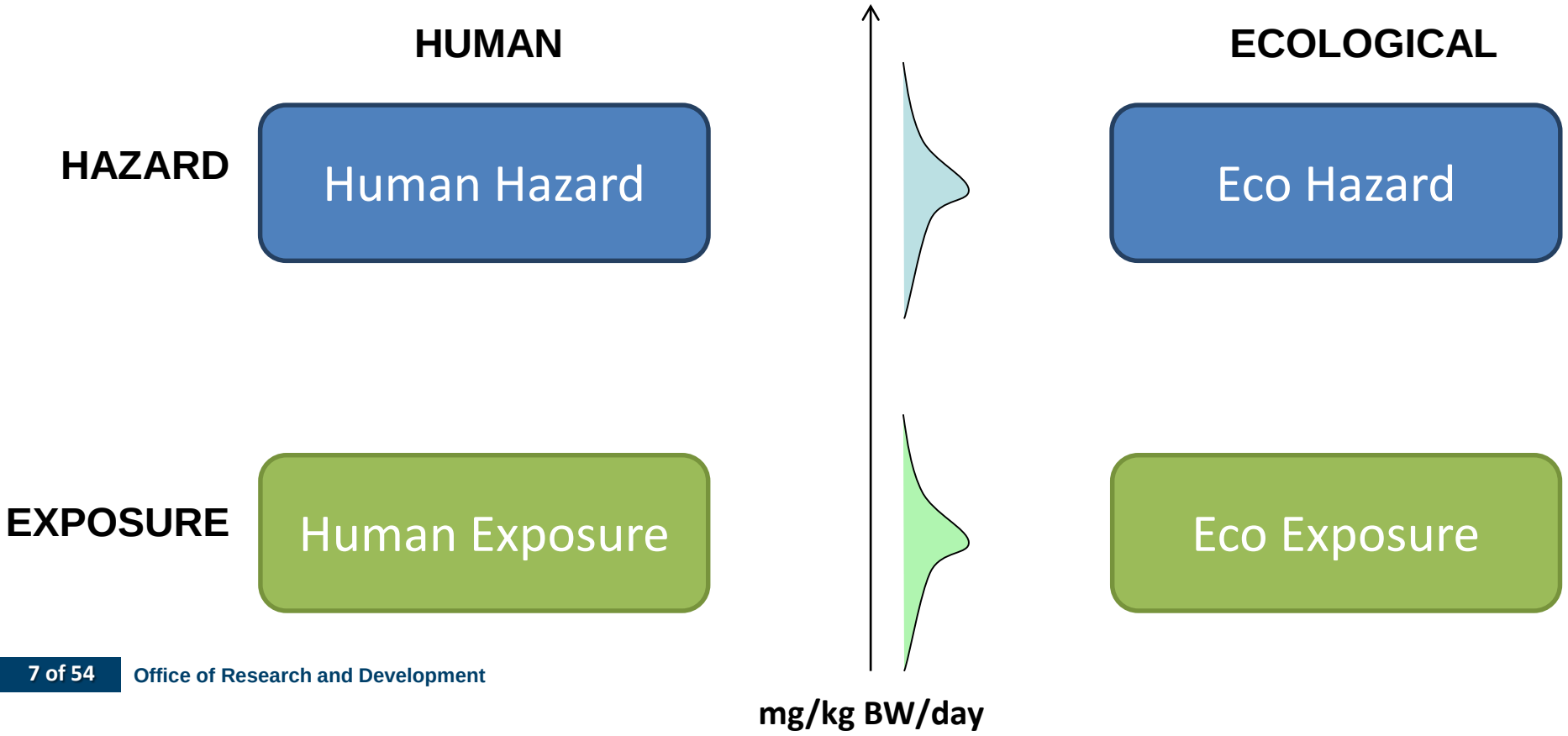
Application to U.S. EPA Endocrine Disruptor Screening Program (EDSP)



High Throughput Chemical Risk Prioritization

Prioritization as in Wetmore *et al*. (2015)

July and December 2014 FIFRA Scientific Advisory Panels reviewed research as it applies to the Endocrine Disruptor Screening Program



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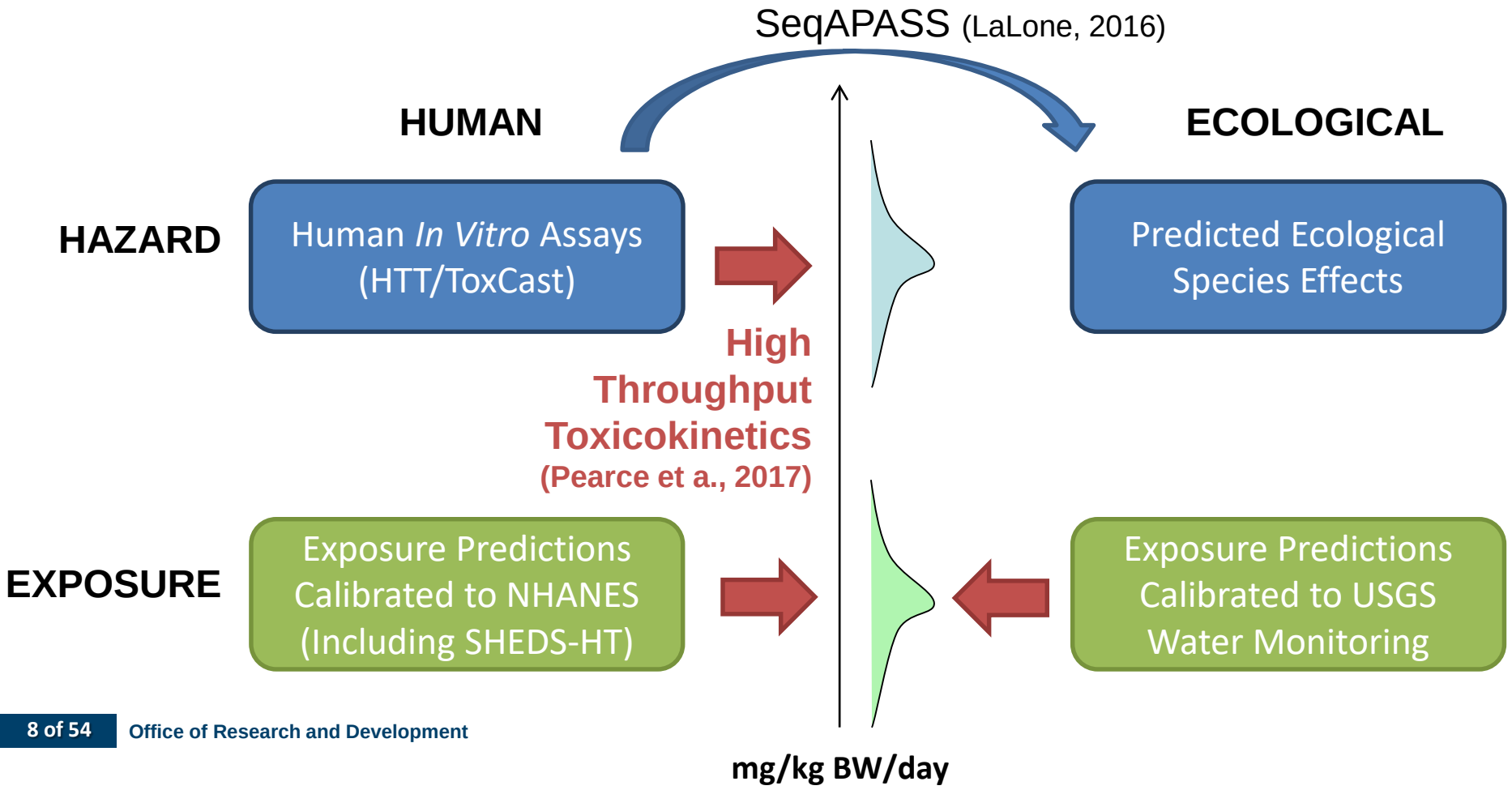


High Throughput Risk Prioritization in Practice

mg/kg bw/day

ToxCast-derived Receptor Bioactivity Converted to mg/kg/day with HTTK

ExpoCast Exposure Predictions

Near Field
Far Field

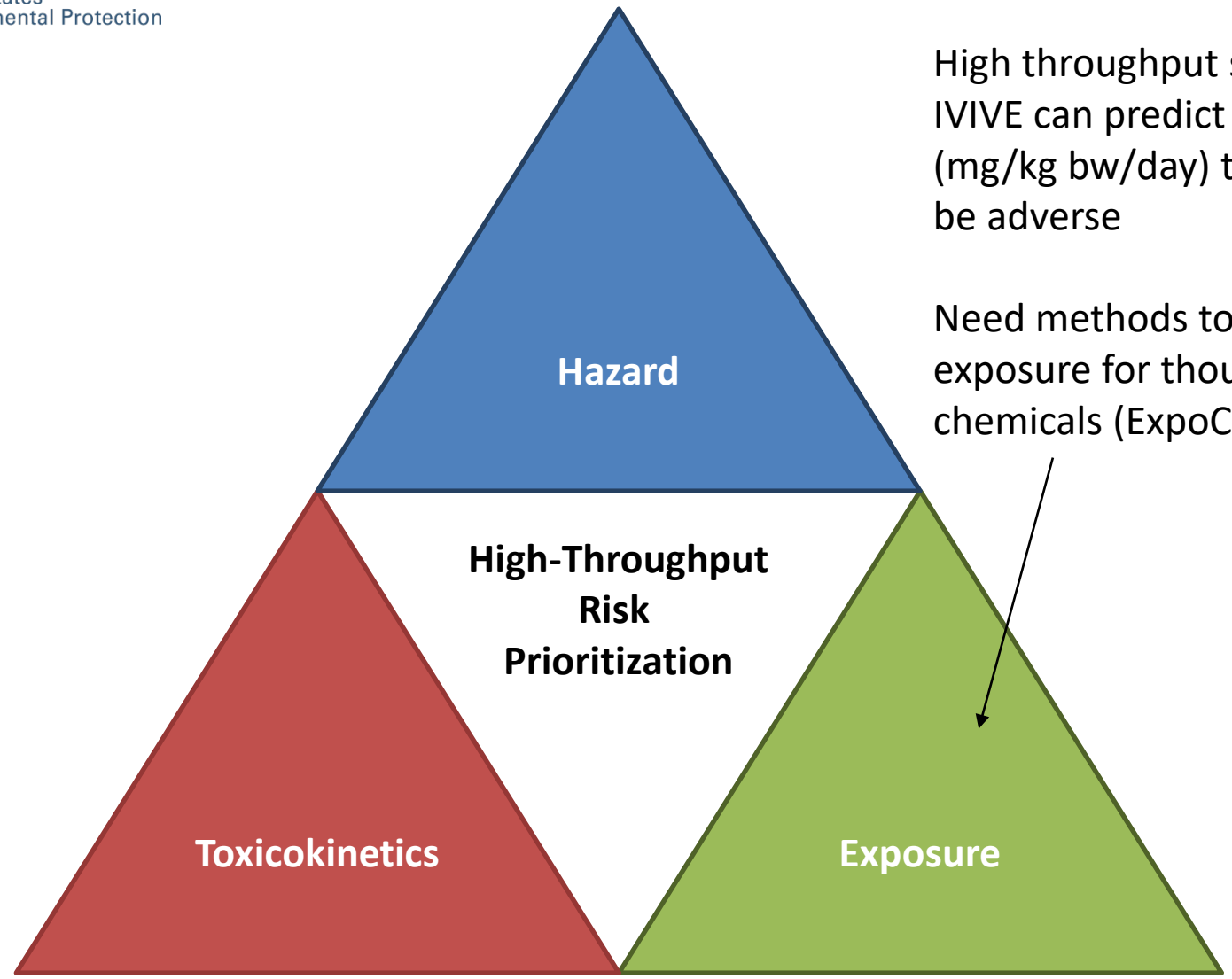
ToxCast Chemicals

December, 2014 Panel:
"Scientific Issues Associated with Integrated Endocrine Bioactivity and Exposure-Based Prioritization and Screening"

ToxCast: Toxicity Forecaster
ExpoCast: Exposure Forecaster

Rapid Exposure and Dosimetry Project provides ExpoCast research

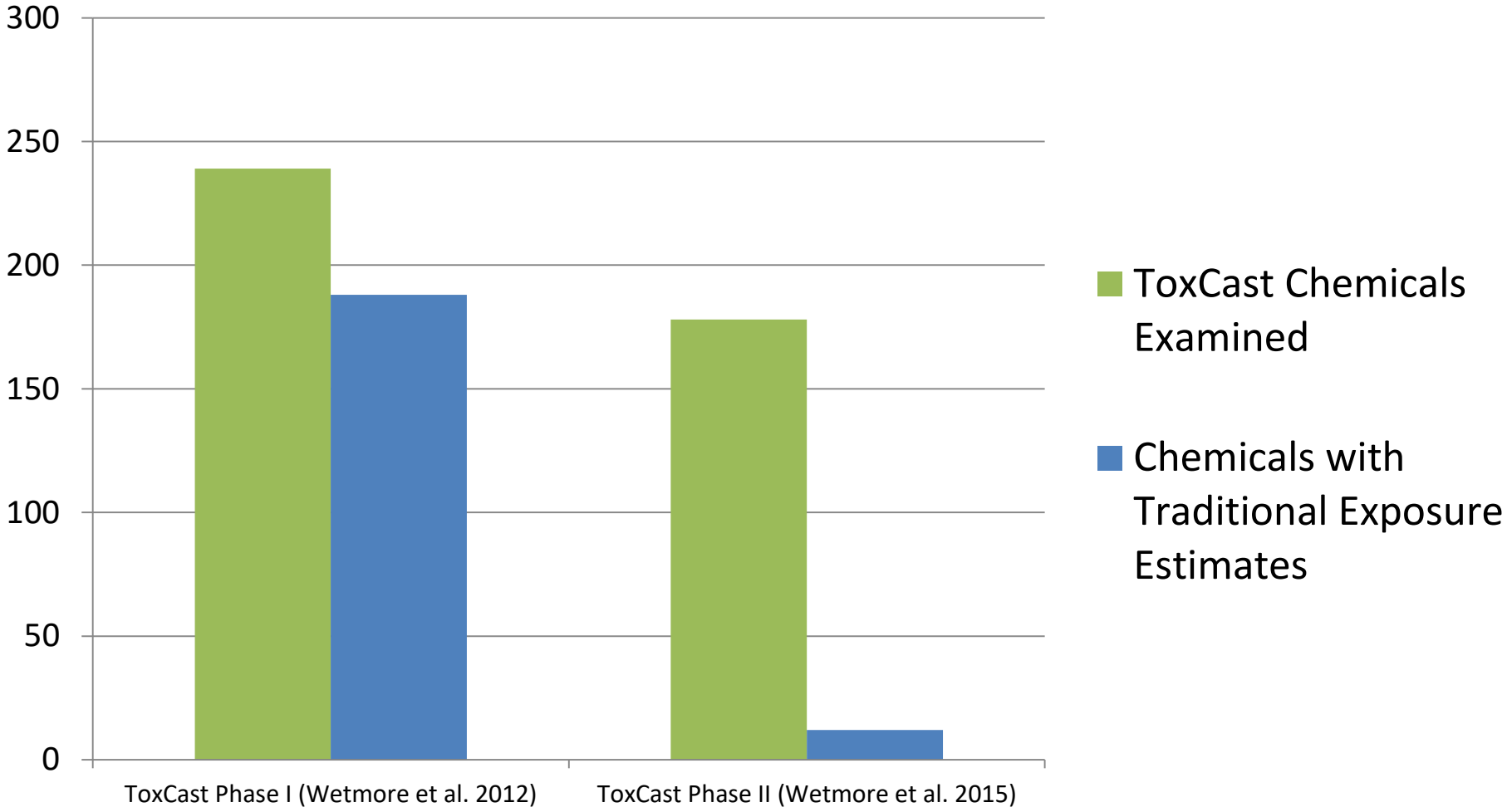
High Throughput Exposure



High throughput screening + IVIVE can predict a dose (mg/kg bw/day) that might be adverse

Need methods to forecast exposure for thousands of chemicals (ExpoCast)

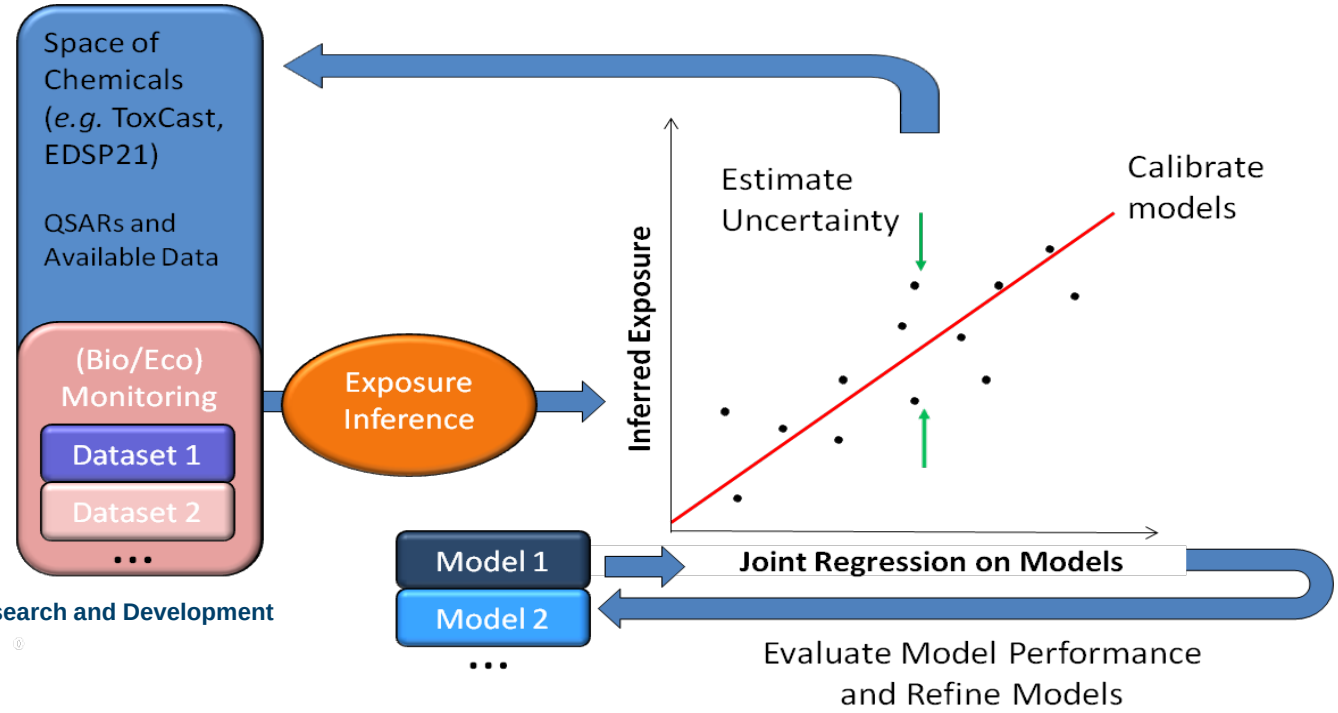
The Need for High Throughput Exposure



- Egeghy et al. (2012) – Most chemicals lack exposure data

Consensus Exposure Predictions with the SEEM Framework

- We incorporate multiple models into consensus predictions for 1000s of chemicals within the **Systematic Empirical Evaluation of Models (SEEM) framework** (Wambaugh et al., 2013, 2014)
- We evaluate/calibrate predictions with available monitoring data
- This provides information similar to a sensitivity analysis: What models are working? What data are most needed? This is an iterative process.
- To date we have relied on median U.S. population exposure rates only



Exposures Inferred from NHANES

- Annual survey, data released on 2-year cycle.
- Different predictive models provide different chemical-specific predictions
  - Some models may do a better job form some chemical classes than others overall, so we want to evaluate performance against monitoring data
- Separate evaluations can be done for various demographics

National Health and Nutrition Examination Survey

CDC, Fourth National Exposure Report (2011)

Heuristics of Exposure

Wambaugh *et al.* (2014)

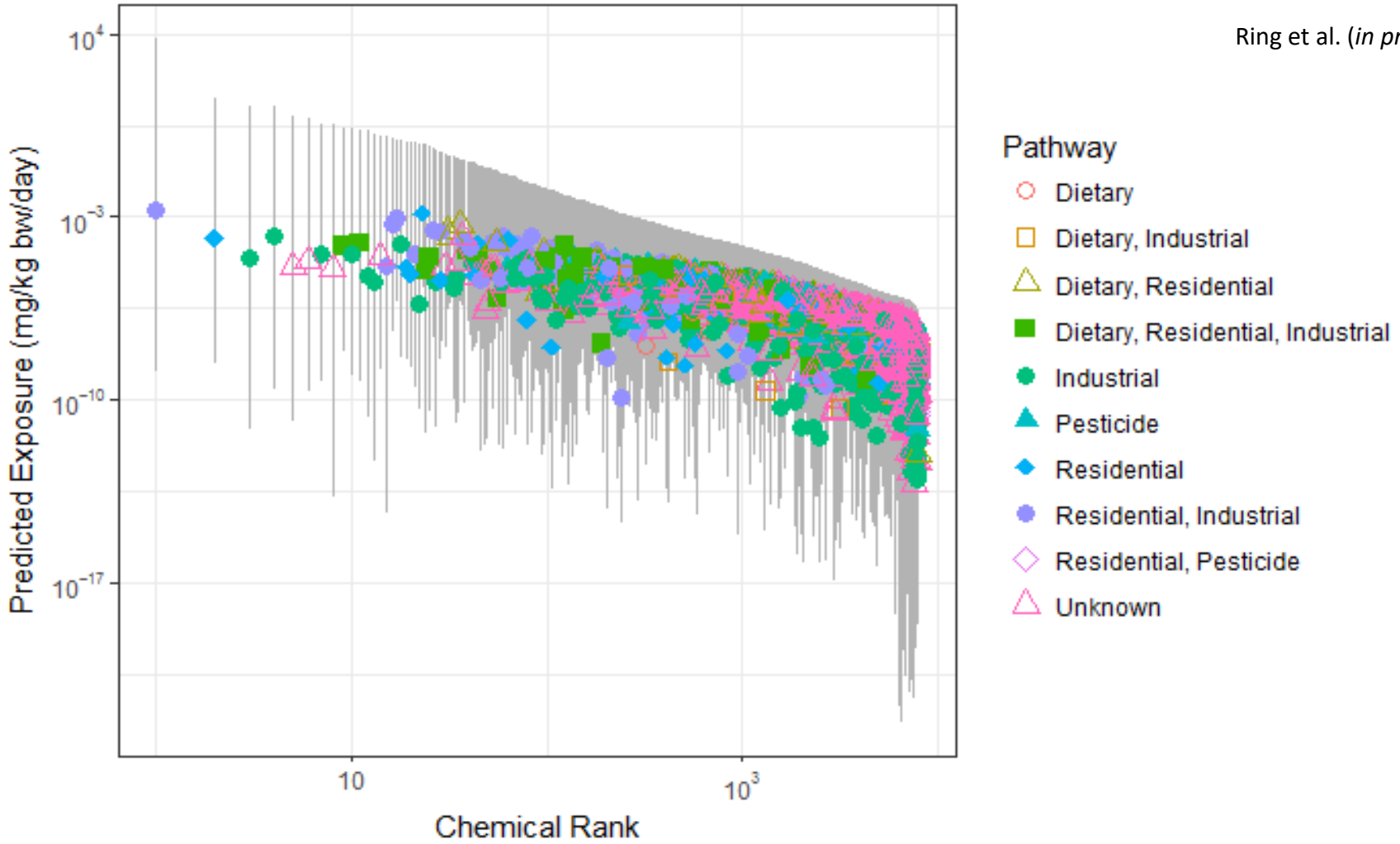
Five descriptors explain roughly 50% of the chemical to chemical variability in median NHANES exposure rates

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

Human Exposure Predictions for 134,521 Chemicals

Ring et al. (*in prep.*)



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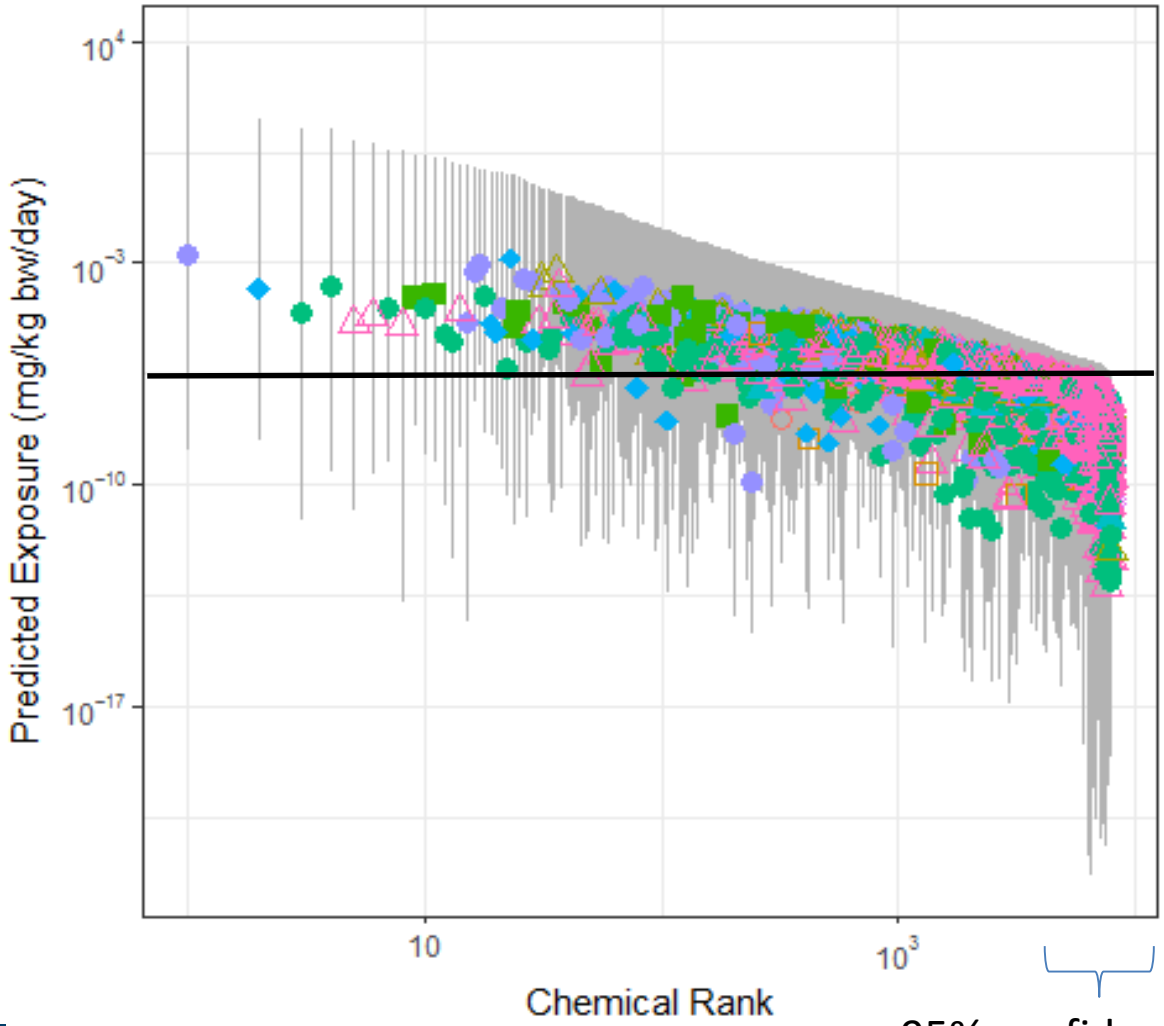
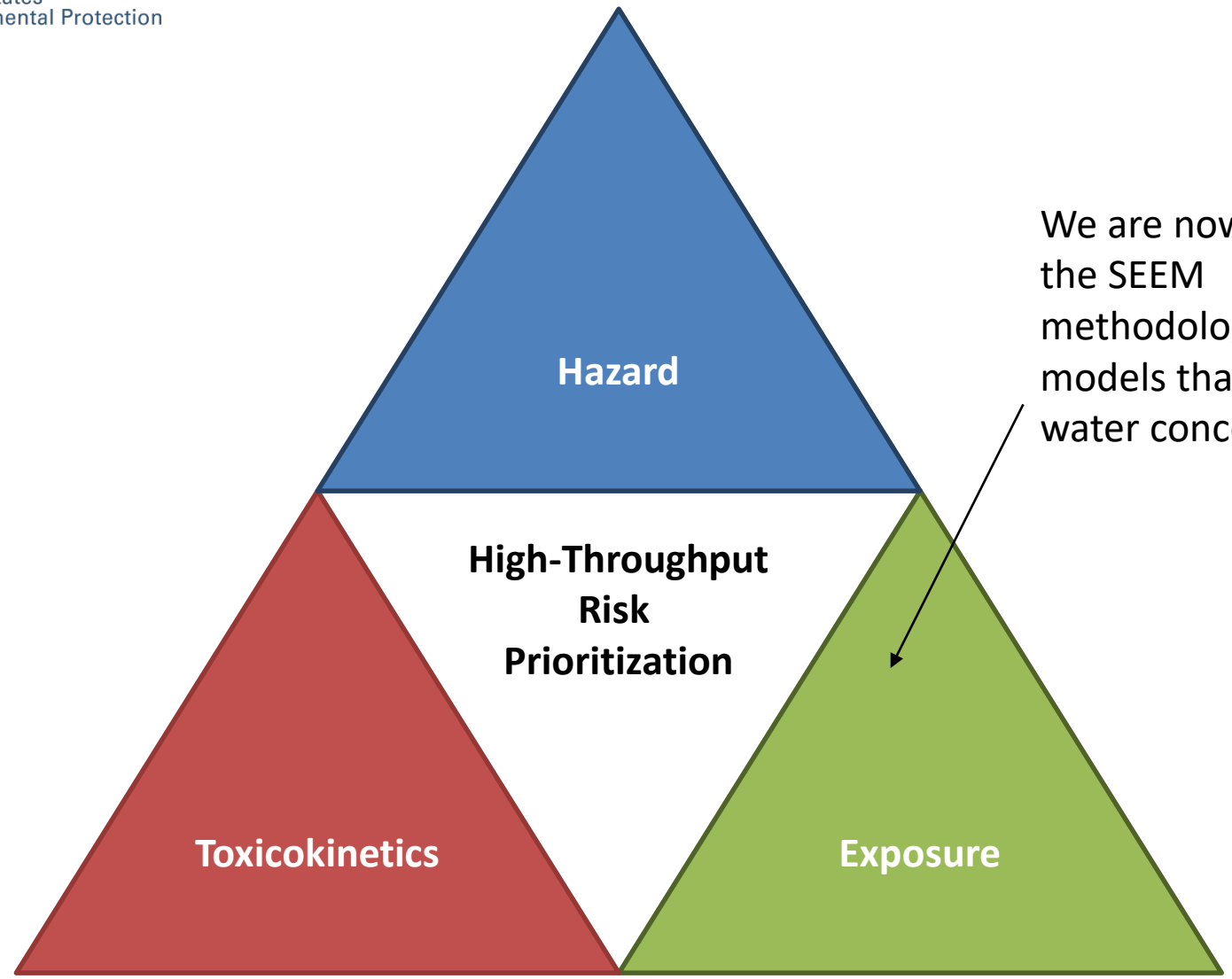


Lowest NHANES limit of detection (LOD) roughly corresponds to ~10^{-6} mg/kg BW/day

95% confident that median population would be <LOD for thousands of chemicals

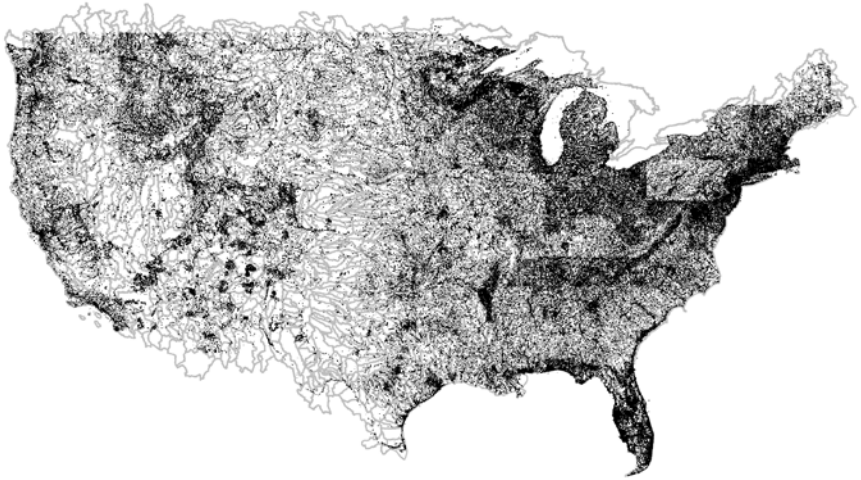
Water Concentrations



We are now applying the SEEM methodology to models that predict water concentrations

USGS National Water Quality Assessment (NAWQA) Data

https://www.waterqualitydata.us/portal/



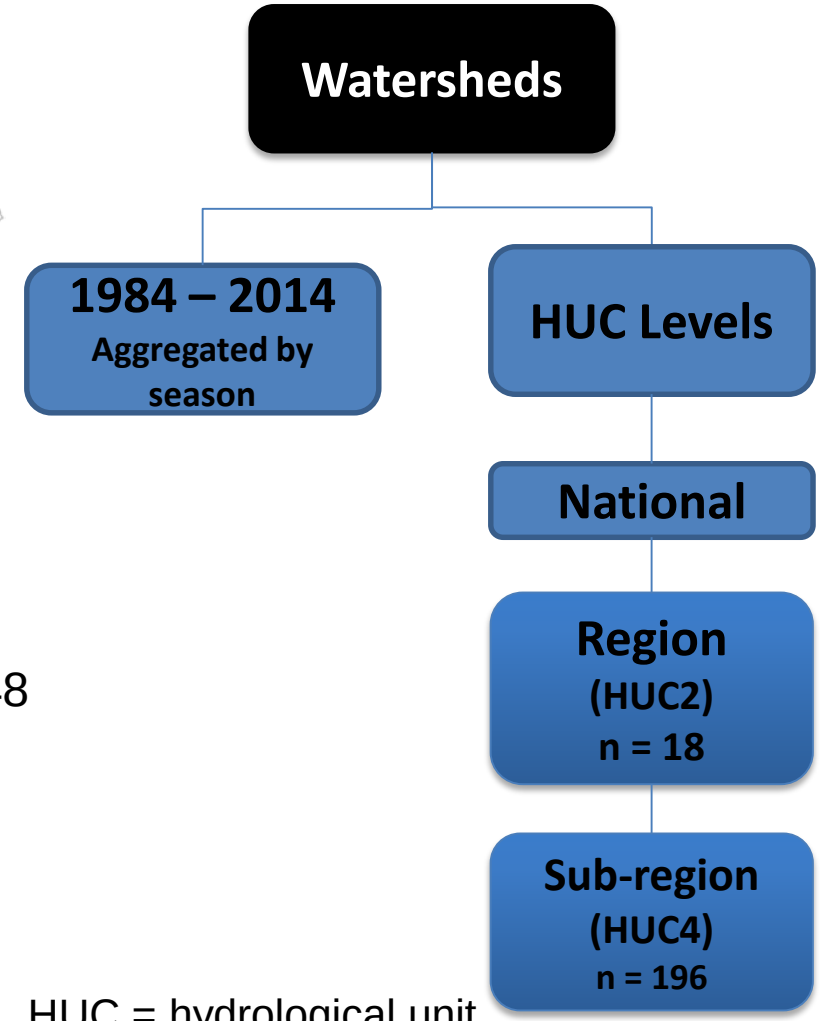
Surface Water Sampling Sites

> 600,000 surface water sites in lower 48

> 700 individual chemicals

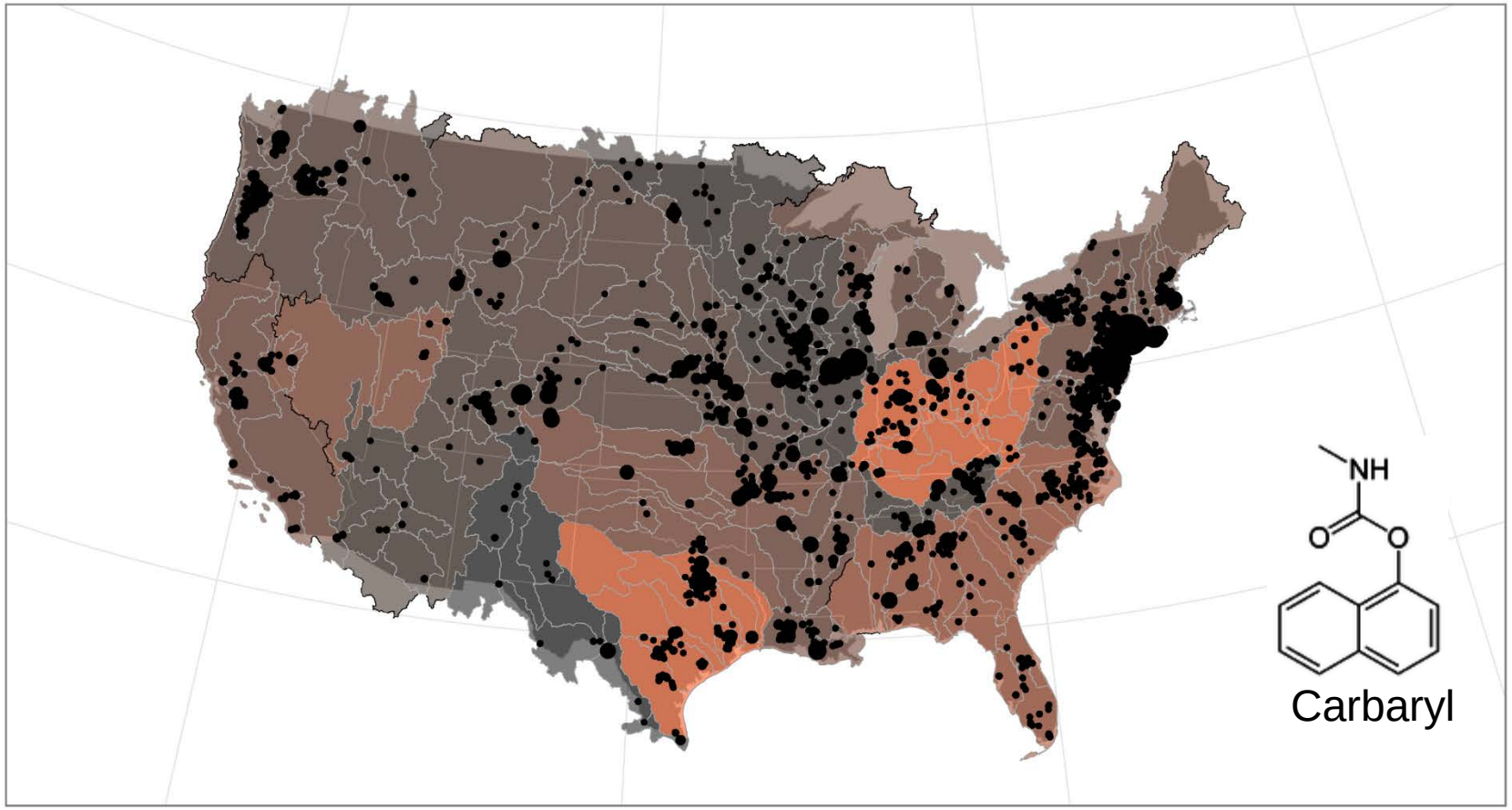
GPS, date, and time stamps

LOD indication



HUC = hydrological unit

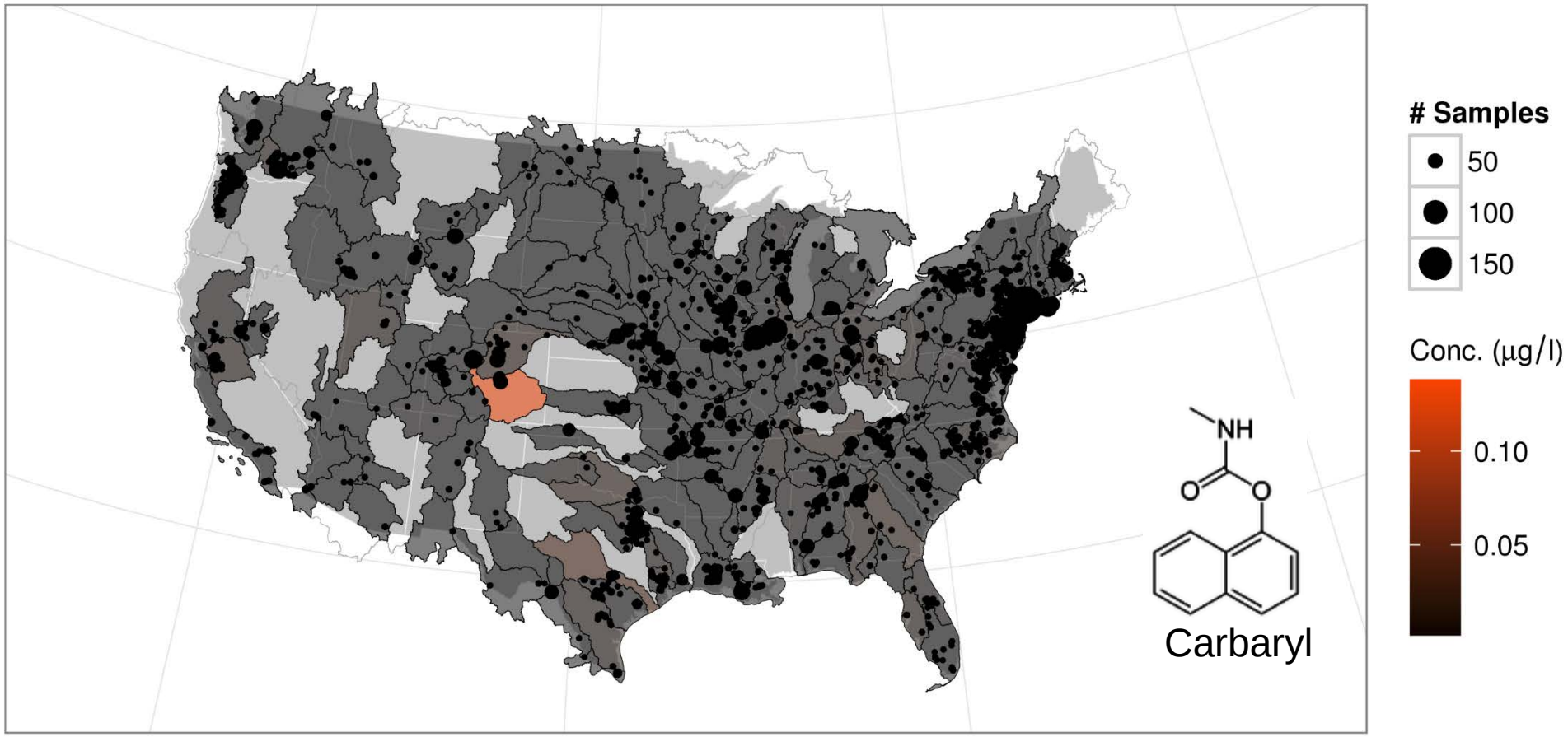
Regional Watersheds (HUC2)



Setzer et al., (in prep)

Slide from Parichehr Saranjampour

Sub-Regional Watersheds (HUC4)



Setzer et al., (in prep)

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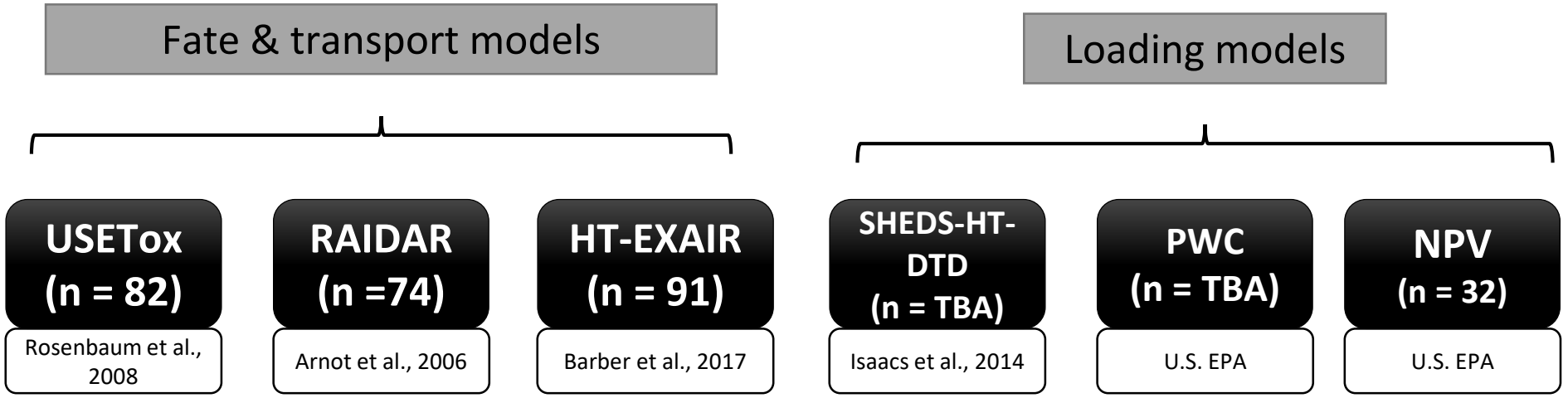
Predicting Water Concentrations for Thousands of Chemicals

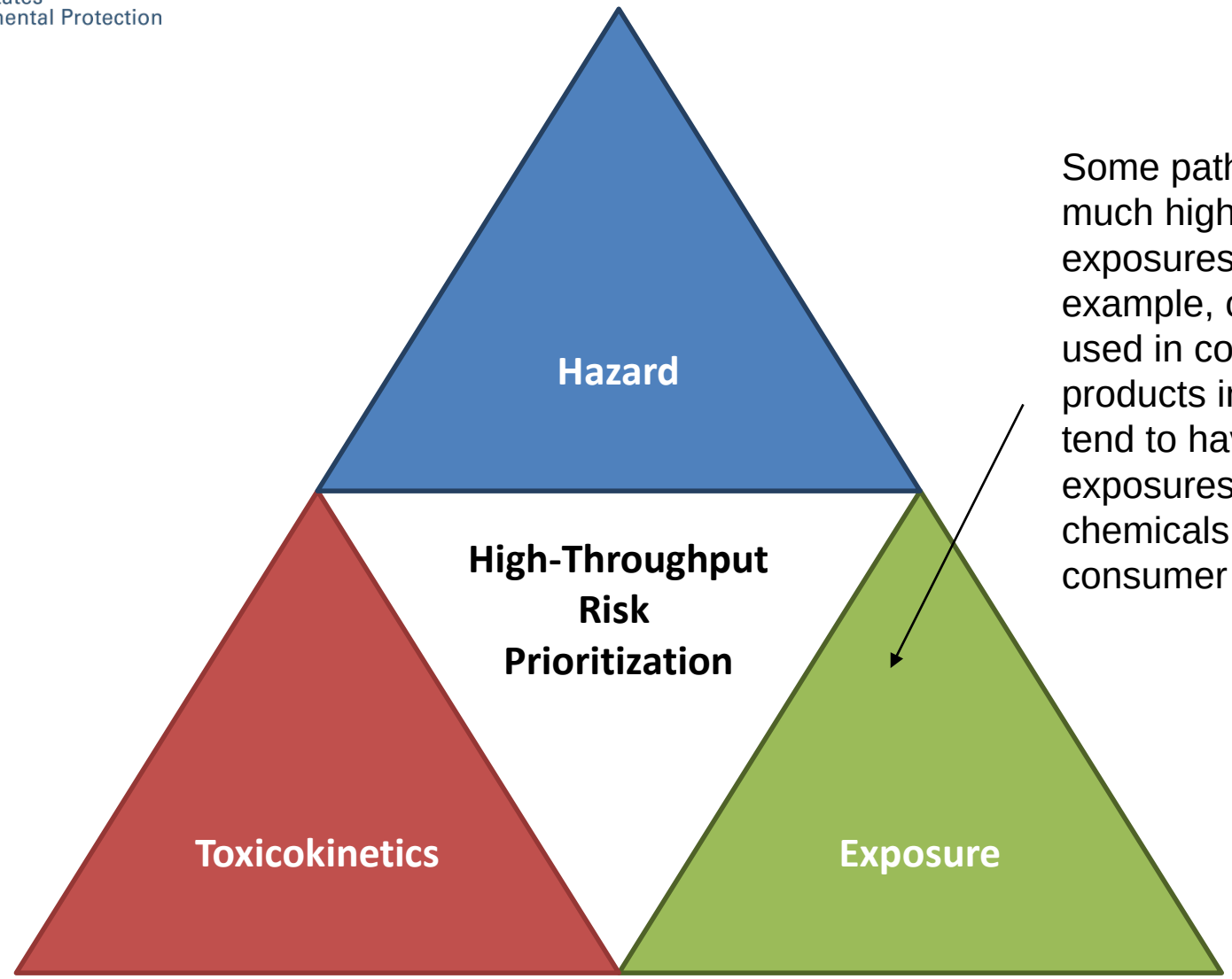


μ = geometric mean water concentrations

log (μ) = fate and transport models * loading models

Saranjampour et al., (in prep)

Idenifying Exposure Pathways

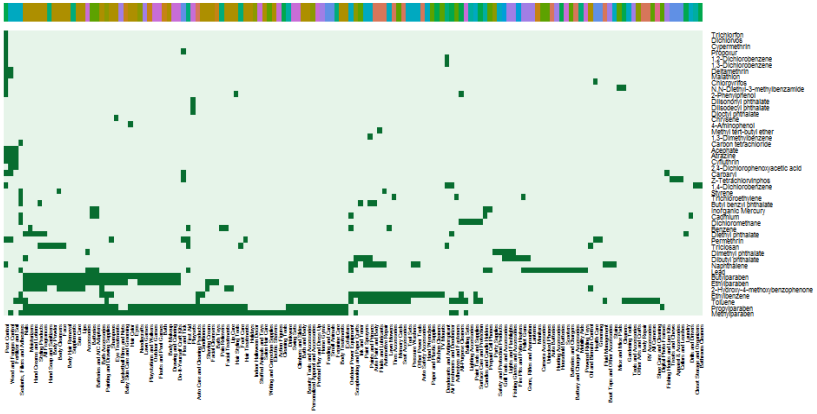


Some pathways have much higher average exposures. For example, chemicals used in consumer products in the home tend to have higher exposures. But what chemicals are in consumer products?

Chemical Use Identifies Relevant Pathways

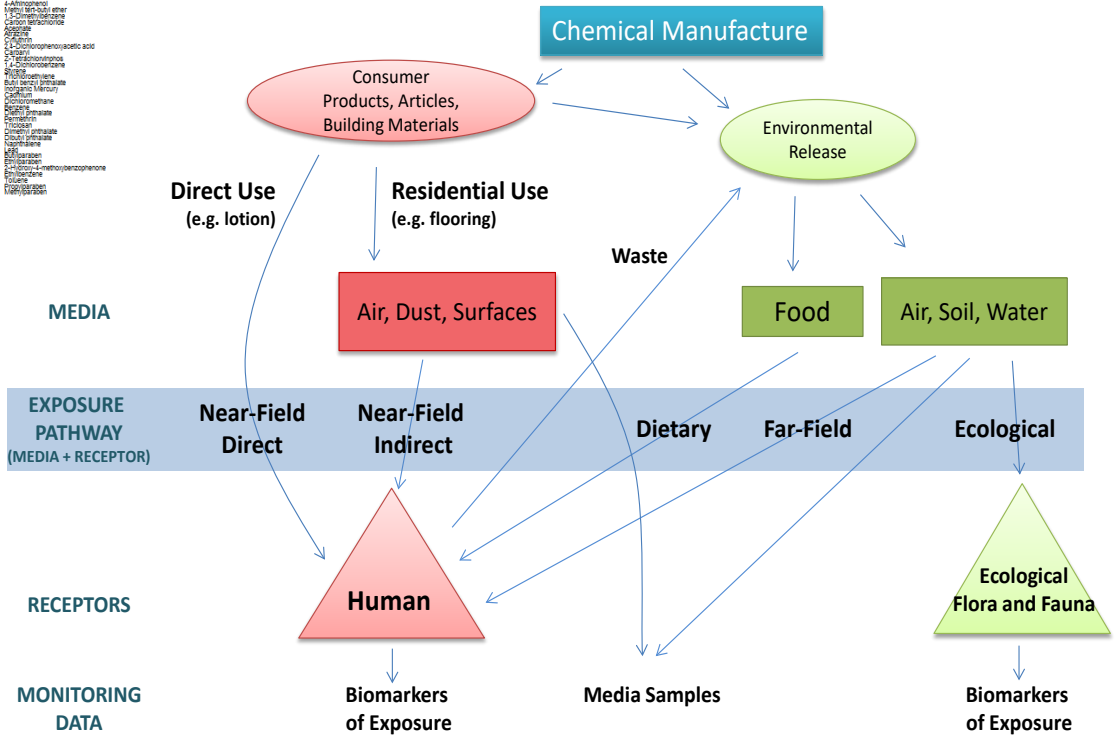
>2000 chemicals with Material Safety Data Sheets (MSDS) in CPCPdb (Goldsmith *et al.*, 2014)

106 NHANES Chemicals



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

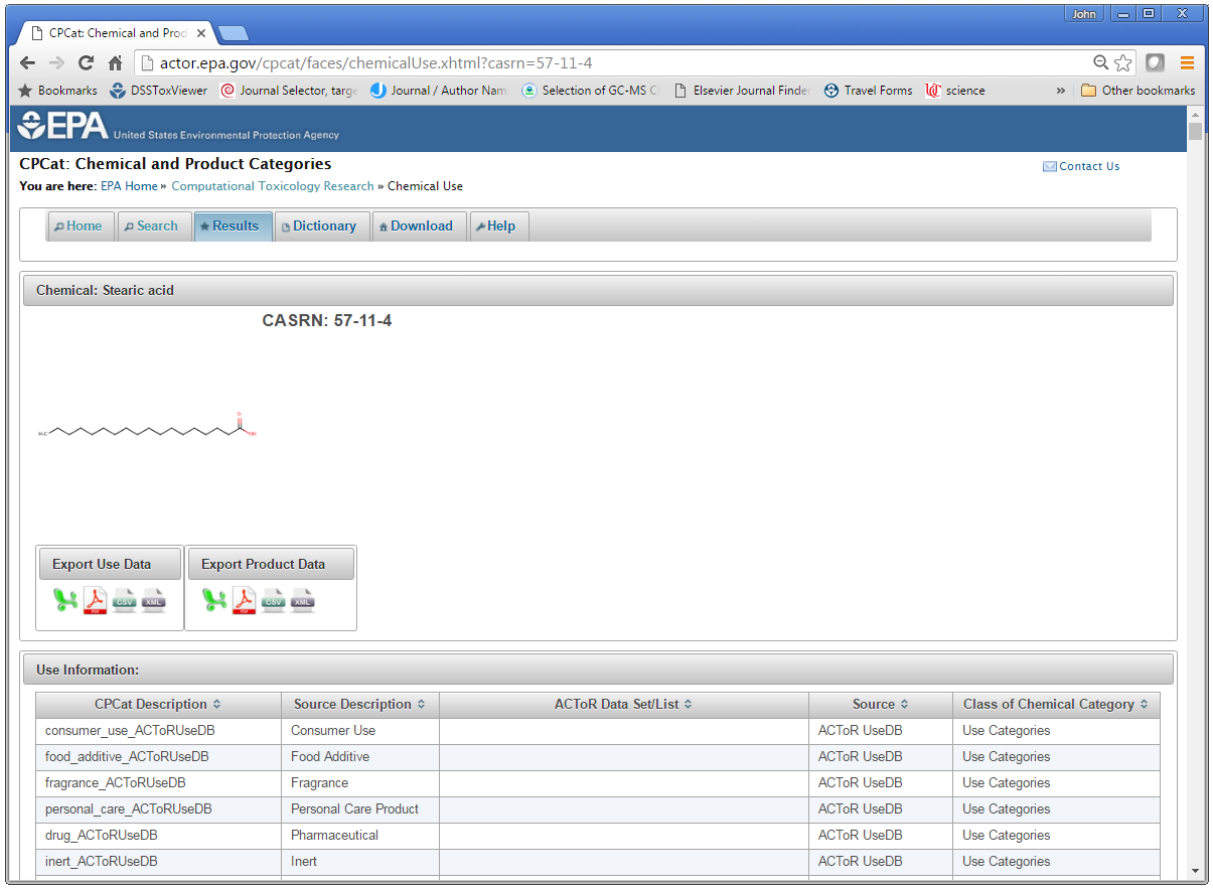
Some pathways have much higher average exposures!



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

CPdat: Chemical Use Information for ~30,000 Chemicals

- Chemical-Product database (CPdat) maps many different types of use information and ontologies onto each other
- Includes CPCPdb (Goldsmith, et al., 2014) with information on ~2000 products from major retailors
- Largest single database has coarsest information: ACToR UseDB



http://**actor.epa.gov/cpcat/**

Dionisio *et al.* (2015)

Predicting Exposure

- EPA's public CPdat (http://actor.epa.gov/cpcat/) includes every chemical safety sheet from a major U.S. retailer (>2000 chemicals) but there are many thousands of other chemicals (Goldsmith et al, 2015)
- We use applied statistics, including machine learning techniques, to learn from the data we have to fill in the gaps (Wambaugh et al., 2014, Isaacs et al., 2016, Phillips et al., 2017)
  - This is similar to how Netflix can guess how much you will like a movie

The New York Times

Internet

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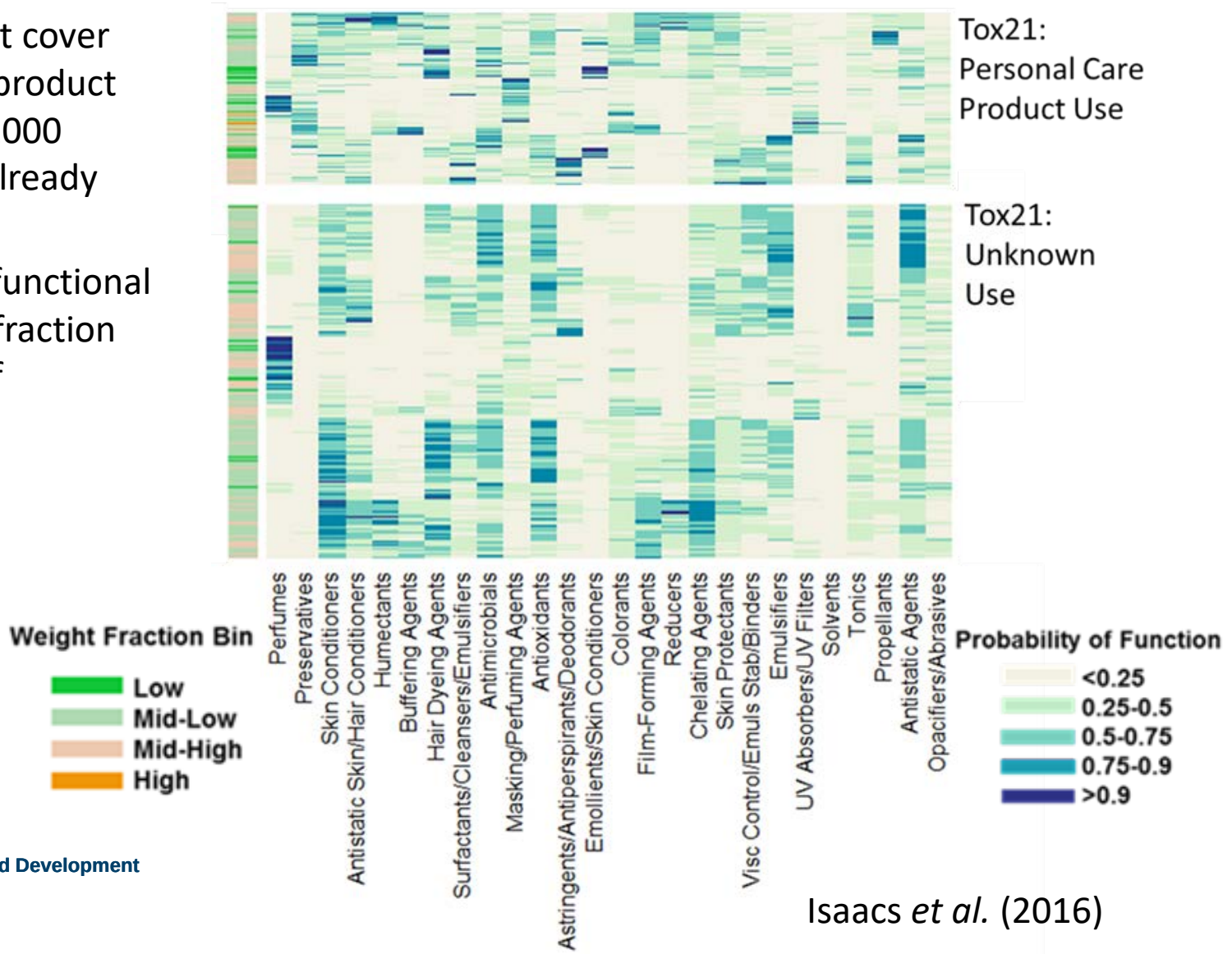
A $1 Million Research Bargain for Netflix, and Maybe a Model for Others

By STEVE LOHR
Published: September 21, 2009

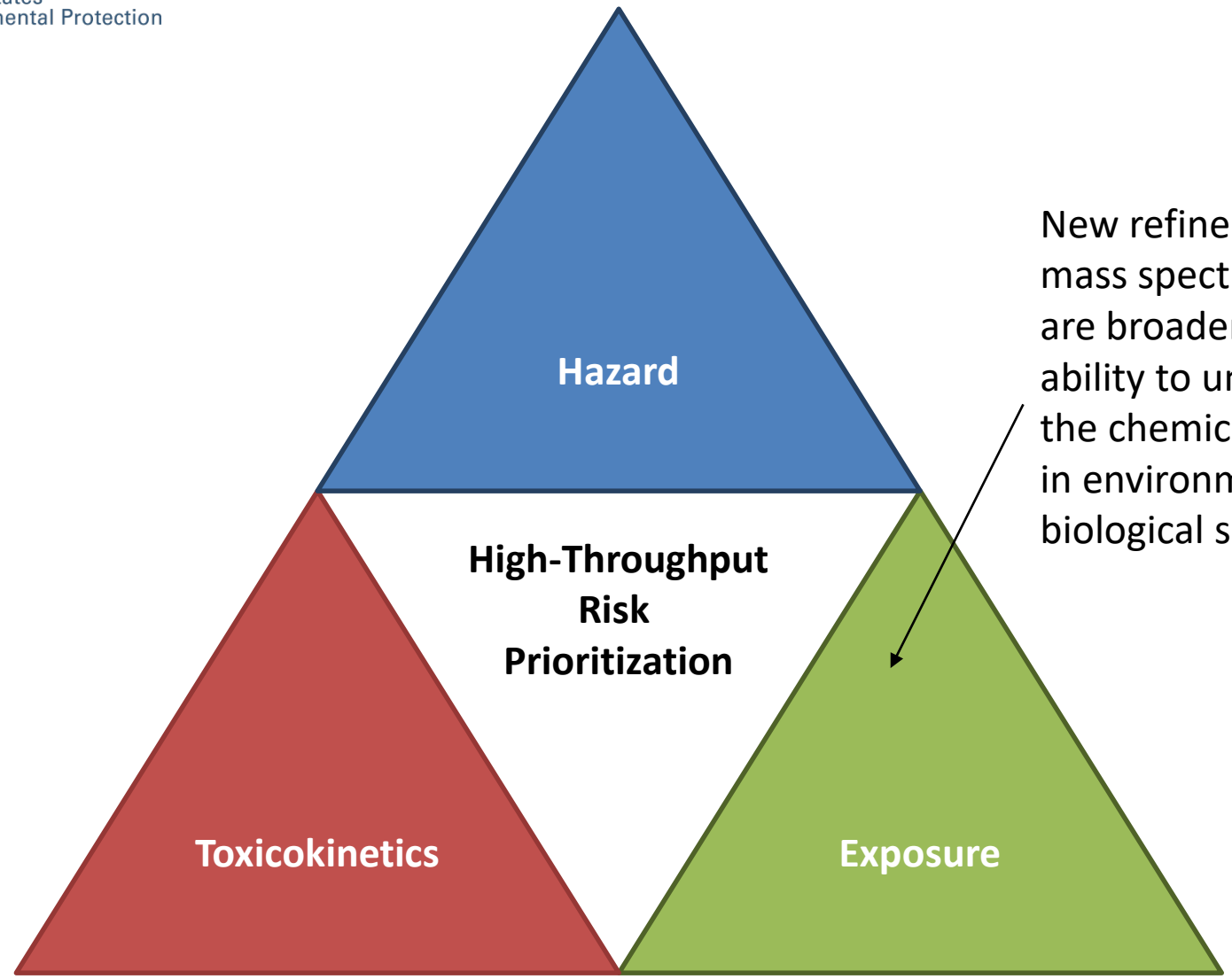
Predicting Chemical Constituents

- CPCPdb does not cover every chemical-product combination (~2000 chemicals, but already >8000 in Tox21)
- We can predict functional use and weight fraction for thousands of chemicals



Isaacs *et al.* (2016)

Non-Targeted Analysis



New refinements to mass spectrometry are broadening our ability to understand the chemicals present in environmental and biological samples

Non-Targeted and Suspect-Screening Analysis

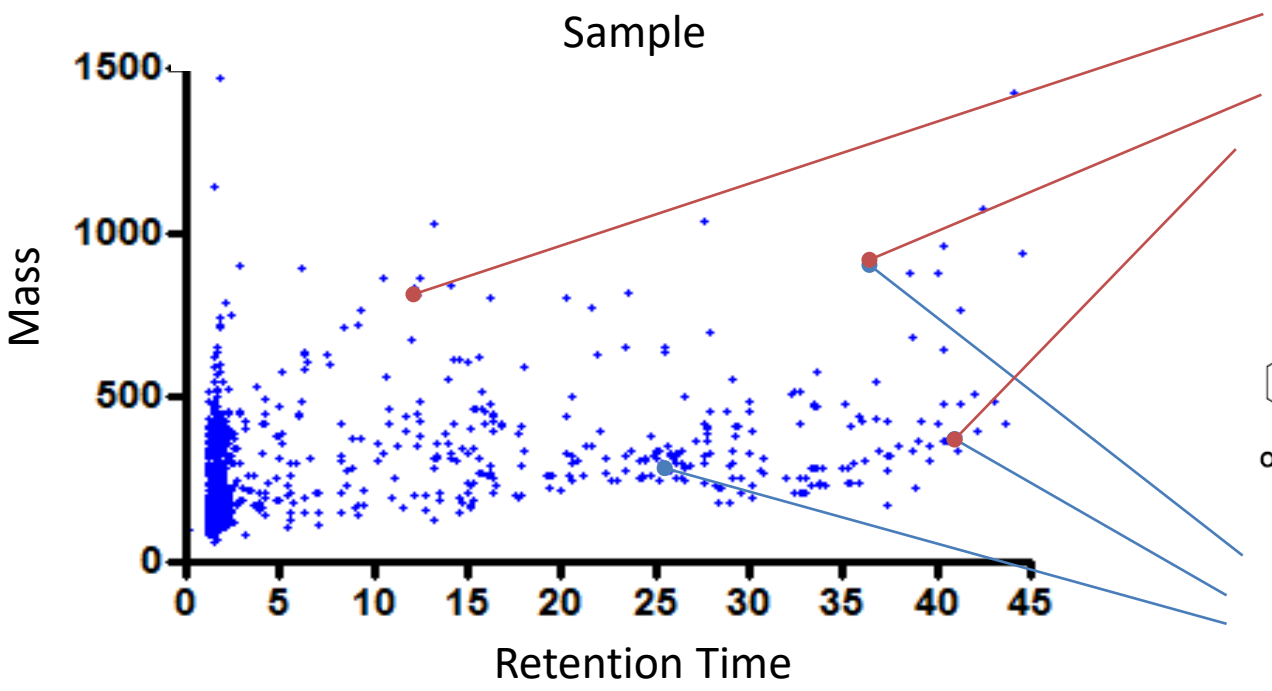
- Models present one way forward, but new analytic techniques may also allow insight in to chemicals composition of products and the greater environment
- EPA is coordinating a comparison of non-targeted screening workflows used by leading academic and government groups (led by Jon Sobus and Elin Ulrich)
  - Examining house dust, human plasma, and silicone wristbands (O'Connell, et al., 2014)
  - Similar to NORMAN Network (Schymanski et al., 2015) analysis of water
- Published analysis on house dust (Rager et al., 2016)

"I'm searching for my keys."

- 100 consumer products from a major U.S. retailer were analyzed, tentatively identifying 1,632 chemicals, 1,445 which were not in EPA's database of consumer product chemicals (Phillips *et al., submitted*)

Suspect Screening in House Dust

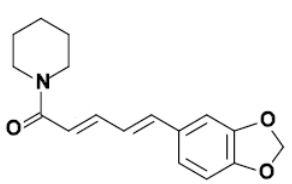
947 Peaks in an American Health Homes Dust Sample

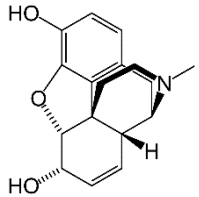


Each peak corresponds to a chemical with an accurate mass and predicted formula:

$C_{17}H_{19}NO_3$

Multiple chemicals can have the same mass and formula:





Is chemical A present, chemical B, both, or some other chemical (neither)?

We are expanding our reference libraries using ToxCast chemicals to enable greater numbers and better accuracy of confirmed chemicals

See Rager et al., (2016)

Appropriate Skepticism for Non-Targeted Analysis and Suspect Screening

United States Environmental Protection Agency

"As chemists we are obliged to accept the assignment of barium to the observed activity, but as nuclear chemists working very closely to the field of physics we cannot yet bring ourselves to take such a drastic step, which goes against all previous experience in nuclear physics. It could be, however, that a series of strange coincidences has misled us."

Hahn and Strassmann (1938)

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Hahn and Strassmann (1938)

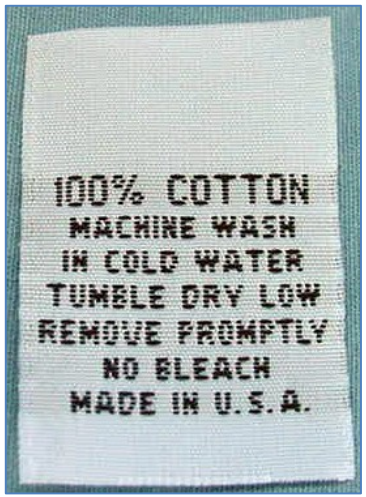
1944 Nobel Prize in Chemistry for "discovery of the fission of heavy nuclei"

ExpoCast Consumer Product Scan

United States Environmental Protection Agency

$Log_{10}(\mu g/g)$

The chemicals found in a cotton shirt



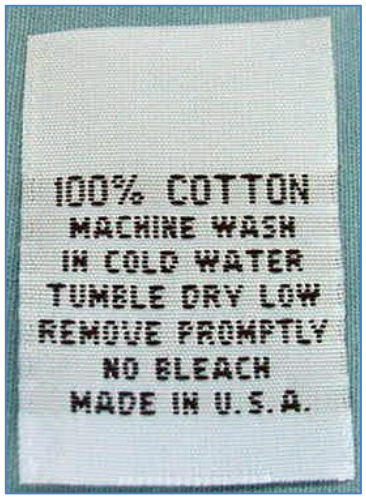
Phillips et al. (submitted)

ExpoCast Consumer Product Scan

United States Environmental Protection Agency

$Log_{10}(\mu g/g)$

⬅ Chemicals that are present



⬅ Chemicals that are absent (but found in other products)

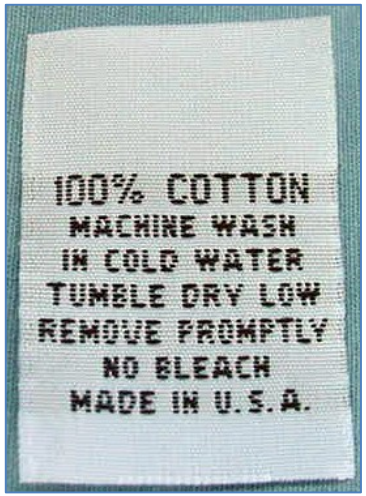
Phillips et al. (submitted)

ExpoCast Consumer Product Scan

United States Environmental Protection Agency

$Log_{10}(\mu g/g)$

The chemicals found in a cotton shirt



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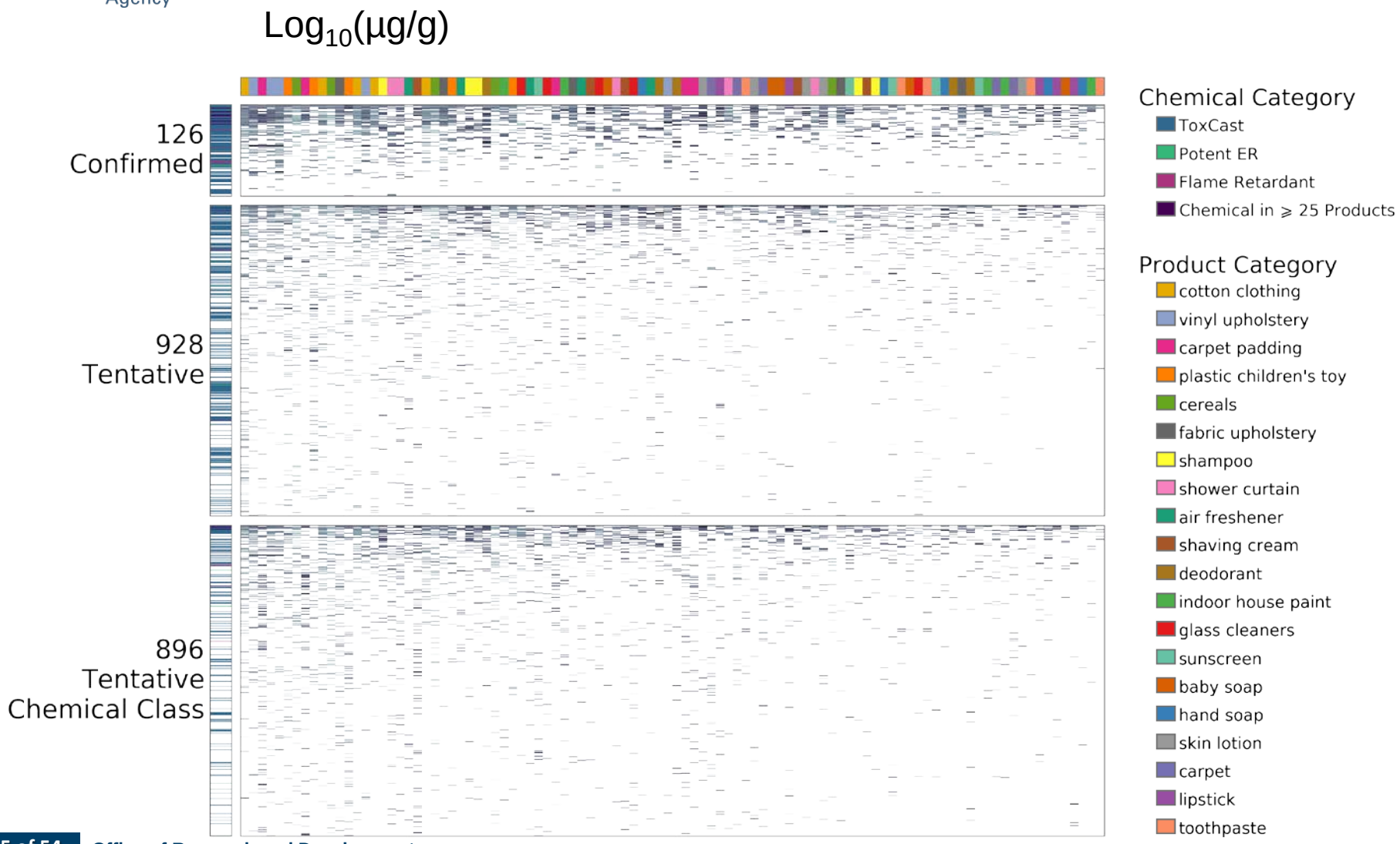


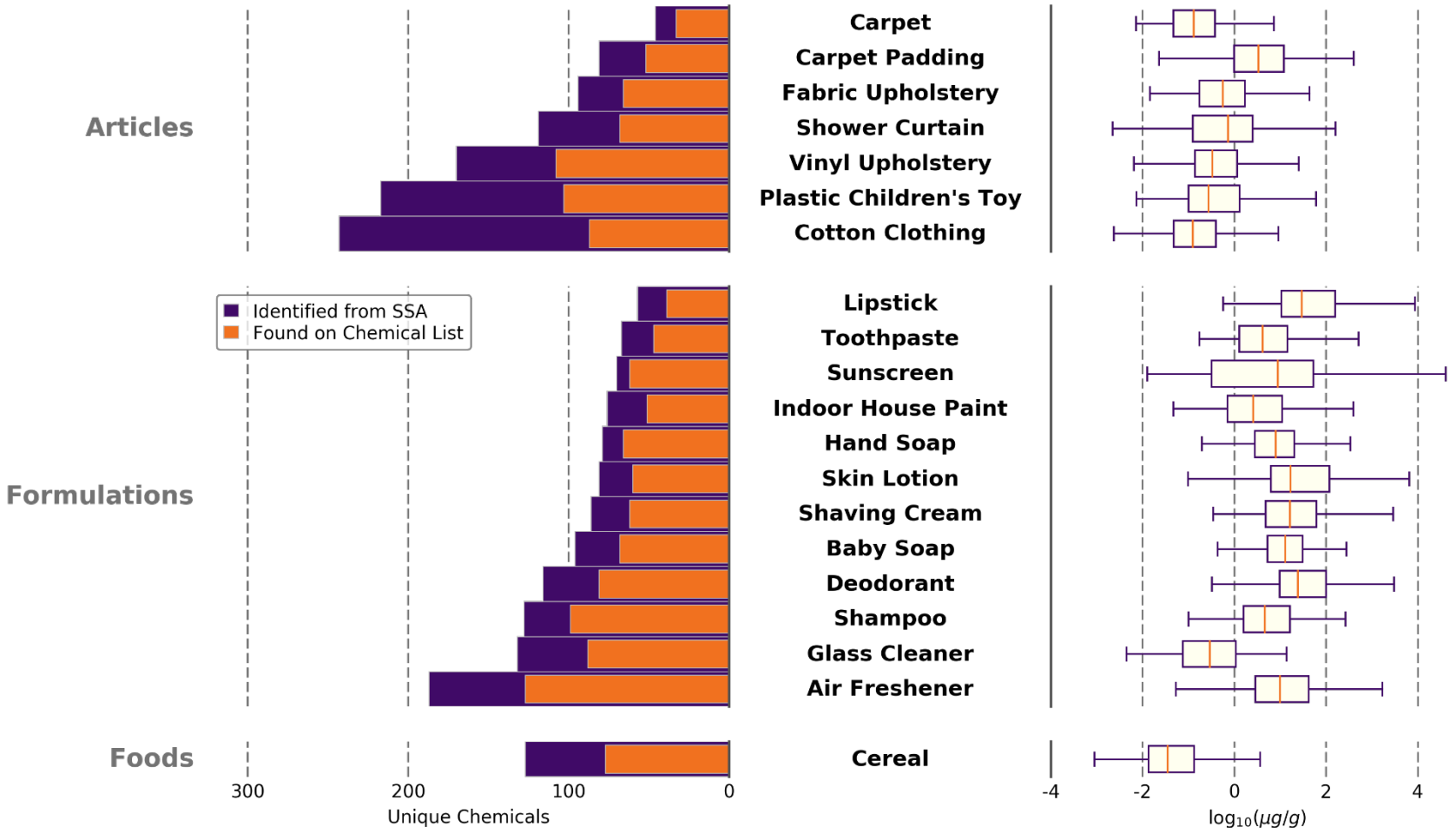
Of 1,632 chemicals, 1,445 were not present in our database from the major retailer (CPCPdb)

Phillips et al. (submitted)

Product Scan Summary

United States Environmental Protection Agency

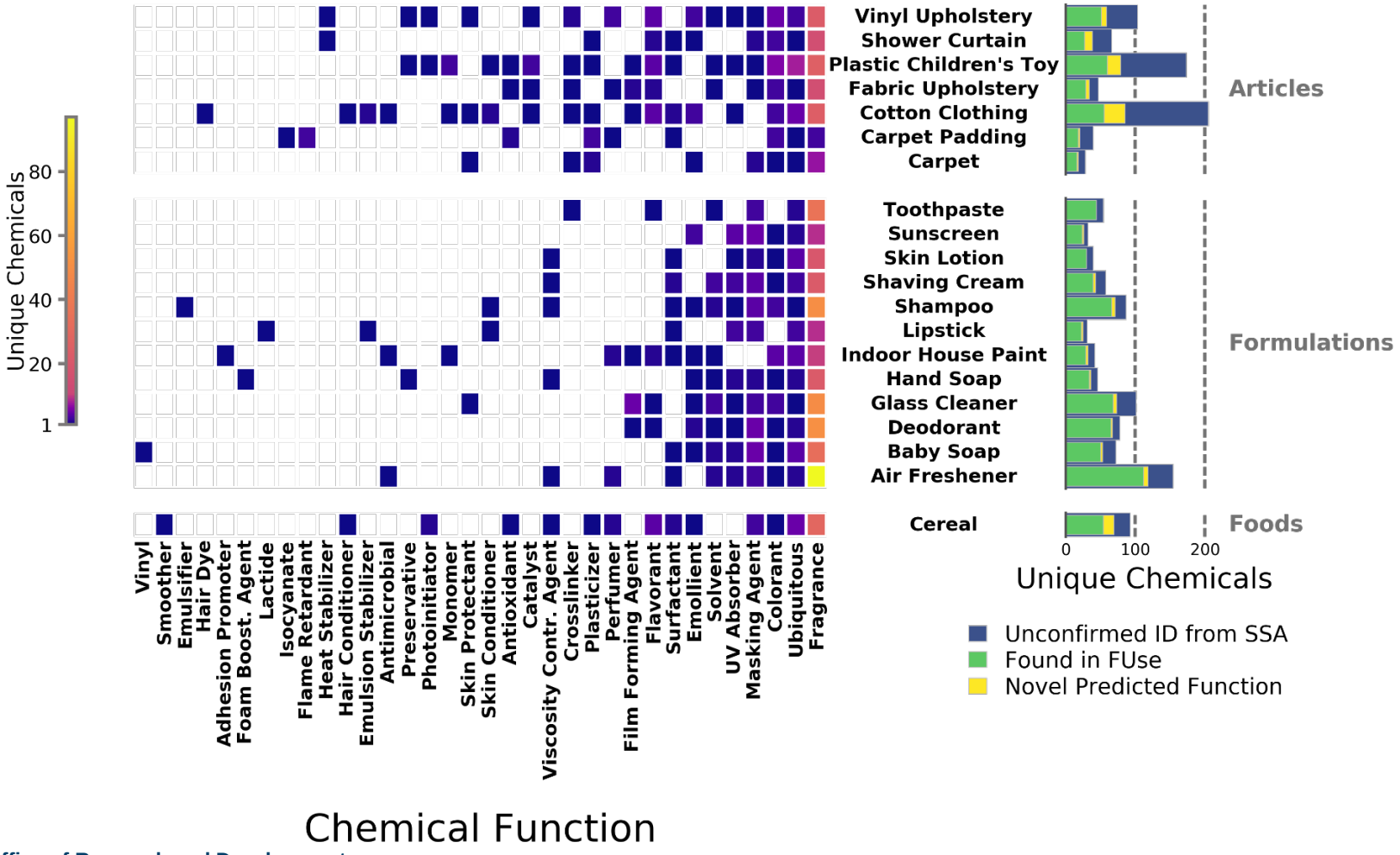
Of 1,632 chemicals confirmed or tentatively identified, 1,445 were not present in CPCPdb



Phillips *et al.* (*submitted*)

Predicting Chemical Function

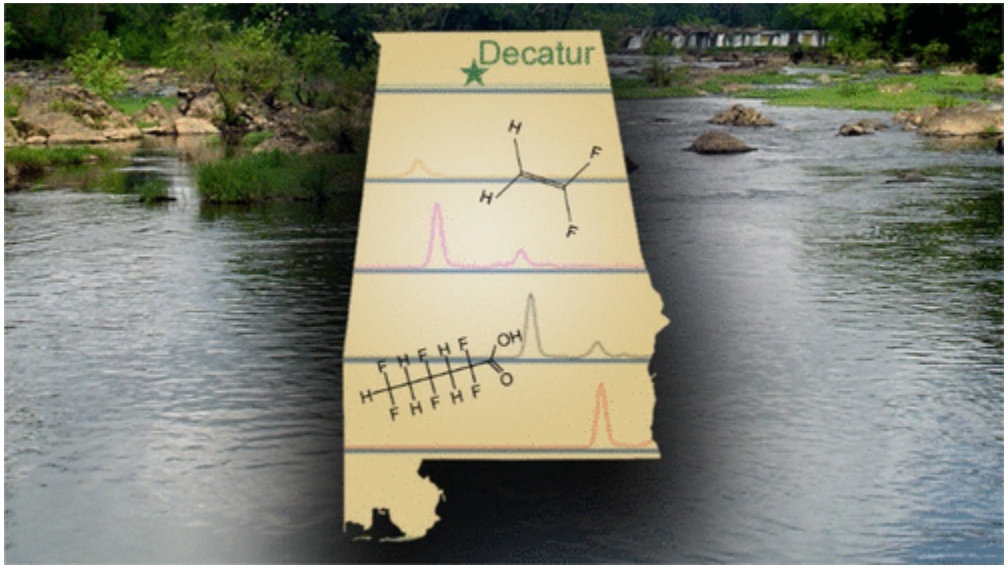
Using the methods of Phillips *et al.*, (2017):



Phillips *et al.* (*submitted*)

Analysis of Drinking Water

High resolution mass spectrometry was used to investigate the occurrence and identity of replacement fluorinated compounds in surface water and sediment of the Tennessee River near Decatur, Alabama



A series of nine polyfluorinated carboxylic acids was discovered

Phillips *et al.* (2017)

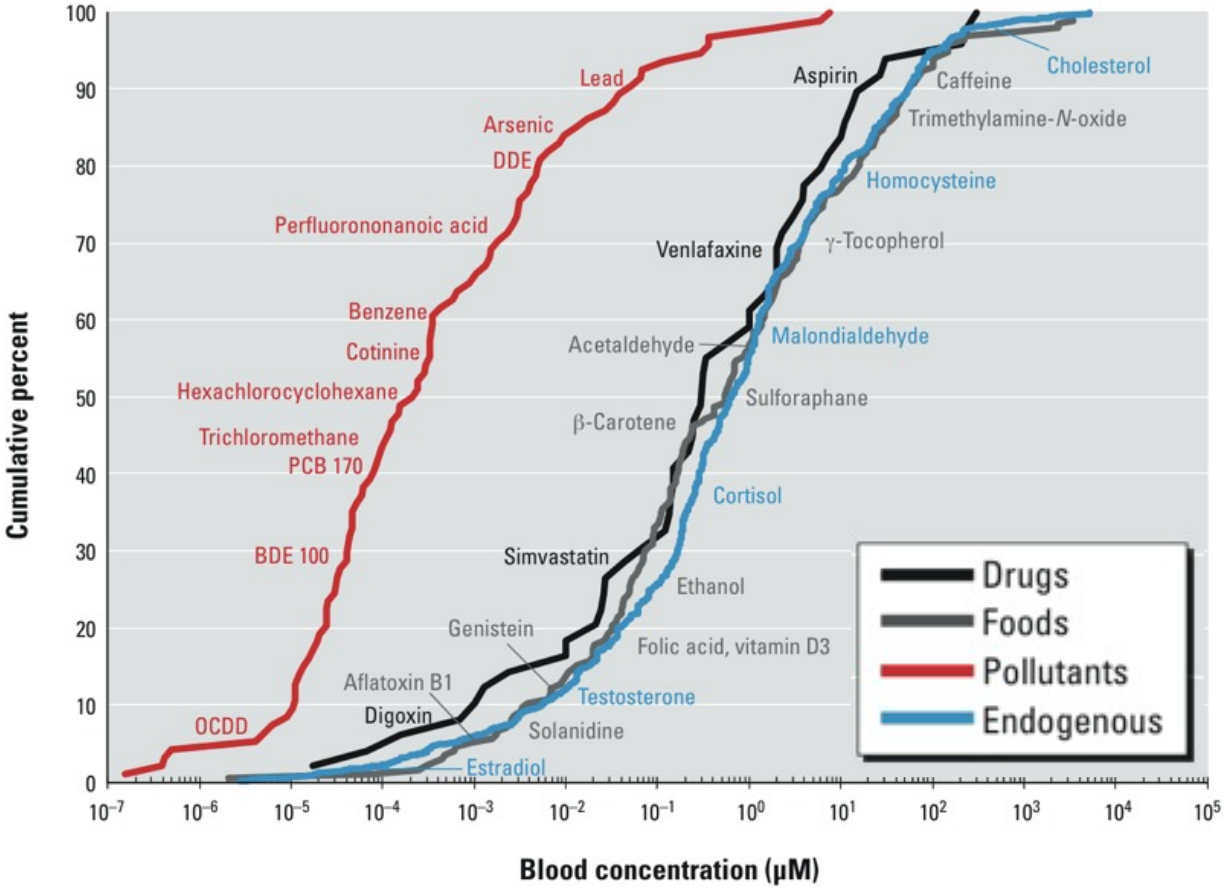
Caveats to Non-Targeted Screening

- **Chemical presence in an object does not mean that exposure occurs**
- **Only some chemical identities are confirmed, *most are tentative***
  - Can use formulation predictor models as additional evidence
- **Chemical presence in an object does not necessarily mean that it is bioavailable**
  - Can build emission models
- **Small range for quantitation leads to underestimation of concentration**
- **Product de-formulation caveats:**
  - Samples are being homogenized (e.g., grinding) and are extracted with a solvent (dichloro methane, DCM)
  - Only using one solvent (DCM, polar) and one method GCxGC-TOF-MS
  - Varying exposure intimacy, from carpet padding to shampoo to cereal
- **Exposure alone is not risk, need hazard data**

Expanded Biomonitoring

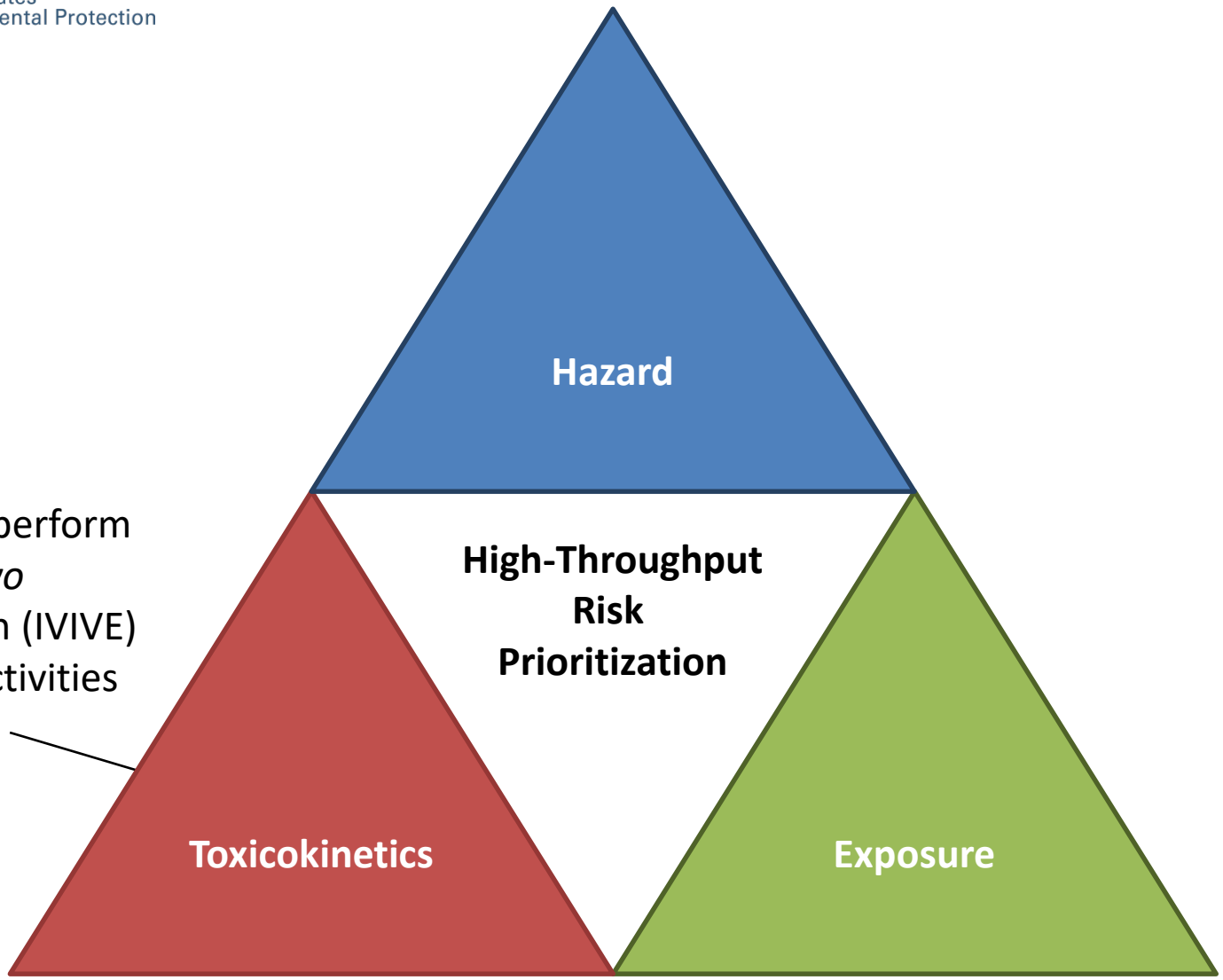
- Moving beyond NHANES chemicals
  - Non-targeted analysis of blood may be possible
  - Not just a matter of sensitivity, must also "filter out" endogenous, food, and drug chemicals

Rappaport et al. (2014)

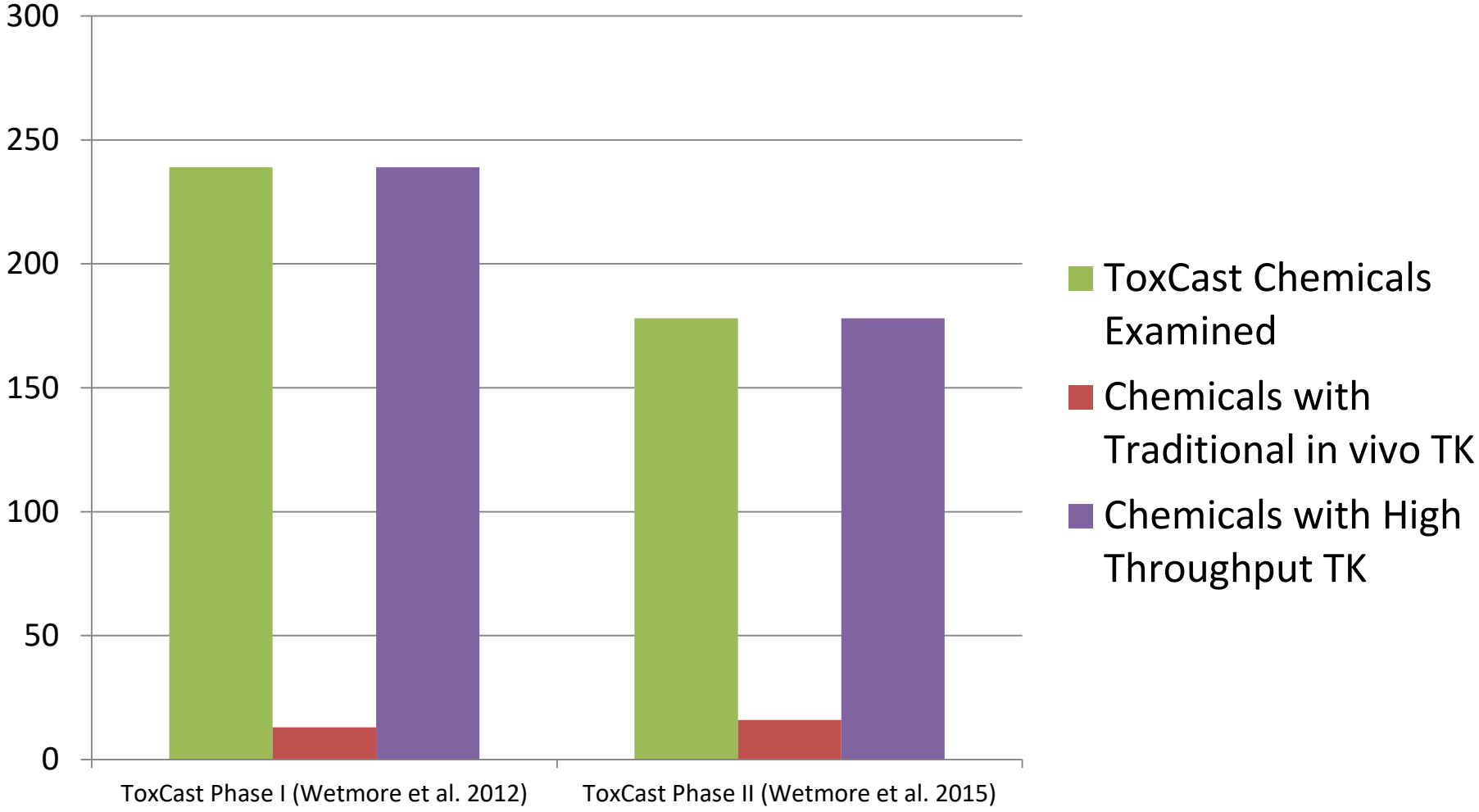


Toxicokinetics for IVIVE

We want to perform *in vitro-in vivo* extrapolation (IVIVE) of ToxCast activities



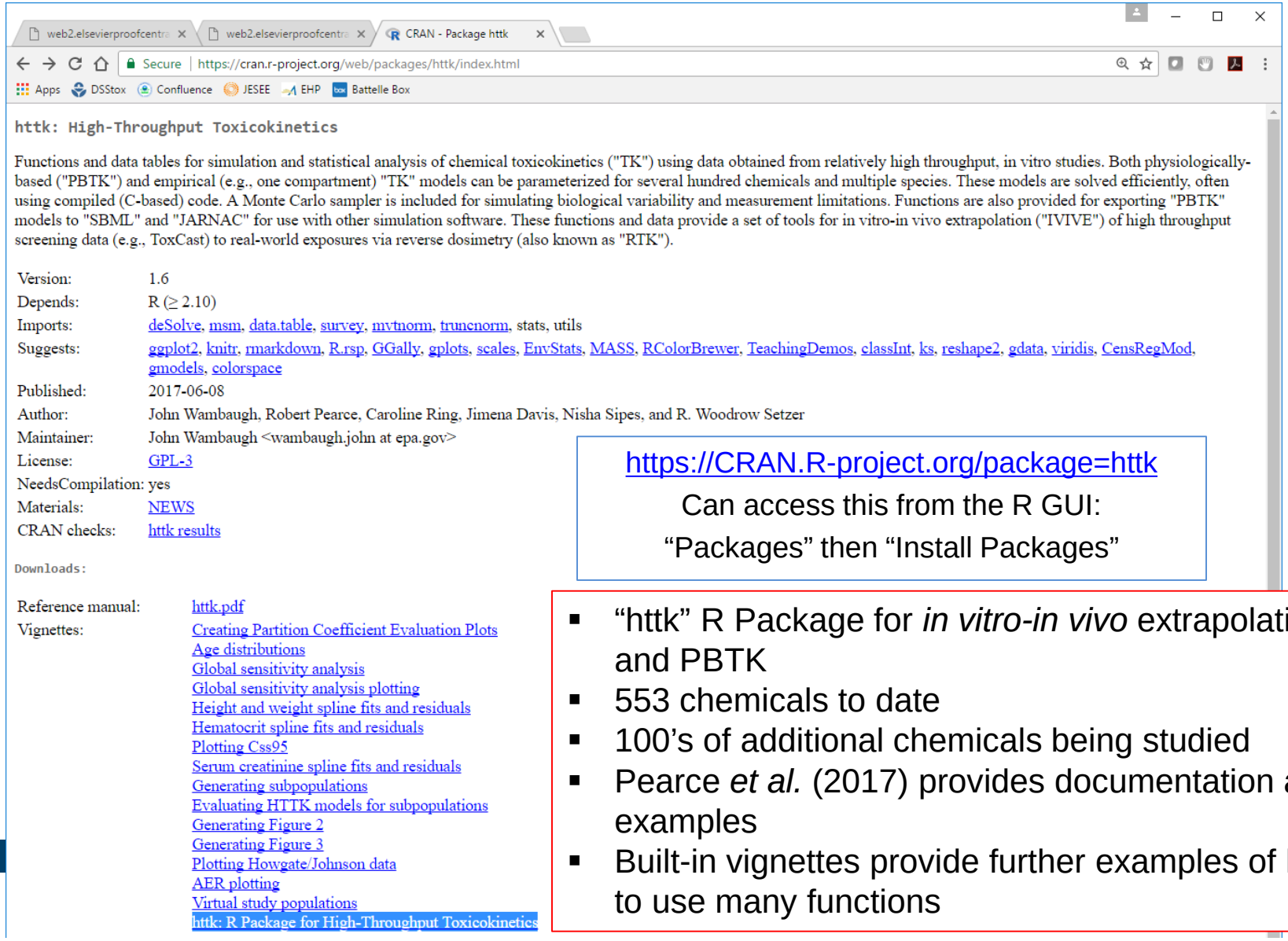
The Need for *In Vitro* Toxicokinetics



- Studies like Wetmore et al. (2012, 2015), addressed the need for TK data using *in vitro* methods

High Throughput Toxicokinetics

United States Environmental Protection Agency



web2.elsevierproofcentra | web2.elsevierproofcentra | CRAN - Package httk

Secure | https://cran.r-project.org/web/packages/httk/index.html

Apps | DSStox | Confluence | JESEE | EHP | Battelle Box

httk: High-Throughput Toxicokinetics

Functions and data tables for simulation and statistical analysis of chemical toxicokinetics ("TK") using data obtained from relatively high throughput, in vitro studies. 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 and measurement limitations. Functions are also provided for exporting "PBTK" models to "SBML" and "JARNAC" for use with other simulation software. These functions and data provide a set of tools for in vitro-in vivo extrapolation ("IVIVE") of high throughput screening data (e.g., ToxCast) to real-world exposures via reverse dosimetry (also known as "RTK").

Version:	1.6
Depends:	R (≥ 2.10)
Imports:	deSolve, msm, data.table, survey, mvtnorm, truncnorm, stats, utils
Suggests:	ggplot2, knitr, rmarkdown, R.rsp, GGally, gplots, scales, EnvStats, MASS, RColorBrewer, TeachingDemos, classInt, ks, reshape2, gdata, viridis, CensRegMod, gmodels, colorspace
Published:	2017-06-08
Author:	John Wambaugh, Robert Pearce, Caroline Ring, Jimena Davis, Nisha Sipes, and R. Woodrow Setzer
Maintainer:	John Wambaugh <wambaugh.john at epa.gov>
License:	GPL-3
NeedsCompilation:	yes
Materials:	NEWS
CRAN checks:	httk results

Downloads:

Reference manual:	httk.pdf
Vignettes:	Creating Partition Coefficient Evaluation Plots
	Age distributions
	Global sensitivity analysis
	Global sensitivity analysis plotting
	Height and weight spline fits and residuals
	Hematocrit spline fits and residuals
	Plotting Css95
	Serum creatinine spline fits and residuals
	Generating subpopulations
	Evaluating HTTK models for subpopulations
	Generating Figure 2
	Generating Figure 3
	Plotting Howgate/Johnson data
	AER plotting
	Virtual study populations
	httk: R Package for High-Throughput Toxicokinetics

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

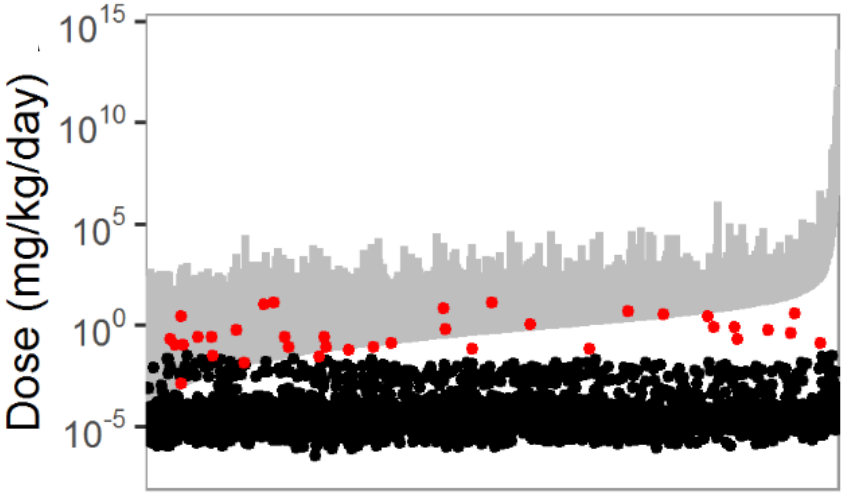
Can access this from the R GUI:

"Packages" then "Install Packages"

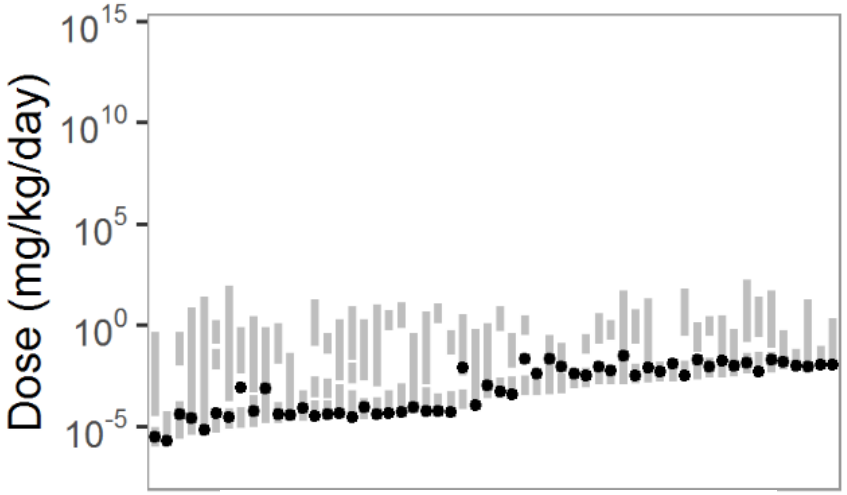
- "httk" R Package for *in vitro-in vivo* extrapolation and PBTK
- 553 chemicals to date
- 100's of additional chemicals being studied
- Pearce *et al.* (2017) provides documentation and examples
- Built-in vignettes provide further examples of how to use many functions

Using HTTK Predicted C_{max} for Risk Prioritization

Screening for toxicity has blind spots and exposure forecasts are highly uncertain, yet:



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

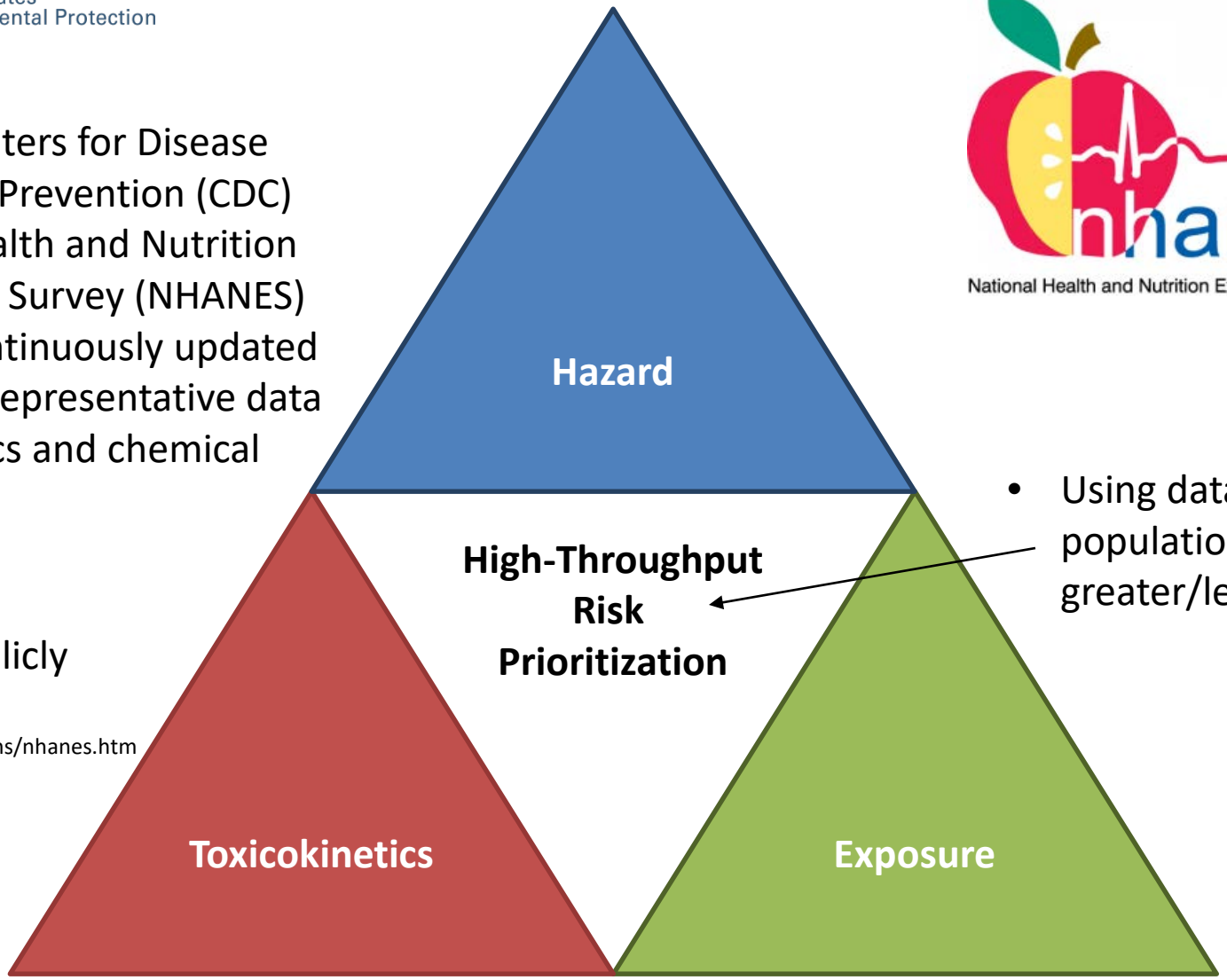
Sipes et al., (2017)

Further Analyzing the CDC NHANES Data

EPA United States Environmental Protection Agency

The U.S. Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination Survey (NHANES) provides continuously updated statistically representative data on biometrics and chemical exposure

nhanes National Health and Nutrition Examination Survey



- Using data to identify populations with greater/lesser risk

Data sets publicly available:
http://www.cdc.gov/nchs/nhanes.htm

Population simulator for HTTK

Correlated Monte Carlo sampling of physiological model parameters

Sample NHANES quantities

Sex
Race/ethnicity
Age
Height
Weight
Serum creatinine

Predict physiological quantities

Tissue masses
Tissue blood flows
GFR (kidney function)
Hepatocellularity

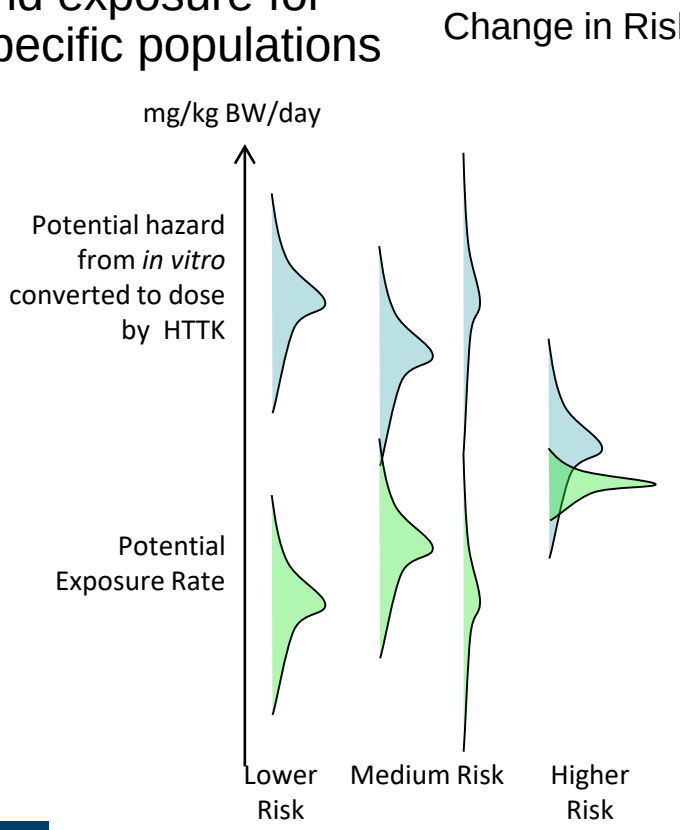
Regression equations from literature
(+ residual marginal variability)

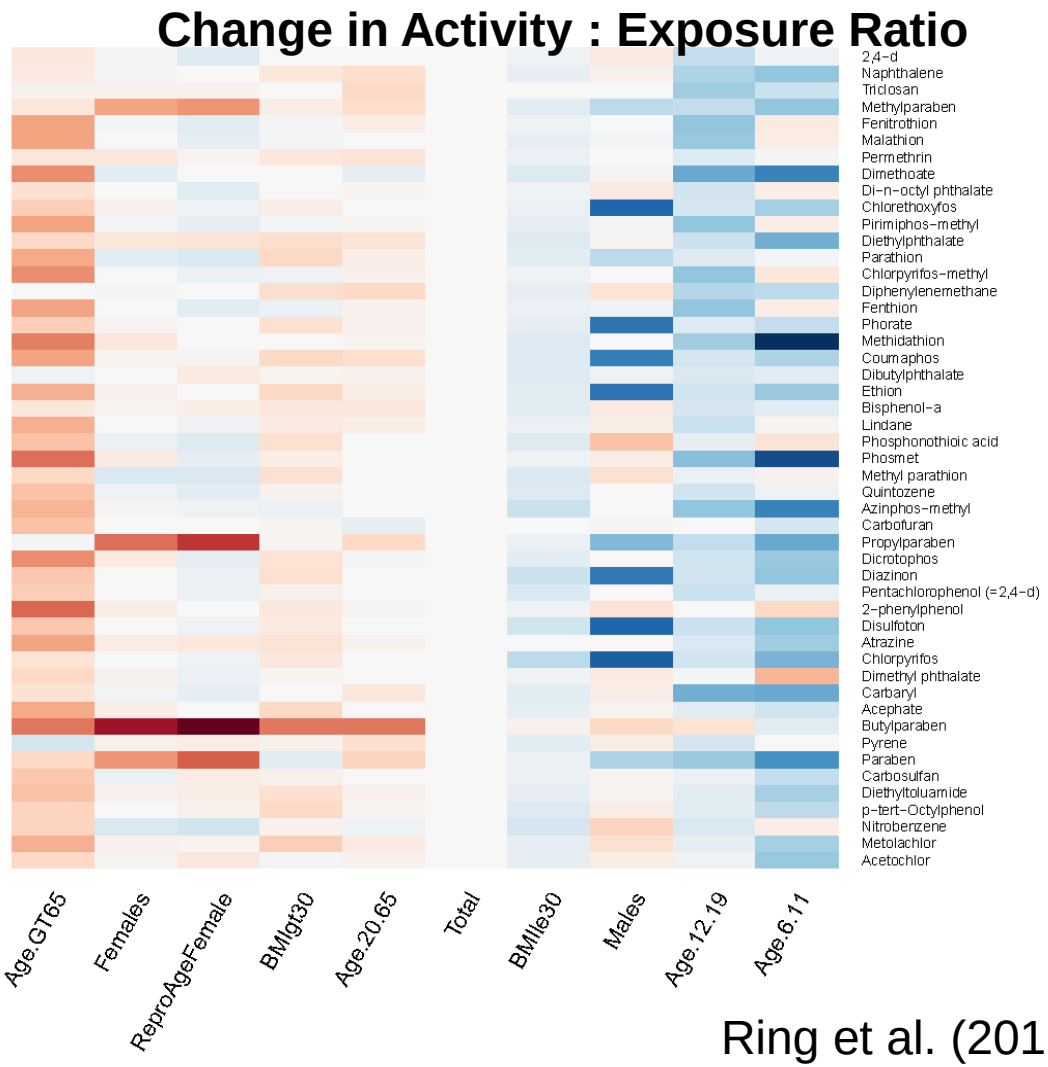
(Similar approach used in SimCYP [Jamei et al. 2009], GastroPlus, PopGen [McNally et al. 2014], P3M [Price et al. 2003], physB [Bosgra et al. 2012], etc.)

Ring *et al*. *(in press)*

Toxicokinetic IVIVE:
Convert HTS µM to mg/kg/day

- We use HTTK to calculate margin between bioactivity and exposure for specific populations

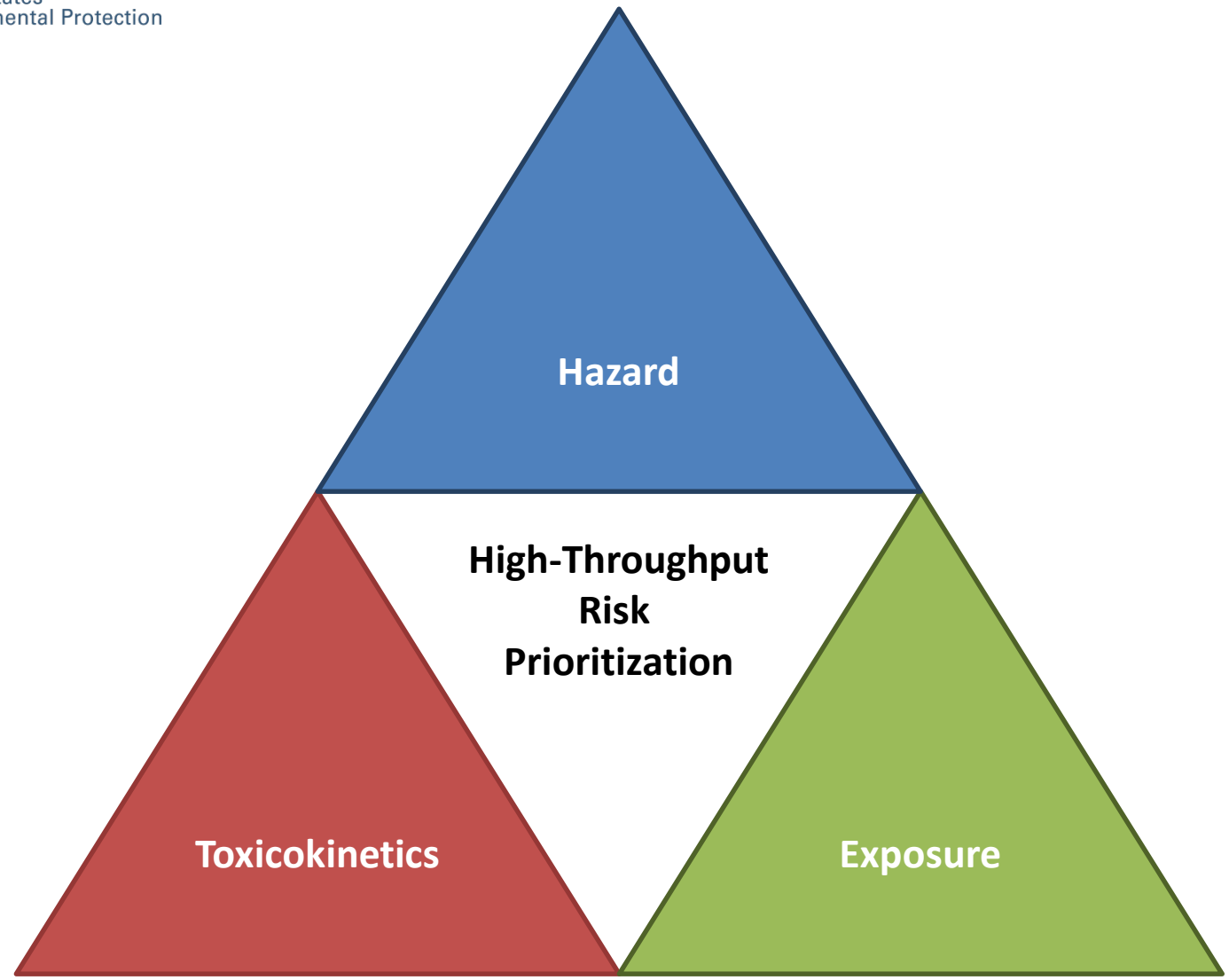




Ring et al. (2017

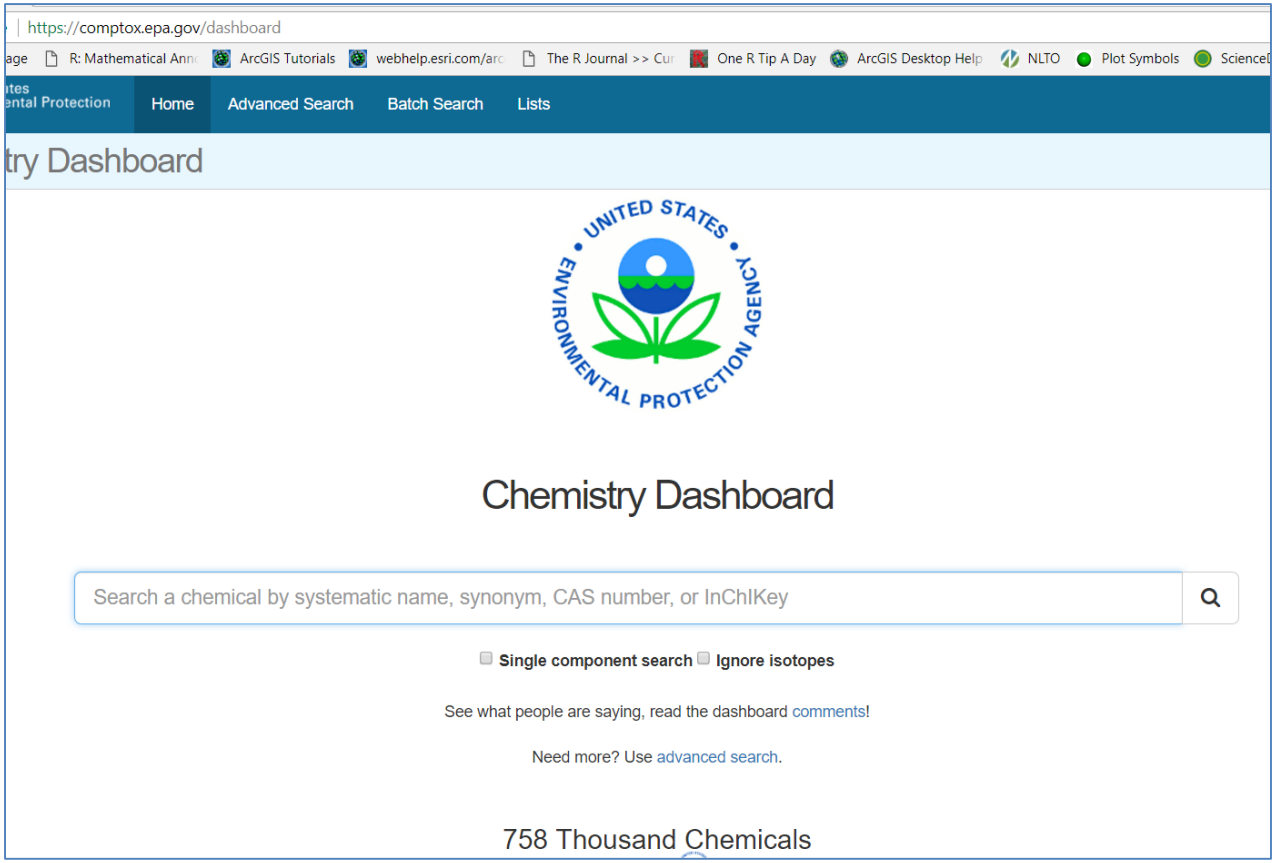
Public Chemical Assessment Tools from EPA ORD

United States Environmental Protection Agency



A Google for Chemicals

http://comptox.epa.gov/dashboard/



Examples:

“Stearic Acid”

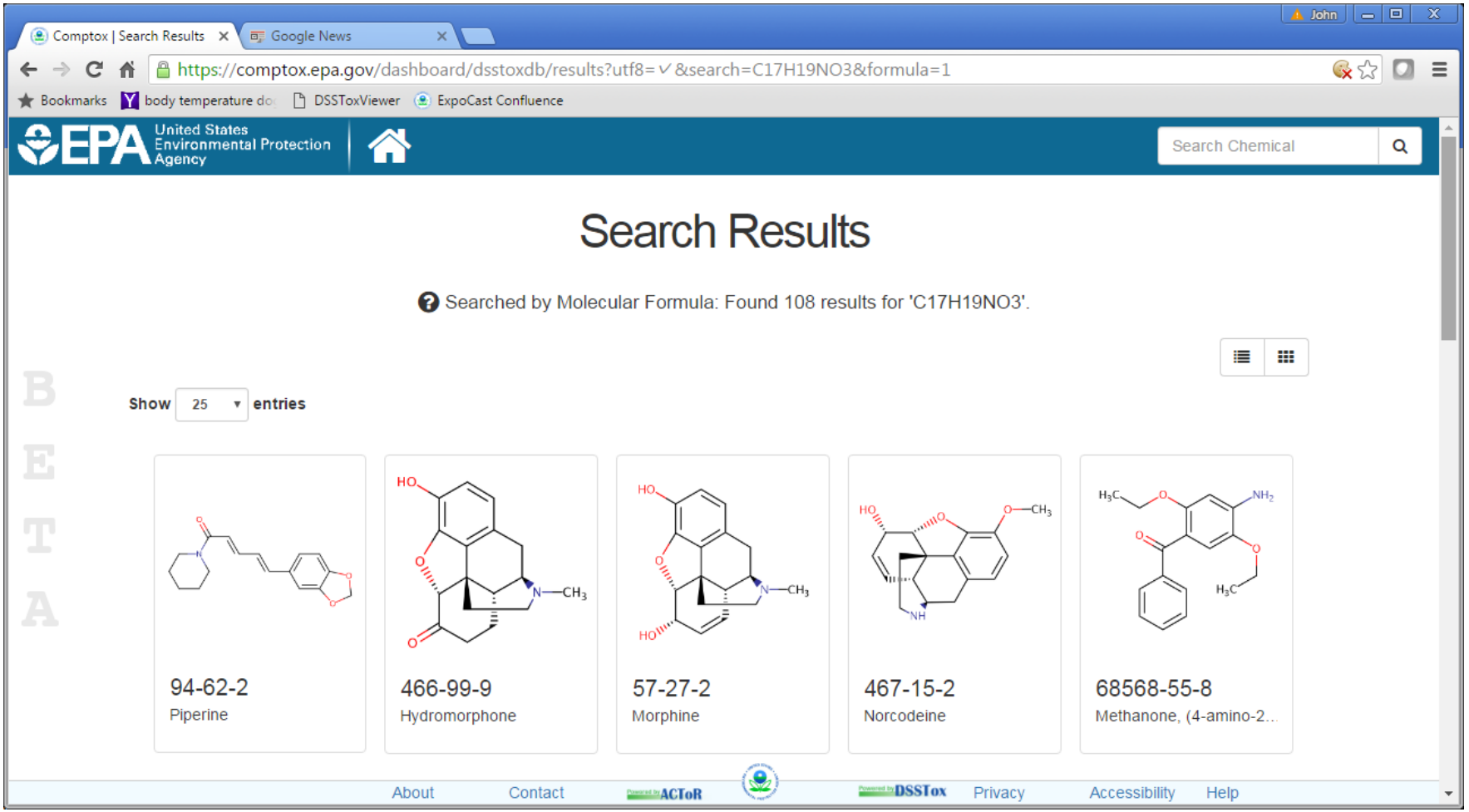
“Bisphenol A”

“C17H19NO3”

Technical leads Tony Williams, Richard Judson, et al. (NCCT)

A Google for Chemicals

http://comptox.epa.gov/dashboard/



Technical leads Tony Williams, Richard Judson, et al. (NCCT)

Public Chemical Assessment Tools from EPA ORD

United States Environmental Protection Agency

Dashboards:	**Chemistry Dashboard (one stop shop):** http://comptox.epa.gov/dashboard/ **iCSS Dashboard (ToxCast data):** http://actor.epa.gov/dashboard/ **CPdat:** http://actor.epa.gov/cpcat/
Underlying Databases:	**DSStox** (Distributed structure-searchable toxicity (DSSTox) public database, Richard et al., 2002) **ToxRefDB** (Animal Study data, Martin et al., 2009) **CPCPdb** (Consumer Product Chemical Pathways databse, Goldsmith et al, 2014)
R Packages:	**httk: High-Throughput Toxicokinetics** (Pearce et al., *in press*) https://cran.r-project.org/web/packages/httk/index.html **tcpl: ToxCast Data Analysis Pipeline** (Filer et al., 2014) https://cran.r-project.org/web/packages/tcpl/index.html

Conclusions

- We would like to know more about the risk posed by thousands of chemicals in the environment – which ones should we start with?
  - High throughput screening (HTS) provides a path forward for identifying potential hazard
  - Exposure and dosimetry provide real world context to hazards indicated by HTS
- Using *in vitro* methods developed for pharmaceuticals, we can relatively efficiently predict TK for large numbers of chemicals, but we are limited by analytical chemistry
- Using high throughput exposure approaches we can make coarse predictions of exposure
  - We are actively refining these predictions with new models and data
  - In some cases, upper confidence limit on current predictions is already many times lower than predicted hazard
- Expanded monitoring data (exposure surveillance) allows evaluation of model predictions
  - Are chemicals missing that we predicted would be there?
  - Are there unexpected chemicals?
- All data being made public:
  - R package "httk": **https://CRAN.R-project.org/package=httk**
  - The Chemistry Dashboard (A "Google" for chemicals) **http://comptox.epa.gov/**
  - Consumer Product Database: http://**actor.epa.gov/cpcat**/

United States Environmental Protection Agency

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