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Tools Fit for Chemical Risk Prioritization

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June 20, 2017

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

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Introduction

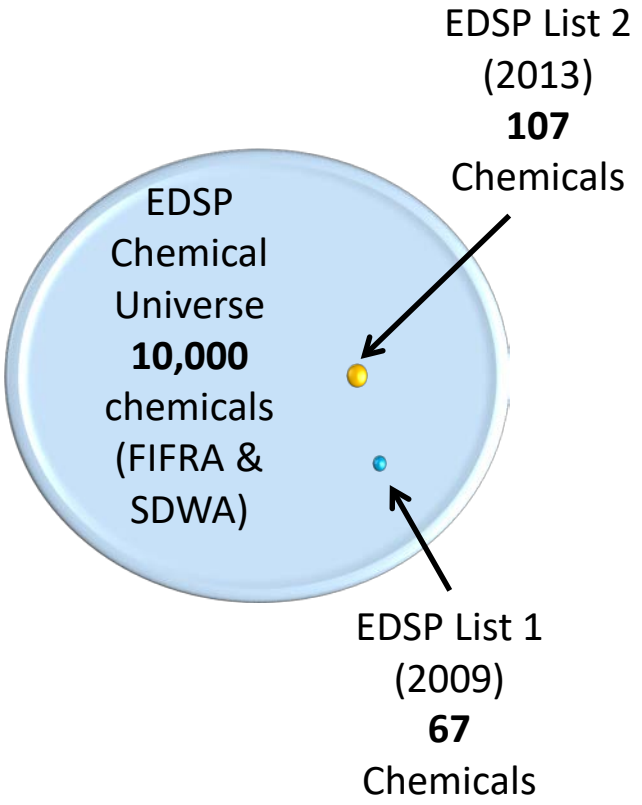
The timely characterization of the human and ecological risk posed by thousands of existing and emerging commercial chemicals is a critical challenge facing EPA in its mission to protect public health and the environment

November 29, 2014

Scale of the Problem

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

Endocrine Disruptor Screening Program (EDSP) Chemical List	Number of Compounds
Conventional Active Ingredients	838
Antimicrobial Active Ingredients	324
Biological Pesticide Active Ingredients	287
Non Food Use Inert Ingredients	2,211
Food Use Inert Ingredients	1,536
Fragrances used as Inert Ingredients	1,529
Safe Drinking Water Act Chemicals	3,616
TOTAL	**10,341**

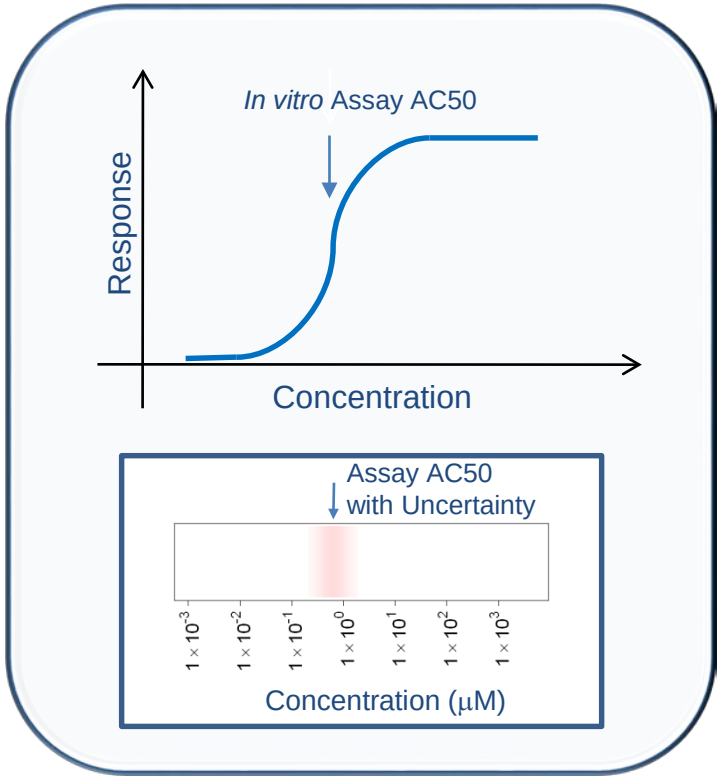


So far 67 chemicals have completed testing and an additional 107 are being tested

December, 2014 Panel: "Scientific Issues Associated with Integrated Endocrine Bioactivity and Exposure-Based Prioritization and Screening" DOCKET NUMBER: EPA–HQ–OPP–2014–0614

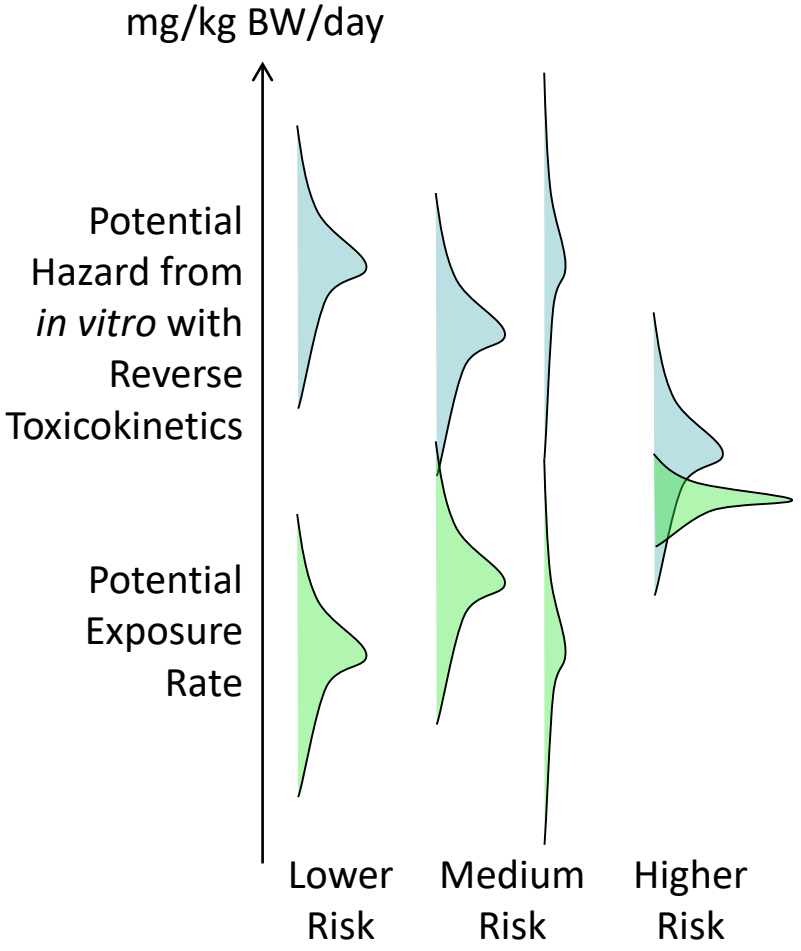
High-Throughput Bioactivity

- **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 (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, Filer *et al.*, 2016)
- All data is public: http://comptox.epa.gov/

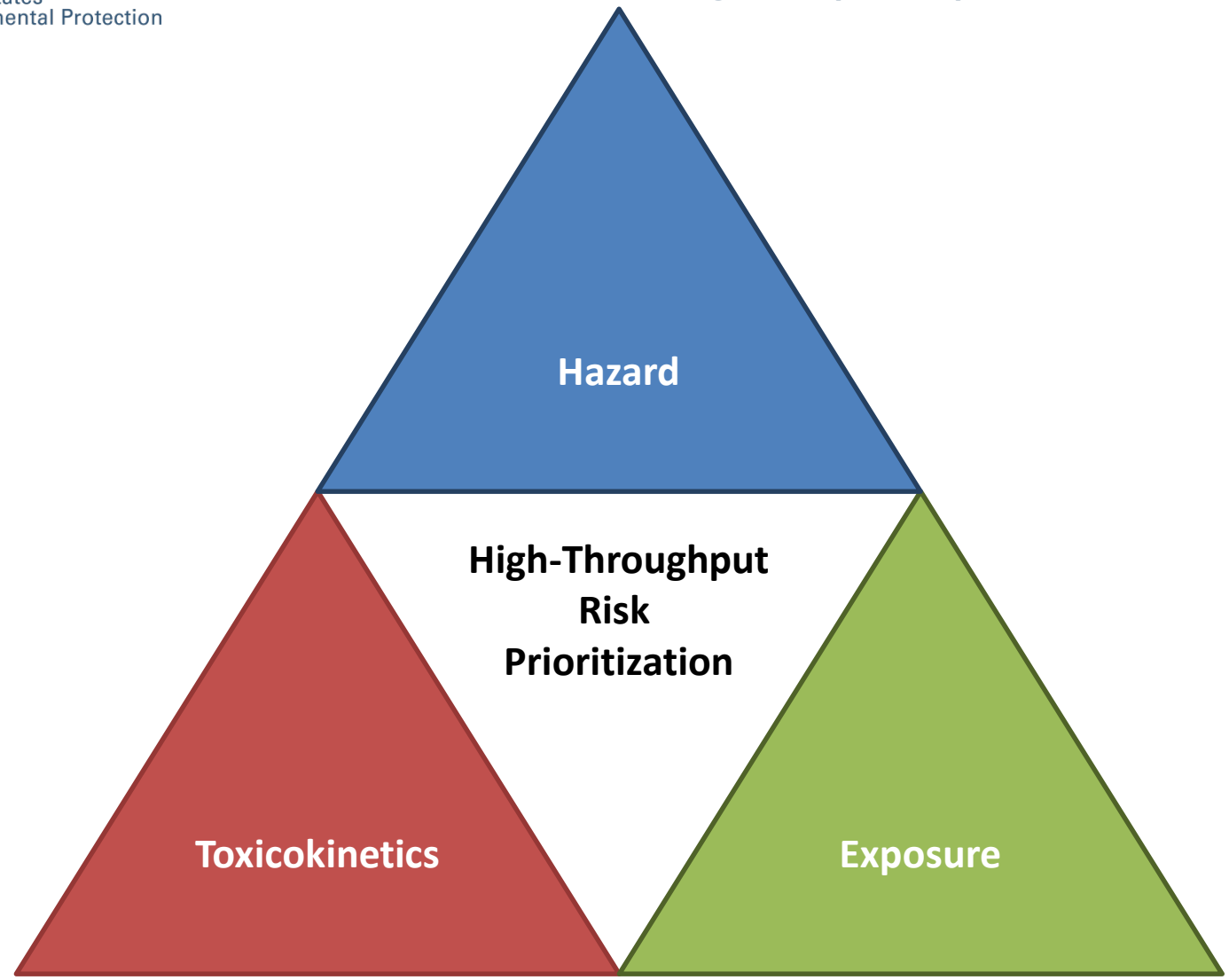


High Throughput Risk Prioritization

- **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)



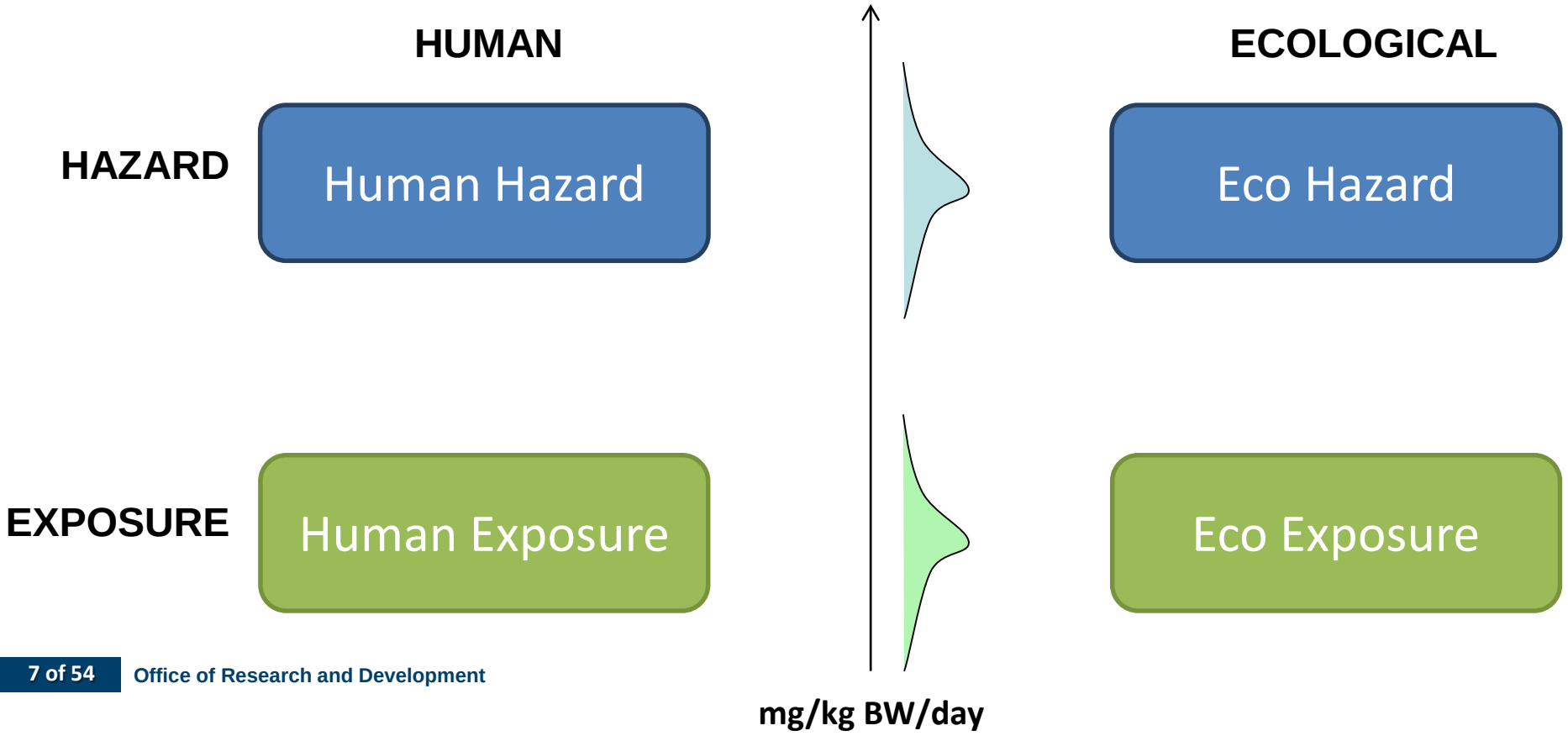
Application to U.S. EPA Endocrine Disruptor Screening Program (EDSP)



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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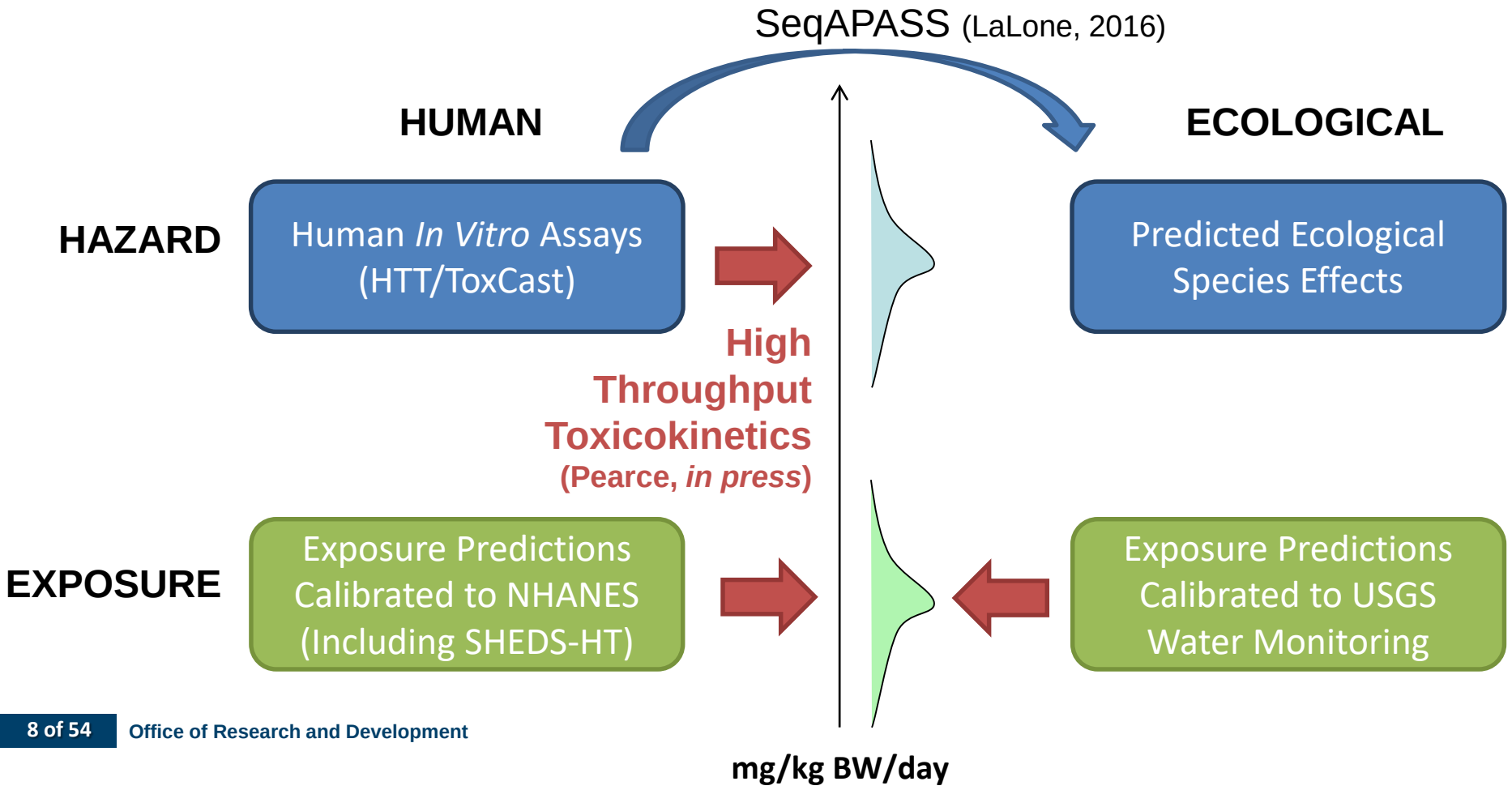


High Throughput Risk Prioritization in Practice

mg/kg bw/day

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

ExpoCast Exposure Predictions

Near Field

Far Field

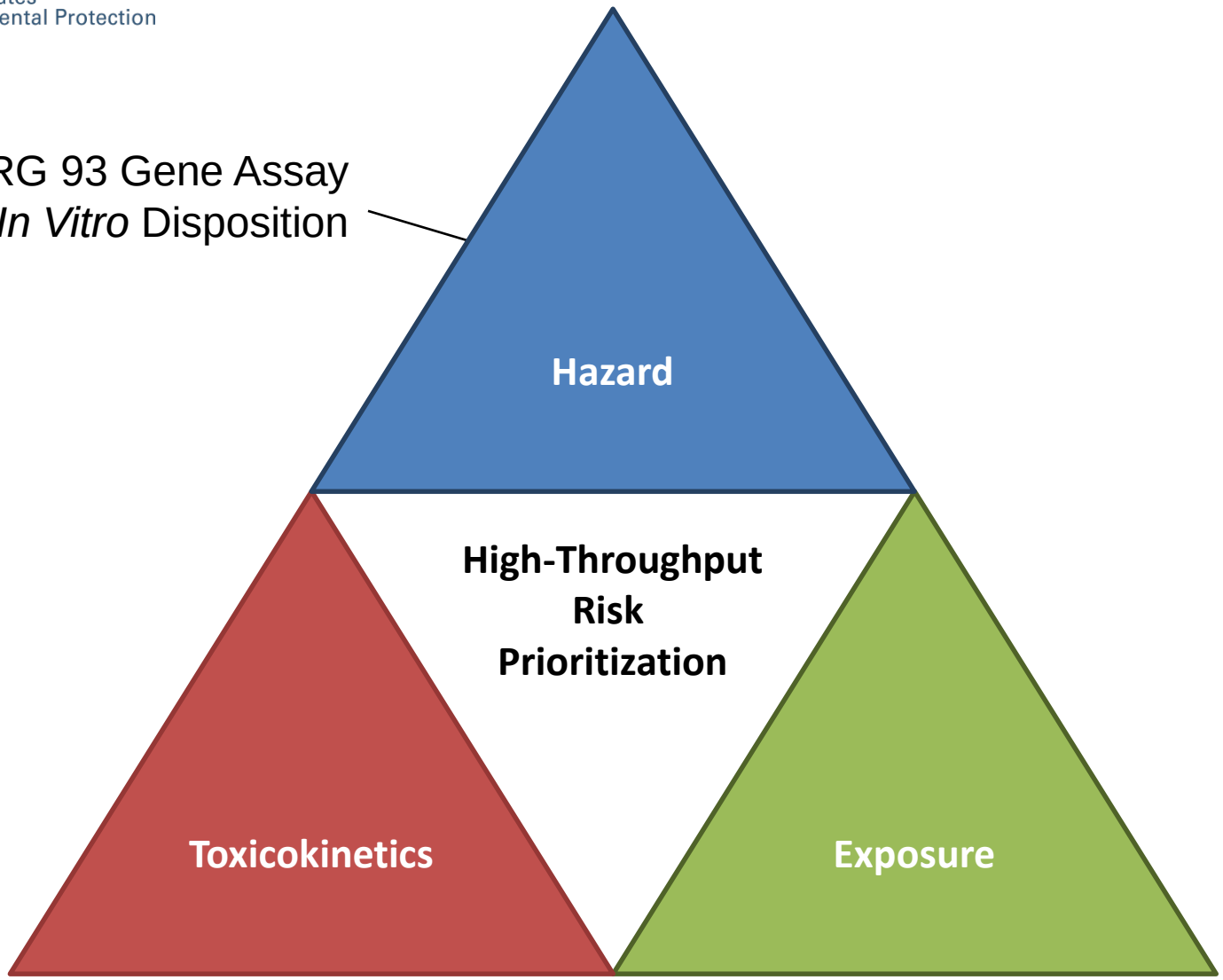
ToxCast Chemicals

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

Rapid exposure and dosimetry project helps establish exposure context for ToxCast high throughput screening

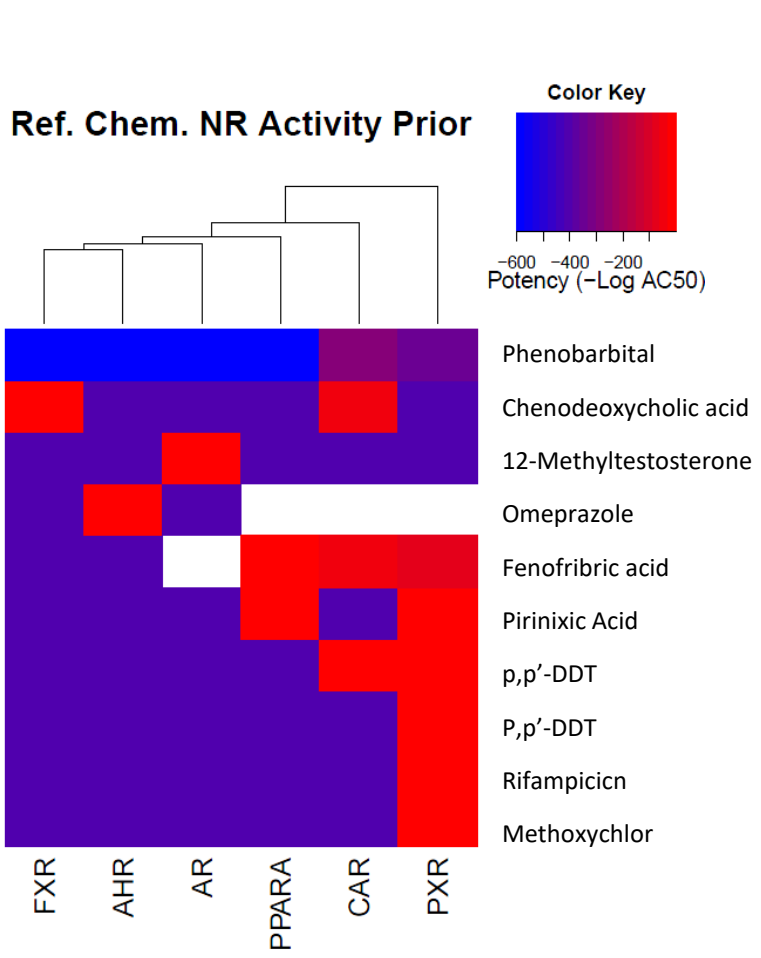
New ToxCast Developments

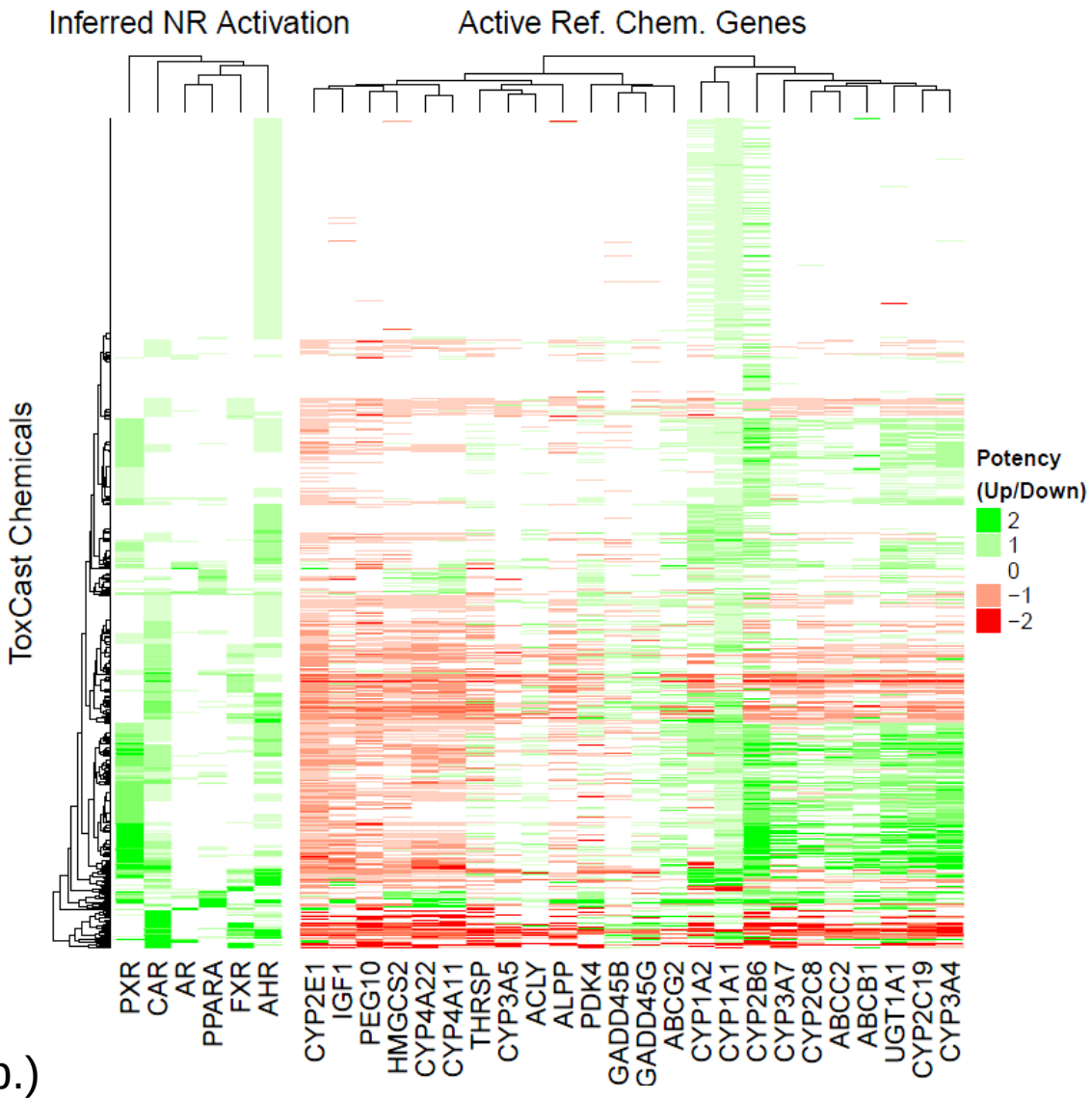
- HepaRG 93 Gene Assay
  - *In Vitro* Disposition



ToxCast HepaRG Assay

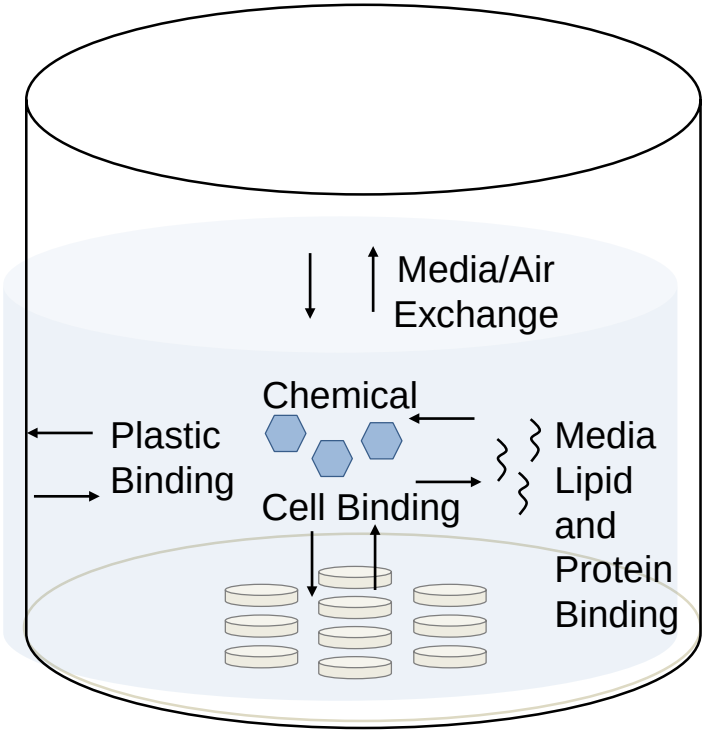
Inferred NR activation using 93 genes and reference chemicals for 1060 ToxCast chemicals in a metabolically competent (HepaRG) system





Franzosa et al. (in prep.)

In Vitro Disposition Assay:
Determining Concentration in Cells



Zaldívar Comenges (2012)

Collaboration with U.S. National Toxicology Program Evaluating Armitage et al. (2014) and Fischer (2017) models

- 100 to 200 chemicals, using acoustic liquid handling to randomize and expose
- MCF-7 cells
- 1, 6, and 24 hours
- 10 µM

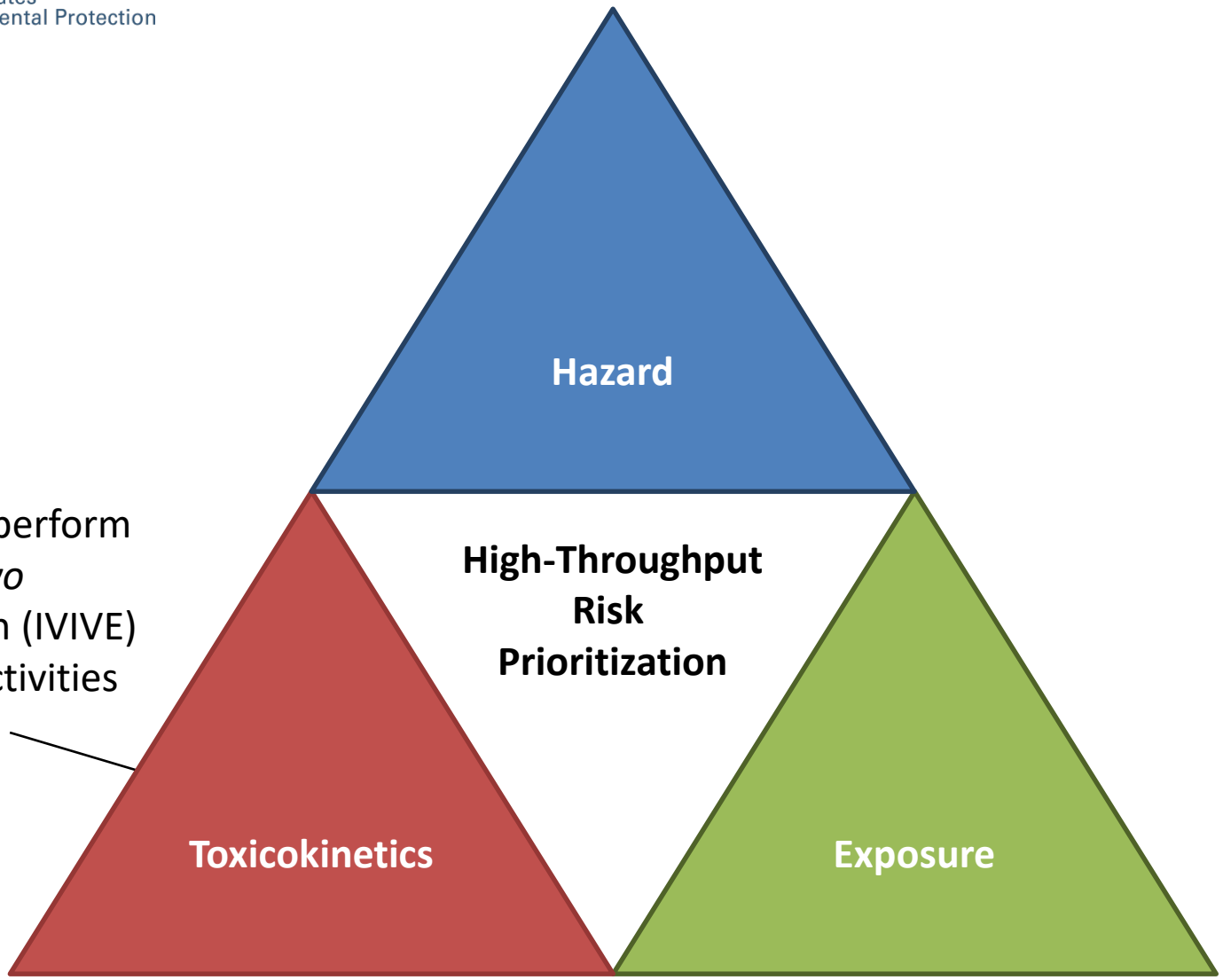
	Plating condition	FBS (high/low)	Measured compartment
1	Medium – cells	High	Medium
2	Medium – cells	Low	Medium
3	Medium + cells	High	Medium
4	Medium + cells	Low	Medium
5	Medium + cells	High	Cells/plastic
6	Medium + cells	Low	Cells/plastic
7	Medium + cells	High	Cells, medium, and plastic

- LC-MS/MS, using a Thermo Q Exactive Plus system with high resolution

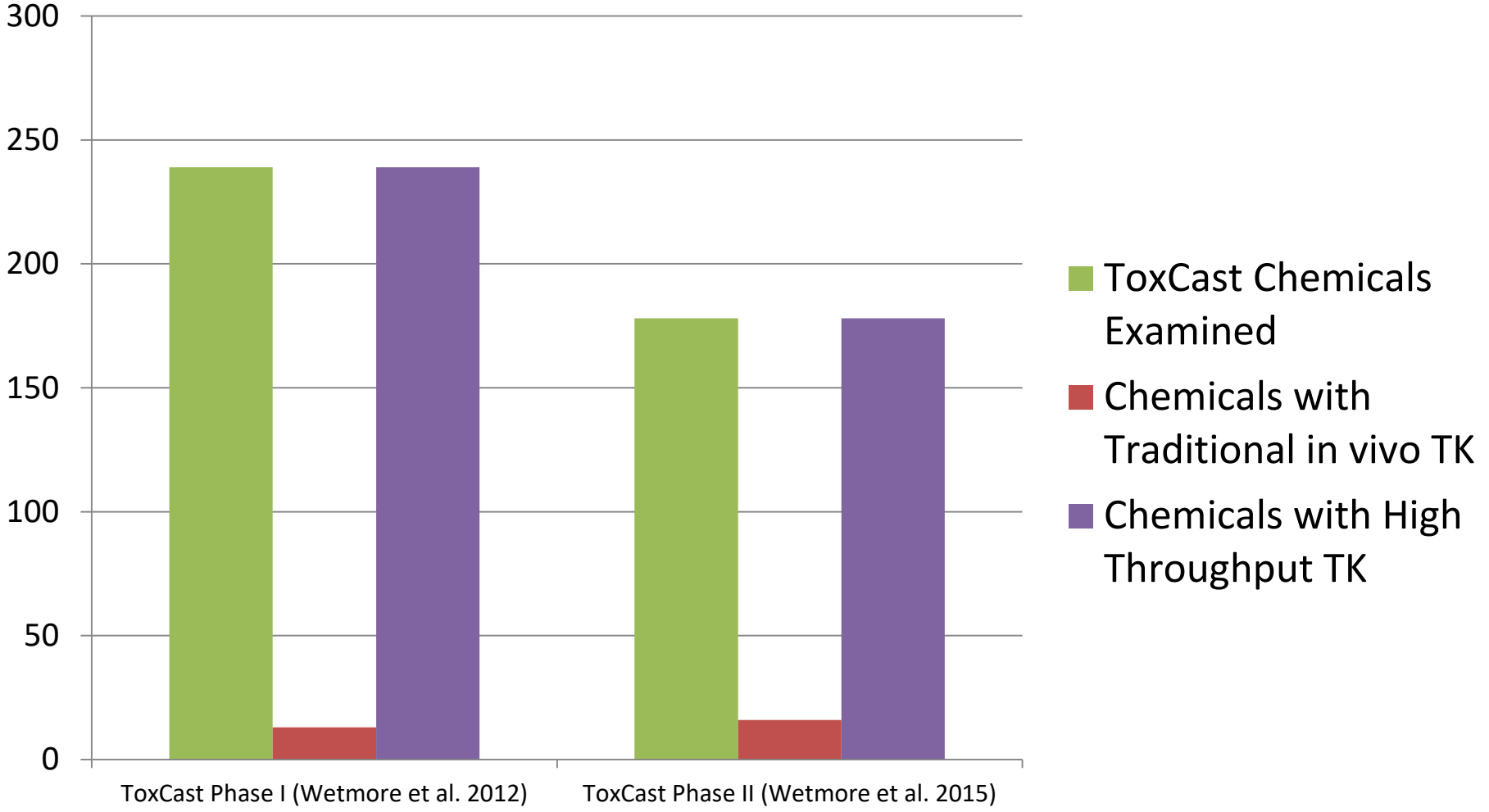
Katie Paul-Friedman, Mike Devito

Toxicokinetics for IVIVE

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



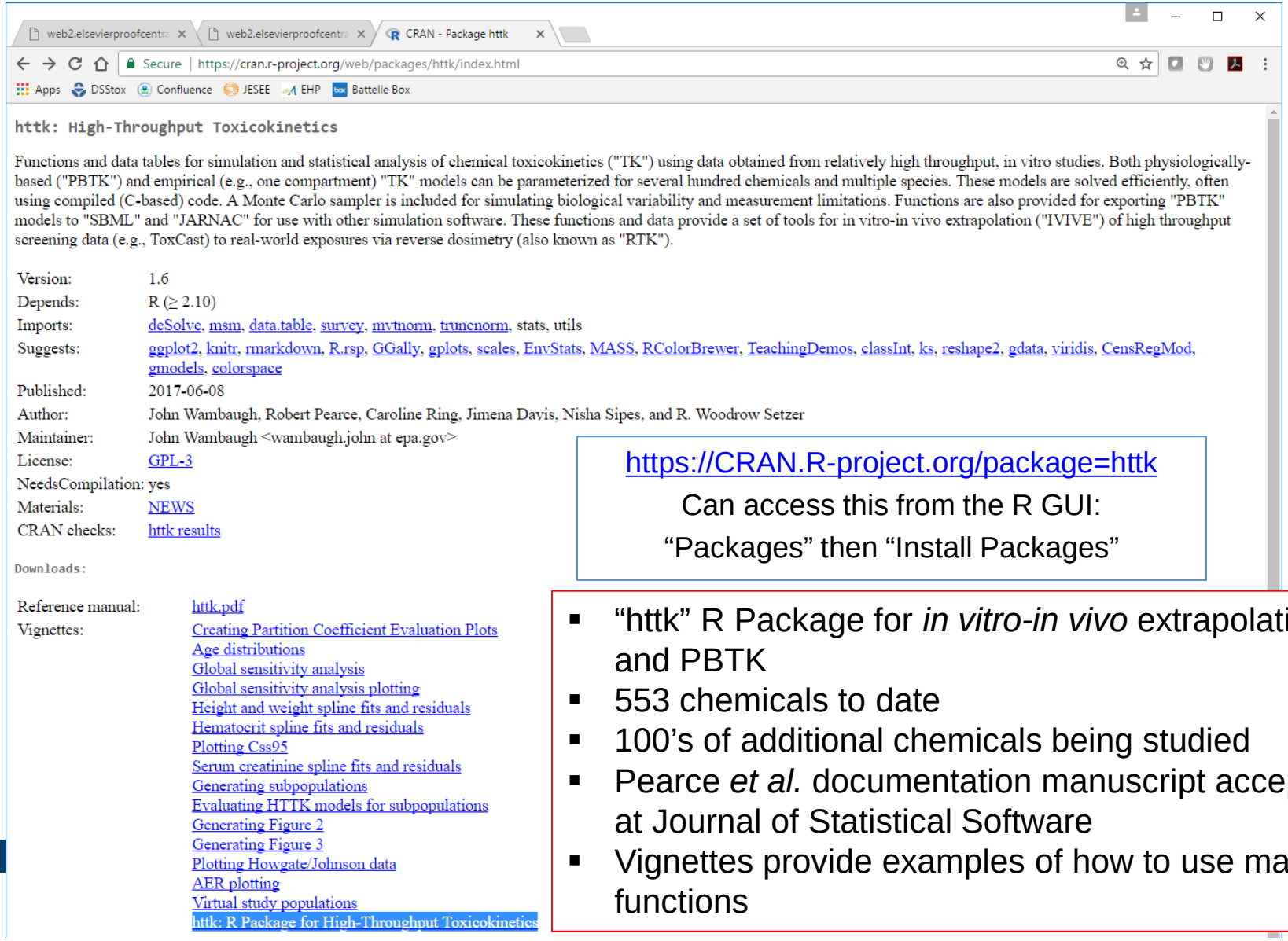
The Need for *In Vitro* Toxicokinetics



- 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

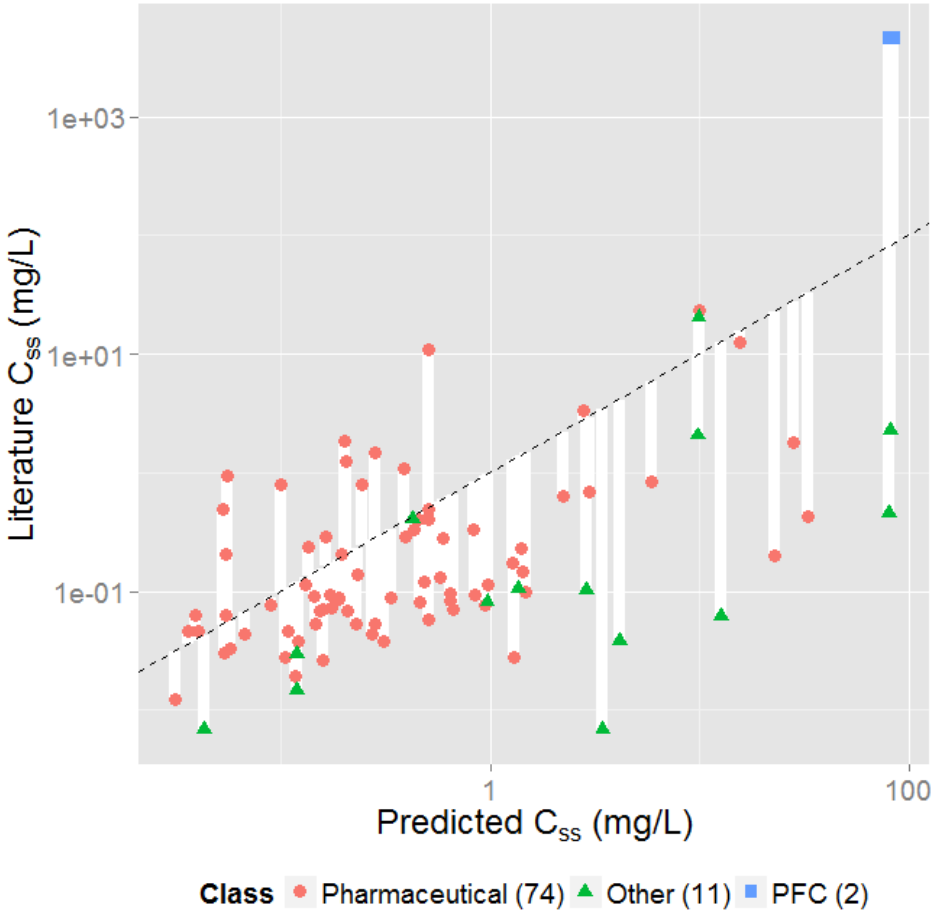
https://CRAN.R-project.org/package=httk

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.* documentation manuscript accepted at Journal of Statistical Software
- Vignettes provide examples of how to use many functions

Using *in vivo* Data to Evaluate RTK

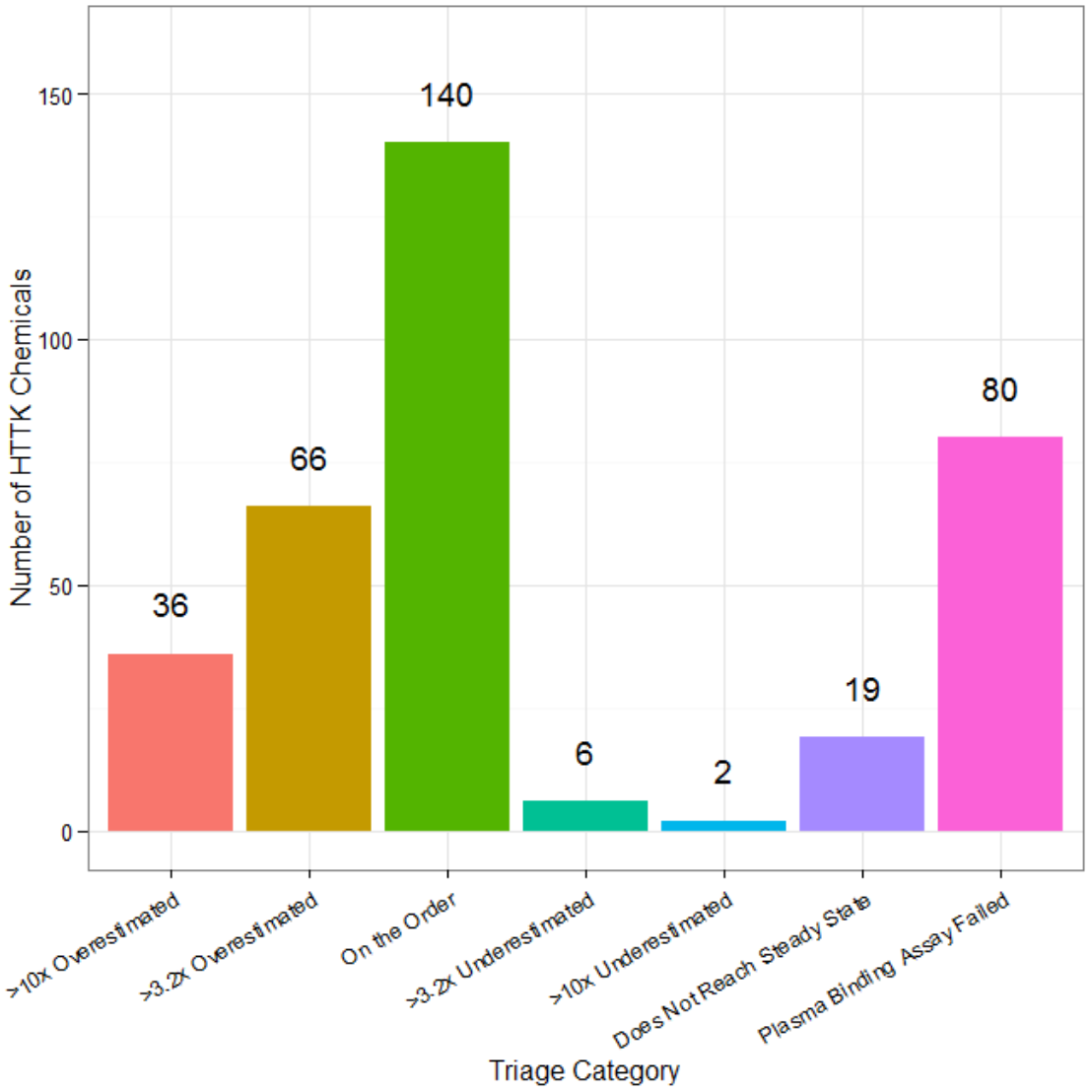


- When we compare the C_{ss} predicted from *in vitro* HTTK with *in vivo* C_{ss} values determined from the literature we find limited correlation (R^2 ~0.34)
- The dashed line indicates the identity (perfect predictor) line:
  - Over-predict for 65
  - Under-predict for 22
- The white lines indicate the discrepancy between measured and predicted values (the residual)

Wambaugh et al. (2015)

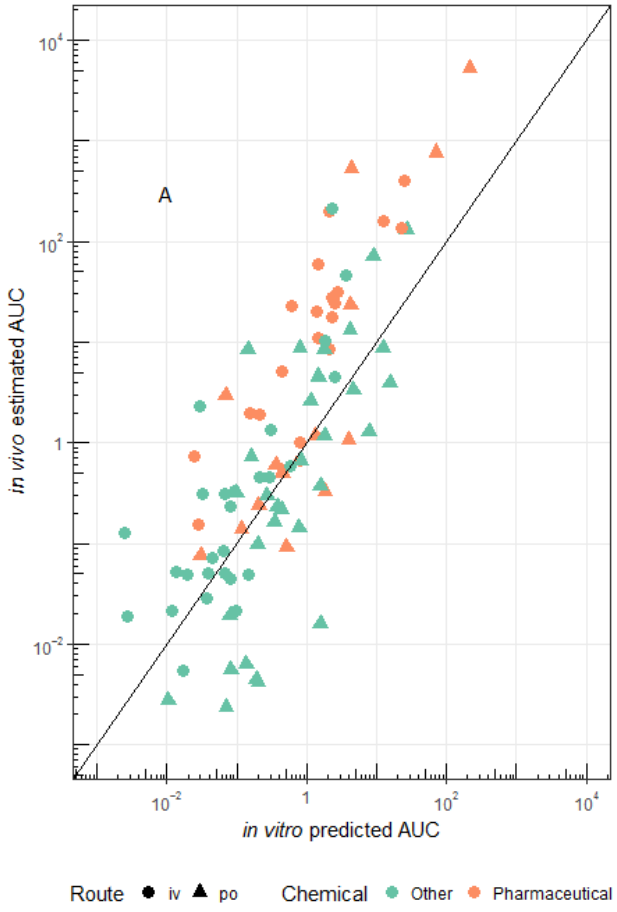
Toxicokinetic Triage

- Through comparison to *in vivo* data, a cross-validated (random forest) predictor of success or failure of HTTK has been constructed
- Add categories for chemicals that do not reach steady-state or for which plasma binding assay fails
- All chemicals can be placed into one of seven confidence categories



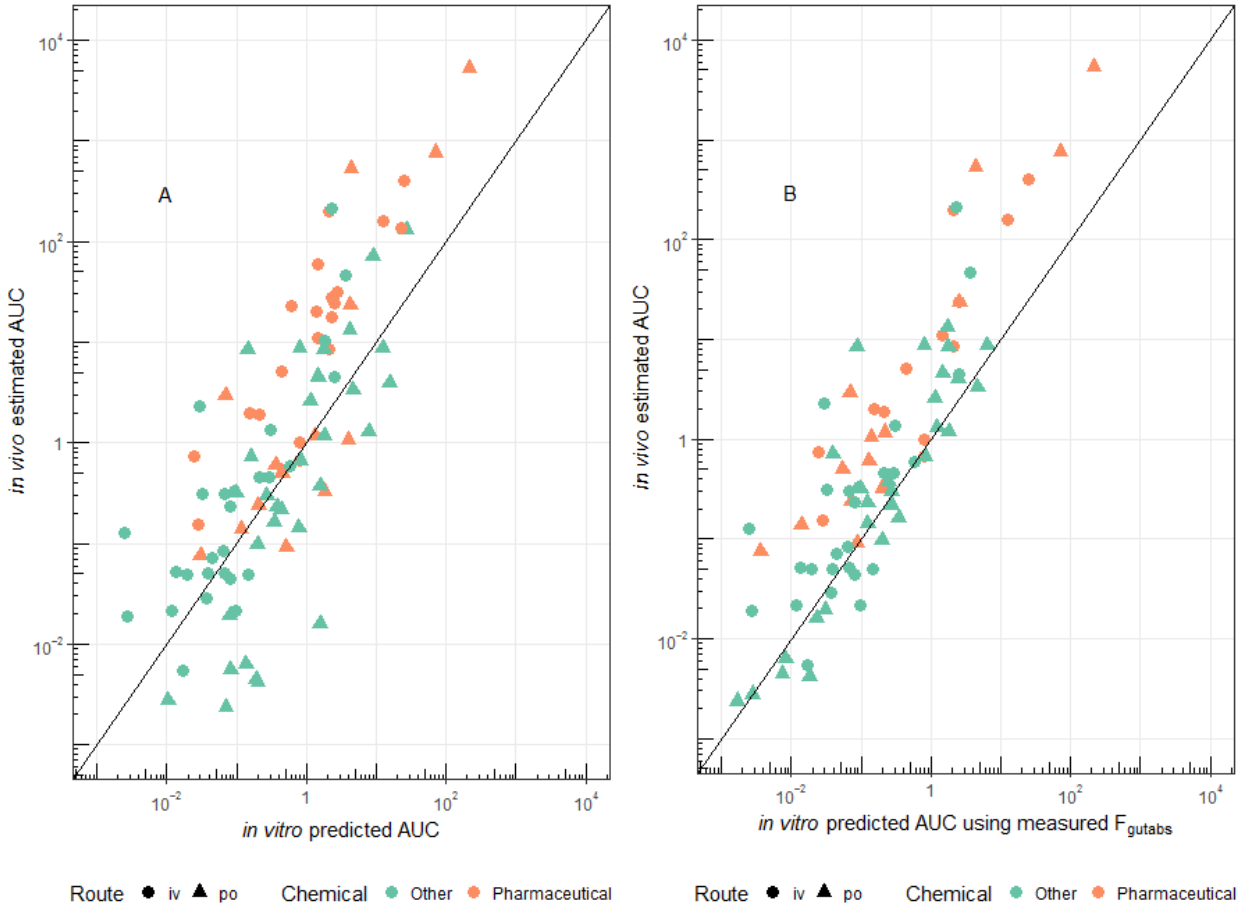
Wambaugh et al. (2015)

Analyzing New *In Vivo* Data (Rat)



- Oral and *iv* studies for 26 ToxCast compounds
  - Collaboration with NHEERL (Mike Hughes and Jane Ellen Simmons)
  - Additional work by Research Triangle Institute (Tim Fennell)
- Can estimate
  - Fraction absorbed
  - Absorption Rate
  - Elimination Rate
  - Volume of Distribution

Analyzing New *In Vivo* Data (Rat)



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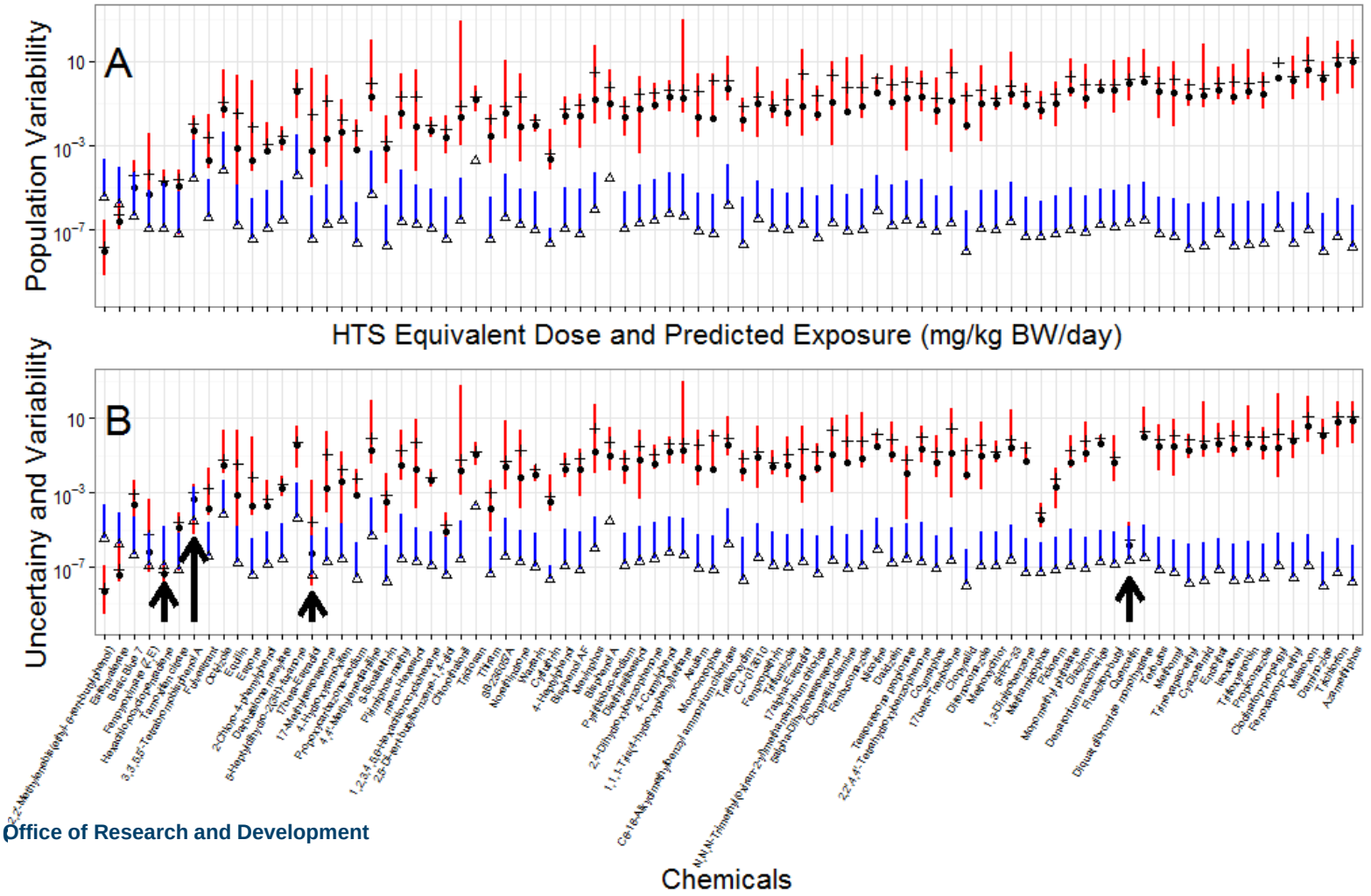
Cyprotex (ToxCast) is now measuring bioavailability (CACO2) for many HTTK chemicals

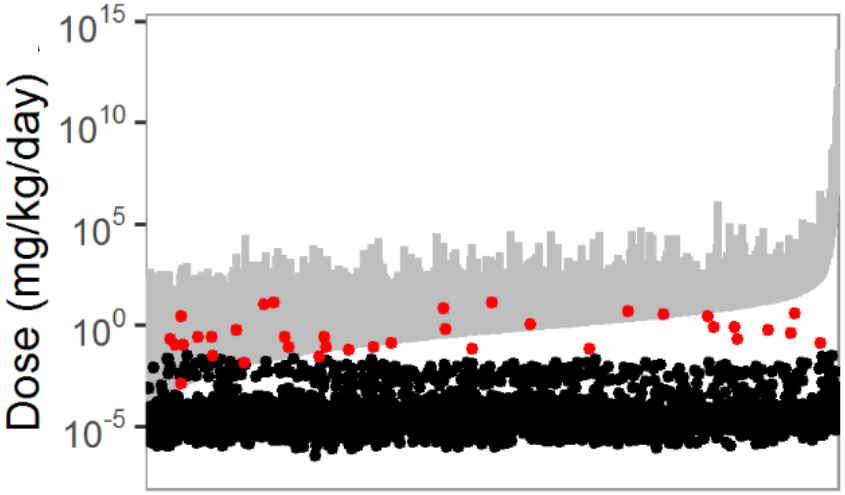
Propagating Measurement Uncertainty

Now using Bayesian analysis of measurement error to assess confidence in HTTK predictions

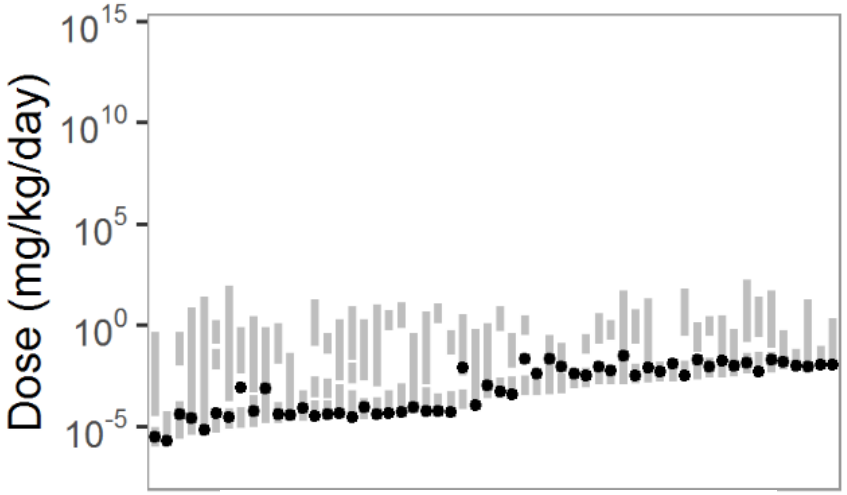


Using HTTK Predicted C_{max} for Risk Prioritization

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



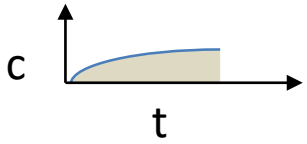
56 compounds with potential *in vivo* biological interaction at or above estimated environmental exposures

Sipes et al., under revision

IVIVE with HTTK PBPK Model

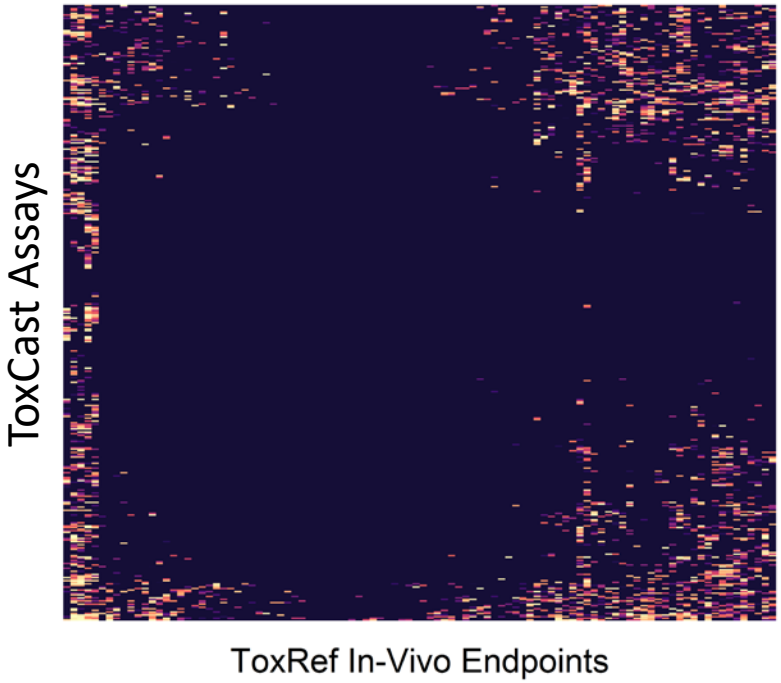
United States Environmental Protection Agency

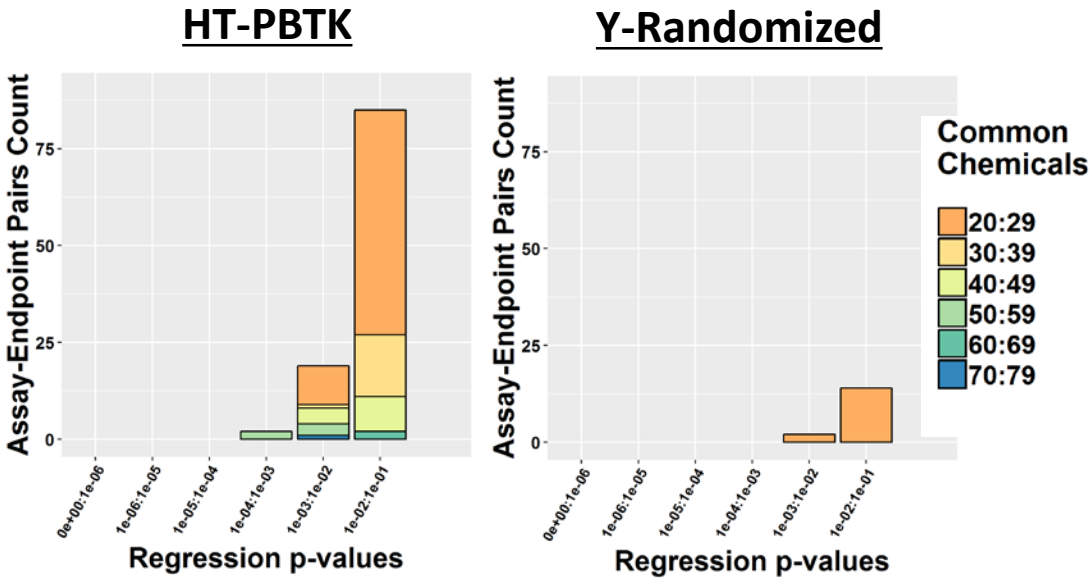
ToxRefDB *in vivo* LEL dose (mg/kg/day) → **HT-PBTK** → **HT-PBTK transformed concentration (µM)** **vs.** **ToxCast AC50 (µM)**



Plasma concentration determined by **HT-PBTK** shows **greater correlation** with **ToxCast AC50** than dose alone or y-randomization result

HT-PBTK *p*-Values

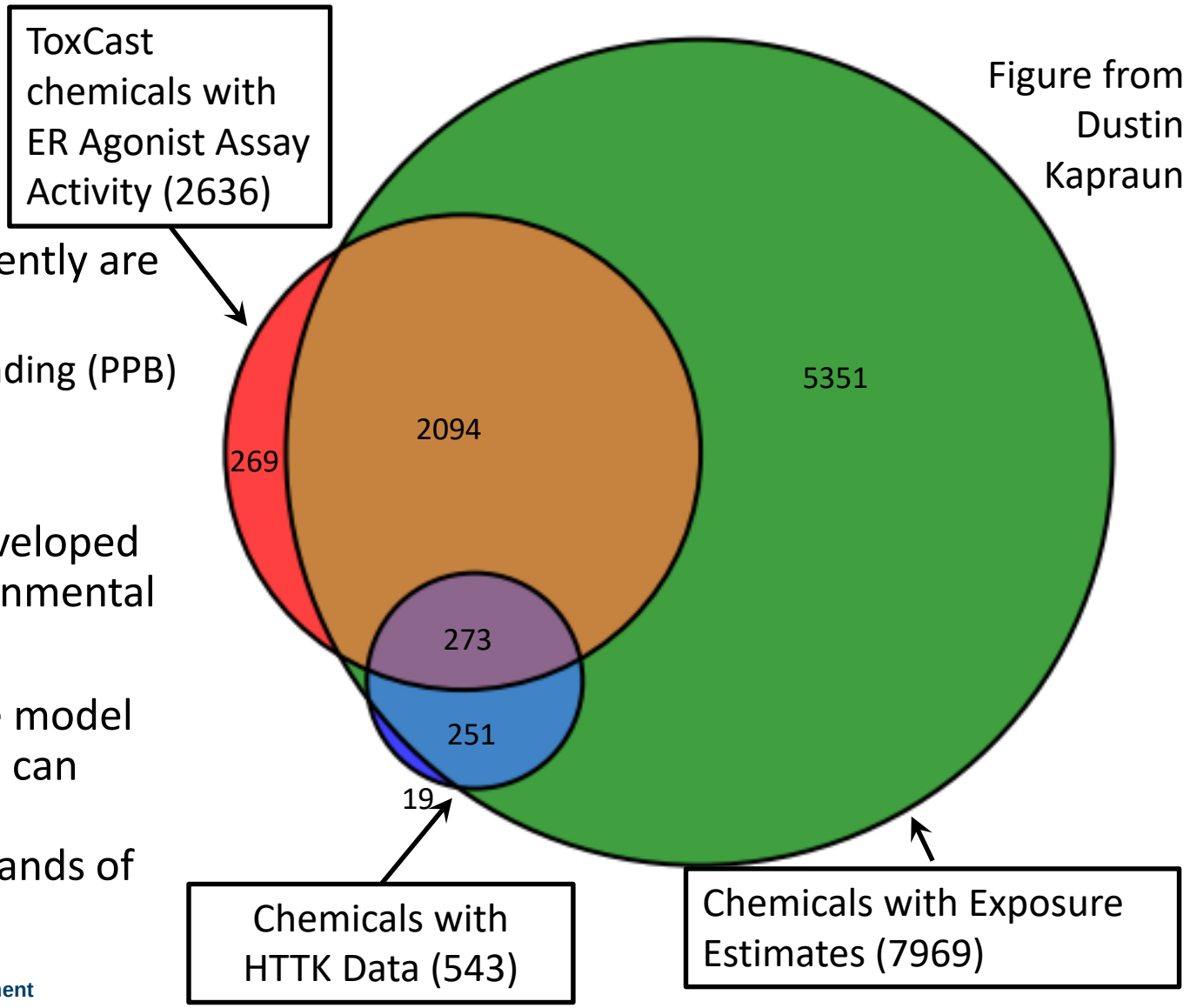




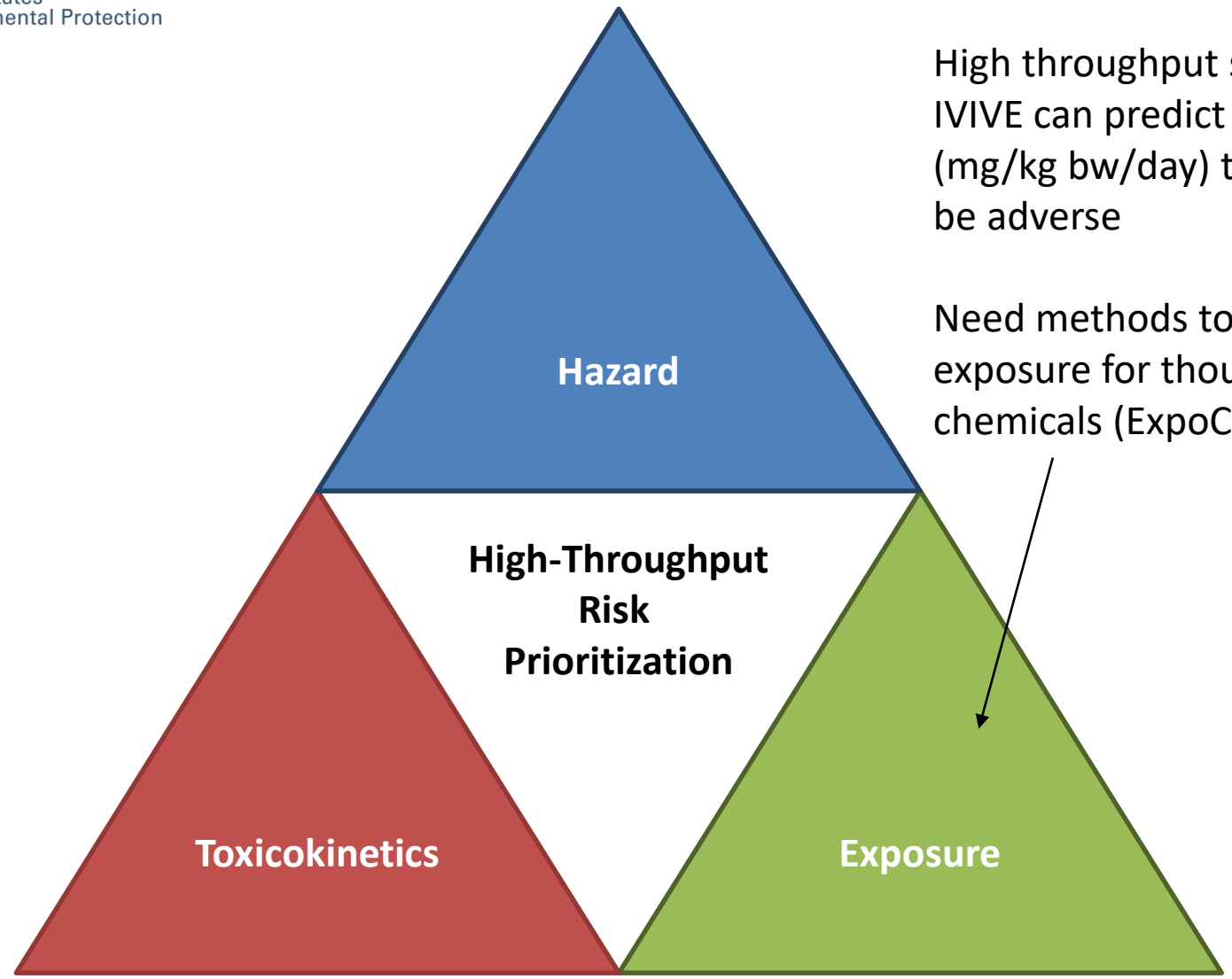
Analysis led by Greg Honda

Predicting Critical TK Parameters

- Two parameters currently are key to HTTK model:
  - Plasma protein binding (PPB)
  - Hepatic clearance (metabolism)
- Ingle *et al.* (2016) developed PPB model for environmental chemicals
- If a hepatic clearance model can be developed we can provide tentative TK predictions for thousands of more chemicals



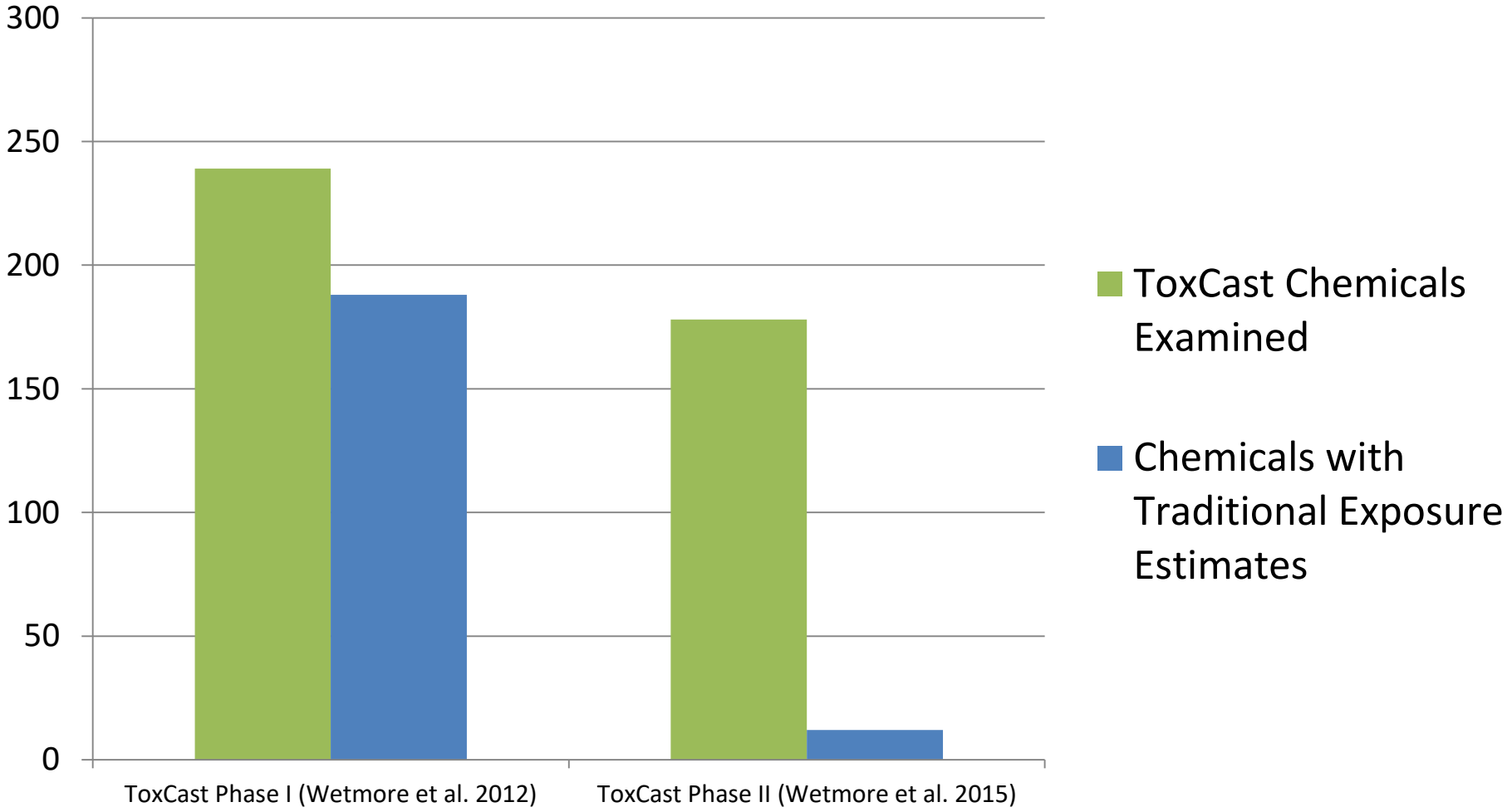
High Throughput Exposure



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

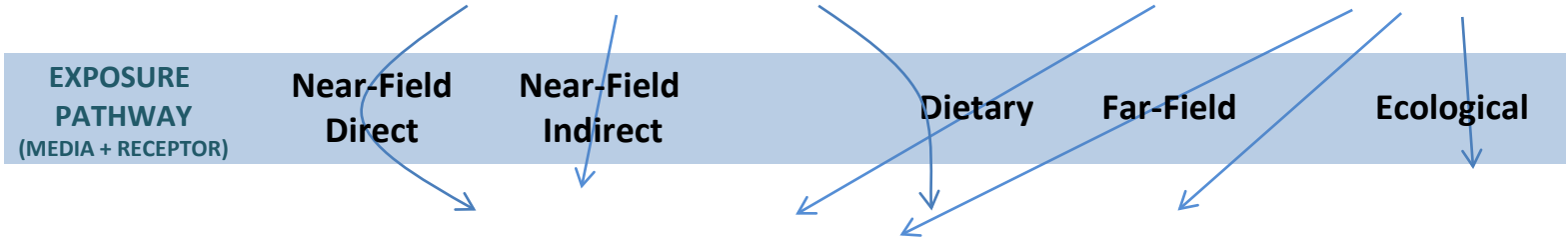
Need methods to forecast exposure for thousands of chemicals (ExpoCast)

The Need for High Throughput Exposure



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

The Exposure Event is Often Unobservable

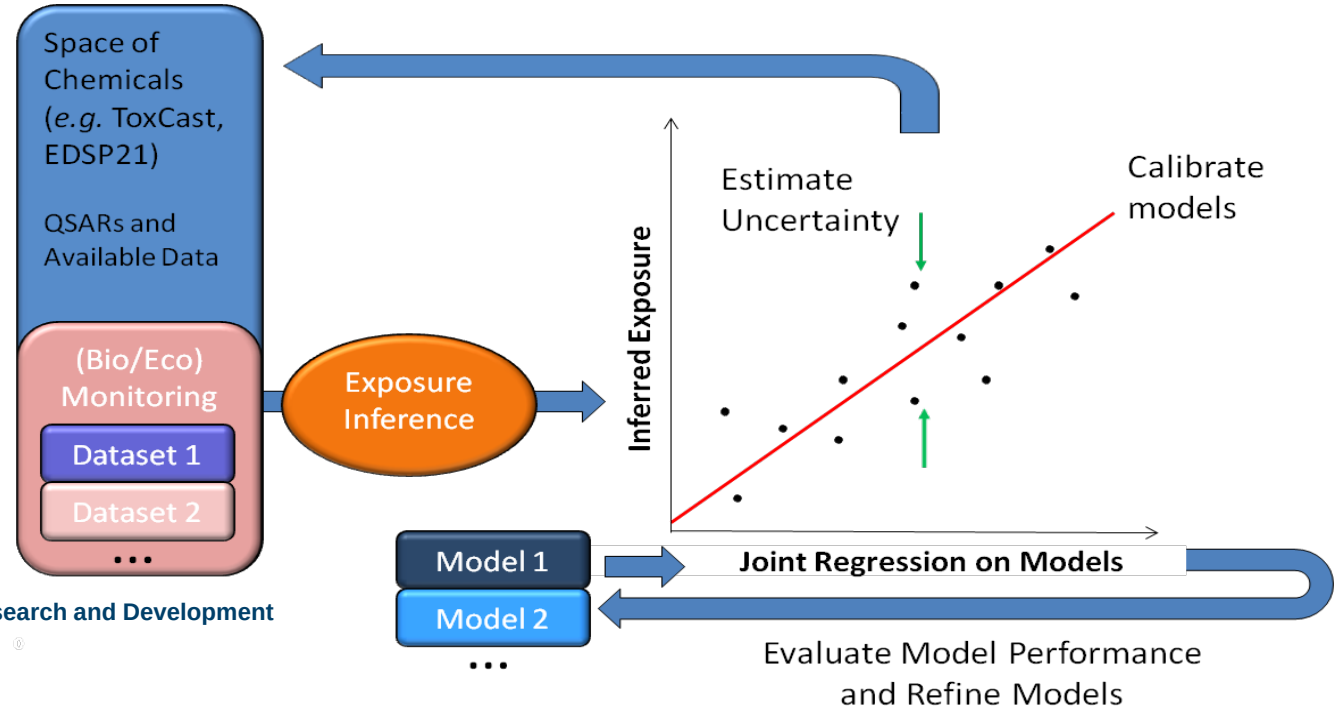


- The exposure pathway is the actual interaction of the receptor and media, e.g. consuming potato chips
- For humans in particular, these events are often unobserved and for many reasons (including ethics and privacy) may remain unobservable
  - *Did you eat the serving size or the whole bag of potato chips?*
- **Either predict** exposure using data and models up-stream of the exposure event
- **Or infer** exposure pathways from down-stream data, especially biomarkers of exposure

Figure modified from original by Kristin Isaacs

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 across as many chemical classes as possible to allow extrapolation
  - Attempt to identify correlations and errors empirically



Exposures Inferred from NHANES

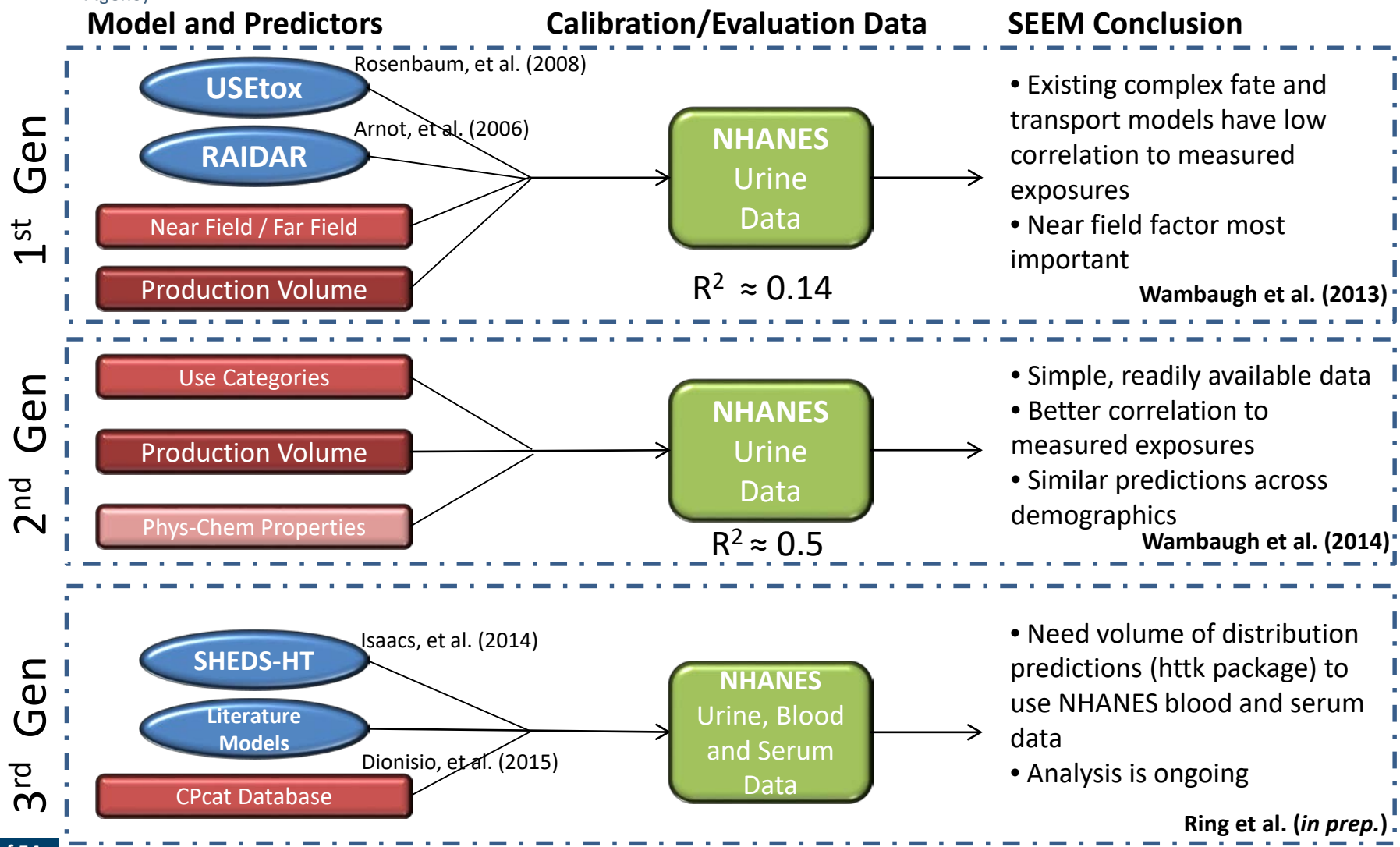
- Annual survey, data released on 2-year cycle.
- Different predictive models provide different chemical-specific predictions
  - Some models may do a better job form some chemical classes than others overall, so we want to evaluate performance against monitoring data
- Separate evaluations can be done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

National Health and Nutrition Examination Survey

CDC, Fourth National Exposure Report (2011)

SEEM Evolution

United States Environmental Protection Agency



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:

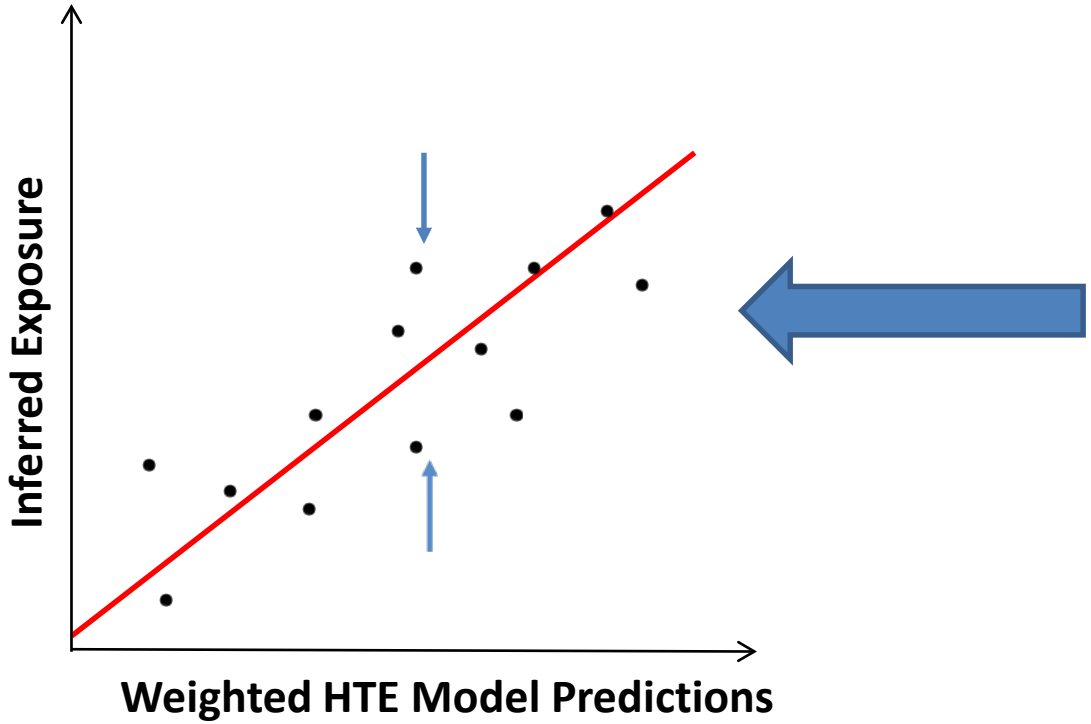
- Industrial and Consumer use
- Pesticide Inert
- Pesticide Active
- Industrial but no Consumer use
- Production Volume

SEEM is a Linear Regression

United States Environmental Protection Agency

Multiple regression models:

Log(Parent Exposure) = a + m * log(Model Prediction) + b* Near Field + ε



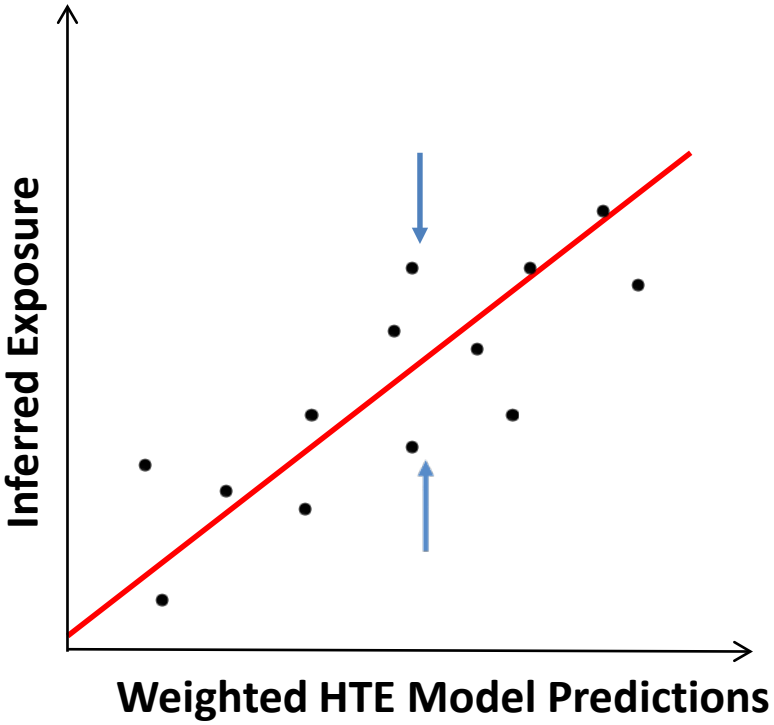
$\varepsilon \sim N(0, \sigma^2)$
Residual error, unexplained by the regression model

SEEM is a Linear Regression

United States Environmental Protection Agency

Multiple regression models:

Log(Parent Exposure) = a + m * log(Model Prediction) + b* Near Field + ε



Not all models have predictions for all chemicals

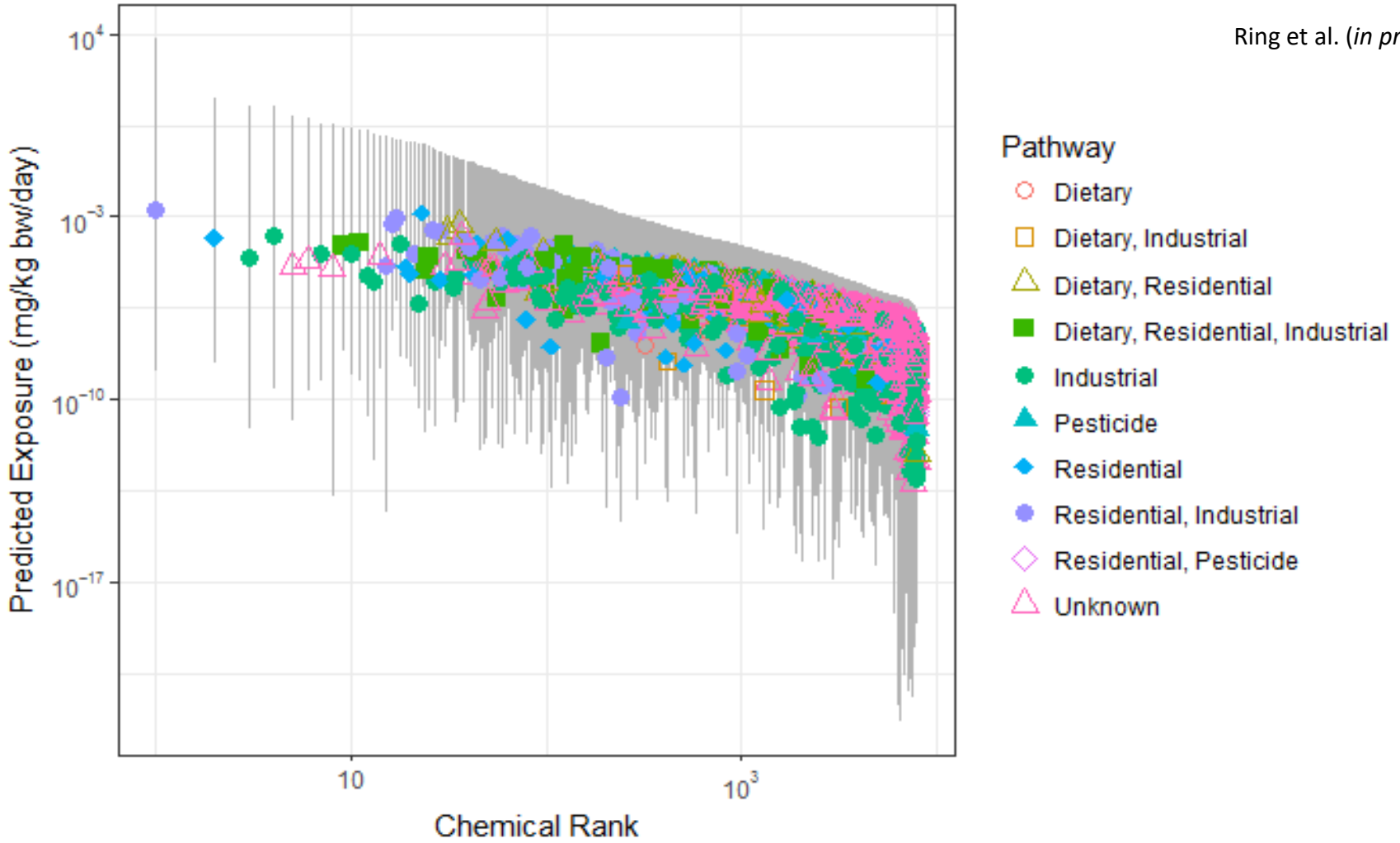
- We can run SHEDS-HT (Isaacs et al., 2014) for ~2500 chemicals

What do we do for the rest?

- Assign the average value?
- Zero?

Human Exposure Predictions for 134,521 Chemicals

Ring et al. (*in prep.*)



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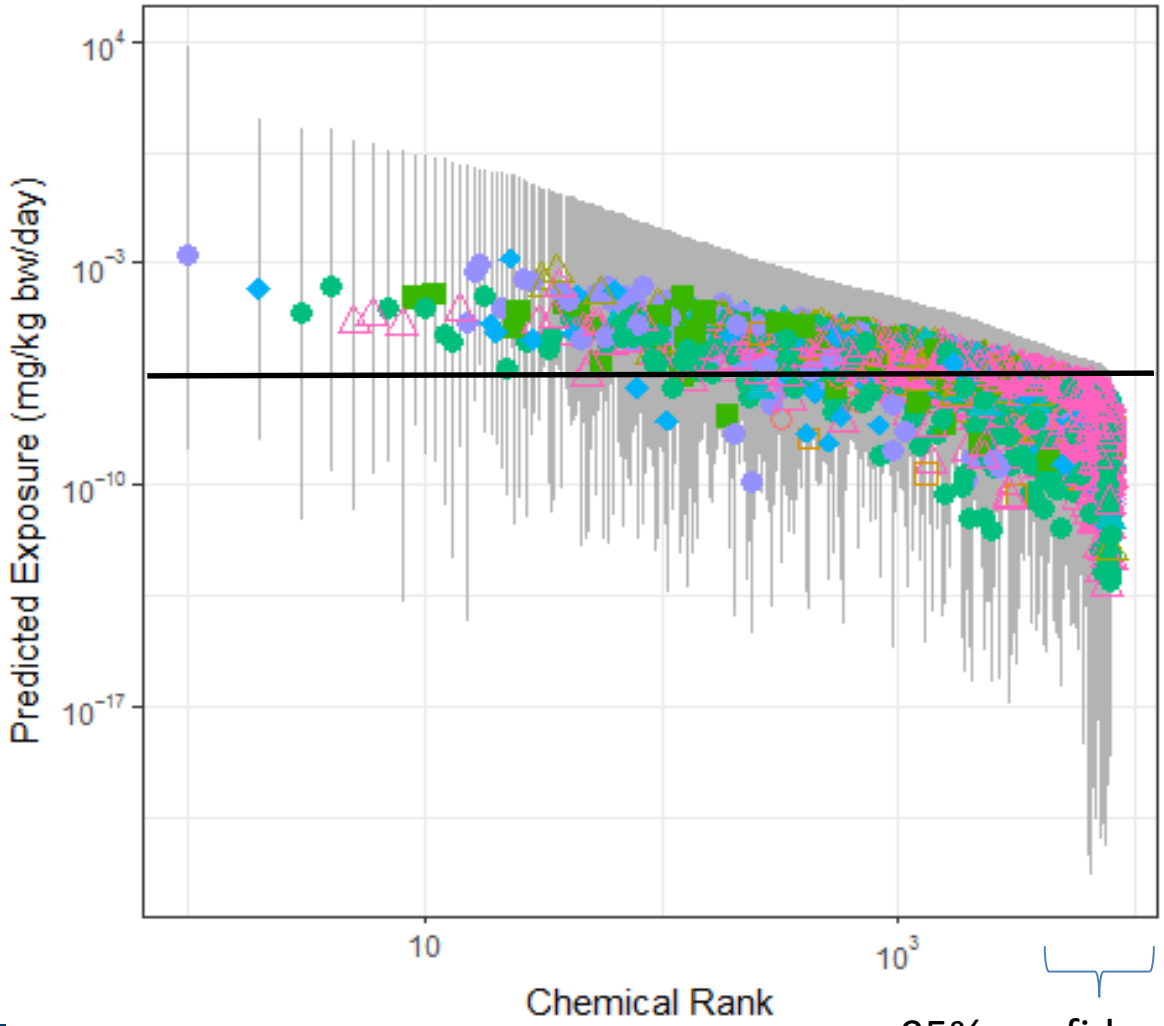


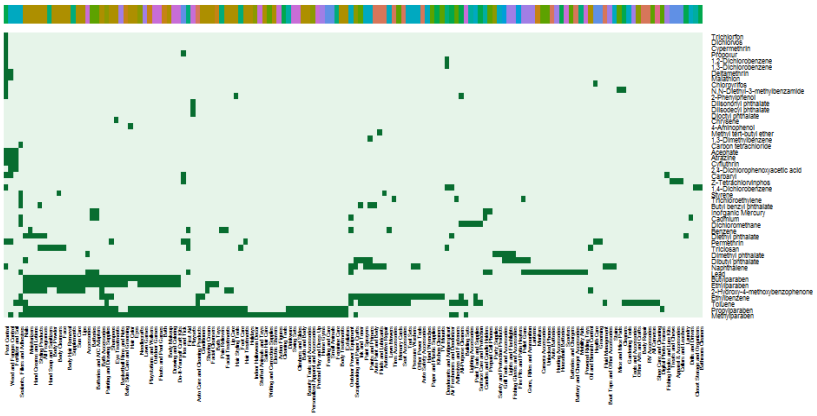
Lowest NHANES limit of detection (LOD) roughly corresponds to ~10^{-6} mg/kg BW/day

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

Chemical Use Identifies Relevant Pathways

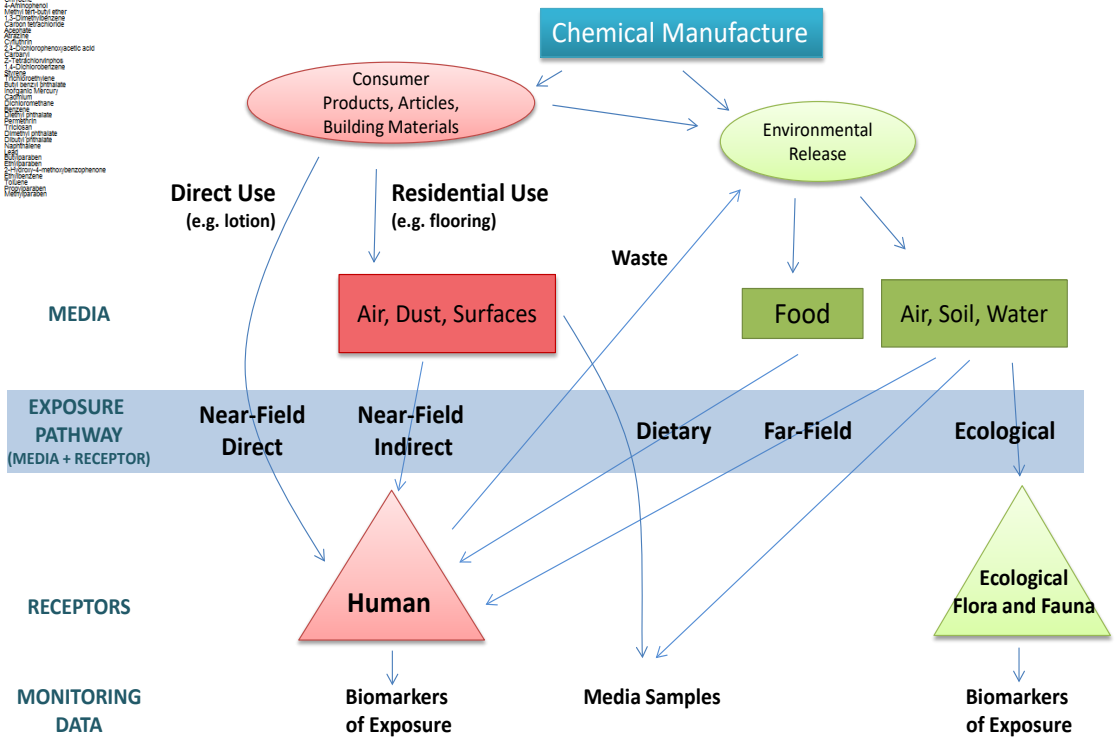
>2000 chemicals with Material Safety Data Sheets (MSDS) in CPCPdb (Goldsmith *et al.*, 2014)

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

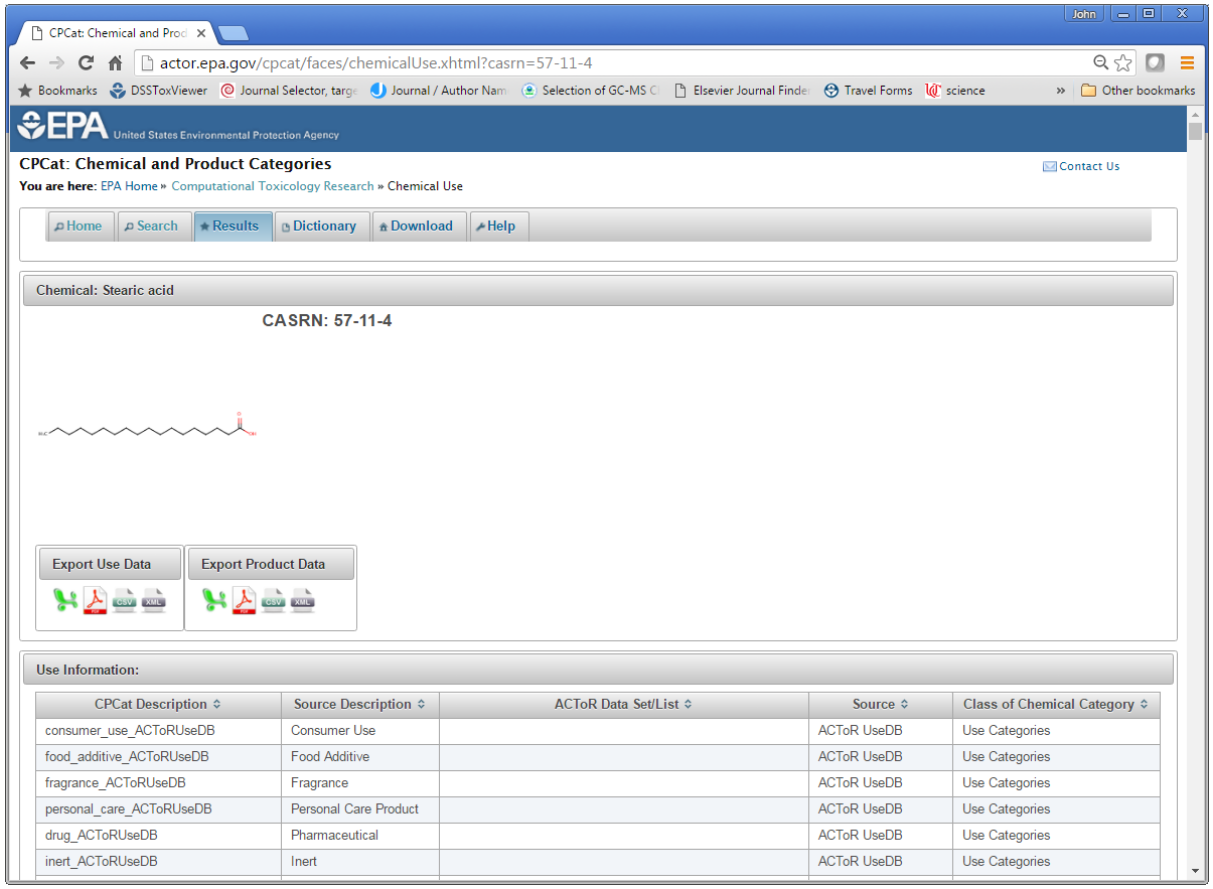
Some pathways have much higher average exposures!



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

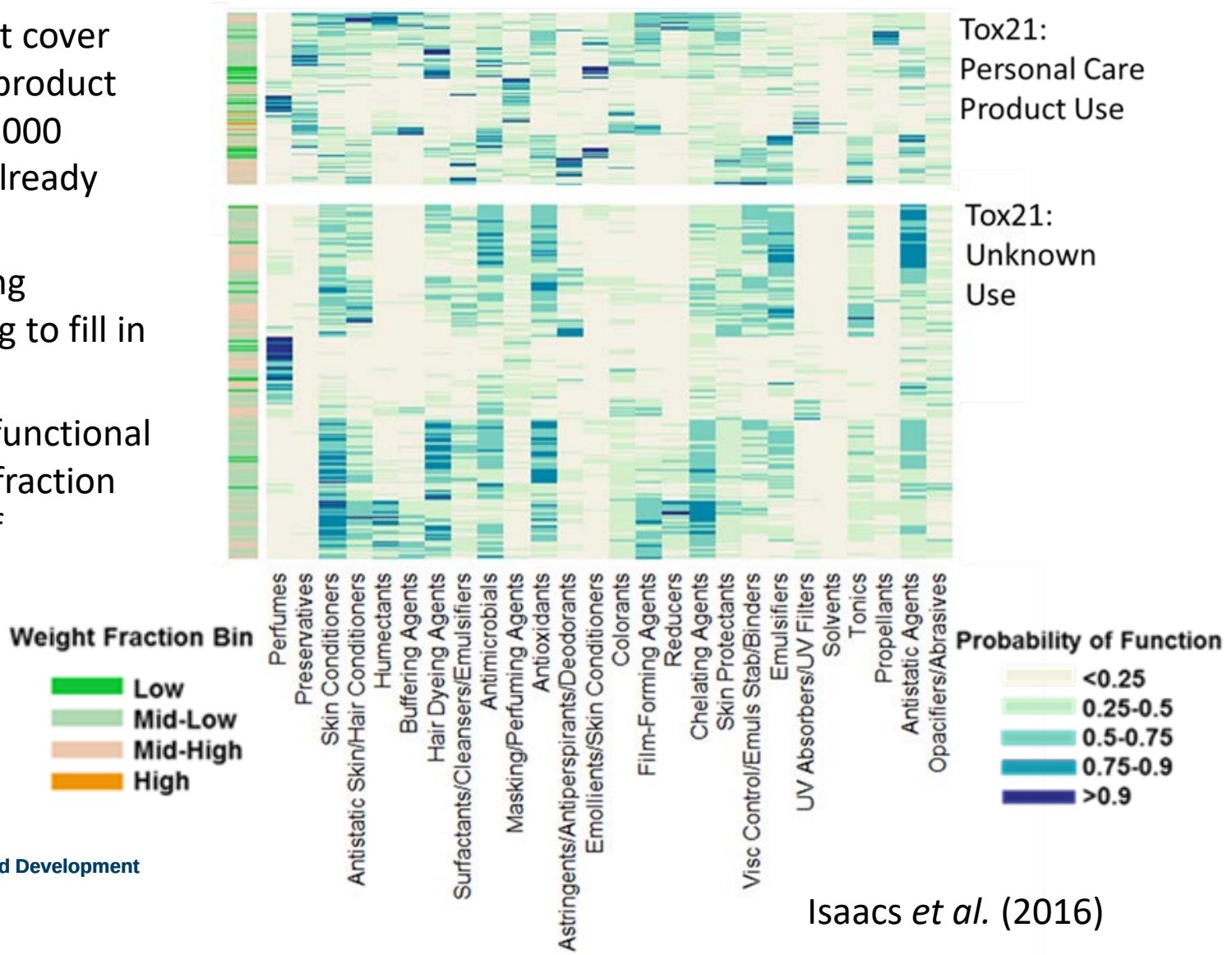


http://**actor.epa.gov/cpcat/**

Dionisio *et al.* (2015)

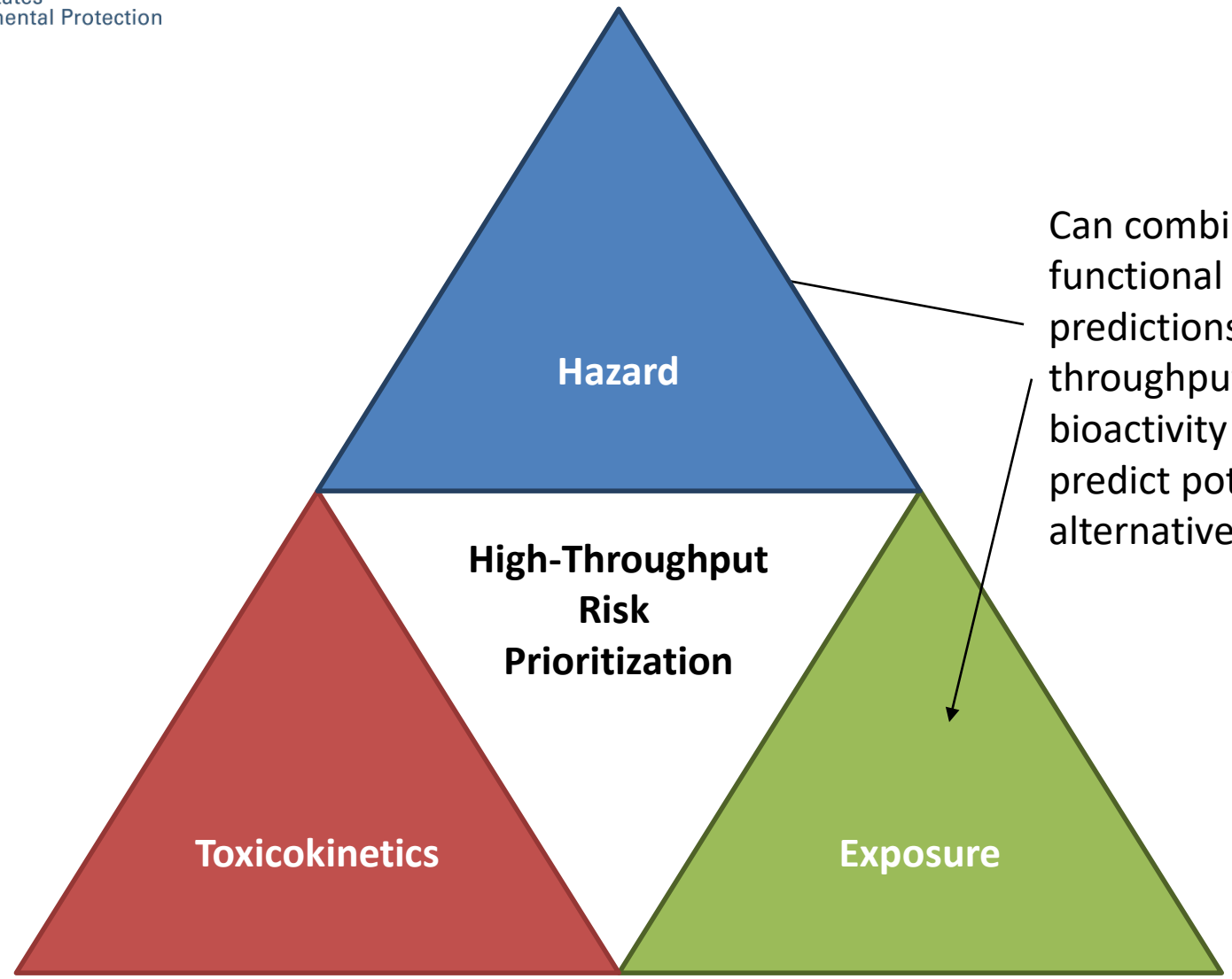
Predicting Chemical Constituents

- CPCPdb does not cover every chemical-product combination (~2000 chemicals, but already >8000 in Tox21)
- We are now using machine learning to fill in the rest
- We can predict functional use and weight fraction for thousands of chemicals



Isaacs *et al.* (2016)

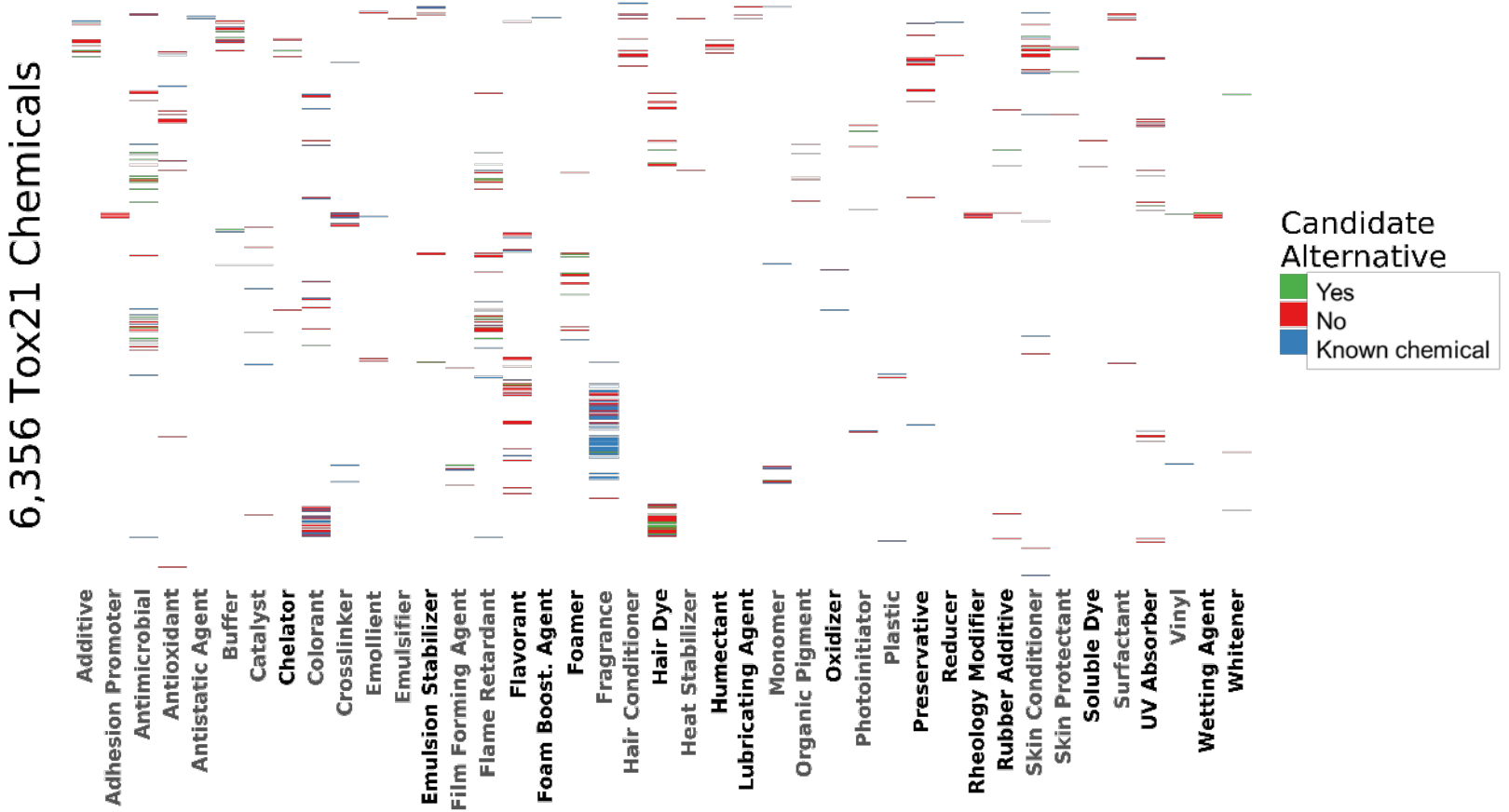
Chemical Alternatives



Can combine functional use predictions with high throughput bioactivity data to predict potential alternatives

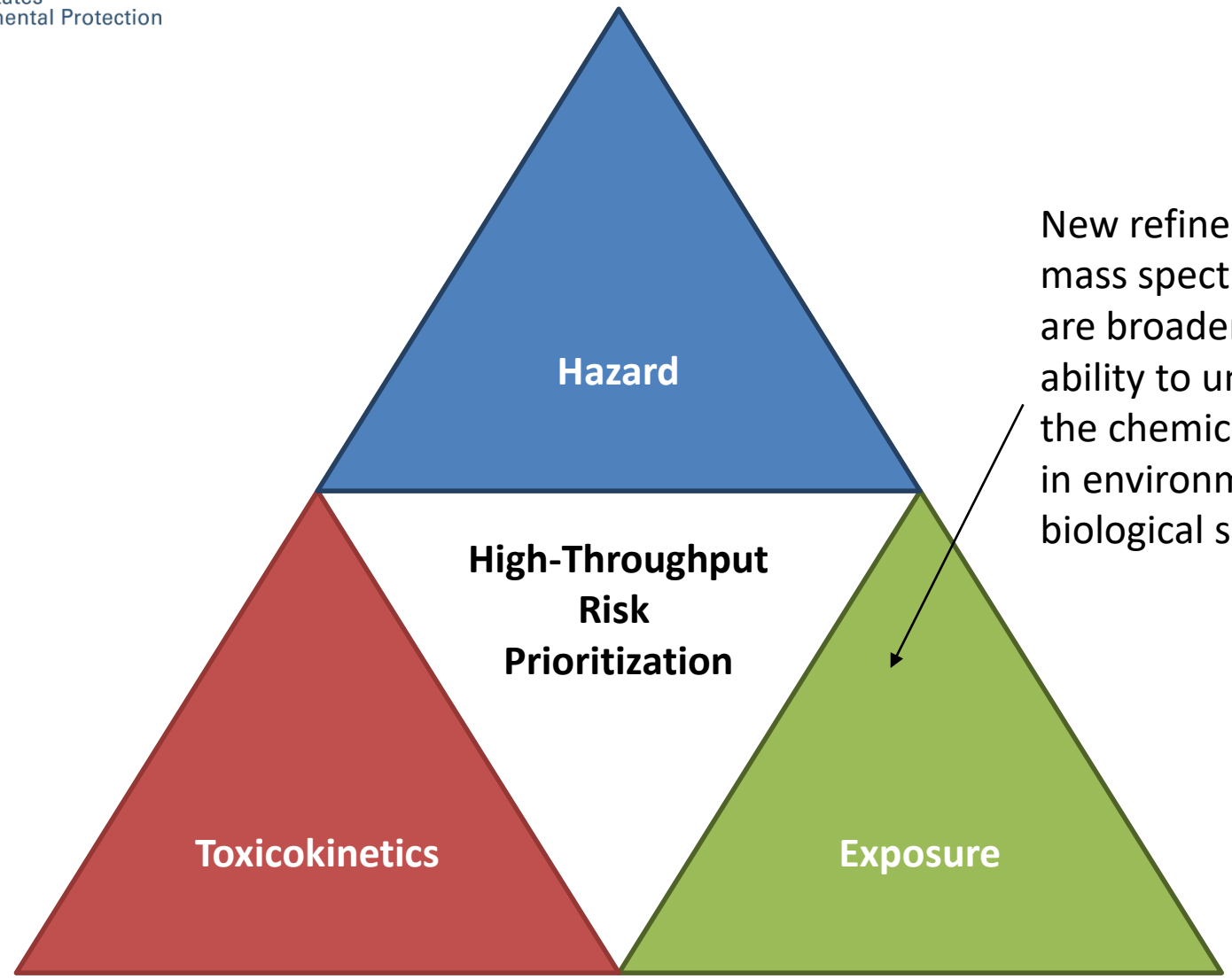
Screening for Alternatives By Function and Bioactivity

Comparing a metric of bioactivity (across a number of Tox21 assays) for predicted “functional substitutes” against a threshold value derived from existing chemicals with that function identified 648 “candidate alternatives”



Phillips et al., (2017)

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

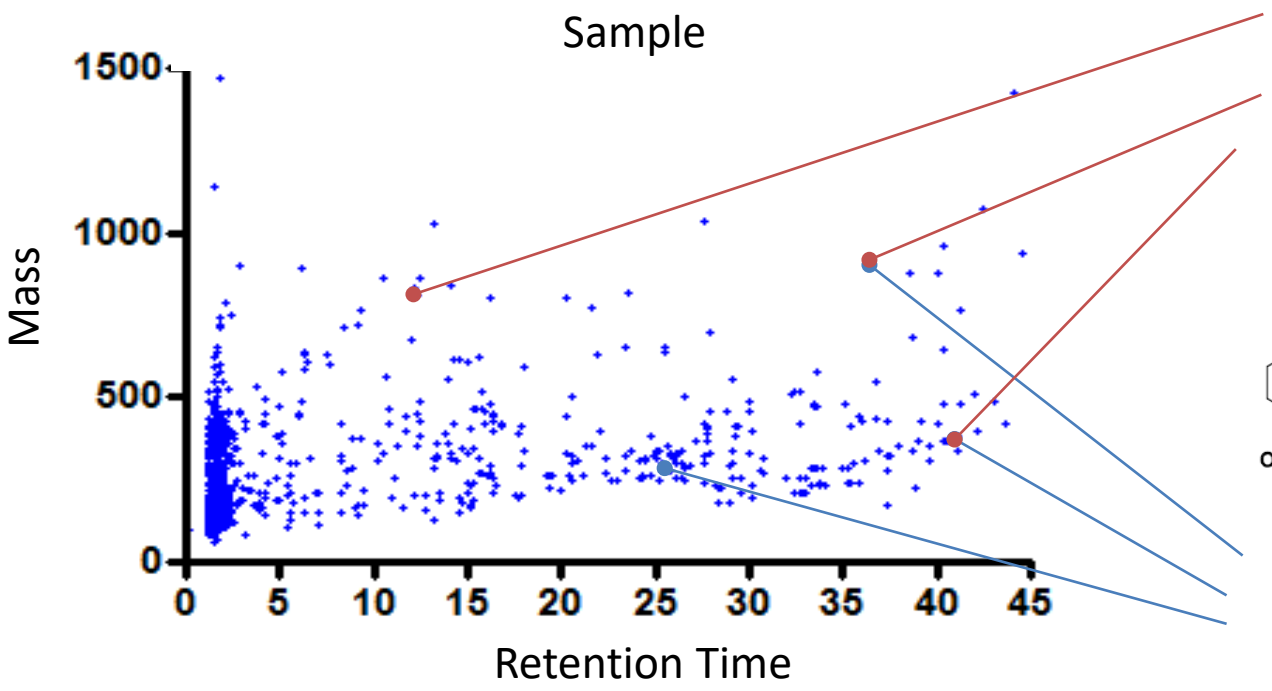
- Models present one way forward, but new analytic techniques may also allow insight in to chemicals composition of products and the greater environment
- EPA is coordinating a comparison of non-targeted screening workflows used by leading academic and government groups (led by Jon Sobus and Elin Ulrich)
  - 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

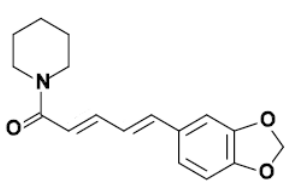
947 Peaks in an American Health Homes Dust Sample

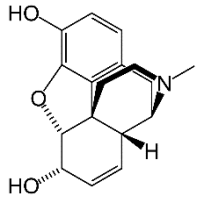


Each peak corresponds to a chemical with an accurate mass and predicted formula:

$C_{17}H_{19}NO_3$

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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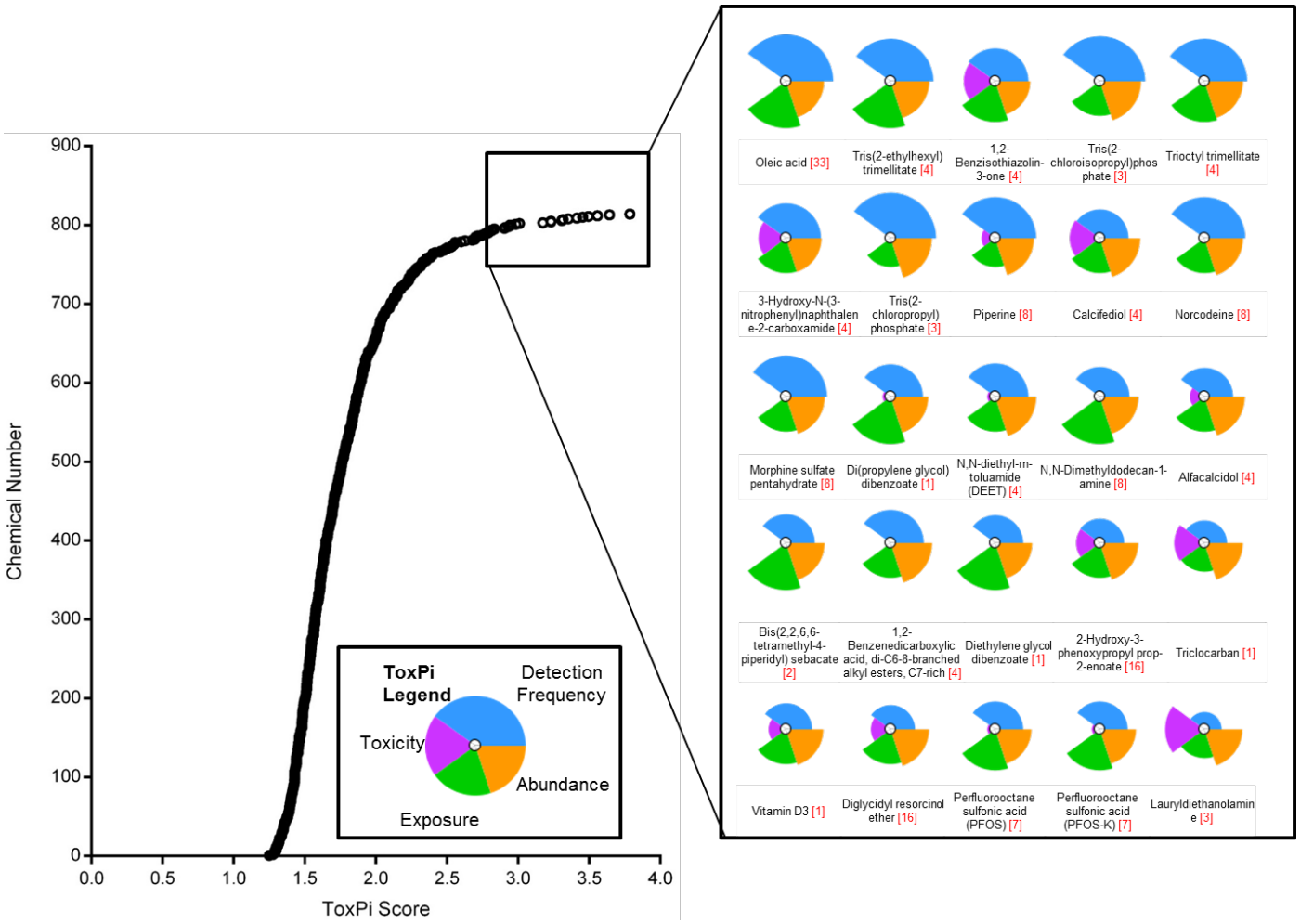
Hahn and Strassmann (1938)

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

Chemical Forensics

United States Environmental Protection Agency



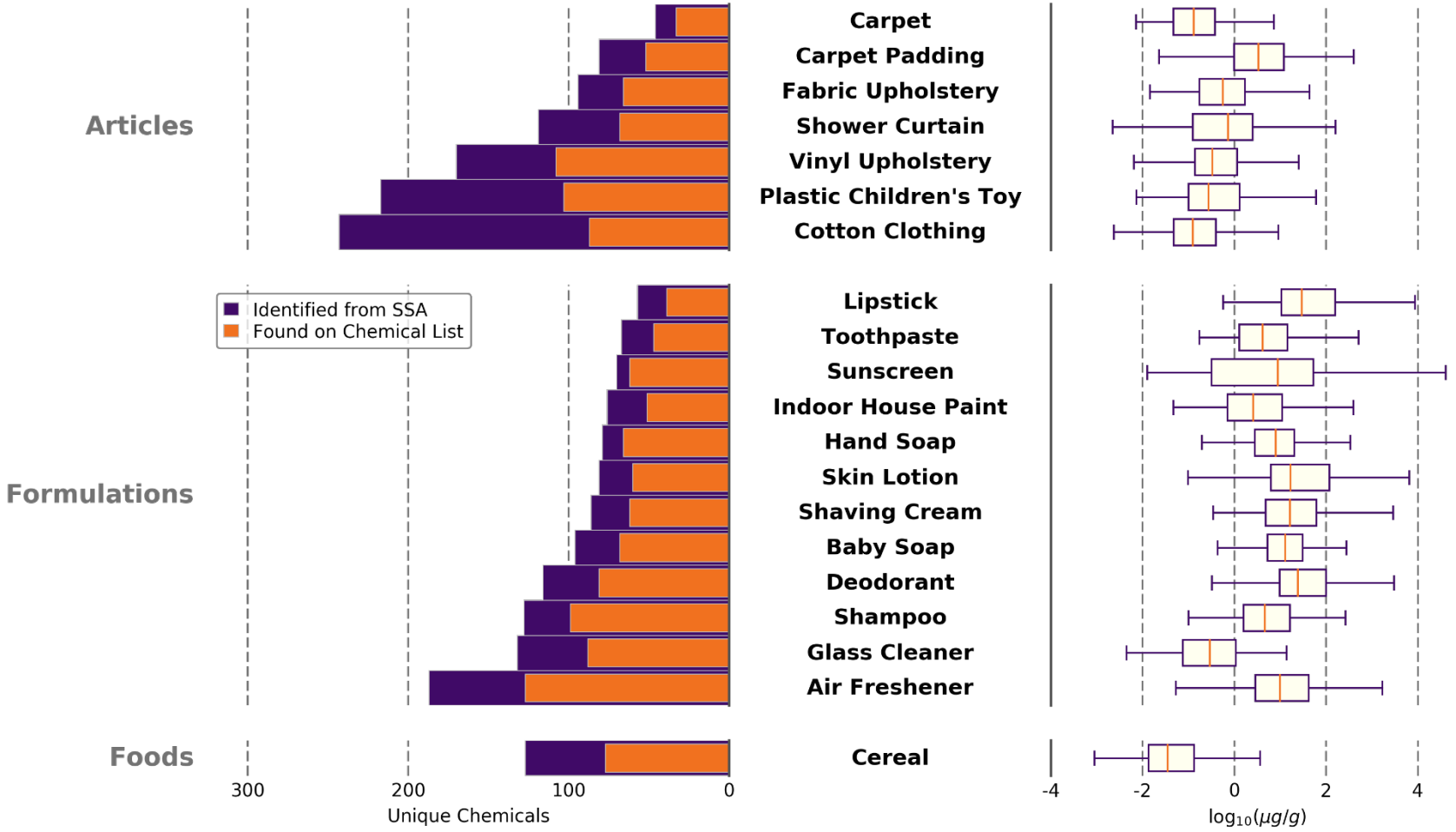
High throughput exposure and toxicity predictions can discriminate between possibilities based upon risk

Tools developed for predicting chemical use can provide evidence for/against chemical identities

Rager *et al*., (2016)
Phillips *et al*., (*submitted*)

Product Scan Summary

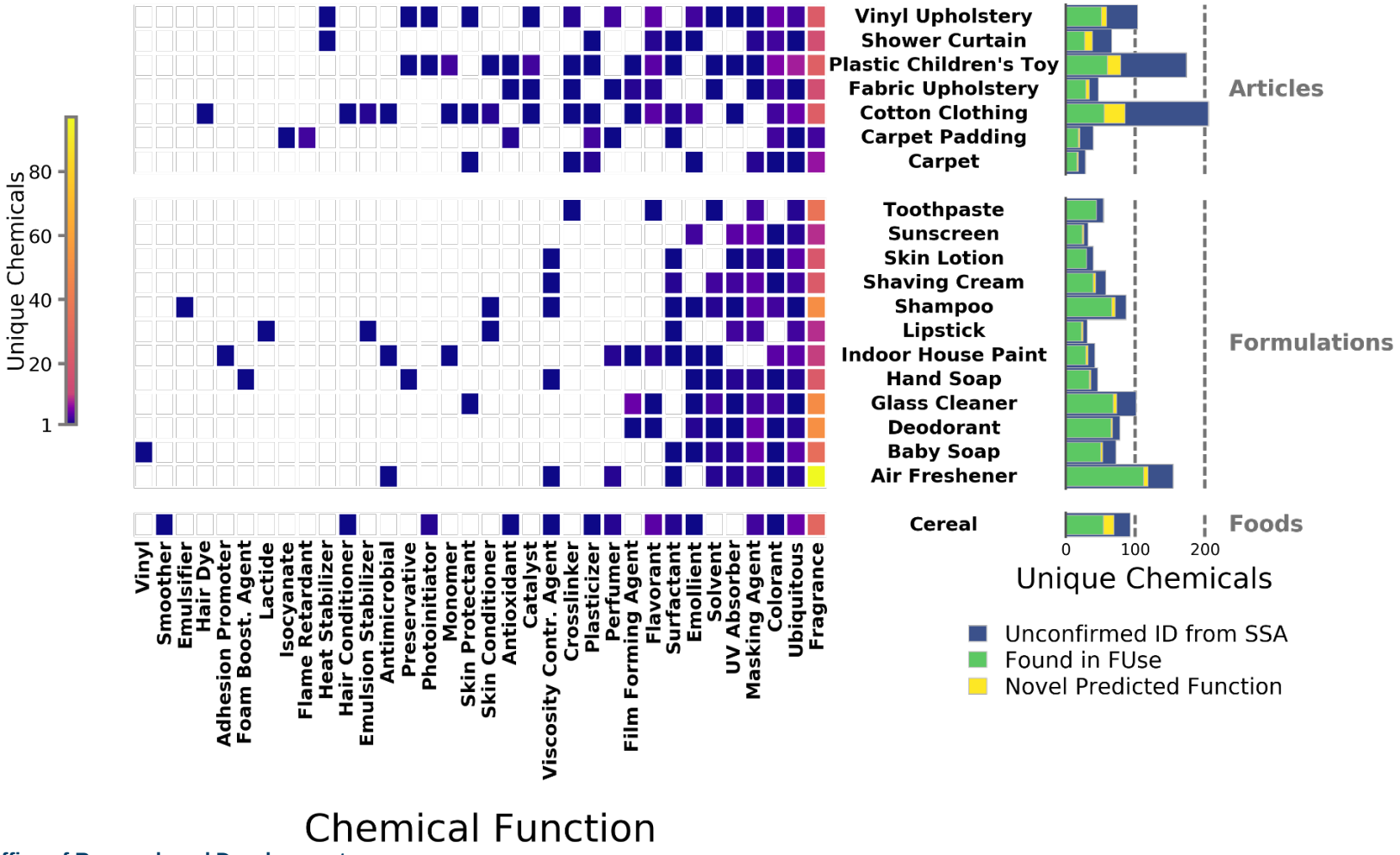
Of 1,632 chemicals confirmed or tentatively identified, 1,445 were not present in CPCPdb



Phillips *et al.* (*submitted*)

Predicting Chemical Function

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



Phillips *et al.* (*submitted*)

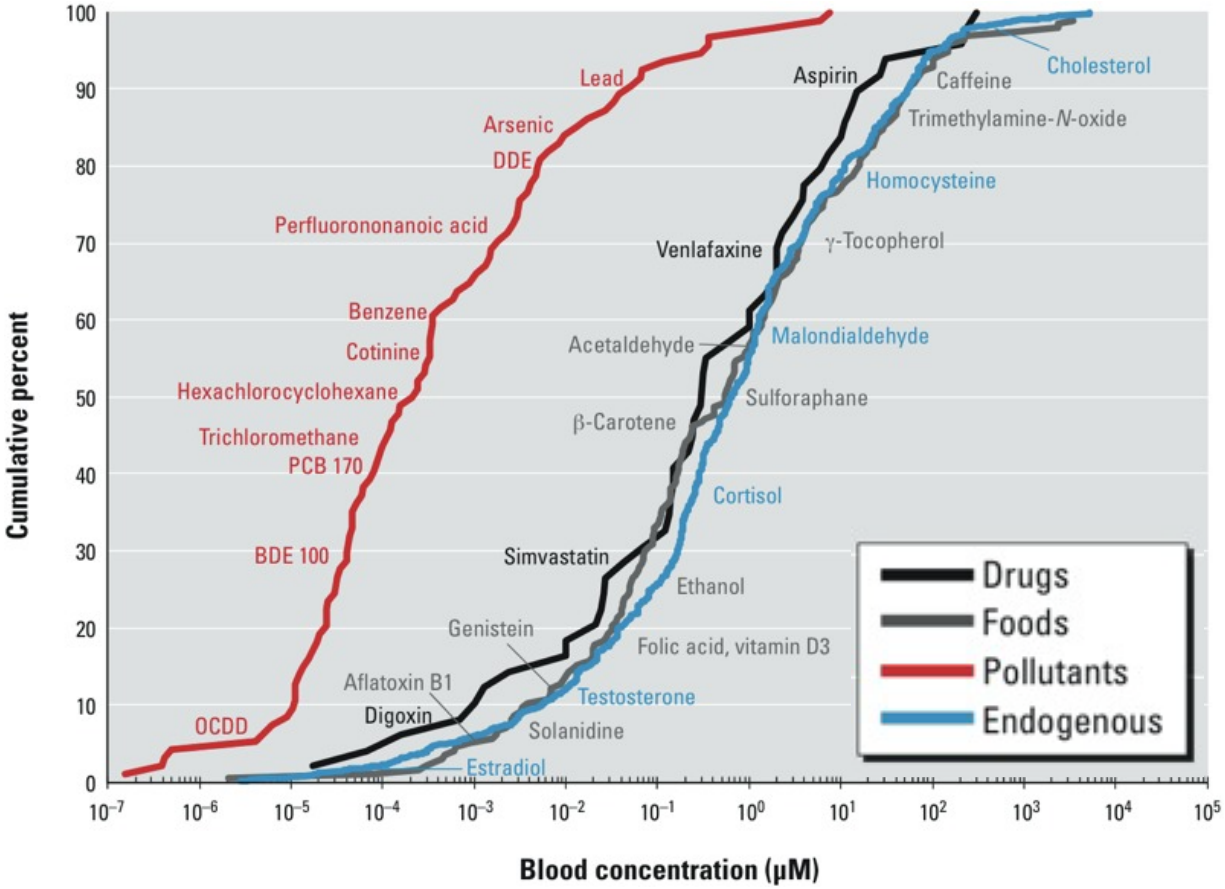
Caveats to Non-Targeted Screening

- **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

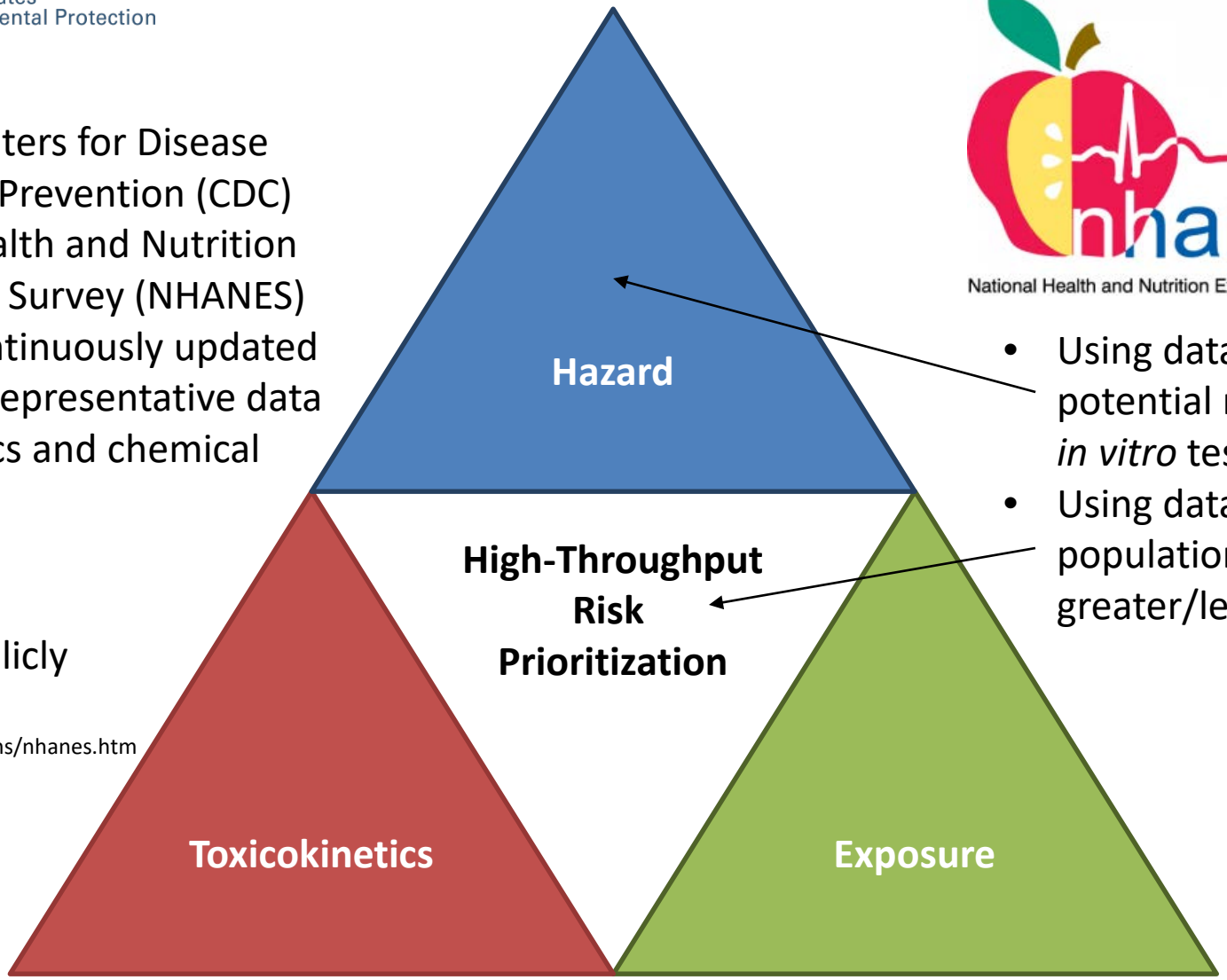
Rappaport et al. (2014)



Further Analyzing the CDC NHANES Data

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

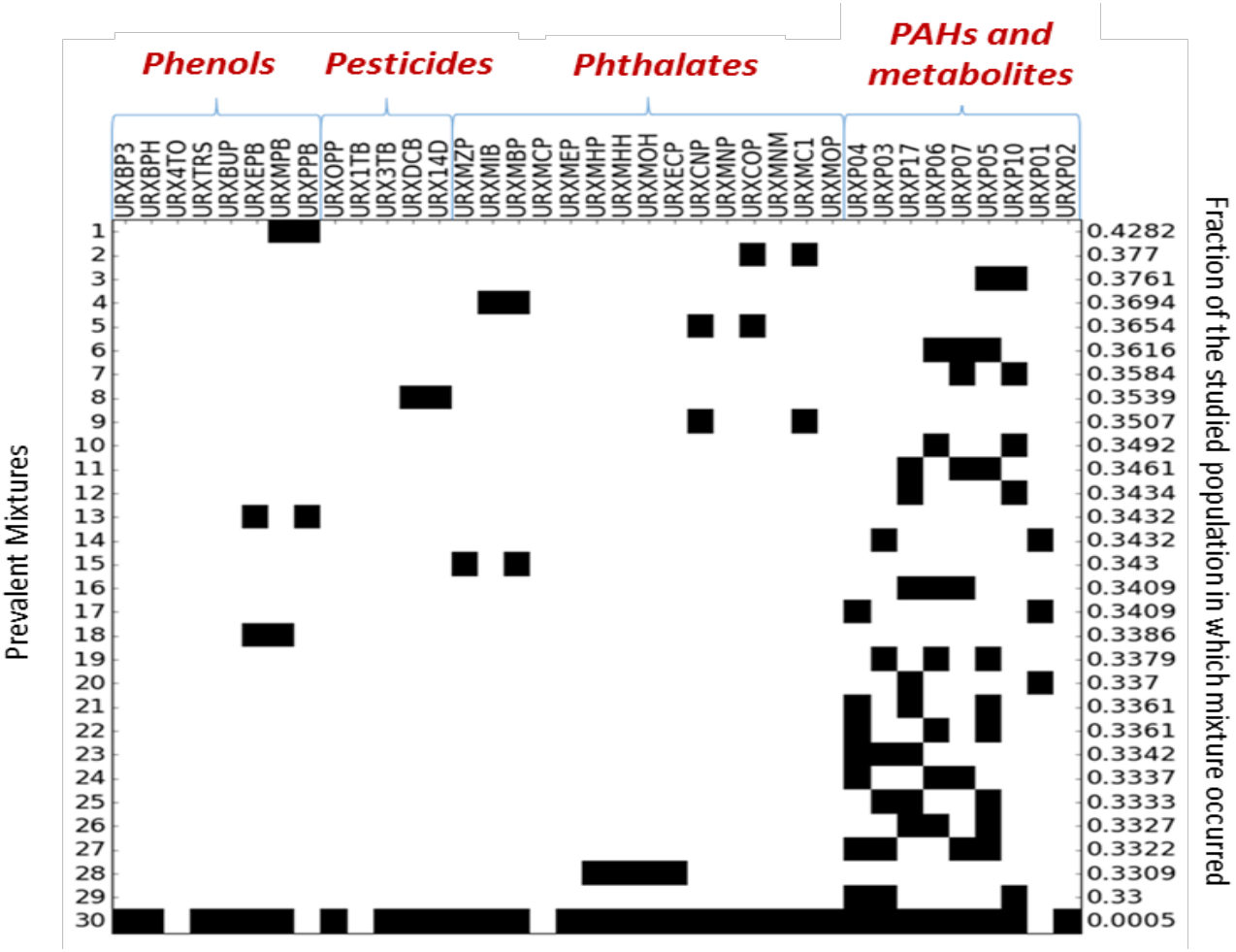
Data sets publicly available:
http://www.cdc.gov/nchs/nhanes.htm



- Using data to identify potential mixtures for *in vitro* testing
- Using data to identify populations with greater/lesser risk

Identifying Prevalent Mixtures

- Chemical mixtures present in consumer products and biomonitoring samples are being analyzed
- We are using data-mining methods that identify combinations of items (chemicals) that occur frequently in a database of observations
- Identified a few dozen mixtures present in >30% of U.S. population



Frequent itemset mining used to identify combinations of NHANES group B chemicals occurring in individuals at a concentration greater than the population median

Kapraun *et al., (in press)*

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)

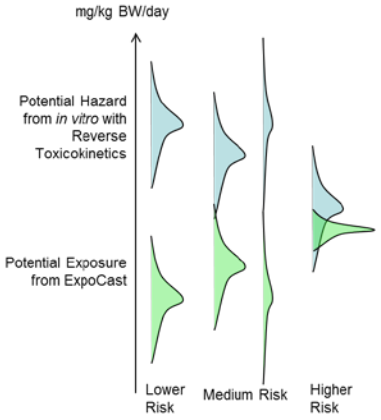
(Similar approach used in SimCYP [Jamei et al. 2009], GastroPlus, PopGen [McNally et al. 2014], P3M [Price et al. 2003], physB [Bosgra et al. 2012], etc.)

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

Life-stage and Demographic Specific Predictions

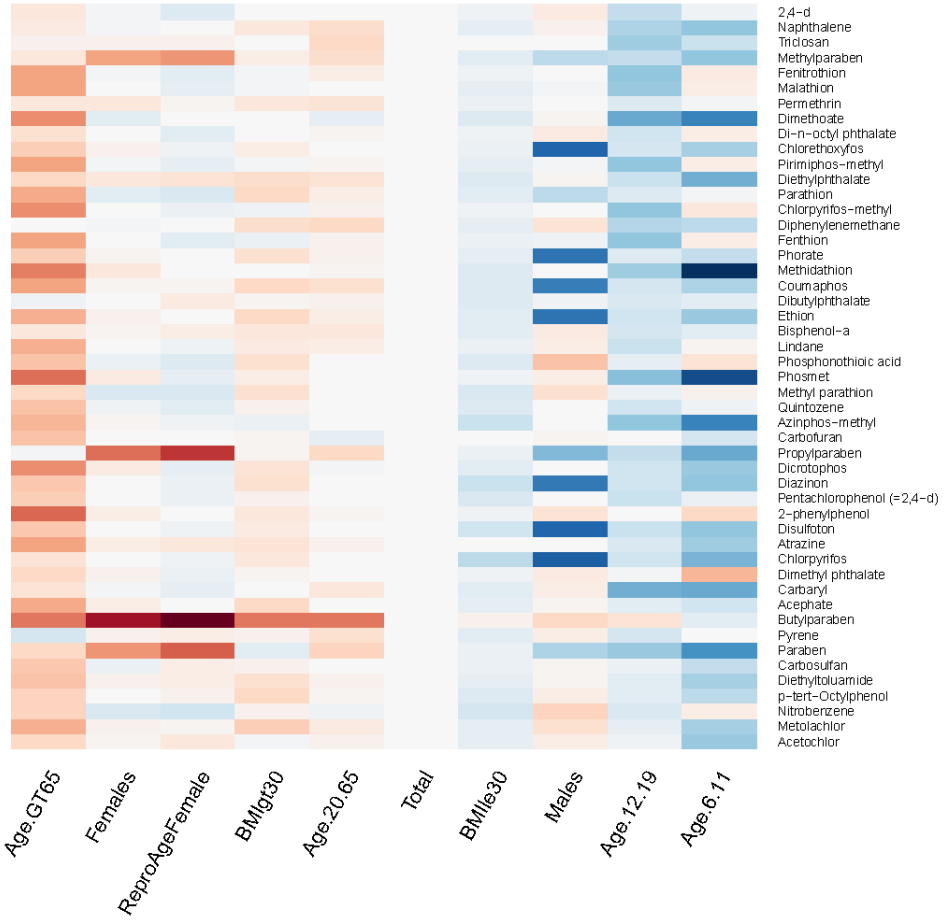
- Wambaugh *et al.* (2014) predictions of exposure rate (mg/kg/day) for various demographic groups

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



Change in Risk

Change in Activity:Exposure Ratio



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

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**/

EPA United States Environmental Protection Agency

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

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