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Agency

Chemical Priority Setting in the 21st Century

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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

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EPA Office of Research and Development

United States Environmental Protection Agency

- The Office of Research and Development (ORD) is the scientific research arm of EPA
  - 558 peer-reviewed journal articles in 2016
- Research is conducted by ORD's three national laboratories, four national centers, and two offices
  - Includes **National Center for Computational Toxicology** and **National Exposure Research Laboratory**
- 14 facilities across the country and in Washington, D.C.
- Six research programs
  - Includes **Chemical Safety for Sustainability**
- Research conducted by a combination of Federal scientists; contract researchers; and postdoctoral, graduate student, and post-baccalaureate trainees

ORD Facility in
Research Triangle Park, NC

Chemical Regulation in the United States

- Park *et al.* (2012): At least 3221 chemicals 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)
- Most other chemicals, ranging from industrial waste to dyes to packing materials are covered by the recently updated Toxic Substances Control Act (TSCA)
  - Previously, thousands of chemicals on the market were either "grandfathered" in or were allowed without experimental assessment of hazard, toxicokinetics, or exposure
  - Thousands of new chemical use submissions are made to the EPA every year
  - **Due to TSCA reform, methods are being developed to prioritize these existing and new chemicals for testing**

November 29, 2014

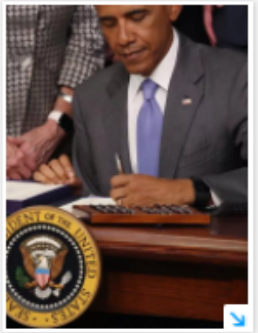
TSCA Reform

- **The Toxic Substances Control Act (TSCA):**
  - Passed: October 11,1976
  - Amended: June 22, 2016
- Prioritizing existing chemicals for risk evaluation starting with 10 chemicals:
  - The purpose of prioritization is to designate a chemical substance as either High-Priority for further risk evaluation, or Low-Priority for which risk evaluation is not warranted at the time.
  - Upon completion of a risk evaluation (other than those requested by a manufacturer), EPA must designate at least one additional High-Priority chemical to take its place, thus ensuring that the EPA's risk evaluation queue always remains full.

USA TODAY

Obama signs bipartisan chemical safety bill

Gregory Korte, USA TODAY Published 12:24 p.m. ET June 22, 2016 | Updated 12:29 p.m. ET June 22, 2016



(Photo: Mark Wilson, Getty Images)

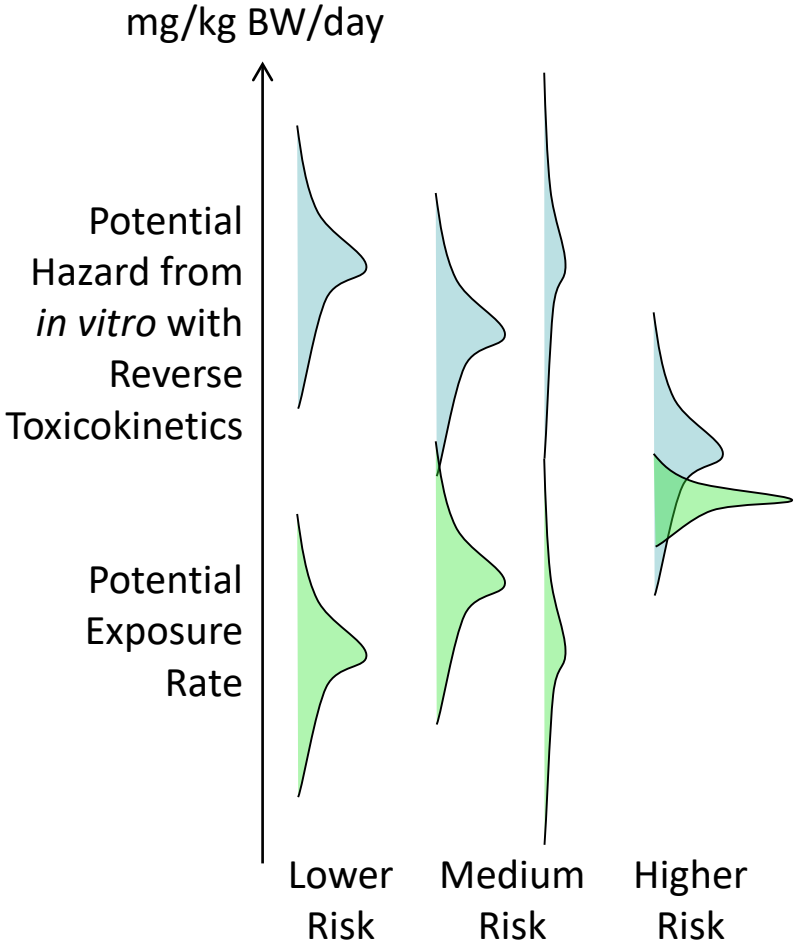
WASHINGTON —
The Frank R. Lautenberg Chemical Safety for the 21st Century Act is the first major update to environmental legislation in two decades, overhauling the process for regulating toxic chemicals, allowing the Environmental Protection Agency to ban substances like asbestos, and limiting the secrecy around those chemicals after 10 years.

But that's not the only reason why President Obama chose to sign the bill Wednesday in a public ceremony at the White House: It's also a rare example of bipartisanship from a Congress widely seen as unable to agree on much of

- "[P]otentially exposed or susceptible subpopulation" means a group of individuals within the general population identified by the Administrator who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, or the elderly.

Chemical Risk = Hazard + Exposure

- National Research Council (1983) identified chemical risk as a function of both inherent hazard and exposure
- To address thousands of chemicals, we need to use "high throughput methods" to prioritize those chemicals most worthy of additional study
- **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) linking hazard and exposure



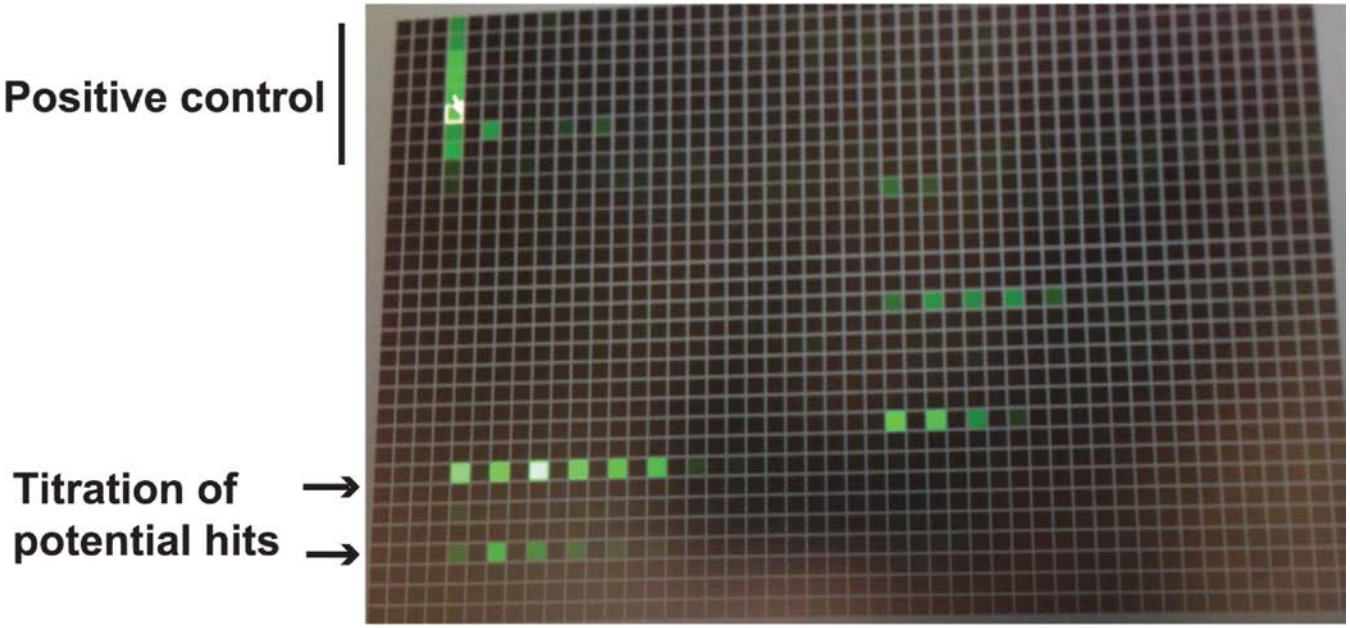
High-throughput Screening

Hertzberg and Pope (2000):

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

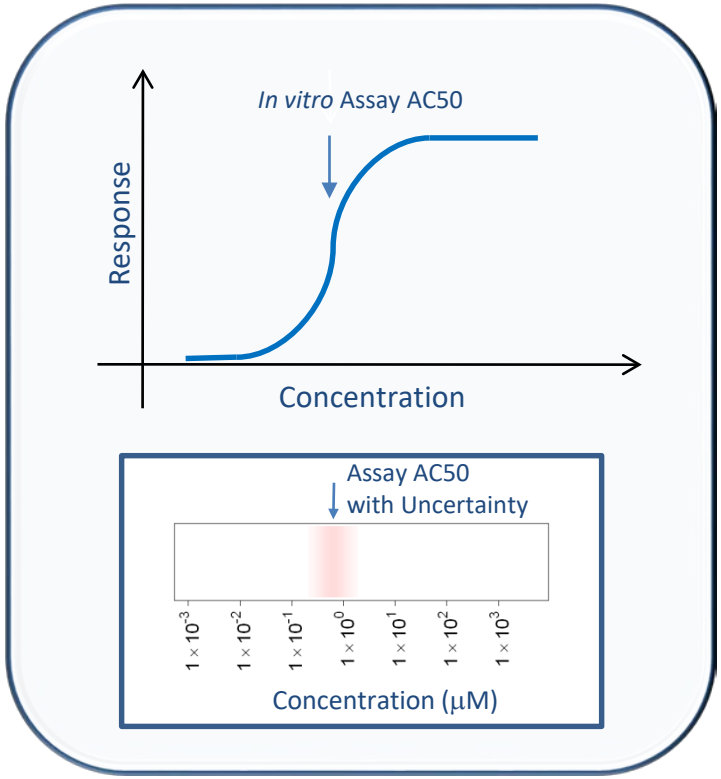
- "Key advances over the past few years include new fluorescence methods, detection platforms and liquid-handling technologies."

Kaewkhaw et al. (2016)



High-Throughput Bioactivity

- We might 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 – AC50 – and efficacy if data described by a Hill function, Filer *et al.*, 2016)
- All data is public: http://comptox.epa.gov/dashboard/



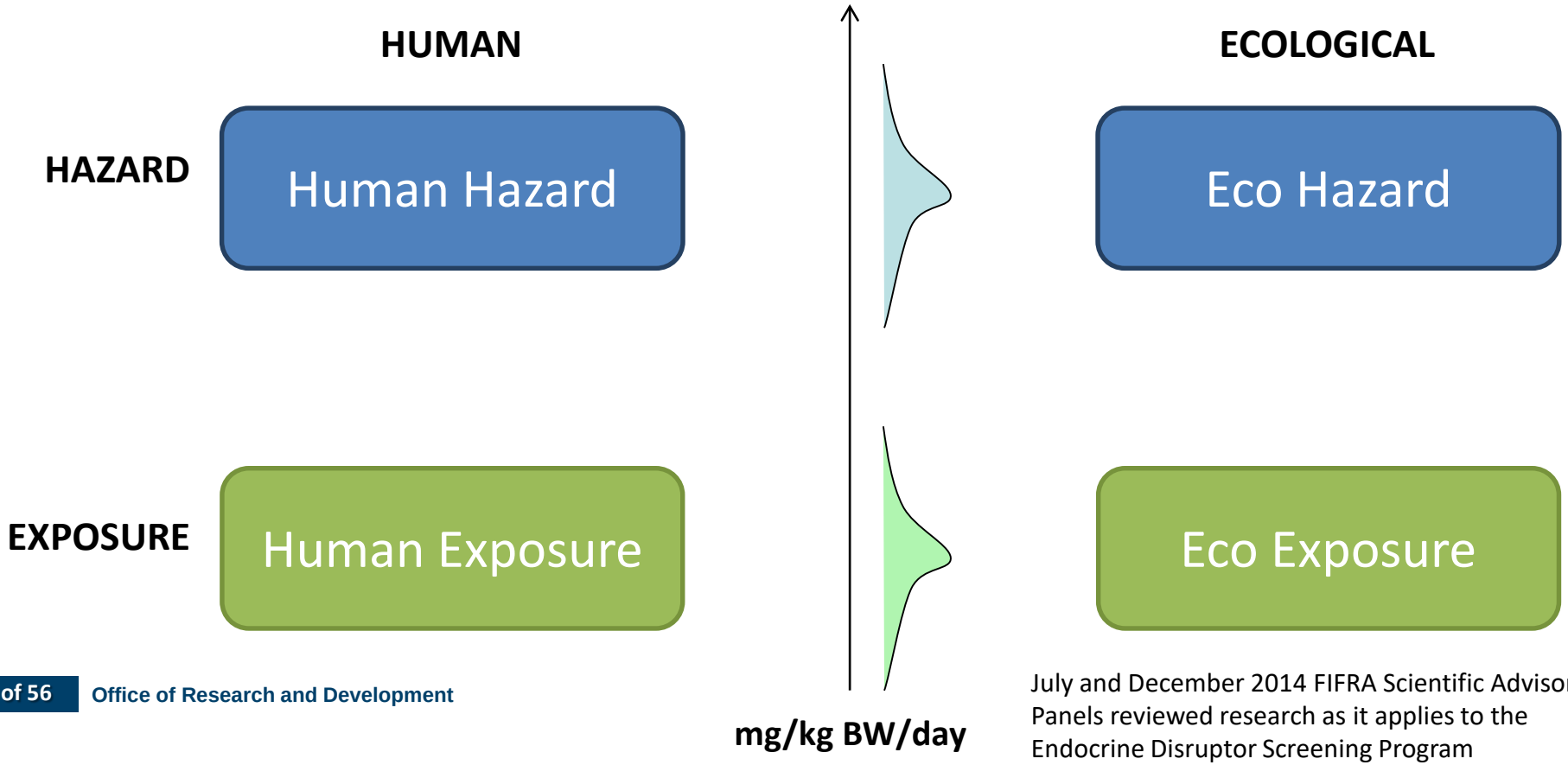
2017 National Academies Report

"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"

Effects of Environmental Chemicals on Hormones

The Endocrine Disruptor Screening Program (EDSP) uses a two tiered approach to screen pesticides, chemicals, and environmental contaminants for their potential effect on estrogen, androgen and thyroid hormone systems. The EDSP is outlined in two Federal Register Notices published in 1998.

All pesticide actives and chemicals in drinking water



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

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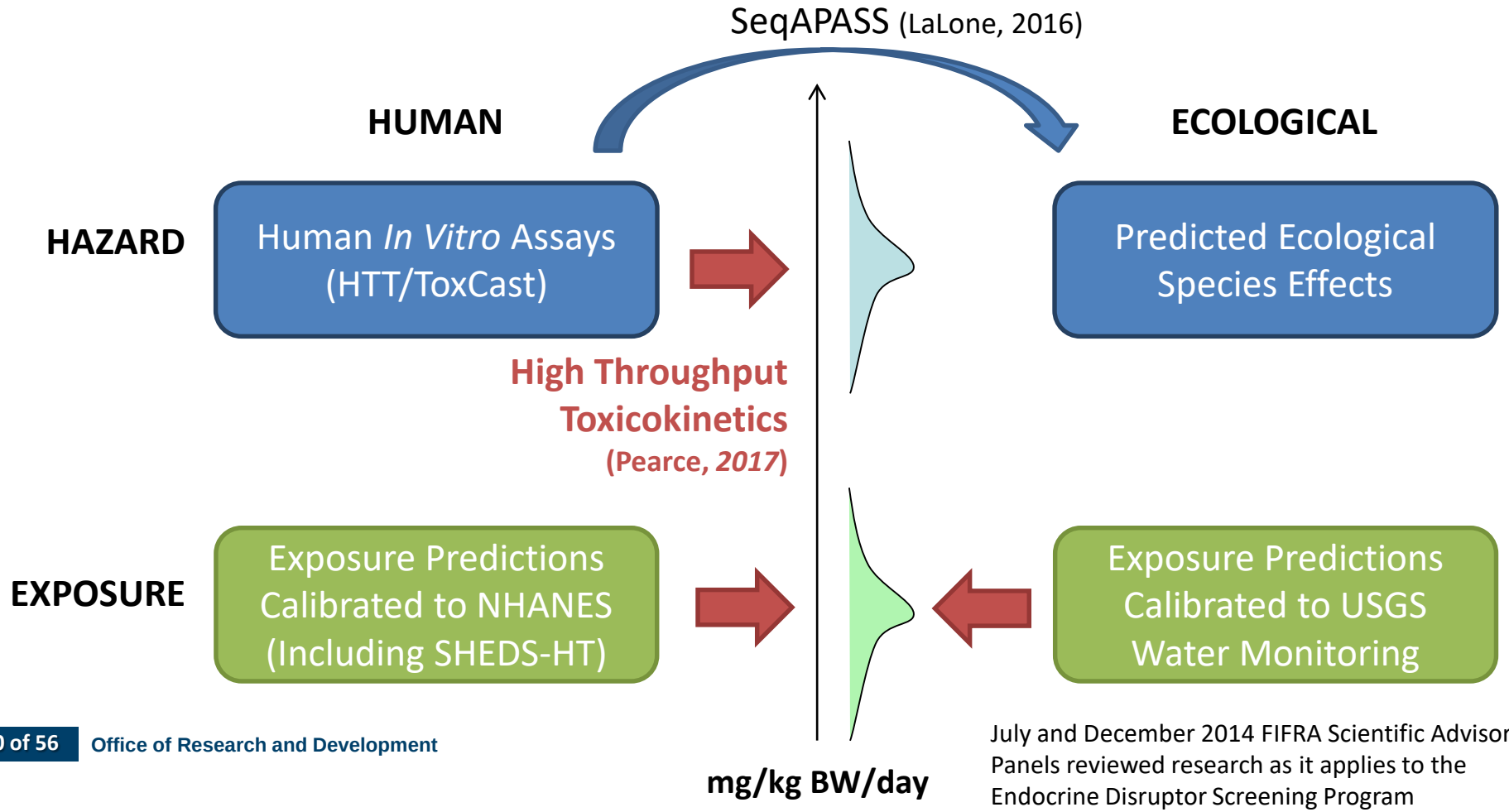

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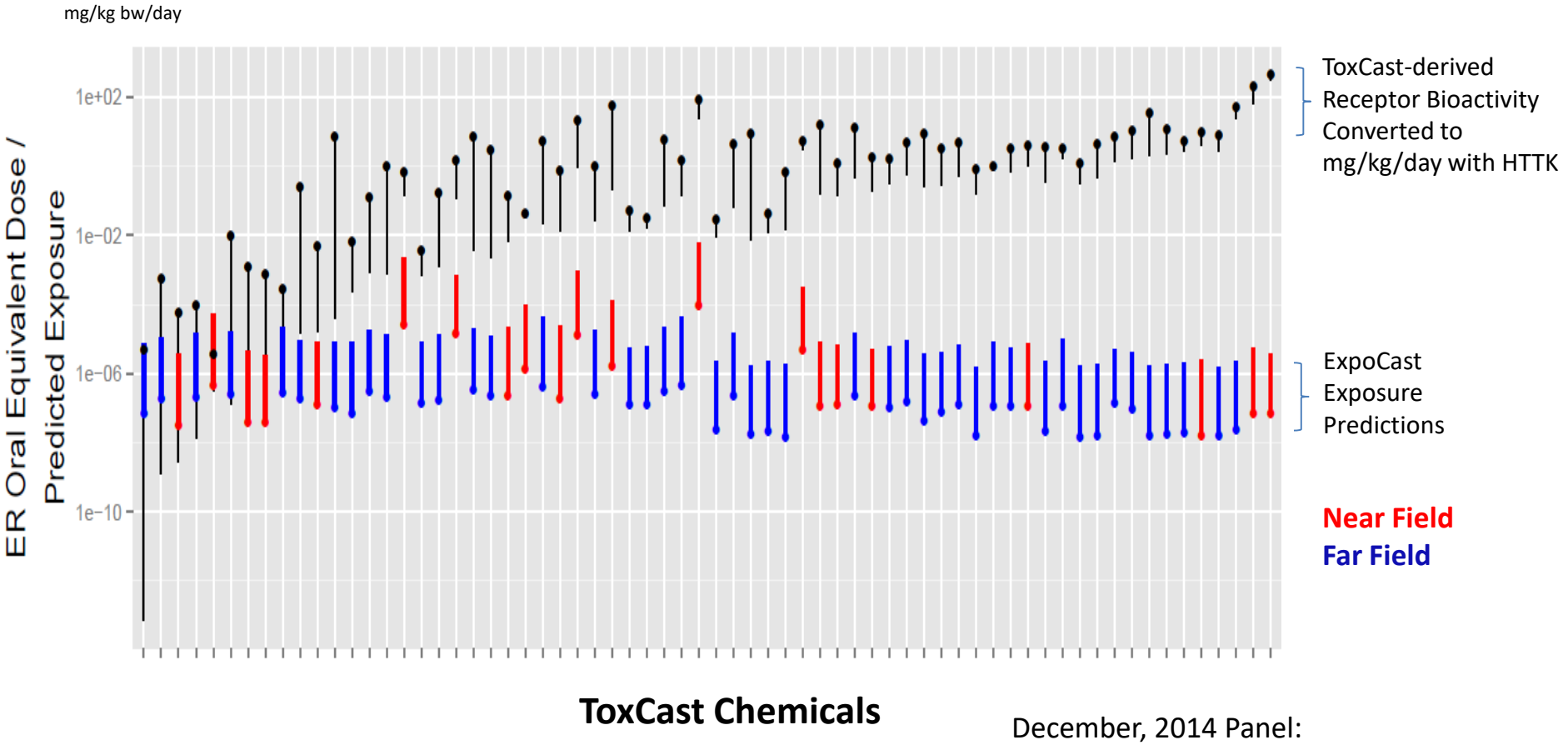
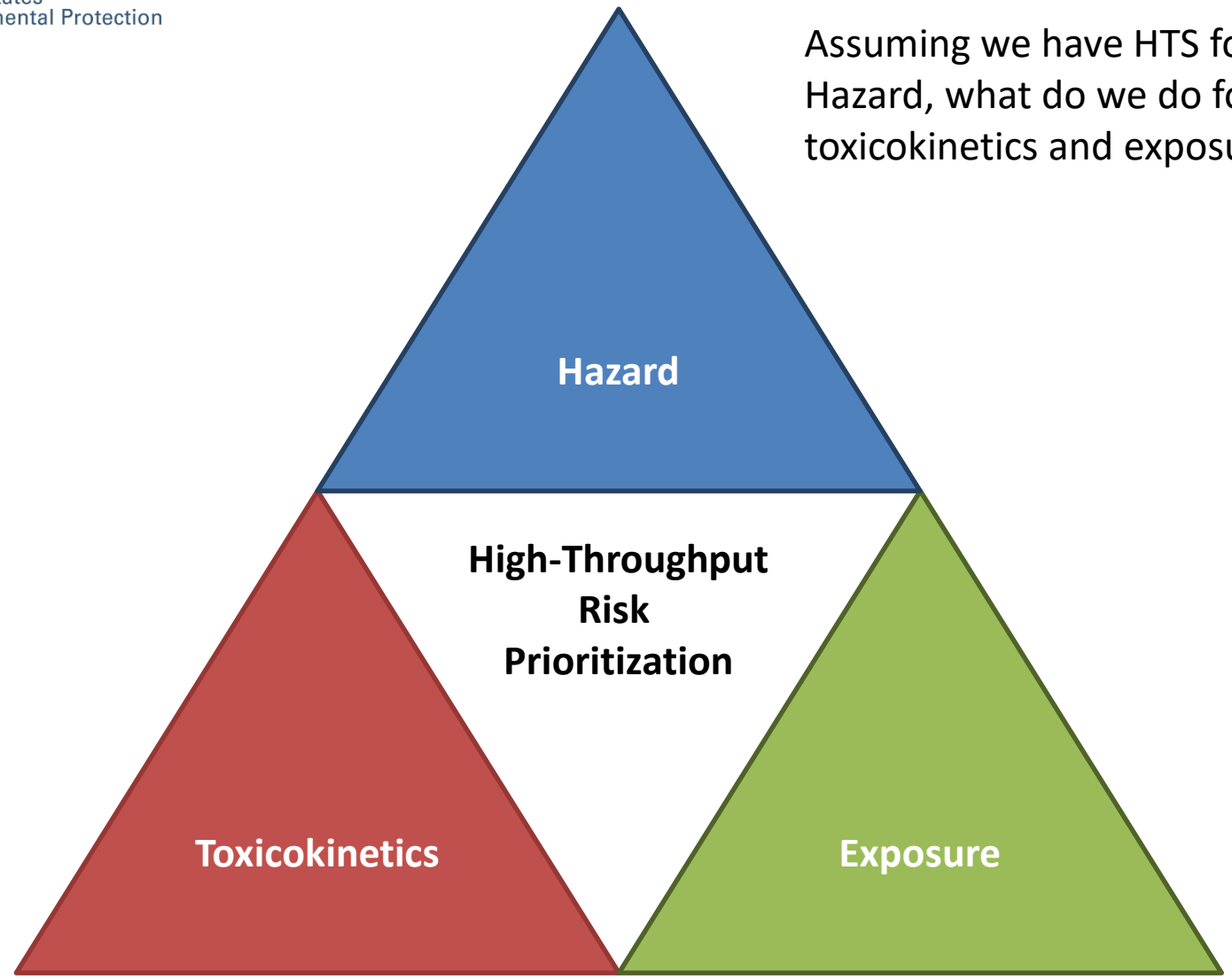
High Throughput Risk Prioritization in Practice



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

Risk-Based Prioritization

Assuming we have HTS for Hazard, what do we do for toxicokinetics and exposure?



Forecasting Exposure is a Systems Problem

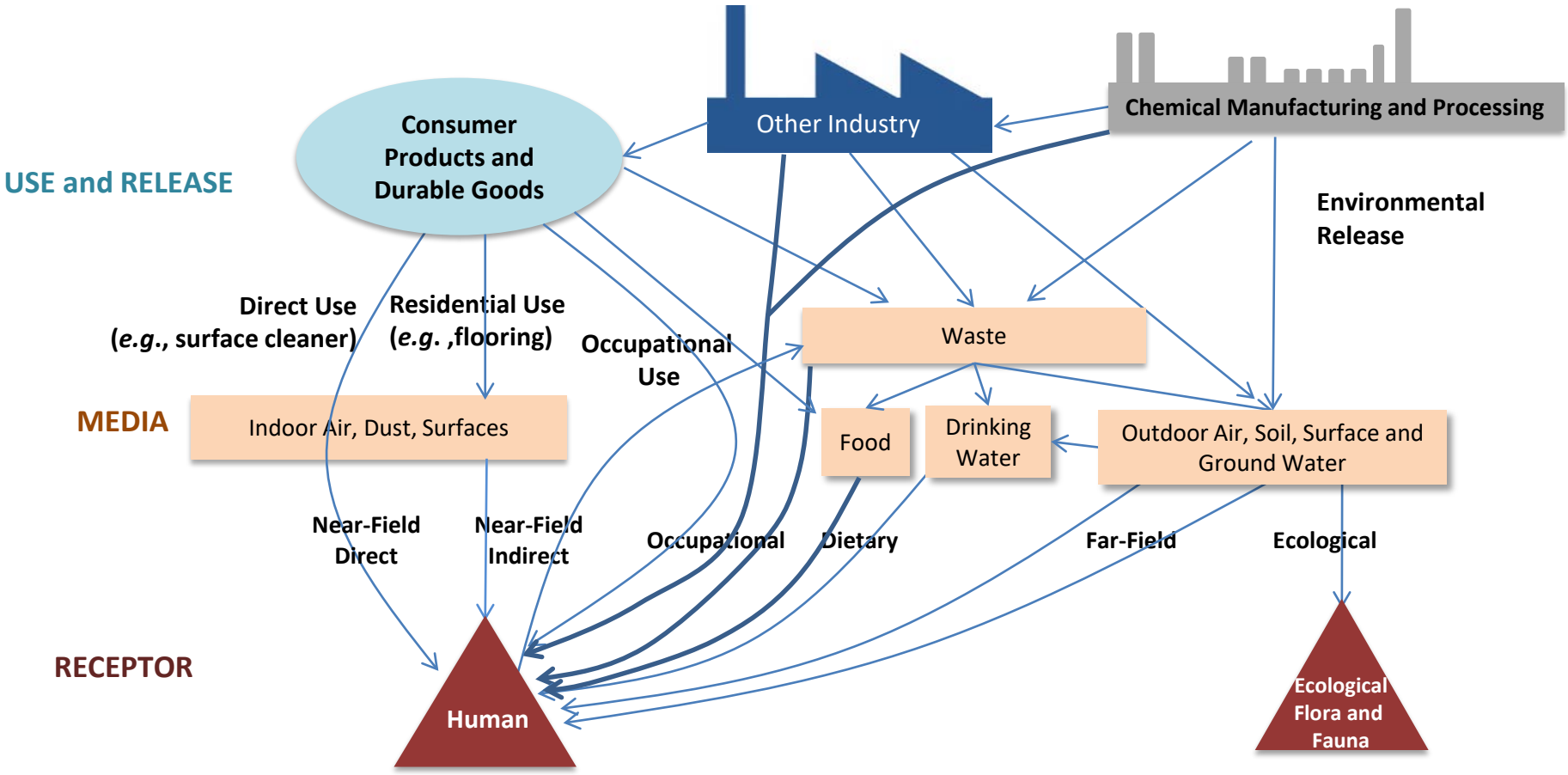


Figure from Kristin Isaacs

Exposure Pathway: Media+Receptor

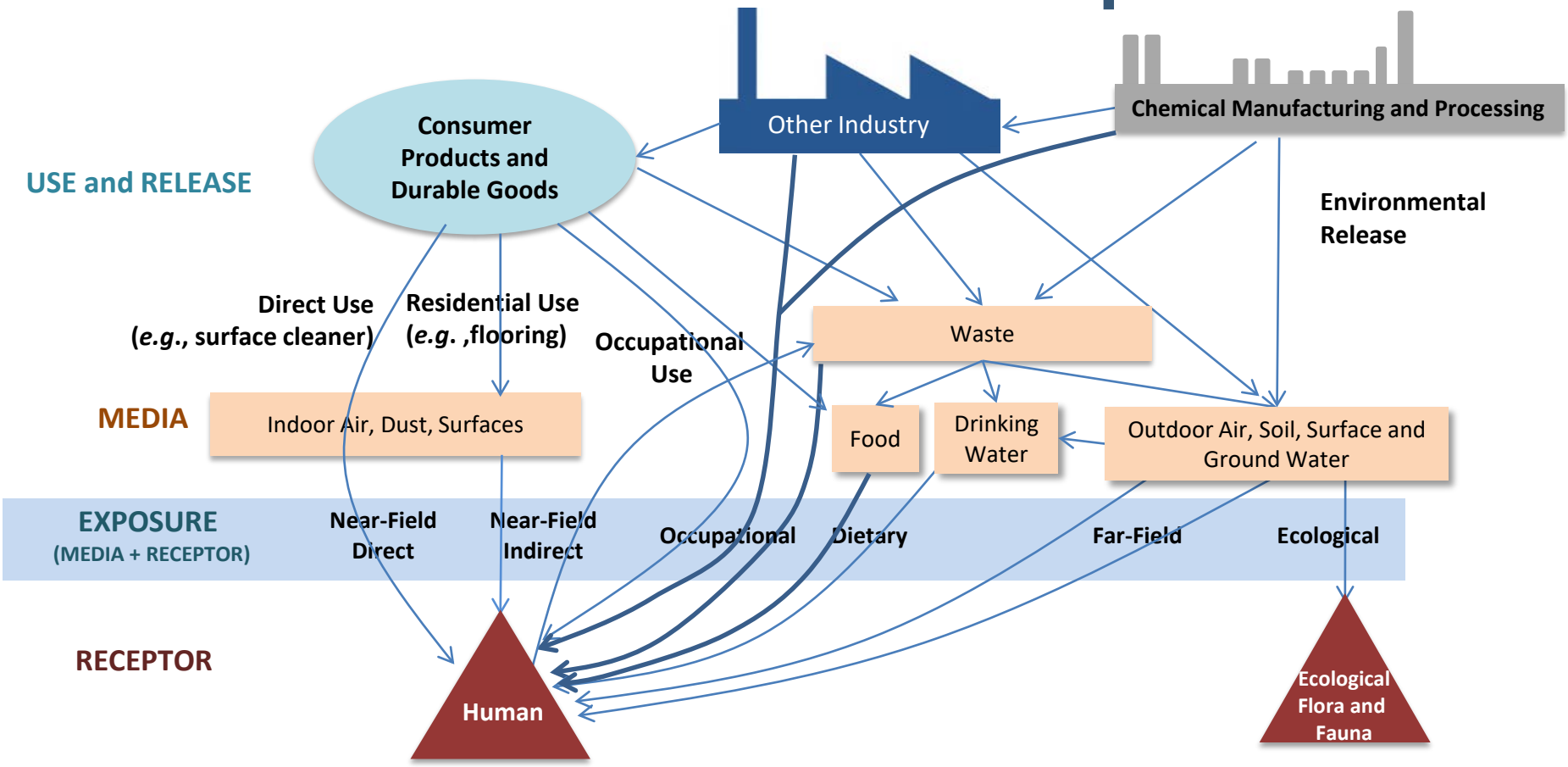
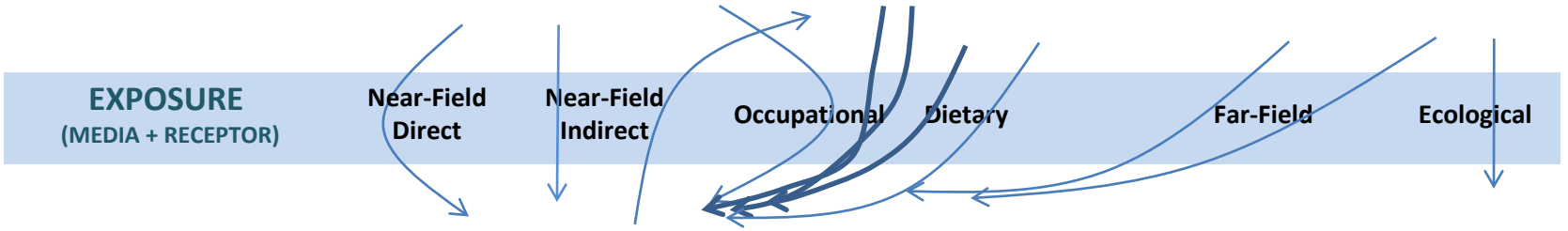


Figure from Kristin Isaacs

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

Inferring Exposure from Monitoring Data

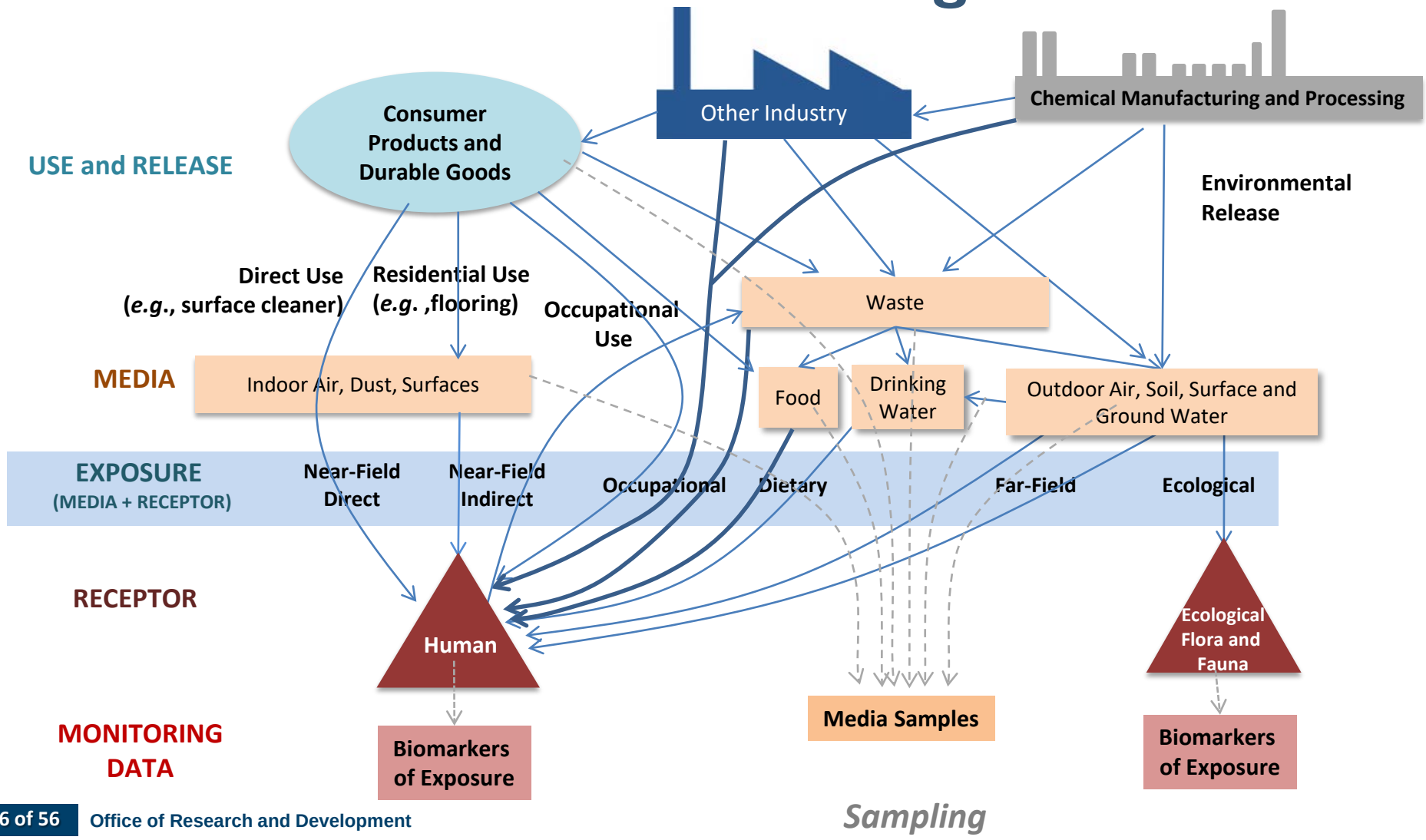


Figure from Kristin Isaacs

Consumer Exposure

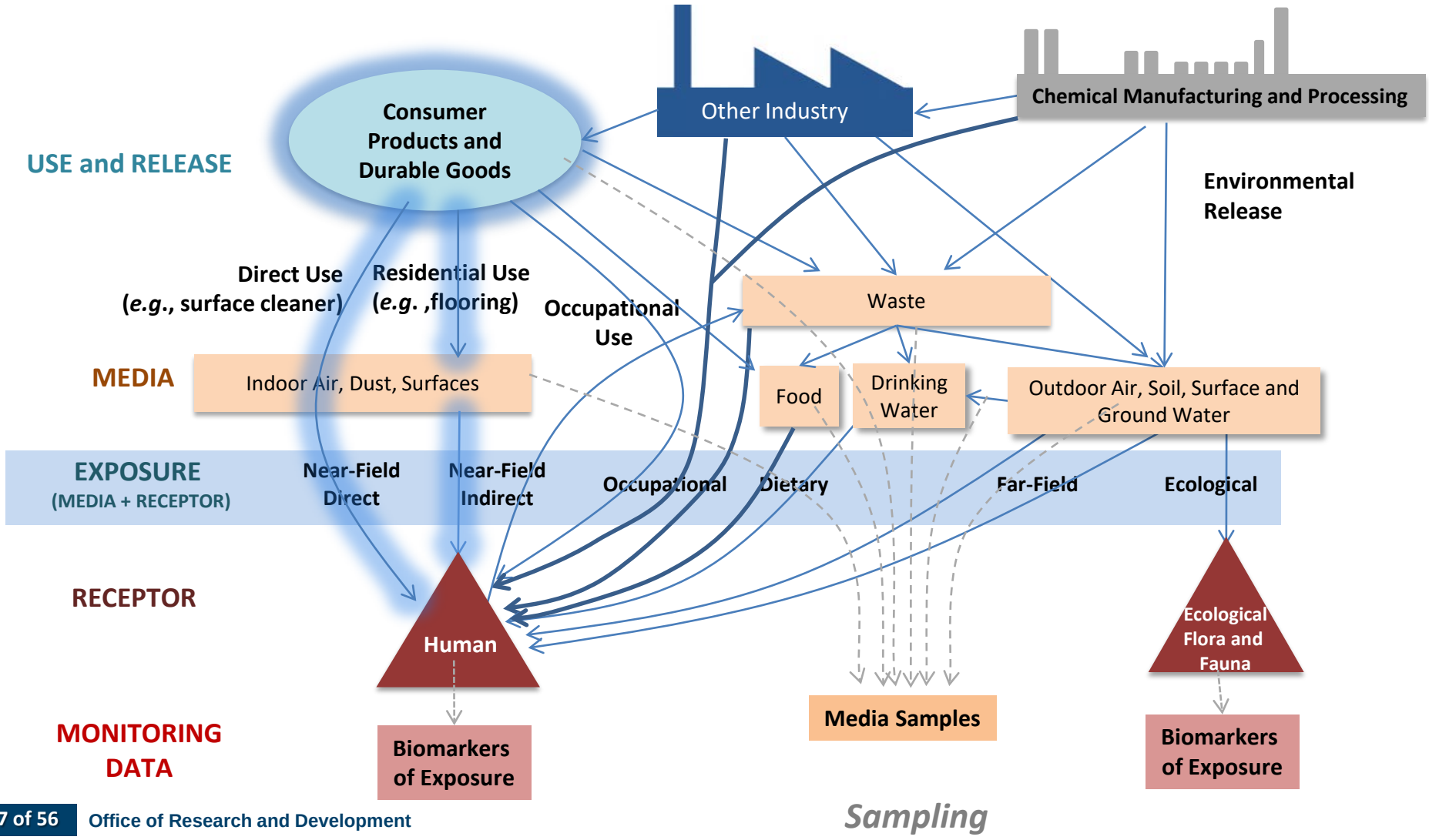


Figure from Kristin Isaacs

Occupational Exposure

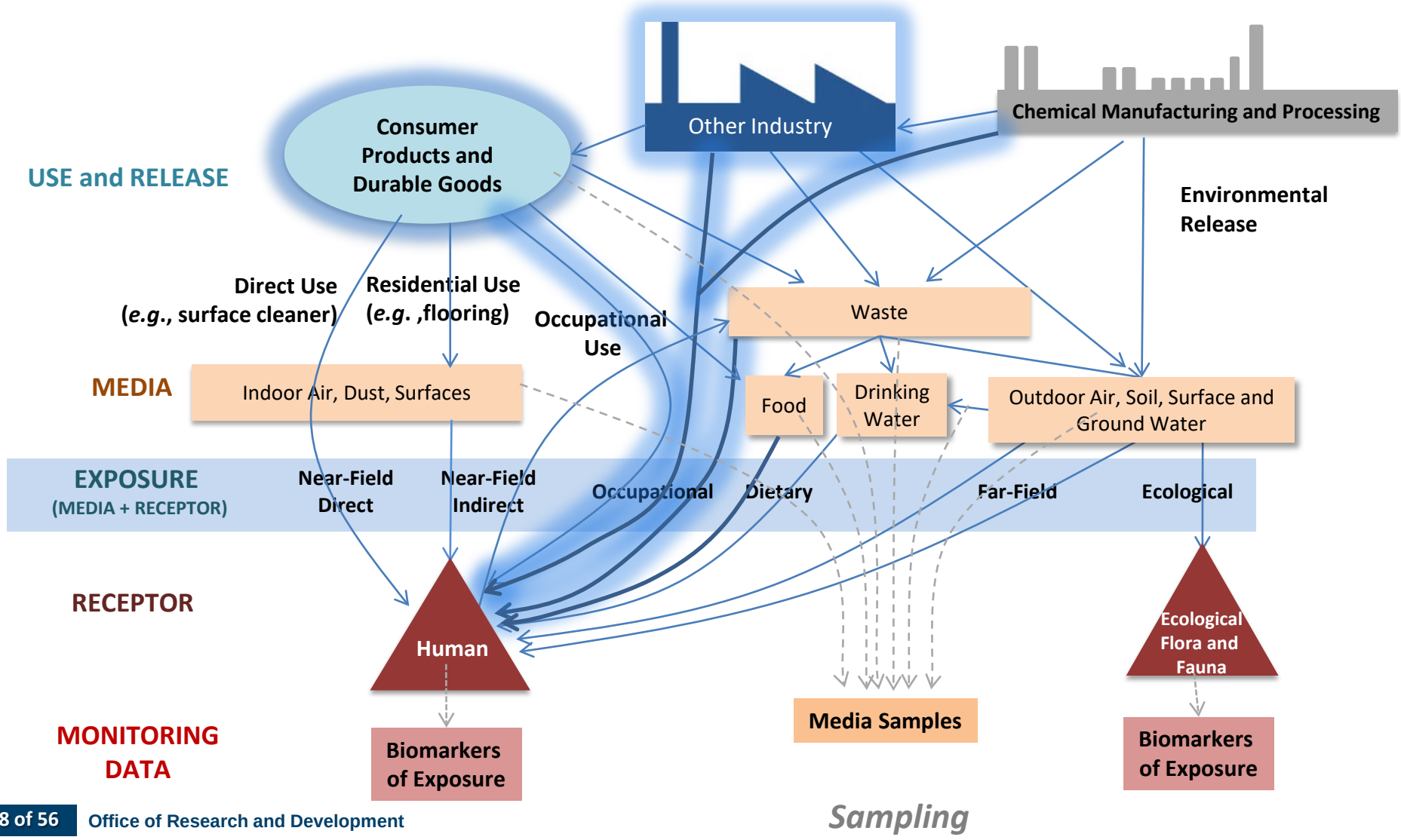


Figure from Kristin Isaacs

Ambient Exposure

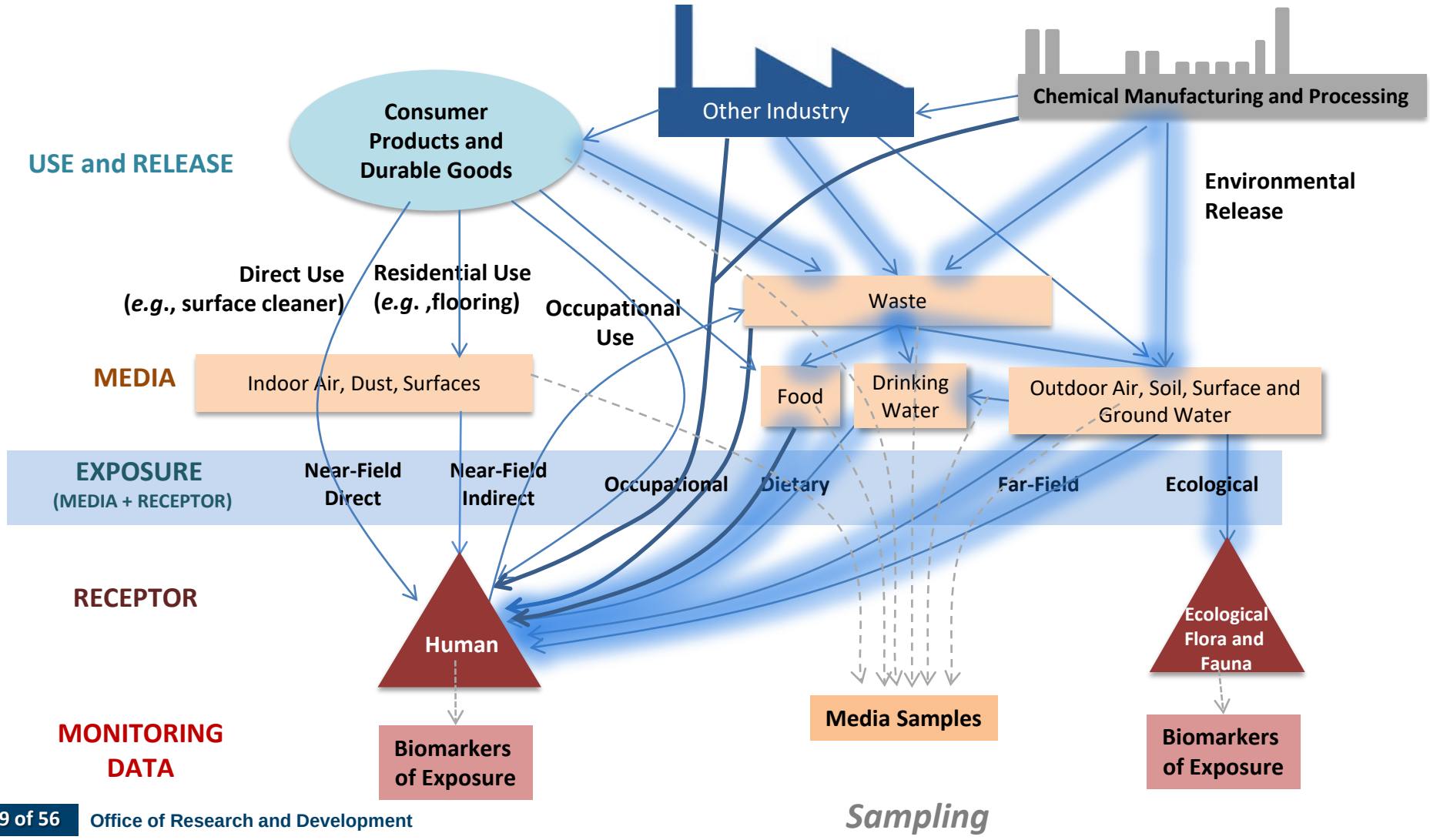
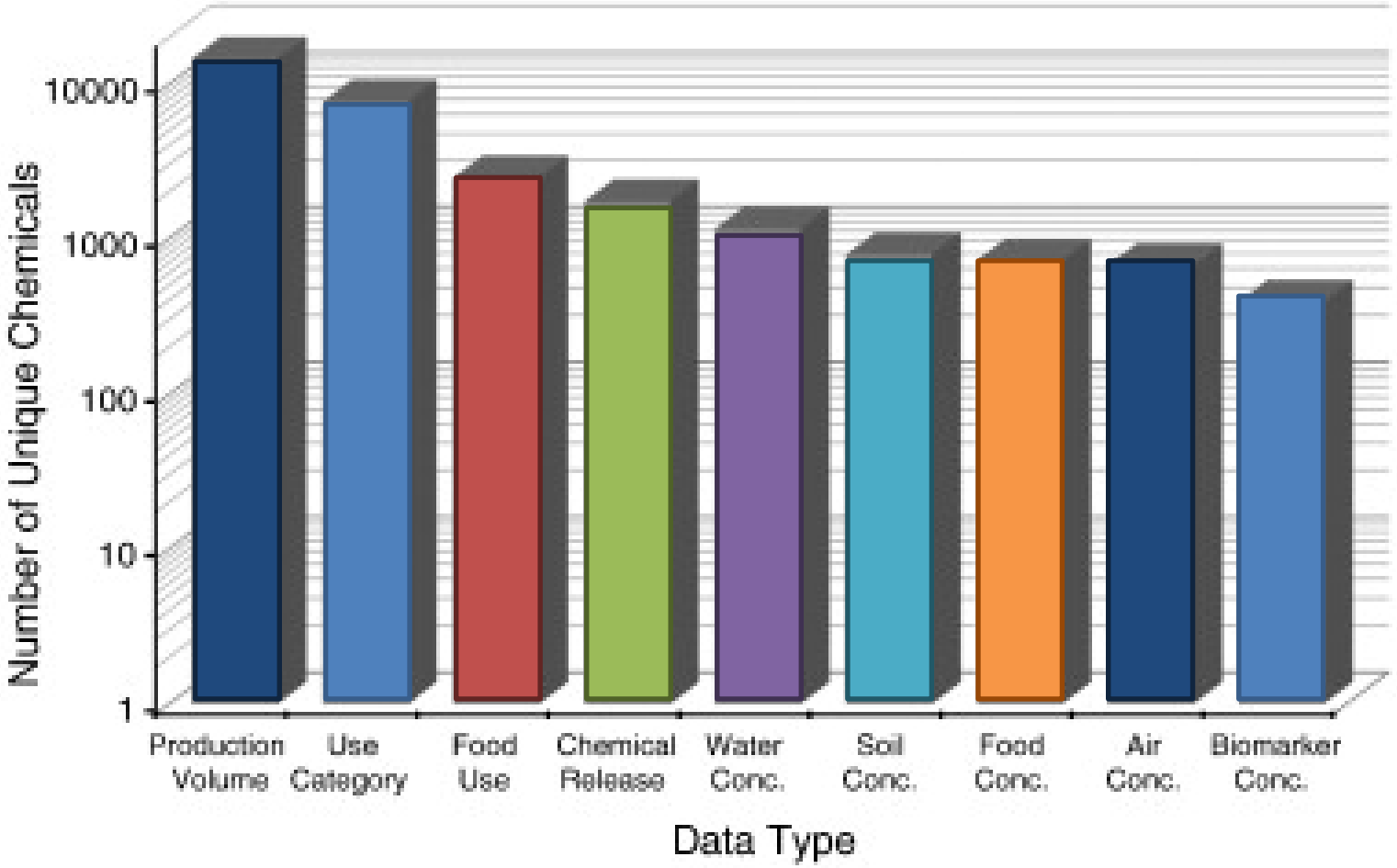


Figure from Kristin Isaacs

Limited Available Data for Exposure Estimations



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

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

Urinary Bisphenol A (2,2-*bis*[4-Hydroxyphenyl] propane)

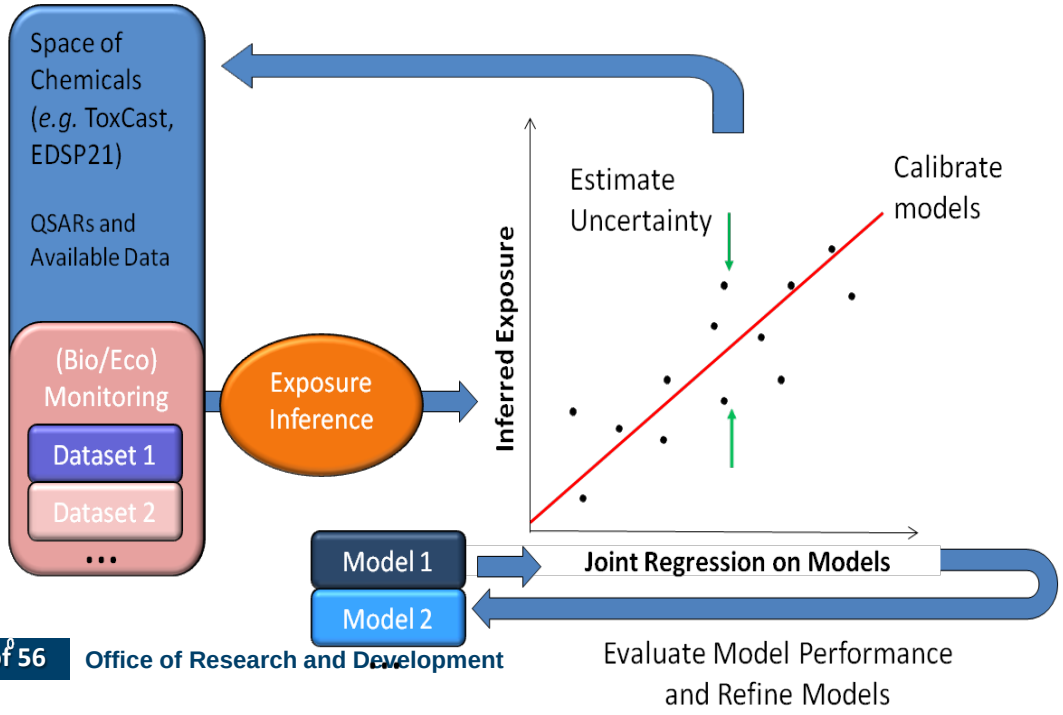
Geometric mean and selected percentiles of urine concentrations (in µg/L) for the U.S. populatio and Nutrition Examination Survey.

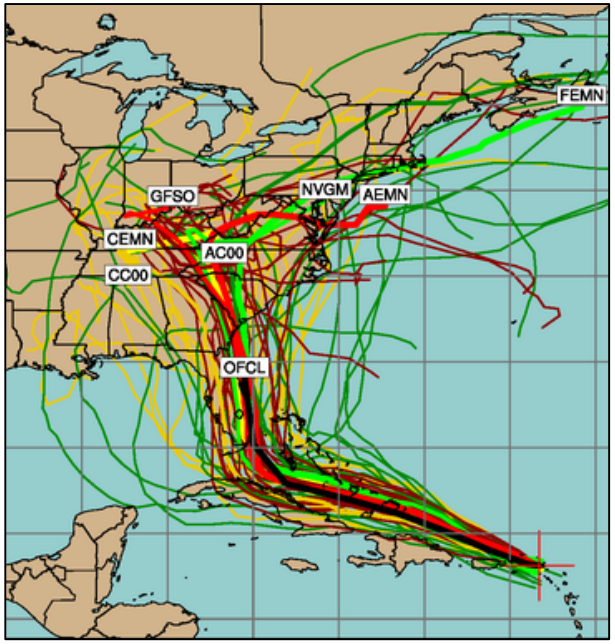
	Survey years	Geometric mean (95% conf. interval)	Selected percentiles (95% confidence interval) 50th	75th	90th
Total	03-04	2.64 (2.38-2.94)	2.80 (2.50-3.10)	5.50 (5.00-6.20)	10.6 (9.40-
	05-06	1.90 (1.79-2.02)	2.00 (1.90-2.00)	3.70 (3.50-3.90)	7.00 (6.40-
	07-08	2.08 (1.92-2.26)	2.10 (1.90-2.30)	4.10 (3.60-4.60)	7.70 (6.80-
Age group					
6-11 years	03-04	3.55 (2.95-4.29)	3.80 (2.70-5.00)	6.90 (6.00-8.30)	12.6 (9.50-
	05-06	2.86 (2.52-3.24)	2.70 (2.30-2.90)	5.00 (4.40-5.80)	13.5 (9.30-
	07-08	2.46 (2.20-2.75)	2.40 (1.90-3.00)	4.50 (3.70-5.50)	7.00 (6.30-
12-19 years	03-04	3.74 (3.31-4.22)	4.30 (3.60-4.60)	7.80 (6.50-9.00)	13.5 (11.8-
	05-06	2.42 (2.18-2.68)	2.40 (2.10-2.70)	4.30 (3.90-5.20)	8.40 (6.50-
	07-08	2.44 (2.14-2.78)	2.30 (2.10-2.60)	4.40 (3.70-5.50)	9.70 (7.30-
20 years and older	03-04	2.41 (2.15-2.72)	2.60 (2.30-2.80)	5.10 (4.50-5.70)	9.50 (8.10-
	05-06	1.75 (1.62-1.89)	1.80 (1.70-2.00)	3.40 (3.10-3.70)	6.40 (5.80-
	07-08	1.99 (1.82-2.18)	2.00 (1.80-2.30)	3.90 (3.40-4.60)	7.40 (6.60-

CDC, Fourth National Exposure Report (2011)

Consensus Exposure Predictions with the SEEM Framework

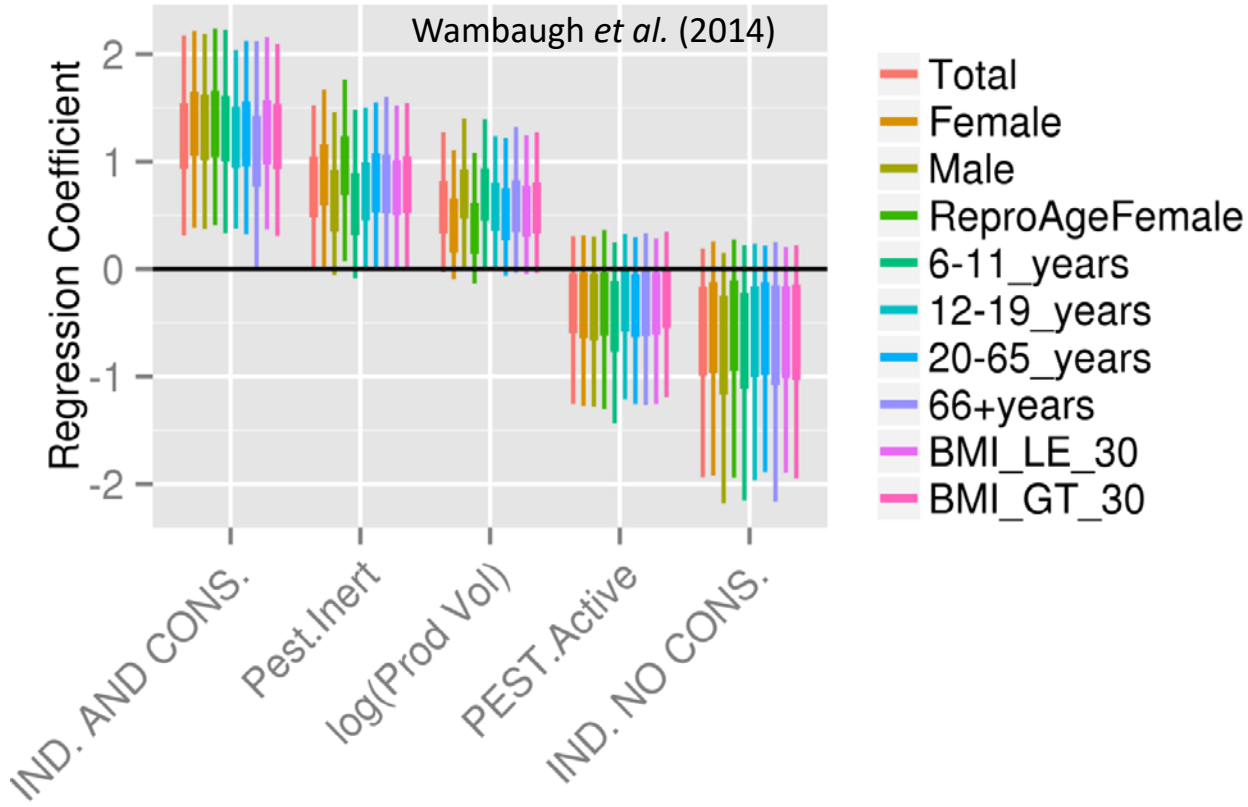
- We incorporate multiple models into consensus predictions for 1000s of chemicals within the **Systematic Empirical Evaluation of Models (SEEM) framework**
- We evaluate/calibrate predictions with available monitoring data
- This provides information similar to a sensitivity analysis: What models are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





Integrating Multiple Models

Heuristics of Exposure



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

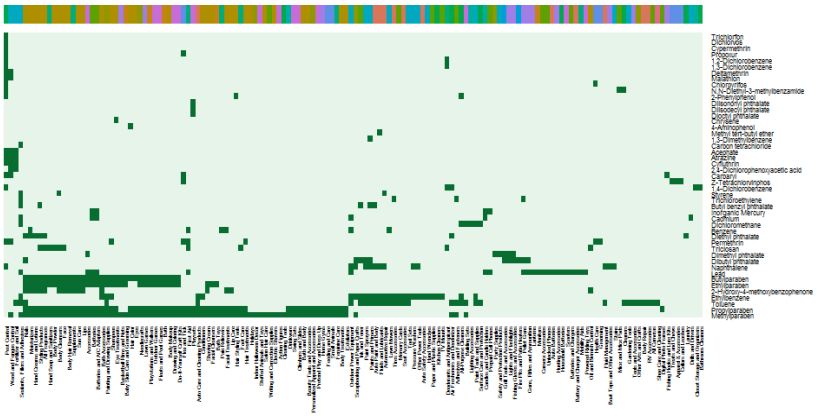
Same five predictors work for all NHANES demographic groups analyzed – stratified by age, sex, and body-mass index:

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

Chemical Use Identifies Relevant Pathways

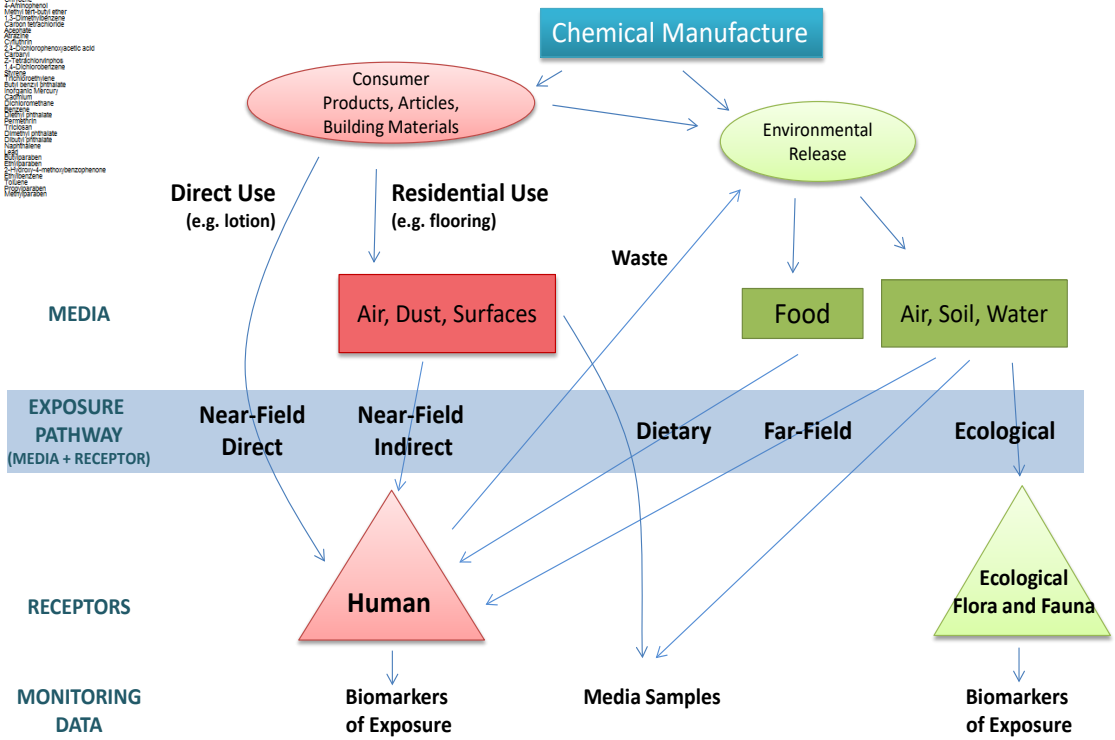
>2000 chemicals with Material Safety Data Sheets (MSDS) in CPCPdb (Goldsmith *et al.*, 2014)

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

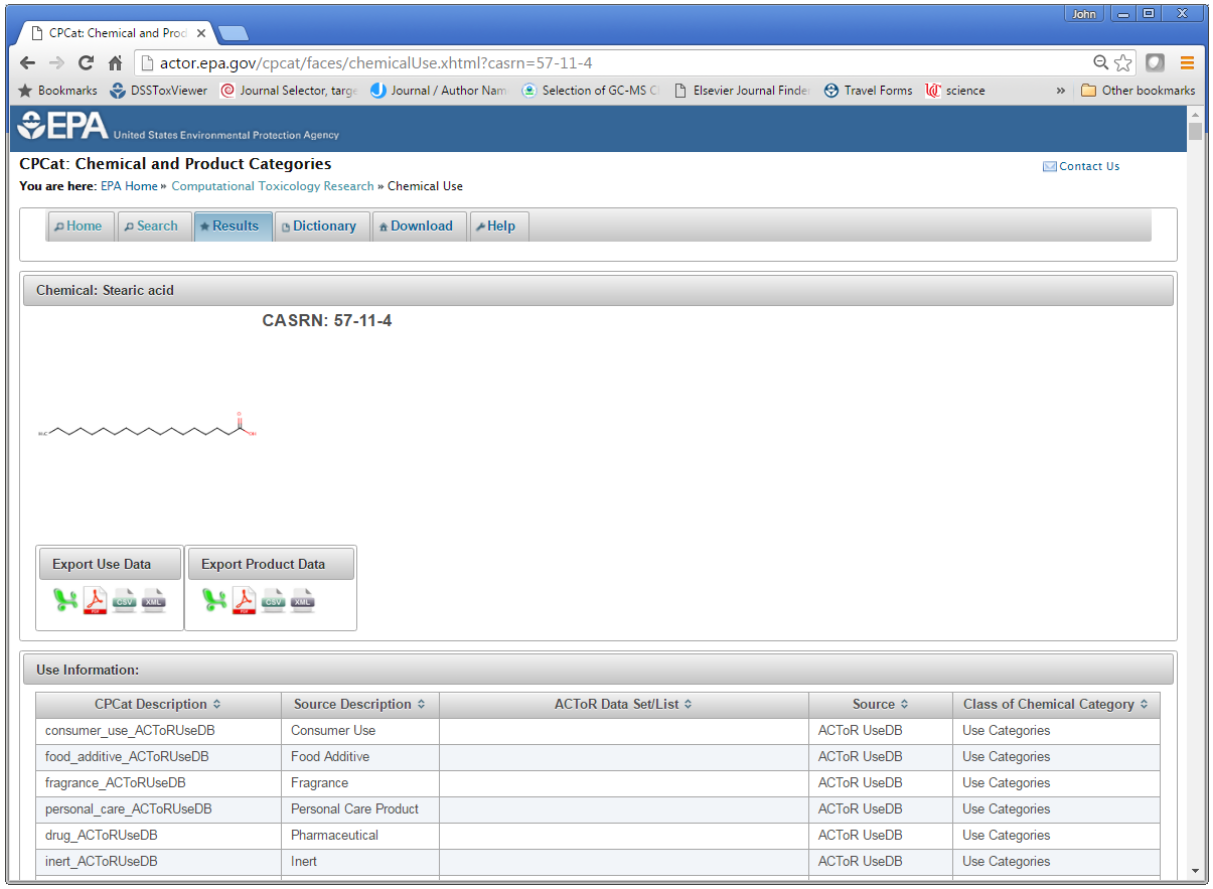
Some pathways have much higher average exposures!



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

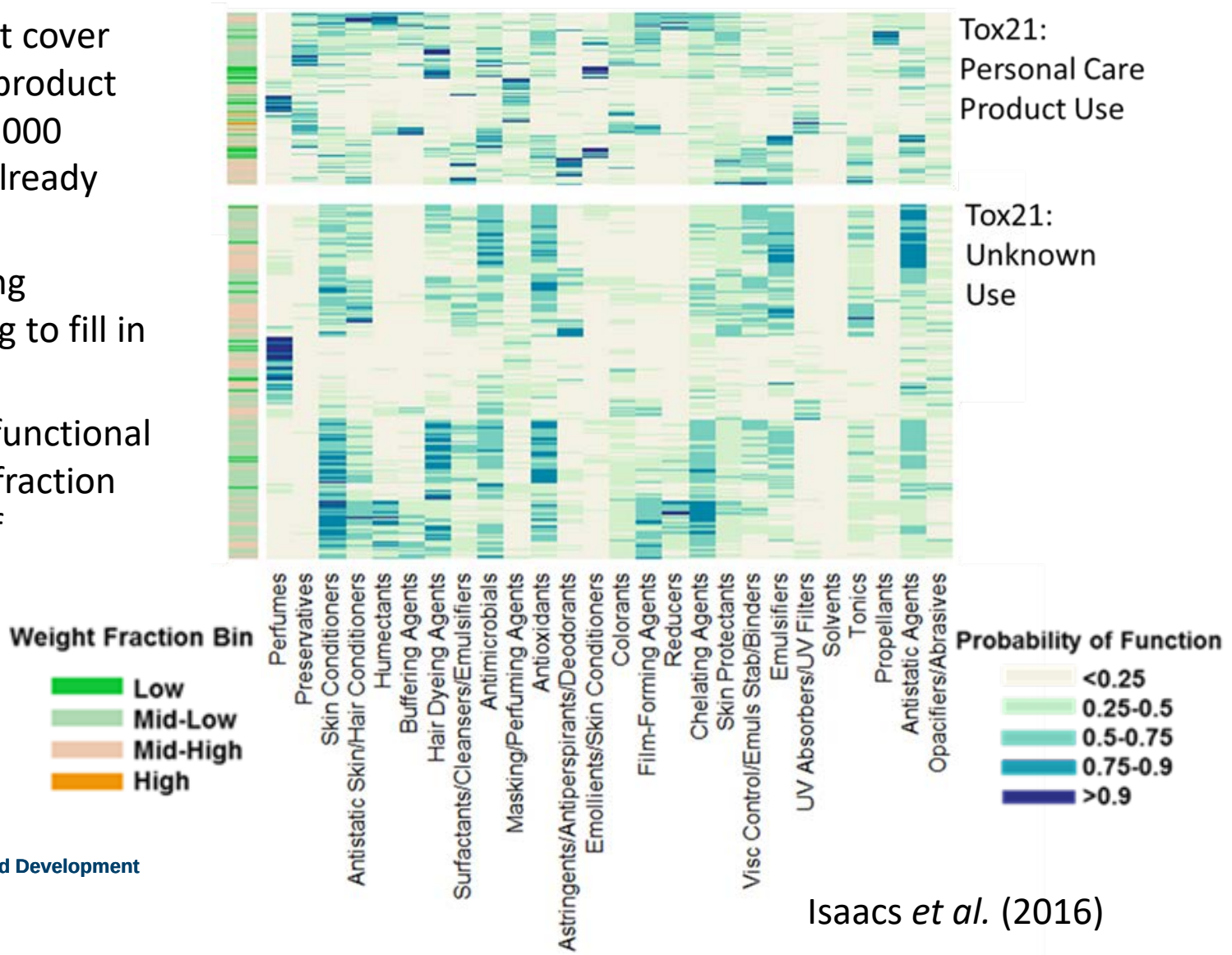


http://**actor.epa.gov/cpcat/**

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)

Non-Targeted and Suspect-Screening Analysis

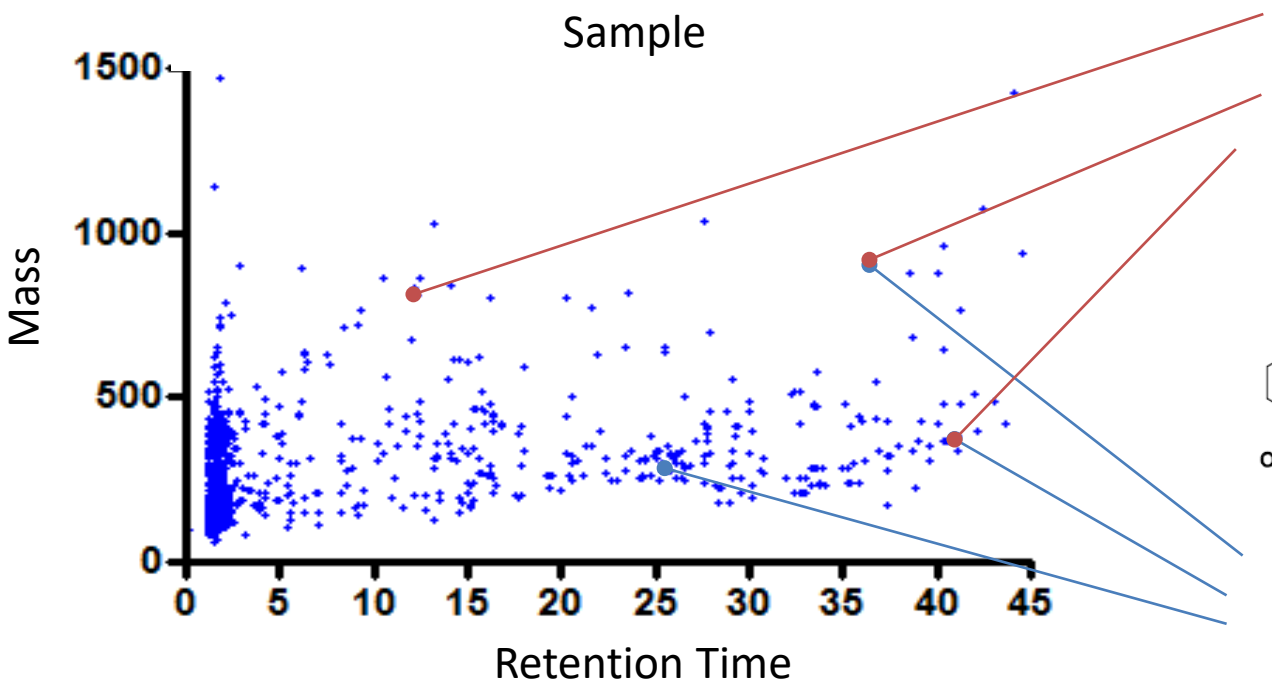
- Models present one way forward, but new analytic techniques may also allow insight in to chemicals composition of products and the greater environment
- EPA is coordinating a comparison of non-targeted screening workflows used by leading academic and government groups (led by Jon Sobus and Elin Ulrich)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

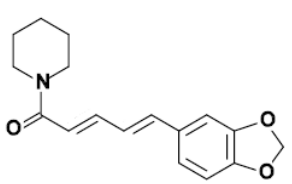
947 Peaks in an American Health Homes Dust Sample

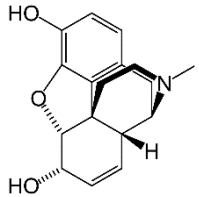


Each peak corresponds to a chemical with an accurate mass and predicted formula:

$C_{17}H_{19}NO_3$

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

"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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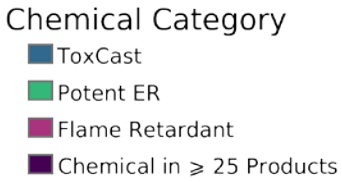
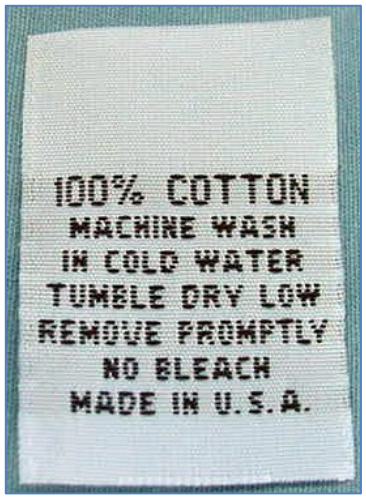
Hahn and Strassmann (1938)

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

Measuring Chemicals in Household Items



The chemicals found in a cotton shirt

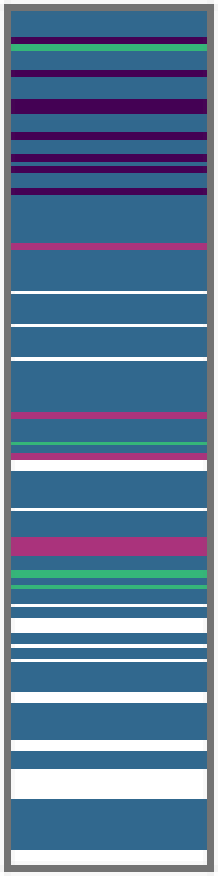


Phillips et al. (submitted)

Measuring Chemicals in Household Items

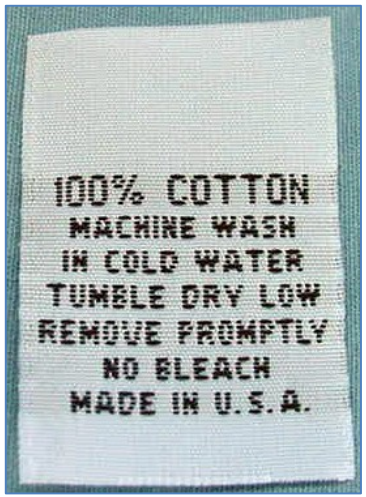
United States Environmental Protection Agency

126 Confirmed



⬅ Chemicals that are present

Chemical Category
- ToxCast
- Potent ER
- Flame Retardant
- Chemical in ⩾ 25 Products

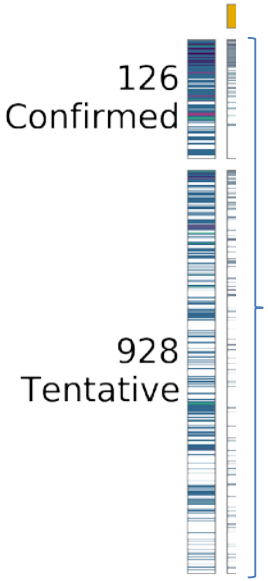


⬅ Chemicals that are absent (but found in other products)

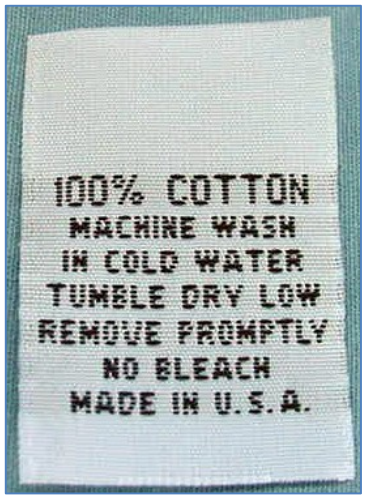
Phillips et al. (submitted)

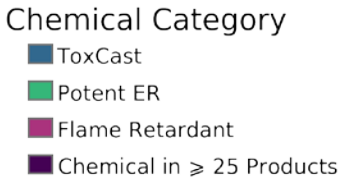
Measuring Chemicals in Household Items

United States Environmental Protection Agency



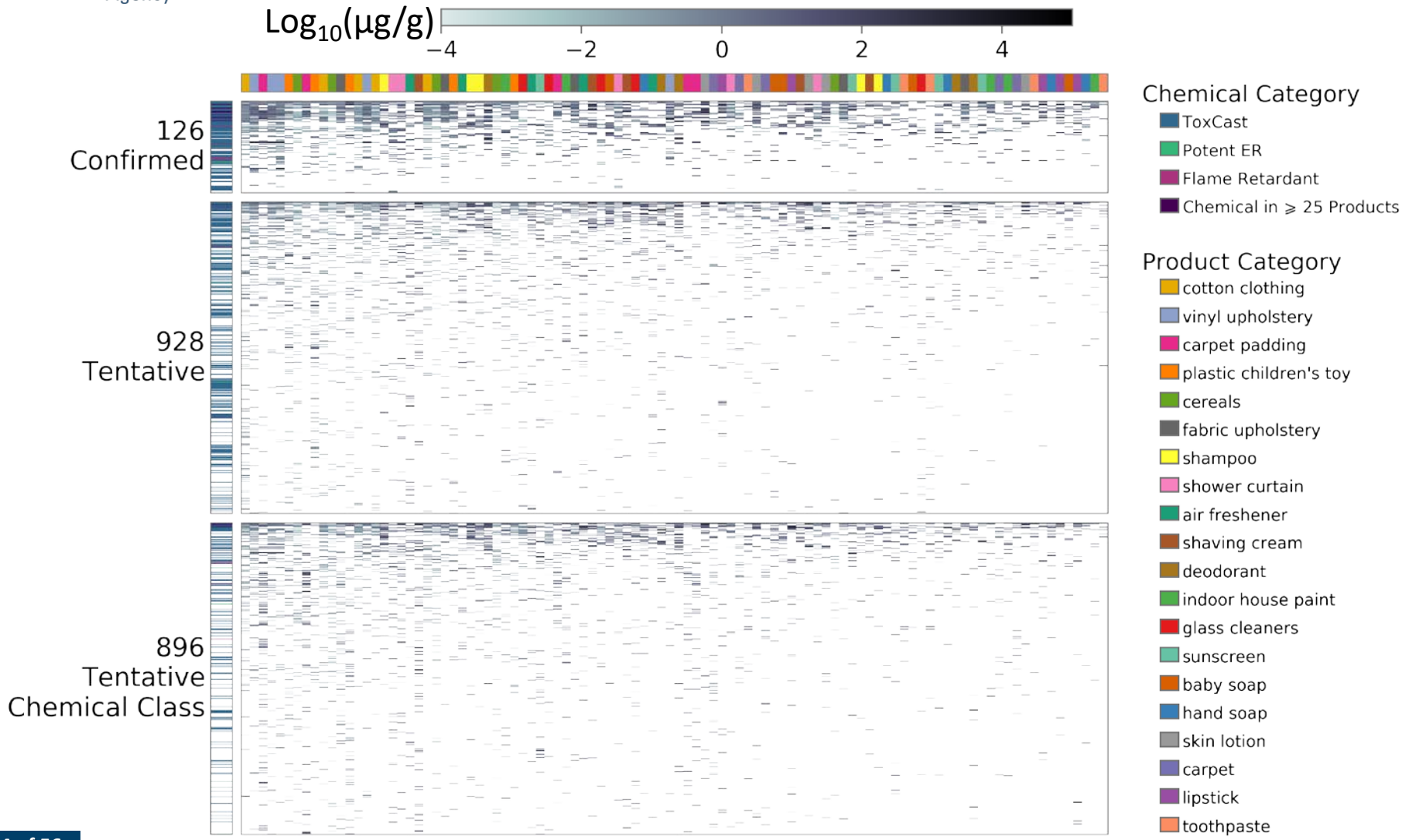
The chemicals found in a cotton shirt





Phillips et al. (submitted)

Measuring Chemicals in Household Items

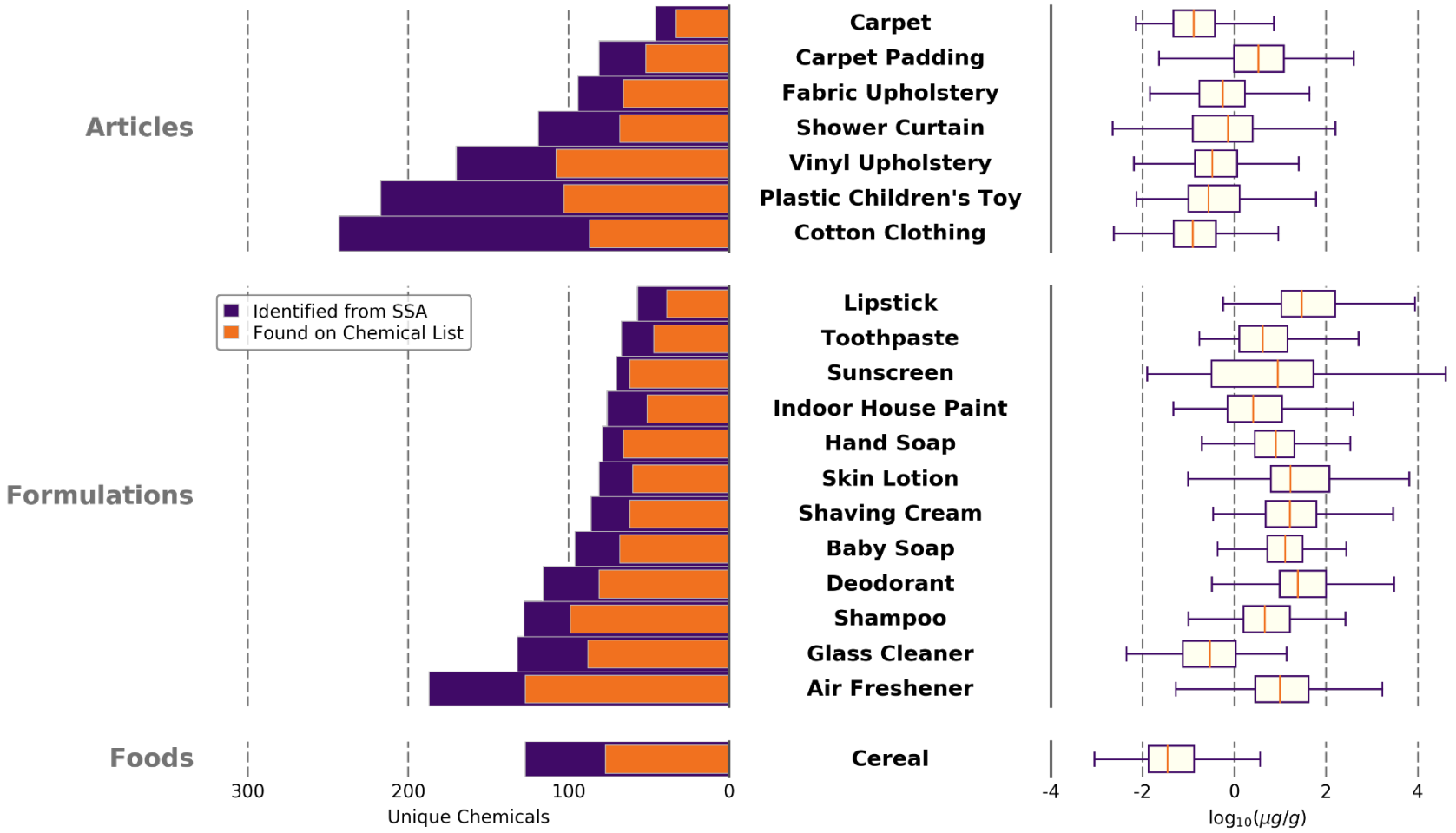


Phillips et al. (submitted)

Product Scan Summary

United States Environmental Protection Agency

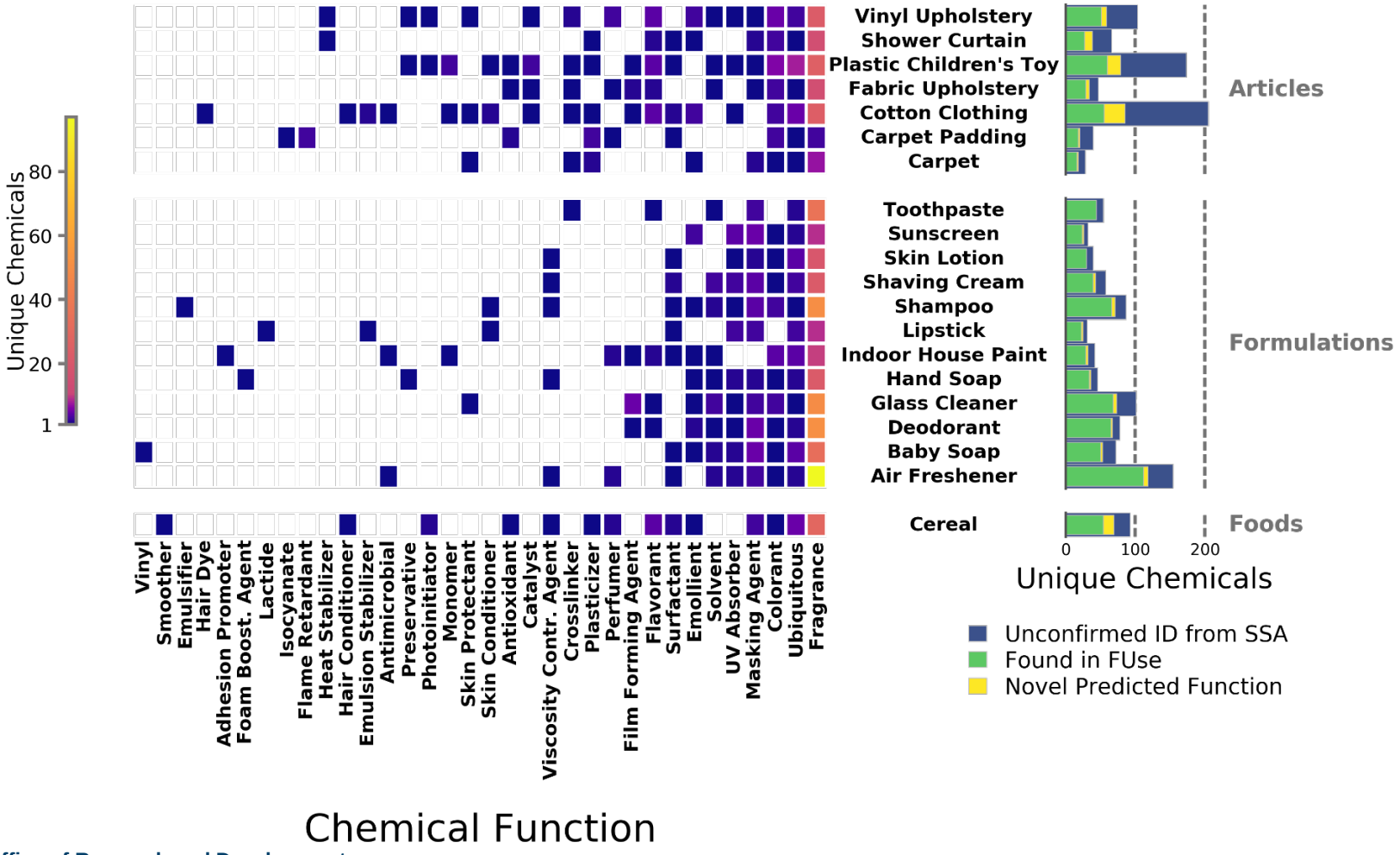
Of 1,632 chemicals confirmed or tentatively identified, 1,445 were not present in CPCPdb



Phillips *et al.* (*submitted*)

Predicting Chemical Function

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



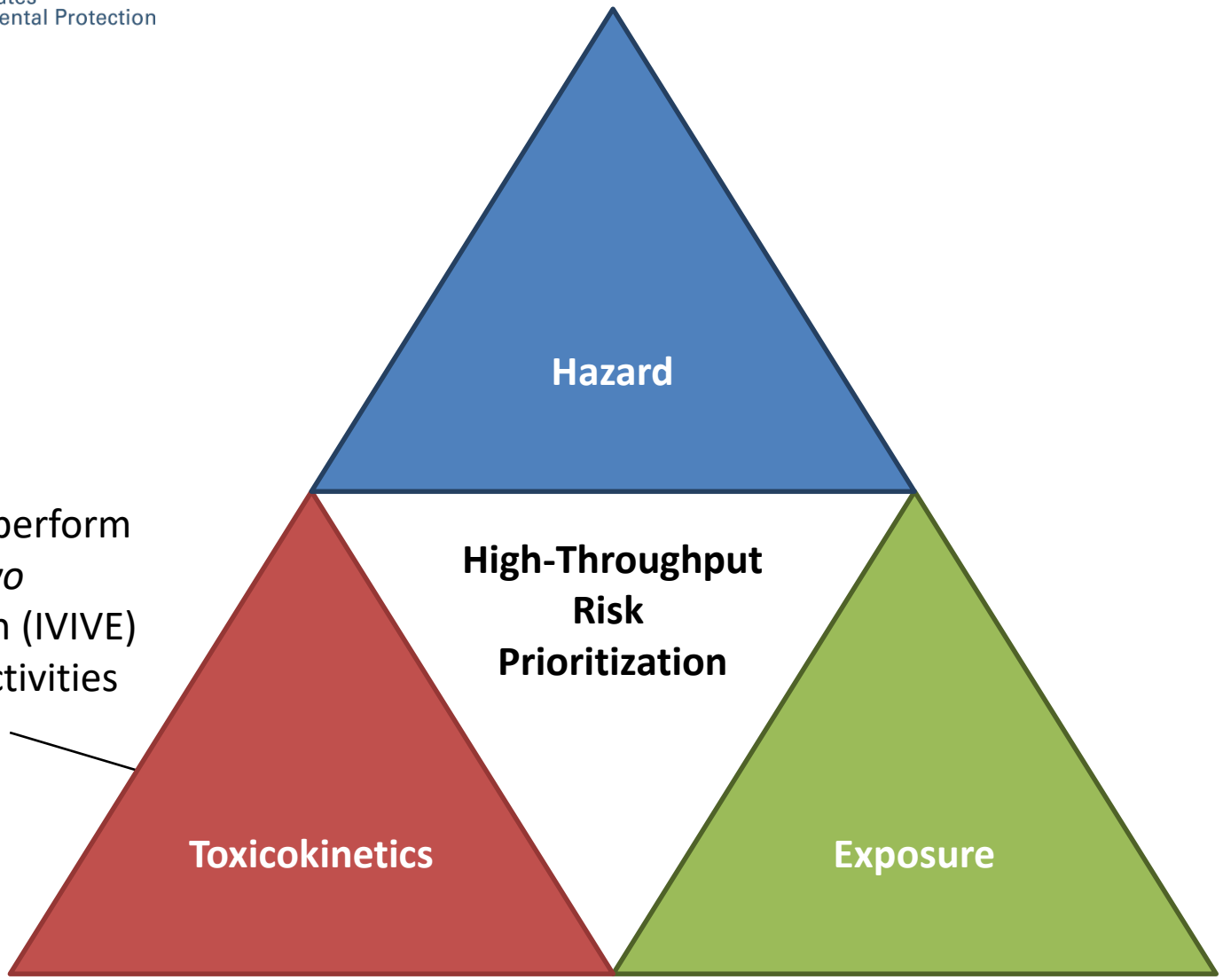
Phillips *et al.* (*submitted*)

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**

Toxicokinetics for IVIVE

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



In Vitro - In Vivo Extrapolation (IVIVE)

Definition:
IVIVE is the utilization 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

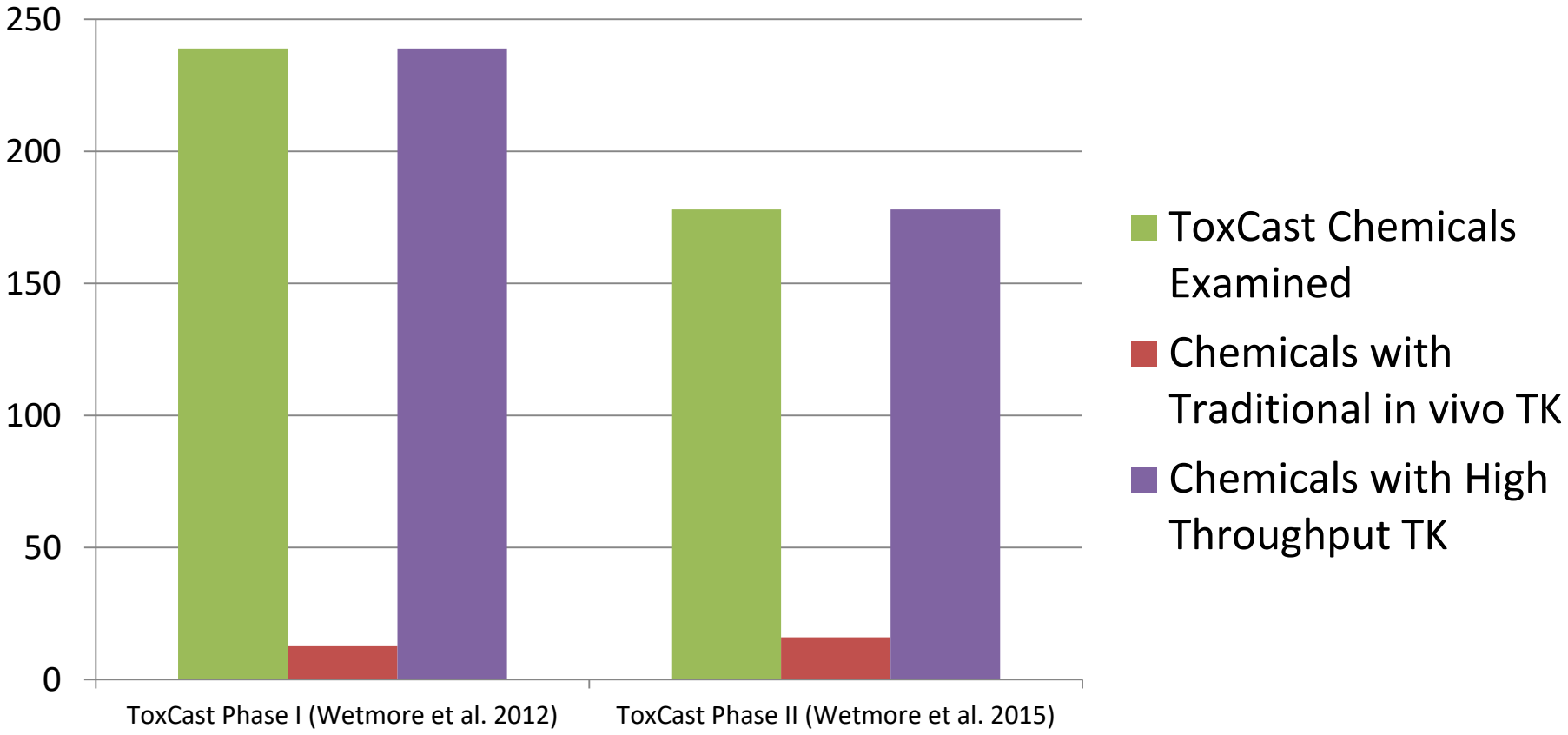
- IVIVE-PD/TD (Pharmacodynamics/Toxicodynamics):
  - Effect of molecules/chemicals at biological target *in vivo*
  - Assay design/selection important
  - Perturbation as adverse/therapeutic effect, reversible/ irreversible

- Both contribute to predict *in vivo* effects

Slide from Barbara Wetmore

Addressing The Need for *In Vitro* Toxicokinetics

- Studies like Wetmore et al. (2012, 2015) generate TK data using *in vitro* methods

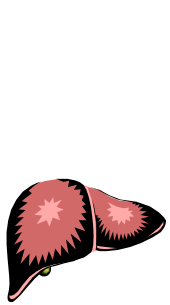


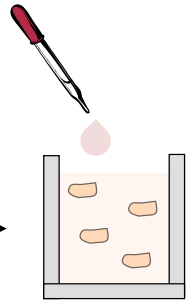
High Throughput Toxicokinetics (HTTK)

- Toxicokinetics (TK) provides a bridge between toxicity and exposure assessment by predicting tissue concentrations due to exposure
  - However traditional TK methods are resource intensive

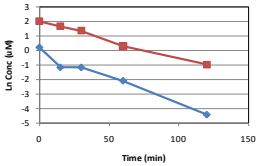
- Relatively high throughput TK (HTTK) methods have been used by the pharmaceutical industry to determine range of efficacious doses and to prospectively evaluate success of planned clinical trials (Jamei, *et al.*, 2009; Wang, 2010)
  - A key application of HTTK has been “reverse dosimetry” (also called Reverse TK or RTK)
  - RTK can approximately convert *in vitro* HTS results to daily doses needed to produce similar levels in a human for comparison to exposure data (starting off with Rotroff, *et al*., 2010)

Characterizing Human *In Vivo* Toxicokinetics Using *In Vitro* Assays





Human Hepatocytes (10 donor pool)

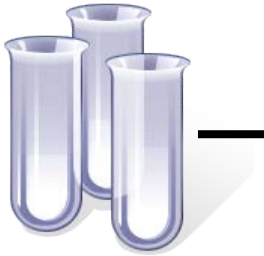


Intrinsic Hepatic Clearance (Cl_{int})

Measurements require chemical-specific methods for concentration

In Vitro - In Vivo Extrapolation

Predicted Plasma Concentrations



Human Plasma (6 donor pool)

Plasma Protein Binding (f_{up})

Rotroff et al. (2010) 35 chemicals
Wetmore et al. (2012) +204 chemicals
Wetmore et al. (2015) +163 chemicals

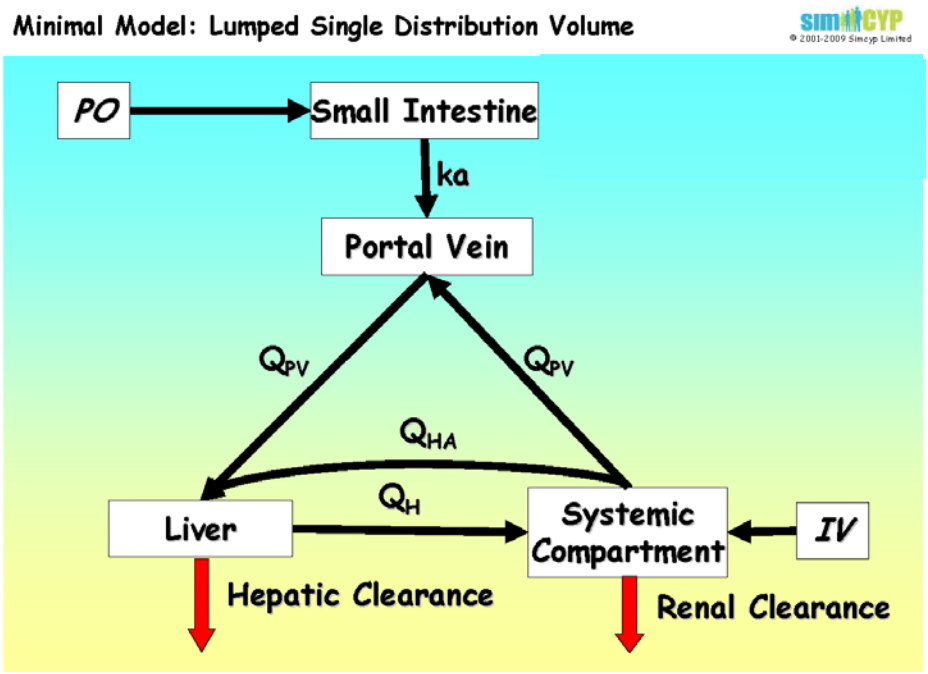
Figure from Barbara Wetmore

A Basic Model Allows HTTK

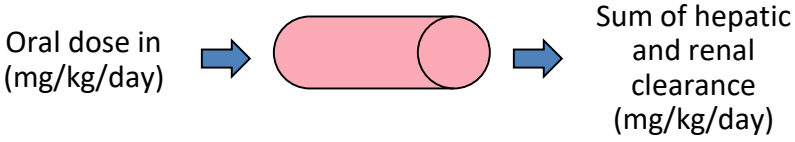
- *In vitro* plasma protein binding (fraction unbound in plasma – f_{up}) and intrinsic hepatic metabolic clearance (Cl_{int}) assays allow approximate hepatic and renal clearances to be calculated
- At steady state this allows conversion from concentration to administered dose
- 100% bioavailability assumed

$$C_{ss} = \frac{\text{oral dose rate}}{\left(GFR * F_{up}\right) + \left(Q_l * F_{up} * \frac{Cl_{int}}{Q_l + F_{up} * Cl_{int}}\right)}$$

GFR: Glomerular filtration rate (kidney)
Q_l: Liver blood flow

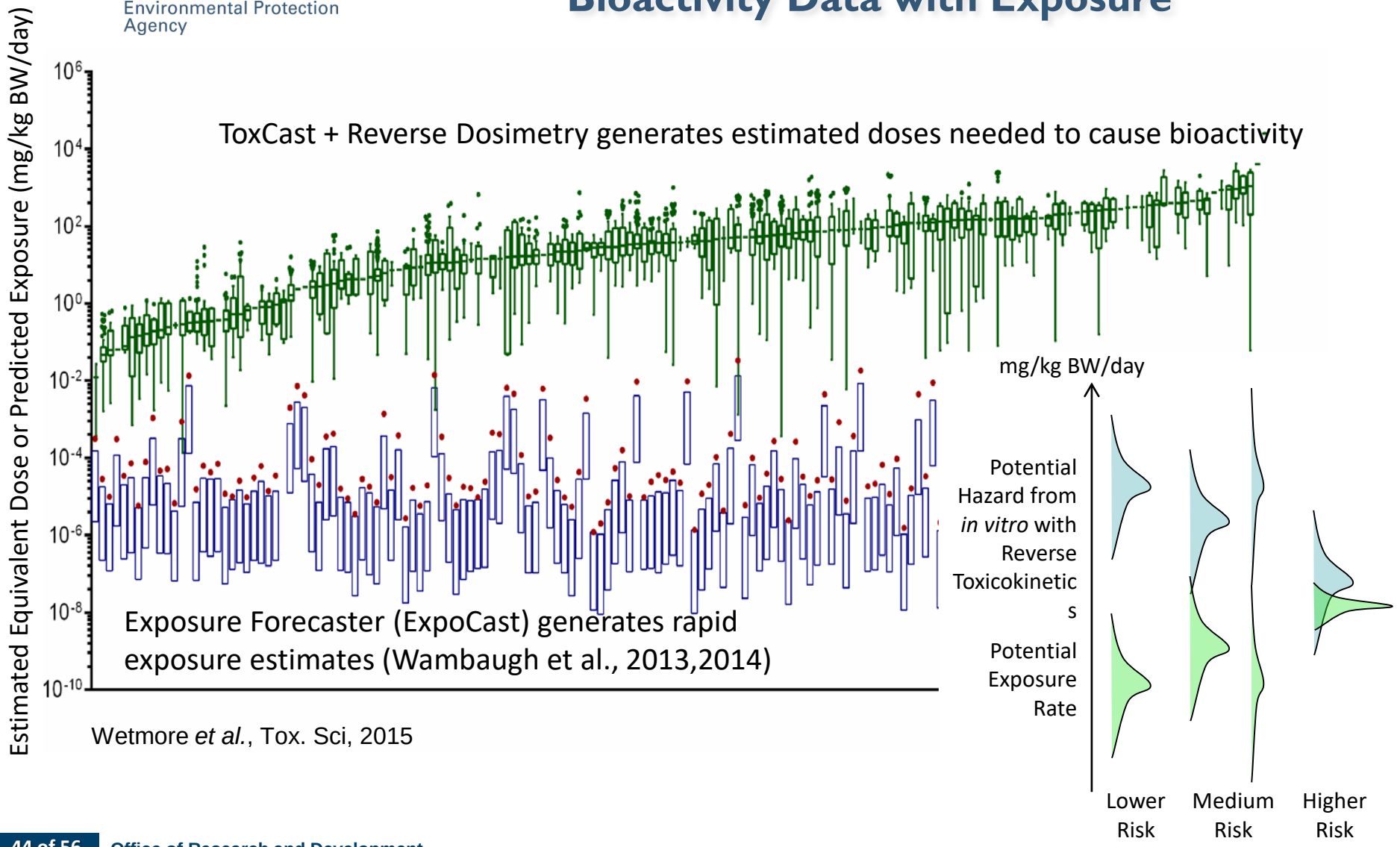


Jamei *et al.* (2009)



Incorporating Dosimetry-Adjusted ToxCast Bioactivity Data with Exposure

United States Environmental Protection Agency

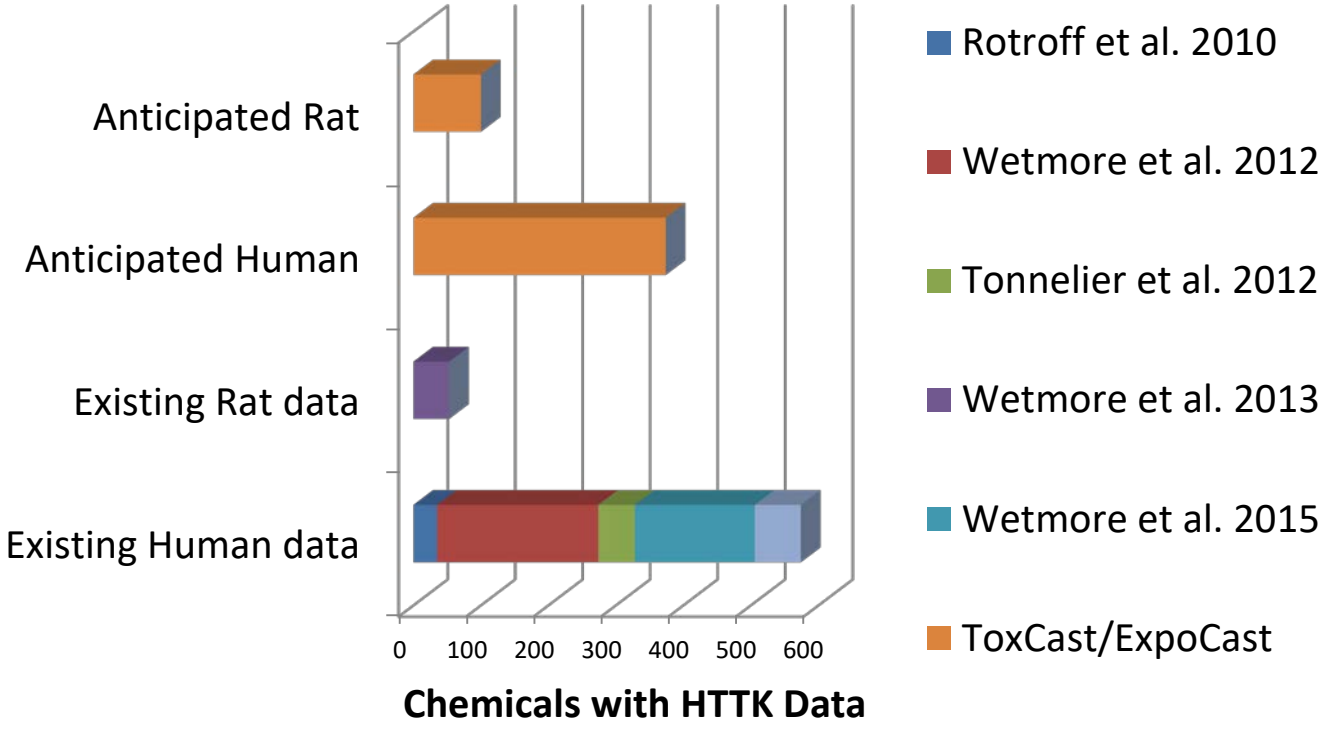


Wetmore *et al.*, Tox. Sci, 2015

Chemicals with HTTK Data

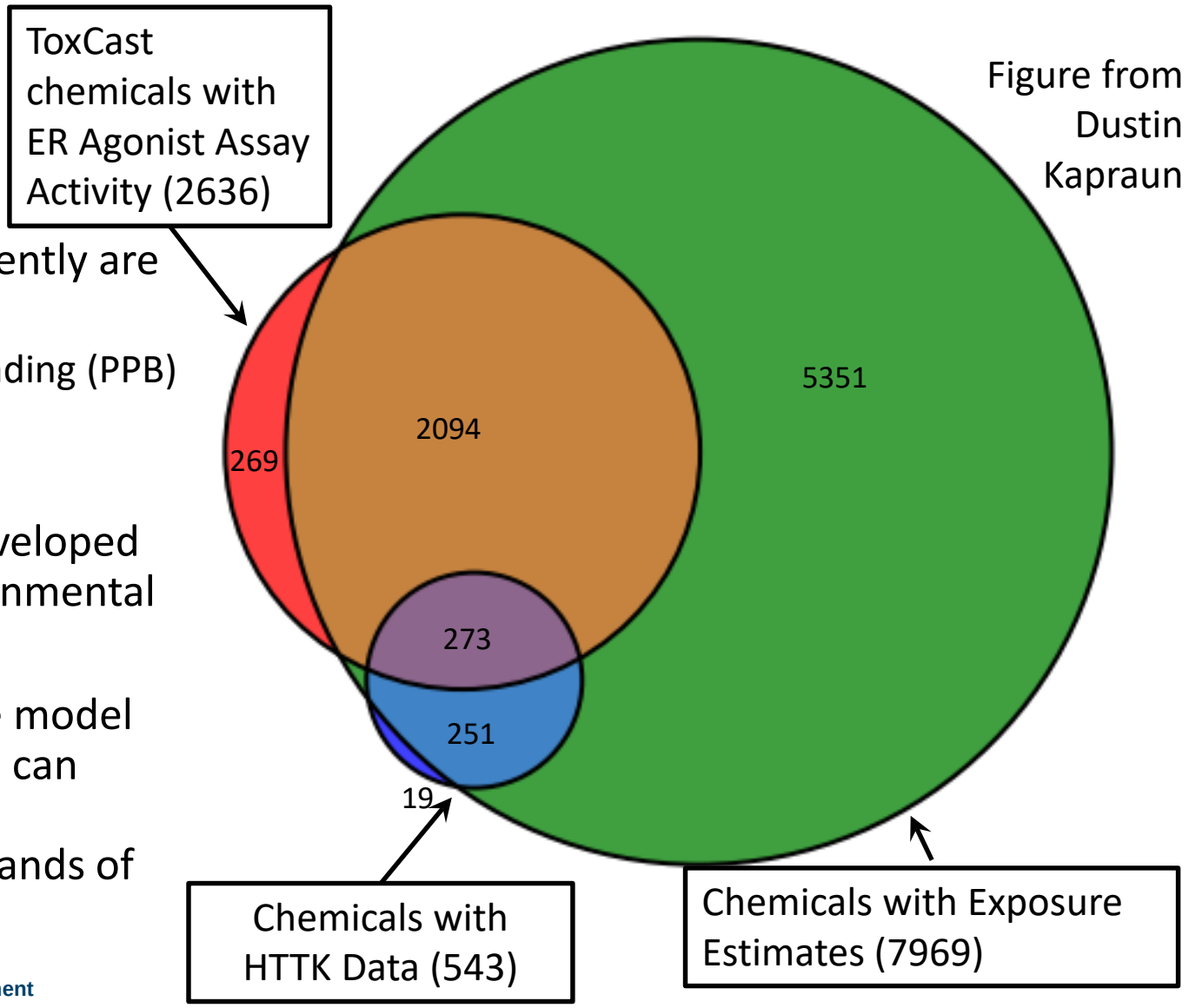
Measurement of *in vitro* clearance and binding both require chemical-specific analytical chemistry methods – these can be difficult to develop

Methods are appropriate for chemicals that are soluble, non-volatile only



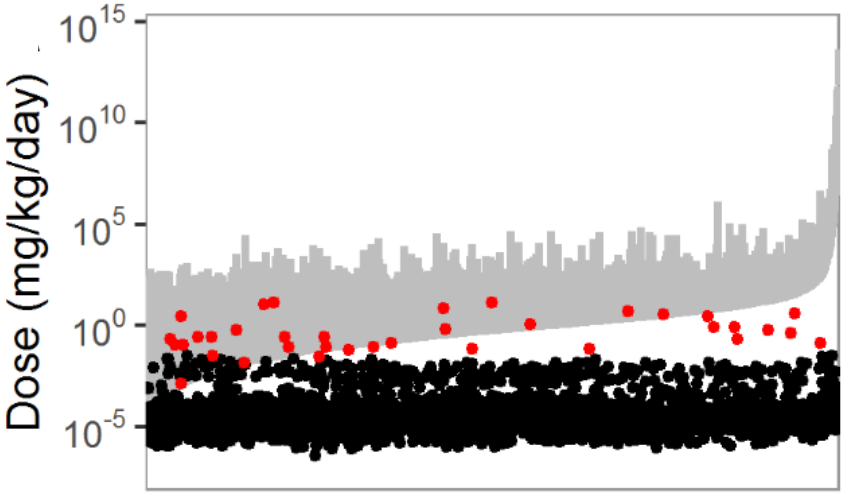
Predicting Critical TK Parameters

- 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

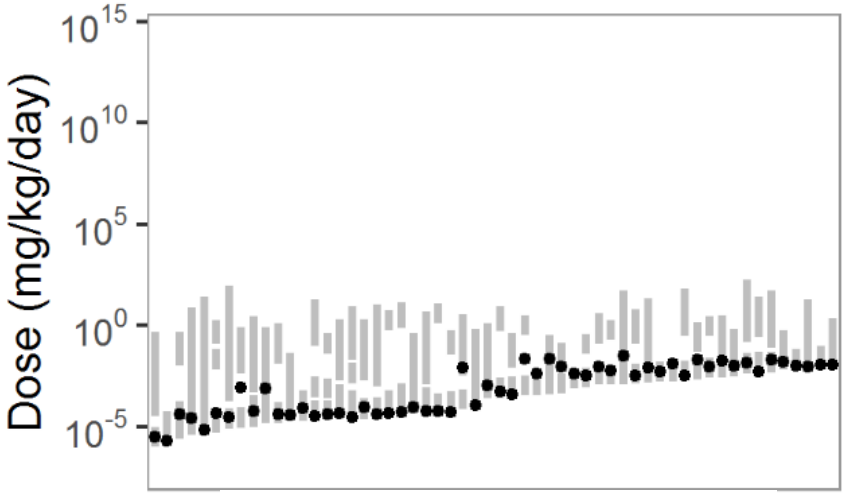


Using Predicted HTTK for Risk Prioritization

Sipes et al. 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

Sipes et al., (2017)

Modern U.S. Population Simulator for HTTK

Correlated Monte Carlo sampling of physiological model parameters

Sample quantities from

Sex
Race/ethnicity
Age
Height
Weight
Serum creatinine

Ring *et al*. (2017)

Modern U.S. Population Simulator for HTTK

Correlated Monte Carlo sampling of physiological model parameters

Sample quantities from

nhanes
National Health and Nutrition Examination Survey

Sex
Race/ethnicity
Age
Height
Weight
Serum creatinine

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

Ring *et al*. (2017)

Modern U.S. Population Simulator for HTTK

Correlated Monte Carlo sampling of physiological model parameters

Sample quantities from

Sex
Race/ethnicity
Age
Height
Weight
Serum creatinine

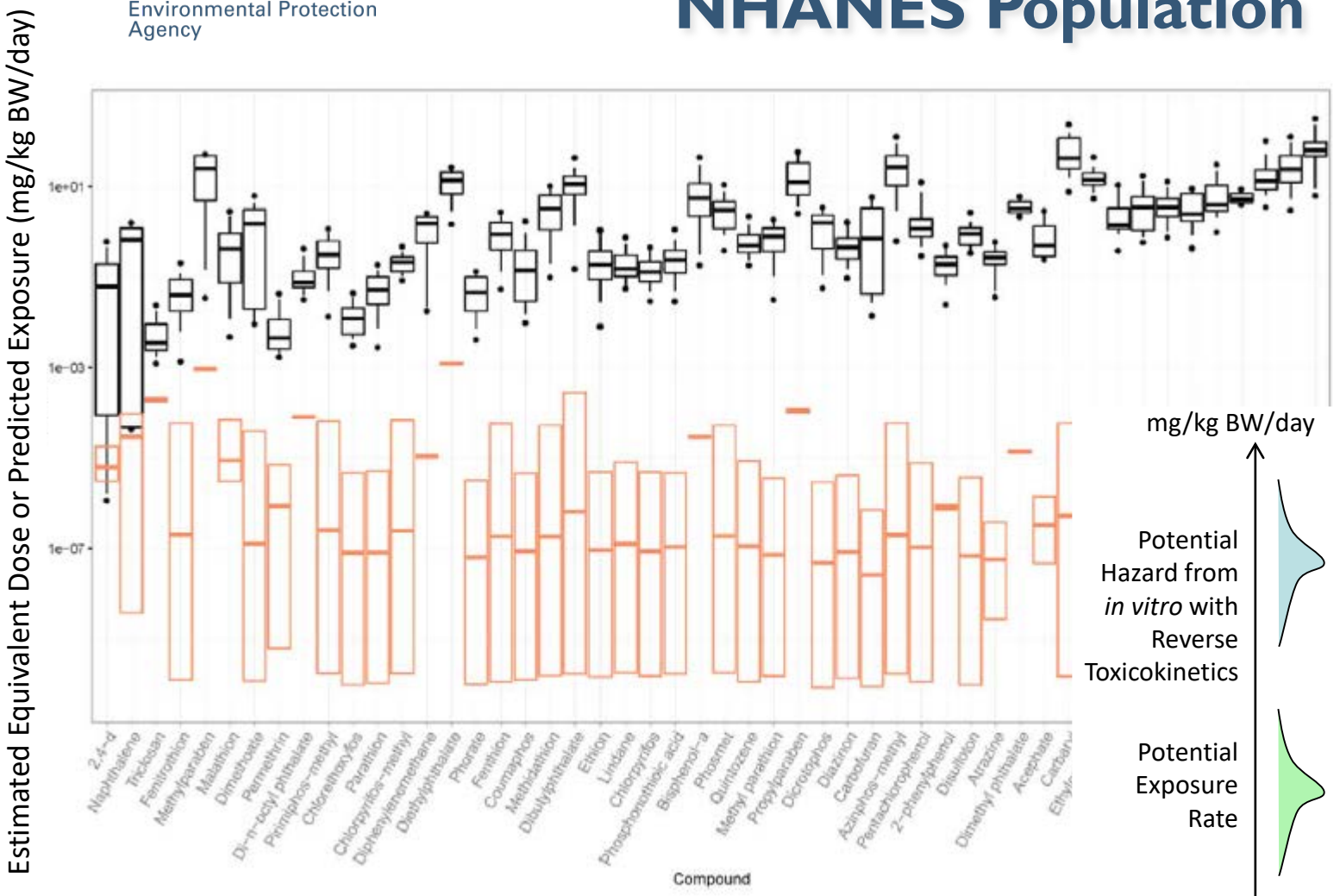
Use equations from literature
(McNally *et al.*, 2014)
(+ residual marginal variability)

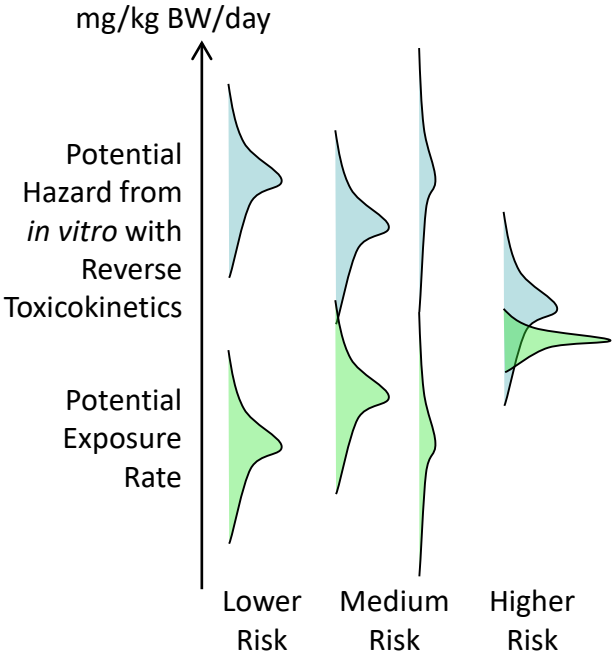
Predict physiological quantities

Tissue masses
Tissue blood flows
GFR (kidney function)
Hepatocellularity

Ring *et al*. (2017)

Risk-Based Ranking for Total NHANES Population

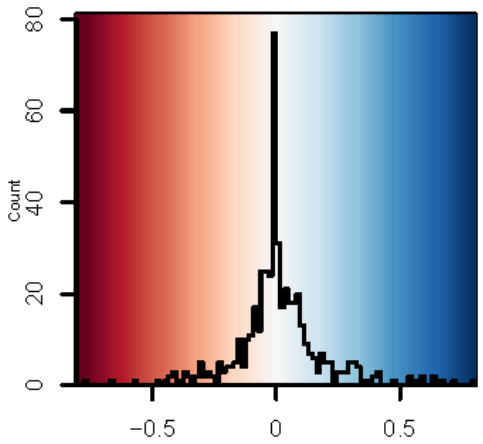




Ring *et al*. (2017)

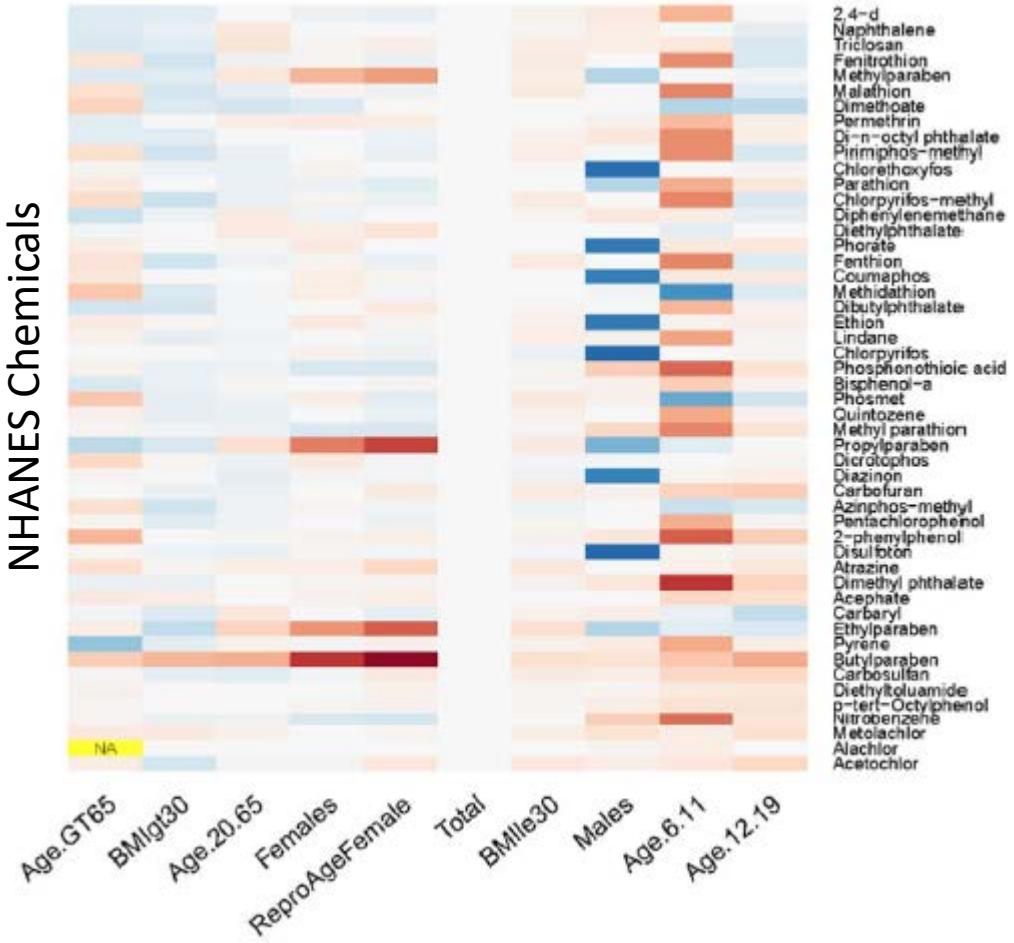
Life-stage and Demographic Variation in Exposure

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



Change in Exposure Relative to Total Population

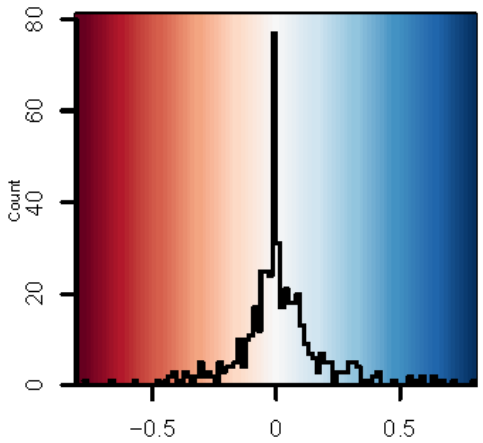
Change in Exposure (mg/kg bodyweight/day)



Ring *et al.* (2017)

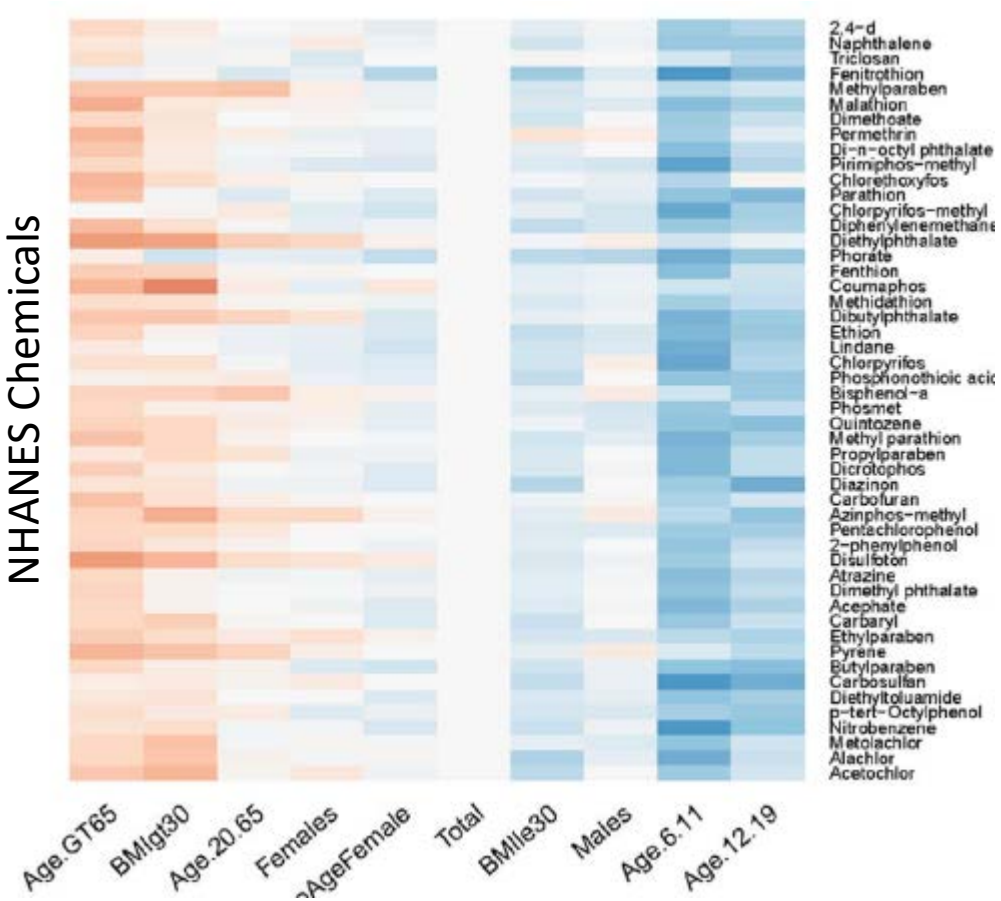
Life-stage and Demographic Variation in Exposure

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



Change in Plasma Concentration Relative to Total Population

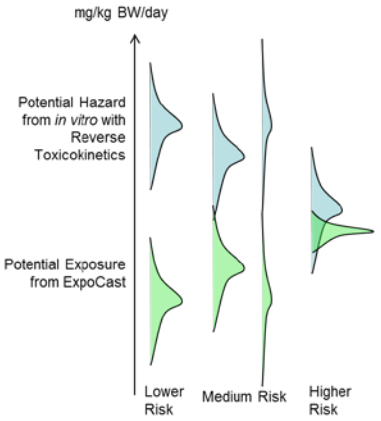
Change in Toxicokinetics (µM/unit exposure)

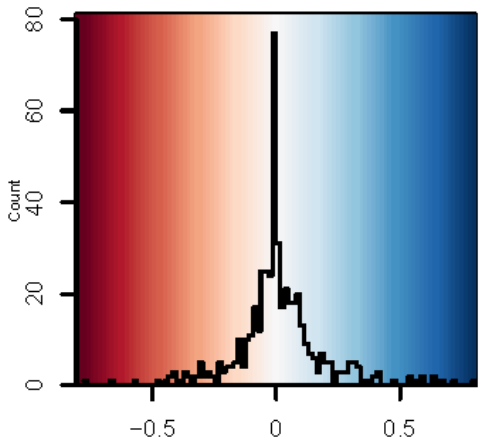


Ring *et al.* (2017)

Life-stage and Demographic Specific Predictions

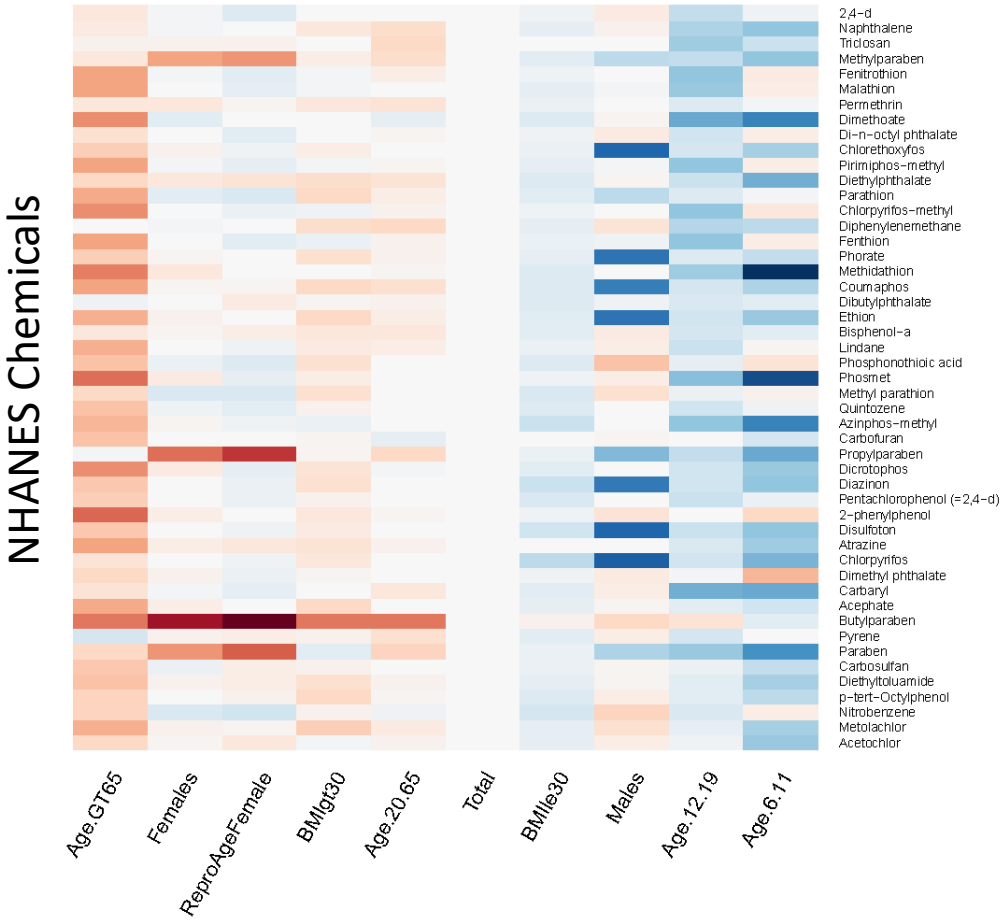
- Can calculate margin between bioactivity and exposure for specific populations





Change in Risk Relative to Total Population

Change in Activity:Exposure Ratio



Ring *et al*. (2017)

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 high throughput exposure approaches we can make coarse predictions of exposure
- Expanded monitoring data (exposure surveillance) allows evaluation of model predictions
  - Are chemicals missing that we predicted would be there?
  - Are there unexpected chemicals?
- 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
- 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

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

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