EPA
United States
Environmental Protection
Agency

Exposure Based Priority Setting for Chemical Safety

John Wambaugh
National Center for Computational Toxicology
Office of Research and Development
U.S. Environmental Protection Agency

Presentation to NCSU Bioinformatics Research Center, January 10, 2018

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

orcid.org/0000-0002-4024-534X

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
- 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)

November 29, 2014

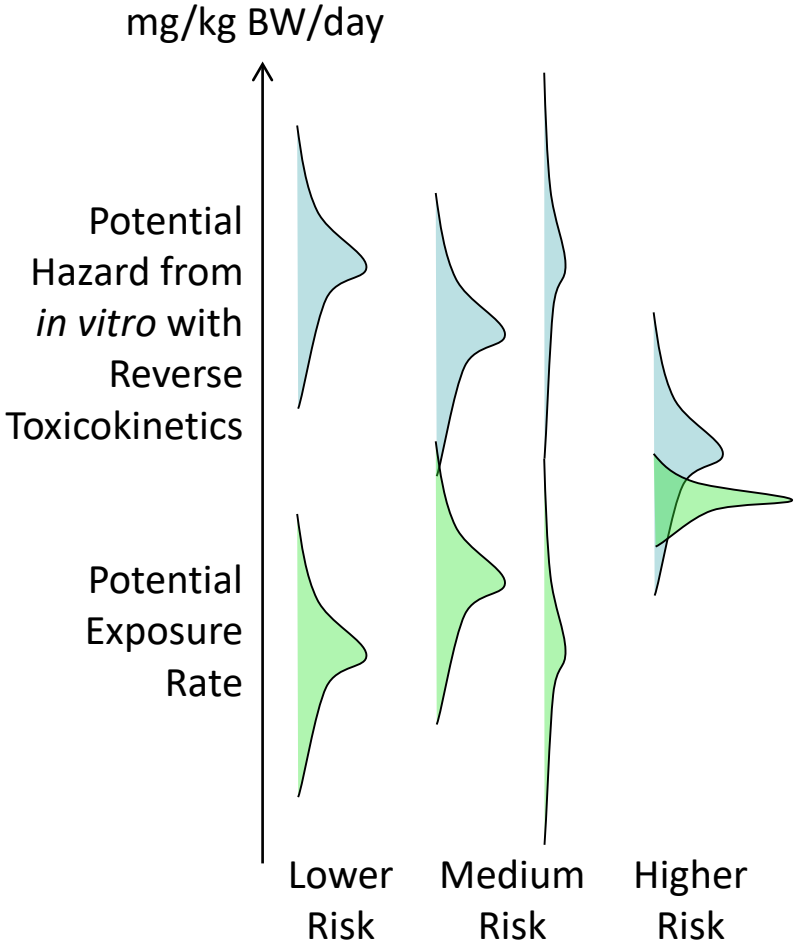
Chemical Regulation in the United States

- Most other chemicals, ranging from industrial waste to dyes to packing materials are covered by the recently updated Toxic Substances Control Act (TSCA)
  - 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
  - **Methods are being developed to prioritize these existing and new chemicals for testing**

November 29, 2014

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

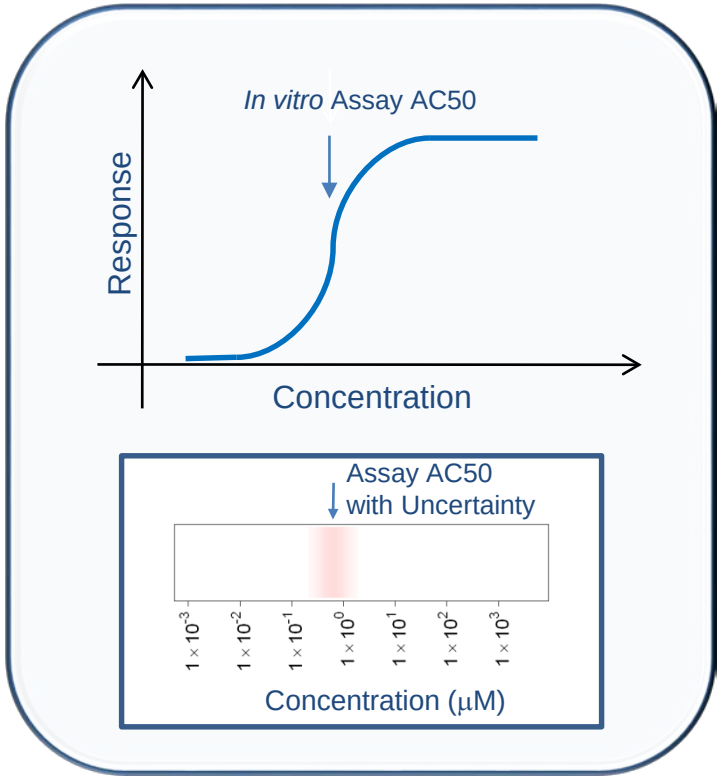
- We might estimate points of departure (concentrations causing relevant bioactivity) *in vitro* using high throughput screening (HTS)

- **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/



Risk Assessment in the 21st Century

United States Environmental Protection Agency

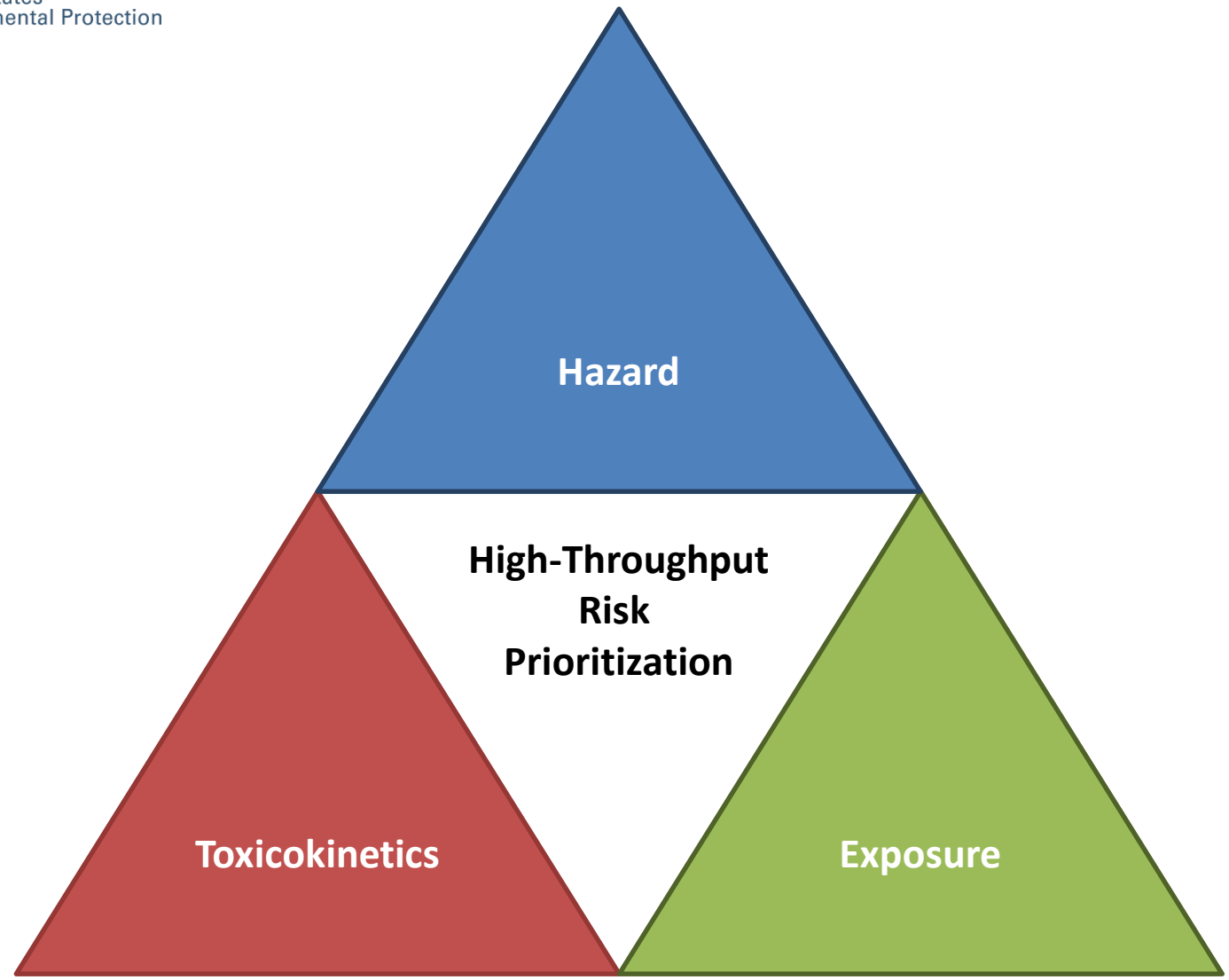
"Translation of high-throughput data into risk-based rankings is an important application of exposure data for chemical priority-setting. Recent advances in high-throughput toxicity assessment, notably the ToxCast and Tox21 programs (see Chapter 1), and in high-throughput computational exposure assessment (Wambaugh et al. 2013, 2014) have enabled first-tier risk-based rankings of chemicals on the basis of margins of exposure…"

"…The committee sees the potential for the application of **computational exposure science** to be highly valuable and credible for comparison and **priority-setting among chemicals in a risk-based context**."

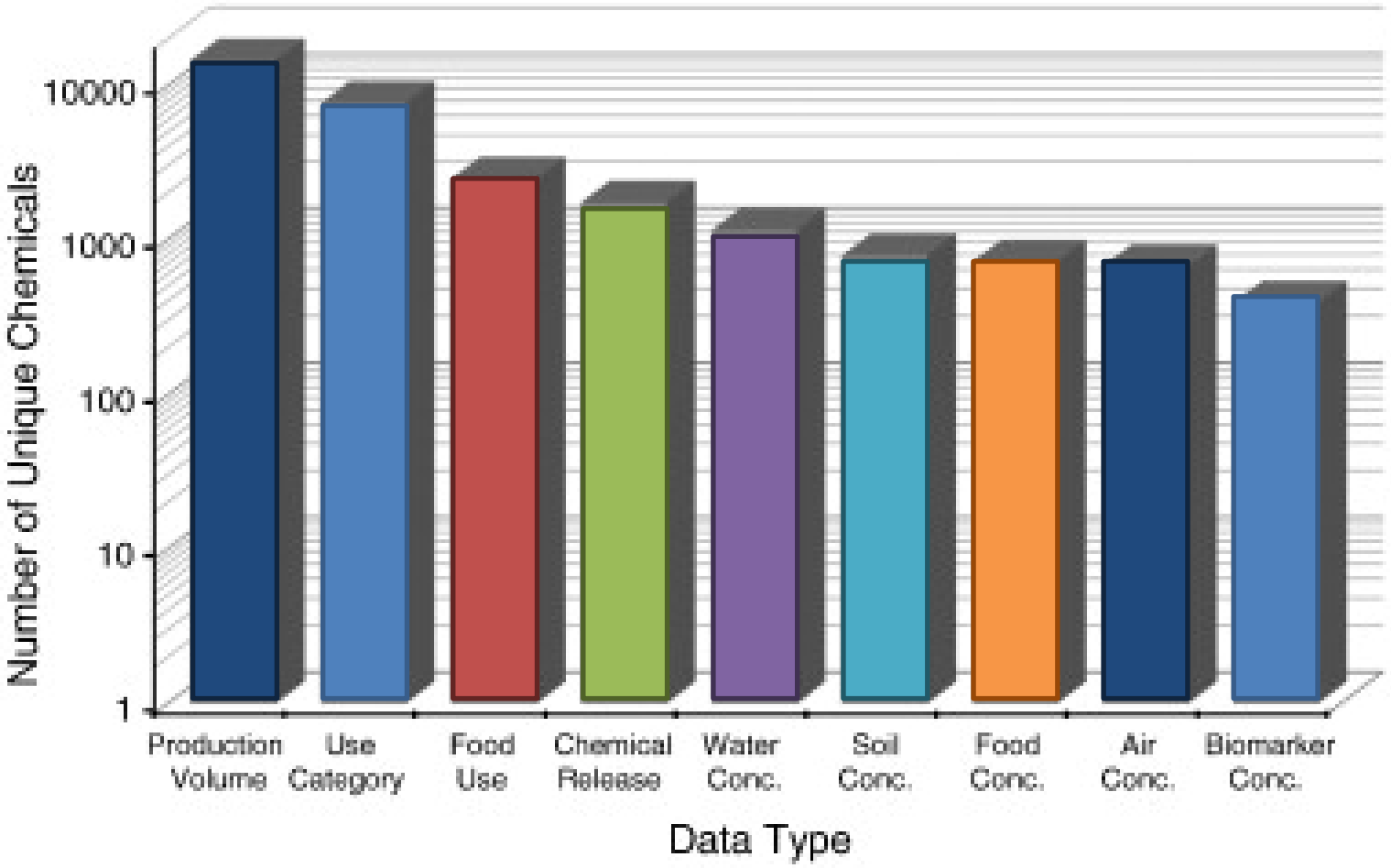
January 5, 2017

Three Components for Chemical Risk

United States Environmental Protection Agency



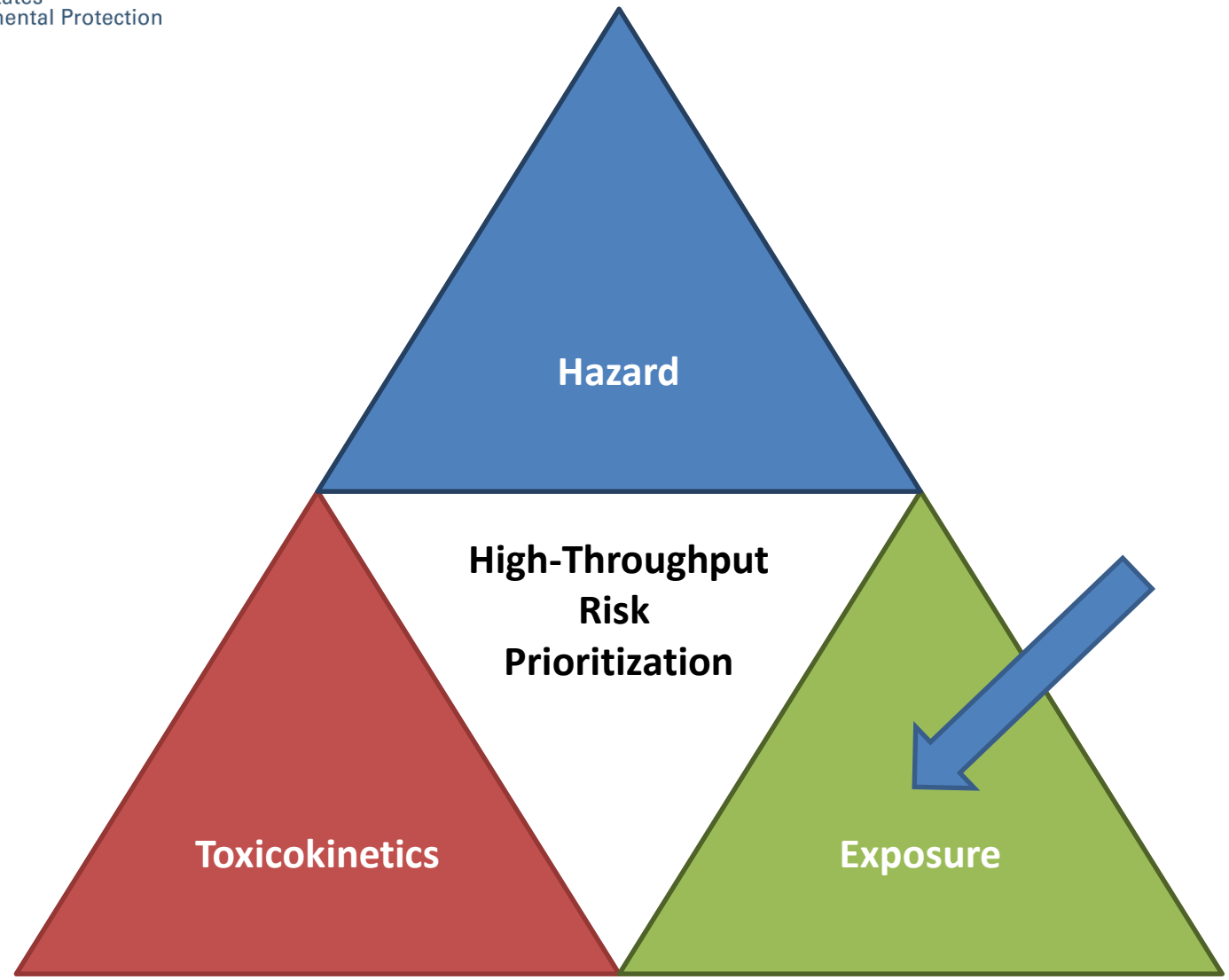
Limited Available Data for Exposure Estimations



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

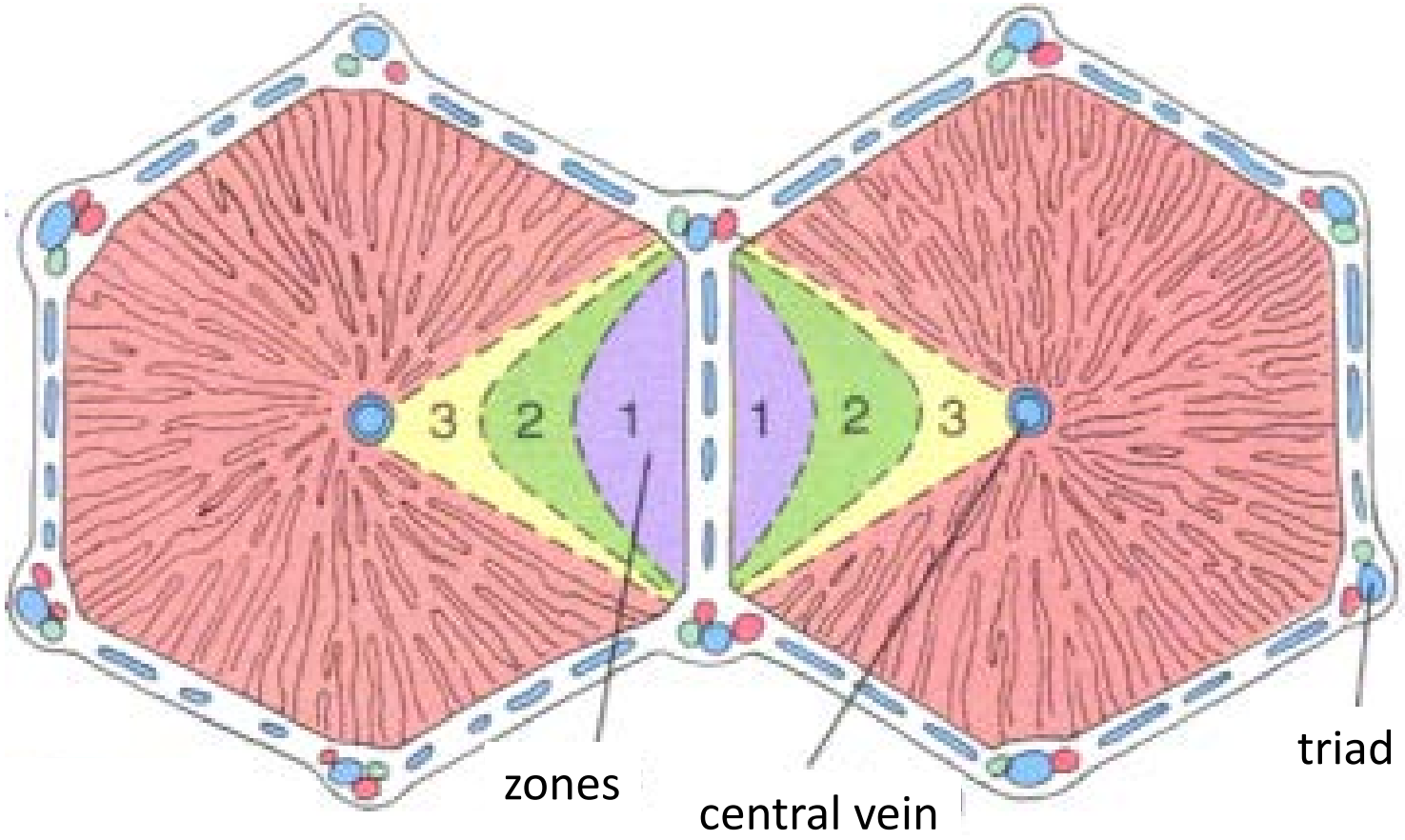
New Exposure Data and Models

United States Environmental Protection Agency



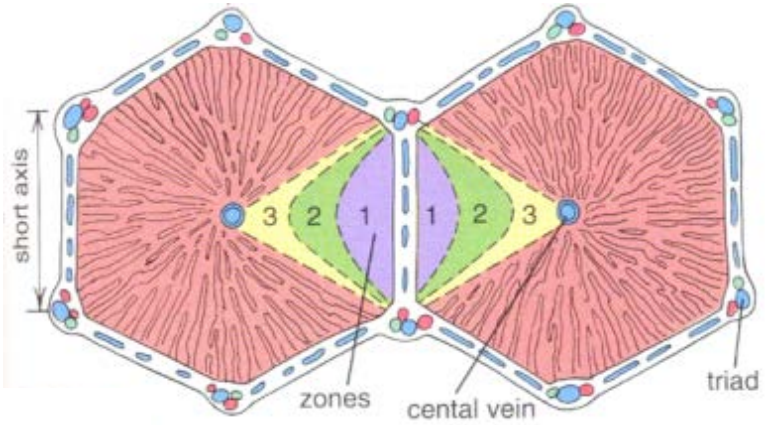
Computational Approaches: Modeling

The liver is composed of hepatic lobules



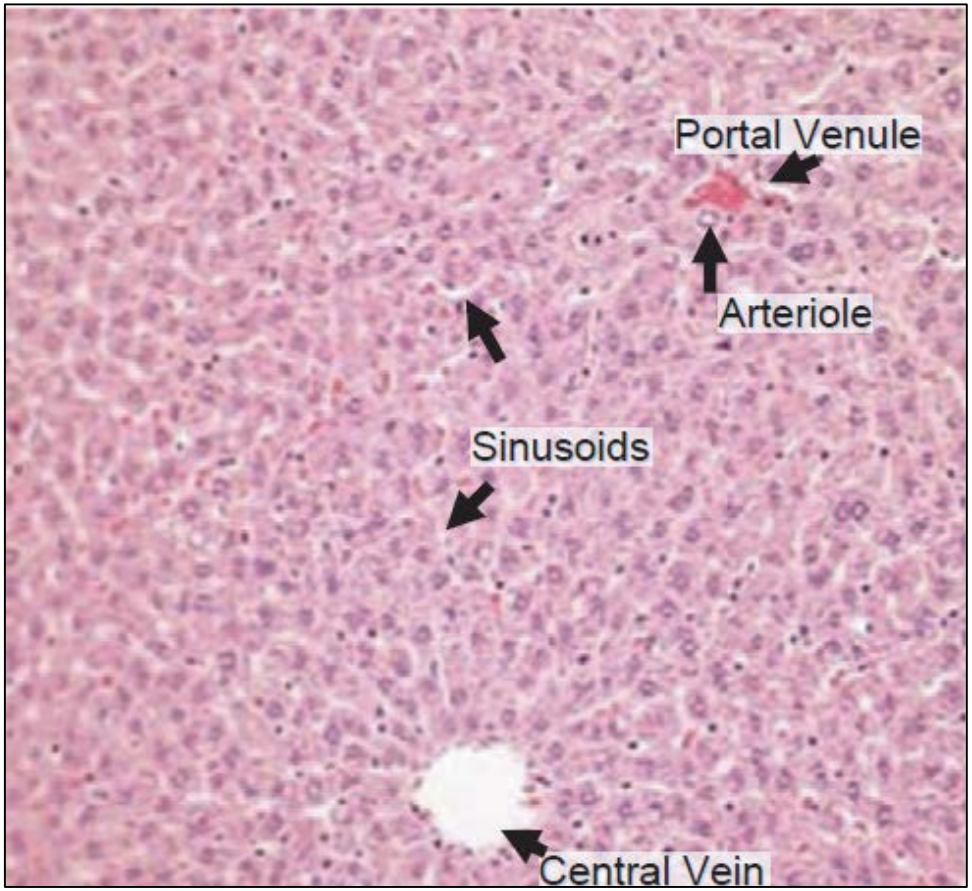
University of South Dakota

When Models Meet Real Biological Variability



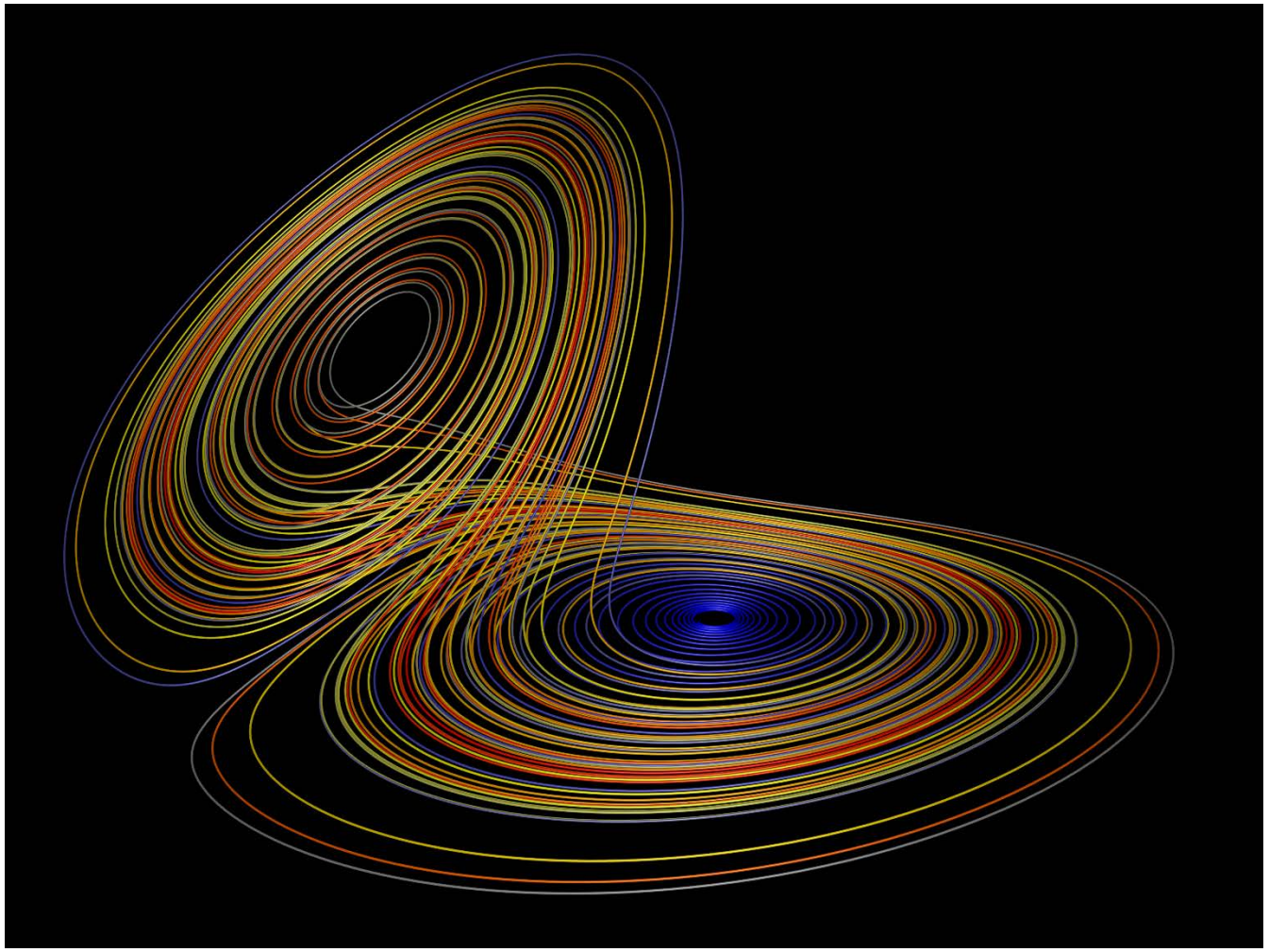
- Actual lobules are much messier (variable) (Crawford, et al., 1988)
- Further, pathology calls are actually quite subjective
- You need to understand both the system being modeled and the data generation process

Rockett et al. (2006)



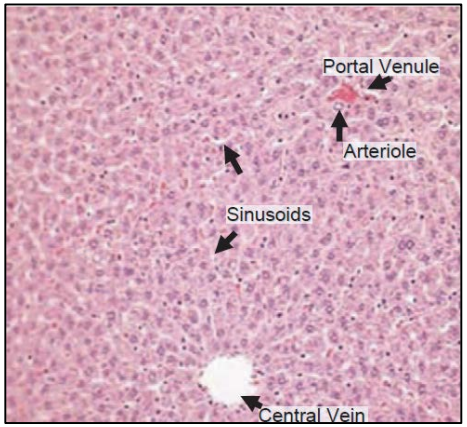
Emergent Phenomena

- The underlying rules of system may constrain the observed states
- For example, each hepatocyte needs to get oxygen
- Heaptocyte state depends on degree of hypoxia, endogenous chemical signaling, and history of exposure to exogenous chemicals



Lorenz Attractor, Paul Bourke (1997)

Pattern Recognition



Rockett et al. (2006)

Teatra Sociale, Como, Italy

- The underlying rules of system
- Each hepatocyte needs to get oxygen, state depends on degree of hypoxia, endogenous chemical signaling, and history of exposure to exogenous chemicals

What do we know about exposure?

Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination Survey (NHANES) provides an important tool for monitoring public health

Large, ongoing CDC survey of US population: demographic, body measures, medical exam, biomonitoring (health and exposure), …

Designed to be representative of US population according to census data

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

Includes measurements of:

- Body weight
- Height
- **Chemical analysis of blood and urine**

The Structure of Chemical Exposure

United States Environmental Protection Agency

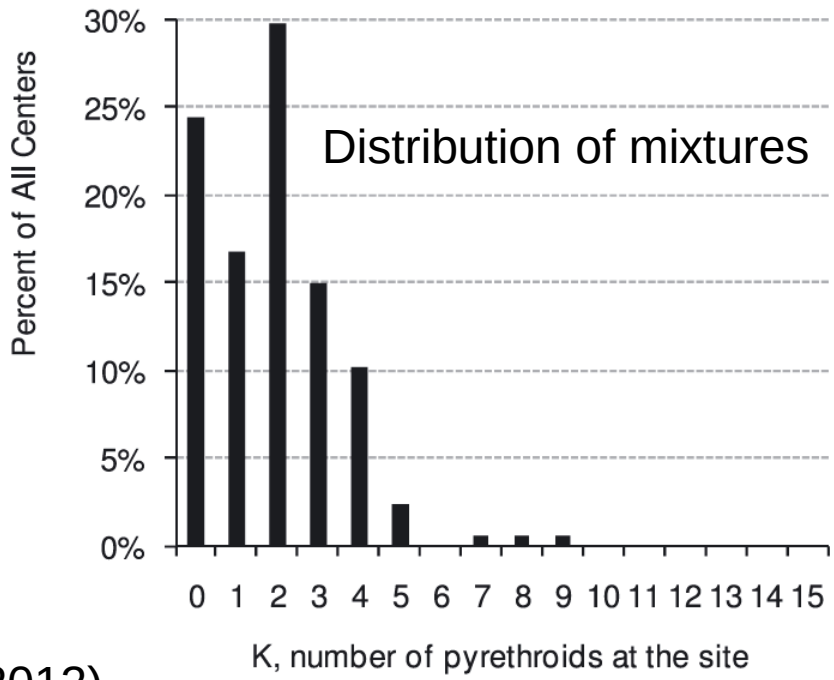
finch species

	Cuba	Hispanolia	Jamaica	Puerto Rico	Guadeloupe	
Loxigilla noxis	0	0	0	0	1	**1**
Melanospiza richardsoni	0	0	0	0	0	**0**
Tiara olivacea	1	1	1	1	0	**4**
Tiara bicolor	0	1	1	1	1	**4**
Tiara canora	1	0	0	0	0	**1**
Loxipasser anoxanthus	0	0	1	0	0	**1**
	2	**2**	**3**	**2**	**2**	**11**

chemical species

	site 1	site 2	site 3	site 4	site 5	
chemical 1	1	0	0	0	1	**2**
chemical 2	1	1	0	1	1	**4**
chemical 3	0	0	0	0	1	**1**
chemical 4	1	0	0	0	0	**1**
chemical 5	0	0	1	0	0	**1**
chemical 6	0	0	1	0	0	**1**
	3	**1**	**2**	**1**	**3**	**10**

- For **n** chemicals **2^n** combinations are possible
  - However, not all are observed
- Diamond (1975): Not all finch species present on all islands of Caribbean
- Tornero-Velez et al. (2012): Not all chemical combinations present at all sites



Tornero-Velez et al. (2012)

Kapraun et al. (2017) EHP

- Targeted analytical chemistry used to quantitate concentration of specific chemicals in urine
  - Samples must be divided up for each chemical tested
  - NHANES cohort divided up to allow enough sample for testing all chemicals

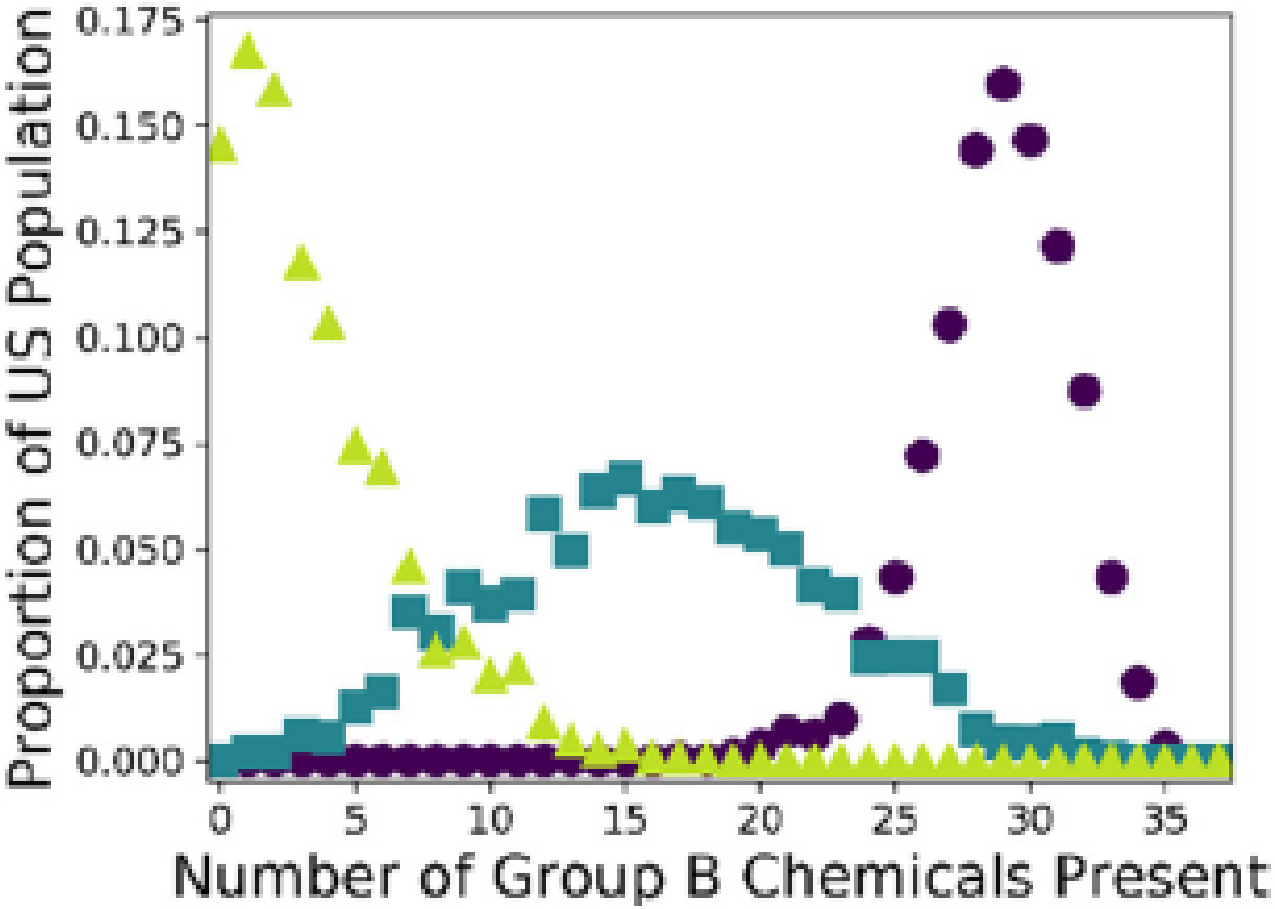
Table 4. Summary information for each of the National Health and Nutrition Examination Survey (NHANES) 2009–2010 subsamples.

Category	Subsample A	Subsample B	Subsample C
Number of subjects	2,741	2,736	2,132
Number of chemicals	29	37	40
Maximum weight	476,883.0	426,061.1	413,068.1
Minimum weight	14,002.7	13,975.1	12,659.3
Sum of weights	258,281,689.4	272,911,664.0	226,021,580.6
Records needed	18,445.1	19,528.5	17,854.1

- We will focus on “Sub-sample B” PAHs, Phenols, Pesticides, and Phthalates

Co-Occurrence of Chemicals in Individuals

The number of chemicals (out of 37) “present” in individuals depends upon where you set the limit

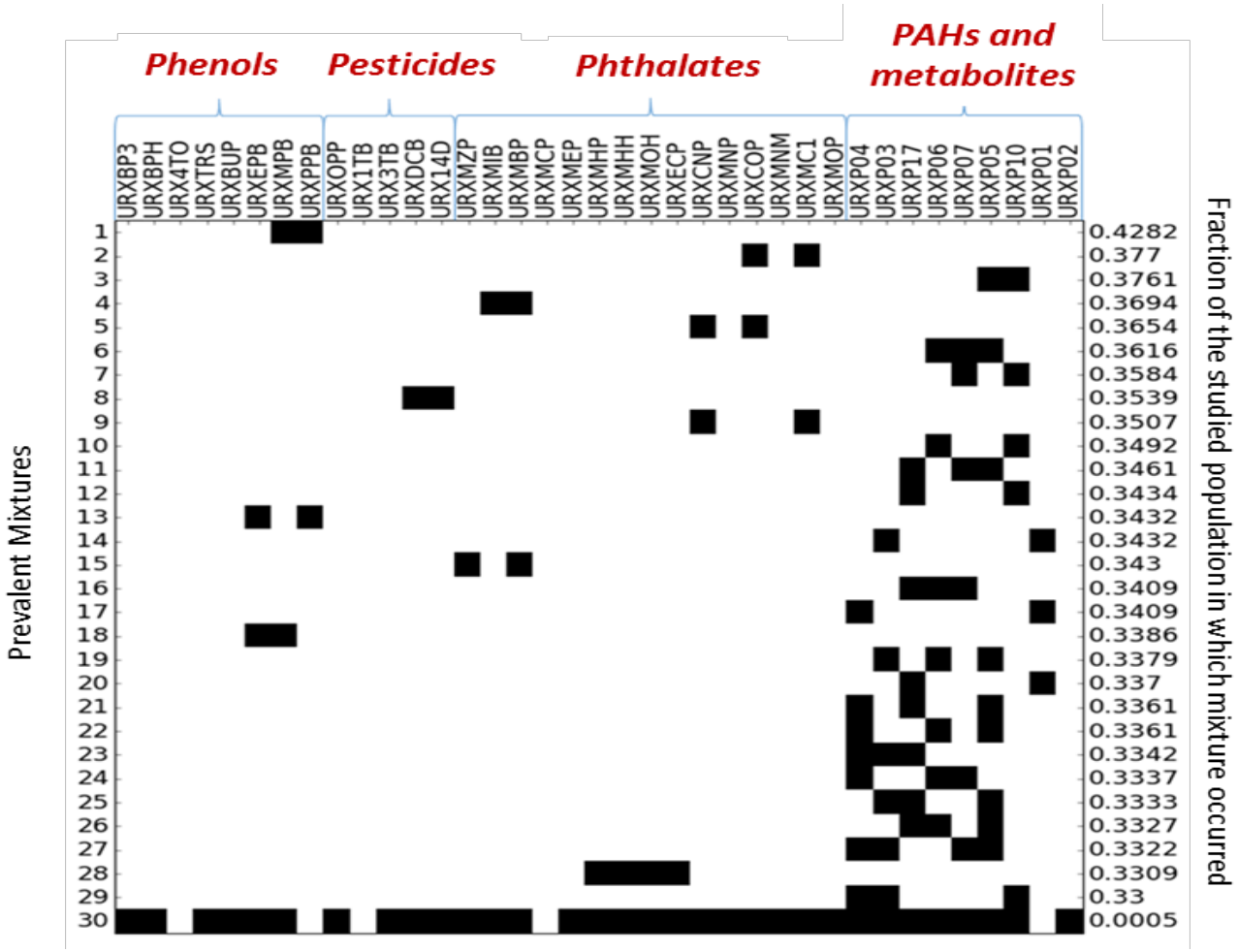


Ideally we would use some sort of chemical toxicity informed point of departure but don’t have that for all chemicals

Kapraun et al. (2017)

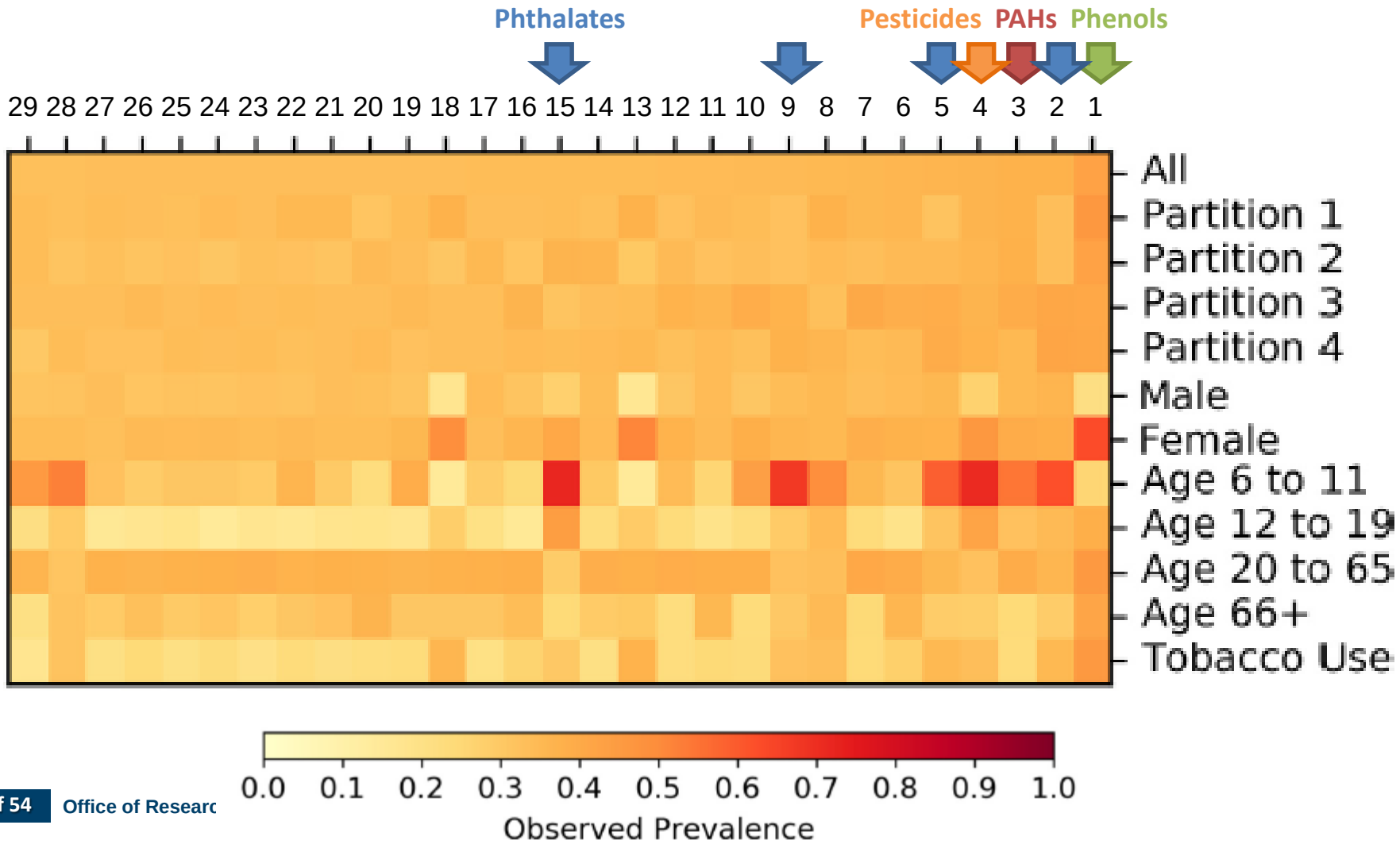
Identifying Prevalent Mixtures

- We are using data-mining methods (frequent itemset mining or FIM, Borgelt, 2012) to identify combinations of items (chemicals) that co-occur together within samples from same individual
- Used total population median concentration as threshold for “presence”
- Identified a few dozen mixtures present in >30% of U.S. population



Kapraun et al. (2017)

Demographic-Specific Prevalence of Combinations

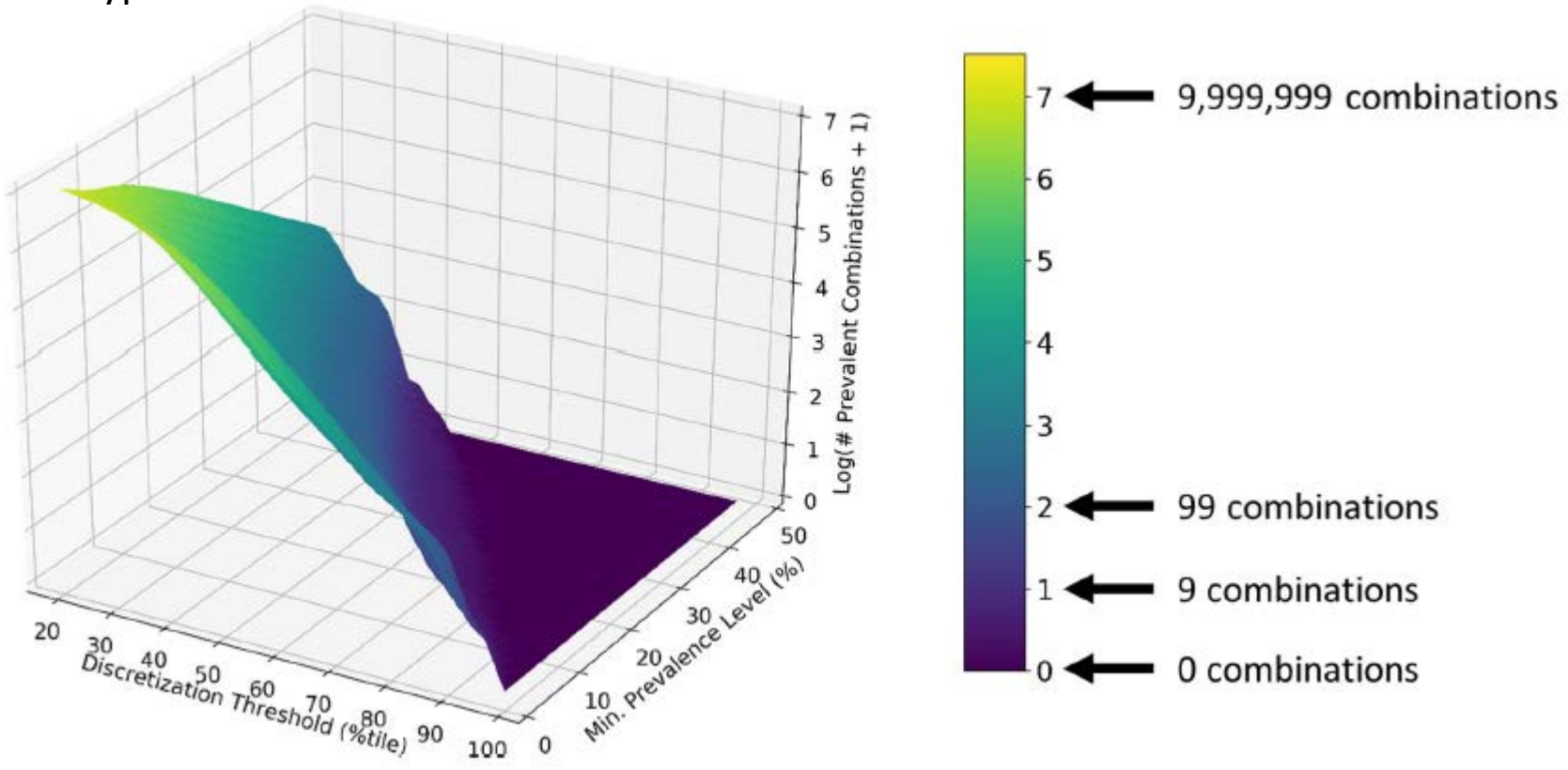


Kapraun et al. (2017)

United States Environmental Protection Agency

A Testable Number of Combinations

While high throughput screening (HTS) allows thousands of tests, there are millions of hypothetical combinations



"Exposure based priority setting" (NAS, 2017) allows identification of most important mixtures to test

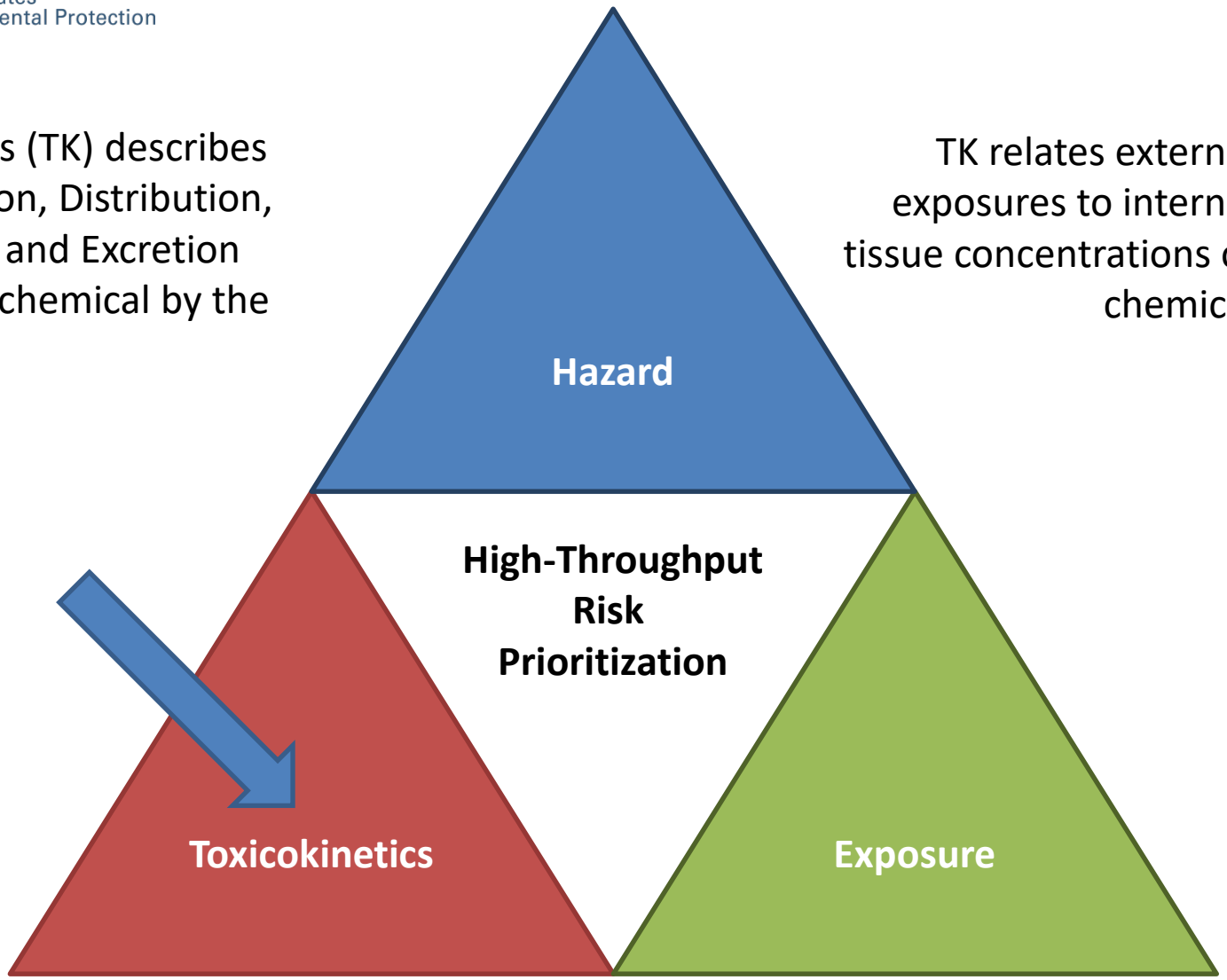
Kapraun et al. (2017)

High Throughput Toxicokinetics (HTTK)

United States Environmental Protection Agency

Toxicokinetics (TK) describes the Absorption, Distribution, Metabolism, and Excretion (ADME) of a chemical by the body

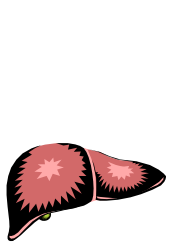
TK relates external exposures to internal tissue concentrations of chemical

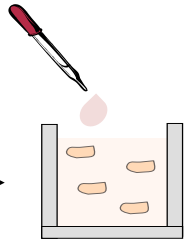


High-Throughput Toxicokinetics (HTTK)

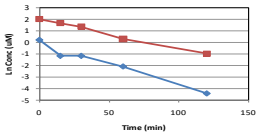
United States Environmental Protection Agency

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





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

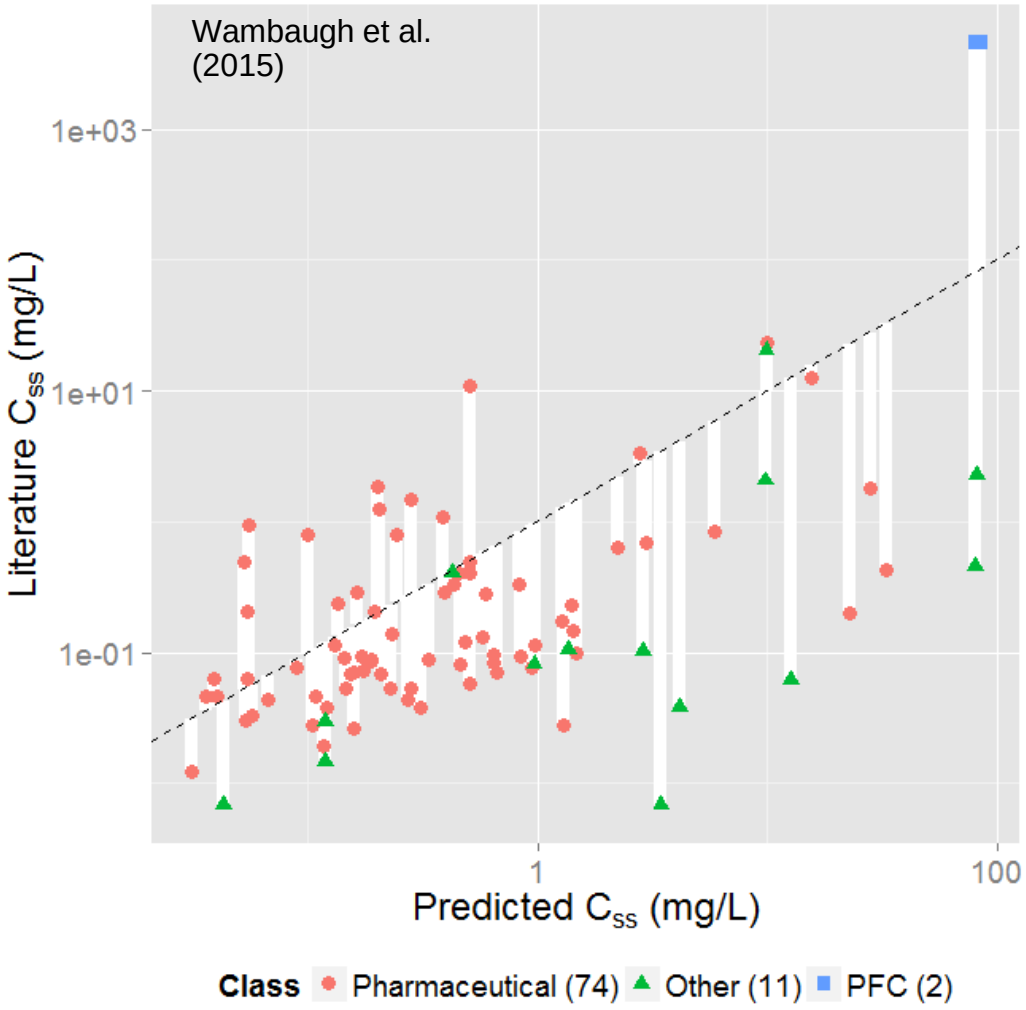
Human Plasma (6 donor pool)

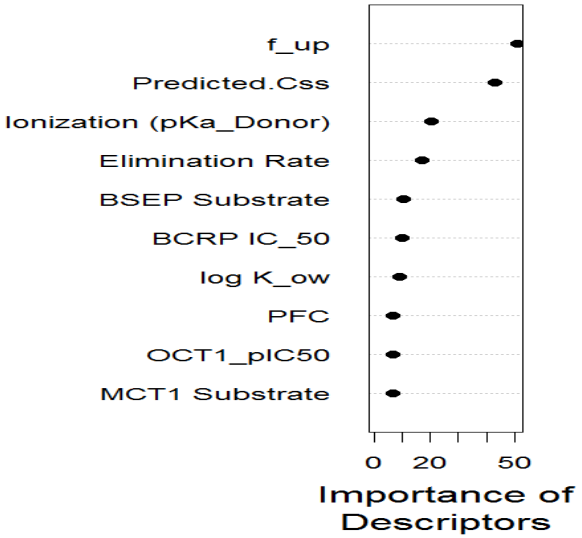
Plasma Protein Binding (f_{up})

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

Figure from Barbara Wetmore

Evaluating Predictions of Steady-State Plasma Concentration (C_{ss})

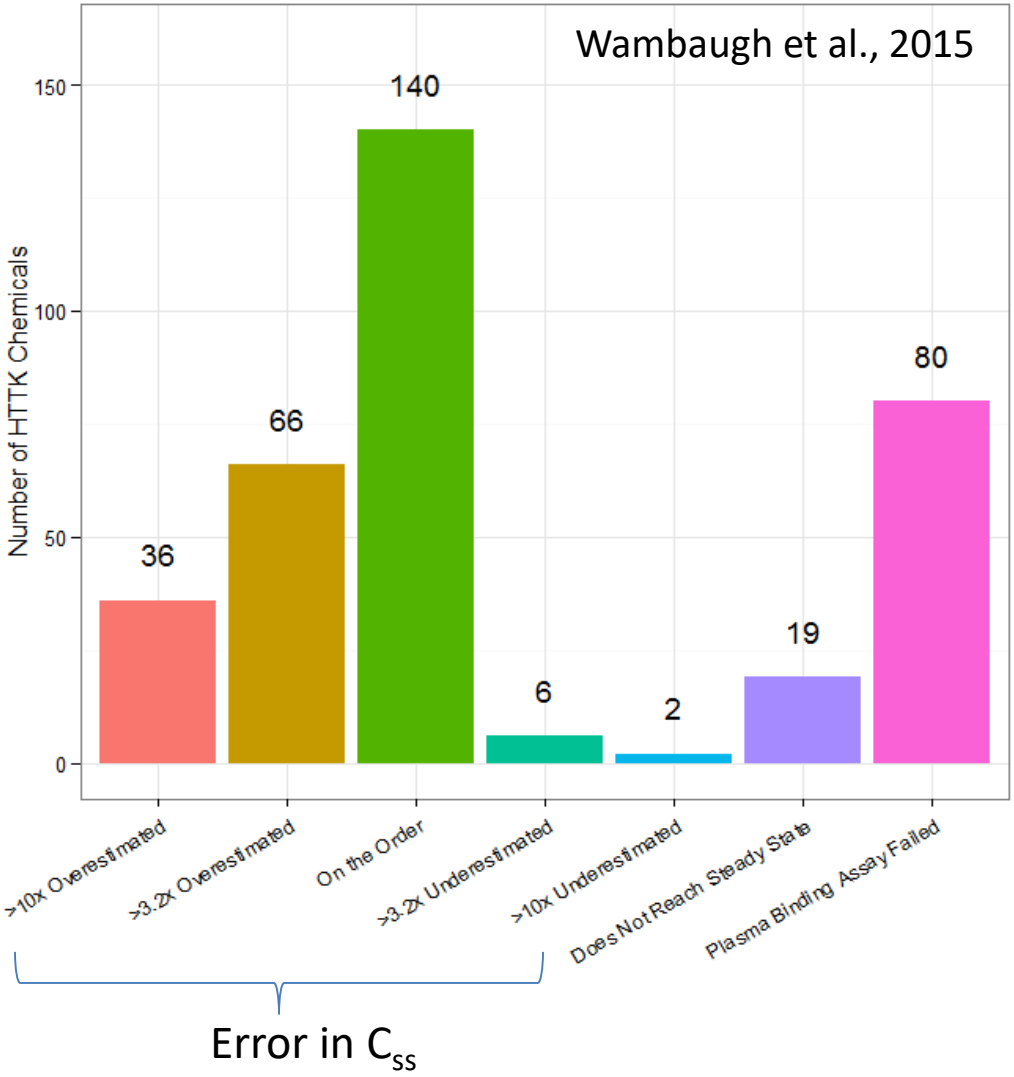




- When we compare the C_{ss} predicted from *in vitro* HTTK with *in vivo* C_{ss} values determined from the literature we find limited correlation (R^2 ~0.34)
- The dashed line indicates the identity (perfect predictor) line:
  - Over-predict for 65
  - Under-predict for 22
- The white lines indicate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

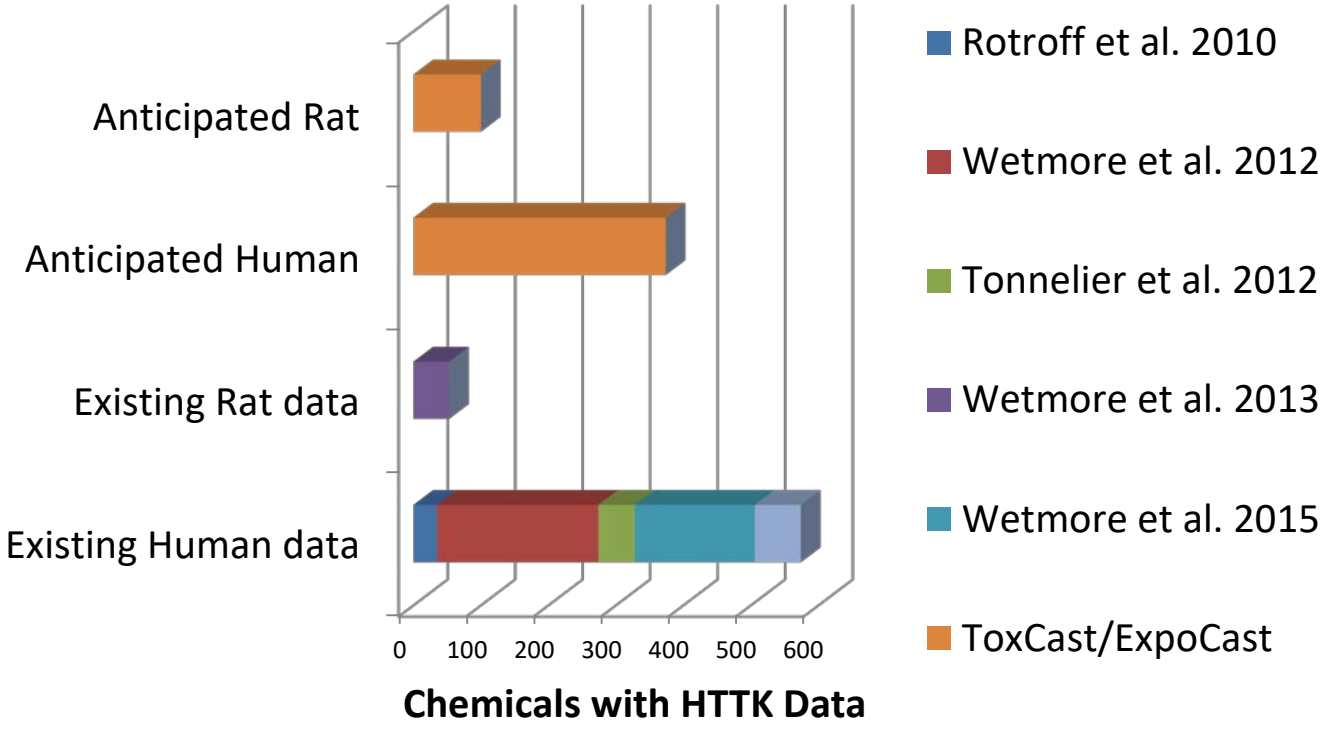
Predicting Error in HTTK Predictions

- For most compounds in the environment there will be no clinical trials
- Uncertainty must be well characterized
  - We compare to *in vivo* data to get **empirical estimates of HTTK uncertainty**
  - Any approximations, omissions, or mistakes should work to increase the estimated uncertainty when evaluated systematically across chemicals
- Through comparison to *in vivo* data, a cross-validated (Random Forest, Breiman, 2001) predictor of success or failure of HTTK has been constructed
- We also have categories for chemicals that do not reach steady-state or for which plasma binding assay fails



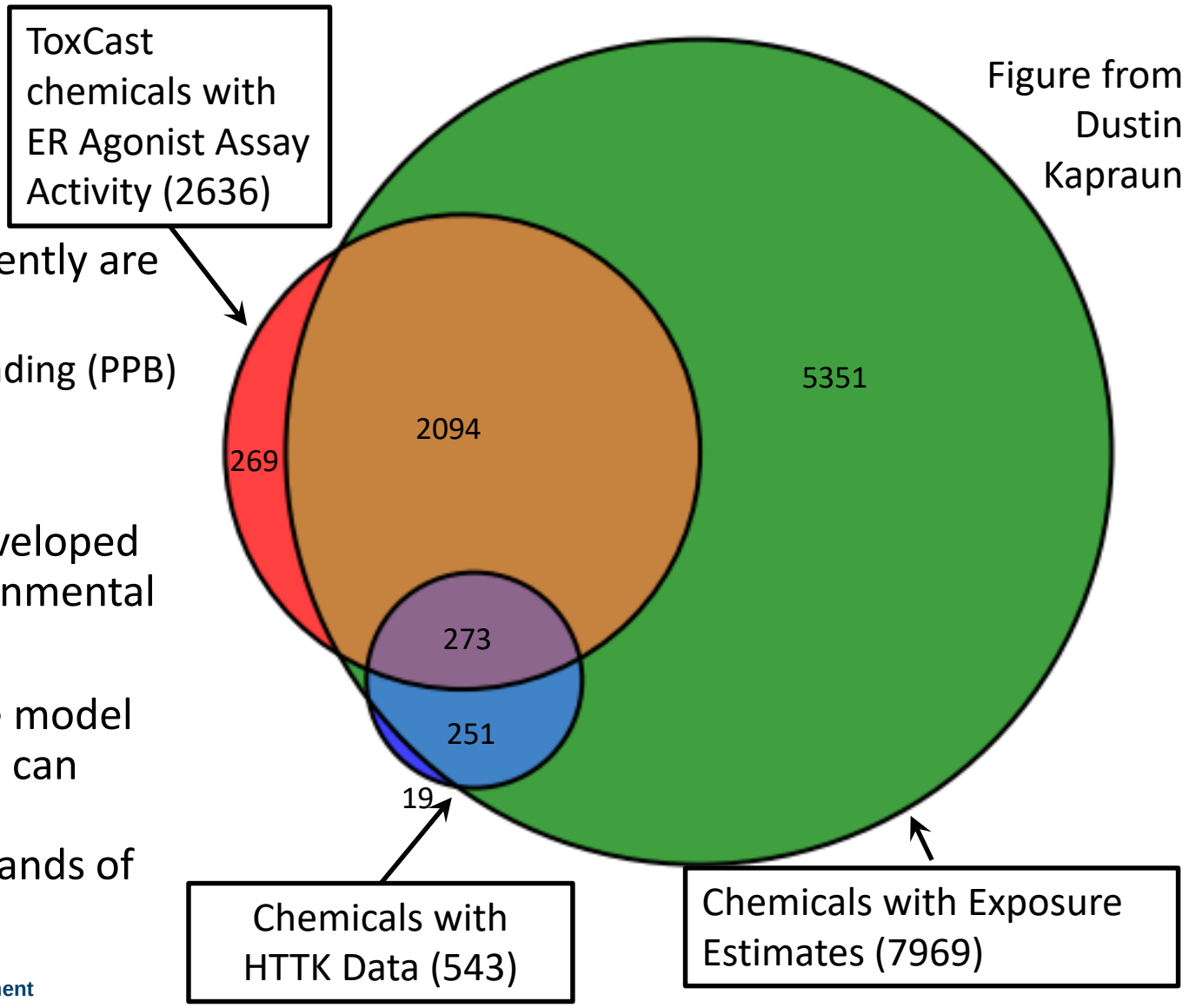
Chemicals with HTTK Data

- 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



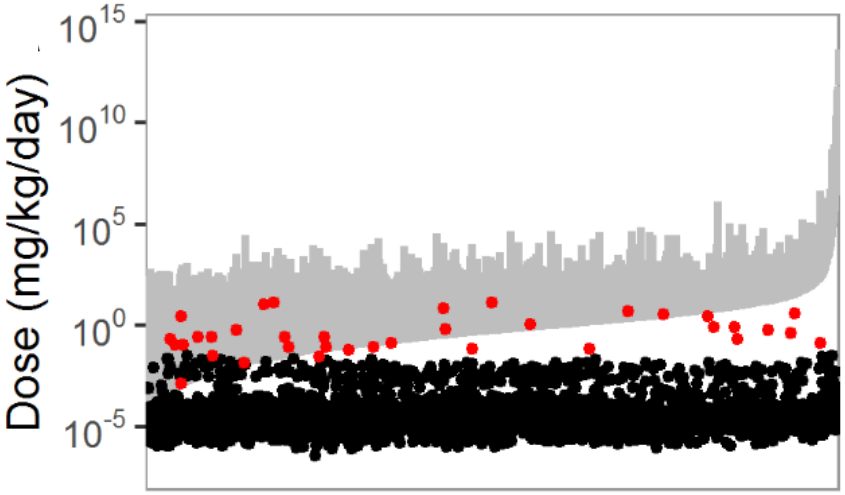
Predicting Critical TK Parameters

- 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

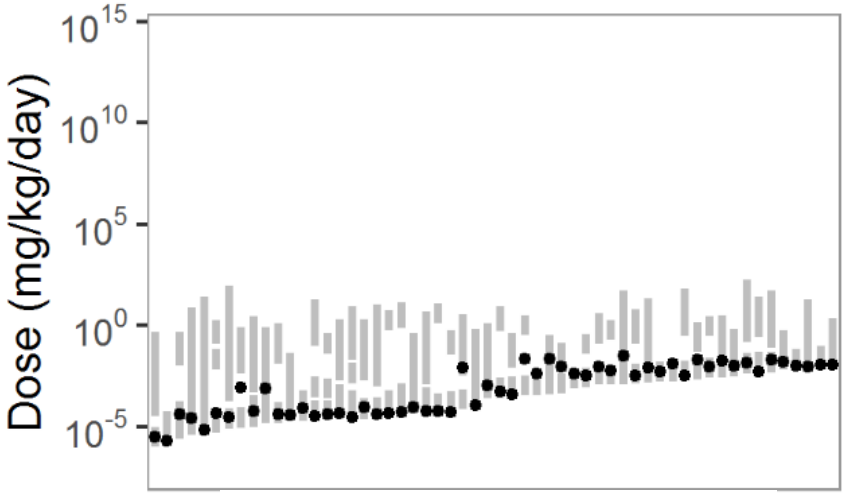


Using Predicted HTTK for Risk Prioritization

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

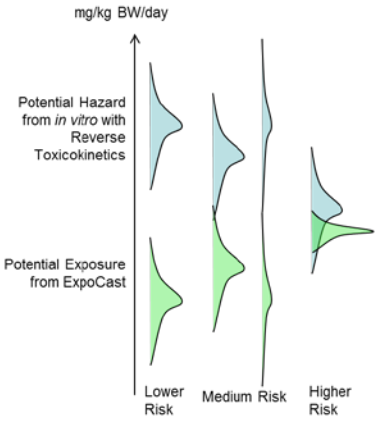


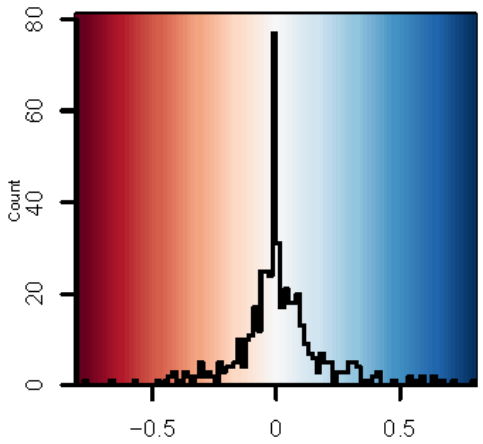
56 compounds with potential *in vivo* biological interaction at or above estimated environmental exposures

Sipes et al., (2017)

Life-stage and Demographic Specific Predictions

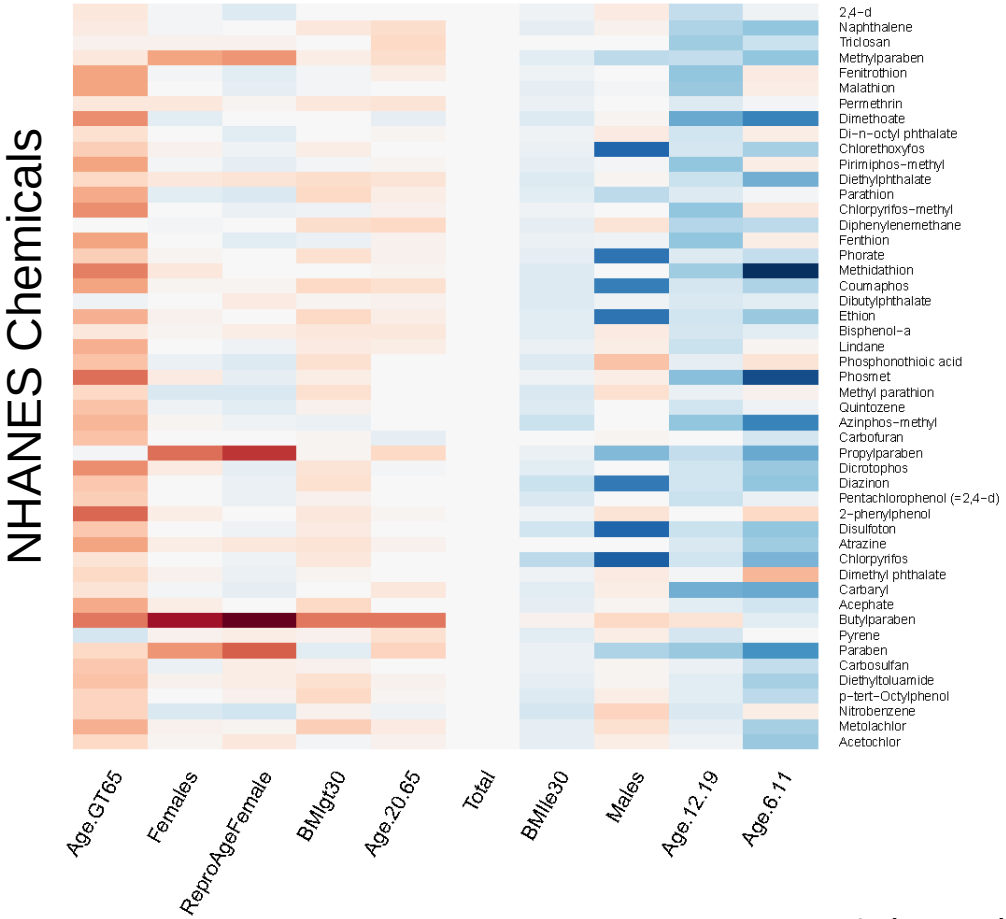
- Can calculate margin between bioactivity and exposure for specific populations





Change in Risk Relative to Total Population

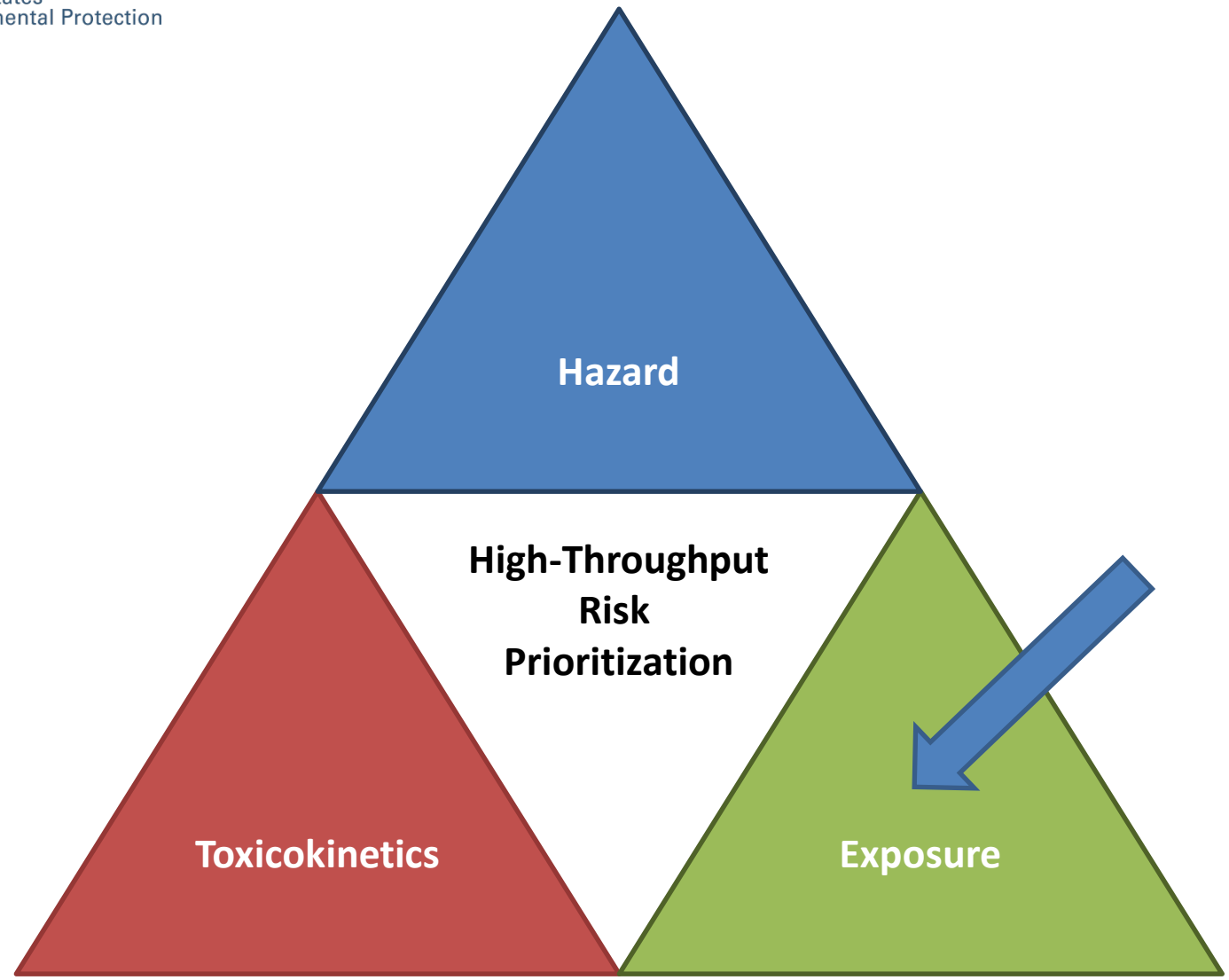
Change in Activity:Exposure Ratio



Ring *et al*. (2017)

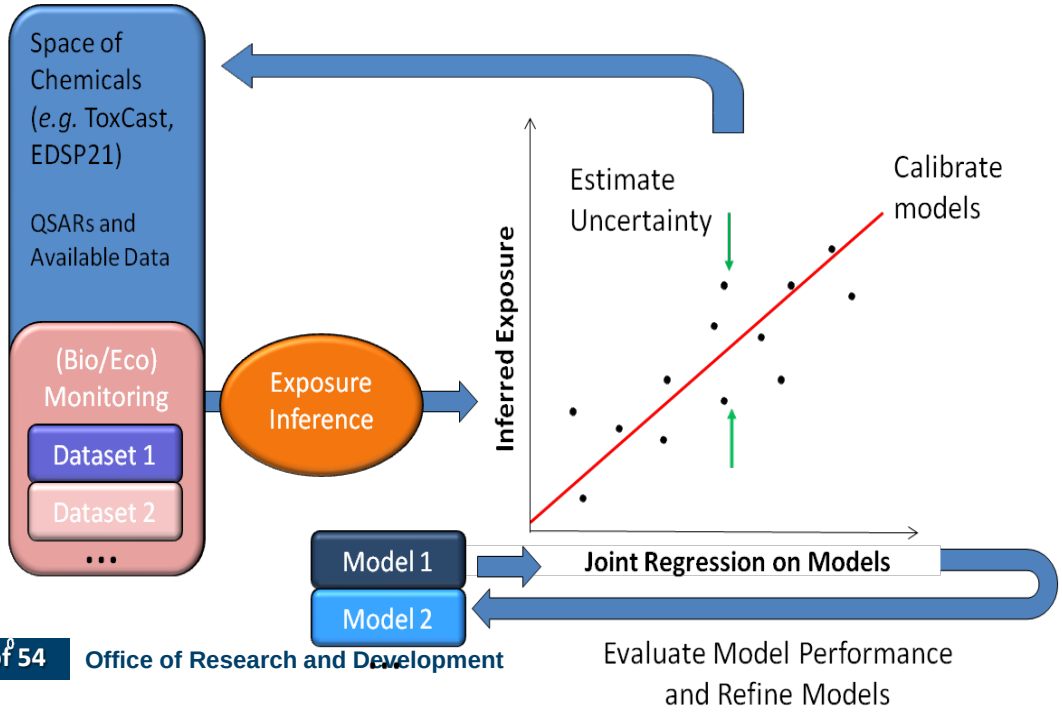
New Exposure Data and Models

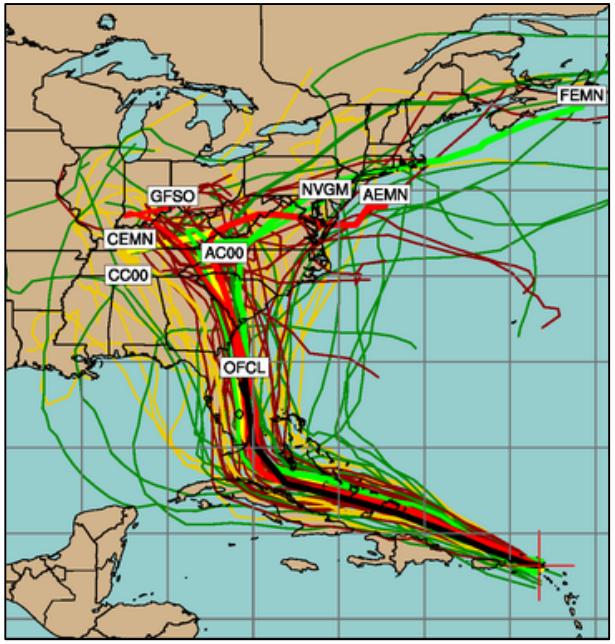
United States Environmental Protection Agency



How Do We get Exposed to Chemicals?

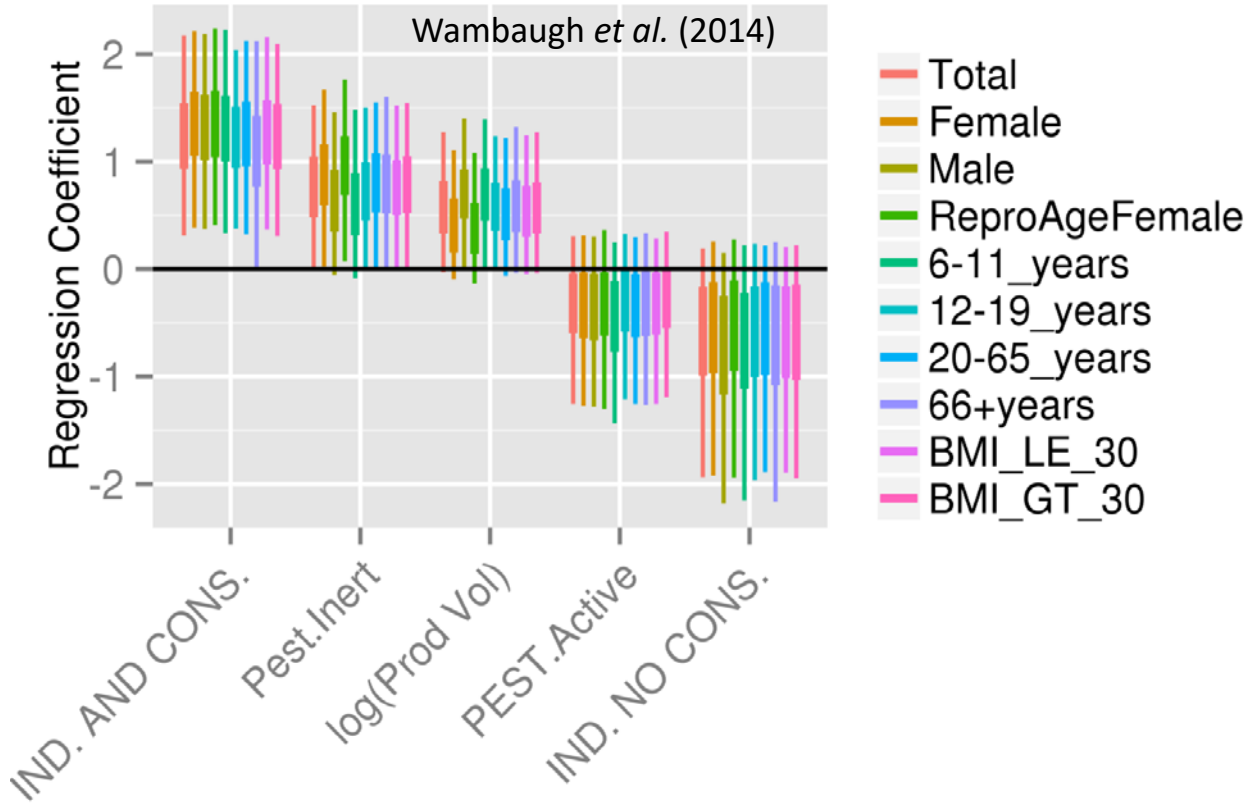
- We incorporate multiple models into consensus predictions for 1000s of chemicals within the **Systematic Empirical Evaluation of Models (SEEM) framework** (Wambaugh et al., 2013, 2014)
- We evaluate/calibrate predictions with available monitoring data
- This provides information similar to a sensitivity 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





Integrating Multiple Models

Heuristics of Exposure



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

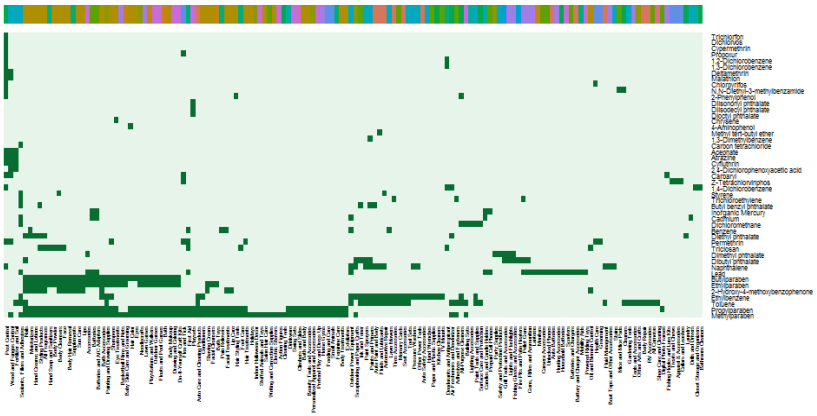
Same five predictors work for all NHANES demographic groups analyzed – stratified by age, sex, and body-mass index:

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

Chemical Use Identifies Relevant Pathways

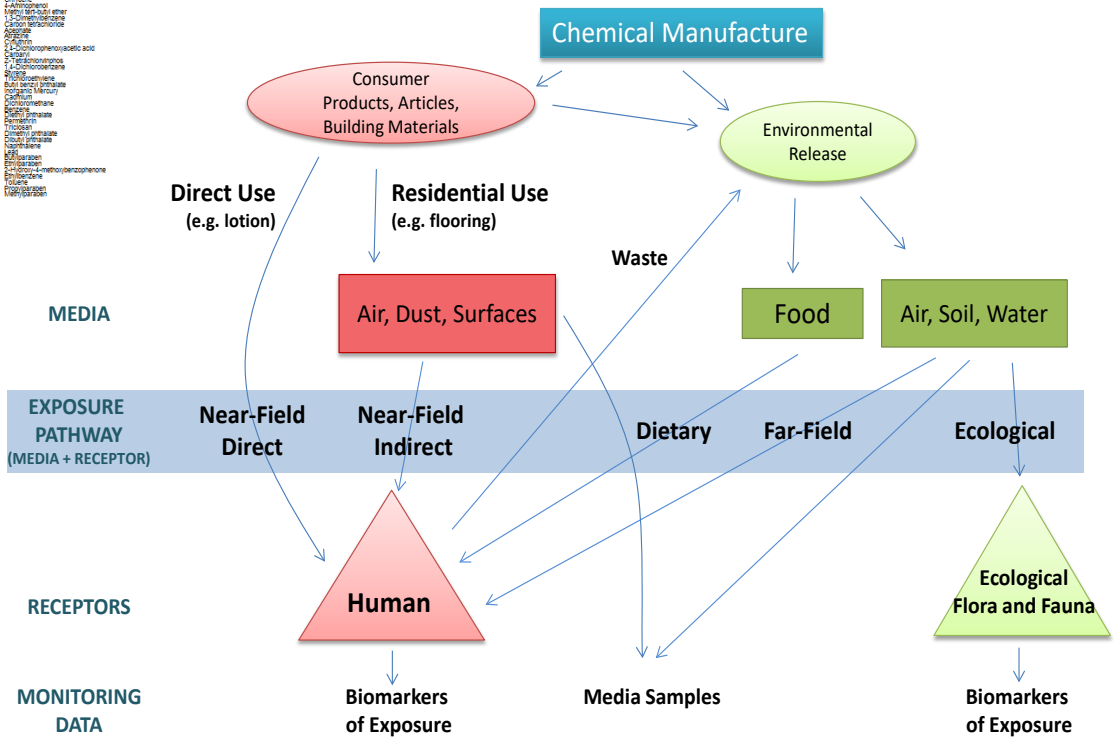
>2000 chemicals with Material Safety Data Sheets (MSDS) in CPCPdb (Goldsmith *et al.*, 2014)

106 NHANES Chemicals



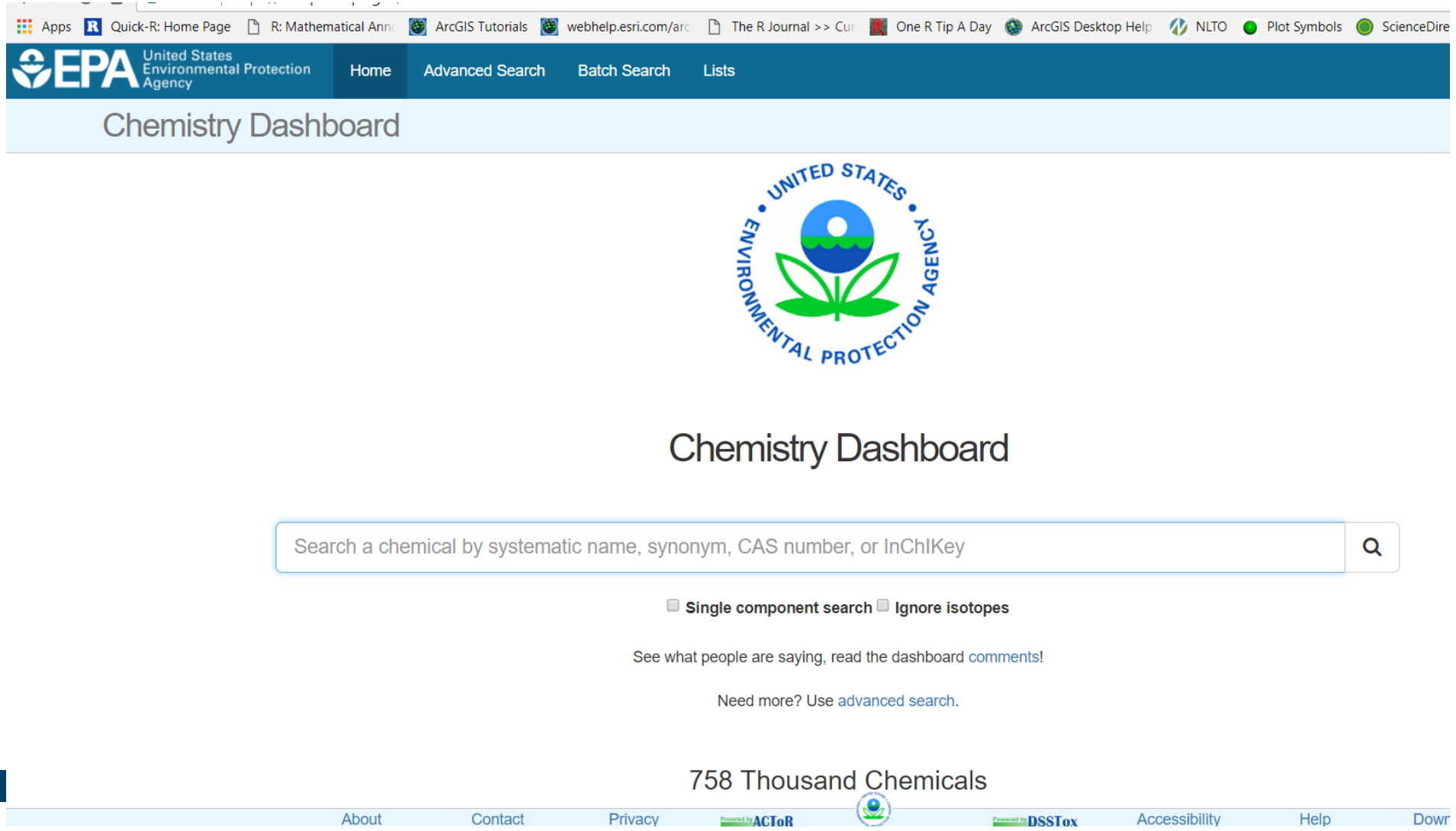
- Apparel
- Auto and Tires
- Baby
- Beauty
- Craft and Party Supply
- Electronics
- Grocery
- Health
- Home
- Home Improvement
- Patio and Garden
- Pets
- Sports and Outdoors
- Toys

Some pathways have much higher average exposures!

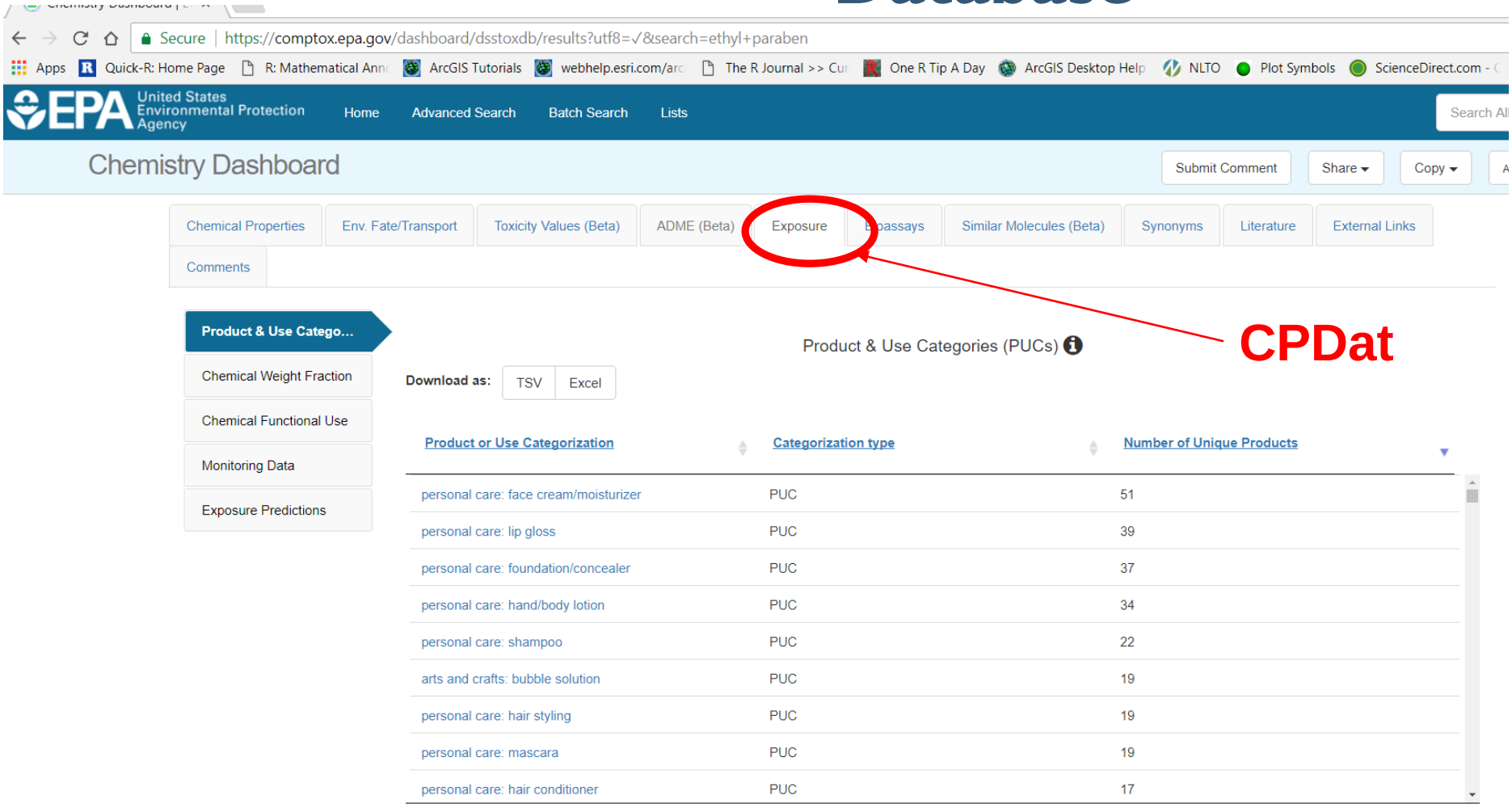


Near field sources have been known to be important at least since 1987 – see Wallace, *et al.*

The Chemistry Dashboard
http://comptox.epa.gov/

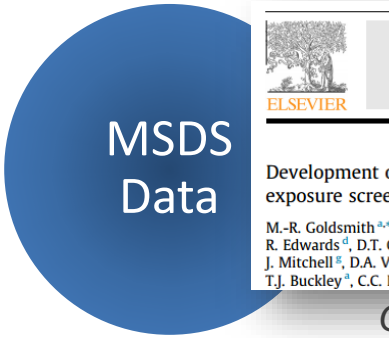


Chemicals and Products Database



Chemical Use: Chemicals and Products Database

United States Environmental Protection Agency




Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

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

M.-R. Goldsmith, C.M. Grulke, R.D. Brooks, T.R. Transue, Y.M. Tan, A. Frame, P.P. Egeghy, R. Edwards, D.T. Chang, R. Tornero-Velez, K. Isaacs, A. Wang, J. Johnson, K. Holm, M. Reich, J. Mitchell, D.A. Vallero, L. Phillips, M. Phillips, J.F. Wambaugh, R.S. Judson, T.J. Buckley, C.C. Dary

Occurrence and quantitative chemical composition


Contents lists available at ScienceDirect

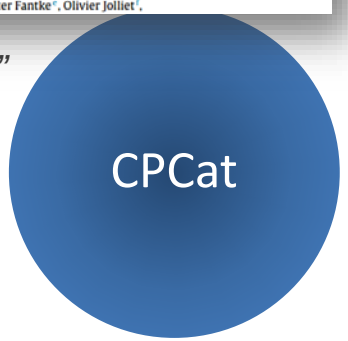
Toxicology Reports

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

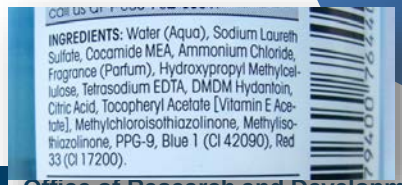
Exploring consumer exposure pathways and patterns of use for chemicals in the environment

Kathie L. Dionisio, Alicia M. Frame, Michael-Rock Goldsmith, John F. Wambaugh, Alan Liddell, Tommy Cathey, Doris Smith, James Vail, Alexi S. Ernstoff, Peter Fantke, Olivier Jolliet

Broad "index" of chemical uses



Occurrence data


INGREDIENTS: Water (Aqua), Sodium Laureth Sulfate, Cocamide MEA, Ammonium Chloride, Fragrance (Parfum), Hydroxypropyl Methylcellulose, Tetrasodium EDTA, DMDM Hydantoin, Citric Acid, Tocopheryl Acetate [Vitamin E Acetate], Methylchloroisothiazolinone, Methylisothiazolinone, PPG-9, Blue 1 (CI 42090), Red 33 (CI 17200).

Targeted and non-targeted measurement of chemicals in consumer products

Also available as R Package

Slide from Kristin Isaacs

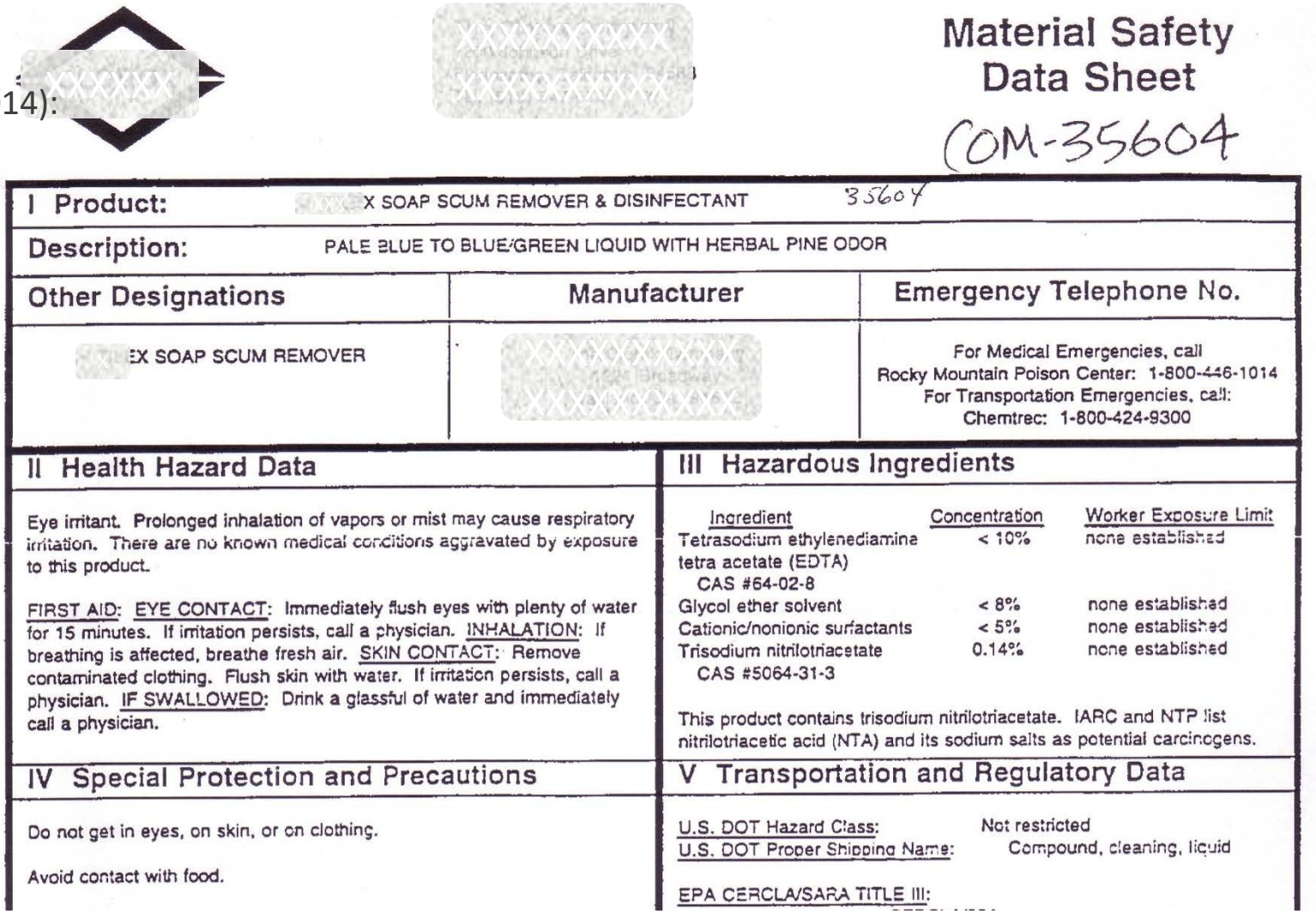
Material Safety Data Sheets

United States Environmental Protection Agency

Goldsmith et al. (2014):

- ~20,000 product-specific Material Safety Data Sheets (MSDS) curated
- ~2,400 chemicals

Product-specific uses determined using web spider to click through categories (e.g., home goods, bath soaps, baby) to find each product



Material Safety Data Sheet

COM-35604

I Product:	X SOAP SCUM REMOVER & DISINFECTANT 35604	
Description:	PALE BLUE TO BLUE/GREEN LIQUID WITH HERBAL PINE ODOR	
Other Designations	Manufacturer	Emergency Telephone No.
EX SOAP SCUM REMOVER		For Medical Emergencies, call Rocky Mountain Poison Center: 1-800-446-1014 For Transportation Emergencies, call: Chemtrec: 1-800-424-9300

II Health Hazard Data

Eye irritant. Prolonged inhalation of vapors or mist may cause respiratory irritation. There are no known medical conditions aggravated by exposure to this product.

FIRST AID: EYE CONTACT: Immediately flush eyes with plenty of water for 15 minutes. If irritation persists, call a physician. INHALATION: If breathing is affected, breathe fresh air. SKIN CONTACT: Remove contaminated clothing. Flush skin with water. If irritation persists, call a physician. IF SWALLOWED: Drink a glassful of water and immediately call a physician.

III Hazardous Ingredients

Ingredient	Concentration	Worker Exposure Limit
Tetrasodium ethylenediamine tetra acetate (EDTA) CAS #64-02-8	< 10%	none established
Glycol ether solvent	< 8%	none established
Cationic/nonionic surfactants	< 5%	none established
Trisodium nitrilotriacetate CAS #5064-31-3	0.14%	none established

This product contains trisodium nitrilotriacetate. IARC and NTP list nitrilotriacetic acid (NTA) and its sodium salts as potential carcinogens.

IV Special Protection and Precautions

Do not get in eyes, on skin, or on clothing.

Avoid contact with food.

V Transportation and Regulatory Data

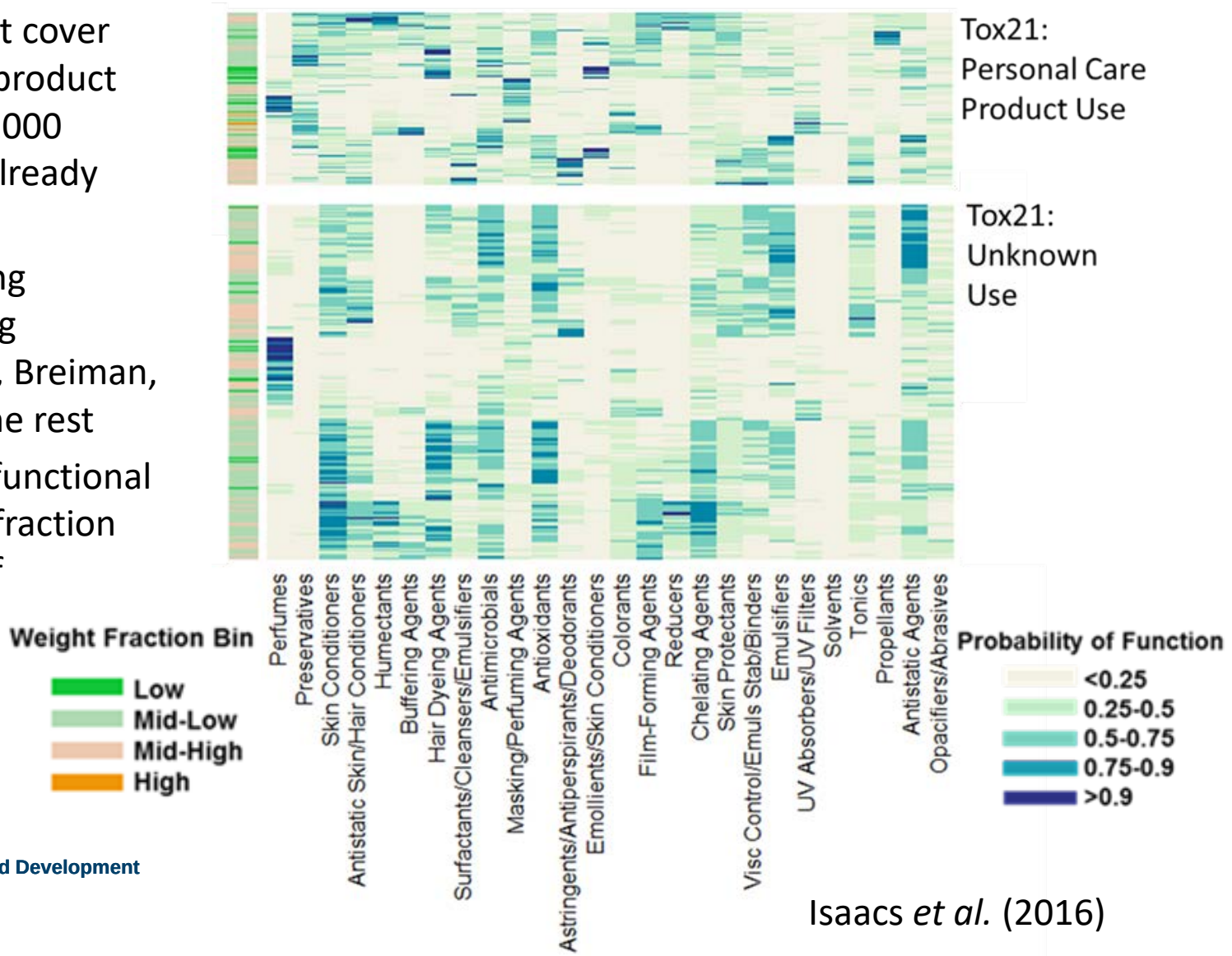
U.S. DOT Hazard Class: Not restricted

U.S. DOT Proper Shipping Name: Compound, cleaning, liquid

EPA CERCLA/SARA TITLE III:

Predicting Chemical Constituents

- CPCPdb does not cover every chemical-product combination (~2000 chemicals, but already >8000 in Tox21)
- We are now using machine learning (Random Forest, Breiman, 2001) to fill in the rest
- We can predict functional use and weight fraction for thousands of chemicals

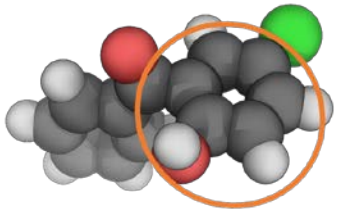


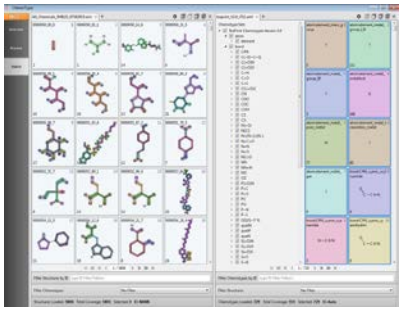
Isaacs *et al.* (2016)

Predicting Function Based on Structure

Chemical Structure and Property Descriptors

Use Database (FUSE)





Prediction of Of Potential Alternatives from Chemical Libraries

Random Forest Based Classification Models (Breiman, 2001)

Each functional model evaluated on the basis of balanced accuracy, 5-fold CV, and Y-randomization classification errors

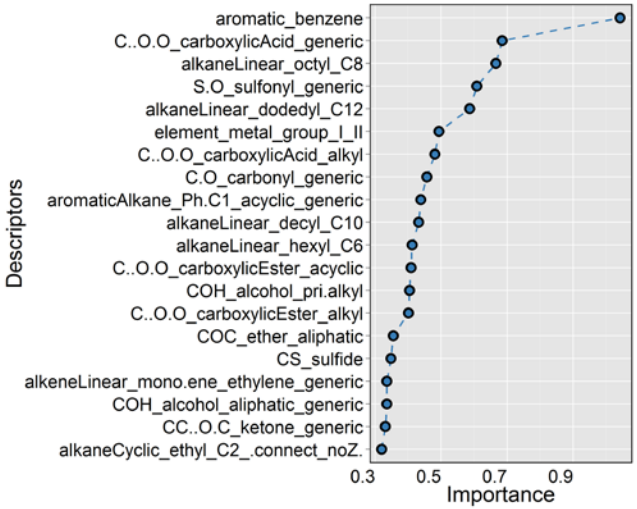
Phillips et al. (2017)

Understanding Use Predictions

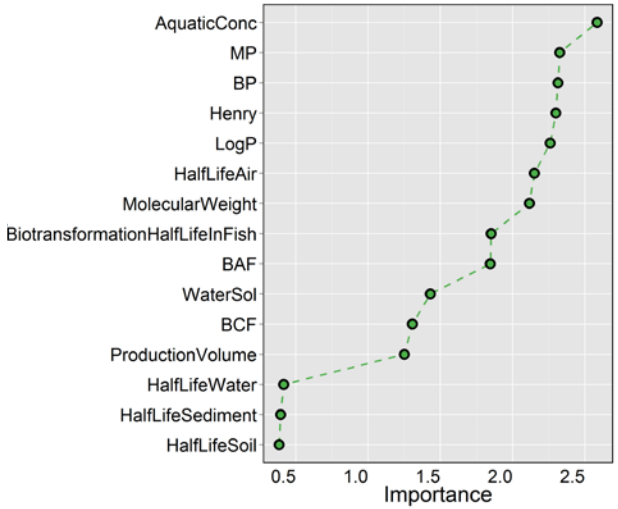
- Each functional model evaluated on the basis of balanced accuracy, 5-fold CV, and Y-randomization classification errors

Random Forest Importance for Viscosity Controller Functional Use (Failed Model)

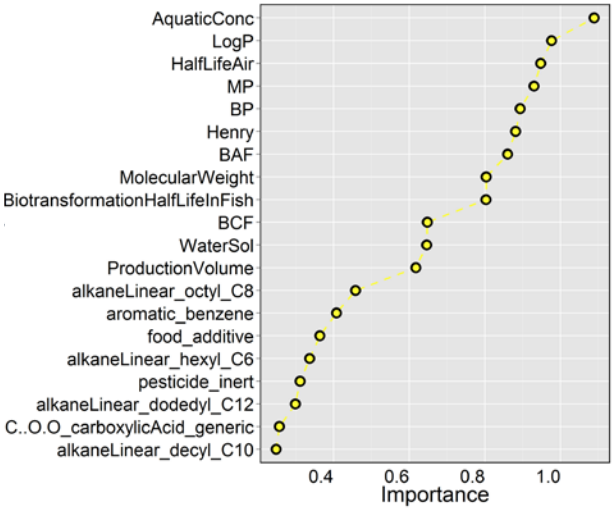
ToxPrint



EPI Suite



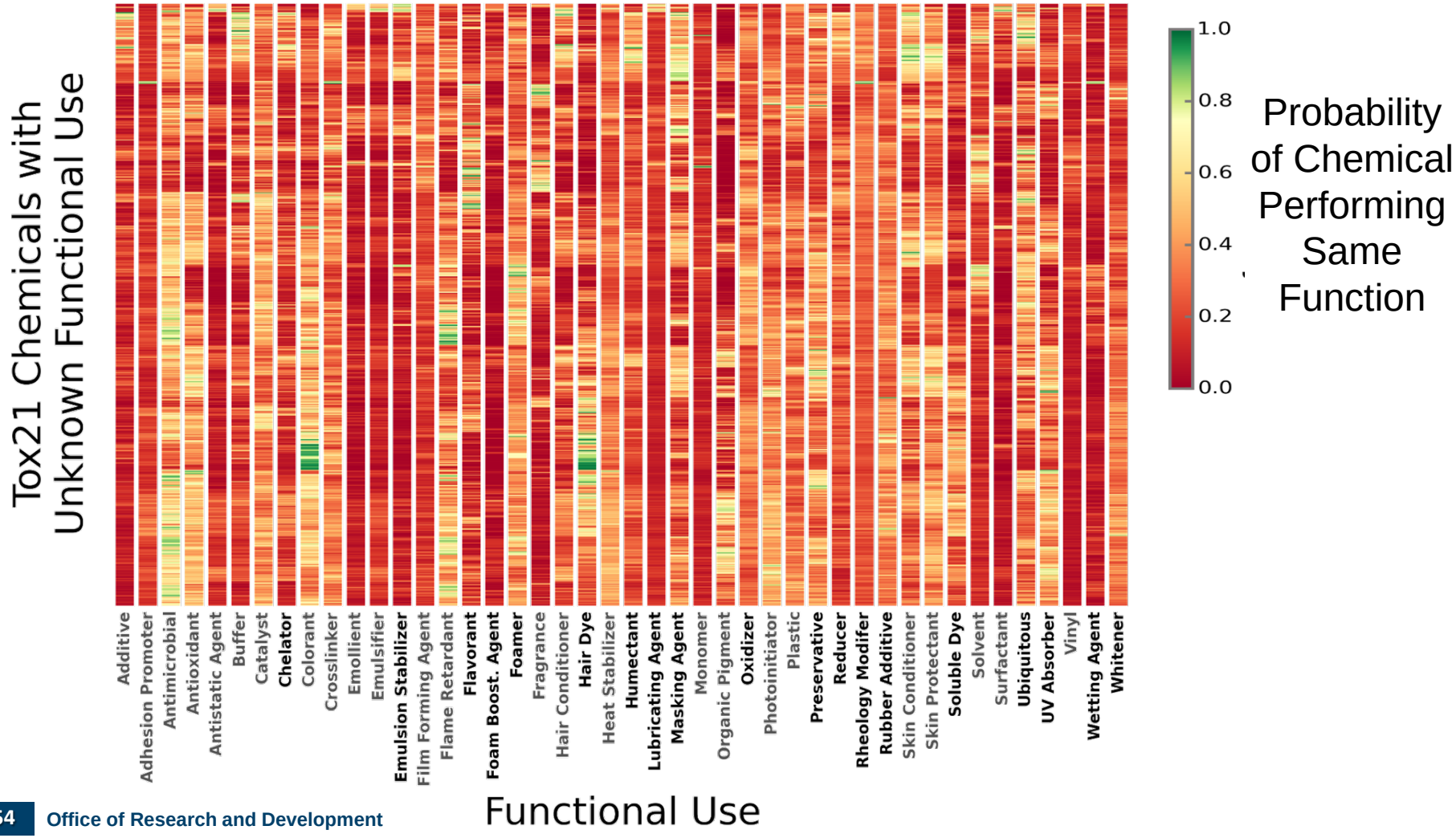
ToxPrint + EPI Suite



Viscosity controllers can be used to ***thicken*** or ***thin out*** mixtures of chemicals..

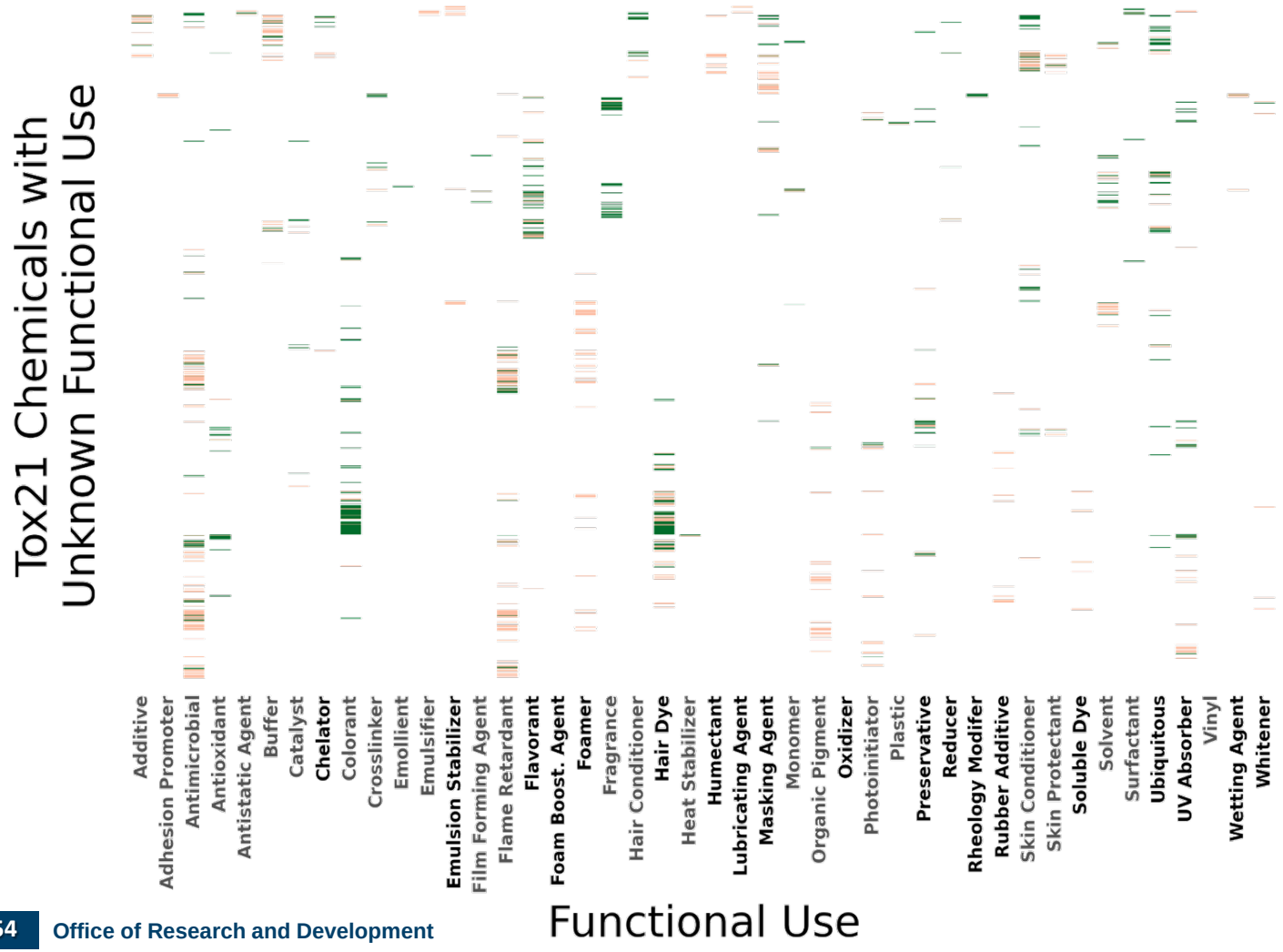
Phillips et al. (2017)

Screening for Alternatives By Function and Bioactivity



Phillips et al. (2017)

Screening for Alternatives By Function and Bioactivity



Phillips et al. (2017)

Non-Targeted and Suspect-Screening Analysis

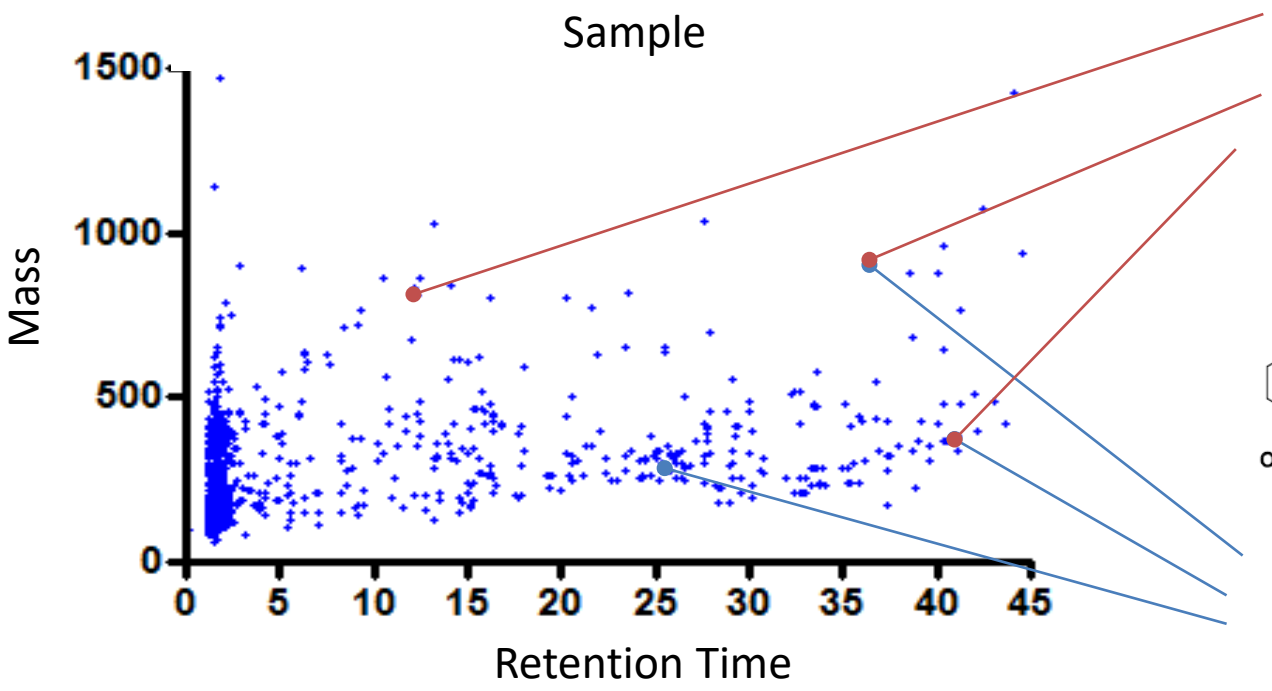
- Models present one way forward, but new analytic techniques may also allow insight in to chemicals composition of products and the greater environment
- EPA is coordinating a comparison of non-targeted screening workflows used by leading academic and government groups (led by Jon Sobus and Elin Ulrich)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

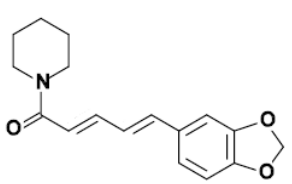
947 Peaks in an American Health Homes Dust Sample

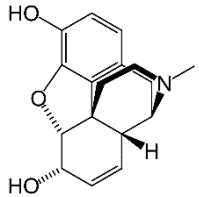


Each peak corresponds to a chemical with an accurate mass and predicted formula:

$C_{17}H_{19}NO_3$

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)

Appropriate Skepticism for Non-Targeted Analysis and Suspect Screening

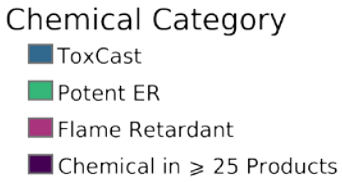
"As chemists we are obliged to accept the assignment of barium to the observed activity, but as nuclear chemists working very closely to the field of physics we cannot yet bring ourselves to take such a drastic step, which goes against all previous experience in nuclear physics. It could be, however,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

Hahn and Strassmann (1938)

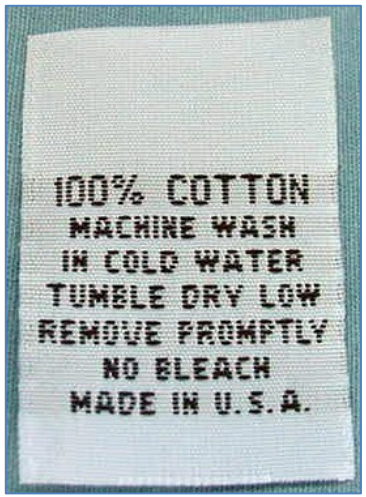
1944 Nobel Prize in Chemistry for "discovery of the fission of heavy nuclei"

Measuring Chemicals in Household Items

United States Environmental Protection Agency



The chemicals found in a cotton shirt

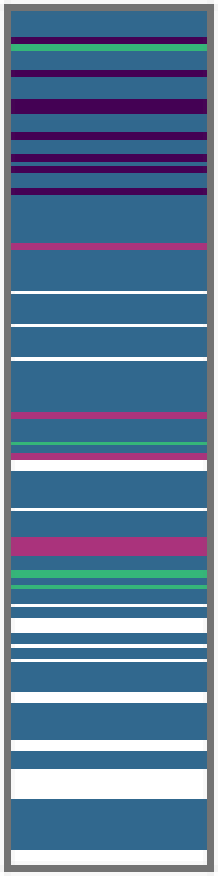


Phillips et al. (submitted)

Measuring Chemicals in Household Items

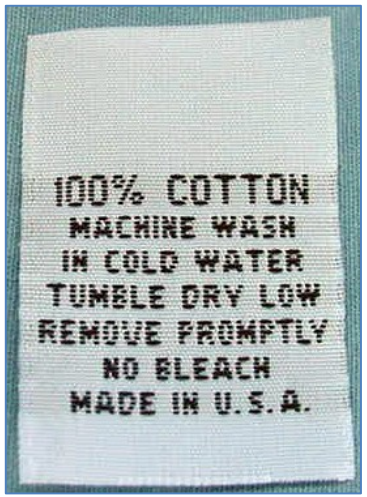
United States Environmental Protection Agency

126 Confirmed



⬅ Chemicals that are present

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

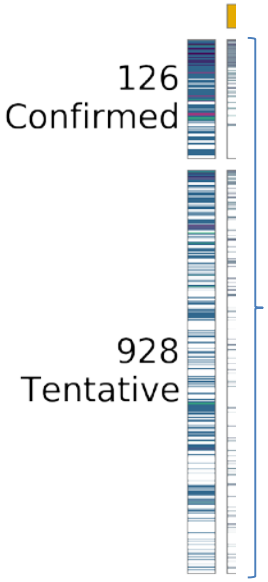


⬅ Chemicals that are absent (but found in other products)

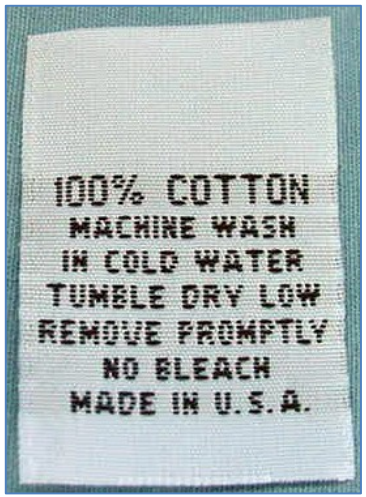
Phillips et al. (accepted)

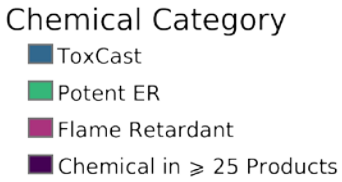
Measuring Chemicals in Household Items

United States Environmental Protection Agency



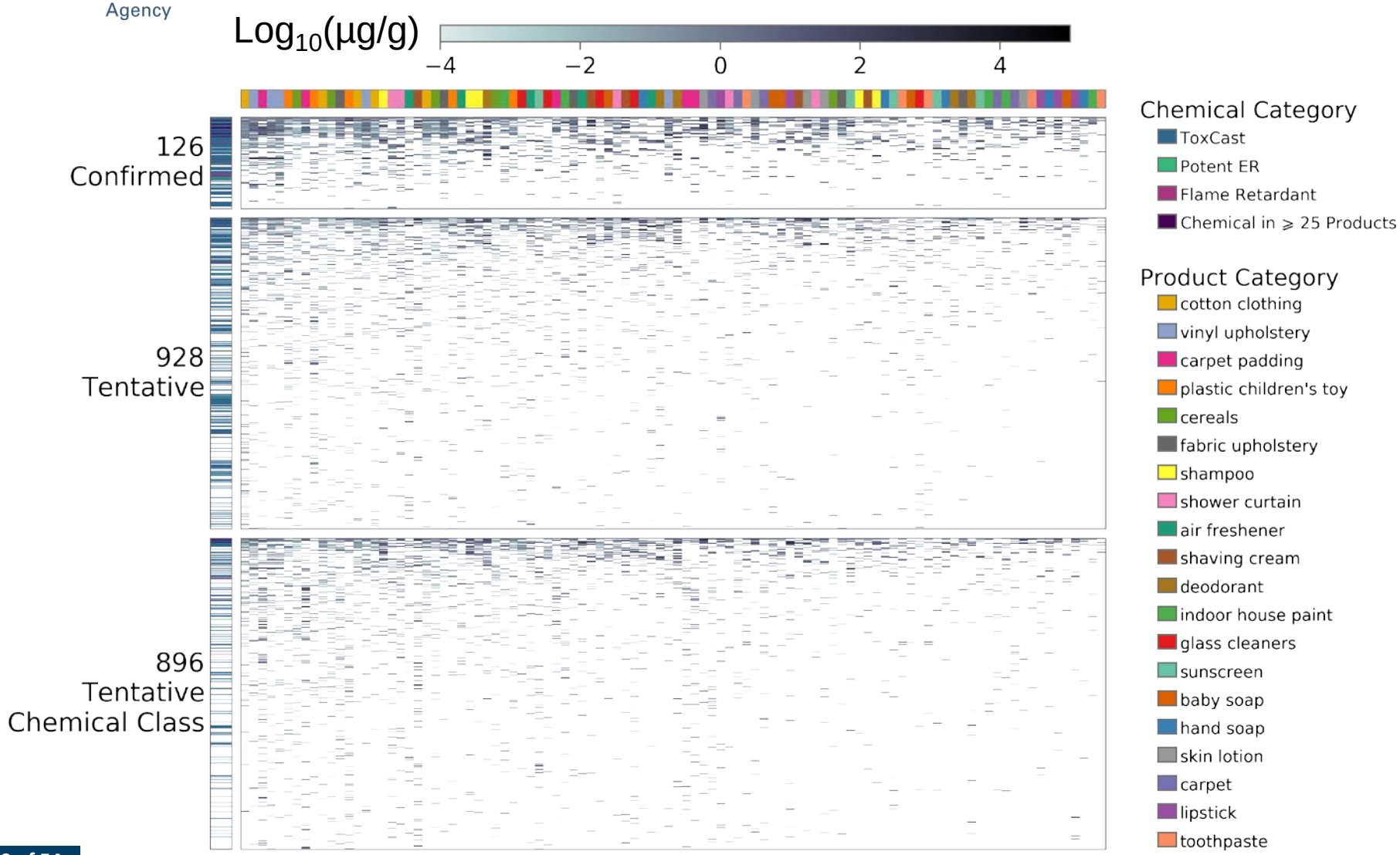
The chemicals found in a cotton shirt





Phillips et al. (accepted)

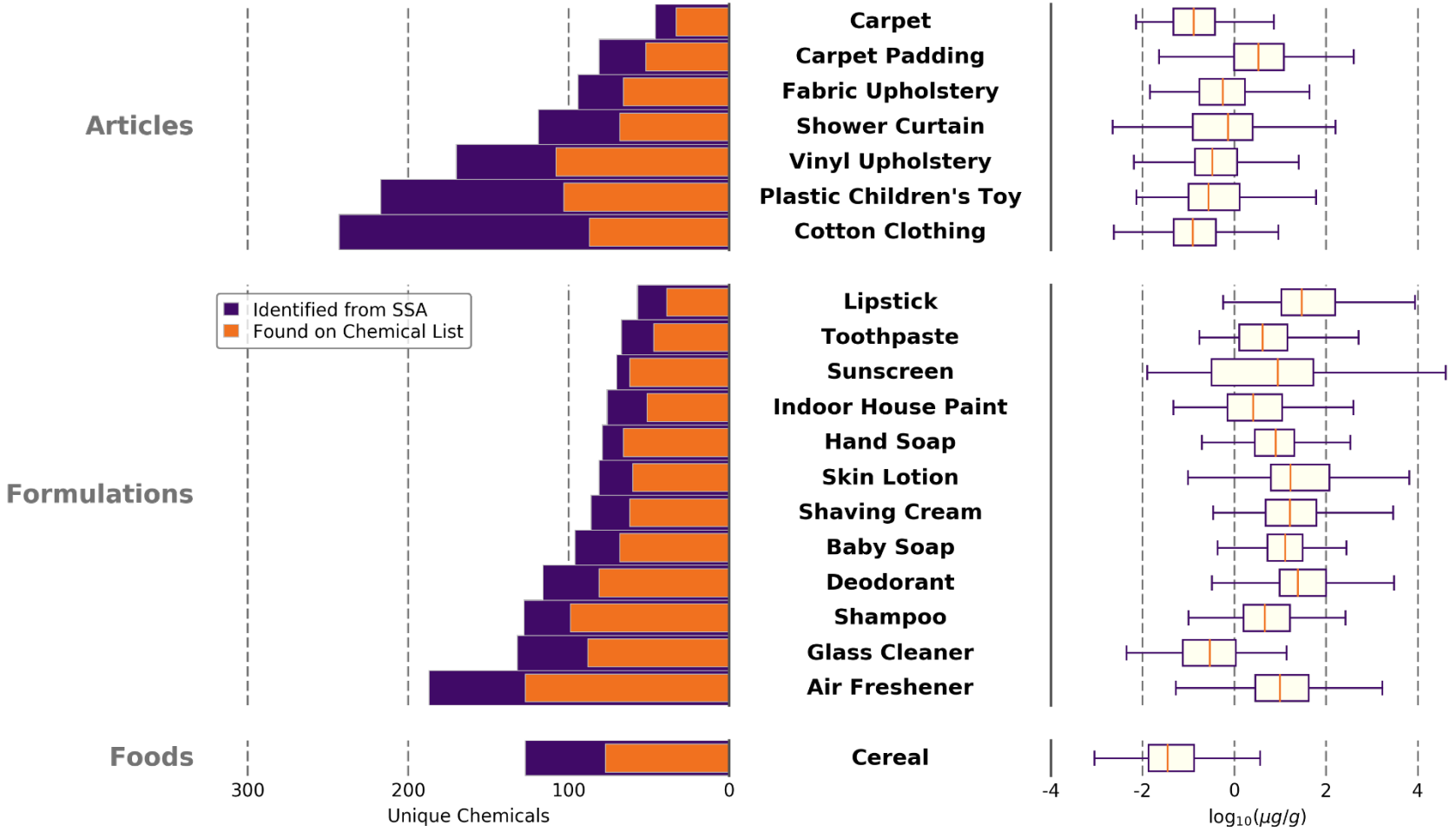
Measuring Chemicals in Household Items



Phillips et al. (accepted)

Product Scan Summary

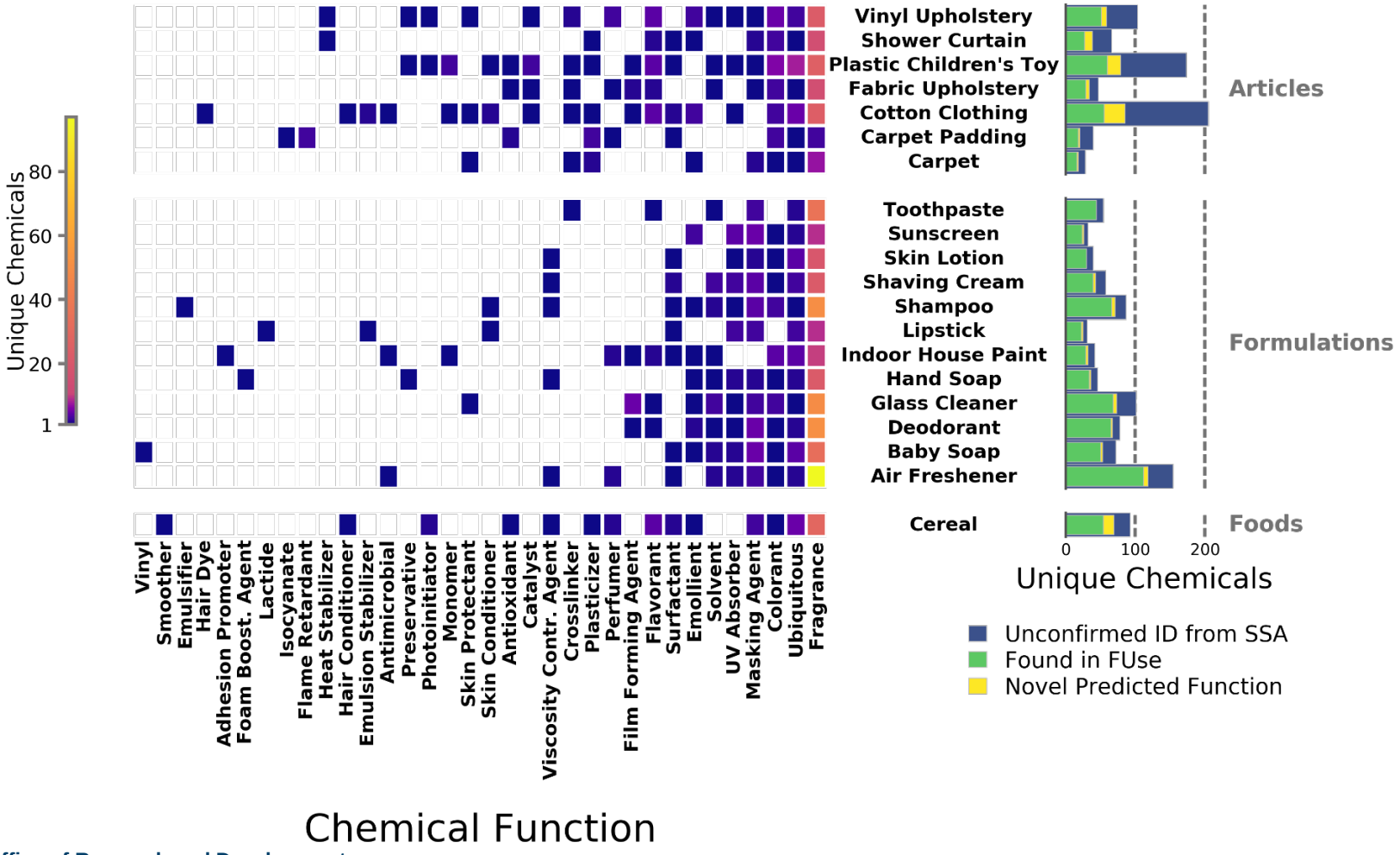
Of 1,632 chemicals confirmed or tentatively identified, 1,445 were not present in CPCPdb (Goldsmith, et al., 2015)



Phillips et al. (accepted)

Predicting Chemical Function

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



Phillips et al. (accepted)

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**

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, but the real world is full of more mixtures than we can test
- Exposure-based priority setting allows identification of the most relevant mixtures
- New informatic tools are needed to analyze complex data characterizing human exposure
- New analytical chemistry tools (i.e., non-targeted analysis or NTA) are needed to develop the data to understand what and how we are exposed to
  - These NTA tools present their own informatics challenges
- Finally, 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

EPA United States Environmental Protection Agency

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

NCCT
Chris Grulke
Greg Honda*
Richard Judson
Andrew McEachran*
Robert Pearce*
Ann Richard
Risa Sayre*
Woody Setzer
Rusty Thomas
John Wambaugh
Antony Williams

NRMRL
Yirui Liang*
Xiaoyu Liu

NHEERL
Linda Adams
Christopher Ecklund
Marina Evans
Mike Hughes
Jane Ellen Simmons

NERL
Craig Barber
Namdi Brandon*
Peter Egeghy
Hongtai Huang*
Brandall Ingle*
Kristin Isaacs
Seth Newton
Katherine Phillips
Paul Price
Jeanette Reyes*
Jon Sobus
John Streicher*
Mark Strynar
Mike Tornero-Velez
Elin Ulrich
Dan Vallero
Barbara Wetmore

*Trainees

Lead CSS Matrix Interfaces:
John Kenneke (NERL)
John Cowden (NCCT)

Collaborators

Arnot Research and Consulting
Jon Arnot
Battelle Memorial Institute
Anne Louise Sumner
Anne Gregg
Chemical Computing Group
Rocky Goldsmith
National Institute for Environmental Health Sciences (NIEHS) National Toxicology Program
Mike Devito
Steve Ferguson
Nisha Sipes
Research Triangle Institute
Timothy Fennell
ScitoVation
Harvey Clewell
Kamle Mansouri
Chantel Nicolas
Silent Spring Institute
Robin Dodson
Southwest Research Institute
Alice Yau
Kristin Favela
Summit Toxicology
Lesa Aylward
Tox Strategies
Caroline Ring
University of California, Davis
Deborah Bennett
Hyeong-Moo Shin
University of Michigan
Olivier Jolliet
University of North Carolina, Chapel Hill
Alex Tropsha

References

- Borgelt, C. (2012). Frequent item set mining. Wiley Interdisciplinary Reviews: Data Mining and Knowledge Discovery, 2(6), 437-456.
- Breiman, L. (2001). Random forests. Machine learning, 45(1), 5-32.
- Breyer, Stephen. Breaking the vicious circle: Toward effective risk regulation. Harvard University Press, 2009
- Diamond JM. Assembly of species communities. Pp. 342–444 in Cody ML, Diamond JM (eds). Ecology and Evolution of Communities. Cambridge, MA: Belkap Press, 1975.
- Dionisio, Kathie L., et al. "Exploring Consumer Exposure Pathways and Patterns of Use for Chemicals in the Environment." Toxicology Reports (2015)
- Egeghy, P. P., et al. (2012). The exposure data landscape for manufactured chemicals. Science of the Total Environment, 414, 159-166.
- Filer, Dayne L.. "The ToxCast analysis pipeline: An R package for processing and modeling chemical screening data." US Environmental Protection Agency: http://www. epa. gov/ncct/toxcast/files/MySQL% 20Database/Pipeline_Overview. pdf (2014)
- Goldsmith, M. R., et al. (2014). Development of a consumer product ingredient database for chemical exposure screening and prioritization. Food and chemical toxicology, 65, 269-279.
- Hahn, O., & Straßmann, F. (1938). Über die Entstehung von Radiumisotopen aus Uran durch Bestrahlen mit schnellen und verlangsamten Neutronen. Naturwissenschaften, 26(46), 755-756.
- Hertzberg, R. P., & Pope, A. J. (2000). High-throughput screening: new technology for the 21st century. Current opinion in chemical biology, 4(4), 445-451.
- Ingle, Brandall L., et al. "Informing the Human Plasma Protein Binding of Environmental Chemicals by Machine Learning in the Pharmaceutical Space: Applicability Domain and Limits of Predictability." Journal of Chemical Information and Modeling 56.11 (2016): 2243-2252.
- Kaewkhaw, R., et al. (2016). Treatment paradigms for retinal and macular diseases using 3-D retina cultures derived from human reporter pluripotent stem cell linestreatment design using PSC-Derived 3-D retina cultures. Investigative ophthalmology & visual science, 57(5), ORSFl1-ORSFl11.
- Kapraun, Dustin et al., "A Method for Identifying Prevalent Chemical Combinations in the US Population," Environmental Health Perspectives, 2017
- Kavlock, Robert, et al. "Update on EPA's ToxCast program: providing high throughput decision support tools for chemical risk management." Chemical research in toxicology 25.7 (2012): 1287-1302.
- National Academies of Sciences, Engineering, and Medicine. (2017). Using 21st century science to improve risk-related evaluations. National Academies Press.
- National Research Council. (1983). Risk Assessment in the Federal Government: Managing the Process Working Papers. National Academies Press.
- National Research Council. (2007) Toxicity testing in the 21st century: a vision and a strategy. National Academies Press.
- O'Connell, S. G., Kincl, L. D., & Anderson, K. A. (2014). Silicone wristbands as personal passive samplers. Environmental science & technology, 48(6), 3327-3335.
- Park, Youngja, H., et al. "High-performance metabolic profiling of plasma from seven mammalian species for simultaneous environmental chemical surveillance and bioeffect monitoring." Toxicology 295:47-55 (2012)
- Pearce, Robert, et al. "httk: R Package for High-Throughput Toxicokinetics." Journal of Statistical Software, 2017
- Phillips, Katherine A., et al. "High-throughput screening of chemicals as functional substitutes using structure-based classification models." Green Chemistry (2017).
- Rager, J. et al. (2016). Linking high resolution mass spectrometry data with exposure and toxicity forecasts to advance high-throughput environmental monitoring. Environment international, 88, 269-280.
- Ring, Caroline, et al., "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability", Environment International, 2017
- Rotroff, Daniel, et al., (2010) "Incorporating human dosimetry and exposure into high-throughput in vitro toxicity screening." Tox. Sciences 117(2), 348-58
- Schymanski, E. L., et al. (2015). Non-target screening with high-resolution mass spectrometry: critical review using a collaborative trial on water analysis. Analytical and bioanalytical chemistry, 407(21), 6237-625
- Schmidt, Charles W. "TOX 21: new dimensions of toxicity testing." Environmental health perspectives 117.8 (2009): A348.
- Sipes, Nisha, et al. (2017) "An Intuitive Approach for Predicting Potential Human Health Risk with the Tox21 10k Library", Environmental Science and Technology
- Tonnelier, A., Coecke, S., & Zaldívar, J. M. (2012). Screening of chemicals for human bioaccumulative potential with a physiologically based toxicokinetic model. Archives of toxicology, 86(3), 393-403.
- Tornero-Velez et al. (2012) "Biogeographical Analysis of Chemical Co-Occurrence to Identify Priorities for Mixtures Research": Risk Analysis, 32(2) 224-236
- Wambaugh, John F., et al. "High-throughput models for exposure-based chemical prioritization in the ExpoCast project." Environmental science & technology 47.15 (2013): 8479-848.
- Wambaugh, John F., et al. "High Throughput Heuristics for Prioritizing Human Exposure to Environmental Chemicals." Environmental science & technology (2014).
- Wang, Y.-H. (2010). "Confidence Assessment of the Simcyp Time-Based Approach and a Static Mathematical Model in Predicting Clinical Drug-Drug Interactions for Mechanism-Based CYP3A Inhibitors." Drug Metabolism and Disposition 38(7), 1094-1104
- Wetmore, Barbara A., et al. "Integration of dosimetry, exposure and high-throughput screening data in chemical toxicity assessment." Toxicological Sciences (2012): kfr254.
- Wetmore, Barbara A., et al., "Incorporating population variability and susceptible subpopulations into dosimetry for high-throughput toxicity testing. Toxicological sciences 2014;142:210-224
- Wetmore, Barbara A., et al. "Incorporating High-Throughput Exposure Predictions with Dosimetry-Adjusted In Vitro Bioactivity to Inform Chemical Toxicity Testing." Toxicological Sciences 148.1 (2015): 121-136.