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Looking Beyond the Lamppost:
High Throughput Measurement and Modeling for Chemical Prioritization

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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

ILSI North America 2019
Food Packaging Conference:
Scientific Advances and Challenges in Safety Evaluation of Food Packaging Materials
April 2-3, 2019

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

EPA Office of Research and Development

- The Office of Research and Development (ORD) is the scientific research arm of EPA
  - 626 peer-reviewed journal articles in 2017 and 562 so far for 2018

- Research is conducted by ORD's three national laboratories, four national centers, and two offices organized to address:
  - Hazard, exposure, risk assessment, and risk management

- 13 facilities across the United States

- Research conducted by a combination of Federal scientists (including uniformed members of the **Public Health Service)**; contract researchers; and postdoctoral, graduate student, and post-baccalaureate trainees

ORD Facility in Research Triangle Park, NC

Moving Beyond the Lamp Post

- 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)
  - Some chemicals are well studied, others not so much

- Park *et al.* (2012): At least 3221 chemical signatures in pooled human blood samples, many appear to be exogenous
  - What do we know about these chemicals?
  - Are they endogenous/exogenous?
  - Nutrients/therapeutics?

"I'm searching for my keys."

Chemical Regulation in the United States

- Most non-food additive, pharmaceutical, or pesticidal chemicals, ranging from industrial waste to dyes to packing materials, are covered by the Toxic Substances Control Act (TSCA)

- Thousands of chemicals on the market were "grandfathered" in without assessment, see: Judson et al. (2009), Egeghy et al. (2012), Wetmore et al. (2015)

"Tens of thousands of chemicals are listed with the Environmental Protection Agency (EPA) for commercial use in the United States, with an average of 600 new chemicals listed each year."
U.S. Government Accountability Office

November 29, 2014

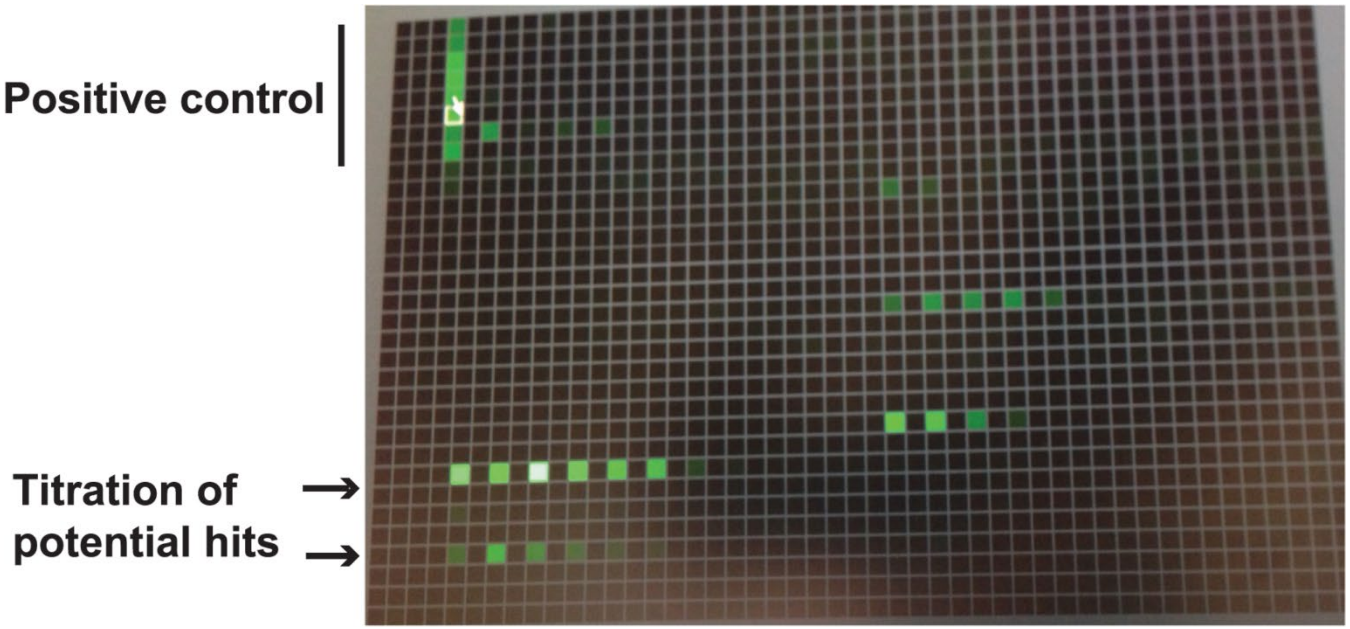
High-throughput Screening

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."

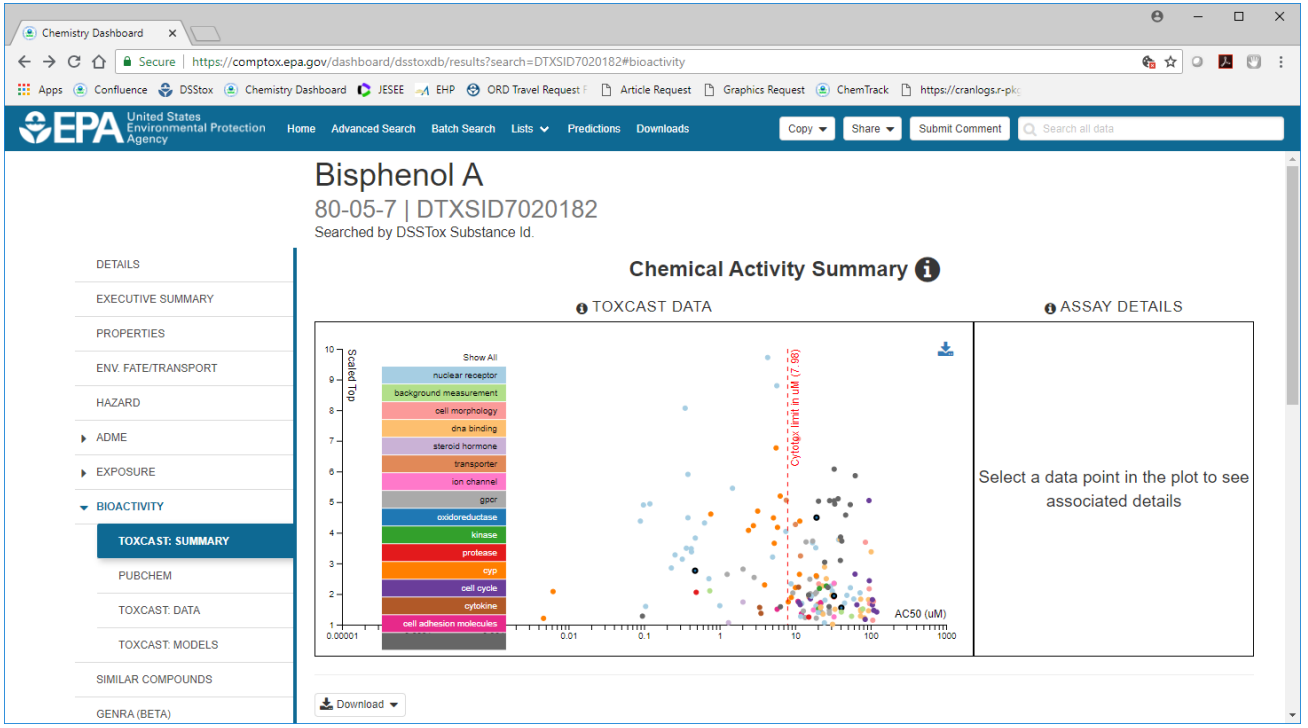
Kaewkhaw et al. (2016)



Toxicity Testing in the 21st Century

- **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)



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

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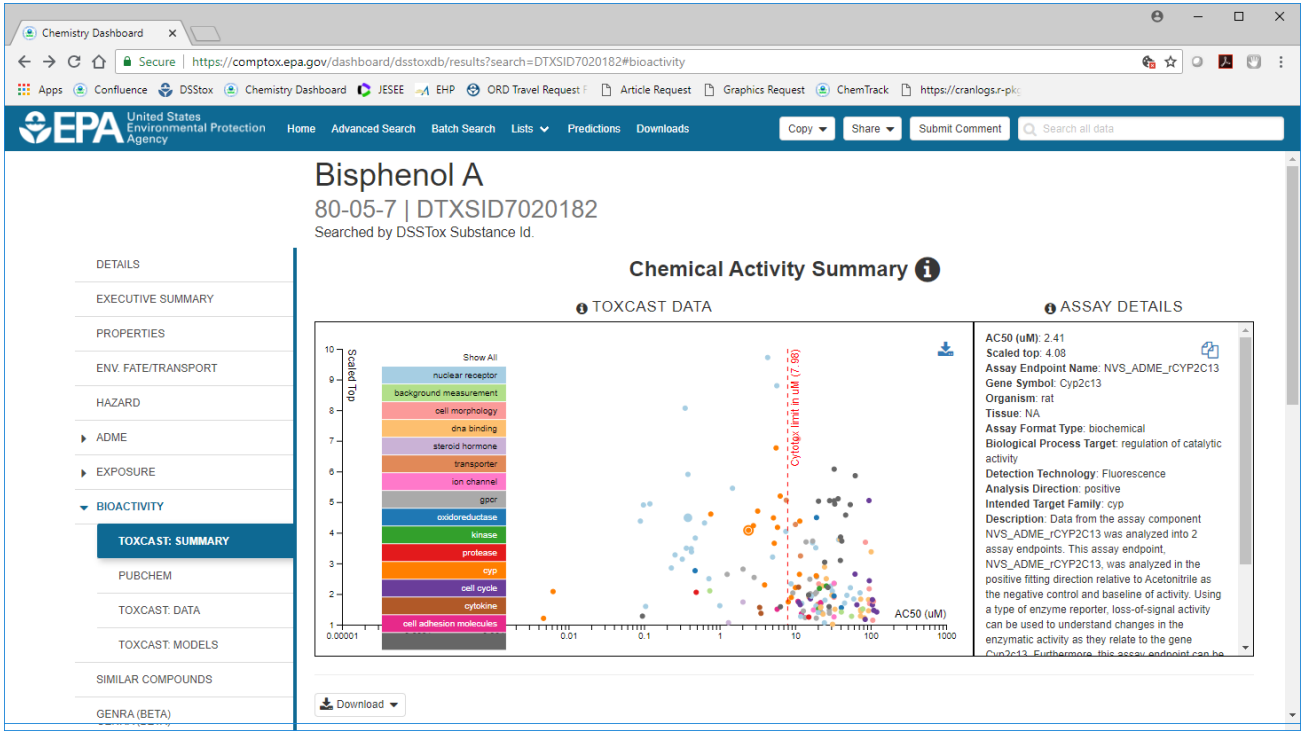
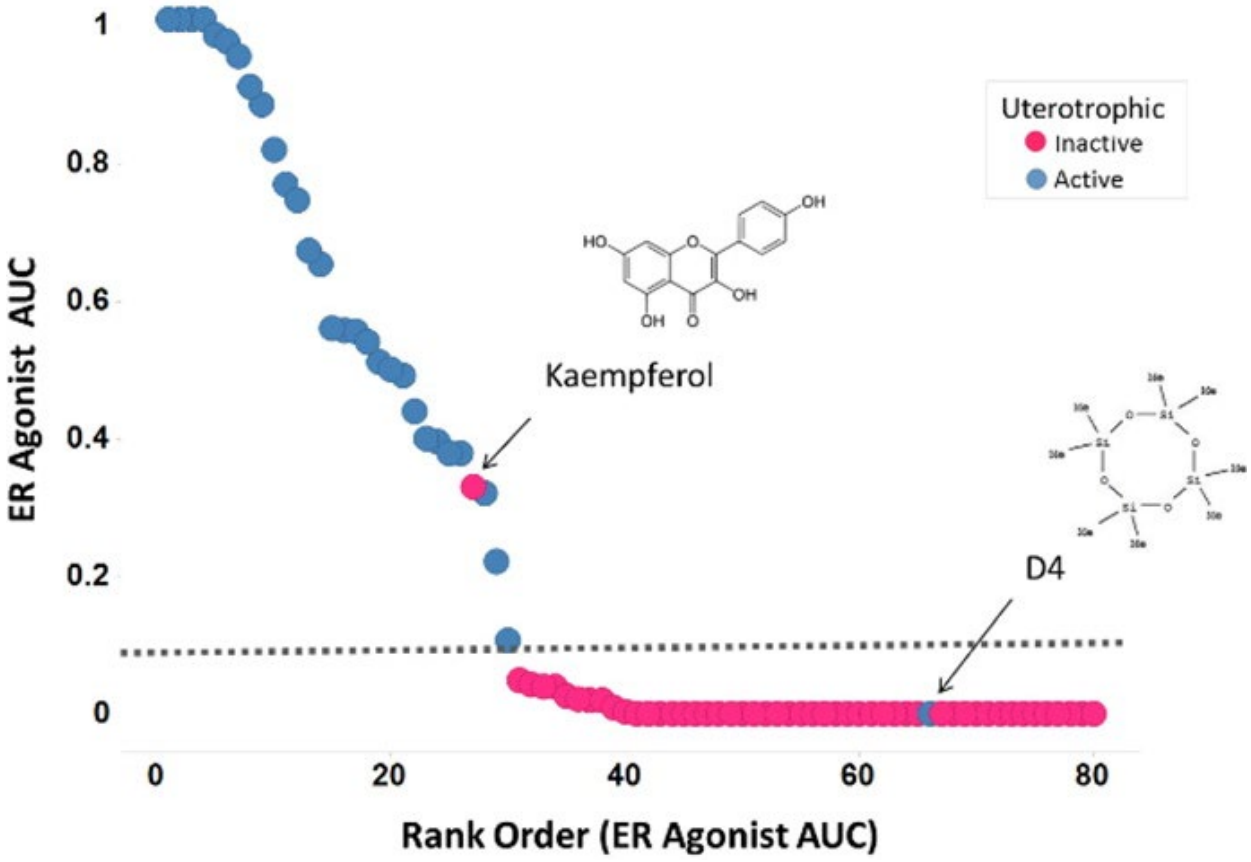


https://comptox.epa.gov/dashboard/

New Approach Methodologies

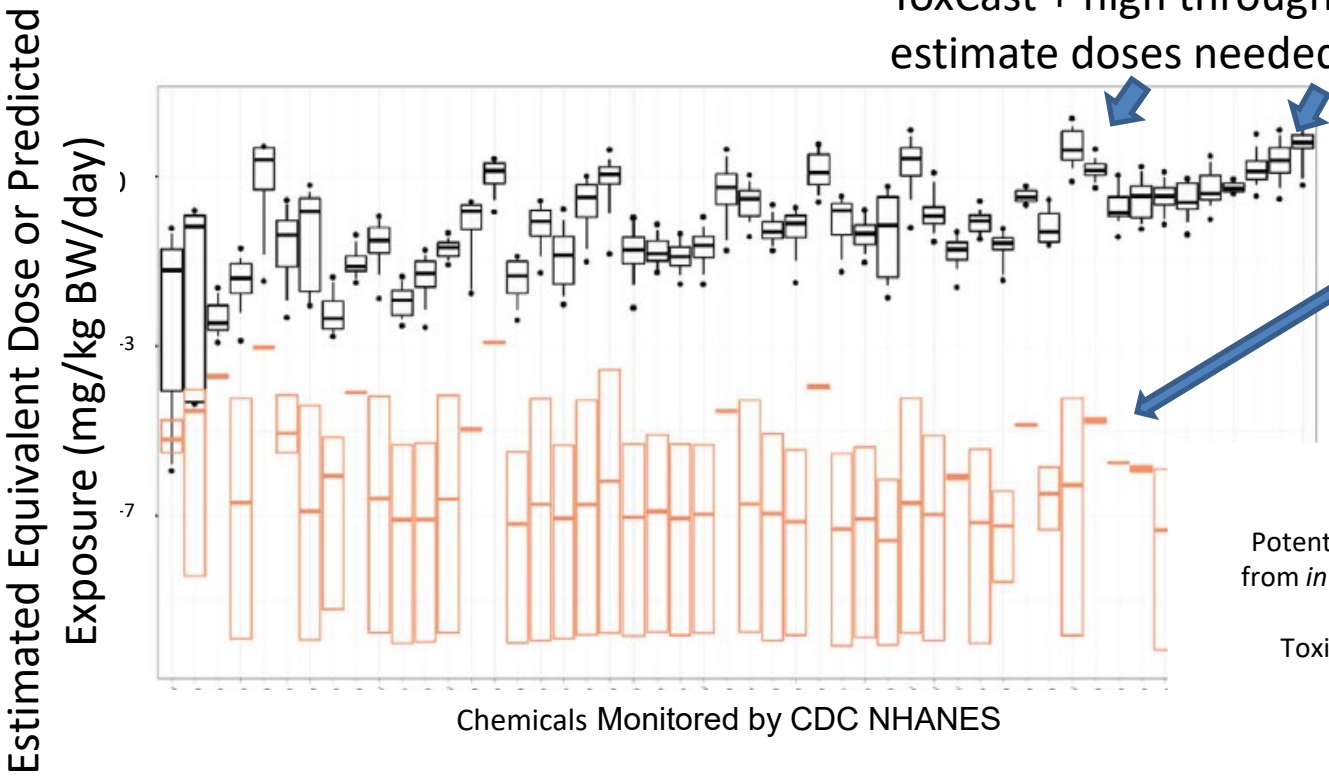
- New approach methodologies (NAMs) are being considered to inform prioritization of chemicals for testing and evaluation (Kavlock et al., 2018)
- *In vivo* uterotrophic assay has been replaced with in vitro assays to screen chemical for endocrine disruption (EPA, 2015)
- EPA has released a "A Working Approach for Identifying Potential Candidate Chemicals for Prioritization" (EPA, 2018)



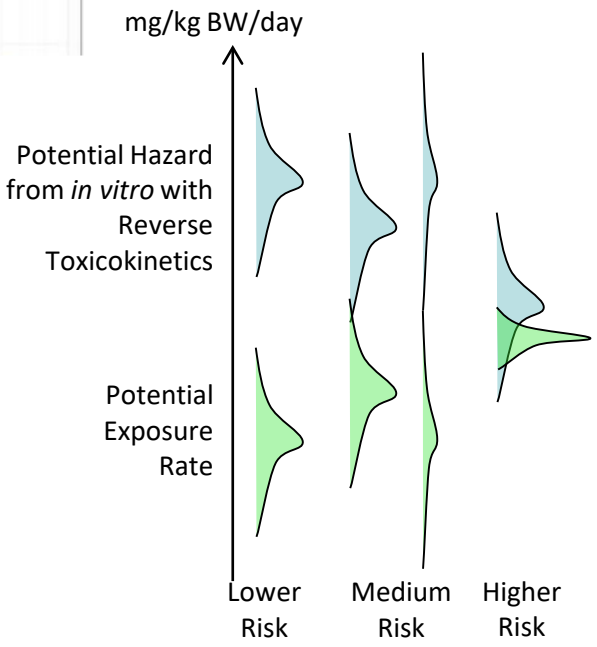
Browne et al. (2015)

Selecting Candidates for Prioritization

ToxCast + high throughput toxicokinetics can estimate doses needed to cause bioactivity



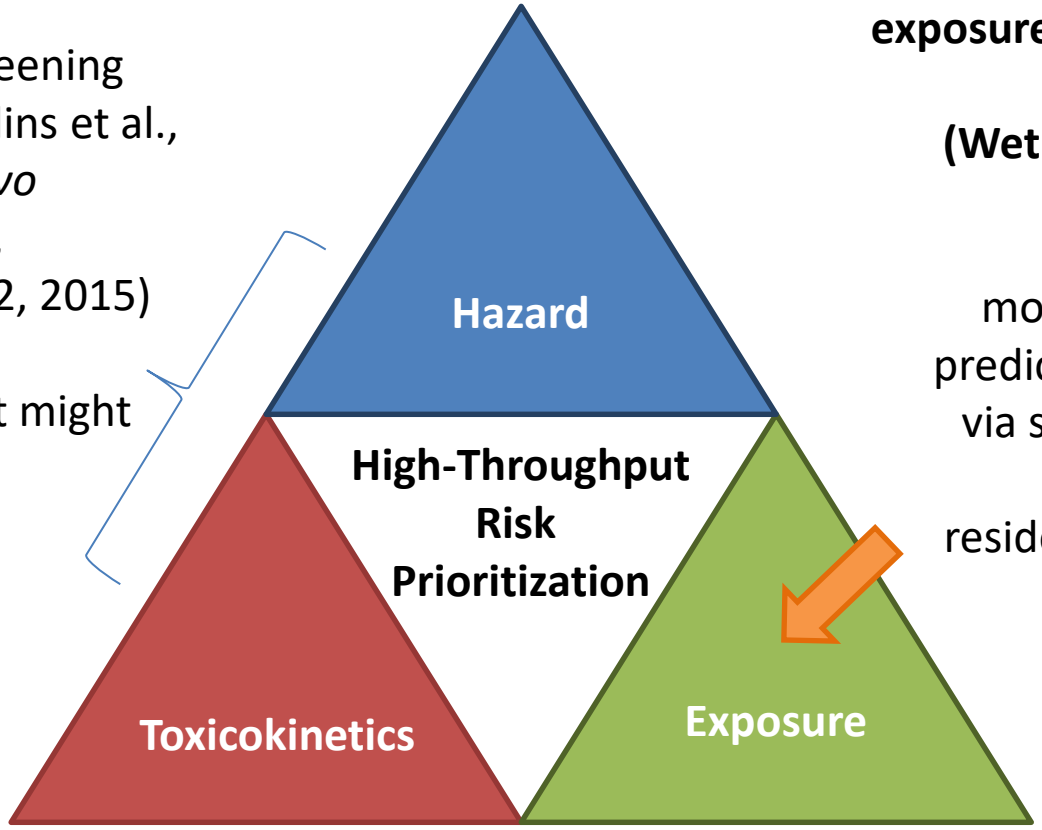
Exposure intake rates can be inferred from biomarkers (Wambaugh et al., 2014)



Ring *et al*. (2017)

Risk = Hazard x Exposure

High throughput screening (Dix et al., 2006, Collins et al., 2008) + *in vitro-in vivo* extrapolation (IVIVE, Wetmore et al., 2012, 2015) can predict a dose (mg/kg bw/day) that might be adverse



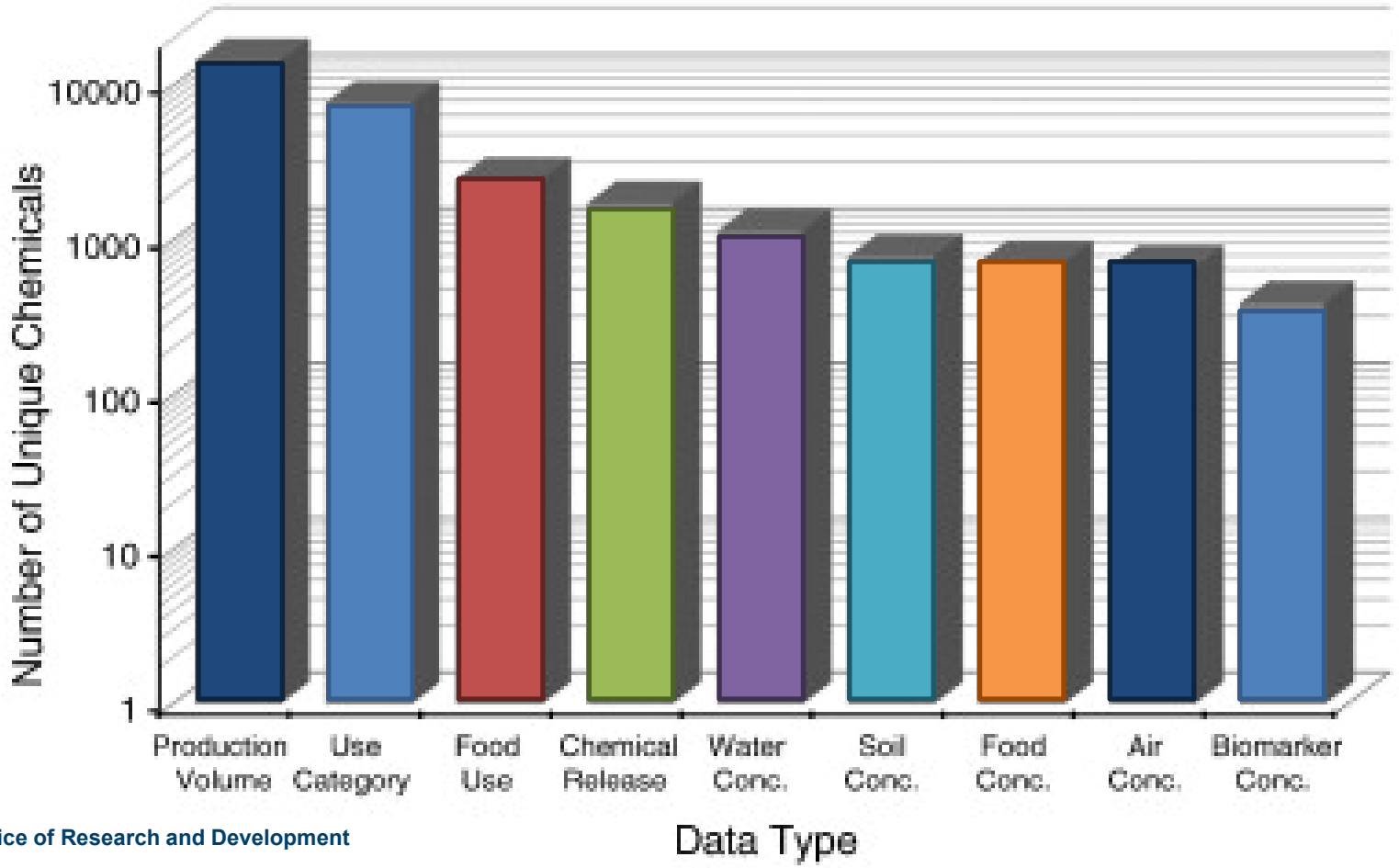
We need methods to forecast exposure for thousands of chemicals (Wetmore et al., 2015)

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

NRC (1983)

Limited Available Data for Exposure Estimation

Most chemicals lack public exposure-related data beyond production volume (Egeghy et al., 2012)



United States Environmental Protection Agency

Biomonitoring Data

The National Health and Nutrition Examination Survey (NHANES) provides targeted biomonitoring data of chemicals and metabolites in human blood and urine

Chemicals in the *Fourth Report: Updated Tables, March 2018*

CDC's *Fourth National Report on Human Exposure to Environmental Chemicals: Updated Tables* provides exposure data on the following chemicals or classes of chemicals. The *Updated Tables* contain cumulative data from national samples collected beginning in 1999–2000 and as recently as 2015-2016. Not all chemicals were measured in each national sample. The data tables are available at http://www.cdc.gov/exposurereport. An asterisk (*) indicates the chemical has been added since publication of the *Fourth Report* in 2009.

Phthalate and Phthalate Alternative Metabolites

Mono-benzyl phthalate (MBzP)
Mono-3-hydroxybutyl phthalate (MHBP)*
Mono-n-butyl phthalate (MnBP)
Mono-2-methyl-2-hydroxypropyl phthalate (MHiBP)*
Mono-isobutyl phthalate (MiBP)
Mono-cyclohexyl phthalate (MCHP)
Mono-ethyl phthalate (MEP)
Mono-2-ethylhexyl phthalate (MEHP)
Mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)

Organophosphorus Insecticides: Dialkyl Phosphate Metabolites

Diethylphosphate (DEP)
Dimethylphosphate (DMP)
Diethylthiophosphate (DETP)
Dimethylthiophosphate (DMTP)
Diethyldithiophosphate (DEDTP)
Dimethyldithiophosphate (DMDTP)

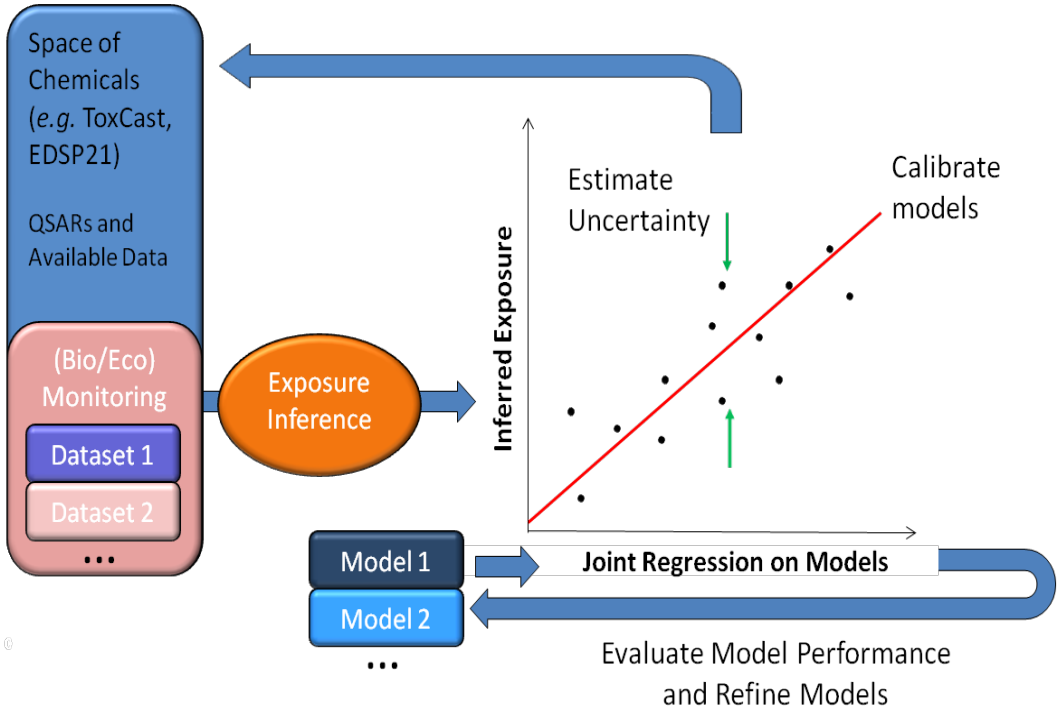
Pyrethroid Metabolites

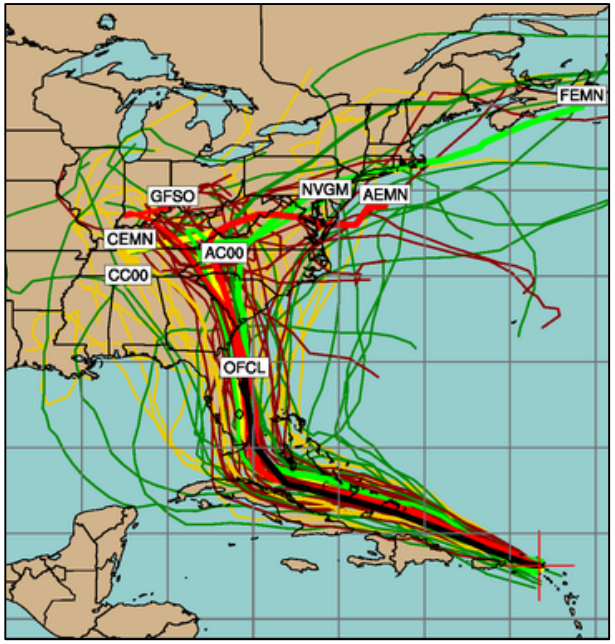
trans-3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (trans-DCCA)
cis-3-(2,2-Dibromovinyl)-2,2dimethylcyclopropane carboxylic acid (cis-DBCA)
4-Fluoro-3-phenoxy-benzoic acid*
3-Phenoxybenzoic acid*

There are hundreds of chemicals, and yet Park *et al.* (2012) and others have seen evidence for many others

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)** (Wambaugh et al., 2013, 2014)
- *Each chemical with measured intake rate provides an additional evaluation of exposure model predictions*
- Evaluation is similar to a sensitivity analysis: What models are working? What data are most needed?

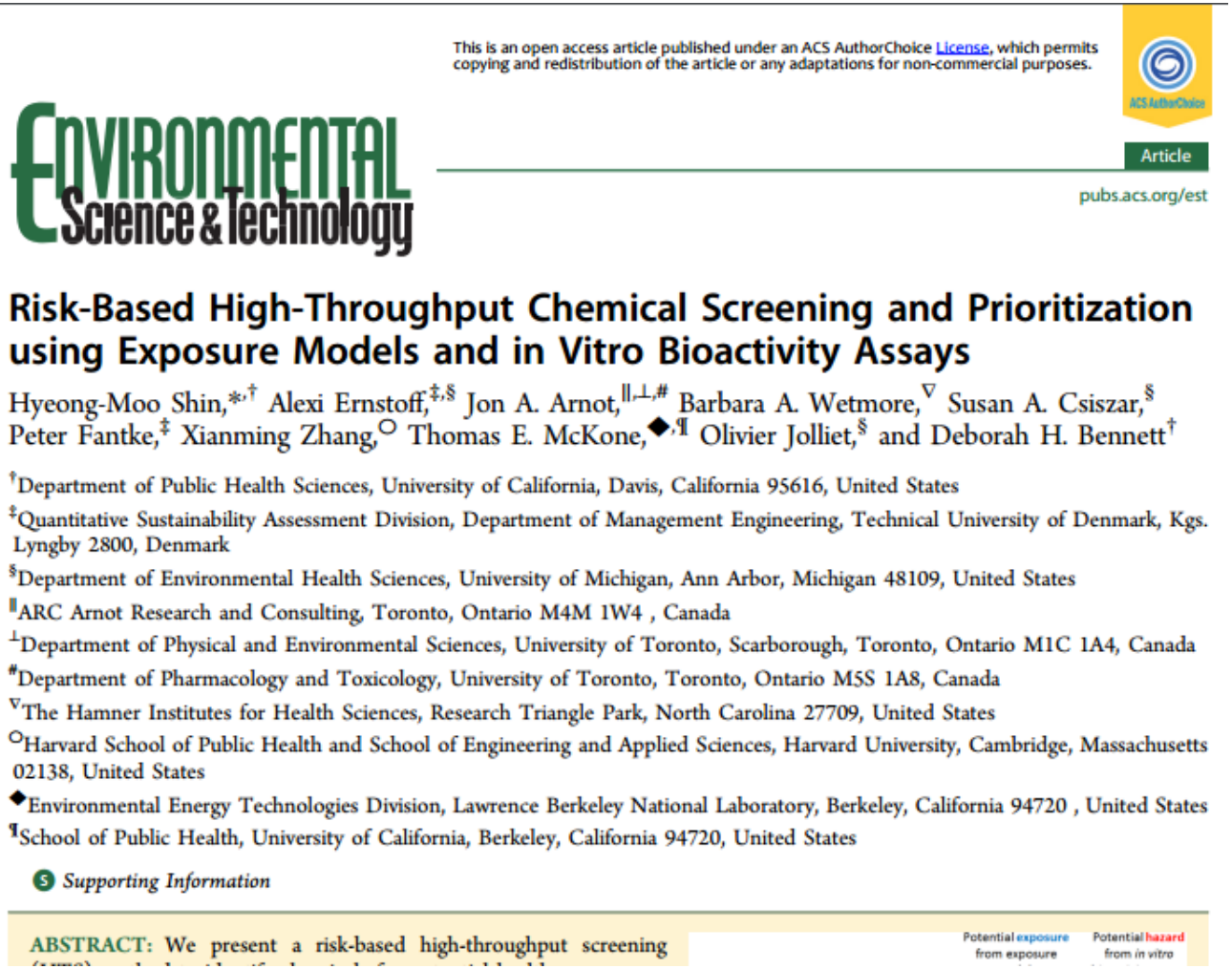




Integrating Multiple Models

Knowledge of Exposure Pathways Limits High Throughput Exposure Models

"In particular, the assumption that 100% of [quantity emitted, applied, or ingested] is being applied to each individual use scenario is a very conservative assumption for many compound / use scenario pairs."



Environmental Science & Technology

Article

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

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[¶]School of Public Health, University of California, Berkeley, California 94720, United States

Supporting Information

ABSTRACT: We present a risk-based high-throughput screening

Potential exposure from exposure

Potential hazard from in vitro

EPA United States Environmental Protection Agency

Ring et al. (2019)

Predicting Pathways

We use the method of Random Forests to relate chemical structure and properties to exposure pathway

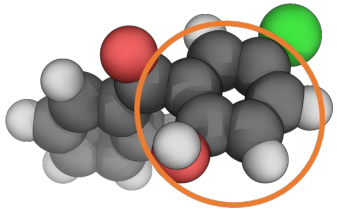
	NHANES Chemicals	Positives	Negatives	OOB Error Rate	Positives Error Rate	Balanced Accuracy	Sources of Positives	Sources of Negatives
Dietary	24	2523	8865	27	32	73	FDA CEDI, ExpoCast, CPDat (Food, Food Additive, Food Contact), NHANES Curation	Pharmapendium, CPDat (non-food), NHANES Curation
Near-Field	49	1622	567	27	25	73	CPDat (consumer_use, building_material), ExpoCast, NHANES Curation	CPDat (Agricultural, Industrial), FDA CEDI, NHANES Curation
Far-Field Pesticide	94	1480	6522	20	36	80	REDs, Swiss Pesticides, Stockholm Convention, CPDat (Pesticide), NHANES Curation	Pharmapendium, Industrial Positives, NHANES Curation
Far Field Industrial	42	5089	2913	19	17	81	CDR HPV, USGS Water Occurrence, NORNAN PFAS, Stockholm Convention, CPDat (Industrial, Industrial_Fluid), NHANES Curation	Pharmapendium, Pesticide Positives, NHANES Curation

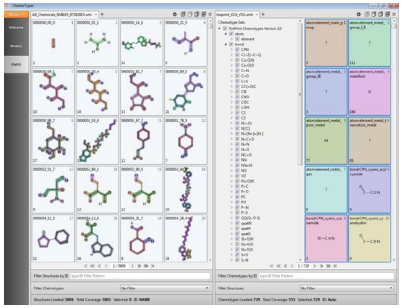
Predicting Function Based on Structure

United States Environmental Protection Agency

Machine Learning Based Classification Models
(Random Forest, Breiman, 2001)

Chemical Structure and Property Descriptors





Use Database (FUSE)

Prediction of Of Potential Alternatives from Chemical Libraries

Phillips et al. (2017)

Collaboration on High Throughput Exposure Predictions

Jon Arnot, Deborah H. Bennett, Peter P. Egeghy, Peter Fantke, Lei Huang, Kristin K. Isaacs, Olivier Jolliet, Hyeong-Moo Shin, Katherine A. Phillips, Paul S. Price, Caroline Ring, R. Woodrow Setzer, John F. Wambaugh, Johnny Westgate

Ring et al., 2019

Predictor	Reference	Chemicals Predicted	Pathways
EPA Inventory Update Reporting and Chemical Data Reporting (CDR) (2015)	US EPA (2018)	7856	All
Stockholm Convention of Banned Persistent Organic Pollutants (2017)	Lallas (2001)	248	Far-Field Industrial and Pesticide
EPA Pesticide Reregistration Eligibility Documents (REDs) Exposure Assessments (Through 2015)	Wetmore et al. (2012, 2015)	239	Far-Field Pesticide
Food Contact Substance Migration Model (2017)	Biryol et al. (2017)	940	Dietary
United Nations Environment Program and Society for Environmental Toxicology and Chemistry toxicity model (USEtox) Industrial Scenario (2.0)	Rosenbaum et al. (2008)	8167	Far-Field Industrial
USEtox Pesticide Scenario (2.0)[48]USEtox Pesticide Scenario (2.0)	Fantke et al. (2011, 2012, 2016)	8167	Far-Field Pesticide
Risk Assessment IDentification And Ranking (RAIDAR) Far-Field (2.95)	Arnot et al. (2008)	7511	Far-Field Industrial and Pesticide
EPA Stochastic Human Exposure Dose Simulator High-Throughput (SHEDS-HT) Near-Field Direct (2017)	Isaacs (2017)	1119	Consumer (Near-Field)
SHEDS-HT Near-field Indirect (2017)	Isaacs (2017)	645	Consumer
Fugacity-based INdoor Exposure (FINE) (2017)	Bennett et al. (2004), Shin et al. (2012)	1221	Consumer
RAIDAR-ICE Near-Field (0.804)	Arnot et al., (2014), Zhang et al. (2014)	615	Consumer
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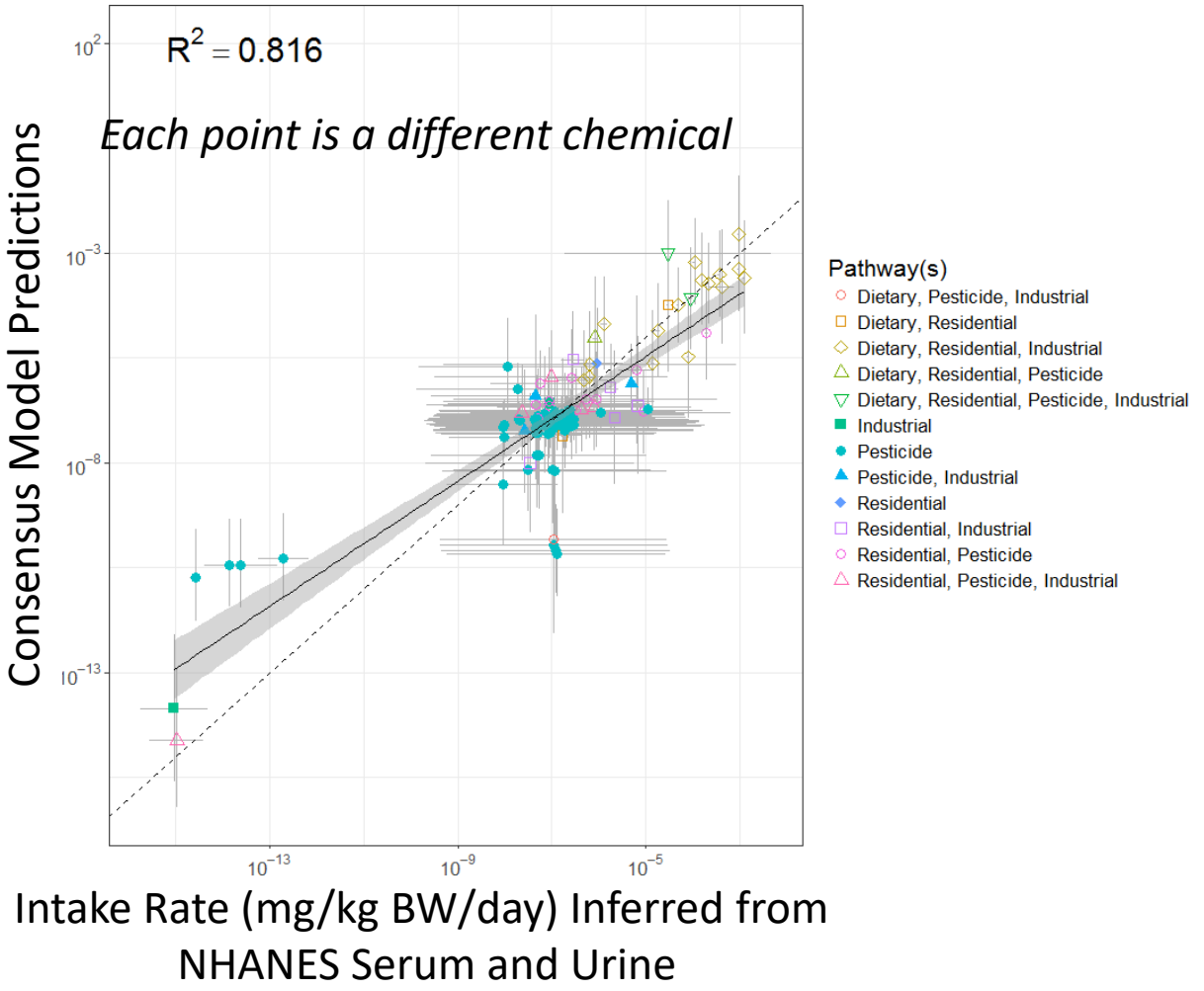
USEtox Dietary Scenario (2.0)	Jolliet et al. (2015), Huang et al. (2016), Ernstoff et al. (2017)	8167	Dietary

Pathway-Based Consensus Modeling of NHANES

- New machine learning tools provide improved high throughput exposure estimates by matching chemicals to exposure pathways and associated calibrated exposure models.

- Exposure predictors (data and models) have been grouped into four pathways (residential, dietary, pesticidal, and industrial) and calibrated via Bayesian multivariate regression using human intake rates inferred for 114 chemicals from a large bio-monitoring survey.



Ring et al., 2019

Consensus Modeling of Median Chemical Intake

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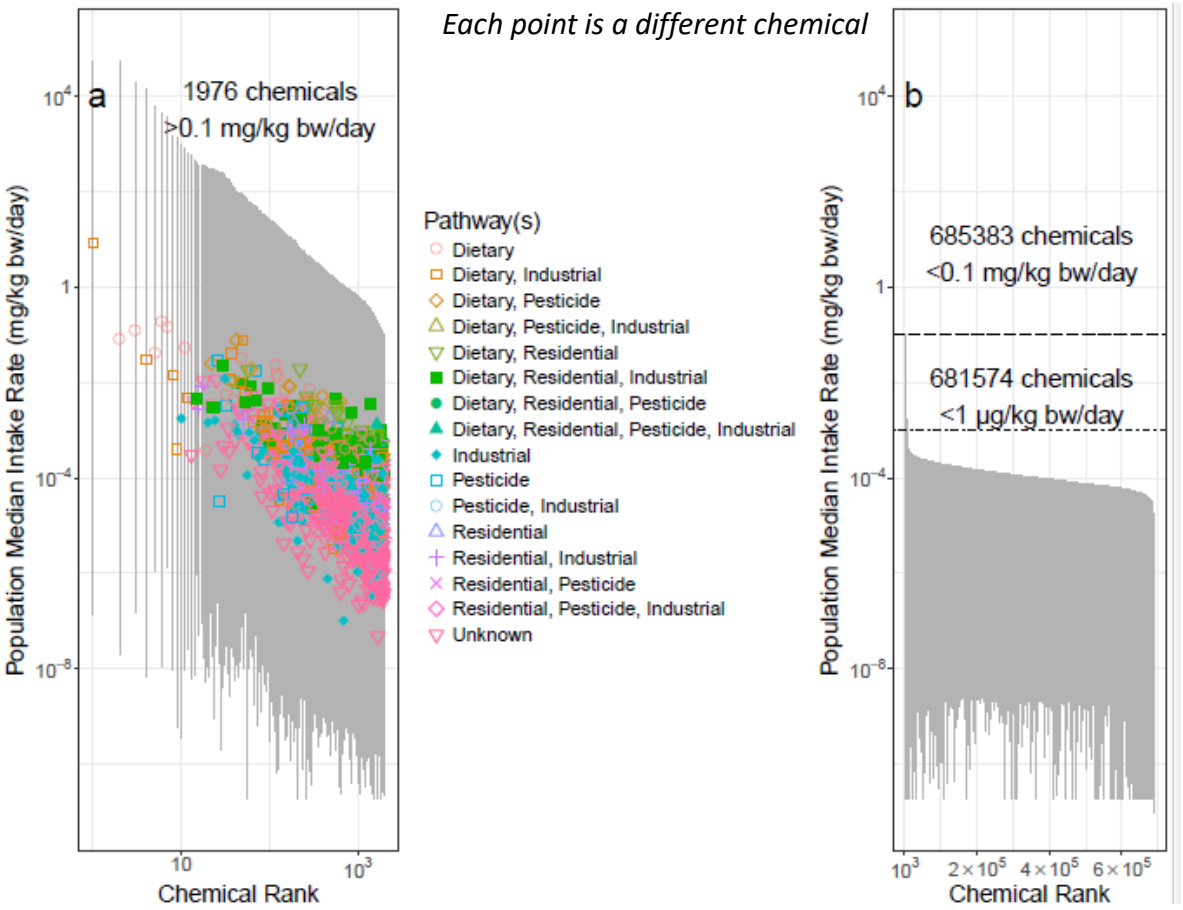

Ring et al., 2019

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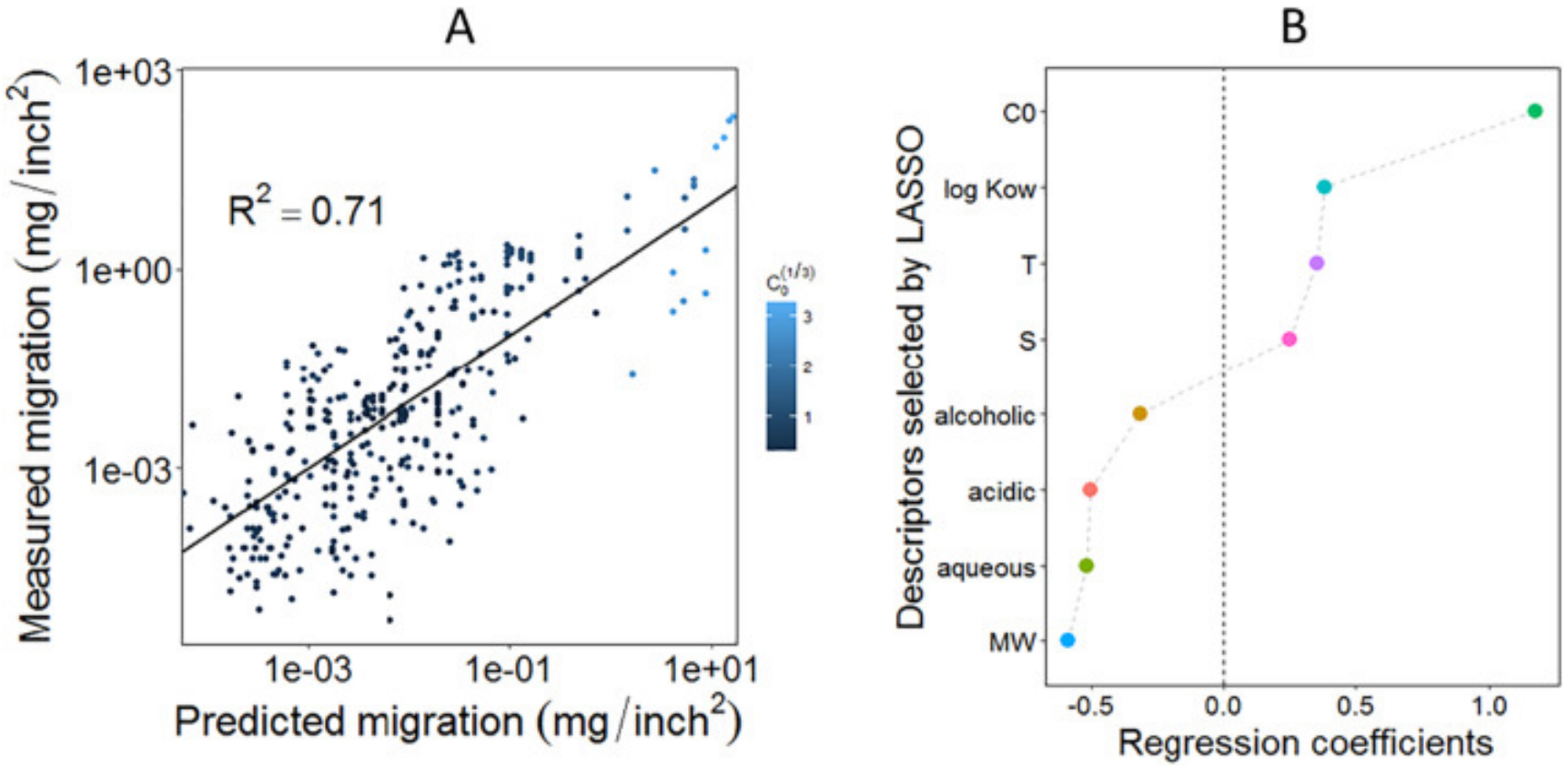
High Throughput Food Migration Model

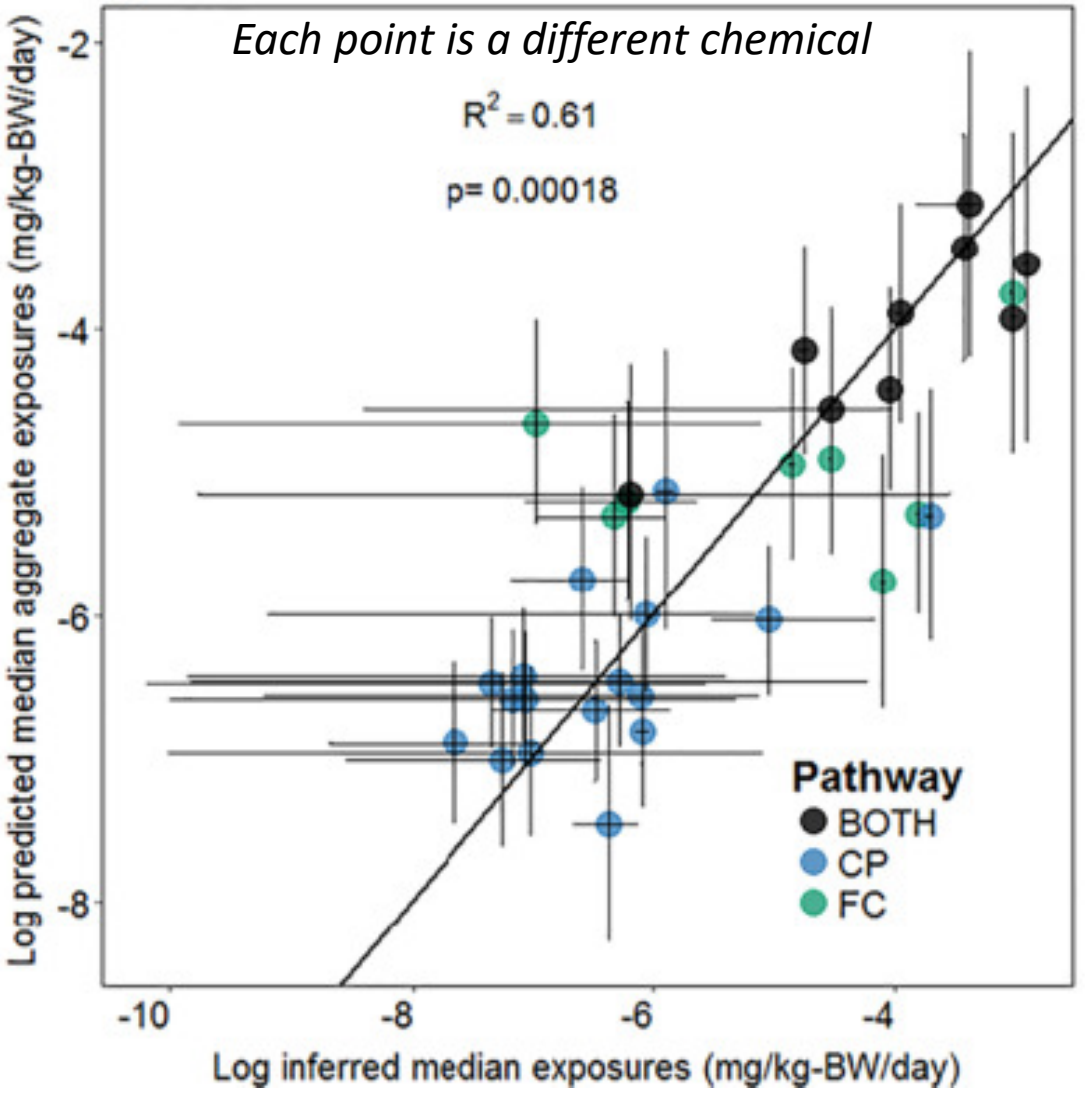


Prediction via linear regression

Biryol et al. (2017)

High Throughput Food Migration Model

Comparing relative contribution of consumer product (CP) and food contact (FC) exposure pathways to NHANES data

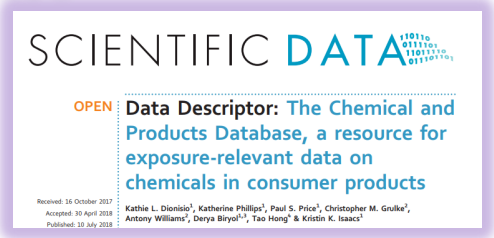


Biryol et al. (2017)

What Do We Know About Chemical Use? The Chemicals and Products Database

MSDS Data

Occurrence and quantitative chemical composition

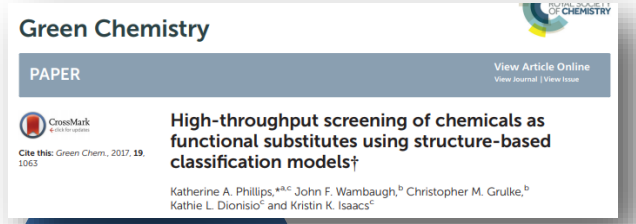


Broad "index" of chemical uses

CPCat

CPDat

EPA United States Environmental Protection Agency
Chemistry Dashboard

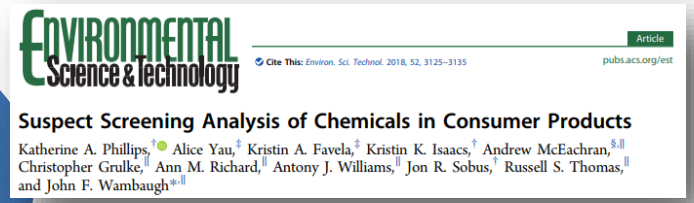


Functional Use Data

The roles that chemicals serve in products

Ingredient Lists

Occurrence data



Measured Data

Measurement of chemicals in consumer products

https://comptox.epa.gov/dashboard

Slide from Kristin Isaacs

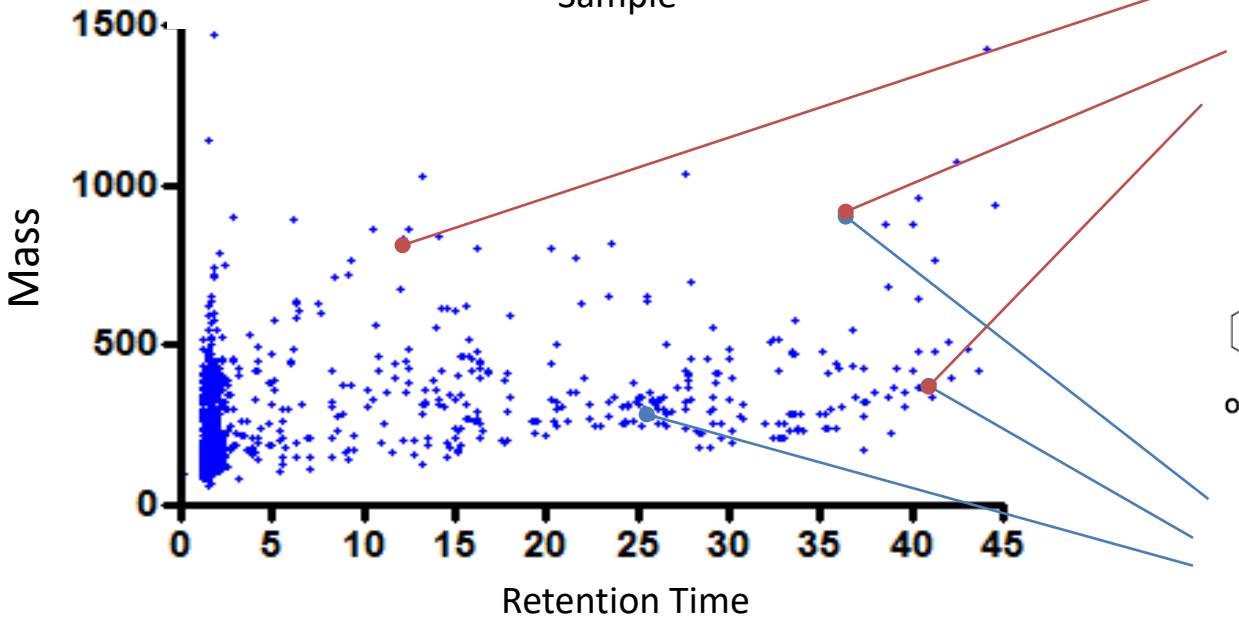
Improving Exposure Pathway Characterization and Model Evaluation

- Targeted Analysis:
  - We know the chemical for which we are looking
  - 10s – 100s of chemicals
- Computer enhanced analysis:
  - We have no preconceived lists
  - 1,000s – 10,000s of chemicals
- Ongoing development of methods for various matrices including environmental and biological media

- Goal is to develop tools, databases, and workflows for rapid analysis of any sample for chemicals of interest, i.e. ***exposure forensics***

Identifying Mass Spectrometer Features

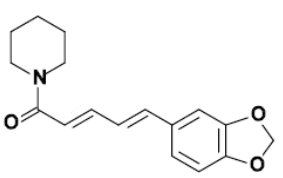
947 Peaks in an American Health Homes Dust Sample

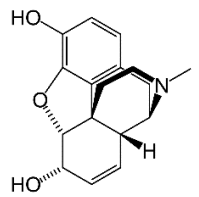


Liquid chromatography peaks corresponds to a chemical with an accurate mass and predicted formula:

$C_{17}H_{19}NO_3$

Multiple chemicals can have the same mass and formula:





Is chemical A present, chemical B, or both?

Slide from Jon Sobus

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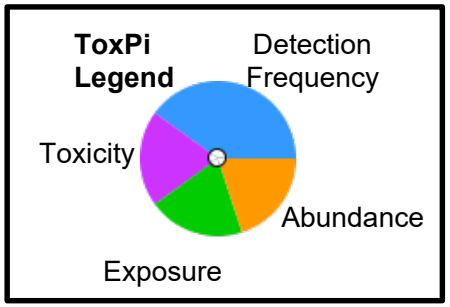
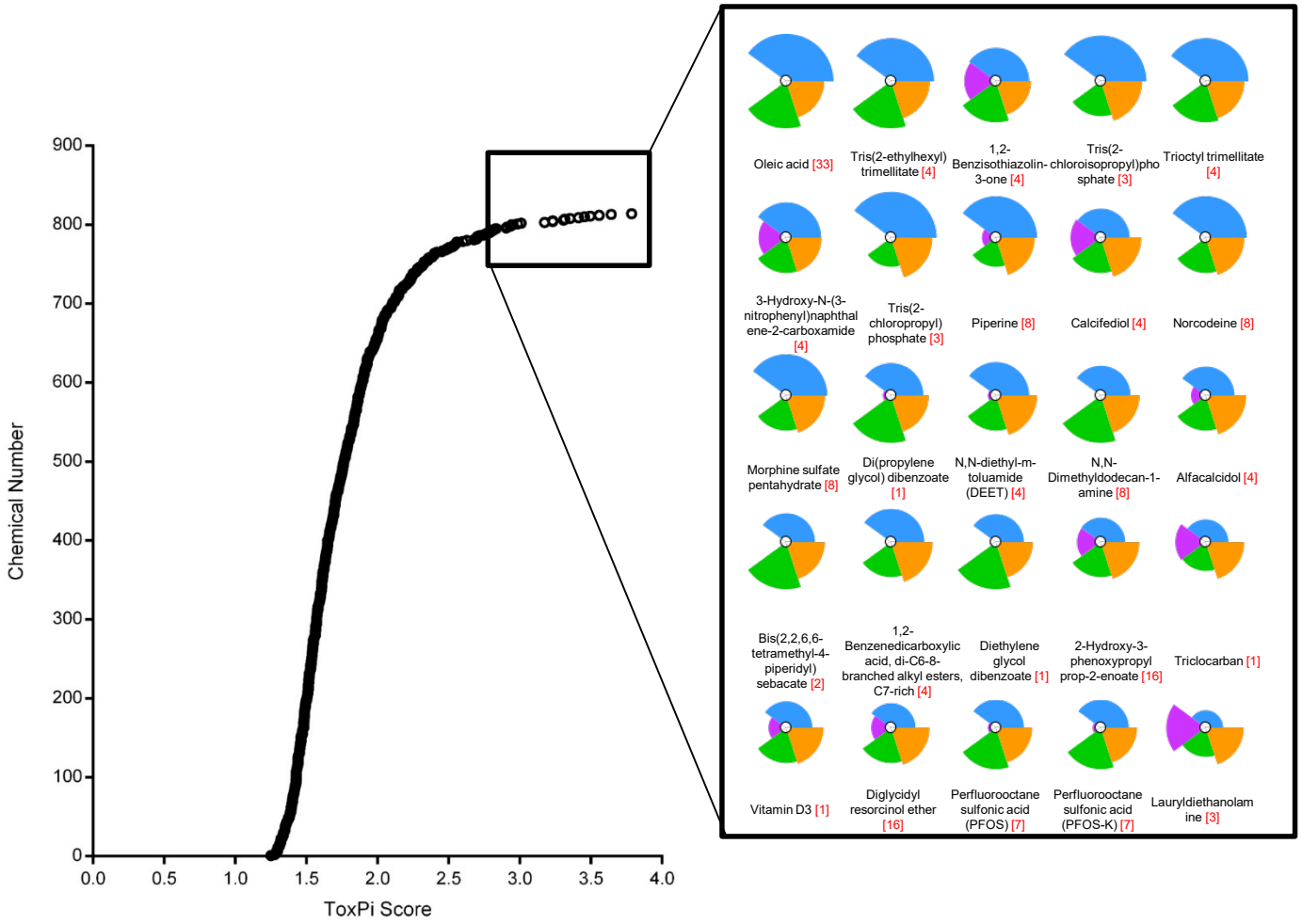
1944 Nobel Prize in Chemistry for "discovery of the fission of heavy nuclei"

Hahn and Strassmann (1938)

Prioritizing Chemical Matches





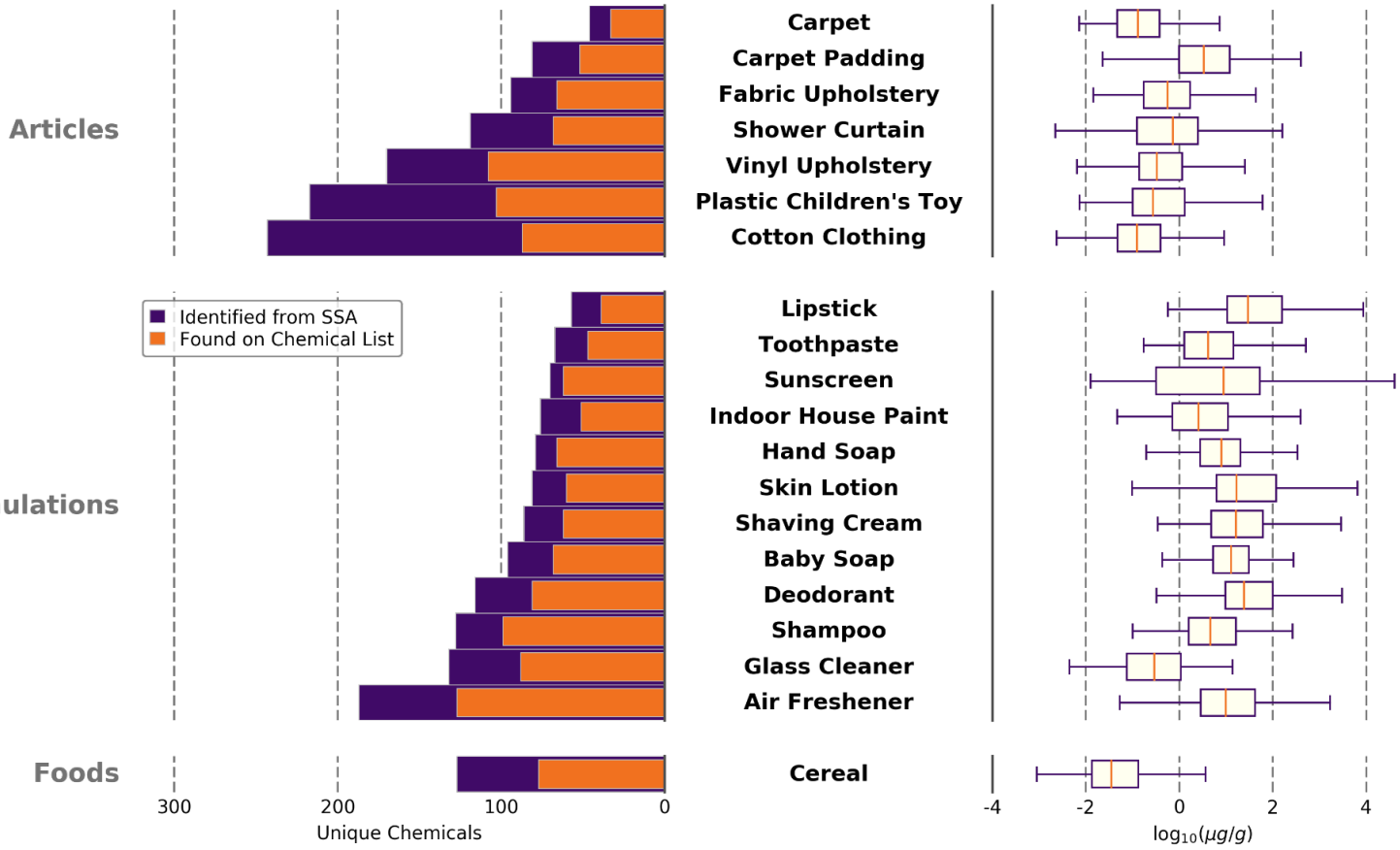
Rager et al. (2016)

Household Item Pilot Study

Analyzed 5 examples each of 20 diverse household items.

Not all categories relevant to TSCA, but included to illustrate the flexibility of the approach.

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



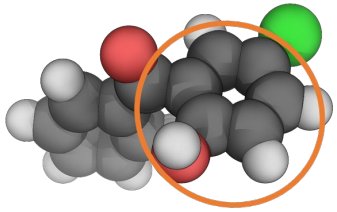
Phillips *et al.* (*submitted*)

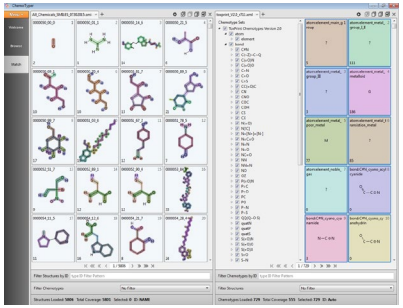
Predicting Function Based on Structure

United States Environmental Protection Agency

Machine Learning Based Classification Models
(Random Forest, Breiman, 2001)

Chemical Structure and Property Descriptors





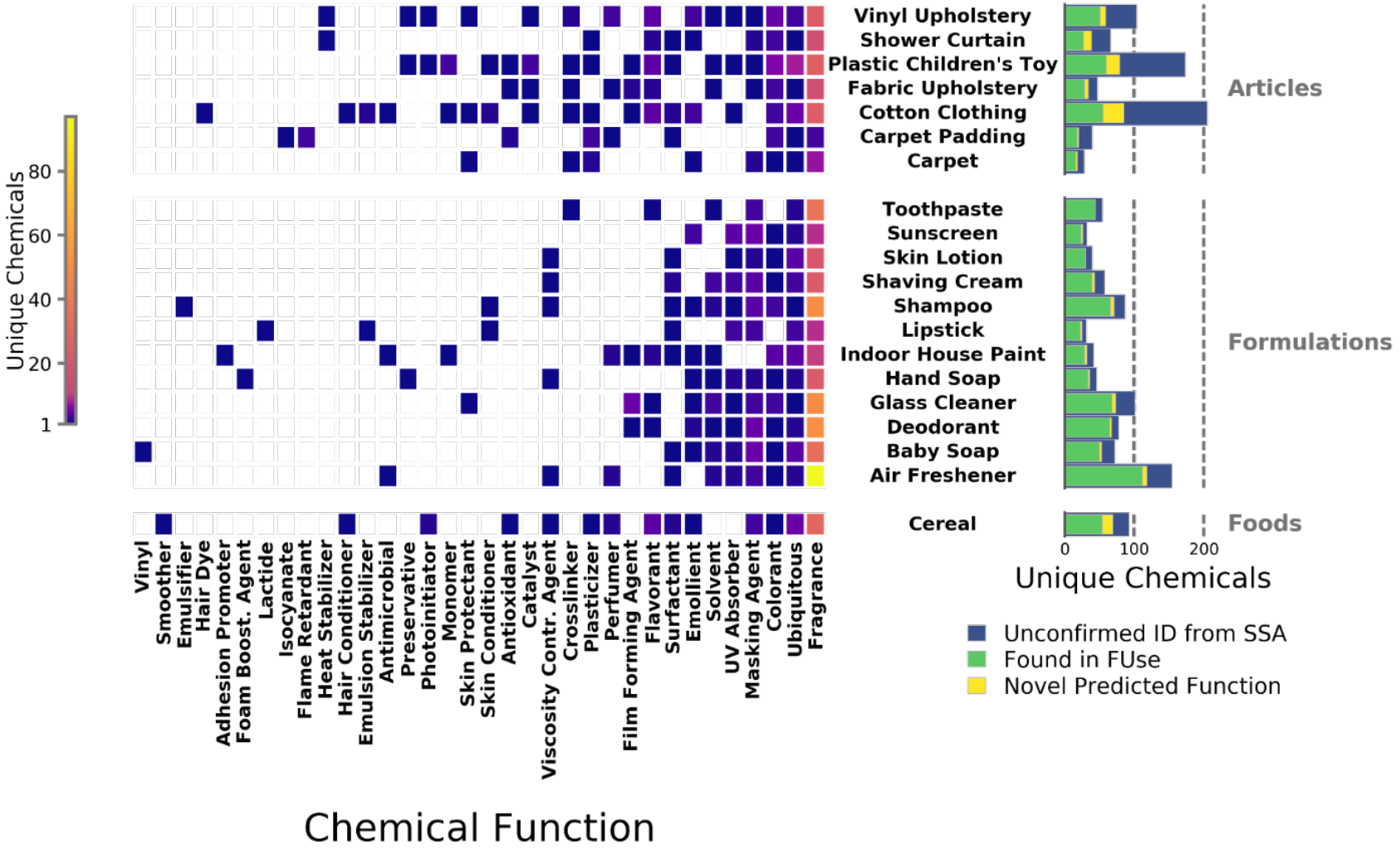
Use Database (FUSE)

Prediction of Of Potential Alternatives from Chemical Libraries

Phillips et al. (2017)

Identifying Chemicals via Predicted Chemical Function

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



Phillips et al. (*2018*)

Conclusions

- New approach methodologies (NAMs) for hazard and toxicokinetics use a blend of *in vitro* and *in silico* methods evaluated with *in vivo* data

- Currently exposure NAMs are purely *in silico*, but are evaluated and calibrated using measured data

"I'm searching for my keys."

- New machine learning tools provide improved high throughput exposure estimates by matching chemicals to exposure pathways and associated calibrated exposure models

- Gaps include:
  - Relative lack of evaluation data (114 NHANES chemicals vs. 800,000 in DSStox database
  - Lack of dietary exposure models
  - Lack of reference data for "negatives" – i.e., chemicals for which there is definitely no exposure by a certain pathway

ExpoCast Project (Exposure Forecasting)

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References

- Borassi, Michele, et al. "On the solvability of the six degrees of kevin bacon game." International Conference on Fun with Algorithms. Springer, Cham, 2014.
- Borgelt, Christian. "Frequent item set mining." Wiley Interdisciplinary Reviews: Data Mining and Knowledge Discovery 2.6 (2012): 437-456.
- Breyer, Stephen. Breaking the vicious circle: Toward effective risk regulation. Harvard University Press, 2009
- Collins, James J., and Carson C. Chow. "It's a small world." Nature 393.6684 (1998): 409.
- Diamond, Jared M. "Assembly of species communities." Ecology and evolution of communities (1975): 342-444.
- Egeghy, P. P., et al. (2012). The exposure data landscape for manufactured chemicals. Science of the Total Environment, 414, 159-166.
- Filer, Dayne L., et al. "tcpl: the ToxCast pipeline for high-throughput screening data." Bioinformatics 33.4 (2016): 618-620.
- Hertzberg, Robert P., and Andrew J. Pope. "High-throughput screening: new technology for the 21st century." Current opinion in chemical biology 4.4 (2000): 445-451.
- Hopkins, Brian. "Kevin Bacon and graph theory." Problems, Resources, and Issues in Mathematics Undergraduate Studies 14.1
- Judson, Richard, et al. "The toxicity data landscape for environmental chemicals." Environmental health perspectives 117.5 (2008): 685-695.
- Kaewkhaw, Rossukon, et al. "Treatment paradigms for retinal and macular diseases using 3-D retina cultures derived from human reporter pluripotent stem cell lines." Investigative ophthalmology & visual science 57.5 (2016): 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 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.
- 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)
- Schmidt, Charles W. "TOX 21: new dimensions of toxicity testing." (2009): A348-A353.
- Tornero-Velez, Rogelio, Peter P. Egeghy, and Elaine A. Cohen Hubal. "Biogeographical analysis of chemical co-occurrence data to identify priorities for mixtures research." Risk Analysis: An International Journal 32.2 (2012): 224-236.
- Travers, Jeffrey, and Stanley Milgram. "An experimental study of the small world problem." Social Networks. Academic Press, 1977. 179-197.
- USGAO. "Toxic substances: EPA has increased efforts to assess and control chemicals but could strengthen its approach." (2013).
- Watts, Duncan J. Six degrees: The science of a connected age. WW Norton & Company, 2004.
- Watts, Duncan J., and Steven H. Strogatz. "Collective dynamics of ‘small-world’ networks." nature 393.6684 (1998): 440.
- 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.