United States Environmental Protection Agency

ExpoCast
exposure forecasting

New Approach Methodologies for Exposure from EPA's ExpoCast Project

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SCIENTIFIC ADVISORY COMMITTEE ON ALTERNATIVE TOXICOLOGICAL METHODS
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United States Environmental Protection Agency

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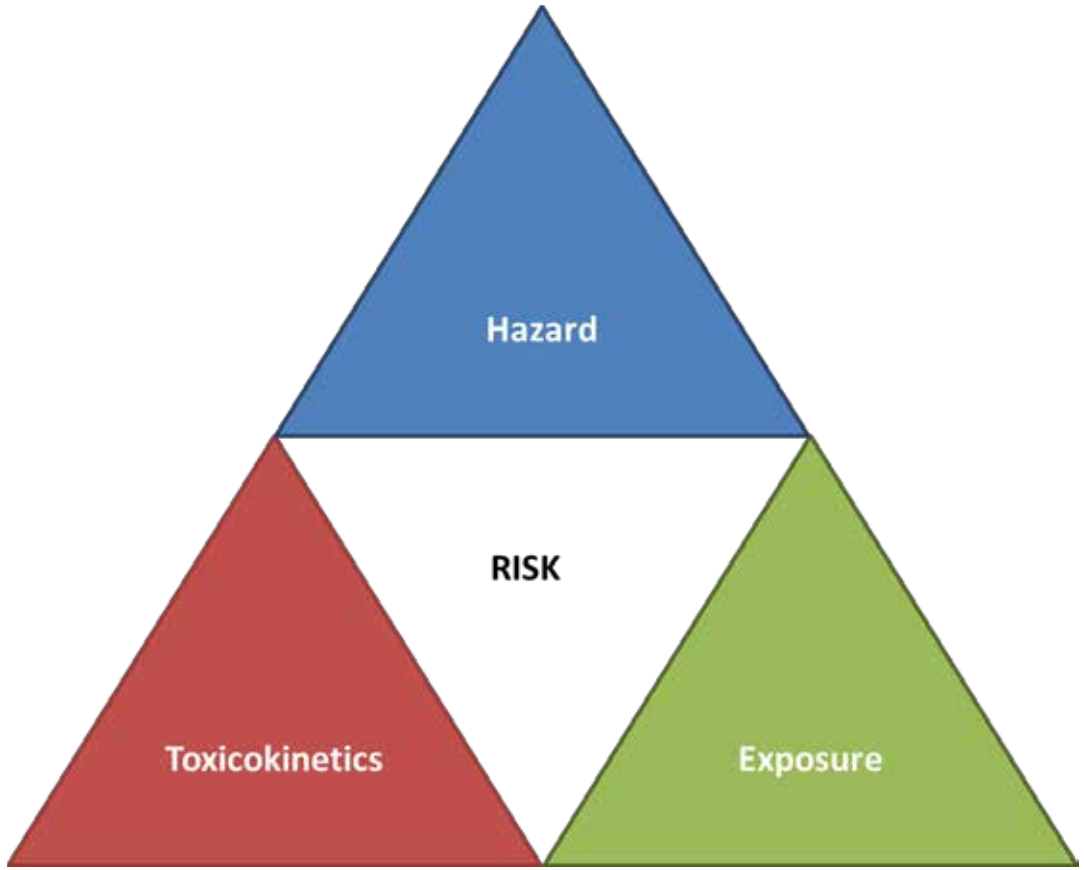
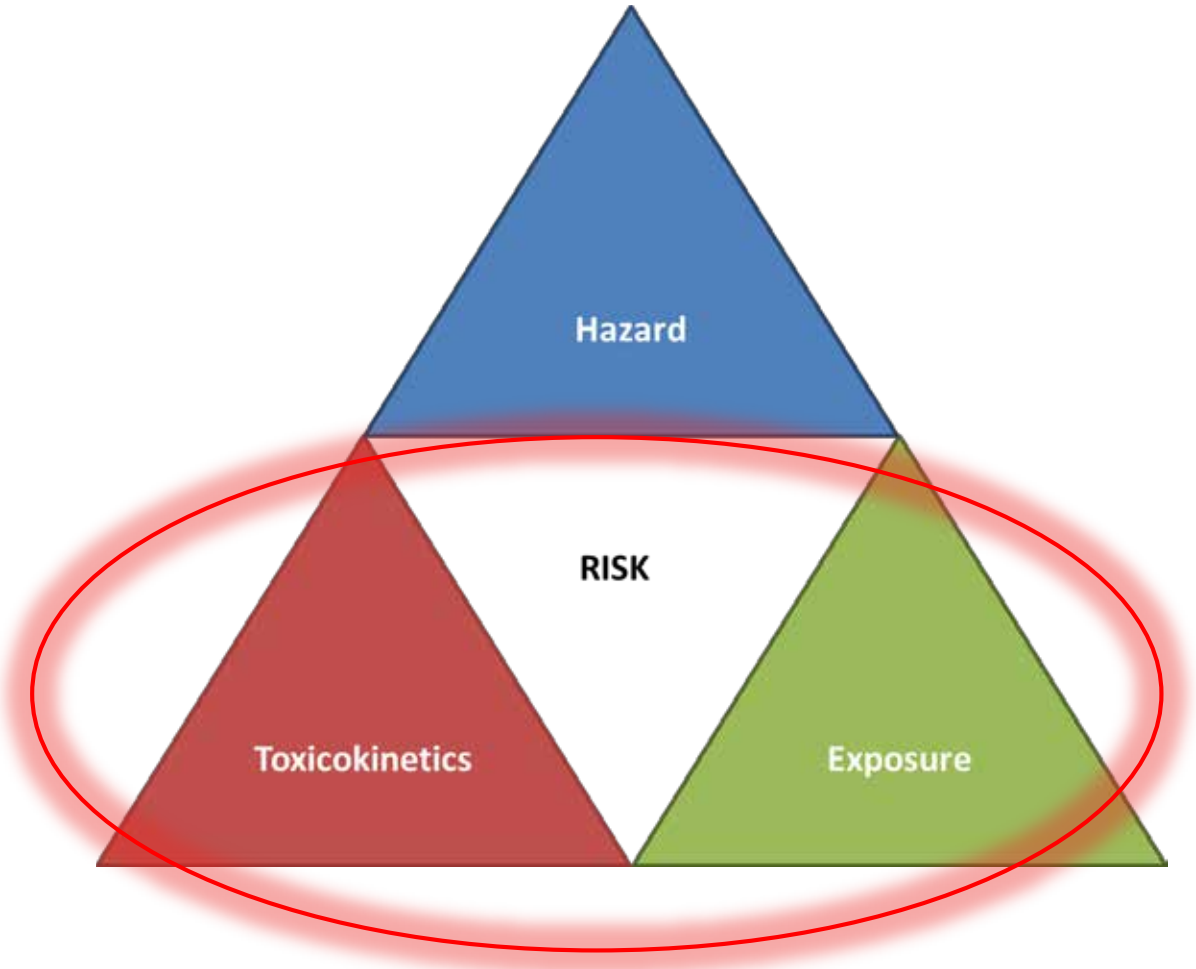
Risk is Multifaceted

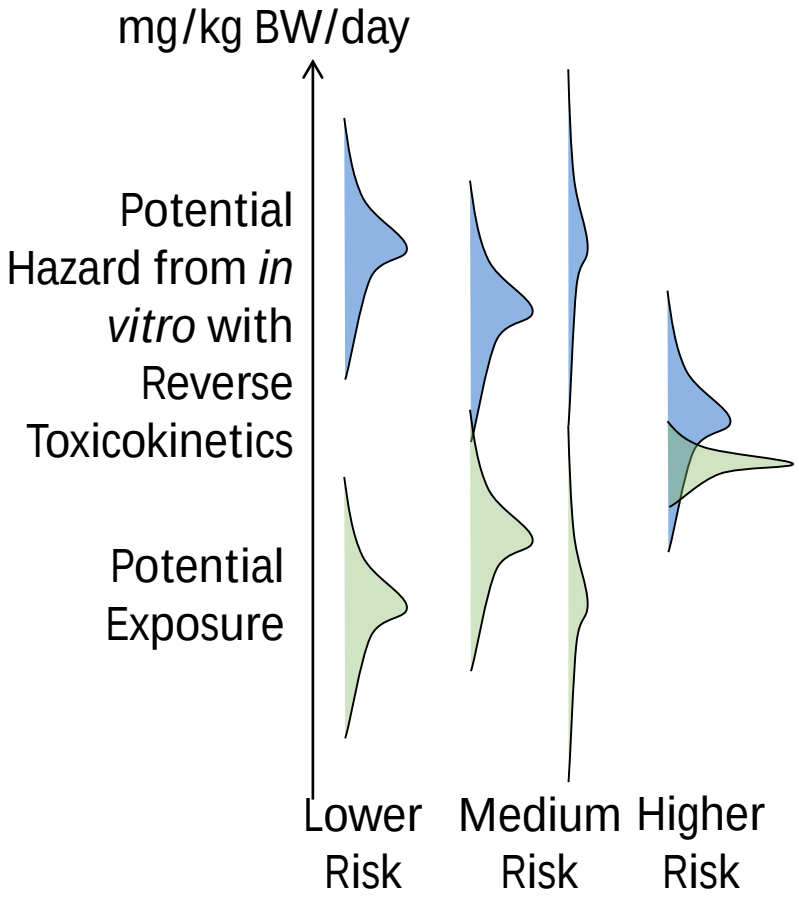


- EPA is charged with evaluating risks associated with 1000s of chemicals in commerce
  - For example, as of June 2017 there were **67,709** chemicals on the TSCA Inventory
- Evaluating chemicals for risk to humans or the environment requires information on hazard and exposure potential
- Exposure potential quantifies the degree of contact between a chemical and a receptor
- Toxicokinetic information is required to bridge hazard and exposure (what real-world exposure is required to produce an internal concentration consistent with a potential hazard?)

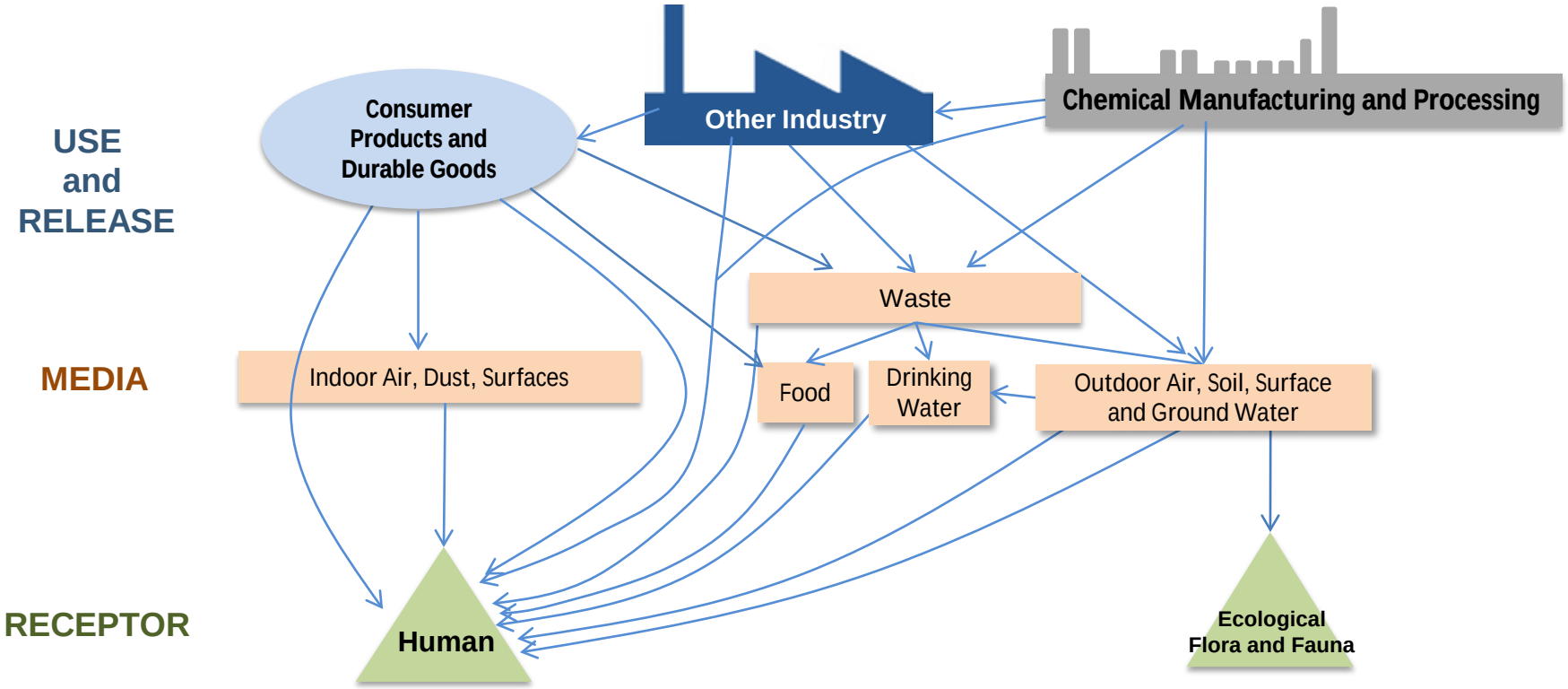
Risk is Multifaceted



EPA's ExpoCast Project



Forecasting Exposure is a Systems Problem



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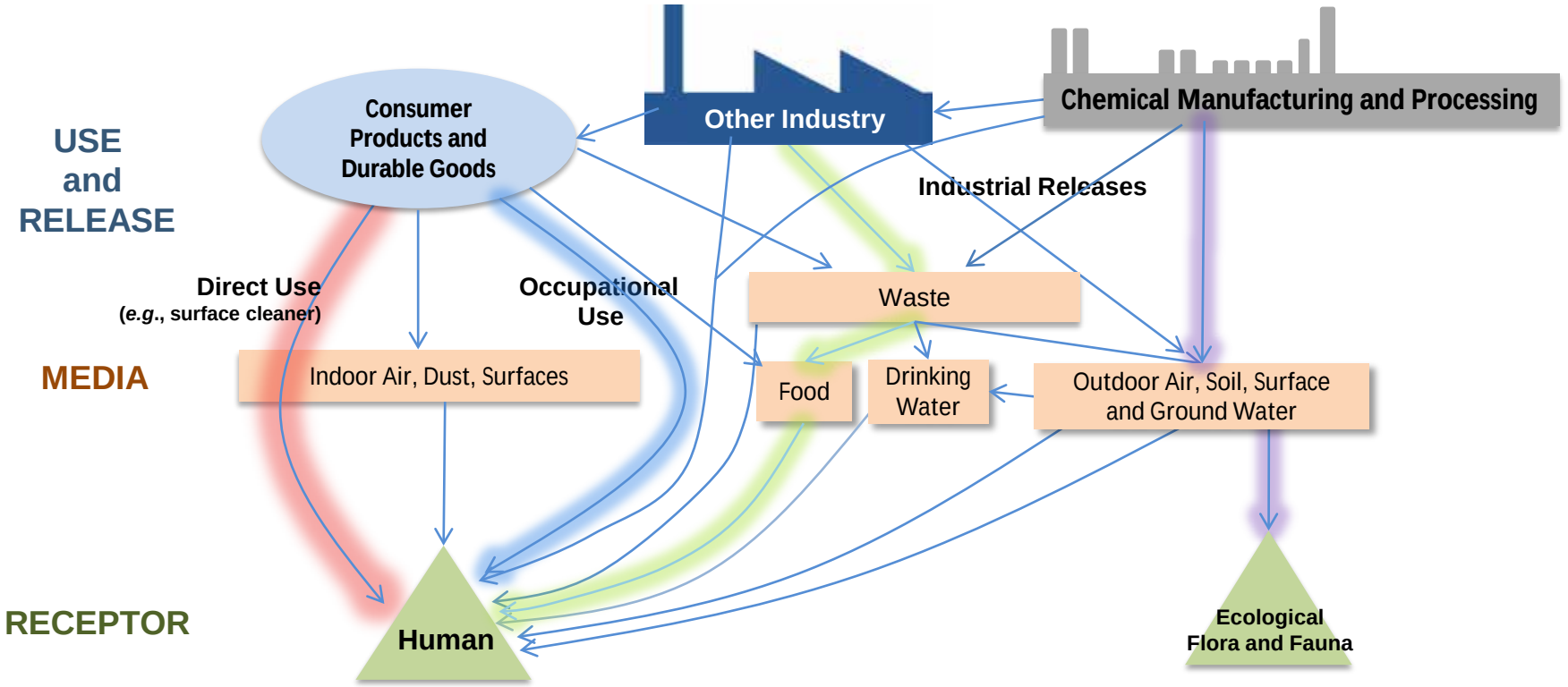


EPA Considers 4 Pathway Types:

Consumer

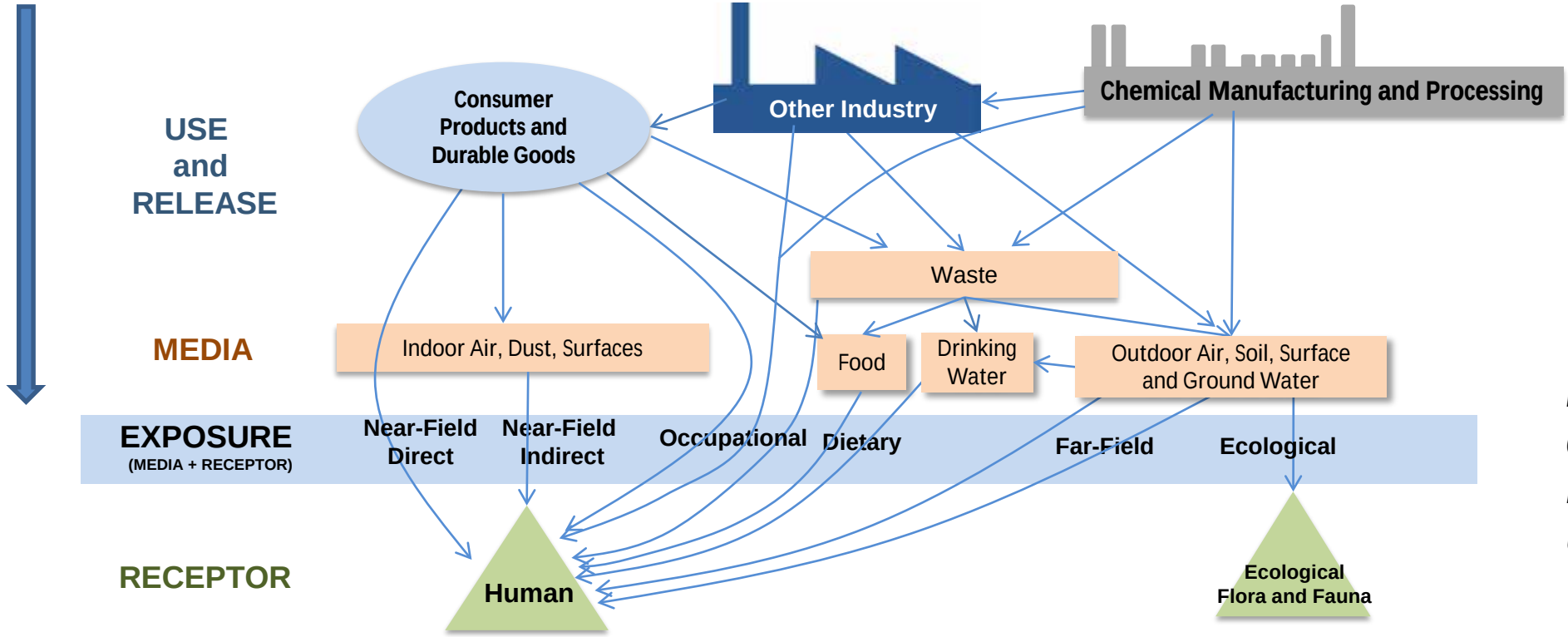
Occupational

Ambient

Ecological

Forecasting Exposure is a Systems Problem

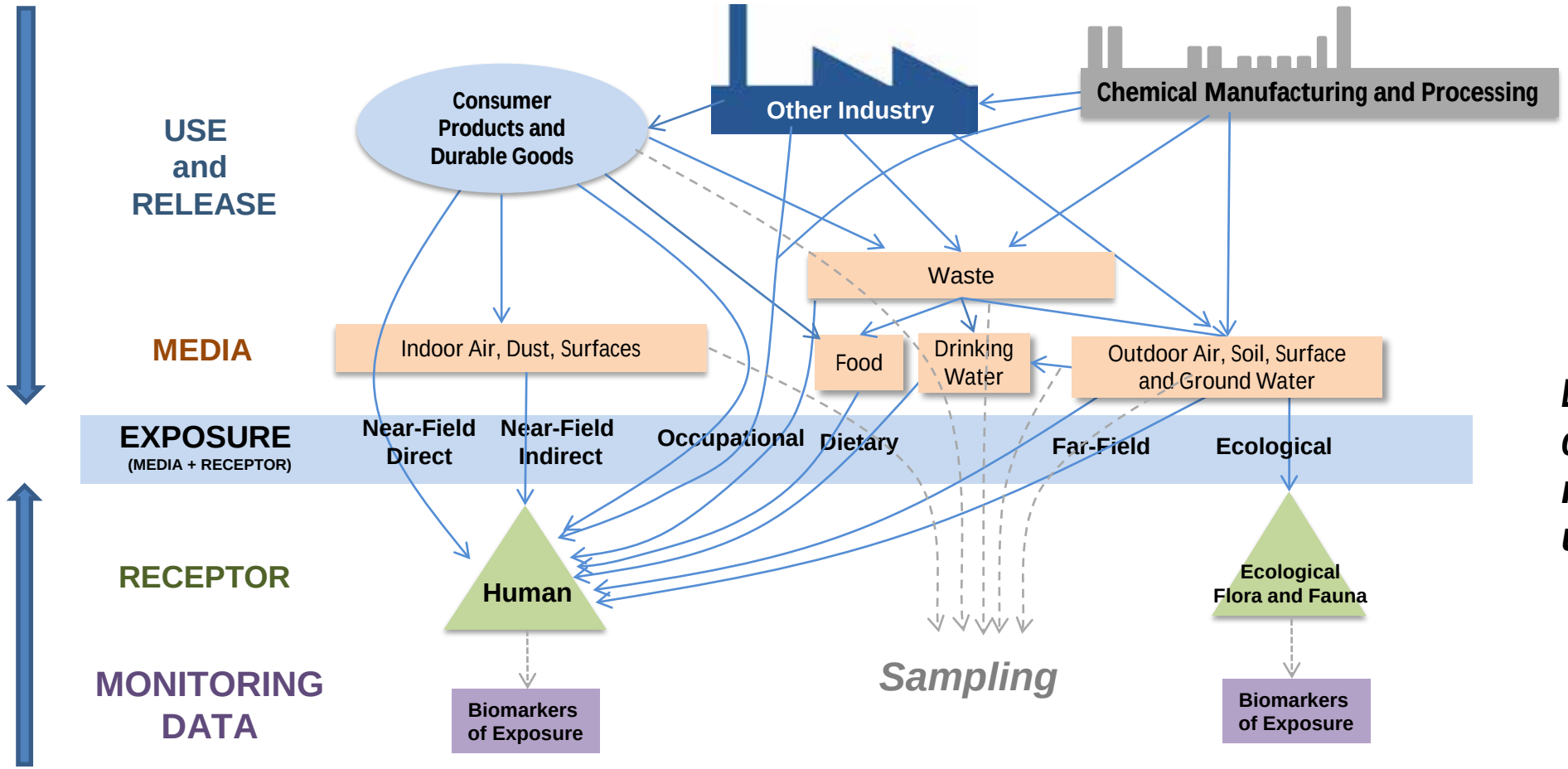
Forward Models for Pathways



Exposure (e.g., chemical intake in mg/kg/day) is unobservable

Forecasting Exposure is a Systems Problem

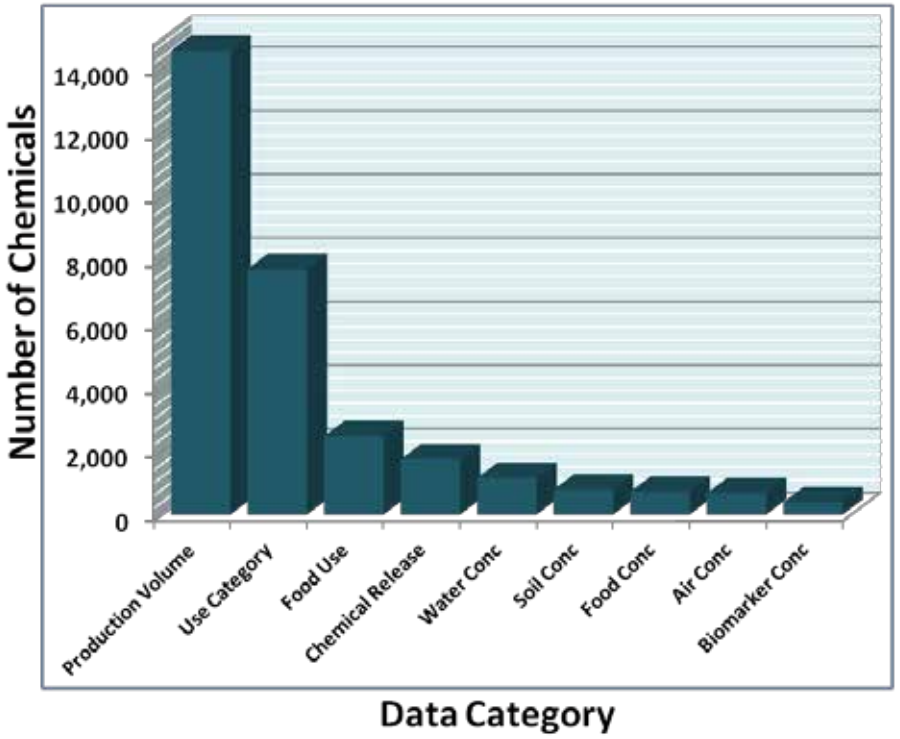
Forward Models for Pathways



Exposure (e.g., chemical intake in mg/kg/day) is unobservable

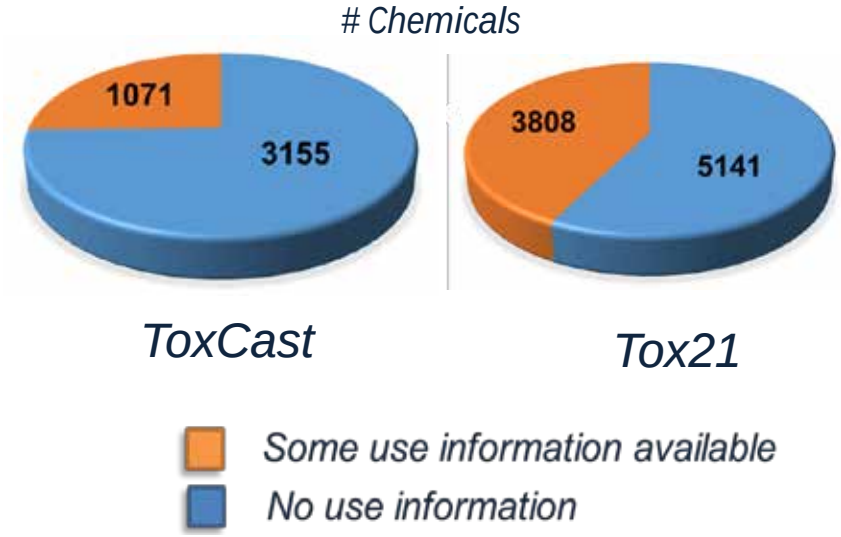
Evaluation

Traditional Exposure Data Are Limited



Egeghy et al. (2012)

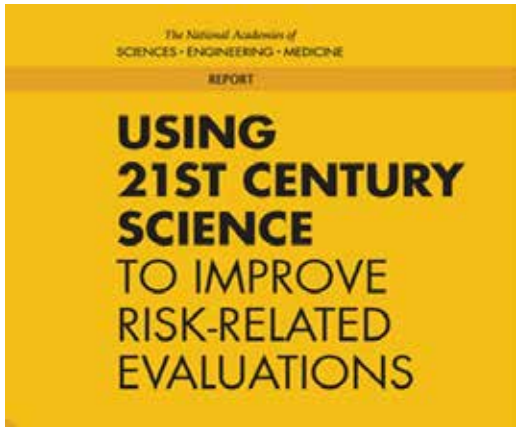
Use category information for chemicals being tested via high throughput screening at EPA



The ExpoCast project and its collaborators are working to fill gaps in exposure data for 1000s of chemicals using high-throughput ***new approach methodologies (NAMs)*** *for exposure*

New Approach Methodologies and Exposure

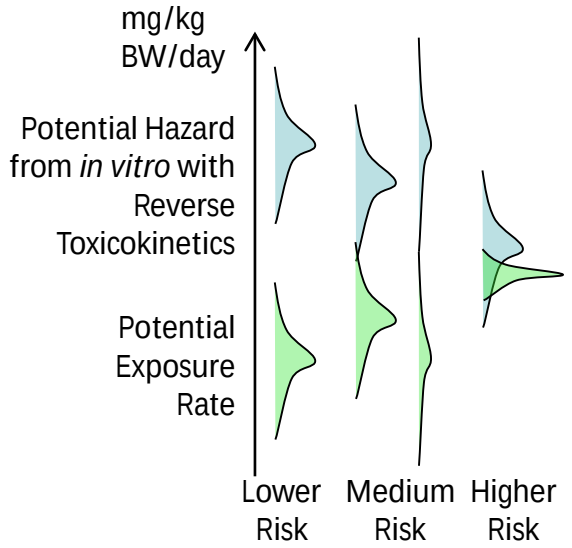
*"NAMs were taken in a broad context to **include in silico approaches**, in chemico and in vitro assays, as **well as the inclusion of information from the exposure of chemicals** in the context of hazard assessment"*



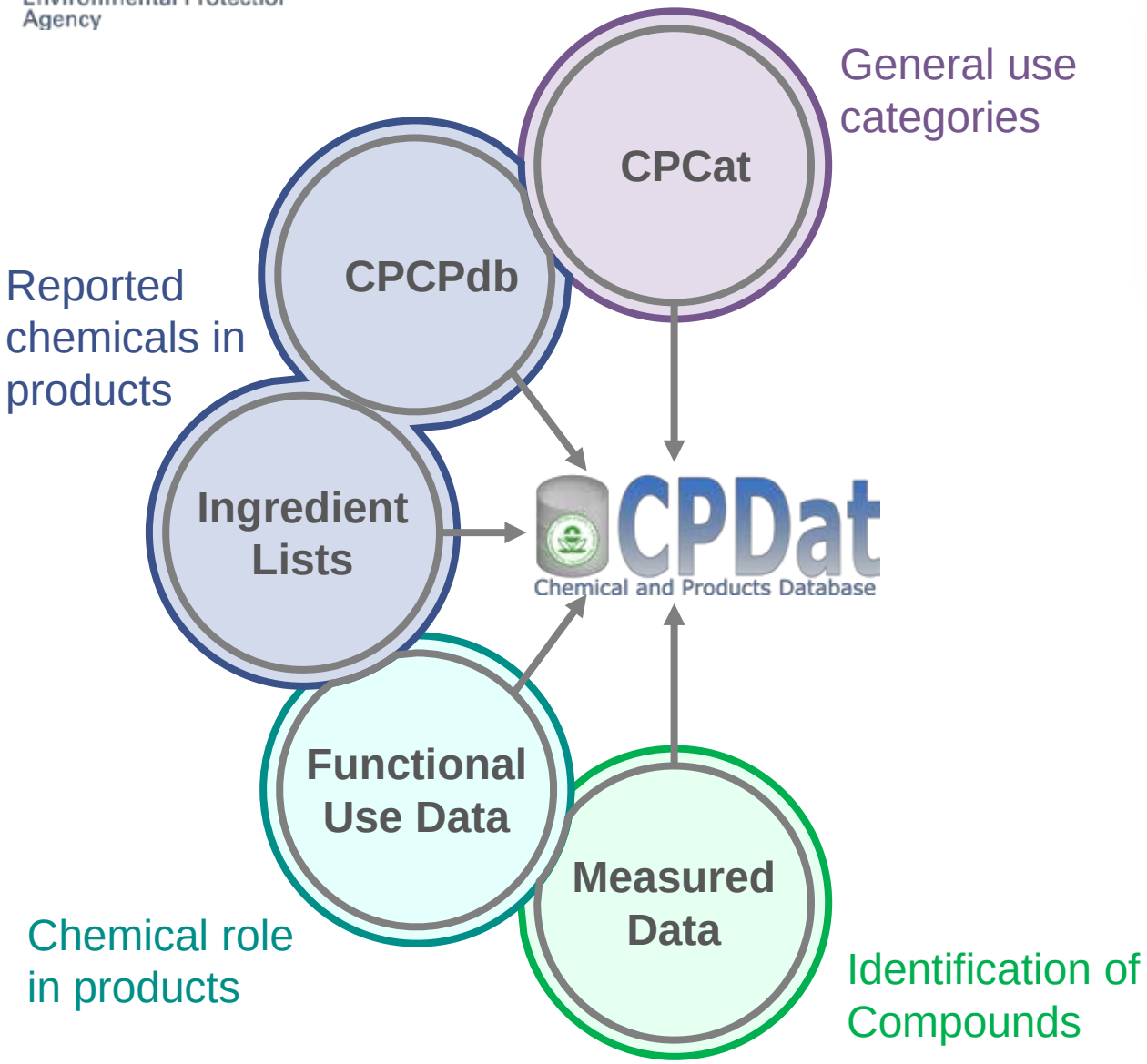
*"…the committee sees the potential for the application of **computational exposure science** to be highly valuable and credible for comparison and priority-setting among chemicals in a risk-based context."*

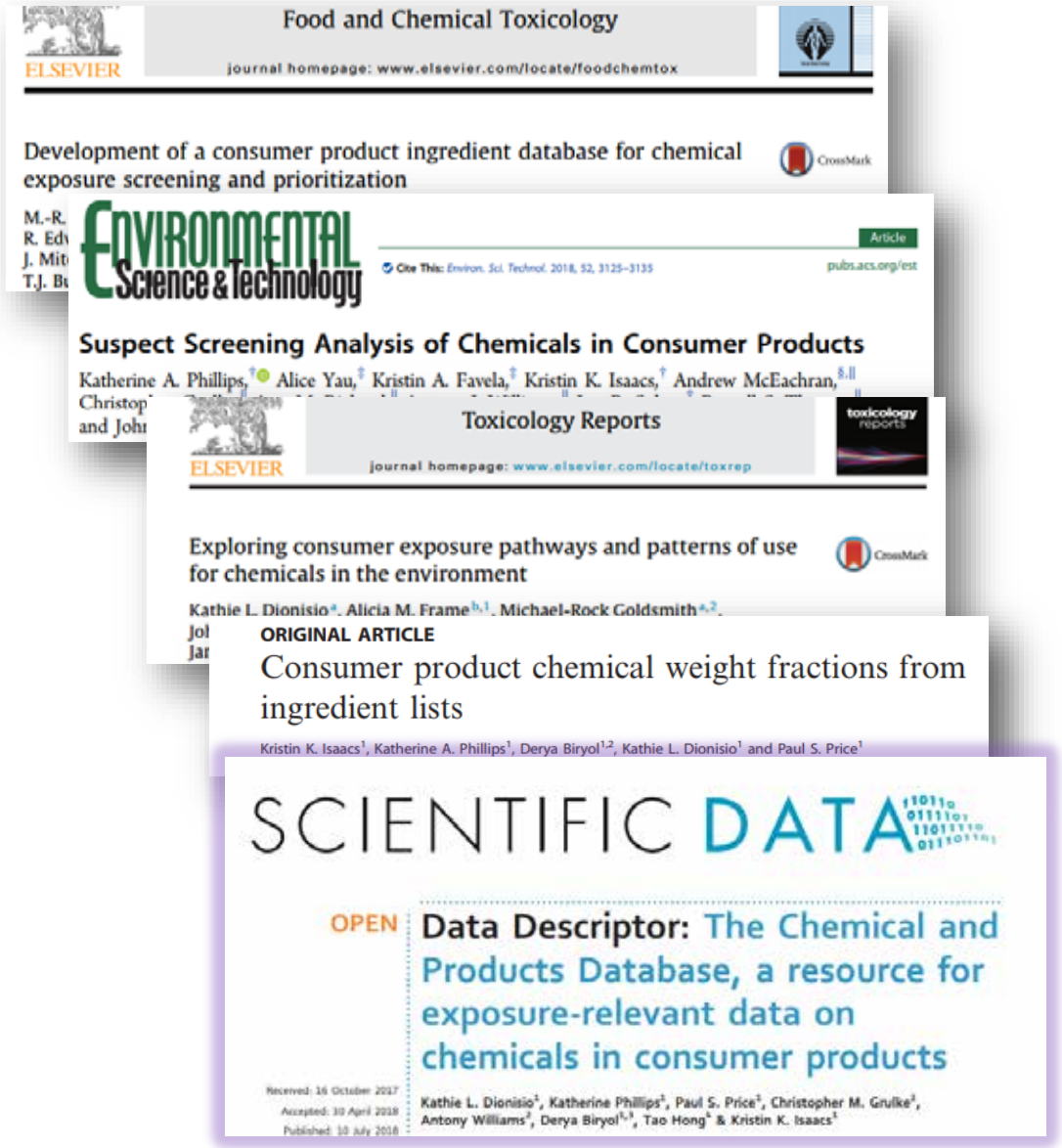
Eight Classes of NAMs for Exposure

- ***Chemical descriptors*** that provide information on chemicals in an exposure context (e.g., how chemicals are used)
- ***Machine-learning approaches*** that use these descriptors to fill gaps in existing data
- ***High-throughput exposure models*** for various pathways
- ***High-throughput measurements*** to fill gaps in monitoring data
- High-throughput approaches for measuring and predicting chemical ***toxicokinetics***
- New ***evaluation frameworks*** for integrating models and monitoring to provide consensus exposure predictions
- All these pieces together provide the tools for high-throughput ***chemical prioritization***



Chemical Descriptor NAMs

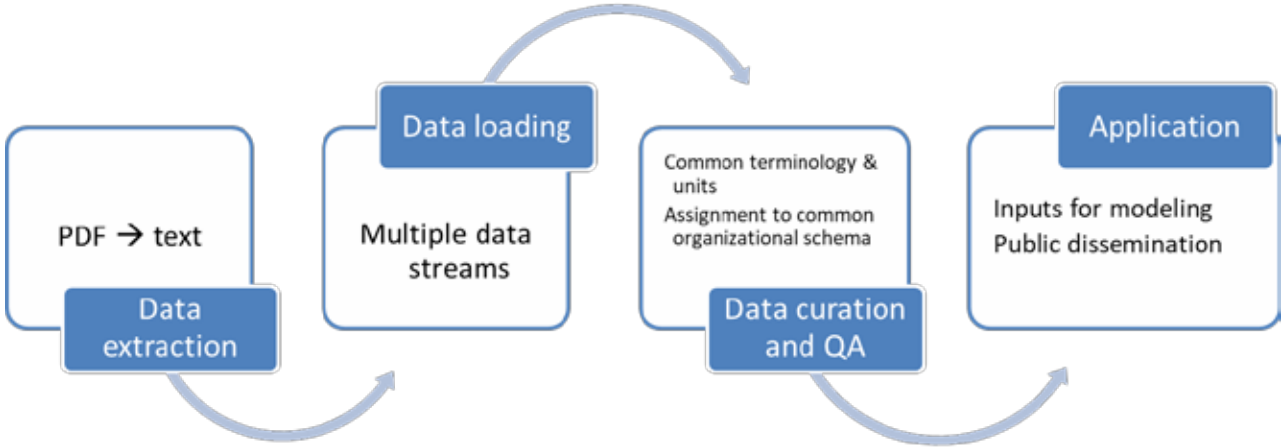




https://comptox.epa.gov/dashboard

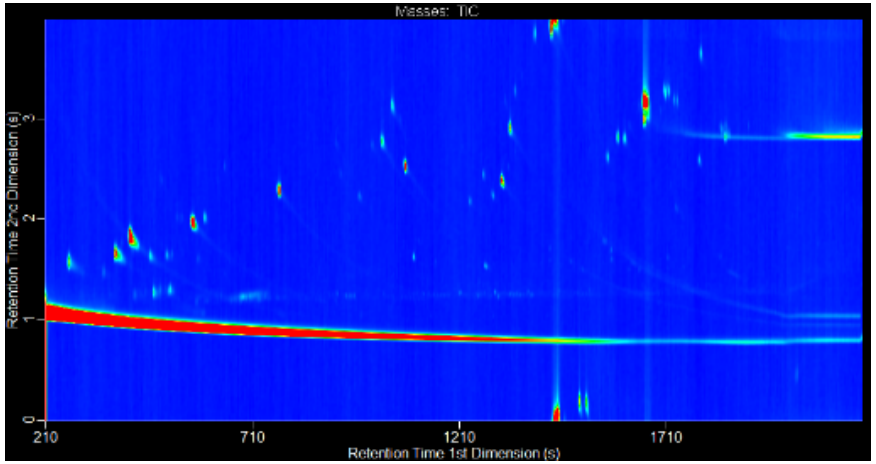
Chemical Descriptor NAMs

- We are using informatics approaches to obtain and curate additional chemical descriptor information
- Data from chemical use, monitoring, and release domains
- Public data sources: reports, open literature, databases
- Focus on expanding to critical pathways (e.g., occupational)



High-throughput Measurement NAMs

High Resolution Mass Spectrometry



- Targeted Analysis:
  - We know exactly what we're looking for
  - 10s – 100s of chemicals
- Non-Targeted Analysis (NTA):
  - We have no preconceived lists
  - 1,000s – 10,000s of chemicals
- Ongoing consumer product scanning and blood sample monitoring via contract (NTA and confirmation of tentative IDs with available standards
- Development of significant in-house capabilities
- EPA is coordinating a comparison of non-targeted screening workflows used by leading academic and government groups using known chemical mixtures (ToxCast) and standardized environmental/biological samples
- Goal is to develop tools, databases, and workflows for rapid analysis of any sample for chemicals of interest, i.e. ***exposure forensics***

NTA Studies in the ExpoCast Project

Consumer Products

- Pilot study of 20 classes of products, including clothing, personal care products, carpet padding, cleaners
- 5 products from each category
- GC X GC/MS
- Phillips *et al.*, *Env. Sci. Tech*. 2018

Recycled Materials

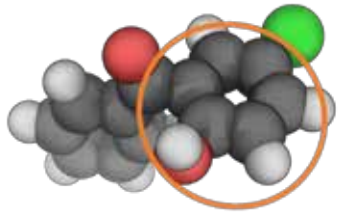
- Products from six categories of recycled products, including building materials, paper products, toys, and clothing
- 20 products per category with 50% recycled material, 8 products virgin materials
- GC X GC/MS
- Lowe *et al.*, in prep

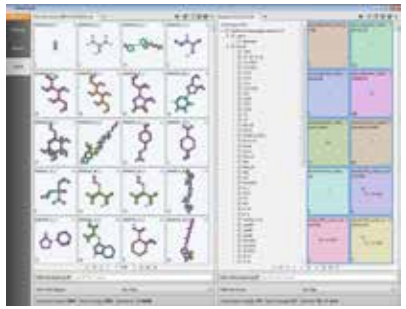
Residential Dust

- Dust samples from 56 U.S. homes in the American Health Homes Survey
- LC/MS
- Rager *et al.*, *Env. Int.*, 2016

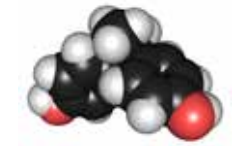
Machine Learning NAMs

Training Sets of Chemical Descriptor NAMS





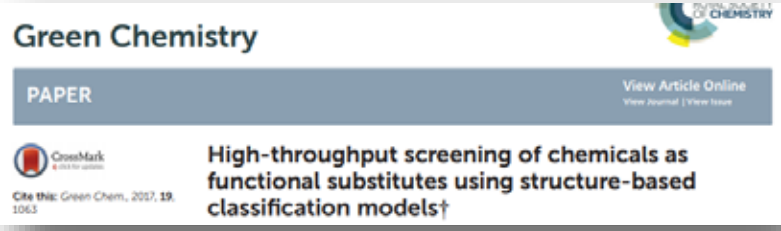
Prediction of Potential Alternatives from Chemical Libraries



YES NO

Machine Learning Based Classification Models

(Random Forest, Breiman, 2001)


Green Chemistry

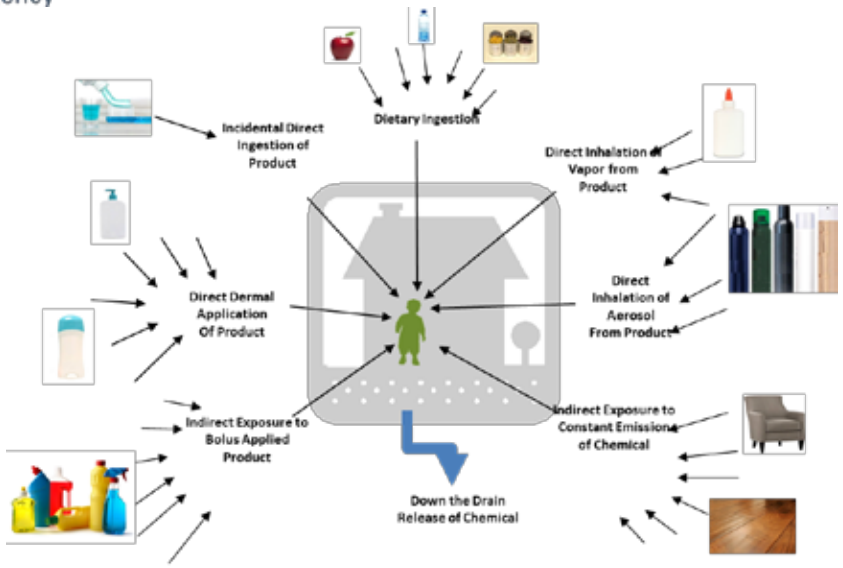
PAPER

View Article Online

High-throughput screening of chemicals as functional substitutes using structure-based classification models†

Phillips *et al.* (2017)

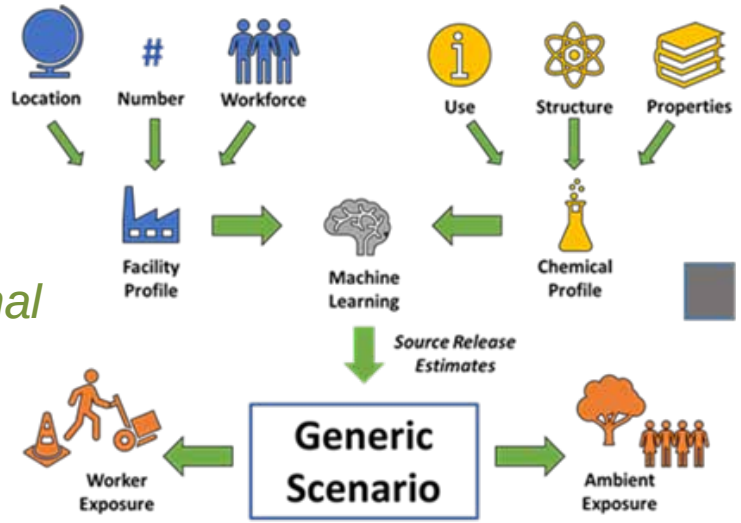
High Throughput Exposure Model NAMs



Consumer

Isaacs *et al.* (2014)

Occupational



Ambient

Meyer *et al.* (2017)

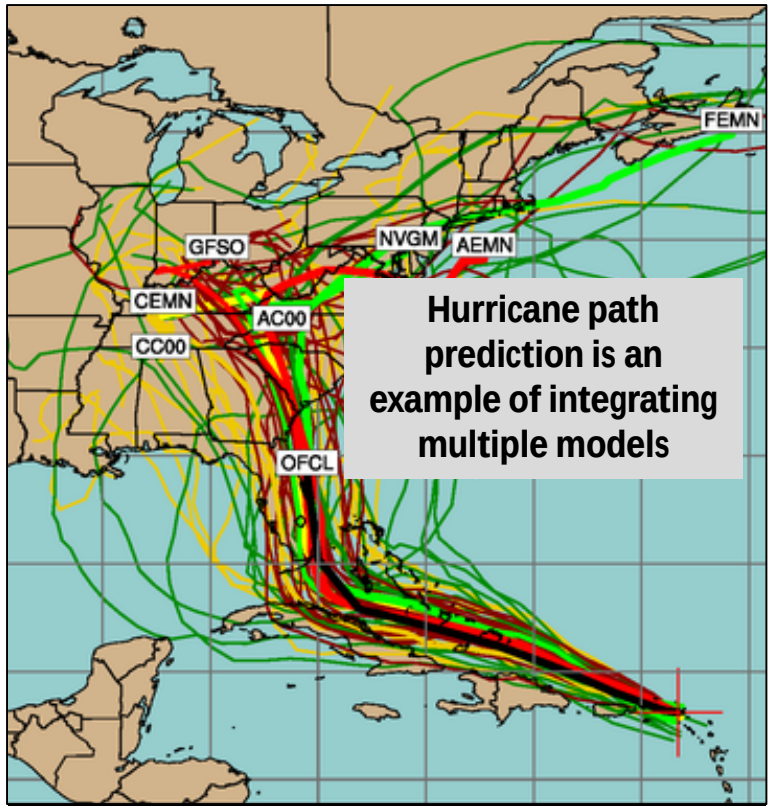
Biryol *et al.* (2017)

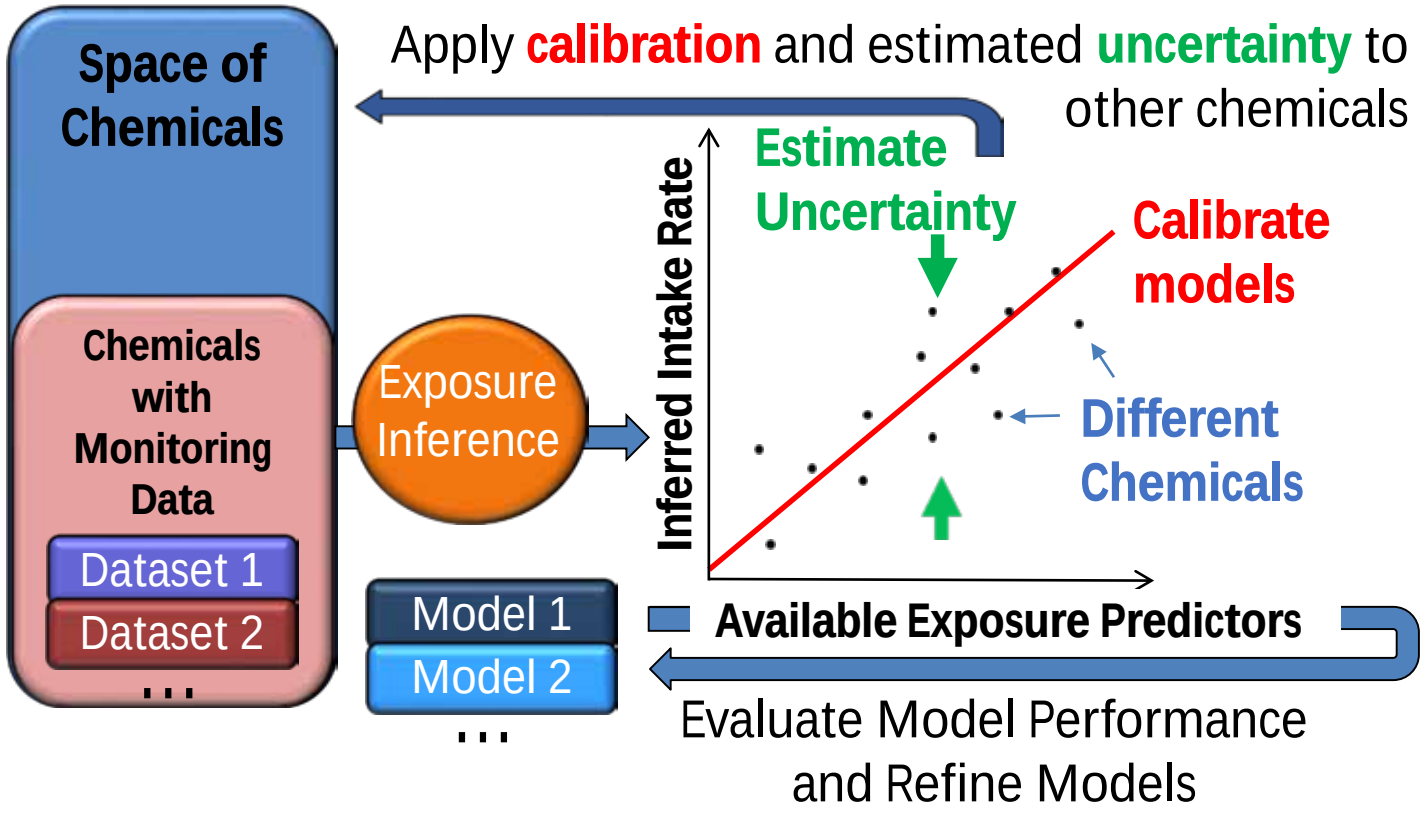
Ecological

Barber *et al.* (2017)

Evaluation NAMs: The SEEM Framework

- We use Bayesian methods to incorporate multiple pathway models into consensus predictions for 1000s of chemicals within the **Systematic Empirical Evaluation of Models (SEEM)**



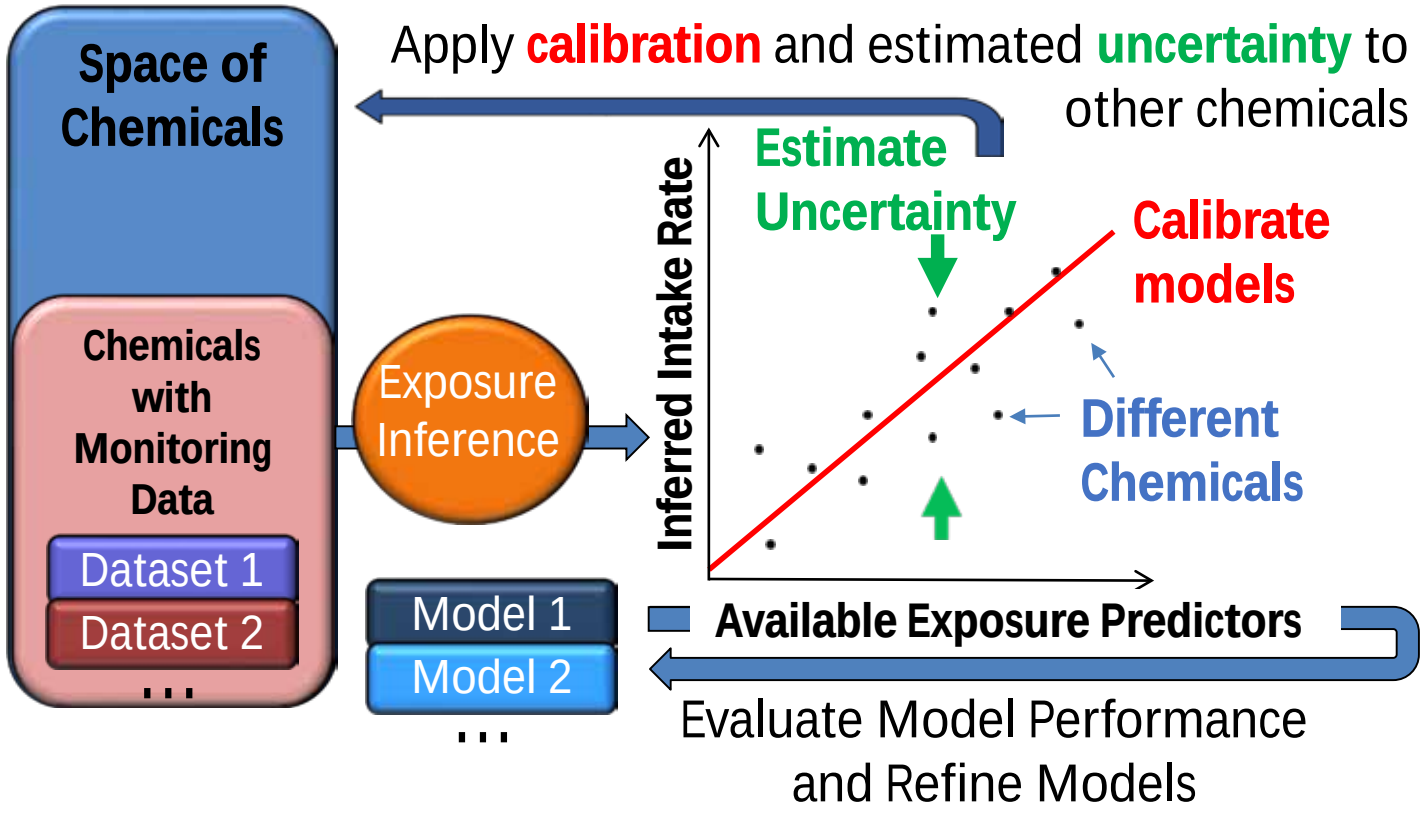


Material from John Wambaugh

Evaluation NAMs: The SEEM Framework

- We use Bayesian methods to incorporate multiple pathway models into consensus predictions for 1000s of chemicals within the **Systematic Empirical Evaluation of Models (SEEM)**

- ExpoCast is developing SEEM Models for multiple receptors and pathways
- **Human** (Wambaugh et al., 2013, 2014; Ring et al., 2018)
  - Evaluated with NHANES biomonitoring data
- **Ecological** (Sayre et al., *in prep*)
  - Evaluated with USGS water data
- **Occupational** (planned)
  - Evaluated with OSHA occupational monitoring data



Material from John Wambaugh

Human SEEM Model (3rd Generation) Collaboration

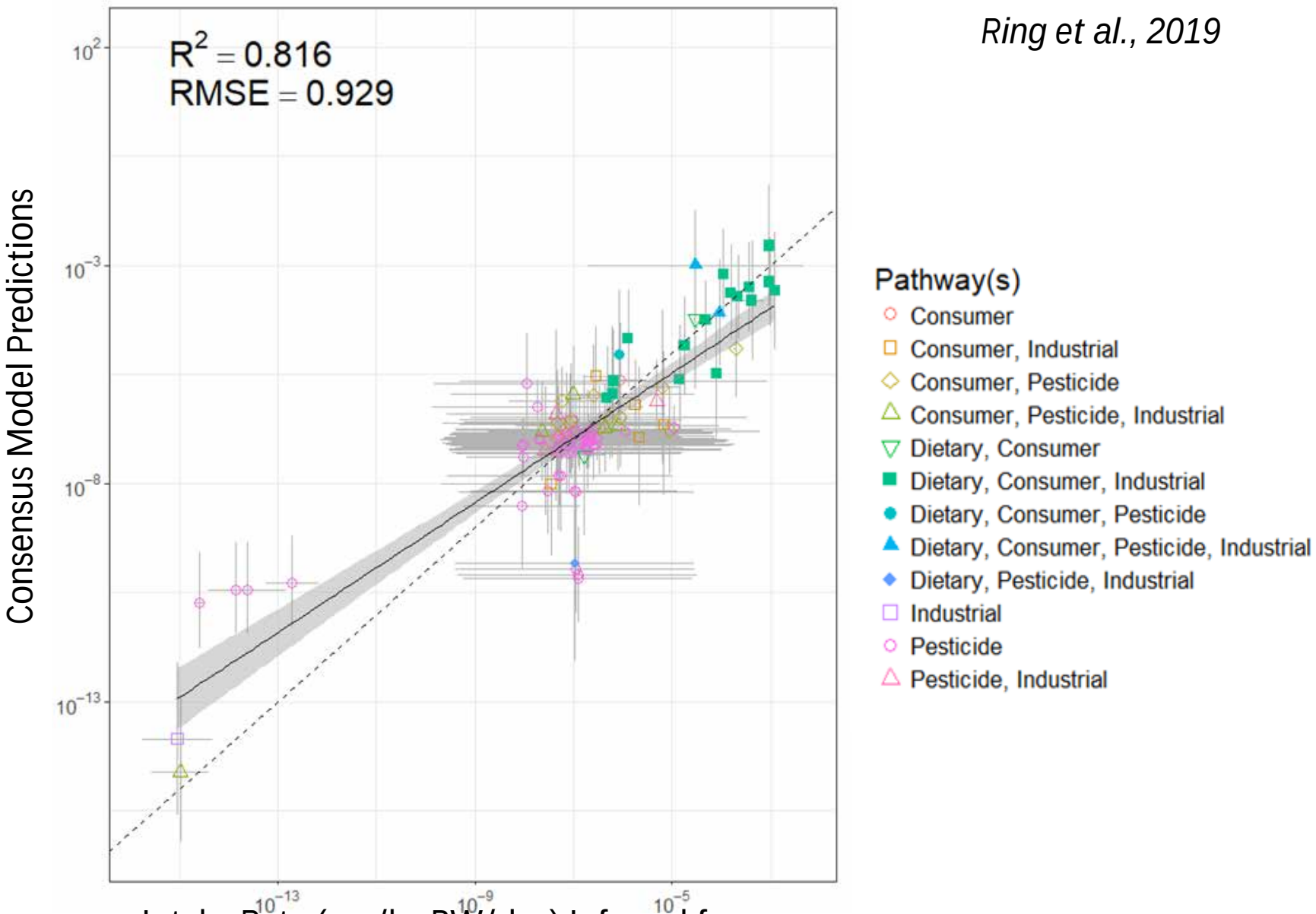
Jon Arnot, Deborah H. Bennett, Peter P. Egeghy, Peter Fantke, Lei Huang, Kristin Isaacs, Olivier Jolliet, Hyeong-Moo Shin, Katherine A. Phillips, Caroline Ring, R. Woodrow Setzer, John F. Wambaugh, Johnny Westgate

Predictor (including Models)	Reference(s)	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
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)	Fantke et al. (2011, 2012, 2016)	940	Far-Field Pesticide
Risk Assessment IDentification And Ranking (RAIDAR) Far-Field (2.02)	Arnot et al. (2008)	8167	Far-Field Pesticide
EPA Stochastic Human Exposure Dose Simulator High Throughput (SHEDS-HT) Near-Field Direct (2017)	Isaacs (2017)	7511	Far-Field Industrial and Pesticide
SHEDS-HT Near-field Indirect (2017)	Isaacs (2017)	1119	Residential
Fugacity-based INdoor Exposure (FINE) (2017)	Bennett et al. (2004), Shin et al. (2012)	645	Residential
RAIDAR-ICE Near-Field (0.803)	Arnot et al., (2014), Zhang et al. (2014)	1221	Residential
USEtox Residential Scenario (2.0)	Jolliet et al. (2015), Huang et al. (2016,2017)	615	Residential
USEtox Dietary Scenario (2.0)	Jolliet et al. (2015), Huang et al. (2016), Ernstoff et al. (2017)	8167	Dietary

Material from John Wambaugh

Human SEEM3: Pathway-Based Consensus Modeling

- Machine learning models were built for each of four exposure pathways
- Pathway predictions can be used for large chemical libraries
- Use prediction (and accuracy of prediction) as a prior for Bayesian analysis
- Each chemical may have exposure by multiple pathways



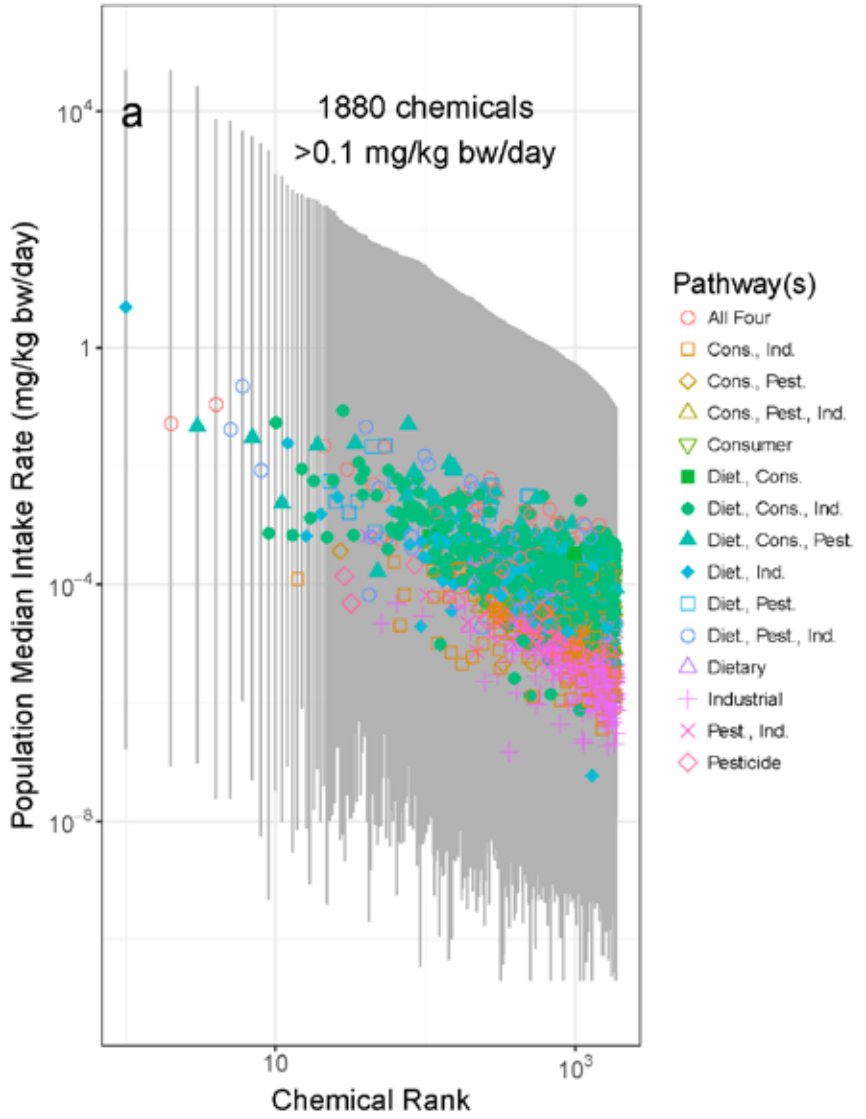
Ring et al., 2019

Material from John Wambaugh

Human SEEM3: Consensus Modeling of Median Chemical Intake

Ring et al., 2019

- We extrapolate to predict relevant pathway(s), median intake rate, and credible interval for each of 479,926 chemicals
- Of the chemicals evaluated, 30% have less than a 50% probability for relevance to any of the four pathways and are considered outside the “domain of applicability”
- This approach identifies 1,880 chemicals for which the median population intake rates may exceed 0.1 mg/kg bodyweight/day.



Material from John Wambaugh

Human SEEM3: Consensus Modeling of Median Chemical Intake

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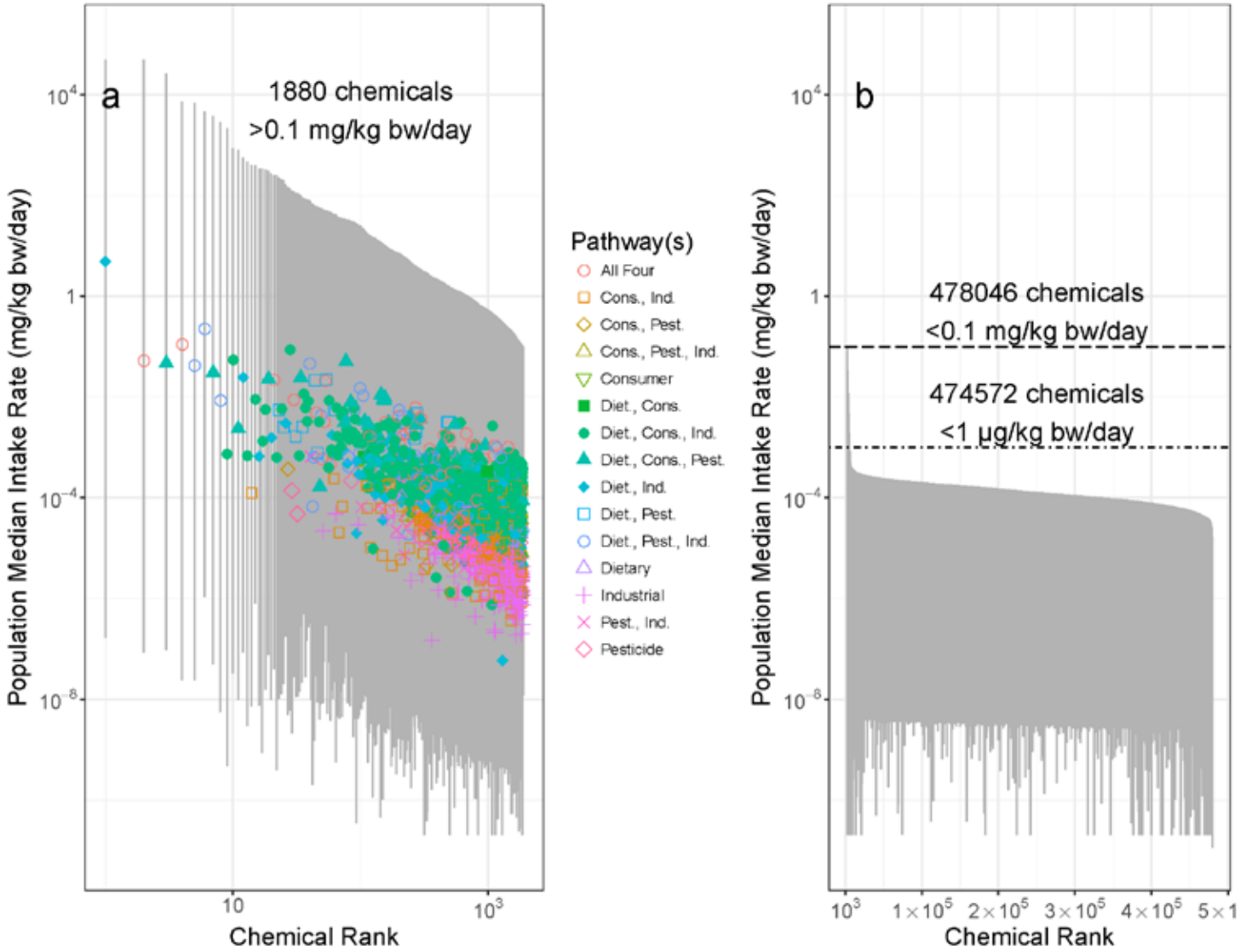
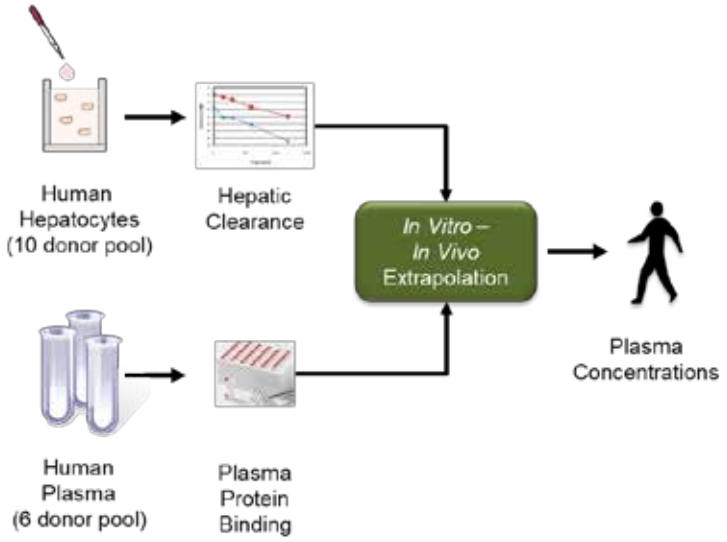
- Of the chemicals evaluated, 30% have less than a 50% probability for exposure via any of the four pathways and are considered outside the “domain of applicability”
- This approach identifies 1,880 chemicals for which the median population intake rates may exceed 0.1 mg/kg bodyweight/day.
- There is 95% confidence that the median intake rate is below 1 µg/kg BW/day for 474,572 compounds.



Material from John Wambaugh

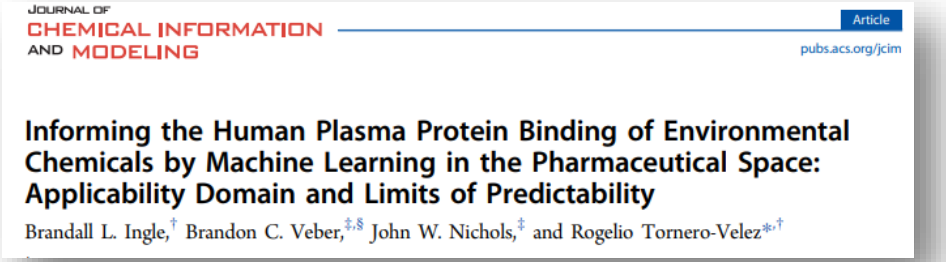
Toxicokinetics NAMs

- Chemical-specific data for toxicokinetics (TK) are as sparse as for exposure
- High throughput TK methods have provided data for nearly 1000 chemicals over the past decade
- However, thousands of chemicals remain requiring machine learning and QSAR approaches



Rotroff et al. (2010) 35 chemicals
Wetmore et al. (2012) +204 chemicals
Wetmore et al. (2015) +163 chemicals
Wambaugh et al. (in prep.) + ~300 chemicals

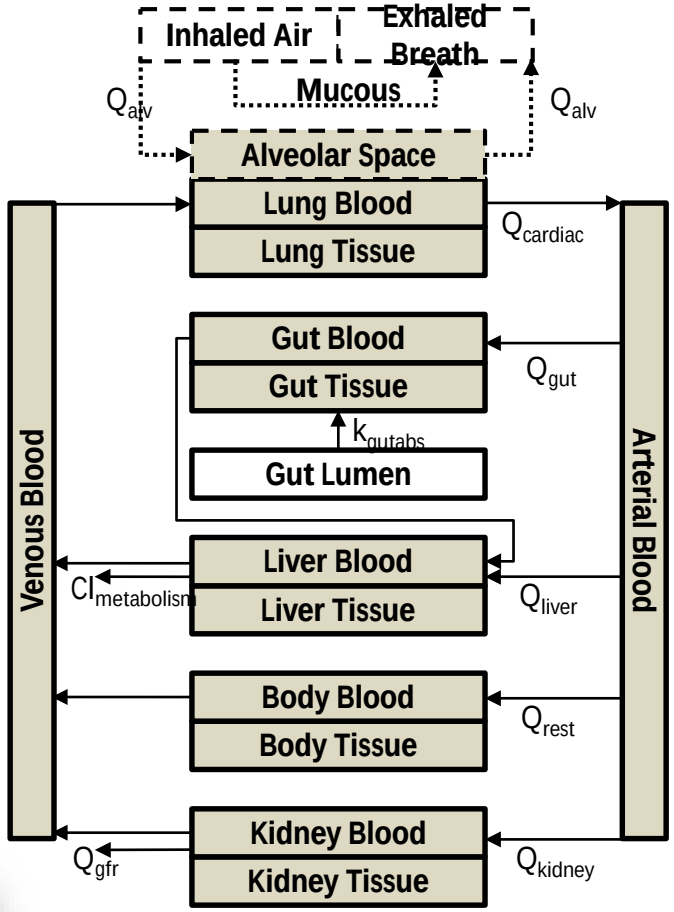
***In vitro* Measurements**


JOURNAL OF CHEMICAL INFORMATION AND MODELING — Article — pubs.acs.org/jcim

Informing the Human Plasma Protein Binding of Environmental Chemicals by Machine Learning in the Pharmaceutical Space: Applicability Domain and Limits of Predictability

Brandall L. Ingle,[†] Brandon C. Veber,[‡,§] John W. Nichols,[‡] and Rogelio Tornero-Velez*[,†]

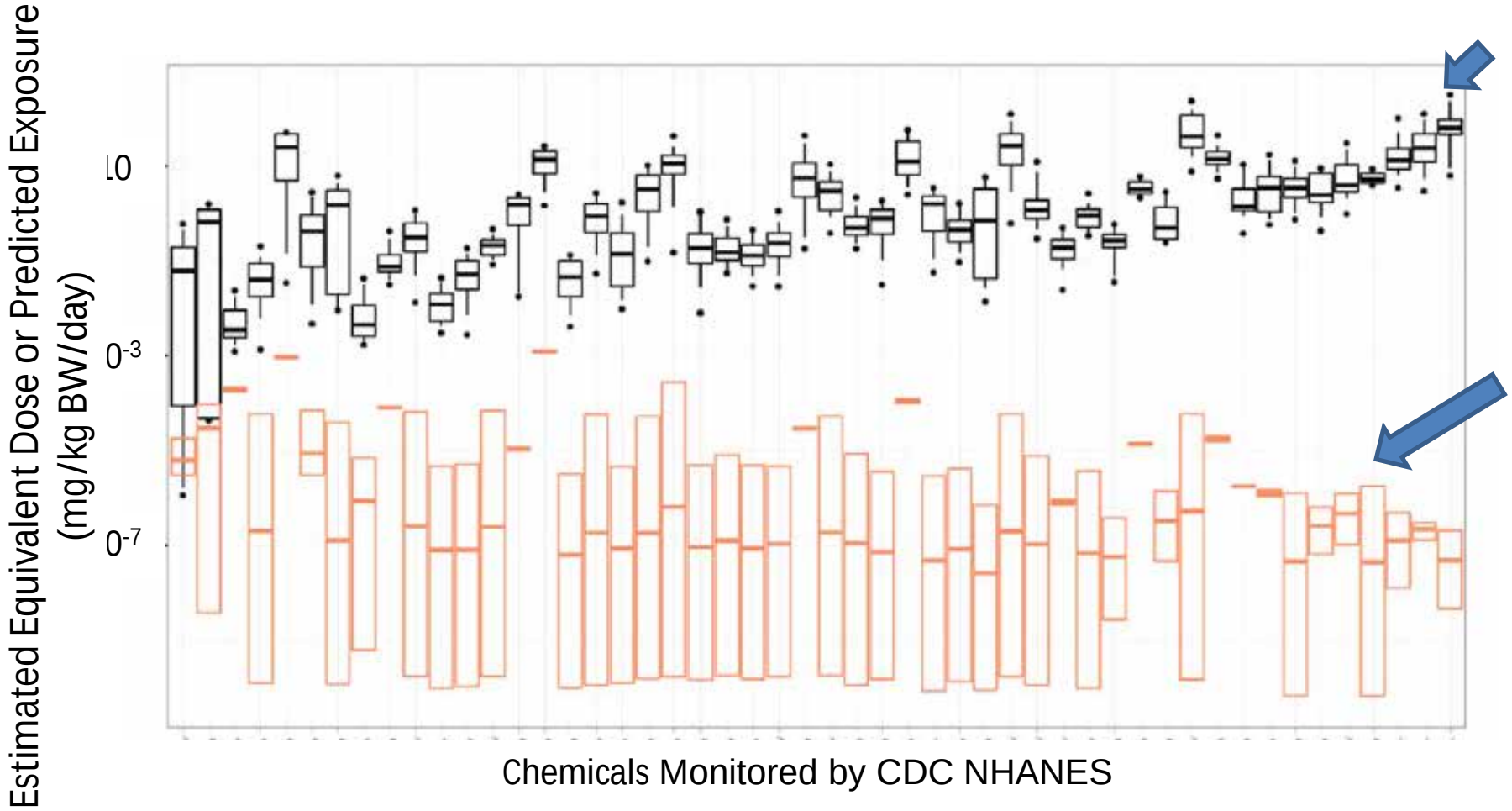
Machine Learning Models



Generic Physiologically-Based Toxicokinetic Models

Material from John Wambaugh

Prioritization NAMs: Risk-Based Evaluation in Practice



High throughput *in vitro* screening + toxicokinetics NAMs can estimate doses needed to cause bioactivity (e.g., Wetmore *et al.*, 2015)

Consensus exposure rates with uncertainty (e.g., Ring *et al.*, 2018)

Summary

- Estimates of human and ecological exposures are required as critical input to risk-based prioritization and screening of chemicals.

- The ExpoCast project seeks to develop the data, tools, and evaluation approaches required to generate rapid and scientifically-defensible:
  - Exposure predictions for the full universe of existing and proposed commercial chemicals.
  - The toxicokinetic data required to relate bioactive concentrations identified in high-throughput screening to predicted real world doses (i.e. *in vitro-in vivo extrapolation*).

- We are developing and applying computational and analytical new approach methodologies for exposure science and toxicokinetics that are appropriate for application to 1000s of chemicals.

- Rapid prediction of chemical exposure and bioactive doses allows prioritization based upon risk.

ExpoCast Project (Exposure Forecasting)

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***Trainees**

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