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High-Throughput Predictive Approaches to Evaluating Chemicals in Food Contact Materials: Migration, Exposure, and Alternatives Identification

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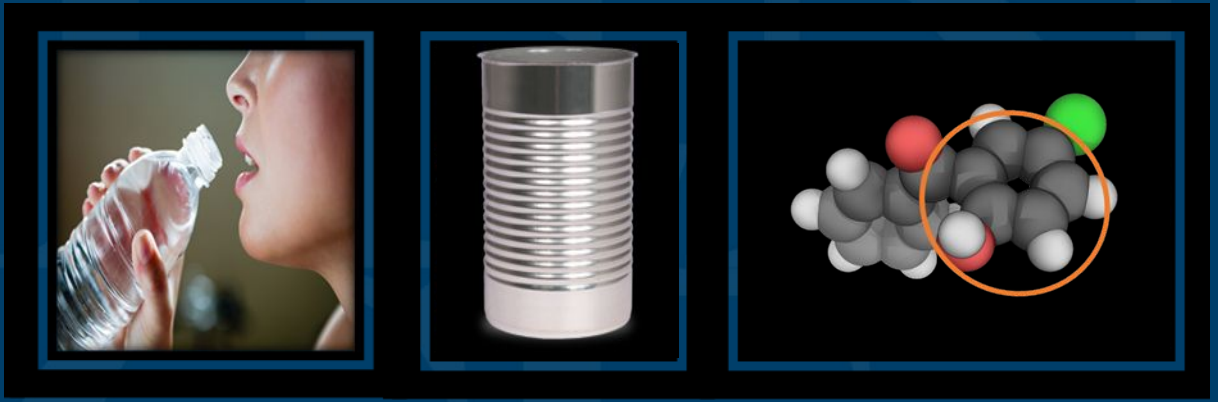

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Forum: Identifying and Evaluating Alternative Materials: The Case of BPA-Free Can Linings
UC Berkeley Center for Green Chemistry
November 4, 2016

Scientific Problem

- The timely characterization of the human and ecological risk posed by thousands of existing and emerging commercial chemicals is a critical challenge facing EPA in its mission to protect public health and the environment
- Tens of thousands chemicals in commerce have yet to be fully evaluated
- Example: EPA's Endocrine Disruptor Screening Program chemical list contains over 10,300 chemicals. Only 67 have undergone *in vivo* testing; 103 currently being tested

November 29, 2014

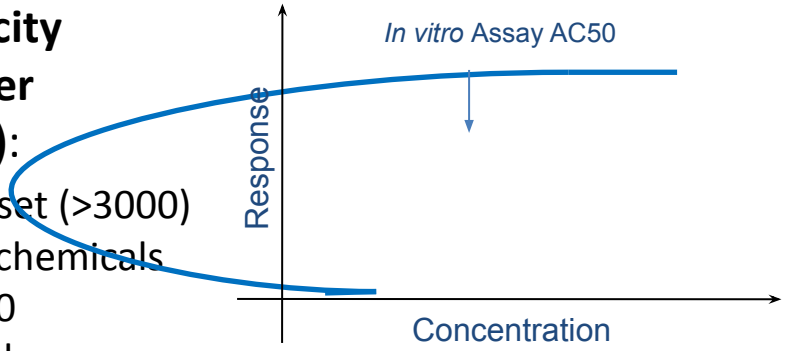
Material from John Wambaugh

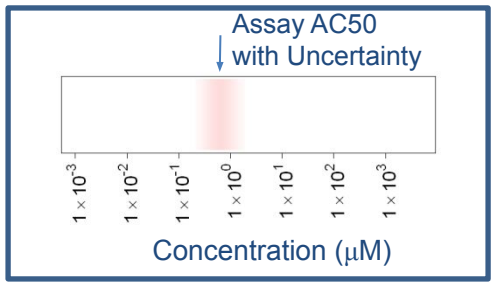
New High-Throughput Screening (HTS) Methods for Evaluating Hazard

- **Tox21**: Examining >10,000 chemicals using ~50 assays intended to identify interactions with biological pathways (Schmidt, 2009)

- **EPA Toxicity Forecaster (ToxCast)**:

  For a subset (>3000) of Tox21 chemicals run >1000 additional assay endpoints (Judson et al., 2010)



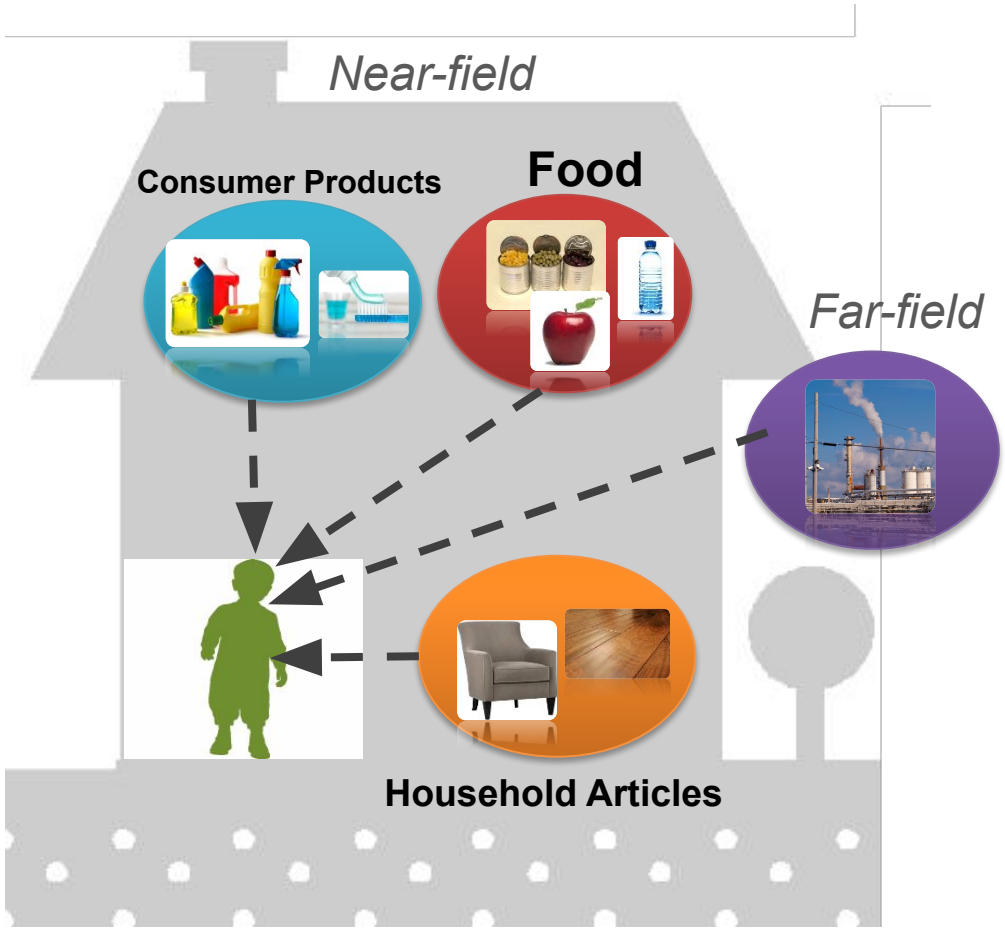


- Most assays conducted in dose-response format (identify 50% activity concentration – AC50 – and efficacy if data described by a Hill function)
- Data are being revised, new chemicals tested, new assays added
- All data are made public:

http://comptox.epa.gov/dashboard/

Material from John Wambaugh

Exposure Predictions are Needed to Provide Real-World Context to HTS Data



- Must consider multiple **exposure** pathways

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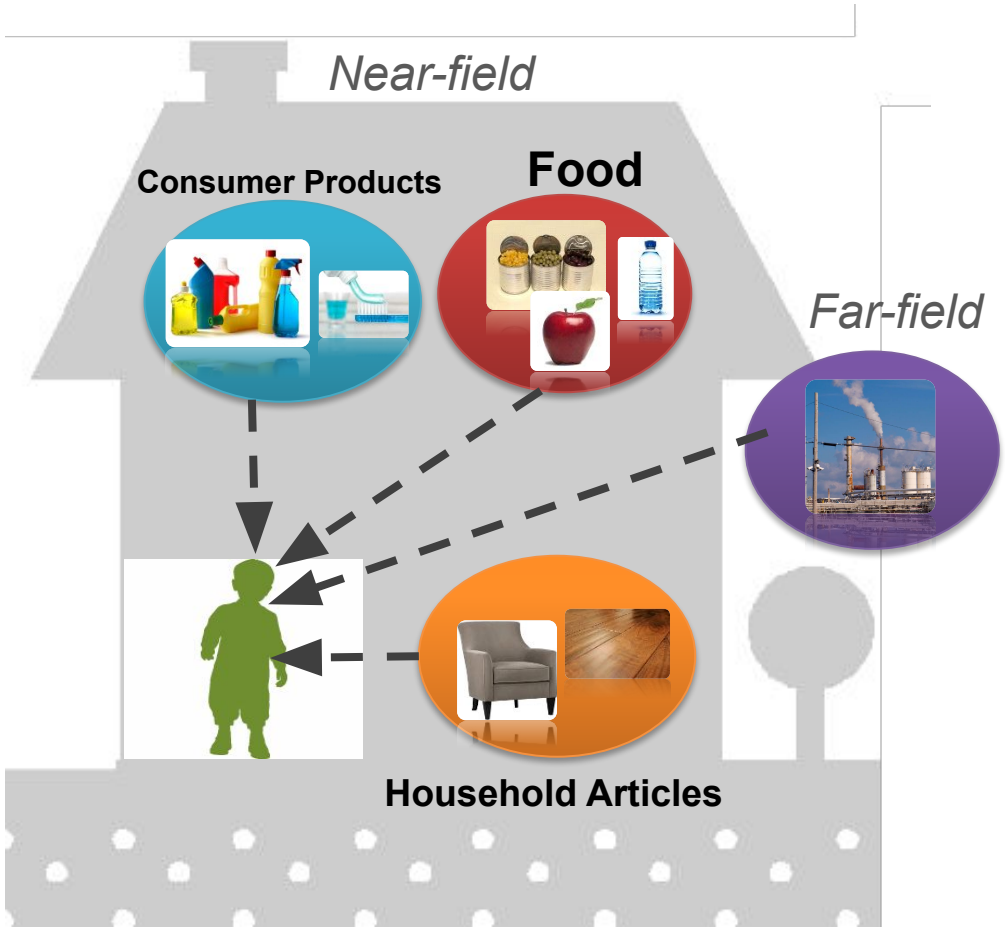

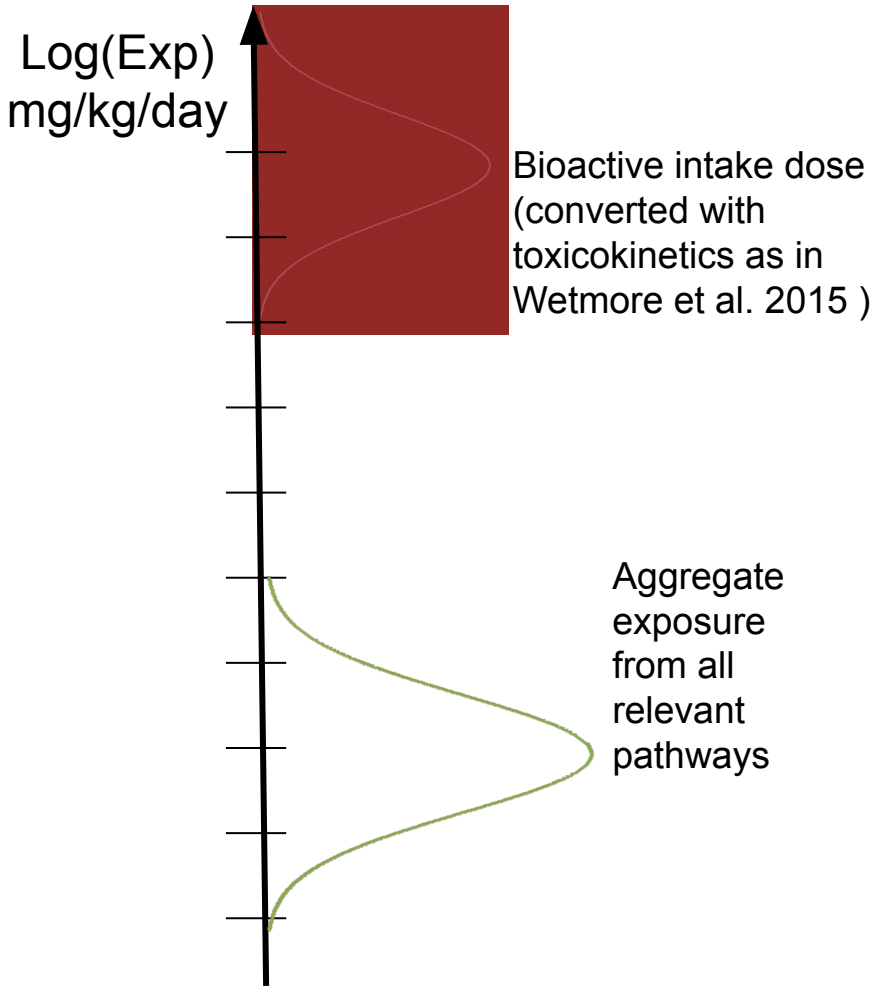

- Must consider multiple **exposure** pathways

- Comparing exposure to bioactivity allows for ***risk-based prioritization***

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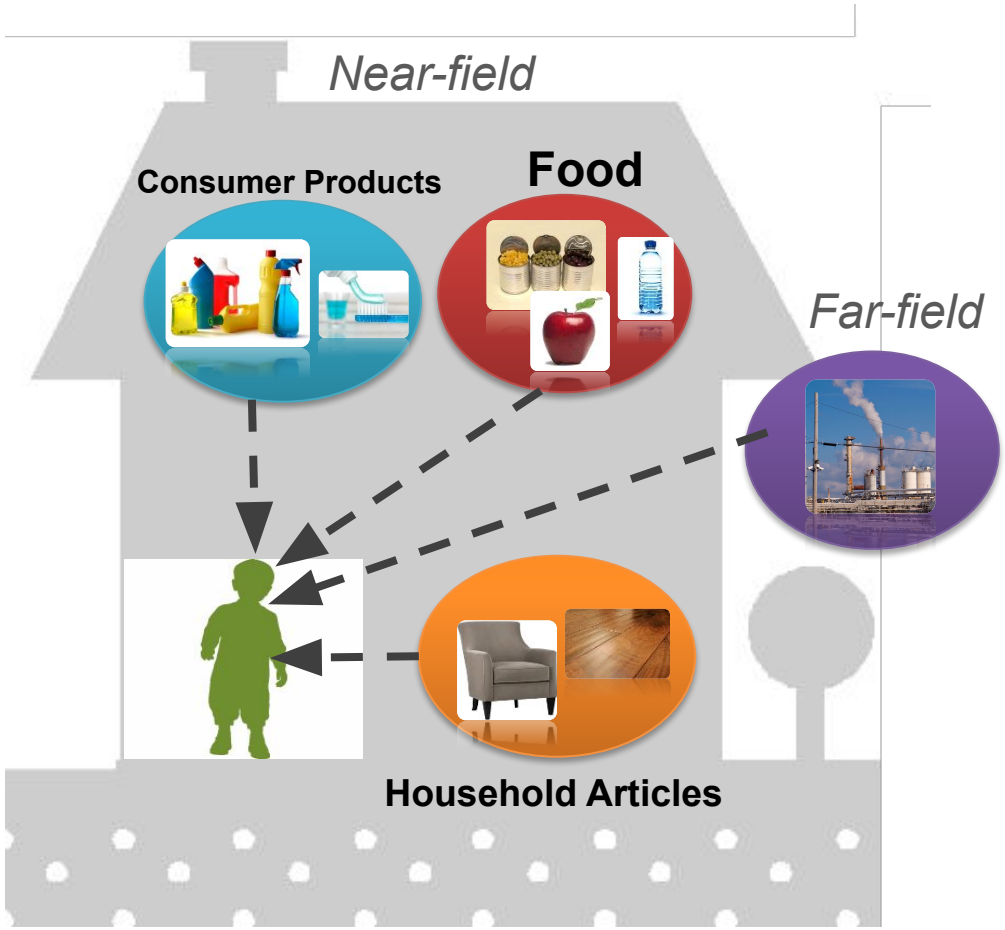

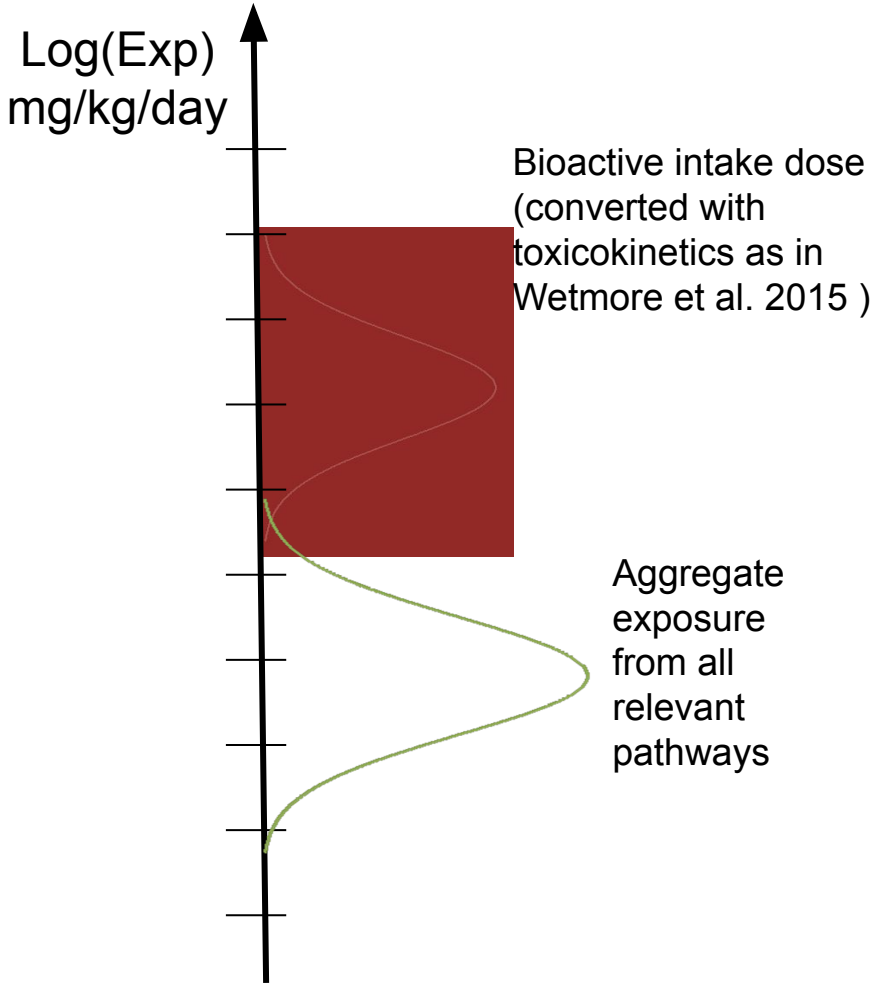

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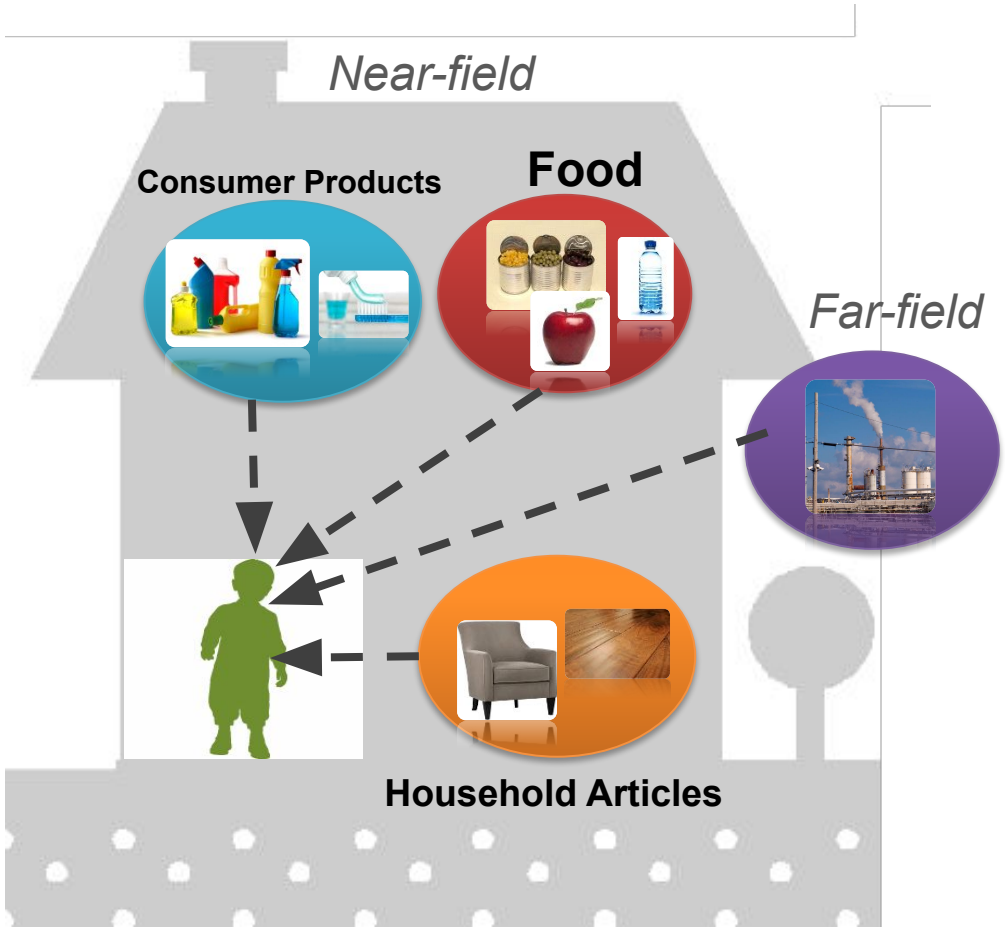

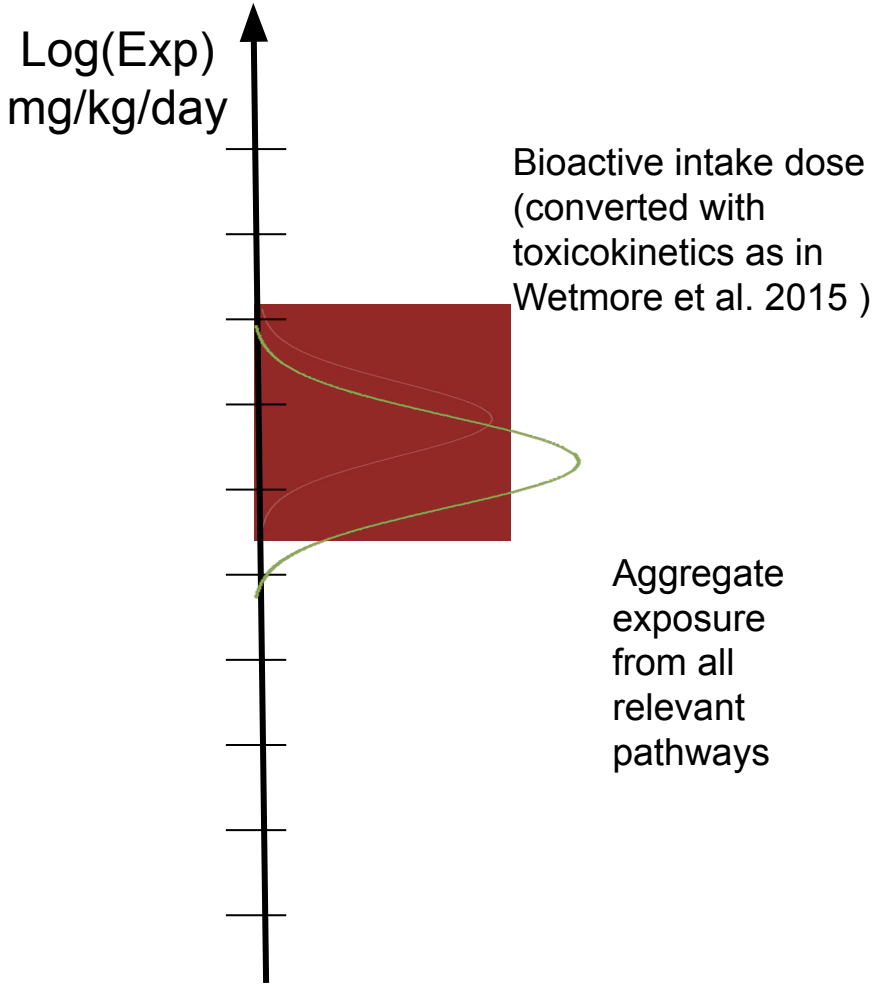

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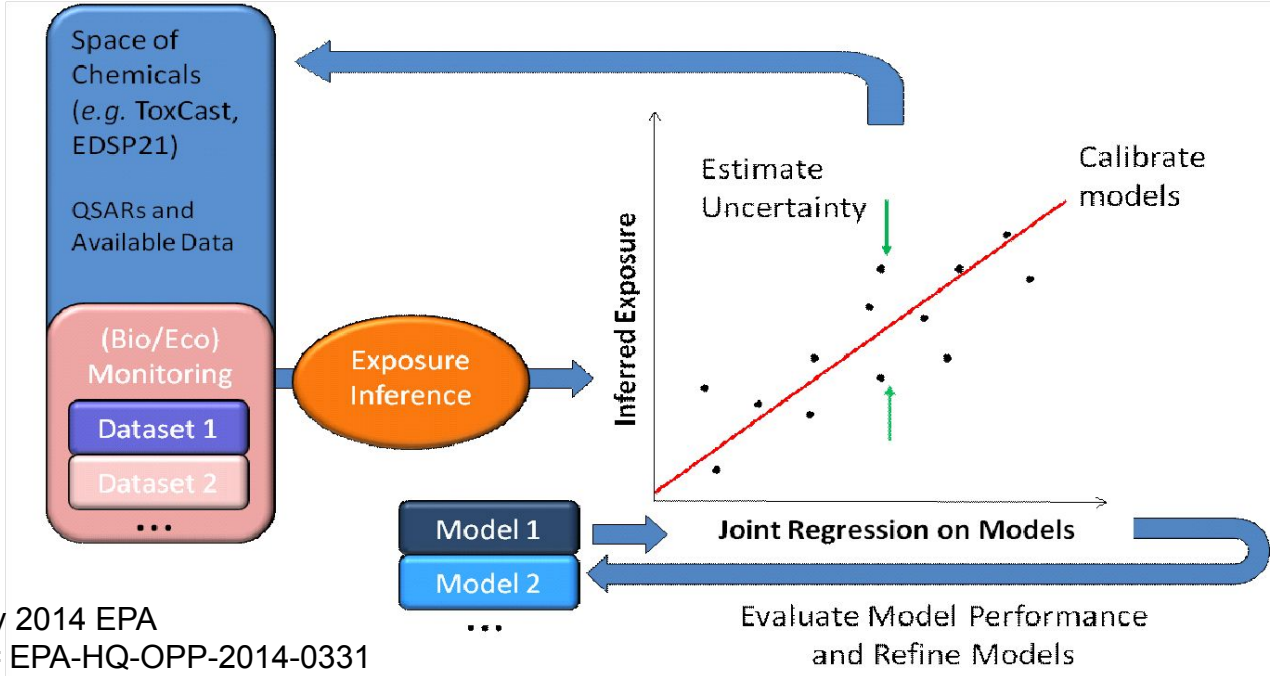
Consensus Exposure Predictions with the SEEM Framework

- Incorporate multiple models into consensus predictions for 1000s of chemicals within the **Systematic Empirical Evaluation of Models (SEEM) framework** (Wambaugh et al., 2013, 2014)
- Evaluate/calibrate predictions with available monitoring data across as many chemical classes as possible to allow extrapolation
- Allows for correction of bias associated with individual models, evaluation of predictive power, and development of a consensus forecast



Evaluated by the July 2014 EPA
FIFRA SAP Docket # EPA-HQ-OPP-2014-0331

ExpoCast Predictive Tools Relevant to Evaluation of Alternative Chemicals Having Food Contact Pathways

- HT models of population exposure for food contact substances (FCS)
  - Empirical methods for predicting chemical migration
- Development of models and methods for screening large libraries of chemicals for “functional substitutes” and “candidate alternatives”

High-Throughput Predictions of Exposure from Food Contact Pathways

- Exposure is simply *Food Concentration X Food Consumption*
- BUT…How do we implement a HT method for ExpoCast? We identified **1659** chemicals identified as present in polymer or plastic FCS
  - USFDA's Inventory of Effective Food Contact Substance (FCS) Notifications and List of Indirect Additives Used in Food Contact Substances
  - European data on plastics and surface coatings
- How do we approach generating migration for chemicals with different properties, from packaging with different compositions and configurations, under different storage conditions, into food substrates having different characteristics?
- Data-driven empirical model
  - High uncertainty, but applicable to many chemicals

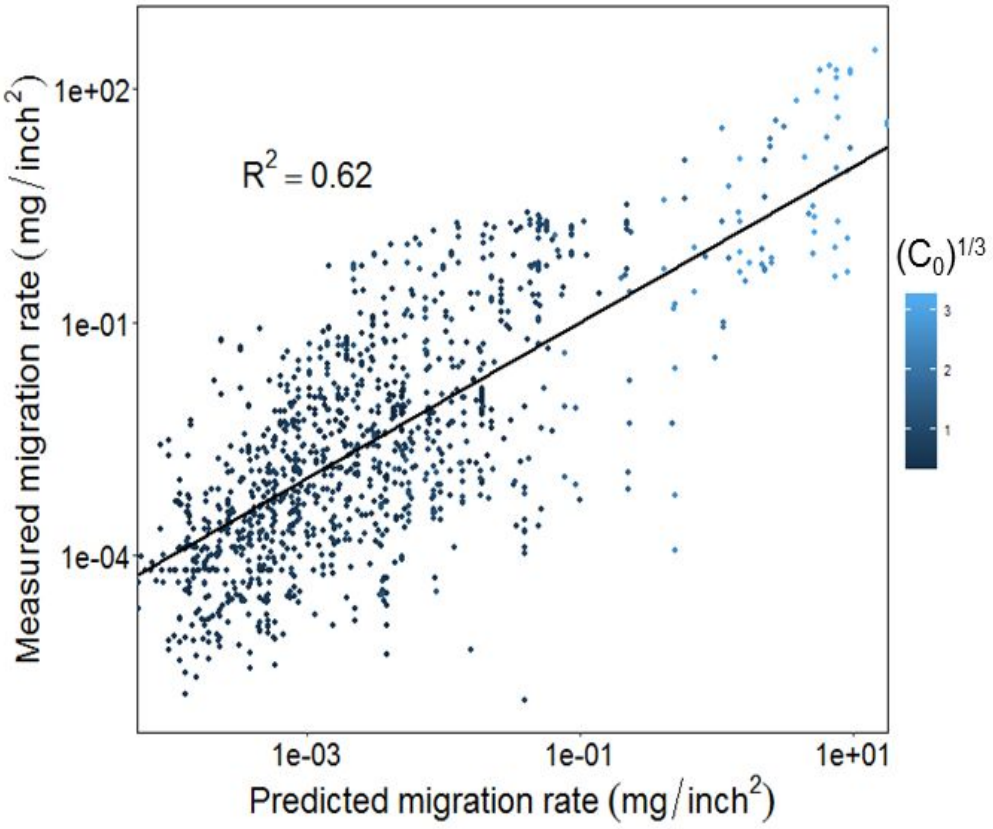
Prediction of Migration

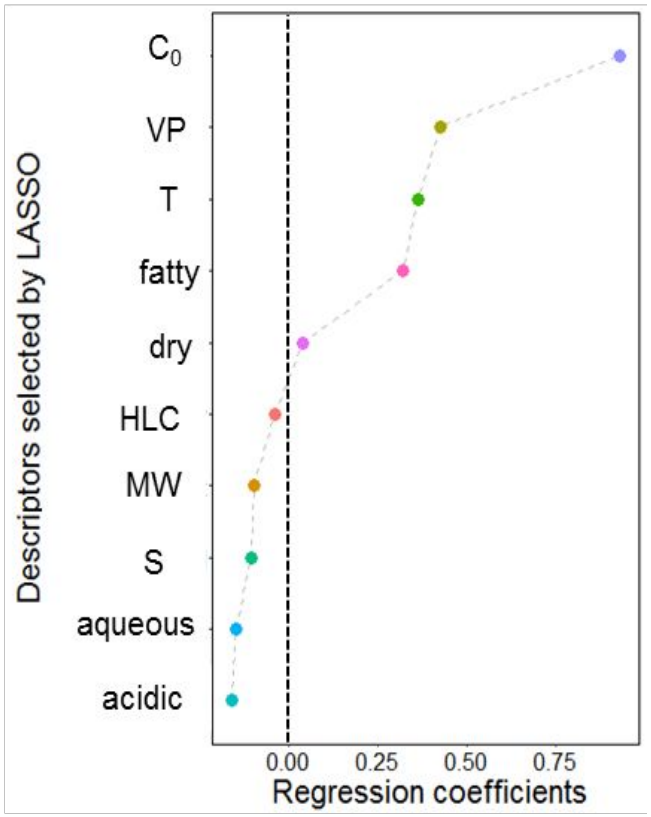
United States Environmental Protection Agency

- FDA database of migration (ug/cm2) measurements with experimental data from polymer FCS
  - 50 chemicals
  - Examined steady state or maximal migration during test
  - 1209 observations at different conditions
- Built linear regression model for migration level
- Least Absolute Shrinkage and Selection (LASSO) algorithm to identify best subset of parameters

Parameter Category	Parameter	Description
FCS Properties	C_0	Initial concentration of chemical migrant in the FCS (g/g)
Food Properties	Food Type Category (Food or food simulant)	Alcoholic, Aqueous, Acidic, Dry, Fatty
Food Storage Conditions	Temperature	°C
Chemical Properties	MW	Molecular weight
	S	Solubility in water (mg/L)
	VP	Vapor Pressure (Pa)
	LogP	Log (octanol/water partition coefficient)
	HLC	Henry's law constant (Pa-m3/mole)

Resulting Migration Model

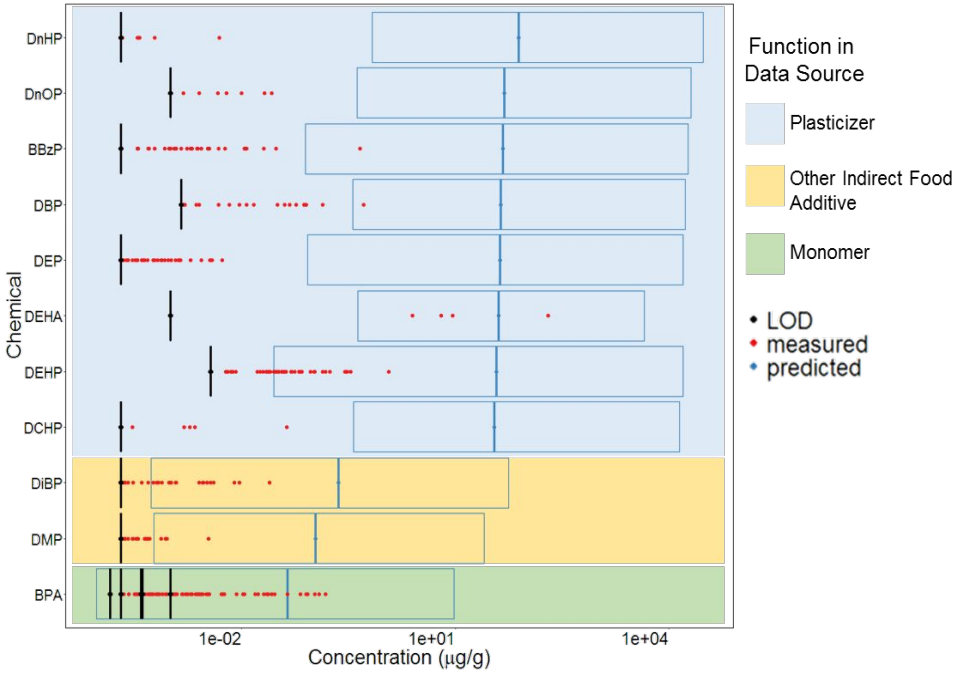




- Most important predictors were initial concentration, vapor pressure, and temperature
- LogP and alcoholic food type were eliminated
- Vapor pressure, solubility, and LogP were correlated

Estimating HT Food Concentrations for Chemicals Identified in Polymer Food Contact Substances

- C_0 distributions assigned to the 1659 FCS chemicals by using **function** information from data sources and migration database
- Migration model predictions for 15 **food groups**: combinations of food storage temperatures and food category
- Food concentration calculated using standard assumption of 6 dm2 packaging contacting 1 kg food



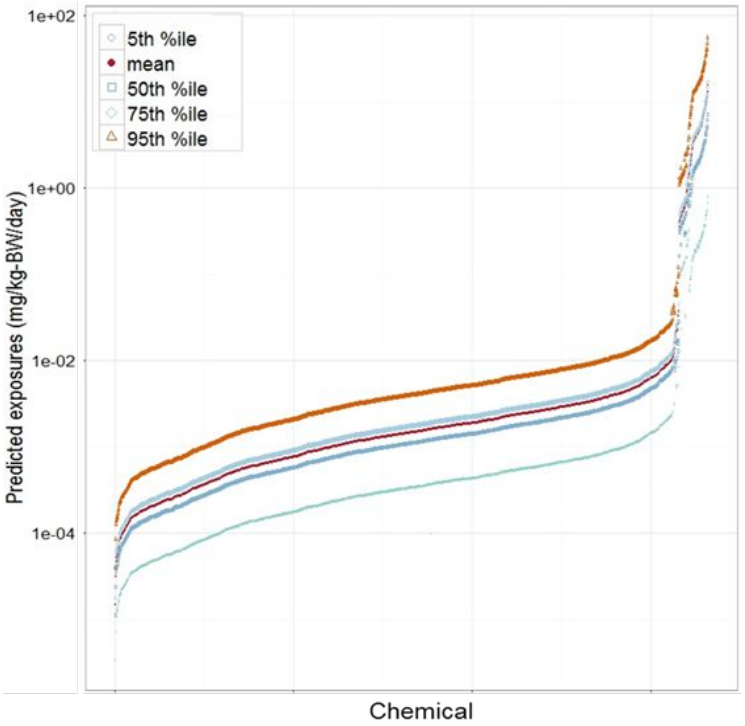
Measured concentrations (N=276) versus maximum estimated with HT migration model

Predicting Population Exposures

- NHANES-WWEIA two-day food diaries for the years 2009-2010 (9651 diary-days)
- Food codes mapped to the migration model **food groups**
- Daily consumption of each food group calculated for each diary
- Standard FDA factors describing amount of diet contacting polymer packaging and distribution of diet across food type applied
- Chemicals assumed to be in all packaging (no chemical-specific prevalences)
- Population exposures calculated

(7000 food codes)

Code 11111000: *Milk, cow's, fluid, whole* → Migration Food Group "*Fatty Chilled*"

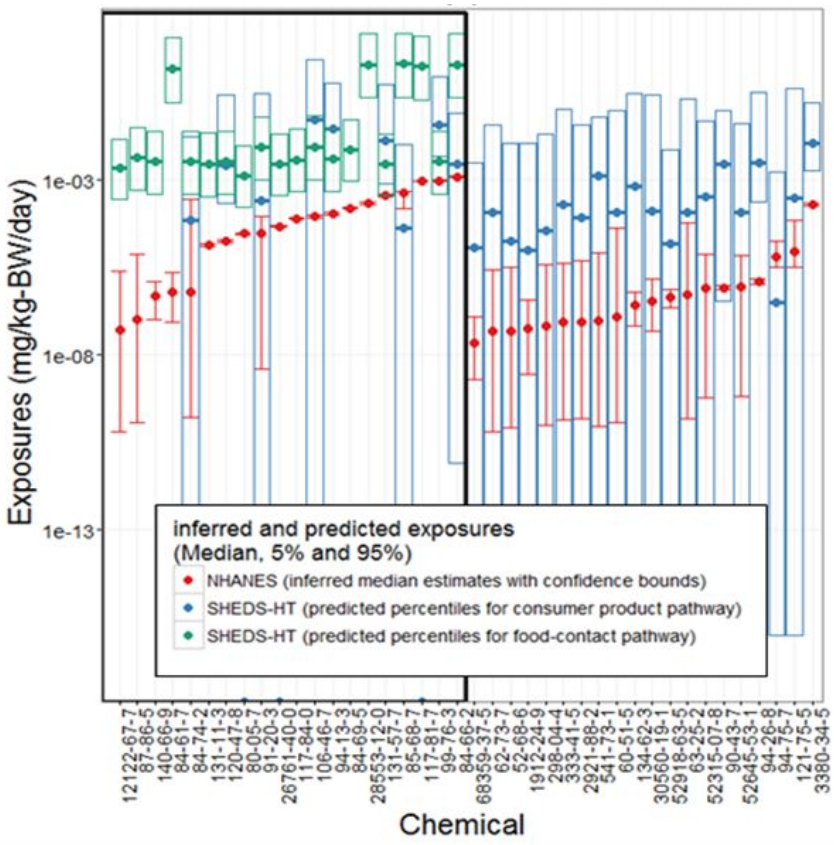


Exposure = Concentration X Consumption

Comparison with Exposures Inferred from NHANES Biomarkers and Consumer Product Exposures

United States Environmental Protection Agency

Exposure were overestimated (as expected) given assumptions…



Exposures inferred from NHANES biomonitoring data as in Wambaugh et al., 2013; 2014.

Biryol et al., submitted

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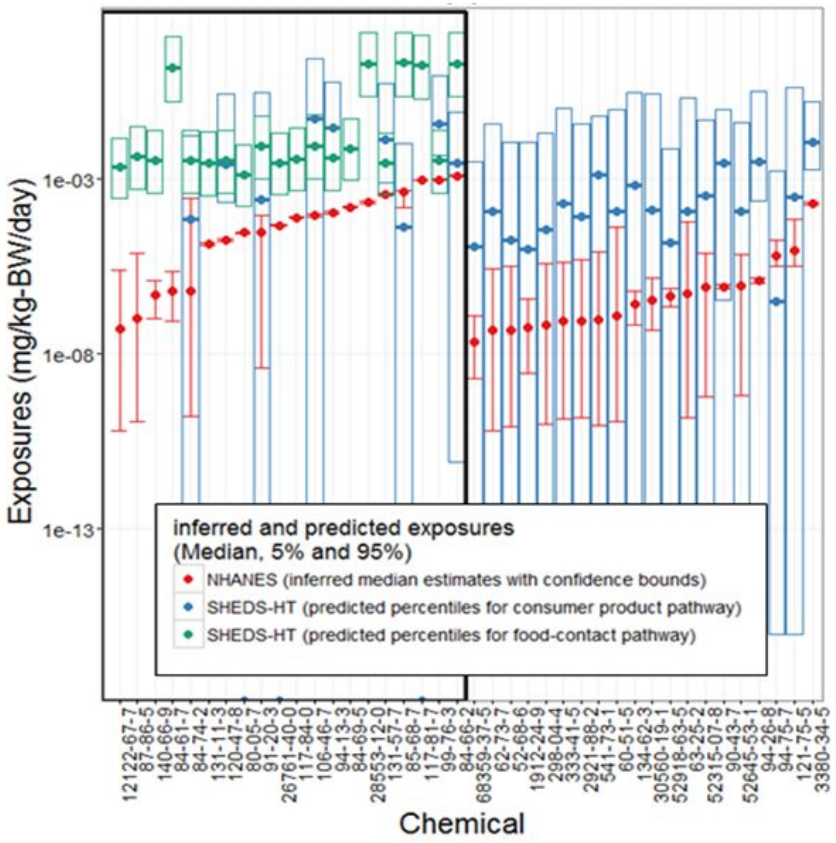
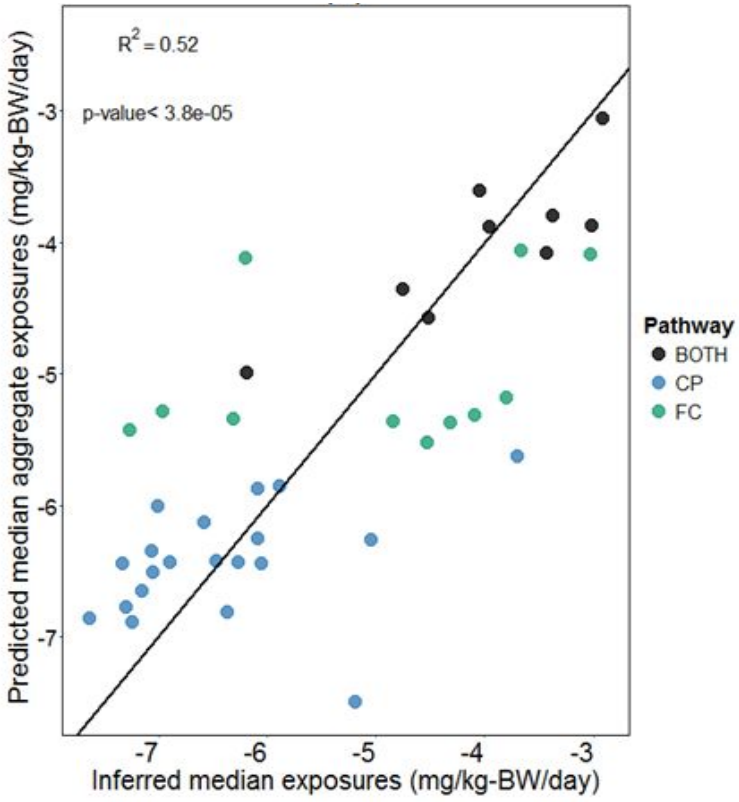


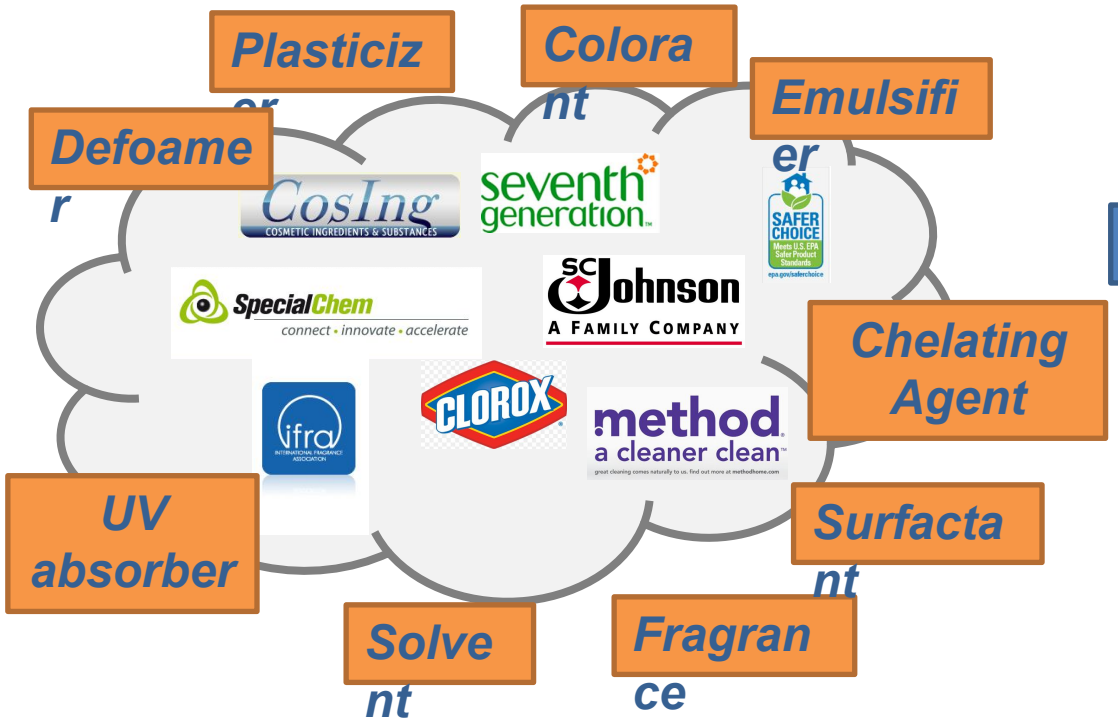
Exposures inferred from NHANES biomonitoring data as in Wambaugh et al. Environmental Science and Technology, 2014.

…but correlated with inferences and also associated with inferences when included in an initial aggregate model with consumer product exposures



Biryol et al., submitted

Databases and Models for Predicting Function of Chemicals



Functional Use (FUse) Dataset
14,000+ Chemicals
200+ Functions

Allows for Modeling of Function in Terms of Chemical Properties or Structures

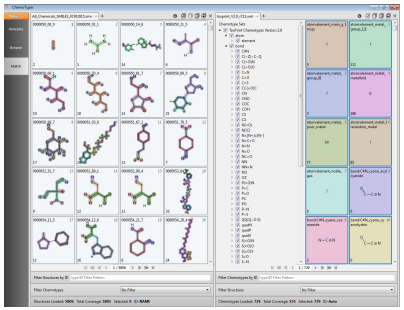
- ***Fill gaps in quantitative information***
- ***Refined heuristics of exposure***
- ***Other applications***

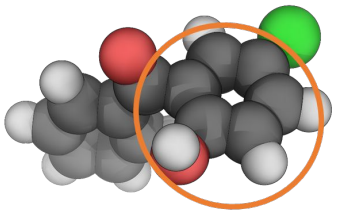
Isaacs et al., 2016

Classification Models for Chemical Function

United States Environmental Protection Agency

Chemical Structure and Property Descriptors





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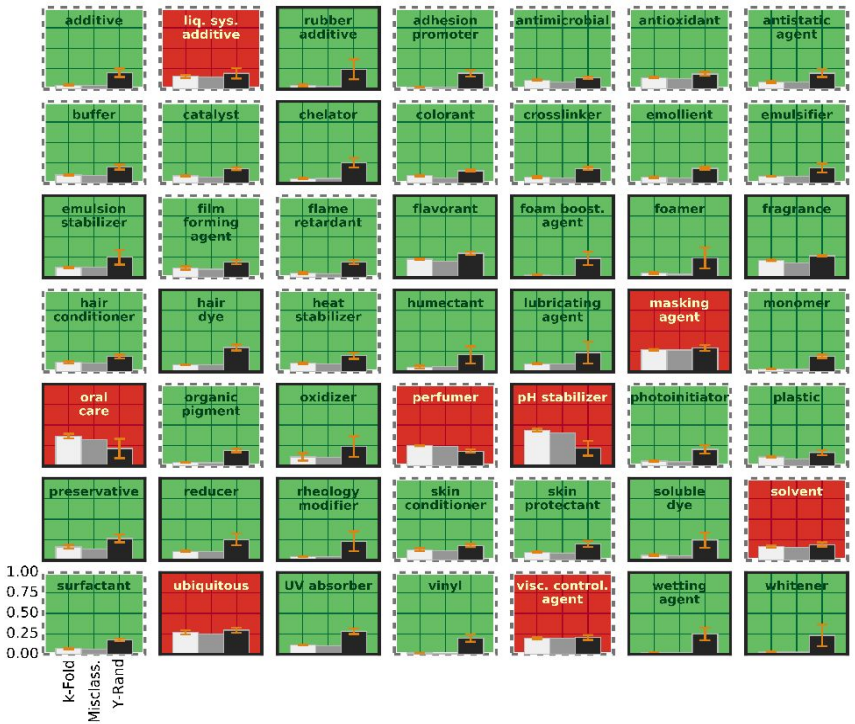
Chemical Function Information

FUSE



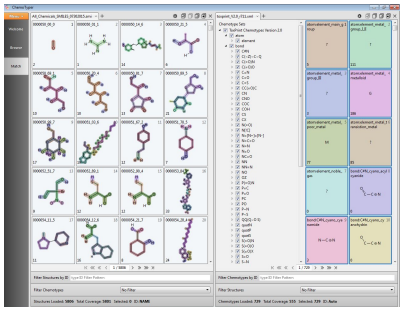
Machine-Learning Based Classification Models

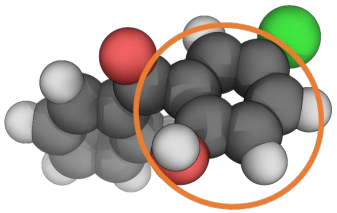
Prediction of Of Potential "Functional Substitutes"

Classification Models for Chemical Function

United States Environmental Protection Agency

Chemical Structure and Property Descriptors





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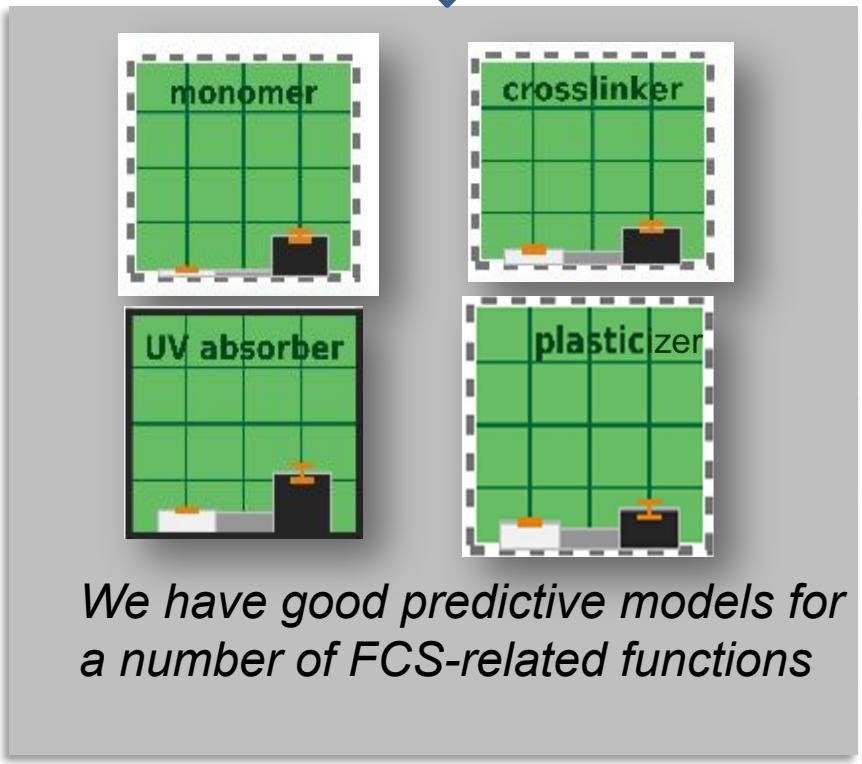
Chemical Function Information

FUSE



Machine-Learning Based Classification Models

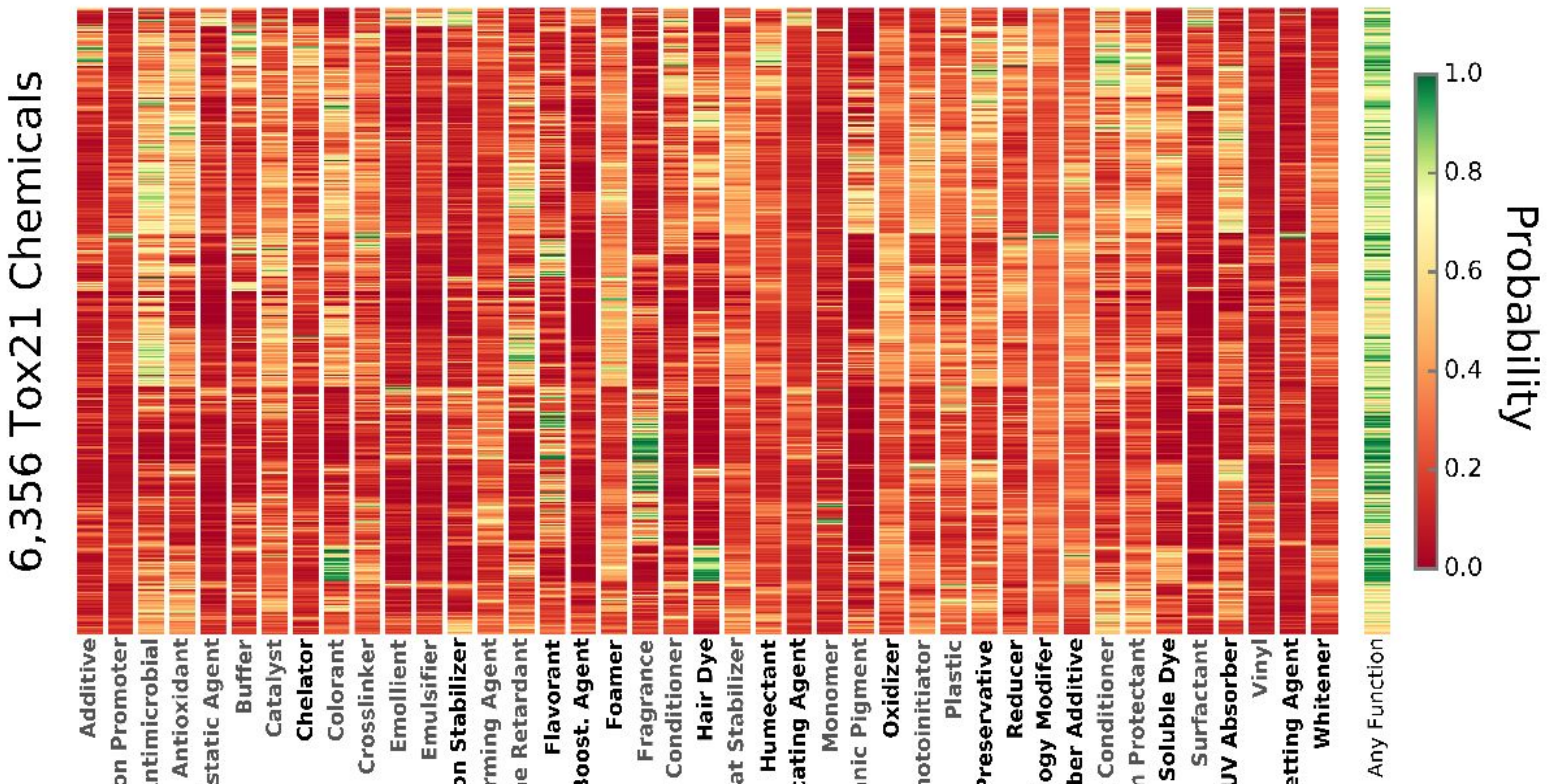
Structural Descriptors

Structural and Physicochemical Descriptors

Prediction of Of Potential "Functional Substitutes"

Application: Screening for Alternatives By Function and Bioactivity

United States Environmental Protection Agency



Phillips et al., submitted

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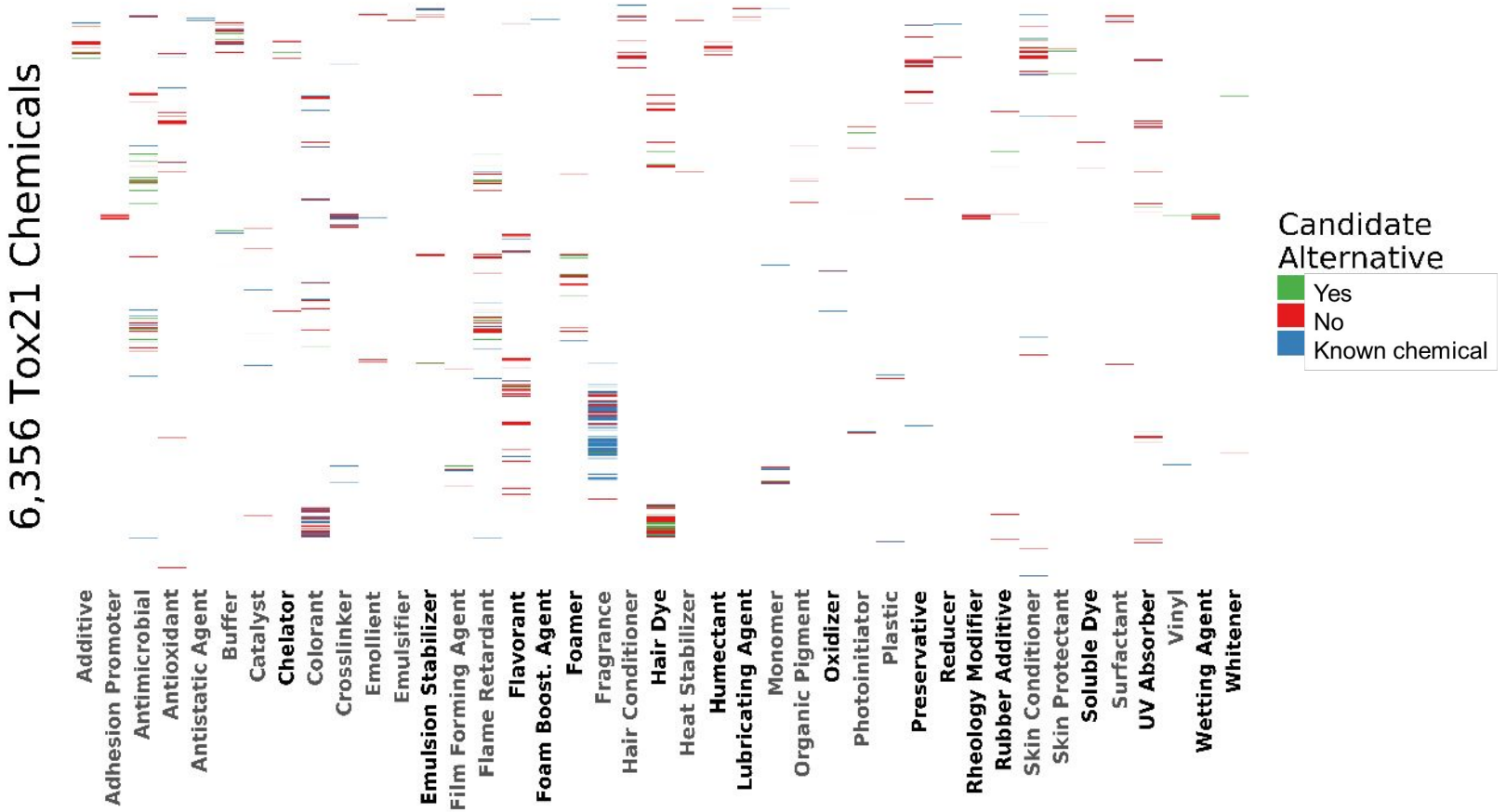


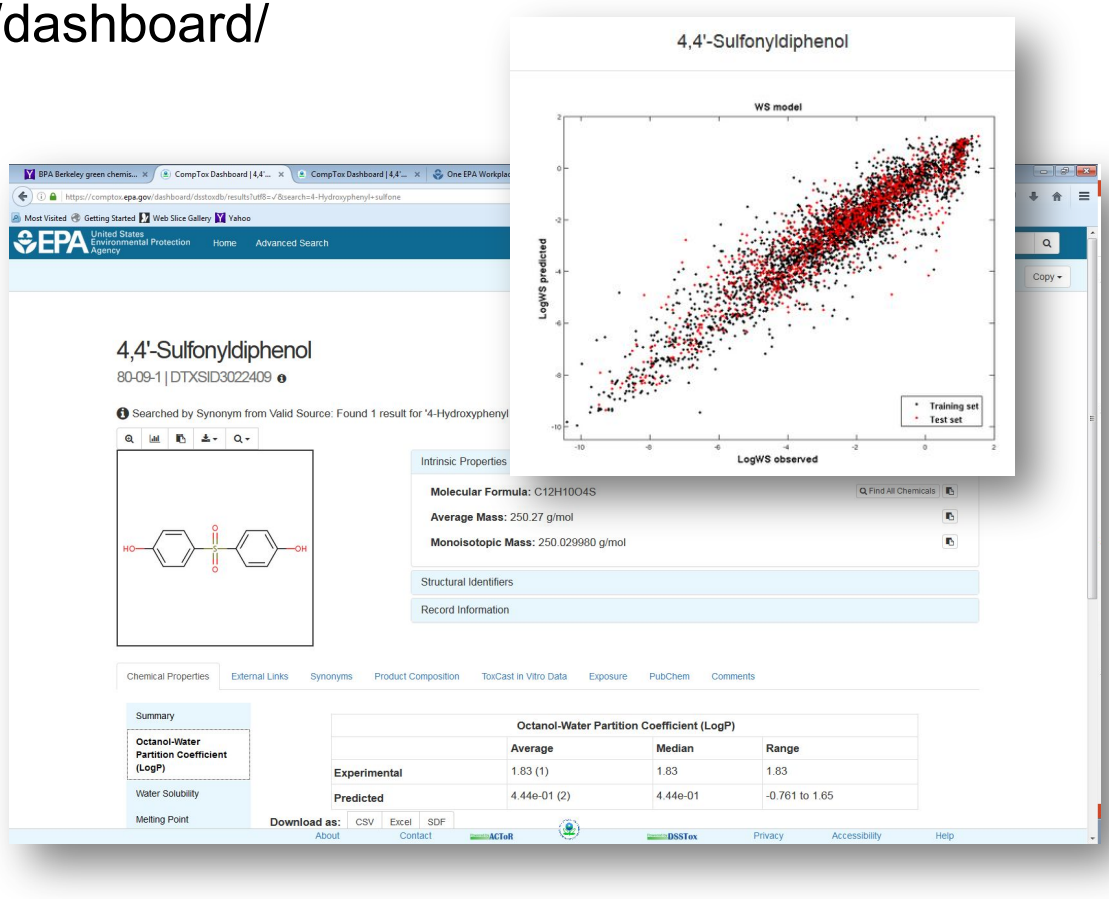
- **Comparing a metric of bioactivity (across a number of Tox21 assays) for predicted "functional substitutes" against a threshold value derived from existing chemicals with that function identified 648 "candidate alternatives"**

Phillips et al., submitted

A New Source of Curated HT Chemical Information

http://comptox.epa.gov/dashboard/

- Data on over 700,000 chemicals
- Property predictions when QSAR models available
- New curated structural information being incorporated
- Will allow us to expand the prediction of functional substitutes to larger libraries of chemicals



Technical leads Tony Williams, Richard Judson, et al. (NCCT)

Conclusions

- US EPA is generating high-throughput predictive models for use in risk-based prioritization of chemicals for further study
- While our HT migration and exposure predictions by their nature have higher uncertainty than focused single-chemical assessments, the data and approaches could inform evaluation of alternatives when no other information is available
- HT dietary exposure framework could incorporate refined data that could improve exposure estimates (e.g. refined composition information, chemical occurrence in packaging, even measured migration or concentration data)
- Aggregate predictions from ExpoCast can also inform “background” exposures for proposed alternatives (i.e. from sources other than FCS applications)
- We are working to expand the application of classification models for functional use to identify previously unknown compounds that could be further evaluated as alternatives for existing chemicals

EPA United States Environmental Protection Agency

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

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References

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