United States Environmental Protection Agency

Symposium on New Data Streams for 21st Century Exposure Science

New Data from EPA's Exposure Forecasting (ExpoCast) Project

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The views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the U.S. EPA

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High Throughput Risk Prioritization in Practice

ToxCast-derived Receptor Bioactivity Converted to mg/kg/day with HTTK

ExpoCast Exposure Predictions

Near Field

Far Field

Prioritization as in Wetmore *et al*. (2015) Bioactivity, Dosimetry, and Exposure Paper

ToxCast Chemicals

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

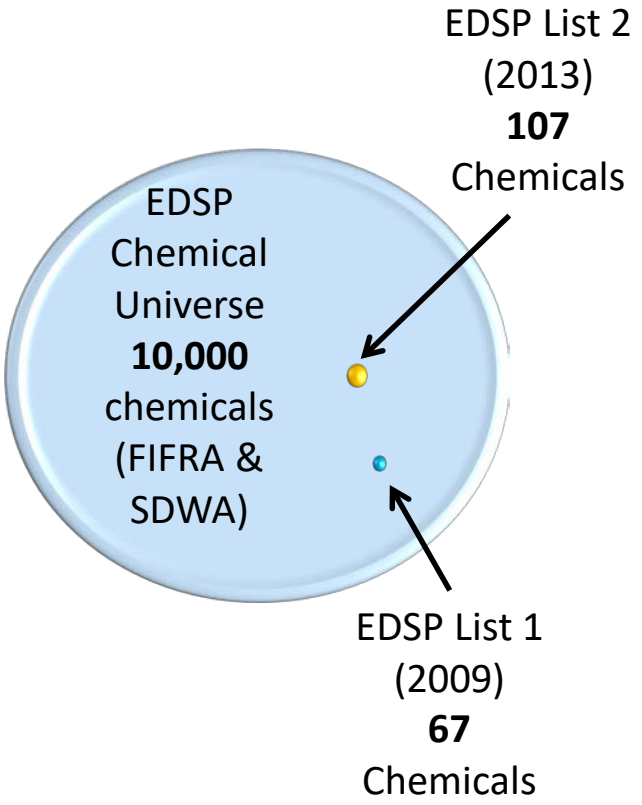
Rapid exposure and dosimetry project helps establish exposure context for ToxCast high throughput screening

Led by Kristin Isaacs and John Wambaugh

Scale of the Problem

- Park *et al*. (2012): At least 3221 chemicals in humans, many appear to be exogenous

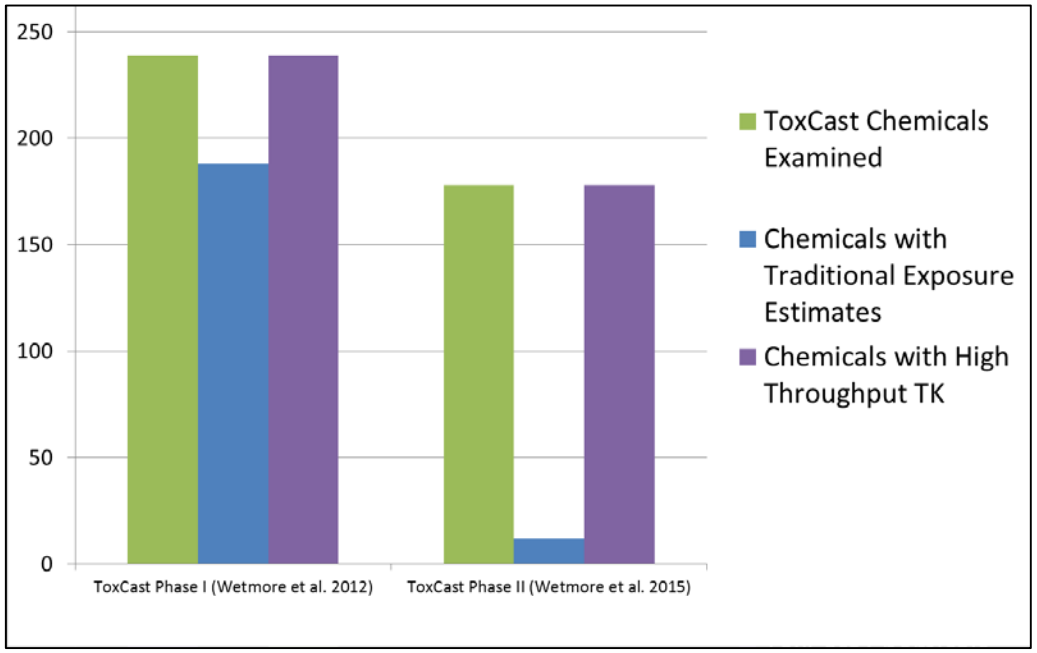
Endocrine Disruptor Screening Program (EDSP) Chemical List	Number of Compounds
Conventional Active Ingredients	838
Antimicrobial Active Ingredients	324
Biological Pesticide Active Ingredients	287
Non Food Use Inert Ingredients	2,211
Food Use Inert Ingredients	1,536
Fragrances used as Inert Ingredients	1,529
Safe Drinking Water Act Chemicals	3,616
TOTAL	**10,341**



So far 67 chemicals have completed testing and an additional 107 are being tested

December, 2014 Panel: "Scientific Issues Associated with Integrated Endocrine Bioactivity and Exposure-Based Prioritization and Screening" DOCKET NUMBER: EPA–HQ–OPP–2014–0614

Exposure Data are Lacking But New Tools Can Provide New Information



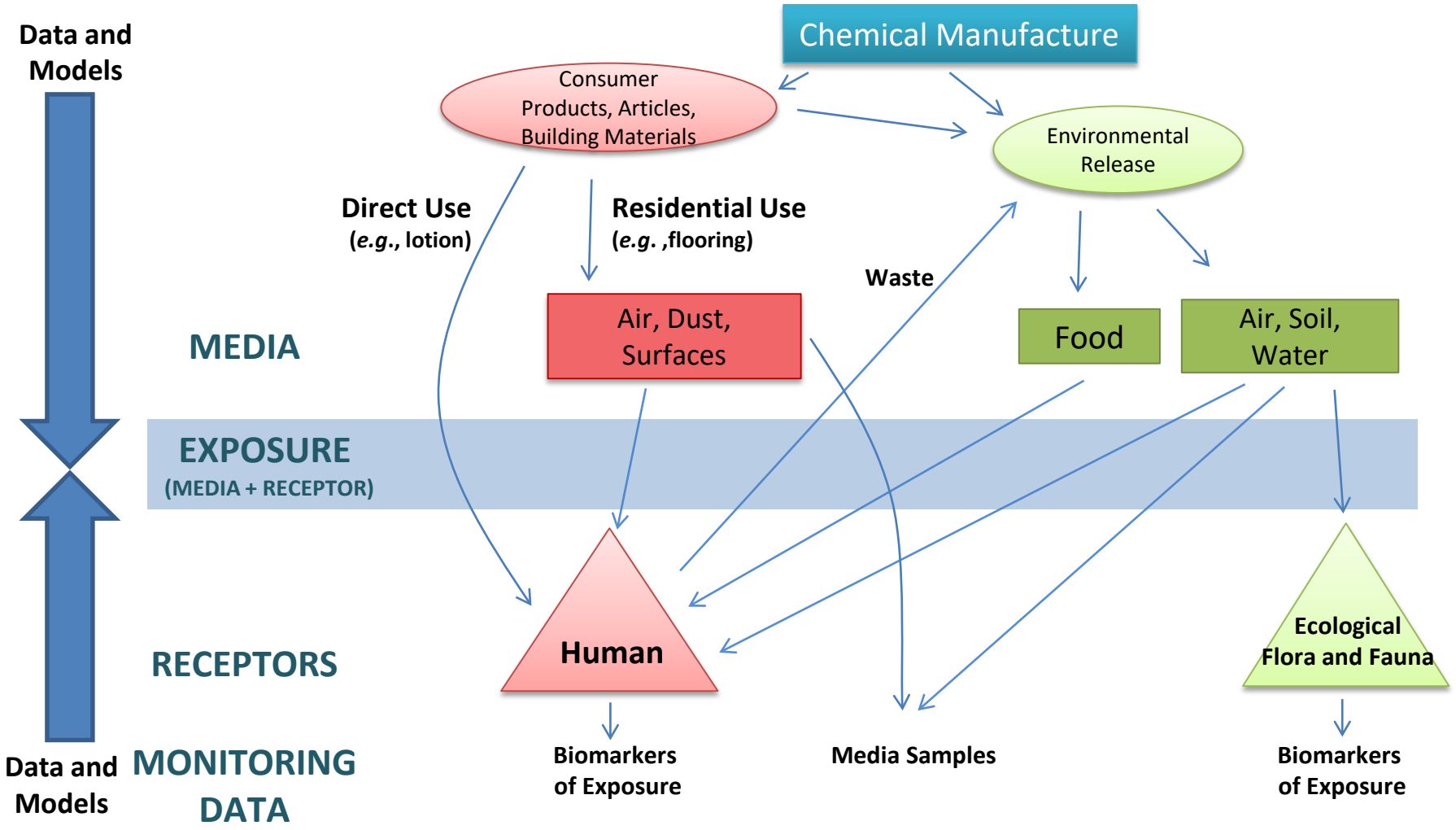


"I'm searching for my keys."

With non-targeted/suspect screening we now have the tools to provide monitoring data greatly beyond the "looking under the lamp post"

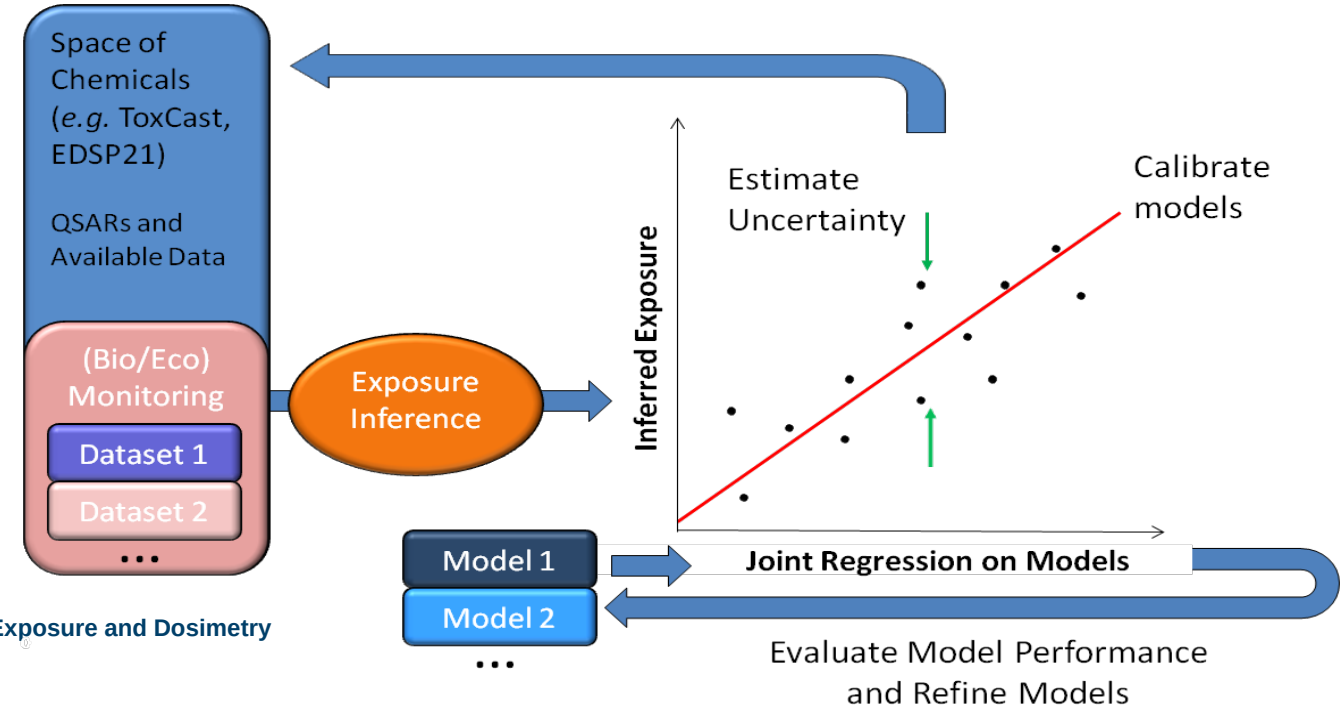
- For non-pesticide chemical space, there is a paucity of data for providing context to HTS data (Egeghy *et al.* (2012))

Evaluating Exposure Models

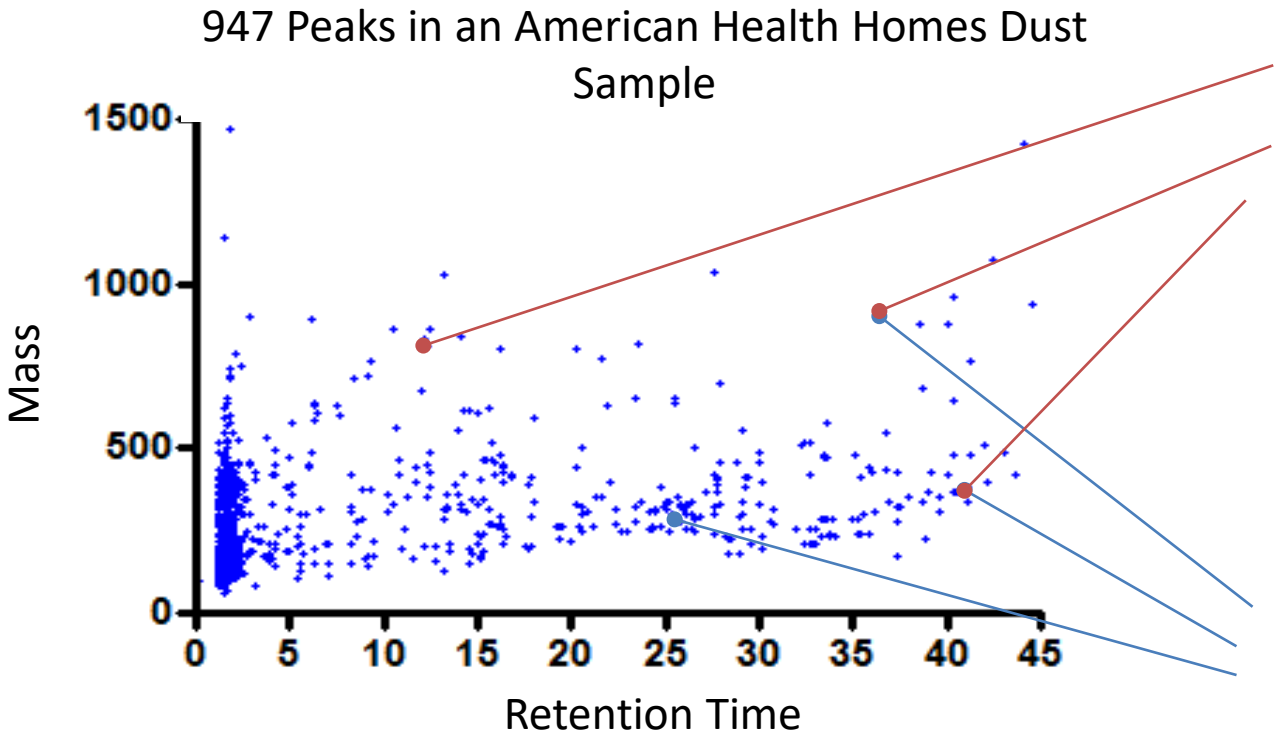


Consensus Exposure Predictions with the SEEM Framework

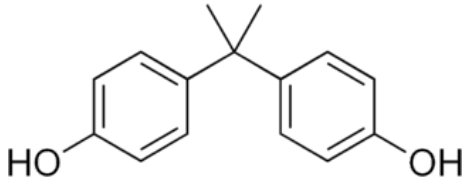
- Incorporate multiple models into consensus predictions for 1000s of chemicals within the **Systematic Empirical Evaluation of Models (SEEM) framework** (Wambaugh et al., 2013, 2014)
- Evaluate/calibrate predictions with available monitoring data across as many chemical classes as possible to allow extrapolation
- Analogous efforts for both human and ecological exposures



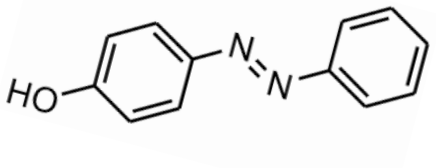
Suspect Screening and Non-Targeted Analytical Chemistry



Each peak corresponds to a mass of a chemical or (depending on technique) fragments of that compound



Multiple chemicals can have the same fragments or overall mass



Is chemical A present, chemical B, or both?

Rager, J.E., Strynar, M.J., Liang, S., McMahen, R.L., Richard, A.M., Grulke, C.M., Wambaugh, J.F., Isaacs, K.K., Judson, R., Williams, A.J., Sobus, J.R. "Linking high resolution mass spectrometry data with exposure and toxicity forecasts to advance high-throughput environmental monitoring" Environment International, 88, 269-280 (2016).

Pilot Projects to Reduce Uncertainty and Expand Validation Domain

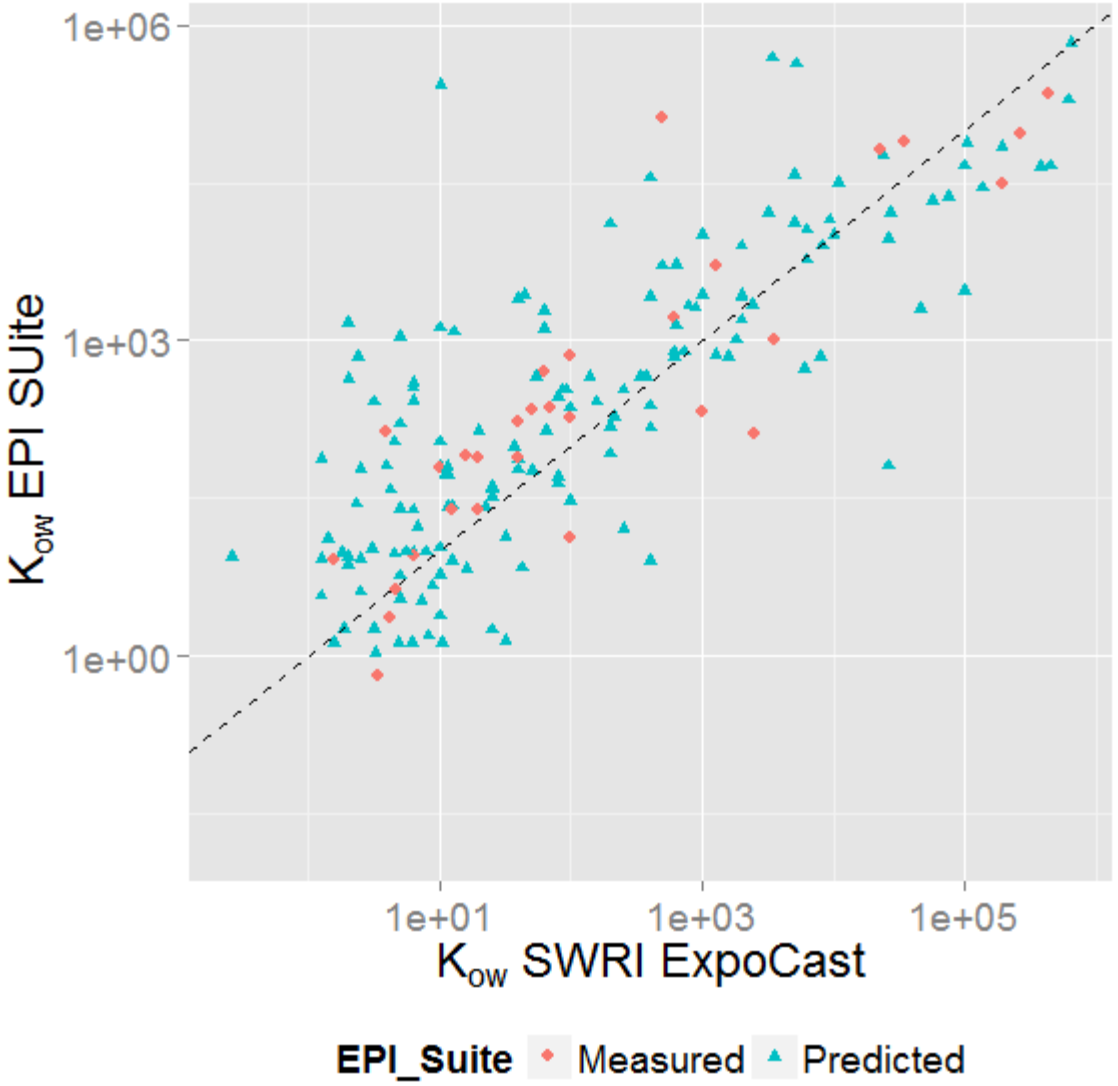
Phase I (Pilot) Examining capabilities and feasibility

Project	Pilot Project Scope
High throughput chemical property measurement (e.g., log P)	200 chemicals
Determine the chemical constituents of products, materials, articles	20 classes of product, 5 samples each
Determine chemical emission rate from specific products, materials, articles	100 materials
Screening for occurrence of large numbers of chemicals in blood samples	500 individuals

- Expands application domain of physical chemical property computational models
- Better understanding of what chemicals are associated with household products
- Better understanding of chemicals in the indoor environment
- Expands validation domain of human biomonitoring chemicals

Pilot Study: HT Phys-Chem

- 200 chemicals selected for measurement of hydrophobicity/lipophilicity (Kow), vapor pressure, Henry's law constant, and ionization equilibria (*i.e.*, pKa)
- Chemicals include a mix of those with known (measured) values and chemistries that may have been under=represented in training sets
- For K_{ow}, R^2 for chemicals with measured values (*i.e.*, in EPI Suite's training set) was 0.76, while for other chemicals R^2 was 0.62.



Pilot Study: Emission of Chemicals from Products

- Battelle measured emission of for 12 target SVOCs (e.g., flame retardants) from fabric clothing and upholstery
- Developed LCMS and GCMS methods with detection in the 1-1,000 ng/mL range
- Standard micro chamber emission tests: 10-hr sampling at 37°C and ~20% RH on 17 fabric samples with 2 duplicates, 8 blanks, and in-chamber spikes of one fabric sample
- Samples extracted and analyzed by GCMC and LCMS
- Data delivered and being analyzed; quantifiable data for 10 chems (7 LCMS, 3 GCMS)


Socks


Carpet Cushion


Tent


Leather


Carpet Padding

Material from Battelle Memorial Institute

Pilot Study: Analysis of Consumer Products

- 20 classes of product, 5 samples each
- Samples chosen to reflect range of products within category (e.g. spray and gel air fresheners, baby and adult sunscreens)
- Articles and formulations





Air freshener
Baby soap
Carpet
Carpet padding
Cereals
Cotton clothing
Deodorant
Fabric upholstery
Glass cleaners
Hand soap
Indoor house paint
Lipstick
Plastic children's toys
Shampoo
Shaving cream
Shower curtain
Skin lotion
Sunscreen
Toothpaste
Vinyl upholstery

Results from Kristen Favela and Alice Yau (SWRI)

Method for Screening Product Compositions

- Southwest Research Institute conducted analytical chemistry screening for large numbers of chemicals in consumer products and articles of commerce
  - Five sample products were arbitrarily selected from -each of twenty different categories
- Products were analyzed using two dimensional gas chromatograph (GC) x GC Time of Flight Mass Spectrometry
  - Chemical presence and approximate quantitation relative to reference chemicals (internal standards) was determined
  - All dilutions and extractions used Dichloromethane (DCM) *(Hexane:Ether was also examined initially, but had a higher background)*
  - Dilution level and processing were tailored to Mass spectra for some each sample; 1x, 10x and/or 100x
- Data processing
- GC features were matched to NIST 07 spectral database for tentative chemical identification
  - Compounds within some chemical classes are very similar, making definitive identifications difficult
  - Some peaks have a large, unresolved region of hydrocarbons in the C17-C32 range
    - Classifications used to manage hydrocarbon regions were ambiguous

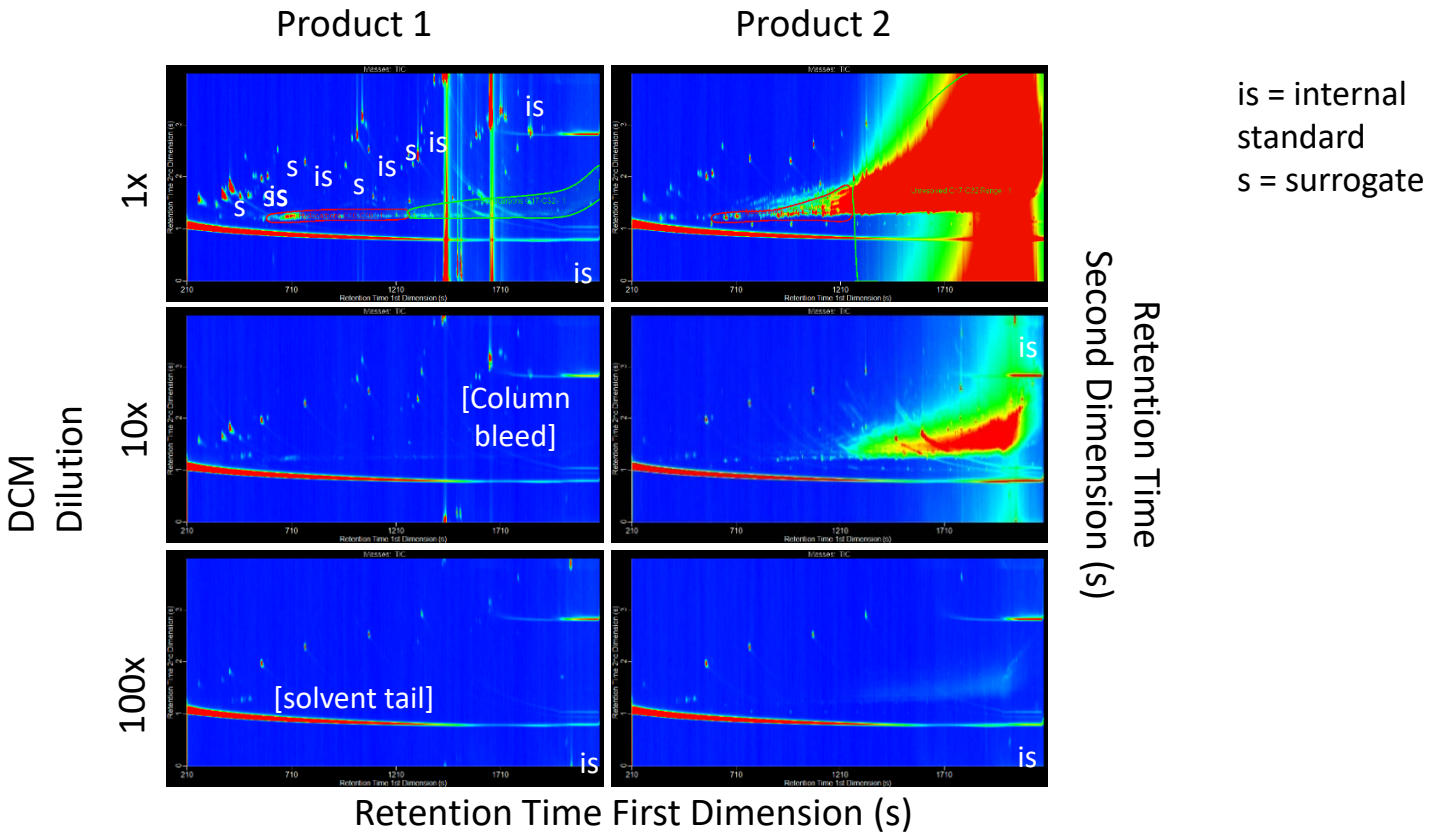
Results from Kristen Favela and Alice Yau (SWRI)

Caveats to Non-Targeted Screening

- Chemical presence in an object does not necessarily mean that it is bioavailable
- Samples are being homogenized (e.g., grinding)
- Chemicals are extracted with a solvent (CDM)
- Varying degrees of intimacy of exposure – carpet padding to shampoo to cereal
- Chemical presence in an object does not mean that exposure occurs
- We are not assessing toxicity of chemical exposure here – exposure alone is not risk

Chromatographs for Baby Toys

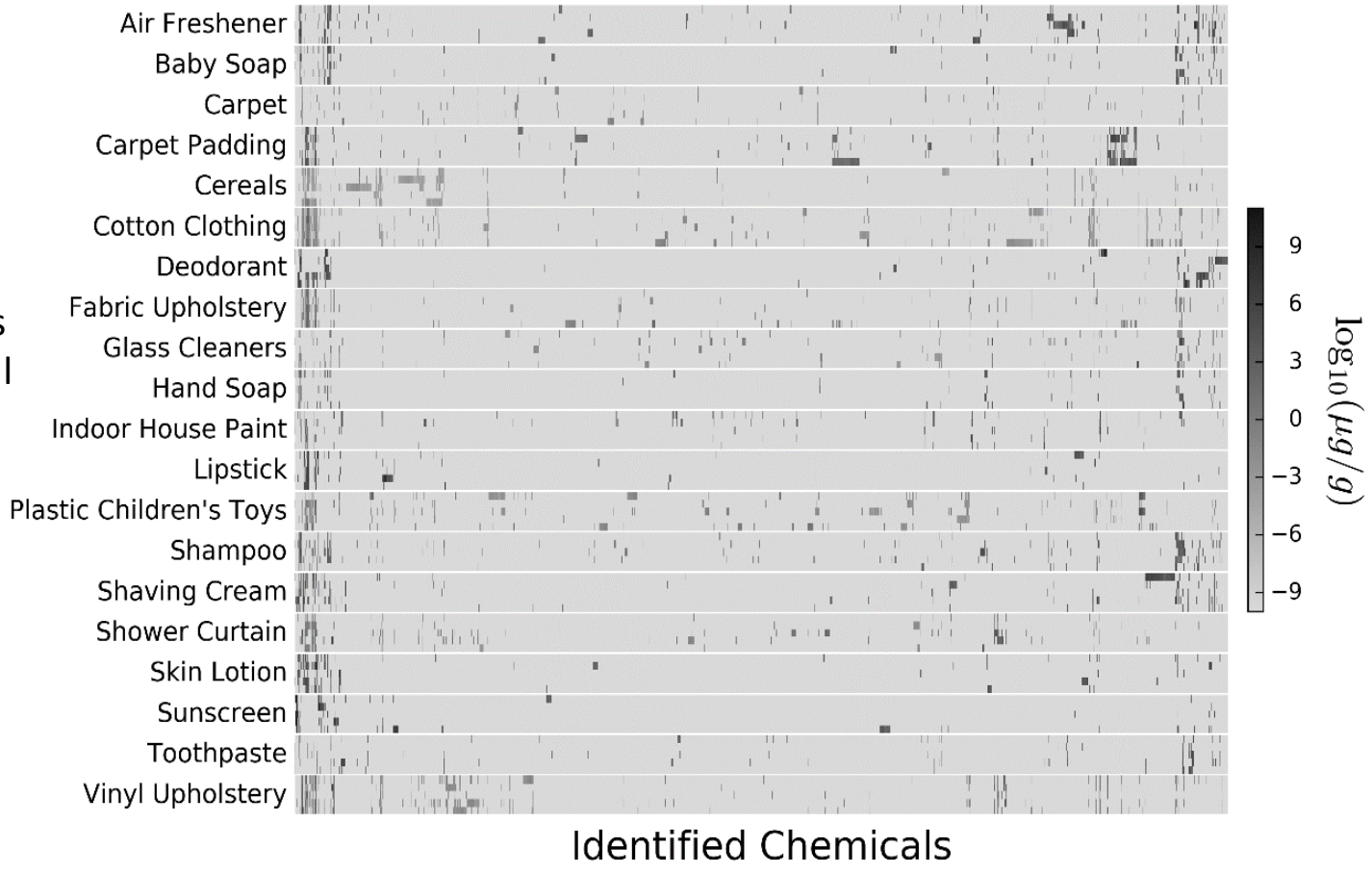
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is = internal standard
s = surrogate

Tentative and Confirmed Chemicals

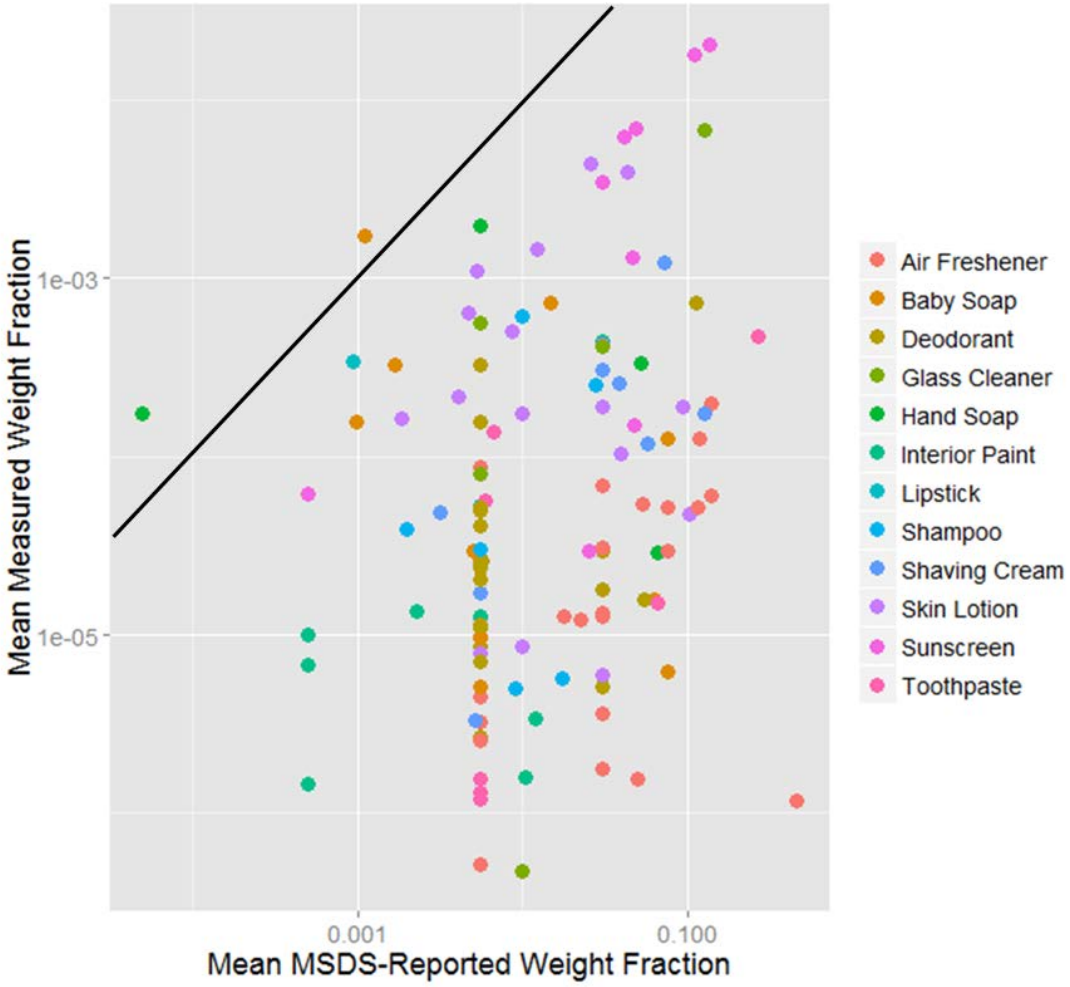
- **3,803** chemical signatures
- **1,605** tentative chemical identifications
- **126** confirmed chemical identifications



Coverage of Chemical Lists of Interest

- 187 of 1797 chemicals with previously known consumer product use (CPCPdb)
- 520 of 8948 Tox21 chemicals
- 393 of 3805 ToxCast chemicals
- 11 of 96 ToxCast ER active chemicals
- 17 of 178 EDSP List 1 and 2 chemicals
- 94 of 1172 ToxRefDB chemicals
- 32 of 452 NHANES chemicals
- 1 of 670 pharmaceuticals (Obach, 2008)
- 9 of 67 flame retardants

Evaluation – Approximate Chemical Concentrations vs. Formulation



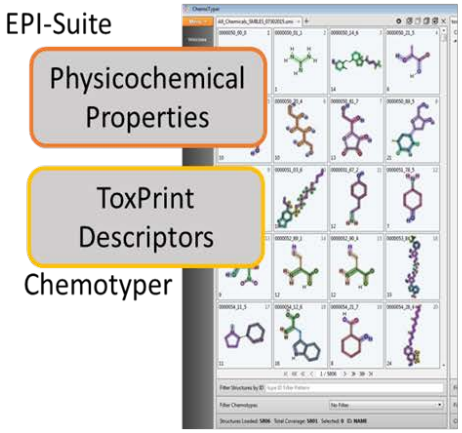
- For some chemicals we can compare to concentrations expected in generic formulations that were developed for SHEDS-HT
- 125 Unique Product Category/Chemical Pairs Found in both HT Measurement and MSDS Data
- As seen in Rager et al. (2016), we underestimate concentration of chemicals that occur at high concentrations

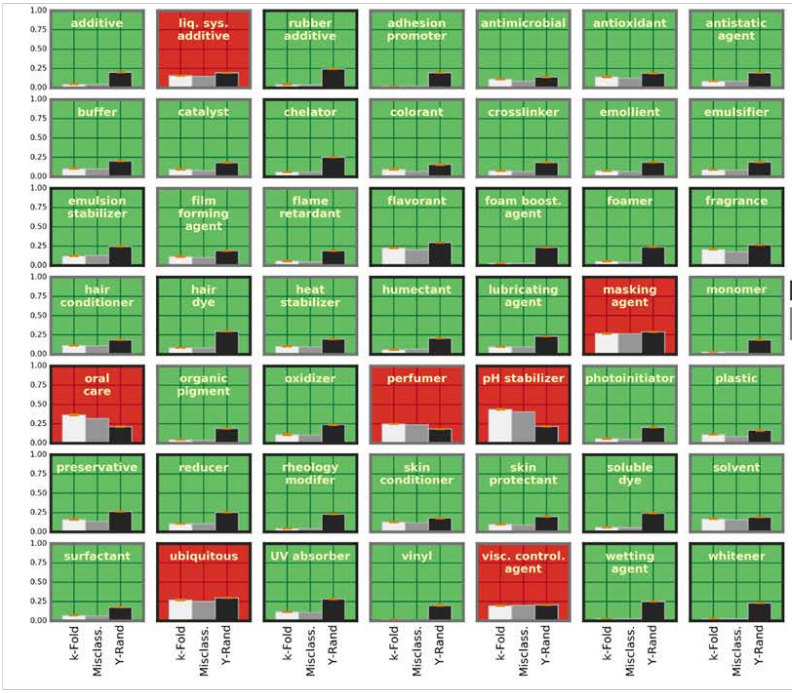
Figure from Kristin Isaacs

We found many new chemicals in consumer products- why are they there?

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Collect CASRN and functional uses from online data sources

Curate chemical-specific property and structure descriptors

Develop machine-learning based QSPR classification models for each chemical function

Functional Use (FUse) Database and Classifier Models

Reported Functional Uses of Identified Chemicals

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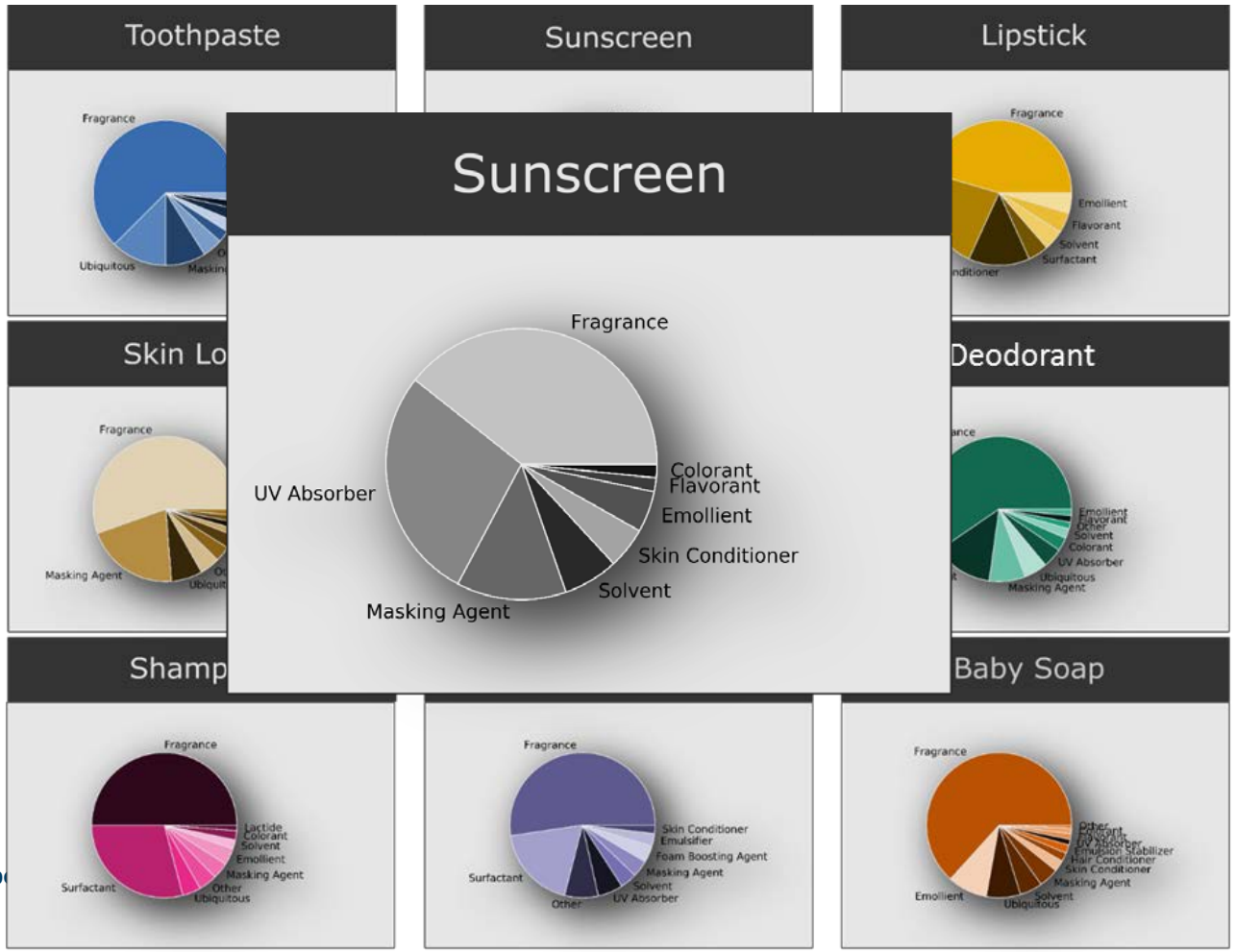
- 556 unique chemicals found in products and FUse



Reported Functional Uses of Identified Chemicals

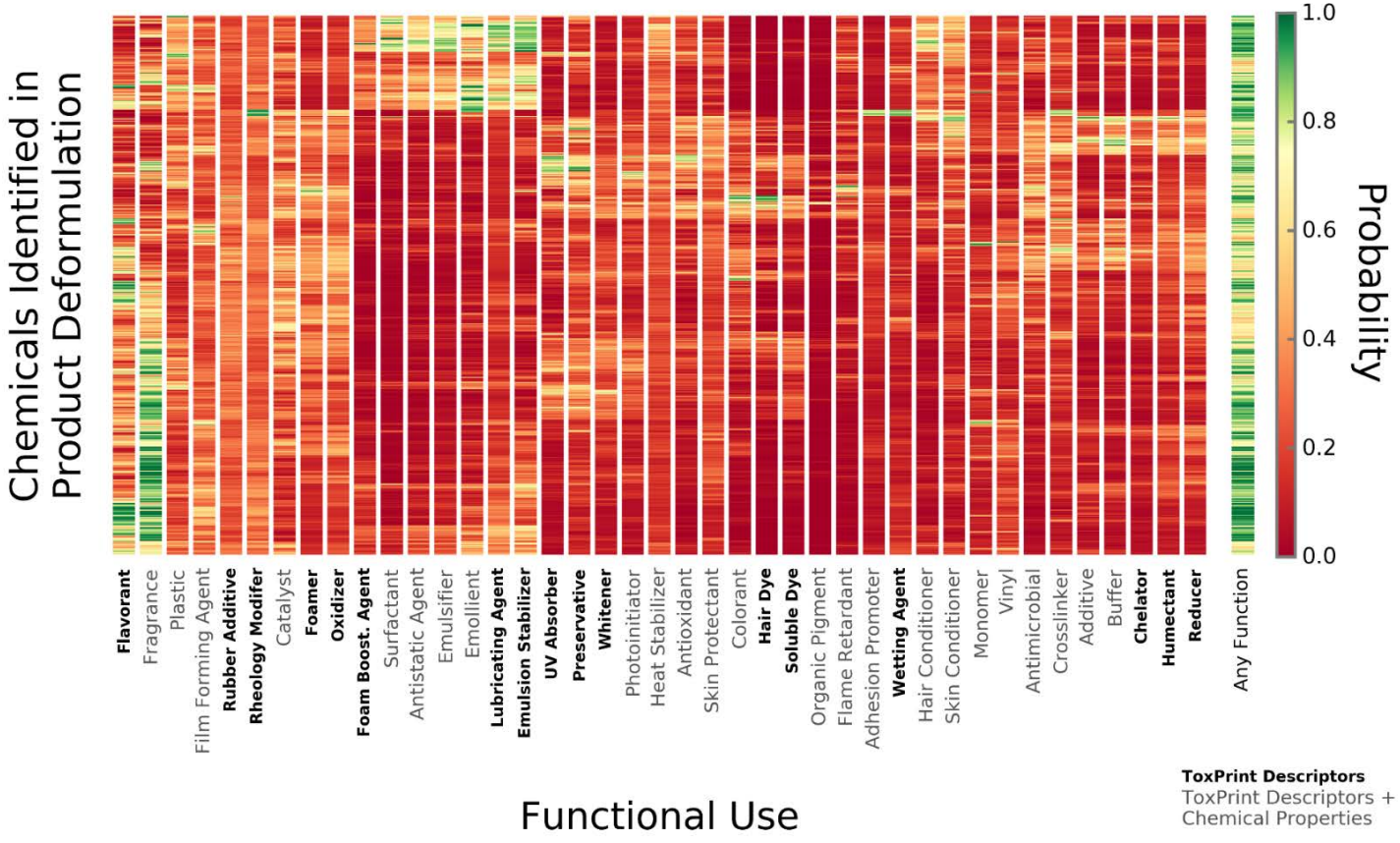
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- 556 unique chemicals found in products and in database of chemical function information



Predicted vs. Actual Functional Uses

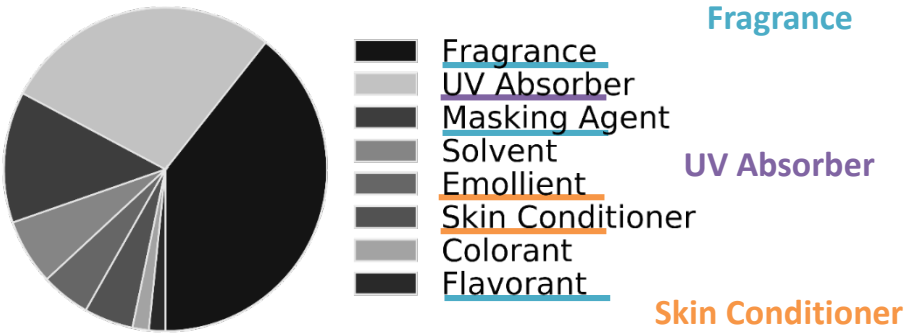
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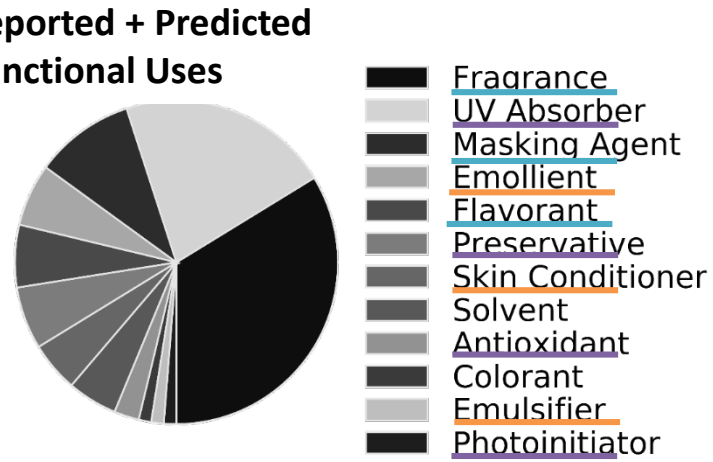
- 1347 identified chemicals had enough information to apply function models
- 850 chemicals a function predicted with a probability of 80% or higher

Comparison of Functional Uses in Sunscreen

Reported Functional Uses (in FUse)



Reported + Predicted Functional Uses



Use	Number of Chemicals	
	Reported	Reported + Predicted
Fragrance	33	40
UV Absorber	17	25
Skin Conditioner	6	10
Solvent	4	4
Colorant	1	1

Follow-up to Product Composition Pilot Study

- Case study of products in feminine care products (collaboration with Office of Health Assessment, National Toxicology Program)

- Case study of chemicals in recycled versus virgin materials
  - 7 categories of products including clothing, food contact materials, paper products, children's toys, tire crumb rubber-derived products, other housewares

Summary

- In ExpoCast, we are using a combination of forward modeling and reverse inference from biomarkers to predict exposure pathways and rates
- We are collecting new high-throughput data for parameterizing and evaluating our models
- Non-targeted and suspect screening provides an important new tool for acquiring evaluation data but important limitations must be noted
- New chemical-specific information on properties and emission rates will improve predictive models for these parameters and broaden the universe of chemicals for which pathway-specific exposure models can be applied
- These new data will ultimately reduce uncertainty in exposure model predictions used in risk-based prioritization

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

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