United States Environmental Protection Agency

Advances in EPA's Rapid Exposure and Dosimetry Project

Kristin Isaacs
National Exposure Research Laboratory
Office of Research and Development
U.S. Environmental Protection Agency
ORCID: 0000-0001-9547-1654

John Wambaugh
National Center for Computational Toxicology
Office of Research and Development
U.S. Environmental Protection Agency
ORCID: 0000-0002-4024-534X

Interagency Alternatives Assessment Webinar

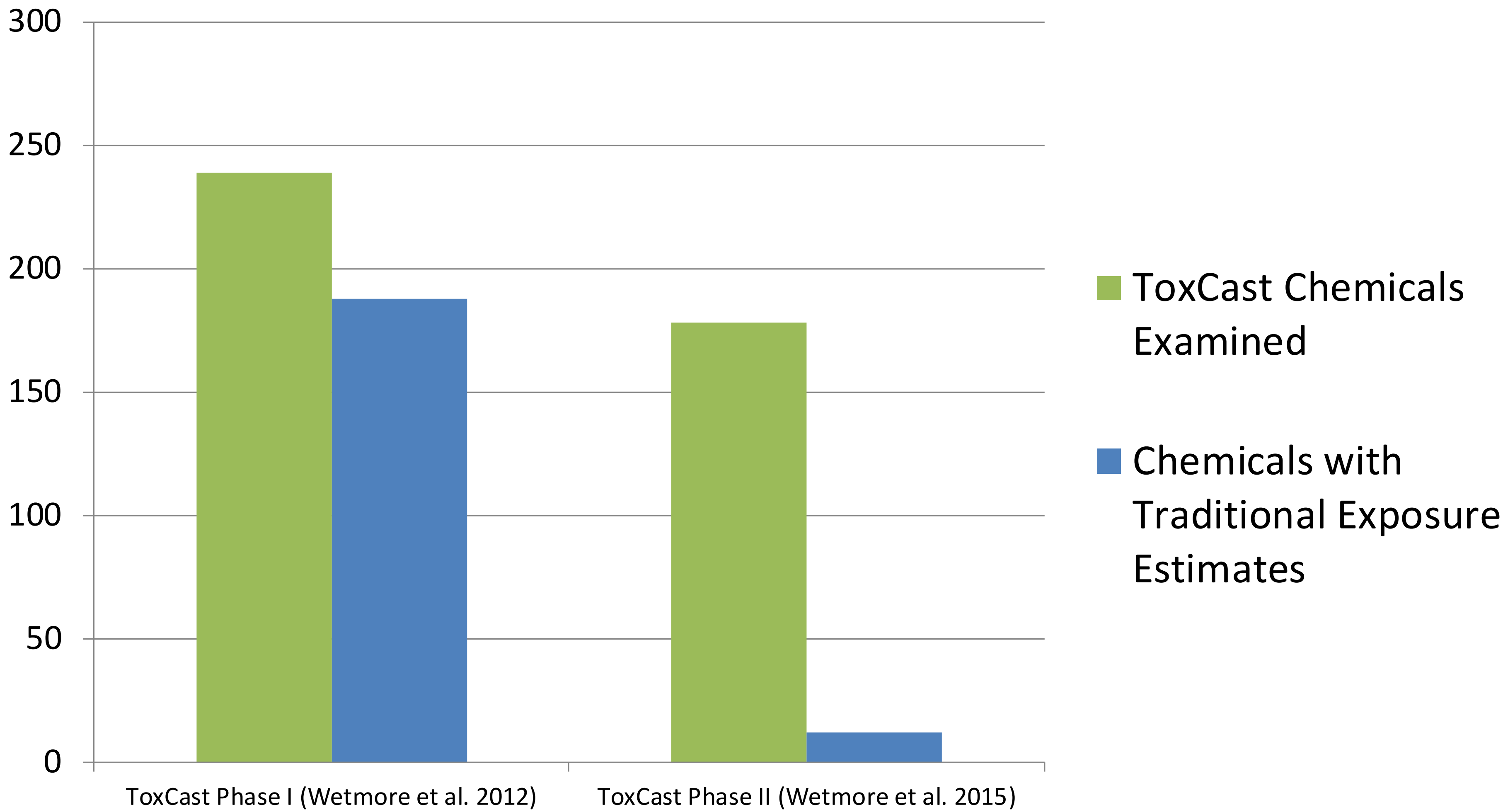
February 25, 2016

Introduction

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

November 29, 2014

Available Data for Exposure Estimations



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

Thinking About Exposure

United States
Environmental Protection
Agency

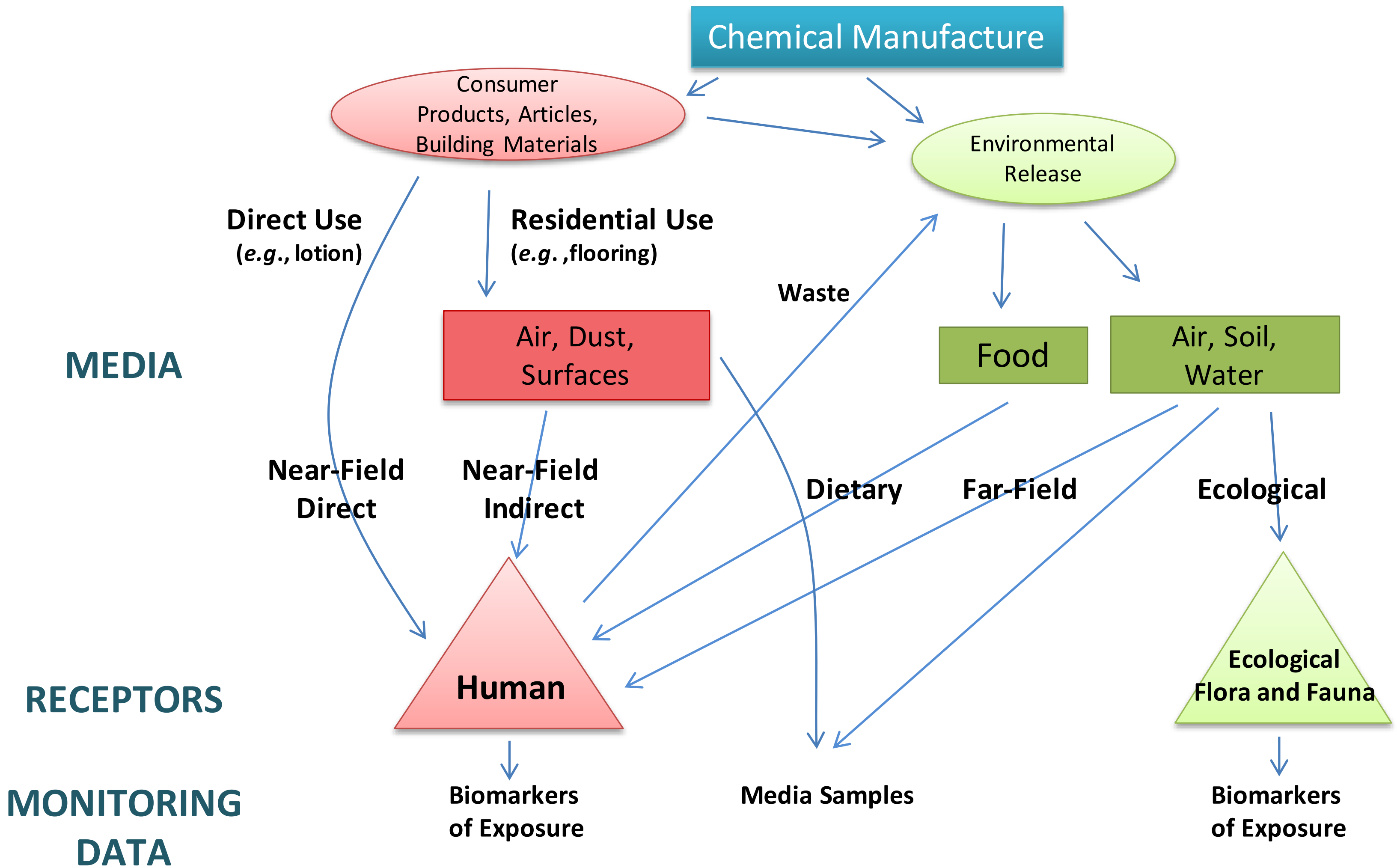


Figure from Kristin Isaacs

Exposure Pathways

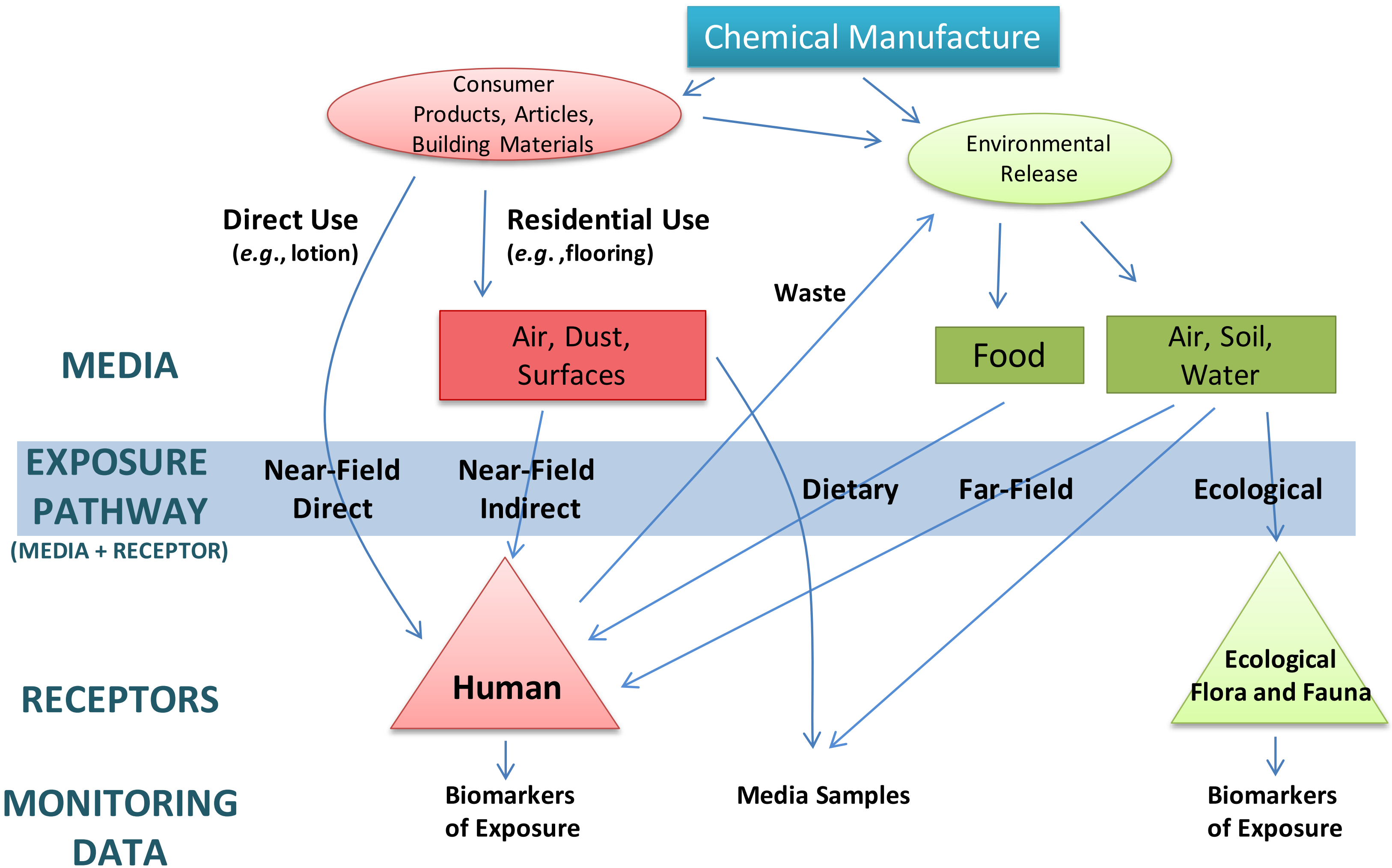
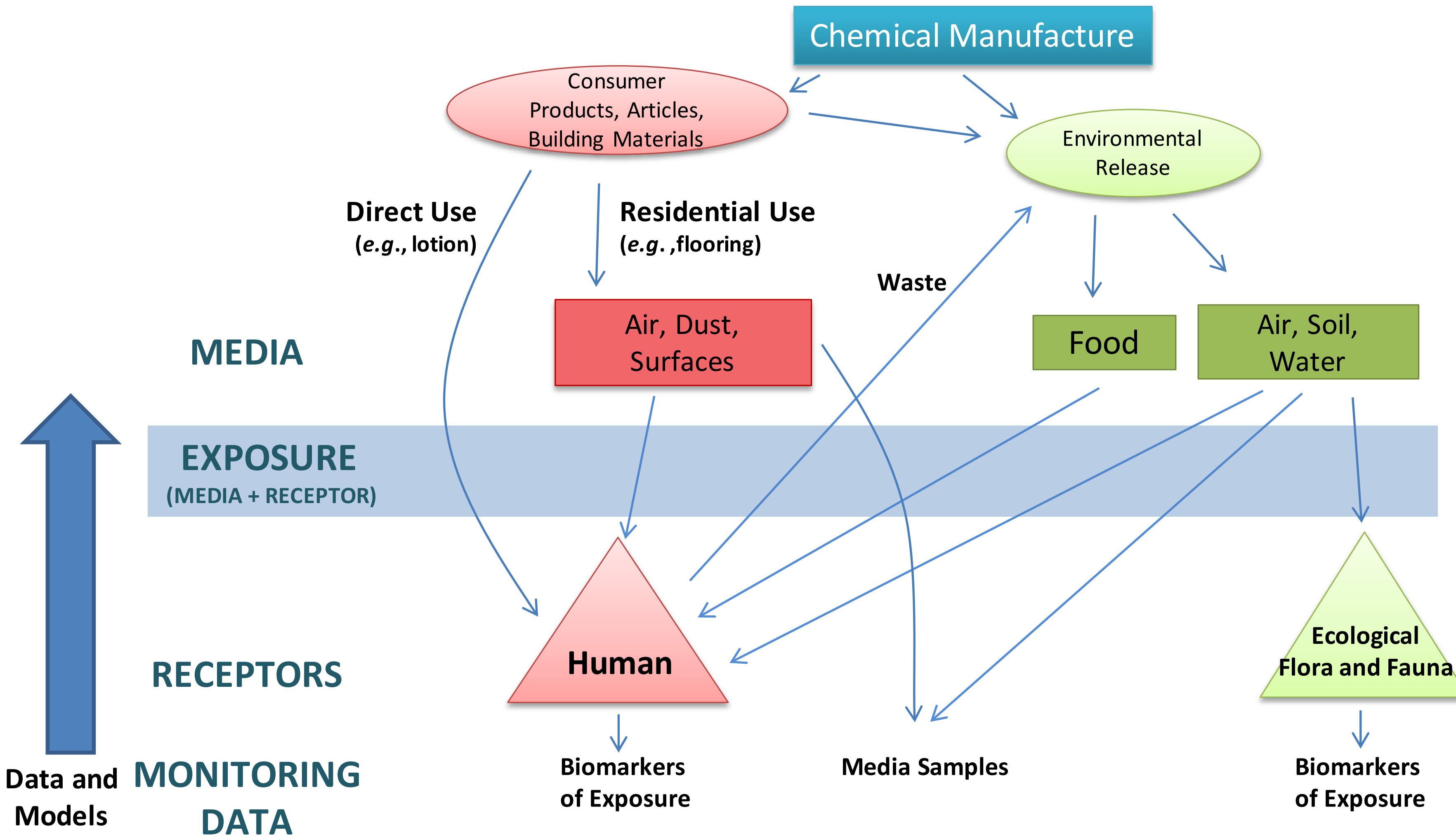


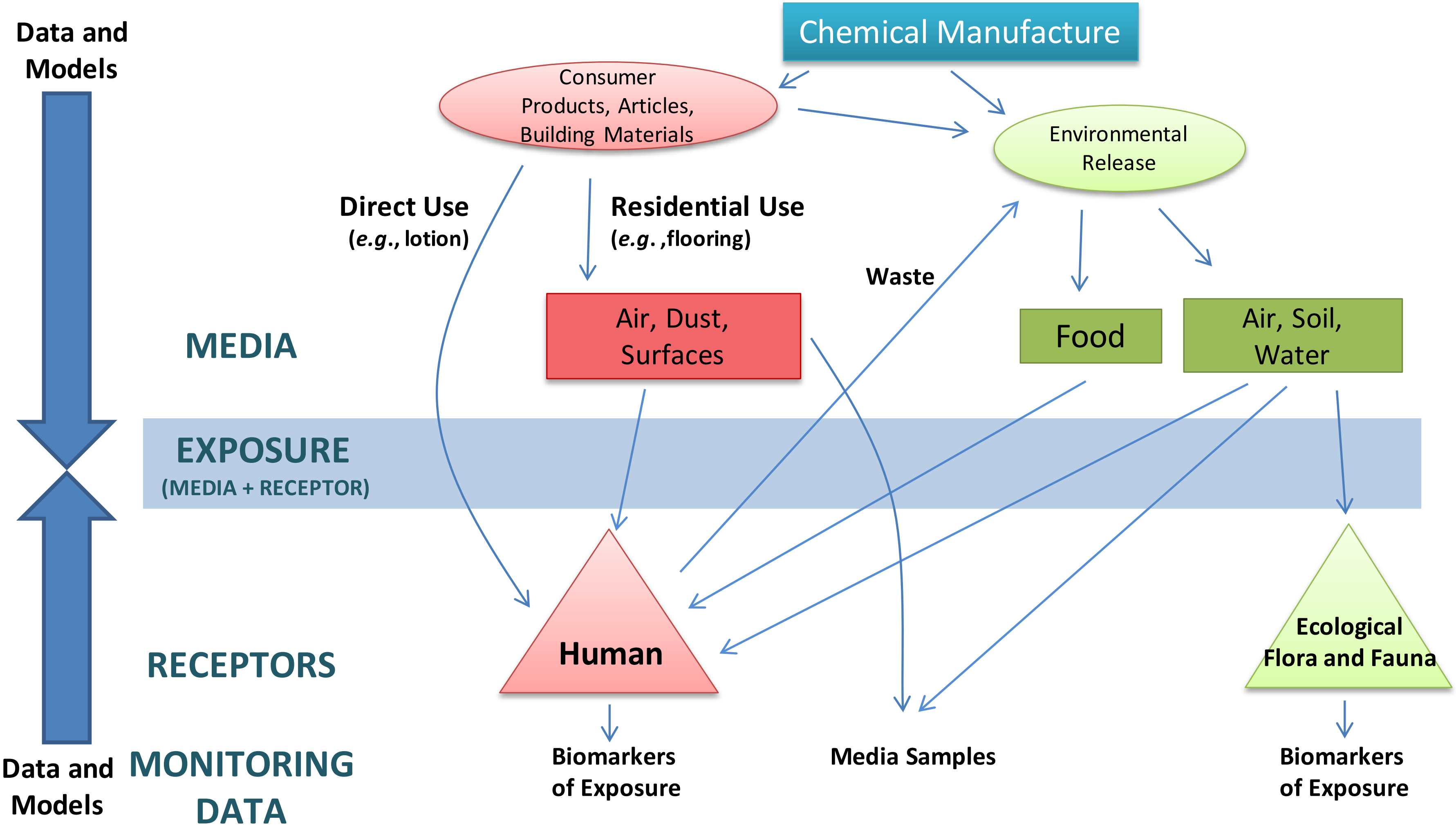
Figure from Kristin Isaacs

Exposure Monitoring

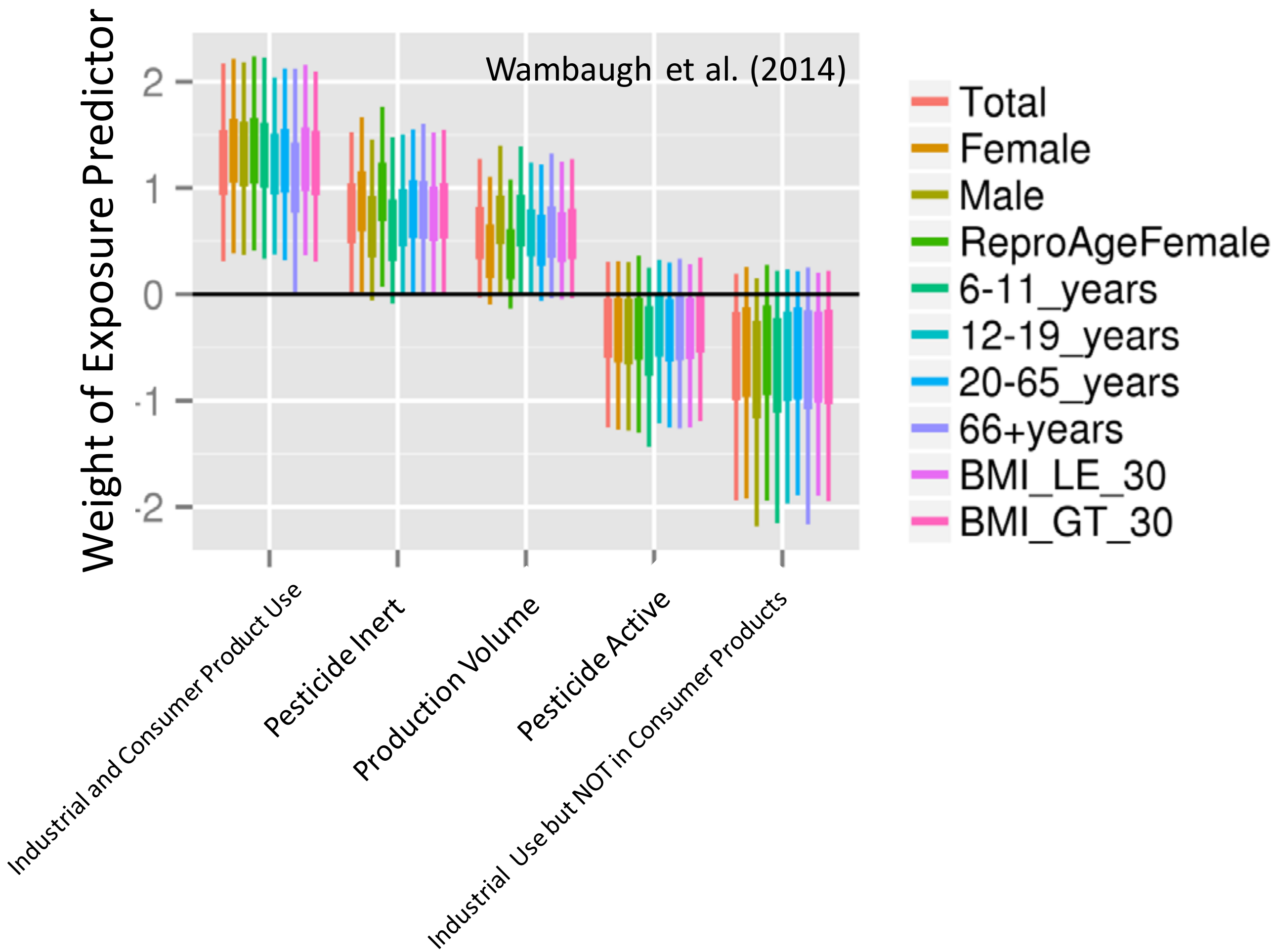


- Centers for Disease Control monitors a few hundred specific chemicals in urine and blood of U.S. citizens

Evaluating Exposure Models



Predicting Exposure



We incorporate multiple computer models into consensus predictions for 1000s of chemicals

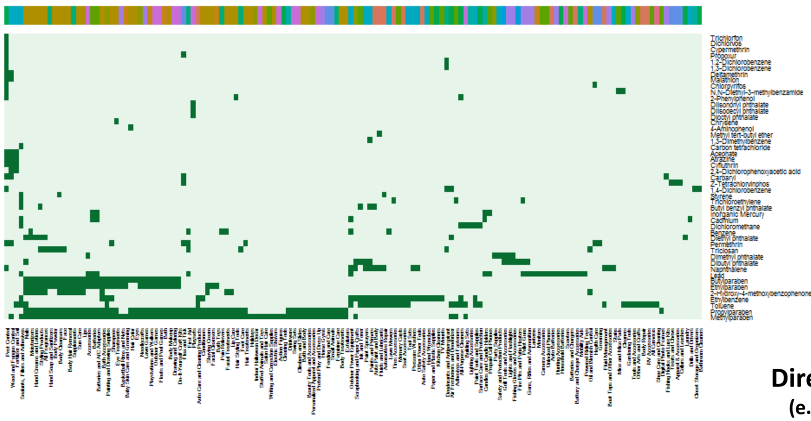
Same five predictors work for all NHANES demographic groups analyzed – stratified by age, sex, and body-mass index:

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

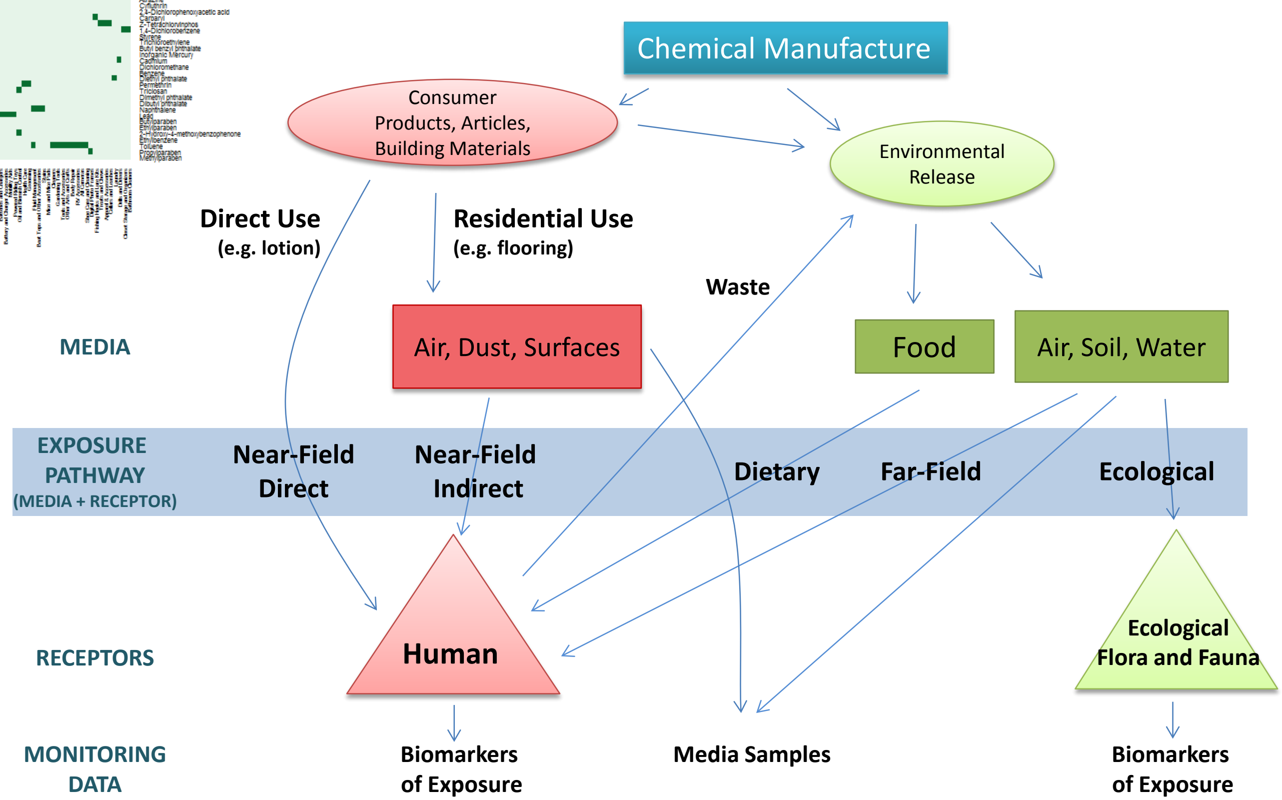
Chemical Use Identifies Relevant Pathways

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

105 NHANES Chemicals

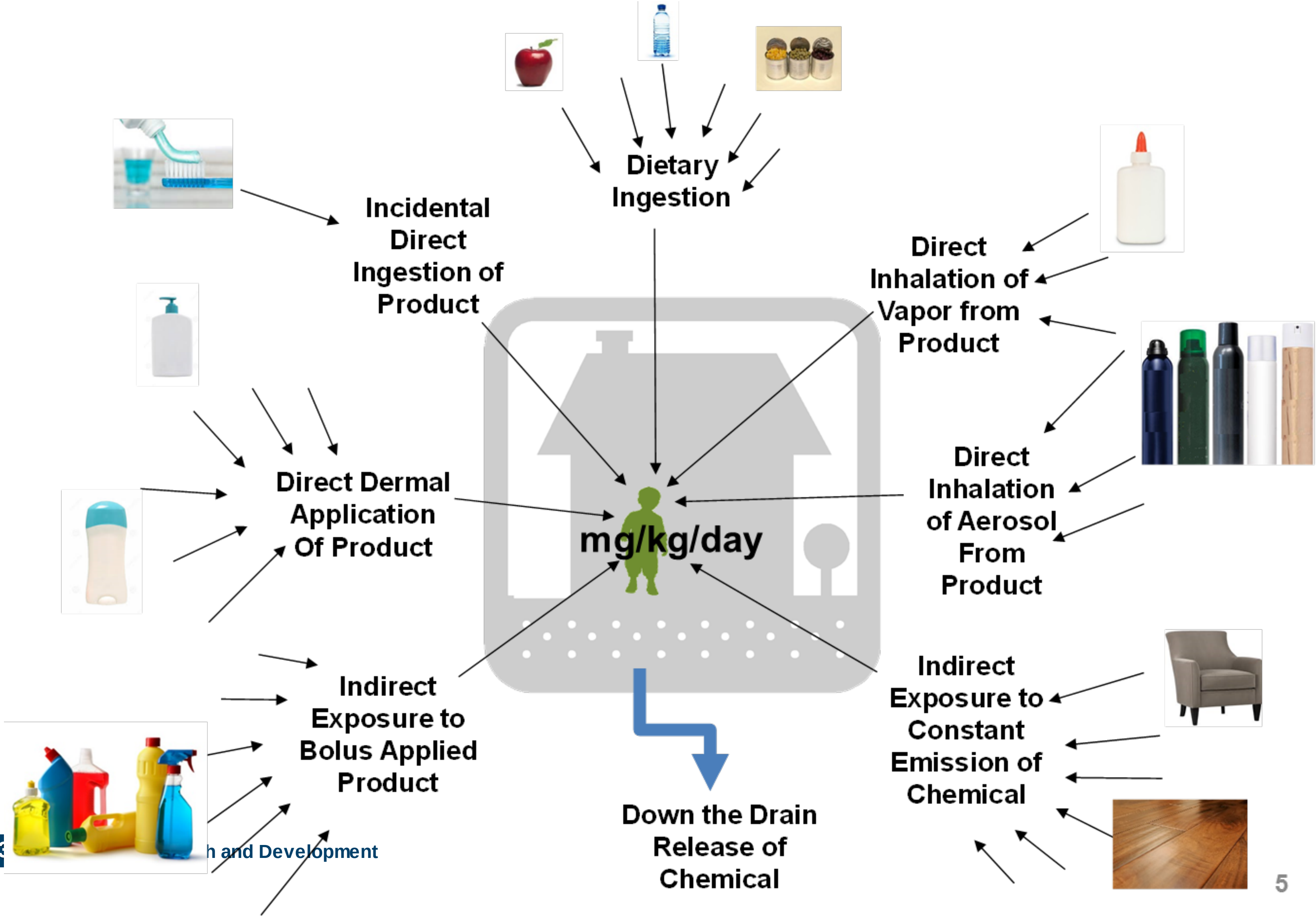


- Apparel
- Auto and Tires
- Baby
- Beauty
- Craft and Party Supply
- Electronics
- Grocery
- Health
- Home
- Home Improvement
- Patio and Garden
- Pets
- Sports and Outdoors
- Toys

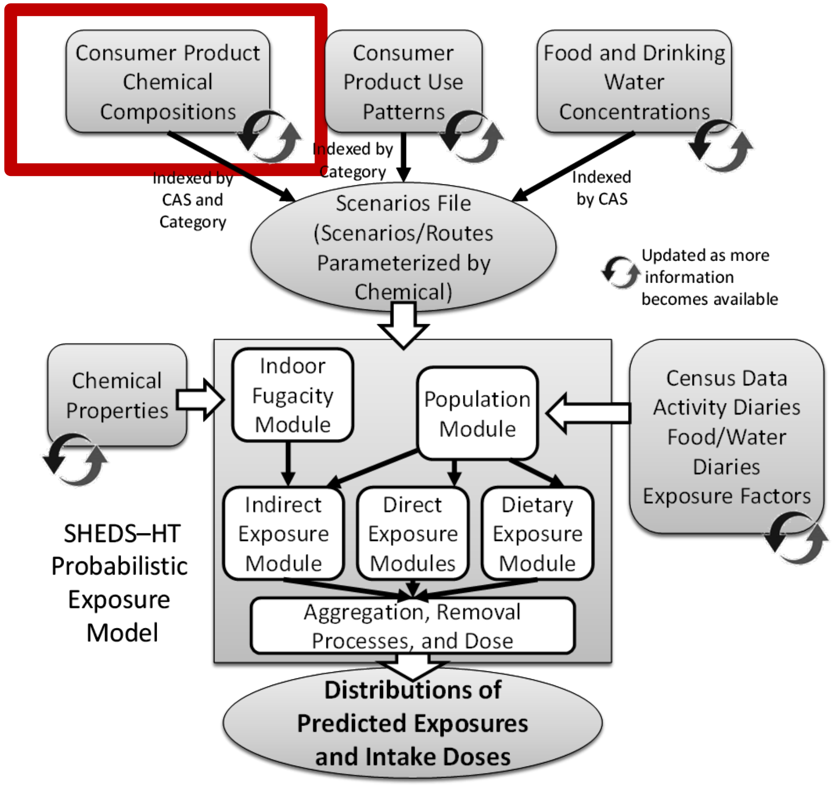


Office of Research and Development

Advancing Near-Field Models: SHEDS-HT



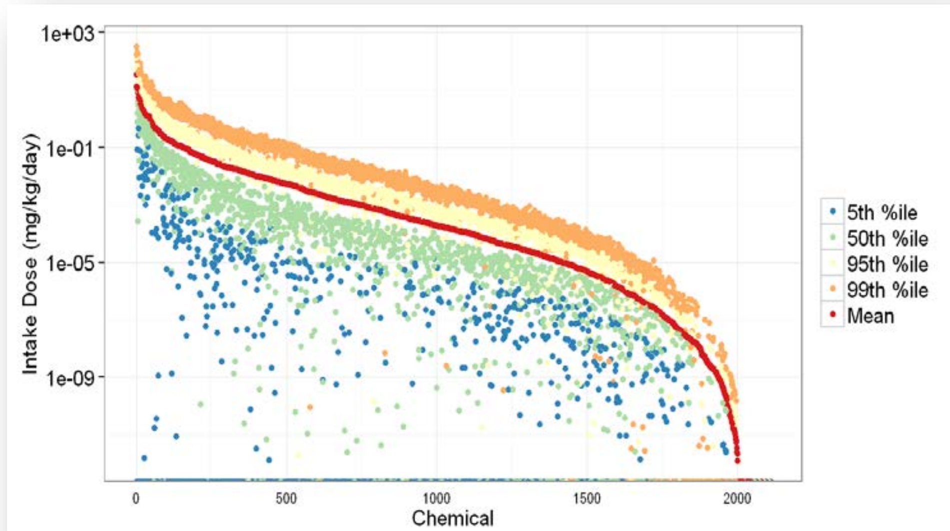
Advancing Near-Field Models: SHEDS-HT



Environmental Science & Technology
Article
pubs.acs.org/est

SHEDS-HT: An Integrated Probabilistic Exposure Model for Prioritizing Exposures to Chemicals with Near-Field and Dietary Sources

Kristin K. Isaacs,[*,†] W. Graham Glen,[‡] Peter Egeghy,[†] Michael-Rock Goldsmith,[§,○] Luther Smith,[‡] Daniel Vallero,[†] Raina Brooks,[‖] Christopher M. Grulke,[⊥,○] and Halûk Özkaynak[†]



USE: What chemicals are in consumer products and articles?

FUNCTION: Why are they there?

COMPOSITION: At what weight fractions are they present?

Chemical Use Research

- Chemical and Product Categories Database (CPCat)
  - Cross-lab effort
  - Effort to curate data and harmonize use categories across many different public data sources
  - Chemical to use-category linkages
  - Publically available: http://actor.epa.gov/cpcat

Chemical and Product Categories Database (CPCat)

United States Environmental Protection Agency

- Information on the use of 40,000 unique chemicals Chemical and Product Categories Database (CPCat)
- Curated across many different public data sources
- Indexed by a set of 800 harmonized *terms* describing how chemicals are used
- Terms are combined into*cassettes* to provide refined categories of chemicals with potential uses

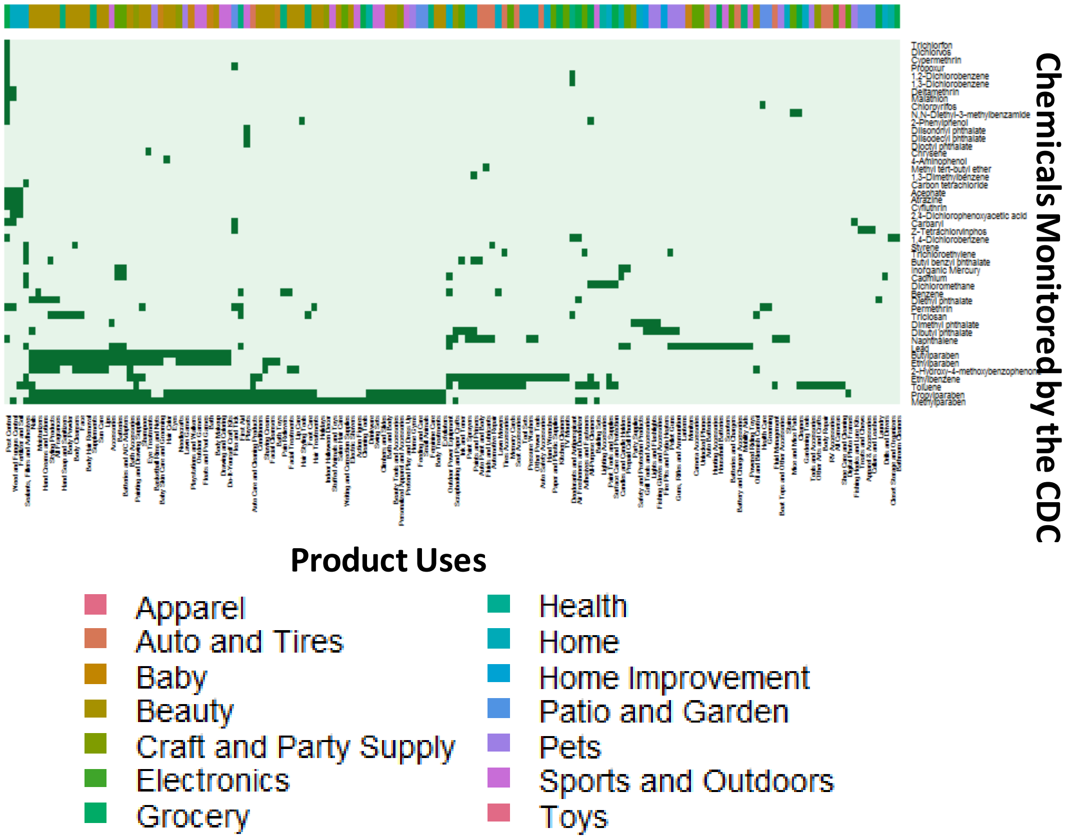
Publically available: http://actor.epa.gov/cpcat

Original data source	Class of categories	Original categories	CPCat cassettes	Chemicals
ACToR Data Sets and Lists	General-use	131	173	35,838
ACToR UseDB	General-use	15	15	31,622
CDR 2012:				
Consumer	General-use	34	36	3,321
Industrial Function	Functional-use	34	27	5,023
Industrial Sector	Industrial sector-use	42	43	5,226
DfE	Functional-use	11	9	444
Dow	Functional-use	19	18	104
DrugBank	Therapeutic-use	582	460	1,754
2006 IUR	General-use	19	24	1,152
KemI	Functional-use	61	31	876
NICNAS	General-use	17	17	177
Retail Product Categories	Product-use	359	191	2,778
SPIN:				
detpcat	General-use	781	284	6,491
Industrial Sector	Industrial sector-use	580	221	4,603
NACE	Industrial sector-use	57	52	7,745
UC62	General-use	61	59	9,059
Toxome	Functional-use	16	16	442

*Dionisio, K. L., et al. (2015). "Exploring consumer exposure pathways and patterns of use for chemicals in the environment." Toxicology Reports **2**: 228-237.*

Composition Data: Consumer Product Chemical Profile Database (CPCPdb)

- Analyzed Materials Safety Data Sheets (MSDS) for ~20,000 products sold by a major U.S. retailer
- MSDS indicated most constituent chemicals and in some cases, weight fraction
- Annotated each product with putative usage based on how chemical was sold on-line – e.g., home goods, bath toys
- Provides some of the most detailed information within CPCat
- New MSDS datasets have subsequently been collected
- ~300 new consumer product categories have been developed for exposure modeling: considering product type, subtype, form (e.g. spray), targeted population (e.g. women, children)

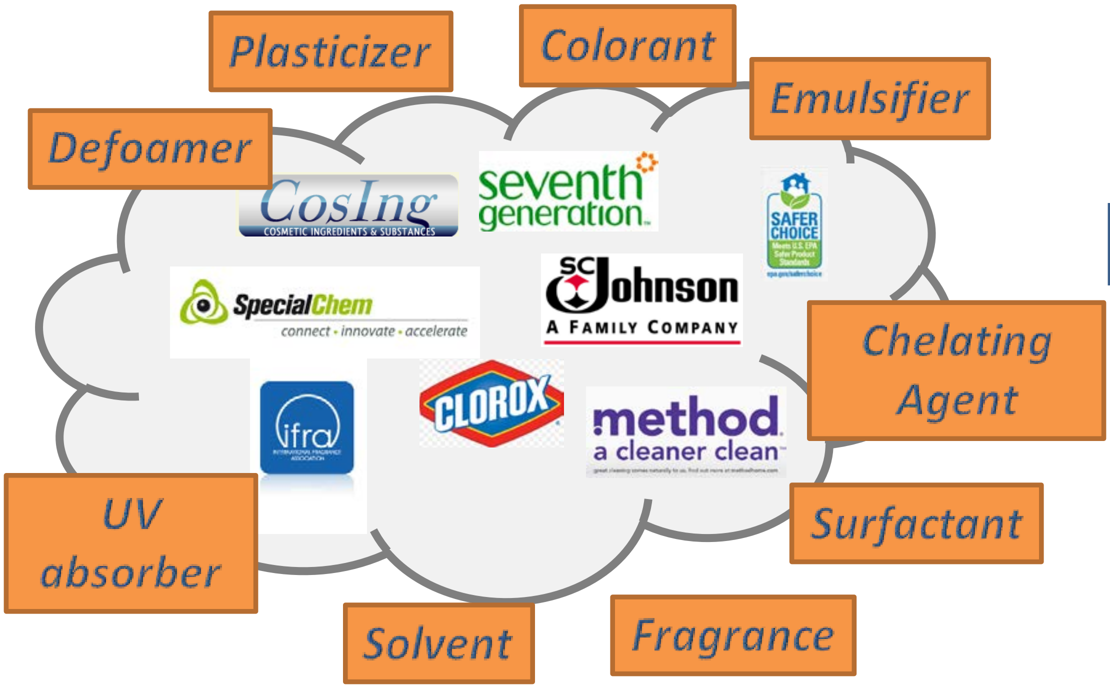


Goldsmith et al., *Food and Chemical Toxicology*. 2014.

What Do We Do When We Don't Know How a Chemical is Used?

- Unfortunately we are lacking specific use information for 1000s of known chemicals
- Including a large part of the Tox21 library
- How might we go about predicting chemical use and ultimate exposure potential?
- *Function* may be key
- Use machine learning to fill in data gaps

Expanding the Use Information in CPCat to Include Chemical Functional Use



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

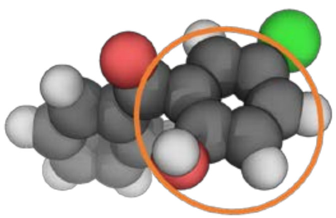
Will Allow for Modeling of Function in Terms of Chemical Properties or Structures

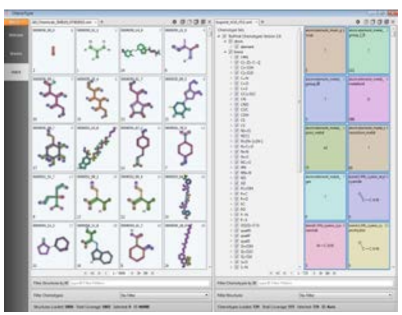
United States Environmental Protection Agency

Predicting Function Based on Properties and Structure

Chemical Structure and Property Descriptors

Use Database (FUSE)





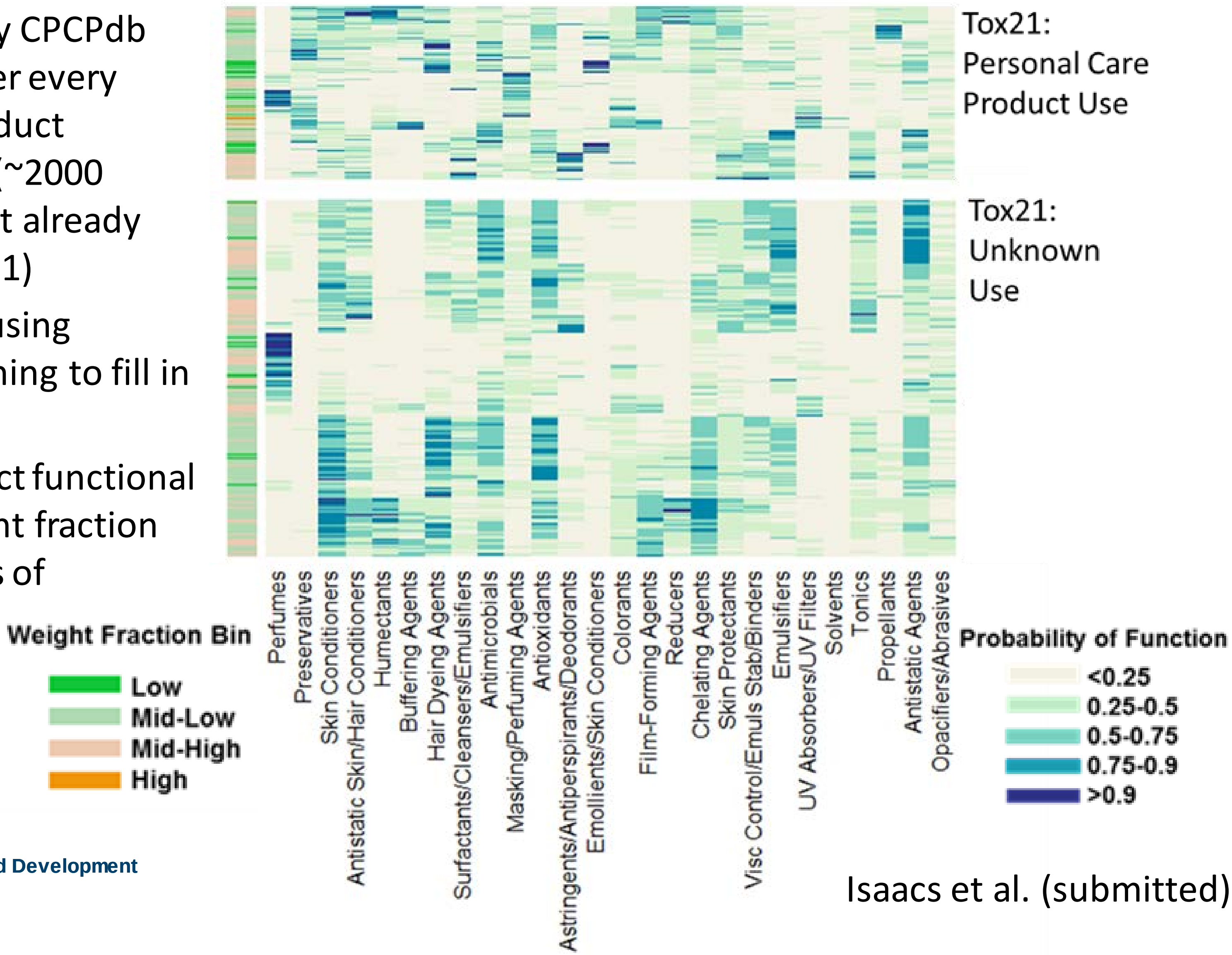
Prediction of Of Potential Function from Chemical Libraries

Machine-Learning Based Classification Models

Material from Katherine Phillips

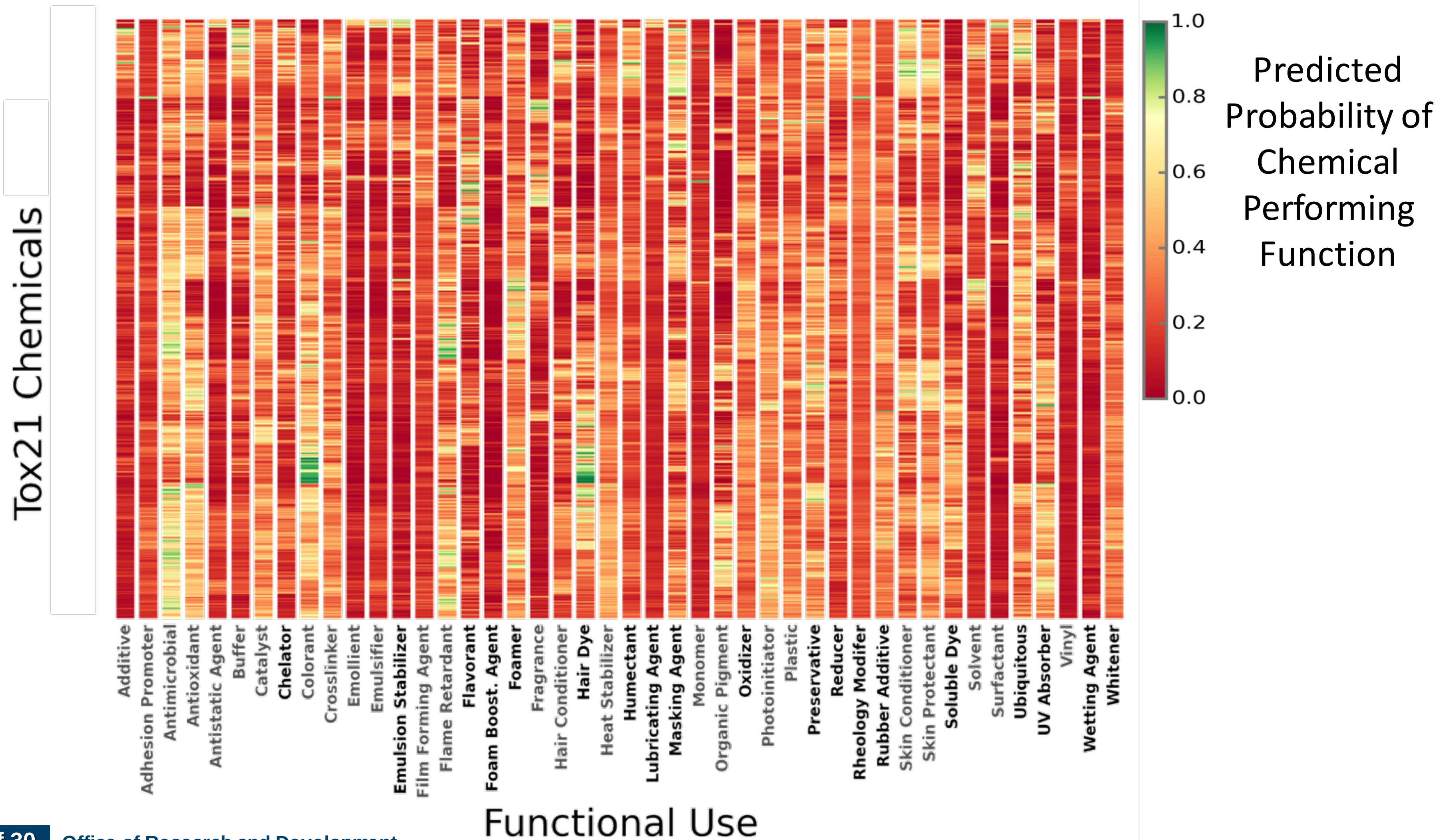
Predicting Chemical Constituents

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



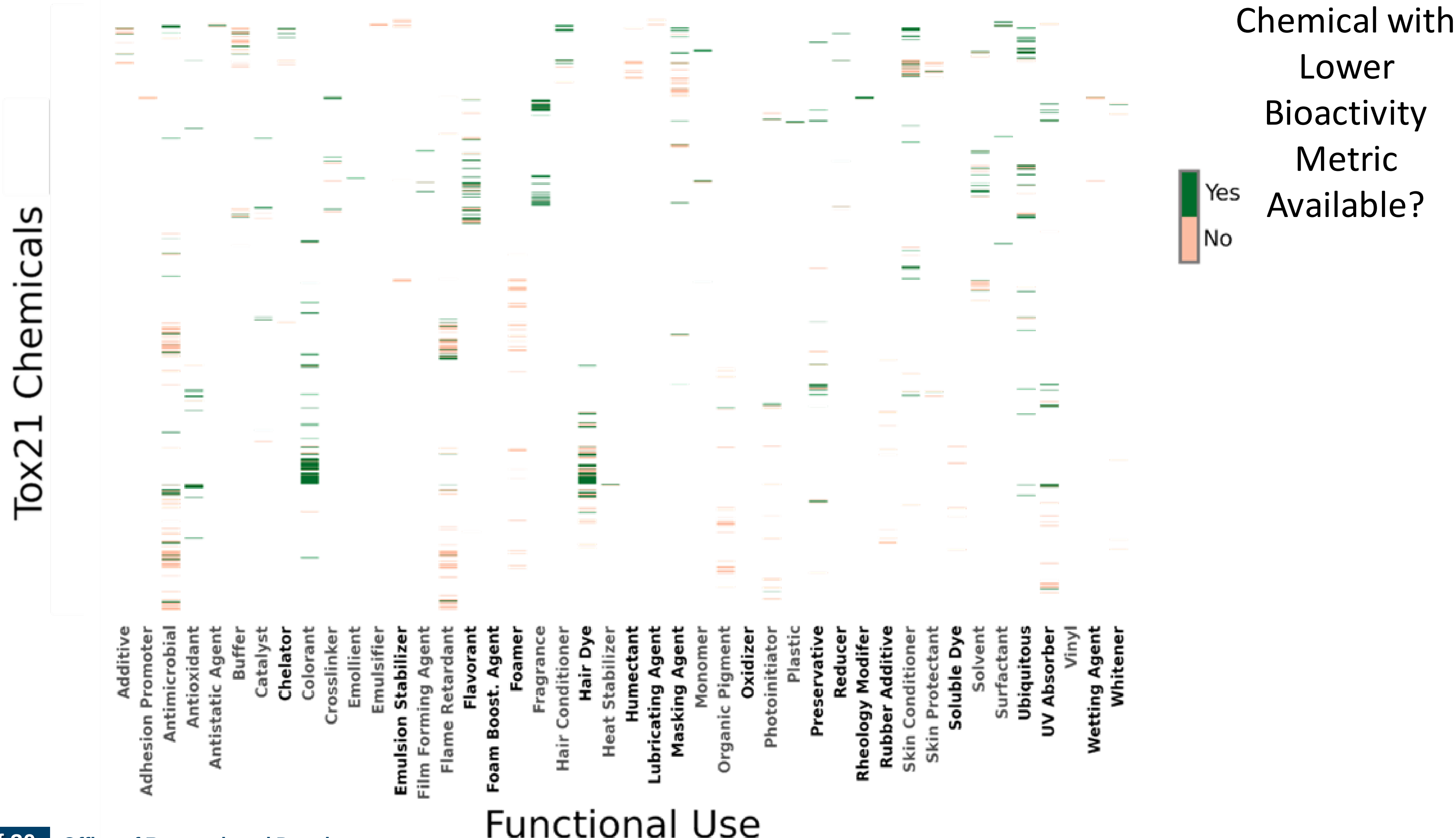
Isaacs et al. (submitted)

Screening for Potential Alternatives By Function and Bioactivity



Material from Katherine Phillips

Screening for Alternatives By Function and Bioactivity

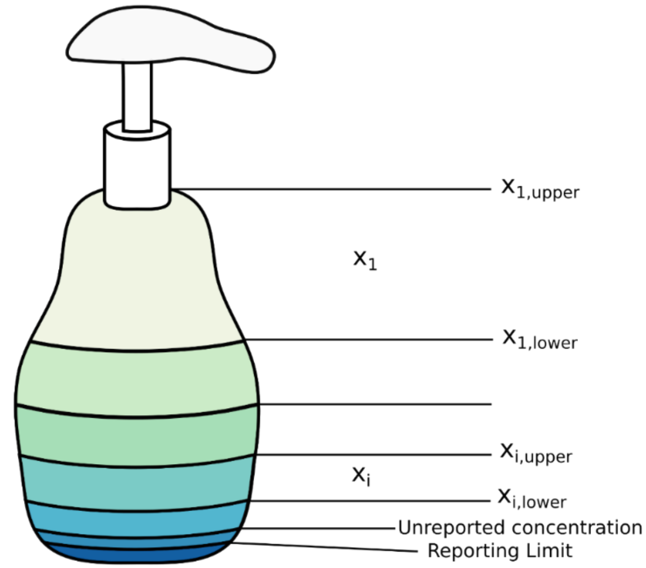


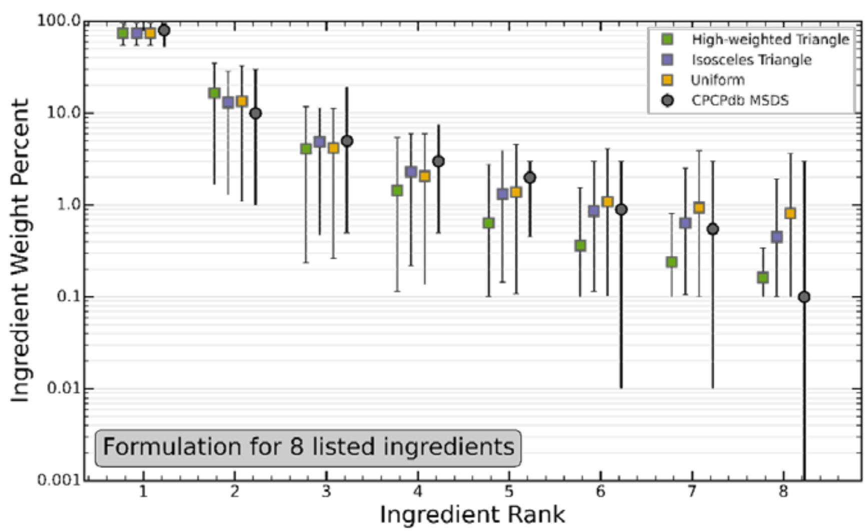
 Office of Research and Development

Material from Katherine Phillips

Predicted Concentrations from Ingredient Lists

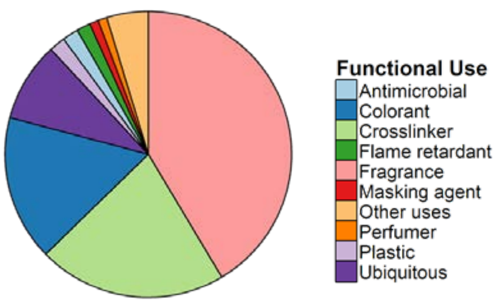
- When a list of ingredients
  - Is presented in descending order by weight fraction
  - Includes all ingredients above a cut off weight fraction
- The weight fraction of a chemical is constrained by:
  - The rank of the chemical in the list
  - The length of the list
  - The cut off for reporting



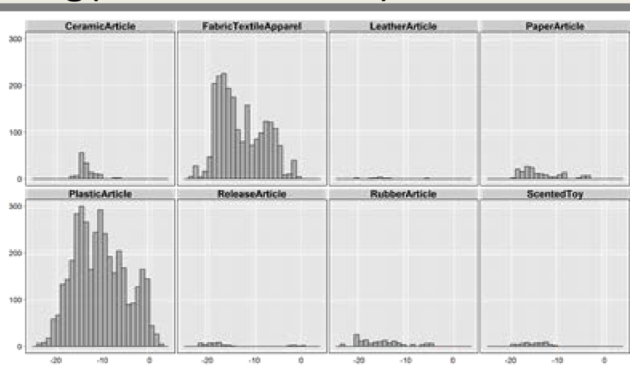


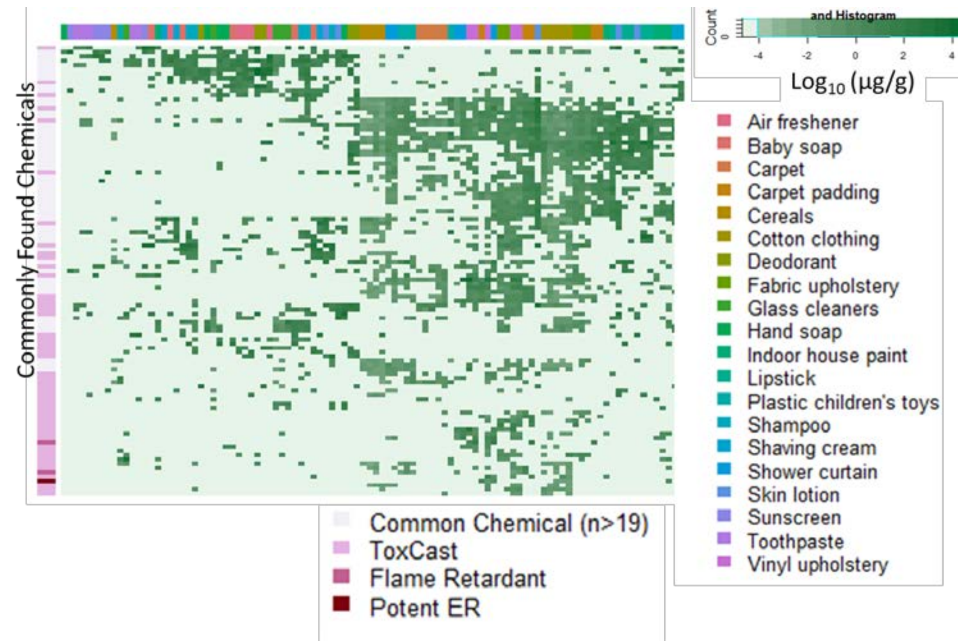
Moving Forward from Formulations to Articles

Danish EPA Surveys on Chemicals in Consumer Products



Log(Concentration) distributions





ExpoCast/RED HT Measurement Contract

Material from John Wambaugh, Alice Yau (SWRI) and Katherine Phillips

Pilot Projects to Reduce Uncertainty and Expand Validation Domain

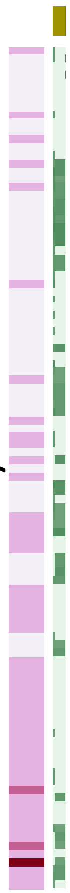
Project	Pilot Project Scope
High throughput chemical property measurement (e.g., log P)	200 chemicals
Determine the chemical constituents of products, materials, articles	20 classes of product, 5 samples each
Determine chemical emission rate from specific products, materials, articles	100 materials
Screening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

ExpoCast Consumer Product Scan

United States Environmental Protection Agency

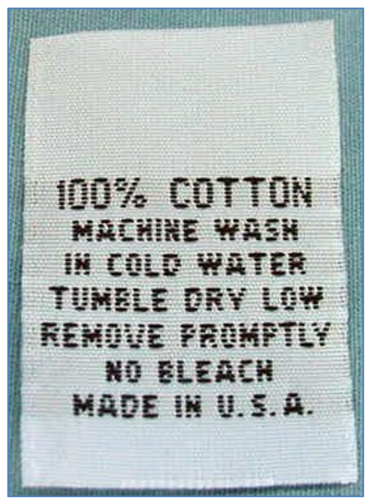
Commonly Found Chemicals

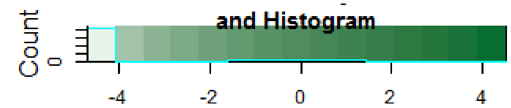


Scanned 5 examples each of 20 class of consumer products

Found >3500 chemicals in total across the 100 products

The chemicals found in a cotton shirt





Log_{10} (µg/g)

- 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

GC-MS with DCM Extraction

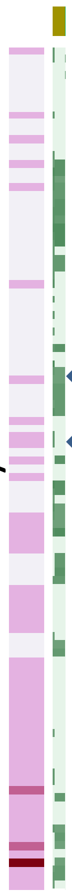
- Common Chemical (n>19)
- ToxCast
- Flame Retardant
- Potent ER

Results from Alice Yau (SWRI)

ExpoCast Consumer Product Scan

United States Environmental Protection Agency

Commonly Found Chemicals

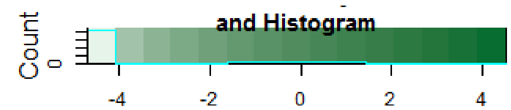


Scanned 5 examples each of 20 class of consumer products

Found >3500 chemicals in total across the 100 products

Dark green is a high concentration

Light green is not detected



Log_{10} (µg/g)

- 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

GC-MS with DCM Extraction

- Common Chemical (n>19)
- ToxCast
- Flame Retardant
- Potent ER

Results from Alice Yau (SWRI)

ExpoCast Consumer Product Scan

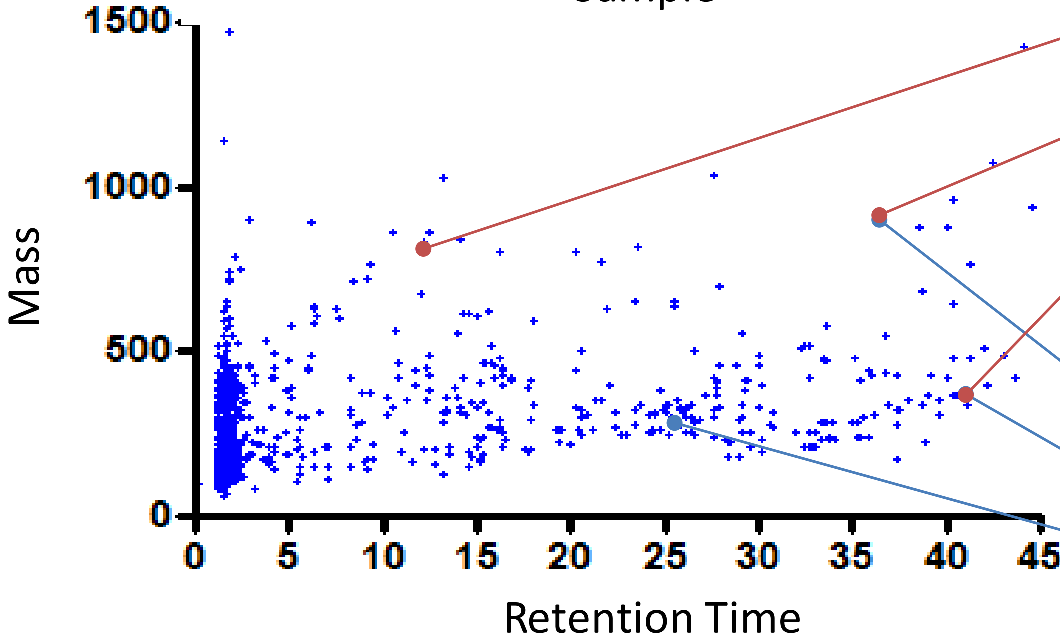
GCXGC-MS with DCM Extraction

Results from Alice Yau (SWRI)

United States Environmental Protection Agency

Suspect Screening and Non-Targeted Analytical Chemistry

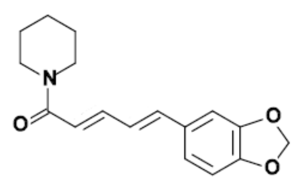
947 Peaks in an American Health Homes Dust Sample

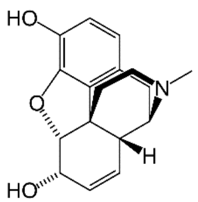


Each peak corresponds to a chemical with an accurate mass and predicted formula:

$$C_{17}H_{19}NO_3$$

Multiple chemicals can have the same mass and formula:





Is chemical A present, chemical B, or both?

We are now expanding our identity libraries using reference samples of ToxCast chemicals

See Rager et al., Environment International (In Press)

United States Environmental Protection Agency

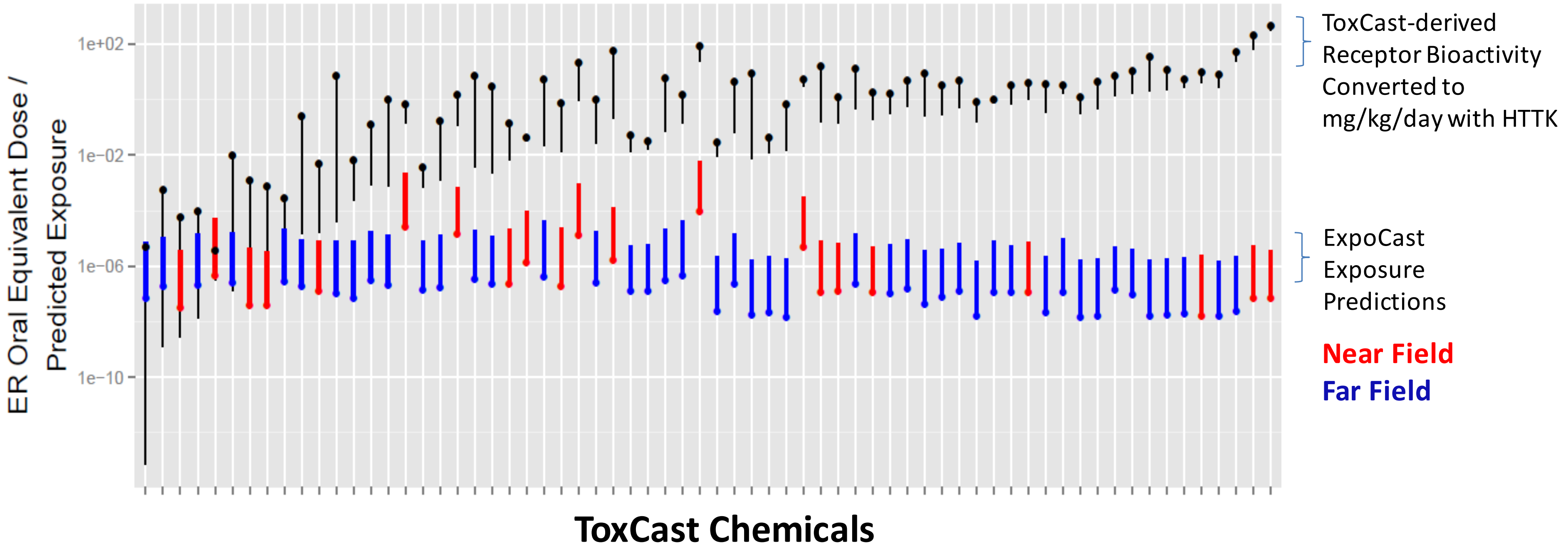
Applying Non-Targeted Screening

- ExpoCast consumer product scanning and blood sample monitoring
- EPA is also analyzing house dust from American homes – can identify 50% of the mass but only 2% of the chemicals Rager et al., Environment International (In Press)

"I'm searching for my keys."

- EPA is coordinating a comparison of the abilities of leading academic, government, and industry non-targeted screening groups to assess strengths and weaknesses

High Throughput Risk Prioritization in Practice



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

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

DOCKET NUMBER:
EPA–HQ–OPP–2014–0614

Conclusion

- We would like to know more about the risk posed by thousands of chemicals in the environment – which are most worthy of further study?
  - Exposure provides real world context to hazards indicated by high-throughput bioactivity screening

- Using **high throughput exposure** approaches we can make coarse predictions of exposure
  - We are actively refining and better validating these predictions with new models and data
  - In some cases, upper confidence limit on current predictions is already many times lower than predicted hazard

Collaborators

Arnot Research and Consulting
Jon Arnot
Battelle Memorial Institute
Anne Louise Sumner
Anne Gregg
Chemical Computing Group
Rocky Goldsmith
Hamner Institutes
Harvey Clewell
Cory Strope
Barbara Wetmore
National Institute for Environmental Health Sciences (NIEHS)
Mike Devito
Steve Ferguson
Nisha Sipes
Kyla Taylor
Kristina Thayer
Netherlands Organisation for Applied Scientific Research (TNO)
Sieto Bosgra
Research Triangle Institute
Timothy Fennell
Silent Spring Institute
Robin Dodson
Southwest Research Institute
Alice Yau
Kristin Favela
Summit Toxicology
Lesa Aylward
University of California, Davis
Deborah Bennett
University of Michigan
Olivier Jolliet
University of North Carolina, Chapel Hill
Alex Tropsha

EPA United States Environmental Protection Agency

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

NCCT
Chris Grulke
Richard Judson
Dustin Kapruan*
Chantel Nicolas*
Robert Pearce*
James Rabinowitz
Ann Richard
Caroline Ring*
Woody Setzer
Rusty Thomas
John Wambaugh
Antony Williams

NRMRL
Yirui Liang*
Xiaoyu Liu

NHEERL
Jane Ellen Simmons
Marina Evans
Mike Hughes

*Trainees

NERL
Craig Barber
Brandy Beverly*
Derya Biryol*
Kathie Dionisio
Peter Egeghy
Kim Gaetz
Brandall Ingle*
Kristin Isaacs
Katherine Phillips*
Paul Price
Mark Strynar
Jon Sobus
Mike Tornero-Velez
Elin Ulrich
Dan Vallero