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

EPA United States Environmental Protection Agency

High Throughput Chemical Safety

John Wambaugh
National Center for Computational Toxicology
U.S. E.P.A. Office of Research and Development

STEM in the Park Educator ExternTrip

October 25, 2017

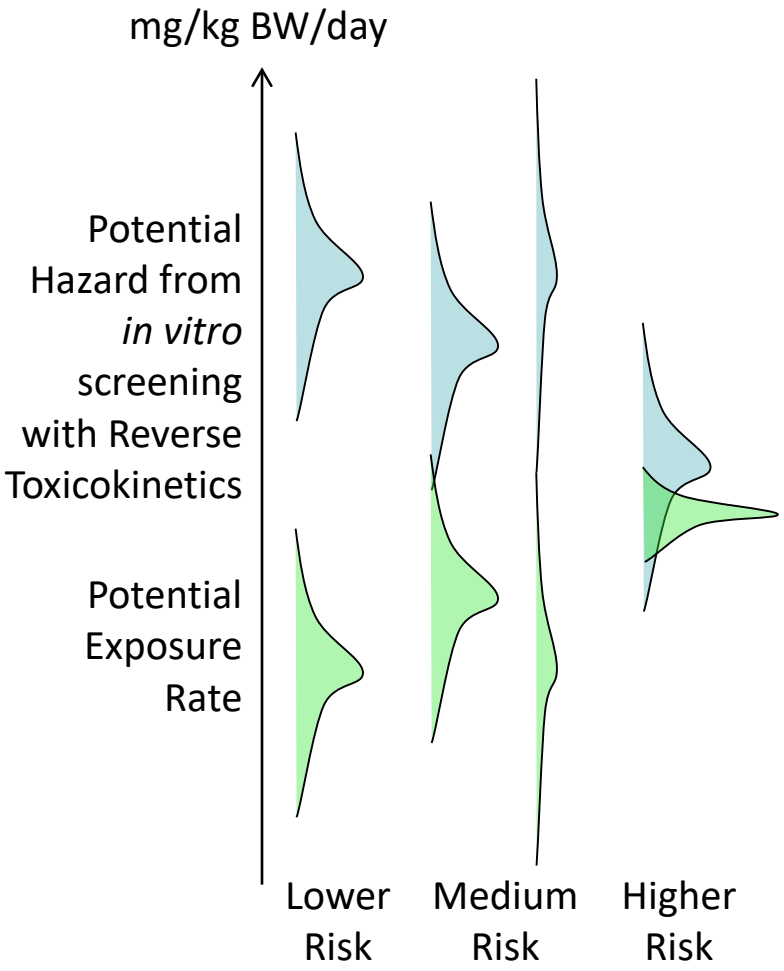
Chemical Regulation in the United States

- Park *et al.* (2012): At least 3221 chemicals in pooled human blood samples, many appear to be exogenous
- 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)
- Most other chemicals, ranging from industrial waste to dyes to packing materials are covered by the recently updated Toxic Substances Control Act (TSCA)
  - Thousands of chemicals on the market were either "grandfathered" in or were allowed without experimental assessment of hazard, toxicokinetics, or exposure
  - Thousands of new chemical use submissions are made to the EPA every year
  - **Methods are being developed to prioritize these existing and new chemicals for testing**

November 29, 2014

Chemical Risk = Hazard + Exposure

- "High Throughput" methods allow rapid assessment of potential hazard using "drug discovery" tools
- **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)



- All data are made public: http://comptox.epa.gov/dashboard/

EPA's Rapid Exposure and Dosimetry Project

We do exposure forecasting or "ExpoCast"

Co-leaders Kristin Isaacs and John Wambaugh

NCCT
Chris Grulke
Greg Honda
Richard Judson
Andrew McEachran
Robert Pearce
Ann Richard
Risa Sayre
Woody Setzer
Rusty Thomas
John Wambaugh
Antony Williams

NRMRL
Yirui Liang
Xiaoyu Liu

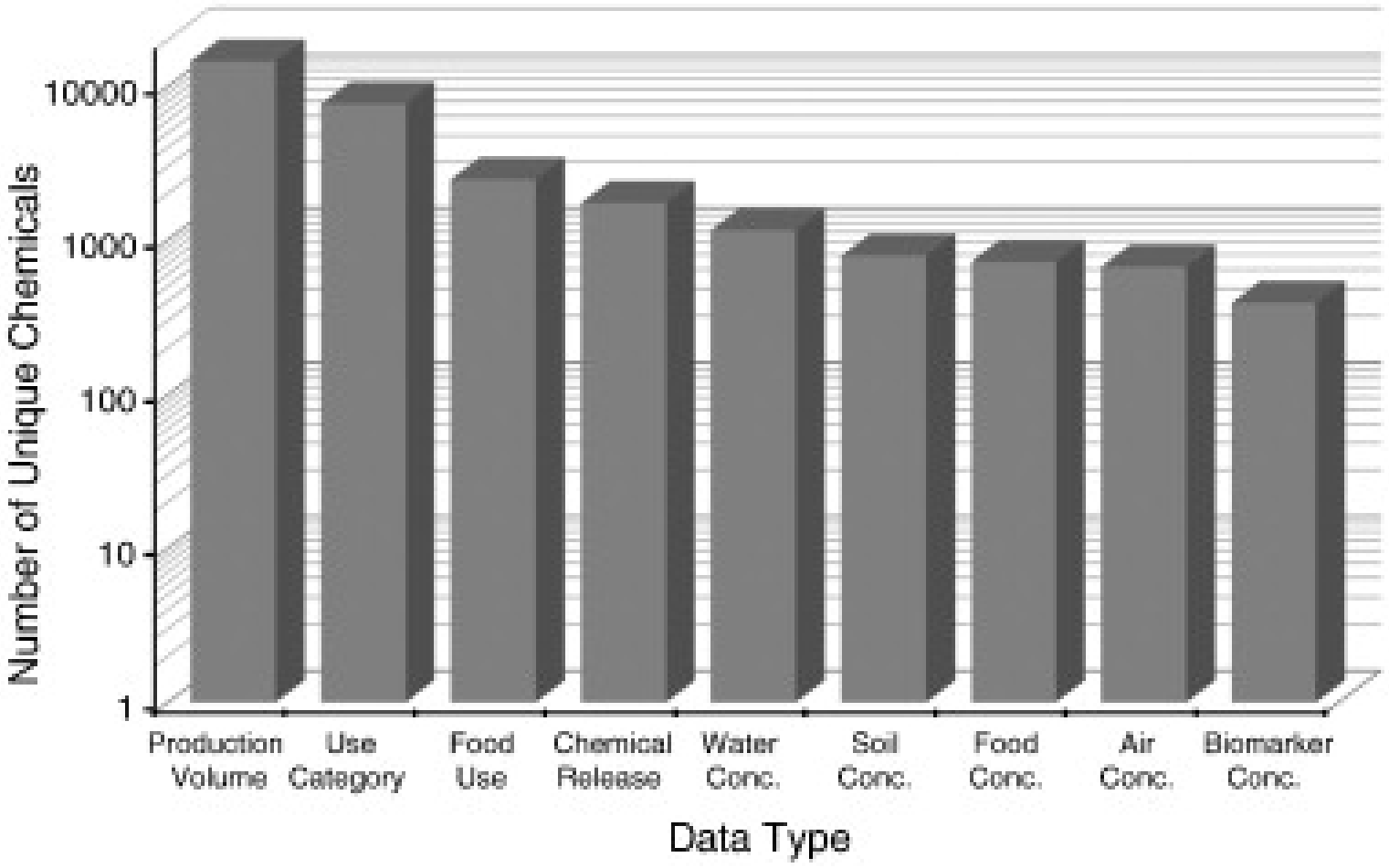
NHEERL
Linda Adams
Christopher Ecklund
Marina Evans
Mike Hughes
Jane Ellen Simmons

NERL
Craig Barber
Namdi Brandon
Peter Egeghy
Hongtai Huang
Brandall Ingle
Kristin Isaacs
Dawn Mills
Seth Newton
Katherine Phillips
Paul Price
Jeanette Reyes
Jon Sobus
John Streicher
Mark Strynar
Mike Tornero-Velez
Elin Ulrich
Dan Vallero
Barbara Wetmore

We develop exposure and toxicokinetic models, statistical methods, and chemical analyses of environmental samples including water, dust, blood, and household products

Lead CSS
Matrix Interfaces:
John Kenneke (NERL)
John Cowden (NCCT)

Limited Available Data for Exposure Estimations



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

Thinking About Exposure

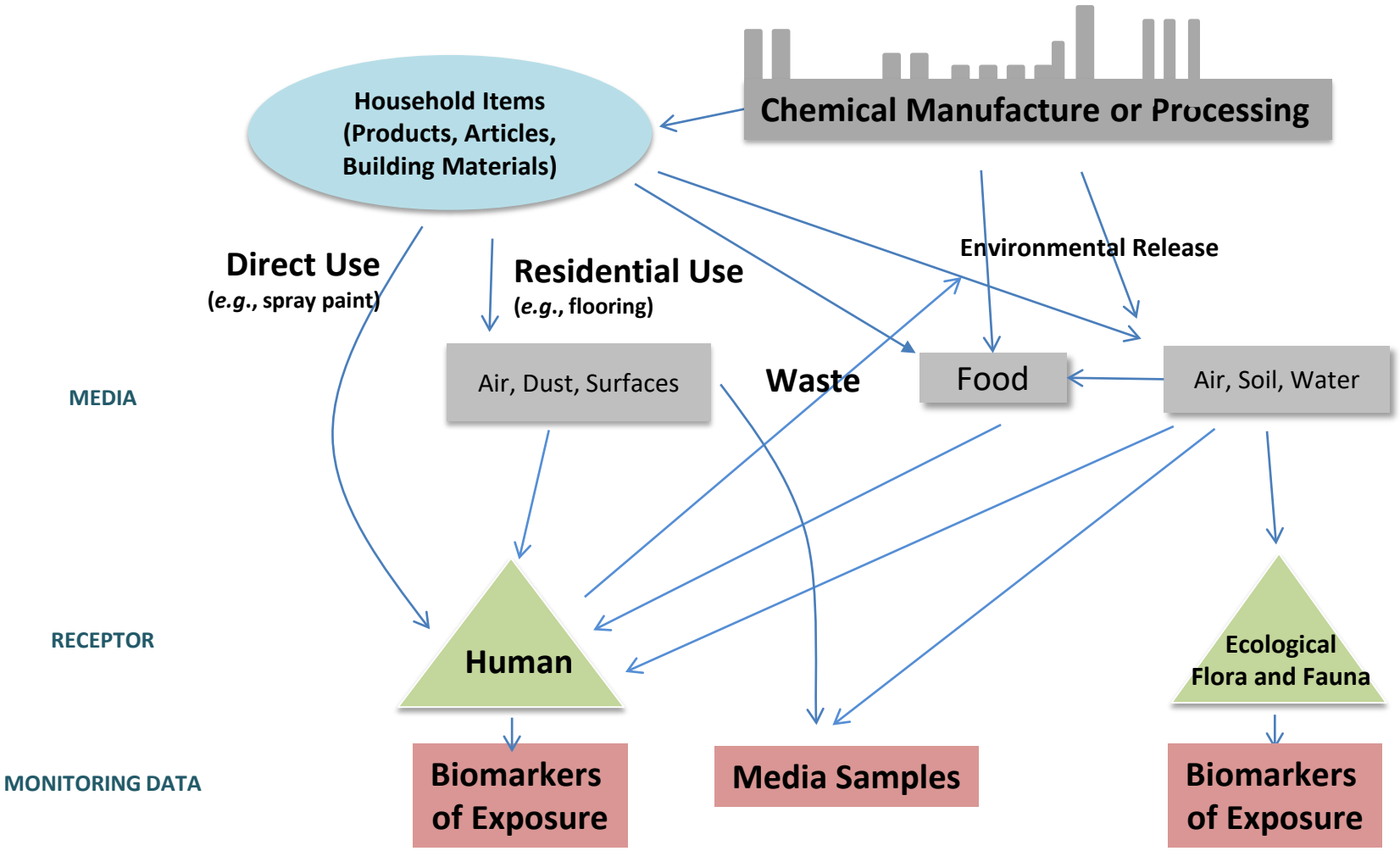


Figure from Kristin Isaacs

Exposure Pathways

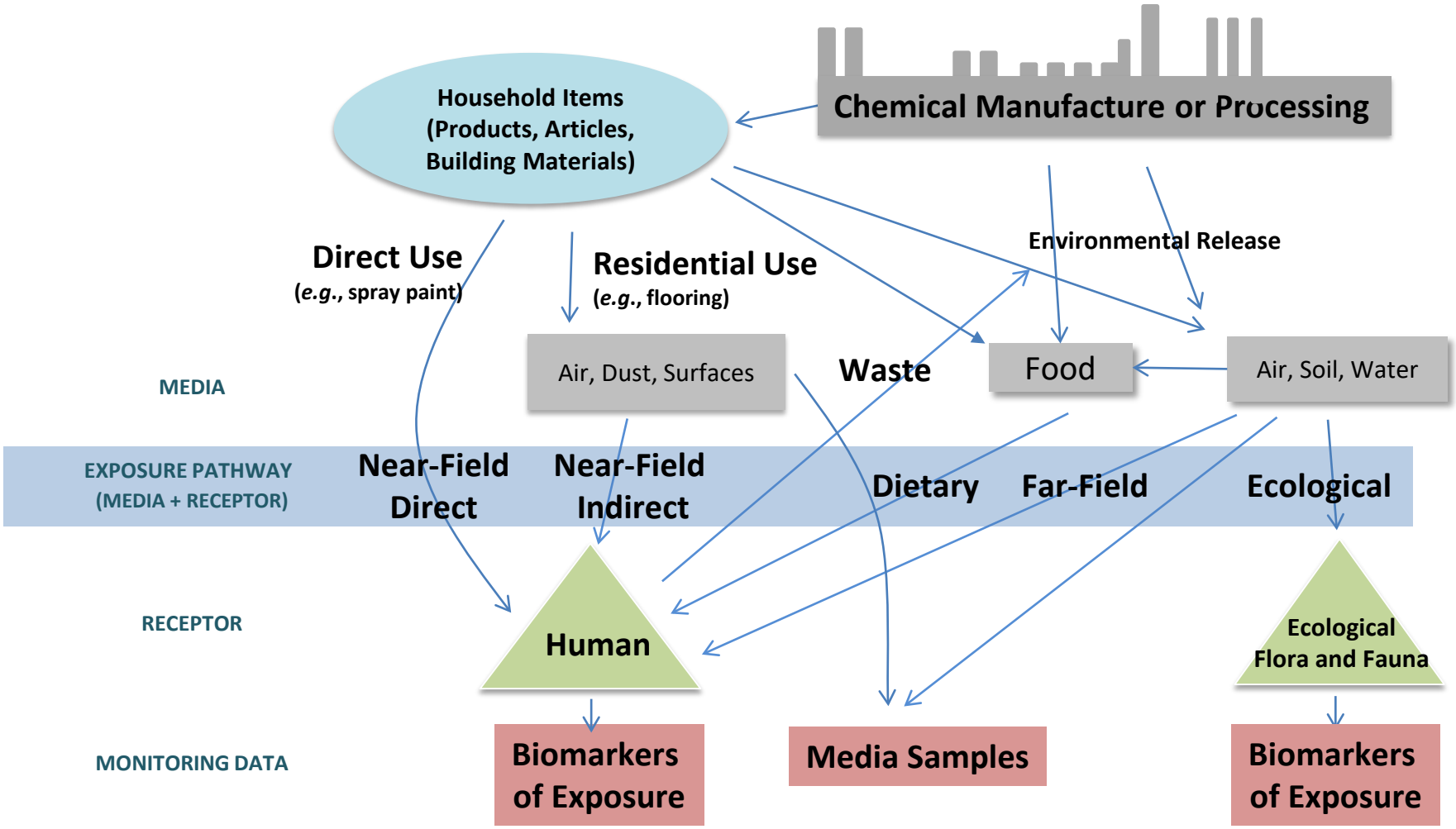


Figure from Kristin Isaacs

Predicting Exposure

- Some pathways have much higher average exposures. For example, chemicals used in consumer products in the home tend to have higher exposures. (Wambaugh et al., 2014)
  - But what chemicals are in consumer products?

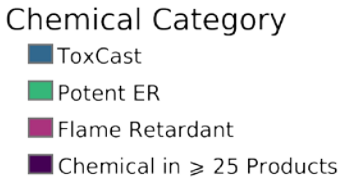
- EPA's public CPdat (http://actor.epa.gov/cpcat/) includes every chemical safety sheet from a major U.S. retailer (>2000 chemicals) but there are many thousands of other chemicals (Goldsmith et al, 2015)

- We use applied statistics, including machine learning techniques, to learn from the data we have to fill in the gaps (Wambaugh et al., 2014, Isaacs et al., 2016, Phillips et al., 2017)
  - This is similar to how Netflix can guess how much you will like a movie

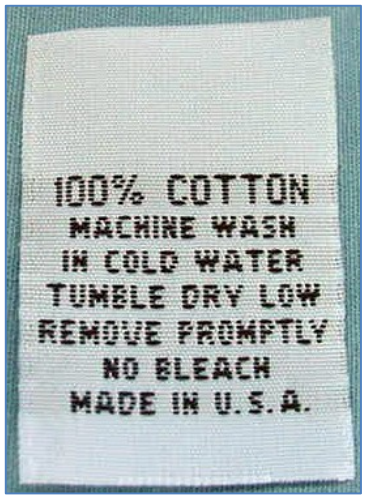
- ExpoCast: Exposure Forecaster Project

ExpoCast Consumer Product Scan

United States Environmental Protection Agency



The chemicals found in a cotton shirt



Phillips et al. (submitted)

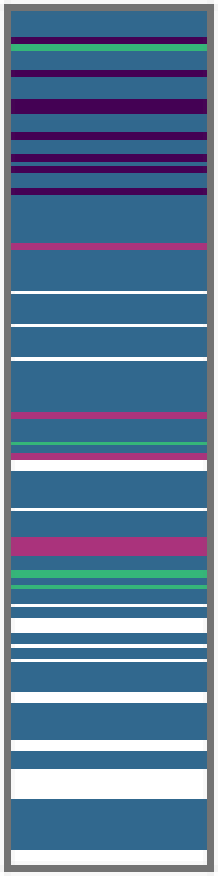
ExpoCast Consumer Product Scan

United States Environmental Protection Agency

$Log_{10}(\mu g/g)$

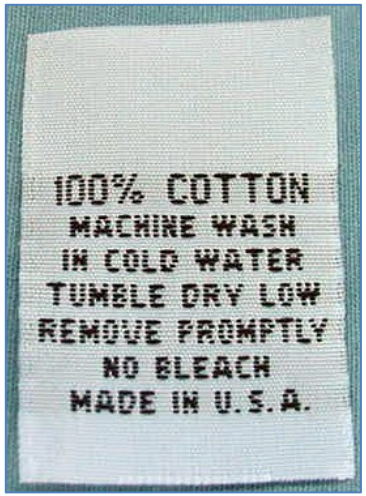
−4 −2 0 2 4

126 Confirmed



⬅ Chemicals that are present

Chemical Category
- ToxCast
- Potent ER
- Flame Retardant
- Chemical in ⩾ 25 Products

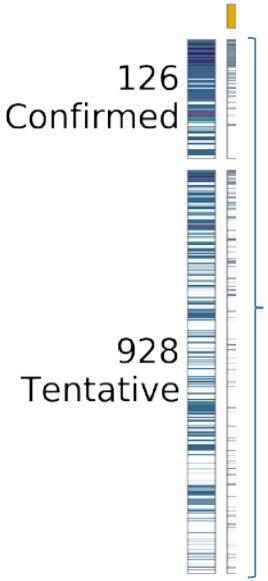


⬅ Chemicals that are absent (but found in other products)

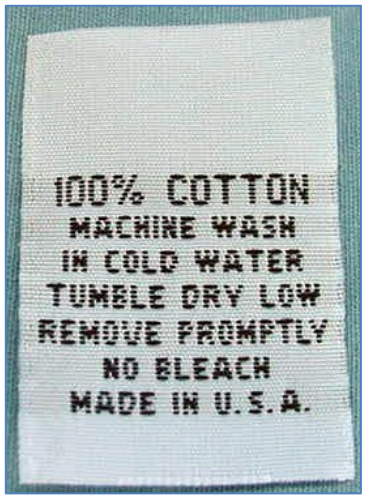
Phillips et al. (submitted)

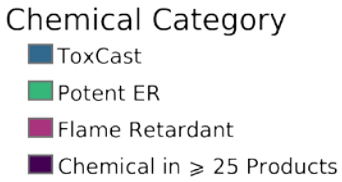
ExpoCast Consumer Product Scan

United States Environmental Protection Agency



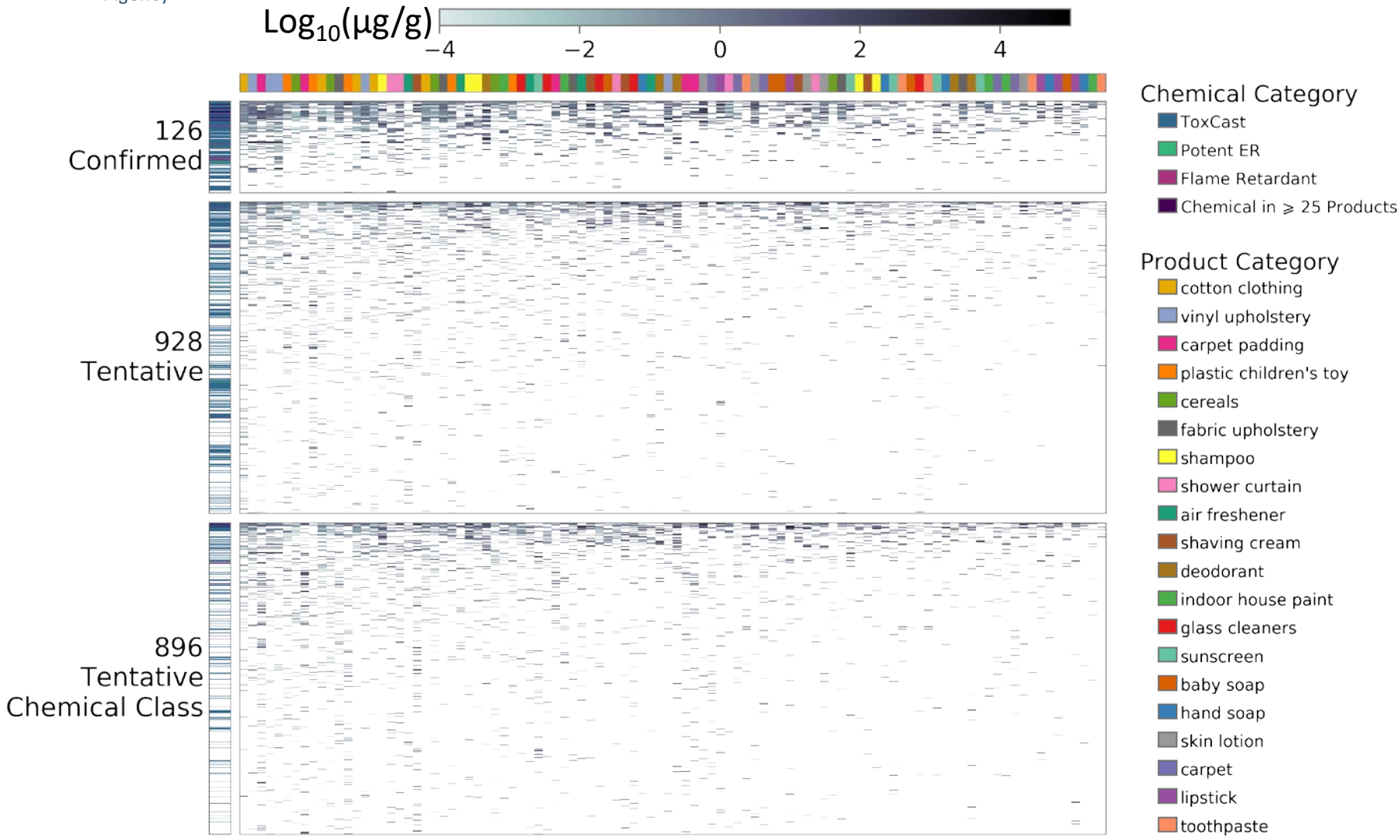
The chemicals found in a cotton shirt





Phillips et al. (submitted)

ExpoCast Consumer Product Scan



Of 1,632 chemicals, 1,445 were not present in our database from the major retailer (CPCPdb)

Phillips et al. (submitted)

Where We Are Today

- Understanding 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
- **Toxicity is hazard and exposure**
  - **Exposure alone is not risk**
- Product analysis caveats:
  - Samples are being homogenized (e.g., grinding) and are extracted with a solvent (dichloro methane, DCM)
  - Only using one solvent (DCM, polar) and one method GCxGC-TOF-MS
  - Varying exposure intimacy, from carpet padding to shampoo to cereal
- **Only some chemical identities are confirmed, *most are tentative***
- **Chemical presence in an object does not mean that exposure occurs**
- **Chemical presence in an object does not necessarily mean that it is bioavailable**

EPA United States Environmental Protection Agency

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

NCCT
Chris Grulke
Greg Honda*
Richard Judson
Andrew McEachran*
Robert Pearce*
Ann Richard
Parichehr Saranjampour*
Risa Sayre*
Woody Setzer
Rusty Thomas
John Wambaugh
Antony Williams

NRMRL
Yirui Liang*
Xiaoyu Liu

NHEERL
Linda Adams
Christopher Ecklund
Marina Evans
Mike Hughes
Jane Ellen Simmons

*Trainees

NERL
Craig Barber
Namdi Brandon*
Peter Egeghy
Jarod Grossman*
Hongtai Huang*
Brandall Ingle*
Kristin Isaacs
Sarah Laughlin-Toth*
Seth Newton
Katherine Phillips
Paul Price
Jeanette Reyes*
Jon Sobus
John Streicher*
Mark Strynar
Mike Tornero-Velez
Elin Ulrich
Dan Vallero
Barbara Wetmore

Lead CSS Matrix Interface:
John Kenneke (NERL)
John Cowden (NCCT)

Collaborators

Arnot Research and Consulting
Jon Arnot
Battelle Memorial Institute
Anne Louise Sumner
Anne Gregg
Chemical Computing Group
Rocky Goldsmith
National Institute for Environmental Health Sciences (NIEHS) National Toxicology Program
Mike Devito
Steve Ferguson
Nisha Sipes
Netherlands Organisation for Applied Scientifi Research (TNO)
Sieto Bosgra
Research Triangle Institute
Timothy Fennell
ScitoVation
Harvey Clewell
Chantel Nicolas
Silent Spring Institute
Robin Dodson
Southwest Research Institute
Alice Yau
Kristin Favela
Summit Toxicology
Lesa Aylward
Tox Strategies
Caroline Ring
University of California, Davis
Deborah Bennett
Hyeong-Moo Shin
University of Michigan
Olivier Jolliet
University of North Carolina, Chapel Hill
Alex Tropsha

References

- Breyer, Stephen. Breaking the vicious circle: Toward effective risk regulation. Harvard University Press, 2009.
- Egeghy, Peter P., et al. "The exposure data landscape for manufactured chemicals." *Science of the Total Environment* 414: 159-166 (2012)
- Goldsmith, M-R., et al. "Development of a consumer product ingredient database for chemical exposure screening and prioritization." *Food and chemical toxicology* 65 (2014): 269-279.
- Isaacs, Kristin K., et al. "Characterization and prediction of chemical functions and weight fractions in consumer products." *Toxicology Reports* 3 (2016): 723-732.
- Judson, Richard S., et al. "In vitro screening of environmental chemicals for targeted testing prioritization: the ToxCast project." *Environmental Health Perspectives* 118.4 (2010): 485.
- National Research Council. Toxicity testing in the 21st century: a vision and a strategy. National Academies Press, 2007.
- 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)
- Phillips, Katherine A., et al. "High-throughput screening of chemicals as functional substitutes using structure-based classification models." Green Chemistry (2017).Rager, Julia E., et al. "Linking high resolution mass spectrometry data with exposure and toxicity forecasts to advance high-throughput environmental monitoring." *Environment International* 88 (2016): 269-280.
- Schmidt, Charles W. "TOX 21: new dimensions of toxicity testing." *Environ Health Perspectives* 117.8 (2009): A348-A353.
- Wambaugh, John F., et al. "High Throughput Heuristics for Prioritizing Human Exposure to Environmental Chemicals." *Environmental Science & Technology* (2014).