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How Exposure Science can be Integrated into the Assessment of Ingredient Safety

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21st Century Approaches to Assessing Food Ingredient Safety
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Introduction

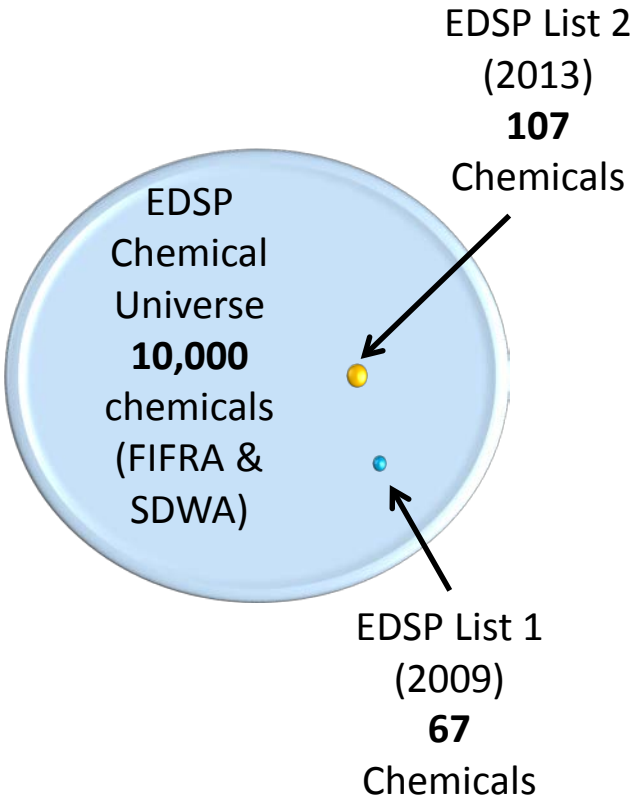
The timely characterization of the human and ecological risk posed by thousands of existing and emerging commercial chemicals is a critical challenge facing EPA in its mission to protect public health and the environment

November 29, 2014

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

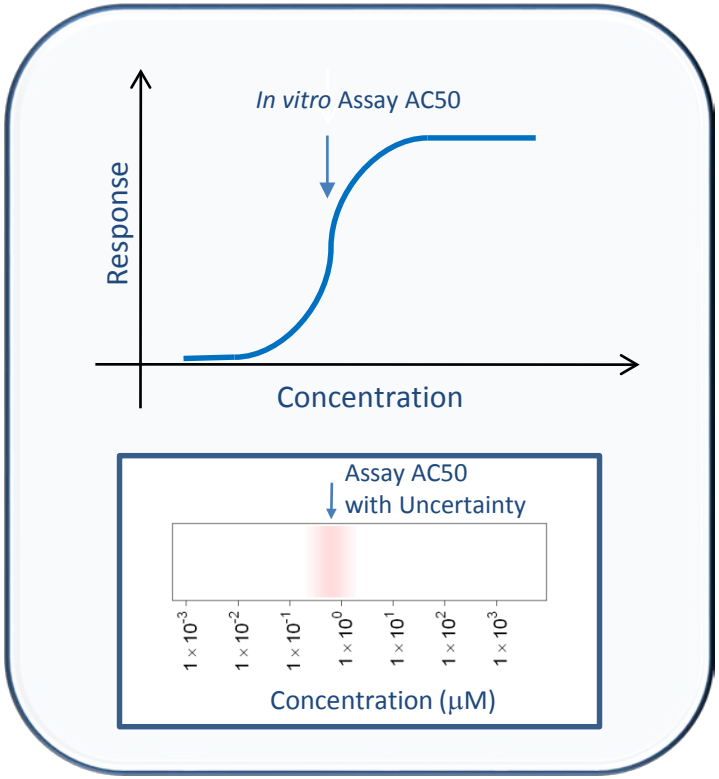
December, 2014 Panel: "Scientific Issues Associated with Integrated Endocrine Bioactivity and Exposure-Based Prioritization and Screening"
DOCKET NUMBER: EPA–HQ–OPP–2014–0614

High-Throughput Bioactivity

- **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)

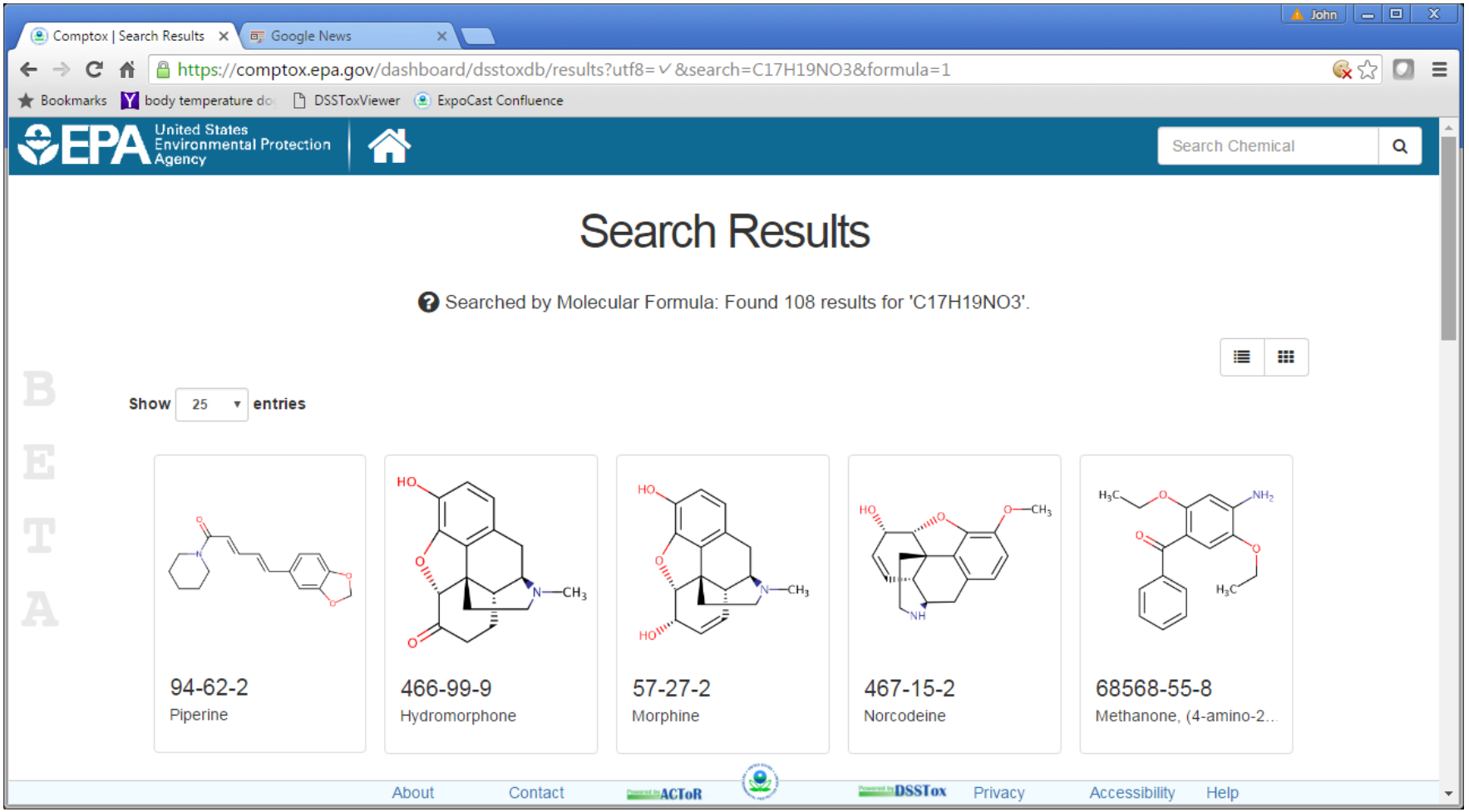


- Most assays conducted in dose-response format (identify 50% activity concentration – AC50 – and efficacy if data described by a Hill function)
- Data are being revised, new chemicals tested, new assays added
- All data are made public:

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

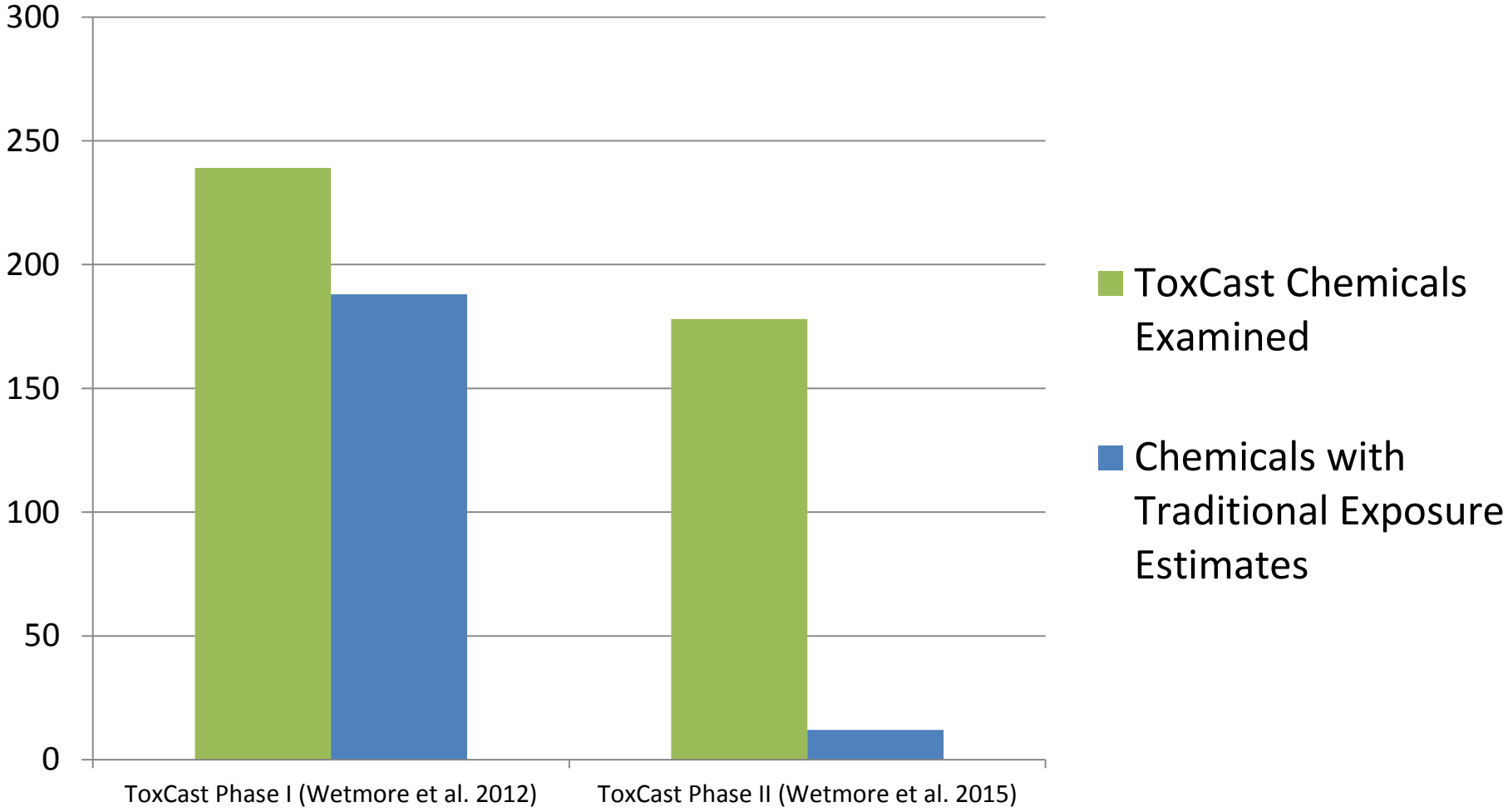
A Google for Chemicals

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



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

Limited Available Data for Exposure Estimations



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

Thinking About Exposure

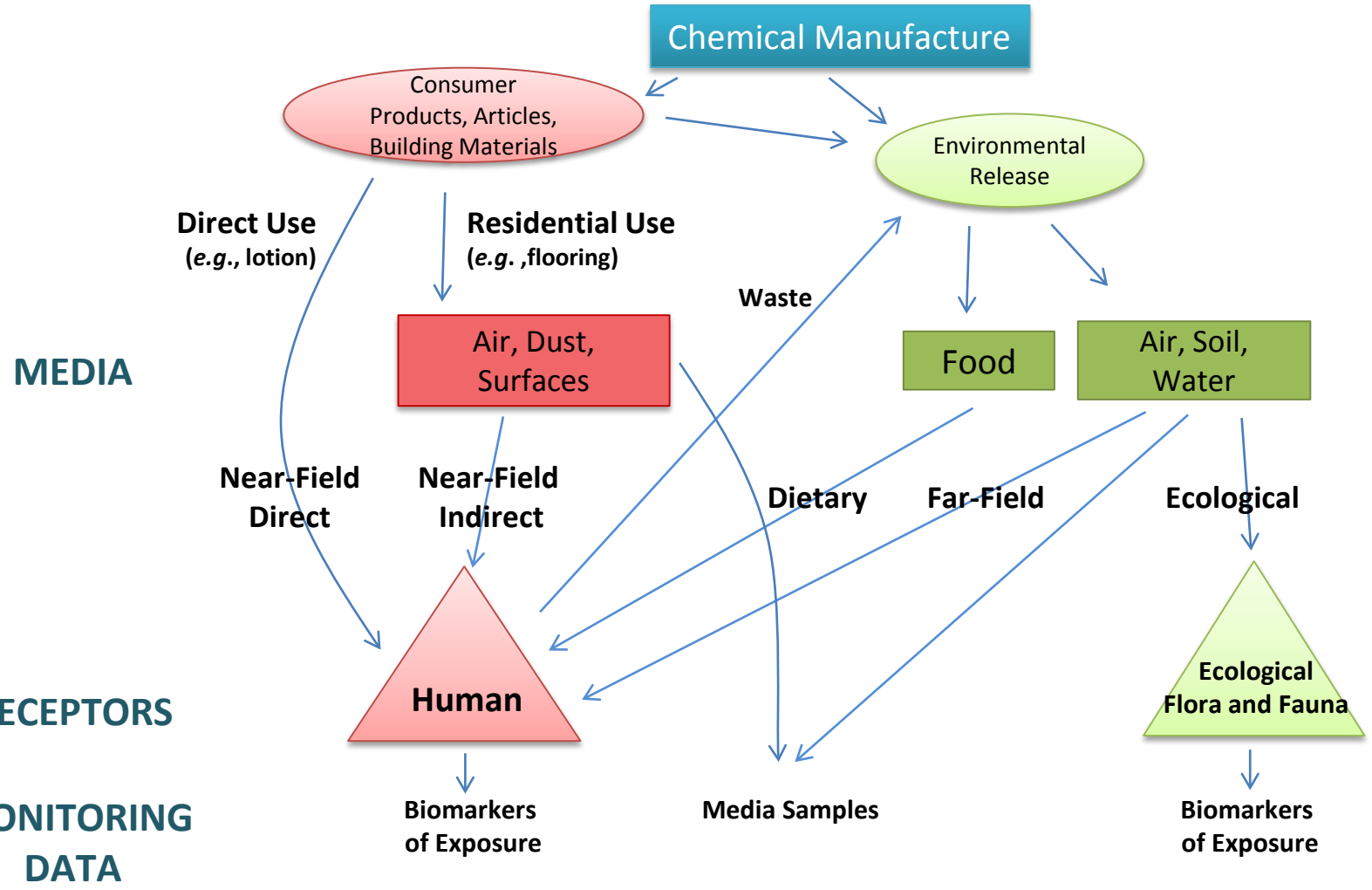


Figure from Kristin Isaacs

Exposure Pathways

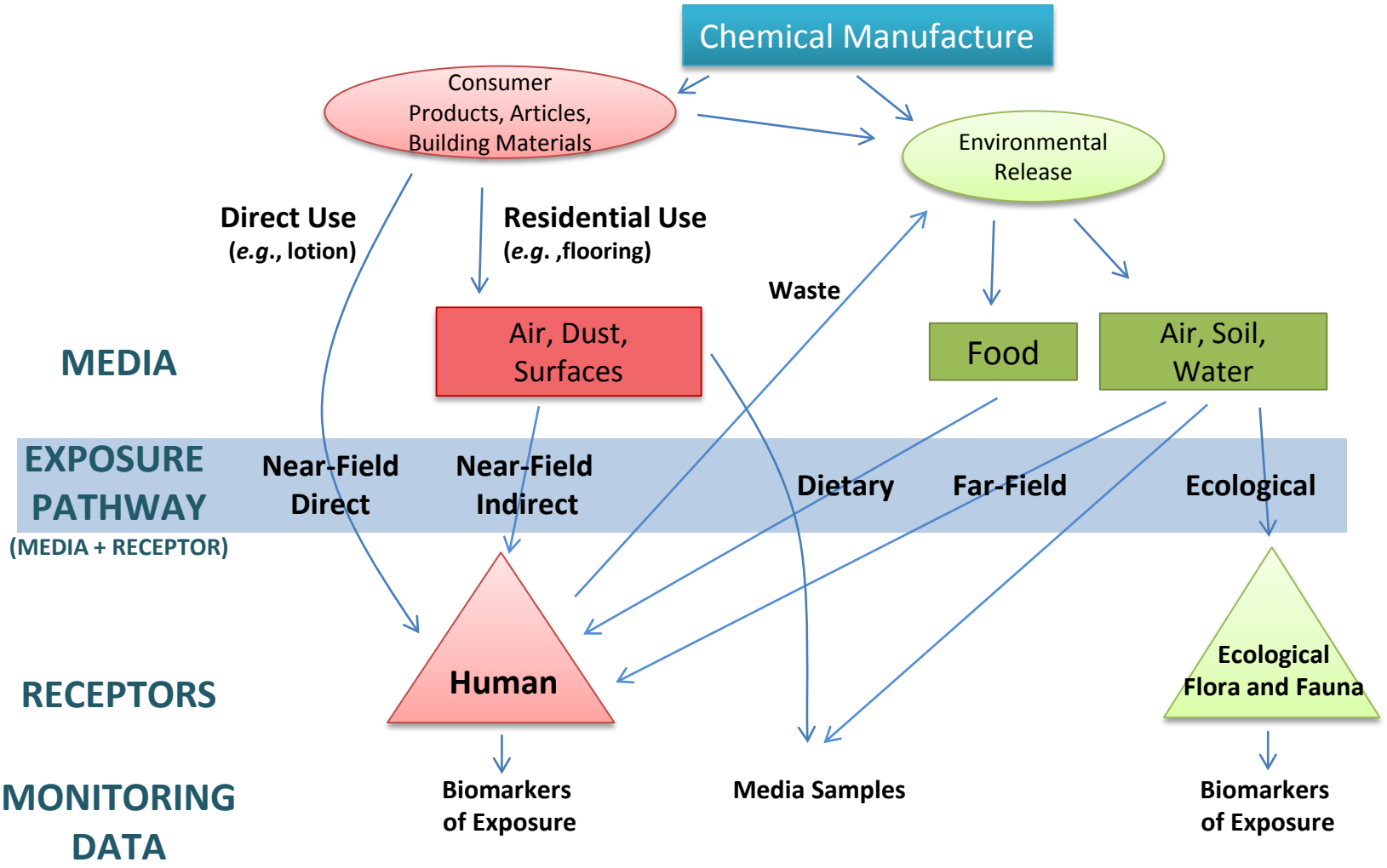
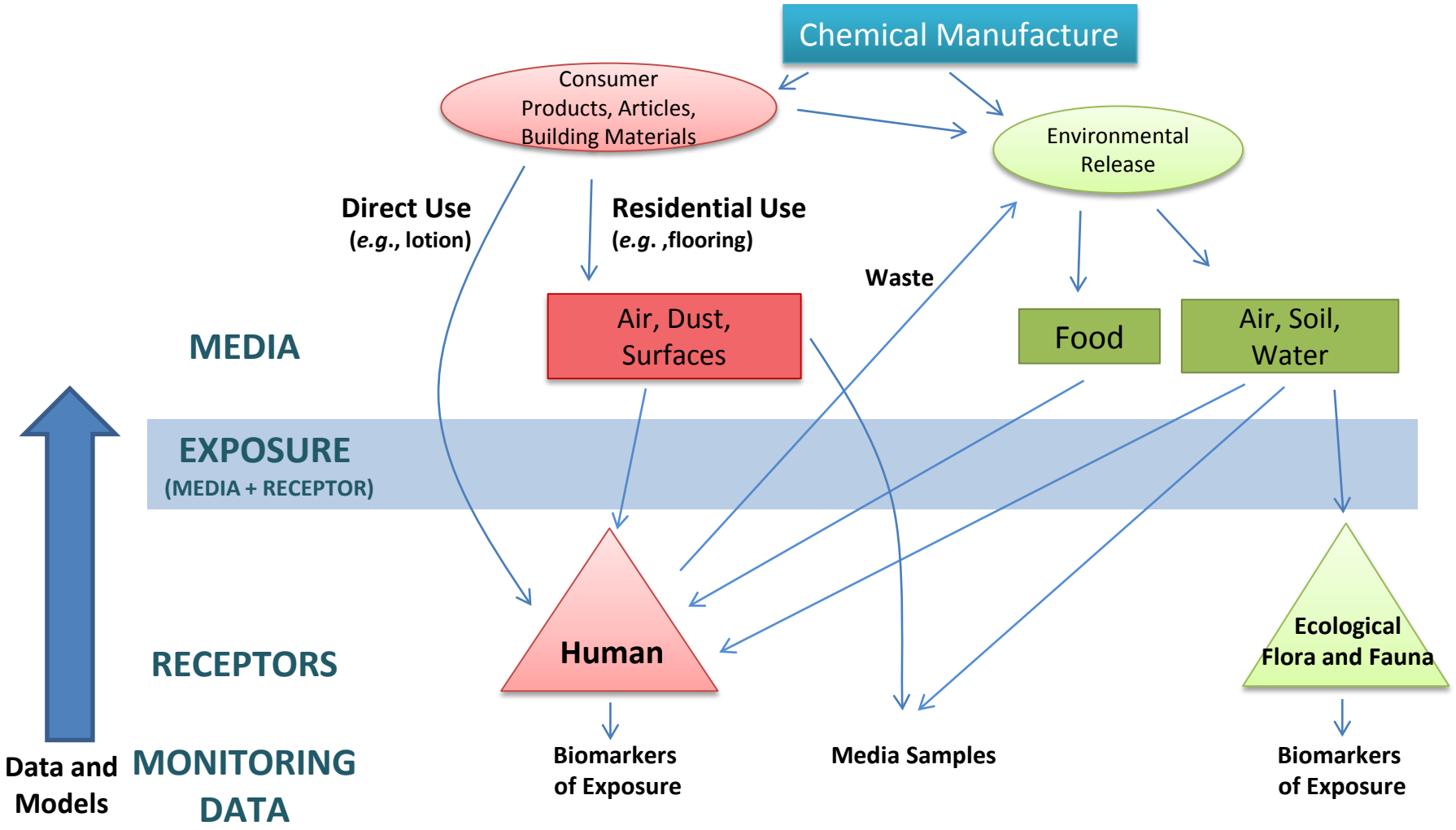


Figure from Kristin Isaacs

Exposure Monitoring



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

Figure from Kristin Isaacs

Evaluating Exposure Models

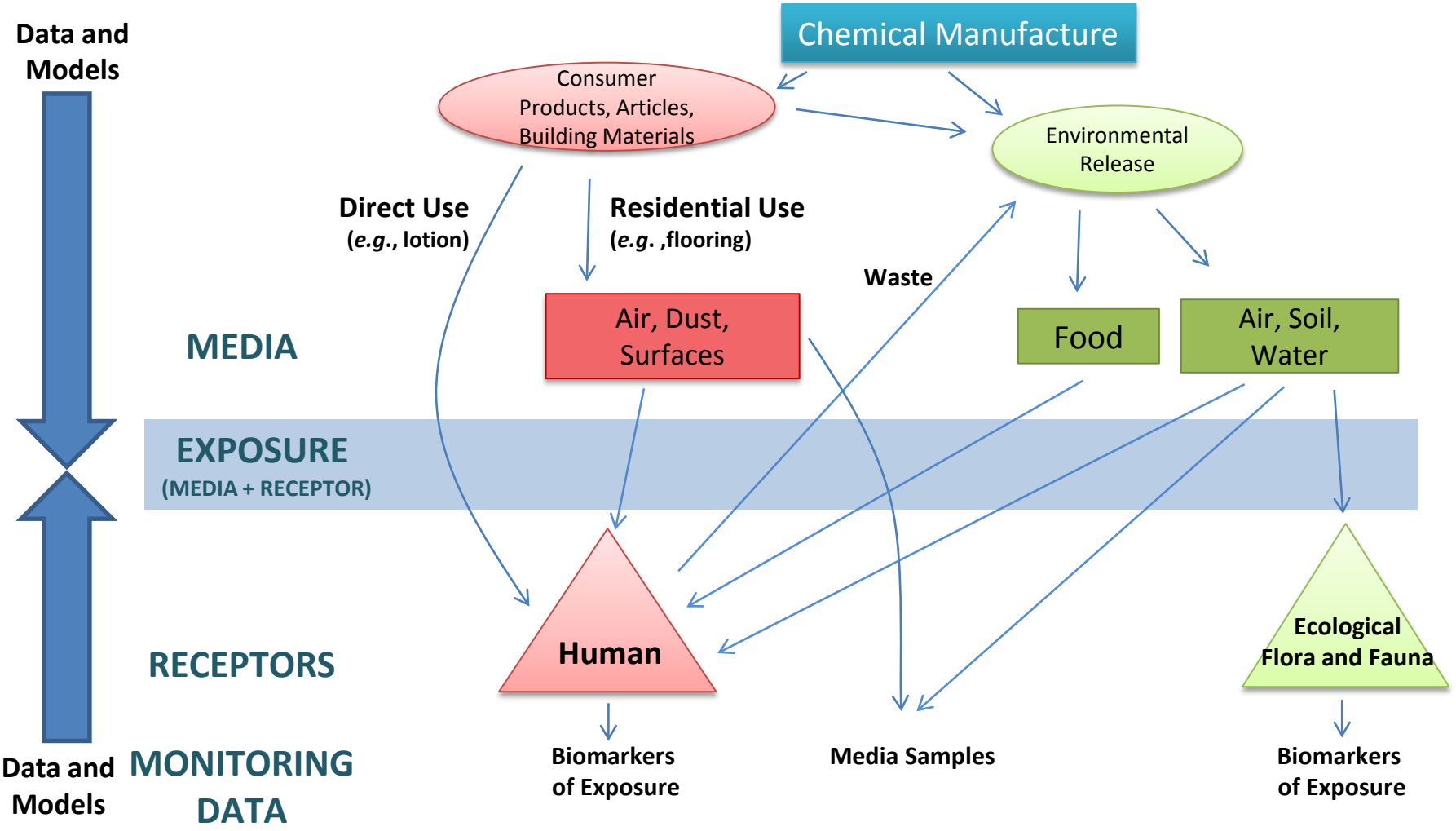
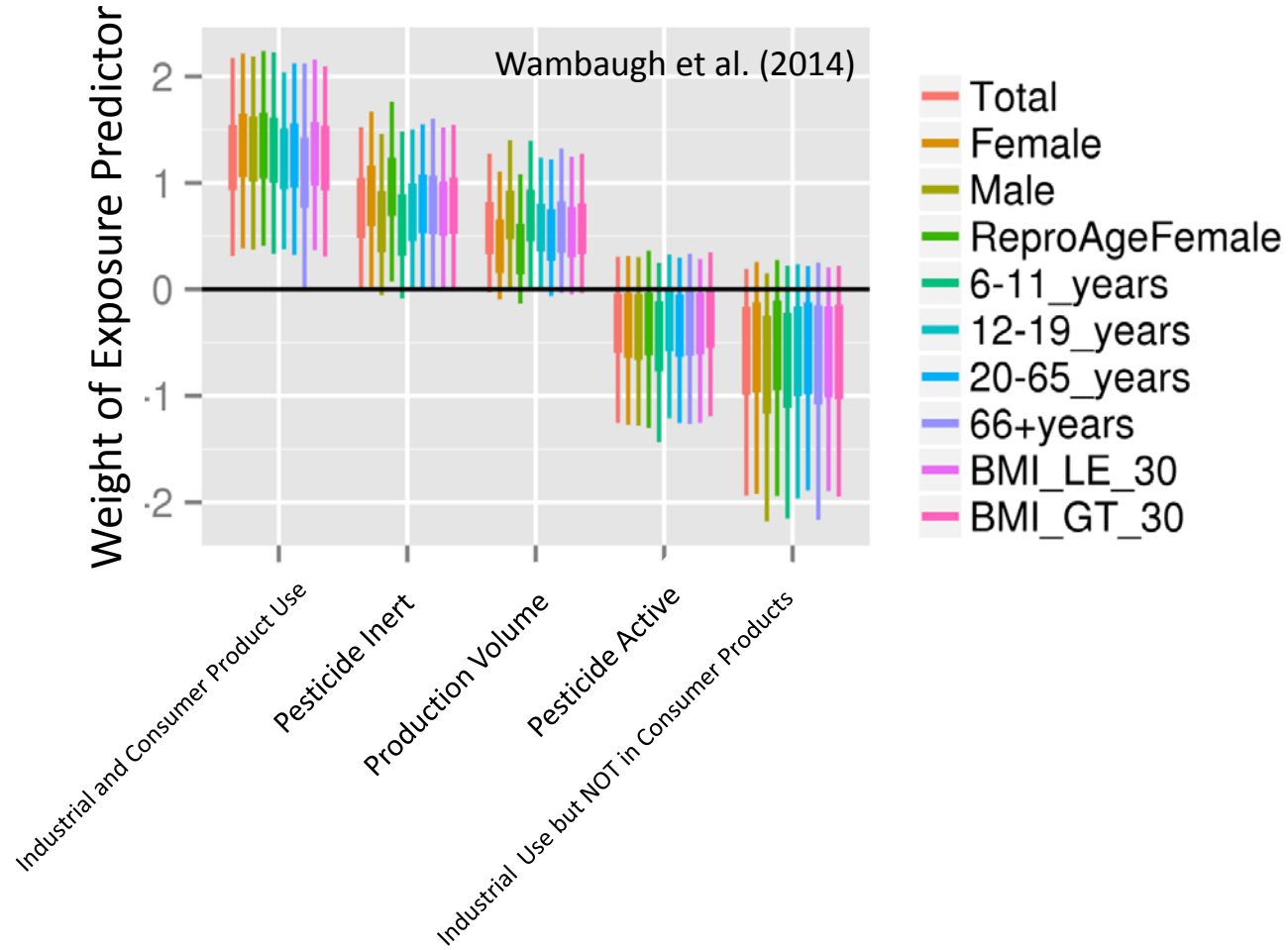


Figure from Kristin Isaacs

Predicting Exposure



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

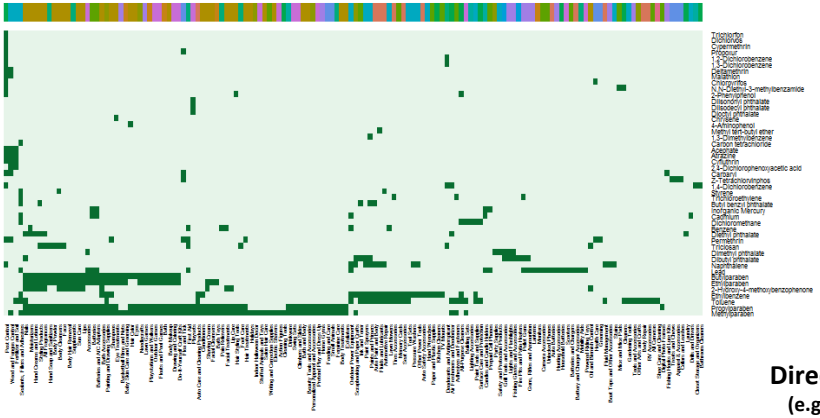
Same five predictors work for all NHANES demographic groups analyzed – stratified by age, sex, and body-mass index:

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

Chemical Use Identifies Relevant Pathways

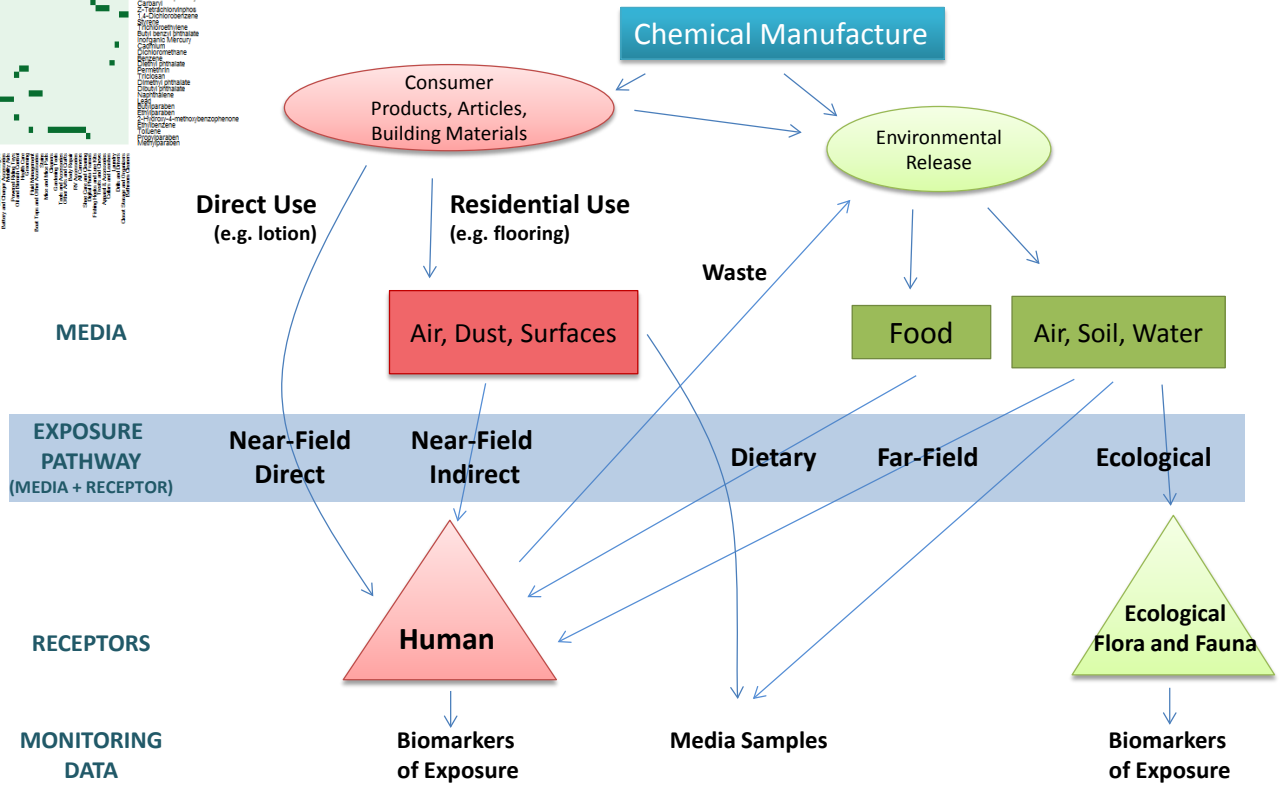
>2000 chemicals with Material Safety Data Sheets (MSDS) in CPCPdb (Goldsmith *et al.*, 2014)

105 NHANES Chemicals



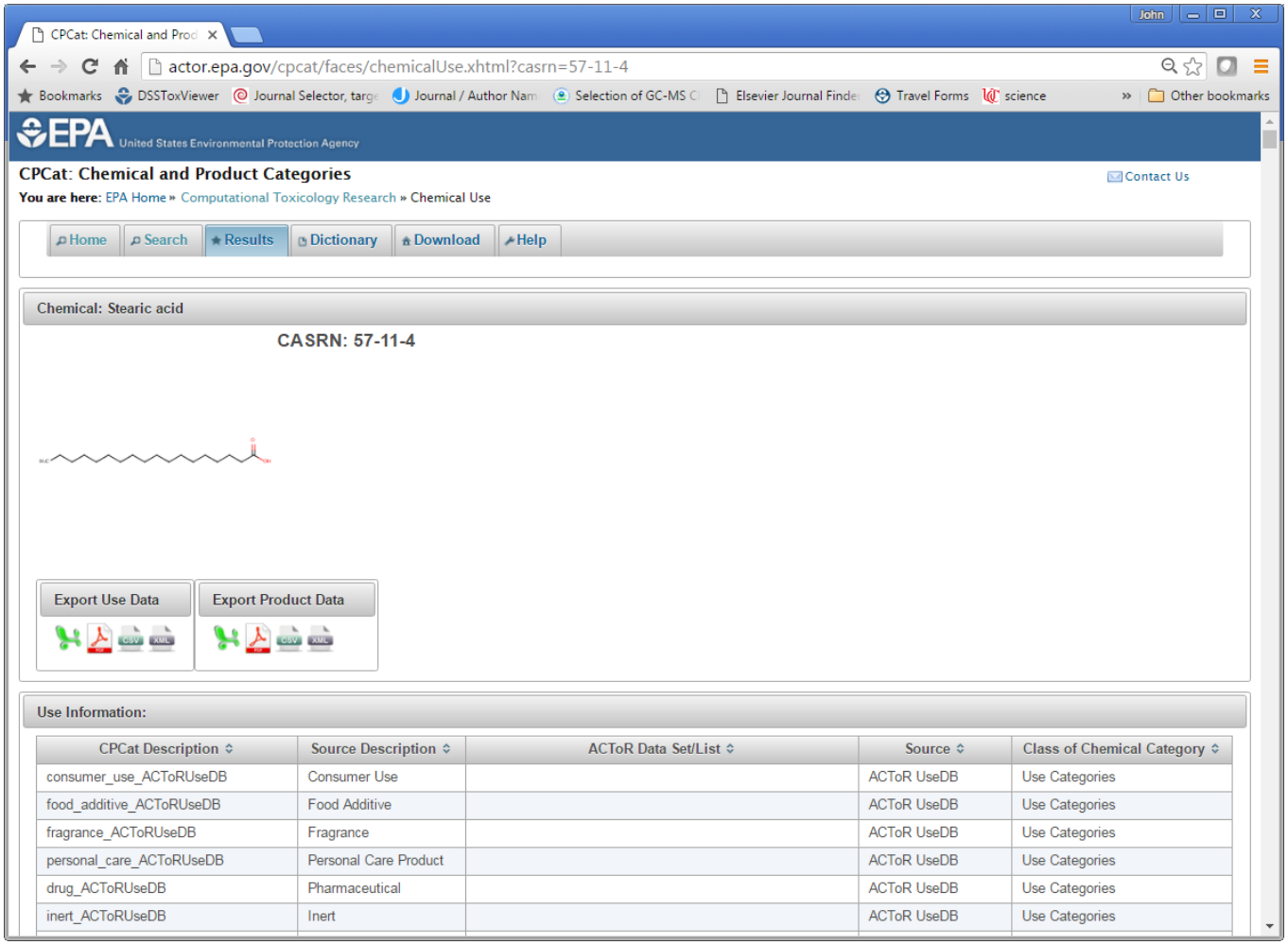
- Apparel
- Auto and Tires
- Baby
- Beauty
- Craft and Party Supply
- Electronics
- Grocery
- Health
- Home
- Home Improvement
- Patio and Garden
- Pets
- Sports and Outdoors
- Toys

…and some pathways have much higher average exposures!



CPcat: Chemical Use Information for >30,000 Chemicals

- Chemical-Product Categories (CPcat) database maps many different types of use information and ontologies onto each other
- Includes CPCPdb (Goldsmith, et al., 2014) with information on >2000 products from major retailors
- Largest single database has coarsest information: ACToR UseDB

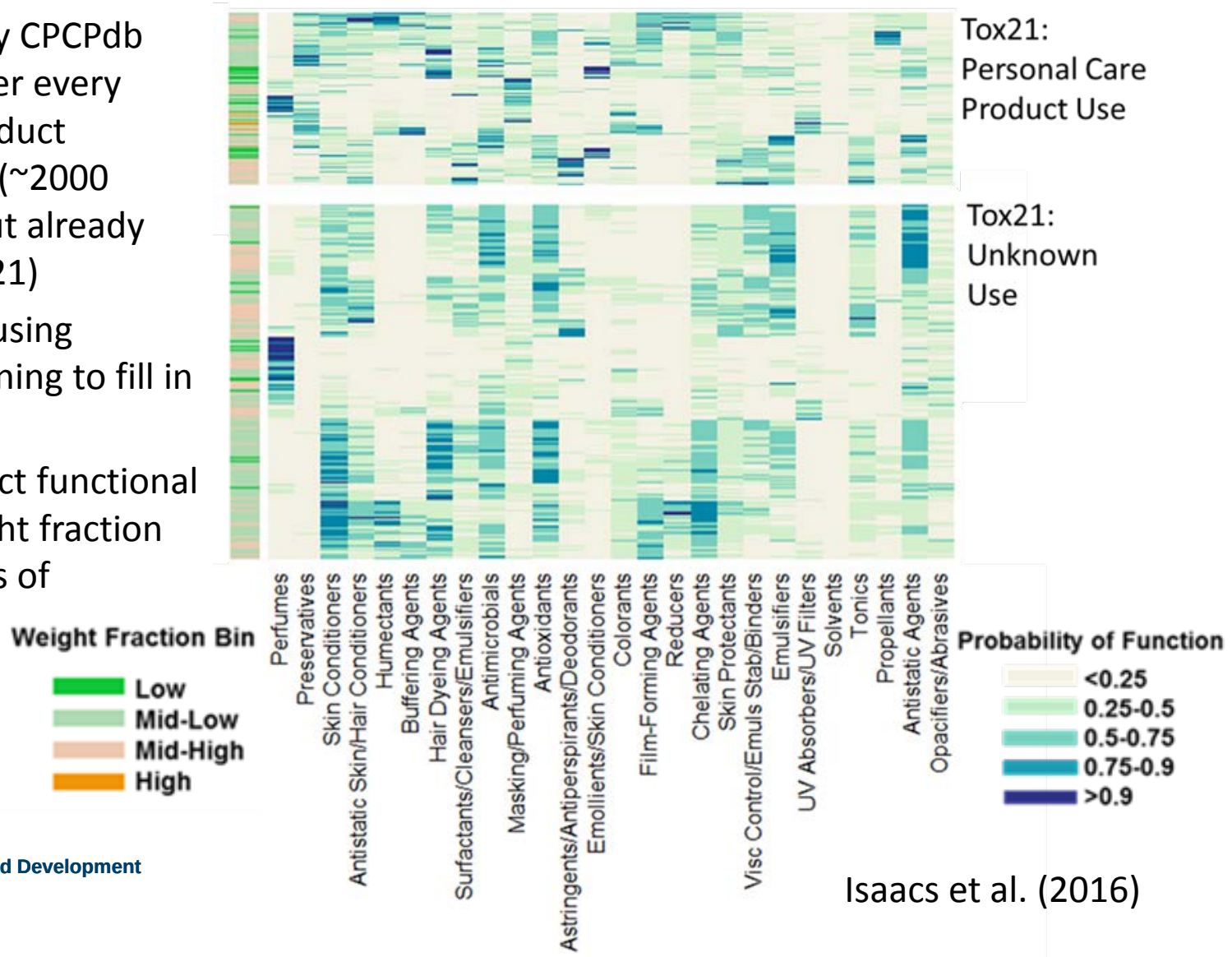


http://actor.epa.gov/cpcat/

Dionisio et al. *(2015)*

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. (2016)

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

Targeted vs. Non-Targeted Screening

- Of 106 chemicals with urine biomarkers in CDC NHANES, roughly half were below the limit of detection (Wambaugh et al., 2014)
- Park et al. (2012) found evidence of thousands of exogenous chemicals in blood

  - Differences in sensitivity
  - Differences in screening method – targeted vs. non-targeted screening

Targeted vs. Non-Targeted Screening

- When we do a targeted analysis for a particular analyte, you typically gain accuracy and precision (and quantification) but are deliberately focusing on only part of the story
- Targeting eliminates background to focus on analyte

Targeted vs. Non-Targeted Screening

- Non-targeted approach considers the “background”
- Need to take into account transformation (e.g., metabolism)
- Need to control for background (e.g., endogenous chemicals)

Applying Non-Targeted Screening

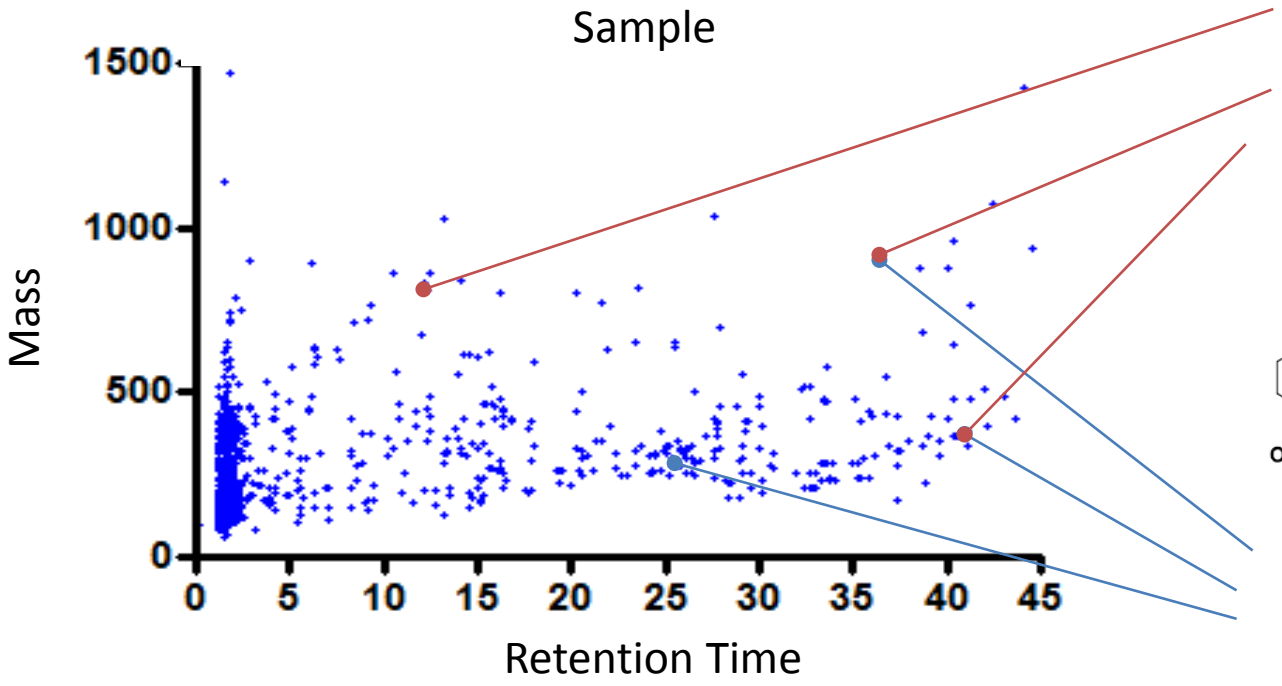
- Ongoing ExpoCast contract consumer product scanning and blood sample monitoring
- EPA has developed significant in house capabilities
  - Published on analysis of house dust from American homes – can identify 50% of the mass but only 2% of the chemicals *Rager et al., Environment International (2016)*

"I'm searching for my keys."

- 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 (Sobus and Ulrich)

Suspect Screening and Non-Targeted Analytical Chemistry

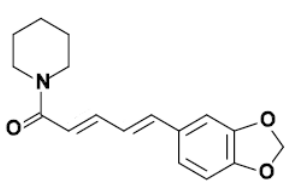
947 Peaks in an American Health Homes Dust Sample

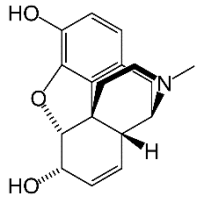


Each peak corresponds to a chemical with an accurate mass and predicted formula:

$C_{17}H_{19}NO_3$

Multiple chemicals can have the same mass and formula:





Is chemical A present, chemical B, both, or some other chemical (neither)?

We are expanding our reference libraries using ToxCast chemicals to enable greater numbers and better accuracy of confirmed chemicals

See Rager et al., Environment International (2016)

Appropriate Skepticism for Non-Targeted Analysis and Suspect Screening

"As chemists we are obliged to accept the assignment of barium to the observed activity, but as nuclear chemists working very closely to the field of physics we cannot yet bring ourselves to take such a drastic step, which goes against all previous experience in nuclear physics. It could be, however, that a series of strange coincidences has misled us."

Hahn and Strassmann (1938)

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Hahn and Strassmann (1938)

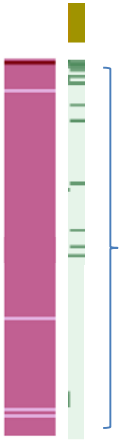
1944 Nobel Prize in Chemistry for "discovery of the fission of heavy nuclei"

ExpoCast Consumer Product Scan

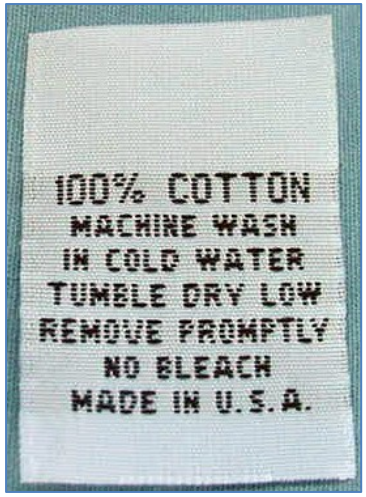
In Preparation: Katherine Phillips et al.
"Product Deformulation to Identify Exposure Pathways for ToxCast Chemicals"

A total of 3803 unique chemical signatures were observed in test objects. Of these, 1506 were associated with a tentative chemical identification and 126 had confirmed chemical identities.

- Flame Retardant
- Common Non-ToxCast
- ToxCast Chemical
- Estrogen Active



The chemicals found in a cotton shirt



Phillips et al. (in preparation)

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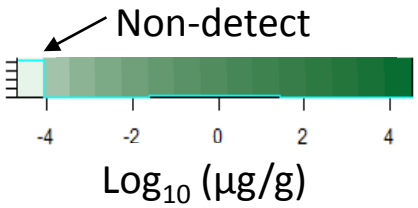

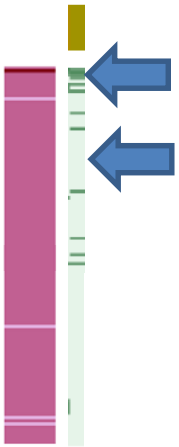

Dark green is a high concentration

Light green is not detected

Phillips et al. (in preparation)

ExpoCast Consumer Product Scan

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"Product Deformulation to Identify Exposure Pathways for ToxCast Chemicals"

A total of 3803 unique chemical signatures were observed in test objects. Of these, 1506 were associated with a tentative chemical identification and 126 had confirmed chemical identities.

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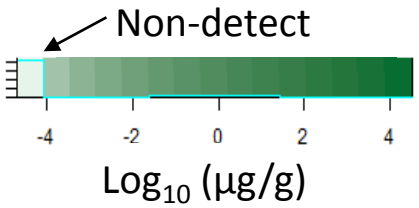
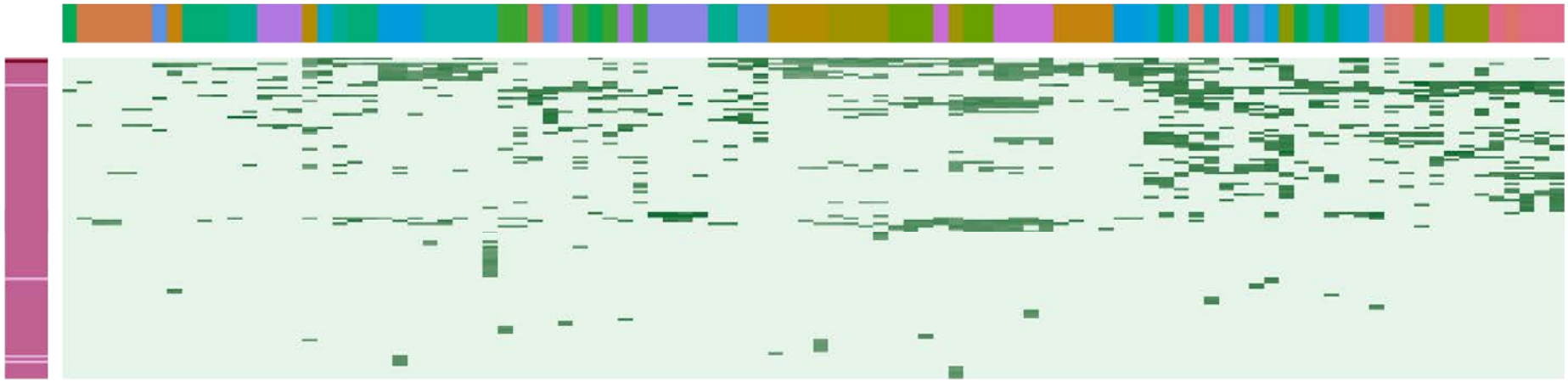
- Common Non-ToxCast
- ToxCast Chemical
- Estrogen Active

Test objects consisted of five arbitrary products in each of the following twenty categories:

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

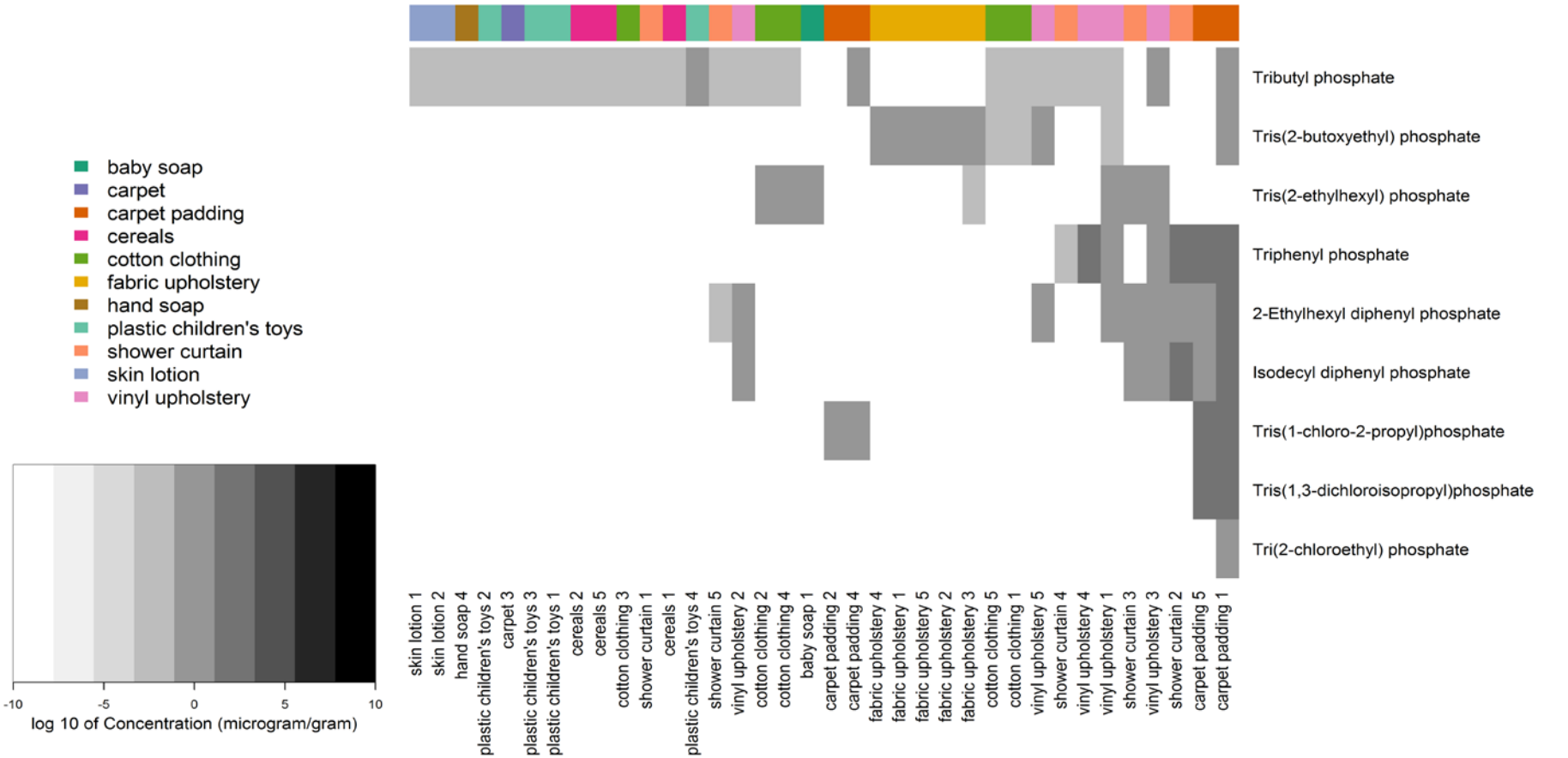




Phillips et al. (in preparation)

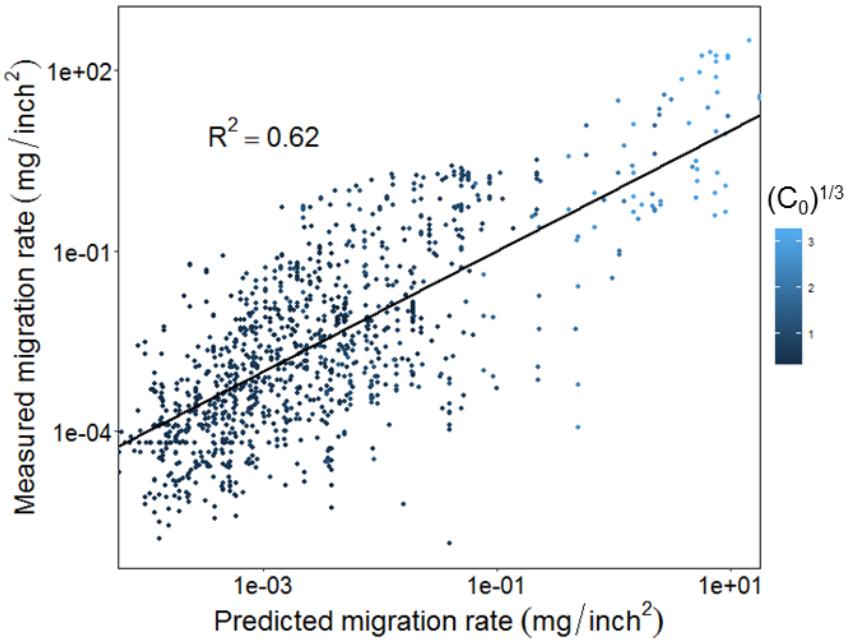
ExpoCast Consumer Product Scan

Known flame retardant chemicals:

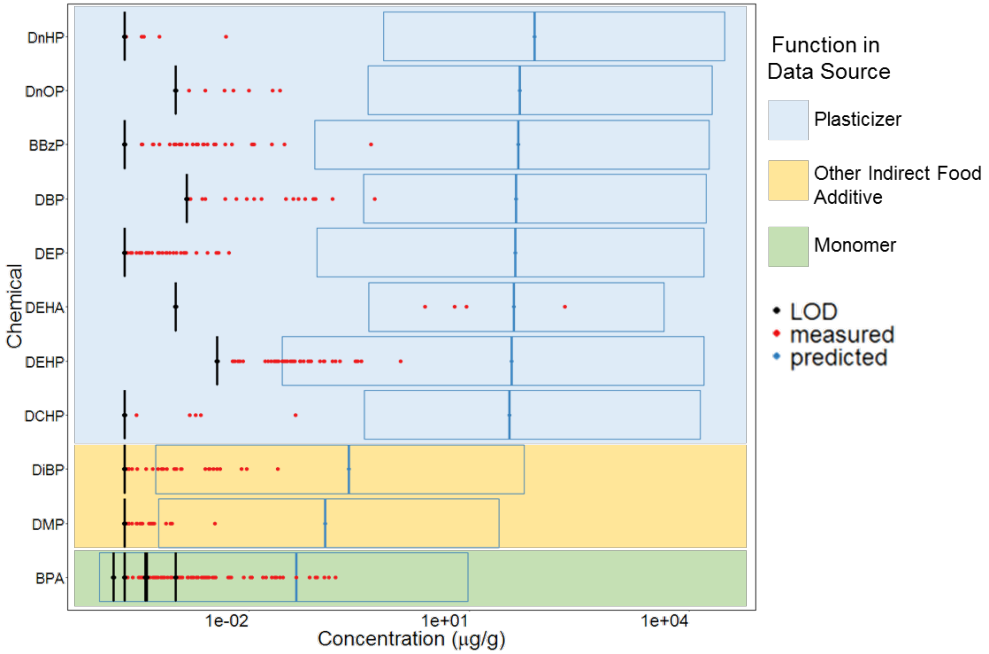


Phillips et al. (in preparation)

Modeling Chemical Migration



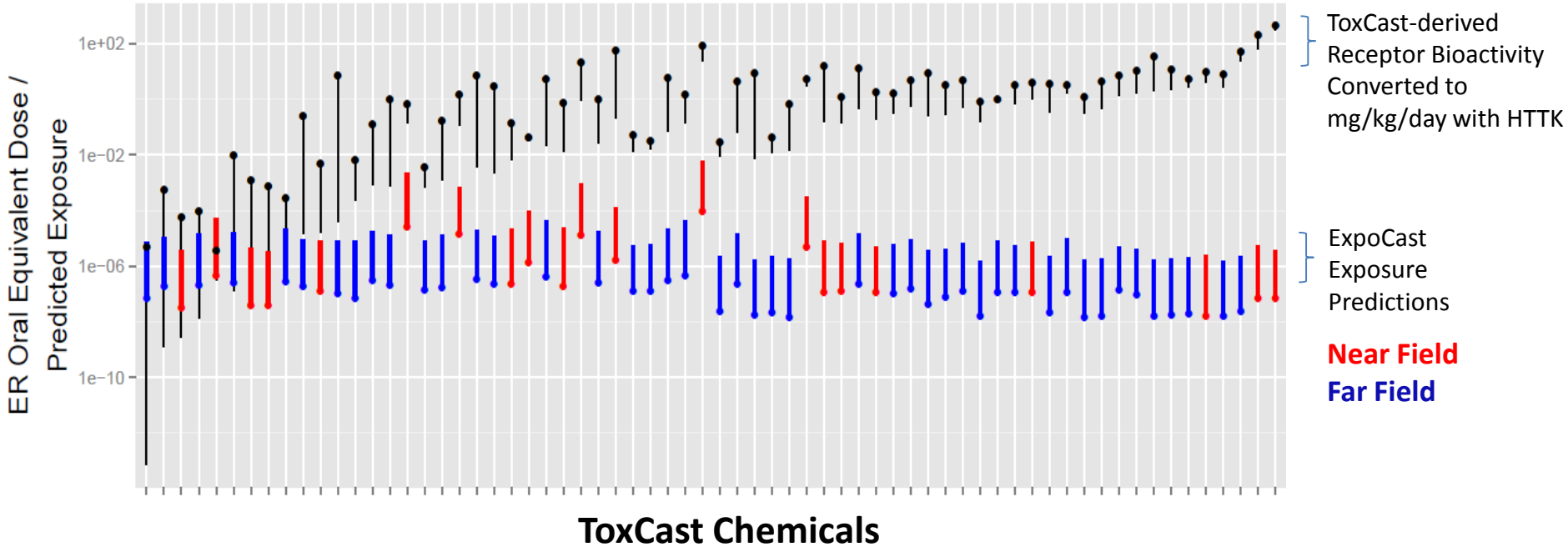
Results of the regression model for migration rate (MR) and regression coefficients for 1209 measurements of 50 chemicals



Comparison of 276 measured food concentrations with maximum concentrations predicted with the migration model

Biryol et al. (submitted)

High Throughput Risk Prioritization in Practice



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

December, 2014 Panel:
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DOCKET NUMBER:
EPA–HQ–OPP–2014–0614

Public Comp Tox Tools from EPA

United States Environmental Protection Agency

Dashboards:

Chemistry Dashboard (one stop shop):
http://comptox.epa.gov/dashboard/
iCSS Dashboard (ToxCast data):
http://actor.epa.gov/dashboard/
CPcat:
http://actor.epa.gov/cpcat/

Underlying Databases:

DSStox (Distributed structure-searchable toxicity (DSSTox) public database, Richard et al., 2002)
ToxRefDB (Animal Study data, Martin et al., 2009)
CPCPdb (Consumer Product Chemical Pathways database, Goldsmith et al, 2014)

R Packages:

httk: High-Throughput Toxicokinetics (Pearce et al., *in press*)
https://cran.r-project.org/web/packages/httk/index.html
tcpl: ToxCast Data Analysis Pipeline (Filer et al., 2014)
https://cran.r-project.org/web/packages/tcpl/index.html
toxboot: Bootstrap Methods for 'ToxCast' High Throughput Screening Data (Watt et al., *in preparation*)
https://cran.r-project.org/web/packages/toxboot/index.html

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
- Monitoring is tricky, and there are trade offs between the precision of targeted monitoring for specific chemicals and non-targeted screening for all exogenous chemicals
- Expanded monitoring data (exposure surveillance) allows evaluation of model predictions
  - Are chemicals missing that we predicted would be there?
  - Are there unexpected chemicals?

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

EPA United States Environmental Protection Agency

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