Exposure-Based Screening and Priority Setting

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Considerations of Exposure Dose, and Metabolism in 3R's

10th World Congress on Alternatives and Animal Use in the Life Sciences
Seattle, WA

August 21, 2017

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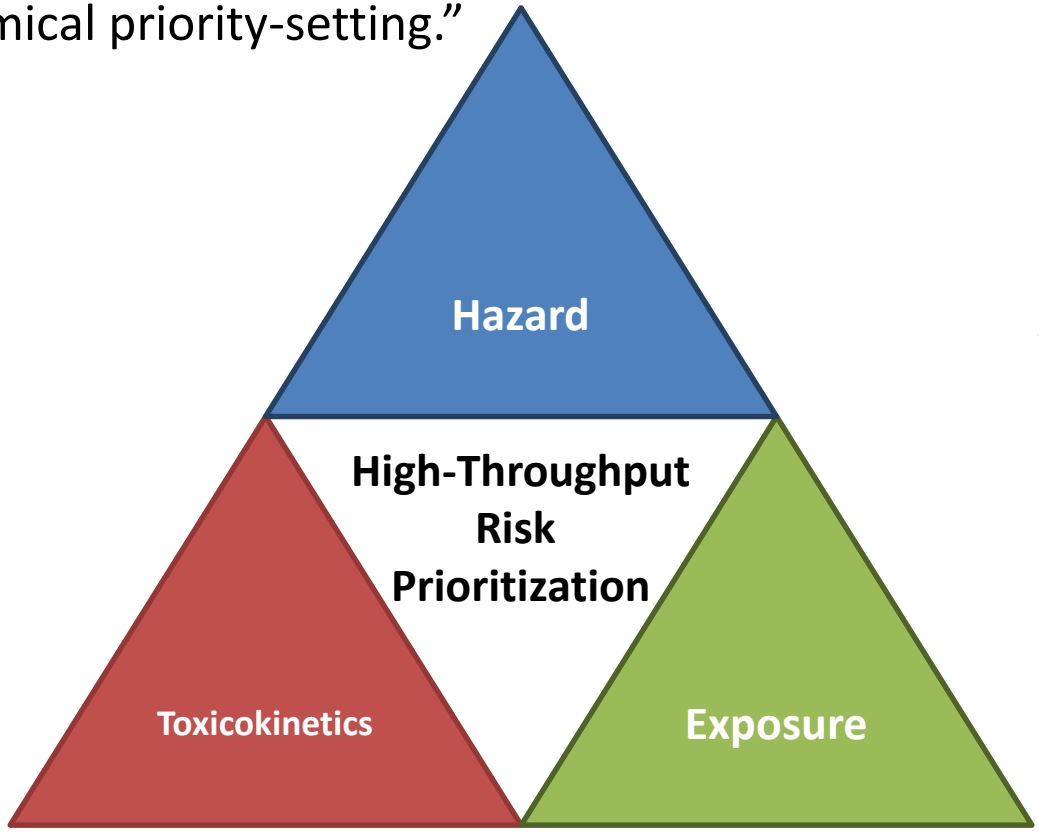
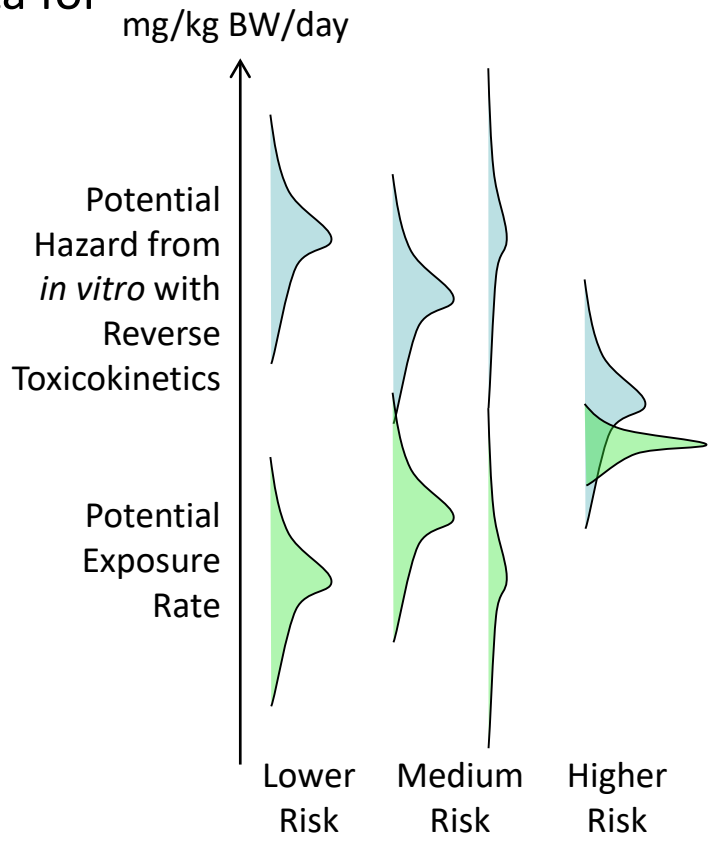
Introduction

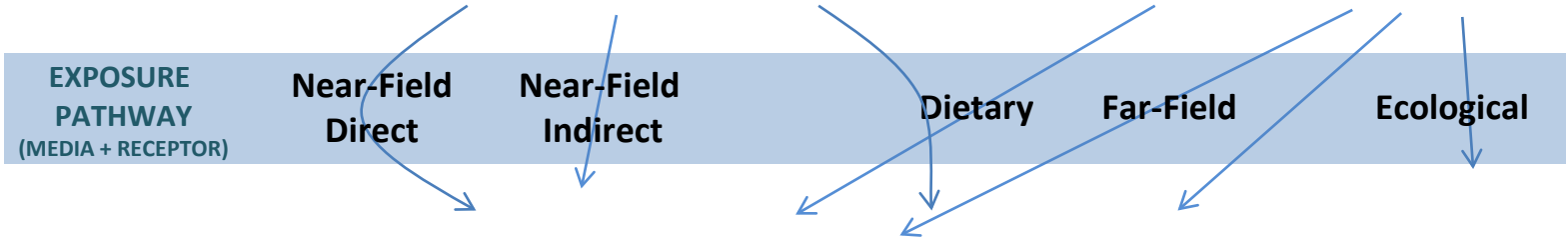
Risk Assessment in the 21st Century (NAS, 2017):

"Translation of high-throughput data into risk-based rankings is an important application of exposure data for chemical priority-setting."





The Exposure Event is Often Unobservable

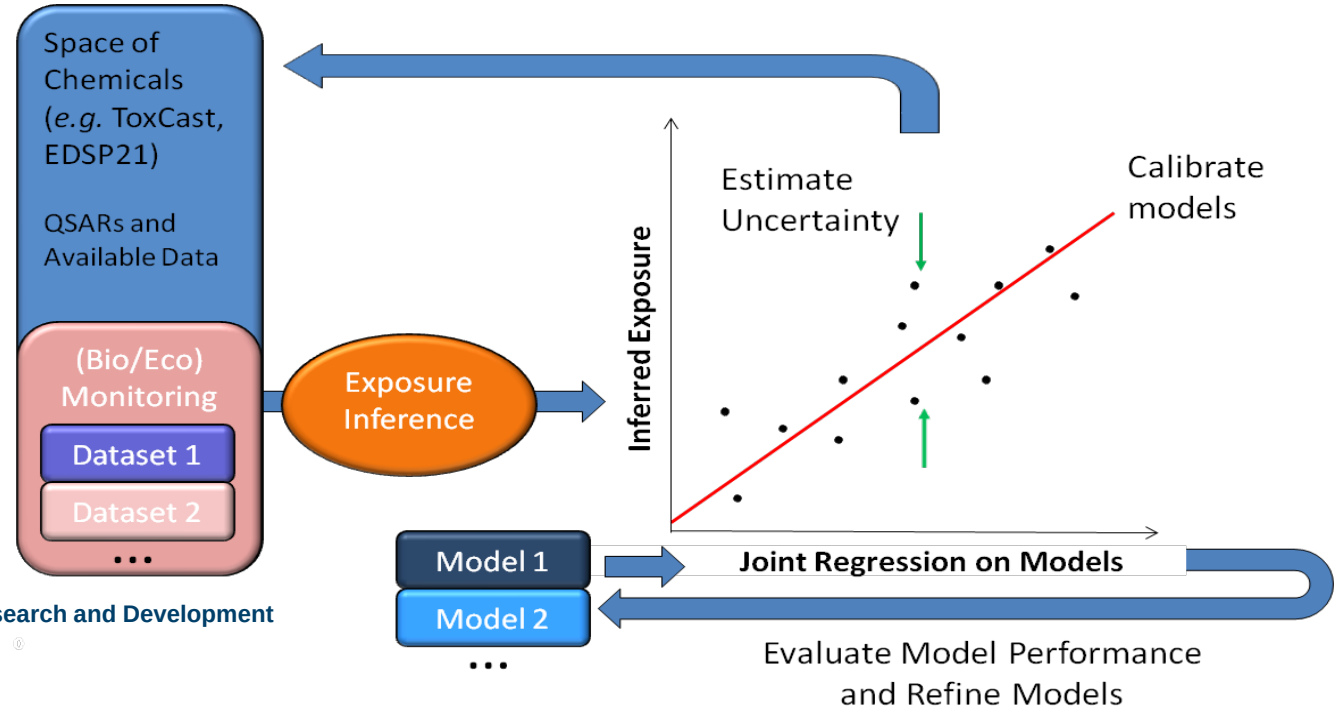


- The exposure pathway is the actual interaction of the receptor and media, e.g. consuming potato chips
- For humans in particular, these events are often unobserved and for many reasons (including ethics and privacy) may remain unobservable
  - *Did you eat the serving size or the whole bag of potato chips?*
- **Either predict** exposure using data and models up-stream of the exposure event
- **Or infer** exposure pathways from down-stream data, especially biomarkers of exposure

Figure modified from original by Kristin Isaacs

Consensus Exposure Predictions with the SEEM Framework

- We incorporate multiple models into consensus predictions for 1000s of chemicals within the **Systematic Empirical Evaluation of Models (SEEM) framework** (Wambaugh et al., 2013, 2014)
- We evaluate/calibrate predictions with available monitoring data across as many chemical classes as possible to allow extrapolation
  - Attempt to identify correlations and errors empirically



Exposures Inferred from NHANES

- Annual survey, data released on 2-year cycle, includes biomonitoring for chemical exposure
- Use as “ground truth” for evaluating models
- Different predictive models provide different chemical-specific predictions
  - Some models may do a better job form some chemical classes than others overall, so we want to evaluate performance against monitoring data
  - SHEDS-HT (Isaacs et al., 2014) is predictive of indoor exposures

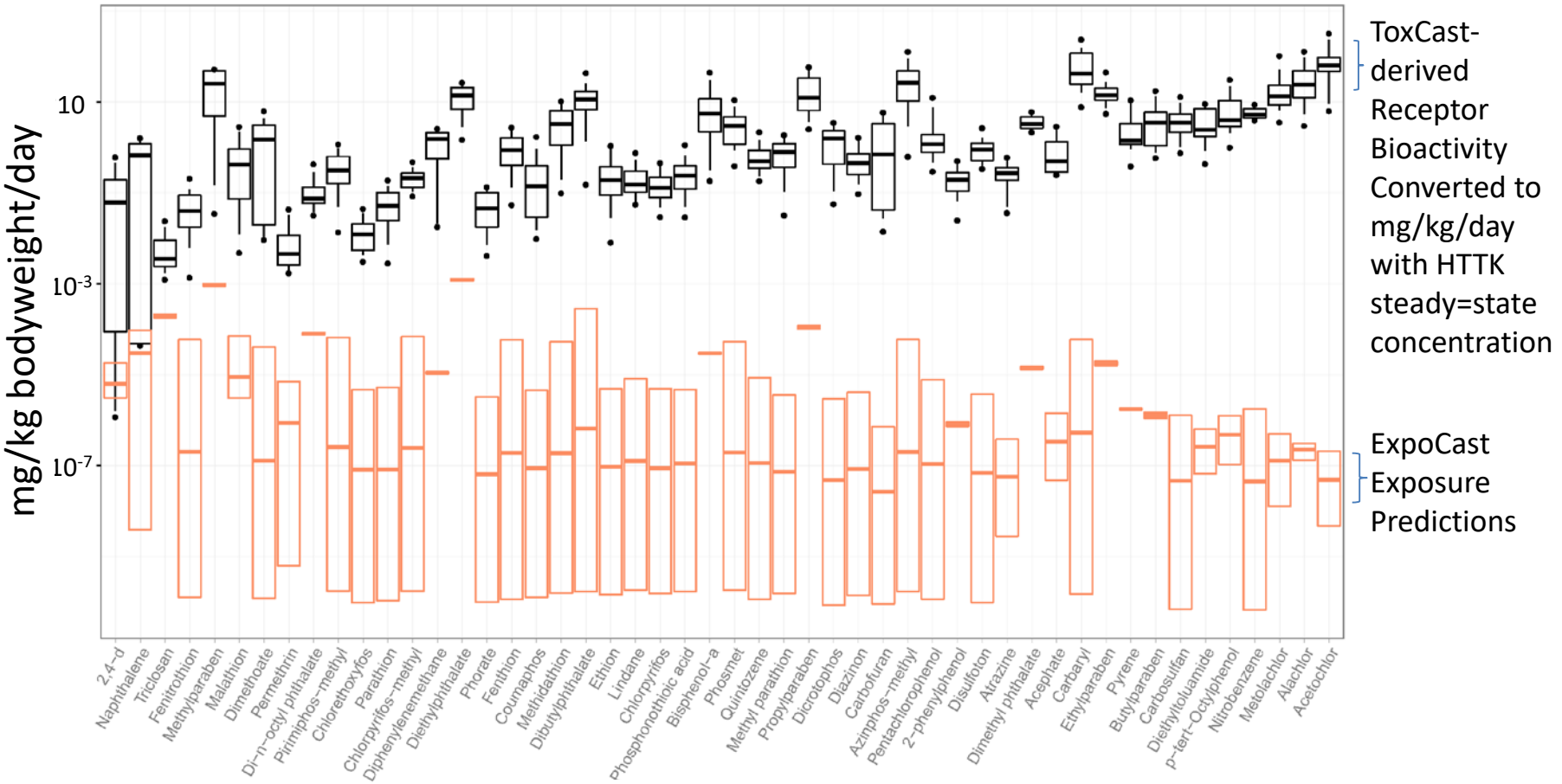
National Health and Nutrition Examination Survey

CDC, Fourth National Exposure Report (2011)

Exposure-Based Priority Setting: Using HTS Data (ToxCast)

United States Environmental Protection Agency

Priority chemicals have smaller predicted margin between hazard and exposure



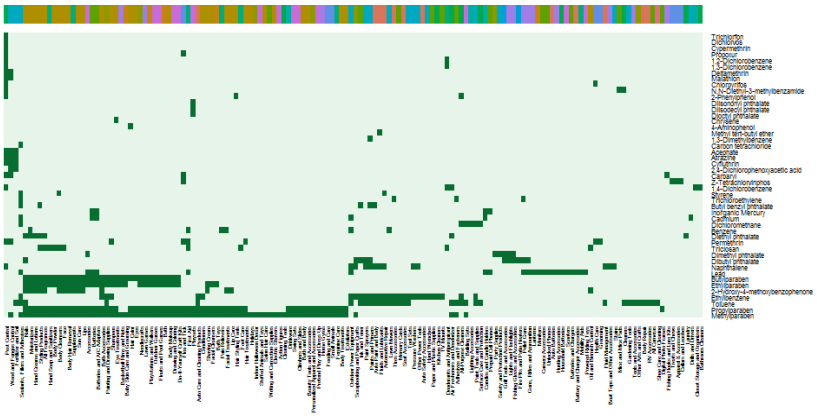
ToxCast Chemicals with NHANES data

Figure from Ring et al., (2017), see also Wetmore et al. (2015)

Chemical Use Identifies Relevant Pathways

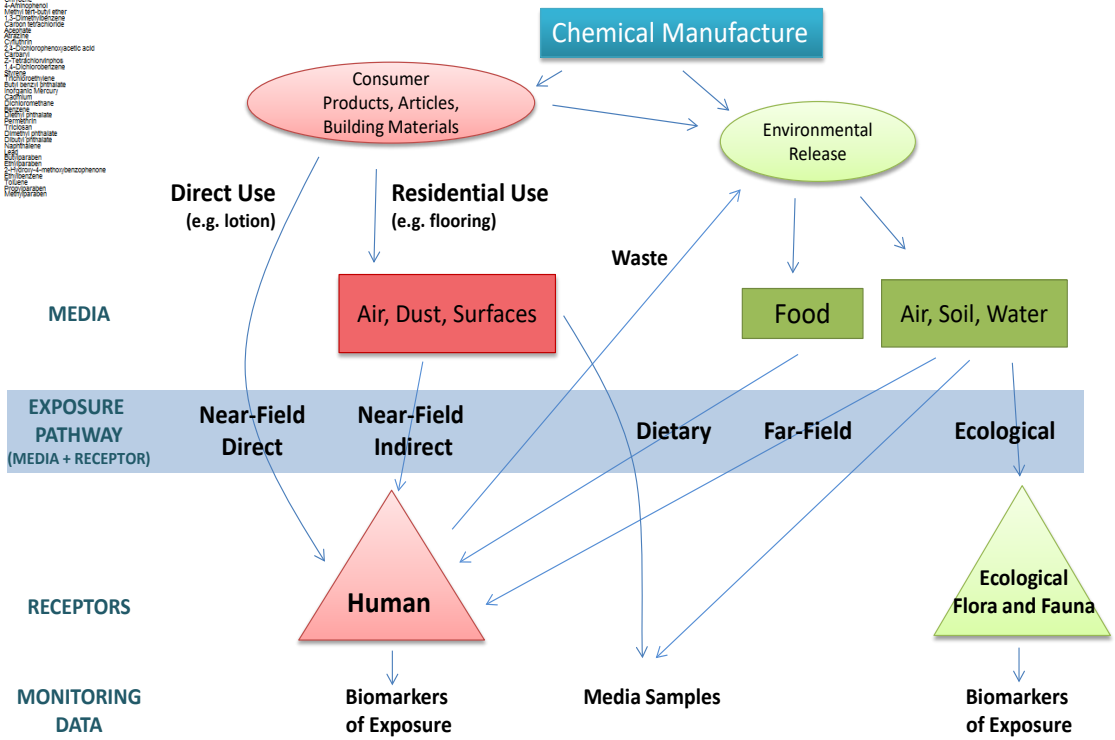
Chemical-Product Database (https://actor.epa.gov/cpcat/) provides chemical use information (Dionisio et al., 2015)

106 NHANES Chemicals



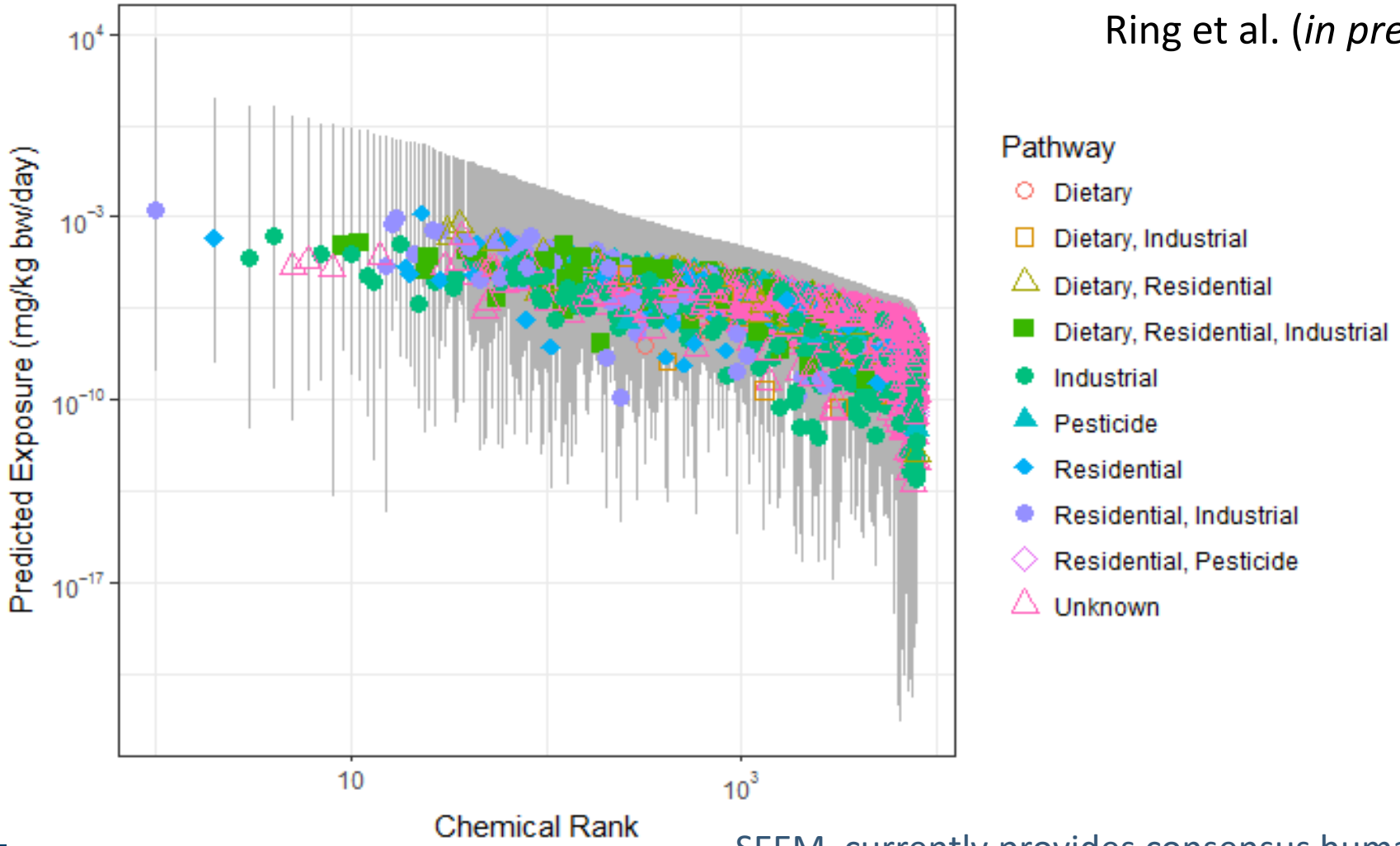
- Apparel
- Auto and Tires
- Baby
- Beauty
- Craft and Party Supply
- Electronics
- Grocery
- Health
- Home
- Home Improvement
- Patio and Garden
- Pets
- Sports and Outdoors
- Toys

Some pathways have much higher average exposures!



Near field sources have been known to be important at least since 1987 – see Wallace, *et al.*

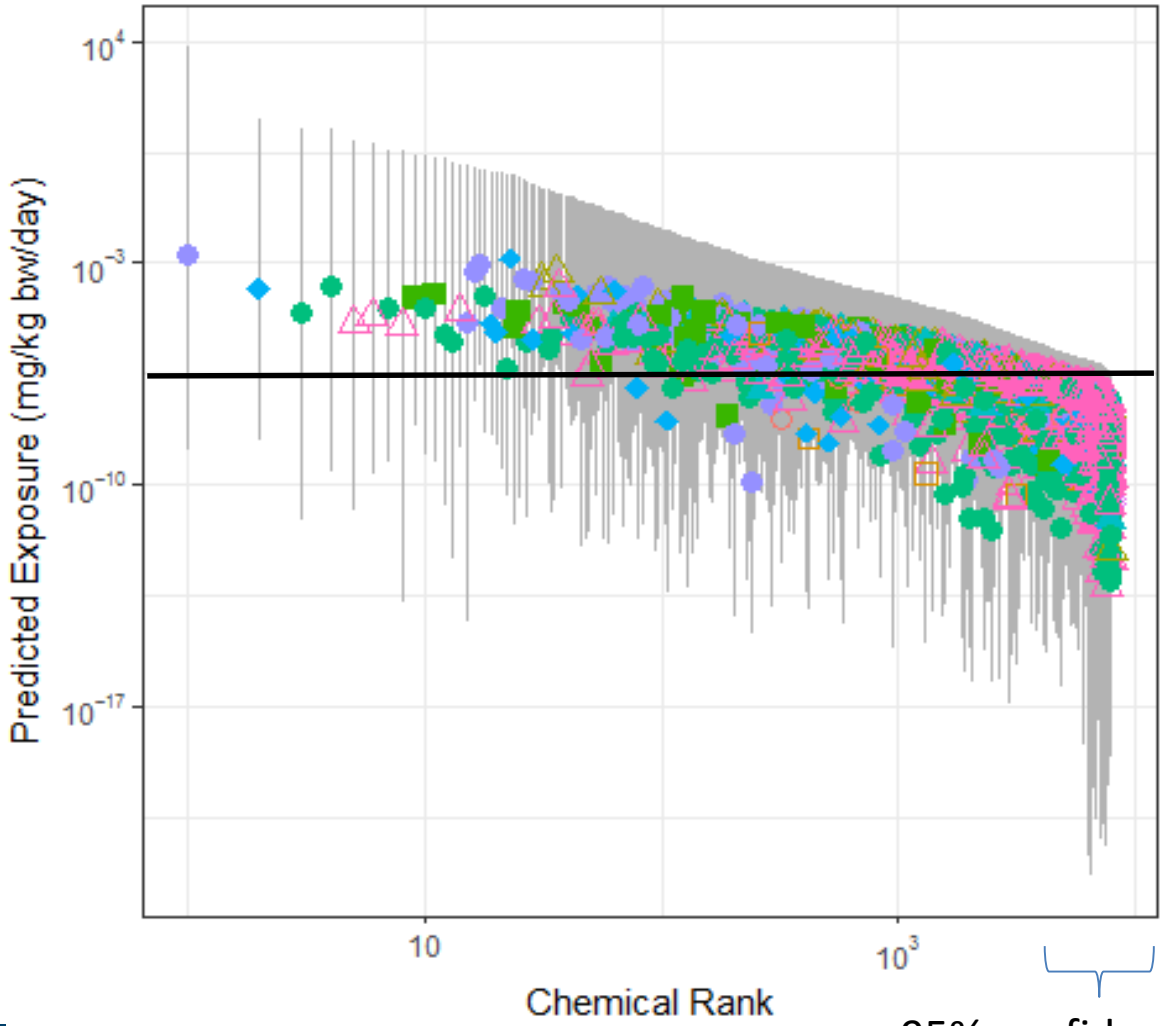
High Throughput Exposure Predictions



Ring et al. (*in prep.*)

SEEM currently provides consensus human exposure predictions for 134,521 chemicals

High Throughput Exposure Predictions



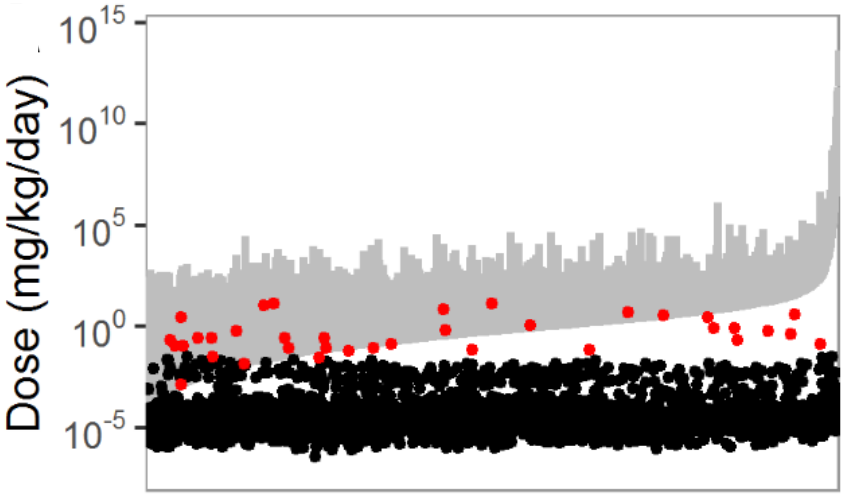
Ring et al. (*in prep.*)

Lowest NHANES limit of detection (LOD) roughly corresponds to ~10^{-6} mg/kg BW/day

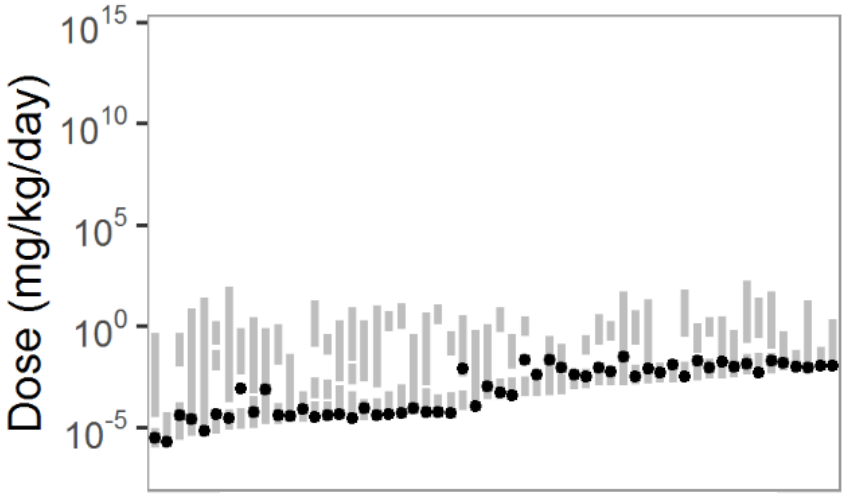
95% confident that median population would be <LOD for thousands of chemicals

Exposure-Based Priority Setting: Using HTS Data (Tox21)

Tox21 has screened >8000 chemicals – compare in vitro active concentrations with HTTK predicted maximum plasma concentrations



Dose range for all 3925 Tox21 compounds eliciting a 'possible'-to-'likely' human *in vivo* interaction alongside estimated daily exposure



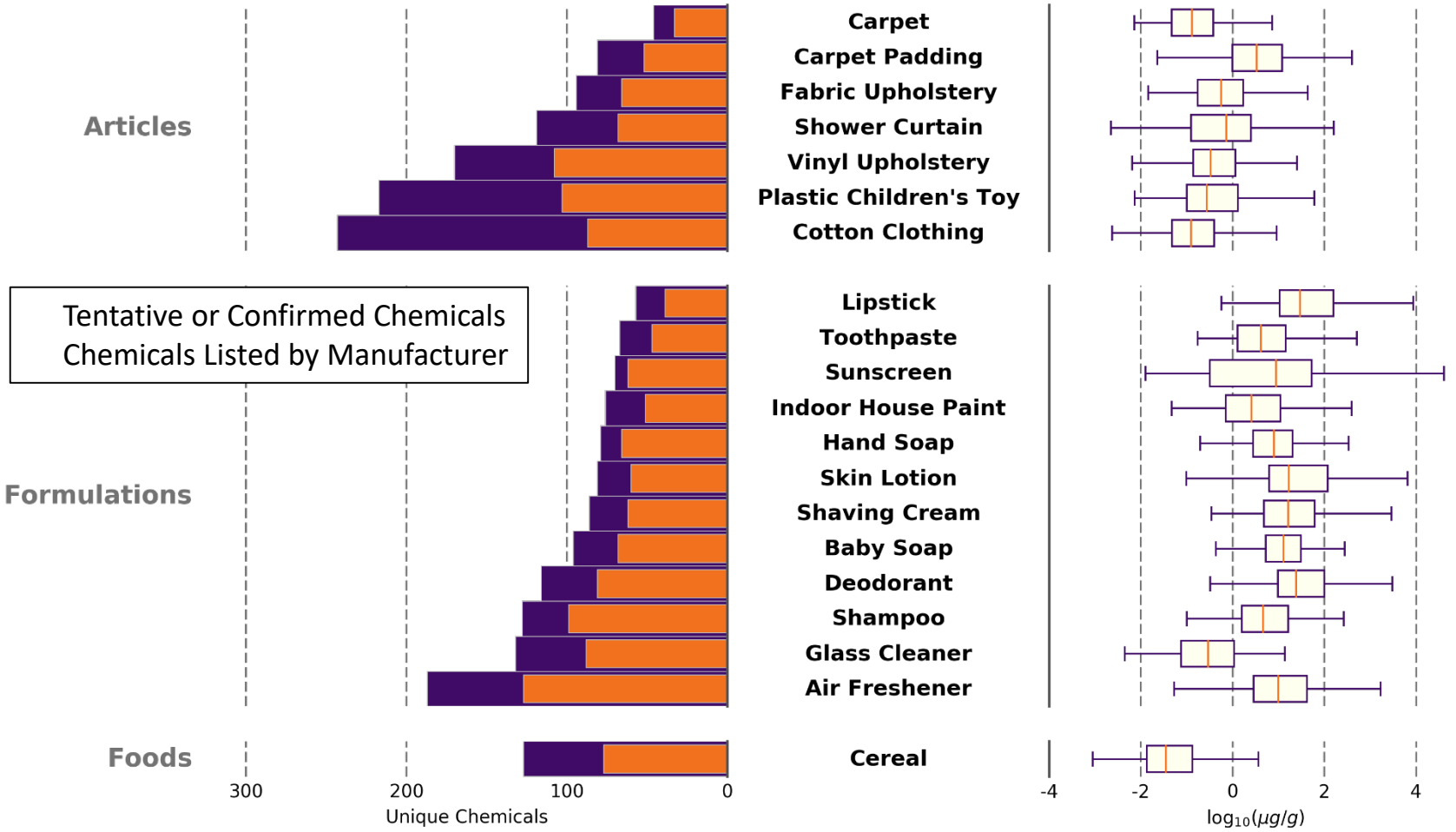
56 compounds with potential *in vivo* biological interaction at or above estimated environmental exposures

Sipes et al., in press

Other Approaches to Exposure:
Exposure Surveillance with Non-Targeted Analysis

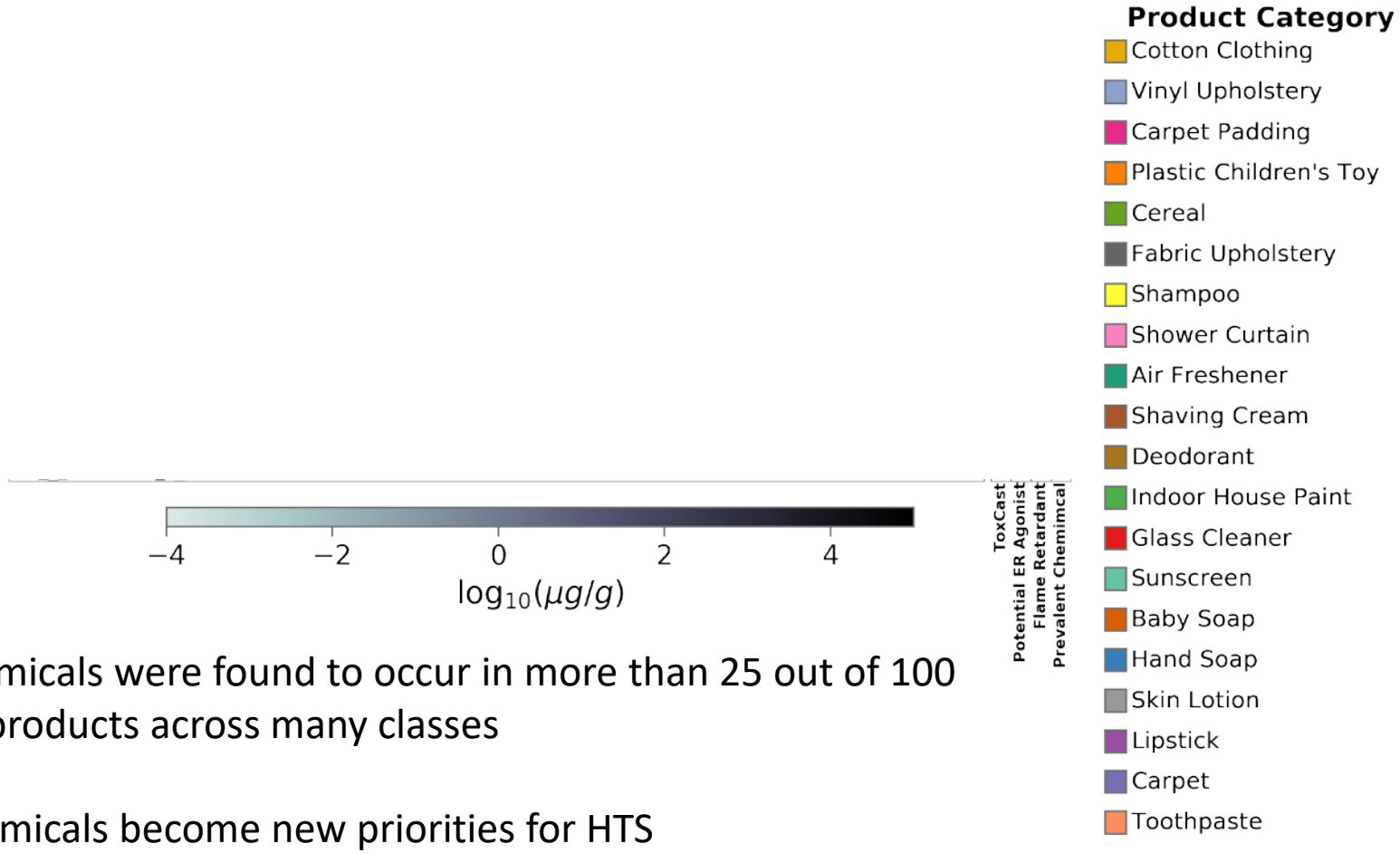
United States Environmental Protection Agency

Scanned 5 examples each of 20 class of consumer products
Of 1,632 chemicals, 1,445 were not present in CPCPdb (Goldsmith et al., 2014)



Phillips *et al.* (*submitted*)

Exposure-Based Priority Setting: Environmental Monitoring



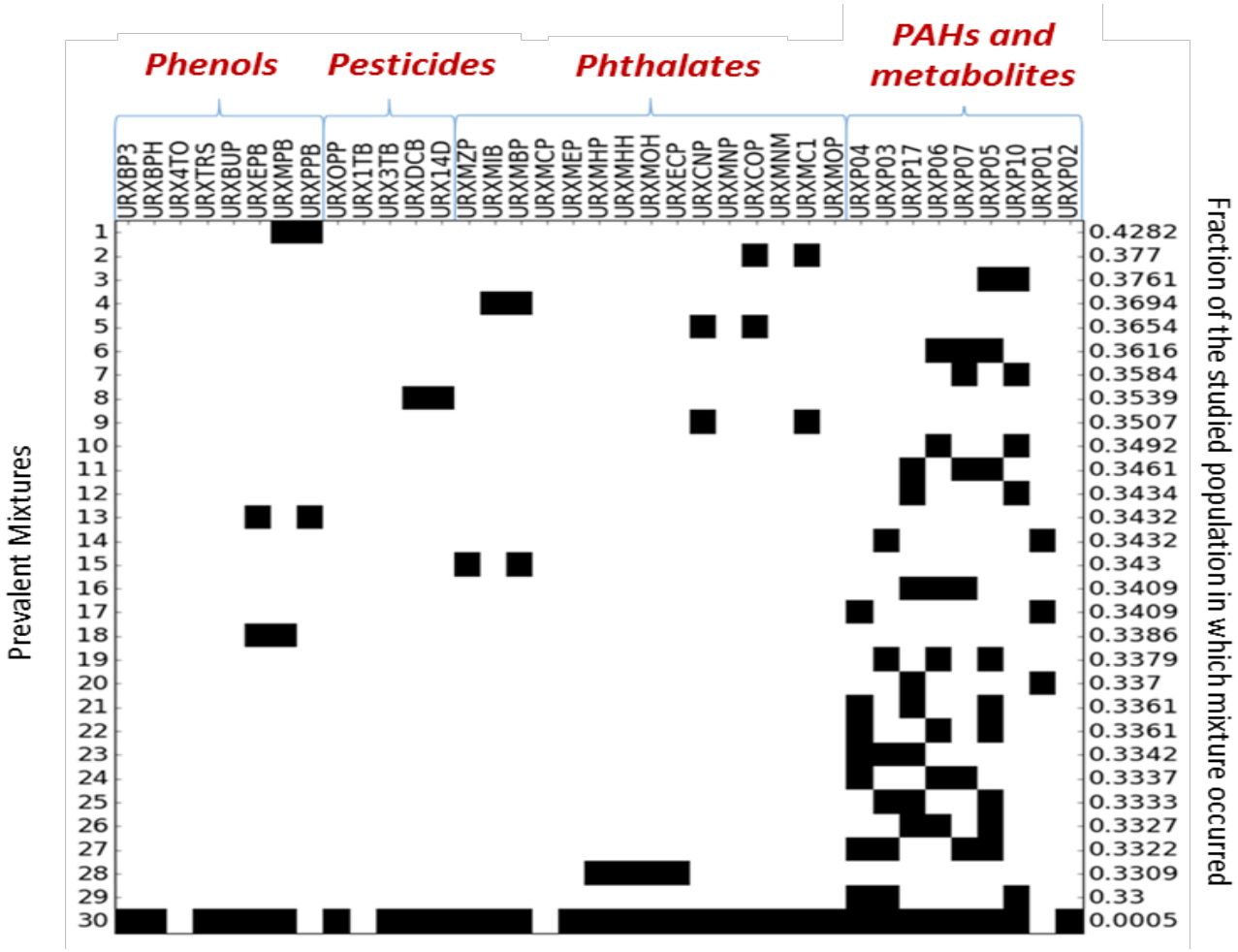
Some chemicals were found to occur in more than 25 out of 100 different products across many classes

These chemicals become new priorities for HTS

Phillips *et al.* (*submitted*)

Exposure-Based Priority Setting: Biomonitoring of Mixtures

- Data-mining methods identify chemical combinations that occur frequently
- We have identified a few dozen mixtures present in >30% of U.S. population
  - These mixtures become priorities for HTS
- Currently limited by targeted nature of biomonitoring
  - Non-targeted analysis?



Frequent itemset mining used to identify combinations of NHANES group B chemicals occurring in individuals at a concentration greater than the population median

Kapraun *et al., (in press)*

Exposure-Based Priority Setting

- If you have *in vitro* high-throughput screening (HTS) data then high throughput exposure models allow risk-based calculations
  - Chemicals with smaller margins become priorities for follow-up research
- We can use non-targeted analysis to scan our environment for presence of chemicals
  - Understudied but commonly occurring chemicals become priorities for HTS
- Data analytics allows the identification of commonly occurring mixtures in biological matrices like plasma and urine
  - Mixtures occurring in large fractions of the population become priorities for HTS
  - Observational discovery of mixtures avoids combinatorial explosion for testing

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EPA United States Environmental Protection Agency

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

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