Advances in Exposure Science and the Improved Characterization of Combined Exposures

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Disclaimer and Conflict of Interest Statement

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The author declares that they have no conflict of interest.

Technical Glossary

AEP: Aggregate Exposure Pathway. A framework for storing data on exposure and dosimetry.

CPDat: Chemical and Products Database. A US EPA database containing data on composition of consumer products, general chemical use, functional use, and product measurements.

CompTox Dashboard: A US EPA community data resource for environmental chemistry information that includes physicochemical, environmental fate and transport, exposure, usage, *in vivo* toxicity, and *in vitro* bioassay data. (https://comptox.epa.gov/dashboard)

CHEM: Combined Human Exposure Model. Longitudinal human exposure model under development at EPA.

Frequent Itemset Mining: Data mining method to identify prevalent combinations occurring in dataset.

Hazard Quotient: Exposure divided by a reference dose.

Hazard Index: Sum of hazard quotients for co-occurring (cumulative) exposures.

MCR: Maximum Cumulative Ratio. Ratio of hazard index to maximum hazard quotient.

NAMs: New Approach Methodologies. New methods for assessing a substance's toxicity or biological activity.

Natural Language Processing: Programs that allow the extraction of specific data from free text.

NHANES: National Health and Nutrition Examination Survey.

NTA: Nontargeted Analysis. Analytical chemistry studies in which chemical structures of unknown compounds are postulated without the aid of suspect lists.

PUC: Product use category. The consumer product categorization schema used in CPDat, which allows for linking to consumer exposure algorithms in US EPA models.

Random Forest Modeling: A learning method for classification that operates by constructing a number of decision trees and developing consensus predictions.

SHEDS-HT: Stochastic Human Exposure and Dose Simulation (High-Throughput) model. A screening-level, minimally parametrized population-based human exposure model for consumer products; uses data from CPDat as input.

Suspect Screening: Analytical chemistry studies in which observed but unknown features (generally defined in high-resolution mass spectrometry experiments by an accurate mass, retention time, and mass spectrum) are compared against a database of chemical suspects to identify plausible hits.

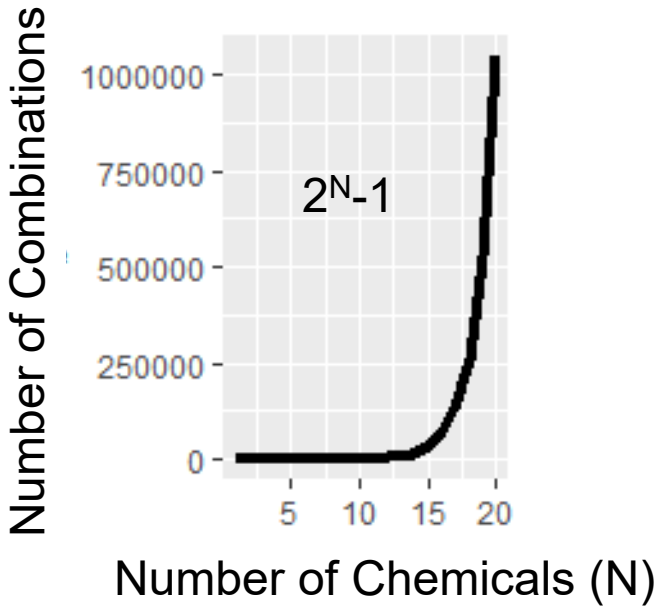
QSUR: Quantitative Structure-Use Relationship. Machine-learning models for predicting chemical function or use from chemical structure.

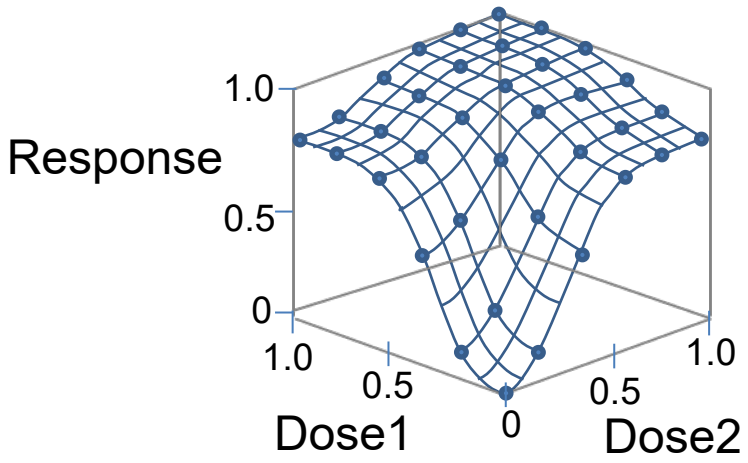
UVCB: A substance with Unknown or Variable composition such as a Complex reaction product or Biological material.

Challenge of Combined Exposure to Multiple Chemicals

- Mixture toxicity is a function of a combinations of chemicals that reach an individual
- Exposures need not be concurrent; one chemical's effects may persist and affect the toxicity of a later exposure to a second chemical
- Humans and ecological receptors are exposed to very large numbers of complex mixtures
- The combination of exposures from all sources form an individual's exposome
- Difference in individuals' exposomes have been shown to have significant impacts on human health

Challenges in Assessing Combined Exposure to Multiple Chemicals

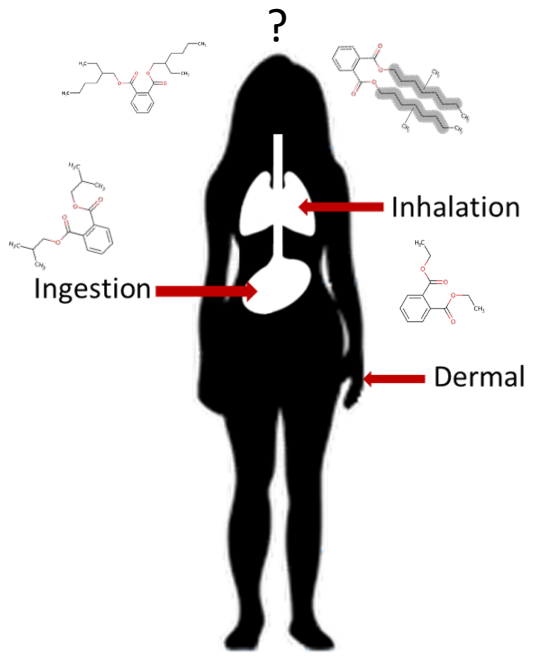




- Single chemical toxicity assessments are relatively straightforward. A single dose-response curve, defined by 3–5 doses, predicts the response for any dose. This allows toxicity assessments to be performed independently from exposure assessments.
- For mixtures toxicity assessments:
  - The number of unique combinations of the doses of N chemicals is 2^N-1.
  - The number of dose combinations required to generate an N-dimensional response surface is k^N.
  - This results in too many possible mixtures to exhaustively test.
- **Toxicologists need guidance from exposure assessors on which combinations of chemicals should be tested.**
  - **Which combinations of chemicals actually co-occur in exposed populations? and**
  - **What is the relevant range of dose for each chemical?**

Exposure Science Can Inform Scoping, Design, and Interpretation of Toxicological Mixtures Assessments

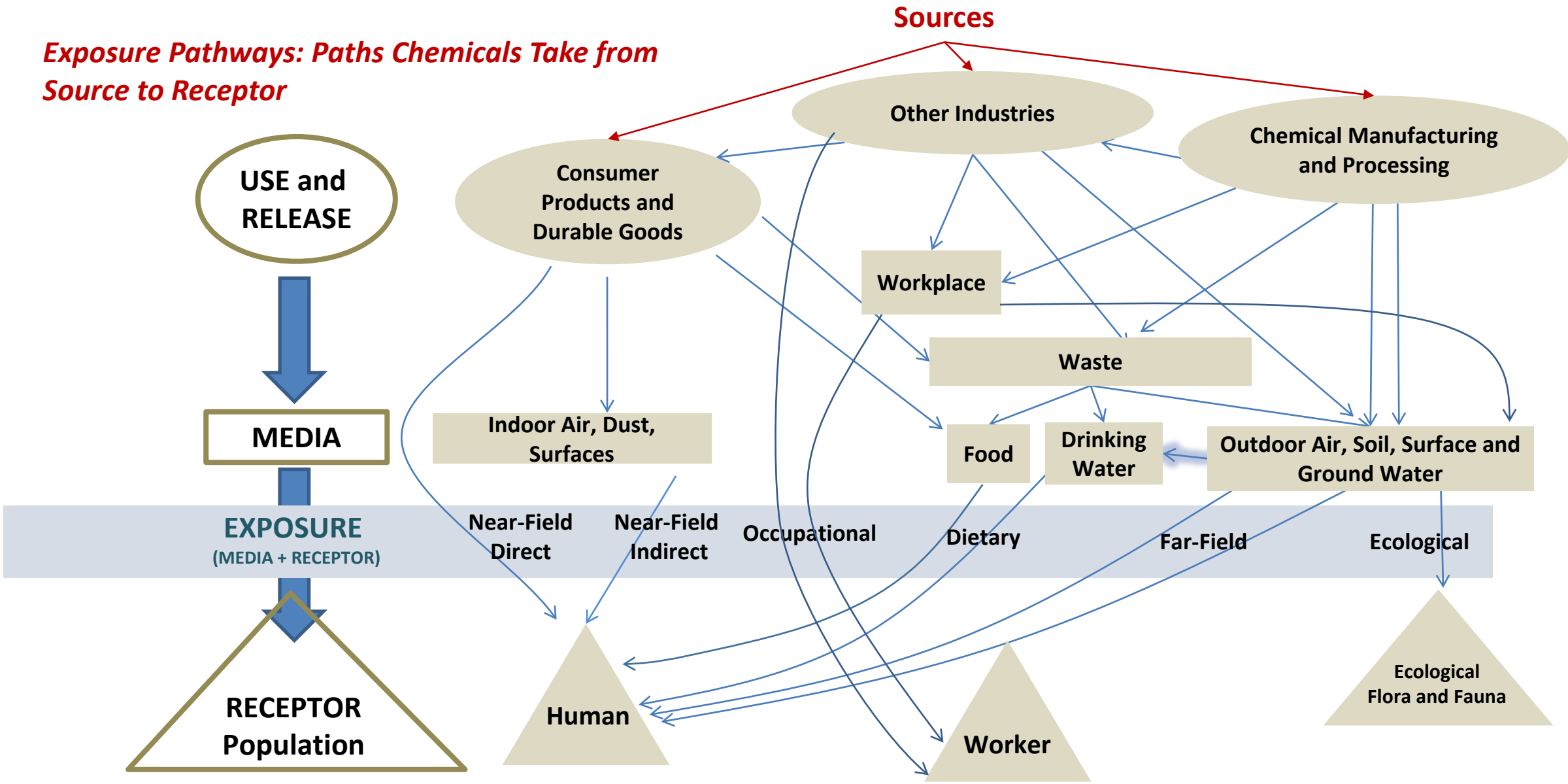
Real-World Combined Exposures



- Identification of priority real-world mixtures for testing
  - Identification of the most important real-world co-exposures (chemical combinations)
- Selecting doses for *in vitro* and targeted *in vivo* studies
  - Selection of doses that reflect those encountered under real exposure conditions
- Interpreting hazard findings for populations and individuals exposed to mixtures
  - Assessment of contribution of component hazards to overall risk and likelihood of cumulative impacts

How Do Combined Exposures Arise?

Exposure Pathways: Paths Chemicals Take from Source to Receptor



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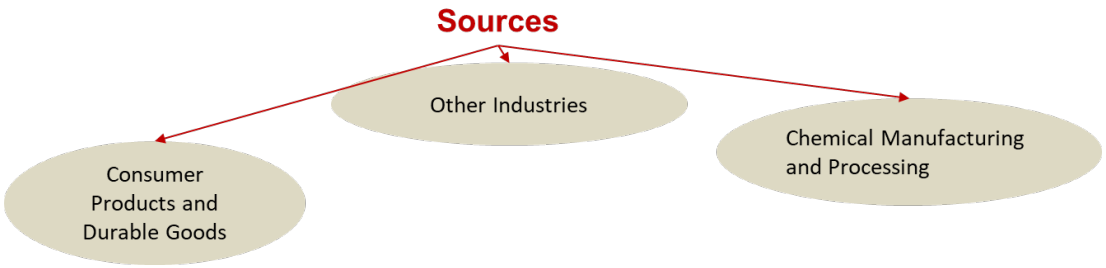
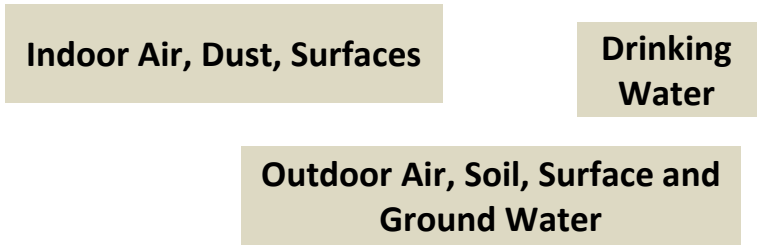
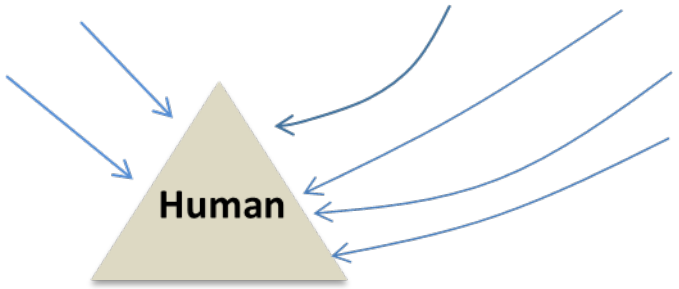






Chemical co-occurrence within chemical sources

- Chemicals that occur in the same consumer product
- Co-release of chemicals from one source
- UVCBs

Chemical co-occurrence in environmental media

- House dust
- Site-specific exposures/Superfund sites
- Drinking water

Cumulative exposures at the receptor level from multiple sources and exposure pathways

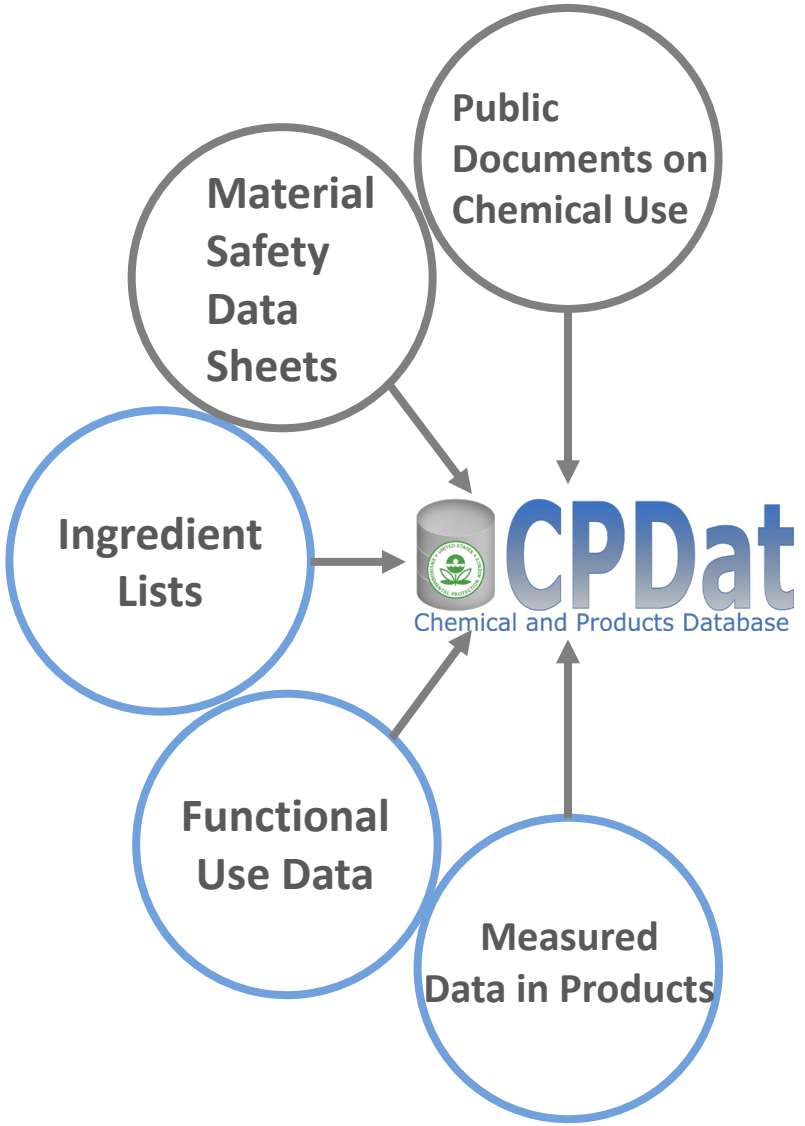
- Dietary exposures to phthalates in food contact materials and
- Dermal exposures to phthalates in cosmetics

Exposure Science Is Providing Data and Tools Needed to Address Combined Exposures

- Data describing how chemicals are used in products and processes, how they are released, and how they are distributed in environmental media are essential in determining single chemical and combined exposures.
- Modeling tools that help estimate exposures and fill gaps in these data also are needed.
- Advances in exposure science, including **informatic (data-based), measurement, and modeling** approaches, are improving our ability to characterize chemical releases from sources; chemical concentrations in environmental media, indoor air, drinking water, and the workplace; and the resulting exposures and doses.

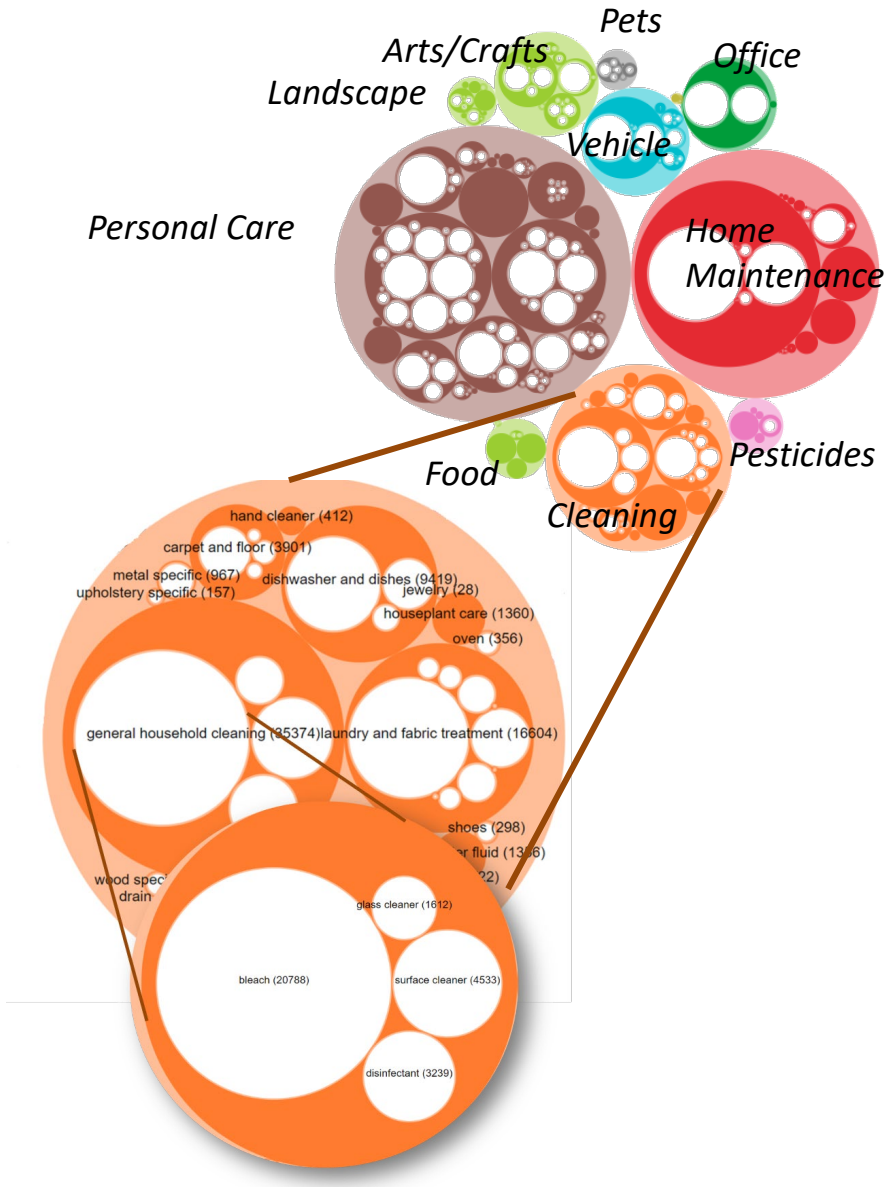
The Chemicals and Products Database (CPDat)

- Provides a means to organize information on chemicals in consumer products for exposure assessments (Dionisio et al., 2018)
- Composed of data on chemical use and consumer product composition from a variety of public sources; includes measured, modeled, and reported data
- Organized around a set of consumer product use categories (PUCs) that are designed to support exposure modeling (Isaacs et al., 2020)
- All data are curated in a robust, well-documented manner using US EPA curation tools



The Chemicals and Products Database (CPDat)

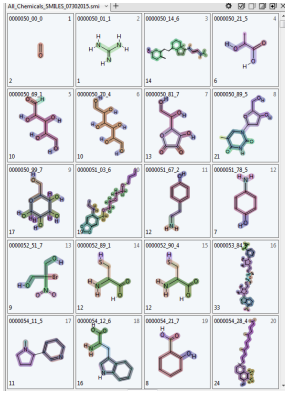
- CPDat currently contains curated information extracted from over 500,000 documents reflecting data on over 35,000 unique chemical substances
- Chemical composition of more than 29,000 individual consumer products
- Currently mapping additional products to product categories using natural language processing
- Public CPDat releases available at https://doi.org/10.23645/epacomptox.5352997 and summary data available on the CompTox Chemicals Dashboard (Williams et al., 2017) https://comptox.epa.gov/dashboard/

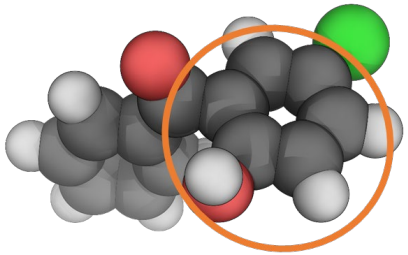


Filling Gaps in Chemical Use Data with Quantitative Structure-Use Relationship (QSUR) Models

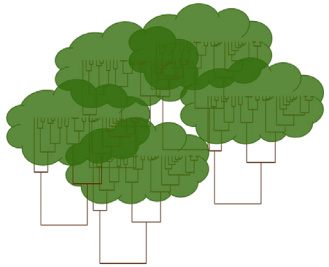
Structure-based models have been used to extrapolate known information about chemical function and consumer product weight fraction (Isaacs et al., 2016, Phillips et al., 2017) to data-poor chemicals

Chemical Structure and Property Descriptors





Random Forest Machine-Learning Models

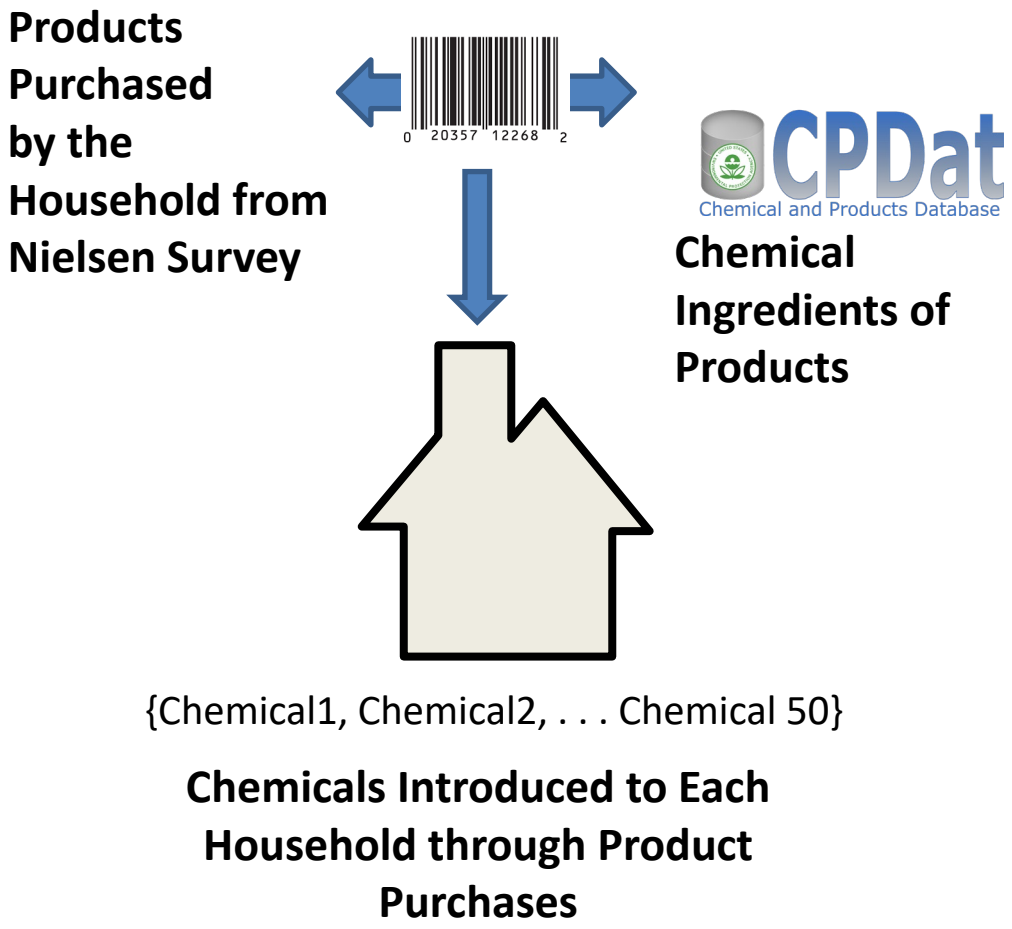


Predict Probability of Chemical Performing 41 Functions

Solvent?
Colorant?
Plasticizer?

Identifying Chemical Co-exposures Using Consumer Product Data

- CPDat data were combined with purchasing data to inform identification of real-world co-exposures (Stanfield et al., 2020)



Identifying Chemical Co-exposures Using Consumer Product Data

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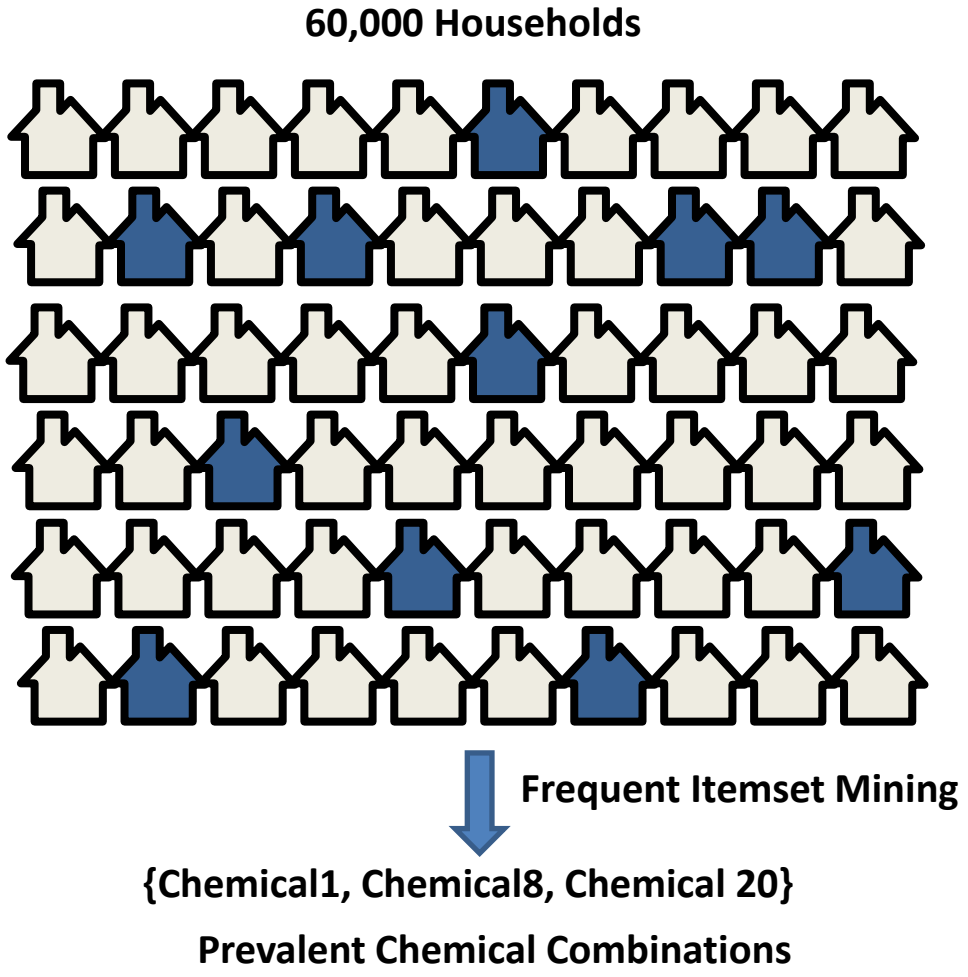
- Frequent itemset mining (FIM) was used to identify the most frequent chemical combinations introduced to households.



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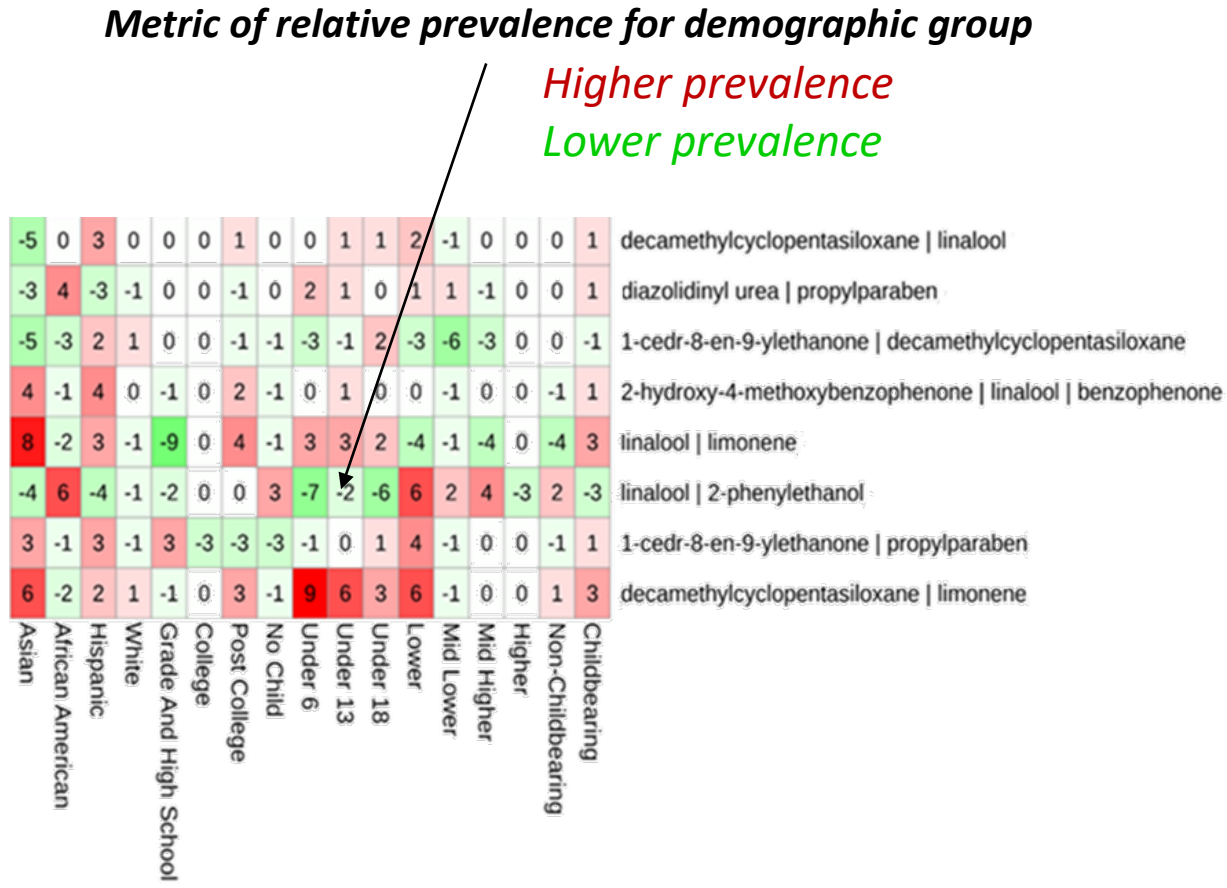
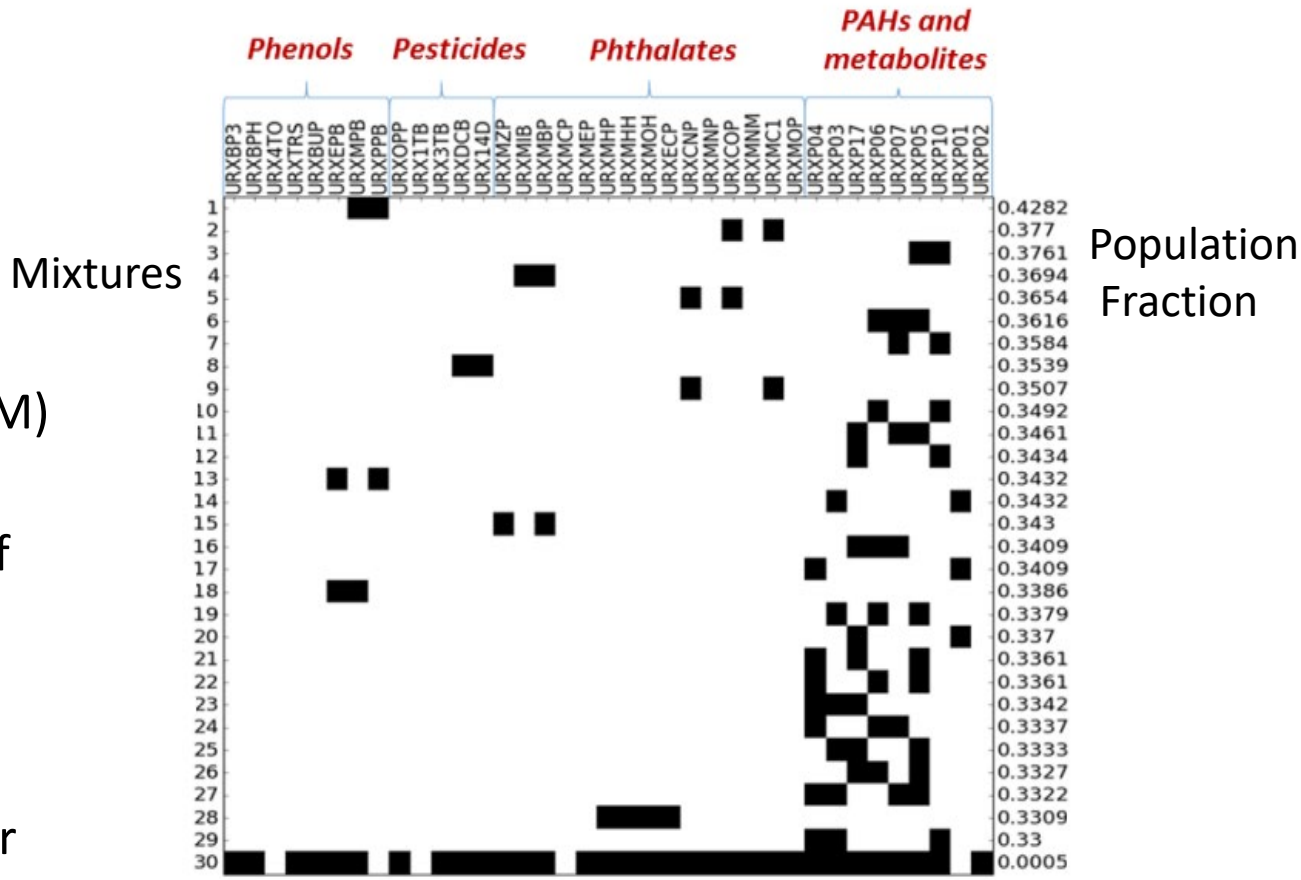
- Frequent itemset mining (FIM) was used to identify the most frequent chemical combinations introduced to households.
- By combining with bioactivity data and predictions, we could identify relevant combinations of endocrine-active chemicals for various demographic groups. These results are informing a pilot study of mixture bioactivity.



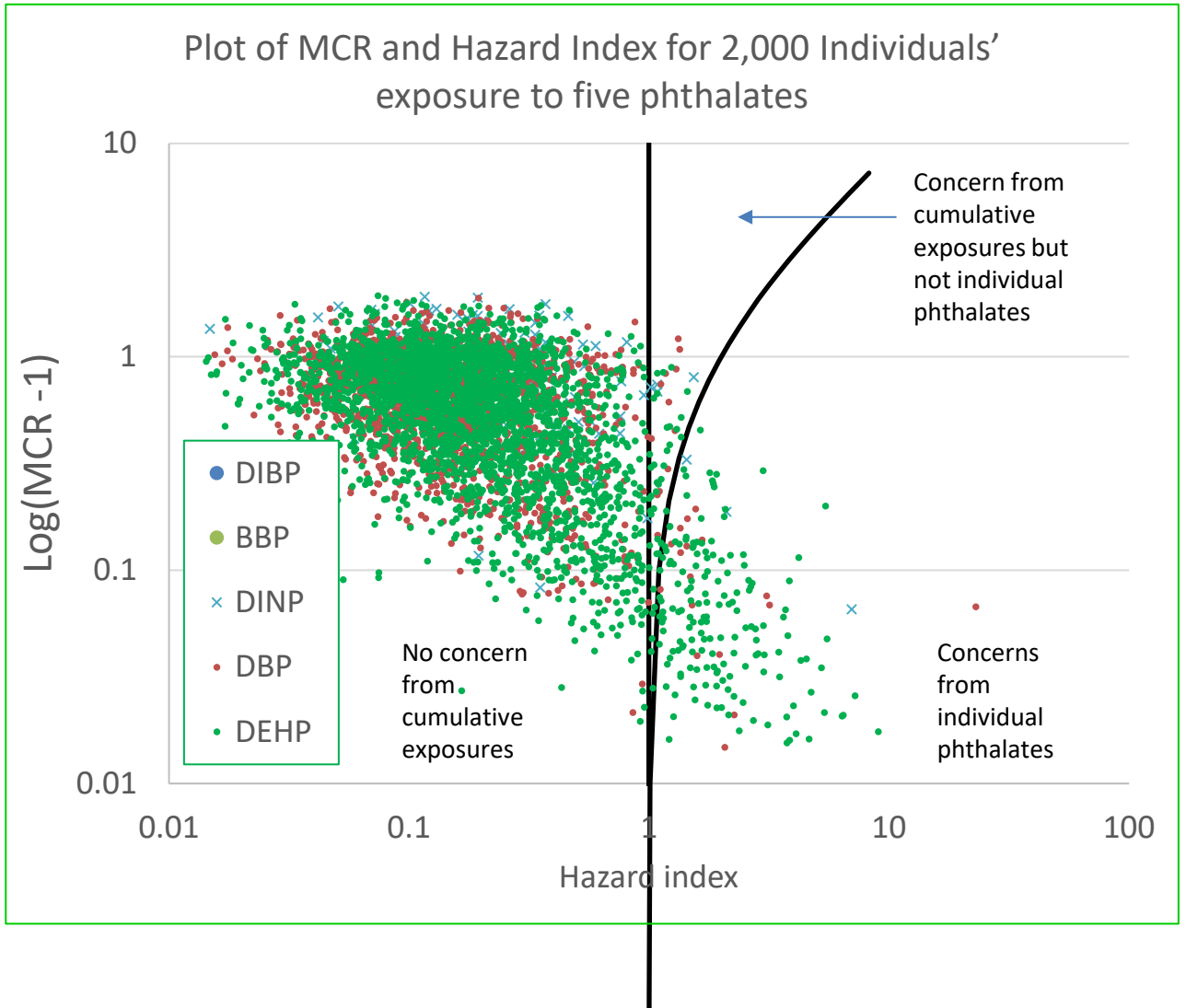
Biomonitoring Data Provide Gold-Standard Information on Combined Exposures

- Kapraun et al., (2017) mined biomonitoring data from the NHANES study to identify prevalent chemical combinations
- Measured concentrations were discretized to presence/absence using a fixed threshold
- Examined co-occurrence within three groups of chemicals measured in unique subsamples of the study population, using frequent itemset mining (FIM)
- Identified 90 chemical combinations consisting of relatively few chemicals that occur in at least 30% of the US population
- Identified three “super combinations” of chemicals that occurred in a smaller fraction of the population
- But these approaches only look for a limited number of known chemicals



Addressing Risk: Maximum Cumulative Ratio (MCR) and Combined Exposures

- Maximum Cumulative Ratio is ratio of the combined hazard index (HI, sum of the hazard quotients) divided by the hazard quotient from the largest contribution by any one chemical (Price and Han, 2011).
- Reyes and Price (2018) examined cumulative phthalate exposures in 2,000 individuals.
- Plotting MCR against hazard index for each individual identifies those with combined exposures that separately pose no risk but in combination could pose a risk.



Phthalate and Phthalate Pairs That Drive Cumulative Toxicity

- DINP was found to be the most common single driver of combined toxicity followed by DEHP
- DEHP: DINP, DINP: DIDP, DEHP: DIDP are the pairs of phthalates that drive toxicity for the most exposed individuals
- This suggests that studies of the interaction of phthalates should focus on these three pairs of phthalates

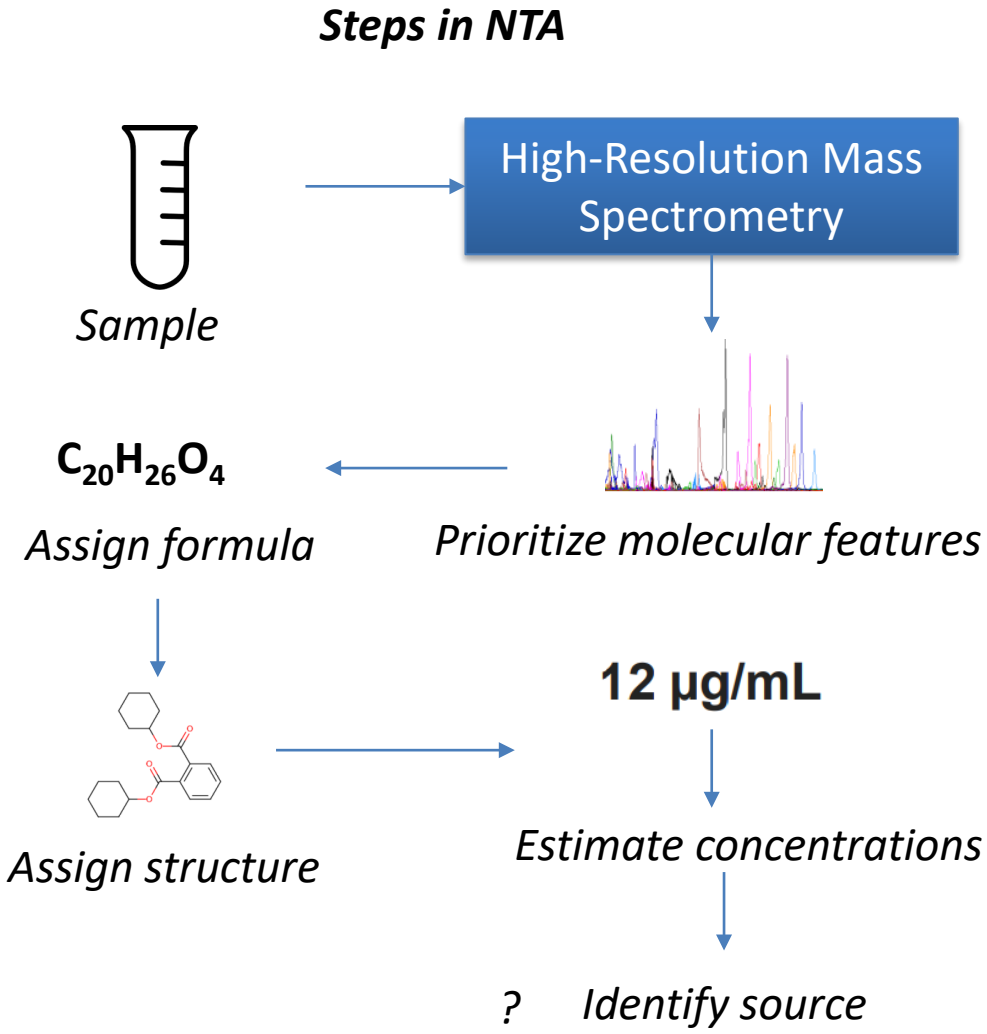
Frequency of phthalate pairs producing the highest HQ in individuals

	DEHP	DINP	DIDP	DBP	BBP	DIBP
DEHP		12	2	1	0	0
DINP	---		5	1	0	0
DIDP	---	---		0	0	0
DBP	---	---	---		0	0
BBP	---	---	---	---		0
DIBP	---	---	---	---	---	

Reyes and Price (2018)

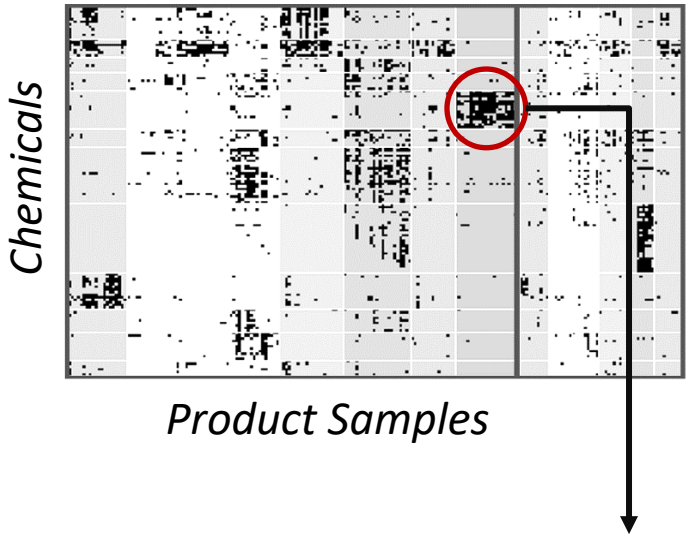
Advancing Knowledge of Chemical Sources, Media, and Receptors with Nontargeted Analysis

- Traditional monitoring approaches address well-studied chemicals (on the order of 100 to a few thousand)
- Other known but data-poor chemicals number in the 1,000s–100,000s
- How many unknown chemicals are there?
- New high-resolution mass spectrometry–based suspect-screening and nontargeted analysis (NTA) methods are characterizing data-poor chemicals in the environment and identifying unknown chemicals



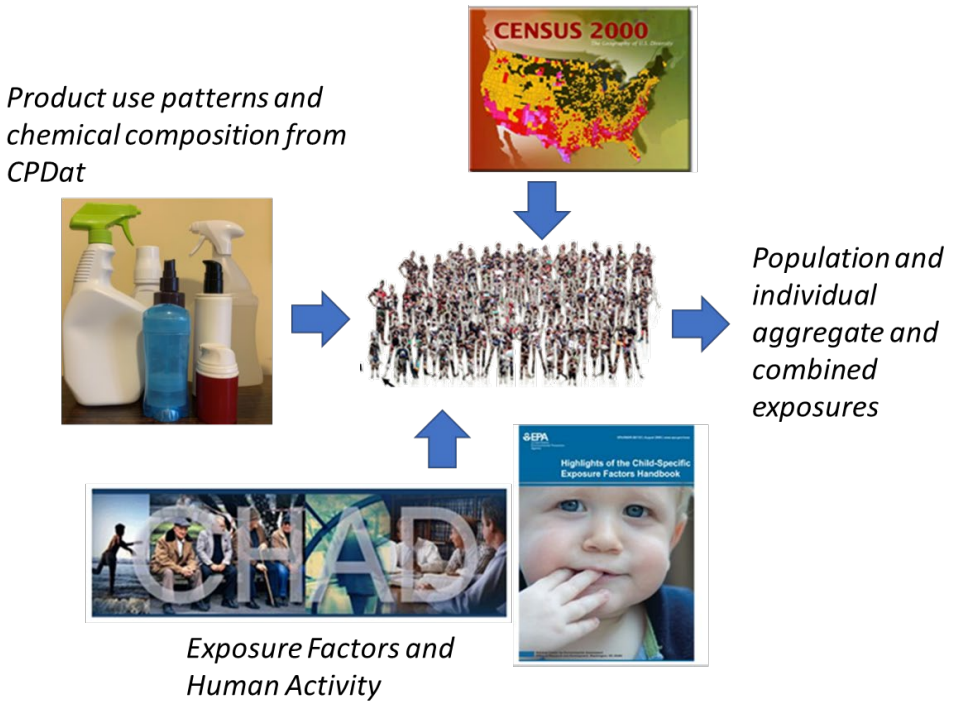
Advancing Knowledge of Chemical Sources, Media, and Receptors with Nontargeted Analysis

- NTA has recently been used to characterize chemicals in:
  - House dust (Rager et al., 2016)
  - Consumer products (Phillips et al., 2018)
  - Drinking water (Newton et al., 2018)
  - Waste and surface water (Murrell and Dorman, 2020)
- We also used NTA in concert with cluster analysis to identify groups of chemicals co-occuring in differently types of consumer products, including products derived from recycled tires (Lowe et al., 2021)



15 substances co-occuring in samples: intermediates, rubber components, and processing aids used in the manufacture of rubber products and rubber tires, or in rubber recycling

Modeling Approaches Informing Cumulative Exposure Assessment

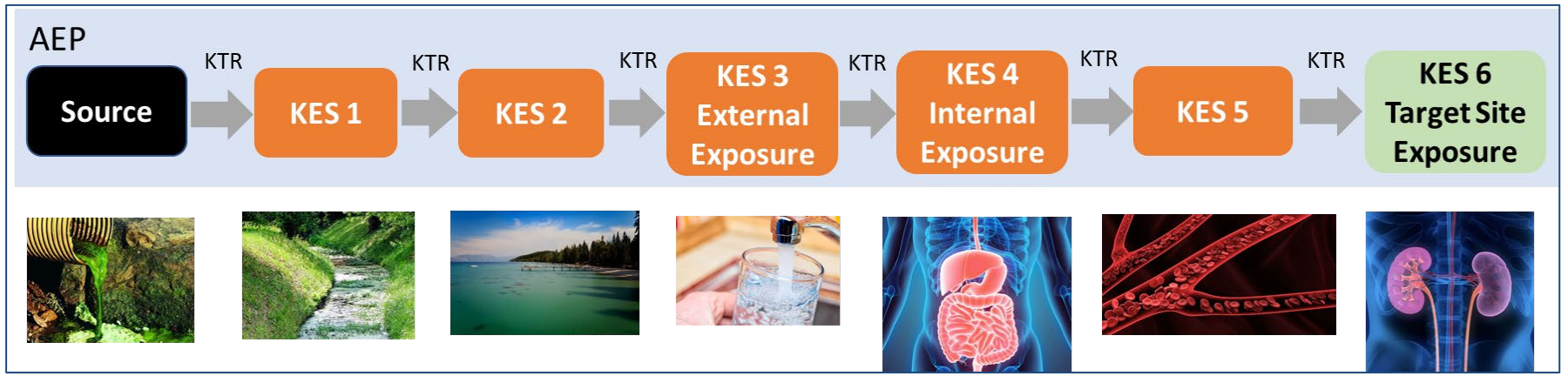


https://github.com/humanexposure/shedshtrpackage

- Population-based consumer models are being developed that can determine the aggregate and cumulative exposures from many sources (consumer products). The models integrate data on:
  - The human behaviors that drive exposures
  - The ingredients in consumer products
- Can be used in concert with toxicokinetic or dosimetry models to develop estimates of internal doses appropriate for NAMs-based mixtures assessment
- Models for modeling cross-sectional single day and longitudinal exposures are available.
  - High-Throughput Stochastic Human Exposure and Dose Simulation model (SHEDS-HT, Isaacs et al., 2016)
  - Combined Human Exposure Model (CHEM)

Aggregate Exposure Pathway: A Framework to Organize Exposure Information

- Use the same concept of causal events and acyclic graphs (edges and nodes) as the adverse outcome pathway (AOP) framework
- Links directly to AOP
- Integrates the processes of:
  - Release and transport of chemicals
  - Exposure
  - Toxicokinetic processes (absorption, distribution, metabolism, and excretion)



Summary and Conclusions

- Advances in exposure science have increased the amount of data available and provided the tools necessary to identify and characterize the specific combinations of chemicals that commonly occur in varying demographics of the US population.
- These data can inform the design of hazard studies for chemical mixtures by identifying the specific chemicals that co-occur in sources of exposure and the doses at which they occur.
- When combined with toxicity information, quantitative exposure estimates enable risk-based analyses of combined exposures, including identification of the drivers of mixture risks.

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