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SUSPECT SCREENING OF POOLED HUMAN SERUM SAMPLES

Katherine Phillips

March 28, 2024

Office of Research and Development
Center for Computational Toxicology and Exposure

United States Environmental Protection Agency

DISCLAIMER: The views expressed in this presentation are those of the authors and do not necessarily reflect the views or policies of the United States EPA.

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THANK YOU!!


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Annette Rice

SWRI
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Alice Yau

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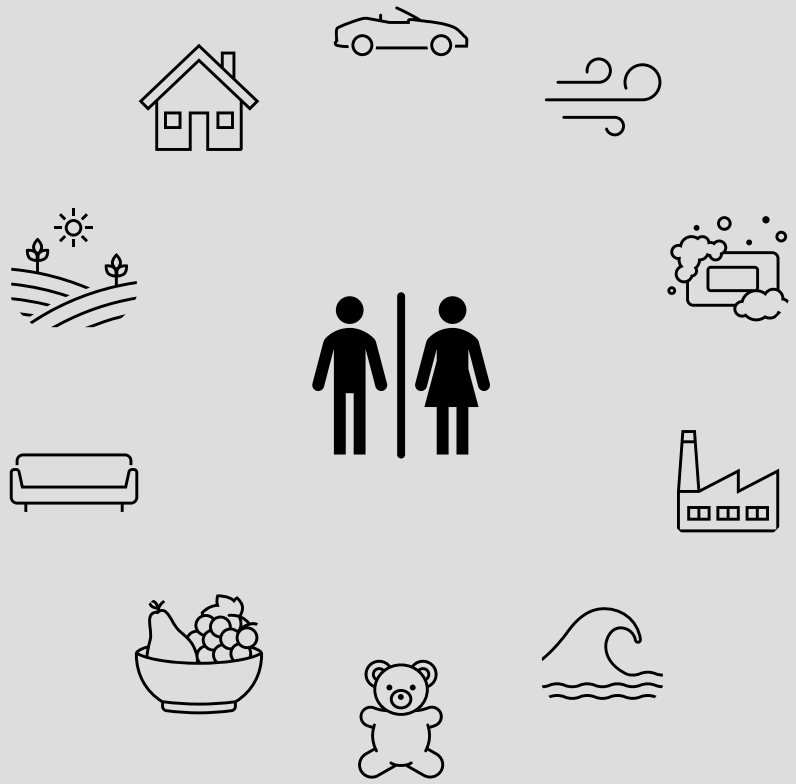
CHEMICAL EXPOSURE

- Humans interact with thousands of chemicals on a regular basis
- We often don't know precisely…
  - …which chemicals we contact in our everyday lives
  - …the quantities of those chemicals
  - …the ultimate fate of those chemicals in our bodies



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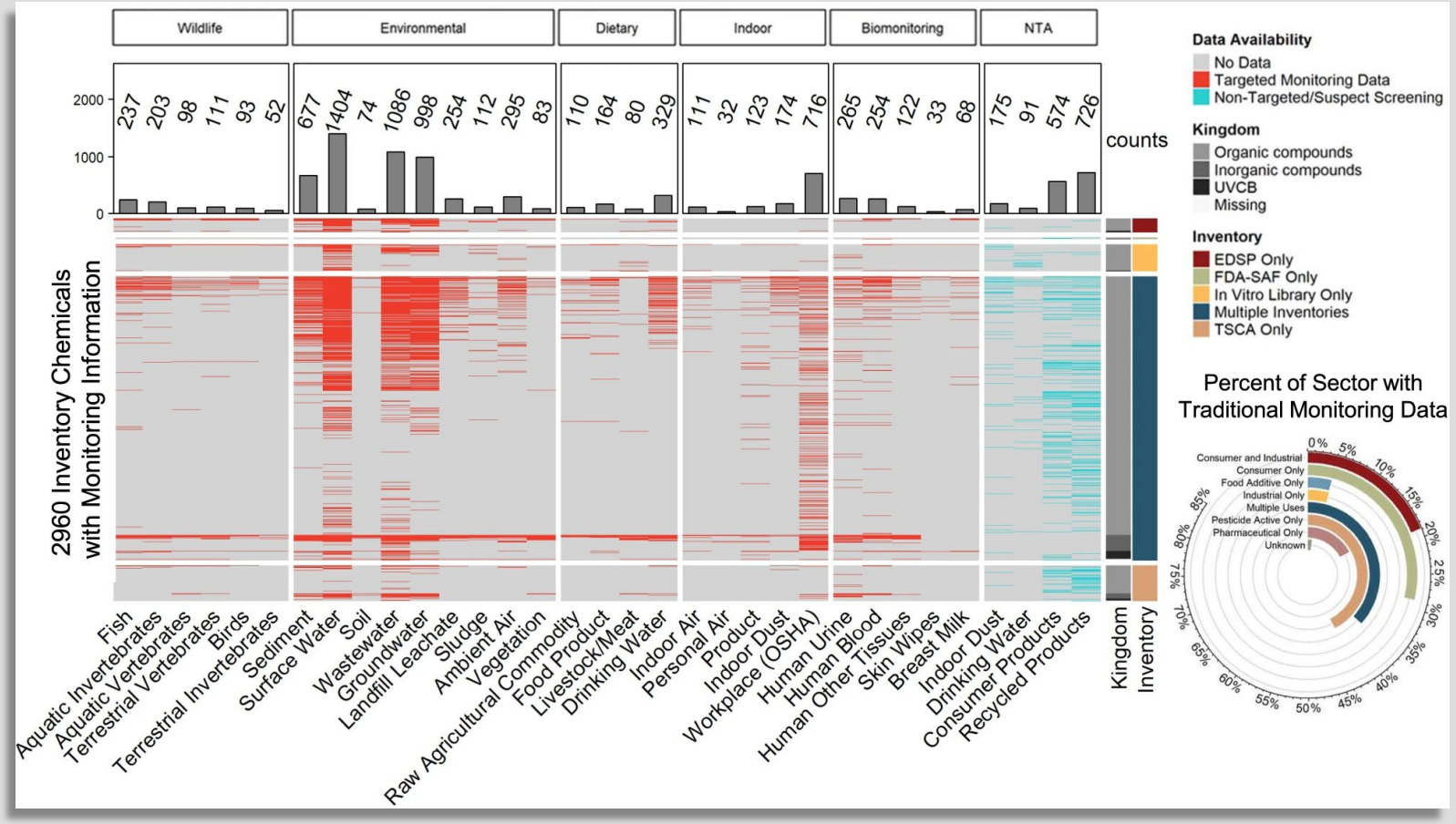
EXPOSURE LANDSCAPE

- A recent effort to assess the landscape of available data for assisting in chemical exposure assessment showed there is a lack in monitoring data for many relevant media (Isaacs, *JESEE*, 2022)
- New Approach Methods (NAMs) are needed to fill these data gaps
- Analytical Chemistry to the rescue!



Isaacs et al., *J. Expo. Sci. Environ. Epi.*, 2022

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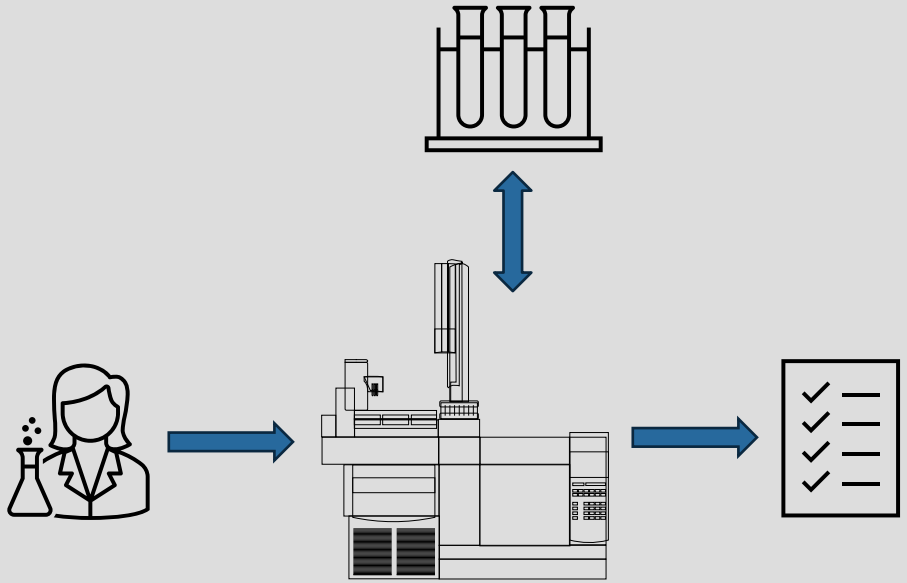
TARGETED ANALYSIS

- Targeted Analysis can identify 10s—100s of chemicals, but need to know what chemicals you're looking for



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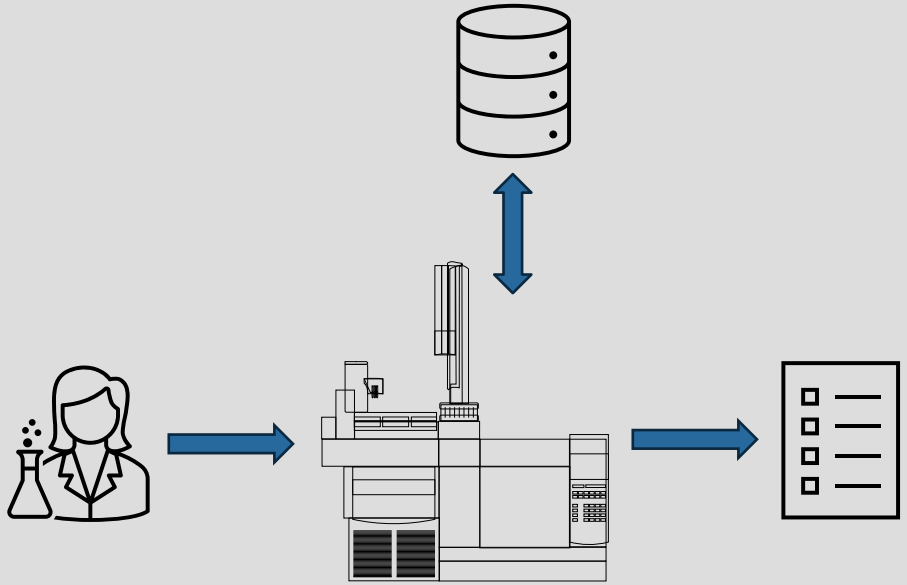
SUSPECT SCREENING ANALYSIS

- Targeted Analysis can identify 10s—100s of chemicals, but need to know what chemicals you're looking for
- Suspect Screening Analysis can identify 1000s—10000s of chemicals, need to have a library of chemicals (suspects) to match with



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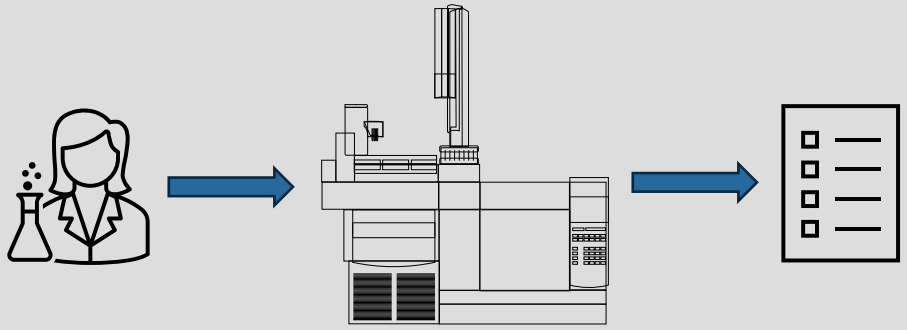
NON-TARGETED ANALYSIS

- Targeted Analysis can identify 10s—100s of chemicals, but need to know what chemicals you're looking for
- Suspect Screening Analysis can identify 1000s—10000s of chemicals, need to have a library of chemicals (suspects) to match with
- Non-targeted Analysis also can identify 1000s—10000s of chemicals, but uses inherent chemical information to propose candidate chemicals



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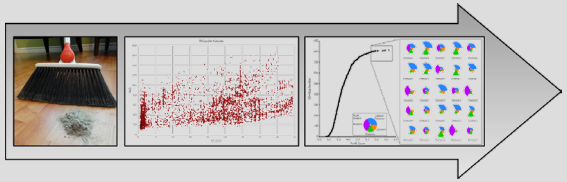
HISTORY OF NTA AT EPA



Rager et al., *Env. Int.*, 2016

Attempted to rank chemicals tentatively identified in dust for confirmation using measured abundance, detection frequency, bioactivity, and exposure.

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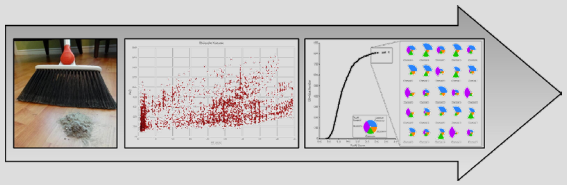
HISTORY OF NTA AT EPA

Looked at a 100 different products across 20 product categories



Rager et al., *Env. Int.*, 2016

Phillips et al., *Env. Sci. & Tech.*, 2018

Looked at a 160 different products across 5 product categories

Stanfield et al., *in preparation*

Used water filters to sample drinking water from 9 homes.

Newton et al., *Env. Poll.*, 2018

Compared chemical signature of recycled and virgin products across 7 product categories

Lowe et al., *Env. Sci. & Tech.*, 2021

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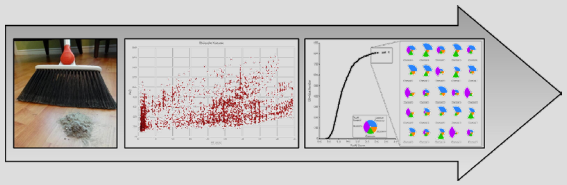
HISTORY OF NTA AT EPA

Chemical Sources and Releases



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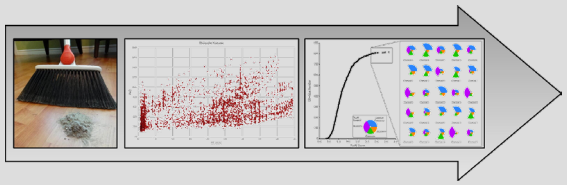

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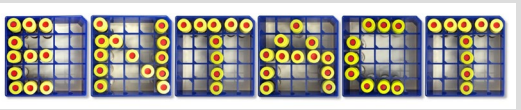
Methods Development



Ulrich et al., *Analyt. & Bioanalyt. Chem.*, 2018

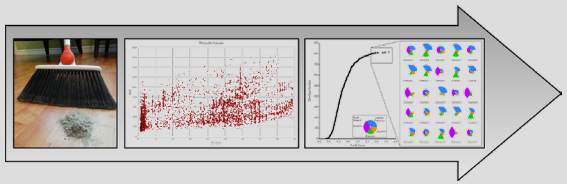
Sobus et al., *J. Expo. Sci. & Env. Epi.*, 2017

Newton et al., *Analyt. & Bioanalyt. Chem.*, 2020

EPA's Non-Targeted Analysis Collaborative Trial (ENTACT) has sought to quantify variability in NTA/SSA results from lab-to-lab

HISTORY OF NTA AT EPA

Chemical Sources and Releases



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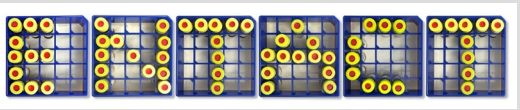

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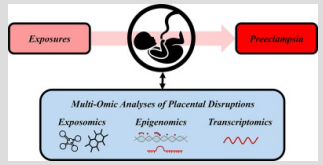
Exposure Biomarkers

Phillips et al., *Env. Sci. & Tech.*, 2024



Chao et al., *Env. Int.*, 2022

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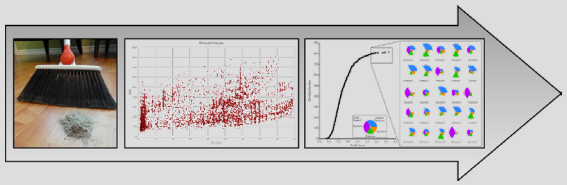

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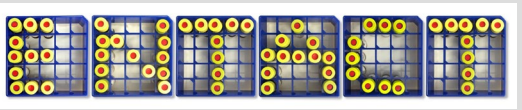

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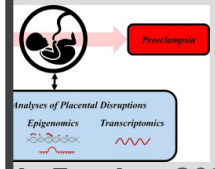

l., *Env. Int.*, 2022

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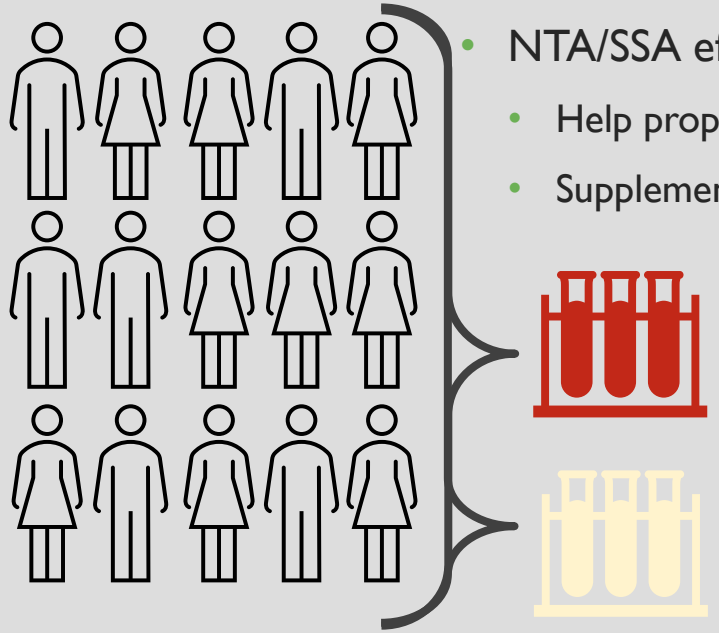
APPLICATION TO BIOMONITORING

- Biomonitoring efforts allow public health scientist to surveil different sets of chemicals to see if they occur in all, part, or none of the population
- Very specific *cohort sampling* (i.e., choosing people from a population) is performed to ensure the *specimen sample* (e.g., blood, urine, etc.) is representative of the population of interest
- However, these are mostly targeted efforts and can therefore miss many chemicals due to time and cost constraints
- NTA/SSA efforts can
  - Help propose chemicals for further inclusion in biomonitoring
  - Supplement standard biomonitoring efforts



BIOMONITORING CALIFORNIA
MEASURING CHEMICALS IN CALIFORNIANS

nhanes
The Nation's Mobile Health Survey

HBM4EU

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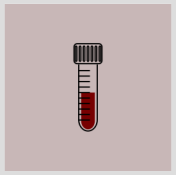
STUDY WORKFLOW

NIEHS Clinical Research Unit Specimen Bank

3500 Individuals

Convivence Sample, not Representative (like NHANES)

NIST SRM



Standard Reference Material that can be used to compare Samples against

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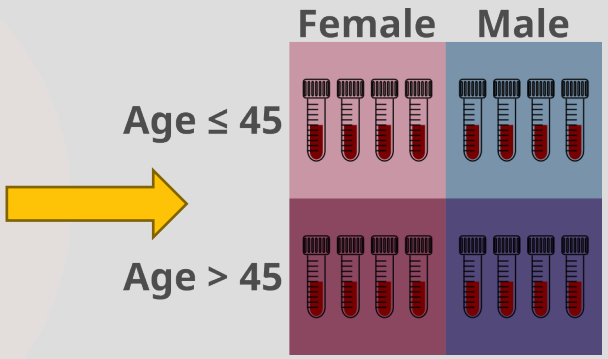
STUDY WORKFLOW

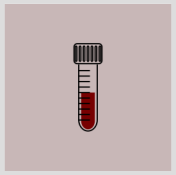
NIEHS Clinical Research Unit Specimen Bank

3500 Individuals



Pooled samples made up of 25 individual samples; stratified by age and sex.

NIST SRM



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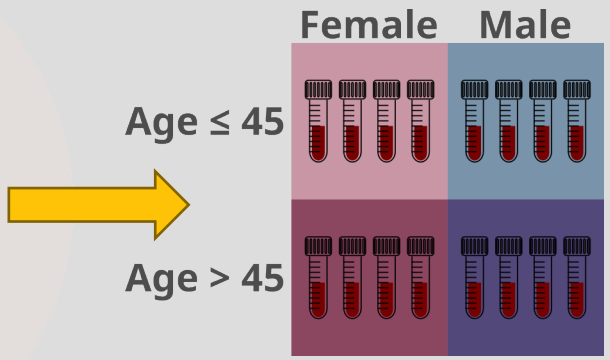
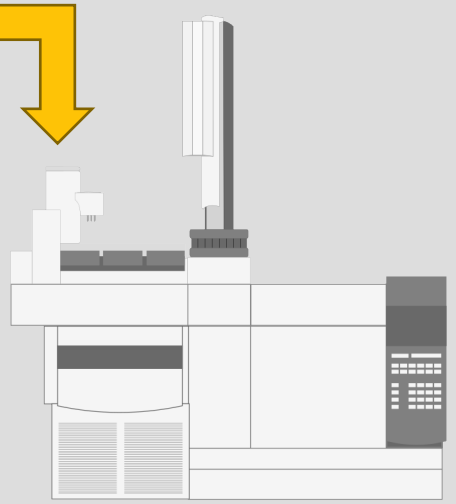
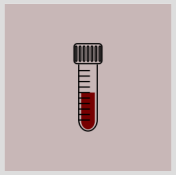




SSA: Low-resolution GC
Confirmation: High-resolution GC

NIST SRM



STUDY WORKFLOW

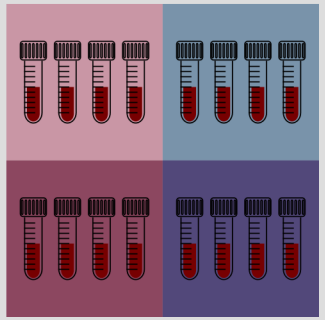
NIEHS Clinical Research Unit Specimen Bank

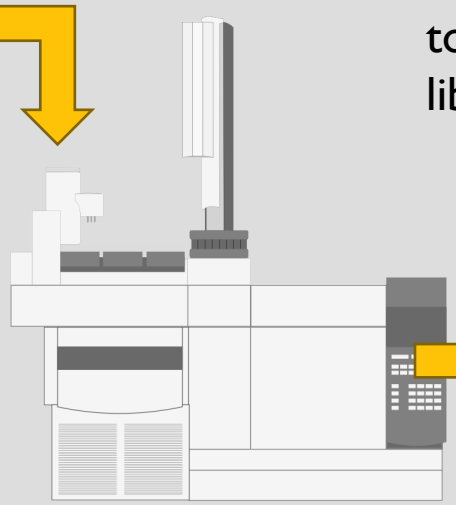
3500 Individuals

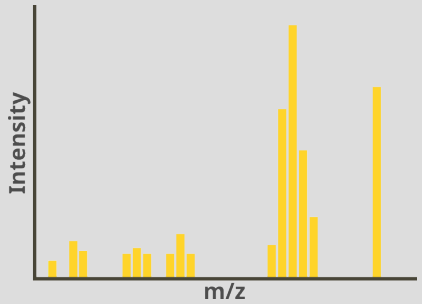
Female Male

Age ≤ 45

Age > 45



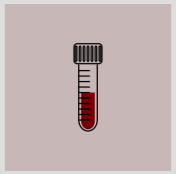




SSA: Low-resolution GC
Confirmation: High-resolution GC

Thousands of spectra that need to be matched to a chemical library and reviewed for accuracy.

NIST SRM



NIST 2014 Spectral Library was used.

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QUALITY OF SSA IDENTIFICATIONS

- Chemical Confirmation
  - Requires having a reference standard to ensure that compound truly is identified in a sample
  - Really is targeted analysis
  - We chose 11 chemicals
- Tentative Identification
  - We have manually reviewed spectra and feel some confidence that this chemical is in the sample
  - Without confirmation (timely and expensive) we can not actually say that this chemical is in the sample though
- Tentative Isomer Identification
  - We have some idea about the structure/chemical makeup of this chemical but cannot say with confidence that it is there

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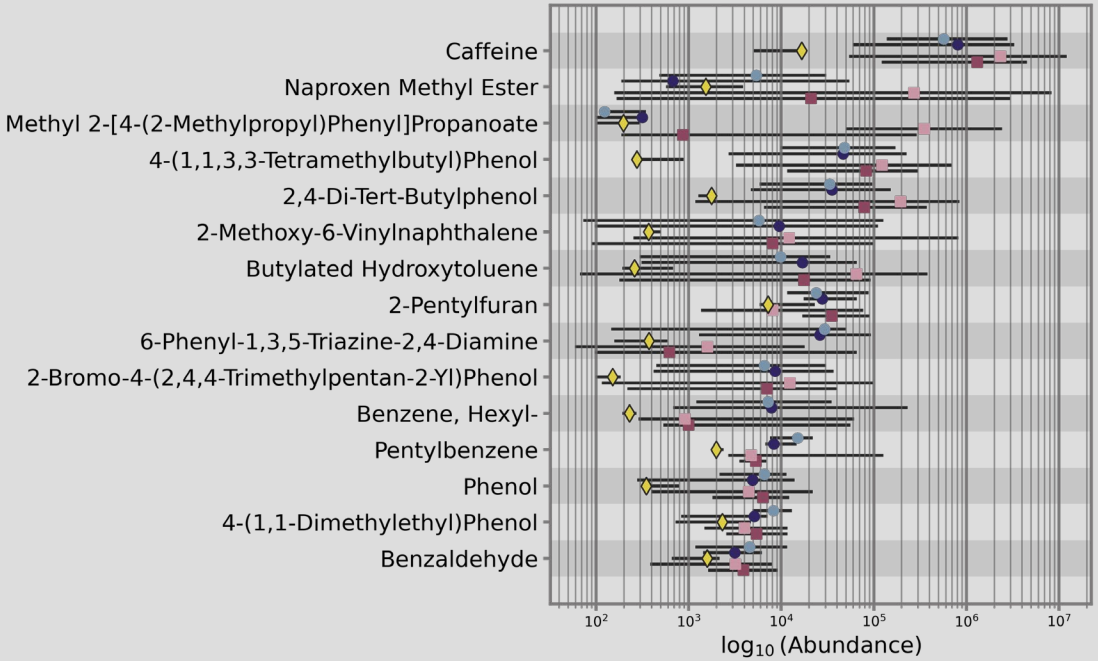
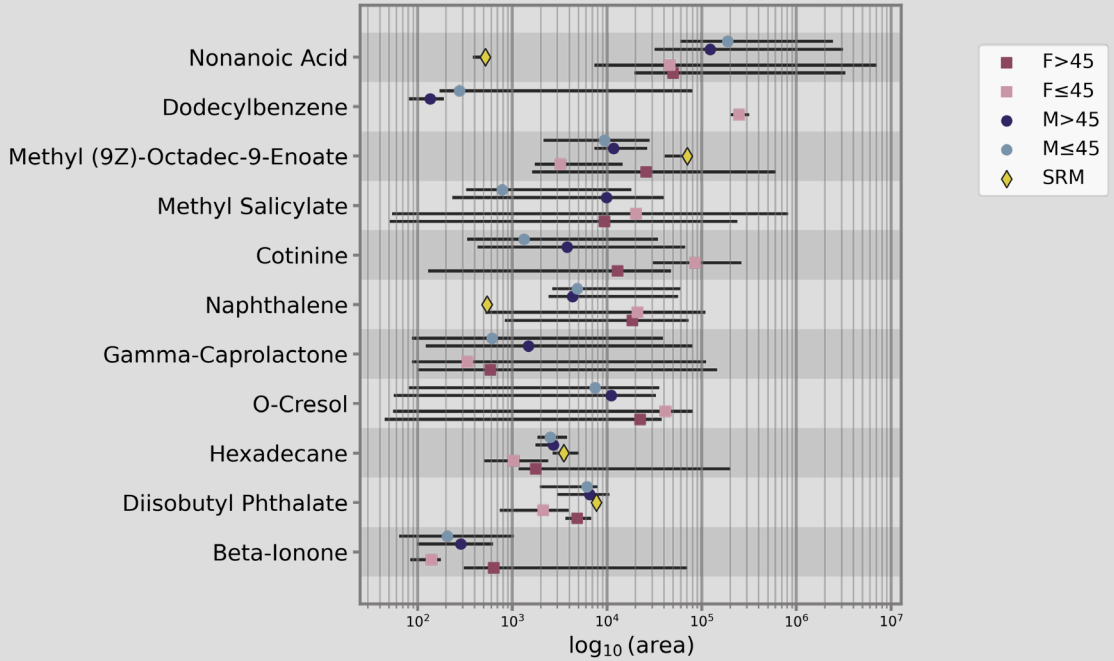
COMPARISON TO SRM VALUES

TENTATIVE



CONFIRMED



Only 5 of the 11 confirmation chemicals were found in the SRM, but all 11 were found in at least one pooled sample.

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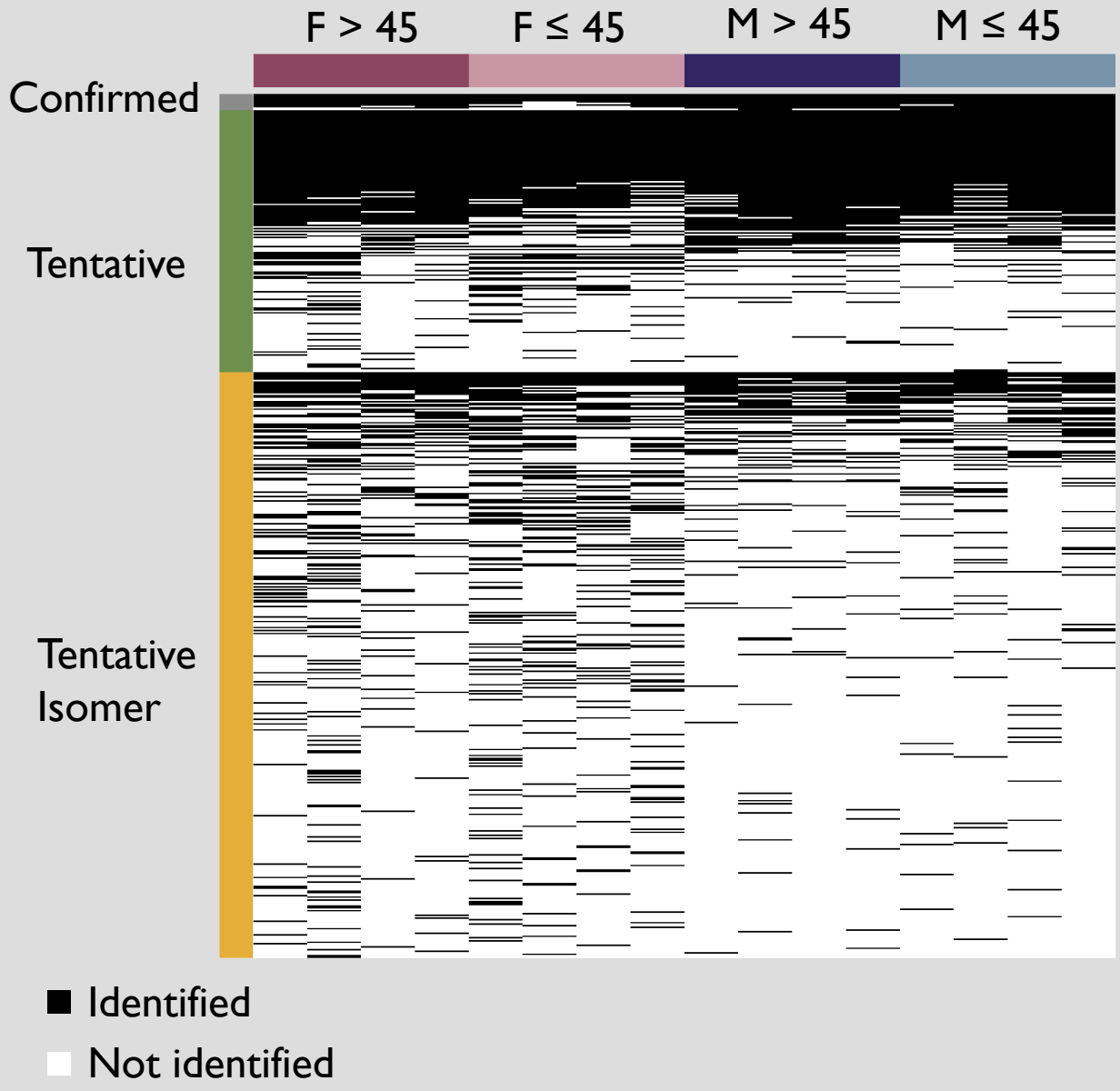
THE LAY OF THE LAND

- Heatmaps allow us to survey the identifications made across the entirety of the study
- Visually, we can see there is consistency in our identification procedure across the stratified groups for the Confirmed and Tentative Identifications
- There is less so with Tentative Isomers, which is to be expected
- Rearranging (i.e., sorting the heatmap) can provide even more interesting areas to explore



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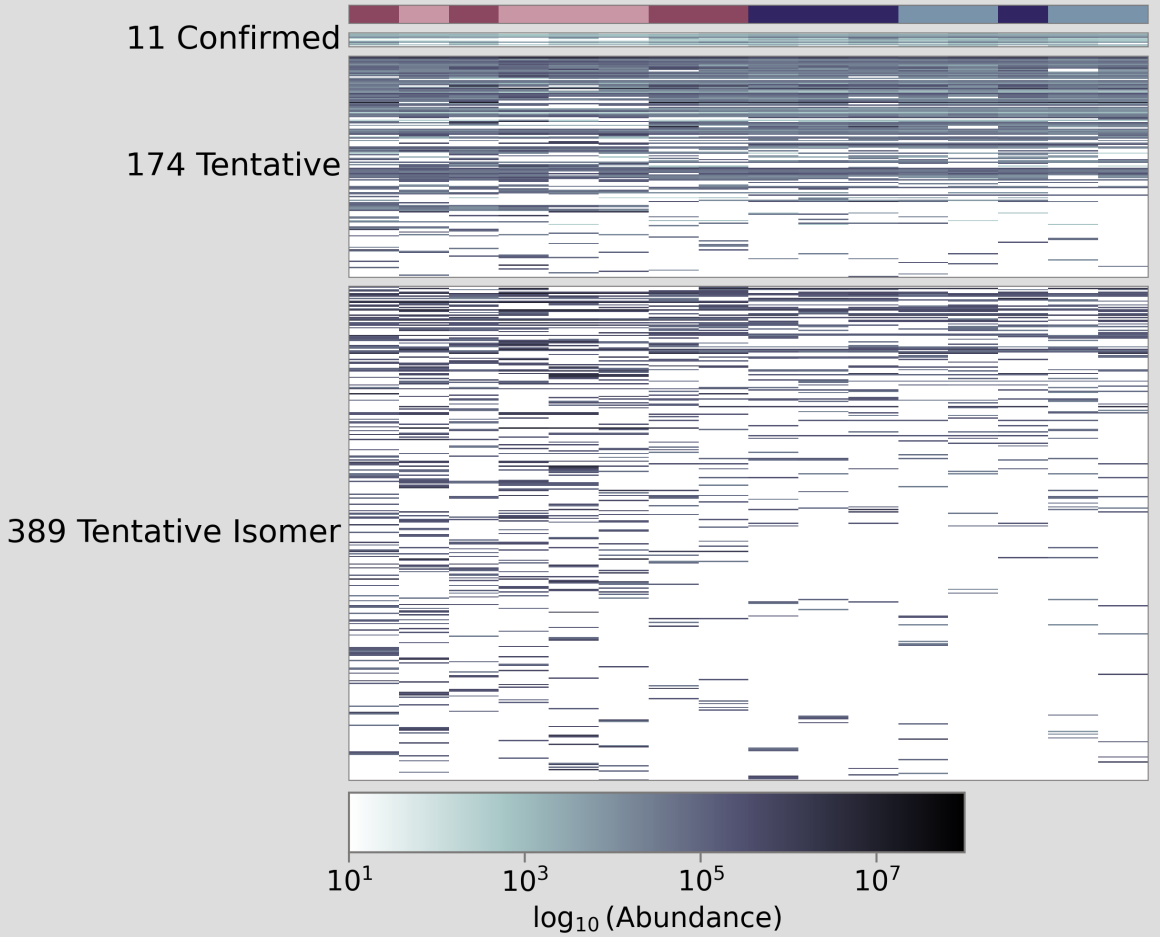
THE LAY OF THE LAND

- All spectra were matched against the NIST 2014 MS Library
  - Matches were manually reviewed for correctness
  - Matches were tagged as tentative, potentially relevant, long-chain biological, phthalates, vitamins, hydrocarbons, and sterols
- 544 total IDs were made, but some the same substance could have been identified at the Confirmed, Tentative, and/or Tentative Isomer levels



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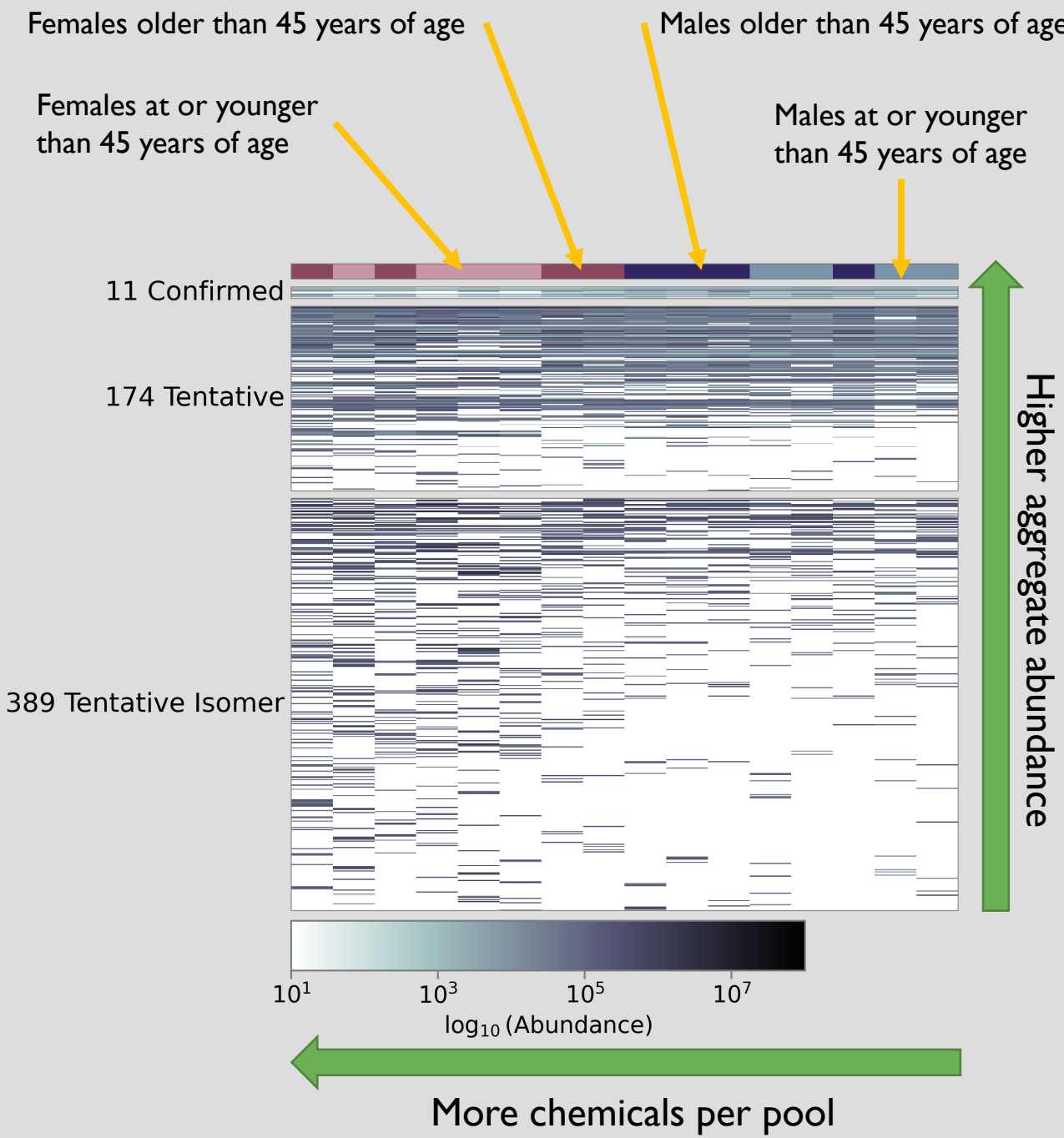

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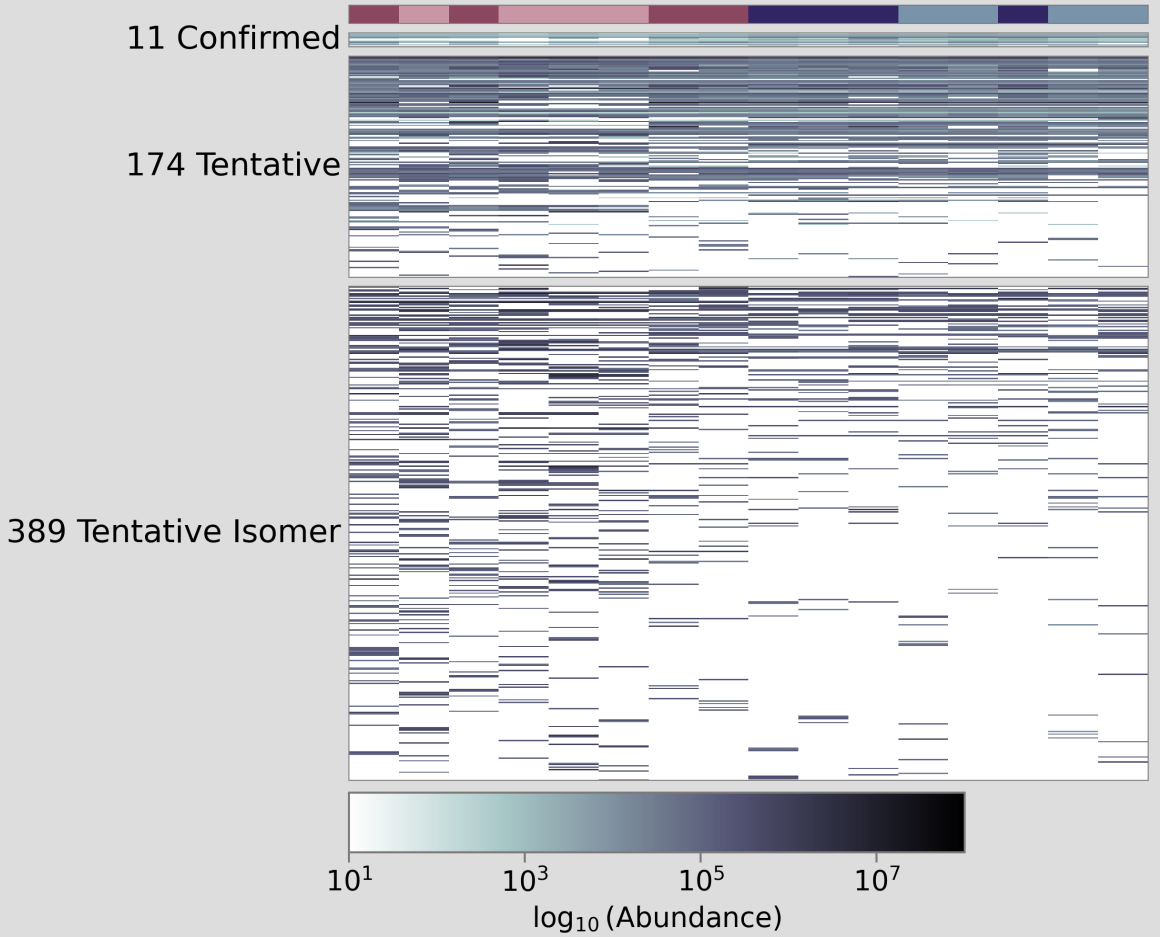
How can we begin to link compounds to sources/releases via "Exposure Forensics"?



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EXISTING DATABASES

HUMAN METABOLOME DATABASE

- "Database containing detailed information about small molecule metabolites found in the human body" -- https://hmdb.ca/
- Collection is literature derived and curated to include molecules <1500 Da and concentrations higher than >1µM

BLOOD EXPOSOME DATABASE

- "Catalogue of chemicals (endogenous and exogenous) that are expected and detected in human blood specimens" -- https://bloodexposome.org/
- Collection of chemicals that were associated with blood via text mining approaches

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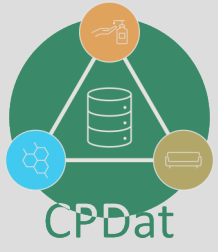
While useful, neither database provides a direct way to tie chemicals/metabolites in the database to an exposure source.

ANNOTATED DATA SOURCES



CompTox Chemicals Dashboard v2.3.0

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Inxight Drugs

Retired in Jan. 2021

- CPDat provides information on chemicals in consumer products and industrial processes and annotates them to various types of uses
- MMDB annotates chemical substances to various environmental, ecological, and biological media in which they have been identified
- CompTox Chemicals Dashboard provides many lists that link chemicals to pharmaceuticals, environmental clean up sites, etc.

- Inxight is based of FDA's Global Substance Registration System (GSRS) and provides chemicals that are associated with pharmaceutical uses in the US
- Pillbox contained information on both active and inactive ingredients contained in over-the-counter and prescription drugs available in the U.S.

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SUBSTANCE SOURCE TYPES

CompTox Chemicals Dashboard v2.3.0

NIH National Center for Advancing Translational Sciences

Inxight Drugs

CPDat

MMDB

Pillbox @NIH

- Annotated to different Substance Source Types (SSTs), or sources from which a substance could originate:
  - Endogenous
  - Food/Nutrient
  - Drug
  - Commerce
  - Contaminant
- Substances can be annotated to multiple SSTs

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QUICK ASIDE

Ways to view categorical data

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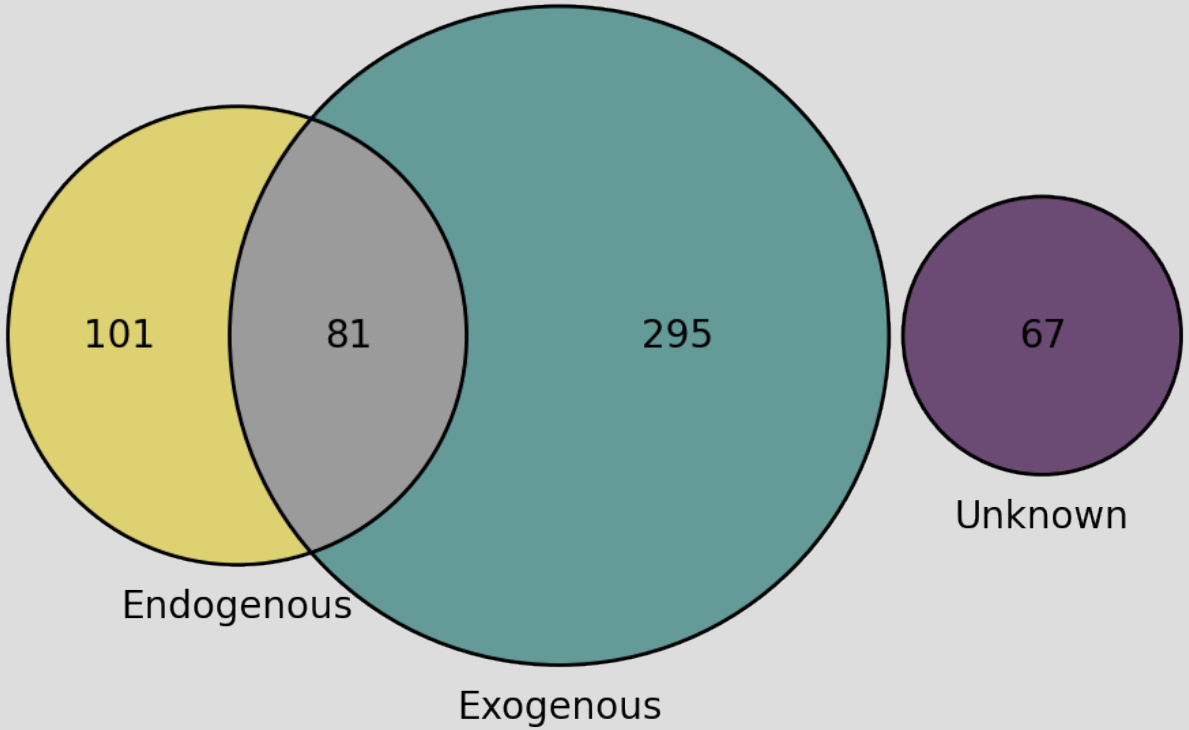
CATEGORICAL DATA

- Venn Diagrams are used to view overlap and quantities of categorical data (sets).
- If we were only looking at 3 sets, Venn Diagrams are great.
- They can easily show the size of one set to others and the proportional amount of overlap between sets.



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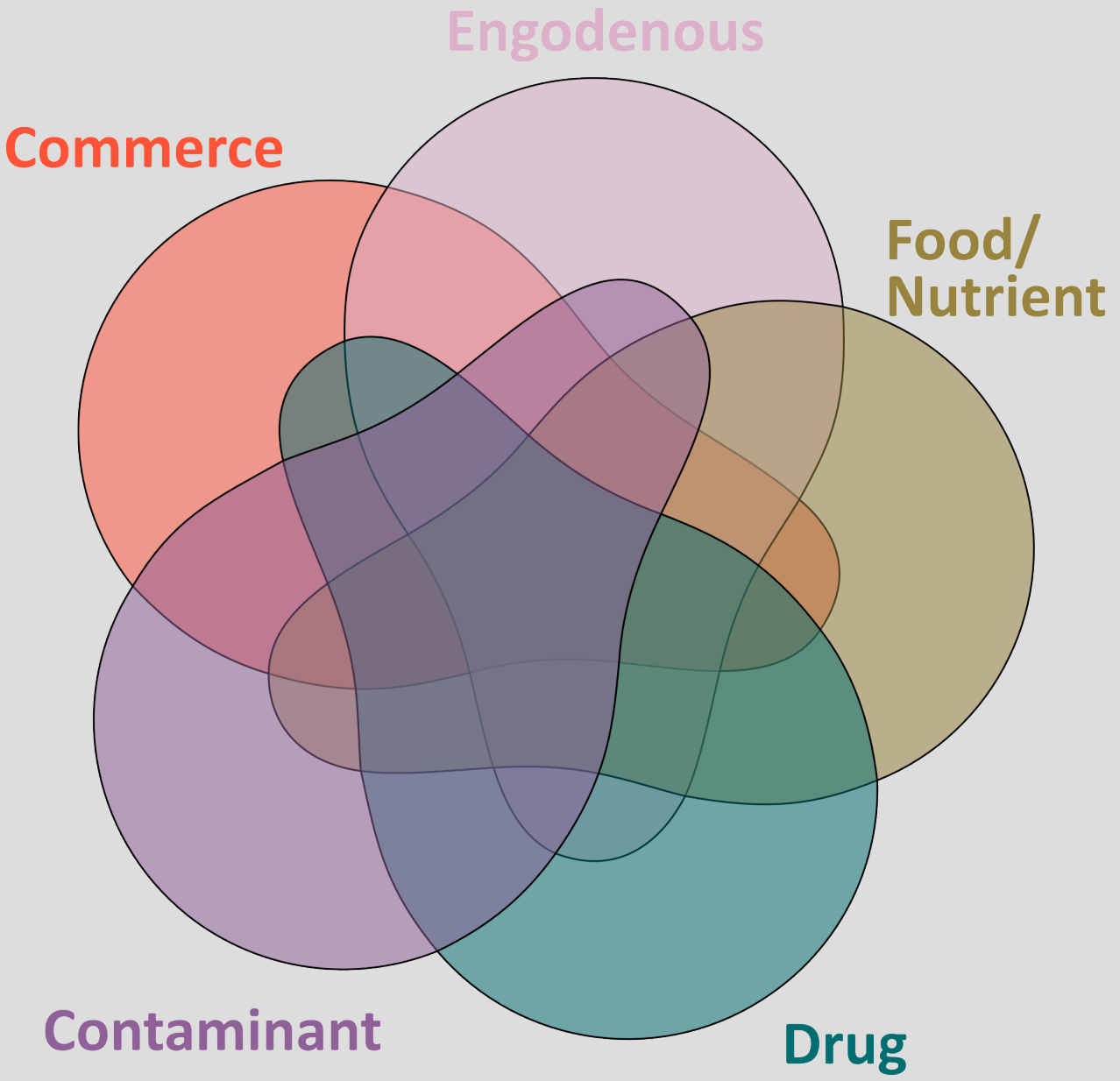
- If we were only looking at 3 sets, Venn Diagrams are great.
- They can easily show the size of one set to others and the proportional amount of overlap between sets.
- For more than 4 categories Venn Diagrams become very difficult to interpret and can no longer show adequate proportions between sets and their overlaps.



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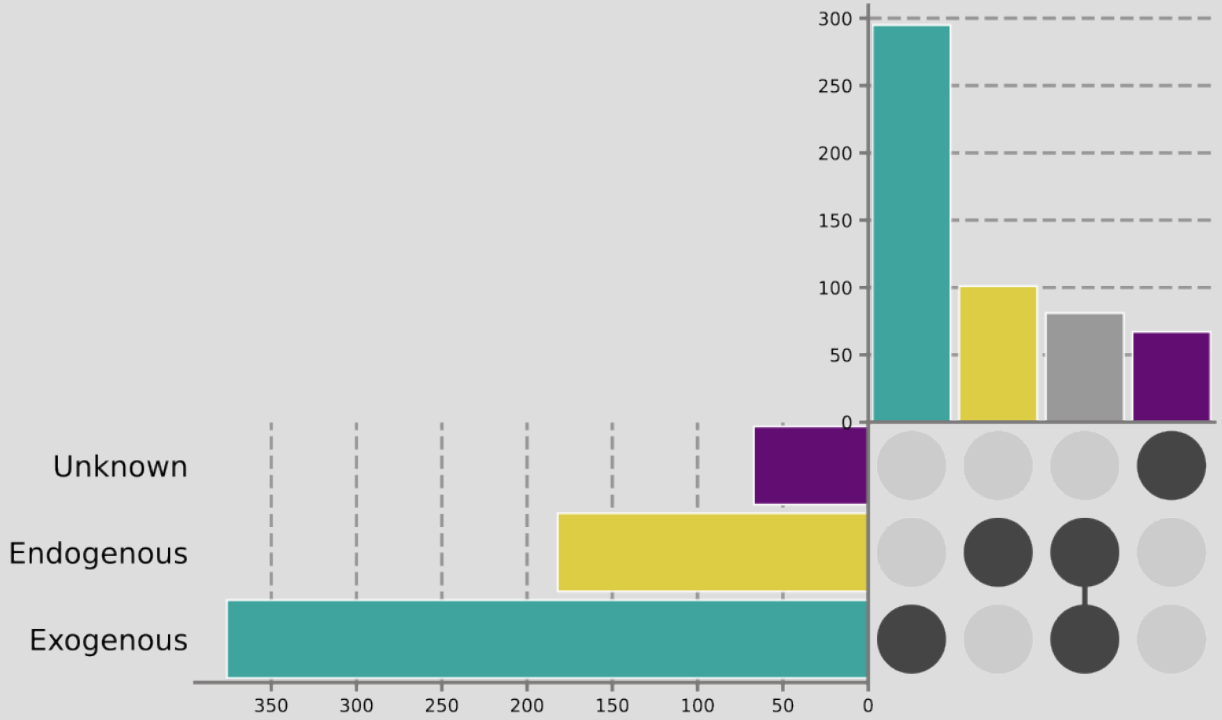
UPSET PLOTS

- UpSet plots provide a cleaner way of looking at categorical data, with more than 4 categories.
- Developed by Alexander Lex and others at Harvard in 2014 (doi:10.1109/TVCG.2014.2346248)



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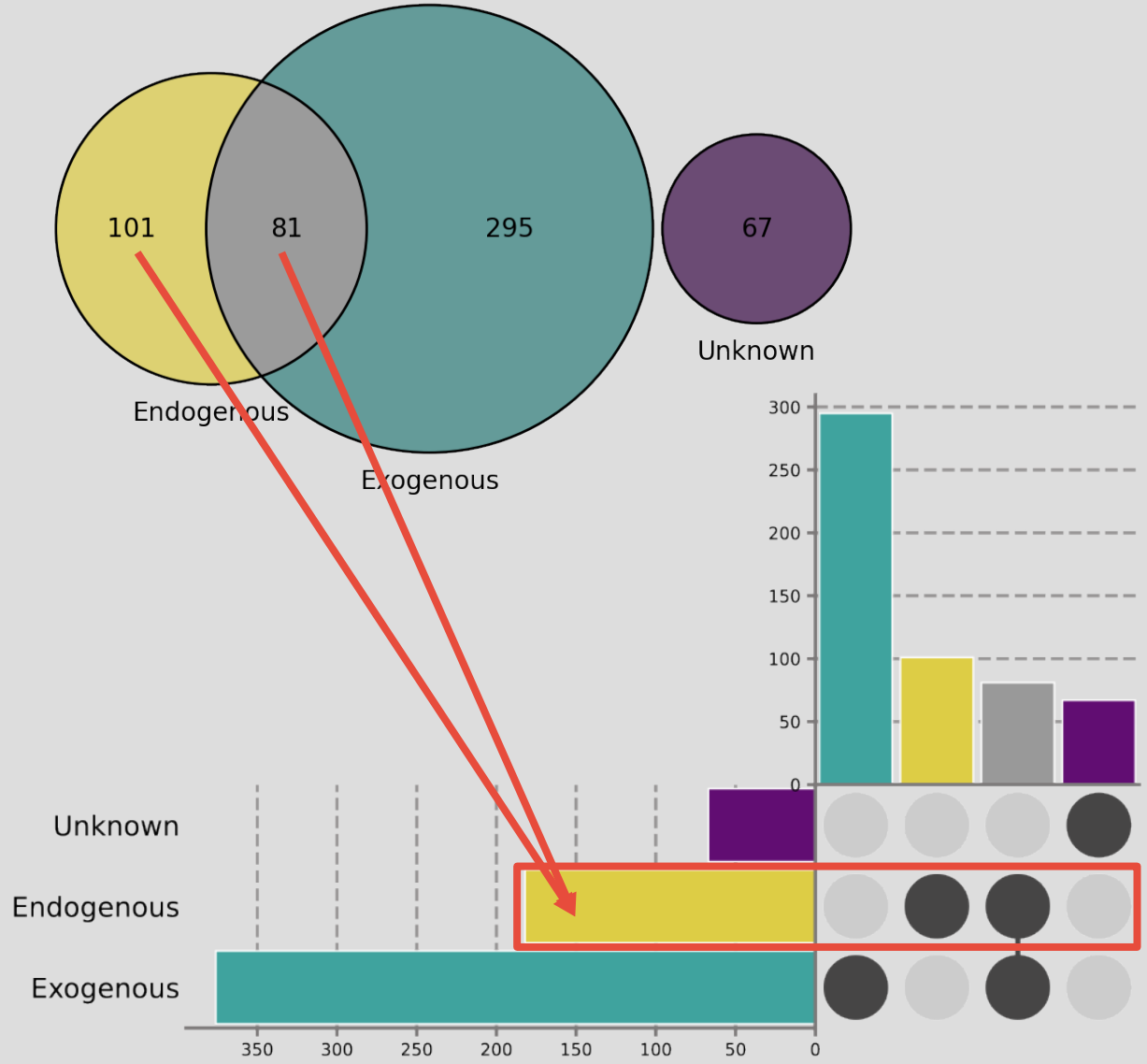
UPSET PLOTS

- One set of axes shows the total number of items belong to each category (set)



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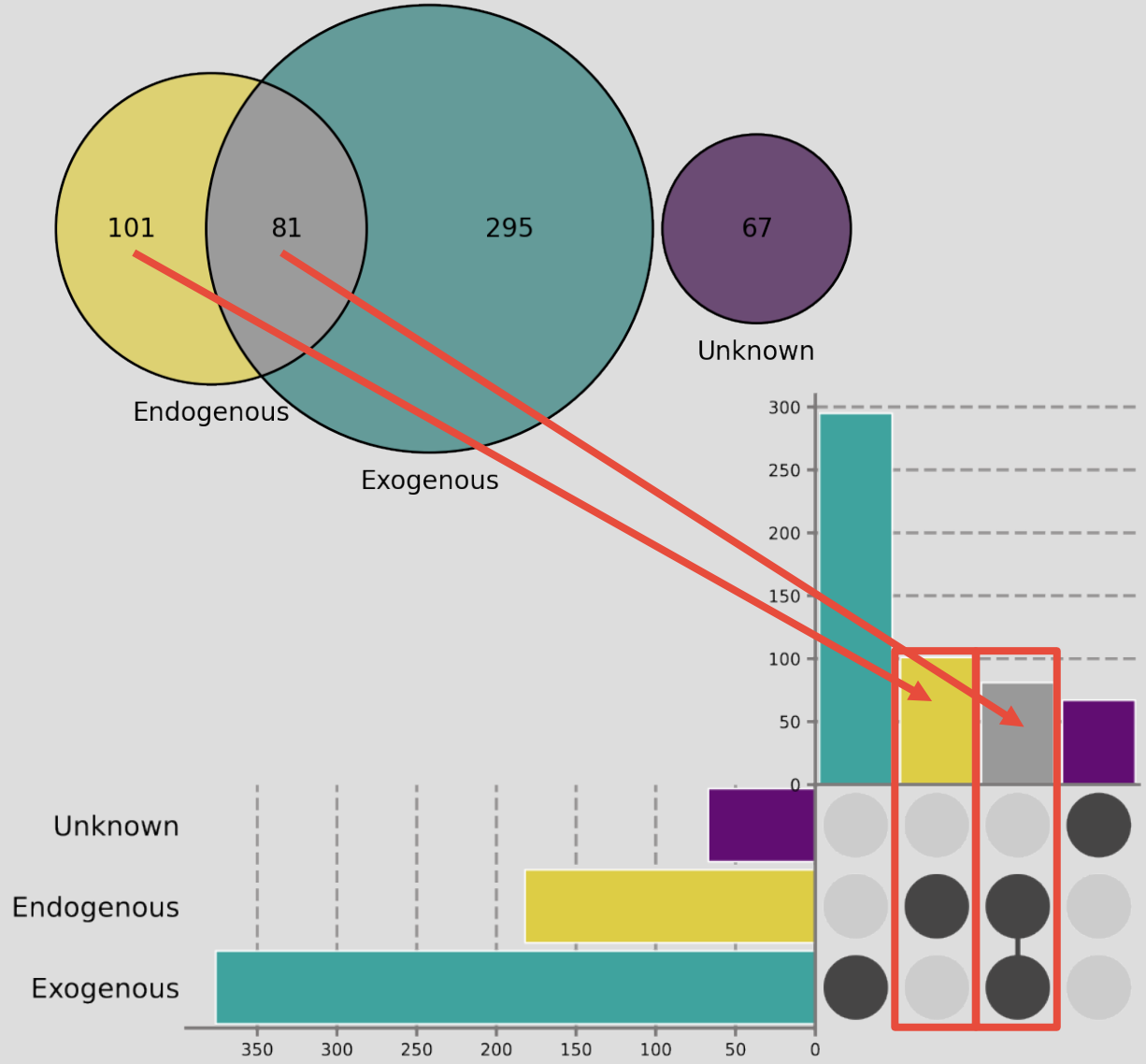
UPSET PLOTS

- One set of axes shows the total number of items belong to each category (set)
- Another set of axes shows the number of items that overlap between sets (unions) and then number of items that do not overlap



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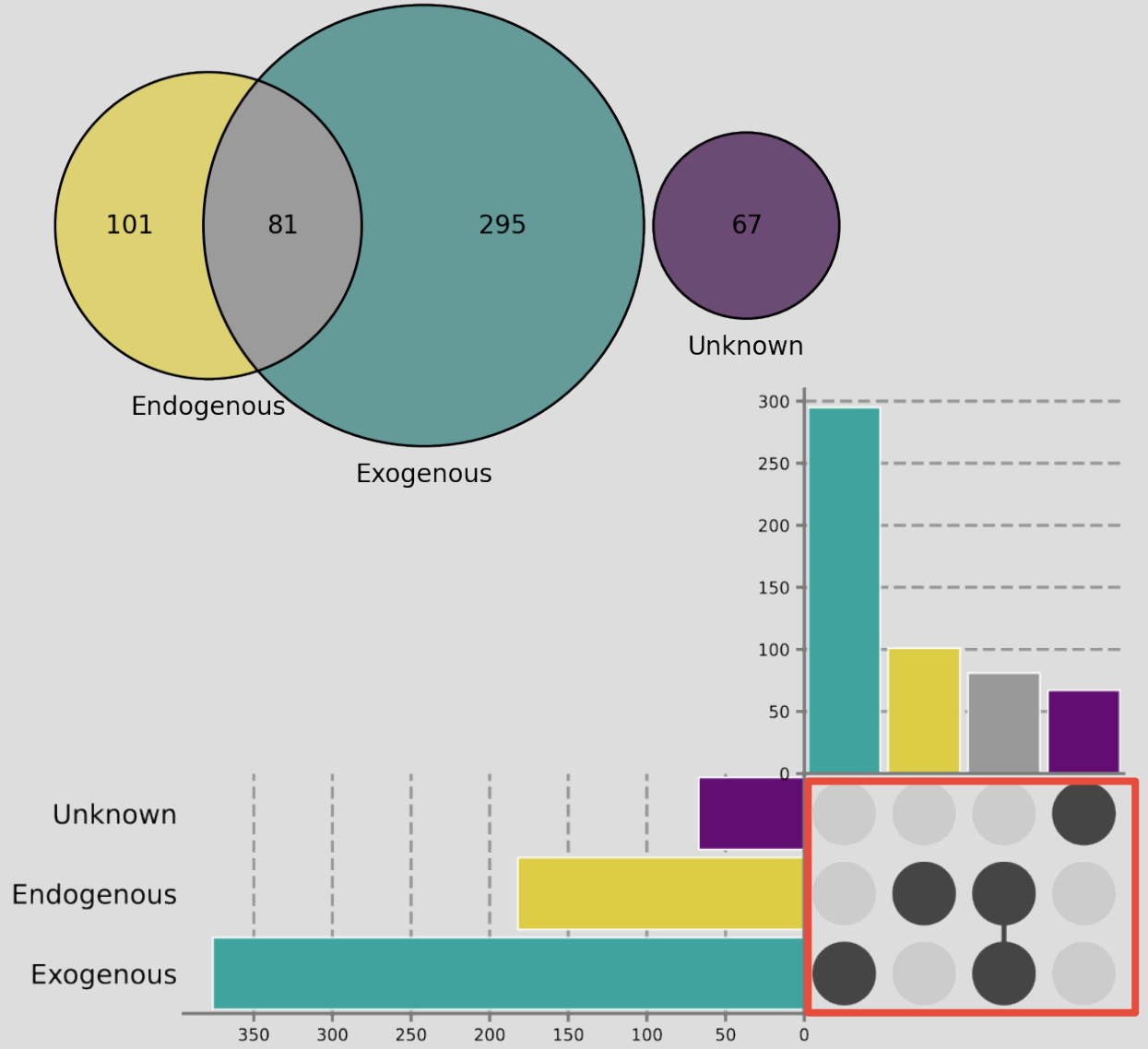

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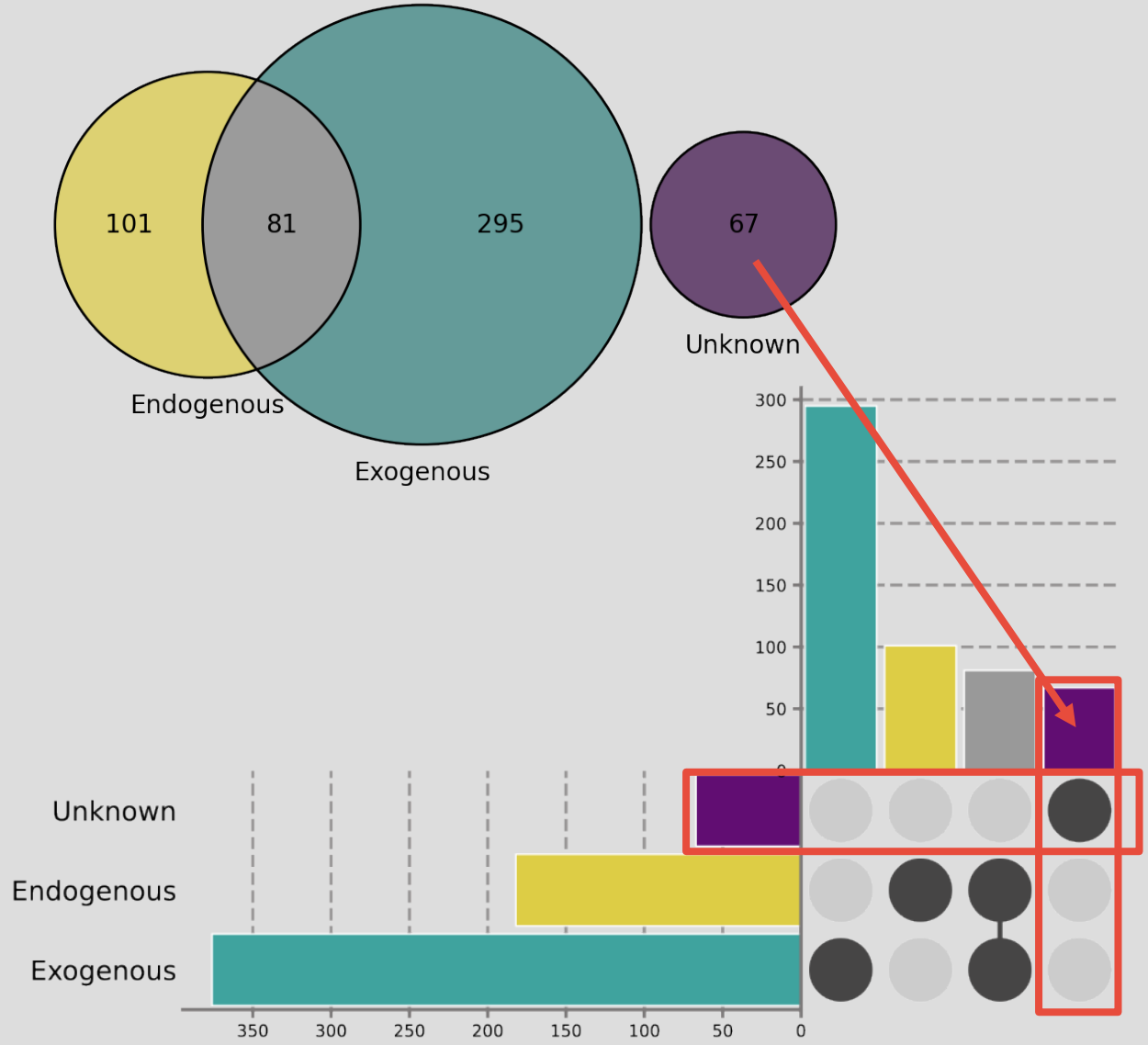
- Another set of axes shows the number of items that overlap between sets (unions) and then number of items that do not overlap
- Filled circles show which categories belong to a union, lines connect multiple categories within a union
- Categories with no connections can be show too



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BACK TO BUSINESS

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SOURCE SUBSTANCE TYPES

- Annotated to different types of sources from which a substance could originate:
  - Endogenous
  - Food/Nutrient
  - Drug
  - Commerce
  - Contaminant
- Substances can be annotated to multiple SSAs

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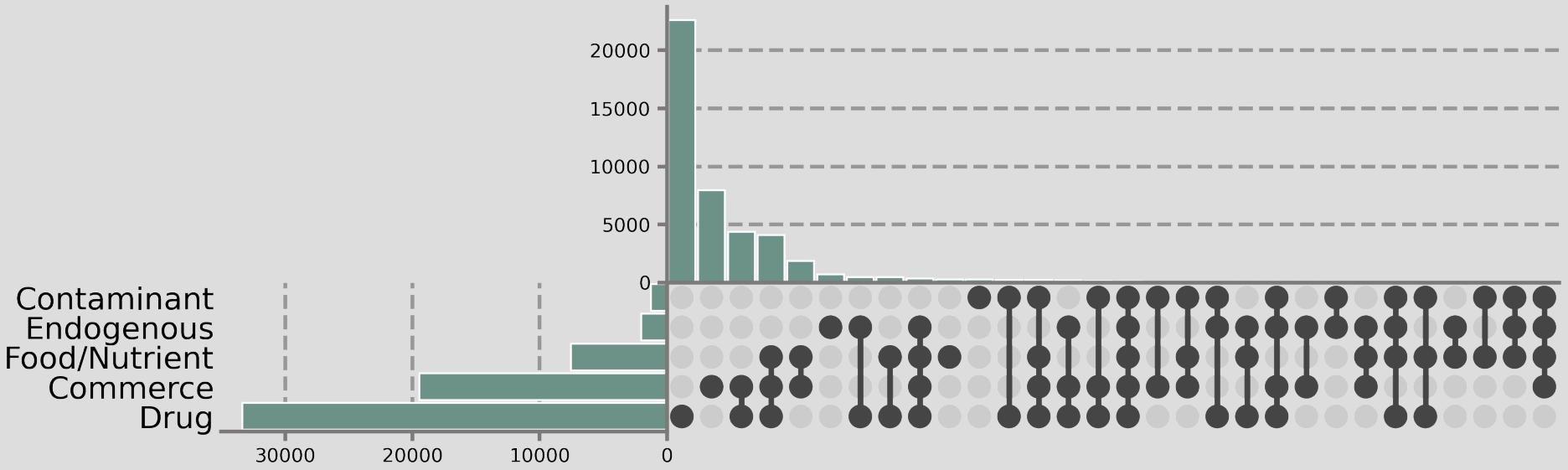
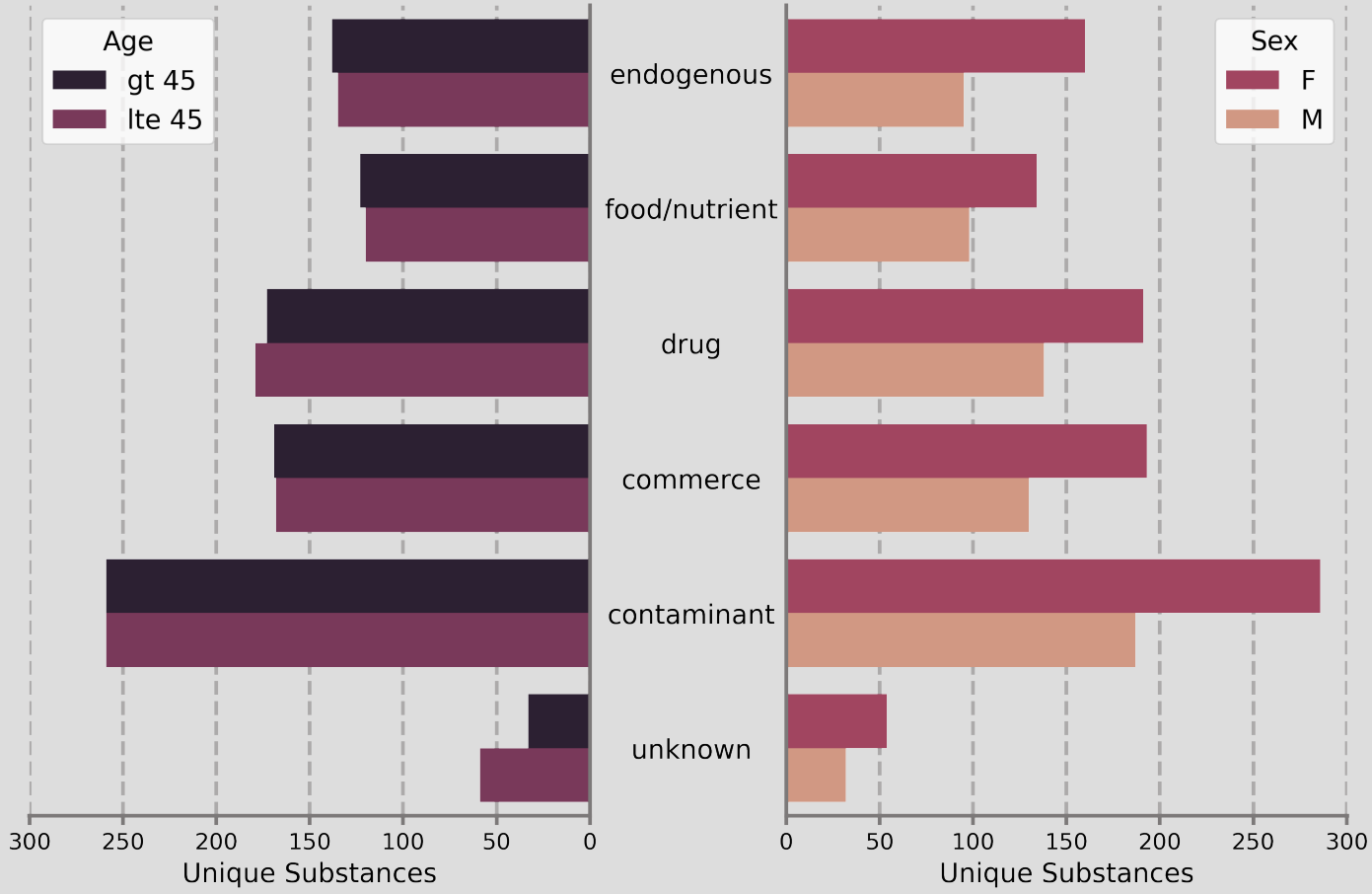
SOURCE SUBSTANCE TYPES



- +44k substances were collected and annotated to source substance types (SSTs)
- Many more substances were annotated to "Drug" and "Commerce"
- Most substances could be annotated to at least on SST, but 67 were not found in any of our data sources

SOURCE SUBSTANCE TYPES FOR IDENTIFIED SUBSTANCES

- Grouping identified substances by source substance annotations, we still see that there are more chemicals in females for all categories
- Not enough of a difference with ages to be too noticeable



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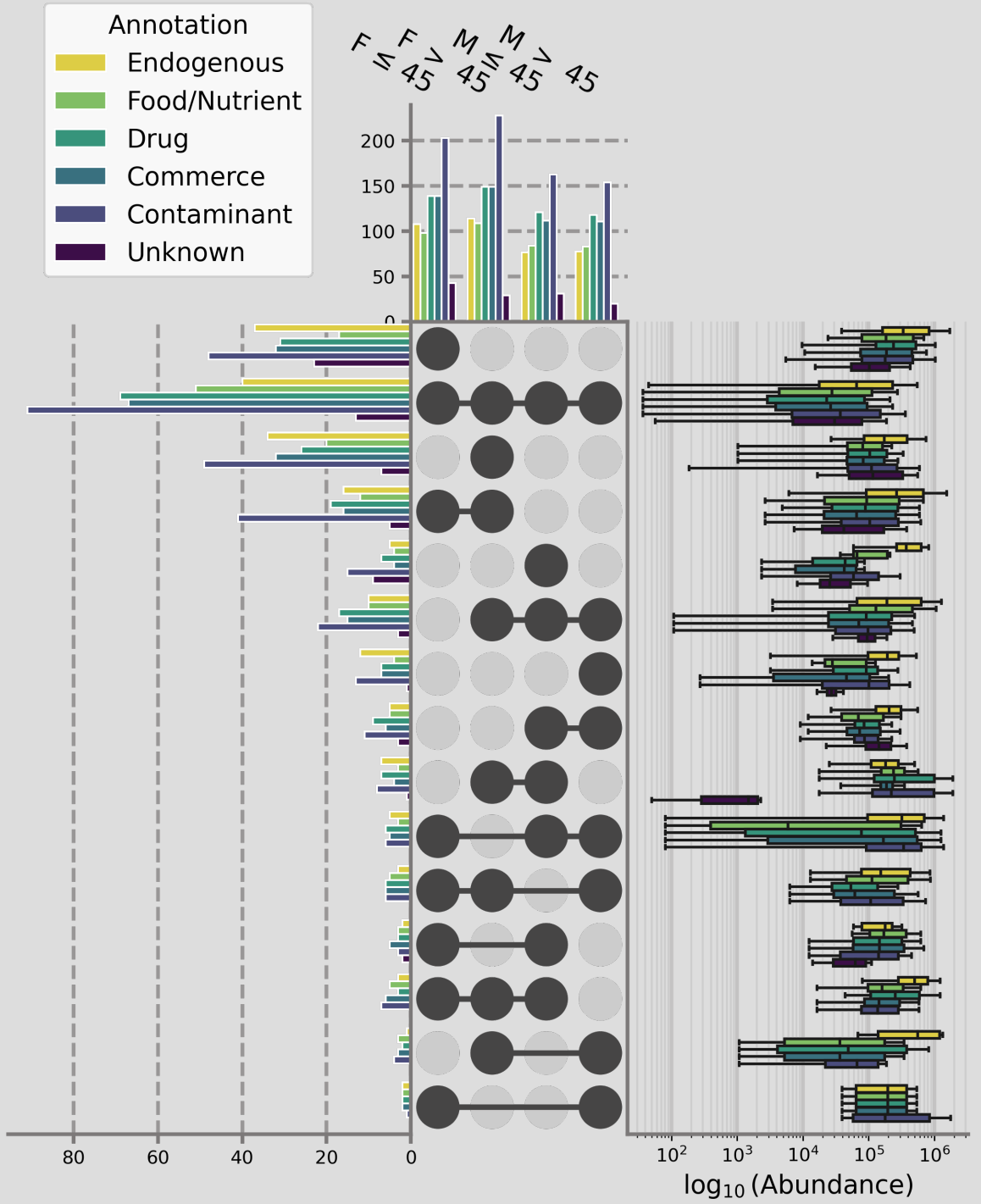
STRATIFICATION ACROSS POOLS

- Women at or younger than age 45 had most chemicals, and more chemicals unique to their demographic
- Women older than 45 were close behind
- Even the intersection of chemicals unique to all women had more chemicals than the younger men
- That said, we se pretty high numbers of endogenous, food, and drug



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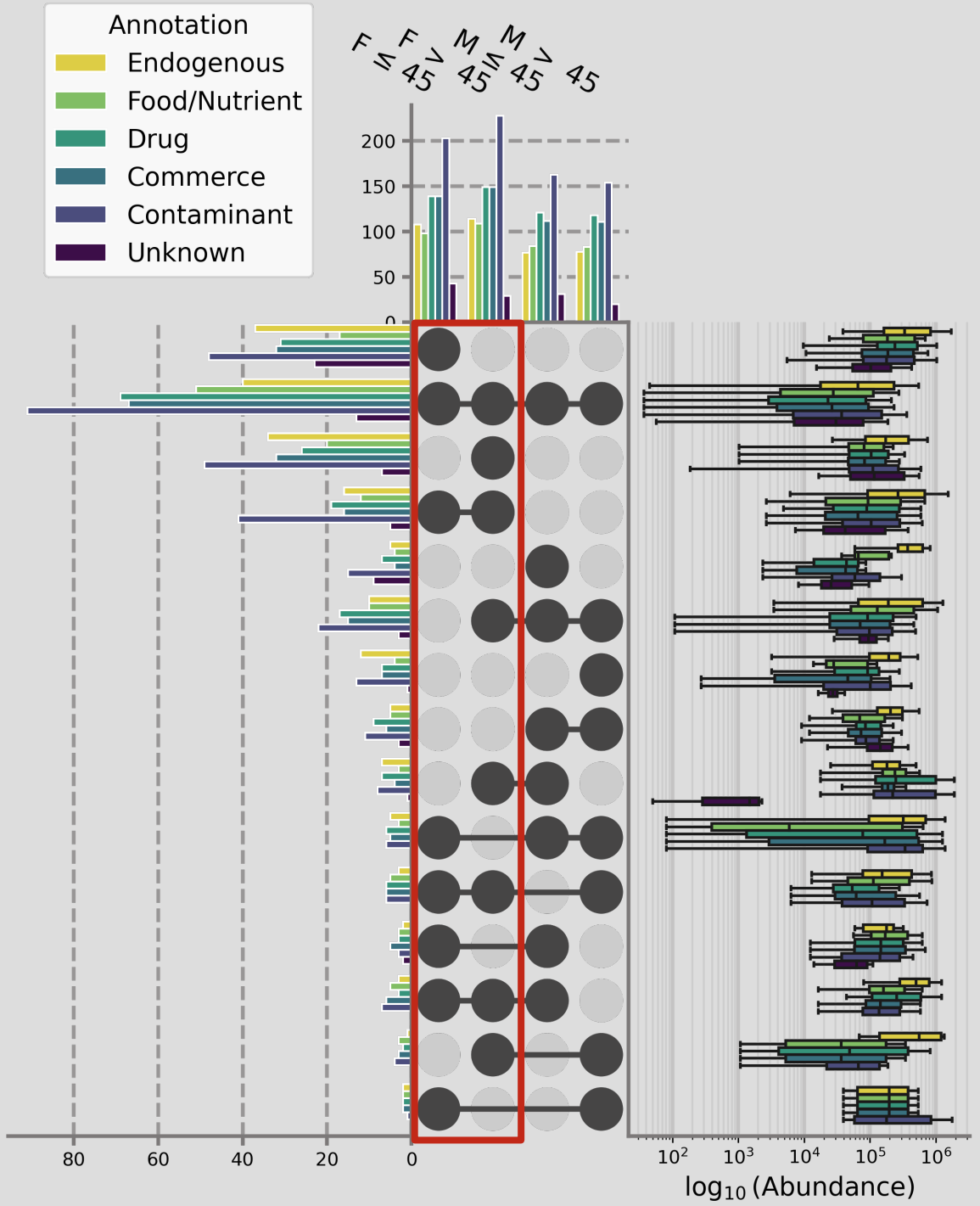

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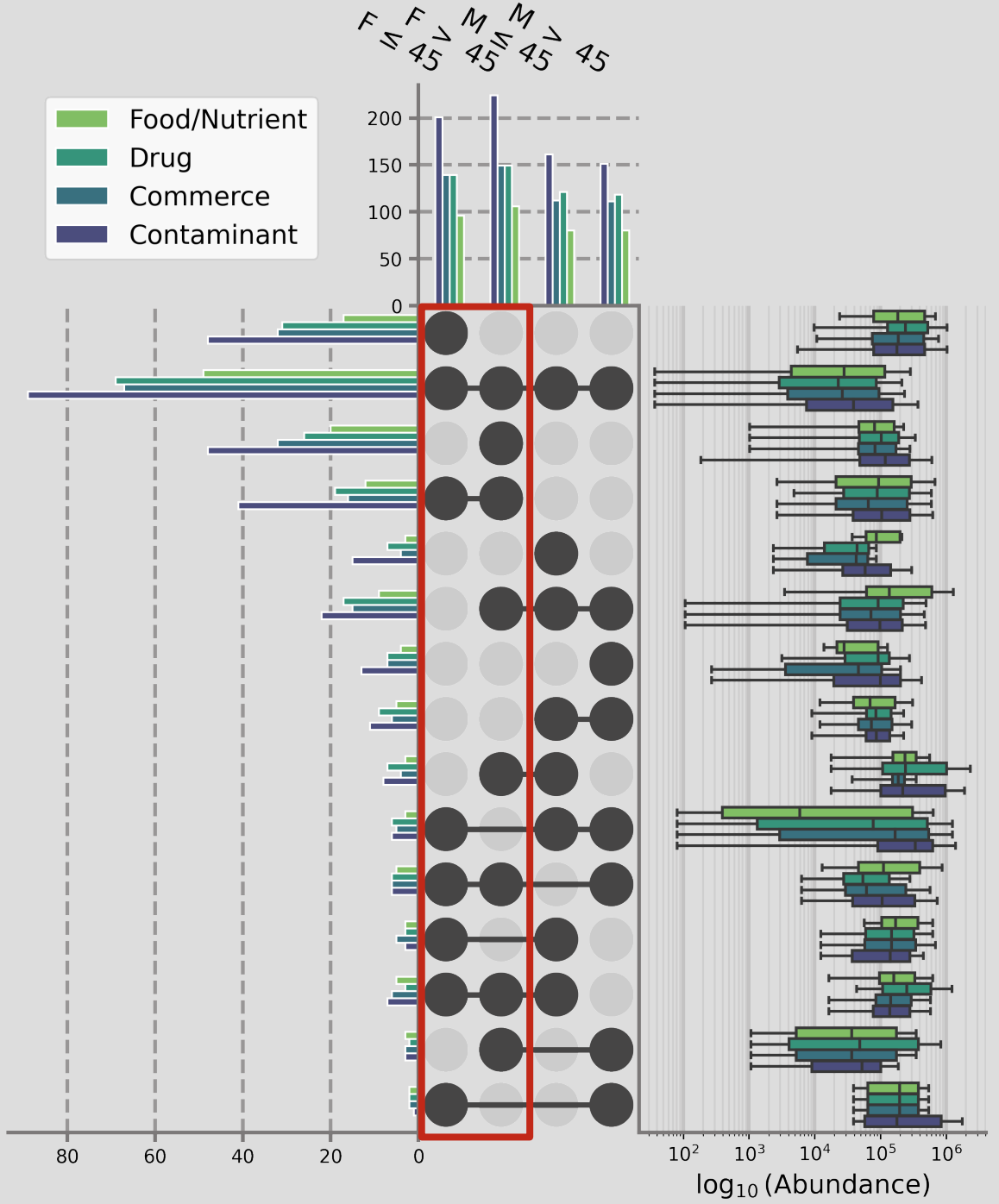
- That said, we se pretty high numbers of endogenous, food, and drug
- Subtracting out all substances that were annotated to "Endogenous" or were "Unknown" shows higher "Contaminants" typically



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STRATIFICATION ACROSS

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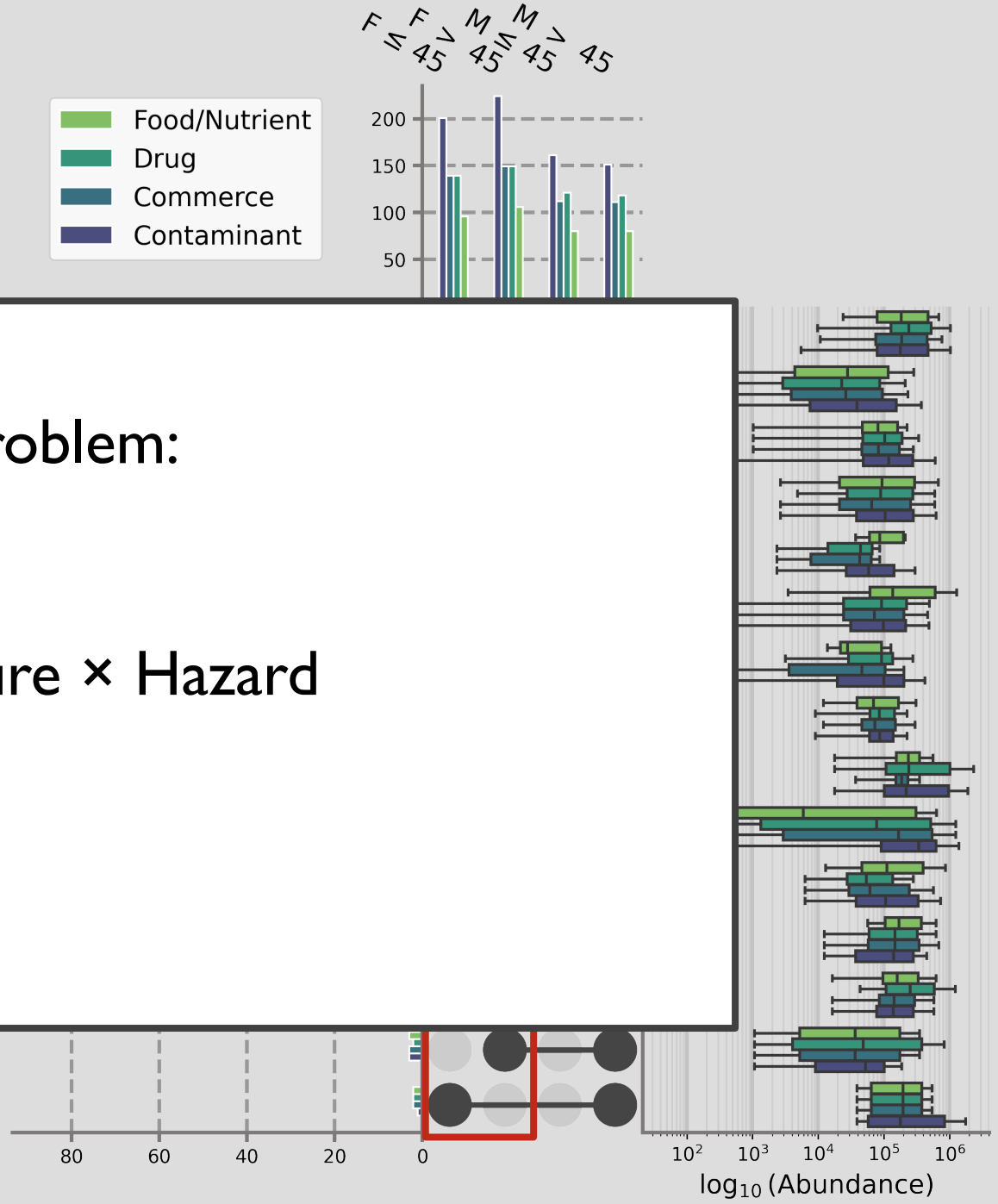
Exposure is only half of the problem:

Risk = Exposure × Hazard



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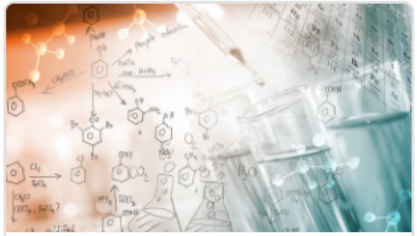
COMPTOX TOOLS

- EPA's Center for Computational Toxicology and Exposure provides many tools to the public that may be useful for assessing risk to chemicals

ChemExpo Knowledgebase

The Chemical Exposure Knowledgebase (ChemExpo) is an interactive tool for exploring and searching information on how chemicals are used in commerce and in consumer products.

ChemExpo Resource Hub



Cheminformatics Modules

Cheminformatics analysis modules provide high-quality chemical structures, experimental and predicted physicochemical properties, environmental fate and transport information, and linked toxicity data.

Cheminformatics Resource Hub

CompTox Chemicals Dashboard

The CompTox Chemicals Dashboard provides publicly-accessible chemistry, toxicity, and exposure information for over one million chemicals. This information includes physicochemical data, hazard data, and much more.

CompTox Chemicals Dashboard Resource Hub

GenRA Tool

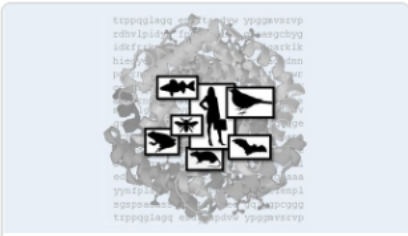
The Generalized Read-Across (GenRA) tool is an algorithmic approach to permit objective and reproducible read-across predictions of *in vivo* toxicity and *in vitro* bioactivity.

GenRA Resource Hub

ECOTOX Knowledgebase

The Ecotoxicology (ECOTOX) Knowledgebase is a comprehensive database providing information on adverse effects of single chemical stressors to ecologically relevant aquatic and terrestrial species.

ECOTOX Resource Hub



SeqAPASS Tool

The Sequence Alignment to Predict Across Species Susceptibility (SeqAPASS) tool is a fast, online screening tool that allows researchers and regulators to extrapolate toxicity information across species.

SeqAPASS Resource Hub

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COMPTOX TOOLS

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- The Cheminformatics Modules provides a way to access contextualized hazard profiles for chemicals via the Hazard Comparison Tool

https://www.epa.gov/comptox-tools/cheminformatics

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HAZARD PROFILES

- Obtained Human Health Effects hazard profiles for 535 (out of 544) substances identified in the study
- Only kept substances that had at least one hazard value of "Medium", "High", or "Very High"
- Left 441 substance for analysis

The Hazard Comparison Dashboard is a prototype tool and a compilation of information sourced from many sites, databases and sources including U.S. Federal and state sources and international bodies that saves the user time by providing information in one location. The data are not reviewed by USEPA – the user must apply judgment in use of the information. The results do not indicate EPA's position on the use or regulation of these chemicals.

			VH - Very High	H - High	M - Medium	L - Low	I - Inconclusive	No Data	Authoritative	Screening	*QSAR Model*
			Human Health Effects							Ecotoxicity	Fate
			Acute Mammalian Toxicity				Neurotoxicity	Systemic Toxicity			
DTXSID	CAS	Name	Oral	Inhalation	Dermal	Carcinogenicity	Genotoxicity Mutagenicity	Endocrine Disruption	Reproductive	Developmental	Repeat Exposure	Single Exposure	Repeat Exposure	Single Exposure	Skin Sensitization	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Exposure
DTXSID5025607	93-15-2	1,2-Dimethoxy-4-(2-propen-1-yl)b	M	I	L	VH	VH		I	I			M		I	L	M	H		*M*	L	*H*
DTXSID3022455	131-11-3	Dimethyl phthalate	L	H	L	I	L	H	L	L	I		I	M	I	L	H	M	M	*M*	L	*M*
DTXSID7021780	84-66-2	Diethyl phthalate	M	H	L	I	L	H	H	M	L		H	M	H	H	M	M	M	*M*	M	*H*
DTXSID4021268	122-34-9	Simazine	M	H	L	VH	L	H	H	H	H		H	M	I	H	H	VH	VH	*H*	L	*M*
DTXSID6024204	21087-64-9	Metribuzin	M	I	M	I	L	H	H	H	I	I	H	I	L	L	L	VH	VH		L	*M*
DTXSID2021781	84-74-2	Dibutyl 1,2-benzenedicarboxylate	L	H	L	H	L	H	H	H			L	M	H	L	H	VH	H	*L*	M	*M*
DTXSID5032498	3380-34-5	Triclosan	L	VH	L	I	VH	H	M	M	H	I	M	I	I	H	H	VH	VH	*H*	L	*M*
DTXSID3024102	22224-92-6	Fenamiphos	VH	VH	VH	L	L		H	H	H	H	H		L	L	H	VH	VH			*M*
DTXSID7020182	80-05-7	Bisphenol A	L	L	L	I	L	H	H	H			M	M	H	L	VH	H	VH	*M*	L	*H*
DTXSID0023951	5234-68-4	Carboxin	M	I	M	L			H	M			H				H	H	H			*H*
DTXSID9020453	60-57-1	Dieldrin	VH	VH	VH	VH	VH	H	H	H	H	H	H		I	VH	VH	VH	VH		VH	*L*
DTXSID6020561	72-20-8	Endrin	VH	I	H	I	L	H	H	H	H	H	H	H	I	L	I	VH	VH		VH	*L*
DTXSID6022345	789-02-6	o,p'-DDT	*I*				*L*	H	H	H					*H*	*H*		*VH*	VH		VH	*L*
DTXSID7020895	2385-85-5	Mirex	H	I	M	VH	L	H	M	H	H	H	H	H	I	H	I	VH	VH		VH	*L*
DTXSID1021956	117-84-0	Di-n-octyl phthalate	L	I	L	I	*VH*	H	H	M	I	I	M	I	I	L	L	H		*M*	VH	*M*
DTXSID001016032	822-73-1	Bicyclo[2.2.1]hept-2-ene, 1-methy	*L*				*I*	*L*		*H*								*M*			*M*	
DTXSID001016101	19893-77-7	Camphorlactone	*L*				*L*	*L*		*H*								*M*			*I*	
DTXSID001016137	NOCAS_1016137	2,2,3,3,4,4,4-Heptafluorobutyl 9-o	*I*				*L*	*I*		*H*								*L*			*L*	
DTXSID001016220	2193055-35-3	Butyl 4,7,10,13,16,19-docosahexae	*L*				*H*	*L*		*H*								*VH*			*L*	
DTXSID001016656	93306-10-6	Isobutyl 3-(perhydro-5-oxo-2-fury	*L*				*L*	*L*		*L*								*M*			*I*	
DTXSID00147020	10523-35-0	2-Nonylpyridine	*I*				*L*	*H*		*L*								*VH*			M	M
DTXSID00181964	27563-67-3	N-Methyldodecanamide	*L*				*L*	*L*		*H*								*H*			*L*	*M*
DTXSID0020232	58-08-2	Caffeine	H	H	L	I	VH	H	H	H	I	I	M	I	I	L	L	L	H	*M*	L	*M*
DTXSID0020498	120-61-6	Dimethyl terephthalate	L	I	L	I	L	*L*	I	M	I		L	M	I	L	M	M		*M*	L	*VH*
DTXSID0020606	103-23-1	Bis(2-ethylhexyl)hexanedioate	L	I	L	VH	VH	H	M	H	I	I	L	I	I	L	I	VH	VH	*L*	L	*VH*

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Vegosen and Martin, *Clean Tech. & Environ. Policy*, 2020

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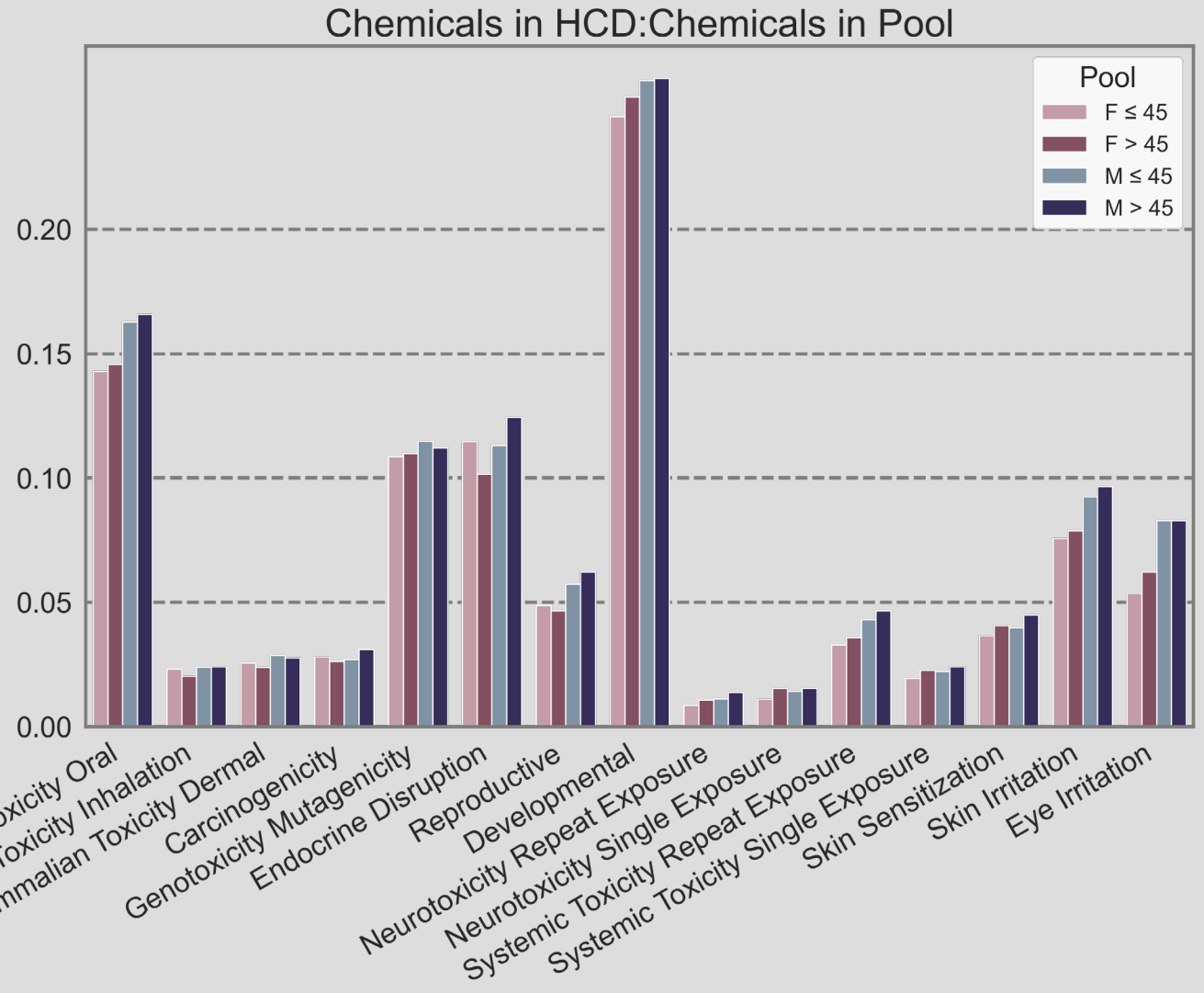
HAZARD PROFILES

- Proportional to the number of chemicals identified in serum:
  - Males tend to have more substances that "Medium" or higher hazard values
- That being said, females still have more chemicals in total that have high hazard values



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SUMMARY

- NTA/SSA of pooled samples can be an effective way to surveil chemicals to which populations may be exposed
- Our samples showed there were more chemicals in females than in males
- Through mapping chemicals to potential sources of exposure, many substances in females could be traced back to endogenous compounds, but there were still more exogenous substances in females
- While females may have higher exposures to more substances, using Hazard Profiles, we find that a larger proportion of the substances in males have a higher human health effect hazard profile.