

Non-Target Dust Analysis and Other Approaches for Identifying Compounds of Concern in the Indoor Environment

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Sources of Indoor Chemicals



Flame Retardants
BDEs + OP-FRs



Plasticizer,
Phthalates



Cosmetic and personal
care ingredients



Pesticides +
Flea Control



Skin Oils



Surfactants +
Cleaning Agents

Plus Many More



~ 300
chemicals

Only fraction of chemicals
measured or evaluated for
health effects in children

~ 8,000
chemicals
High volume

Can readily study the ones with
commonly evaluated measured
concentrations and biomarkers

What about the rest?

Which are important?

9.5 Trillion pounds of chemicals /year

Picture source: www.othot.com

What do we need to know?

- To assess potential harmful effects of chemicals to humans, we need
 - Exposure
 - Toxicity

Outline of Today's Talk

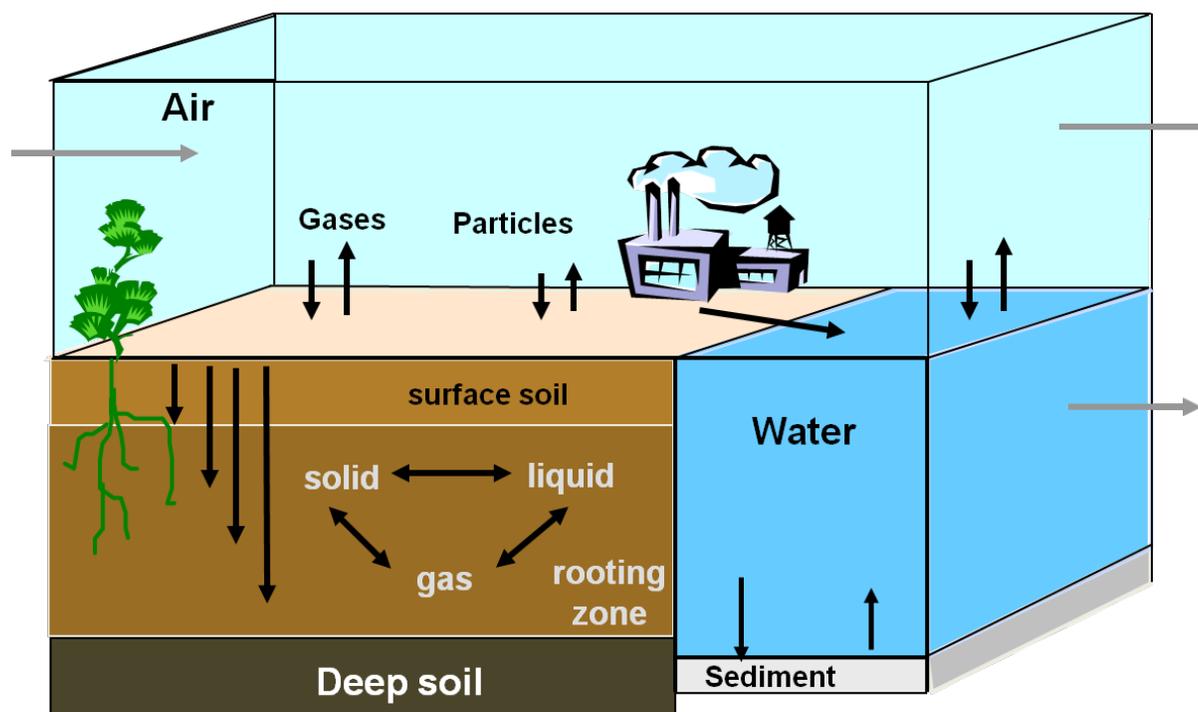
- Two examples of compounds with indoor source
- Challenges of modeling exposure from source
- Finding compounds we should worry about
 - Models driven by database information
 - Non-targeted dust
 - Combining databases and literature review (ECHO)
 - Functional Use information (EPA)
- Where do we go from here?

Old-fashioned example – PAHs

CalTOX Outdoor Model

Exposure Pathways:

- inhalation
- food ingestion

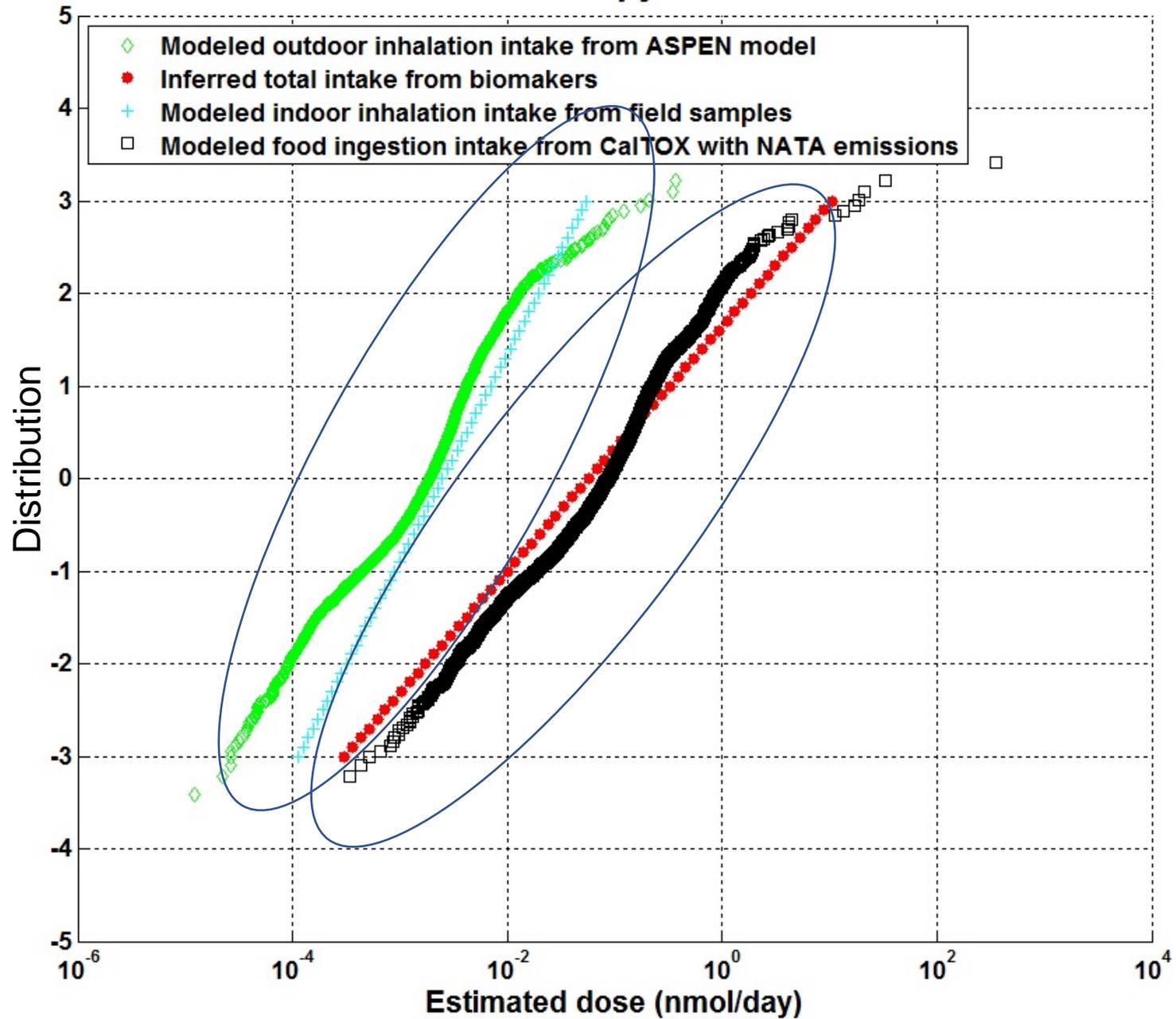


McKone, 1993
Shin et al. 2013

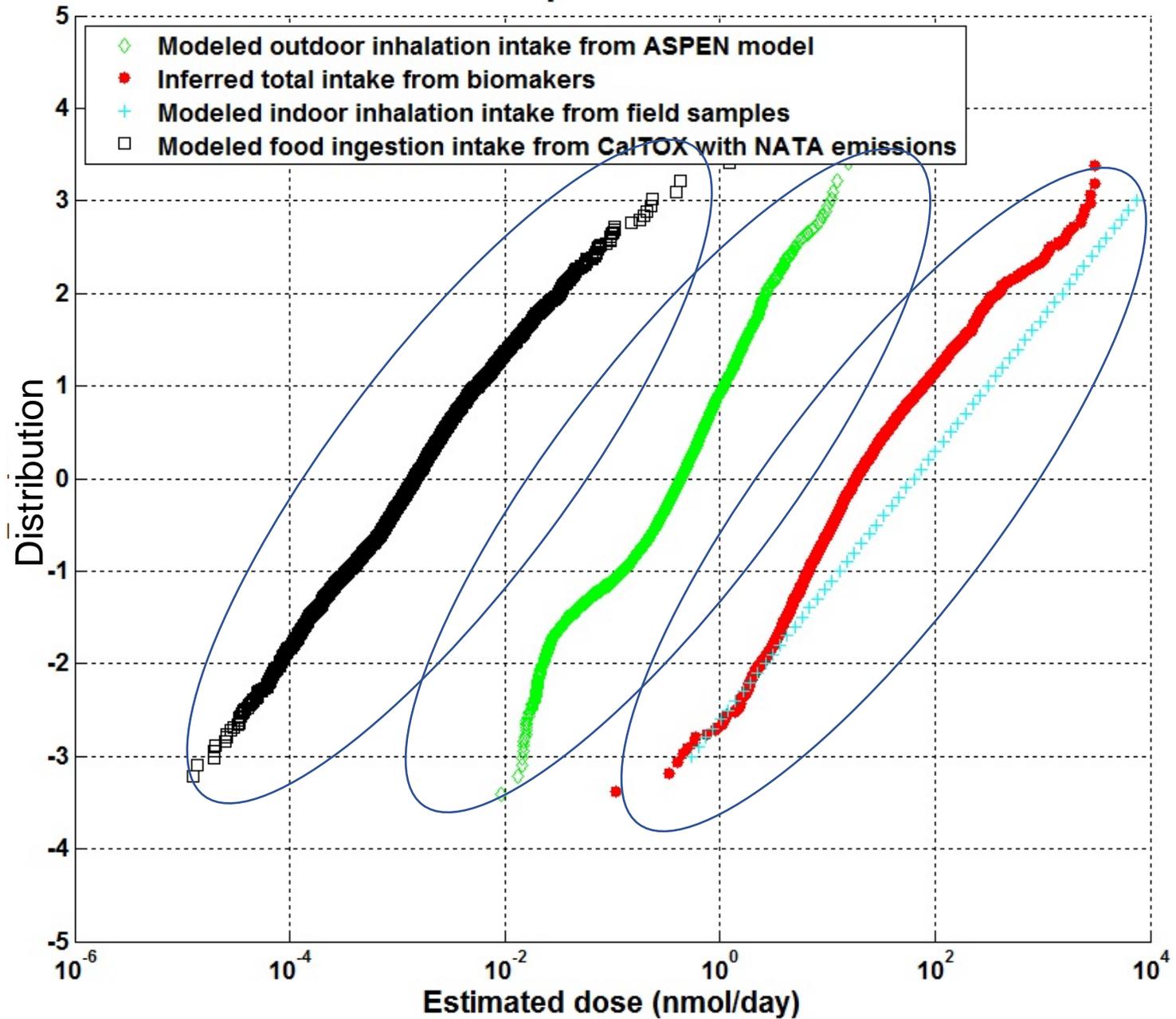
Compare Models to Intake Rates Inferred from NHANES

- PAHs - Naphthalene, benzo(a)pyrene
- Measured in urine samples from the 2001-2002 NHANES survey (biomarkers)
- Emission data are available at the county-level in the 2002 EPA NATA data (input for outdoor air and for CalTOX for food ingestion)
- Field data provide indoor exposure levels
- Human exposure and intake from multiple sources (indoor air, outdoor air, and food)

benzoapyrene



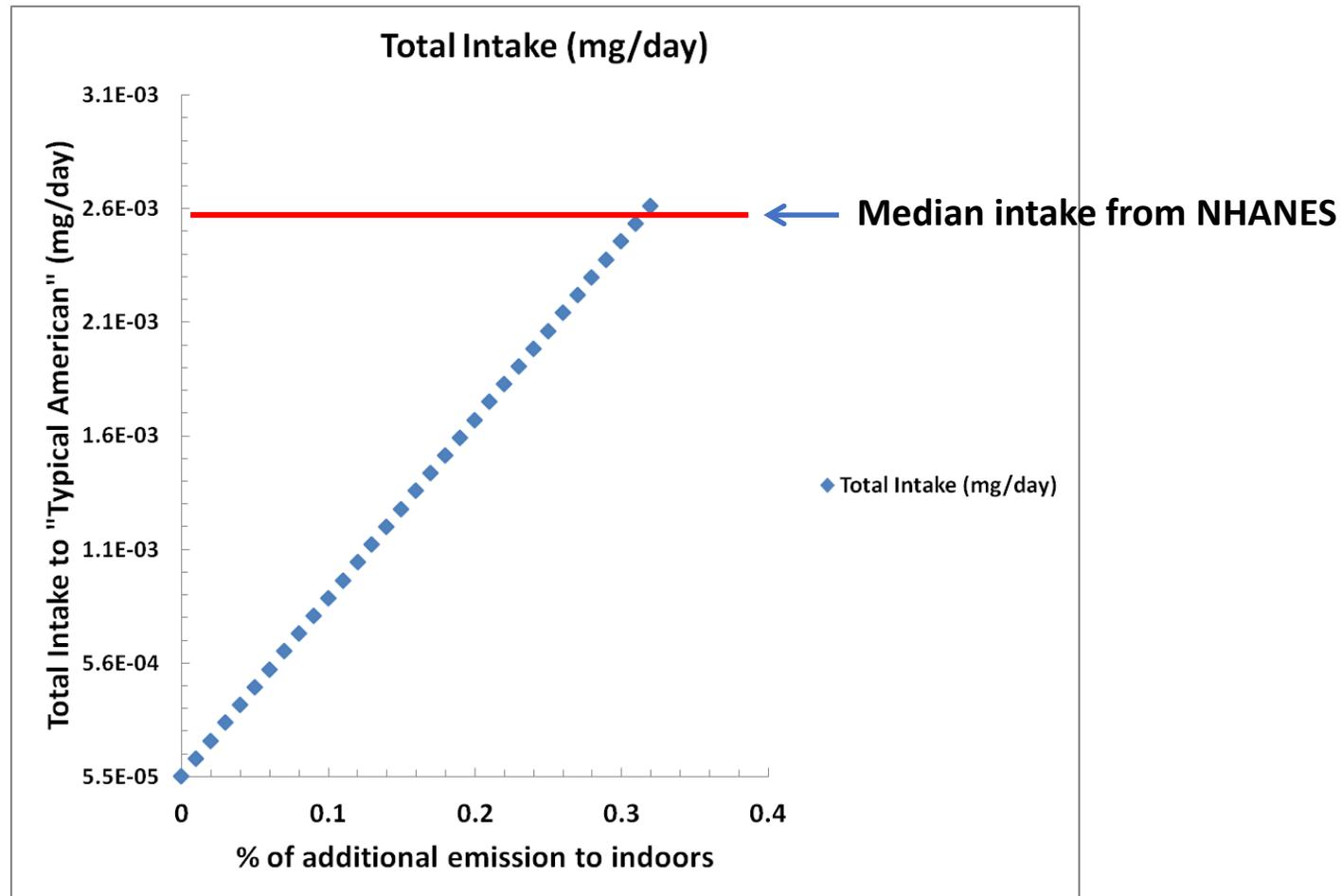
naphthalene



Contribution of Naphthalene Indoor Emission on Total Intake

$$\begin{aligned} \text{Total Intake} &= \text{Outdoor Intake} + \text{Indoor Intake} \\ &= \text{Outdoor Intake} + \text{Indoor Emission} \times \text{Indoor Intake per unit Indoor Emission} \\ &= \text{Outdoor Intake} + \frac{\text{Outdoor Emission} \times \% \text{ to indoors}}{\# \text{ of household}} \times \text{Indoor Intake per unit Indoor Emission} \end{aligned}$$

Sensitivity of Indoor Emission on Naphthalene Total Intake



Take Home Message

- If your difference in the source to dose relationship is significant between sources, exposure is very sensitive to emission patterns

Finding a compound of interest – Almost by Chance?

- Professor Mark Zylka was looking for environmental clues to causes of autism, and was concerned with transcriptional changes that inhibit mitochondrial function.
- He developed a high-throughput screening assay and ran the EPA ToxCast compounds through the assay
- One group of compounds of particular interest based on the assay were the strobilurin fungicides, fenamidone, azoxystrobin, fluoxastrobin, pyraclostrobin, and trifluoxystrobin, a relatively new class of fungicides and, have increased steadily in variety and use since introduced in 1996.
- Azoxystrobin and pyraclostrobin were both used on strawberries.

Logical Next Step, Surprise Finding

- Two individuals in North Carolina then bought strawberries, wiped their hands prior to eating the strawberries, ate some strawberries, wiped their hands after eating the strawberries, and then wiped the strawberries
- The strawberries had the two fungicides, levels on the hands were greater after eating the strawberries
- The surprise – One individual had really high levels before eating the strawberries. Why?
- Dr. Zylka did some sleuthing....

(12) **United States Patent**
Cornish et al.

(10) **Patent No.:** **US 8,138,196 B2**
(45) **Date of Patent:** **Mar. 20, 2012**

(54) **ANTIFUNGAL WALLBOARDS AND BUILDING MATERIALS AND METHODS FOR THE PRODUCTION THEREOF**

(75) Inventors: **Alexander Cornish**, Basel (CH); **Anja Greiner**, Weinheim (DE); **John R. James**, Greensboro, NC (US); **Gertrude Knauf-Beiter**, Stein (CH); **Johann Steiner**, Basel (CH)

(73) Assignee: **Syngenta Crop Protection, Inc.**, Greensboro, NC (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 958 days.

(21) Appl. No.: **11/917,167**

(22) PCT Filed: **Jun. 13, 2006**

(86) PCT No.: **PCT/GB2006/002167**

§ 371 (c)(1),
(2), (4) Date: **Jun. 5, 2008**

(87) PCT Pub. No.: **WO2006/134347**

PCT Pub. Date: **Dec. 21, 2006**

(65) **Prior Publication Data**

US 2008/0280929 A1 Nov. 13, 2008

Related U.S. Application Data

(60) Provisional application No. 60/690,403, filed on Jun. 14, 2005.

(51) **Int. Cl.**

A01N 43/54 (2006.01)

E04C 2/26 (2006.01)

(52) **U.S. Cl.** **514/269; 52/309.3**

(58) **Field of Classification Search** None
See application file for complete search history.

(56) **References Cited**

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Primary Examiner — Shanon A Foley

(74) *Attorney, Agent, or Firm* — William A. Teoli, Jr.

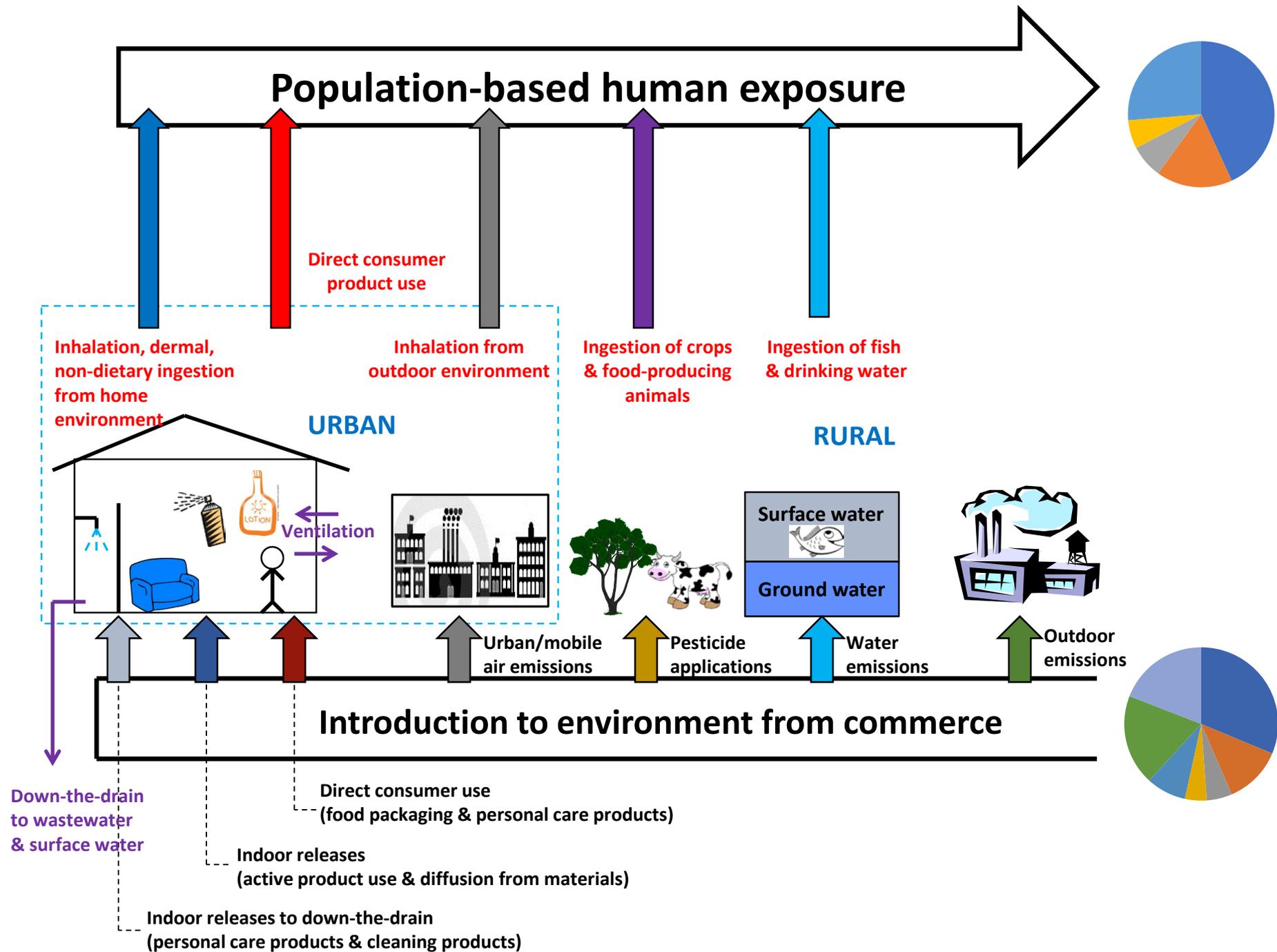
(57) **ABSTRACT**

The present invention relates to, inter alia, methods for the treatment of wallboards and the treated wallboards. In particular, the invention relates to the treatment of wallboards with a fungicidally effective amount of a strobilurin or strobilurin-type fungicide. In a particular embodiment the fungicide is azoxystrobin. The invention also provides for the treatment of wallboards and building materials with combinations of fungicides present in synergistic amounts.

6 Claims, No Drawings



- PURPLE[®] drywall is unique because it resists moisture, mold and mildew.
- Appears to contain Azoxystrobin, first introduced in around 2009
- This story is really interesting
- We need a good way to catch these things



Modeling Challenge

- Three groups were given a list of 192 compounds with high-throughput toxicological estimates and asked to estimate exposure
- Meant only to be a “Tier 1” estimate, not actual exposure
- Goal → Be conservative

Calculating Exposure

- Emissions
 - Need some sort of mass estimates
 - Emissions Estimates in EPA Databases - Toxics Release Inventory Program (TRI), National Emissions Inventory (NEI)
 - Total Production Volumes (TPV) required as surrogate for emission estimate
- **Problem: How are releases disaggregated between personal care use, indoor use, and outdoor emissions?**
- Use Data
 - Used EPA's [CPCat database](#) (Chemical & Product Categories)
 - Database includes ~43,000 chemicals with use classifications

Use Scenarios

- **Direct intake** – directly ingested or inhaled
- **Food/oral contact** – contact food or placed in mouth
- **Direct dermal** – directly applied to skin
- **Dermal contact** – items we touch
- **Indoor emissions** – emitted to indoor environments
- **Passive indoor emissions** – items placed in indoor environments
- **Emissions near indoors** – emissions occurring in close proximity to homes
- **Pesticide applications**
- **Outdoor emissions**

Near Field
Direct

Near Field
Indirect

Far Field Direct

Far Field Indirect

Calculating Exposure

- Intake Fraction
 - Here we use a model to estimate how much exposure there is for a specified use scenario
 - Chemical properties required
 - Utilized a variety of models
- Both sources and exposure models are equally important

Use Scenarios

Intake Fraction (iF) from Chemical Properties & Models

Quantity (Emitted, applied, ingested) (Q)

Intake Rate (iR) by Use Scenarios

Oral Equivalent Dose (OED)

- Direct Intake
- Food/oral contact
- Direct dermal
- Dermal contact
- Indoor emissions
- Passive indoor emissions
- Emissions near indoors
- Pesticide applications
- Outdoor releases

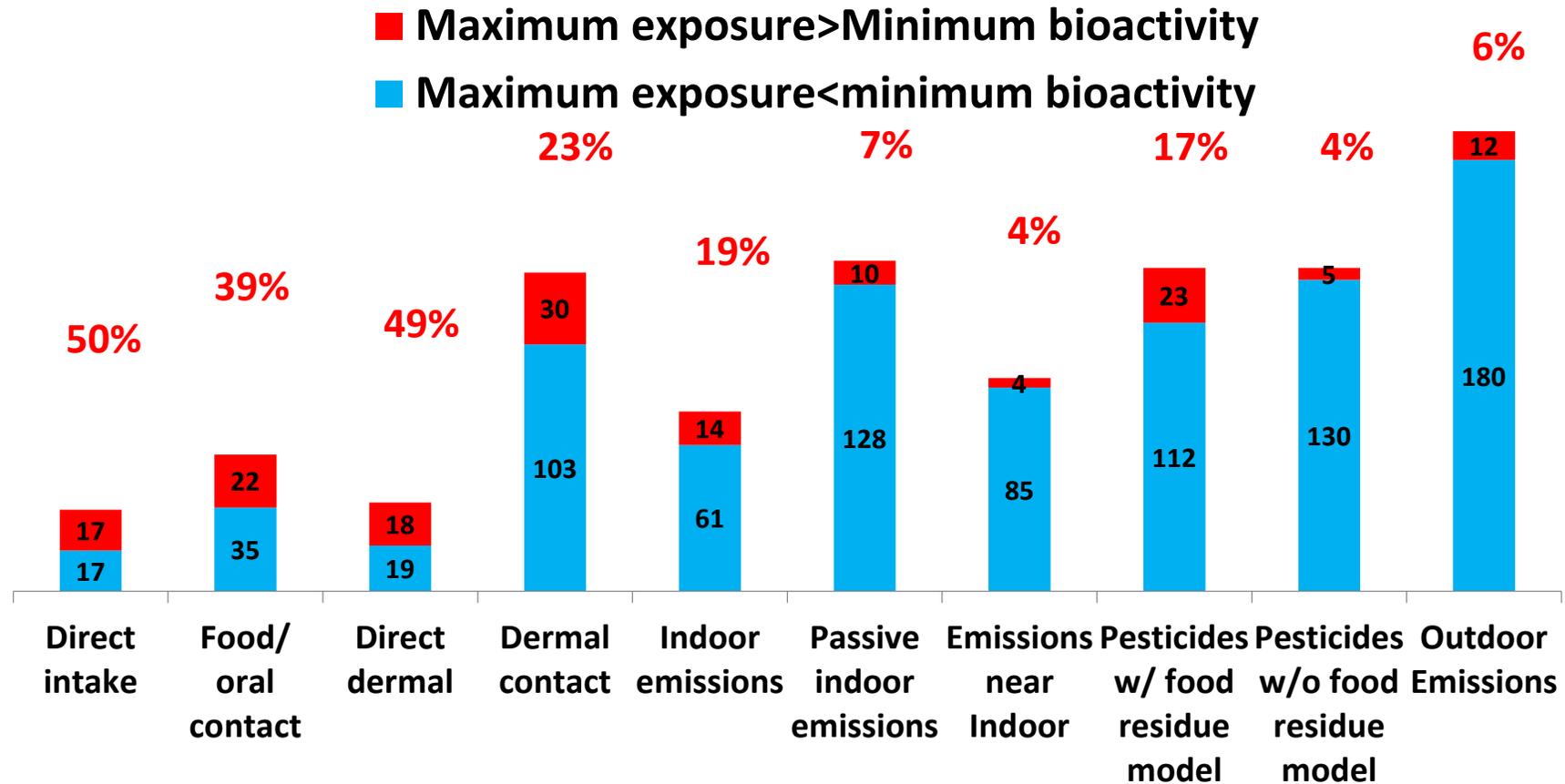
Divide by BW (kg)

Compare iR and OED for each category

$$\begin{matrix} \text{mg} \\ \hline \text{mg} \end{matrix} \times \text{mg/day} = \text{mg/kg/day} \longleftrightarrow \text{mg/kg/day}$$

Max exposure > Minimum bioactivity ?

Screening Results: 52 compounds out of 192

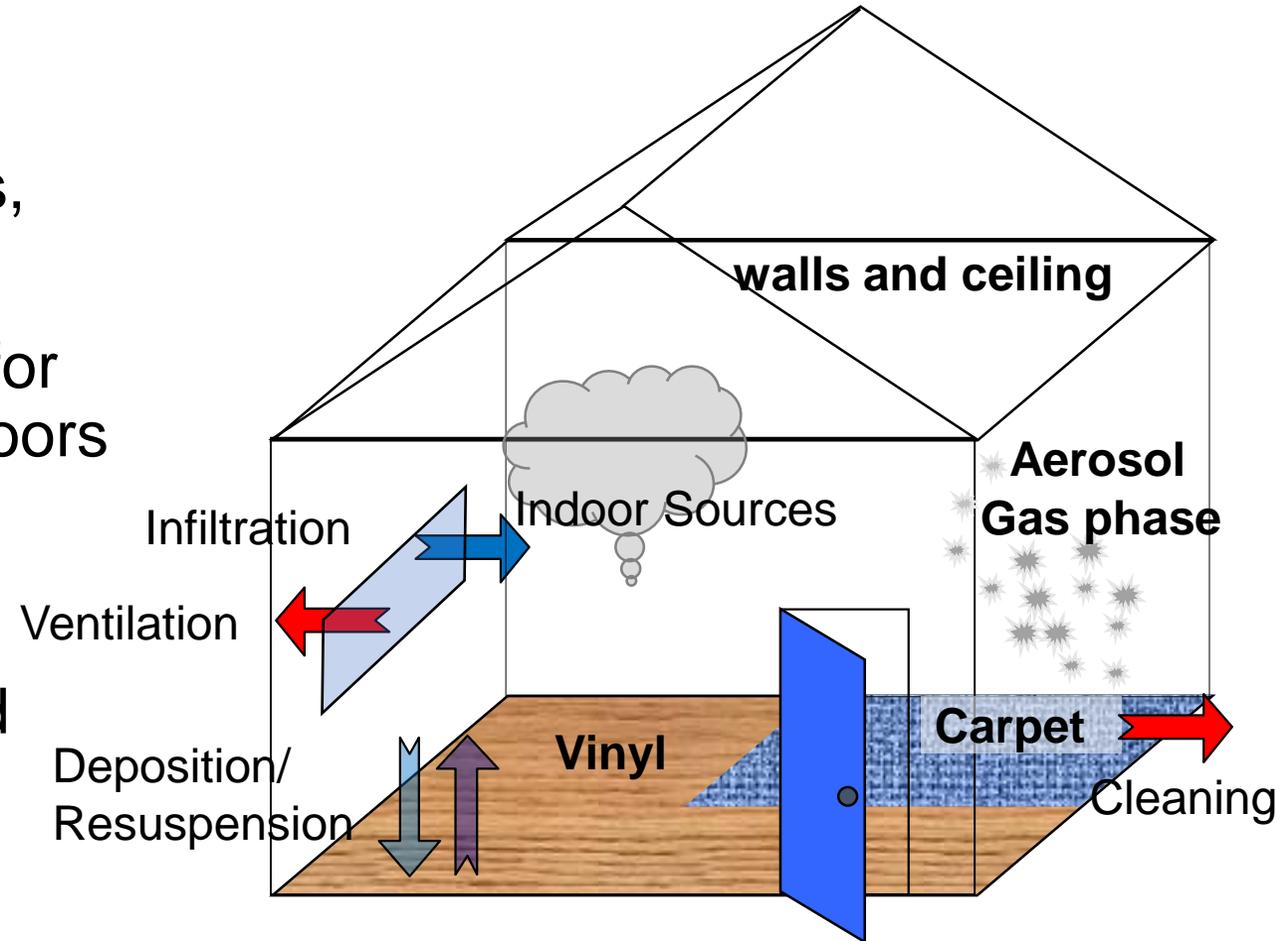


What do results mean?

- Does not imply risk → results have many uncertainties!
 - emissions/use patterns/chemical properties (input parameters)
 - intake fractions (model calculations)
 - bioactivity estimates (In vitro assay data, scaling)
- Simply means we should look more carefully at the individual compound
- More curation of use categories, filling gaps
- Sources
 - Need refined estimates of use by category
 - Some estimates not conservative → importation of products

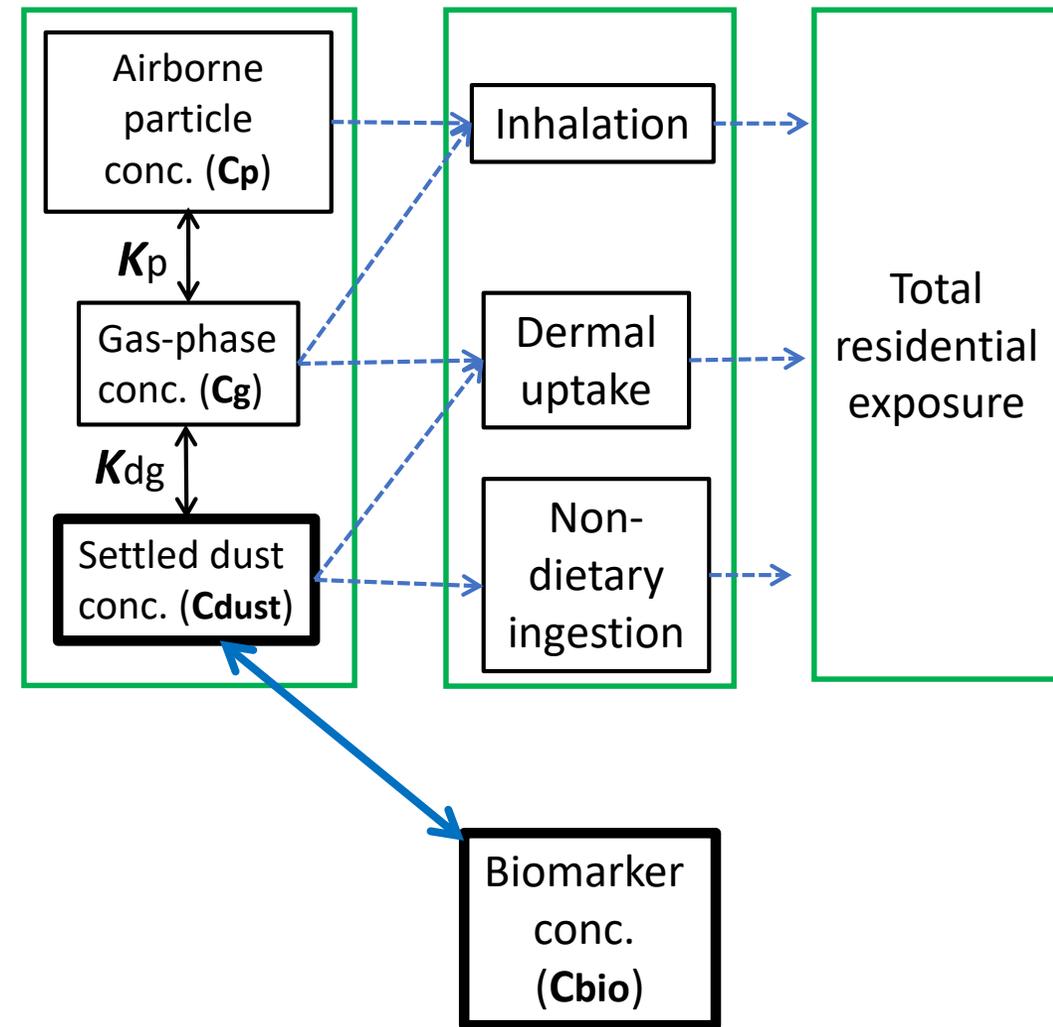
Dust: Marker of SVOC Source

- Known to be a reservoir for many compounds released indoors
 - Phthalates, PBDEs, Pesticides, PFCs, personal care product ingredients
- Has low temporal variability, particularly for compounds with long residence time indoors
- For SVOCs with low VP and high K_{oa} , favorably partition to dust
 - More likely to have levels that exceed LOD
 - More compounds can be analytically quantified



Why Dust for Exposure?

- **Exposure occurs** via inhalation, dermal uptake, non-dietary ingestion of dust
- Dust concentrations
 - **Correlated** with indoor air, other indoor surfaces, biological samples
 - Used as a surrogate for human exposure in epidemiologic studies
 - Used to reconstruct total residential exposure with partitioning relationships
 - Dust is known to be a reservoir for SVOCs released indoors

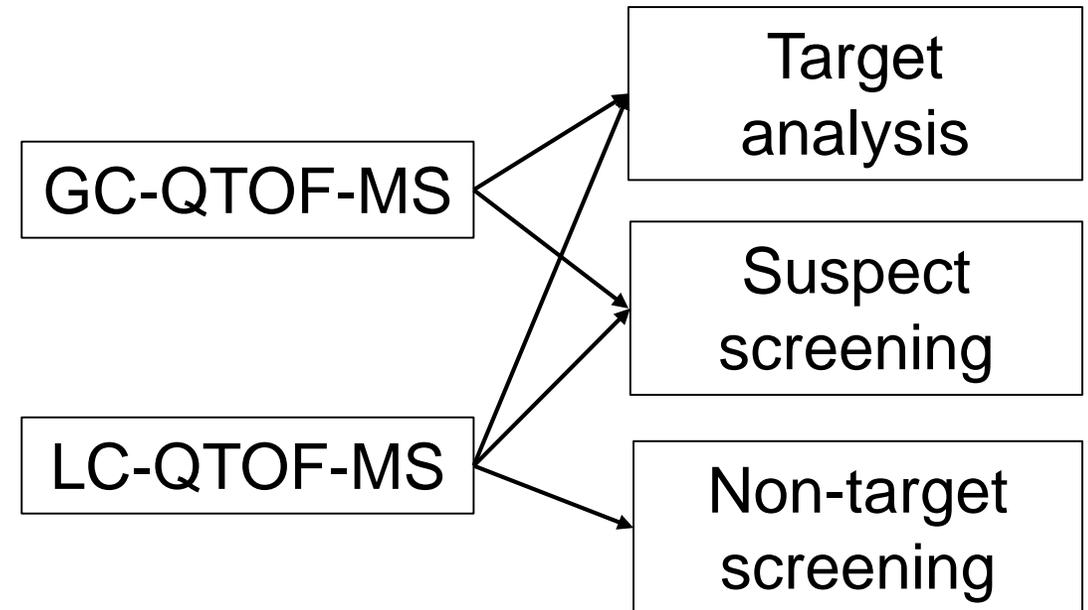


Objectives

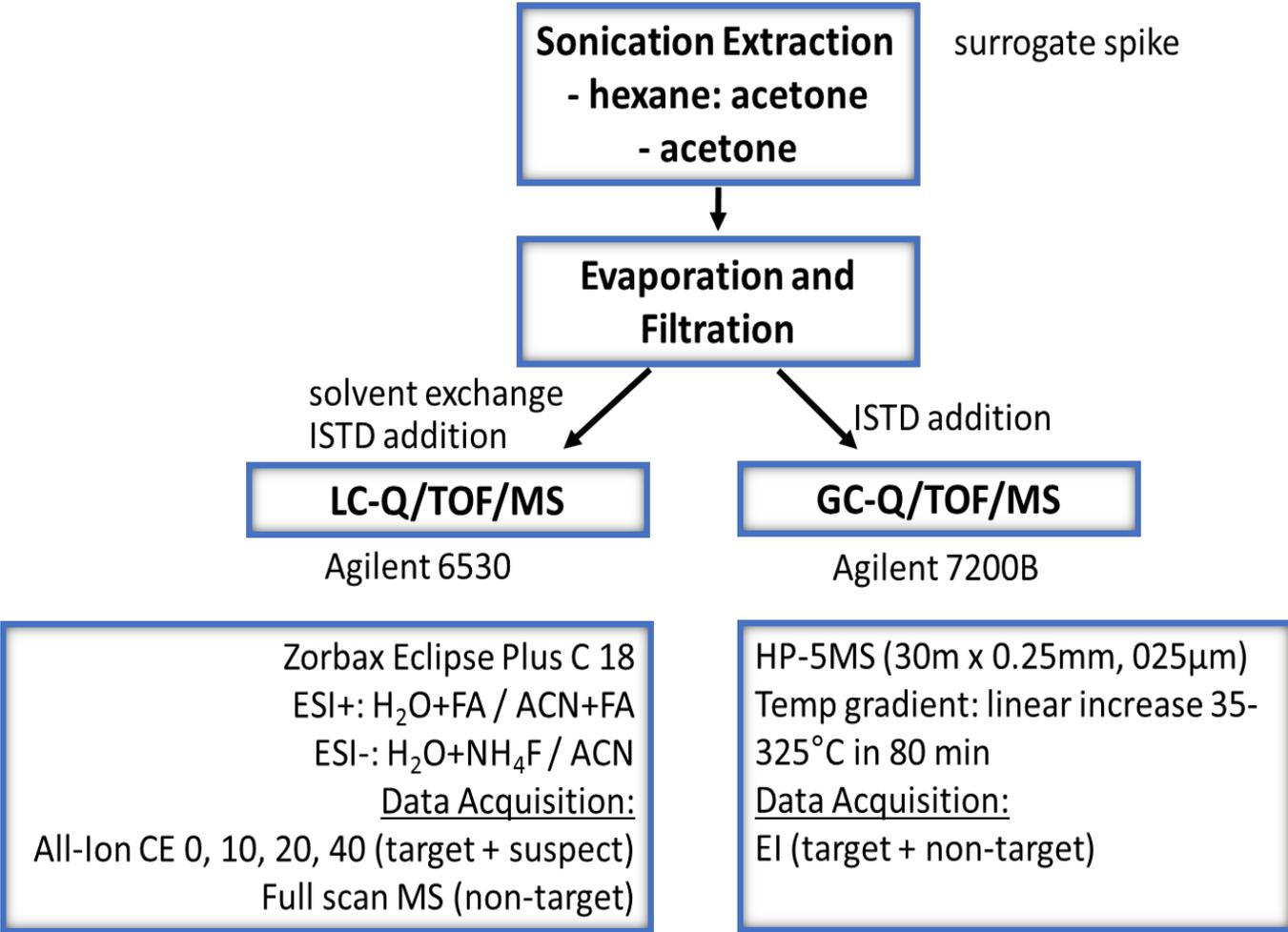
- Identify a broader range of compounds in dust to improve our understanding of potential sources
- Dust was Investigated by both **LC-MS** and **GC-MS** analytical platforms with three analytical approaches, **target, suspect screening, and non-target**. Moschet et al. ES&T
- Consider results in the context of consumer products and potential toxicity

Sample Collection and Analysis

- Dust samples were collected using a high-volume small surface sampler (**HVS3**) from the main living area of **38** homes in Northern California (**2015-2016**)
- Analyzed known chemical classes → **target**
- Now include expected compounds using existing databases or libraries → **suspect screening**
- Also identify previously unknown compounds through high-resolution mass spec → **non-target**
- **Standards purchased to confirm identity of suspect and non-targeted**



Dust Extraction



- Sieved through a 106 µm
- Extraction optimized for LC-Q/TOF-MS and GC-Q/TOF-MS without losing chemicals on clean-up, relying instead on the resolution and mass accuracy of the instruments to support identification
- 3 mL of hexane:acetone (3:1), vortexed, sonication.
- Dust is extracted a second time using 100% acetone following the same procedure.
- The combined extract is evaporated to 1 mL under nitrogen and filtered through a 0.2 µm PTFE filter. This extract is split into GC and an LC fractions.
- GC fraction spiked with dibromooctafluoro-bisphenol (DBOFB).
- The LC fraction is further evaporated and solvent exchanged with methanol, and again evaporated. After that, deionized water is added to produce a final ratio of water/methanol of 50:50. An internal standard mixture of 9 chemicals is added.

LC-Q/TOF Analysis

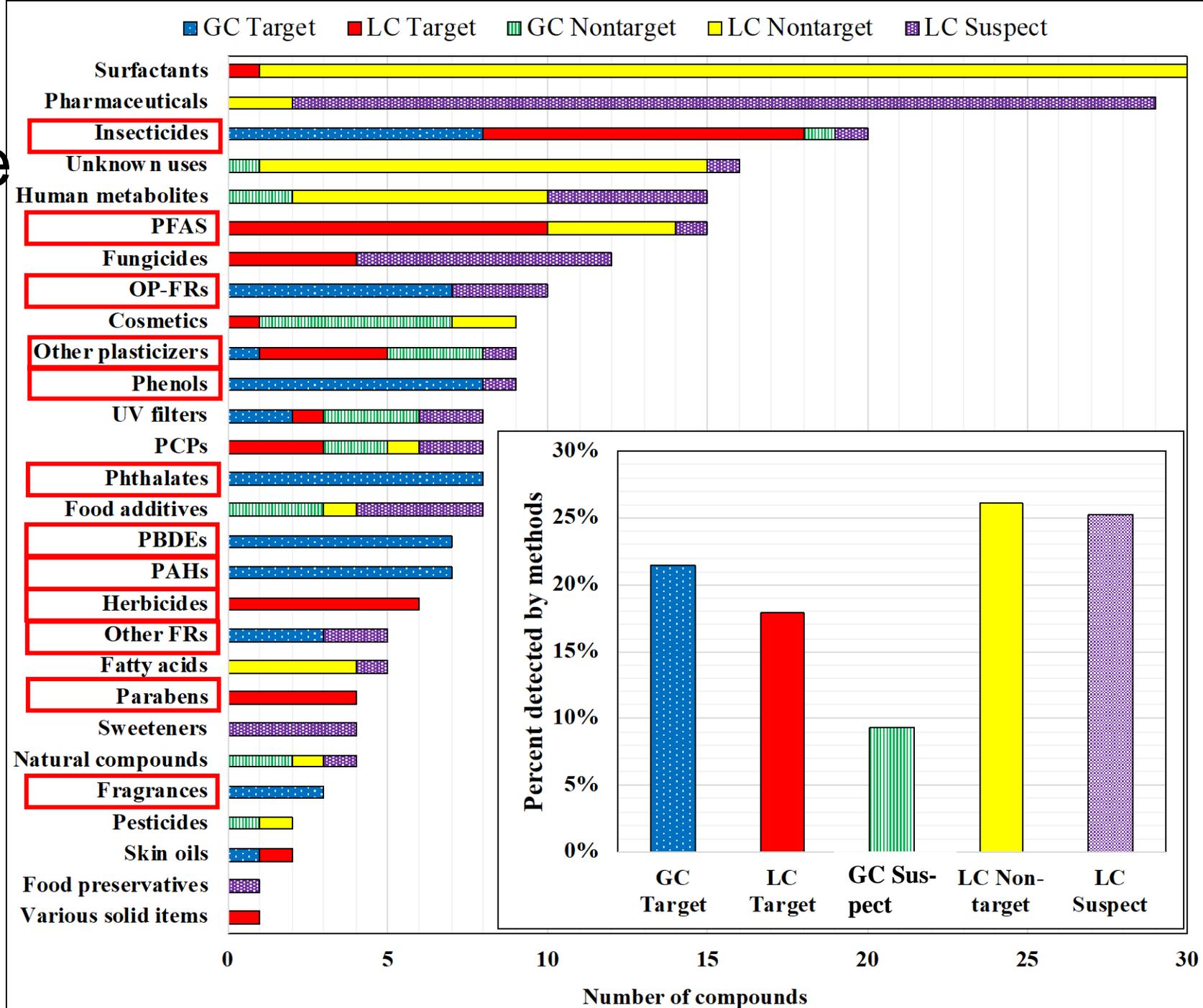
- LC-Q/TOF analysis is performed by injecting 10 μL of extract. For chromatographic separation a Zorbax Eclipse Plus C18 column (100 mm, 2.5 mm, 1.8 μm , Agilent Technologies, Inc.) is used.
- The following mobile phases are used in a 23 min run at a flow rate of 0.35 mL/min:
 - positive ionization mode: A) deionized water plus 0.1% formic acid, B) acetonitrile plus 0.1% formic acid;
 - negative ionization mode: A) deionized water plus 1mM ammonium fluoride, B) acetonitrile.
- The Q/TOF is run in the 2 GHz, extended dynamic range mode at 4 spectra/second. Acquisition is done in data independent All-Ions fragmentation mode using collision energies (CE) of 0, 10, 20, and 40. MS settings were optimized separately in positive and negative ionization modes using the target compounds.

GC Analysis

- The GC separations carried out using a HP-5MS (30 m x 0.25 mm, 0.25 μm) column and the Q/TOF 7200B run are (EI) mode. A 78 min run with a linear temperature gradient from 35°C-325°C was chosen to be optimal for separating 102 target chemicals and all major peaks in the analysis of a dust extract.
- The optimized extraction and analytical method for both instrumental platforms was validated by extracting a triplicate of a standard reference house dust (NIST SRM 2585) and comparing the results to the concentrations of the 14 target compounds that had certified values.

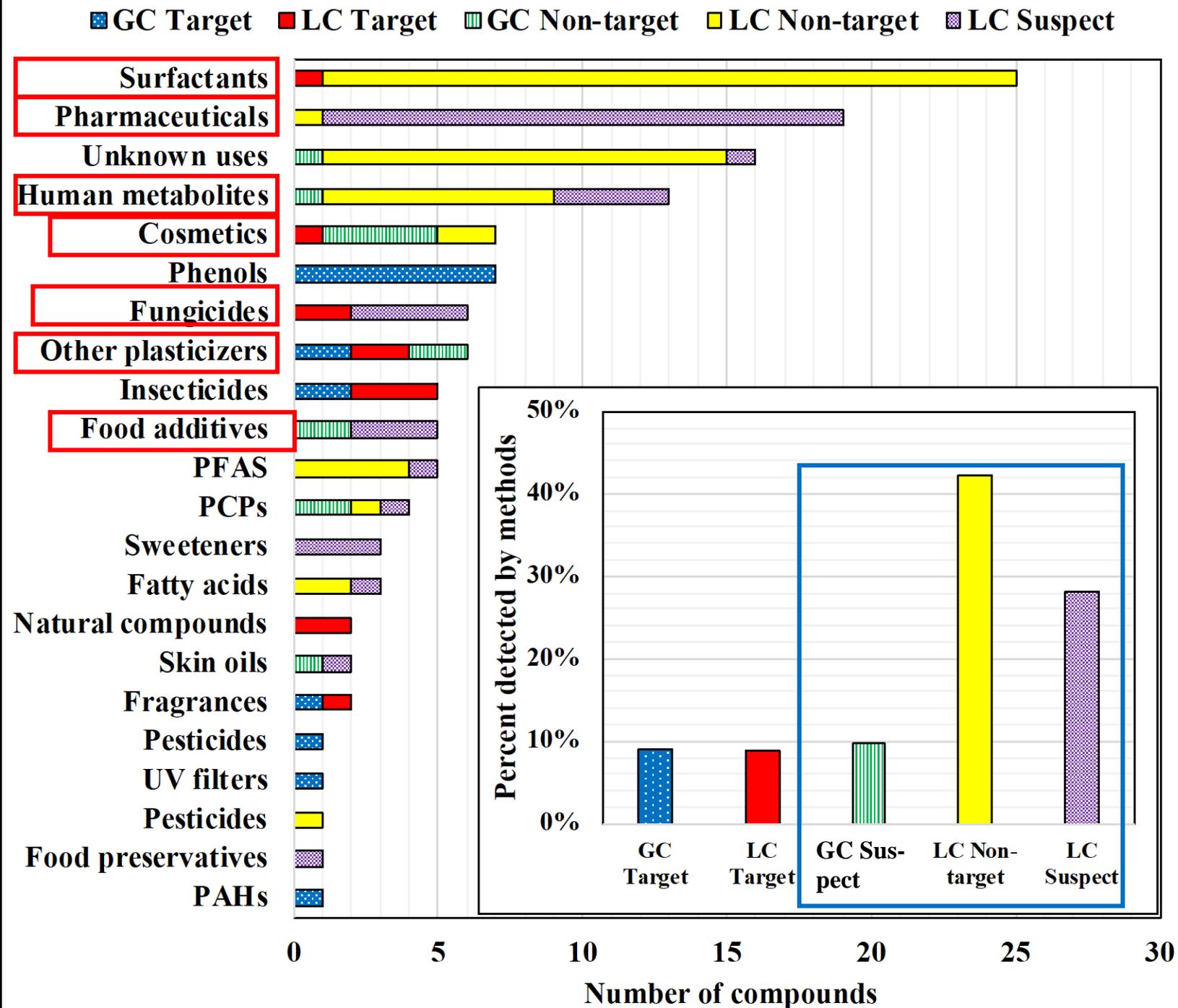
A total of 257 compounds were detected by different analytical instruments/approaches

- Traditional compound classes identified via target methods



Of these, 135 were newly-measured compounds

- 81% from GC suspect, LC suspect and LC non-target
- GC suspect screening found many cosmetic ingredients and other plasticizers
- LC suspect screening found many pharmaceuticals, fungicides, and food additives
- True non-target found many surfactants and human metabolites

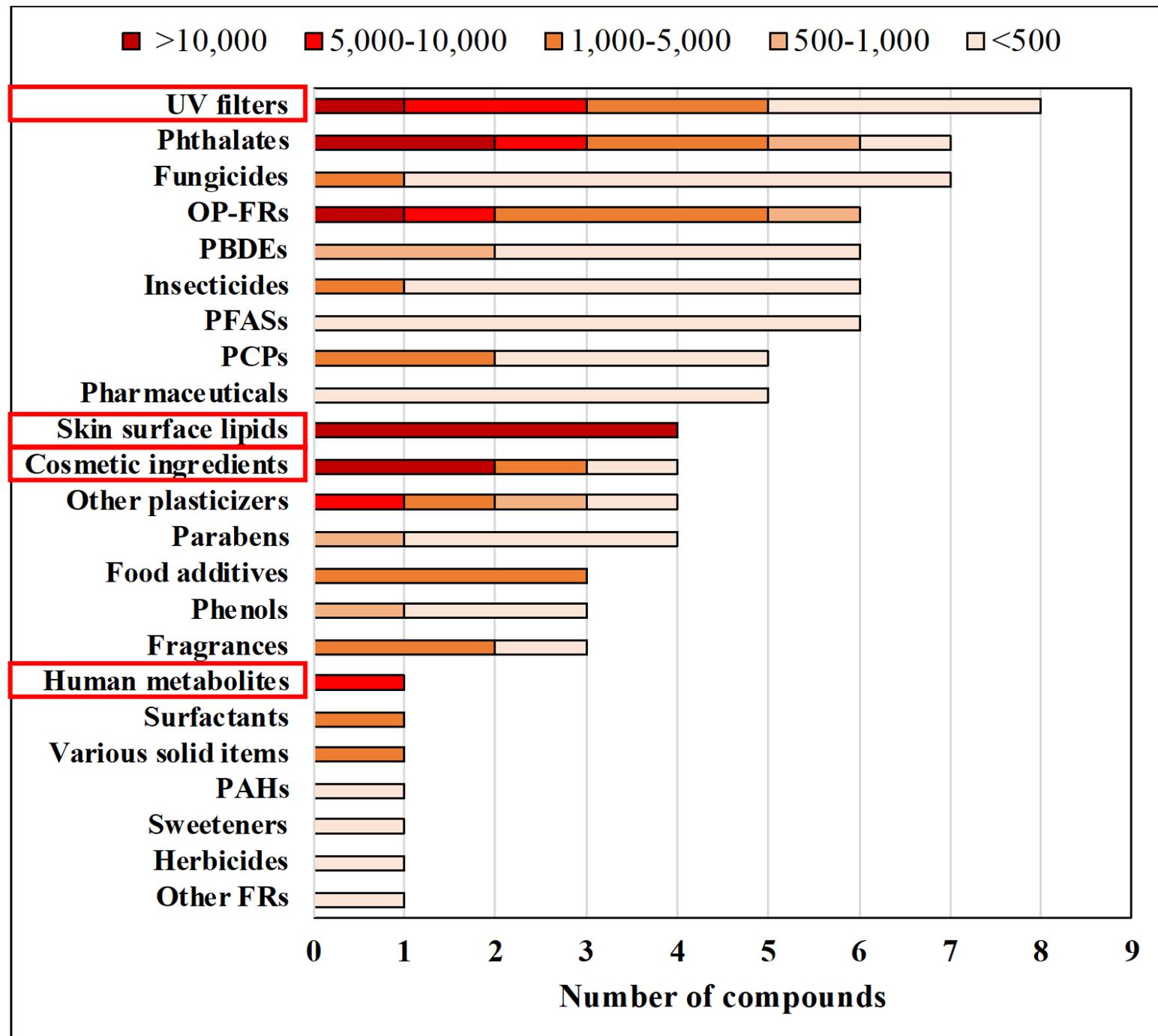


Relevance to consumer products

- Cosmetic ingredients – likely in dust due to skin flakes, and dust gives us a good way to access what compounds may be in products used in homes
- Alternative Plasticizers - Three compounds not previously measured in dust were near ubiquitous, indicates how quickly markets shift
- Fungicides – Compounds applied to fruit were frequently detected indoors
- Industrial Compounds – Ingredients of coatings and rubber widely detected in dust

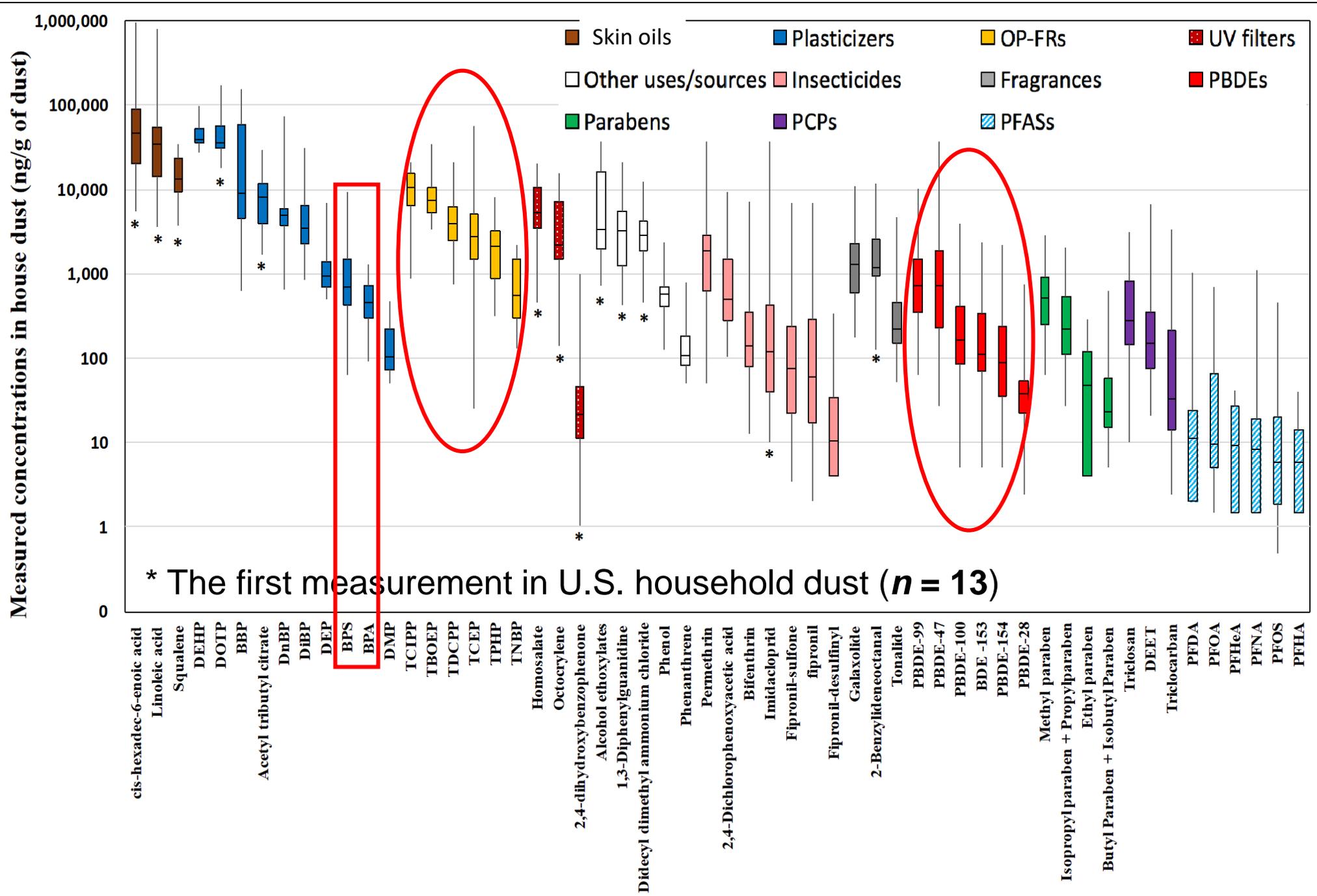
Median conc.
(ng/g of dust) for
88 compounds
detected in more
than **50%** of
samples

- Compound classes w/ high concentrations: humans and their activities, and possibly pets, play as sources of SVOCs in the indoor environment



Dust conc.
for **56**
target
compounds
detected in
more than
50% of
samples

Reflect recent
changes in
consumer use
and changes in
product
formulation and
regulations
affecting **PBDEs**
and **BPA**

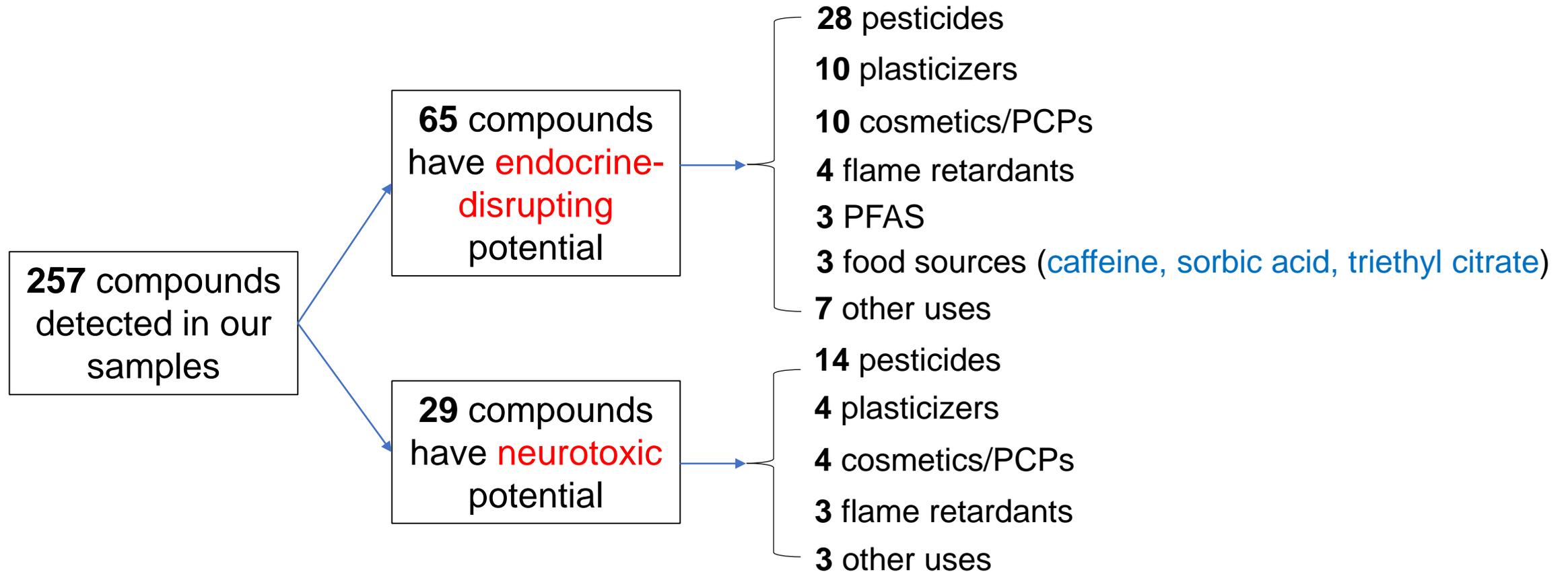


in-vitro Assays and Models, primarily ToxCast

- **Neurological assays** – calcium, ligand, potassium, and sodium ion-channel assays directly from ToxCast Database. Integrated neural network activity assay
- **Endocrine Processes** - The four main processes were evaluated, estrogen, androgen, thyroid, and steroidogenic
 - Model with 18 *in vitro* HTS assays measuring estrogen receptor
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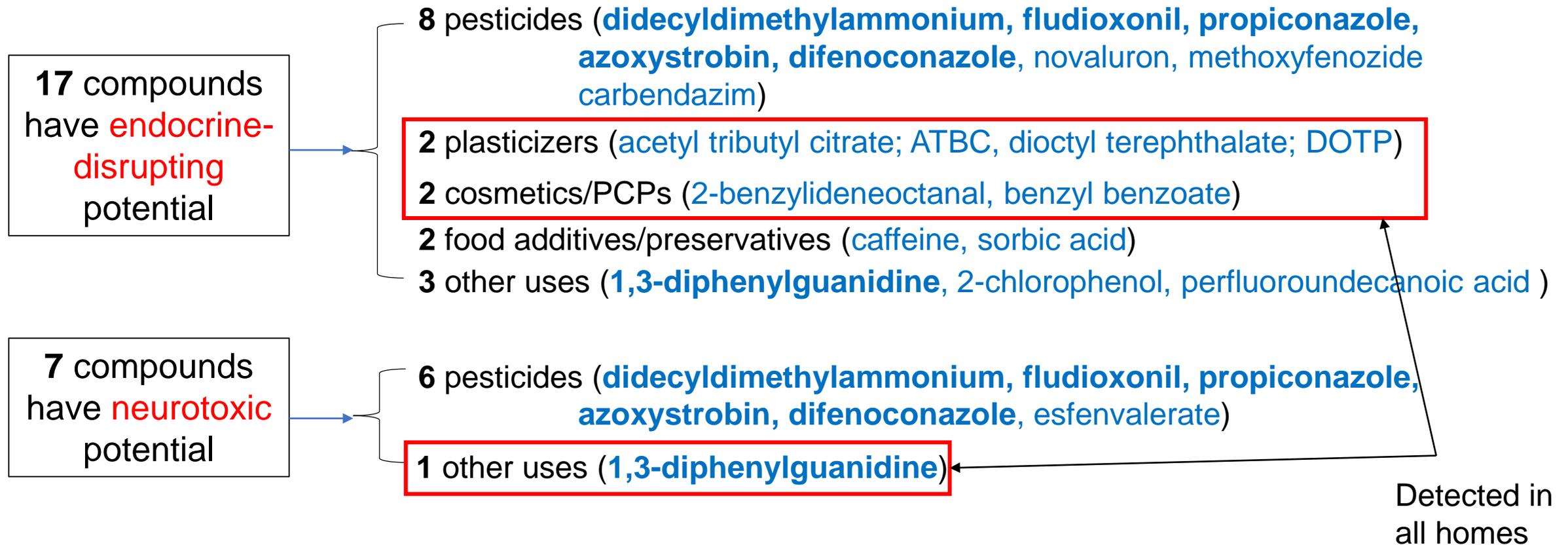
Compounds with endocrine-disrupting or neurotoxic potential

- Utilizing results from *in vitro* high-throughput screening assays (Friedman et al. 2016; Kleinstreuer et al. 2017, Rotroff et al. 2014, Strickland et al. 2018)



Compounds with endocrine-disrupting or neurotoxic potential

- Among **135** newly-detected compounds in our samples

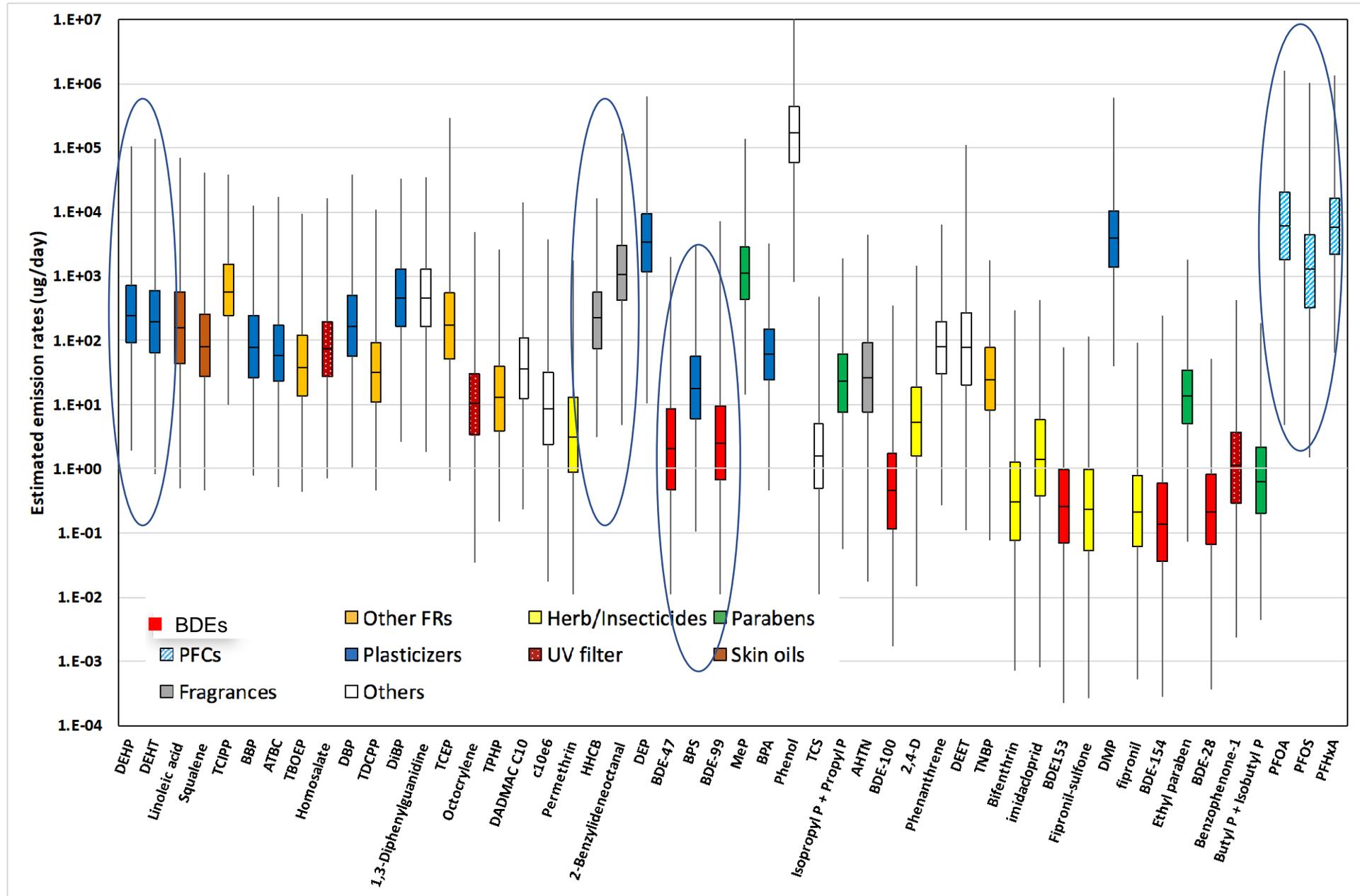


Searching for Other Compounds

We also developed lists of potentially interesting compounds from other sources, matched those with potential unconfirmed matches, and confirmed a portion of them, shown to the right

Compound Name	Number of Detects	Type of Compound
Prometon	2	herbicide
DDM/Dichlorophen	1	an anticestodal agent, fungicide, germicide, and antimicrobial agent
3-Iodo-2-propynyl-N-butylcarbamate	11	a member of the carbamate family of biocides, preservative used globally in the paints & coatings, wood preservatives, personal care, and cosmetics industries,
Bisphenol AF	4	used in various plastic products and other resins including epoxy resins.
Dihexyl phthalate	17	plasticizer
TCP / Tricresylphosphate	6	a plasticizer in nitrocellulose, acrylate lacquers, varnishes, and in polyvinyl chloride

Estimated Emission Rates for Target (ng/d)



Summary

- Quantified a large number of SVOCs with high confidence
 - In total, **257** compounds were detected in one or more samples
 - **135** compounds were quantified **for the first time** in U.S. household dust
 - **78%** of compounds were fully confirmed with **reference standards** or tentatively confirmed with **matching mass spectral libraries**
- Support the idea that dust can serve as a marker of use
 - Measured **13** food additives, sweeteners, preservatives → via **direct food intake**
 - Measured **11** compounds (e.g., **skin oils and cosmetic ingredients**) in dust also measured in **skin wipe**
 - Identification of compounds used in building and consumer products
 - Relatively new chemicals (e.g., **OP-FRs, BPS**) were measured at concentrations higher than those for controversial or banned chemicals in consumer products (e.g., **PBDEs, BPA**).



ECHO

Environmental influences
on Child Health Outcomes

A program supported by the NIH

Mapping Chemicals across Routes of Exposure and Body Burden: Data Gaps and Opportunities for ECHO

Debbie Bennett, Edo Pellizzari, David Balshaw, Paloma Beamer, Rebecca Boyles, Asa Bradman, Jessie Buckley, Timothy Fennell, Eliseo Guallar, Kurunthachalam Kannan, Richard Miller, Aolin Wang, Yeyi Zhu, Tracey Woodruff for the ECHO Program

ISES-ISEE Joint Annual Meeting

August 28, 2018

Environmental influences on Child Health Outcomes (ECHO)



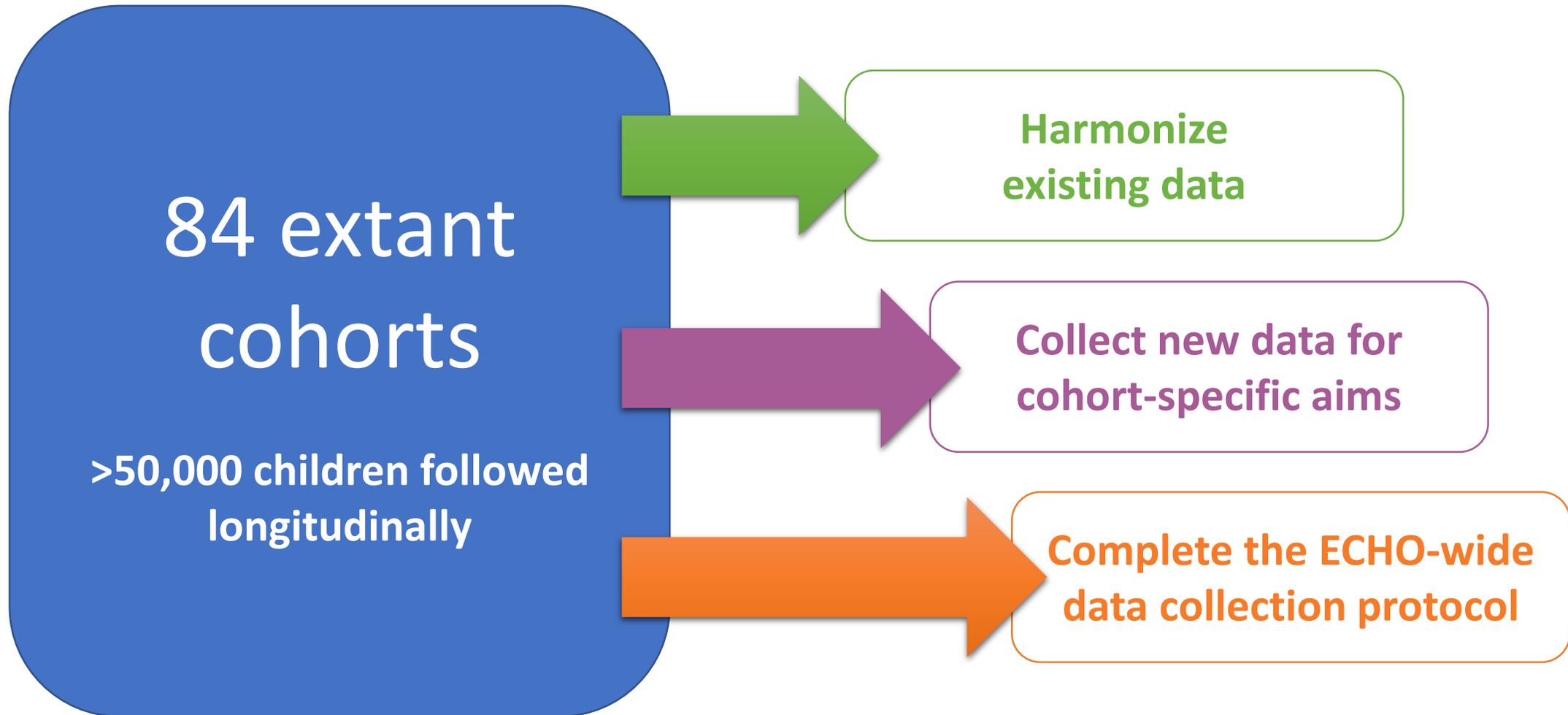
ECHO'S PROGRAM OBJECTIVES:

- Improve the health of children and adolescents by conducting observational and intervention research that will inform high-impact programs, policies, and practices.
- Institute best practices for conducting Team Science in the 21st century, giving researchers the tools to work collaboratively to improve child health.

ECHO'S OVERARCHING SCIENTIFIC GOAL:

- Answer crucial questions about the effects of a **BROAD** range of **EARLY** environmental influences on child health and development

ECHO Pediatric Cohorts



ECHO's health outcomes

Focus on key pediatric outcomes that have a high public health impact

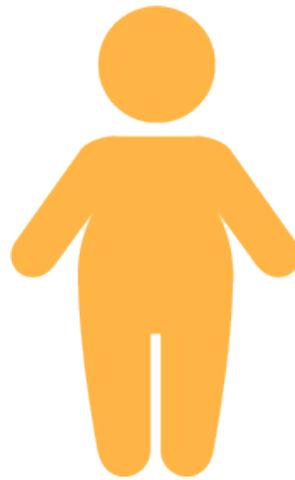
PRE-, PERI-
AND POSTNATAL



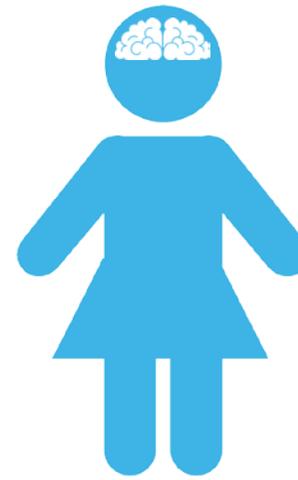
UPPER AND LOWER
AIRWAY



OBESITY



NEURO-
DEVELOPMENT



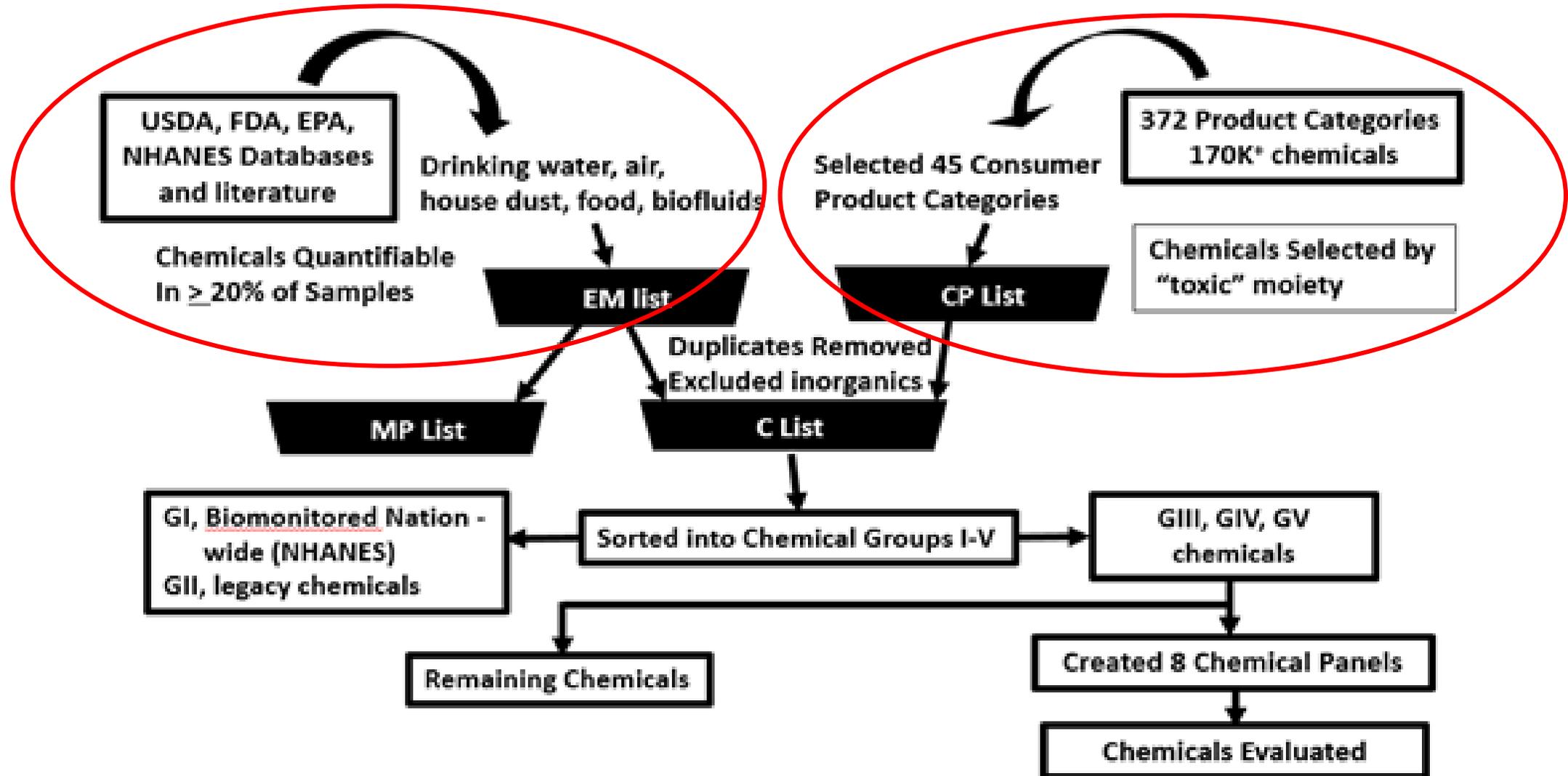
POSITIVE HEALTH



Our approach for identifying chemicals of interest for ECHO

- Published literature, government databases, and other sources contain understudied chemicals that may impact health outcomes of interest in ECHO
- Consider compounds with likely exposure based on use, production volume, and chemical properties
- Use factors related to exposure and health effects/toxicity to create groups of chemicals that
 - High and low priority for biomonitoring in ECHO
 - Require further research to fill voids in knowledge

Selecting Compounds



Compounds placed into 1 of 5 groups

- 1) Compounds currently included in NHANES → 116 (includes 74 VOCs)
- 2) Legacy chemicals → 71 (primarily PCBs, OC pesticides), well studied, not further evaluated
- 3) Prevalent in environmental media, perhaps limited biomonitoring → 248
- 4) Have EPA predicted exposures, little measurement data → 261
- 5) Little or no information, but use and “toxic” moiety of interest → 148

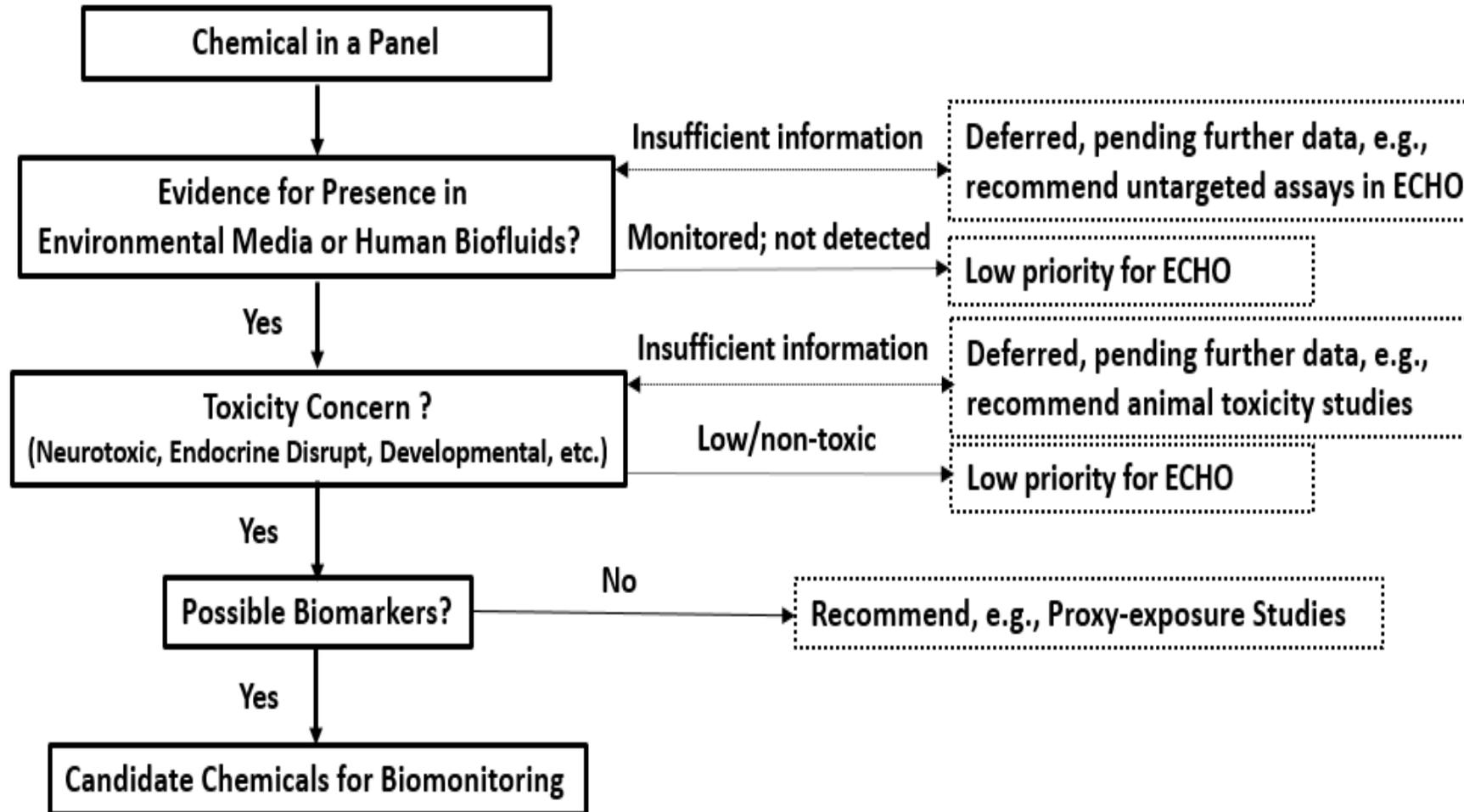
Break into 2 approaches

- 1) Prescribed approach
- 2) High-throughput approaches

Prescribed Approach for Evaluation

- Divided into Chemical Panels – 171 compounds
 - Alternate Flame Retardants, Organophosphorus-based Flame Retardants, Environmental Phenols, Alternative Plasticizers, Perfluorinated Compounds, Pesticides, Aromatic Amines, and Quaternary Amines
 - Included relevant compounds from Groups 3 (75 compounds), Group 4 (66 compounds), and Group 5 (30 compounds)
- Panels were divided among team members and literature reviews focusing on measured exposures and toxicity were conducted using a semi-structured approach

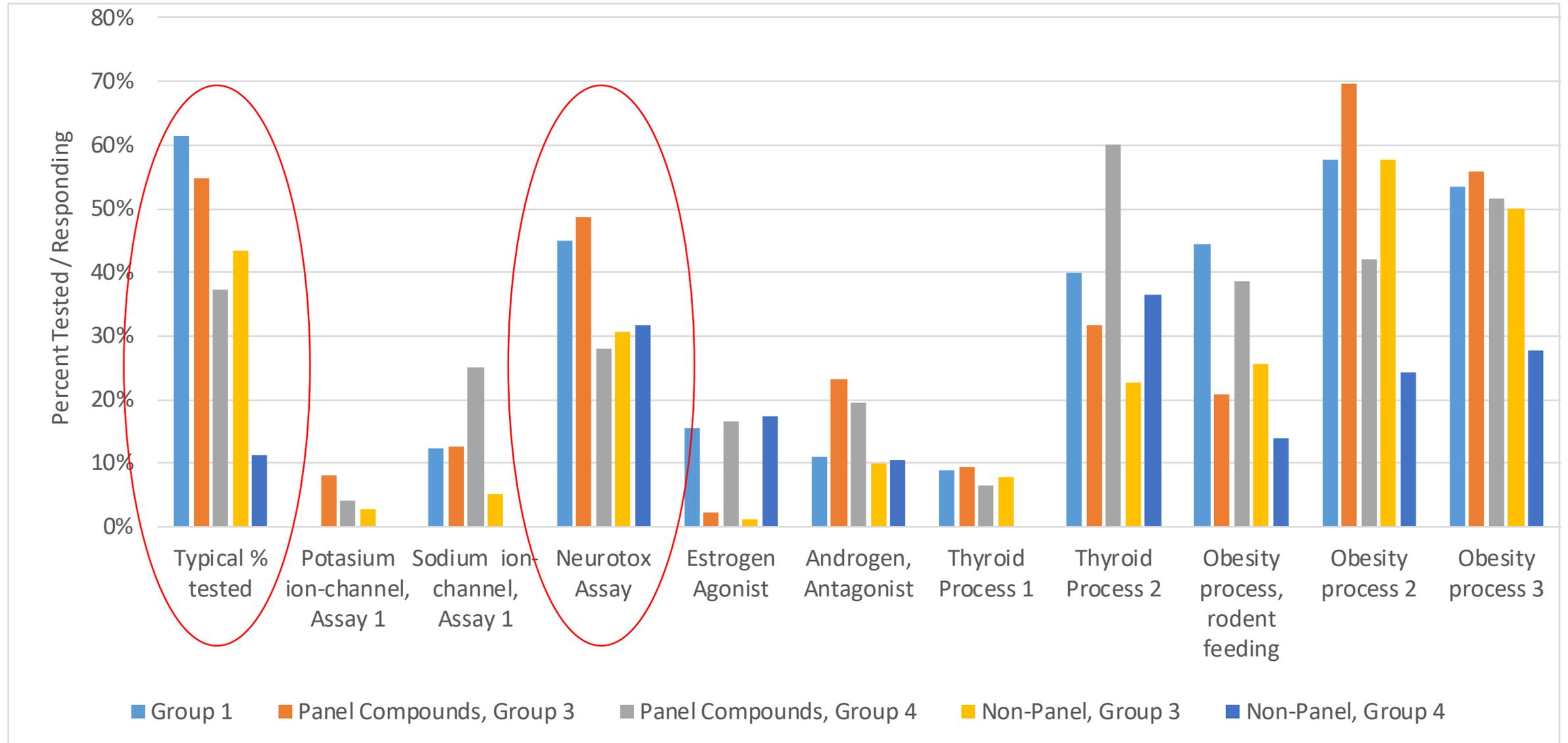
Identifying Candidate Chemicals for Biomonitoring



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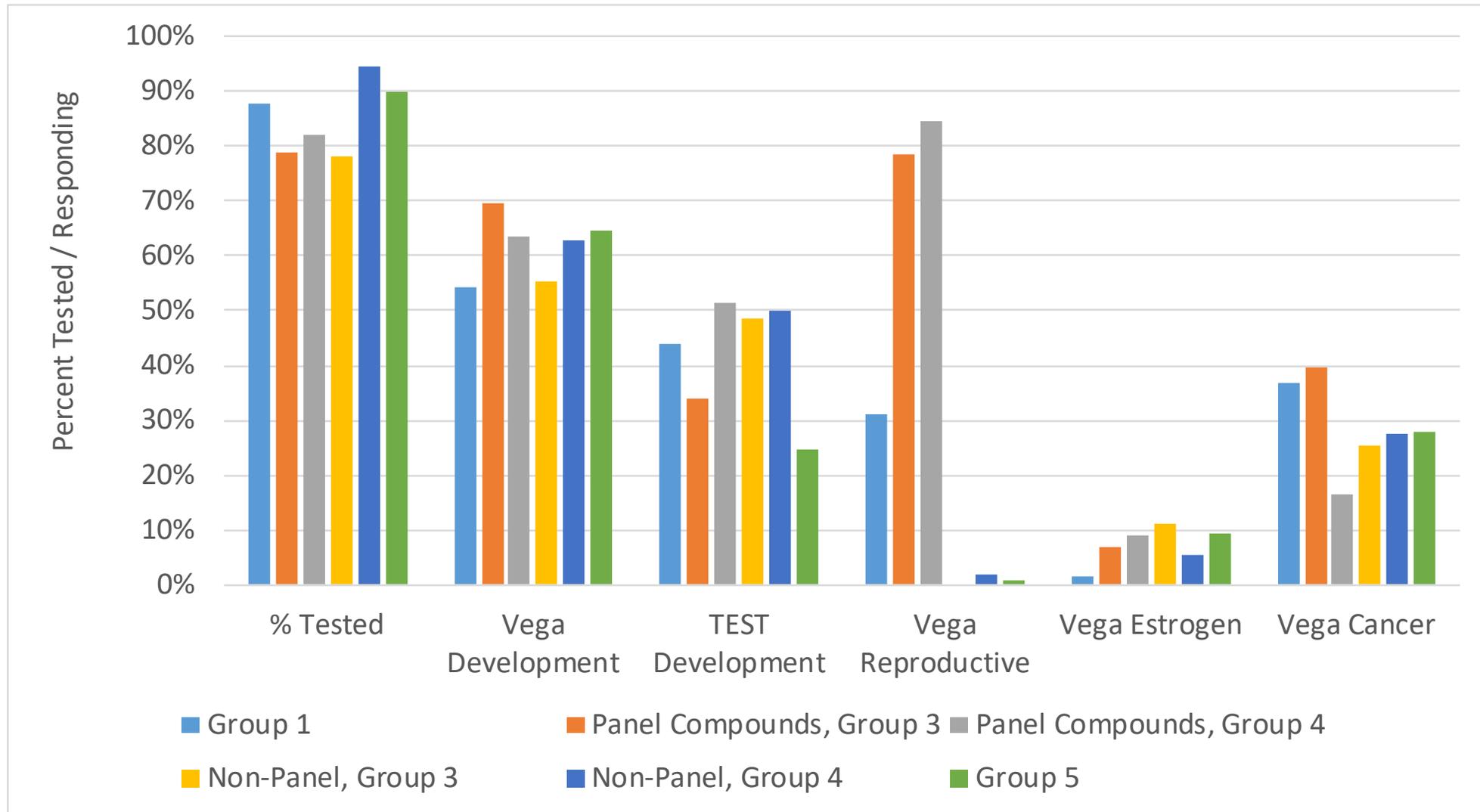
Selected In-vitro testing results, % tested and % hits



Predictive Modeling for Toxicity

- **Endocrine Disruption** - Endocrine Disruptome[®] model, prediction tool that uses molecular docking to predict the binding of compounds to 14 different human nuclear receptors including: androgen, estrogen, glucocorticoid, liver X, and thyroid. Only applied to chemical panels.
- **Toxicity Estimator Software Tool (TEST)** - U.S. EPA developed model that estimates the toxicity using Quantitative Structure Activity Relationships (QSARs) methodologies. Developmental Toxicity (DevTox) and Bioconcentration Factor (BCF) modules utilized.
- **VEGA** – A consortium of models based on QSARs methodologies. Specifically, Developmental, Developmental/Reproductive, Estrogen-binding, and Carcinogenicity modules.
- **CarcinoPred-EL** - Predicts carcinogenicity using three novel ensemble classification models that use seven types of molecular fingerprints and three machine learning methods.

Predictive Modeling for Toxicity Results



Revisiting Alternative Plastics

In vivo/In vitro

	Human Study/Risk Assess.
	<i>In vivo</i> animal studies
	<i>In vitro</i> experiments
	No or Sparse Data

Docking/QSAR Models

	Toxicant-High reliability
	Toxicant-Medium reliability
	Toxicant-Low reliability
	Not likely a Toxicant
	No prediction

In Vitro

	>6 hits
	3-5 hits
	1-2 hits
	No hits
	Not tested

Name	Health Effects/Toxicity						ToxCast Tests <i>In Vitro</i>	
	<i>In vivo</i>				Docking/ QSAR Models			
	Endocrine	Developmental	Reproductive	Neurotoxicity	Endocrine	Developmental	Reproductive	Number of Hits
Di-(2-ethyl hexyl) adipate (DEHA)								
Dibutylated hydroxytoluene (BHT)								
Acetyl tributyl citrate (ATBC)								
2,2,4-trimethyl 1,3-pentanediol diisobutyrate (TXIB)								
Tri-2-ethylhexyl trimellitate (TETM)								
Bis-(2- ethylhexyl)-1,4-benzenedicarboxylate (DEHT)								
Di-butyl adipate (DBA)								
Di(2-ethylhexyl) phosphate (DEHP)								
Diocetyl succinate (DOS)								
Di-butyl sebacate (DBS) [dibutyl decanedioate]								
Di-isononyl- cyclohexane-1, 2-dicarboxylate (DINCH)								
Diocetyl terephthalate (DOTP)								
O-toluene sulfonamide (OTSA)								

Preliminary Results for Alternative Plasticizers

- Thirteen APs were evaluated. Exposure reported through biomarkers for 5 chemicals, while 11 have been measured in environmental media. Toxicity evidence variable.
- 1 recommended for biomonitoring in ECHO based on presence in biofluids or environmental media as well as available toxicological data:
 - Di-(2-ethyl hexyl) adipate (DEHA); Bis-(2-ethylhexyl)-1, 4-benzenedicarboxylate [Bis-(2-ethylhexyl)-1, 4-terephthalate (DEHT)]; Di-isononyl- cyclohexane-1, 2-dicarboxylate (DINCH); Di(2-ethylhexyl) phosphate
- 8 deferred Pending Further Data
 - Dibutylated hydroxytoluene (BHT); Acetyl tributyl citrate (ATBC); 2,2,4-Trimethyl 1,3-pentanediol diisobutyrate (TXIB); Tri-2-ethylhexyl trimellitate (TETM); Dioctyl succinate (DOS) Di-butyl sebacate (DBS) [dibutyl decanedioate]; Dioctyl terephthalate (DOTP); o-Toluene sulfonamide (OTSA)
- 1, Di-butyl adipate (DBA) was considered low priority based on very low levels measured in environmental media
- All but 1 panel now complete, and are being reviewed for consistency before final recommendations

Reviewing Approach

- Adding chemicals to the biomonitoring repertoire will enhance our understanding:
 - Of endocrine disruption, developmental, reproductive and neurotoxic effects in children
 - Of chemical mixture interactions on health effects
- Defined a Process for identifying and ranking chemicals for biomonitoring in ECHO
- Surveyed Government databases, literature and Consumer Products database – yielded over 600 understudied chemicals with potential for health effects in children,
- Applied QSAR/docking predictive models and *in vitro* models/assays
- Created 8 chemical panels – 116 chemicals subjected to in-depth evaluation
- Surveyed published literature:
 - Prevalence in environmental media and human exposure,
 - Known health effects/toxicity relevant to ECHO,
 - Existence of biomarker for biomonitoring.

Conclusions by the Numbers

- Ranked 116 chemicals:
 - Recommended nearly 50 chemicals for biomonitoring in ECHO,
 - Deferred nearly 40 chemicals pending additional data → often specific recommendations are provided
 - Recommended 26 chemicals as low priority for biomonitoring in ECHO.
- Future Opportunities:
- Of 134 compounds with *in-vitro* data and postulated exposure, 65 activate at least 3 assays → literature reviews should focus on exposure, or non-target exposure work can be done to look for exposure
- Of 427 compounds with predictive model testing, 213 suspected of being toxic on in at least 2 models → recommended that *in-vitro* testing be completed

Other Approaches Being Utilized

- EPA is doing great work to study the chemical compositions to determine what use the chemical likely serves in a product, such as fragrance or thickener
- Different “functions” have typical concentration ranges, for example, fragrances typically have low concentrations
- Using QSAR type models to classify compounds
- This is being used in their models to try to refine model based estimates of exposure

Recommendations

- Keep an eye out for compounds highlighted through detailed, individual work
- Look for compounds of potential concern highlighted through other methods
- Conduct more toxicity testing on compounds with potential exposure
- Look for potential exposure of compounds highlighted through toxicity screening

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