
Photo source: http://www.pulseheadlines.com

Leveraging mass spectrometry data to understand maternal and fetal exposome in pregnancy

September 19, 2018

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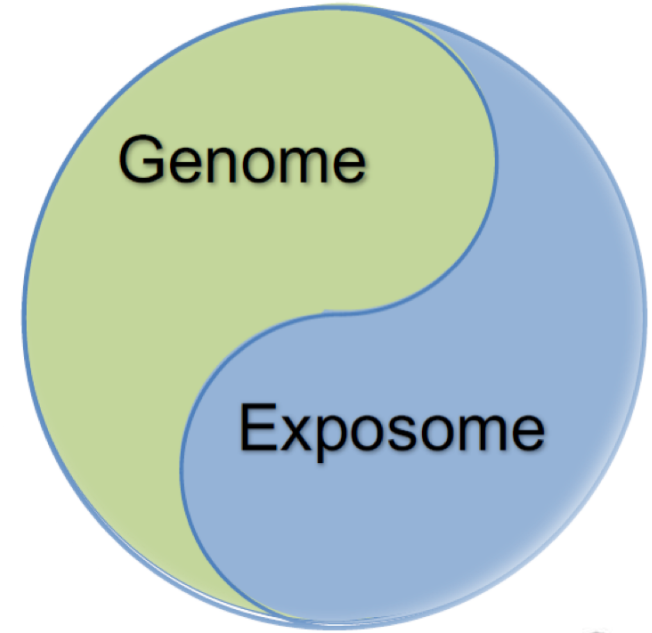
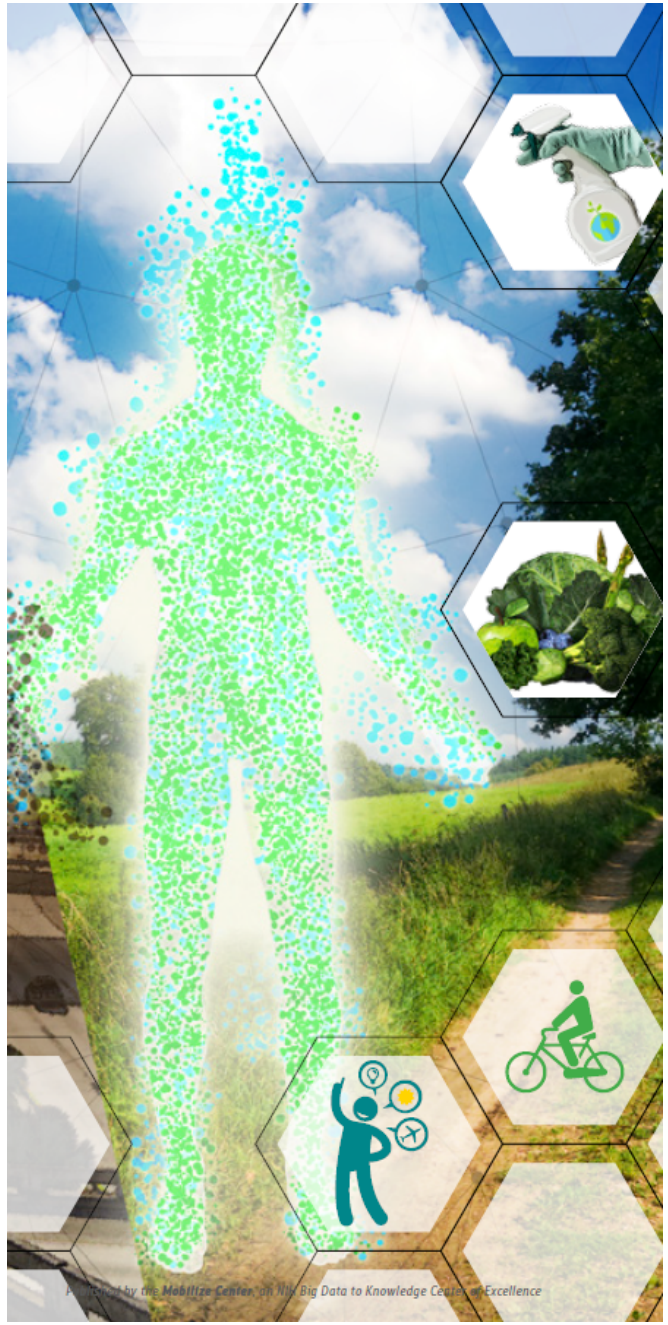
Christopher Wild (2005):
Complementing the Genome with an

"Exposome"





Exposome encompasses:
the ***totality*** of human environmental exposures
from conception onwards

Picture source: D.P. Jones, Yale symposium presentation 2017; Jessica Young's FYC6230 Blog; K. Sainani, BCR 2016

Chemisome: the chemical components of the human ***<u>exposome</u>***

[*i.e.*, totality of human environmental exposures from conception onwards (Wild 2005)]

Slide modified from T.J. Woodruff, with permission

Only <3% of the ~8,000 high-use chemicals are being biomonitored (targeted method)

Goal:

- ***Characterize*** the pregnancy chemisome
- ***Prioritize*** chemicals of interest for further investigation

How? – *Suspect Screening*

Research

Environmental Health Perspectives 2018
doi.org/10.1289/EHP2920

A Suspect Screening Method for Characterizing Multiple Chemical Exposures among a Demographically Diverse Population of Pregnant Women in San Francisco

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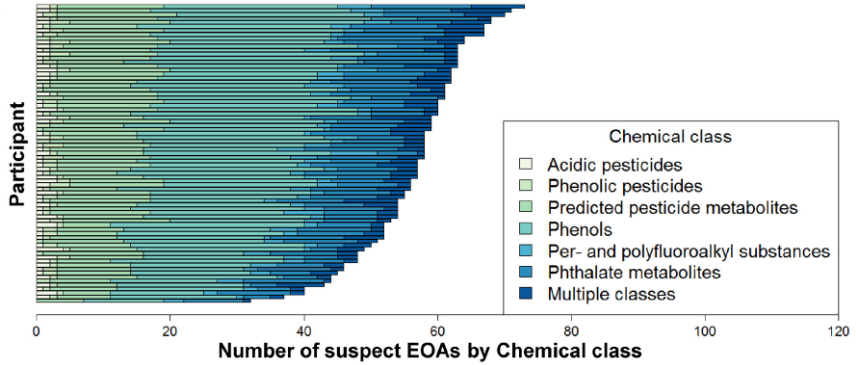
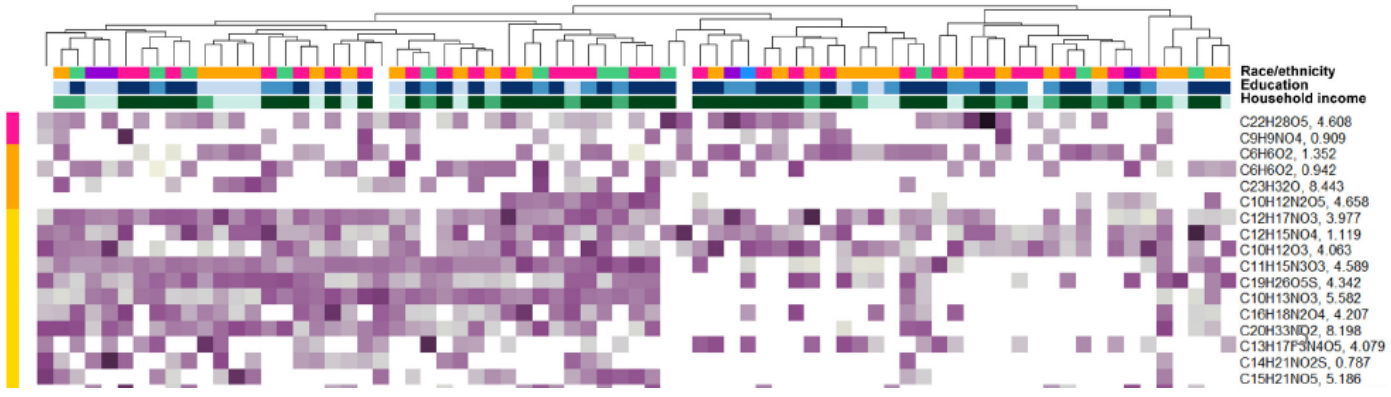




Required Analytical Platform: High Resolution Mass Spectrometer

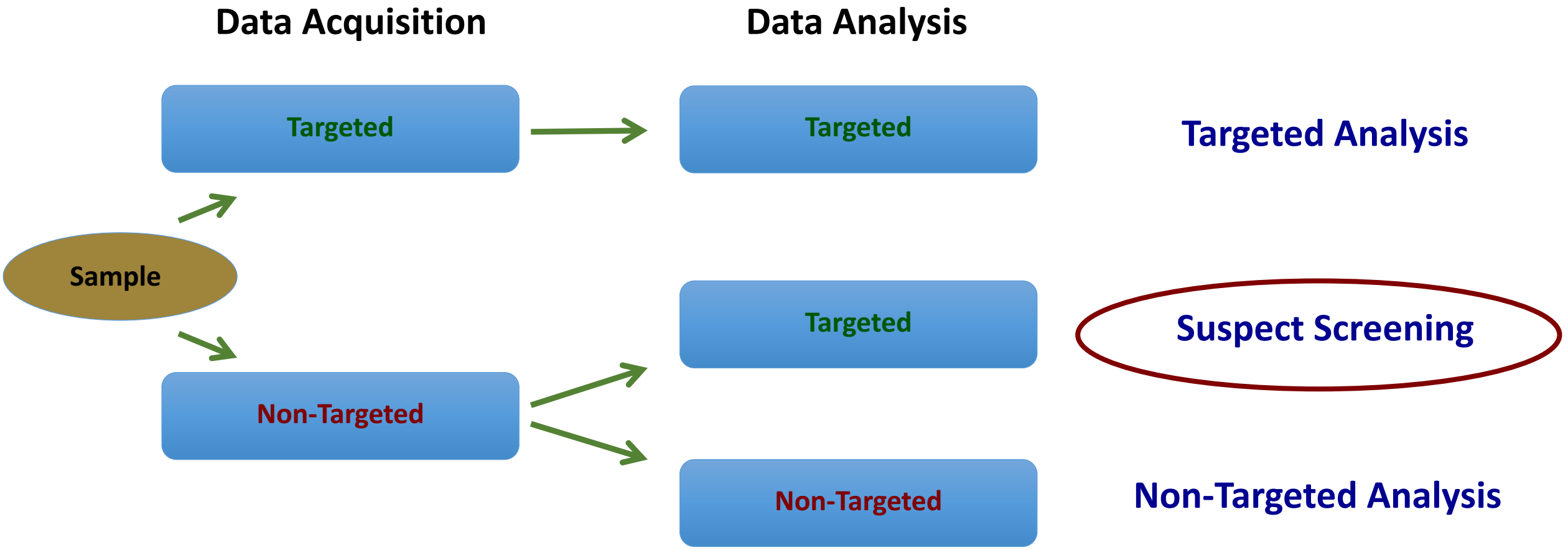
Usually used in tandem with chromatography

Separation of molecules by ionization, and sorting by them by mass (m/z, molecular weight)

Current advances allow **sub-2ppm mass accuracy**

Allows unambiguous assignment of formula to measured masses

Types of Analyses Available Through HRMS



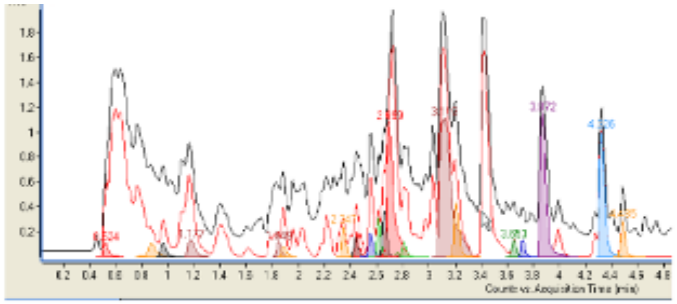
Types of Analyses Available Through HRMS

- Targeted Analysis
  - Reference standard available (RT, HRMS, MS/MS)
  - Acquisition: Targeted; Analysis: Targeted
- Suspect Screening
  - Prior information available BUT no reference standard available
  - Acquisition: Non-Targeted; Analysis: Targeted
- Non-Targeted Analysis
  - NO prior information available
  - Acquisition: Non-Targeted; Analysis: Non-Targeted

Suspect Screening: High-Res Mass Spec (HRMS) + Database

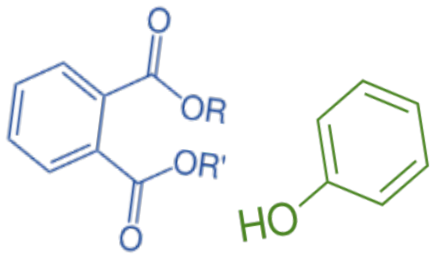
Human serum samples

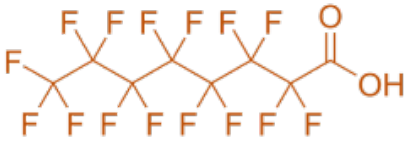
HRMS



Mass peaks

+





PubChem

Chemistry Dashboard

Suspect Chemical Database ("Road Map")

Detected Suspect Features

(mass matched to candidate chemicals in our database)

Confirmation (reference standards)

Suspect Features Detection (and Confirmation)

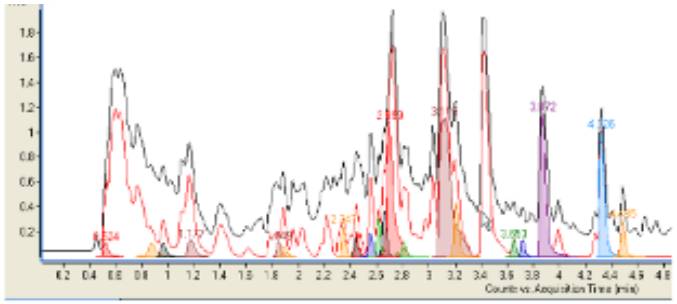
- "Find by Formula"
  - Accurate mass
  - Isotope pattern
  - Peak Shape
  - (Retention Time)

	Values to match	Mass
Formula Matching	Mass tolerance	+/- 10ppm
Negative Ions	Charge carrier	-H
(Retention Time Matching)	RT Tolerance	+/- 0.15 min
Scoring	Mass score contribution	100
	Isotope abundance score contribution	60
	Isotope spacing score contribution	50
	(Retention time score contribution)	100
	Expected MS mass variation	2.0mDa + 5.6ppm
	Expected MS isotope abundance variation	7.5%
Result Filters	Do not match if target score	<70
	Warn if the unobserved 2nd ion's abundance is expected to be	>50
	Do not match if the unobserved 2nd ion's abundance is expected to be	>200

Initial study

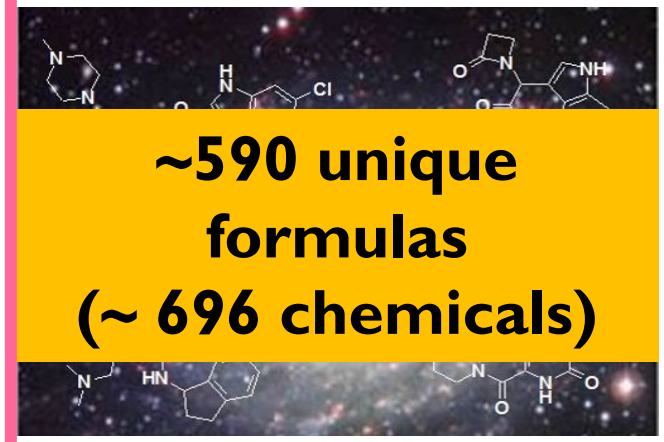
75
Maternal serum samples

HRMS



Mass peaks

+



~590 unique formulas (~ 696 chemicals)

In-house Database

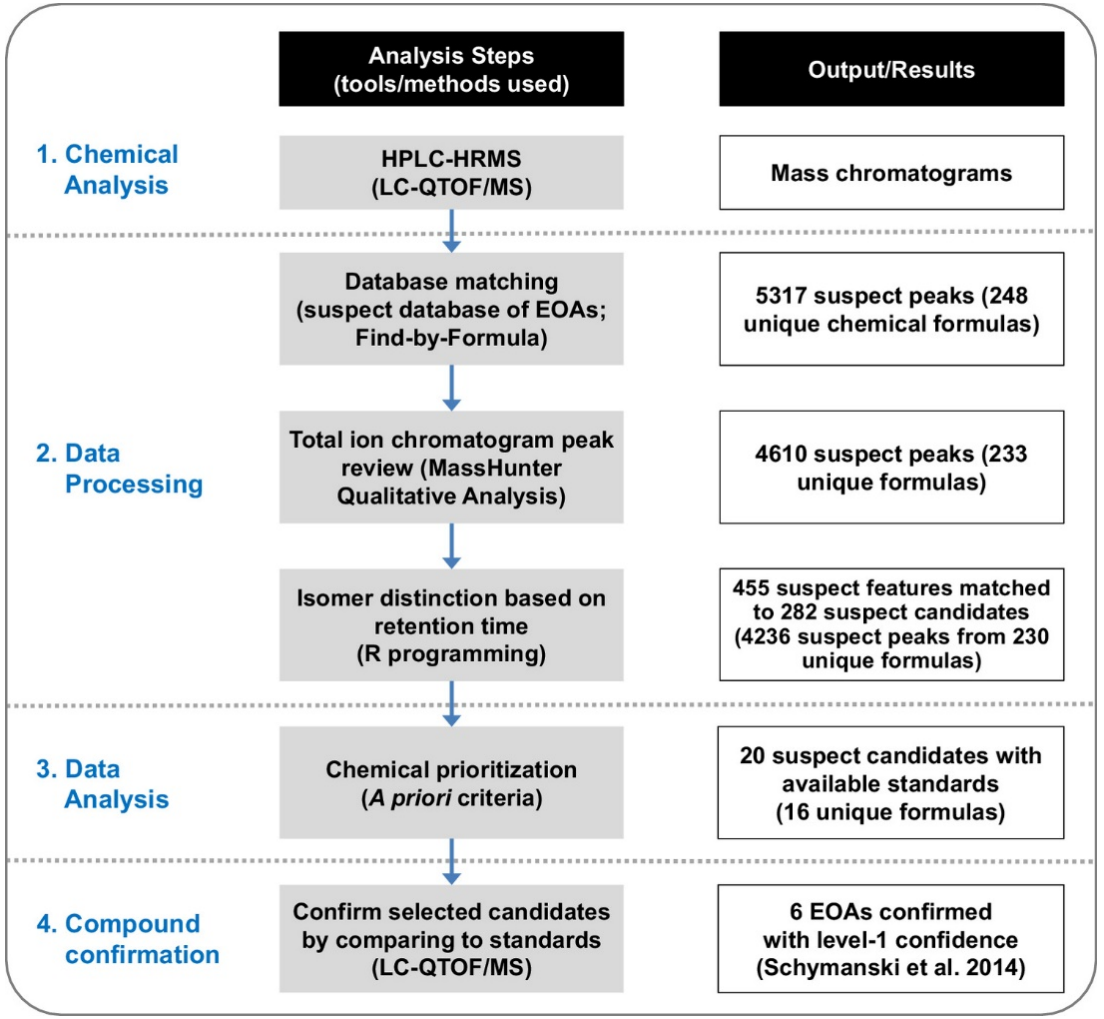
Environmental Organic Acids

Suspect Chemical Database

In-House Database (696):

environmental phenols (bisphenols, parabens etc), pesticides, perfluorinated compounds, flame retardants, phthalate metabolites

Suspect screening of EOAs in 75 maternal serum samples

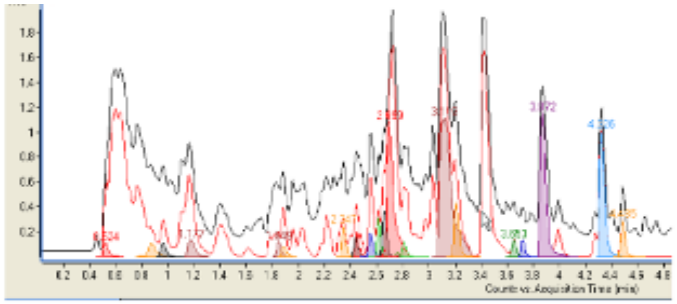


Current study extends the database & sample size

75
Maternal serum samples

HRMS

LC-QTOF/MS



Mass peaks

UCSF Medical Center

ZUCKERBERG SAN FRANCISCO GENERAL Hospital and Trauma Center

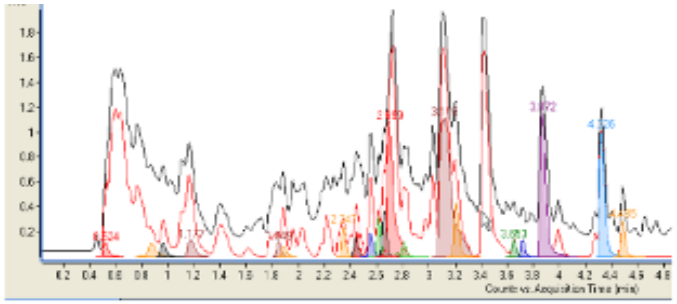
Maternal serum collected at delivery

- **Questionnaires at 2nd trimester (demographics & consumer product use)**
- **Medical records: birth outcomes**

Study design

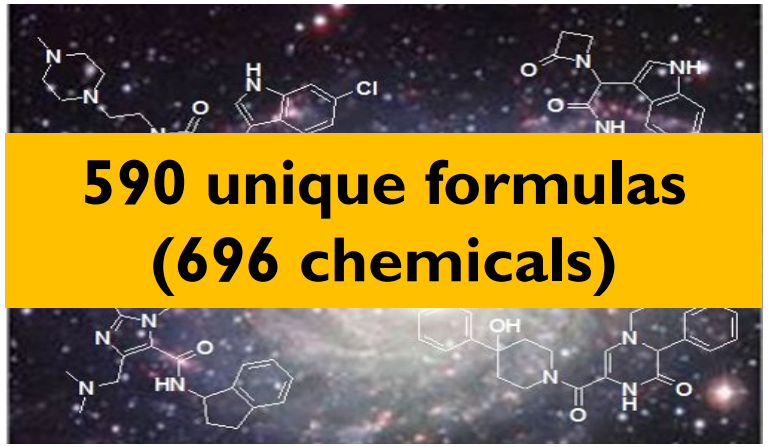
75
Maternal serum samples

HRMS



Mass peaks

+



590 unique formulas (696 chemicals)

Suspect Chemical Database ("Road Map")

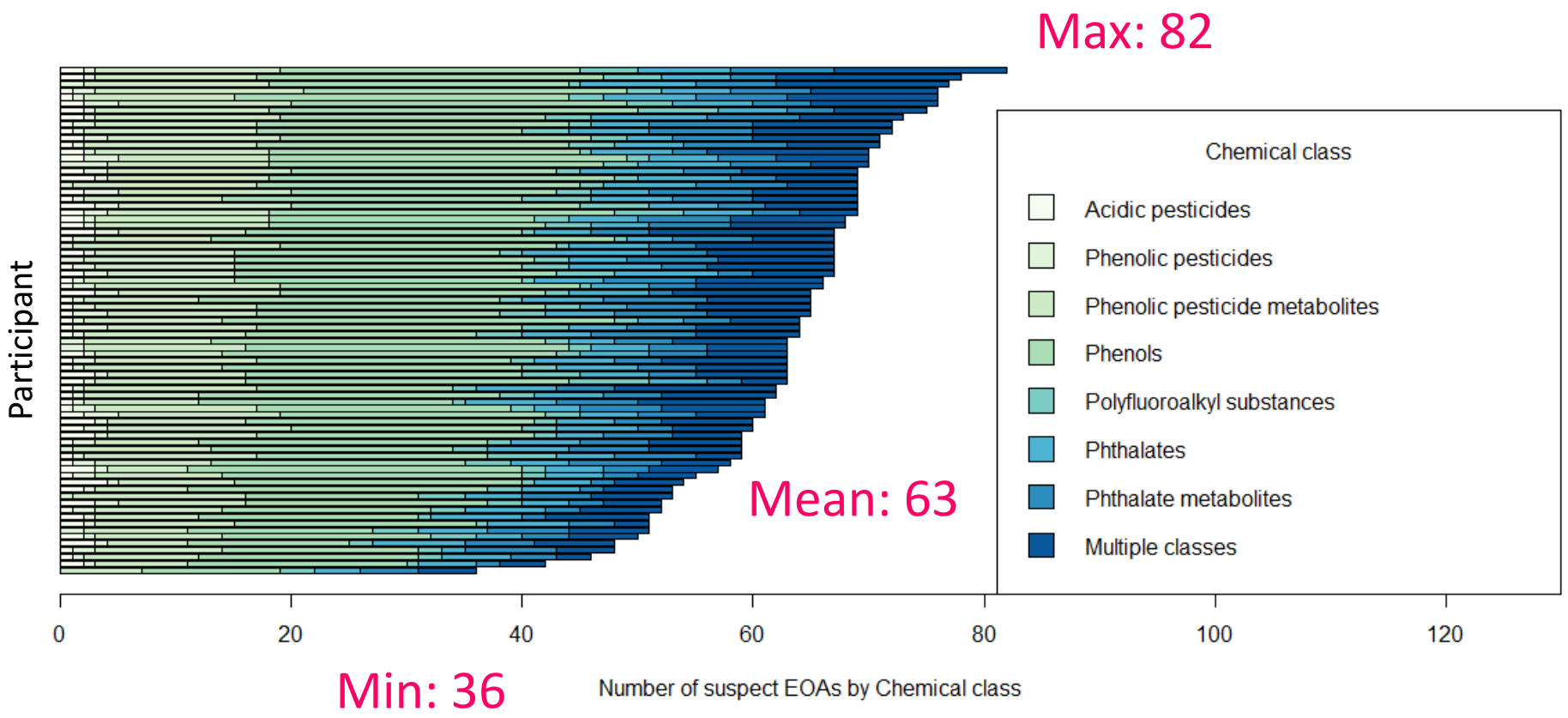
Detected Suspect Features

(mass matched to candidate chemicals in our database)

Priority Chemical Evaluation/ Confirmation/ Association Analysis with Birth Outcomes / Consumer Product Use

Results

Number of suspect EOAs by chemical class (N=75)



Aim 1: Suspect EOAs with detection frequency (DF) ≥ 80%, ranked by DF

15 suspect EOAs (formulas) matched to 27 compounds

Suspects identified after FbF			Information on Matched EOAs			External information		
						Biomonitored?		
Chemical formula	RT (mean)	DF	# isomers	Names	Chemical class	NHANES	CA[a]	HPV[b]
C8HF17O3S	5.502	75	1	Perfluorooctane sulfonic acid	Polyfluoroalkyl substances	√	√	
				2,4-bis(1,1-Dimethylethyl)phenol				
				2,6-bis(1,1-Dimethylethyl)phenol				
				4-Octylphenol				
C14H22O	6.719	74	4	4-tert-Octylphenol	Phenols	√	√	√
				Butyl decyl phthalate				
				Diheptyl phthalate				
C22H34O4	7.560	72	3	Diisoheptyl phthalate	Phthalates			
C10H14O2	4.029	70	1	4-Butoxyphenol	Phenols			
				2-Methylphenol				√
C7H8O	1.999	70	2	4-Methylphenol	Phenols			√
C8H8O3	1.931	66				√	√	√
							√	
							√	
						√	√	
C16H22O4	5.139	65	5	Monooctyl phthalate	Phthalate metabolites	√		
C15H22O3	5.132	64	1	3,5-Di-tert-Butylsalicylic acid	Phenols			
				2-Isopropoxyphenol				
C9H12O2	4.553	64	2	4-Propoxyphenol	Phenols			
C11H14O2	5.129	63	1	Methyl eugenol	Phenols			
C12H17NO3	3.977	63	1	Promecarb metabolite	Phenolic pesticide metabolites			*
C16H22O4	4.773	63	5	Same as above. They are isomers, compounds with the same molecular formula (mass) but different structure (RT).				
C12H15NO4	1.119	61	1	Carbofuran metabolite	Phenolic pesticide metabolites			*
C16H26O2	6.153	61	1	Octylphenol monoethoxylate	Phenols			
C20H26O4	4.457	61	1	Dicyclohexyl phthalate (DCHP)	Phthalates		√	

Over half of the matched chemicals have not been biomonitored

Abbreviations: EOA, environmental organic acid; DF, detection frequency; RT, retention time (in minutes); NHANES, National Health and Nutrition Examination Survey; HPV, high production volume.

Summary of the confirmed compounds, uses and available health hazard information from suspect screening of pregnant women (N=75).

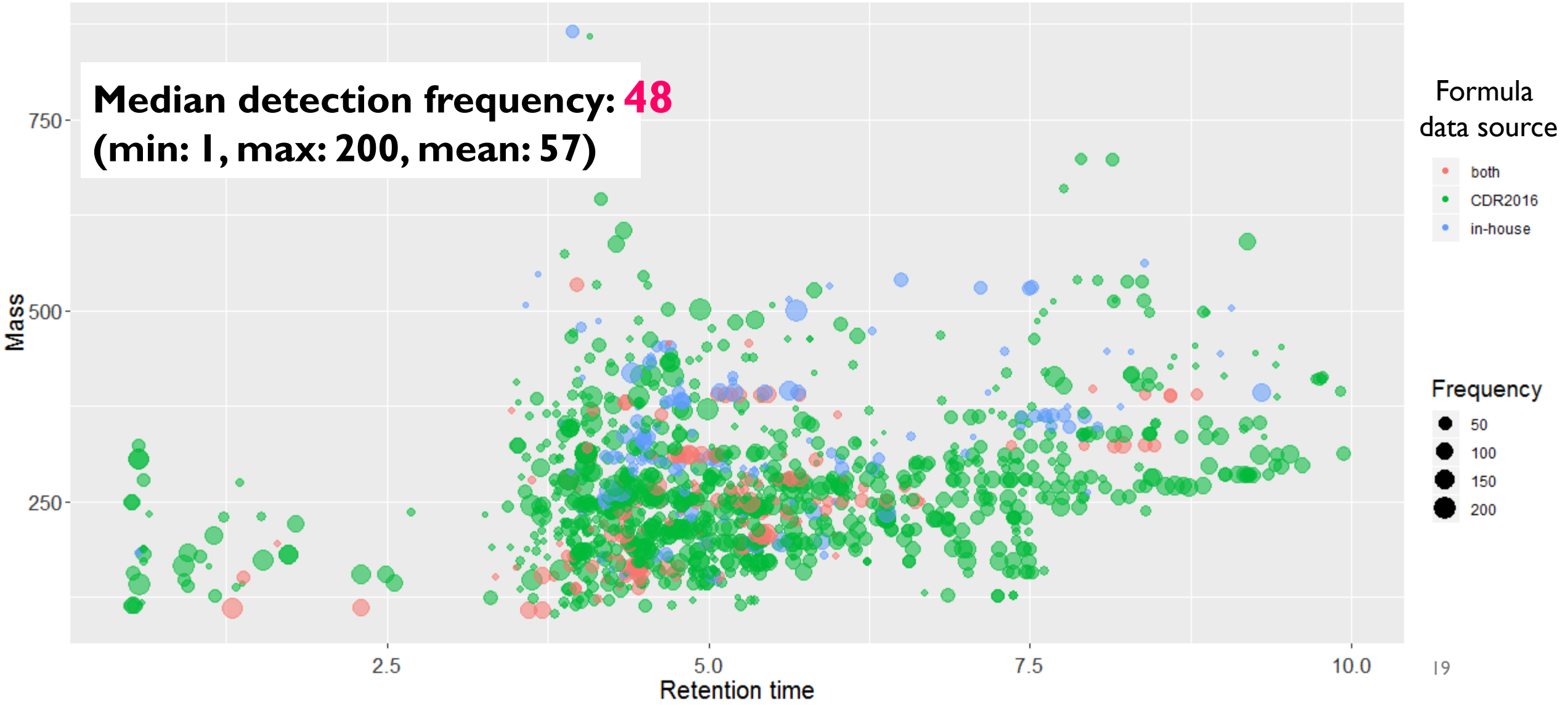
Chemical Name (CASRN)	Selected Chemical Uses from EPA's CPCat Database	Health Hazard Information
2,4-Di-tert-butylphenol (96-76-4)	Toys; Personal care products; Manufacturing	Estrogenic effects
3,5-Di-tert-butylsalicylic acid (19715-19-6)	Not available	No information
2,4-Dinitrophenol (51-28-5)	Cosmetics; Pesticides; Pharmaceuticals; Coloring agents	Cataract formation; Causing genetic defects; Damaging fertility and the fetus
Pyrocatechol (120-80-9)	Cosmetics; Food additives; Pesticides; Pharmaceuticals; Manufacturing	Possible human (Group 2B) carcinogen
2'-Hydroxyacetophenone (118-93-4)	Fragrances; Food additives; Pesticides; Pharmaceuticals; Manufacturing	No information
4-Hydroxycoumarin (1076-38-6)	Pharmaceuticals	No information
CPCat: Chemical and Product Categories		

10-50 million pounds per year
EPA 2017 CDR

Condensed information based on the cassettes obtained from the U.S. EPA's Chemical and Product Categories (CPCat) database (Dionisio et al. 2015; U.S. EPA 2014).

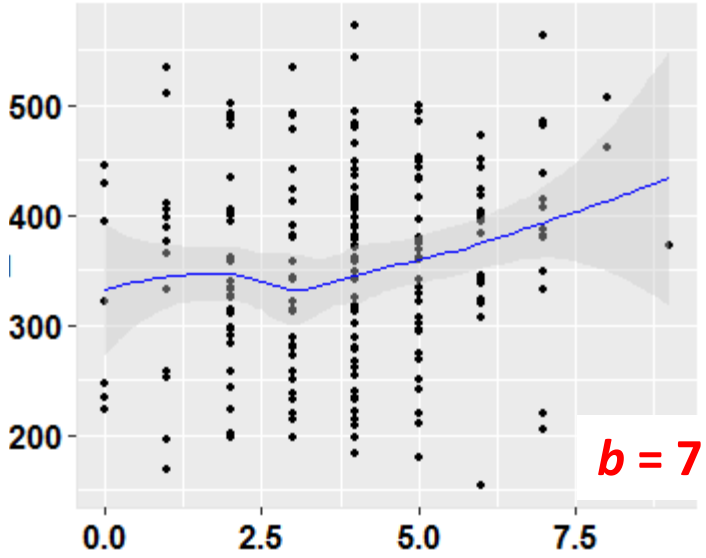
Results from LC-QTOF/MS + Suspect Screening

Overview of 1220 suspect features (mass matches) detected across 200 serum samples



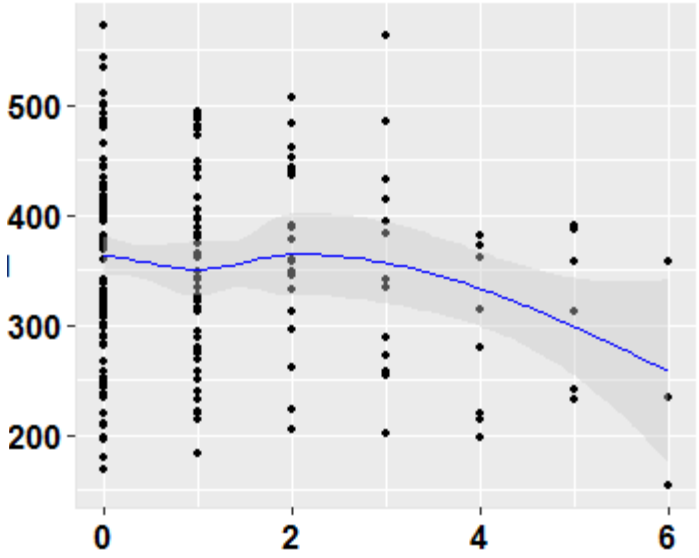
Number of suspect features by # of daily consumer product use and by birth outcomes

*p<0.05



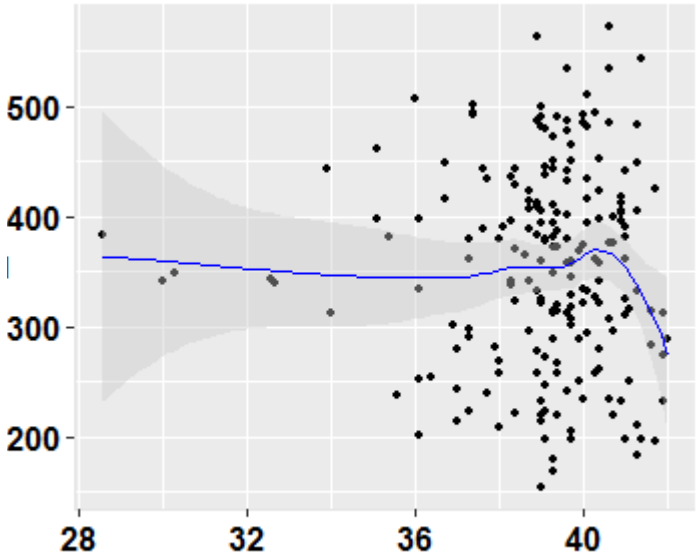
b* = 7.5

 # Personal care product used daily

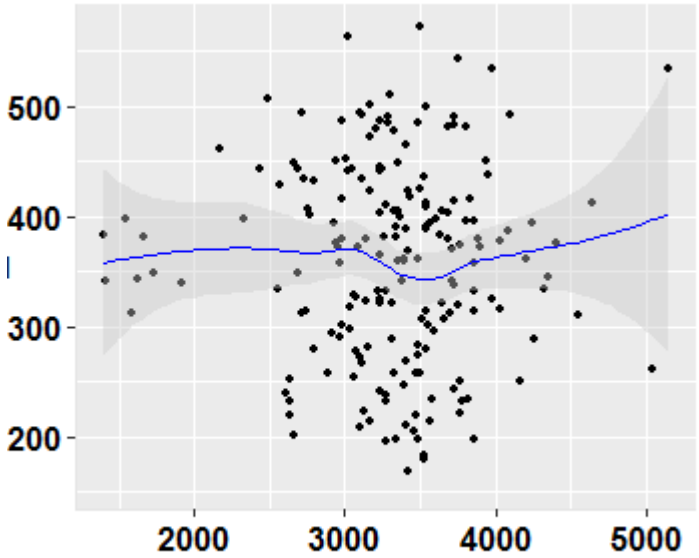


***b* = -10.0**

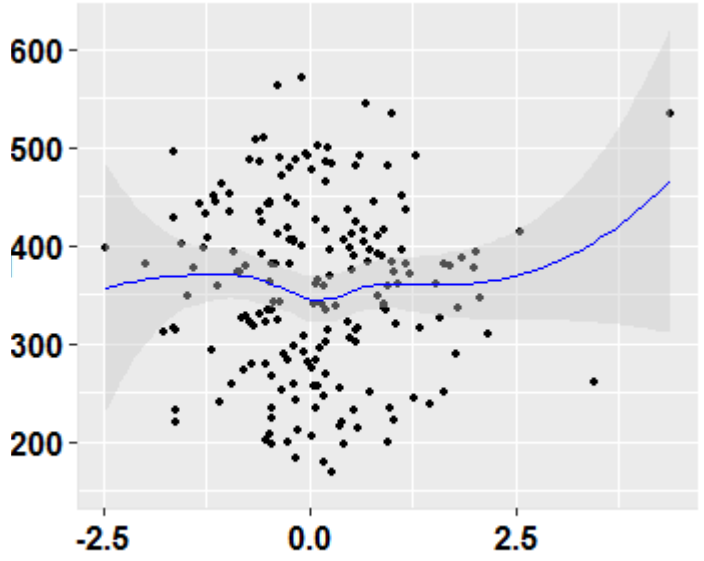
 # Household cleaning product used daily



Gestational age (weeks)



Birth weight (grams)



Birth weight (Z score)

Summary

- Suspect Screening a viable method to more holistically characterize a broad spectrum of environmental chemicals and to identify novel, ubiquitously present compounds and thus prioritize chemicals for targeted method development

Strengths/Limitations

- Relatively large sample size for suspect screening analysis
- Sparse data (lower sensitivity compared to the targeted method)
- Needing further confirmation with reference standards
- Restricted chemical space (EOA library_

Ongoing work/Future directions

- Screening for broader array of chemicals ~3,000
- Develop computational techniques for workflow/chemical analysis
- Additional biological samples

Acknowledgements

Tracey J. Woodruff
Marina Sirota
Rachel Morello-Frosch
Roy R. Gerona
Jackie M. Schwartz
Thomas Lin
Naomi Stotland
Marya Zlatnick
Erin DeMicco
Brittany Tadwilliams
Cheryl Godwin De Medina
Lizbeth Cabrera
Junesoo Park (DTSC)
Miaomiao Wang (DTSC)
Juliet Kinyua (DTSC)
Ting Jiang (DTSC)
Vincent Bessonneau (Silent Spring)
Jon Sobus (US EPA)
Jarod Grossman (Agilent)
Antony Williams (US EPA)
Seth Newton (US EPA)

All CiOB2 study participants

Sirota Lab

Funding

U.S. Environmental Protection Agency (RD-83543301, RD-83564301)
National Institute of Environmental Health Sciences (P01ES022841, R01ES027051)
March of Dimes Prematurity Research Center at Stanford
Preterm Birth Initiative at UCSF

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Pregnancy Exposures to Environmental Chemicals Children's Center

University of California, San Francisco
Preterm Birth Initiative

march of dimes
prematurity research center
at Stanford University

Thank you!

Suspect Screening Blog Post:
prheucsf.blog (Eng/Chinese)

EHP paper: EHP2920
(covered by the ***NY Times***)

PRHE is hiring postdocs!


Photo source: pulseheadlines.com

Contact: PRHE@ucsf.edu

Program on Reproductive Health and the Environment