Polyfluoroalkyl Substances: A Translational Research Story from the Ohio River Valley

Partnerships for Environmental Public Health Webinar

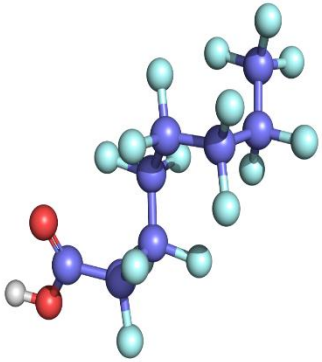
June 13, 2018

Susan M. Pinney, PhD
Professor
University of Cincinnati College of Medicine
Dept. of Environmental Health
Deputy Director, Center for Environmental Genetics
susan.pinney@uc.edu

UNIVERSITY OF Cincinnati

CEG
Center for Environmental Genetics

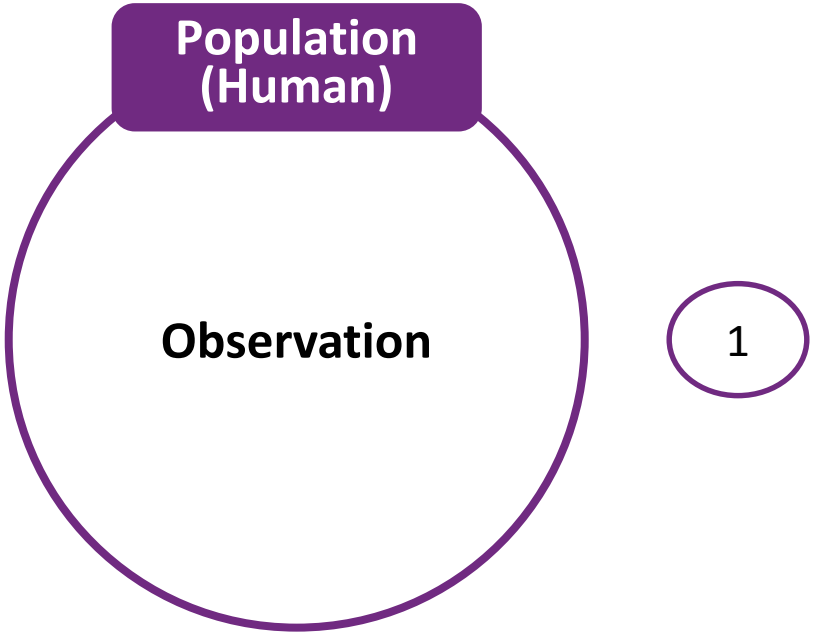
Perfluorooctanoate (PFOA)



- $C_8F_{15}O_2$
- PFOA is a catalyst for polymerization of trifluoroethylene to produce Teflon.
- PFOA is a residual contaminant in non-stick and soil-resistant compounds
- Also has a strong potential to bioaccumulate
  - PFOA half-life: 2.6 to 3.8 years in humans
  - PFOA half-life: hours to ~7 days in mice

- Not metabolized in people; stored in serum liver, and kidney before excretion.
- Large amount released into the Ohio River (near Parkersburg W Va), starting in the 1980s
  - drinking water was contaminated.
- US manufacturers eliminated PFOA emissions and product content at the end of 2015.

PFCs and BCERP



Population Observation

- Elevated PFC levels in NHANES leads to Pilot Study in BCERP Puberty Study Cohorts, including Cincinnati

Timeframe: 2005

Who was involved:

CDC; Antonia Calafat

Cincinnati BCERP; NIEHS Program Directors

Data Source:

- Calafat AM, Wong L, Kuklenyik Z, Reidy JA, Needham LL. Polyfluoroalkyl chemicals in the US population: Data from the National Health and Nutrition Examination Survey (NHANES) 2003–2004 and comparisons with NHANES 1999–2000. Environ Health Perspect. 2007b;115(11):1596–1602.
- Hiatt RA, Haslam SZ, Osuch J. The Breast Cancer and the Environment Research Centers: Transdisciplinary research on the role of the environment in breast cancer etiology. Environ Health Perspect. 2009;117:1814–1822.

PFOA exposure to girls in greater Cincinnati and the San Francisco Bay Area

Cohort study at three sites in the USA:

New York City (Mt. Sinai, Mary Wolff, PI); Cincinnati (U of Cincinnati, Cincinnati Children's Hospital Medical Center, **Frank Biro, PI**); San Francisco Bay area (Kaiser Permanente, Larry Kushi, PI).

Recruit girls at 6-8 years; total 1239 girls

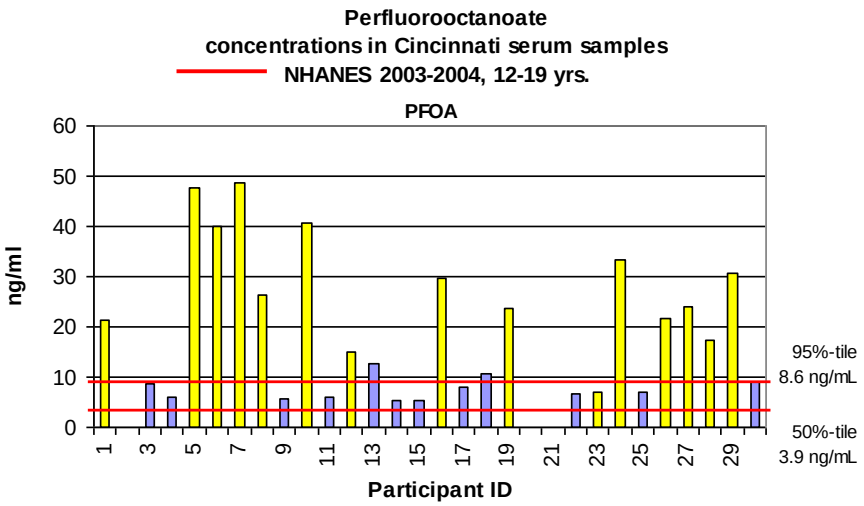
Blood serum (Cincinnati and San Francisco) for environmental biomarkers (including PFCs in serum. N=704).

Sent to CDC Environmental Health Laboratory for analyses.

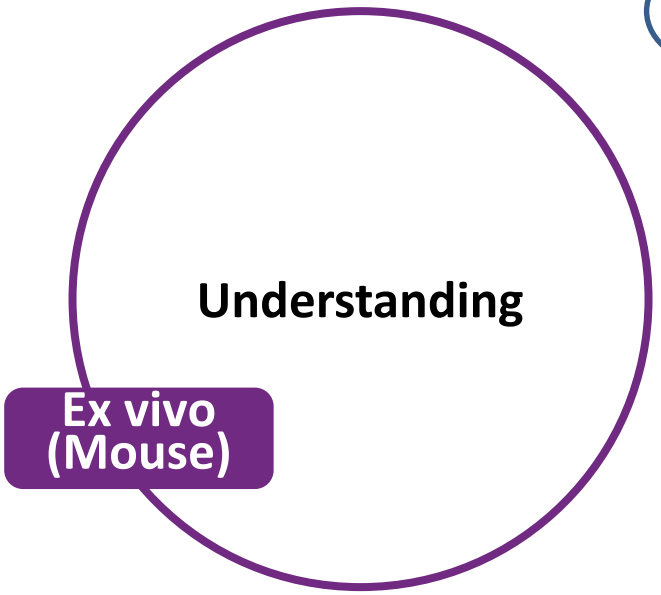
PFAS – Analyses conducted with solid phase extraction, high performance liquid chromatography, tandem mass spectron

Results:

Higher levels of perfluorooctanoic acid (PFOA or C-8) than in US children (NHANES study)



PFCs and BCERP



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Ex vivo Understanding

- PFOA stimulates mammary gland development in C57Bl/6 **mice**

Timeframe: 2006-2008

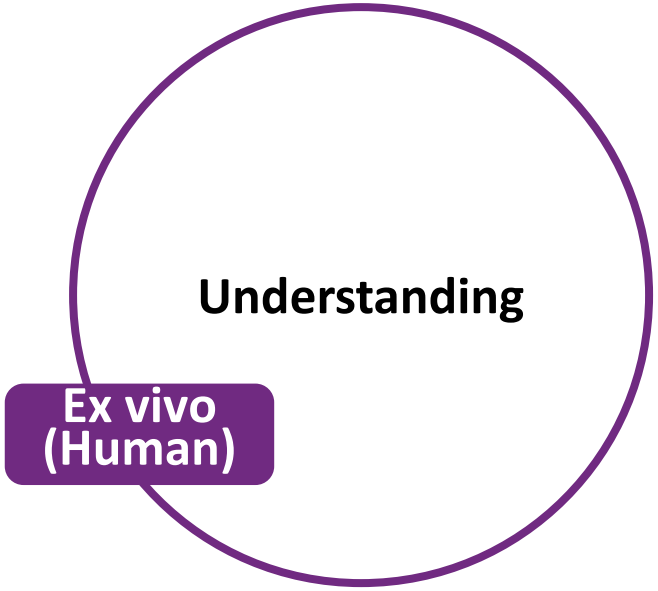
Who was involved:

Haslam Lab; Michigan State University

Cincinnati BCERP

Data Source: Zhao, Y, Tan YS, Haslam, SZ, Yang C (2010). Perfluorooactanoic acid effects on steroid hormone and growth factor levels mediate stimulation of peripubertal mammary gland development in C57Bl/6 mice. *Toxicol Sci* 115:214-224. [Epub ahead of print, Jan 29] DOI: 10.1093/toxsci/kfq030

PFCs and BCERP



3

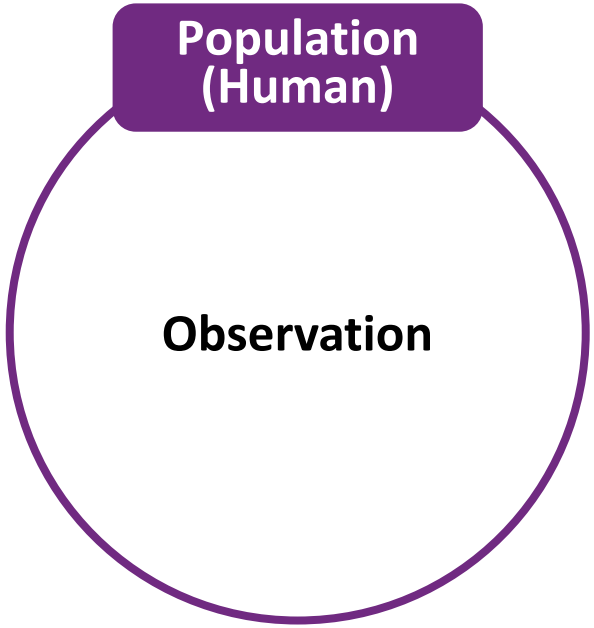
Ex vivo Understanding

- Is PFC exposure associated with puberty development in **girls?**

Timeframe: 2006-2008
Who was involved:
Cincinnati BCERP
Cincinnati Community Members
Haslam Lab; Michigan State University

Data Source: Pinney SM, Windham GC, Biro FM, Kushi LH, Herrick RL, Yaghjyan L, Calafat A, Kato K, Succop P, Bornschein R. Age At Puberty In Relation To Prepubertal Measures Of PFOA – New Findings. International Society of Environmental Epidemiology, Barcelona, Spain, September, 2011.

PFCs and BCERP



4

Population Observation

- Expanded PFC analysis to all girls aged 6-8 in the Cincinnati and California Cohorts

Timeframe: (2008, 2009)
Who was involved:
Cincinnati BCERP
California BCERP

Data Source: Pinney SM, Biro FB, Windham G, Herrick RL, Yaghjyan L, Calafat AM, Succop P, Sucharew H, Ball KM, Kayoko K, Kushi LH, Bornschein R. Serum biomarkers of polyfluoroalkyl compounds in young girls in greater Cincinnati and the San Francisco Bay area. Environmental Pollution 2014 Jan 184:327-34. Epub 2013 Oct 1. PMID: 24095703.

Puberty Main Study: 704 girls
Site-Specific BCERC PFOA biomarker Levels

Location	Number of Subjects	Number of Subjects above LOD	LOD (ng/mL)	% above LOD	Range of PFOA Levels (ng/mL)	Median PFOA Level (ng/mL)
Cincinnati	353	352	0.1	99.7%	<LOD-55.9	7.3
Kaiser	351	351	0.1	100	2.4-18.2	5.8

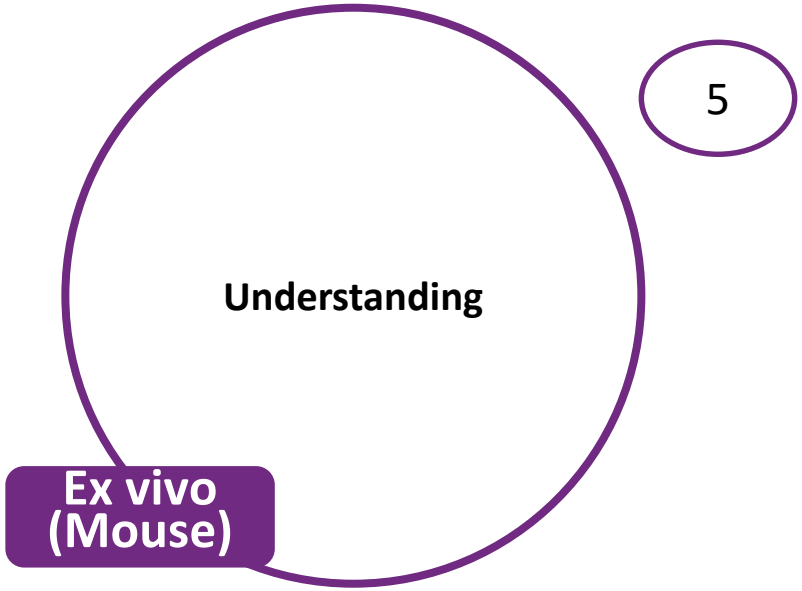
Median level for NHANES 12-19 year old children in the US, in 2005-2006, was 3.8 ng/mL

Number of study participants with PFOA serum concentrations greater than the NHANES 2005-2006 95th percentile value

Location	Total #	>8.4 ng/ml (NHANES 95th %)	
		#	%
Cincinnati	353	136	38.5%
Kaiser	351	50	14.3%

Data Source:Pinney SM, Biro FB, Windham G, Herrick RL, Yaghjyan L, Calafat AM, Succop P, Sucharew H, Ball KM, Kayoko K, Kushi LH, Bornschein R. Serum biomarkers of polyfluoroalkyl compounds in young girls in greater Cincinnati and the San Francisco Bay area. Environmental Pollution 2014 Jan 184:327-34. Epub 2013 Oct 1. PMID: 24095703.

PFCs and BCERP



5

Ex vivo Understanding

- General research on EGFR signaling and progesterone receptor binding

Timeframe: 2009-2014

Who was involved:

Haslam Lab; Michigan State University

Data Sources:

Aupperlee et al., 2014 Epidermal growth factor receptor (EGFR) signaling is a key mediator of hormone-induced leukocyte infiltration in the pubertal female mammary gland. Endorinology 155(6), 2301-13. doi: 10.1210/en.2013-1933

Zhao et al. 2012. Perfluorooctanoic acid effects on ovaries mediate its inhibition of peripubertal mammary gland development in Balb/c and C57Bl/6 mice. Reprod Toxicol. 2012 Jul;33(4):563-76. doi: 10.1016/j.reprotox.2012.02.004.

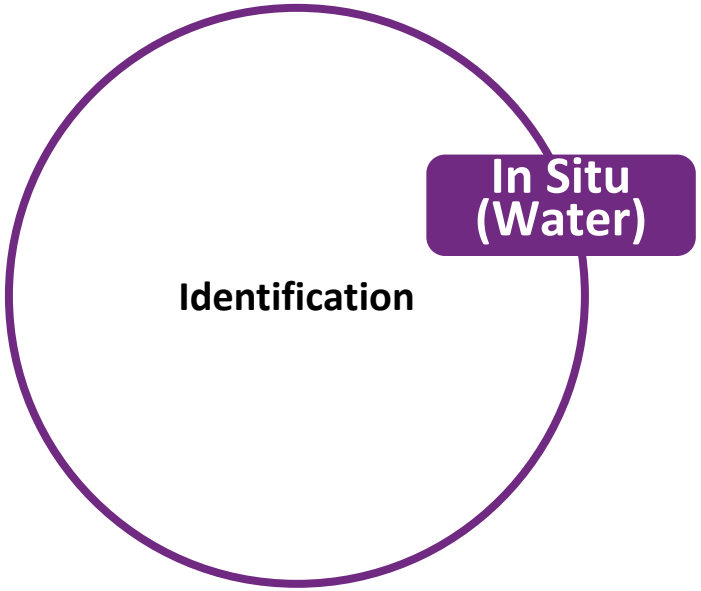
Santos, SJ, Haslam, SZ, Conrad, SE. 2010. Signal transducer and activator of transcription 5a mediates mammary ductal branching and proliferation in the nulliparous mouse. Endocrinology. 2010 Jun;151(6):2876-85. doi: 10.1210/en.2009-1282.

Zhang et al. 2010. Tip30 deletion in MMTV-Neu mice leads to enhanced EGFR signaling and development of estrogen receptor-positive and progesterone receptor-negative mammary tumors. Cancer Res. 2010 Dec 15;70(24):10224-33. doi: 10.1158/0008-5472.

Yang, et al. 2009. Differential effects of peripubertal exposure to perfluorooctanoic acid on mammary gland development in C57Bl/6 and Balb/c mouse strains. Reprod Toxicol. 2009 Jun;27(3-4):299-306. doi: 10.1016/j.reprotox.2008.10.003.

Santos et al. 2009. Progesterone receptor A-regulated gene expression in mammary organoid cultures. J Steroid Biochem Mol Biol. 2009 Jul;115(3-5):161-72. doi: 10.1016/j.jsbmb.2009.04.001.

PFCs and BCERP



6

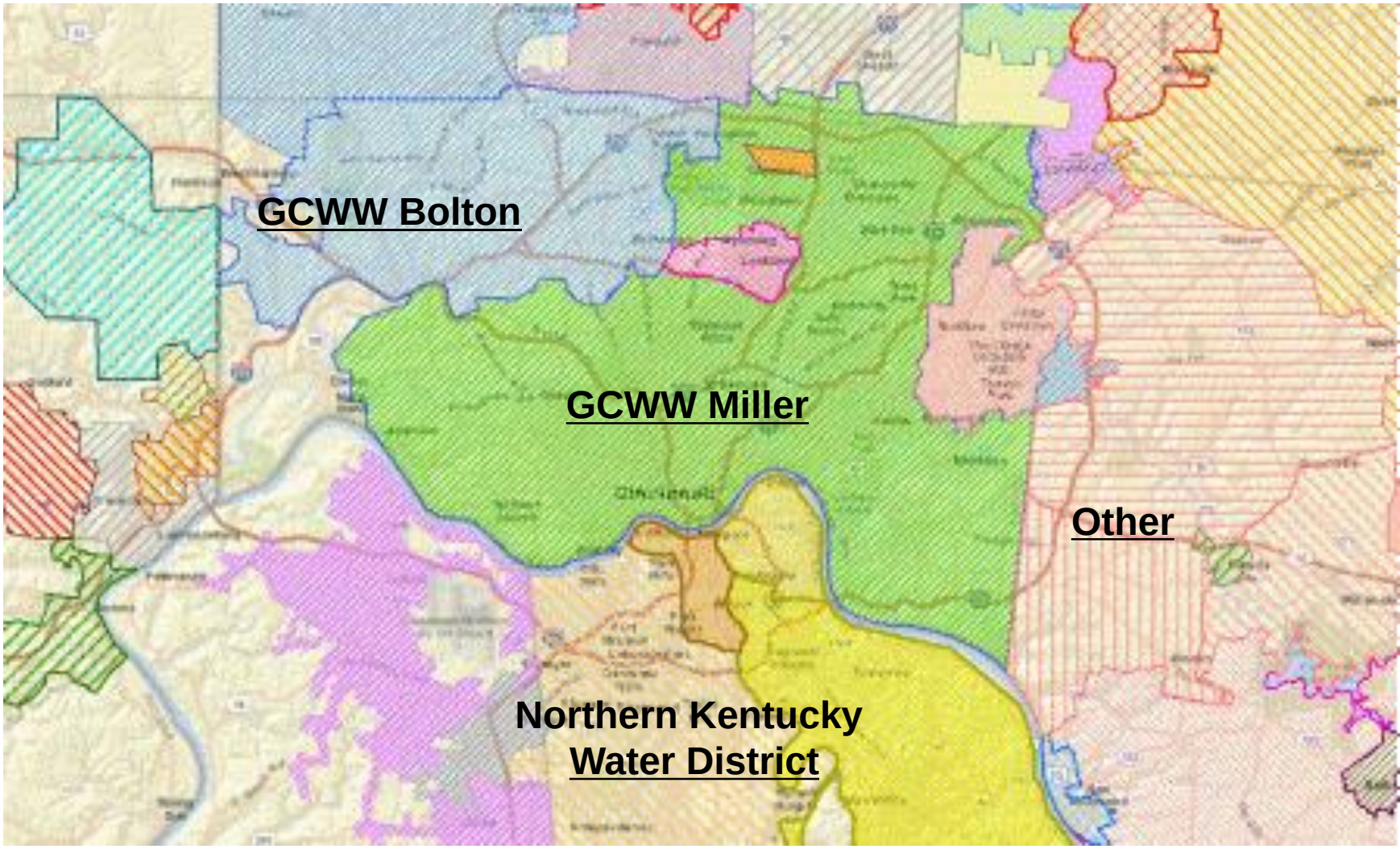
Exposure Identification

- Identified drinking water as probable exposure pathway

Timeframe: (2010-2013)
Who was involved:
Cincinnati BCERP
Cincinnati Community Members

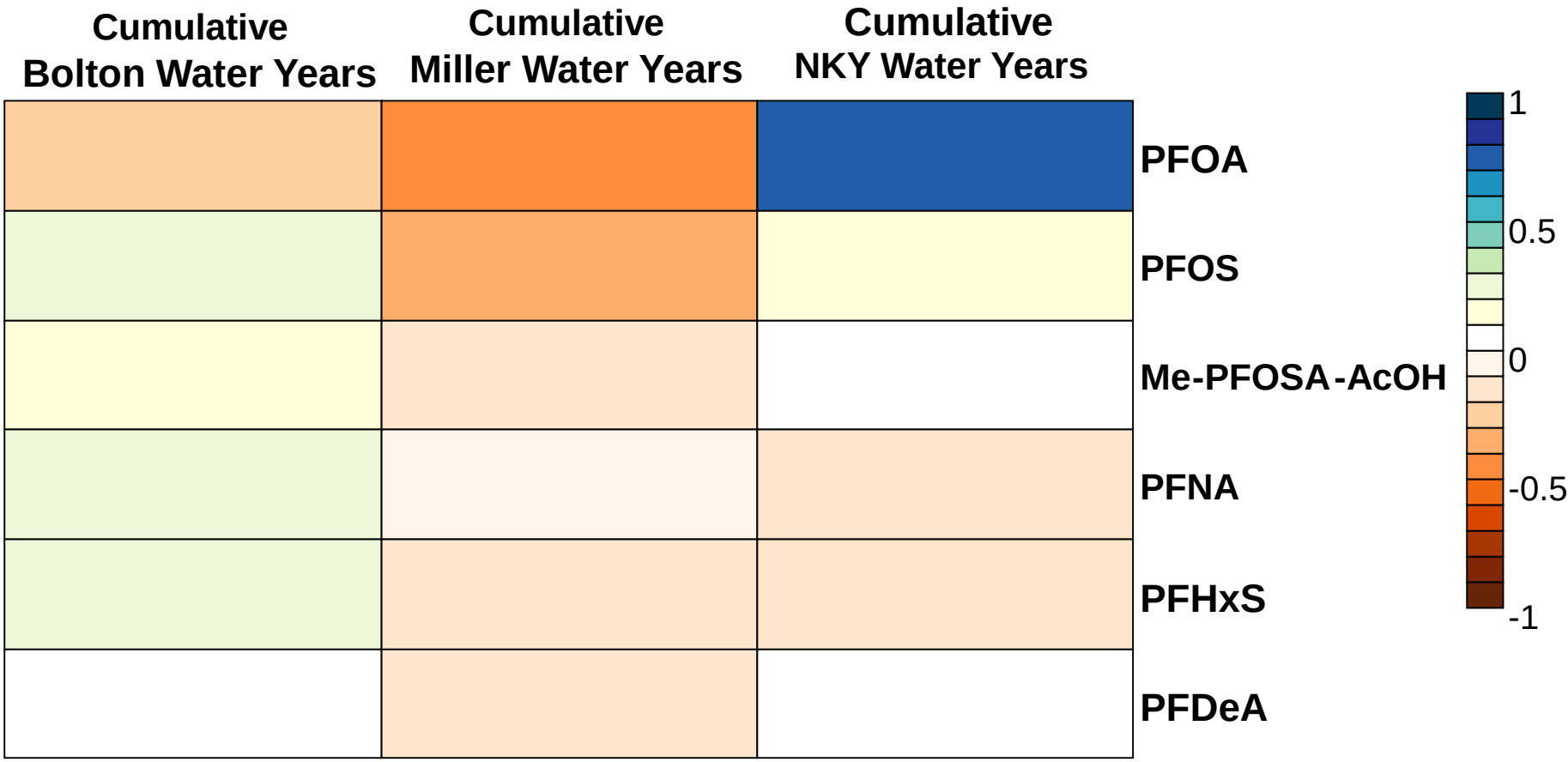
Data Source: Pinney SM, Biro FB, Windham G, Herrick RL, Yaghjyan L, Calafat AM, Succop P, Sucharew H, Ball KM, Kayoko K, Kushi LH, Bornschein R. Serum biomarkers of polyfluoroalkyl compounds in young girls in greater Cincinnati and the San Francisco Bay area. Environmental Pollution 2014 Jan 184:327-34. Epub 2013 Oct 1. PMID: 24095703.

Water Sources For Study Participants

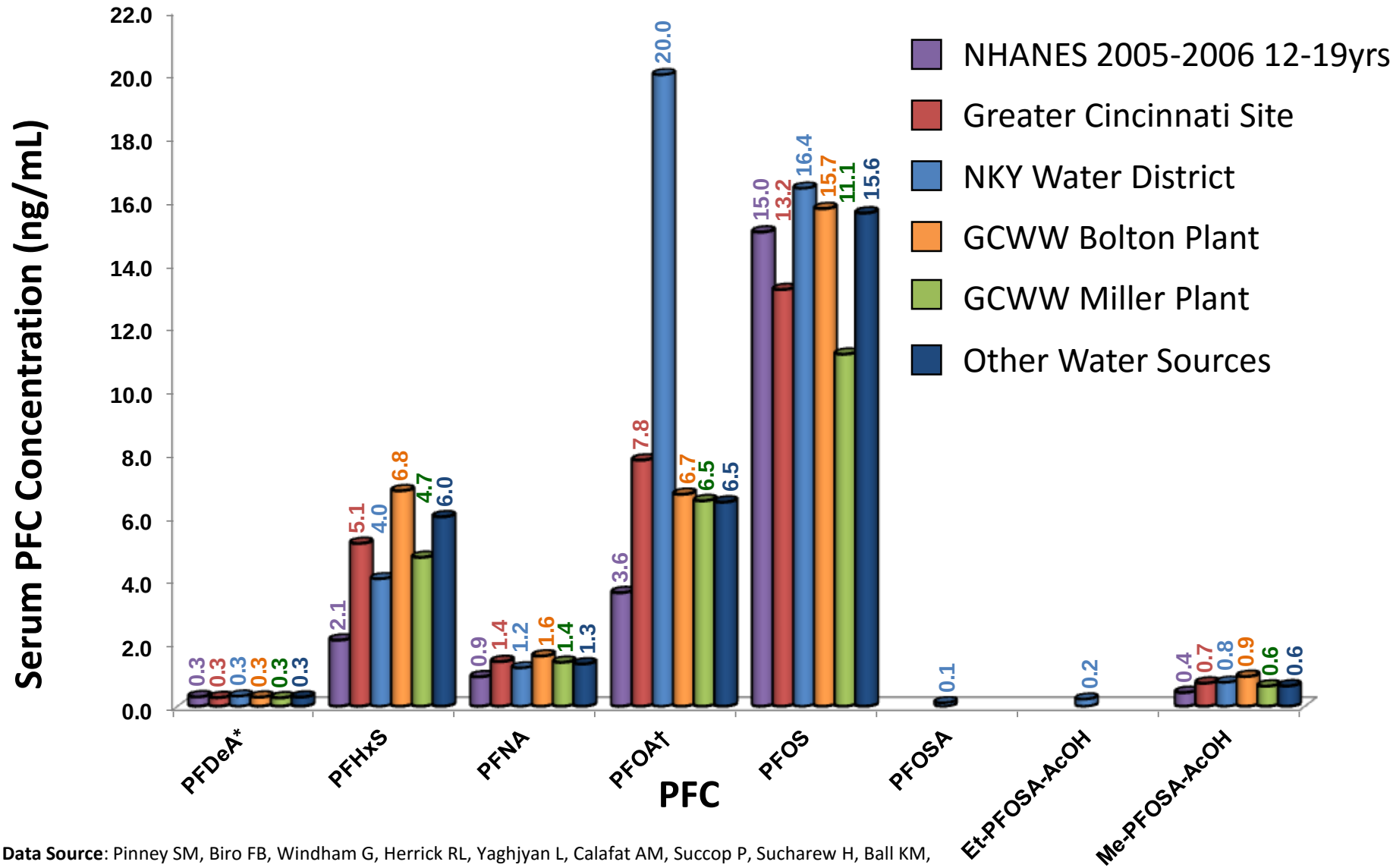


Linking of water source to residential address done by Robert Herrick, MECEH fellow, Environmental Pollution, 2013

Correlation between cumulative years of drinking water with serum PFC

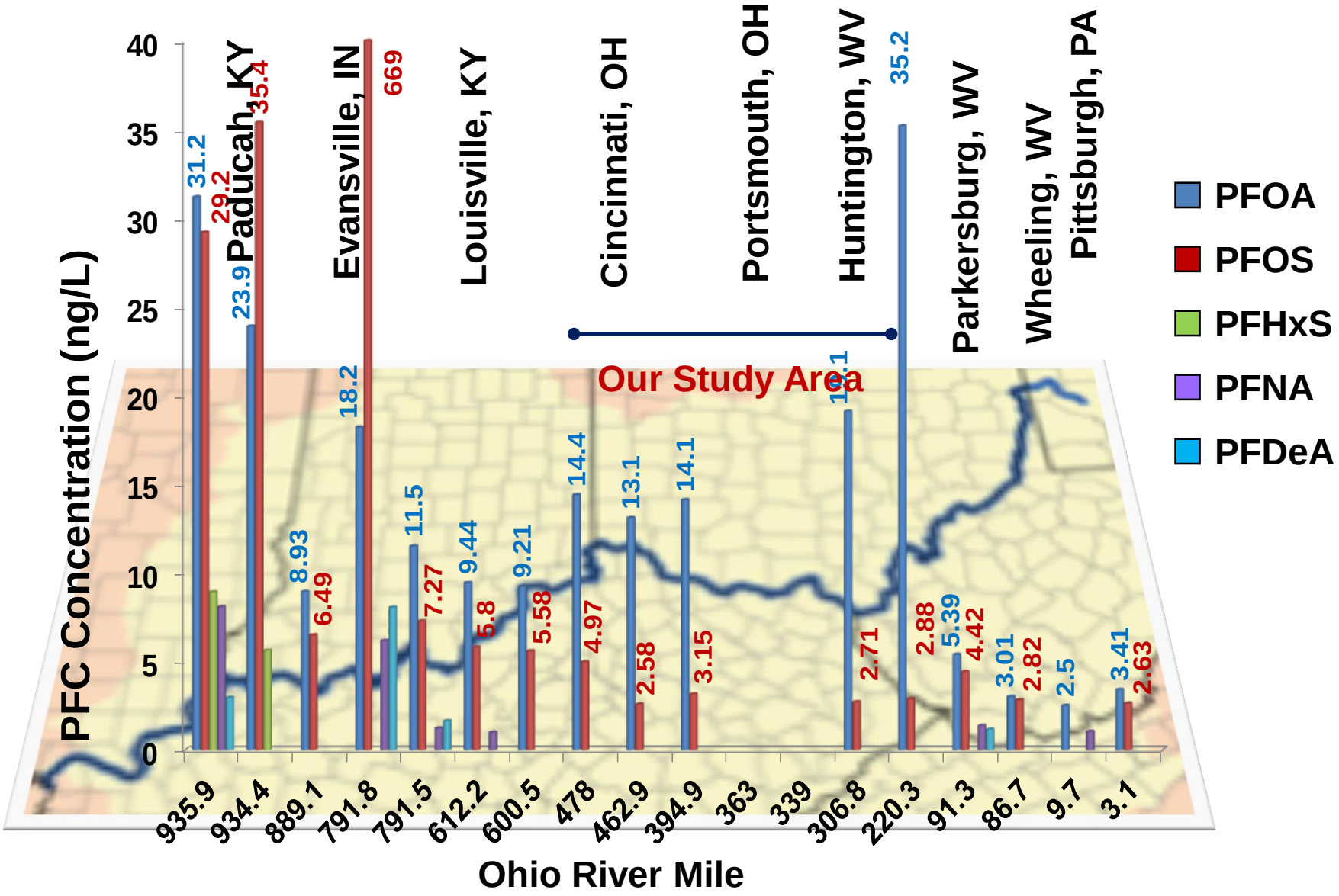


Geometric Means of Measured PFCs
GC Site - Water Source at Enrollment

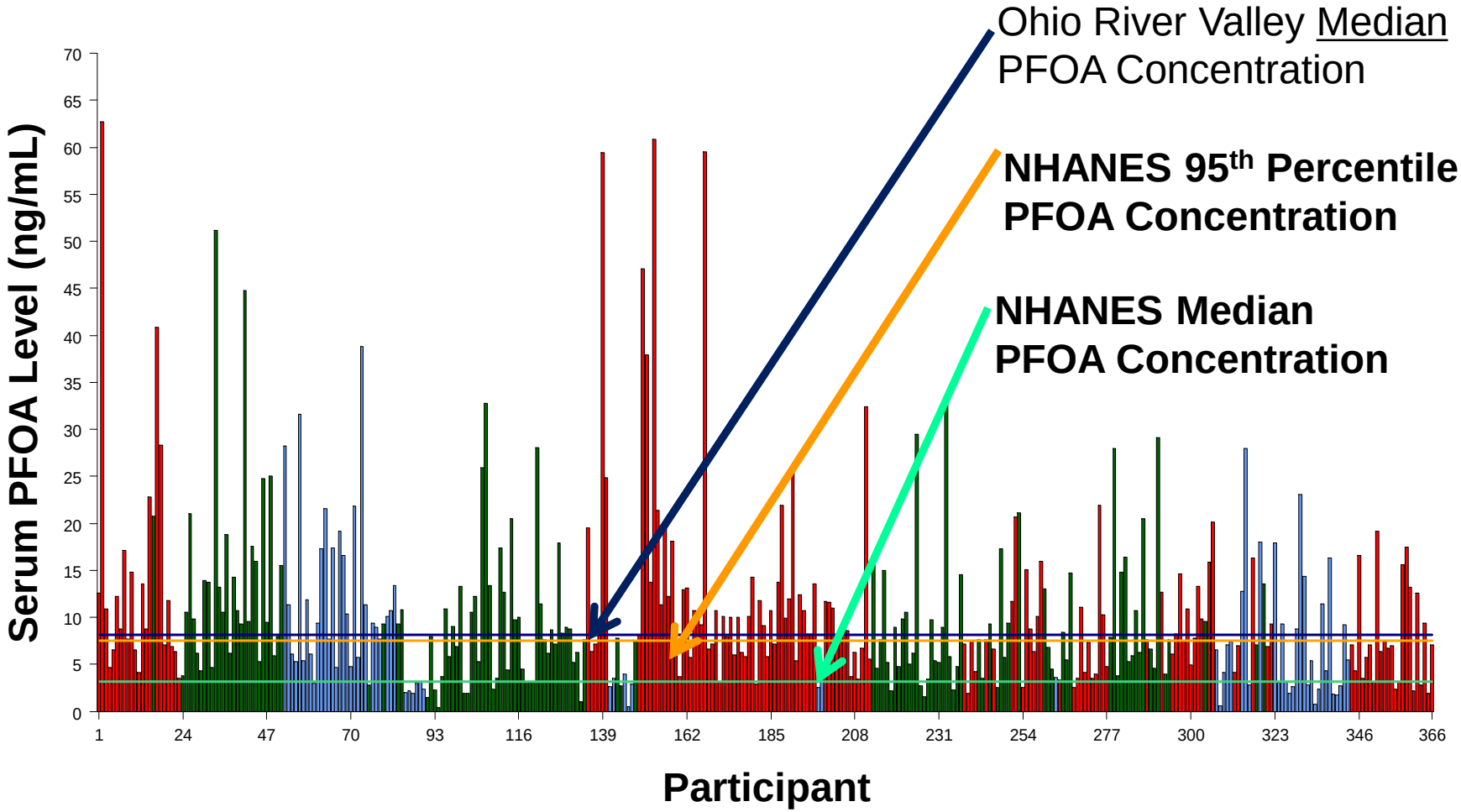


Data Source: Pinney SM, Biro FB, Windham G, Herrick RL, Yaghjyan L, Calafat AM, Succop P, Sucharew H, Ball KM, Kayoko K, Kushi LH, Bornschein R. Serum biomarkers of polyfluoroalkyl compounds in young girls in greater Cincinnati and the San Francisco Bay area. Environmental Pollution 2014 Jan 184:327-34. Epub 2013 Oct 1. PMID: 24095703.

PFCs in the Ohio River, Sept. 2009

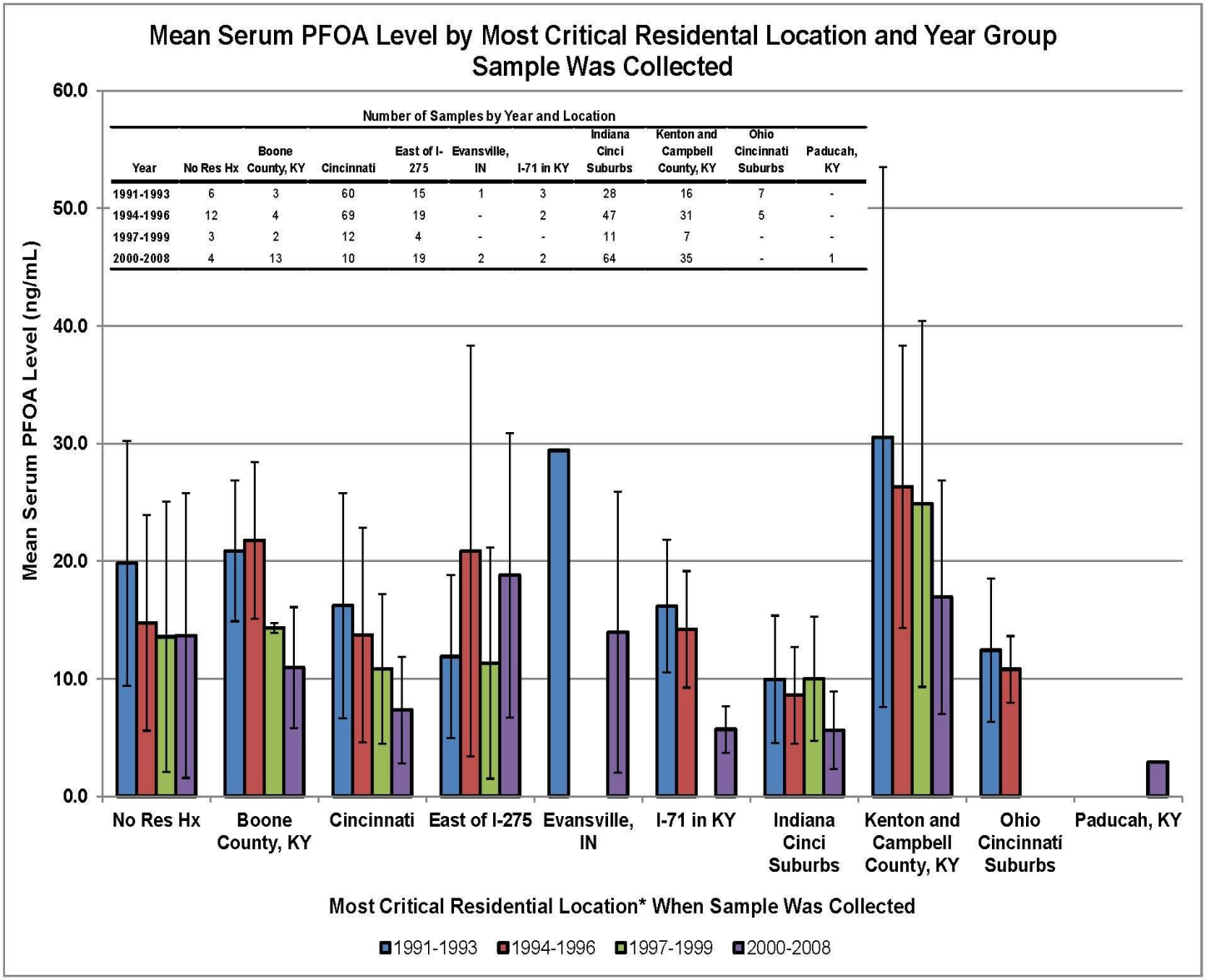


Ohio River Valley Study
Serum PFOA Levels of Study Participants (N=372)
Median: 8.1 ng/mL
Range: 0.3 to 62.7 ng/mL



Addition of historical samples (Fernald Community Cohort)

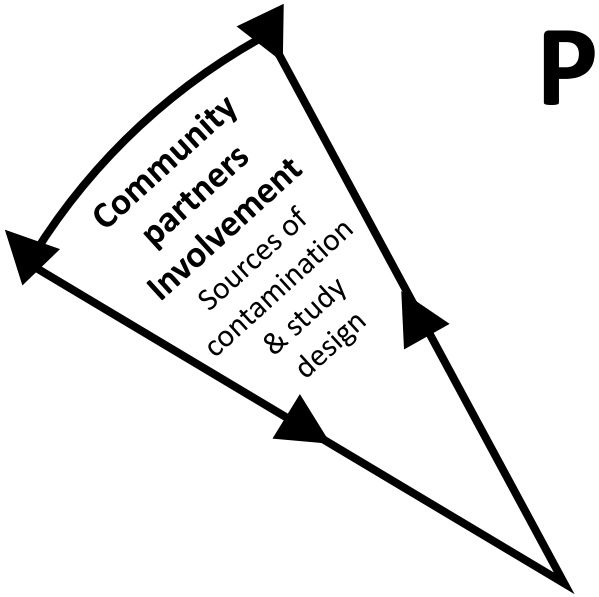
http://med.uc.edu/eh/research/projects/fcc



Number of Samples by Year and Location

Year	No Res Hx	Boone County, KY	Cincinnati	East of I-275	Evansville, IN	I-71 in KY	Indiana Cinci Suburbs	Kenton and Campbell County, KY	Ohio Cincinnati Suburbs	Paducah, KY
1991-1993	6	3	60	15	1	3	28	16	7	-
1994-1996	12	4	69	19	-	2	47	31	5	-
1997-1999	3	2	12	4	-	-	11	7	-	-
2000-2008	4	13	10	19	2	2	64	35	-	1

Herrick RL, Buckholz JM, Biro FM, Calafat AM, Ye X, Xie C, Pinney SM. Polyfluoroalkyl substance exposure in the Mid-Ohio River Valley, 1991-2012. *Environmental Pollution* 2017; 228: 50-60. doi: 10.1016/j.envpol.2017.04.092. PMID:28505513



PFCs and BCERP

Community

Individual biomarker results were mailed to parents of the girls.

Meetings held with parents

Surveyed parents (and participants of other studies after received results)

Timeframe:

Who was involved:

Community partners (Ann Hernick, Kathy Ball, Gail Greenberg and Peggy Monroe)

Cincinnati BCERP

Data Source: Grantee Submitted Trx Example

Hernick AD, Brown MK, Pinney SM, Biro FM, Ball KM, Bornschein RL. Sharing Unexpected Biomarker Results with Study Participants. *Environ Health Perspect* 2011; 119:1-5. PMID: 20876037

BREAST CANCER AND THE ENVIRONMENT RESEARCH PROGRAM (BCERP)
"GROWING UP FEMALE"
A study of the effect on environmental exposures on mammary development and potential breast cancer risk

PFC SAMPLE RESULTS

PFCs (Perfluorochemicals) are manmade chemicals used in products that resist heat, water, oil, grease and stains. They are present in metal plating, computer semi-conductors, film processing, fire-fighting foams and grease- and water-resistant coatings. Two examples (types) of this group of chemicals are **PFOA** (Perfluorooctanoic acid or C-8) and **PFOS** (Perfluorooctane Sulfonate).

Participant Name _____ Date of Birth _____

- **Most of the PFC blood serum samples were collected between 2005 and 2006**
- **PFC levels were measured at the Centers for Disease Control Environmental Laboratory**
- **Average GUF participant results are based on 353 girls, age 6-8 years old, in Greater Cincinnati**

Type of PFC	GUF Girl's Result	Average of GUF (Cincinnati) Girls	NHANES 95th Percentile
PFOA		7.3 ng/mL	8.4 ng/mL
PFOS		13.6 ng/mL	38.5 ng/mL

The CDC does not provide printed laboratory results for individual participants.

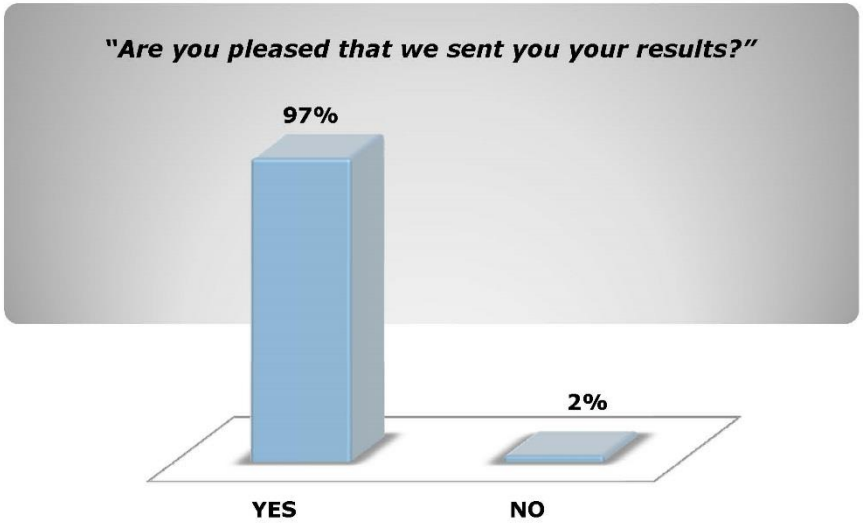
This report is produced by the research staff of BCERP/Growing Up Female under the direction of Dr. Frank Biro and Dr. Susan Pinney.

PLEASE SEE ENCLOSED INFORMATION ABOUT PFCs, RECENT PUBLICATIONS, AND THE IMPACT OF THESE FINDINGS

Questions should be addressed to the Growing Up Female study line at 513-636-8592.

Hernick AD, Brown MK, Pinney SM, Biro FM, Ball KM, Bornschein RL. Sharing Unexpected Biomarker Results with Study Participants. *Environ Health Perspect* 2011; 119:1-5. PMID: 20876037

Comprehension and Perceptions of Study Participants Upon Receiving Perfluoroalkyl Substance Exposure Biomarker Results

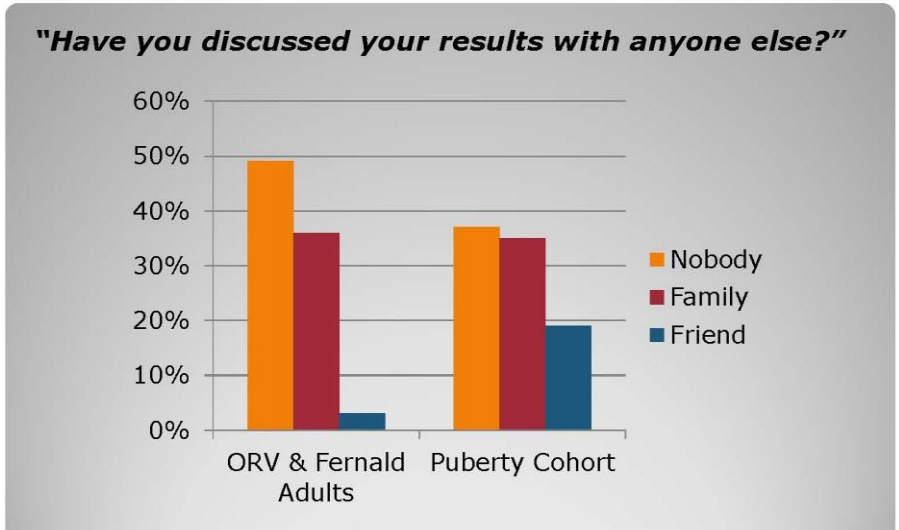


An overwhelming majority were pleased to have received their PFOA/PFOS results.

Agreement table and Kappa statistic for Fernald cohort

	Actual PFOA serum concentration (ng/mL)			
Perceived PFC Level	***> 13.0***	***> 5.60***	***< 5.60***	Total
High	36 (72%)	4 (12%)	0 (0%)	40 (43%)
Medium	9 (18%)	13 (38%)	2 (22%)	24 (26%)
Low	5 (10%)	17 (50%)	7 (78%)	29 (31%)
	50	34	9	93

Kappa = 0.382, 95% CI: 0.247 - 0.517



Many reported that they talked to no one about their serum concentrations of PFOA and PFOS. Those who did were most likely to talk to family members; only 8% of the adult participants and 3% of the parents of the girls reported that they discussed their results with a health professional.

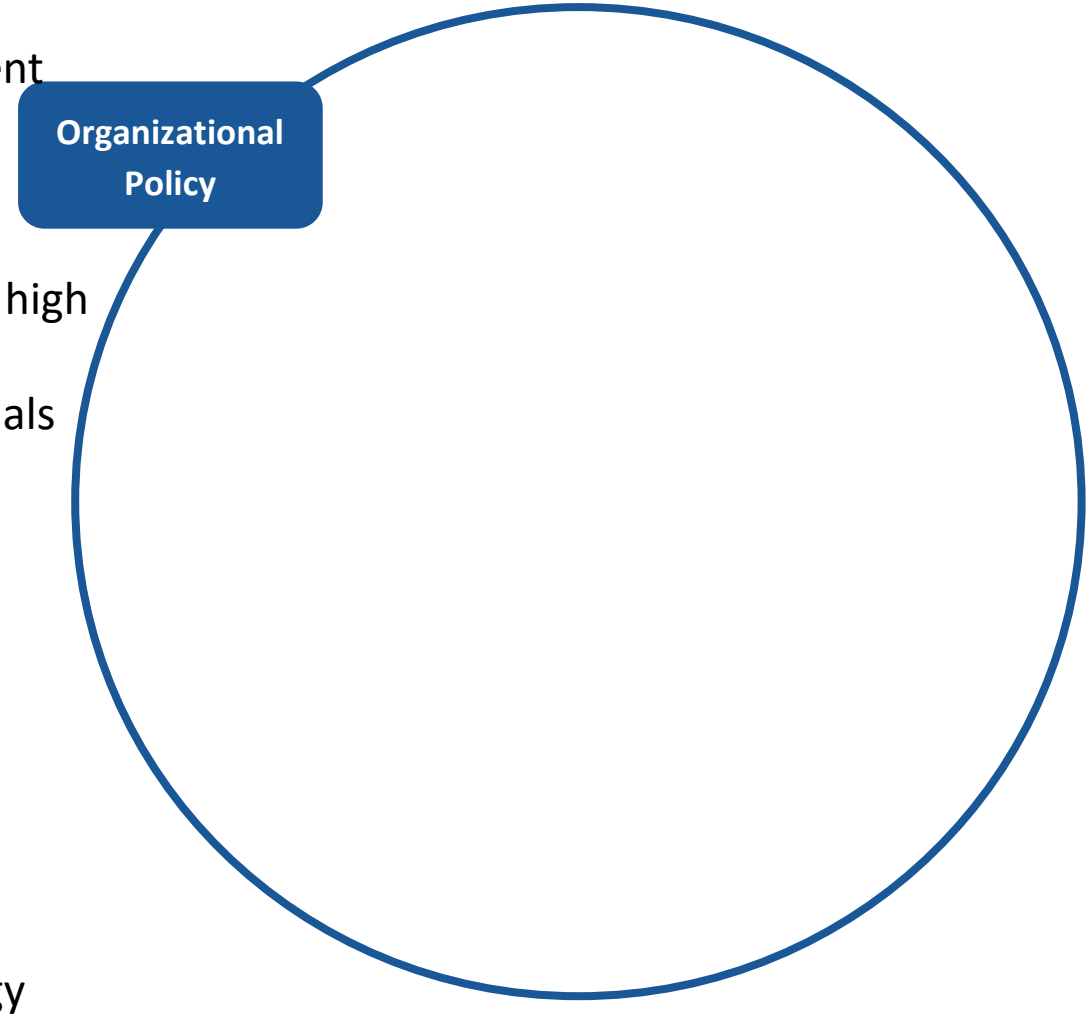
Manuscript resubmitted, 5/30/2018

PFCs and BCERP

7

Organizational Policy

- Partnered with water treatment departments to reduce exposure through water filtering
- Question about whether very high values should be shared with physicians, public health officials



Timeframe: 2007-2012

Who was involved:

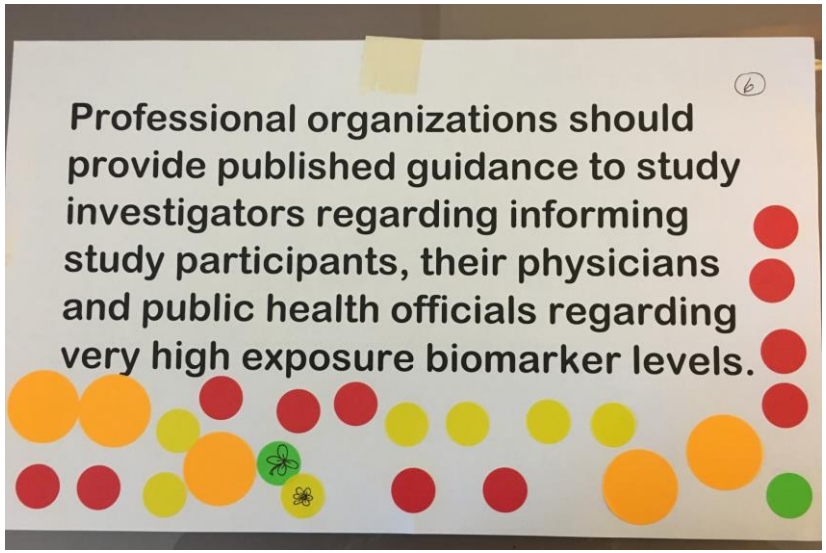
Cincinnati BCERP (Drs. Robert Bornschein, Susan Pinney)
Cincinnati Water Department
Northern Kentucky Water Department
Cincinnati Health Department
American College of Epidemiology

Data Source: Grantee Submitted Trx Example

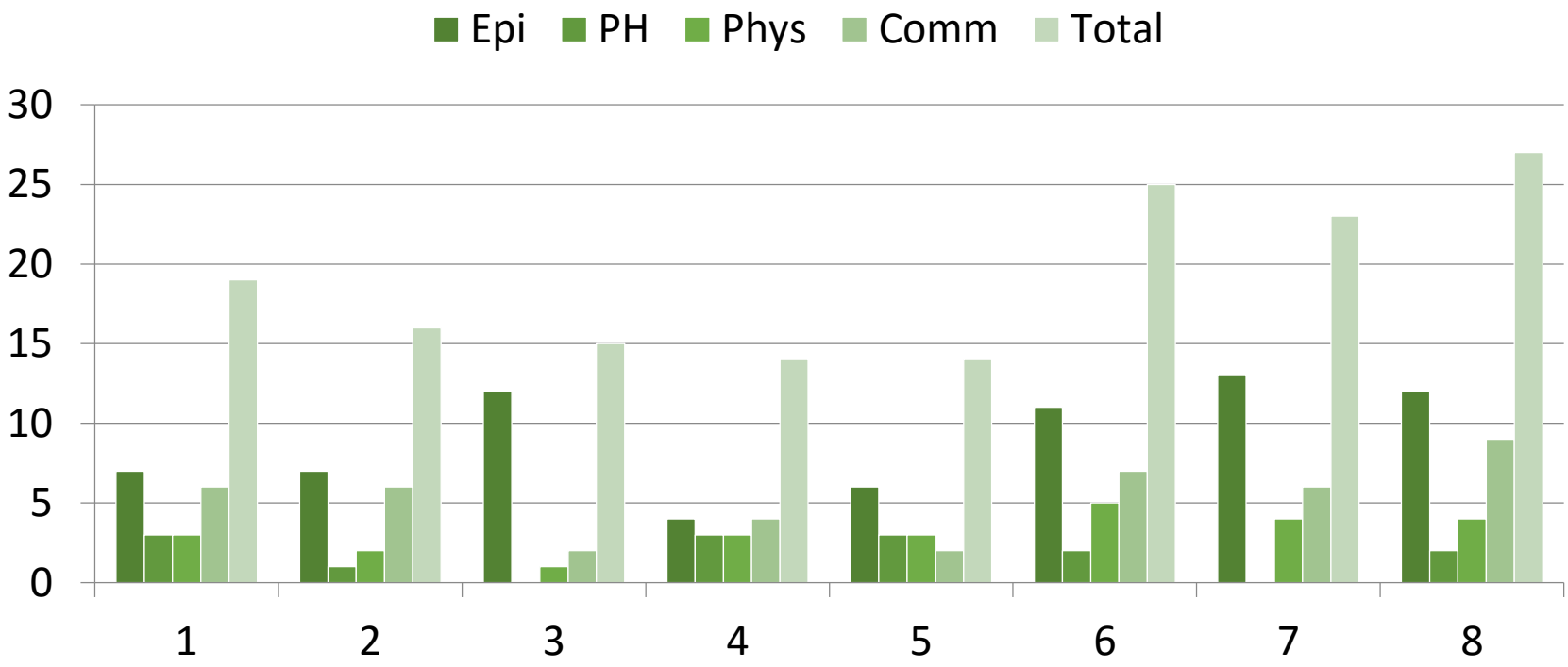
Very high levels of individual exposure biomarkers: A void in guidance for study investigators

- Some persons are found to have **very high concentrations of environmental biomarkers** in blood or urine, higher than 2x the 95th percentile value for the US population.
  - Random incidental findings
  - Communities with known exposures
- **Should physicians and/or public health officials be given this information?**
- (Information would be shared with physicians or public health officials only after the study participant signed a release.)

Workshop: American College of Epidemiology, September 2017



Workshop: Number of votes for each statement



6. Professional organizations should provide published guidance to study investigators regarding informing study participants, their physicians and public health officials regarding very high exposure biomarker levels.

7. Researchers have some responsibility to find out why the extreme result occurred.

8. There is a need for researchers to inform their study participants of very high levels of exposure biomarkers

PFCs and BCERP

Change in Environmental Exposures

8

Change in Environmental Exposure

- Continued monitoring of girls' PFC levels after the water filtering intervention was implemented

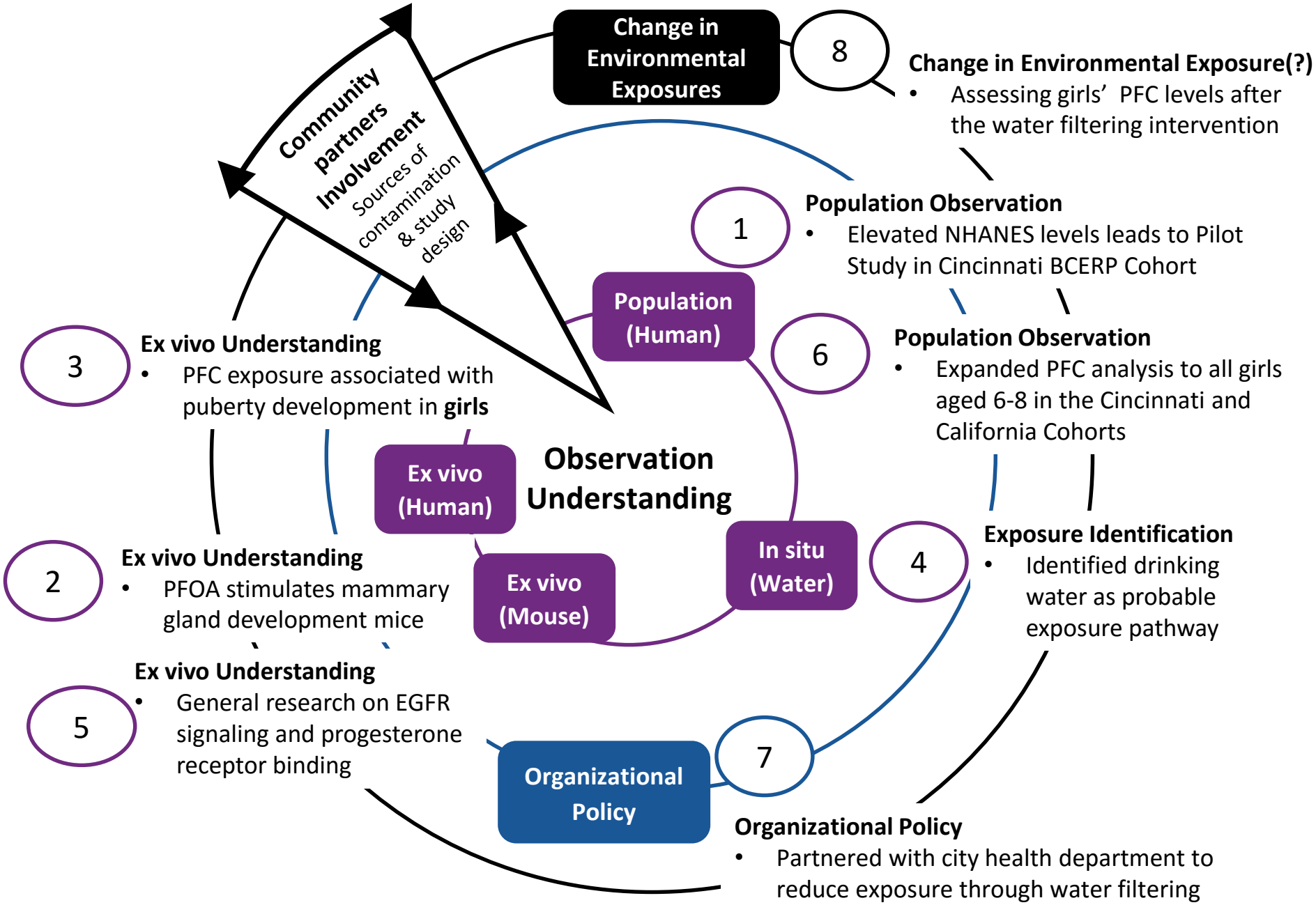
Timeframe: 2011 – 2014

Who was involved:

Cincinnati BCERP

CDC

Data Source: Grantee Communication to PO


Change in Environmental Exposures
8
Change in Environmental Exposure(?)
• Assessing girls' PFC levels after the water filtering intervention
Community partners Involvement
Sources of contamination & study design
1
Population Observation
• Elevated NHANES levels leads to Pilot Study in Cincinnati BCERP Cohort
Population (Human)
6
Population Observation
• Expanded PFC analysis to all girls aged 6-8 in the Cincinnati and California Cohorts
3
Ex vivo Understanding
• PFC exposure associated with puberty development in girls
Ex vivo (Human)
Observation Understanding
In situ (Water)
4
Exposure Identification
• Identified drinking water as probable exposure pathway
2
Ex vivo Understanding
• PFOA stimulates mammary gland development mice
Ex vivo (Mouse)
Ex vivo Understanding
5
• General research on EGFR signaling and progesterone receptor binding
7
Organizational Policy
Organizational Policy
• Partnered with city health department to reduce exposure through water filtering

Acknowledgments

- Funding for these projects was provided by the NIEHS and NCI through the
  - Breast Cancer and Environment Research Program (U01 ES/CA 12770, U01 ES/CA 1280112800)
  - University of Cincinnati Center for Environmental Genetics (P30-ES006096)
  - UCSF Clinical & Translational Science Institute (NIH/NCRR UL1 RR024131)
  - University of Cincinnati (R21 ES-017176).
  - The Molecular Epidemiology in Children's Environmental Health training grant (T32-ES10957).
  - Extreme Personal Exposure Biomarker levels: Guidance for Study Investigators (Workshop grant) (R13 ES027347

Collaborators

UC/CCHMC

- Frank M. Biro
- Changchun Xie
- Paul Succop
- **Robert Bornschein**
- Armand Antommaria
- Jeanette Buckholz
- Alex Daniels
- Cecily Fassler
- Courtney Giannini
- Robert Herrick
- Ketrell McWhorter

California Department of Public Health
Gayle Windham

Division of Laboratory Sciences, CDC
Antonia M. Calafat, Kayoko Kato

Division of Research, Kaiser Permanente - Lawrence H. Kushi

Kettering Laboratory
Dept. of Environmental Health
University of Cincinnati

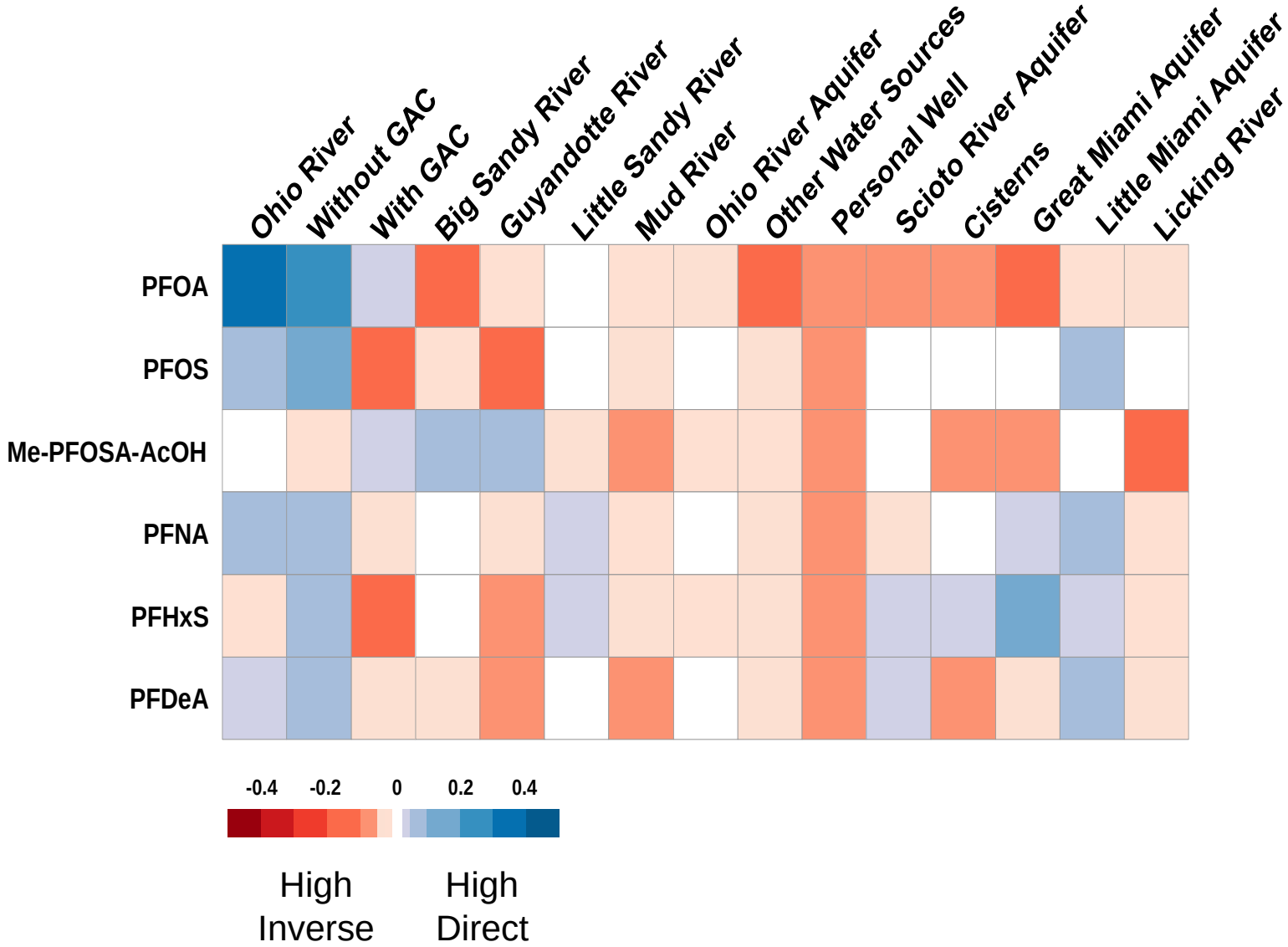
Extra Slides

Outline

- PFOA exposure to girls in greater Cincinnati and the San Francisco Bay Area.

- Polyfluroalkyl substance (PFAS) exposure in the Mid-Ohio River Valley, 1991-2012
  - Adults in Huntington WV, Portsmouth OH, Northern Kentucky.
  - Historical measurements from adults in the Fernald Community Cohort

Ohio River Valley Study
PFAS and Water Source Correlations



Addition of historical samples
(Fernald Community Cohort)

- 9782 in entire Fernald Community Cohort
  - Cohort of persons in a medical monitoring program established because of living near to a uranium refinery, followed for 18 years
  - 160,000 banked biospecimens going back to 1990; available to researchers who apply for use
  - http://med.uc.edu/eh/research/projects/fcc

- Selected subset eligible for PFAS study (N=210)
- 1. Lived at some point in time after 1980 at locations where consuming water from the Ohio River:

- 2. Had at least two archived serum samples collected at different times, as early as 1990