# Update on the California Teachers Study

Peggy Reynolds, Ph.D.

*Biomonitoring California Scientific Guidance Panel*
*November 3, 2016*

CANCER **PREVENTION** INSTITUTE
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# Outline

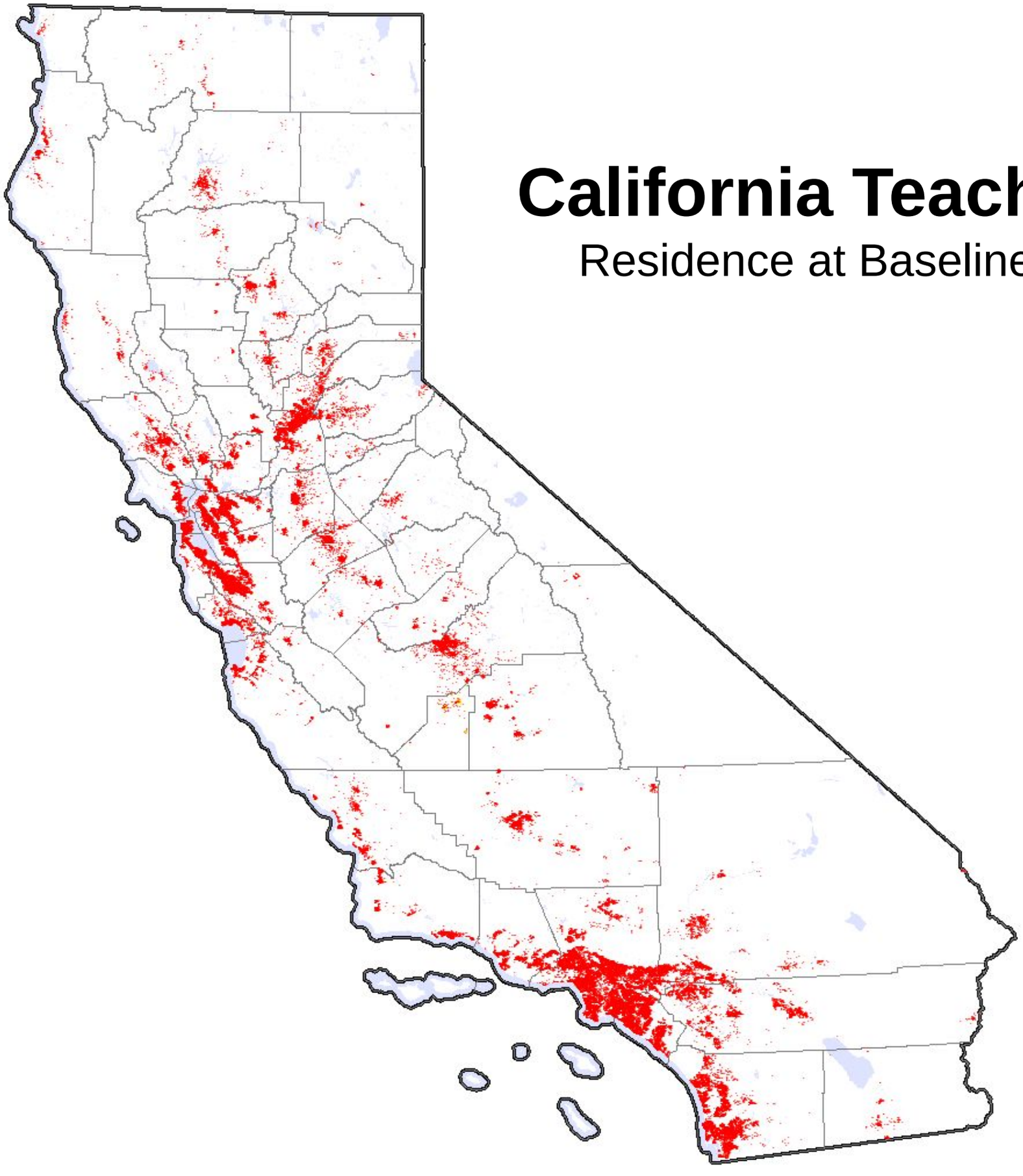
- About the California Teachers Study (CTS)
- CTS Study of Persistent Organic Pollutants (POPs)
  - Update
  - Recent Results
- Ancillary Studies
  - POPs and Mammographic Density
  - Exposures During the Menopausal Transition

# CTS Overview

- Initially funded with breast cancer tobacco tax $
  - One time allocation to CDPH (CDHS) CCR
- Recruitment via mailing to active and retired female State Teachers Retirement System members in 1995
- Final cohort=133,479
- Statewide, geographically diverse
- Largest prospective study specifically designed to study breast cancer
- Now with over 20 years of follow-up, a valuable source of information on women’s health

# California Teachers Study

Residence at Baseline (1995-1996)



# CTS Follow-Up

- Active follow-up via questionnaires, newsletters, sub-studies
  - Five questionnaires to date - questionnaire 6 in process
- Passive follow-up for California residents via linkage to:
  - California Cancer Registry
  - Hospital discharge data
  - State and national death files
- Cancer diagnoses through 2015:
  - 20,193 cases of all sites combined
  - 7,019 cases of invasive breast cancer
  - 1,685 cases of *in situ* breast cancer
- Mortality through 2013:
  - 26,076 deaths from all causes (26,800 to date)
  - 7,071 cancer deaths
  - 1,384 deaths due to breast cancer
- CTS Biobank
  - Over 20,000 biospecimens to date

# CTS Steering Committee

## Areas of Interest/Expertise

| Institution | Investigators | Research Emphasis |
|---|---|---|
| CPIC | Peggy Reynolds<br>David Nelson<br>Pamela Horn-Ross | ↗Social and environmental factors, GIS<br>↗Statistical methods<br>↗Nutrition/diet |
| COH | Leslie Bernstein<br>James Lacey<br>Sophia Wang<br>Susan Neuhausen<br>Jessica Clague | ↗Hormonal carcinogenesis<br>↗Physical activity<br>↗Genetics<br>↗Biologic mechanisms<br>↗Innovative data management |
| UCI | Hoda Anton-Culver<br>Argyrios Ziogas<br>Hannah Park | ↗Genetics |
| USC | Dennis Deapen<br>Eunjung Lee<br>Rich Pinder | ↗Augmentation mamoplasty<br>↗Mammographic density<br>↗Cognitive function<br>↗Integration of outcome data |

# Sample Ancillary CTS Grants

- Case-control study of endometrial cancer
- Hormone therapy, mammographic density and breast cancer risk
- Physical activity and cancers of the ovary and endometrium
- The built environment and breast cancer risk
- Tobacco and breast cancer risk
- Cadmium exposure and breast and endometrial cancer risk
- Air pollution and cardiopulmonary mortality
- Hazardous air pollutants and breast cancer risk
- Residential mobility and environmental exposures
- Persistent organic pollutants and breast cancer risk
- Persistent organic pollutants and mammographic density
- Light at night and breast cancer risk
- UM1 for biospecimen collection
- Windows of susceptibility and the menopausal transition

# CALIFORNIA TEACHERS STUDY



The California Teachers Study (CTS) is a prospective study of 133,479 current and former public school teachers or administrators who participate in the California State Teachers Retirement System (STRS). The initiation of the cohort was supported by the State of California through revenues generated by cigarette taxes for the purpose of supporting breast cancer research. The CTS was developed by a consortium of investigators from the California Department of Health Services, the Cancer Prevention Institute of California, the University of California, Irvine, and the University of Southern California.

New Biospecimens


Newsletters


Publications

## Of Interest Story:

CTS researcher Dr. Leslie Bernstein is among the most accomplished researchers working in cancer epidemiology today. Among her many research achievements; she was instrumental in identifying physical activity as means for reducing breast cancer risk. She is involved in a host of projects, including those based in the CTS, to unravel the links between hormone exposures, obesity, physical activity and cancer. Read More of the Story »

# Persistent Organic Pollutants and Breast Cancer: Chemicals Old and New

- Specific Aims
  - Screen for major predictors of PBDEs
  - Assess breast cancer risk for both “old” and “new” POPs
  - Explore windows of susceptibility
- Chemicals of interest
  - Endocrine disruptors
  - Legacy chemicals (“the old”)
    - Polychlorinated biphenyls (PCBs)
    - Organochlorine pesticides (eg. DDT/DDE)
  - Brominated flame retardants (“the new”)
    - Polybrominated biphenyl ethers (PBDEs)
  - Other
    - Per- and polyfluoroalkyl substances (PFASs)
- Collaboration with DTSC Environmental Chemistry Laboratory

*Funded by CBCRP grant #16ZB-8501 – (2010-2016)*

# CTS POPs: Status of Assays

- PBDEs: assays completed for 19 congeners (n=2,155)
- PFASs: assays completed for 12 compounds (n=2,159)
- PCBs: assays completed for 15 congeners (n=793)**
- OCPs: assays completed for 7 pesticides (n=793)**

** PCBs and OCPs are currently being finalized for an additional final batch of 1,383 samples, pending QA/QC review.

# CTS and POPs: Locations of Participants

# Characteristics of Participants (n=2,155)*

**Age**

| | N | % |
|---|---|---|
| 40-49 years | 114 | 5% |
| 50-59 years | 307 | 14% |
| 60-69 years | 861 | 40% |
| 70-79 years | 692 | 32% |
| 80-94 years | 181 | 8% |

**Mean age = 67 years; range = 40 to 94 years**

**Race/ethnicity**

| | N | % |
|---|---|---|
| White | 1,751 | 81% |
| Black | 104 | 5% |
| Hispanic | 127 | 6% |
| Asian/Pacific Islander | 125 | 6% |
| Other | 48 | 2% |
| Total: | 2,155 | 100% |

*** among those with completed PBDE assays; includes 902 diagnosed with invasive breast cancer and 1,253 cancer-free controls.**


Environmental Science & Technology Letters

Letter

pubs.acs.org/journal/estlcu

# Preliminary Associations between the Detection of Perfluoroalkyl Acids (PFAAs) in Drinking Water and Serum Concentrations in a Sample of California Women

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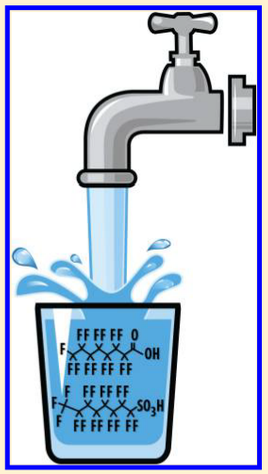
Supporting Information

**ABSTRACT:** This study compared detection of perfluoroalkyl acids (PFAAs) in public drinking water with PFAA serum concentrations for 1566 California women. PFAA occurrence in drinking water from U.S. EPA's third Unregulated Contaminant Monitoring Rule (UCMR3) database was linked by residential zip code to study participants. Detectable water concentrations of perfluorooctanoic acid (PFOA) ranged from 0.020 to 0.053 μg/L and of perfluorooctanesulfonic acid (PFOS) from 0.041 to 0.156 μg/L. Forty percent of detectable concentrations exceeded the 2016 Health Advisory Level of 0.07 μg/L for combined PFOA and PFOS concentrations. Serum concentrations of PFOS and PFOA significantly differed between participants with and without detectable measures of these compounds in water (Wilcoxon $P \leq 0.0007$). Median serum concentrations of PFOS and PFOA were 29% and 38% higher, respectively, among those with detectable levels in water compared to those without detectable levels. Validation of this approach and replication of these results in other study populations are warranted.




## INTRODUCTION

Perfluoroalkyl acids (PFAAs) are a subset of the poly- and perfluoroalkylsubstances (PFASs), a class of compounds that have been widely used for over 60 years to impart nonstick, waterproof and stain-resistant coatings to a variety of consumer products, including cookware, food packaging, clothing, carpeting, and textiles.[1−3] PFASs are also active ingredients in aqueous film forming foams (AFFF) used to extinguish hydrocarbon-based fuel fires at airports, oil refineries, military bases, and firefighter training facilities.[4] PFAAs are highly resistant to biodegradation and are among the most persistent of environmental pollutants.[1,3,5] A growing body of scientific evidence for the two most studied members of PFASs, perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA), suggests potentially toxic effects including tumor induction, hepatoxicity, developmental toxicity, immunotoxicity, endocrine disruption, and neurotoxicity.[2,3,6−13] Consequently, PFASs, especially PFOS and PFOA, have become the focus of considerable public health concern.

Although U.S. and California biomonitoring data indicate widespread human exposures,[14−16] routes of exposure have not been fully elucidated.[3,17−20] Drinking water can be a significant

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# US EPA Measurements of Chemicals in Public Water Systems (PWSs)

- Unregulated Chemicals Monitoring Report (UCMR)
  - All PWSs serving more than 10,000 people, and
  - 800 representative PWSs serving 10,000 or fewer people
- Latest round (UCMR3, 2013-15) included some PFASs

# Study Population

- Drawn from the POPs breast cancer case-control study, nested within the California Teachers Study
- Blood samples collected January 2011-September 2013
- Analyzed for 12 PFASs
- Address at the time of blood draw was geocoded
- 1,333 participants lived in a zip code with UCMR3 data (40% cases, 60% controls)

➢Women were matched by residential zip codes to drinking water systems tested for these chemicals

# PFASs measured

| | PFAS in Serum | | PFAS in Water (UCMR3) |
|---|---|---|---|
| | DF (%) | GM (ng/mL) | DF (%) |
| PFBuS | 18 | NR | 0.0 |
| PFHxS | 99.9 | 1.62 | 0.8 |
| PFOS | 99.8 | 6.8 | 3.3 |
| PFHpA | 74 | 0.054 | 0.4 |
| PFOA | 99.9 | 2.46 | 2.0 |
| PFNA | 99.7 | 0.92 | 0.0 |
| PFDeA | 95 | 0.22 | NA |
| PFUA | 96.8 | 0.13 | NA |
| PFDoA | 11 | NR | NA |
| PFOSA | 74 | 0.036 | NA |
| EtPFOSAAcOH | 84.5 | 0.031 | NA |
| MePFOSAAcOH | 98.4 | 0.2 | NA |

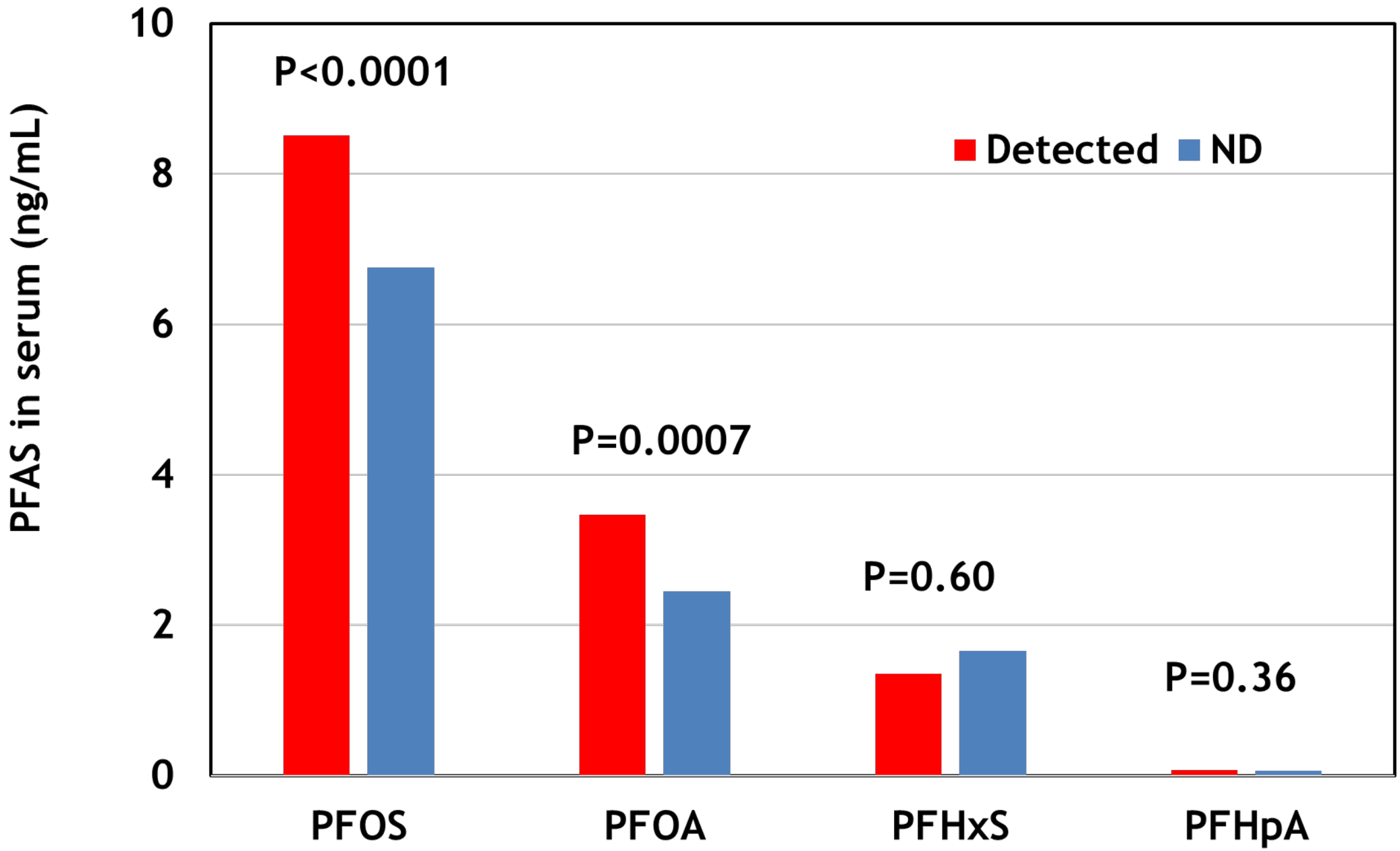
Similar to NHANES

# Results

- All water PFAS levels were below the previous US EPA Health Advisories
  - 400 ng/L for PFOA
  - 200 ng/L for PFOS
- 40% exceeded the new US EPA Health Advisory (May 2016)
  - 70 ng/L for PFOA and PFOS combined


**Women with PFAS detected in their water had 38% higher PFOA and 29% higher PFOS in their blood**

# Serum PFASs (GM) in Women with Detected and Non-Detected PFASs in their Drinking Water



# Study Limitations

- Method Detection Limits of the UCMR3 data are relatively high; PFASs could be under-reported.
- Only 109 (7%) of our study participants lived in a residence in a zip code supplied by a PWS that had detected at least one PFAS
- Some zip codes encompass more than one PWS
- Not designed to test effect of drinking water
  - Assumed ingestion of home tap water

# Study Strengths

- The distribution of age, racial/ethnic characteristics and disease status (cases/controls) were similar across the categories of PFAS water detections
- Majority (70%) lived in same address for over 15 years
- Single occupation
- Similar results when examining only controls (n=944)

# Conclusions

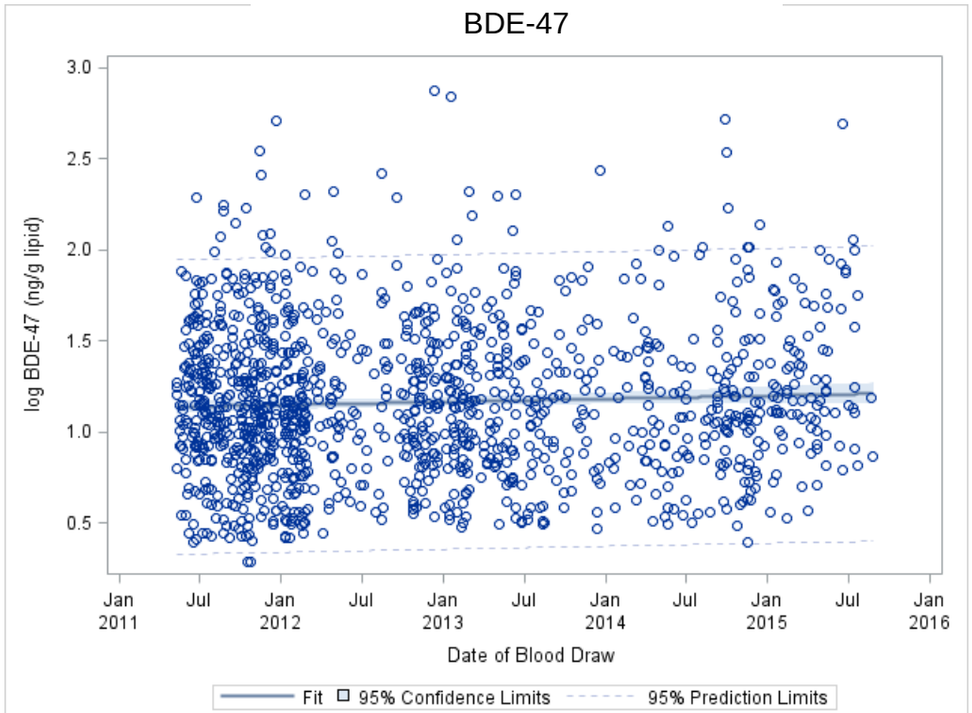
- First study to demonstrate an association between levels of PFOA and PFOS in serum with their presence in drinking water supplies among a ***population with no previously recognized water contamination***
- In agreement with other studies pointing to the need to reduce PFAS in drinking water

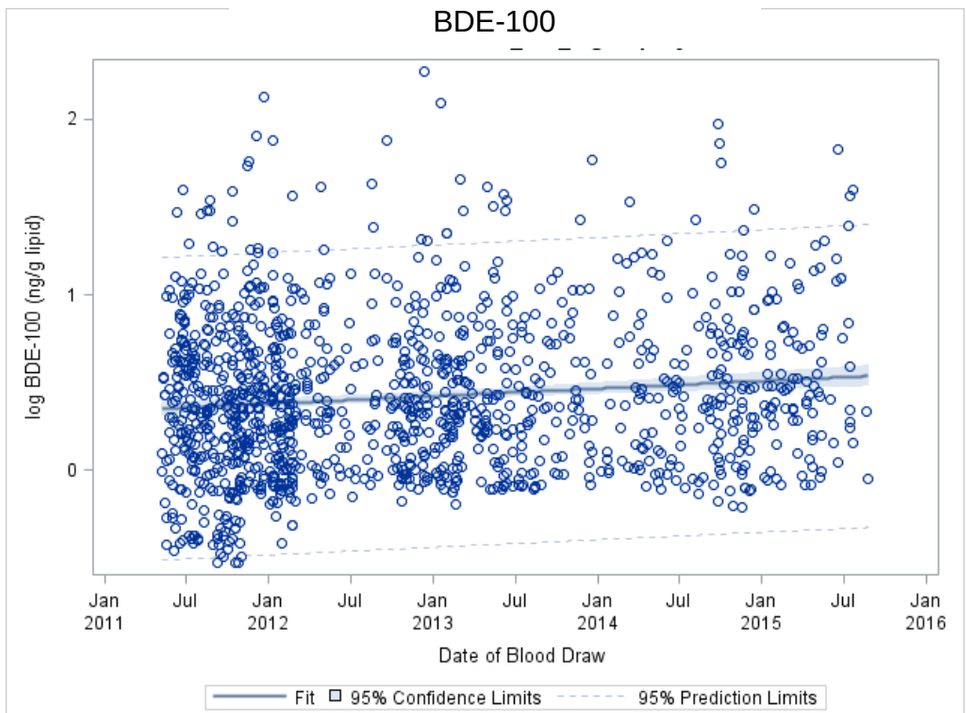
**Associations are probably underestimated**

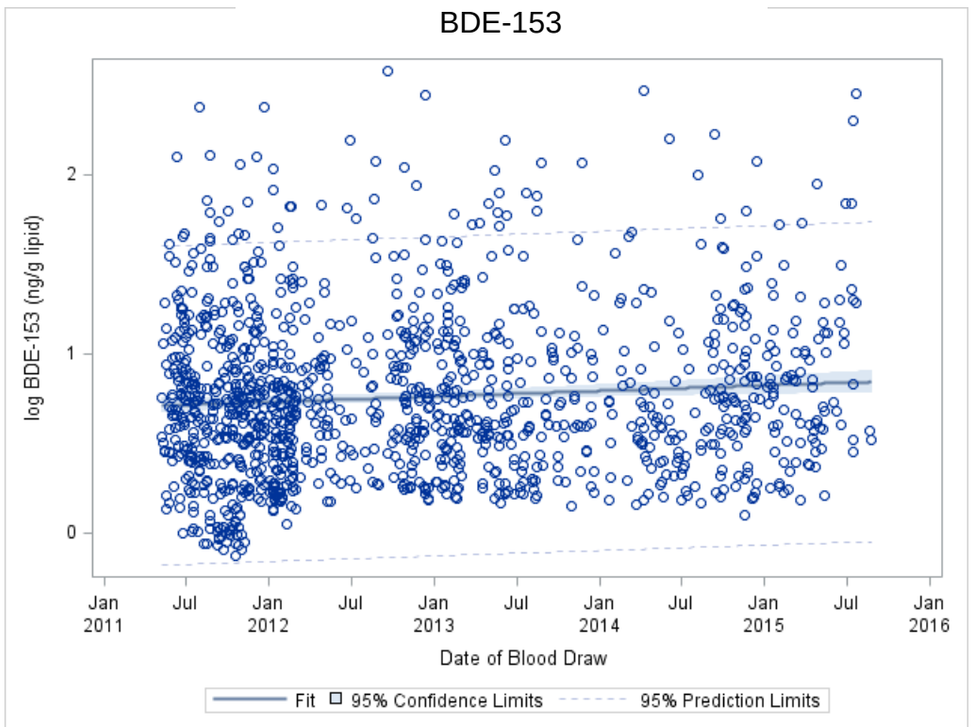
# Are Levels of the Study Chemicals Changing in the Population Over Time?

- A few studies in biota, human serum and breast milk
  - Inconsistencies in methods/measurement/time periods
  - Small sample sizes
  - Mixed results
- PRELIMINARY assessment in the CTS POPs study
  - Large statewide sample of older women
  - Samples collected January 2011-September 2015
  - Controls only:
    - PBDEs n=1,253
    - PFASs n=1,257
  - Most commonly detected compounds
    - 3 PBDEs
    - 8 PFASs
  - Trends estimated from generalized linear models

# PBDEs: Time Trends (preliminary)*

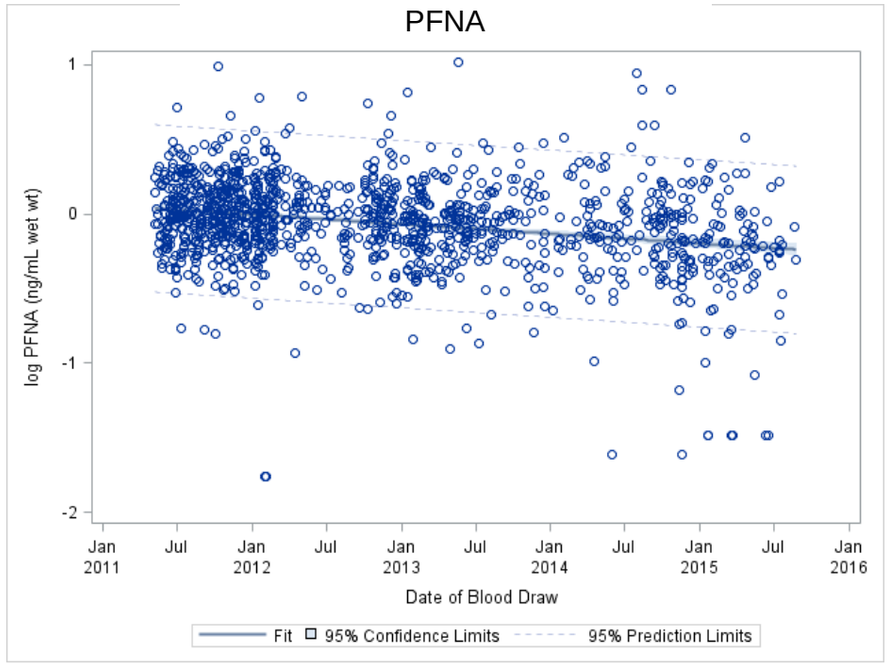


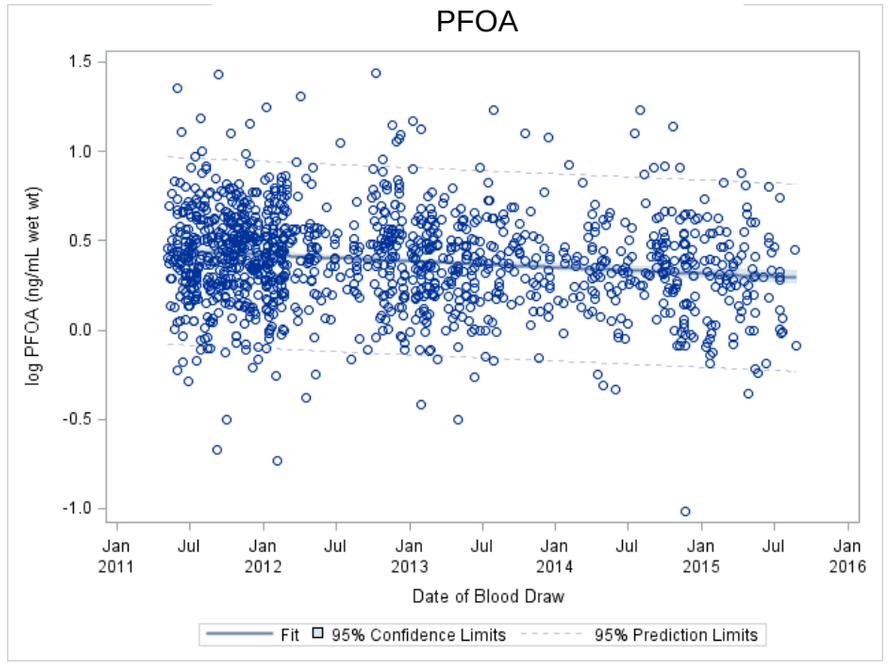



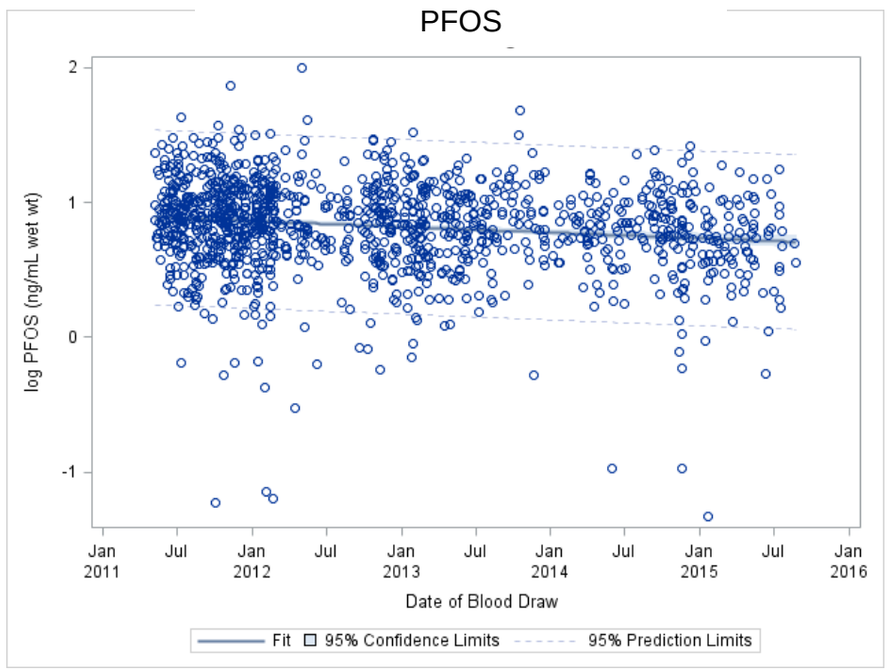



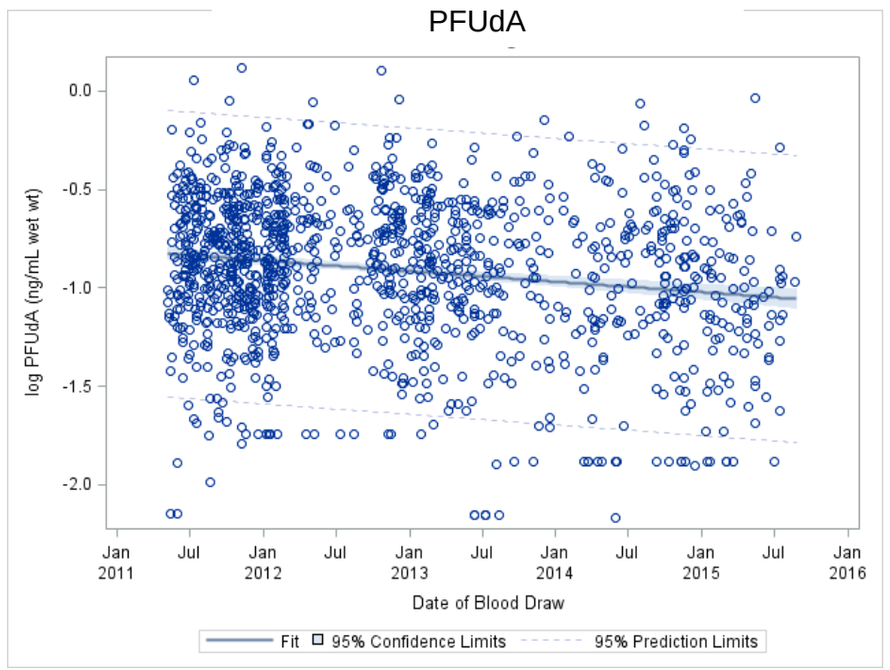

* Estimated from generalized linear models (controls only, n=1,253)

# PFASs: Time Trends (preliminary)*



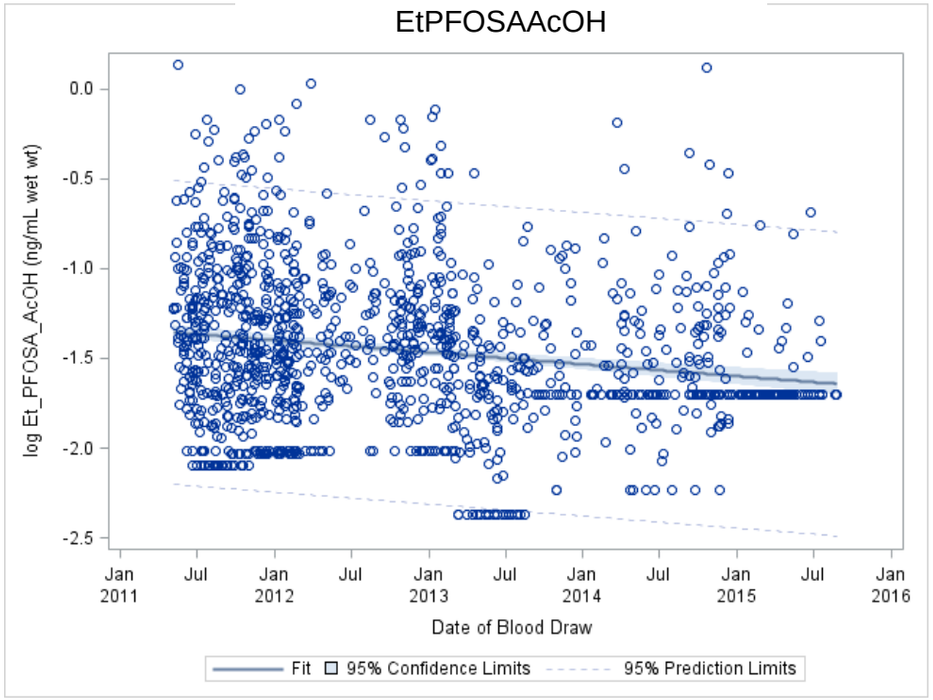



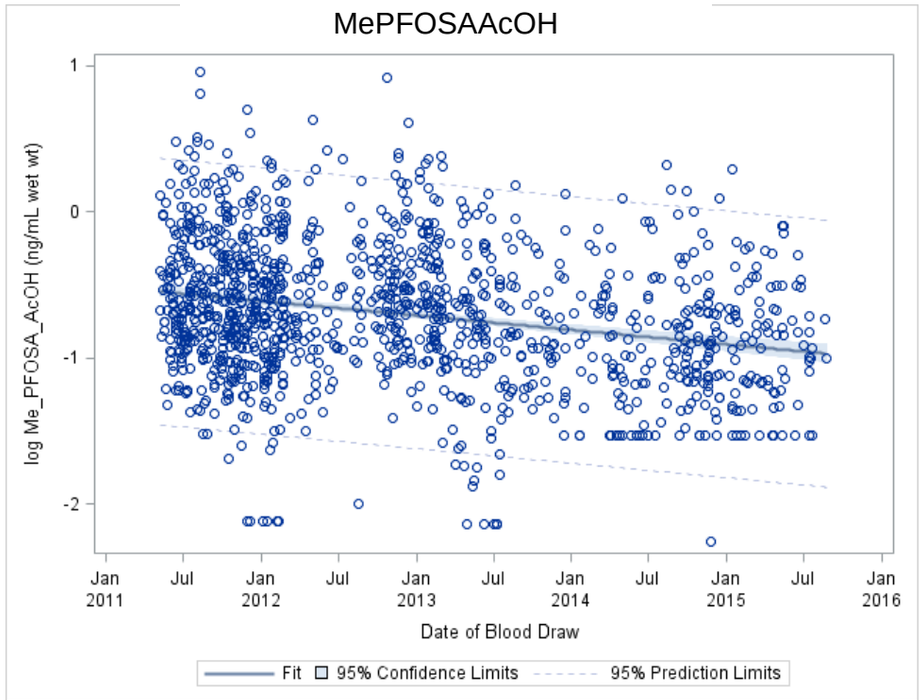



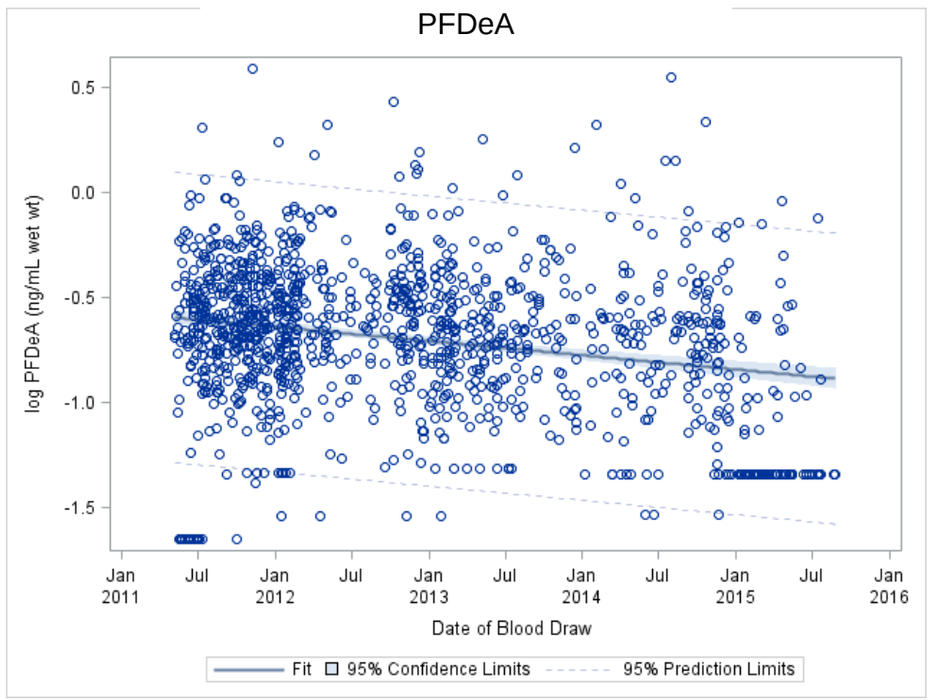



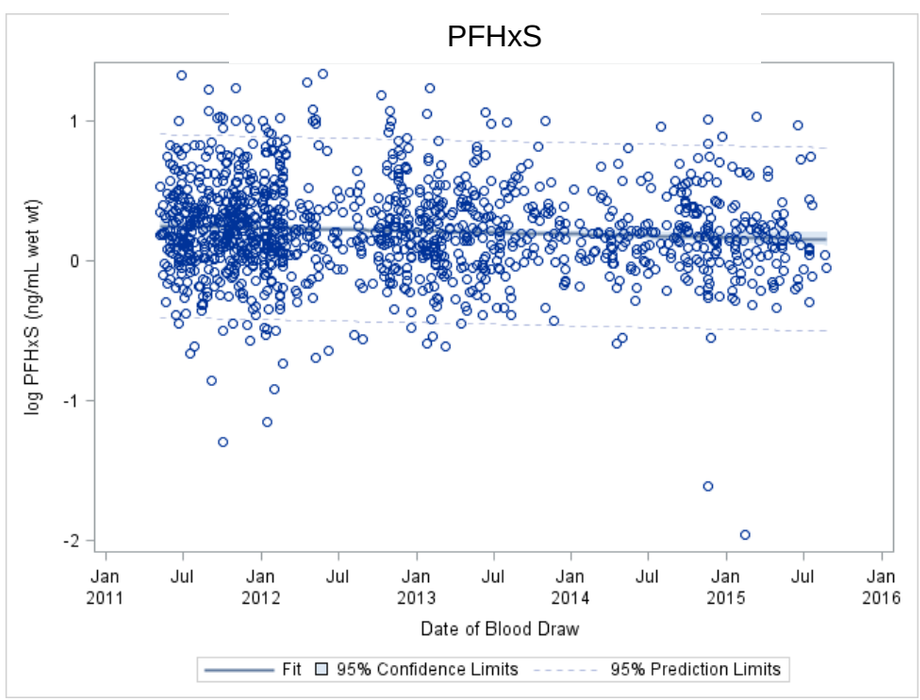

* Estimated from generalized linear models (controls only, n=1,257)

# PFASs: Time Trends (preliminary)*




* Estimated from generalized linear models (controls only, n=1,257)

# CTS and POPs Research Team

## Cancer Prevention Institute of California

- Peggy Reynolds, Susan Hurley, David Nelson, Andrew Hertz, Julie Von Behren, Pam Horn-Ross, Chris Collins

## DTSC Environmental Chemistry Lab

- Myrto Petreas, June-Soo Park

## City of Hope

- Leslie Bernstein

## UC Irvine

- Hoda Anton-Culver

*Funded by the California Breast Cancer Research Program grant # 16ZB-8501*

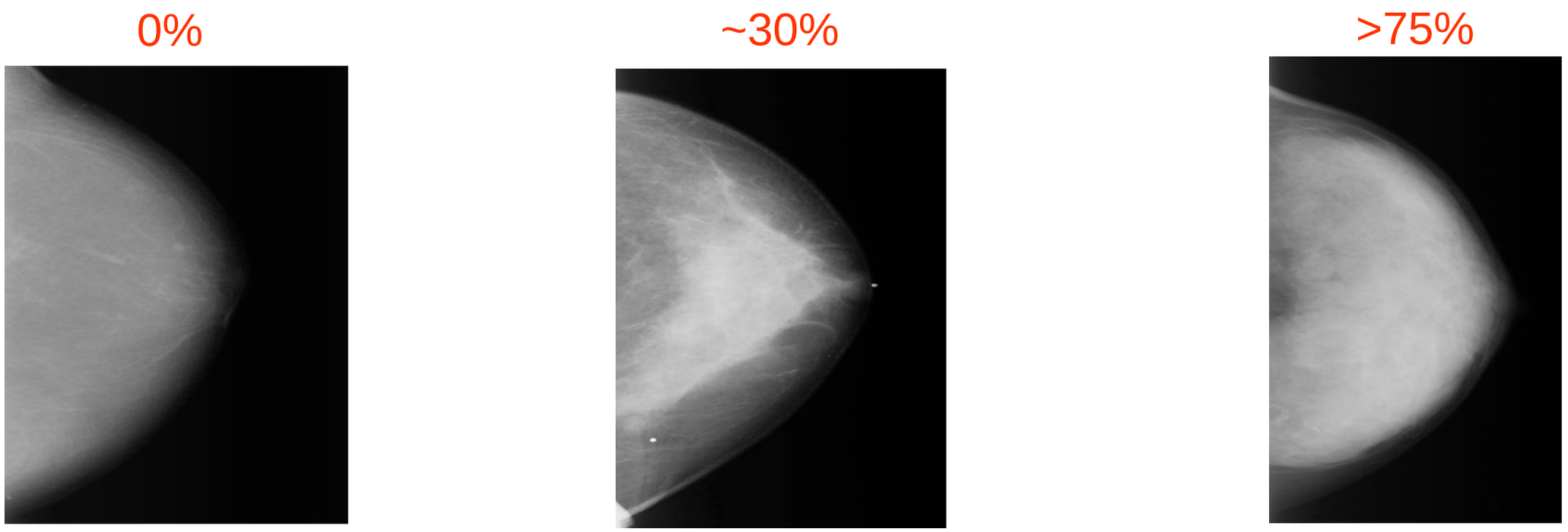
# Funded Studies Ancillary to the POPs study

- Enhanced residential/workplace histories (NCI PQ2 project, PI: P. Reynolds)
- Additional chemical analytes, eg. PFASs (Petreas/Park, ECL)
- Metabolomics/TOF Mass Spec (PI: S. Salihovic, ORU)
- POPs and mammographic density (PI: E. Lee, USC)
- The menopausal transition window of susceptibility (PIs: S. Chen and S. Neuhausen, COH)

# Persistent Organic Pollutants (POPs) and Mammographic Density

(CBCRP IDEA 20IB-0114; PI: Eunjung Lee)

- **Background:** Mammographic density is associated with elevated risk of breast cancer




Adjusted RR (>75% vs. <5%) = 4.6 (McCormack 2006)

- **Hypothesis:** Serum POP levels are positively associated with higher mammographic density

# Persistent Organic Pollutants (POPs) and Mammographic Density

(CBCRP IDEA 20IB-0114; PI: Eunjung Lee)

- **Study participants from:**
  - POPs sub-study of the California Teachers Study (CTS) (PI: Reynolds)
    - ~1300 women without breast cancer
    - 7 organochlorine pesticides, 11 PBDEs, 15 PCBs, 12 PFASs

      (Dr. Petreas, CA Dept Toxic Substances Control)

- **Study design**: Cross-sectional study
  - To recruit 160 postmenopausal CTS women
  - Survey and collect mammograms to assess mammographic density
  - Analysis to investigate the association between serum POPs levels and mammographic density

- **Status**:  Participants selected/mammograms under review

# Environmental Chemicals and Risk of Breast Cancer During the Menopausal Transition

(U01ES026; PIs Shiuan Chen and Susan Neuhausen)

- Co-funded by NIEHS and NCI
  - Breast Cancer and the Environment Research Program (BCERP)
- Designed to be transdisciplinary to:
  - target windows of susceptibility for breast cancer risk
  - integrate experimental models and human studies
    - In vitro, mouse model and human study elements
  - include a community outreach component

**Hypothesis :** During the menopausal transition, when natural hormone levels are actively declining, BPAs and PBDEs, acting as endocrine-disrupting chemicals, promote the development of hormone-responsive breast cancers. They may act individually or have additive or synergistic effects.

# COH BCERP Human Study

- Based on the CTS POPs project
- Women ages 40-58 years with menopausal status recorded at the time of blood draw
- Composition of the study sample:
  - 150 invasive breast cancers, 97 *in situ* breast cancers
  - 416 controls (114 pre-, 68 peri-, 234 post-menopausal)
- AIM: to assess the effects of BPA and PBDE levels in serum of women in the menopausal transition on:
  - Total estrogenic activity, after accounting for endogenous levels
  - Epigenomic changes:
    - miRNA
    - Global and gene-specific methylation
  - Risk of breast cancer

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# COH BCERP Study Acknowledgments


- **Beckman Research Institute of the City of Hope**

  Dr. Shiuan Chen
  Ms. Michele Rakoff
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  Dr. Tim Synold
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  Ms. Mayra Serrano
  Ms. Linda Steele
  Ms. Lauren Carter

- **The Cancer Prevention Institute of California**

  Dr. Peggy Reynolds
  Dr. David Nelson
  Ms. Susan Hurley

- **Environmental Chemistry Lab/Public Health Institute of California**

  Dr. June-Soo Park
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  Dr. Myrto Petreas
  Dr. Swati Anand
  Dr. Sabrina Smith
  Ms. Weihong Guo

*Funded by NIH U01ES026137-01 (Chen/Neuhausen)*


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# CTS and Biomonitoring California

- Statewide representation
- Extensive information on personal health habits/health histories
- Reflects the diversity of California environments
- Special demographic (women, now mostly over 60 yrs old)
- Large sample size
- Collaborative effort
- Parent POPs study funded by CBCRP – with opportunities for expansion via Biomonitoring California and other independently funded research projects:
  - to include additional chemicals of concern
  - to address additional health outcomes and biologic mechanisms

***A special thanks to Biomonitoring California!***

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