PFAS Exposure Assessment for Epidemiological Studies: Lessons from the C8 Studies, and Plans for the Multi-Site PFAS Study

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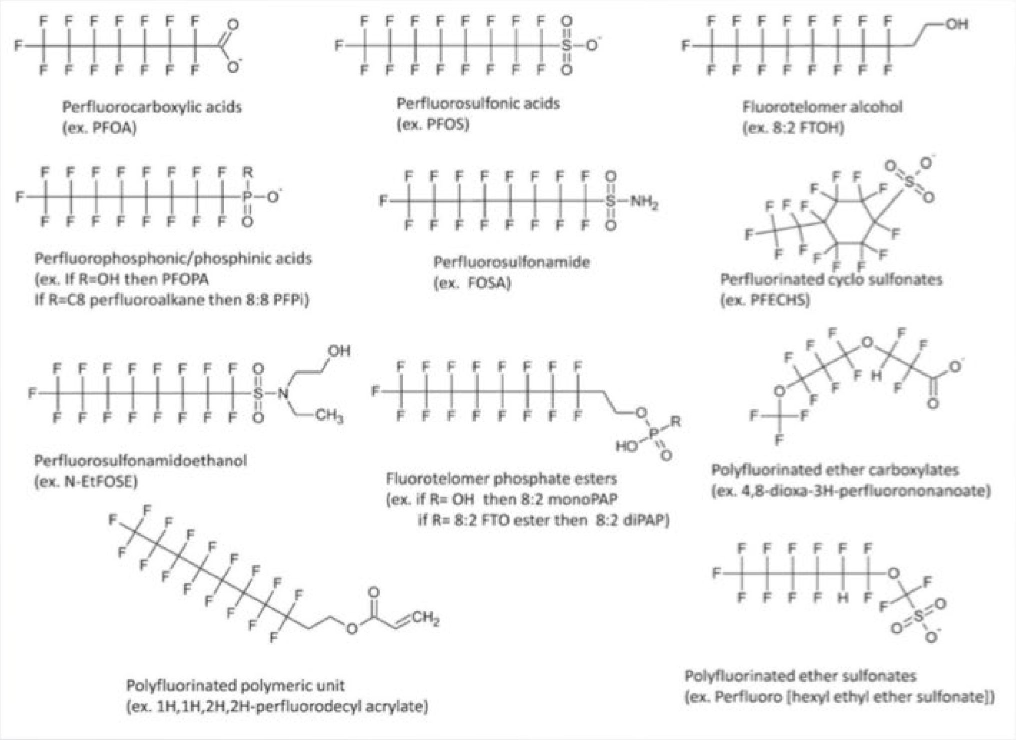
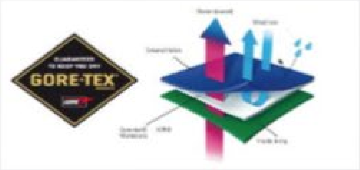
Per- and Polyfluoroalkyl Substances (PFAS)





Slide courtesy of Mark Strynar referencing Lindstrom, Strynar and Libelo, 2011 ES&T

Some Characteristics of PFAS (a.k.a. PFCs)

- Surfactants
- Environmentally persistent (strong C-F bonds)
- Some are bioaccumulative in aquatic species
- Some are bioaccumulative in humans
  - apparent half-lives in years
- Exhibit toxicity in both animal and human studies
- PFOA and PFOS are the most well studied PFAS
  - *mostly* phased out of production in US by 2010
  - still detected in virtually everyone's blood
  - likely ongoing exposures from food, dusts, and for millions of people, contaminated water
- Thousands of other PFAS variations
  - unknown how many are in active commercial use

C8 Science Panel Studies

- 12 related studies, 2007-2016
  - Multi-university research team
  - Funding from settlement of a class action lawsuit brought by citizens in West Virginia and Ohio, exposed mostly via contaminated drinking water (Steenland et al., 2014)
- Access to community data collected under the lawsuit settlement
  - 2005-2006 cross-sectional data for 69,030 people
  - Blood samples, residential histories, water use, health histories
- 32,000 participants enrolled in a prospective cohort study
  - Cancer registry and birth records linkage, neurobehavioral assessments, occupational and environmental dose reconstruction, etc.
- Epidemiological evidence for "probable links" with kidney cancer, testicular cancer, ulcerative colitis, thyroid disease, hypercholesterolemia, and pregnancy-induced hypertension (out of 55 adverse health conditions studied)
- Many journal publications; all study findings described at:

http://www.c8sciencepanel.org/index.html

Exposure Data for C8 Studies

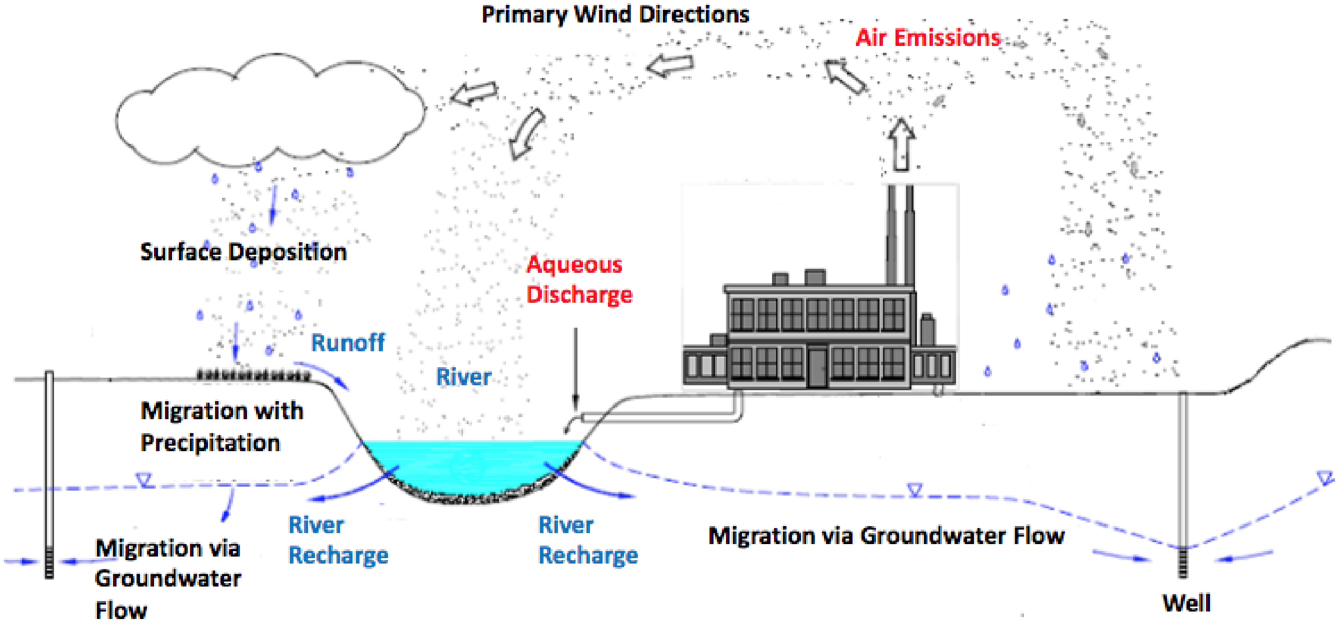
- Measured human serum PFOA concentrations in 2005-2006 ranged from 0.5 to 22,412 ng/mL, with a median of 28 ng/mL (IQR: 14 to 71 ng/mL)
  - US median serum concentration was 3.9 ng/mL at the time
- Water PFOA concentrations from 2002-2005 ranged from 0.03 ng/mL in Mason to 3.49 ng/mL in Little Hocking
  - Strong differences across public water districts
  - Few environmental or biological samples available prior to 2002
  - Detailed annual PFOA emissions data available starting in 1950s
  - How should we classify individual exposures for epidemiological studies?

Exposure Reconstruction for C8 Studies

Retrospective estimation of *individual* year-by-year PFOA exposures

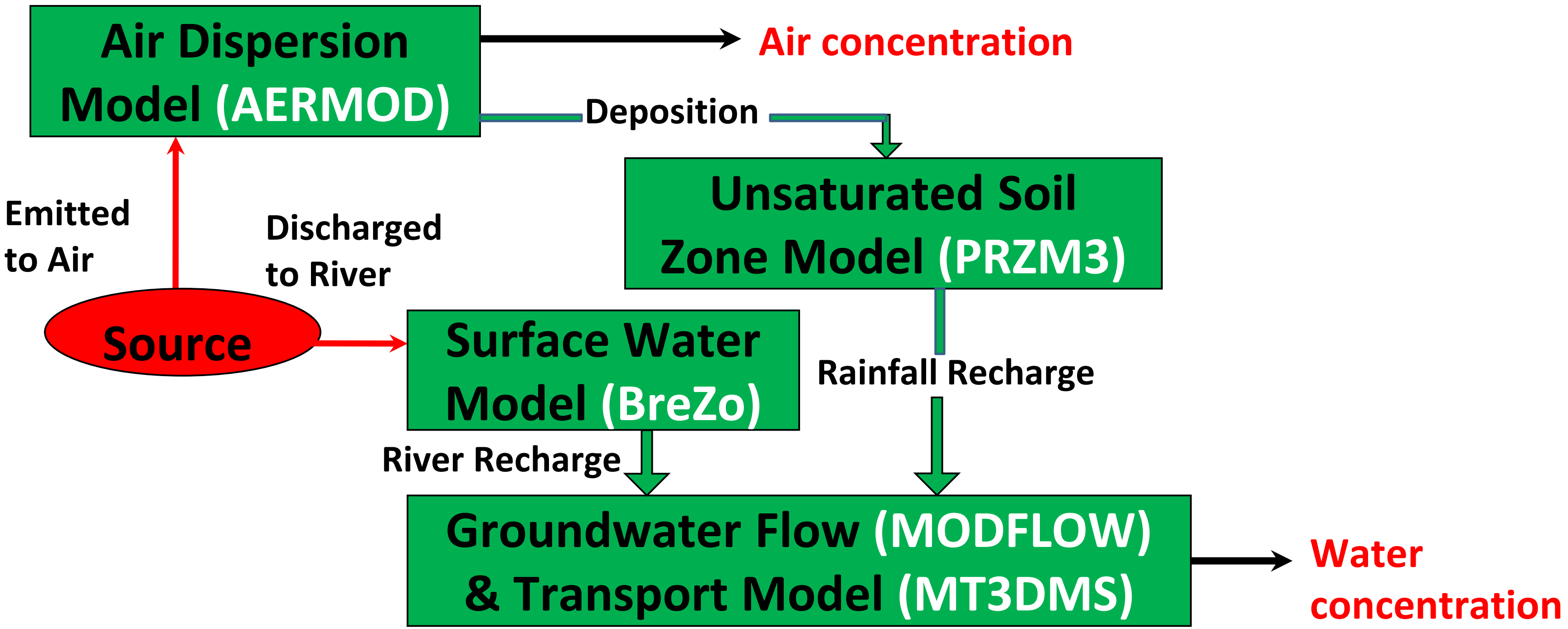
- Fate and transport models used to predict water PFOA concentrations from annual emissions estimates from the Dupont facility (Shin et al., 2011a)
- Individual residential histories and reconstruction of historic public water supply pipe networks used to model water PFOA concentrations over time (Vieira et al., 2013)
- Water consumption rates and modelled water PFOA concentrations used to predict annual dose rates (Shin et al., 2011b)
- Annual dose rates used to predict annual serum concentrations, validated by comparison to 2005-2006 serum measurements (Shin et al., 2011b)
- Modelled serum concentration (or cumulative serum) used as the exposure metric for many of the retrospective epidemiological studies

Schematic Transport Pathways



Source: Data Assessment Report, DuPont (2008)

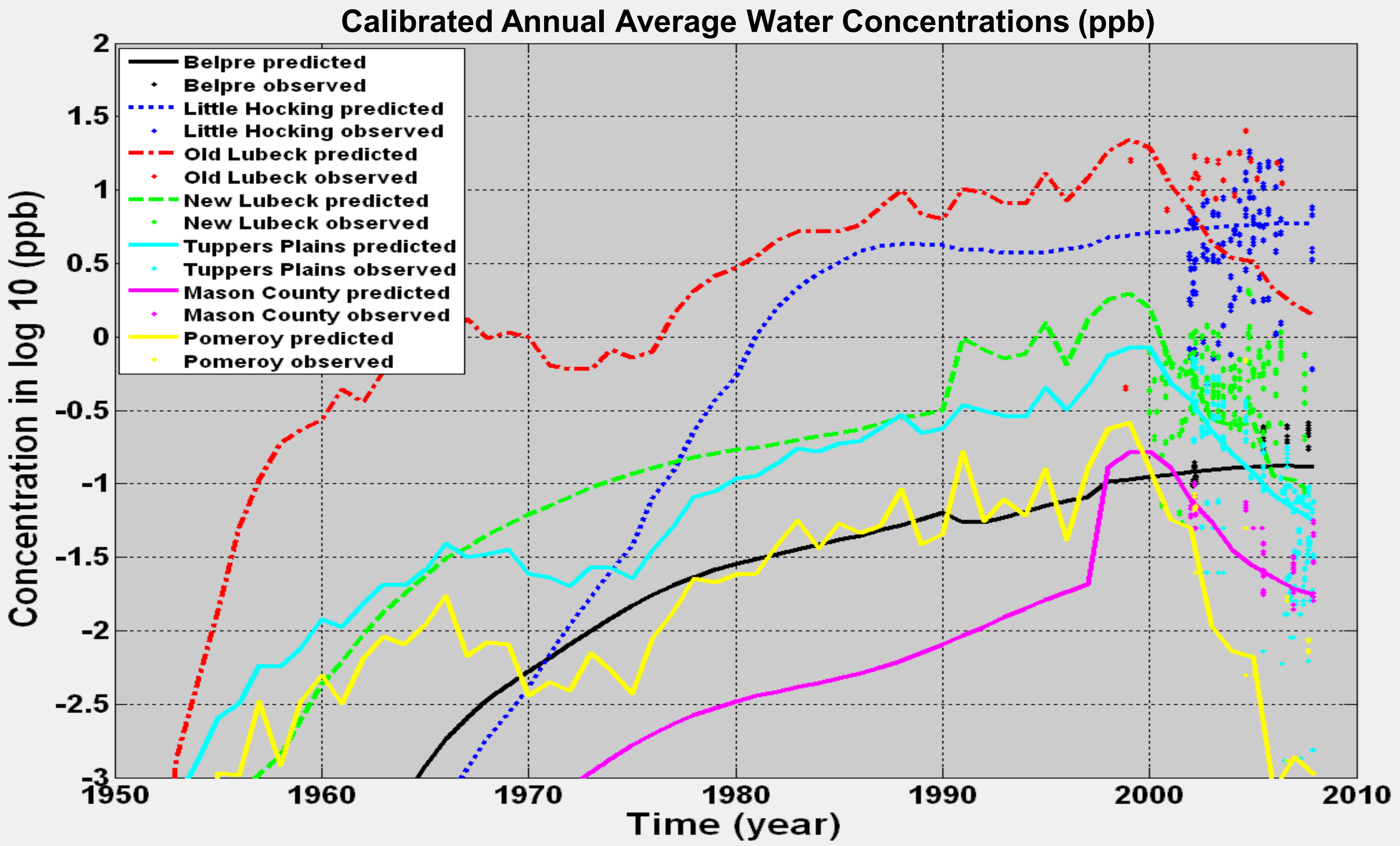
Conceptual Framework of Environmental Modeling



Shin et al., 2010 ES&T

Sources of Input Data and Parameters

Model Component	Type of Input	Example parameter	Data Source
Air	**Emission sources**	Annual emission rate, particle size	DuPont (2008) / Paustenbach(2007)
	Meteorological data	Wind direction and speed	NOAA-NCDC
	Building configuration	Building height, width, size	Paustenbach (2007)
	Receptor information	Terrain elevation	WebGIS
Vadose Zone	Source information	Deposition rate	AEMOD
	Precipitation	Hourly precipitation rate	NOAA-NCDC
	Soil parameters	Soil type, hydrologic soil group	USDA-NRCS-STATSGO
	Soil depth	Depth to groundwater table	DuPont (2003)/WebGIS
Surface Water	Emission sources	Annual liquid emission rate	DuPont (2008) / Paustenbach(2007)
	Bathymetric data	River bottom elevation	DuPont (2003)
	River parameters	River width and depth	GIS
	Mixing parameters	Flow velocity, mixing coefficient	Fisher (1979) /Akan (2006)
		Monthly flow rate	USGS
Groundwater	Source information	PFOA Flux to groundwater table	PRZM3/BREZO
	Hydrological parameters	Hydraulic conductivity	DuPont (2003)
	Geological parameters	Recharge rate	
	Pumping rate	Historical pumping rate	Pipe network/DuPont (2003)


Calibrated Annual Average Water Concentrations (ppb)
Belpre predicted
Belpre observed
Little Hocking predicted
Little Hocking observed
Old Lubeck predicted
Old Lubeck observed
New Lubeck predicted
New Lubeck observed
Tuppers Plains predicted
Tuppers Plains observed
Mason County predicted
Mason County observed
Pomeroy predicted
Pomeroy observed
Concentration in log 10 (ppb)
2
1.5
1
0.5
0
-0.5
-1
-1.5
-2
-2.5
-3
1950
1960
1970
1980
1990
2000
2010
Time (year)

Pharmacokinetic Model

Total Serum Concentration:

$$y_t = y_{t,ww} + y_{t,bc}$$

Background Conc.:

$$y_{t,bc} = \begin{cases} \beta_1 \times (t - 1950) & \text{if } t < 1999 \\ y_{2000,bc} + \beta_2 \times (t - 2000) & \text{if } 2000 < t \leq 2004 \\ y_{2004,bc} & \text{if } t > 2004 \end{cases}$$

DuPont Plant:

$$y_{t,ww} = y_{t-1,ww} \cdot e^{-k} + (1 - e^{-k}) \frac{1}{k \cdot V} I_t$$

- $\mathbf{y_{t,ww}}$ = serum PFOA concentration [μg/L] for year *t* due to DuPont emissions
- $\mathbf{I_t}$ = total mass of PFOA ingested [μg] for year *t*
- **V** = age- and gender-specific volume of distribution for serum [L]
- **k**= excretion rate coefficient for PFOA (= ln2/half-life of 2.3 years) [1/time]
- $\mathbf{y_{t,bc}}$ = background serum PFOA concentration [μg/L] for year *t*
- $\boldsymbol{\beta_1}, \boldsymbol{\beta_2}$ = slope of background concentration from 1950 to 2000 and from 2000 to 2004
- $\mathbf{y_t}$ (= $\mathbf{y_{t,bc}} + \mathbf{y_{t,ww}}$) = serum PFOA concentration [μg/L] for year *t* contributed from background concentration and DuPont emissions

Modelled vs. Measured Serum PFOA

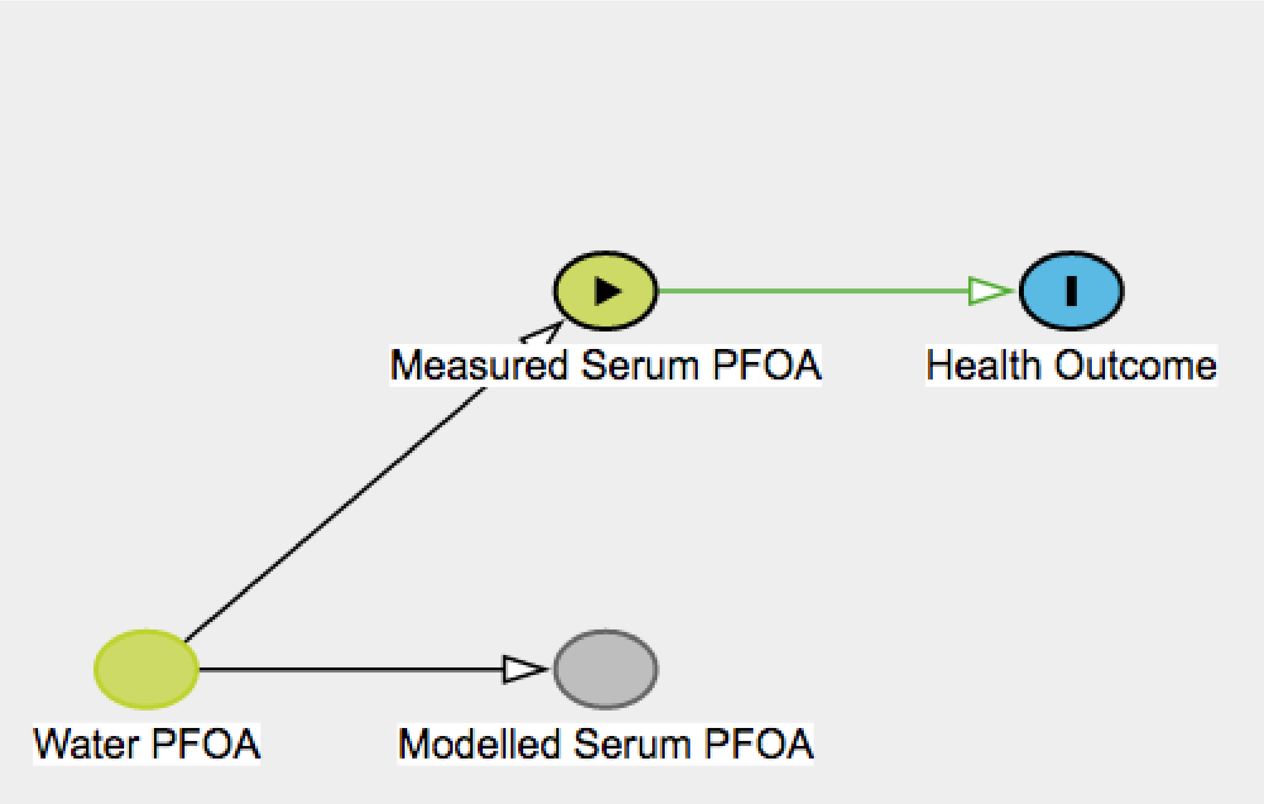
	N*	R_{sp}	Predicted median (ppb)	Observed median (ppb)	Under-prediction (%)	Close-approxim. (%)	Over-prediction (%)
All participants	45,276	**0.67**	10.5	24.3	47.8	**43.3**	8.9
Water consumption	16,138	**0.70**	10.8	26.9	51.4	**41.5**	7.1
Residence in 6 water districts in 2005	25,765	**0.75**	19.5	36.8	39.4	**49.2**	11.4
Same residence & workplace in 6 water districts from 2001 to 2005	1,647	**0.81**	17.0	35.6	42.7	**51.4**	6.0
Same residence & workplace in 6 water districts from 2001 to 2005 and water consumption rate	793	**0.83**	18.2	39.4	38.1	**55.7**	6.2
Same residence & workplace NOT in 6 water districts from 2001 to 2005	1,257	**0.27**	4.8	15.7	70.0	**26.8**	3.2
Bottled water drinkers	2,419	**0.74**	11.1	27.5	50.0	**41.8**	8.1
Non -vegetable growers	34,363	**0.66**	10.3	23.0	46.8	**43.9**	9.4
Vegetable growers	10,913	**0.70**	11.3	28.9	51.1	**41.3**	7.6
Work histories	29,820	**0.68**	9.8	24.6	51.6	**41.4**	7.0

***Excludes DuPont workers and participants without observed serum concentration**

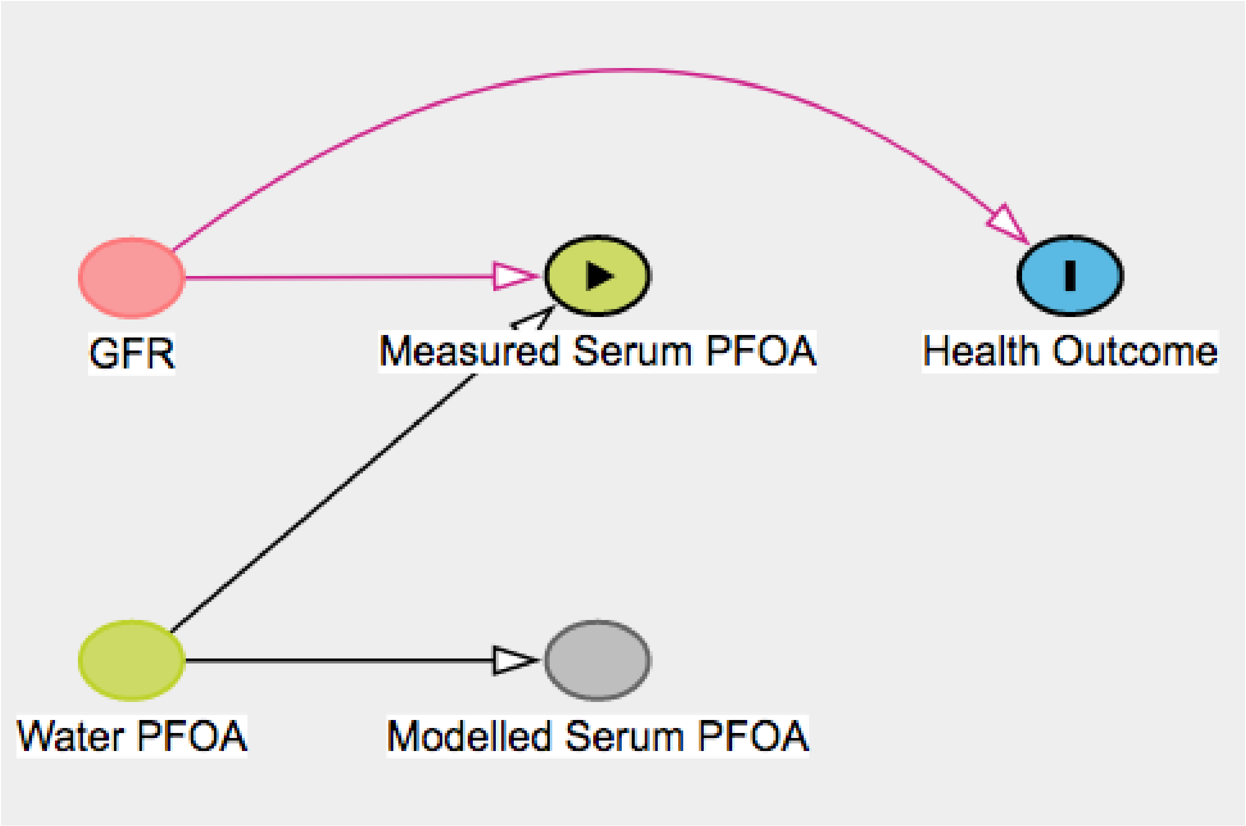
Triangulation: External vs. Internal Exposure

- Measured exposure biomarkers often viewed as gold standard
    - **But** may be subject to physiological confounding or reverse causation in some health association studies--especially for PFAS (Longnecker, 2010; Watkins et al., 2013; Steenland et al., 2018)
- External exposure estimates have more measurement error
    - But error is likely to be non-differential, and associations unlikely to affected by physiological confounding or reverse causation (Weisskopf and Webster, 2017)
    - Epidemiological results in the C8 Studies do not appear to be highly sensitive to the exact exposure assignments (Avanasi et al., 2015; Avanasi et al., 2016)
        - Shared exposure source that is highly disparate across water districts
- Both approaches have threats of bias, but of different types
    - Can put epidemiological effect estimates on same scale using pharmacokinetic models
    - Ideally, do epidemiology using both metrics, and compare results
    - If effect estimates differ substantially, it may indicate bias (Watkins et al., 2013)
    - If effect estimates are similar, can combine exposure metrics for more precise results using formal Bayesian calibration (Shin et al., 2014)

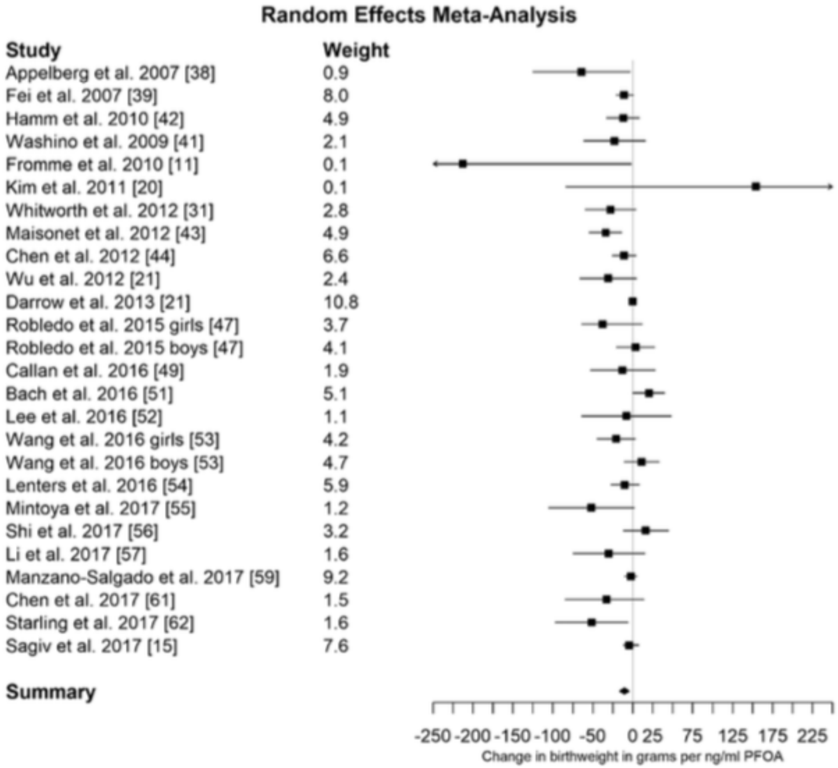
DAG for Causal Effect of PFOA on Health Outcome



Example DAG for Physiological Confounding



Serum PFOA and Birth Weight

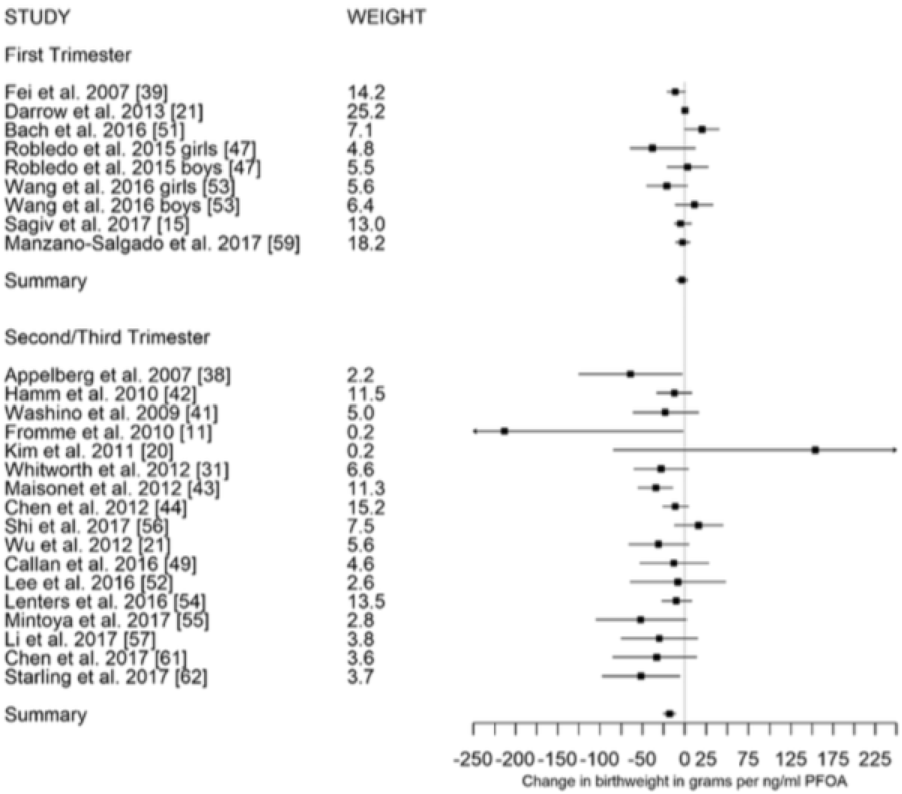


meta-analysis, measured serum:
−10.5 g [95% CI: −16.7, −4.4]
per ng/mL serum PFOA

modelled serum (Savitz, 2012):
-0.1 g [95% CI: -0.2, 0.02]
per ng/mL serum PFOA

(Steenland et al., 2018)

... now stratified by pregnancy period

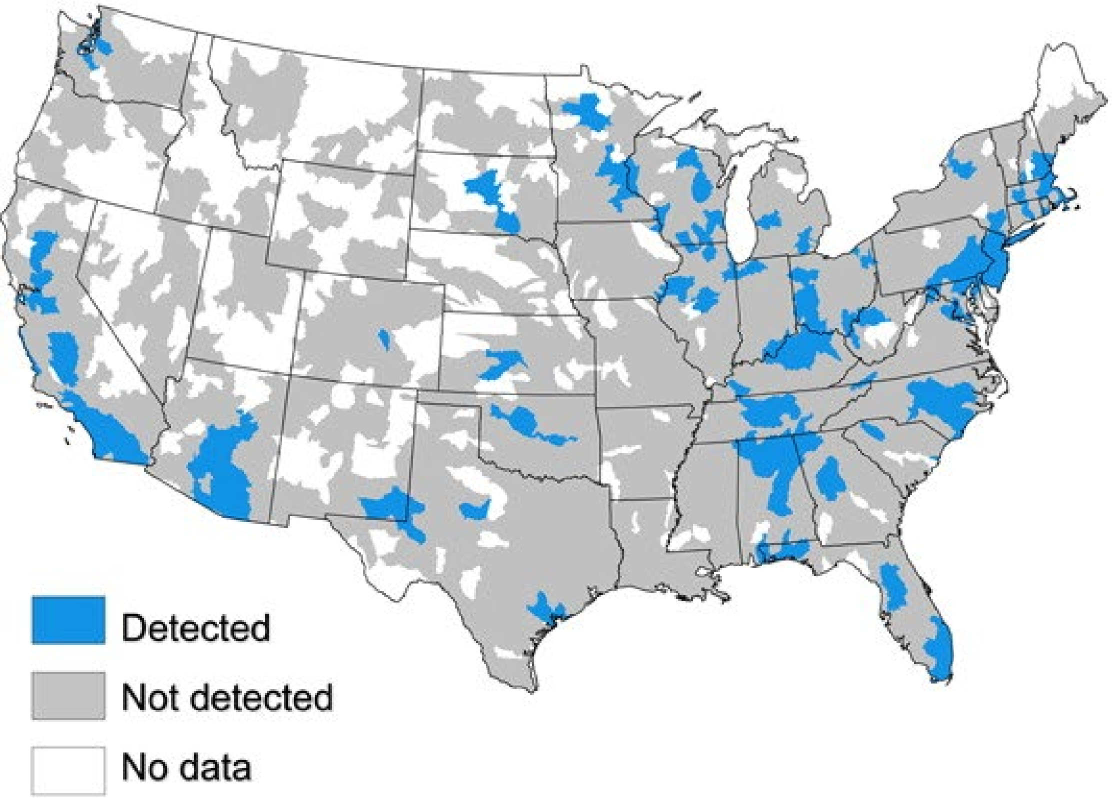


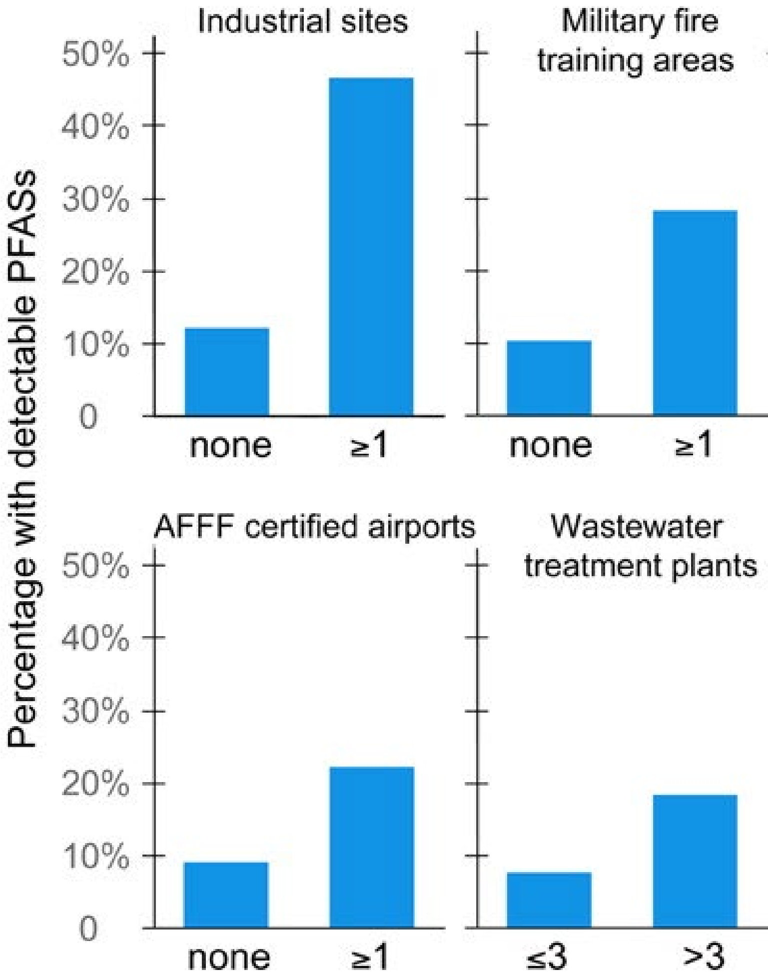
meta-analysis, early pregnancy:
−3.3 g [95% CI: −9.6, 3.0]
per ng/mL serum PFOA

meta-analysis, late pregnancy:
-17.8 g [95% CI: -25.0, -10.6]
per ng/mL serum PFOA

(Steenland et al., 2018)

Hydrological units with detectable PFASs





Hu et al., 2016

CDC/ATSDR Multi-Site PFAS Study

- New 5-year study with 7 sites; all have PFAS in drinking water supplies
  - El Paso County, CO
  - Parchment/Cooper Township, MI, and North Kent County, MI
  - Montgomery and Bucks Counties, PA
  - Gloucester County, NJ
  - Hyannis, MA, and Ayer, MA
  - Hoosick Falls, NY, and Newburgh, NY
  - **Orange County, CA**
- each site will recruit 1000 adults and 300 children for clinical measurements
- shared core protocol, common IRB, and centralized data management
- each site performs local groundwater modeling and historical exposure reconstruction (Shin et al., 2011ab)
- additional site-specific community engagement and research activities

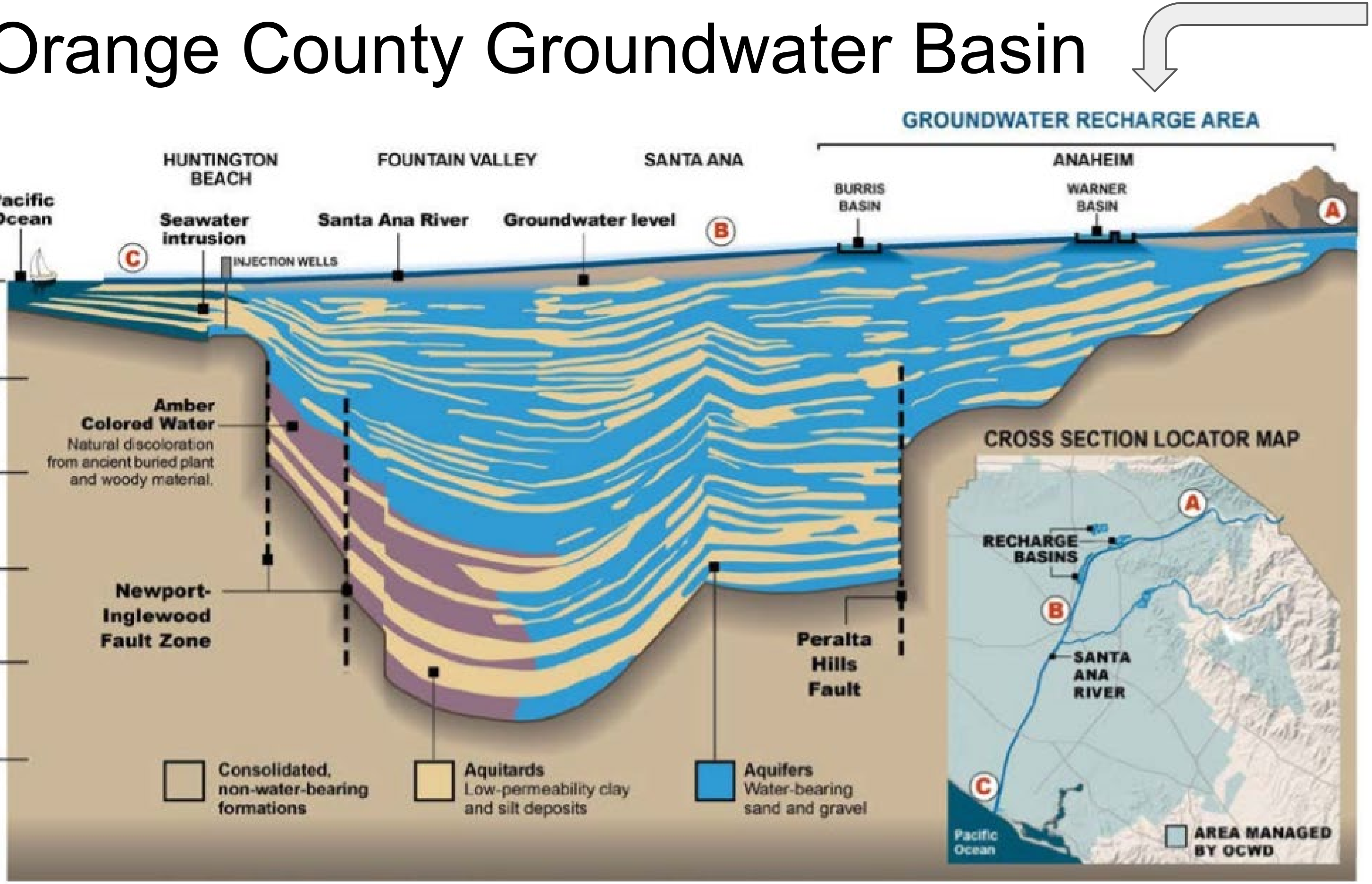
Core Protocol Measurements

- Questionnaire
  - Including residential histories and water consumption
  - self-reported disease histories, validated by medical records
- Fasting blood and urine samples, shipped to CDC
  - PFAS concentrations
  - Biomarkers of immune response, lipid metabolism, kidney function, thyroid function, liver function, and glycemic parameters
- Body measurements and blood pressure
- Neurobehavioral testing
  - WASI-II, NEPSY-II, CPT, SDQ, BRIEF
- Educational records
- Medication list
- Draft protocol: https://www.atsdr.cdc.gov/pfas/PFAS-Research-NOFO.html

PFAS in Orange County, CA

- Over **500,000 people** are served by water systems within 10 miles of UC Irvine Medical Center that had at least one water measurement exceeding EPA Health Advisory (70 ppt for PFOA+PFOS) in UCMR3
    - Anaheim, Orange, Yorba Linda
- Local water utilities use seasonally varying combinations of groundwater, surface water, and/or imported water
- Groundwater supply and quality carefully managed by Orange County Water District (OCWD), but discovered to have PFAS during UCMR3 monitoring

Orange County Groundwater Basin



Recharge from Santa Ana River (mostly **WWTP effluent**), advanced treatment local recycled water, and imported surface water from northern California and the Colorado River.

OCWD, 2009

Other Site-Specific Activities at UC Irvine

- Additional water, soil, and/or stored blood PFAS measurements
- Developing pharmacokinetic models for PFAS in humans
  - Literature-based, validated by linkage of UCMR3 with NHANES biomonitoring data
  - An R package for PFAS pharmacokinetics allowing time-varying exposures
  - Simplified web-based models for public use (e.g., https://www.ics.uci.edu/~sbartell/pfascalc.html)
- Further development of formal Bayesian statistical methods for pharmacokinetic calibration of individual historical exposure estimates using measured biomarkers (e.g., Bartell, 2003; Shin et al., 2014)
- Prospective follow-up of children (cut from budget in Year 1)

Projected Timeline for California Site

- Groundwater modeling and pharmacokinetic modeling underway
- Participant recruitment and clinical measurements on hold for all sites until approval of core protocol by OMB and CDC IRB
  - randomized study invitations vs. targeted recruitment?
- Clinical visits in Years 2-3?
- Complete exposure reconstruction and epidemiological analyses in Years 4-5

Epidemiological analyses using pooled data from all sites at study end

Acknowledgments

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And the rest of the investigators for the multi-university C8 Studies

* Students while working on these studies

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- CDC/ATSDR Cooperative Agreement (U01-TS000308)
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- Research and Education in Green Materials Program at University of California, Irvine (UC-44157)
- C8 Class Action Settlement Agreement (Circuit Court of Wood County, WV)

Dr. Bartell has served as an expert witness for plaintiffs in two medical monitoring lawsuits for PFAS in New Hampshire.