

Perfluorinated Chemicals (PFCs) – Emerging Drinking Water Contaminants

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Office of Science

NJ Department of Environmental Protection

Delaware River Basin Commission

Toxics Advisory Committee

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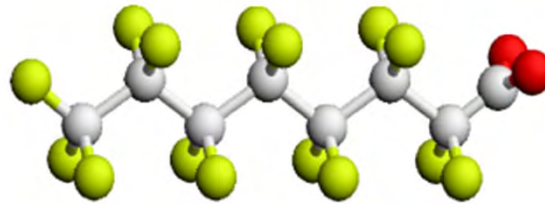


The conclusions expressed in this presentation do not necessarily reflect the policies of NJDEP.

What are perfluorinated chemicals (PFCs)?

- A group of man-made chemicals with:
 - **Totally fluorinated carbon chain** & **charged functional group**

- **Perfluorooctanoic acid (C8):**



- Carbon chain length & functional group vary:
 - Example: Perfluoro**butanoic** acid, C4
 - $\text{CF}_3(\text{CF}_2)_2\text{COO}^-$
 - Example: PFOS – perfluorooctane **sulfonate**
 - $\text{CF}_3(\text{CF}_2)_6\text{SO}_3^-$

Occurrence and Potential Significance of Perfluorooctanoic Acid (PFOA) Detected in New Jersey Public Drinking Water Systems

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After detection of perfluorooctanoic acid (PFOA) in two New Jersey (NJ) public water systems (PWS) at concentrations up to 0.19 $\mu\text{g/L}$, a study of PFOA in 23 other NJ PWS was conducted in 2006. PFOA was detected in 15 (65%) of the

the U.S. population (2). In studies of U.S. populations, the geometric mean serum levels were 3.9 $\mu\text{g/L}$ in 2003–2004 and 3.4 $\mu\text{g/L}$ in 2006 (2, 3). This widespread human exposure is of concern due to PFOA's persistence and toxicity. PFOA has a half-life of several years in humans (4), and caused adverse effects on development, lipid metabolism, liver, and the immune system, and tumors in several organs in animals (5). In some studies, maternal exposures in the general population were associated with decreased birth weight and other measures of fetal growth (6–8), while other studies did not find these effects (9, 10). Some studies of exposed workers found associations with adverse outcomes including diabetes mellitus and increased cholesterol, whereas other studies were negative (5). Preliminary results of a study of almost 70 000 people exposed through drinking water suggest an association with several clinical parameters measured in blood, including increased cholesterol (11, 12).

Sources of exposure to PFOA include consumer products (13), house dust (14), diet (15), and drinking water (16). Exposure also occurs through metabolism and environmental transformation of the related chemical, 8:2 fluorotelomer alcohol, which is widely used in food packaging and other products (17).

PFOA and other perfluorinated chemicals were detected in surface waters (18–23) and drinking water (20, 24, 25) in several countries, and in groundwater contaminated by fire fighting foams (26). Drinking water has been contaminated by sources such as industrial facilities and landfills (16, 27), and by use of a contaminated soil conditioner on agricultural land (20). Blood levels of PFOA are elevated in communities with contaminated drinking water (16, 20), with the median



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Review

Perfluorooctanoic acid (PFOA), an emerging drinking water contaminant: A critical review of recent literature ☆, ☆ ☆

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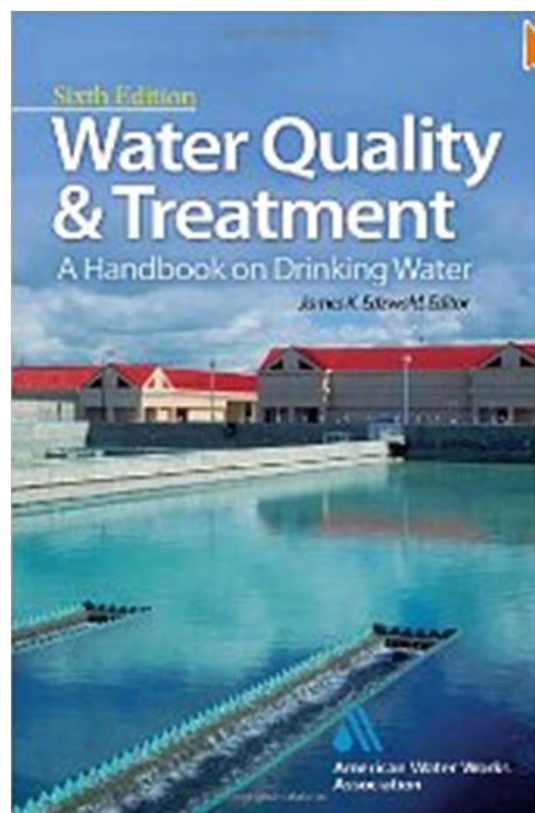
C8

Perfluorinated chemicals

Drinking water contaminants

ABSTRACT

Perfluorooctanoic acid (PFOA) is an anthropogenic contaminant that differs in several ways from most other well-studied organic chemicals found in drinking water. PFOA is extremely resistant to environmental degradation processes and thus persists indefinitely. Unlike most other persistent and bioaccumulative organic pollutants, PFOA is water-soluble, does not bind well to soil or sediments, and bioaccumulates in serum rather than in fat. It has been detected in finished drinking water and drinking water sources impacted by releases from industrial facilities and waste water treatment plants, as well as in waters with no known point sources. However, the overall occurrence and population exposure from drinking water is not known. PFOA persists in humans with a half-life of several years and is found in the serum of almost all U.S. residents and in populations worldwide. Exposure sources include food, food packaging, consumer products, house dust, and drinking water. Continued exposure to even relatively low concentrations in drinking water can substantially increase total human exposure, with a serum:drinking water ratio of about 100:1. For example, ongoing exposures to drinking water concentrations of 10 ng/L, 40 ng/L, 100 ng/L, or 400



Chapter 2. Health and Aesthetic Aspects of Drinking Water

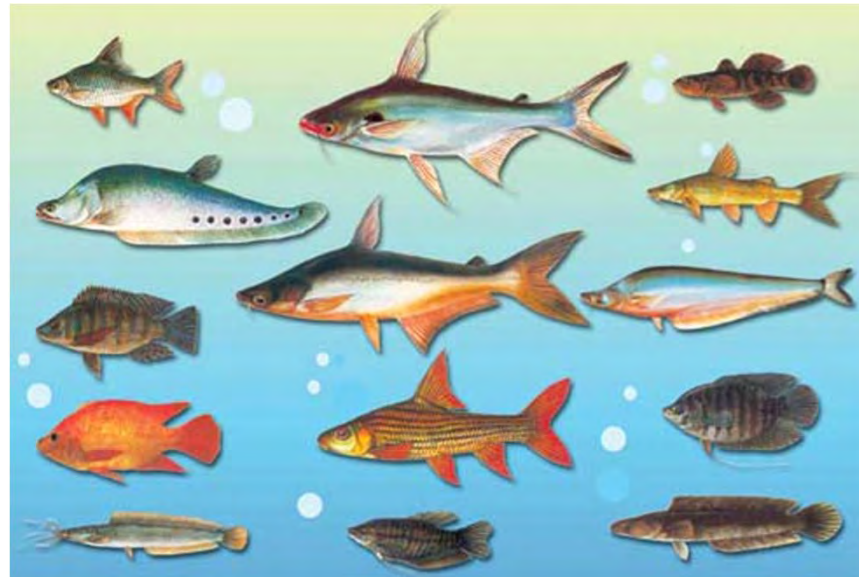
***Gloria B. Post, Ph.D., D.A.B.T., Thomas B. Atherholt, Ph.D.,
and Perry D. Cohn, Ph.D., M.P.H.***

Waterborne Disease	/	2.3
Pathogenic Organisms	/	2.6
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Why is PFOA of interest as a drinking water contaminant?

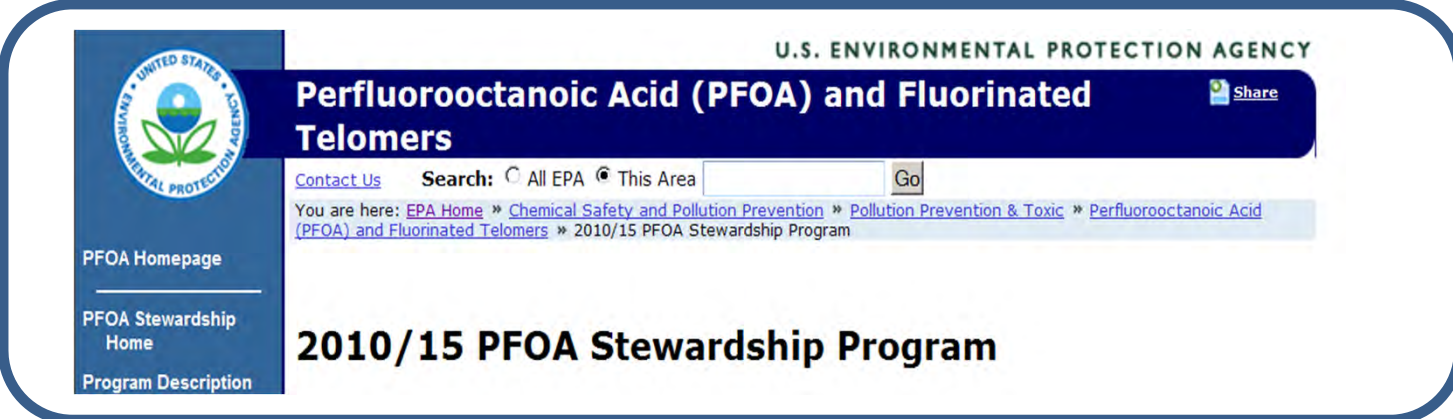
- **Scientific Perspective:**
 - Important differences from other well-studied drinking water contaminants.
 - Large number of recent studies...
...and *MORE* new studies are constantly emerging!
- **Public Health Perspective:**
 - Widespread environmental occurrence & human exposure.
 - Extremely persistent in the environment.
 - Drinking water is an important human exposure route.
 - Long half-life in humans (years).
 - Human & animal data suggest potential health risks from drinking water exposure.

***Wildlife exposure and effects are also important...
...but not addressed here, since our focus is drinking water.***



Production of PFOA

- Produced for over 60 years.
- Currently being **phased out** by voluntary agreement of eight major manufacturers with USEPA.
 - Phase-out includes **other related PFCs** with more than 8 carbons.
 - Production by other manufacturers continues, particularly overseas.
- **Shorter chain PFCs** introduced as **replacements**.
 - Less biologically persistent & less toxic.
 - BUT extremely persistent in the environment, like all PFCs.



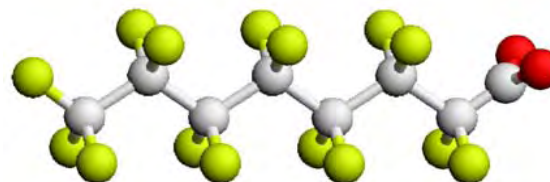
The image is a screenshot of the U.S. Environmental Protection Agency (EPA) website. At the top right, it says "U.S. ENVIRONMENTAL PROTECTION AGENCY". The main heading is "Perfluorooctanoic Acid (PFOA) and Fluorinated Telomers" in a dark blue banner. To the left of this banner is the EPA logo. Below the banner, there is a search bar with "Search:" and radio buttons for "All EPA" and "This Area". Below the search bar, there is a breadcrumb trail: "You are here: EPA Home » Chemical Safety and Pollution Prevention » Pollution Prevention & Toxic » Perfluorooctanoic Acid (PFOA) and Fluorinated Telomers » 2010/15 PFOA Stewardship Program". On the left side of the page, there is a vertical menu with links: "PFOA Homepage", "PFOA Stewardship Home", and "Program Description". The main content area features the heading "2010/15 PFOA Stewardship Program".

Important Properties of PFOA (and other PFCs)

- Contains both hydrophilic & hydrophobic/oleophobic segments.

- *Repels oil and water.*

- *Highly water soluble.*



- C-F bond is one of strongest known in chemistry
 - *Chemically & thermally non-reactive.*
- Unique properties are the basis for:
 - *Commercial and industrial uses.*
 - *Environmental fate & transport.*
 - *Toxicokinetics in humans and other species*

Commercial & Industrial Uses of PFOA*

- Processing aid (solubilizer) in production of fluoropolymer plastic PTFE:
 - Non-stick cookware, waterproof/breathable clothing, and chemical/heat resistant tape and tubing.
 - Present at *very low levels* in final products.



- Water & stain resistant coatings for carpets & upholstery



- Grease-proof food packaging



- Waxes (including ski waxes), polishes, paints, adhesives



- Aqueous fire fighting foams



....and other uses not listed here

* Many of these uses are currently being phased out.

Of PFOA and/or precursors which can degrade to PFOA in the environment & the body

Sources of Environmental Contamination of PFOA

- **Industrial facilities** where made or used.
 - Historical discharges of large amounts to air & water where used as processing aid in fluoropolymer production.



- **Wastewater treatment plants.**



- Land application of:

- **Sludge (“biosolids”)** from WWTP
- **Industrial waste**



- Release of **aqueous fire fighting foams.**

- Firefighter training sites
- Airfields



- **Municipal landfill** leachates.
- Disposal of products used by **small businesses.**
- Runoff of **storm water** and **street dust.**

... and others not listed here.

PFOA Environmental Fate & Transport

- Persistent, Bioaccumulative, and Toxic...

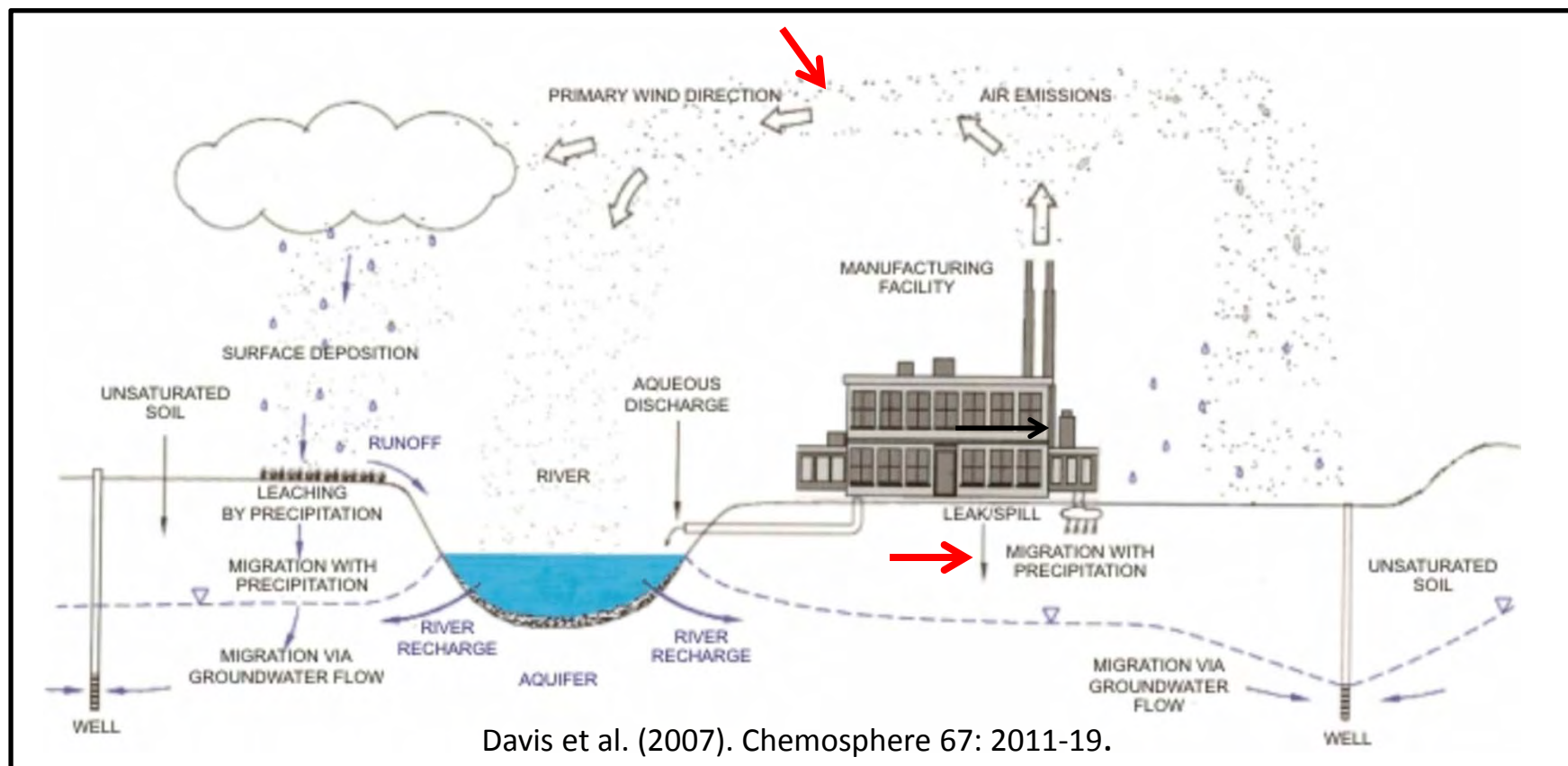
- BUT very different from “classic” PBT chemicals

	PFOA	Dioxins & PCBs
Highly water soluble	YES	NO
Binds well to soil & sediments	NO	YES
Degrades in environment to some extent	NO	YES
Bioaccumulates in fish	NO	YES
Bioaccumulates in lipids	NO	YES
Drinking water is major exposure route	YES	NO

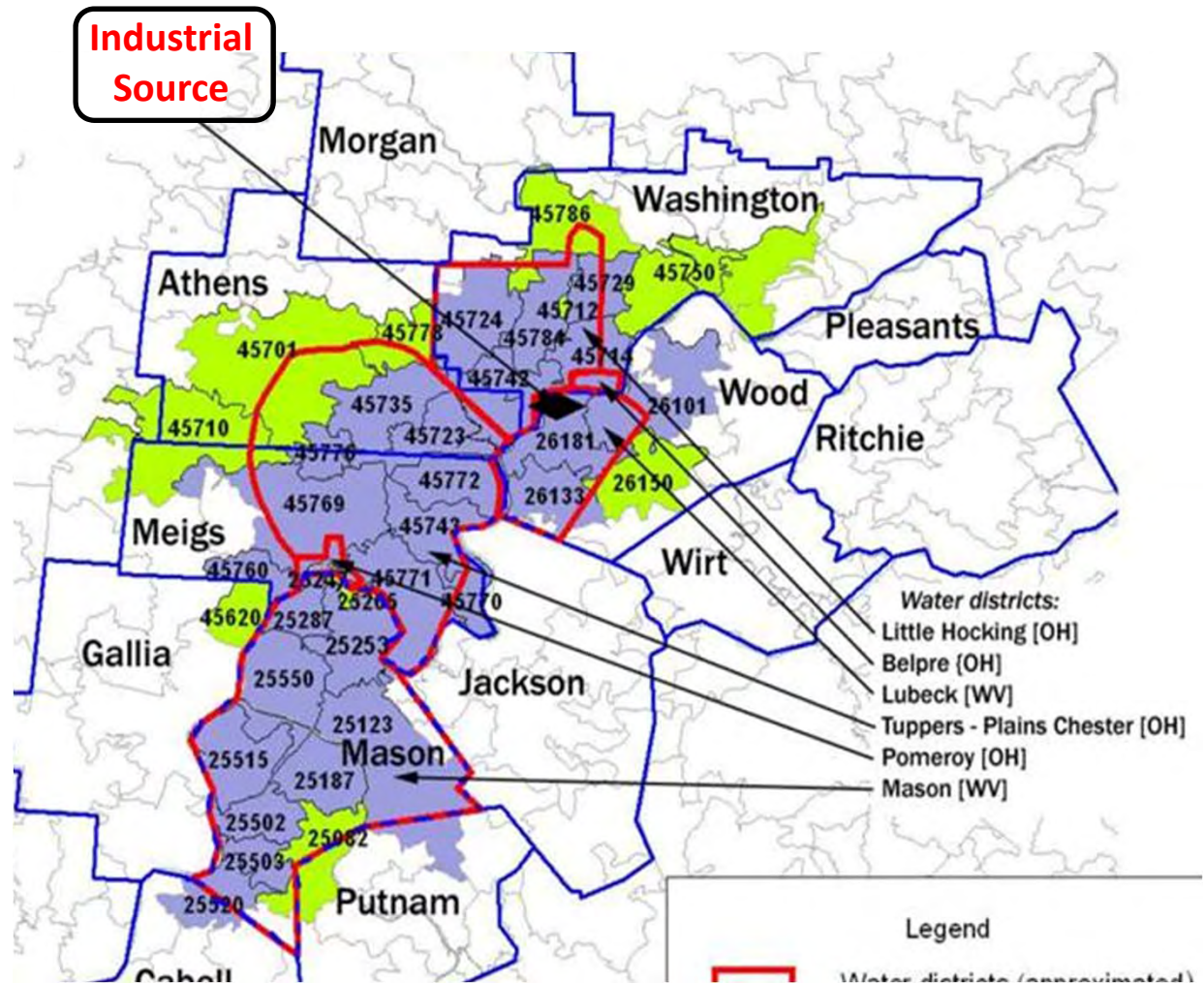
Transport of PFOA after Discharge from Industrial Facility

Two pathways for: Industrial releases \longrightarrow Groundwater:

1. Migration of groundwater plume
2. Air emissions \longrightarrow Soil deposition \longrightarrow Migration to groundwater



Drinking water wells up to ~20 miles from industrial source were contaminated with PFOA through air deposition (WV & Ohio).



Source: S. Frisbee,
 West Virginia Univ.
 School of Medicine. 2008.



This also occurred in New Jersey on a smaller scale.....



Private and Public Wells near Industrial Site

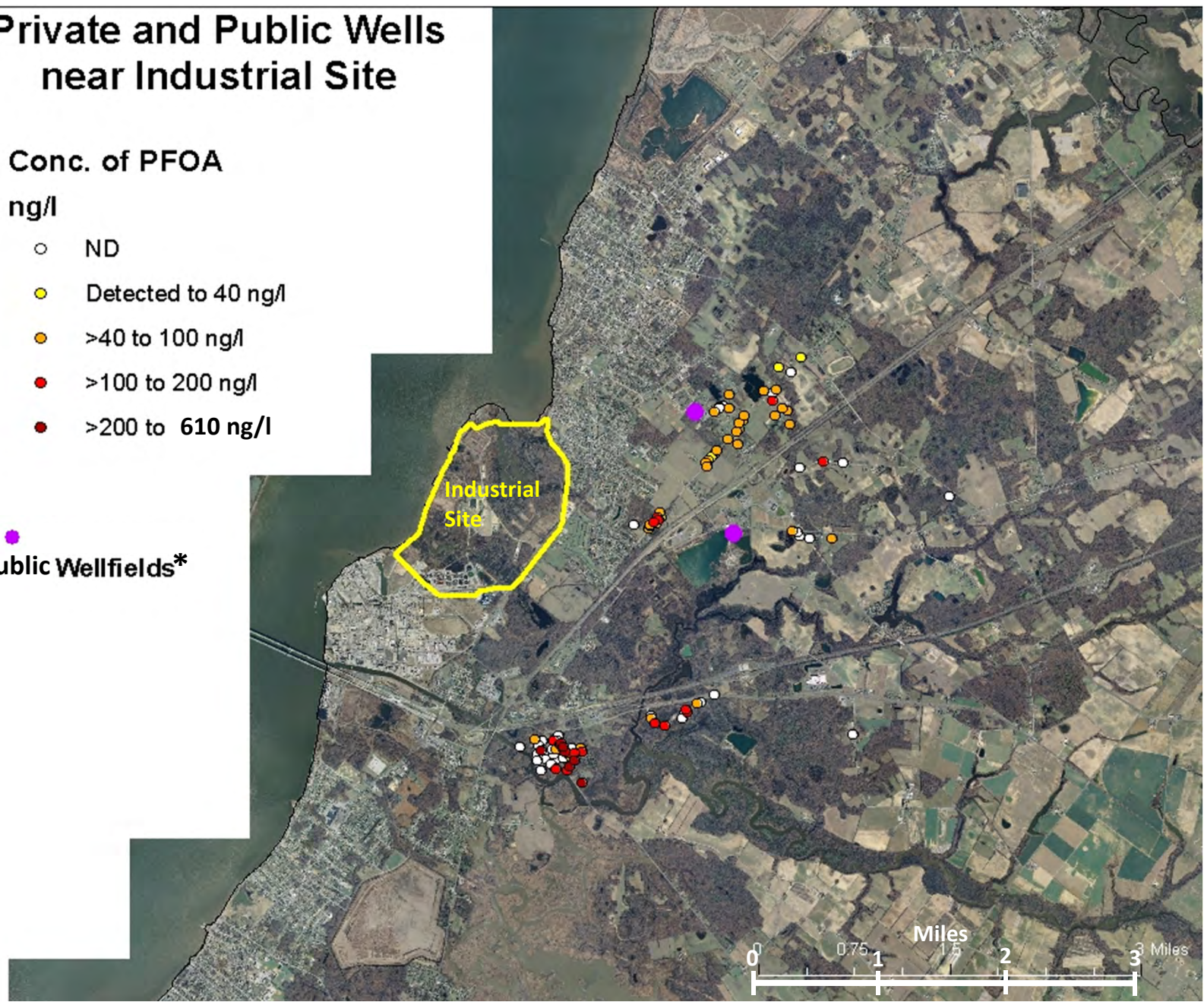
Conc. of PFOA

ng/l

- ND
- Detected to 40 ng/l
- >40 to 100 ng/l
- >100 to 200 ng/l
- >200 to 610 ng/l

Public Wellfields*

Industrial Site



*Detected in public water supply wells at up to 280 ng/L.

Good News!

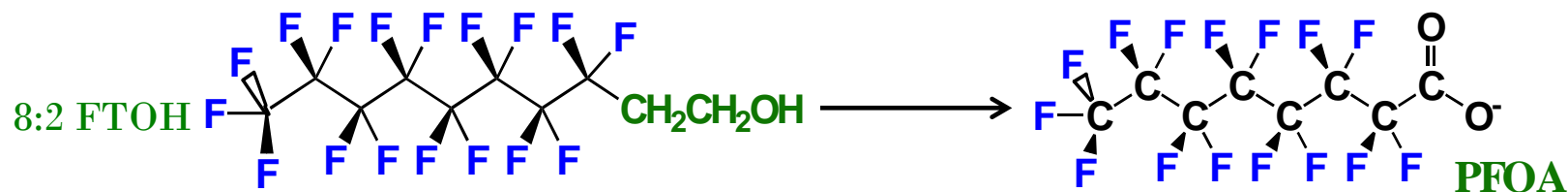
Measures are in place to eliminate exposure to PFOA in drinking water from affected public water supplies & private wells at these Ohio/West Virginia & NJ sites.



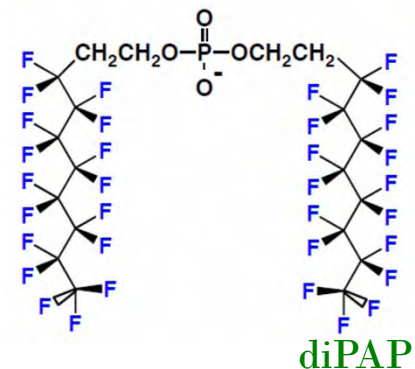
Formation of PFOA* from Precursor Compounds

(*and other PFCs)

- Precursors found in commercial products & industrial processes (e.g. food packaging; carpet & upholstery coatings).
- Fluorotelomer alcohols (FTOH) \longrightarrow PFOA
 - **Atmospheric reactions** (non-biological).
 - **Bacterial metabolism** (WWTP, sludge, & soil).
 - **Metabolic reactions** (humans and other animal species).



- FTOH released from larger molecules (e.g. polyfluoroalkyl phosphate esters (PAPs), ?fluoropolymers?)

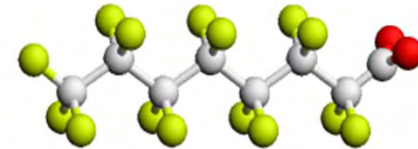


- Contributes to environmental contamination & human exposure.
 - PFOA that is formed is terminal product & does not degrade.

PFOA* Found in Environmental Media Worldwide ***(*and other PFCs)***

Found in many environmental media including...

- Ground water & surface water
- Drinking water (public supplies & private wells)
- Air (indoor & outdoor)
- Sludge (“biosolids”) from WWTP (sewage treatment plants)
- Soil
- Sediments
- Dust (outdoor & indoor)
- Plants, including food crops
- Wildlife, including in remote regions (Arctic)
- Polar ice caps



Voluntary phase-out is in effect, but contamination is expected to continue due to:

- Extreme environmental persistence
- Continued formation from precursors
- Continued production by non-participating manufacturers, especially overseas.

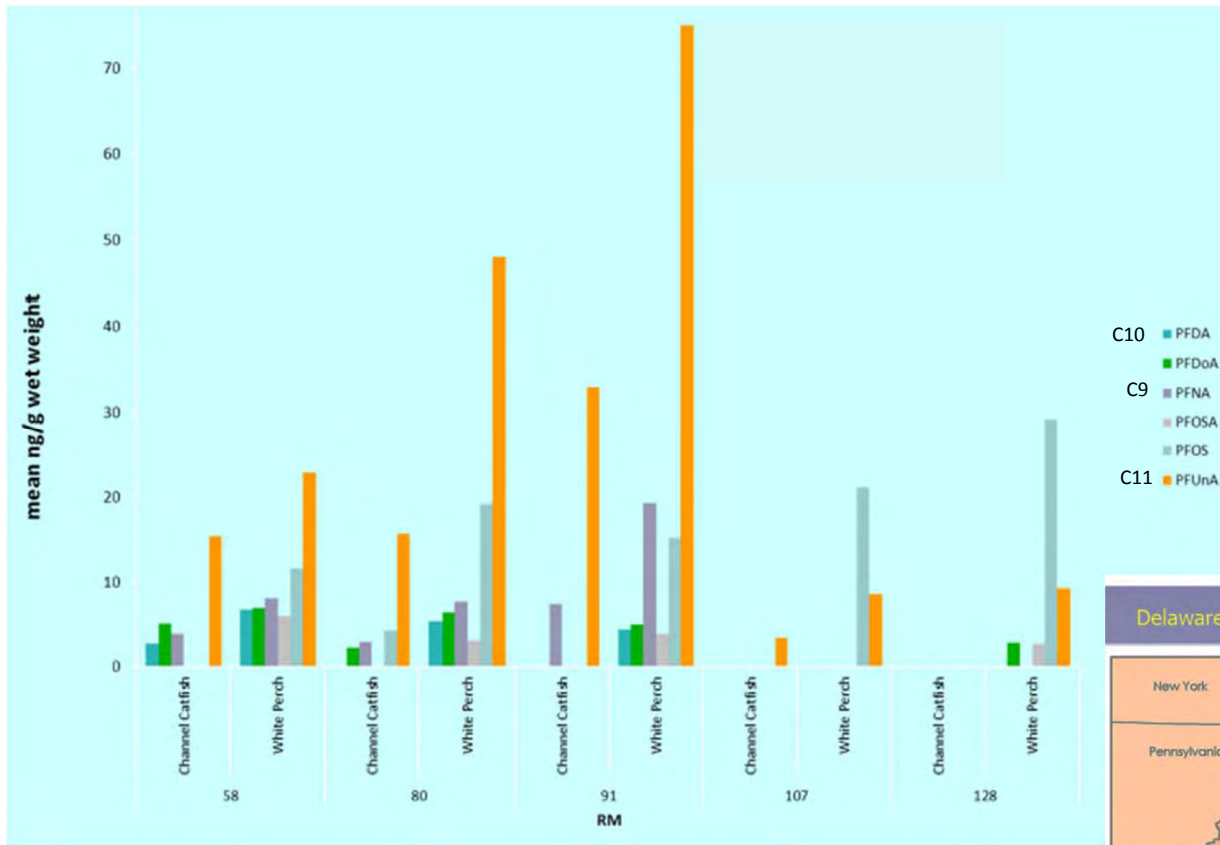
PFC Bioaccumulation in Fish

- Bioaccumulative potential of PFCs in fish increases with increasing carbon chain length.
 - PFOA (C8) is not bioaccumulative in fish.
 - Longer chain **carboxylates** (PFOA homologues) with **9 or more carbons** are bioaccumulative.
 - PFOS & other **sulfonates** with **8 or more carbons** are bioaccumulative.

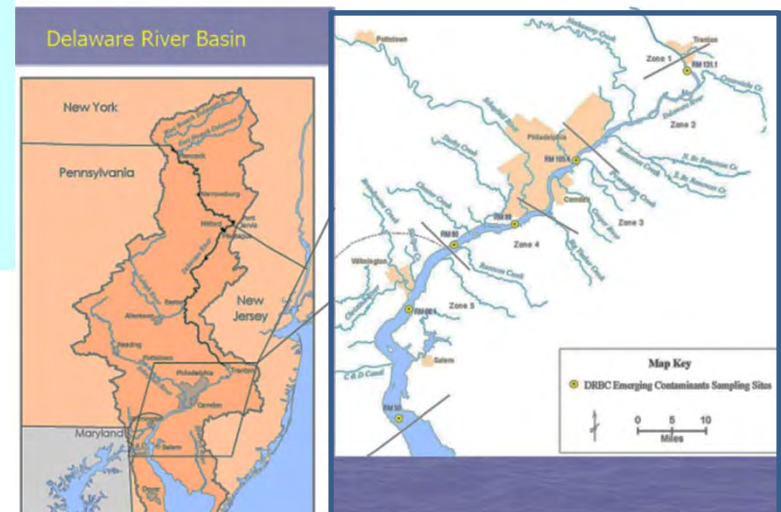


PFCs in Fish Fillets in Tidal Delaware River (2004-07)

(Source: A.R. MacGillivray, Delaware River Basin Commission, 2012)



River Mile



“Units”



Drinking water

- Micrograms per liter (ug/L) = parts per billion (ppb)
- Nanograms per liter (ng/L) = parts per trillion (ppt)



Blood serum

- Nanograms per milliliter (ng/ml)
= parts per billion (ppb)

PFOA Occurrence in Drinking Water

- **Frequently detected** in U.S. & worldwide studies.
- Not removed by conventional water treatment.
 - *Raw water is good indicator of finished water.*
 - *Removed by **Granular Activated Carbon** (not commonly used).*
- **USEPA Unregulated Contaminant Monitoring Rule 3:**
 - *Will provide **national occurrence data** for PFOA & 5 other PFCs by 2017.*



PFOA Occurrence in New Jersey Public Water Supplies (PWS)

- Quantified in 59% of 56 PWS tested ($\geq 4\text{-}5$ ng/L).
 - In two NJDEP statewide studies (2006 & 2009) & additional data submitted by several water companies.
- Found both in surface water & unconfined ground water wells.

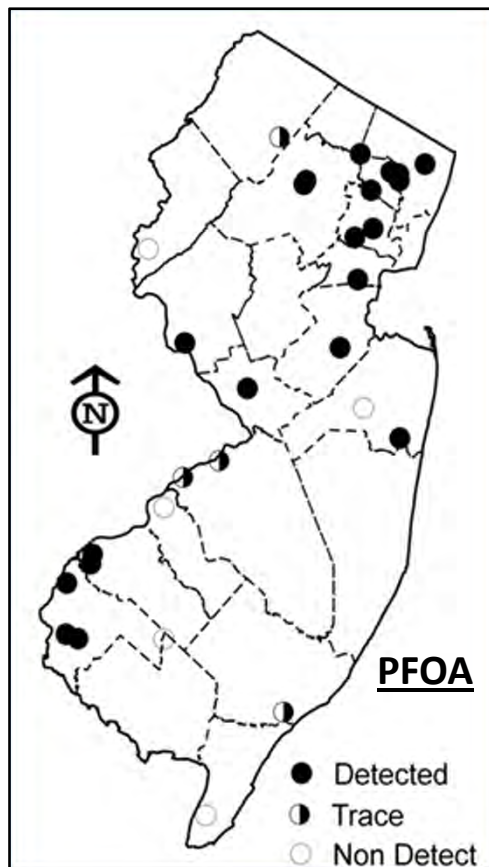


- 12% of PWS had at least one detection \geq NJ Health-based Guidance (0.04 ug/L; 40 ng/L).
- PFOS found less frequently and at lower maximum levels than PFOA.
- 2009 NJDEP study of 30 PWS included PFOA, PFOS, & 8 other PFCs.
 - Participating PWS have been informed of results.
 - Study report not yet final.
- No other state has done similar studies.



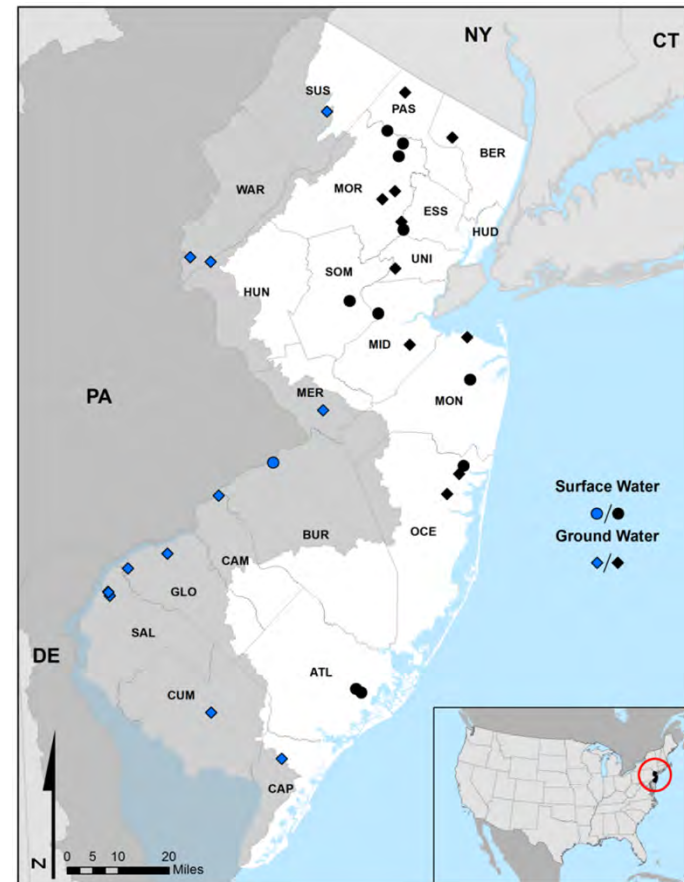
Locations of Public Water Supplies (PWS) Sampled in NJDEP Occurrence Studies

2006 Study
(PFOA & PFOS)*



*NJDEP (2007); Post et al. (2009)

2009 Study
(10 PFCs)**

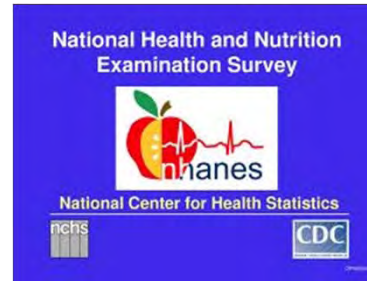


**Includes two additional PWS that monitored for these 10 PFCs.

Human Exposure to PFOA is Ubiquitous

- Found in blood serum of **virtually 100% of general population** in U.S. & other industrialized nations:

- Median: 4 ppb.
- Upper 95th %: 10 ppb.
(NHANES, 2007-8)



- **Persistent** in humans:

- Half-life \geq ~3 years.
- *Much longer than most other organic drinking water contaminants.*

- Serum level is stable measure of internal dose.

- Typical serum levels are in **ppb (ng/ml, ug/L)** range, while typical drinking water levels are in **ppt (ng/L)** range.

- Found in **decades-old** archived serum samples

- 8-10 fold increase in serum levels over ~30-50 year time periods.

# of HALF-LIVES	% REMAINING
1	50%
2	25%
3	12.5%
4	6.3%
5	3.1%
6	1.8%
7	0.8%

Sources of General Population Exposure to PFOA

- **Total** = (Exposure to PFOA) + (Metabolism of Precursors to PFOA)

- **Diet** – an important source

- Food + migration from food packaging
- Detected in wide variety of foods

- *BUT dietary data limited and uncertain*

- Taken up from soil/sludge into crops consumed by humans & livestock



- **Consumer products** including:

- Carpets, upholstery, clothing
- Protective sprays, ski waxes etc.



- ***Non-stick cookware not considered to be major source.***

- **Indoor & outdoor air, house dust**

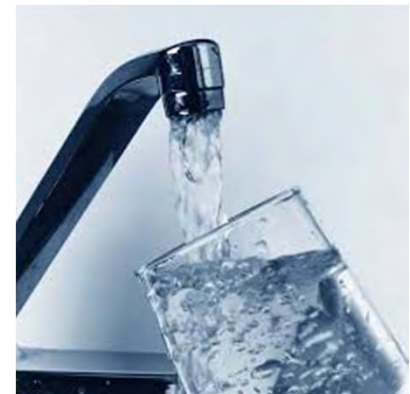
- **Drinking Water**

- *% of total exposure is highly dependent on drinking water concentration*



Drinking Water is an Important Exposure Route for PFOA

- With ongoing exposures, serum levels increase on average by at least **100-fold** the drinking water concentration.
 - Serum:drinking water ratio is higher than 100:1 in children.
- **100:1** (or greater) **serum:drinking water ratio** is valid over wide range of drinking water concentrations.
- **Conclusion: Even relatively low drinking water concentrations substantially increase human serum levels.**



Relationships Between PFOA Drinking Water & Serum Levels Predicted by 100:1 Ratio

<i>Drinking Water Concentration (ug/L)</i>	<i>Increase in Serum Conc. (ug/L)</i>	<i>% Increase in Serum Level *</i>	<i>% Total Exposure From DW*</i>
0.001	0.1	2.5%	2.4%
0.01	1	25%	20%
0.04 **	4	100%	50%
0.1	10	250%	71%
0.4	40	1000%	91%

** Assuming 4 ug/L background serum level (U.S. median).*

*** New Jersey Health-based Guidance.*

Developmental Exposures are Important



- **Developmental effects*** are sensitive endpoints for PFOA toxicity.
- **Prenatal exposure to fetus**
 - PFOA levels are similar in umbilical cord blood & maternal blood.



- **Breast-fed or formula-fed** infants have higher exposures than mother using same drinking water source.**
 - Level in breast milk \geq in mother's drinking water.
 - Infant fluid consumption (ml/kg/day) about 8-fold > than mother's.



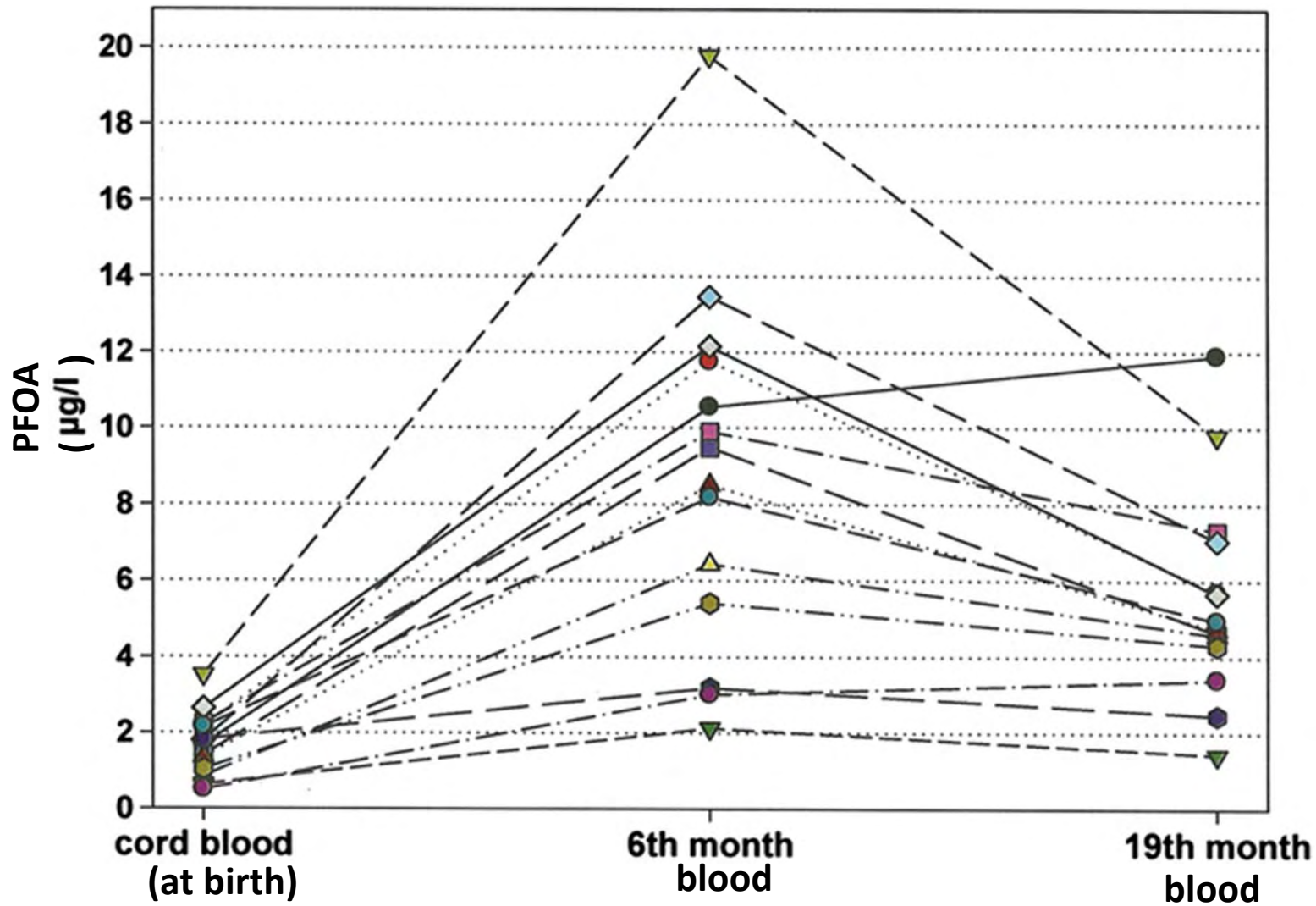
- Young children consume more food & water on body weight basis than adults.
- Hand-to-mouth behavior – house dust.
- More time on floors – treated carpets.



* *Effects resulting from prenatal or early-life exposures.*

** *From powdered or concentrated formula prepared with drinking water.*

Infant Exposure to PFOA Increases During Breast-Feeding & Decreases at Weaning



Fromme et al. 2010. *Env. Sci. & Technol.* 44; 7123-29.



Health Effects of PFOA



- Human epidemiology and animal toxicology data.
- Much information is *very recent*....
.....and **more** is constantly emerging!

Human Epidemiology Studies: General Considerations



- **Advantage:**
 - Human data are most relevant to human risk.
- **Caveats:**
 - Not a “controlled” experiment.
 - Due to nature of the situation under study.
 - Results reported as **associations**.
 - *“Causality not proven.”*
- **Overall conclusions** based on total body of evidence.
 - Positive & negative findings often reported for same endpoint in different study populations.

Human Epidemiology for PFOA

- More data than for many other environmental contaminants.
- **Internal doses** (serum levels) reduces uncertainty about exposures.



- **Three types** of populations :

- Workers (highly exposed).



- Communities with contaminated drinking water.



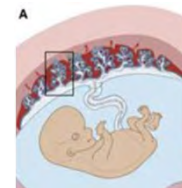
- General population (NHANES & other groups).



- **Timing of exposures** may be important.

- Developmental exposures → effects later in life.

- Most studies not designed to evaluate this.



- Wide variety of effects reported, with some **consistency** among studies for many endpoints.

Occupational Studies



- Workers have much **higher exposures** than other populations.
 - Very high acute exposures to PFOA did not cause mortality or overt toxicity.
 - Several studies evaluated health effects from longer term exposures.
- **Potential limitations** that should be considered in interpreting results:
 - **Small size** limits power to detect increases in disease.
 - Data on exposures & cause of death/disease incidence may be **inaccurate or incomplete**.
 - **Few women** included.
 - **“Control” group** of workers may have relatively high exposures
 - Especially important for PFOA, due to shape of dose-response curve.
 - May be confounded by exposure to **multiple chemicals**.
 - Not designed to detect effects of **developmental exposures**.

(UPDATED)

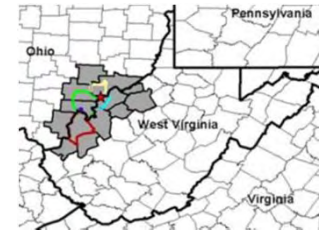
Summary of health endpoints associated with PFOA in multiple human studies.

Endpoints	Workplace					General Population	
	3M— Decatur, AL, USA (PFOA and PFOS)	3M— Cottage Grove, MN, USA	3M— Antwerp, Netherlands (PFOA and PFOS)	DuPont— Parkersburg, WV, USA	Miteni— Italy	C8 Health— Study OH-WV, USA communities with contaminated drinking water near DuPont plant	NHANES— USA
Cancer							
Bladder	+ ^a - ^b	- ^c	NR	+ ^d - ^e	NR	- + +	NR
Kidney	+ ^a	- ^c	NR	+ ^d ± ^e + ^g	NR		NR
Prostate	± ^h	± ^c	NR	- ^d - ^e	NR		NR
Cardio- and cerebro-vascular							
↑Serum Cholesterol	± ⁱ	- ⁱ	- ⁱ	+ ^j , + ^k	+ ^l	+ ^m	+ ⁿ
↑Serum Uric Acid	NR	NR	NR	+ ^j	+ ^l	+ ^o	+ ^p
Diabetes	± ^h	± ^c	NR	± ^e	NR	- ^q	- ^r - ^s - ^t
Hepatic							
↑Serum enzymes	ALT + ⁱ GGT + ⁱ AST - ⁱ AP + ⁱ	ALT - ⁱ GGT - ⁱ AST ± ⁱ AP - ⁱ	ALT - ⁱ GGT - ⁱ AST - ⁱ AP - ⁱ	ALT ± ^j , - ^k GGT + ^j , - ^k AST ± ^j , + ^k AP - ^j	ALT + ^u GGT + ^u AST - ^u AP + ^u	ALT + ^v GGT ± ^v	ALT + ^w GGT + ^w
↓Serum bilirubin	+ ⁱ	- ⁱ	- ⁱ	- ^j , + ^k	+ ^l	+ ^v	- ^w
Renal							
↑Serum calcium, iron, potassium	NR	NR	NR	+ ^j	NR	± ^x	NR
Thyroid							
Thyroid disease	- ^h	NR	NR	NR	NR	+ ^y + ^z	+ ^t
Thyroid hormone	+ ^{aa}	+ ^{aa}	+ ^{aa}	NR	NR ^{bb}	- ^y + ^{cc}	NR
Reproductive hormones							
Estradiol	NR	- ^{dd}	NR	+↑ ^δ ^j	NR	± ↓ [♀] ^x	NR
Testosterone	NR	- ^{dd}	NR	+↑ [♂] ^j	NR	± ↓ ^{boys} ^x	NR

Post et al. 2012. Env. Res. 116: 93-117.



Studies of WV/Ohio Communities with Contaminated Drinking Water -“C8 Health Study”



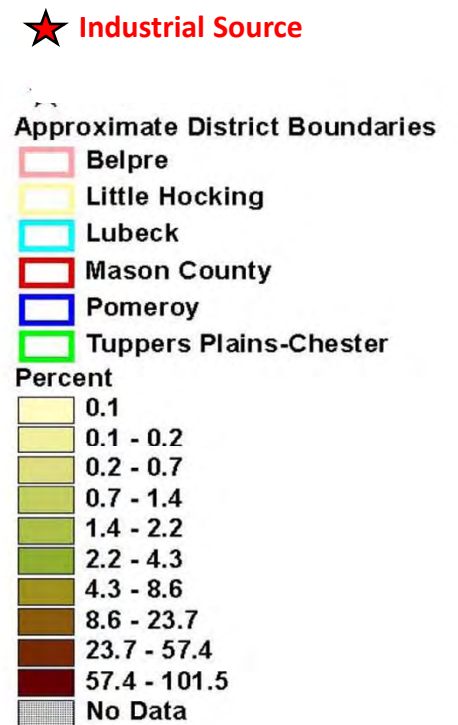
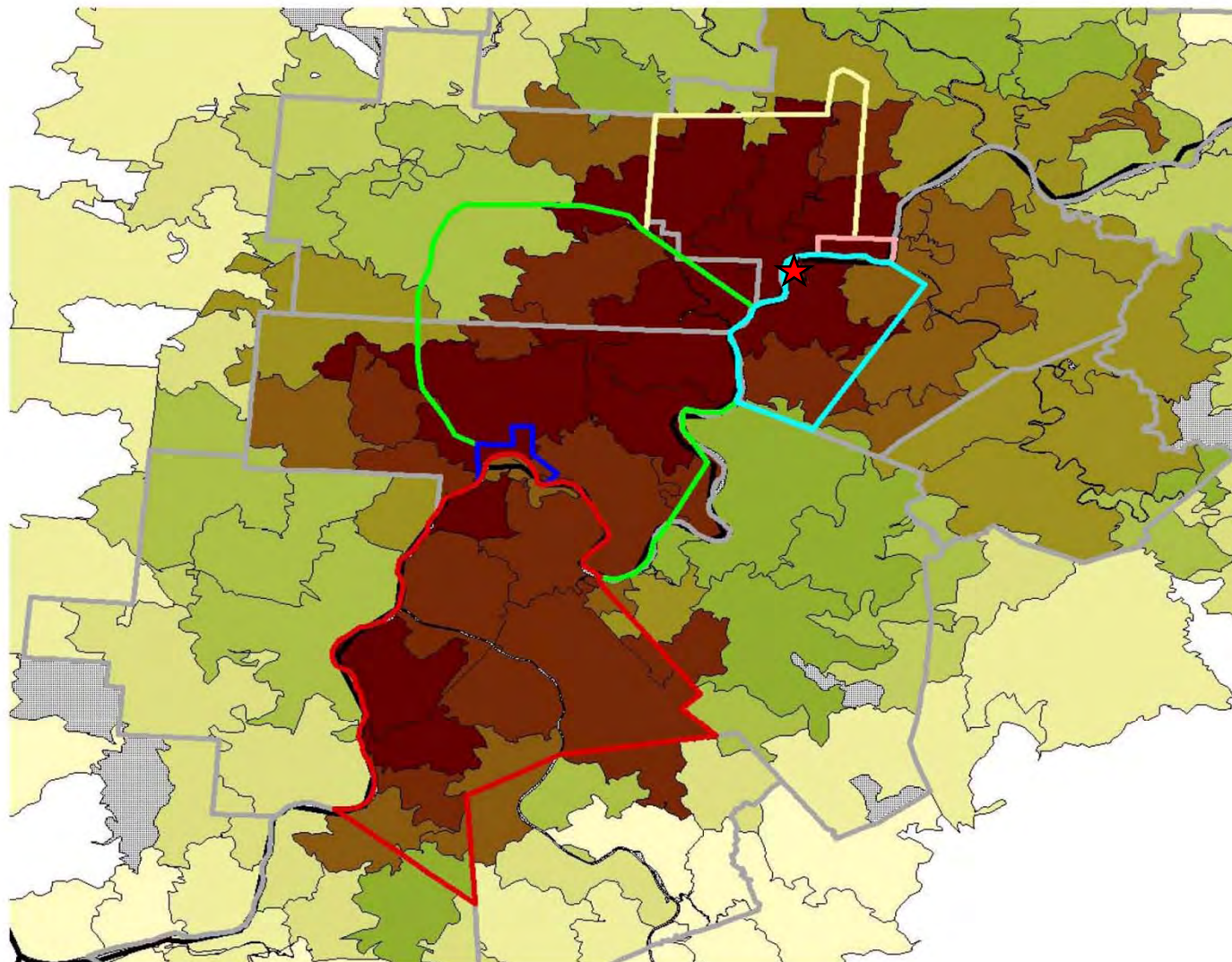
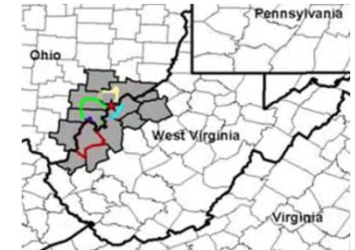
- **Unique study:**
 - **Huge size:** ~70,000 subjects (infants to very elderly).
 - **Wide scope:** Many parameters, sub-studies, & researchers.
- **6 water districts** impacted by fluoropolymer manufacturing emissions for ~50 yrs.
 - Drinking water levels: ≥ 50 ng/L (0.05 ug/L) to over 3000 ng/L (3 ug/L)
 - Includes **public water supply & private well users.**
- Data collected:
 - PFOA serum levels.
 - Clinical laboratory values.
 - Health histories/disease incidence.
- *C8 Science Panel* determined if ***probable links*** between disease & PFOA exposure:
 - Defined as: “... given the scientific evidence available, it is more likely than not that a connection exists between C8 exposure and a particular human disease among class members....”
 - Funded as part of 2004 settlement of class action lawsuit.



C8 Science Panel

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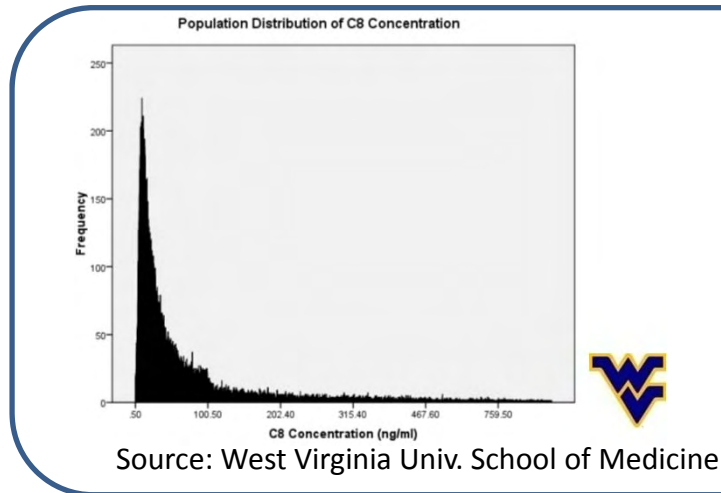
Percent of C8 Study Participants in Relation to Total 2000 Census Population For ZIP Code Tabulation Areas (ZCTAs)



Source: S. Frisbee,
West Virginia Univ.
School of Medicine. 2008.



Drinking Water & Serum PFOA Levels in C8 Health Study



Wide range of serum levels:

- *Bottom 20%: ≤ 10 ug/L*
- Within general population range*
- *Median: 28 ug/L.*
- *Upper 5%: ≥ 482 ug/L.*
- *Maximum: 22,000 ug/L.*
- Includes highly exposed workers.

Water District	Range of PFOA levels reported by water district (ug/L)	Median Serum PFOA level (ug/L)*	Number of Subjects
Little Hocking	1.7-4.3	132.5	8390
Lubeck	0.4-3.9	45.9	8289
Tuppers	0.25-0.37	28.1	9703
Belpre	0.08-0.13	27.1	5388
Mason	0.06-0.1	12.0	10,066
Village of Pomeroy	0.06-0.07	11.6	1560

* **US general population:**
Median serum level: 4 ug/L.
Upper 95th %: 10 ug/L

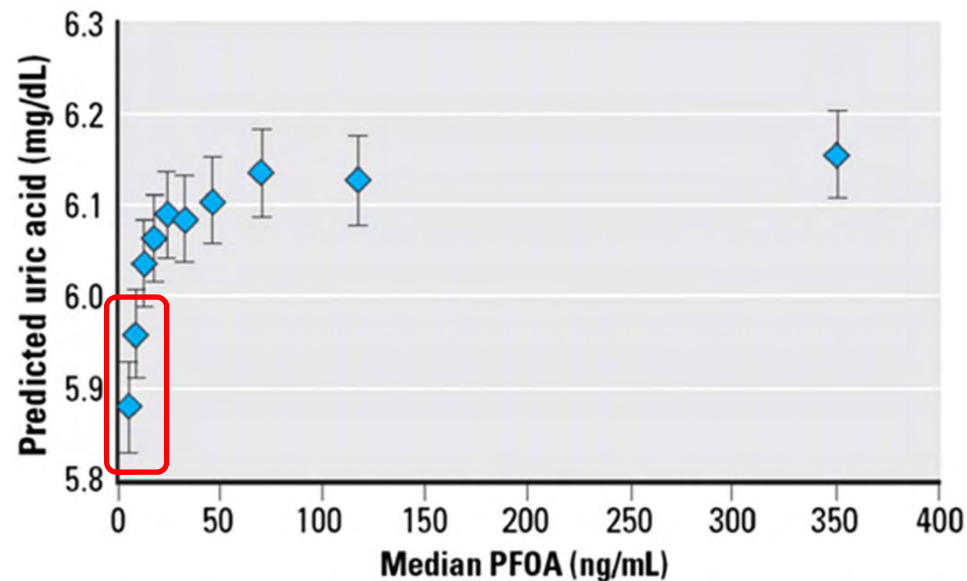
Compare to Health-based Drinking & Ground Water Benchmarks:

NJ Chronic – 0.04 ug/L
MN Chronic – 0.3 ug/L
NC Chronic – 1 ug/L
EPA Short-Term – 0.4 ug/L



Results of C8 Health Study

- Exposure associated with multiple clinical parameters, health endpoints, & diseases.
- Some consistency with worker & general population studies
- Steep dose-response down to lowest exposures (general population range)
 - No apparent threshold for some endpoints



Steenland et al. 2010.
EHP 118: 229-33.

Effects Associated with PFOA Exposure in C8 Health Study

- Testicular cancer*
- Kidney cancer*
- Clinically elevated cholesterol in adults & children*
- Thyroid disease* & changes in *thyroid hormone levels*.
- Pregnancy-induced hypertension*
- Ulcerative colitis*
- Delayed puberty (girls)
- Osteoarthritis
- Clinically elevated uric acid (heart disease risk factor)
- ↑ liver enzyme in serum (marker of liver disease)
- Changes in markers of immune & inflammatory response

**C8 Science Panel conclusion of “Probable Link”.*



C8 Science Panel

Home

C8 Science Panel Conclusion of “No Probable Link” for:

- Cancers other than testicular & kidney cancer
- Rheumatoid arthritis & other autoimmune diseases
- Common infections (cold & flu)
- ADHD & Learning disabilities
- Asthma
- Stroke
- Diabetes (Types 1 & 2)
- Birth defects
- Miscarriage & Stillbirth
- Premature birth & Low Birth Weight
- Liver disease
- Kidney disease
- Osteoarthritis
- Parkinson’s disease
- Heart disease
- High blood pressure



C8 Science Panel

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General Population Studies

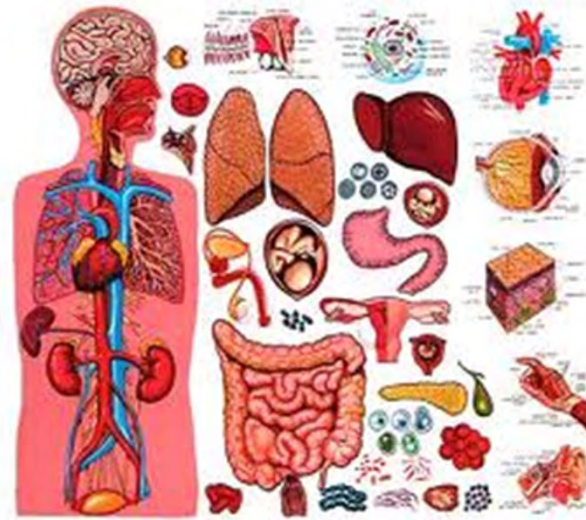


- From U.S. (NHANES) & other countries.
 - Based on internal dose (serum levels).
- Associations with **numerous effects**.
 - Many are **consistent** with worker studies and/or C8 Health Study.
- Relevant to **low-level exposures** from drinking water & other sources.
- *Do not have such data for most other drinking water contaminants.*



Health Effects Associated with PFOA in General Population Studies

- Heart disease
- Thyroid disease
- ↑ cholesterol
- ↑ uric acid (children & adults)
- ↑ serum liver enzymes
- ↓ kidney function
- ↓ fetal growth (birth weight & other measures)
- ↓ vaccine response in children (in 2 study populations)
- ↑ sperm abnormalities
- ↓ fertility (increased time-to-pregnancy)
- ↑ osteoarthritis (women)
- ↑ asthma and IgE (children)



- Prenatal exposure associated with ***effects in adulthood:***
 - Obesity in young women
 - Decreased sperm count in young men
- ***Cancer incidence has not been adequately evaluated.***

Linking Early Environmental Exposures to Adult Diseases



“A growing body of research is beginning to suggest that many chronic adult diseases and disorders, including asthma, diabetes and obesity, may be traced back to exposures that occur during development. “

Conclusions - Human Epidemiology Studies

- Human data suggests need for concern about drinking water exposures...
 - **Consistency** in findings in different populations
 - **Clinical importance** of some endpoints.
 - Associations within **general population** exposure range.
- Such data is not available for most drinking water contaminants.
- Adds to weight of evidence/hazard identification when considered with animal data.
- Important data gap - Effects later in life from developmental (prenatal & early life) exposures.



Animal Toxicity Summary



Studies in Rodents & Monkeys:

- Steep dose-response for mortality
- Weight loss
- Liver toxicity
- Tumors in chronic rat studies
- Effects on lipid metabolism
- Immune system toxicity
- Changes in hormone levels
- Developmental effects
- Neurobehavioral effects

**Unintended exposures of control groups in some studies - may be important due to possibility of steep dose-response within this low dose range.*

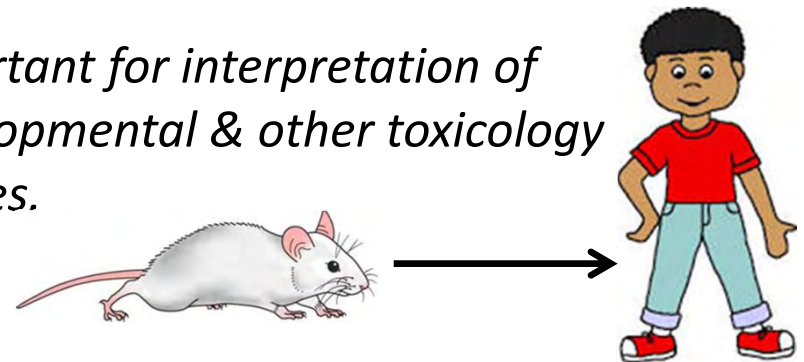
Species & Gender Differences in Persistence of PFOA

Species	Female Half-Life	Male Half-Life
Rat	3 hours	5 days
Mouse	17 days	19 days
Rabbit	7 hours	6 hours
Dog	10 days	25 days
Monkey	30 days	21 days
Human	~3 years or longer	

NOTES:

- *Half-life is dependent on excretion rate.*
- *PFOA and other PFCS are NOT metabolized.*

- Half-lives differ greatly among species:
 - Very different **internal doses** (serum levels) from same **administered dose** (mg/kg/day).
 - **Comparisons** must be based on **serum level**, not administered dose.
- **Female rat** (and M & F rabbit) **not most appropriate human model** due to very short half-life.
 - Rapidly excreted and does not reach sufficient internal dose.
- *Important for interpretation of developmental & other toxicology studies.*



PFOA Chronic Animal Studies - Carcinogenicity

- Liver, testicular, & pancreatic tumors in male rats:

- EPA Science Advisory Board (2006):

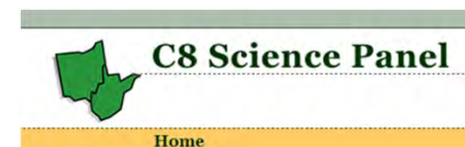
“Likely to be carcinogenic to humans”

based on these rat data.

- Consistent with recent C8 Science Panel (2012):

“Probable link with kidney & testicular cancer”

based on human data.



- Does not cause mutations or DNA damage.
 - Many other carcinogens also are not genotoxic.

- Important **unanswered questions**:

- Cancer & other chronic effects in females in species other than rat (e.g. mouse).
- Cancer & other chronic effects after prenatal and/or early life (developmental) exposures.



PFOA Developmental Effects

- Before 2006, only rat studies were available.
 - Not most appropriate animal model due to rapid excretion by females.

- Many **mouse** studies since 2006
 - Appropriate species – long half-life.



- Developmental exposures:
 - To **fetus** (through dosing of mother) *and/or*
 - To **pups** (through breast milk).



- Most sensitive known animal endpoints.

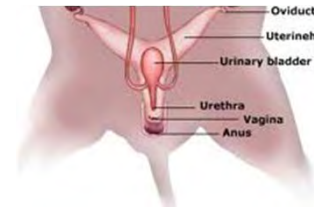
PFOA Developmental Effects in Mice

- Full litter resorptions.
- ↓ pup survival & growth.
- Delayed developmental milestones.
- Sexual maturation:
 - Delay – females.
 - Acceleration – males.
- Neurobehavioral effects in adulthood.
 - From single dose to pups.
- Additional ***low dose*** effects....



PFOA Low-dose Developmental Effects in Mice

- At **lower doses** than other effects – no threshold identified.
- **Timing important:**
 - Early life exposure is critical developmental period.
 - Do not occur from exposures later in life.
- **Obesity** & metabolic hormone changes in early adulthood.
 - In females. Consistent with recent human data.
- **Female reproductive tract**
 - Abnormal structural & microscopic changes from 3 day pup exposure.
- **Delayed mammary gland development.**
 - Very short exposures rapidly cause effects in pups & pregnant/nursing dams.
 - No effects from much higher doses in non-pregnant adults.
 - Pup effects persist into adulthood (permanent change).
 - Most sensitive known endpoint.
 - Drinking water study found effects at serum levels relevant to human environmental exposures.
- *For most other drinking water contaminants, toxicity in animals only at doses much higher than human exposure levels.*



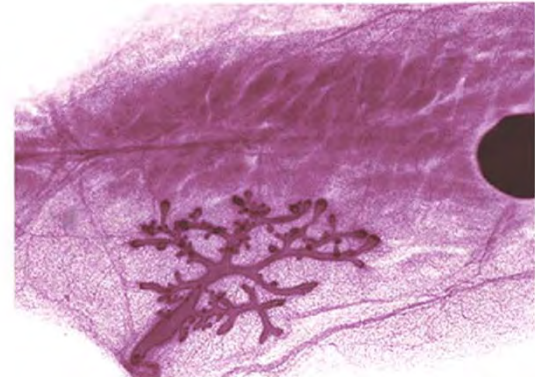
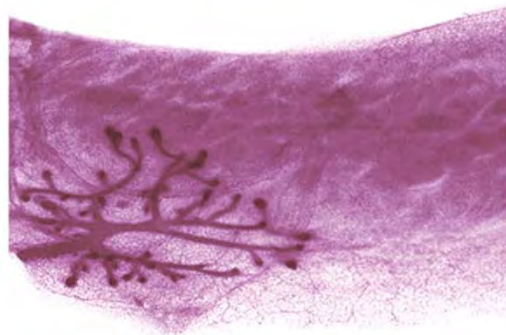
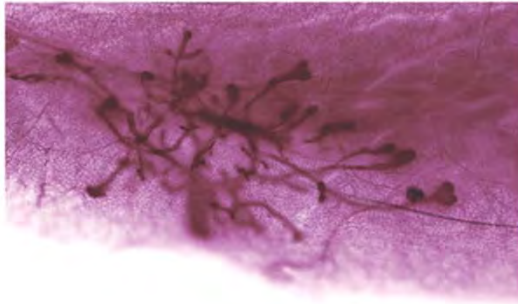
Effects of PFOA on Mammary Gland Development in Mouse Pups

Control

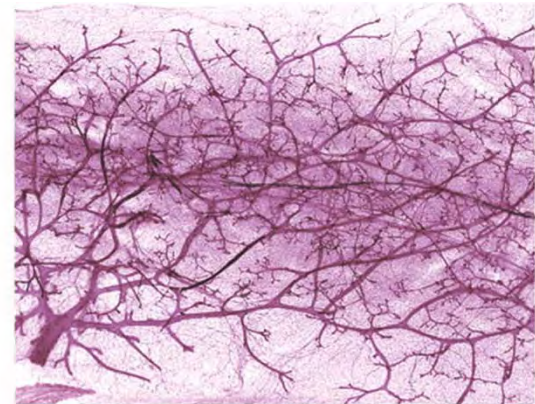
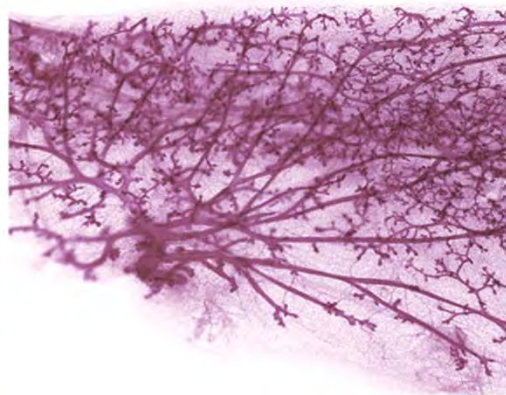
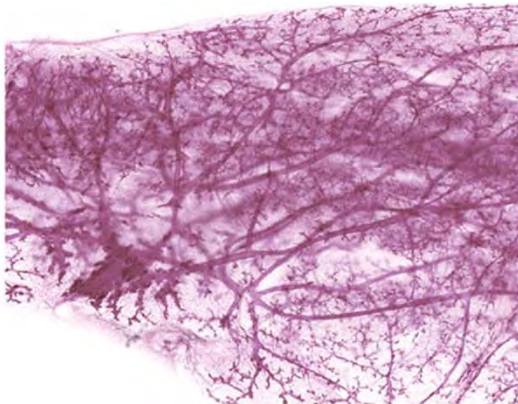
0.3 mg/kg/day

1 mg/kg/day

Age 3 Weeks:



Age 12 Weeks:



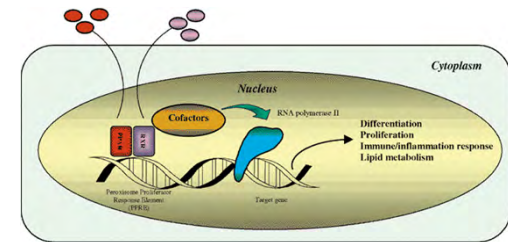
Linking Early Environmental Exposures to Adult Diseases



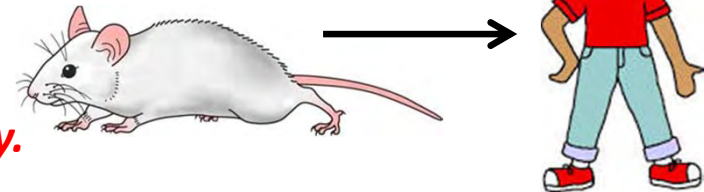
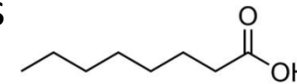
“A growing body of research is beginning to suggest that many chronic adult diseases and disorders, including asthma, diabetes and obesity, may be traced back to exposures that occur during development. “

Mode of Action

- **Chemically inert**
 - Not metabolized to “reactive intermediates” that damage DNA, RNA, or protein.
- Interacts with **receptors** in cell nucleus to change the expression of genes that control biological pathways.
 - Peroxisome Proliferator Activated Receptor-alpha (PPAR- α) and other receptors (CAR, PXR).



- Involved with liver, developmental, immune, and other effects.
- Uncertainties about human relevance of PPAR- α in liver do not necessarily apply to other types of effects.
- Structurally similar to and may interact with receptors in a similar manner as **free fatty acids**.
- Also has **estrogenic** activity.



- **General Conclusion:**
Cannot dismiss human relevance of animal toxicity.
- **BUT** PFOA affects human lipid metabolism differently than “classic” PPAR- α activators:
 - “Classic” activators (drugs): \downarrow cholesterol in both rodents & humans.
 - PFOA: \downarrow cholesterol in rodents, but \uparrow **cholesterol in humans.**

Associations between PFOA, PFOS and changes in the expression of genes involved in cholesterol metabolism in humans [☆]



Tony Fletcher ^{a,1}, Tamara S. Galloway ^{b,1}, David Melzer ^c, Paul Holcroft ^b, Riccardo Cipelli ^b, Luke C. Pilling ^c, Debapriya Mondal ^a, Michael Luster ^d, Lorna W. Harries ^{c,*}

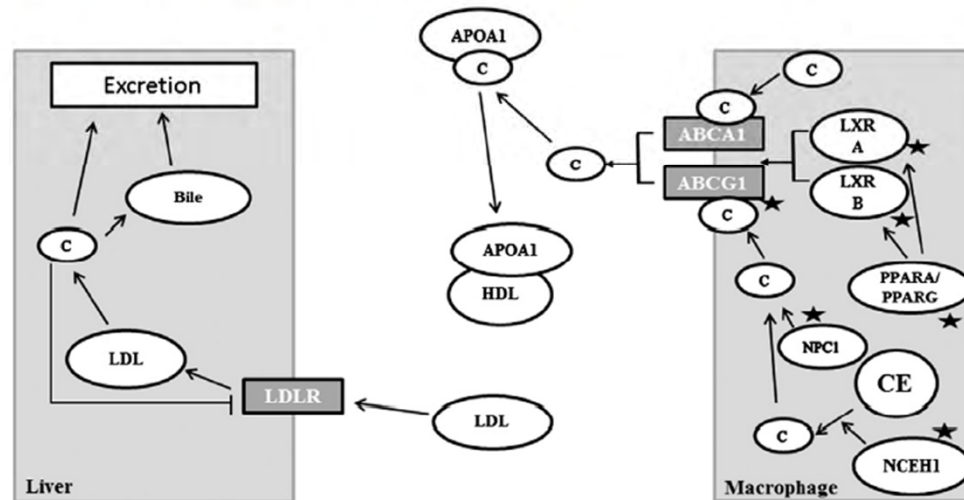


Fig. 3: The reverse cholesterol pathway. “....Transcripts marked with an asterix demonstrate associations with either PFOA or PFOS exposure in any of our analyses...”

Current Drinking Water Guidance

- **New Jersey Health-based Guidance (2007) – 0.04 ppb (40 ng/L)**
 - Intended to protect for **chronic (lifetime) exposure**
 - Based on endpoints identified in USEPA (2005) draft risk assessment.
 - Does not consider recent data including:
 - C8 Health Study & general population human studies.
 - Mouse developmental effects.
 - See NJDEP website or Post et al. (2009) ES&T paper for basis.
- **USEPA Provisional Health Advisory (2009) – 0.4 ppb (400 ng/L)**
 - Intended to protect for **short-term exposure**.
 - Developed rapidly to address emergency situation in Alabama.
 - Lifetime (chronic) Health Advisory currently under development.
- There is **no USEPA or New Jersey enforceable drinking water standard**.



Serum Levels Resulting from Long-term Ingestion Over Range of Drinking Water Concentrations*

<i>Drinking Water Concentration (ug/L)</i>	<i>Increase in Serum Conc. (ug/L)</i>	<i>% Increase in Serum Level *</i>	<i>% Total Exposure From DW*</i>
0.001	0.1	2.5%	2.4%
0.01	1	25%	20%
0.04	4	100%	50%
0.1	10	250%	71%
0.4	40	1000%	91%

Compare to Health-based Drinking Water Guidance:

NJ Chronic – 0.04 ppb

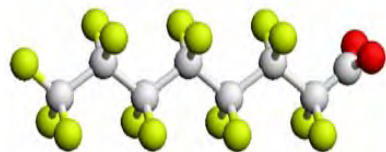
EPA Short-Term – 0.4 ppb

**** Assuming 4 ppb background serum level (U.S. median).***

USEPA Regulatory Status



- Listed on **Contaminant Candidate List 3** for consideration for future drinking water regulation.
- **Unregulated Contaminant Monitoring Rule 3 (UCMR 3):**
 - Includes PFOA & 5 other PFCs.
 - Will provide national occurrence data by 2017.
 - Requires sampling of all large, and subset of small, public water supplies.
 - Reporting Levels are much higher than at commercial labs used in New Jersey studies (4-5 ng/L):
 - PFOA – 20 ng/L.
 - Other PFCs – 10-90 ng/L.
- **If positive Regulatory Determination**, timeframe for proposal of MCL is at least several years after UCMR 3 study is completed.

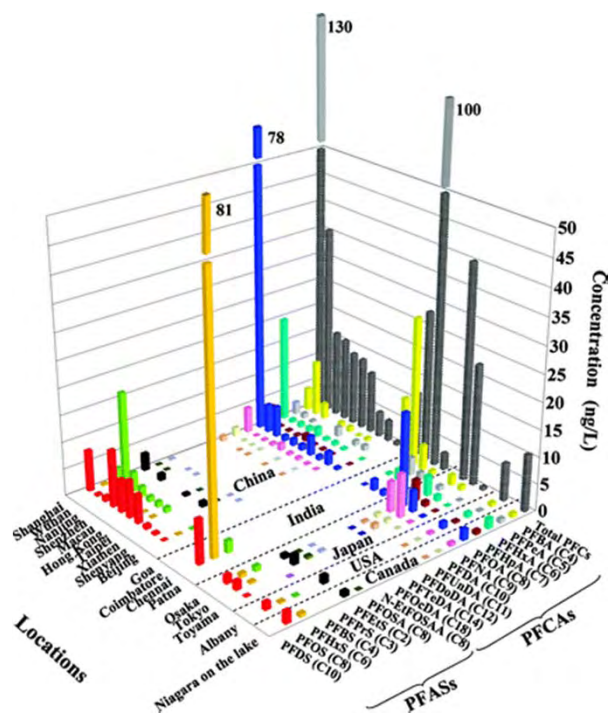


Conclusions - PFOA

- Differs from other well-studied organic drinking water contaminants.
 - *Extreme environmental persistence & long human half-life.*
- Ongoing exposure to even low drinking water concentrations substantially increases total human body burden.
- Numerous health effects, including cancer, have been associated with human exposure.
 - *Many within general population exposure range.*
- Animal toxicity includes low dose developmental effects, some of which persist into adulthood.
 - *Human relevance of animal toxicity cannot be dismissed.*
- Infants are a susceptible sub-population for developmental effects.
 - *Exposures higher than in adults using the same drinking water source.*
- ***SUMMARY: Exposure to even relatively low drinking water levels results in elevated body burdens that may increase the risk of health effects.***

Other Perfluorinated Chemicals

- Mixtures of PFCs are present in drinking water, other environmental media, & human serum.
 - PFOA is *just one member* of large group of PFCs:
 - Toxicology data on others varies from minimal to extensive.
 - **PFOS** has been extensively studied.



- Shorter chain PFCs have been introduced as replacements for PFOA & other long chain PFCs.
 - Excreted more rapidly and generally less toxic.
 - **BUT** extremely persistent in the environment, like all PFCs.
- *Very little data* on toxicity of mixtures and/or toxicological interactions.

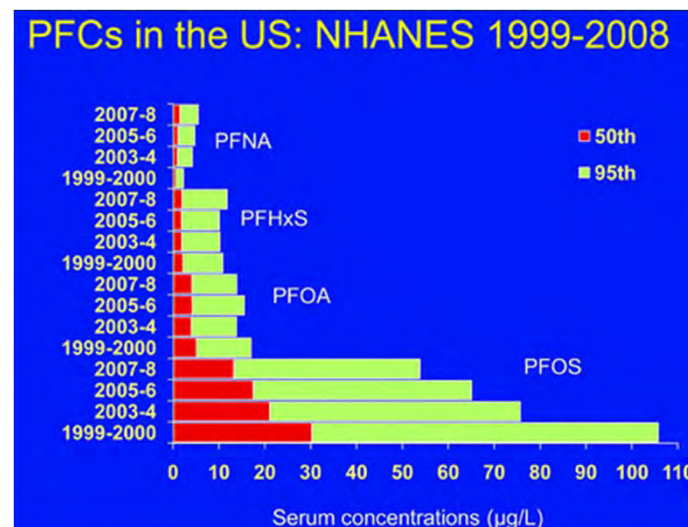
Other PFCs of Potential Concern in Drinking Water

PFOS - Perfluorooctane sulfonate

PFHxS - Perfluorohexane sulfonate

PFNA - Perfluorononanoic acid; C9

..... as well as **PFOA**

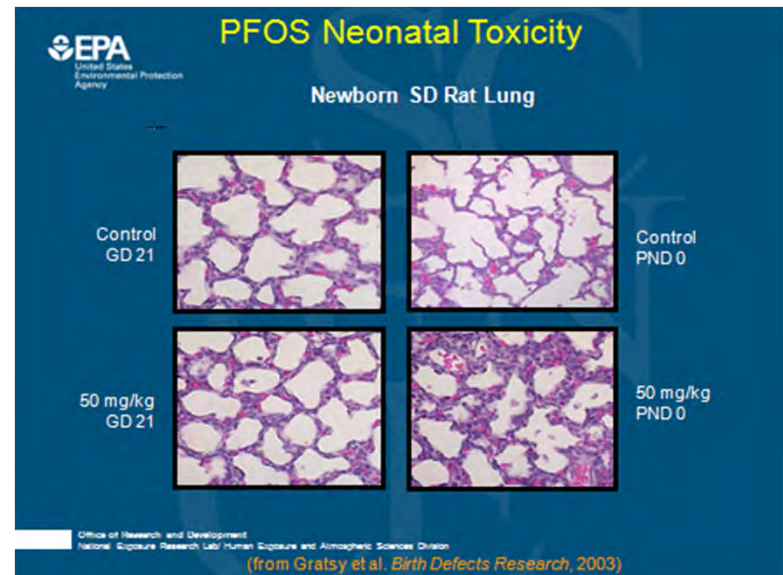


Kato et al. *Environ. Sci. Technol.*
2011. 45: 8037-45

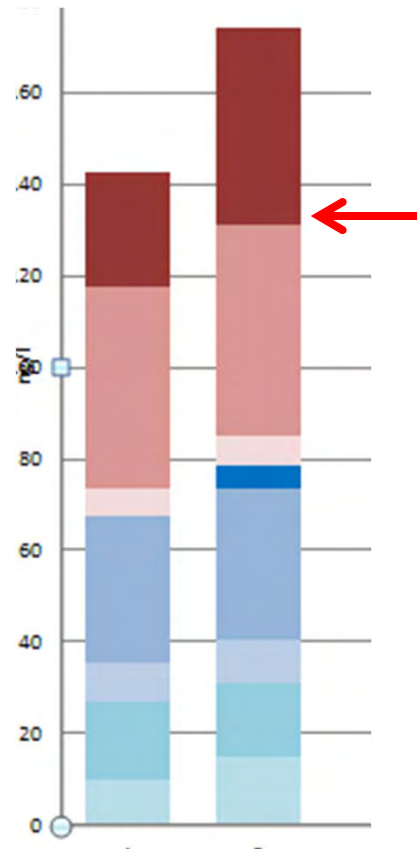
- **Why are these four PFCs of potential concern?**
 - *Found in drinking water.*
 - *Biologically persistent - Long half-life.*
 - *Toxic at relatively low doses.*
 - *More potent than shorter chain PFCs.*
 - *Found in serum of >99% of US population.*
- Their U.S. production has ceased or is being phased out.
- They are included in USEPA nationwide drinking water monitoring.

Health Effects of Sulfonates

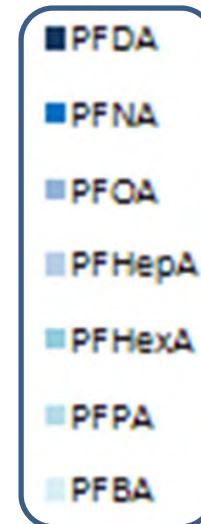
- Similarities and differences with PFOA for:
 - Mode of action.
 - Toxicological effects.
- PFOS
 - Extensively studied humans and animals.
- PFHxS (6 carbon sulfonate) :
 - Longest known human half-life - 8.5 years.
 - But very little toxicology data.



Mixture of PFCs in PWS Surface Water Sources Near an Airfield

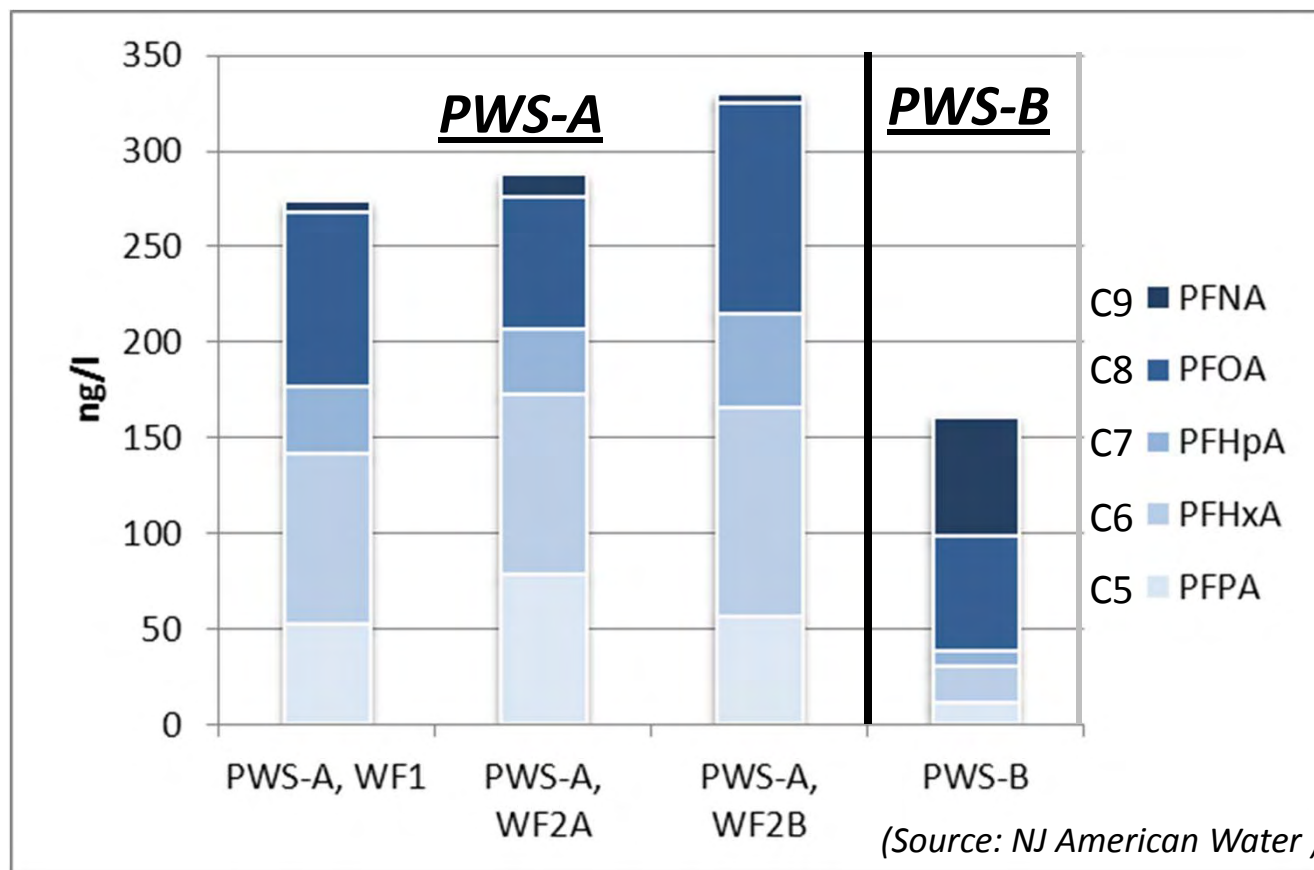
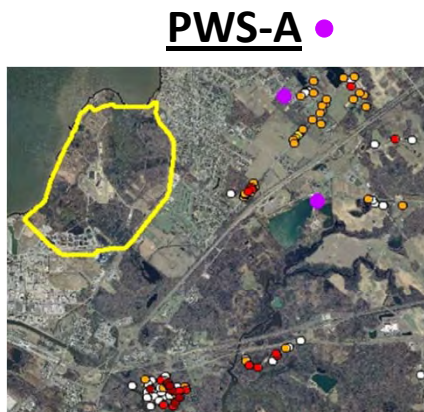


SULFONATES



CARBOXYLATES

Mixtures of Perfluorinated Carboxylates in Raw Water from NJ Public Water Supply Wells Near Industrial Sites*, **

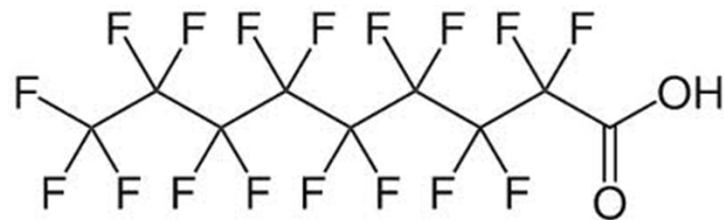


* Measures to eliminate drinking water exposure to PFCs are in place at these locations.

** Perfluorinated sulfonates were not detected.

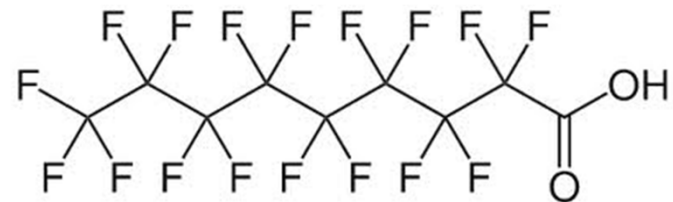
Health Effects of PFNA Summary

- Considerable database for comparison with PFOA.
- Available information suggests:
 - Similar **profile of toxicity** as PFOA.
 - Same **mode of action** as PFOA.
 - More **biologically persistent** than PFOA.
 - More **toxicologically potent** than PFOA.
 - Same *in vivo* effects at lower (or much lower) doses.
 - More intrinsically potent in *in vitro* receptor activation assays.



Industrial Use of PFNA

- Used as **processing aid** in manufacturer of fluoropolymer plastic, polyvinylidene fluoride (PVDF).
 - Analogous to use of PFOA as processing aid in production of fluoropolymer polytetrafluoroethylene (PTFE).
 - Historically discharged to air and water at PVDF manufacturing facilities in a similar manner as for PTFE/PFOA .
- Use is being **phased out** as part of Voluntary Stewardship Program.



Industrial Use of PFNA (continued)

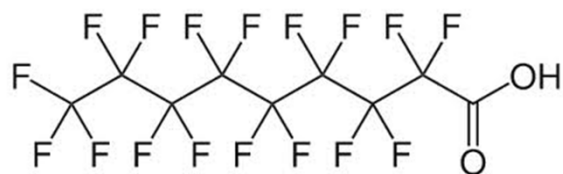


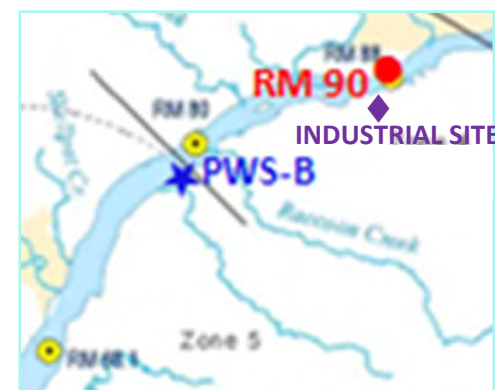
TABLE S2. Commercial PFCA Products Characterization

Product Identification	Figure S1 Process	% Branched Isomers	PERCENT OF TOTAL					
			8 PFO	9 PFN	10 PFD	11 PFU	12 PFDD	13 PFTD
Fluorad [®] FC-143	1	15	99	0.22	≤LOQ	nm	<LOQ	nm
Surflon [®] S-111*	3	0	0.78	74	0.37	20	0.1	5
APFO - DuPont	2	0	99	nd	≤LOQ	<LOQ	<LOQ	nm

*PFC mixture used as processing aid in manufacture of PVDF

Global production of PVDF by the emulsion process (2002)

Producer	Location	Process	Capacity, ktonne/year
	Calvert City, KY, USA	Emulsion	8.4
◆ →	Thorofare, NJ, USA	Emulsion	7.7
	Decatur, AL, USA	Suspension	2.3
	Pierre Bénite, France	Emulsion	2.2
	Tavaux, France	Suspension	5.0
	Ube, Japan	Emulsion?	0.3
	Settsu, Japan	Suspension?	0.1
	Iwaki, Japan	Suspension	1.2
TOTAL			27.2



Source: Prevedouros et al. 2006.
 Environ. Sci. Technol. 40: 32-44.
 Supporting Information.

Perfluorononanoic Acid (PFNA, C9) in Tidal Delaware River Study Area Beginning at River Mile 90 Sampling Site

PWS-B
Raw Groundwater (2011-12)*
*Maximum – 72 ng/L***
 (Source: NJ American Water)

➔ ■ PFNA
 ■ PFOA
 ■ PFHpA
 ■ PFHxA
 ■ PFPA

*Treatment has been installed. PFCs are not detected in finished water.

** Exceeds highest levels found in literature search of US & worldwide drinking water studies.

PFCs in Water From Tidal Delaware River (2007)
 (*not* drinking water source)
*Maximum – 976 ng/L**
 (Source: DRBC, 2012)

PFNA (C9) RM 90

River Miles

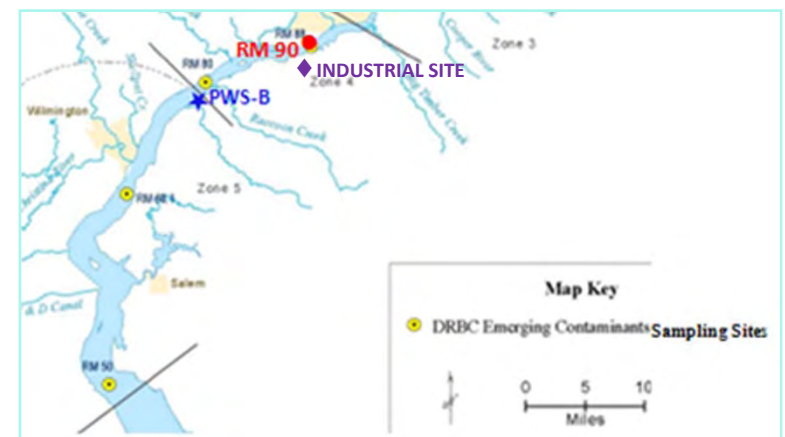
* Exceeds highest levels found in literature search of US & worldwide surface water studies.

PFCs in Fish Fillets in Tidal Delaware River (2004-07)
 (Source: A.R. MacGillivray, Delaware River Basin Commission, 2012)

mean ng/g wet weight

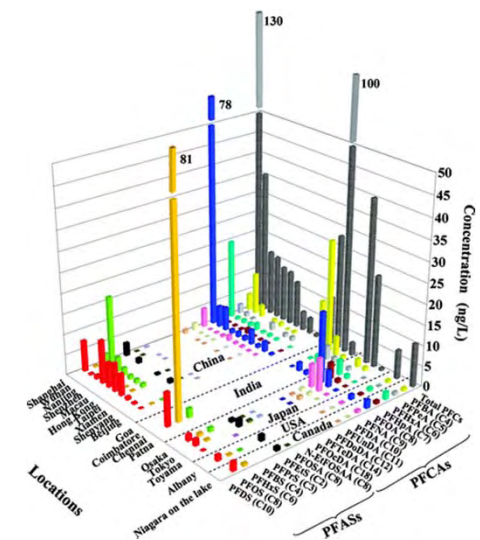
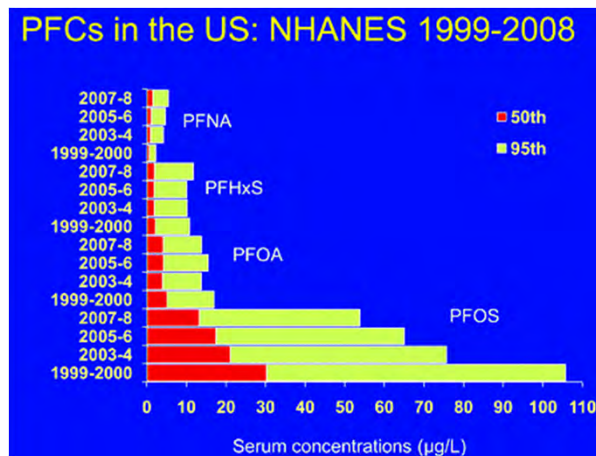
■ PFDA
 ■ PFDoA
 ■ C9
 ■ PFOSA
 ■ PFOS
 ■ C11

RM 91



Conclusions – PFCs other than PFOA

- PFCs other than PFOA also occur in drinking water.
- Available health effects (toxicology & epidemiology) data varies from minimal to extensive.
- All are very persistent in the environment, regardless of long or short biological half-life.
- Several are of potential concern due to occurrence, biological persistence, and potential health effects.
- Future approaches for assessing risks of PFC mixtures must consider similarities & differences in toxic effects & modes of action.



Acknowledgements

Co-Authors

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NJDEP Office of Science

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Thank you!

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