Per- and Poly-Fluoroalkyl Substances (PFAS)

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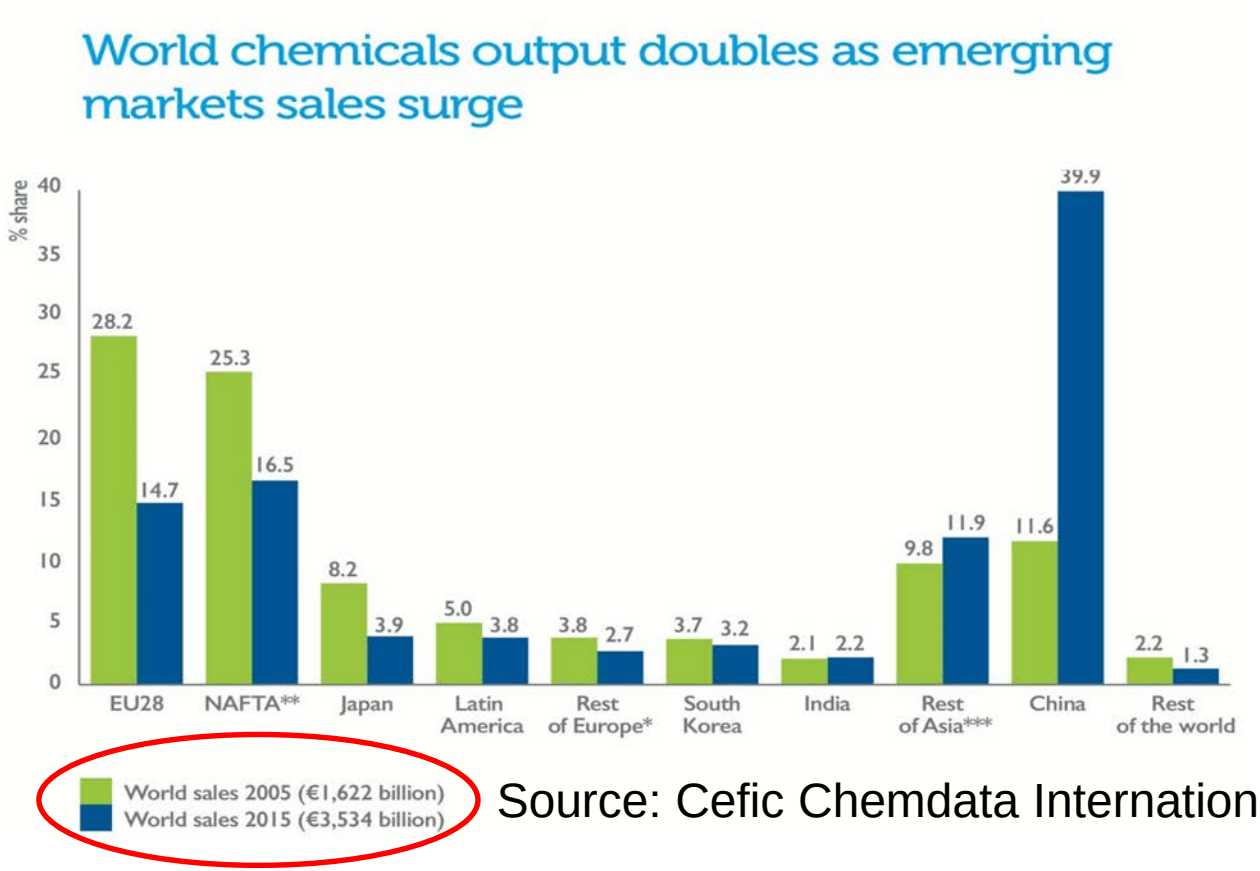
June 14, 2017

Total Chemical Production



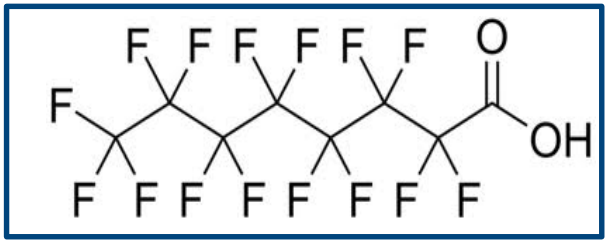
Source: Cefic Chemdata International

Chemicals of Concern

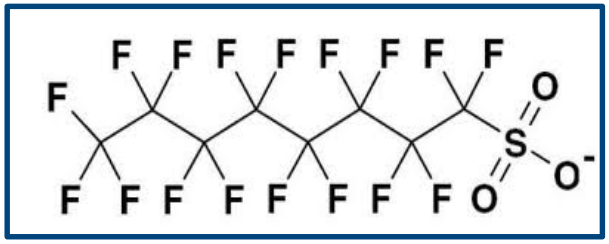
…And closely related alternatives

Per- and Poly-Fluoroalkyl Substances (PFAS)

- **Non-stick, liquid repellant, stain resistance**
  - ***PFOA*** **(C8) used in Teflon**
  - ***PFOS*** **(C8) in Scotchgard and Gore-Tex**
  - **Over 3,000 compounds, many unknown formulations**
- **Aqueous fire fighting foam (AFFF) containing PFASs now showing up widely**
  - **Over 600 military installations**
  - **Airports**
  - **Firefighter training sites**
- **Hundreds of other unknown applications , e.g. cosmetics, dental floss, etc.**



PFOA



PFOS

Exposure to PFOA and PFOS

- **PFOA and PFOS**
  - US production eliminated; use and emissions reduced in US and much of Europe through voluntary agreements
  - Not expected to degrade under typical environmental conditions
  - Not metabolized
  - Slower human elimination rates
    - Half-lives (2-8 years) humans vs. days or weeks in other animals
- **PFOA and PFOS are the most commonly detected perfluoroalkyl acids in environment and human serum**

Geometric mean serum concentrations (µg/L) for US population

Survey years	PFOA	PFOS
1999-2000	**5.21** (4.72-5.74)	**30.4** (27.1-33.9)
2005-2006	**3.92** (3.48-4.42)	**17.1** (16.0-18.2)
2011-2012	**2.08** (1.95-2.22)	**6.31** (5.84-6.82)

Contaminated communities across the US

6NEWS

Erin Brockovich speaks to Hoosick Falls residents

NJSPOTLIGHT
NEWS, ISSUES AND INSIGHT FOR NEW JERSEY
June 8, 2017

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ENERGY & ENVIRONMENT

DEP ACCEPTS PLAN TO CURB TOXIC CHEMICAL IN NJ'S DRINKING WATER

JON HURDLE | JANUARY 11, 2017

Surveys have shown the presence of PFNA in New Jersey's public water systems is much higher than the national rate

StarNews ONLINE

Toxin taints CFPUA drinking water

Utility can't filter out chemical produced upriver at Fayetteville plant

By Vaughn Hagerty StarNews Correspondent
Posted Jun 7, 2017 at 10:31 AM
Updated at 10:38 AM

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Gillibrand calls for CDC public health assessment in Hoosick Falls

By Matthew Hamilton on September 20, 2016 at 1:32 PM

89.3 WFPL Environment

Study Finds Widespread Contamination Of Ohio Valley Drinking Water

By Glynis Board, Ohio Valley ReSource

Study Finds Widespread Contamination Of Oh... 0:00 / 3:39

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HANSI LO WANG

The Washington Post
Democracy Dies in Darkness

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By Brady Dennis August 9, 2016

South Washington County Bulletin

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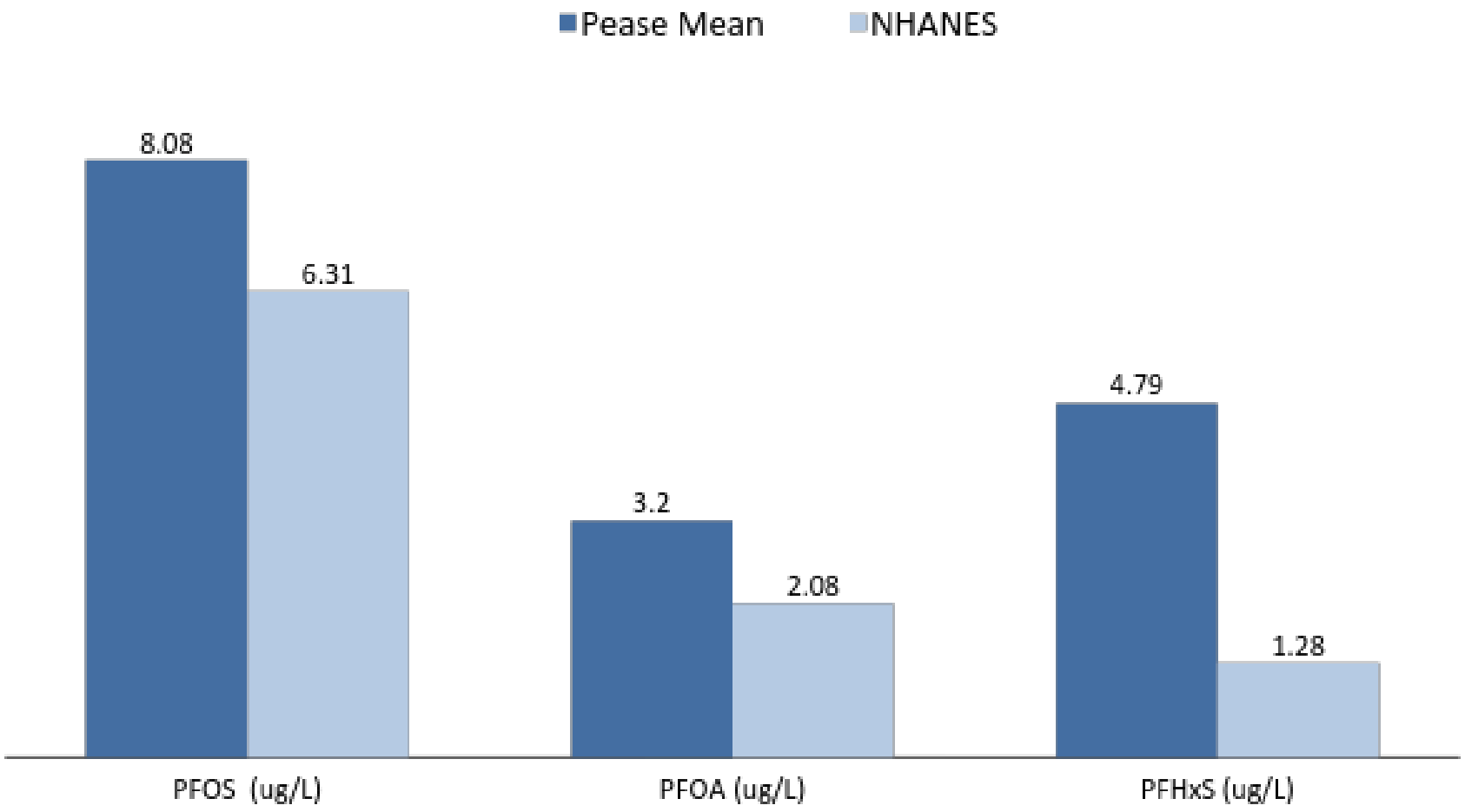
Cottage Grove city water ban affects every area

By Katie Nelson on Jun 5, 2017 at 3:36 p.m.

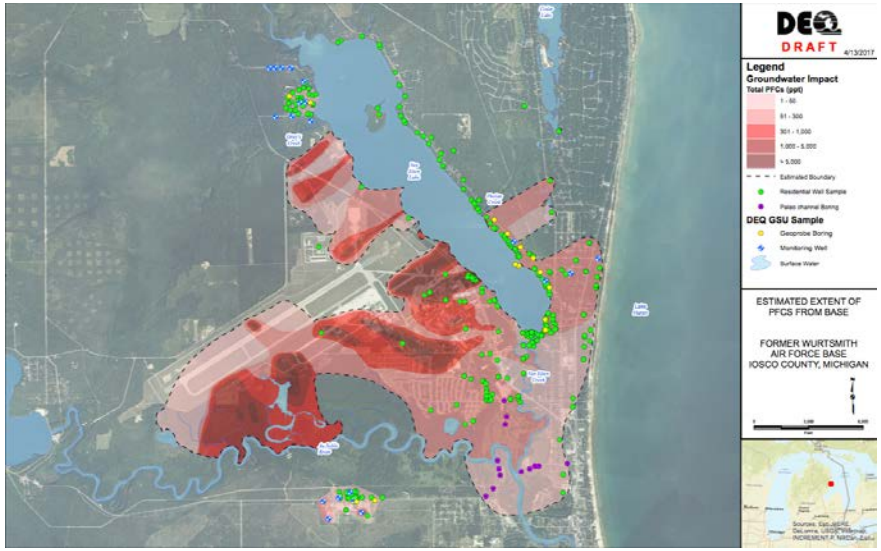
Pease vs NHANES – Blood Levels

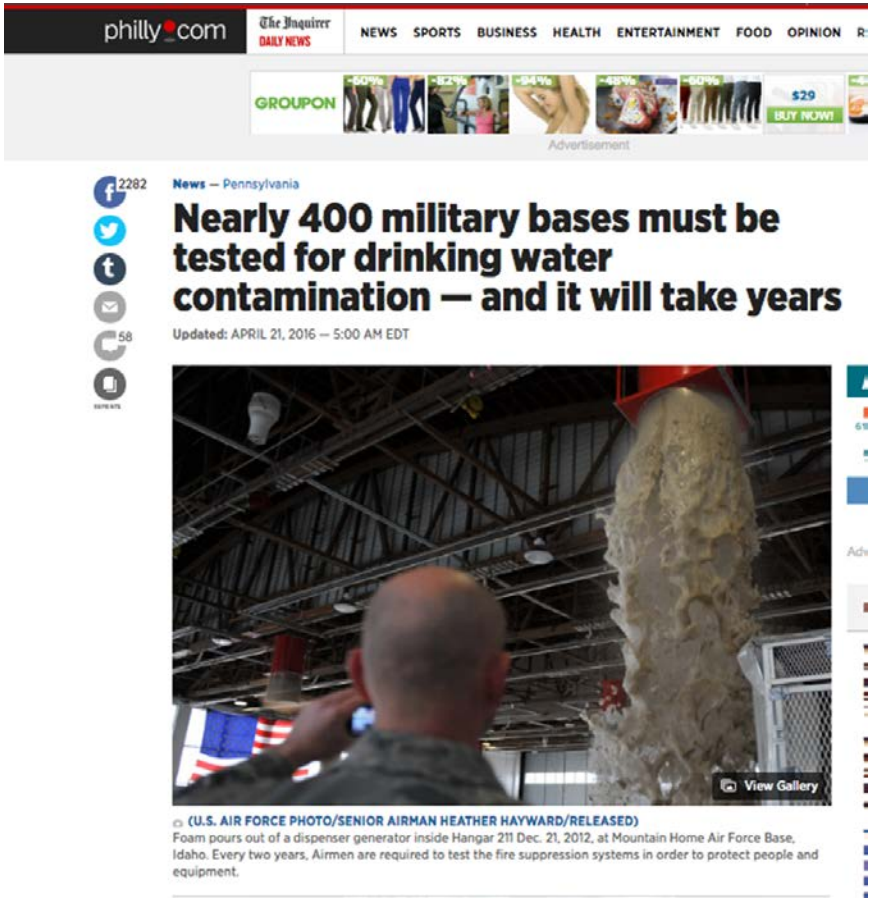


Based on testing of 2,100 Americans in 2011-2012 (NHANES)

*There is no established safe level of PFAS in blood serum and no health advisories for serum levels.

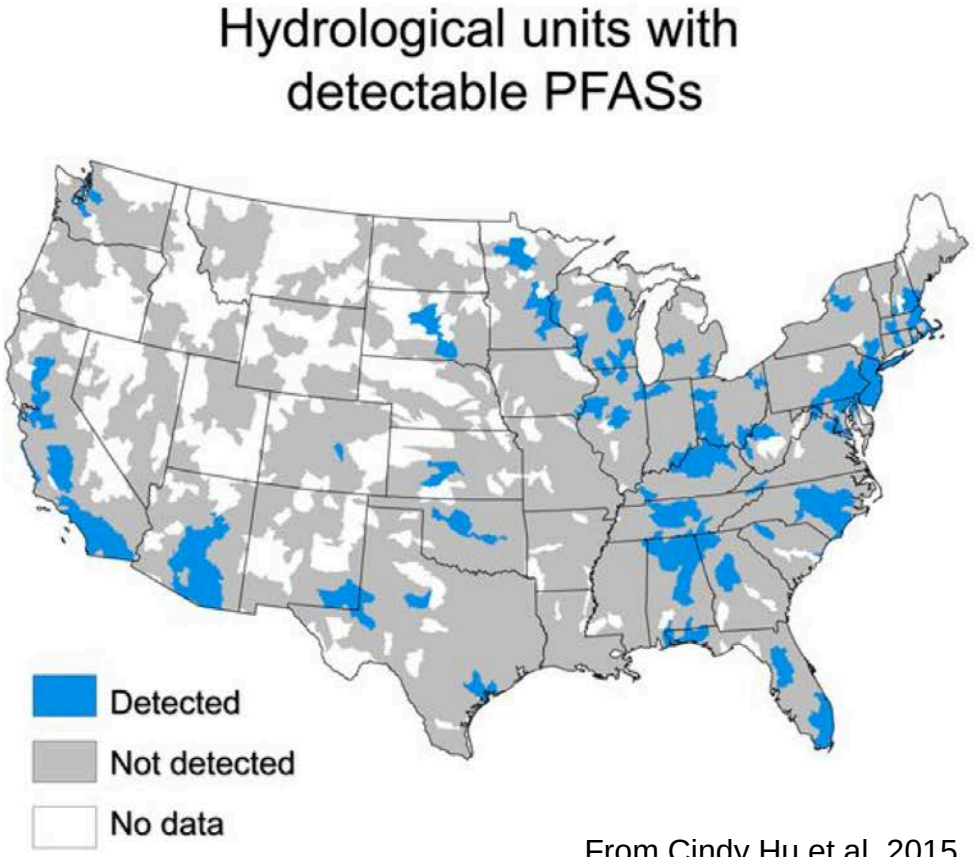
Wurtsmith AFB (Oscoda, MI)



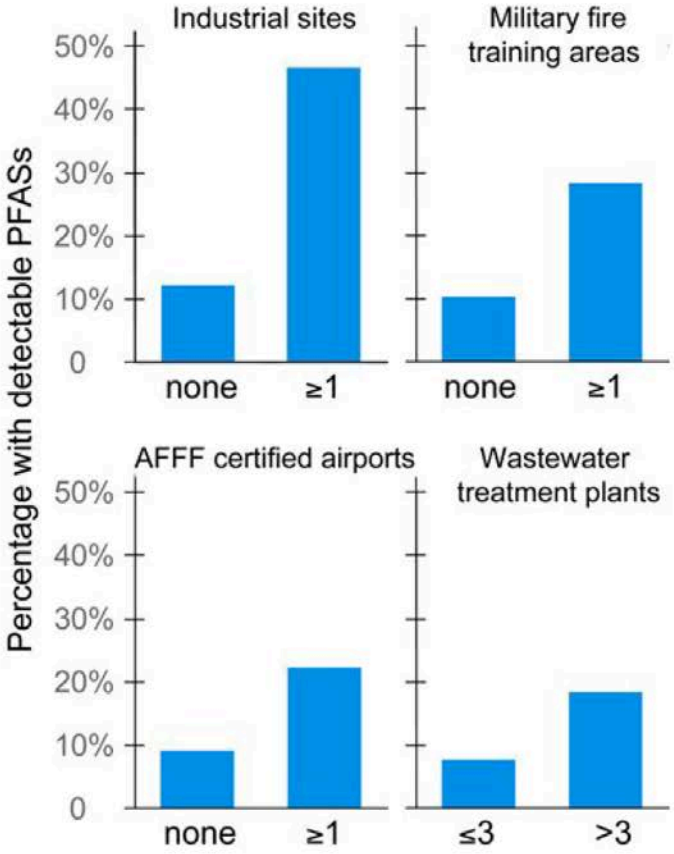


Map Credit: District Health Department No. 2
Photo Credit: Garret Ellison | MLive.com

Watersheds with point sources have higher detection frequencies for PFASs

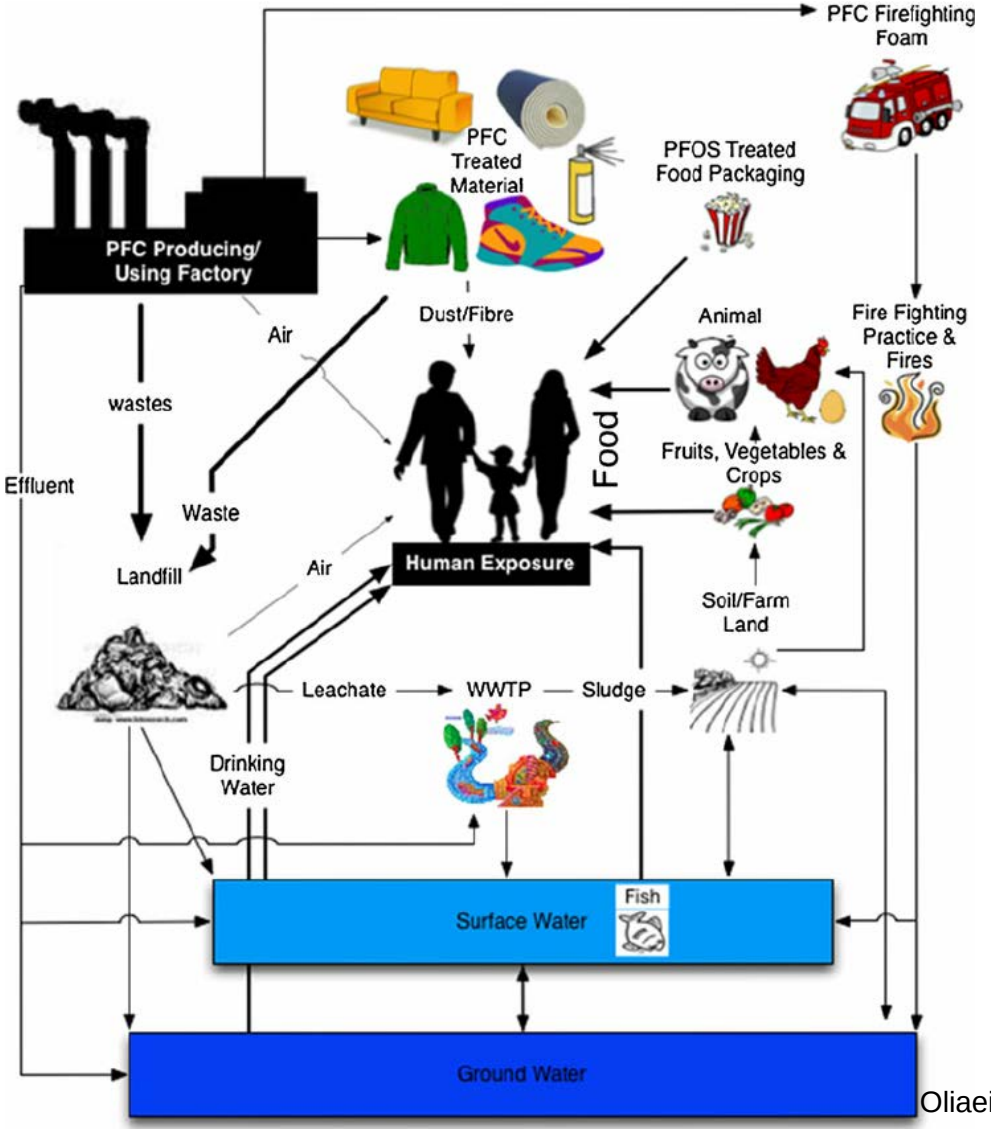


From Cindy Hu et al, 2015



Cindy Hu et al, ES&T Letters, 2016

PFAS Exposure Pathways



Oliaei et al. Environ Sci Pollut Res (2013)

PFAS in Fast food packaging

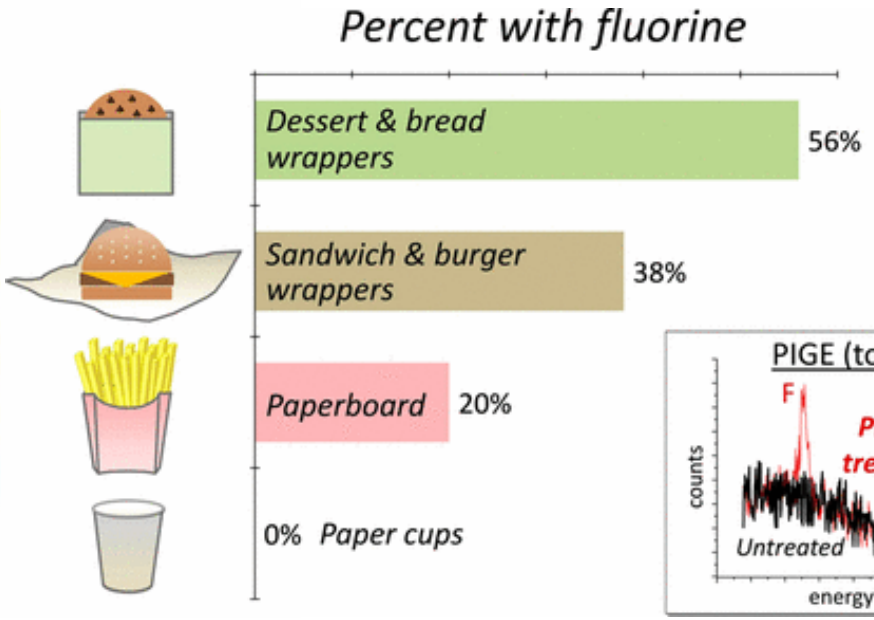
CNN Health » Diet + Fitness | Living Well | Parenting + Family Live TV U.S. Edition +

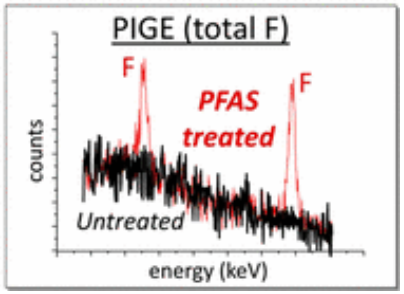
Report finds chemicals in one-third of fast food packaging

By **Ben Tinker**, CNN
Updated 8:33 AM ET, Wed February 1, 2017

Photos: Chemicals in fast food packaging

A study by the Silent Spring Institute found fluorinated chemicals in one-third of the fast food packaging tested. Previous studies have shown PFASs can migrate from food packaging into the food you eat. What types of packaging pose the greatest risk? Click through this gallery to find out.





ENVIRONMENTAL Science & Technology LETTERS
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Fluorinated Compounds in U.S. Fast Food Packaging

Laurel A. Schaider,[*,†] Simona A. Balan,[‡] Arlene Blum,[§,∥] David Q. Andrews,[⊥] Mark J. Strynar,[#] Margaret E. Dickinson,[▽] David M. Lunderberg,[▽] Johnsie R. Lang,[○] and Graham F. Peaslee[@]

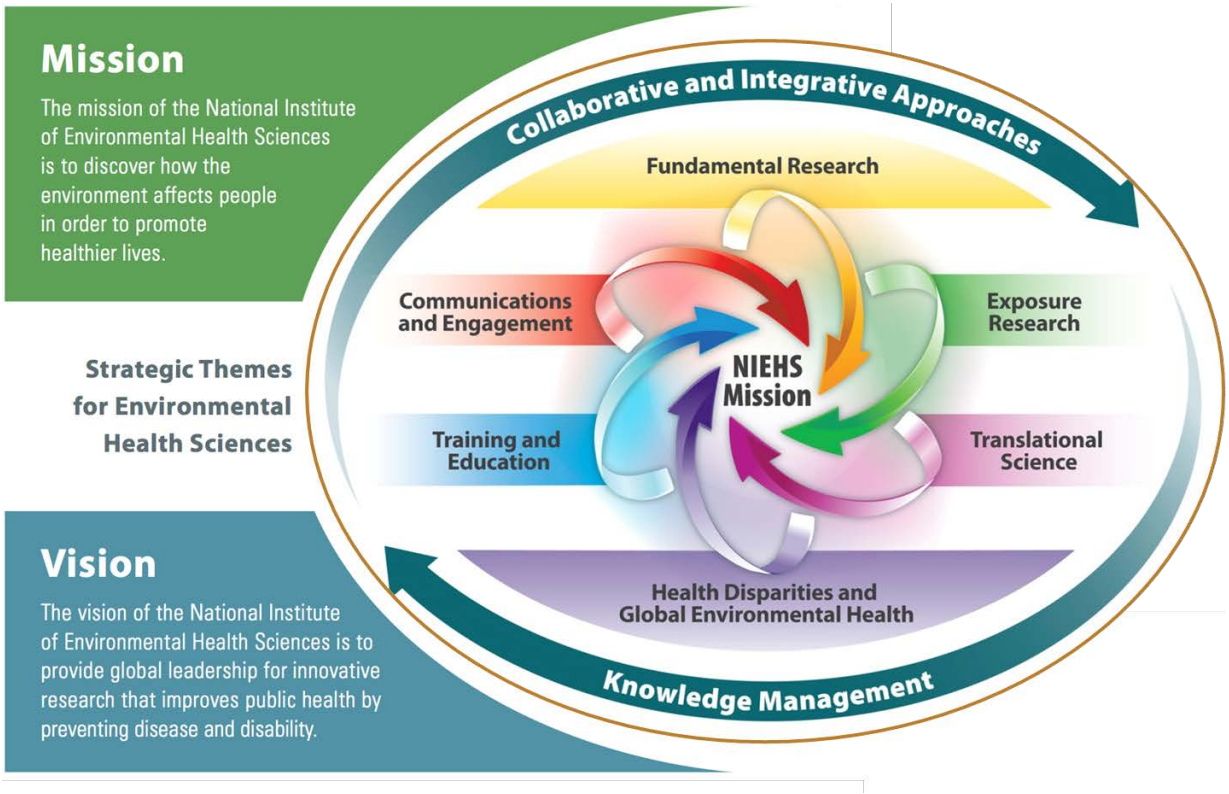
Wide Range of Health Effects of PFAS

PFOS and/or PFOA

- Testicular cancer
- Kidney cancer
- Ulcerative colitis
- High cholesterol
- Pregnancy-induced hypertension
- Thyroid disruption
- Hormonal changes
- Liver malfunction
- Obesity
- Immunotoxicity, incl. interference with child vaccine response
- Lower birth weight and size
- Delayed puberty, decreased fertility, early menopause
- Reduced testosterone
- Prostate cancer
- Ovarian cancer

How we decide what to study

- ✓ Investigator Initiated Research
- ✓ Nominations to the National Toxicology Program
- ✓ NHANES and other biomonitoring
- ✓ MOUs with other Institutes/Agencies /Partners



NIEHS PFOS/PFOA/PFC Active Grant Portfolio

P01, P42, U2C (multi project)	10
R01, R15, R21, R44, & R56	21
U01	1
Total number of grants	**32**

$9,650,647

- 24 Epidemiology/Human studies, 8 Animal/Basic studies

NIEHS PFOS/PFOA/PFCs Active Grant Portfolio

Human Sources & Endpoints

Water, House dust, Diet

- Birthweight
- Fertility & Repro
- Cancer
- Obesity
- Diabetes
- Endocrine function
- Autism ADHD
- CVD
- Immune Outcomes

Animal Systems

Rodents, Zebrafish, *In Vitro*

- Cancer
- Cytotoxicity
- Genotoxicity
- Gene expression
- Oxidative stress
- Signaling pathways

Cohorts ES Grants are Using to Examine PFAS (PFOS/PFOA/PFCs)

Health Outcomes and Measures of the Environment (HOME)

- Birth cohort study in Cincinnati, Ohio with 400+ mother/infant pairs (NIEHS)
- Developmental, and behavioral outcomes.

Healthy Start Study

- Ethnically diverse cohort of 800+ mother/infant pairs (NIDDK)
- Metabolic and behavioral factors during pregnancy

Markers of Autism Risk in Babies-Learning Early Signs (MARBLES)

- Longitudinal cohort of women with a child with autism (NIEHS)
- Environmental exposures and risk factors that may contribute to development of autism

Cohorts ES Grants are Using to Examine PFOS/PFOA/PFCs

Study of Women's Health Across the Nation (SWAN)

- Longitudinal study of 3,000+ ethnically diverse women (NIA)
- Health of women during their middle years

Faroe Islands Birth Cohorts

- Birth cohort studies in the Faroe Islands (NIEHS)
- Postnatal development, neurobehavioral functions, metabolic outcomes, and immune system responses

Project Viva

- Longitudinal Birth Cohort in Eastern MA, (NIDDK)
- Prenatal and child health, diet, neurodevelopment metabolic outcomes, and immune system responses

NTP Immunotoxicity Monograph

- NTP Monograph on Immunotoxicity Associated with Exposure to Perfluorooctanoic Acid or Perfluorooctane Sulfonate
  - Reported immune effects of both PFOA and PFOS
    - Effects on antibody response in animals at some of lowest doses
    - Recent studies reporting similar antibody effects in humans
    - PFOA and PFOS appeared to share some effects and differ for others

- **Studies in animals**
  - Experimental studies
    - PFOA- and PFOS-associated changes in multiple immune measures
    - **Immunosuppression**: reduced antibody response, disease resistance, etc.
    - **Hypersensitivity**: increased airway hypersensitivity
  - Wildlife studies

- **Studies in humans**
  - PFOA- and PFOS-associated measures of immune function or disease
    - **Immunosuppression**: reduced antibody response to vaccines
    - **Hypersensitivity**: increased asthma in children
    - **Autoimmunity**: increased incidence of ulcerative colitis

Action: NTP Conclusions for PFOA

Table 7. PFOA Main Immune Effects Summary Table						
Category of Immune	Immune	Confidence Ratings in the Body of Evidence		Level of Evidence in the Body of Evidence		
Response	Outcomes	Human	Animal	Human	Animal	Hazard Conclusion
Immunosuppression	Antibody response	Moderate	High	Moderate	High	Presumed to be an Immune Hazard to Humans
Hypersensitivity	Asthma and other hypersensitivity-related outcomes	Low	High	Low	High	Presumed to be an Immune Hazard to Humans

PFOA is ***presumed to be an immune hazard to humans*** based on:

- Suppressed antibody response
  - **Animal studies**: High level of evidence
  - **Human studies**: Moderate level of evidence
  - No change in conclusions after considering mechanistic data
- Increased hypersensitivity-related outcomes
  - **Animal studies**: High level of evidence
  - **Human studies**: Low level of evidence
  - No change in conclusions after considering mechanistic data

Action: NTP Conclusions for PFOS

Table 9. PFOS Main Immune Effects Summary Table						
Category of Immune Response	Immune Outcomes	Confidence Ratings in the Body of Evidence		Level of Evidence in the Body of Evidence		Hazard Conclusion
		Human	Animal	Human	Animal	
Immunosuppression	Antibody response	Moderate	High	Moderate	High	**Presumed to be an Immune Hazard to Humans**

PFOS is ***presumed to be an immune hazard to humans*** based on:

- Suppressed antibody response
  - **Animal studies**: High level of evidence
  - **Human studies**: Moderate level of evidence
  - No change in conclusions after considering mechanistic data

Tox 21 Data on PFAS

- PFOS
- PFHxA
- PFOA
- PFDA
- PFNA
- PFHS
- Run in 43 toxicity and/or nuclear receptor assays
- Analyses in process

NTP Study Goals

- Perfluorinated Class Program Update:
- Characterize the chronic toxicity/carcinogenic activity of PFOA, toxicokinetics of several PFASs in the HSD rat, and characterize the toxicities of several PFASs via in vitro and in vivo models
- **With in vivo studies, observed toxicities will be related to internal dose**

Ongoing NTP Studies

- Chronic bioassay: evaluate PFOA toxicity and carcinogenicity in male and female rats. Exposure included a perinatal (GD 6 – PND 21) and non-perinatal component to determine if early life exposure alters response.
  - Study undergoing pathology review
  - Pathology tables expected to be posted during the summer and NTP Technical Report peer reviewed in late 2018
- 28-day toxicity studies: compare toxicity and internal dose of several PFASs in male and female rats
  - 7 PFASs evaluated: PFBS, PFHxS, PFOS, PFHxA, PFOA, PFNA, and PFDA
    - Data undergoing analysis and review
    - Tables expected to posted this summer and reports to follow later this year and 2018

Ongoing and Published NTP Studies

- Toxicokinetic studies: evaluate kinetics of several PFASs after single dose in male and female rats:
  - Evaluated PFBS, PFHxS, PFOS, PFHxA, PFOA, PFDA, and 8:2 fluorotelomer
  - Manuscripts underway
- Immunotoxicity assessment:
  - PFDA evaluation in female rats and mice (poster at SOT)
- Published in vitro studies:
  - In vitro mitochondrial toxicity evaluation of 16 PFASs using rat liver:
    Wallace *et al*. *Toxicology Letters* 2013; 222(3)
  - In vitro assessment of immunotoxicity of 5 PFASs:
    Corsini *et al.* *Toxicology and Applied Pharmacology* 2012; 258(2)
  - In vitro neurotoxicity evaluation of 4 PFASs using PC12 cells:
    Slotkin *et al*. *Environmental Health Perspectives* 2008; 116(6)

NTP Laboratory Studies – Early Life PFOA Exposures

- Enhanced weight gain at low doses, reduced weight gain at high doses
  - Doses higher than 3 mg/kg decrease body weight gain; doses less than 0.3 mg/kg increase weight gain in early/mid-life
  - Doses greater than or equal to 1 mg/kg decrease birthweight
- Hepatocellular hypertrophy, tumors, and inflammation
  - Exposures are prenatal only: 1 mg/kg or less
  - 18 mon after exposure: PFOA exposed CD-1 mice significantly increased liver tumors; PFOA significantly increased hepatocellular hypertrophy and other non-neoplastic lesions in CD-1, 129/Sv, and PPAR-alpha KO mice
  - 90-day old CD-1 mice: dose-dependent increase in hepatic inflammation and hypertrophy, no peroxisome proliferation in livers, mitochondrial dysfunction
  - Papers in clearance: (1) 100% hepatocellular hypertrophy in PFOA-treated CD-1 and 129/Sv mice. All three strains examined show quantitative increases in mitochondrial DNA. (2) Specific gene pathways identified that are associated with phenotypic effects. CD-1 mice exhibit significant changes in CYP genes, and PPAR-alpha KO mice have extensive mitochondrial pathway deficits.
- Behavioral changes
  - Increased motor activity in 18-day old pups; altered methamphetamine response in adults following prenatal exposure to 1 mg/kg or less

NTP Laboratory Studies – Mammary/Breast Effects

- Transfer of PFOA to the offspring
  - PFOA recovery in mouse amniotic fluid and in fetuses
  - Milked mice and PFOA was recovered in milk and mammary tissue
  - Detected in milk of lactating NC women
- Impaired lactation at high doses (5 mg/kg)
  - Led to significantly increased mortality in pups. Related to genes involved in growth and differentiation of the mammary gland.
- Impaired female pubertal mammary development in CD-1 and C57Bl/6 mice
  - All exposures were prenatal and between 0.01 to 5 mg/kg PFOA
  - CD-1 full gestational and late gestational exposures = same results
  - Full gestational exposure: CD-1 stunted growth, fewer terminal end buds, persistent retardation of growth into adulthood, and stromal hyperplasia in late life (18 mon)
  - Late gestation exposure at 1 mg/kg or less: CD-1 altered fat organization, stunted growth and development. At weaning, internal doses overlapped with serum levels reported in people in highly contaminated areas of US.
  - Strain comparison of CD-1 and C57/Bl6 demonstrate no other pubertal effects besides stunted mammary development (prenatal doses of 1 mg/kg or less). Vaginal opening, time to first estrus, and hormones levels compared.

Mouse serum PFOA (ng/ml) associated with mammary gland effects

Days after PFOA ended	Control	0.01 mg/kg	0.1 mg/kg	1.0 mg/kg
7	6.7 ± 1.1 (5)	149.5 ± 11.7 (4)*	1113.5 ± 57.2 (4)*	9163.5 ± 629.7 (3)*
14	4.9 ± 1.2 (4)	95.0 ± 13.3 (3)*	747.7 ± 38.2 (4)*	6448.8 ± 328.3 (5)*
21	< 5, LOQ (5)	29.3 ± 12.5 (4)*	201.0 ± 27.1 (5)*	2250.0 ± 170.8 (5)*
28	< 5, LOQ (5)	8.0 ± 1.0 (5)*	64.0 ± 12.8 (5)*	1249.4 ± 227.6 (5)*
56	< 5, LOQ (5)	< 10, LOQ (5)*	13.1 ± 1.9 (5)*	57.9 ± 18.6 (5)*

Data are presented as mean ± SEM. Significant effects compared to controls by Dunnetts, *p<0.05

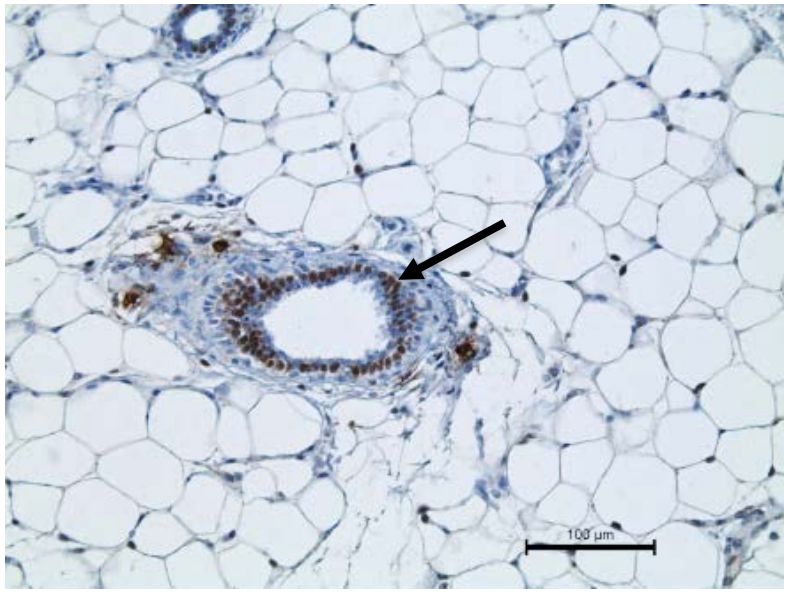
Ohio River Valley children's serum PFOA concentrations:

- ≤600 ng/ml (Ages 2-5; Emmett *et al*., 2006)
- 77.6 ng/ml (Ages <12; Frisbee *et al.*, 2009)
- 59.9 ng/ml (Ages 12-19)

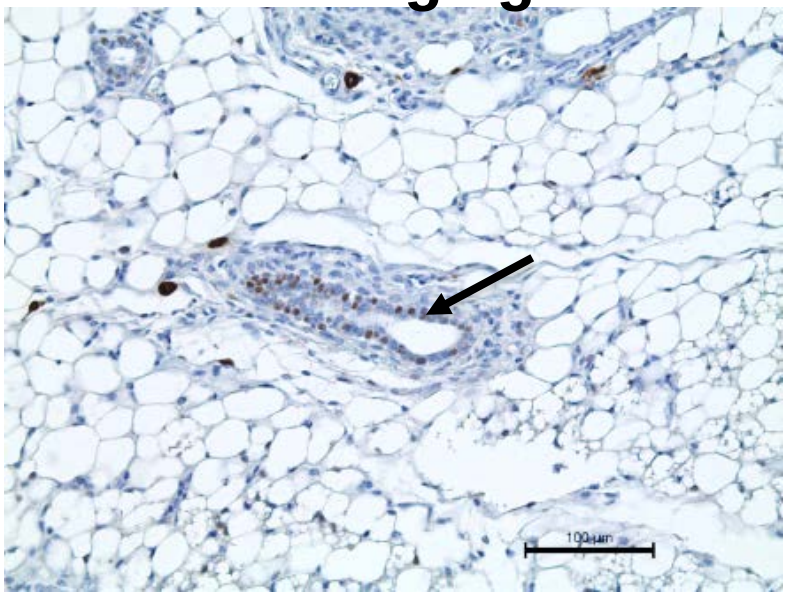
http://www.c8sciencepanel.org/

Mammary adipocyte size and organization is altered by prenatal PFOA

Control



1.0 mg/kg



*Note ER-α staining reduced in ductal epithelium (arrow) of adult animals prenatally PFOA exposed

Prenatal PFOA Induces Early Adult Obesity & Alters Metabolic Hormones

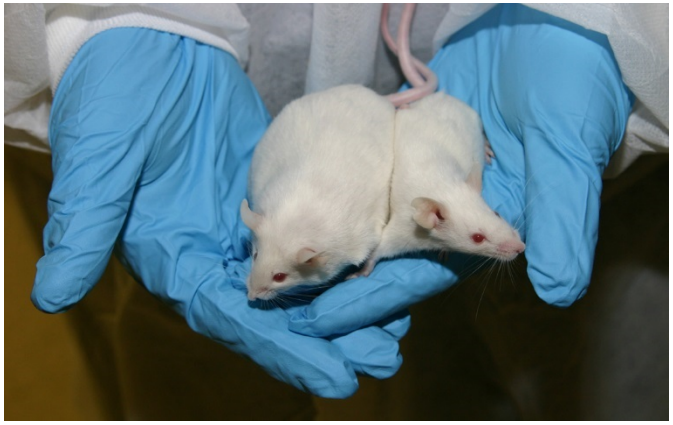
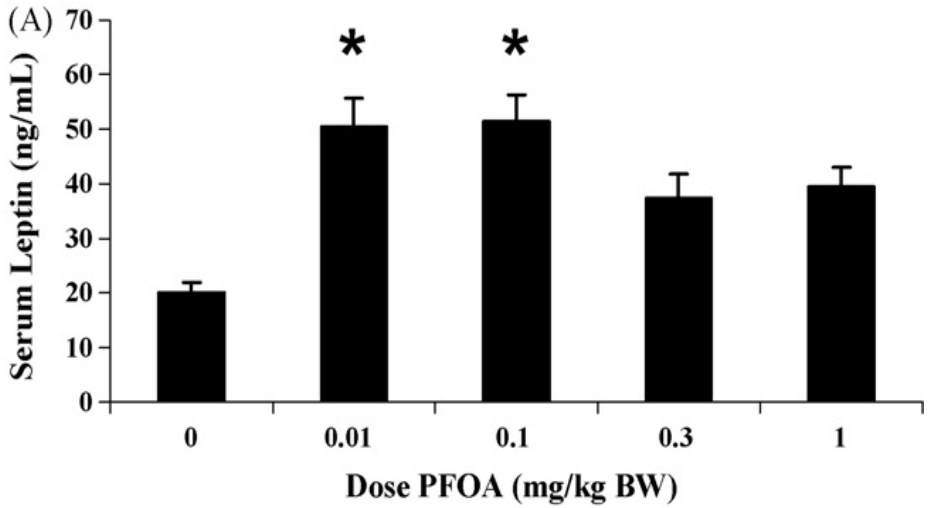
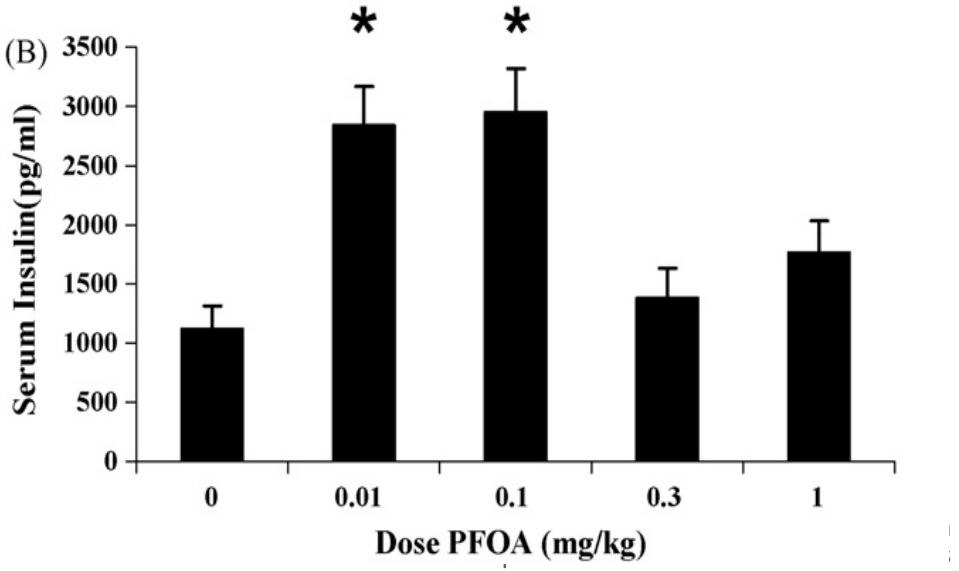


Photo from *Environ Health Perspect* Focus

Data in Hines et al, 2009, *Mol. Cell Endocrinol. 304: 97-105*





Supported in epidemiological studies:

1. Increased gestational weight gain
Int J Environ Res Public Health. 2016
2. Overweight in 20 yr old Danish daughters exposed in utero.
Environ Health Perspect. 2012

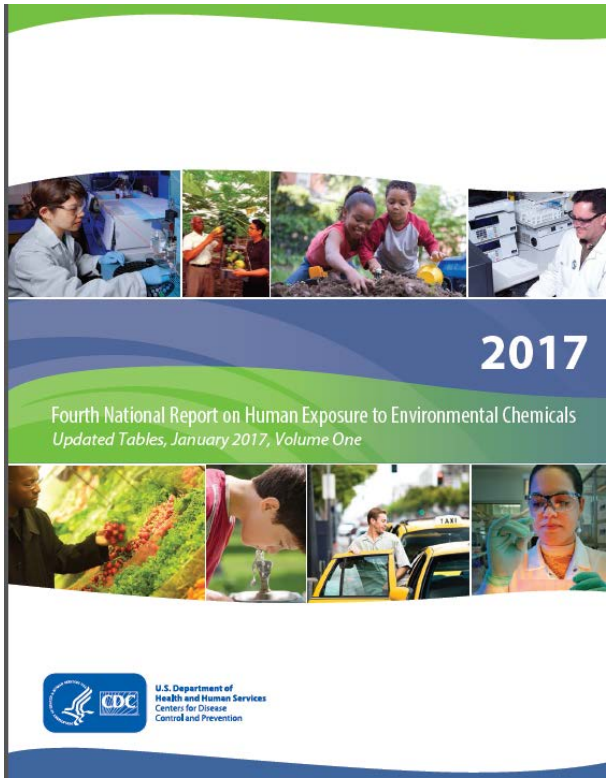
Impact of This Work

- Lower birth weights following PFOA exposure
  - Koustas *et al*., 2014 *Environ Health Perspect* – Navigation Guide – sufficient evidence for link between prenatal PFOA exposure and birthweight deficits in mice
  - 5/8 papers used in meta-analysis were by Fenton *et al.*
- Overweight supported in epidemiological studies
  - Increased gestational weight gain in Danish women; 2016 *Int J Environ Res Public Health*
  - Overweight in 20-yr old Danish daughters exposed in utero; 2012 *Environ Health Perspect*
- Decreased breastfeeding duration in humans
  - Women who had highest levels of serum PFAS lactated shorter time or could not continue as long as they wished.
  - Timmerman *et al*., 2016 *Reprod Toxicol*; Romano *et al*., 2016 *Environ Res*
- Use of mammary data in risk evaluation
  - Tucker *et al*. 2015, Macon *et al*. 2011, White *et al*. 2011
  - German EPA; NJ, NC, MN, and NY environmental protection departments
- Liver data proves human relevant mechanism of action
  - Data also used in NJ Department of Environmental Protection risk evaluation

Ongoing Work on Uncharacterized PFAS

- Blinded evaluations of 22 PFASs:
  - Effects on adipocytes/lipid production (fat deposition)
    - 3T3-L1 cells in culture; measuring lipid production per cell and cell proliferation
  - Metabolism by the liver
    - Collect cells/media post-treatment to measure metabolites
  - Liver effects
    - HepRG cell cultures; human primary hepatocytes
    - Measure proliferation, lipid production, oxidative stress, and mitochondrial dysfunction
    - Transcriptomic evaluation
  - Placental control of energy
    - JEG-3 cells in culture; human placental samples in collaboration with R. Fry (UNC)
    - Measure metabolism and growth-promoting endpoints
- Test in mice once most active PFASs are identified

Biomonitoring: NHANES Data



Perfluoroalkyl and Polyfluoroalkyl Substances: Surfactants

- Perfluorobutane sulfonic acid (PFBuS)
- Perfluorodecanoic acid (PFDeA)
- Perfluorododecanoic acid (PFDoA)
- Perfluoroheptanoic acid (PFHpA)
- Perfluorohexane sulfonic acid (PFHxS)
- Perfluorononanoic acid (PFNA)
- Perfluorooctanoic acid (PFOA)
- n -Perfluorooctanoic acid (n -PFOA)*
- Branched Perfluorooctanoic isomers (Sb-PFOA)*
- Perfluorooctane sulfonic acid (PFOS)
- n -Perfluorooctane sulfonic acid (n -PFOS)*
- Perfluoromethylheptane sulfonic acid isomers (Sm-PFOS)*
- Perfluorooctane sulfonamide (PFOSA)
- 2-(N-Ethyl-perfluorooctane sulfonamido) acetic acid (Et-PFOSA-AcOH)
- 2-(N-Methyl-perfluorooctane sulfonamido) acetic acid (Me-PFOSA-AcOH)
- Perfluoroundecanoic acid (PFUA)

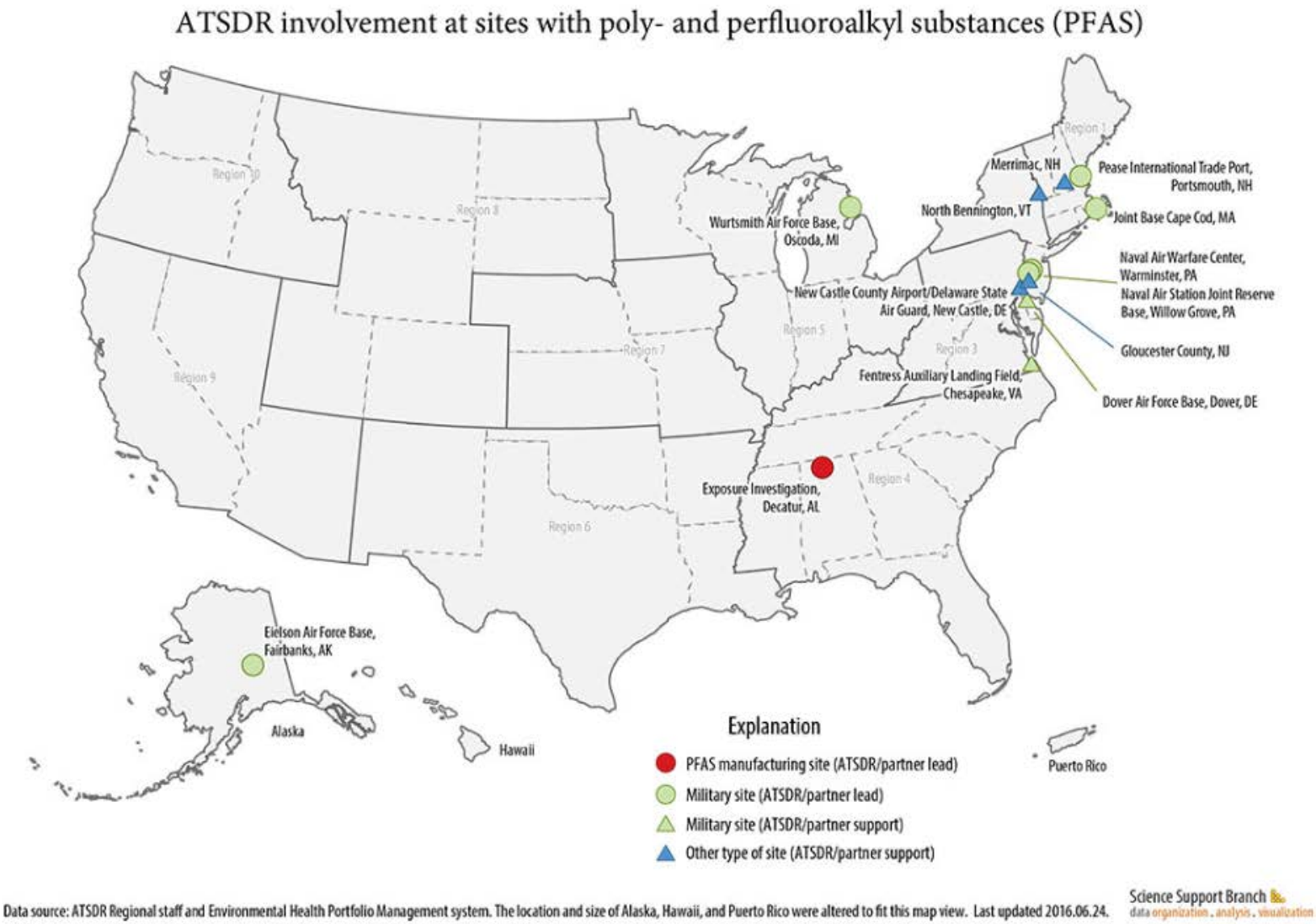


Figure 1. Perfluorinated compound (PFAS) sites with ATSDR, state health department, US Environmental Protection Agency, or Department of Defense involvement

Madrid Statement on Highly Fluorinated Chemicals

"We call on the international community to cooperate in limiting the production and use of PFASs and in developing safer non-fluorinated alternatives."

2015: Environmental Health Perspectives

Acceptable levels

EPA (January 2009):

- Provisional level of 400 ppt for PFOA and 200 ppt for PFOS

Stockholm Convention on Persistent Organic Pollutants (2010)

- PFOS is listed under Annex B of the which restricts use to ‘acceptable purposes’

EPA (May 2016):

- Lifetime level of 70 ppt for total of PFOA and PFOS

States

- New York – 70 ppt
- Vermont – 20 ppt
- New Jersey – 40 ppt
- Minnesota Pollution Control Agency recommends levels at or below 35 parts per trillion for PFOA and 27 parts per trillion for PFOS

"We err on the side of caution, and that's sort of the tradition we have here in Minnesota to really protect the most vulnerable as best we can."

Ed Ehlinger
Minnesota Health Commissioner

PFOS/PFOA replacements – Are they safer?

- Persistence
- Toxicity
- ? Uptake
- ? Target organs
- Water filtration and remediation

Environmental Science & Technology Letters
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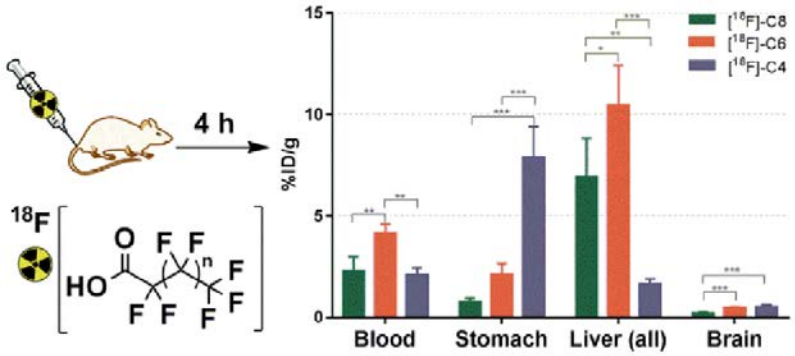
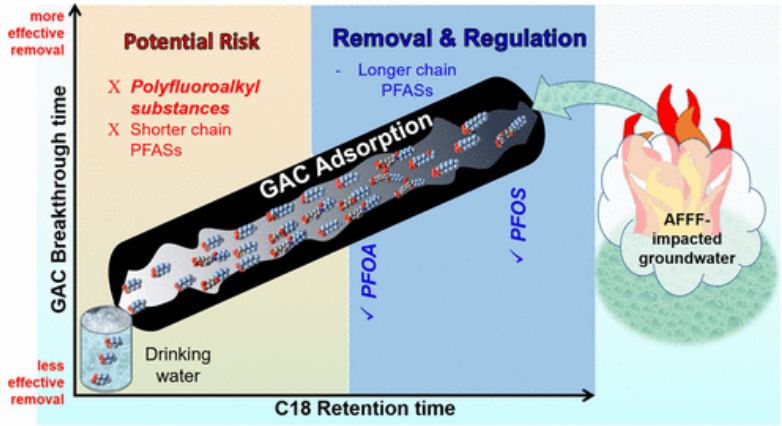
Radiosynthesis and Biological Distribution of ^{18}F-Labeled Perfluorinated Alkyl Substances

Jennifer L. Burkemper,[†] Tolulope A. Aweda,[†] Adam J. Rosenberg,[‡,§] David M. Lunderberg,[∥] Graham F. Peaslee,[⊥] and Suzanne E. Lapi*[,†]





Environ Sci Technol. 2017 Jun 6;51(11):6342-6351. doi: 10.1021/acs.est.7b00970.

Sorption of Poly- and Perfluoroalkyl Substances (PFASs) Relevant to Aqueous Film-Forming Foam (AFFF)-Impacted Groundwater by Biochars and Activated Carbon.

Xiao X[1,2,3], Ulrich BA[2], Chen B[1,3], Higgins CP[2].

Collaboration for investigating short-chain alternatives

NTP
National Toxicology Program
U.S. Department of Health and Human Services

ATSDR
AGENCY FOR TOXIC SUBSTANCES
AND DISEASE REGISTRY

FDA

Thank you!

Strategic Plan Survey
https://www.research.net/r/niehs_strategic_plan

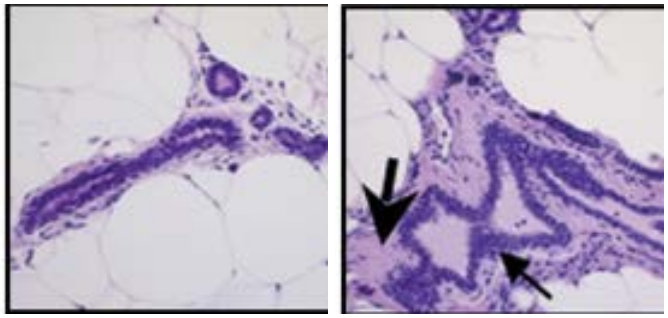
National Institute of Environmental Health Sciences

National Toxicology Program
U.S. Department of Health and Human Services

http://www.niehs.nih.gov

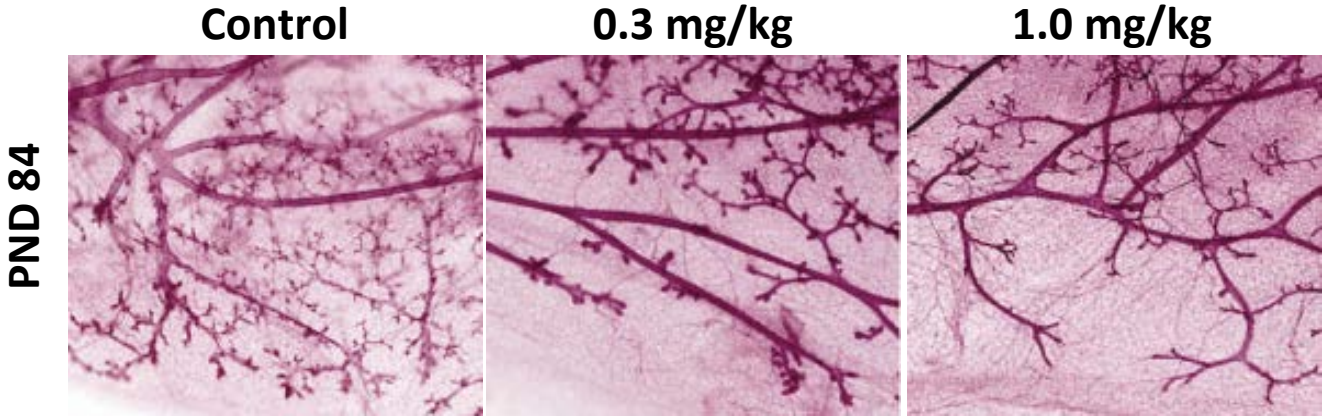
Late life effects on the mammary gland

- **CD-1 mice, GD 1-17 exposure, @ 18 mon**

Control  **5 mg/kg**

White *et al*., 2009

- **CD-1 mice, GD 1-17 exposure**



Macon *et al*., 2011

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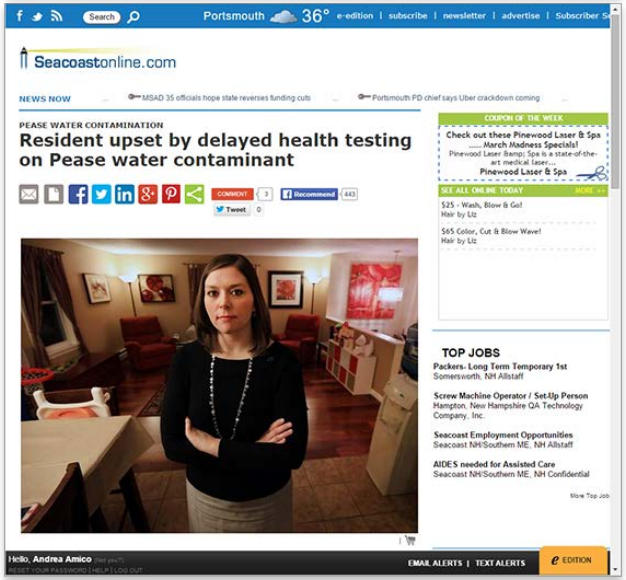
TESTING *for* PEASE

- Pushed for blood testing by NH Health Dept.
- Organized residents
- Recruited health and public health professionals to design research and develop communications and education
- Helped other communities learn how to deal with newly-discovered PFAS contamination
- Presented at professional and activist conferences
- Key planners for June 2017 conference



How we decide what to study…

- Investigator Initiated Research
- Nominations to the National Toxicology Program
- NHANES and other biomonitoring
- MOUs with other Institutes/Agencies