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Links between Human PFAS Exposure, Obesity, & Molecular Mechanisms

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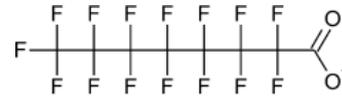
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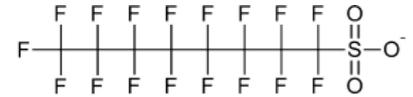
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Perfluoroalkyl Substances (PFAS)

- Used in/as:
 - Stain/water repellent (e.g., carpet, food packaging)
 - Cleaning agents
 - Cosmetics,
 - Firefighting foams
 - Industrial surfactant
- Phased out of use in US
 - Concern over replacements



Perfluorocarboxylic acids
(ex. PFOA)



Perfluorosulfonic acids
(ex. PFOS)



Human PFAS Exposure

- Persistent chemicals
 - Half-lives of 3-7 years
- PFAAs routinely detected in human serum
- Diet is predominant source of exposure in adults
 - Breastmilk for breastfed infants
 - Drinking water contamination



Fromme et al. 2009, Mogensen et al. 2015.

Potential Health Effects of PFAS

- Array of health effects with varying degrees of certainty regarding causality
 - Immunotoxicity
 - Some cancers
 - Neurodevelopment
 - Liver
 - Thyroid function
 - Cholesterol
 - Growth and development
- Special concern about vulnerable populations
 - Fetus, infant, and child



Health Effects of PFAS in Infants & Children



PFAS, Growth, and Adiposity

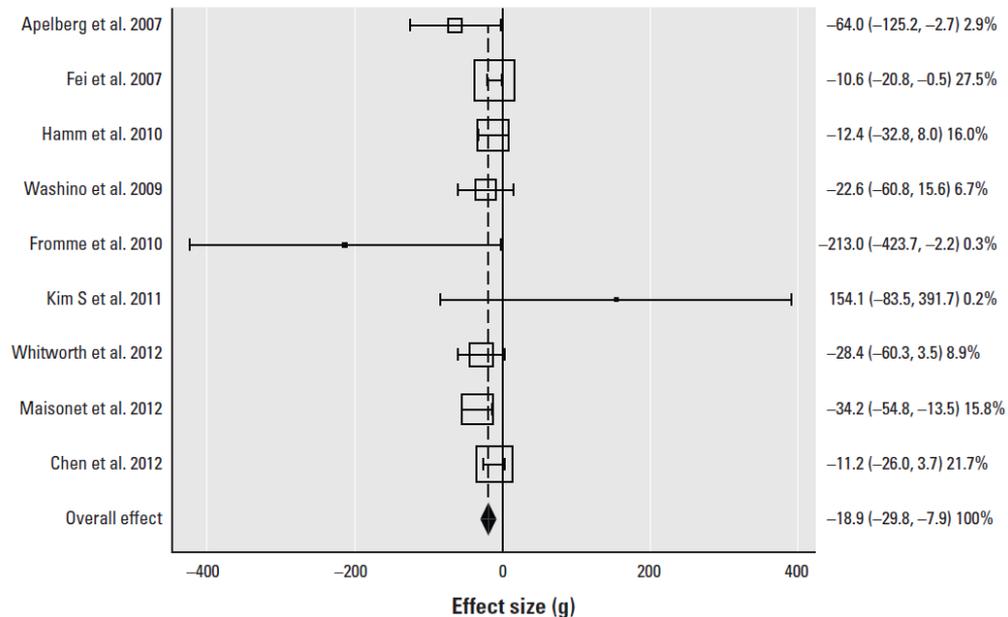
- PFAS can act on biological systems important for growth and metabolism
 - PPAR α and γ
 - Cortisol metabolism (11- β -HSD-2)
 - Lipid and triglyceride metabolism
- Suspected obesogens

Zhao et al. 2011; Taxvig et al. 2012; Vanden Heuvel et al. 2006; Steenland, EHP, 2009



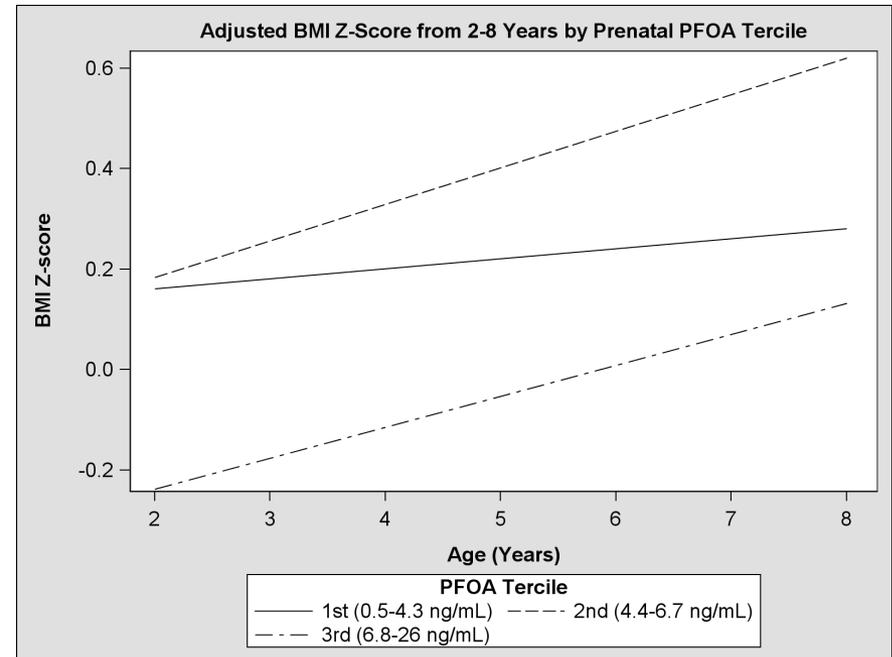
PFOA/PFOS and Fetal Growth

- Animal & human show that PFOA (maybe PFOS) exposure associated with reduced birth weight
 - 1 ng/mL increase in PFOA → 19 gram decrease in BW (95% CI: -30, -7)
 - 1 mg/kg/d increase in PFOA exposure → 23 mg decrease in pup birth weight (95% CI: -29, -16)



PFAS and Child/Adult Adiposity

- Prenatal PFOA/PFOS associated with obesity in some, but not all studies
 - PFOA/PFOS associated with ↑ adiposity at 8, but not 3 years (n~700)
 - PFOA associated with ↑ adiposity at 20 years of age in females, not males (n~600)
- Prenatal PFOA associated with altered growth trajectories (n~285)



PFAS and Breastfeeding

- Pregnancy PFOA/PFOS associated with ↓ breastfeeding duration
- PFAS can influence breast development and lactation hormones
- Potential mechanism explaining PFAS-obesity association



Fei et al., 2010, Romano et al., 2016, Timmerman et al. 2016, Tucker et al. 2015, White et al. 2007, Yang et al. 2009

PFAS and Epigenetics

- PFAS associated with:
 - PFOS and higher LINE-1 methylation
 - PFOA and global DNA hypomethylation
 - DNA methylation of growth-related genes
 - Expression of cholesterol genes
- No studies examining unknown biological pathways (i.e., untargetted approaches)

Watkins et al, Environ Int, 2014; Guerrero-Preston et al., Epigenetics, 2010;
Kobayashi et al., Environ Int, 2014; Fletcher et al., Environ Health Perspect, 2014



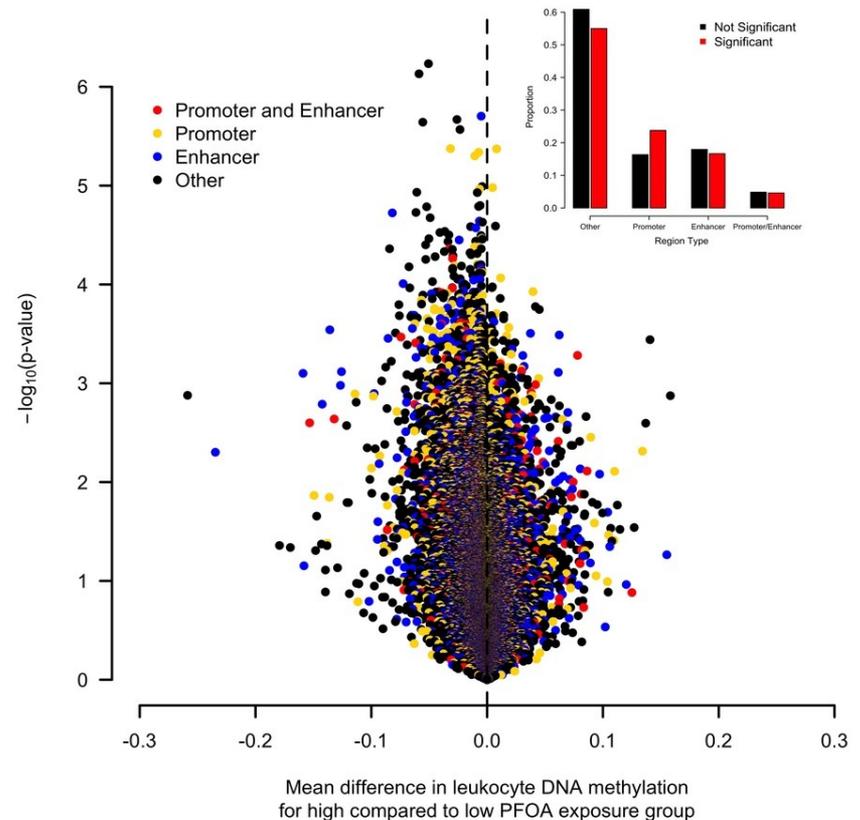
PFOA and DNA Methylation: Pilot Study

- Mother-child pairs in HOME Study
 - Lowest 22 PFOA levels (1.1-3.1 ng/mL)
 - Highest 22 PFOA levels (12-26 ng/mL)
- Leukocyte DNA methylation in infant cord blood
 - Illumina 450K



PFOA & DNA Methylation: Pilot Study

- Excess of associations in promoters
- Hypomethylation of 7 CpG sites in 3 genes
- Notable genes
 - RASA3: Cell growth and differentiation
 - OPRD1: Opioid receptor, associated with obesity
 - HOXD3: Morphogenesis



PFAS in Drinking Water



PFAS Water Contamination



The Detroit News

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EPA joins Michigan in old tannery waste disposal probe

News Feature | March 17, 2017



Whidbey Island Wells Contaminated With Firefighting Chemicals



By Peak Johnson

From contaminants at levels above the

Tap Water Still Unsafe For More Than 200 Burrillville Residents

By AVORY BROOKINS • OCT 24, 2017



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EPA Drinking Water PFOA and PFOS Health Advisory

- Established in May 2016
 - 70 ng/L for PFOA, PFOS, or their sum (ppt)
 - PFOA: ↓ bone formation and accelerated pubertal development
 - PFOS: ↓ offspring weight
- Accounted for susceptibility of fetus and infant
- Non-enforceable and non-regulatory level



Tool for Water-Serum Comparison

- Web app uses PFOA PK to calculate:
 - PFOA after ceasing water exposure
 - PFOA after starting water exposure
- <http://www.ics.uci.edu/~sbartell/pfoacalc.html>

Serum PFOA Calculator for Adults

Please enter the following values, then click on the "submit" button:

1. How much PFOA was in your blood sample?

Starting serum PFOA concentration ($\mu\text{g/L}$, ng/mL , or ppb)

2. How much PFOA is in your drinking water? Enter 0 if you're drinking on

Water PFOA concentration for ongoing consumption (ng/L , or ppt)

Application of PFOA Calculator

- Calculated observed PFOA in Romano et al. 2016 using
 - Background serum PFOA=2 ng/mL
 - Water PFOA levels
- Health implications of current standard

Quartile	RR of quitting BF at 3M	Water PFOA (µg/L)	Serum PFOA (ng/mL)
1 st	Ref	9	3.1
2 nd	1.3	22	4.6
3 rd	1.6	36	6.3
4 th	1.8	70	10



Conclusions

- PFAS exposures may have adverse health effects on developing fetus, infant, and child
 - Mechanisms being elucidated by molecular epidemiology
- Current water-based drinking water health advisory may not be sufficient to protect public health

