Links between Human PFAS Exposure, Obesity, & Molecular Mechanisms

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Perfluoroalkyl Substances (PFAS)

- **Used in/as:**
  - Stain/water repellant (e.g., carpet, food packaging)
  - Cleaning agents
  - Cosmetics,
  - Firefighting foams
  - Industrial surfactant

- **Phased out of use in US**
  - Concern over replacements

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 $\rightarrow$ 19 gram decrease in BW (95% CI: -30, -7)
  - 1 mg/kg/d increase in PFOA exposure $\rightarrow$ 23 mg decrease in pup birth weight (95% CI: -29, -16)

Koustas et al., EHP, 2014; Johnson et al., EHP 2014
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

Kingsley et al., Environ Res, 2017
PFAS in Drinking Water
PFAS Water Contamination

The Detroit News

EPA joins Michigan in old tannery waste disposal probe

News Feature | March 17, 2017

Whidbey Island Wells Contaminated With Firefighting Chemicals

By Peak Johnson

Tap Water Still Unsafe For More Than 200 Burrillville Residents

By AVORY BROOKINS • OCT 24, 2017
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


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 (µg/L, ng/mL, or ppb)

2. How much PFOA is in your drinking water? Enter 0 if you're drinking or Water PFOA concentration for ongoing consumption (ng/L, or ppt)

Bartell, Environmental Health Perspectives, 2017
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

<table>
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<th>Water PFOA (μg/L)</th>
<th>Serum PFOA (ng/mL)</th>
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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