Overview of Putative PFAS Health Effects: Epidemiology

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Brief Orientation to Epidemiologic Research on PFAS and Health

- Distinctive challenges in assessing causal effects of PFAS:
  - Accurate exposure reconstruction due to lack of historical measurements
  - Potential for reverse causality in which disease affects exposure biomarkers
  - Complexity of addressing mixtures of different PFAS chemicals
  - Multiple, ill-defined exposure sources through consumer products

Exposure from Contaminated Drinking Water Supplies

- Source of clear, sometimes extreme gradient in levels of exposure
- Affected community supplies more easily addressed than private wells
- Relatively free of confounding given haphazard location of proximal contamination sites
- Amenable to historical exposure reconstruction
- Variable specific PFAS across locations
- Population size often insufficient for studying rare outcomes

Ubiquitous Background Exposure from Multiple Sources

- Highly prevalent exposure through drinking water, food, food wrapping, other consumer products
- Reflected in biomarkers of exposure since exposure sources are diverse and not amenable to historical reconstruction
- Biomarkers reflect prolonged recent exposure with half-lives of ~2-4 years for long-chain PFAS
- Without clear source, reasons for variation in biomarker levels unclear
  - Susceptible to reverse causation and confounding by biological correlates or presence of disease

Available Research on PFAS and Health Outcomes

- Small number of studies of large populations with substantial exposure due to contaminated drinking water – Mid-Ohio Valley (OH, WV), Ronneby Sweden, Veneto Italy
- ATSDR multi-site study in progress across 7 sites with historical drinking water contamination, most due to proximal military bases
- Hundreds of studies of variation in background exposure – dozens of cohorts that include biospecimens are amenable to investigation

Health Outcomes Most Clearly Affected by PFAS

- Increases in serum cholesterol, particularly LDL, even with modest increases in exposure – shift in distribution, increased proportion with hypercholesterolemia
- Reduced antibody response to vaccines in children, possibly adults
- Elevated liver enzymes, particularly ALT (alanine transferase), indicative of subclinical dysfunction
- Kidney cancer, with recent replication of C8 Science Panel studies in NCI (PLCO) study

Diseases and Health Indicators with Moderate Support

- Ulcerative colitis, based on strong but isolated findings from C8 Health Project
- Testicular cancer, based on strong but isolated findings from C8 Health Project
- Thyroid disease, but inconsistent with respect to hyper- and hypothyroidism, sex-specific effects, and mixed support from studies of thyroid hormones
- Reduced birthweight, consistent small reduction but possibly reverse causality

Potential Consequences of Clinical Biomarker Effects

- Infectious disease – mixed evidence
- Cardiometabolic disease -- negative
- Liver disease – little study

Other Health Outcomes of Interest

- Birth outcomes – miscarriage, preterm birth
- Infant Adiposity
- Neurodevelopment
- Other cancers – prostate, ovary

Reflections on Patterns of Results

- Preponderance of evidence on clinical biomarkers in relation to background variation
- Expected disease consequences of biomarker changes not consistently found
- Very limited research on disease endpoints of interest, especially rare conditions

Key Gaps in Epidemiologic Research on PFAS

- Scarcity of literature on populations with substantial, well-documented variation in environmental exposure
- Insurmountable ambiguity in studies of background exposure variation
- Extensive health research on PFOA and PFOS, some studies of other long-chain PFAS, very little on short-chain recently introduced PFAS
- Quantitative information for establishing regulatory limits in drinking water
- Very little research on environmental pathways other than drinking water

Challenges in Addressing New Forms of PFAS

- Exposure reconstruction requires environmental and pharmacokinetic modeling
  - Shorter half-lives, perhaps more variability in exposure over time
- Brief history of exposure limits ability to study long-term health consequences
- Unclear whether to presume similar health consequences as for legacy PFAS, relative degrees of potential toxicity