Summary

1. Background
2. Health effects review
3. Health studies
Perfluorinated alkyl substances (PFAS, aka PFCs)

Hydrophilic functional group
Hydrophobic/lipophilic fluorinated tail
C-F bond is very strong – does not break down easily
Perfluorinated alkyl substances (PFAS, aka PFCs)

Widely used in the manufacture of products resistant to stains, grease and water.

- Sofas and carpets stain resistant
- Food packaging (microwave popcorn, pizza boxes, parchment paper)
- Water/stain-proof clothing and mattresses
- Production of non-stick cookware
- Some firefighting foams
# A Group of Chemicals

<table>
<thead>
<tr>
<th>Name</th>
<th>Acronym</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfluorobutane sulfonate</td>
<td>PFBS</td>
</tr>
<tr>
<td>Perfluorohexane sulfonate</td>
<td>PFHxS</td>
</tr>
<tr>
<td>Perfluorohexanoic acid</td>
<td>PFHxA</td>
</tr>
<tr>
<td>Perfluorooctanoic acid</td>
<td>PFOA</td>
</tr>
<tr>
<td>Perfluorooctane sulfonate</td>
<td>PFOS</td>
</tr>
<tr>
<td>Perfluorononanoic acid</td>
<td>PFNA</td>
</tr>
<tr>
<td>Perfluorodecanoic acid</td>
<td>PFDA</td>
</tr>
<tr>
<td>8+2 Fluorotelomer alcohol</td>
<td>8:2 FTOH</td>
</tr>
</tbody>
</table>
Half-life

Time it takes for half of the chemical present to be removed from the blood

<table>
<thead>
<tr>
<th></th>
<th>Perfluorooctanoic acid</th>
<th>Perfluorooctane sulfonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>~3 years</td>
<td>PFOA</td>
<td>PFOS</td>
</tr>
<tr>
<td>~5 years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C8 Pease
Properties of Concern

- Widespread presence in general population
- Long half-lives
- Transfer from mother to fetus
- Presence in breast milk
Health Effects Review

1. Endocrine disruption
2. Developmental origins of disease
3. Review some epidemiologic studies
Endocrine Disrupting Chemicals

Chemicals that interfere in some way with the body’s hormone system.
Development and Early Life is Sensitive to Endocrine Disruption

<table>
<thead>
<tr>
<th>Age (weeks)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zygote cleavage; blastocyst implants</td>
<td>2-8 mm</td>
<td>4 mm</td>
<td>6 mm</td>
<td>13 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two-layered embryo forms; amniotic cavity and yolk sac open</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrulation occurs; notochord and beginning of neural tube form</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neural tube closes; heart beats; arm buds, tail, and limb buds form</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implantation occurs; retina (optic cup) and lens (lens pelt) form; leg buds form; brain anlage forms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Webbed fingers and additional ear form; pigment appears in retina, tail, and limb grooves disappearing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (weeks)</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 mm</td>
<td>30 mm</td>
<td>50 mm</td>
<td>81 mm</td>
<td>73 mm</td>
<td>87 mm</td>
<td></td>
</tr>
<tr>
<td>Webbed toes form; bones begin to harden; both straighten; eyelids form</td>
<td>Toes separate; eyelids develop; major parts of brain are present</td>
<td>Chin grows; nostrils separate; face appears human; genitals appear male or female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper limbs begin to appear; genitalia begin to differentiate; fingers are distinct</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>140 mm</td>
<td>190 mm</td>
<td>230 mm</td>
<td>270 mm</td>
<td>330 mm</td>
<td>350 mm</td>
<td></td>
</tr>
<tr>
<td>Blood cells form; all major organs form; head and body hair appear; movements are felt by mother</td>
<td>Fetus may be viable if born; eyelids open; lungs and liver circulation develop; may suck thumbs; fat deposited under skin</td>
<td>Fetus usually viable if born; fat deposits increase; body hair is lost; head hair is well developed; most senses are well developed; fetus turns head down in uterus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 10 |

**Development and Early Life is Sensitive to Endocrine Disruption**

- Zygote cleavage; blastocyst implants
- Two-layered embryo forms; amniotic cavity and yolk sac open
- Gastrulation occurs; notochord and beginning of neural tube form
- Neural tube closes; heart beats; arm buds, tail, and limb buds form
- Implantation occurs; retina (optic cup) and lens (lens pelt) form; leg buds form; brain anlage forms
- Webbed fingers and additional ear form; pigment appears in retina, tail, and limb grooves disappearing
Fetus, Infants and Children

1. Sensitive to endocrine disrupting chemicals
2. Developing enzymes to metabolize chemicals
3. Higher exposure by body weight
Mother:Child Ratio of PFOS

- PFOS was an average of 42% higher in children compared to mothers.
- Persisted until at least 19 years of age.
- Boys older than 5 had significantly higher PFOS child:mother ratios than girls.

C8 Health Study: (Mondal et al. 2012)
Thyroid Hormone

C8 Health Study:
- Prenatal PFOS associated with an increase in $T_4$ among children 1-17 years old (Lopez-Espinosa et al. 2012)

Pregnant Norwegian women:
- PFOS positively associated with thyroid stimulating hormone (TSH) (Wang et al. 2013)
General Health Outcomes of concern for EDCs

- Fertility and Fecundity
- Neurodevelopment
- Immune function
- Timing of puberty
- Metabolic syndrome
- Hormonally sensitive cancers
Examples of specific epidemiologic studies

- For contextual purposes, not a comprehensive literature review
Female reproduction

PFOS associated with lower concentrations of ovarian hormones, $E_2$ (estrogen) and progesterone

(Knox et al. 2011, Barrett et al. 2015)
Female reproduction

PFOA and PFHxS (but not PFOS) associated with increased fecundability (time to pregnancy) and increased odds of infertility (Valez et al. 2015)
Male reproduction

Developmental exposure:
- **PFOA**: Lower sperm concentration and sperm count (Vested et al. 2013)
- **PFOS**: 35% reduction in morphologically normal sperm (Toft et al. 2012)
Neurodevelopment

General Danish Population:
- No association between prenatal PFAS exposure and risk of ADHD or childhood autism (Liew et al. 2015)

C8 Health Study:
- Increase in prevalence of ADHD with increasing prenatal PFHxS exposure (Stein and Savitz 2011)
Immune Function - Children

- Doubled concentrations of PFOS at age 5 were associated with increased odds of falling below a clinically protective level of tetanus and diphtheria antibodies at 7 years of age (Grandjean et al. 2012)

- Maternal serum PFOA associated with decreased vaccine responses and increased frequencies of common cold and gastroenteritis (Granum et al. 2013)
Immune Function - Adults

C8 Health Study
Elevated PFOA associated with:

- Reduced antibody titer rise (especially influenza)
- Increased risk of not attaining antibody threshold for long-term protection

(Looker et al. 2013)
Timing of Puberty

C8 Health Study:
- PFOS exposure associated with longer time to puberty among both boys and girls (~100 days, on average) (Lopez-Espinosa et al. 2012)

Danish cohort:
- Daughters exposed to higher levels of PFOA in utero reached puberty 5.3 months later (Kristensen et al. 2013)
Cholesterol

C8 Health Study:

- In children, increased risk for abnormal total-C and LDL-C with increasing PFOS and PFOA (Frisbee et al. 2011)
- In adults, increase in total-C and LDL-C with increasing PFOS and PFOA (Steenland et al. 2009)
- In women, PFOS was associated with expression of genes involved in cholesterol mobilization and transport (Fletcher et al. 2013)
Hormonally Sensitive Cancers

C8 Health Study (only PFOA was assessed):
- Testicular cancer: 3 fold increase in odds
- Ovarian and prostate cancer: Increased odds (not statistically significant but low statistical power)

(Barry et al. 2013)

Workers: Excess testicular and prostate cancers
Animals: Increased male reproductive organ cancer, delay in mammary gland development
Other Cancers

C8 Health Study (only PFOA was assessed):

- Kidney cancer: 2 fold increase among women (but not men)
- Non-Hodgkin lymphoma: 80% increase among most highly exposed

(Barry et al. 2013)

Workers: Excess kidney and bladder cancer as well as myeloid leukemia
Review of concerns

- Fertility and Fecundity
- Neurodevelopment – ADHD*
- Immune function – children* and adults
- Delayed puberty *
- Cholesterol - children* and adults
- Cancer – testicular and kidney

* Prenatal exposure
Health Studies

1. Ongoing health studies
   - C8
   - Ronneby

2. Types of health studies
C8 Health Project

- 69,030 residents enrolled from 2005-2006
- Demographic data, medical diagnoses, clinical laboratory testing, serum PFCs
- High exposures to PFOA, PFOS levels lower
  - Although drinking water ranged up to 4,900 ng/L

C8 Science Panel Website: [http://www.c8sciencepanel.org/publications.html](http://www.c8sciencepanel.org/publications.html)
Ronneby, Sweden

- Elevated PFOS in drinking water discovered in 2013, 4,000 ng/L
- Air force base
- Fire-fighting foam
- 5,000 households affected

Jakobsson 2015
## Drinking water (ng/L)

<table>
<thead>
<tr>
<th></th>
<th>Pease</th>
<th>Ronneby</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfluorooctane sulfonate (PFOS)</td>
<td>2500</td>
<td>4000</td>
</tr>
<tr>
<td>Perfluorohexane sulfonate (PFHxS)</td>
<td>830</td>
<td>1200</td>
</tr>
<tr>
<td>Perfluoroctanoic acid (PFOA)</td>
<td>350</td>
<td>130</td>
</tr>
<tr>
<td>Perfluorohexanoic acid (PFHxA)</td>
<td>330</td>
<td>340</td>
</tr>
<tr>
<td>Perfluoropentanoic acid (PFPeA)</td>
<td>270</td>
<td>52</td>
</tr>
<tr>
<td>Perfluorooctanoic acid (PFHpS)</td>
<td>120</td>
<td>67</td>
</tr>
<tr>
<td>Perfluorobutane sulfonate (PFBS)</td>
<td>51</td>
<td>140</td>
</tr>
<tr>
<td>Perfluorononanoic acid (PFNA)</td>
<td>17</td>
<td>1.2</td>
</tr>
<tr>
<td>Perfluorodecanoic acid (PFDA)</td>
<td>4.9</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Perfluoroundecanoic acid (PFUnA)</td>
<td>&lt;1</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Perfluorododecanoic acid (PFDoA)</td>
<td>&lt;2</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

4451 5789
Ronneby, Sweden
Preliminary Risk Assessment

- TDI exceeded in formula-fed infants
- No acute health effects
- Probably no increased risk for adverse health effects on individual health in the long run
- Possibly detectable effects on the population level
Ronneby, Sweden
Pilot Study

- Compared blood levels in school children with (n=20) and without (n=20) PFOS in drinking water
- Levels in exposed children highly elevated
Ronneby, Sweden
Exposure Monitoring

- Collected blood from 2,600 affected residents (of ~9,000 total)
- Focus on those under and approaching reproductive age
- In blood: Measuring PFCs, lipids, thyroid hormone, metabolomics, epigenetic markers

Jakobsson 2015
Ronneby, Sweden
Pregnancy Cohort

- ~300 births/year
- Maternal blood from pregnancy, at birth, at 6-8 weeks postpartum and after lactation
- Placenta, colostrum, mature breast milk
- Child immunity
Community Health Guide

1. What is a health study and why would you want one?
2. Framing your concern as a research question
3. A Menu of Health Studies

### Positive things a health study might do:
- Document disease and/or exposure
- Demonstrate a relationship between exposure and disease
- Educate residents about environmental health concerns
- Generate media coverage and motivate the community
- Be useful for political leverage in a campaign
- Create an opportunity for members of your community to get involved
- Be useful in community efforts to protect the health of future generations

### Negative things a health study might do:
- Document no significant relationship between a disease and exposure
- Appear to show that there is no problem
- Give permission to polluters to continue polluting
- Lead to legal issues over confidentiality or lawsuits by polluters
- Be used against your campaign or group
- Overwhelm your organizing efforts and sap members’ energy
- Generate statistics that may undermine your efforts
- Identify health problems that you are unprepared to deal with
- Delay action while waiting for results
Types of Studies

Studies of Exposure
- Environmental or personal exposure monitoring
- Body burden / biomonitoring
- Environmental impact statements

Studies of Outcome
- Community survey
- Analysis of registry data

Studies of the Exposure-Outcome Relationship
- Ecologic study
- Cohort study
- Case-control study

Studies of Contaminated Sites
- Risk assessment
- Public health assessment
Suggestions moving forward

1. Use existing studies, biomonitoring data and community concerns to identify health concerns
2. Frame questions
3. Consider options for addressing those questions
THANK YOU

carignan@hsph.harvard.edu
Exposure Misclassification

How much water did you drink per week?
Drinking water at Pease (ng/L)

<table>
<thead>
<tr>
<th>Perfluorinated Compound</th>
<th>Harrison</th>
<th>Smith</th>
<th>Haven</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfluoropentanoic acid (PFPeA)</td>
<td>7.9</td>
<td>3.5J</td>
<td>270</td>
</tr>
<tr>
<td>Perfluorobutane sulfonate (PFBS)</td>
<td>2J</td>
<td>0.94J</td>
<td>51</td>
</tr>
<tr>
<td>Perfluorohexanoic acid (PFHxA)</td>
<td>8.7</td>
<td>3.9J</td>
<td>330</td>
</tr>
<tr>
<td>Perfluoroheptanoic acid (PFHpS)</td>
<td>4.6J</td>
<td>2.5J</td>
<td>120</td>
</tr>
<tr>
<td>Perfluorohexane sulfonate (PFHxS)</td>
<td>36</td>
<td>13</td>
<td>830</td>
</tr>
<tr>
<td>Perfluorooctanoic acid (PFOA)</td>
<td>9</td>
<td>3.5J</td>
<td>350</td>
</tr>
<tr>
<td>Perfluorononanoic acid (PFNA)</td>
<td>NDU</td>
<td>NDU</td>
<td>17</td>
</tr>
<tr>
<td>Perfluorooctane sulfonate (PFOS)</td>
<td>48</td>
<td>18</td>
<td>2500</td>
</tr>
<tr>
<td>Perfluorodecanoic acid (PFDA)</td>
<td>NDU</td>
<td>4.4J</td>
<td>4.9J</td>
</tr>
<tr>
<td>Perfluoroundecanoic acid (PFUnA)</td>
<td>NDU</td>
<td>17</td>
<td>NDU</td>
</tr>
<tr>
<td>Perfluorododecanoic acid (PFDoA)</td>
<td>NDU</td>
<td>12</td>
<td>NDU</td>
</tr>
<tr>
<td></td>
<td>116.2</td>
<td>49.7</td>
<td>4473</td>
</tr>
</tbody>
</table>
Developmental Origins of Disease

Reproductive Effects of Bisphenol A

BPA Dosing
Pregnancy Day 11
original MOM
GENERATIONS
Table 6-2. Comparison of PFOA content ranges between this study and literature values (in ng PFOA/g sample, unless indicated otherwise)

<table>
<thead>
<tr>
<th>Article category</th>
<th>Literature&lt;sup&gt;a&lt;/sup&gt;</th>
<th>This study&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treated carpeting</td>
<td>200 to 600&lt;sup&gt;b&lt;/sup&gt;</td>
<td>ND (&lt;1.5) to 462</td>
</tr>
<tr>
<td>Carpet-care liquid treated carpeting</td>
<td>200 to 2000&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.6 to 224&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Treated apparel</td>
<td>ND (&lt;20) to 1400&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.4 to 161</td>
</tr>
<tr>
<td>Treated upholstery</td>
<td>ND (&lt;34)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.6 to 293</td>
</tr>
<tr>
<td>Treated home textiles</td>
<td>ND (&lt;20) to 1400&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.8 to 438</td>
</tr>
<tr>
<td>Treated non-woven medical garments</td>
<td>ND (&lt;34)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>46 to 369</td>
</tr>
<tr>
<td>Industrial floor wax and wax removers</td>
<td>0.5 to 60&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7.5 to 44.8</td>
</tr>
<tr>
<td>Stone, tile, and wood sealants</td>
<td>ND (&lt;100)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>477 to 3720</td>
</tr>
<tr>
<td>Membranes for apparel</td>
<td>0.008 to 0.07 ng/cm&lt;sup&gt;2&lt;/sup&gt;&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.1 to 2.5 ng/cm&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Food contact paper</td>
<td>6 to 290&lt;sup&gt;d&lt;/sup&gt;</td>
<td>ND (&lt;1.5) to 4640</td>
</tr>
<tr>
<td>Dental floss/tape</td>
<td>3 to 4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>ND (&lt;1.5) to 96.7</td>
</tr>
<tr>
<td>Thread sealant tape</td>
<td>1800&lt;sup&gt;d&lt;/sup&gt;</td>
<td>ND (&lt;1.5) to 3490</td>
</tr>
<tr>
<td>PTFE cookware</td>
<td>4 to 75&lt;sup&gt;d&lt;/sup&gt;</td>
<td>ND (&lt;1.5) to 4.3</td>
</tr>
</tbody>
</table>

<sup>a</sup> ND: not detected (detection limit in parentheses). <sup>b</sup> Data source: ref 7 (based on theoretical calculations). <sup>c</sup> Calculated by using the recommended coverage and assuming the area density of the carpet is 0.25 g/cm<sup>2</sup>. <sup>d</sup> Data source: ref 17.
Exposure-Disease Conceptual Model

- Source/Emissions
- Media
- Micro-environments

Exposure
- Inhalation
- Ingestion
- Dermal

Absorbed Dose

Biologically Effective Dose

Altered Structure/Function

Susceptibility

Disease
Non-Monotonic Dose Response

Welshons et al. 2003
Gene-Environment

Environmental Inputs interact with our body’s genetic system.

Environmental Inputs
Exposures, Nutrition, Lifestyle

Genetic System

Metabolic Response
Cancer Susceptibility Risk Factors and Other Health Outcomes
Gene-Environment