Insights into PFAS Toxicity from Recent Research and from Previously Undisclosed Documents

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Watersheds with point sources have higher detection frequencies for PFASs.

Cindy Hu et al, ES&T Letters, 2016
EPA Drinking Water Health Advisory Levels

January 2009:
Provisional level of 400 ppt for PFOA and 200 ppt for PFOS

May 2016:
Lifetime level of 70 ppt for total of PFOA and PFOS

2018:
Will ATSDR or EFSA inspire lower and binding limits?
PFAS toxicological characteristics

Highly persistent in the environment, global dissemination
Slightly water soluble, low vapor pressure
Easily absorbed in humans
Elimination half-time in humans: several years
Pass the placental barrier
Lactational transfer results in peak exposures in infancy

Major adverse effects documented in laboratory animals and also reported in humans:
Carcinogenicity
Liver enzymes and serum lipids
Immunotoxicity
Endocrine disruption, including delayed breast development
Fetal toxicity and adverse pregnancy outcomes
Antigen

B cells activated

macrophage presents antigen

macrophage displays antigen

infected cell displays antigen

T cells activated

memory cytotoxic T cells

matures cytotoxic T cells

helper T cells activated

memory helper T cells

plasma cells

antibodies

memory cells

nonspecific killers

(Source: the Human Immune Response System www.uta.edu/chagas/images/immunSys.jpg)
Human immunotoxicity: Advantages of vaccine responses in epidemiological studies:
• ‘Natural experiment’
• Same dose of antigen
• Same age at exposure
• Routine antibody assay
• Clinical relevance
Change in tetanus antibody concentration after booster in 12 adult volunteers

Steepness of increase inversely associated with serum-PFAS

(Kielsen et al., 2015)
Faroe Islands

- Homogeneous, western culture
- High participation rate in prospective studies
- Fishing community with high seafood intake (+ whale)
- Wide range of exposures from traditional food (pilot whale)
- Total population - 48,000
Vaccination

Blood sample

Antibody concentration

Months

Years
SEM for effect of **doubled** serum-PFAS (PFOS/PFOA/PFHxS) at age 5/7 years on serum antibodies (%) at age 7 years

<table>
<thead>
<tr>
<th></th>
<th>Tet</th>
<th>Diph</th>
<th>p (diff)</th>
<th>Joint</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age 5</strong></td>
<td>-55.0</td>
<td>-44.1</td>
<td>0.35</td>
<td>-49.4</td>
<td>-67.6; -21.2</td>
</tr>
<tr>
<td><strong>Age 7</strong></td>
<td>-51.2</td>
<td>-56.9</td>
<td>0.64</td>
<td>-54.7</td>
<td>-73.9; -21.1</td>
</tr>
<tr>
<td><strong>Both</strong></td>
<td>-65.0</td>
<td>-58.5</td>
<td>0.63</td>
<td>-61.5</td>
<td>-77.6; -33.9</td>
</tr>
</tbody>
</table>

Mogensen et al., 2015
Child serum, age 5
$r = 0.50$

Serum concentrations of PFOA correlate with other PFASs, but not as closely as other major PFASs

Grandjean et al., unpublished data
Effect of a **doubled serum-PFOA** at ages 5 and 7 years on serum antibodies (%) at age 7 years

<table>
<thead>
<tr>
<th></th>
<th>Tet</th>
<th>95% CI</th>
<th>Diph</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression (7)</td>
<td>-20.5</td>
<td>-38.2; 2.1</td>
<td>-25.4</td>
<td>-40.9; -5.8</td>
</tr>
<tr>
<td>SEM (5+7)</td>
<td>-38.2</td>
<td>-56.1; -13.0</td>
<td>-34.7</td>
<td>-52.5; -10.2</td>
</tr>
<tr>
<td><strong>Adjusted</strong>*</td>
<td>-29.6</td>
<td>-50.6; 0.4</td>
<td>-26.9</td>
<td>-47.4; 1.5</td>
</tr>
</tbody>
</table>

*adjusted for other PFASs (almost unchanged)  Mogensen et al., 2015
BMC calculations
Serum-PFAS at age 5
Serum antibody at age 7

BMCL at BMR = 5%
~1.3 ng PFOS/mL serum
~0.3 ng PFOA/mL serum for linear curve

Lower for log curve
Higher for BMR = 10%
(2.6 and 0.6 ng/mL)

Environmental Health 2013, 12:35
SYSTEMATIC REVIEW OF IMMUNOTOXICITY ASSOCIATED WITH EXPOSURE TO PERFLUOROOCTANOIC ACID (PFOA) OR PERFLUOROOCTANE SULFONATE (PFOS)

(July 2016)

"The NTP concludes that **PFOS** is presumed to be an immune hazard to humans...”

“The NTP concludes that **PFOA** is presumed to be an immune hazard to humans...”
The lowest curve (dashed) is from a non-breastfed child, and the upper (solid line) is from a child breastfed exclusively for 6 months and partially the following 5 months.
Exposure error in simple linear regression

\[ X: \text{true exposure}, \quad W: \text{measured exposure} \]

Classical additive error: \[ W = X + U \text{ with } U \text{ independent of } X \]

\[ Y = \alpha + \beta \cdot X + \epsilon, \quad \text{Naive Analysis: replace } X \text{ by } W \]

Standard regression analysis assumes no imprecision of the independent variables

Courtesy:
Esben Budtz-Jorgensen
As serum-PFAS in infancy is strongly affected by duration of exclusive breastfeeding, an algorithm was developed to calculate serum-PFAS.
Change (in %) of tetanus and diphtheria antibody concentration at age 5 years associated with a doubling in *calculated* serum-PFOA concentrations in infancy (95% confidence intervals)

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Tetanus</th>
<th>Diphtheria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change</td>
<td>95% CI</td>
</tr>
<tr>
<td>0</td>
<td>-22.3</td>
<td>-35.3, -6.6</td>
</tr>
<tr>
<td>3</td>
<td>-32.8</td>
<td>-47.0, -14.9</td>
</tr>
<tr>
<td>6</td>
<td>-25.8</td>
<td>-39.5, -8.9</td>
</tr>
<tr>
<td>12</td>
<td>-17.8</td>
<td>-31.1, -1.9</td>
</tr>
</tbody>
</table>

Grandjean et al., 2017
Increased risk of infection?

• 359 children aged 1-3 years were monitored for fever and symptoms every 2 weeks for 1 yr (by text messages)
• Days with fever >38.5°, comparison of high and low tertiles of maternal pregnancy serum concentrations
  – Odds of experiencing days with fever above median for PFOA OR: 1.97 (95%CI: 1.07, 3.62)
• Higher exposures to PFOA and PFOS tended to increase the proportion of episodes with both fever and nasal discharge: medium tertile PFOA exposure compared to the low tertile (IRR: 1.38 (95% CI: 1.03,1.86)).
• Likewise, higher exposures to PFOA, PFOS and PFHxS tended to increase the proportion of episodes with fever and coughing.

Dalsager et al., 2016
There was an inverse association between the level of anti-rubella antibodies in the children’s serum at age 3 years and the concentrations of the four PFAS. Furthermore, there was a positive association between the maternal concentrations of PFOA and PFNA and the number of episodes of common cold for the children, and between PFOA and PFHxS and the number of episodes of gastroenteritis (assessed by questionnaire).
Complexities in interpreting PFAS research

- Developmental exposures/vulnerabilities
- Unobservable thresholds
- Unknown target organs/critical effects
- Likely underestimation of risks
- Existence of hypersusceptibility
- Remaining uncertainties
<table>
<thead>
<tr>
<th>Year</th>
<th>Exposure evidence</th>
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<tbody>
<tr>
<td>1968</td>
<td>Organofluoride compounds in human blood</td>
</tr>
<tr>
<td>1976</td>
<td>Organofluorines in workers’ blood</td>
</tr>
<tr>
<td>1981</td>
<td>PFOA found in cord blood (female worker)</td>
</tr>
<tr>
<td>1993</td>
<td>Transfer into milk observed in goats</td>
</tr>
<tr>
<td>1998</td>
<td>PFOS found in general population blood</td>
</tr>
<tr>
<td>2004</td>
<td>PFAS detected in human milk</td>
</tr>
<tr>
<td>2014</td>
<td>Breastfeeding shown to be major source of PFAS exposure in infants</td>
</tr>
<tr>
<td>Year</td>
<td>Description</td>
</tr>
<tr>
<td>------</td>
<td>-------------</td>
</tr>
<tr>
<td>1978</td>
<td>Monkey study: PFOA immunotoxicity</td>
</tr>
<tr>
<td>1992</td>
<td>Leukocyte changes in workers</td>
</tr>
<tr>
<td>2008</td>
<td>Mouse immunotoxicity at serum PFAS concentrations similar to humans</td>
</tr>
<tr>
<td>2012</td>
<td>PFC immunotoxicity in children</td>
</tr>
<tr>
<td>2013</td>
<td>Benchmark Dose calculations suggest that guidelines are far from protective</td>
</tr>
</tbody>
</table>
**Delayed insight or *delayed public access**

<table>
<thead>
<tr>
<th>Research finding</th>
<th>First</th>
<th>Public</th>
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<tr>
<td>PFASs in general population</td>
<td>1976</td>
<td>2001</td>
</tr>
<tr>
<td>PFASs in cord blood</td>
<td>1981</td>
<td>2004</td>
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<td>PFOS immunotoxicity in monkeys</td>
<td>1978</td>
<td>2000*</td>
</tr>
<tr>
<td>Immune cell changes in workers</td>
<td>1992</td>
<td>2018*</td>
</tr>
</tbody>
</table>

**Average delay** 22 years
3M comment on $850 million settlement

• “This agreement reflects 3M’s long-standing commitment to always acting with integrity and conducting business in an ethical and sustainable way. While we have never believed there is a PFC-related health issue, this agreement allows us to move past this litigation and work together with the state on activities and projects to benefit the environment and our communities.”