Adverse effects of PFAS on Immune System Health: Complicating recovery during the COVID-19 Pandemic?

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<table>
<thead>
<tr>
<th>Year</th>
<th>Exposure evidence</th>
</tr>
</thead>
<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>2015</td>
<td>Breastfeeding shown to be major source of PFAS exposure in infants</td>
</tr>
</tbody>
</table>
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.

Mogensen et al., 2015
Serum-PFOA in a woman exposed in utero, via breastfeeding for 12 months and then via diet at 0.33 ng/kg bw per day (EFSA 2020).
<table>
<thead>
<tr>
<th>Year</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<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>PFAS immunotoxicity in children</td>
</tr>
<tr>
<td>2013</td>
<td>Benchmark Dose calculations suggest that guidelines are far from protective</td>
</tr>
<tr>
<td>2020</td>
<td>EFSA considers immunotoxicity the critical effect and lowers tolerable dose</td>
</tr>
</tbody>
</table>

Unpublished
(Source: the Human Immune Response System www.uta.edu/chagas/images/immunSys.jpg)
Change in tetanus antibody concentration after booster in 12 adult volunteers

Steepness of increase inversely associated with serum-PFAS

(Kielsen et al., 2015)
No information on absenteeism among PFAS-exposed 3M employees
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
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...”
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
Exposure error in simple linear regression

$X$: true exposure, $W$: measured exposure

Classical additive error: $W = X + U$ with $U$ independent of $X$

$Y = \alpha + \beta \cdot X + \epsilon$,  Naive Analysis: replace $X$ by $W$

Standard regression analysis assumes no imprecision of the independent variables

Courtesy: Esben Budtz-Jorgensen
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></th>
<th>Diphtheria</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change</td>
<td>95% CI</td>
<td>Change</td>
<td>95% CI</td>
</tr>
<tr>
<td>0</td>
<td>-22.3</td>
<td>-35.3, -6.6</td>
<td>-18.9</td>
<td>-33.2, -1.7</td>
</tr>
<tr>
<td>3</td>
<td>-32.8</td>
<td>-47.0, -14.9</td>
<td>-12.7</td>
<td>-31.0, 10.4</td>
</tr>
<tr>
<td>6</td>
<td>-25.8</td>
<td>-39.5, -8.9</td>
<td>-6.9</td>
<td>-24.1, 14.1</td>
</tr>
<tr>
<td>12</td>
<td>-17.8</td>
<td>-31.1, -1.9</td>
<td>-4.1</td>
<td>-19.4, 14.2</td>
</tr>
</tbody>
</table>

Grandjean et al., 2018
Risk factors for COVID-19

• Elderly
  Have higher accumulated PFAS levels in blood

• Men

• Existing disease, such as
  – Diabetes
    Occur at increased incidence when PFAS exposure is elevated
  – Obesity
Study design

• Plasma from residual volumes from diagnostic blood tests at hospitals (30-70 years)
• All 323 subjects positive for SARS-CoV-2
• Study conducted without informed consent
• All information anonymous on secure server
• Health and demographic information from existing national registers
• Clinical course: no hospitalization, two weeks, or longer, intensive care, and death
• Adjustment for age, sex, chronic disease, ethnicity

https://doi.org/10.1101/2020.10.22.20217562
44 men and 64 women with up to two weeks of hospitalization
94 men and 68 women with longer hospitalization
36 men and 17 women admitted to the intensive care unit (ICU) or deceased
Lung

Perez et al., 2013
PFAS and immune dysfunction

• Lower *antibody response* to some vaccines in children and adults
• More frequent *fever* in children
• …and *hospitalization* for infection
• Likely increased *severity* of COVID-19
• Possible *autoimmunity/allergy*
• Other adverse outcomes possible
Challenges in identifying and preventing PFAS-associated adverse effects

• PFASs used for more than 70 years
• Almost no independent PFAS science before 2000
• Immunotoxicity internally known in 1978
• In humans, antibody response to vaccines
• Most focus on PFASs present in blood
• PFBA low in blood, accumulates in lungs
• Blood concentrations may not reflect retention
• PFBA used as precursor/substitute for legacy PFASs
• Prevention focus on PFASs as a group?
Drinking Water Health Advisory Levels

2009 (U.S.EPA):
Provisional level of 400 ppt for PFOA and 200 ppt for PFOS

2016 (U.S.EPA):
Guidance level of 70 ppt for total of PFOA and PFOS

2020: EFSA proposal for 4 PFASs
TWI (for PFOA+PFNA+PFHxS+PFOS) 8 ng/kg bw · wk
Corresponds to 2.2 ppt in water
STEPP SRP Center

**STEPP Mission**

Address the ubiquitous human health threat of PFASs through rigorous interdisciplinary science to redefine dose exposure benchmarks, develop novel detection techniques, and prepare communities to expect long-term solutions for contaminated sites.

**STEPP Vision**

To avert human and environmental health impacts of PFASs exposure and disseminate lessons learned to help avoid similar contamination problems in the future.