Reduced immune response to vaccinations in children with elevated exposure to perfluorinated compounds

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The Interplay Between Environmental Exposures and Infectious Agents:
Environmental Chemicals and Immune Response
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**Perfluorinated alkyl substances (PFAS) 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
Immunotoxicity

Reported in mice and Rhesus monkeys

Outcomes are fairly crude:
Decreased spleen and thymus weights, lowered total immunoglobulin, and decreased immunocyte cell counts

Decreased antibody responses shown in both mice and monkeys
Mediated through PPARα and non-PPARα dependent pathways

NTP on PFOS and PFOA: “presumed to be an immune hazard to humans... – high level of evidence... from animal studies... and moderate level of evidence from studies in humans”
PFOA: LOAEL higher than highest exposures

PFOS: LOAEL similar to human exposures

(DeWitt et al., 2012)
Human immunotoxicity: Advantages of vaccine responses in epidemiological studies:
• ‘Natural experiment’
• Same dose of antigen
• Same age at exposure
• Routine antibody assay
• Clinical relevance
The higher the **PCB** exposure, the less efficient the response to childhood immunization (here the diphtheria antibody response at 18 months).
Change in tetanus antibody concentration after booster

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
- *Wide range of exposures from traditional food (pilot whale)*
- Total population - 48,000
Antibody concentration responses to vaccinations

Vaccination

Blood sample

Months

Years

3 5 12

5 7
Serum Vaccine Antibody Concentrations in Children Exposed to Perfluorinated Compounds

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Context  Perfluorinated compounds (PFCs) have emerged as important food contaminants. They cause immune suppression in a rodent model at serum concentrations similar to those occurring in the US population, but adverse health effects of PFC exposure are poorly understood.

Objective  To determine whether PFC exposure is associated with antibody response to childhood vaccinations.

Design, Setting, and Participants  Prospective study of a birth cohort from the National Hospital in the Faroe Islands. A total of 656 consecutive singleton births were recruited during 1999-2001, and 587 participated in follow-up through 2008.

Main Outcome Measures  Serum antibody concentrations against tetanus and diphtheria toxoids at ages 5 and 7 years.

Results  Similar to results of prior studies in the United States, the PFCs with the highest serum concentrations were perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA). Among PFCs in maternal pregnancy serum, PFOS showed the strongest negative correlations with antibody concentrations at age 5 years, for which a 2-fold greater concentration of exposure was associated with a difference of −39% (95% CI, −55% to −17%) in the diphtheria antibody concentration. PFCs in the child’s serum at age 5 years showed uniformly negative associations with antibody levels, especially at age 7 years, except that the tetanus antibody level following PFOS exposure was not statistically significant. In a structural equation model, a 2-fold greater concentration of major PFCs in child serum was associated with a difference of −49% (95% CI, −67% to −23%) in the overall antibody concentration. A 2-fold increase in PFOS and PFOA concentrations at age 5 years was associated with odds ratios between 2.38 (95% CI, 0.89 to 6.35) and 4.20 (95% CI, 1.54 to 11.44) for falling below a clinically protective level of 0.1 IU/mL for tetanus and diphtheria antibodies at age 7 years.

Conclusion  Elevated exposures to PFCs were associated with reduced humoral immune response to routine childhood immunizations in children aged 5 and 7 years.

JAMA. 2012;307(4):391-397

www.jama.com
Generalized additive model with 95% confidence limits (lines at the bottom represent individual subjects in cohort)

Anti Tetanus (IU/ml) at 7 years

PFOA at age 5

Grandjean et al., 2012
Odds ratios (ORs) for doubling in child’s age-5 serum-PFAS as predictor of antibodies below 0.1 IU/mL at age 7 years (i.e., the vaccine did not protect against the disease)

<table>
<thead>
<tr>
<th></th>
<th>Tetanus (N=18)</th>
<th>Diphtheria (N=32)</th>
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<tbody>
<tr>
<td></td>
<td>PFOS</td>
<td>PFOA</td>
</tr>
<tr>
<td>OR</td>
<td>2.61</td>
<td>4.20</td>
</tr>
<tr>
<td>95%CI</td>
<td>0.77;</td>
<td>1.54;</td>
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<tr>
<td></td>
<td>8.92</td>
<td>11.44</td>
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<tr>
<td><em>p</em></td>
<td>0.12</td>
<td>0.006</td>
</tr>
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PFOA showed the strongest effect - ORs below 2.0 for other PFASs

Grandjean et al, 2012
Effect of a **doubled serum-PFOA** at ages 5 and 7 years on serum antibodies (%) at age 7 years

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<tr>
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<th>Tet</th>
<th>95% CI</th>
<th>Diph</th>
<th>95% CI</th>
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<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>Adjusted*</td>
<td>-29.6</td>
<td>-50.6; 0.4</td>
<td>-26.9</td>
<td>-47.4; 1.5</td>
</tr>
</tbody>
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*adjusted for other PFASs (almost unchanged)  
Mogensen et al., 2015
Serum concentrations of PFOA correlate with other PFASs, but not as closely as other major PFASs.
Maternal pregnancy serum
$r = 0.25$

Adjustment for PCB exposure barely affected the results

Grandjean et al., unpublished
Follow-up at age 13 years: Antibody concentrations are affected by (unscheduled) booster vaccinations

Grandjean et al., EHP (in press)
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%

N=431
(complete data only)

Environmental Health 2013, 12:35
Increased risk of infection?

• In the Odense Child Cohort (Denmark), 359 children aged 1-3 years were monitored for fever and symptoms every 2 weeks for 1 year (by text messages)
• Days with fever >38.5° (101.3°F), comparison of high and low tertiles of maternal pregnancy serum concentrations:
  – Odds of experiencing days with fever above median for PFOS OR: 2.35 (95%CI: 1.31, 4.11) and PFOA OR: 1.97 (95%CI: 1.07, 3.62)
• Higher exposures to PFOA and PFOS tended to increase the proportion of episodes with fever and nasal discharge: for medium tertile PFOA exposure as 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., Environment International, 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).
Conclusions

• PFASs are *immunotoxic at current exposures*
• Vaccine antibody concentrations are sensitive indicators of immunotoxicity
• Effects of individual PFASs may be difficult to separate in epidemiological studies
• Early development likely represents a highly vulnerable stage (with lactational transfer)
• Likely consequences for infectious disease – and perhaps other adverse health effects
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.