Immunotoxicological findings of PFAS:  
A focus on PFOA and PFOS

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Associations between adverse health outcomes and PFAS serum concentrations in adults and children.

PFAS-exposed experimental animal models also demonstrate multiple adverse health outcomes.
Impacts on the immune system have been documented in humans exposed to PFAS mixtures via drinking water and in animal models exposed to single PFAS.
Why should we care about immunotoxicity with respect to PFAS?
**Immune suppression:**
A reduced ability of the immune system to respond to a challenge from a level considered normal, regardless of whether clinical disease results (DeWitt et al., 2016).

**Immune stimulation:**
Inappropriate immune responses to common substances, i.e., allergic hypersensitivity, or responses to self-antigens, i.e., autoimmunity (DeWitt et al., 2016).
We can evaluate immune system responses in exposed humans, experimental animals, and cellular systems. **Primary outcomes** are those with greater predictive value for overall immunotoxicity or a health effect. **Secondary outcomes** are valuable but are more suggestive than definitive.

<table>
<thead>
<tr>
<th>Table 5. Health Outcome Grouping and Identification of Primary and Secondary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Humans</strong></td>
</tr>
<tr>
<td><strong>Primary Outcomes</strong></td>
</tr>
<tr>
<td>Immune-related diseases and measures of immune function:</td>
</tr>
<tr>
<td>(1) <strong>Immunosuppression</strong> (e.g., otitis, infections, or decreased vaccine antibody response);</td>
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<tr>
<td>(2) <strong>Hypersensitivity-related outcomes</strong> (e.g., atopic dermatitis asthma, total IgE, rhinitis);</td>
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<tr>
<td>(3) <strong>Autoimmunity</strong> (e.g., thyroiditis or ulcerative colitis)</td>
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<tr>
<td><strong>Secondary</strong></td>
</tr>
<tr>
<td><strong>Observational immune endpoints</strong> (e.g., lymphocyte counts, proliferation, cytokine levels, or serum antibody levels)</td>
</tr>
</tbody>
</table>

Table from: NTP, 2016.
What do we know about immunotoxicity of PFOA and PFOS?
PFOA and PFOS can induce suppression of T cell-dependent antibody responses (like a vaccine response) in rodents.

Oral PFOS exposure in male C57BL/6 mice (60d of exposure).

Oral PFOA exposure in female C57BL/6 mice (15d of exposure).

Elevated exposure to PFOA or PFOS was associated with reduced vaccine responses in children and in adults.

The US National Toxicology Program determined that PFOA was presumed to be an immune hazard in humans based, in part, on a high level of evidence that PFOA suppresses the antibody response from animal studies and a moderate level of evidence from studies in humans (US NTP, 2016).

The totality of evidence from human and animal studies, not any one study, allowed the NTP to reach this conclusion.

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### Table 8. Evidence Profile of the Main Findings for PFOS Immunotoxicity

<table>
<thead>
<tr>
<th>INITIAL CONFIDENCE</th>
<th>Risk of Bias</th>
<th>Unexplained Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication Bias</th>
<th>Large Magnitude</th>
<th>Dose Response</th>
<th>Residual Confounding</th>
<th>Consistency Across Human Bodies of Evidence</th>
<th>FINAL CONFIDENCE RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No change for considering across study designs</td>
<td>Moderate</td>
</tr>
<tr>
<td>Initial Moderate</td>
<td>---</td>
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<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
| (4 prospective studies)
| Initial Low        | ---          | ---                        | ---          | ---         | ---             | ---            | ---           | ---                  | ---                        | Low                   |
| (2 cross-sectional studies)
| Confidence Across Human Bodies of Evidence | --- | --- | --- | --- | --- | --- | --- | --- | --- | Moderate |
| Animal             |              |                            |              |             |                 |                |               |                      |                           | High                  |
| Initial High       |              |                            |              |             |                 | ---            | ---           | ---                  | ---                        | High                  |
| (8 mammal studies) | ---          | ---                        | ---          | ---         | ---             | ---            | ---           | ---                  | ---                        | High                  |

References:


PFOA and PFOS are presumed to be immune hazards to humans.

*PFOA suppresses the TDAR* in experimental models (high level of evidence) and humans (moderate level of evidence).

*PFOS suppresses the TDAR* in experimental models (high level of evidence) and humans (moderate level of evidence).

Other immune effects supporting this weight-of-evidence classification:

- Increased hypersensitivity-related outcomes.
- Suppression of innate immune responses (i.e., NK cell function).
- Alterations in disease resistance/infectious disease outcomes.
- Findings of autoimmunity.
A presumed hazard for PFOA and PFOS

Immune suppression

Animal

Immune stimulation

Human

Human equivalent dose (HED) for PFOA-induced immune suppression in mice calculated as 0.0053 mg/kg/day*.

Same HED for developmental toxicity (critical effect) used to calculate the reference dose for PFOA*.

The immune system also is an endpoint sensitive to PFAS.

*US EPA, 2016
Some evidence that GenX, PFHxS, PFDA, PFOA, PFNA, PFUA, PFDoA, PBFuS, PFBS, PFHxA can affect immune endpoints in experimental models and/or exposed humans.

While much of this evidence is observational (secondary outcomes) and not functional (primary outcomes), functional effects can occur at doses below those that affect observational endpoints.

We had evidence of observational immune effects of PFOA and PFOS from late 70s and early 80s. Functional immune endpoints weren’t published until early 2000s.

NC has already acknowledged that evaluation of immune responses is an important step toward public health protection with respect to newly identified PFAS in the Cape Fear River.
Eight states (as of 2016) have drinking water guidelines for PFOA and PFOS that are lower than the US EPA health advisory of 70 ng/L (5.1-35 ng/L for PFOA and 6.5-20 ng/L for PFOS).

<table>
<thead>
<tr>
<th>Agency</th>
<th>PFOA</th>
<th>PFOS</th>
<th>Basis of RfD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>US EPA RfD (2016)</strong></td>
<td>20</td>
<td>20</td>
<td>----</td>
</tr>
<tr>
<td><strong>State RfDs (2016-2019)</strong></td>
<td>2 – 6.1 (6 states)</td>
<td>1.8 – 5 (7 states)</td>
<td>These states consider more sensitive toxicity endpoints as Critical Effect and/or with Database Uncertainty Factor.</td>
</tr>
<tr>
<td>US EPA (2 states)</td>
<td></td>
<td></td>
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<tr>
<td>US EPA (1 state)</td>
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<tr>
<td><strong>ATSDR Minimal Risk Levels (draft, 2018)</strong></td>
<td>3</td>
<td>2</td>
<td>ATSDR MRLs are for intermediate exposures.</td>
</tr>
<tr>
<td><strong>States with RfDs (PFOA and/or PFOS) below US EPA: CA, MA, MI, MN, NH, NJ, NY</strong></td>
<td></td>
<td></td>
<td>Endpoints: increased liver weight, developmental effects (range), decreased antibody response</td>
</tr>
</tbody>
</table>

Data from: SETAC North America Focused Topic Meeting: Environmental Risk Assessment of PFAS. 2019. Modified from presentation of Dr. Gloria Post, NJ DEP.
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Global PFAS Science Panel
(image courtesy of Zhanyun Wang, ETH)