Human Epidemiologic Studies of Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS)

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Primary Health Outcomes

- Immunologic
- Thyroid
- Liver
- Cancer (kidney, liver, testicular, prostate)
- Lipids
- Reproductive
- Other
Literature search

Most recent NTP (2016), US EPA (2016), and ATSDR (2018) reviews

Updated with:

• PubMed
• Google Scholar
• Published review articles
• Bibliographies of all included articles
• Other
From NTP’s 2016 review of PFOS/PFOA and Immunotoxicity

Search string: example
Inclusion-exclusion criteria

**Inclusion**
- Human epidemiologic studies
- PFOA or PFOS
- Exposure: water, blood or urine
- Outcomes expressed as relative risk, mean differences, correlations, regressions, other
- Cohort, case-control, cross-sectional, and ecologic designs

**Exclusion**
- Case-reports
- No comparison group
- Abstracts and studies without original data (e.g. reviews or editorials)
- Results only for multiple perfluoroalkylate substances (PFAS) combined
Evaluating study quality

**Selection:** Were all eligible people, or a random selection of all eligible people, invited to participate?

**Participation:** Of those who were invited to participate, what was the percentage of people who actually agreed to participate and for whom there were sufficient data to be included in the final study analyses?

**Equal groups:** Were there any major socioeconomic or other relevant differences between people with higher or lower PFOA or PFOS levels or between people with or without the outcome of interest?

**Blinding:** Were the researchers measuring the exposure blinded to the outcome status of the participants?

**Exposure levels:** What was the distribution of PFOA or PFOS levels among the study participants? Were exposure levels too low to identify true associations?

**Exposure and outcome methods:** Were validated, generally accepted, or otherwise reasonable methods for assessing exposure and outcome used?

**Confounding:** Is the factor associated with both exposure and outcome, strength of these associations, prevalence of the risk factor?
### Kidney cancer
- Older age
- Gender (males)
- Race (African Americans and American Indians/Alaska Natives)
- Smoking
- Obesity
- Hypertension
- Dialysis
- Occupational exposures: cadmium, pesticides, TCE
- Medications: phenacetin, diuretics
- Exercise and diet (low fruit and vegetable intake, acrylamide, lower alcohol)

### Testicular cancer
- Age
- Race/ethnicity (Caucasian)
- Undescended testicle
- Family history
- HIV infection
- Carcinoma in situ
- Occupations: firefighting and aircraft maintenance
- Organochloride pesticides

### Prostate cancer
- Age
- Race/ethnicity (African American)
- Family history
- Hereditary
- Agent Orange
- Possibly diet
- Geography: North America, northwestern Europe, Australia, and Caribbean islands
- PSA testing

### References:


- Centers for Disease Control and Prevention, [https://www.cdc.gov/cancer/prostate/basic_info/risk_factors.htm](https://www.cdc.gov/cancer/prostate/basic_info/risk_factors.htm)
Other aspects of causal inference

*Modified version of the Bradford Hill criteria*

- Precision (e.g. statistical significance)
- Magnitude of the association
- Dose-response
- Temporality
- Consistency
- Subgroups and susceptibility
- Plausibility
Example of the format used to describe each study

<table>
<thead>
<tr>
<th>Study details</th>
<th>Factors related to bias</th>
<th>Exposure method</th>
<th>Outcome method</th>
<th>Results</th>
<th>Comparison group</th>
<th>Confounding aspects of causal inference</th>
<th>Other aspects of causal inference</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grandjean et al., 2017a</td>
<td>Selection: unclear</td>
<td>Serum near birth, 18 months, age 5</td>
<td>Antibody response: diphtheria Serum IgG age 5</td>
<td>2007-09 cohort: PFOA IgG %change Birth: -18.9 (p=0.03) 18 mo.: 4.1 (p=0.63) 5 yr.: 18.3 (p=0.24)</td>
<td>Percent change for a 2-fold increase in PFAS concentration</td>
<td>Age, sex, PCB concentrations and Cesarean section</td>
<td>Magnitude (O R&gt;1.2): yes</td>
<td>PFAS concentrations highly correlated with breastfeeding duration</td>
</tr>
<tr>
<td>Faroe Islands 2007-09</td>
<td>Participation: unclear</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Statistical significance: yes</td>
<td>Correlation coefficients up to 0.7 for PFAS levels at age 18 months and age 5 years</td>
</tr>
<tr>
<td>Prospective cohort and cross-sectional</td>
<td>Equal groups: unclear</td>
<td></td>
<td></td>
<td>Combined cohort: PFOA IgG %change Birth: -17.8 (p=0.009) 18 mo.: 5.4 (p=0.52) 5 yr.: 3.4 (p=0.73)</td>
<td>No major differences between 1997-2000 and 2007-09 cohorts</td>
<td></td>
<td></td>
<td>Dose-response: linear</td>
</tr>
<tr>
<td>Children ages 5 and under</td>
<td>Blinded: unclear</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Temporal association: yes</td>
<td>44 and 36% had IgG below protective levels for diphtheria and tetanus at age 5, respectively</td>
</tr>
<tr>
<td>N=275-349</td>
<td>Above detection: unclear</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Subgroup only: no</td>
<td></td>
</tr>
<tr>
<td>PFOA</td>
<td>Exposure levels: median (IQR) = 2.8 (2.0-4.5) ng/ml at age 18 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adjustments: unclear</td>
<td></td>
</tr>
</tbody>
</table>
Epidemiologic studies of PFOA and vaccine response: summary

<table>
<thead>
<tr>
<th>Age</th>
<th>Diphtheria Ig age</th>
<th>Tetanus Ig age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 years pre</td>
<td>5 years post</td>
</tr>
<tr>
<td></td>
<td>7 years</td>
<td>13 years</td>
</tr>
<tr>
<td>Birth</td>
<td>-16.2</td>
<td>-22.8</td>
</tr>
<tr>
<td></td>
<td>-18.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-6.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-22.8</td>
<td></td>
</tr>
<tr>
<td>1.5 years</td>
<td>4.2&lt;sup&gt;*&lt;/sup&gt;</td>
<td>-16.3</td>
</tr>
<tr>
<td>5 years</td>
<td>-6.8</td>
<td>-13.3&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>18.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-6.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-25.2</td>
<td>-35.8</td>
</tr>
<tr>
<td>7 years</td>
<td></td>
<td>-20.5</td>
</tr>
<tr>
<td></td>
<td>-25.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-9.2&lt;sup&gt;*&lt;/sup&gt;</td>
<td>2.9&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>13 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-25.3&lt;sup&gt;*&lt;/sup&gt;</td>
<td>-5.6&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Adult</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-8.2&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.23&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Results codes:**
- Negative numbers = PFOA associated with decreased vaccine response
- All results are from the 1997-2000 Faroe Islands cohort except:
  -<sup>a</sup> 2007-09 Faroe Islands cohort
  -<sup>b</sup> Kielsen et al., 2016
- Bolded: statistically significant
- Light orange: cross-sectional analyses (all others are prospective)
Epidemiologic studies of PFOS and vaccine response: summary

<table>
<thead>
<tr>
<th>PFOS Age</th>
<th>Diphtheria Ig age</th>
<th>Tetanus Ig age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 years pre</td>
<td>5 years post</td>
</tr>
<tr>
<td>0</td>
<td>-38.6 -14.0a</td>
<td>-20.6 -10.0</td>
</tr>
<tr>
<td>1.5 years</td>
<td>17.5</td>
<td></td>
</tr>
<tr>
<td>5 years</td>
<td>-16.0 -17.1a</td>
<td>-15.5 -27.6</td>
</tr>
<tr>
<td>7 years</td>
<td>-30.3 -25.6</td>
<td></td>
</tr>
<tr>
<td>13 years</td>
<td>-10.5</td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>-11.9b</td>
<td></td>
</tr>
</tbody>
</table>
Thyroid hormone levels

33 human studies
16 new studies since the 2016 US EPA review
54 different results categorized by age (infants, children, adults), gender, and pregnancy status
Outcomes: serum total T4, free T4, TSH
Overall: mixed results

Thyroid diseases Fewer studies
Some suggestive evidence (e.g. hypothyroidism, “all thyroid diseases”)
Limited by small sample sizes, potential confounding, lack of replication by outcome...

Still updating literature searches and detailed evaluations of study quality
Example: Epidemiologic studies of PFOS/PFOA and thyroid hormones in pregnant women

<table>
<thead>
<tr>
<th>Study</th>
<th>Source</th>
<th>Location</th>
<th>Design</th>
<th>N</th>
<th>Exp</th>
<th>Group</th>
<th>Sex</th>
<th>PFAS</th>
<th>TH</th>
<th>PFOS</th>
<th>Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang et al., 2013</td>
<td>USEPA</td>
<td>Norway</td>
<td>CS</td>
<td>903</td>
<td>Low</td>
<td>Pregnant</td>
<td>Female</td>
<td>Preg</td>
<td>Preg</td>
<td>↓</td>
<td>↑↑ 0 0 ↑↑ 0 0</td>
</tr>
<tr>
<td>Wang et al., 2014</td>
<td>USEPA</td>
<td>Taiwan</td>
<td>CS</td>
<td>283</td>
<td>Low</td>
<td>Pregnant</td>
<td>Female</td>
<td>Preg</td>
<td>Preg</td>
<td>↑↑</td>
<td>↑↑ ↓ ↓ ↑ ↑ ↑</td>
</tr>
<tr>
<td>Webster et al., 2014</td>
<td>USEPA</td>
<td>Vancouver</td>
<td>CS</td>
<td>151</td>
<td>Low</td>
<td>Pregnant</td>
<td>Female</td>
<td>Preg</td>
<td>Preg</td>
<td>↑↑</td>
<td>↑↑ ↓ ↓ ↑ ↑ ↑</td>
</tr>
<tr>
<td>Berg et al., 2015</td>
<td>USEPA</td>
<td>Norway</td>
<td>CS</td>
<td>375</td>
<td>Low</td>
<td>Pregnant</td>
<td>Female</td>
<td>Preg</td>
<td>Preg</td>
<td>↑↑</td>
<td>↑↑ 0 0 ↑↑ 0 0</td>
</tr>
<tr>
<td>Kato et al., 2016</td>
<td>New</td>
<td>Japan</td>
<td>CS</td>
<td>392</td>
<td>Low</td>
<td>Pregnant</td>
<td>Female</td>
<td>Preg</td>
<td>Preg</td>
<td>↑↑</td>
<td>↑↑ ↓ ↓ 0 ↑</td>
</tr>
<tr>
<td>Yang et al., 2016</td>
<td>New</td>
<td>China</td>
<td>CS</td>
<td>157</td>
<td>Low</td>
<td>Pregnant</td>
<td>Female</td>
<td>Preg</td>
<td>Preg</td>
<td>↓</td>
<td>↑   ↑ ↑ ↑↓ ↑↓ ↑</td>
</tr>
<tr>
<td>Preston et al., 2018</td>
<td>New</td>
<td>Boston</td>
<td>CS</td>
<td>718</td>
<td>Low</td>
<td>Pregnant</td>
<td>Female</td>
<td>Preg</td>
<td>Preg</td>
<td>↑↑</td>
<td>↑↑ ↓ ↓ ↓↑ ↑↑ ↑</td>
</tr>
</tbody>
</table>

Results coding:

- ↑↑, statistically significant positive association
- ↓↓, statistically significant inverse association
- Single arrow, not statistically significant
- 0, data not provided; ↑↓, no association
## Study of PFOA and kidney and testicular cancer by Vieira et al 2013

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Kidney cancer</th>
<th>Testicular cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Category</td>
<td>N</td>
</tr>
<tr>
<td>Reference</td>
<td>&lt;3.7 ug/L</td>
<td>187</td>
</tr>
<tr>
<td>Low</td>
<td>3.7-12.8</td>
<td>11</td>
</tr>
<tr>
<td>Medium</td>
<td>12.9-30.7</td>
<td>17</td>
</tr>
<tr>
<td>High</td>
<td>30.8-109</td>
<td>22</td>
</tr>
<tr>
<td>Very high</td>
<td>110-655</td>
<td>9</td>
</tr>
</tbody>
</table>

### Study details

- **Study area:** 13 counties in Ohio and West Virginia, near a Teflon manufacturing plant
- **Incident cancers diagnosed from 1996 to 2005 from the state cancer registries**
- **Exposure based on residential address at diagnosis and modeled serum levels for 1995 (C8 Health Project)**
- **Controls are cancers other than kidney, pancreas, prostate, and liver**
- **Adjusted for age, sex, diagnosis year, smoking, insurance type (e.g. Medicaid)**
Human epidemiologic evidence

Next Steps:
✓ Updated literature searches
✓ Detailed evaluations of bias and confounding
✓ Other health effects