Perfluoroalkyl substances (PFASs) and immunosuppressive effects – Implication on infectious diseases and vaccination responses

Berit Granum
Dept. of Toxicology and Risk Assessment, Norwegian Institute of Public Health

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Disclosure

I declare no conflict of interest
Background

Immunotoxicity – Outcomes

Chemical

Hyper-sensitivity

Rhinitis
Food allergy
Allergic asthma

Auto-immunity

Diabetes type 1
Systemic Lupus Erythematosus (SLE)

Immunostimulation

Inflammation
Exaggerated activation of normal reactions

Immunosuppression

Infections
Cancer
Reduced vaccination responses

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Immune system development

- Extensive development in the fetal period and the first months of life
- Continued immune maturation throughout childhood

Normal maturation dependent upon specific processes

- At different time points
- In different body compartments

Early-life immune system a moving toxicological target for interactions with chemicals
Background

Perfluoroalkyl substances (PFASs)

- Consist of a fully fluorinated carbon chain and different functional groups
  
  - PFOS: perfluorooctane sulfonic acid
  - PFOA: perfluorooctanoic acid

- Widely used
  - E.g. water and oil repellents properties

- Important exposure sources
  
  - Diet
    (fish and other seafood, meat and meat products, eggs and egg products, milk and dairy products and drinking water)
  - Indoor air and house dust
  - Industrial pollution

- Long half-life in humans (3-7 years)

- Do not undergo metabolism

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Regulation – European Union

Regulation of PFOS and PFOA in the European Union

- **PFOS**
  - Prohibited since 2008 and some substances that may be transformed to PFOS

- **PFOA**
  - Prohibited from July 2020
Objective

To undertake a systematic review to develop NTP hazard identification conclusions on the association between exposure to PFOA or PFOS and immunotoxicity based on integrating levels of evidence from human and non-human animal studies with consideration of the degree of support from mechanistic studies.

Published September 2016

Literature searches

- October 2014 and 2015
- May 2016
# Conclusions on immunosuppression

<table>
<thead>
<tr>
<th>Substance</th>
<th>Effects on Humans</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFOS</strong></td>
<td>Reduced vaccination levels</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Suppressed antibody responses in animals</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Some evidence for a reduced ability to respond to infectious diseases</td>
<td></td>
</tr>
<tr>
<td><strong>PFOA</strong></td>
<td>Reduced vaccination levels</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Suppressed antibody responses in animals</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Increased risk of infections in humans</td>
<td>Weaker</td>
</tr>
</tbody>
</table>

Conclusion based on both immunosuppression and hypersensitivity: PFOS and PFOA are presumed to be immune hazards in humans.
## Human studies on prenatal exposure and immunosuppression

### Vaccination responses
- Inverse associations
  - Diphtheria titers (Grandjean et al., 2012)
  - Rubella titers (Granum et al., 2013)

### Infectious diseases
- No associations
  - Hospitalization (Fei et al., 2010)
  - Otitis media (Okada et al., 2012)
- Positive associations
  - Airways infections (Granum et al., 2013)
  - Gastric flu (Granum et al., 2013)
Human studies on prenatal exposure and immunosuppression + new studies

**Vaccination responses**

- **Inverse associations**
  - Diphtheria titers (Grandjean et al., 2012)
  - Rubella titers (Granum et al., 2013)

**Infectious diseases**

- **No associations**
  - Hospitalization (Fei et al., 2010)
  - Otitis media (Okada et al., 2012)
  - Common cold, flu (C8 Project Panel Study, 2012, report only)

- **Positive associations**
  - Airways infections (Granum et al., 2013; Impinen et al., 2018; Impinen et al. in press)
  - Gastric flu (Granum et al., 2013)
  - Fever (Dalsager et al., 2016)
  - Infectious disease occurrence (Goudarzi et al., 2017)

New studies give more evidence for increased risk of infections in humans

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Immunosuppression

Gender differences in exposure-health associations?

- **Goudarzi et al. 2017**
  - PFOS and PFHxS positively associated with total infectious disease, particularly among girls

- **Impinen et al. 2019 in press**
  - Gender differences seen for several PFASs and infectious diseases
  - Significant associations mainly found in girls

Closed circles: girls
Open circles: boy

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Mode of action

Immunotoxicity – Mode of action

- PFOS and PFOA affect immune cells possibly by modulation of gene regulation via PPARs, NF-κB transcription and regulation of apoptosis
  - Both different and shared mechanisms
- Studies on mechanisms are mainly based on animal studies
- Similar findings in humans (Pennings et al. 2016)
  - Indication of a role PPAR-δ
  - Indication of NF-κB activation
  - Induction of several cytokines and immunological adhesion molecules, both at the single gene level and at pathway level

Maternal PFAS levels → Cord blood gene expression → At 3 years: Rubella titers Common cold

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EFSA report December 2018

Risk to human health related to the presence of PFOS and PFOA in food

- Part 1: Risk assessment from the European Food Safety Authority (EFSA) on PFOS and PFOA
  - Derivation of a health-based guidance value based on human epidemiological studies

PFOS
  - Adults: Increase in serum total cholesterol
  - Children: Decrease in antibody response to childhood vaccinations
  - Temporary tolerable intake (TWI): 13 ng/kg bw per week
  - Previous tolerable intake (EFSA 2008): 1 050 ng/kg bw per week (80 times higher)

PFOA
  - Increase in serum total cholesterol
  - Temporary tolerable intake (TWI): 6 ng/kg bw per week
  - Previous tolerable intake (EFSA 2008): 10 050 ng/kg bw per week (1750 times higher)

- A considerable proportion of the population has higher exposure than the TWIs
- Part 2: Ongoing risk assessments of other PFASs

doi: 10.2903/j.efsa.2018.5194
ATSDR report June 2018

Toxicological profile for perfluoroalkyls (Draft for public comment)

- Risk assessment from the Agency of Toxic Substances and Disease Registry (ATSDR)
- Derivation of a health-based guidance value based on animal studies
- Provisional Minimal Risk Levels (MRLs)
  - PFOS: 2 ng/kg bw per day (Delayed eye opening and decreased pup weight, rats)
  - PFOA: 3 ng/kg bw per day (Neurodevelopmental and skeletal effects, mice)
  - PFHxS: 20 ng/kg bw per day (Thyroid follicular cell damage, rats)
  - PFNA: 3 ng/kg bw per day (Decreased body weight and development delays, mice)
- EFSA vs ATSDR
  - PFOS: 13 vs 14 ng/kg bw per week
  - PFOA: 6 vs 21 ng/kg bw per week

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Conclusion

Conclusion - PFASs and immunosuppression

- Increasing evidence for immunosuppressive effects of prenatal exposure to PFASs
- Good accordance between human and animal studies
  - E.g. similar intake values estimated in the EFSA and ATSDR reports
- The Immune system is a sensitive target
  - Lack of validated test guidelines
  - Organ weights included in repeated dose toxicity testing – Insensitive markers of immunotoxicity
  - A need for test guidelines that include functional immune testing
- More focus on adverse immune effects after exposure to environmental chemicals is necessary

Thank you for your attention