NTP Monograph on Immunotoxicity Associated with Exposure to PFOA or PFOS

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NTP Board of Scientific Counselors Meeting
December 15, 2016
Exposure and Immune Effects

- **Perfluoroalkyl acids including PFOA and PFOS**
  - Used extensively in commercial/industrial applications last 50 years
    - food packaging
    - lubricants
    - water-resistant coatings
    - fire-retarding foams

- **PFOA and PFOS**
  - US production eliminated; use and emissions reduced in US and much of Europe through voluntary agreements
  - Not metabolized or expected to degrade in environment

- **Reported immune effects of both PFOA and PFOS**
  - Effects on antibody response in animals at some of lowest doses
  - Recent studies reporting similar antibody effects in humans
  - PFOA and PFOS appeared to share some effects and differ for others
NTP Conducted A Systematic Review

• First OHAT evaluation to use OHAT Approach for Systematic Review and Evidence Integration to reach hazard conclusions

• Objectives

  – To develop NTP hazard identification conclusions on the association between exposure to PFOA or PFOS (or their salts) and immunotoxicity

  – Conclusions for each chemical were reached by integrating evidence from human and animal studies with consideration of the degree of support from mechanistic data
Peer Review Panel Meeting

• July 19, 2016 at NIEHS in Research Triangle Park, NC

• Chair
  – Weihsueh Chiu, PhD – Texas A&M University

• Panel
  – Joseph Braun, PhD – Brown University
  – Emanuela Corsini, PhD – Univeristita degli Sudi di Milano
  – Berit Granum, PhD – Norwegian Institute of Public Health
  – Deborah Keil, PhD, DABT – Montana State University
  – Michael Woolhisser, PhD – The Dow Chemical Company

• BSC Liaison
  – Paul Brandt-Rauf, DrPH, MD, ScD – University of Illinois at Chicago
• To determine whether the scientific information cited in the draft monograph is technically correct and clearly stated, and whether NTP has objectively presented and assessed the scientific evidence.

• To determine whether the scientific evidence presented in the draft NTP monograph supports the NTP’s conclusions regarding whether immunotoxicity is associated with exposure to PFOA or PFOS.
Conclusions Based on Bodies of Evidence

Results Grouped by Same or Related Outcomes

- **Primary outcomes:** Direct health outcomes or endpoints
  - **Example:** Immunosuppression - reduced antibody response

Measures of the Outcome of Interest

**Experimental Animal Data**
- Antibodies to SRBC
- anti-SRBC IgM
- anti-SRBC IgG

**Human Data**
- Antibodies to vaccines
- anti-tetanus IgM
- anti-rubella IgM

**In vitro and Mechanistic Data**
- In vitro antibodies
- Antibody-related mechanistic data
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Draft Conclusions on PFOA Immunotoxicity

- NTP conclusions are based on the highest level-of-evidence conclusions for immune effects on an outcome basis

- PFOA is **presumed to be an immune** hazard to humans based on two separate lines of evidence:
  - (1) PFOA suppressed the antibody response
    - Animal studies: High level of evidence
    - Human studies: Moderate level of evidence
    - No change in conclusions after considering mechanistic data
  - (2) PFOA increased hypersensitivity-related outcomes
    - Animal studies: High level of evidence
    - Human studies: Low level of evidence
    - No change in conclusions after considering mechanistic data
NTP conclusions are based on the highest level-of-evidence conclusions for immune effects on an outcome basis.

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   - Human studies: Moderate level of evidence
   - No change in conclusions after considering mechanistic data

2. PFOA increased hypersensitivity-related outcomes
   - Animal studies: High level of evidence
   - Human studies: Low level of evidence
   - No change in conclusions after considering mechanistic data

The Panel accepted the level of evidence ratings for the antibody response data as written.
NTP conclusions are based on the highest level-of-evidence conclusions for immune effects on an outcome basis.

PFOA is presumed to be an immune hazard to humans based on two separate lines of evidence:

1. PFOA suppressed the antibody response
   - Animal studies: High level of evidence
   - Human studies: Moderate level of evidence
   - No change in conclusions after considering mechanistic data

2. PFOA increased hypersensitivity-related outcomes
   - Animal studies: High-Moderate level of evidence
   - Human studies: Low level of evidence
   - No change in conclusions after considering mechanistic data

The Panel concluded the level of evidence for the animal hypersensitivity-related data was Moderate:
   - Limited number of studies
   - Divergent response to PFOA
Draft Conclusions on PFOA Immunotoxicity

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  - (1) PFOA suppressed the antibody response
    - Animal studies: High level of evidence
    - Human studies: Moderate level of evidence
    - No change in conclusions after considering mechanistic data

  - (2) PFOA increased hypersensitivity-related outcomes
    - Animal studies: High level of evidence
    - Human studies: Low level of evidence
    - No change in conclusions after considering mechanistic data

  *... after downgrading the hypersensitivity data*

The Panel accepted the hazard conclusion for PFOA based on the antibody response data
• Similar evidence base for PFOS with the highest level-of-evidence conclusions for immune effects based on only the antibody response

• PFOS is presumed to be an immune hazard to humans based on:
  
  – PFOS suppressed the antibody response
    • Animal studies: High level of evidence
    • Human studies: Moderate level of evidence
    • No change in conclusions after considering mechanistic data

The Panel accepted the hazard conclusion for PFOS based on the antibody response data
Following the Peer-Review Meeting
- Comments from the public and Peer-Review Panel were considered
- **NTP Monograph** finalized (http://ntp.niehs.nih.gov/go/749926)
- Studies, data, risk of bias, figures available (https://hawcproject.org/assessment/57)

Conclusion - PFOA and PFOS are both *presumed to be an immune hazard to humans*
- Based on bodies of evidence that both chemicals suppressed the antibody response
  - High level of evidence from animal studies
  - Moderate level of evidence from human studies
Thank you