NTP Monograph on Immunotoxicity Associated with Exposure to PFOA or PFOS

Andrew Rooney, PhD
Office of Health Assessment and Translation

NTP Board of Scientific Counselors Meeting
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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.
**Primary outcomes:** Direct health outcomes or endpoints
- **Example:** Immunosuppression - reduced antibody response

- **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
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
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.

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

The Panel accepted the level of evidence ratings for the antibody response data as written.
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-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
• 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

  *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
Final Conclusions on PFOA and PFOS

• 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