NTP
National Toxicology Program

NTP Evaluation Concept

Immunotoxicity Associated with Exposure to PFOA or PFOS

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Outline

- Background and Rationale
- Issues and Key Scientific Questions
- Specific Aims
- Proposed Approach
- Significance
- Questions

Background

Exposure

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

- **PFOA and PFOS**
  - Extremely persistent and widely distributed in the environment
  - No longer manufactured in United States (voluntary agreements)
    - 3M phased out production of PFOS in 2002
    - 8 companies in EPA's PFOA stewardship program
      - will reduce global emission of PFOA and chemicals that breakdown to PFOA
      - will eliminate emissions / product content of PFOA by 2015

Exposure

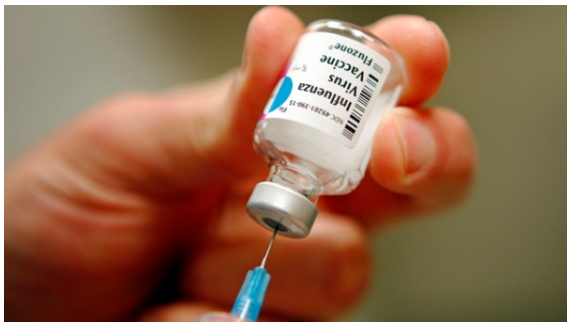
- **PFOA and PFOS are the most commonly detected perfluoroalkyl acids in environment and serum**

Geometric mean of serum concentrations (in µg/L) for US population

Survey years	PFOA	PFOS
1999-2000	**5.21** (4.72-5.74)	**30.4** (27.1-33.9)
2003-2004	**3.95** (3.65-4.27)	**20.7** (19.2-22.3)
2005-2006	**3.92** (3.48-4.42)	**17.1** (16.0-18.2)
2007-2008	**4.12** (4.01-4.24)	**13.2** (12.2-14.2)
2009-2010	**3.07** (2.81-3.36)	**9.32** (8.13-10.7)

National Health and Nutrition Examination Survey data (CDC, 2014)

PFOA and PFOS Immune Effects



- **Studies in humans**
  - Recent (2012-14) reports of PFOA- and PFOS-associated functional immune changes
    - Immune effects in adults in OH and WV
      PFOA contaminated public drinking water
      - Suppressed antibody response to vaccination in adults (Looker, 2014)
      - Increased incidence of ulcerative colitis (autoimmune link) (Steenland, 2013)
    - Immune effects in children in Norway and Faroe Islands (prospective)
      General population level exposure to PFOA and PFOS
      - Suppressed antibody response to vaccination (Granum, 2013;Grandjean, 2012)
- **Studies in animals**
  - Experimental studies
    - Both innate and adaptive immunity including suppression of the antibody response
    - Altered hypersensitivity, inflammatory response and cytokine signaling
  - Wildlife studies
- **Mechanistic studies**

Context

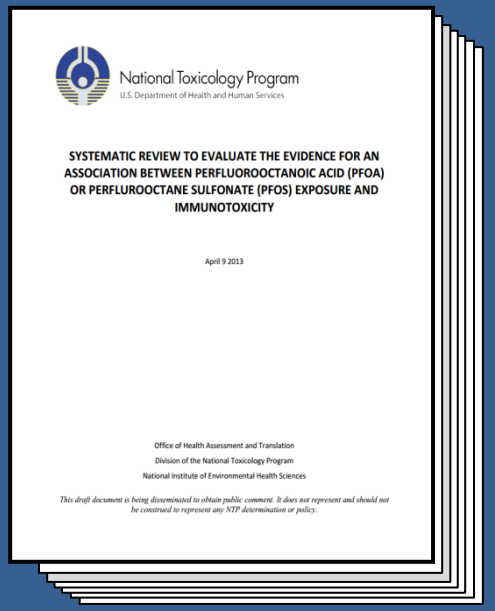
- **PFCs as a class are under toxicological testing at NTP**
  - Immunotoxicity testing for PFOA or PFOS are not currently included because there are sufficient published studies of immunity

- **Federal government assessments of PFOA and PFOS**
  - ATSDR
    - Currently revising the 2009 Draft Toxicological Profile
  - EPA
    - Office of Pollution Prevention and Toxics (OPPTS)
      - 2005 draft health assessment;
      - Ongoing evaluation focused on carcinogenicity
    - Office of Water
      - Currently revising 2014 draft health effects document

Background and Rationale

- **NTP developed case studies to test the OHAT framework for systematic review and evidence integration**
  - Case studies explored the methods for the systematic review
  - Hazard conclusions were not considered
  - Review protocols developed as examples
  - Only subsets of studies were used to test the methods
- **Nominations**
  - Multiple requests to develop hazard identification conclusions for PFOA- and PFOS-associated immunotoxicity

PFOA/PFOS Immunotoxicity


National Toxicology Program
U.S. Department of Health and Human Services

SYSTEMATIC REVIEW TO EVALUATE THE EVIDENCE FOR AN ASSOCIATION BETWEEN PERFLUOROOCTANOIC ACID (PFOA) OR PERFLUROOCTANE SULFONATE (PFOS) EXPOSURE AND IMMUNOTOXICITY

April 9 2013

Office of Health Assessment and Translation
Division of the National Toxicology Program
National Institute of Environmental Health Sciences

This draft document is being disseminated to obtain public comment. It does not represent and should not be construed to represent any NTP determination or policy.

- **Exposure**
- **Human and animal data**
- **Detailed protocol**
- **Do we complete evaluation?**

Issues and Key Scientific Questions

1) **Developing conclusions across the two chemicals**

Proposed Approach:

- Conclusions will be developed for PFOA and PFOS separately
- Ability to make cross-chemical conclusions will then be considered

2) **Relevance of peroxisome proliferator-activated receptor alpha (PPARα) as a mechanism for immune effects given species differences between animal models and humans**

Proposed Approach:

- Immune studies in non-human mammals will be considered directly relevant for human health unless compelling evidence to the contrary is identified during the evaluation
- Immune effects appear partially or wholly independent of PPARα
  - PFOA /PFOS suppression of antibody response in mice (Dewitt, 2012)

Issues and Key Scientific Questions

3) Importance of pronounced differences in elimination rates for PFOA and PFOS between experimental animals and humans

Proposed Approach:

- Known, species, gender, and age differences in elimination will be considered in evaluating the consistency of results reported for a given health effect

- Pharmacokinetic adjustment would be required to evaluate across species consistency

- PFOA and PFOS elimination rates
  - Long half-life in humans (2-8 years)
  - Short half-life in monkeys (weeks to months) & rodents (hours to days)

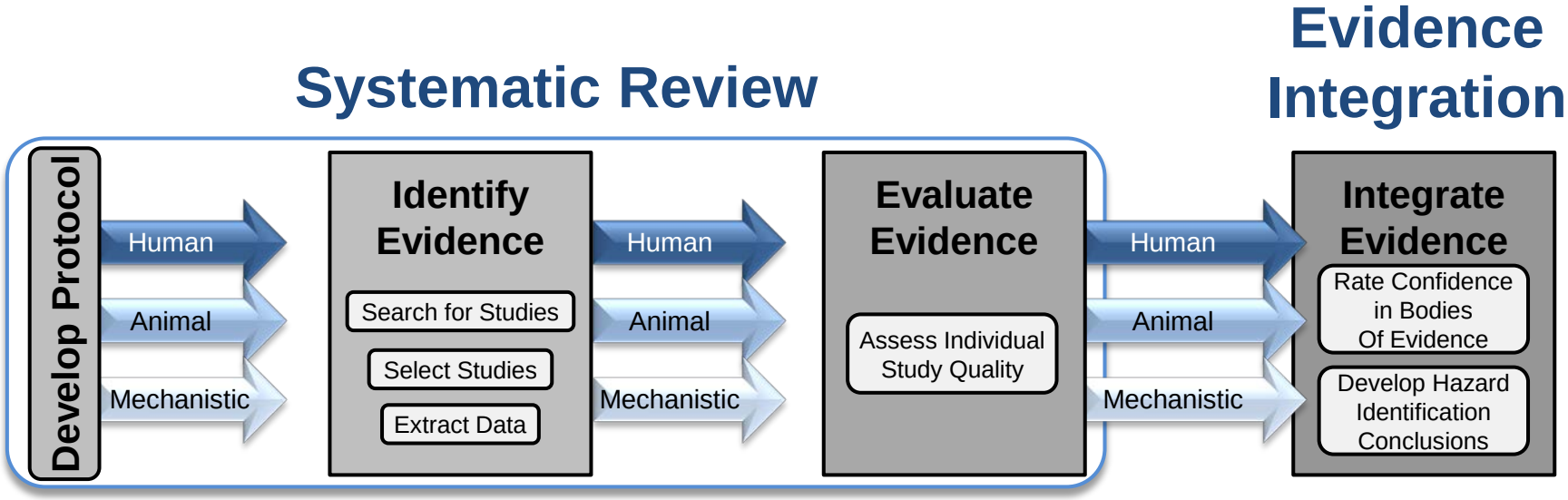
Specific Aims

- The overall objective is to develop hazard identification conclusions whether or not exposure to PFOA or PFOS is associated with immunotoxicity or immune-related health effects

Key Questions (KQ)		
KQ1	Human studies	What is our confidence in the human and animal bodies of evidence for the association between exposure to PFOA or PFOS and immunotoxicity or immune-related health effects?
KQ2	Animal studies	
KQ3	Mechanistic studies	How does the evidence from other relevant studies (e.g., mechanistic or *in vitro* studies) support or refute the biological plausibility of the association between exposure to PFOA or PFOS and immunotoxicity or immune-related health effects?

Proposed Approach

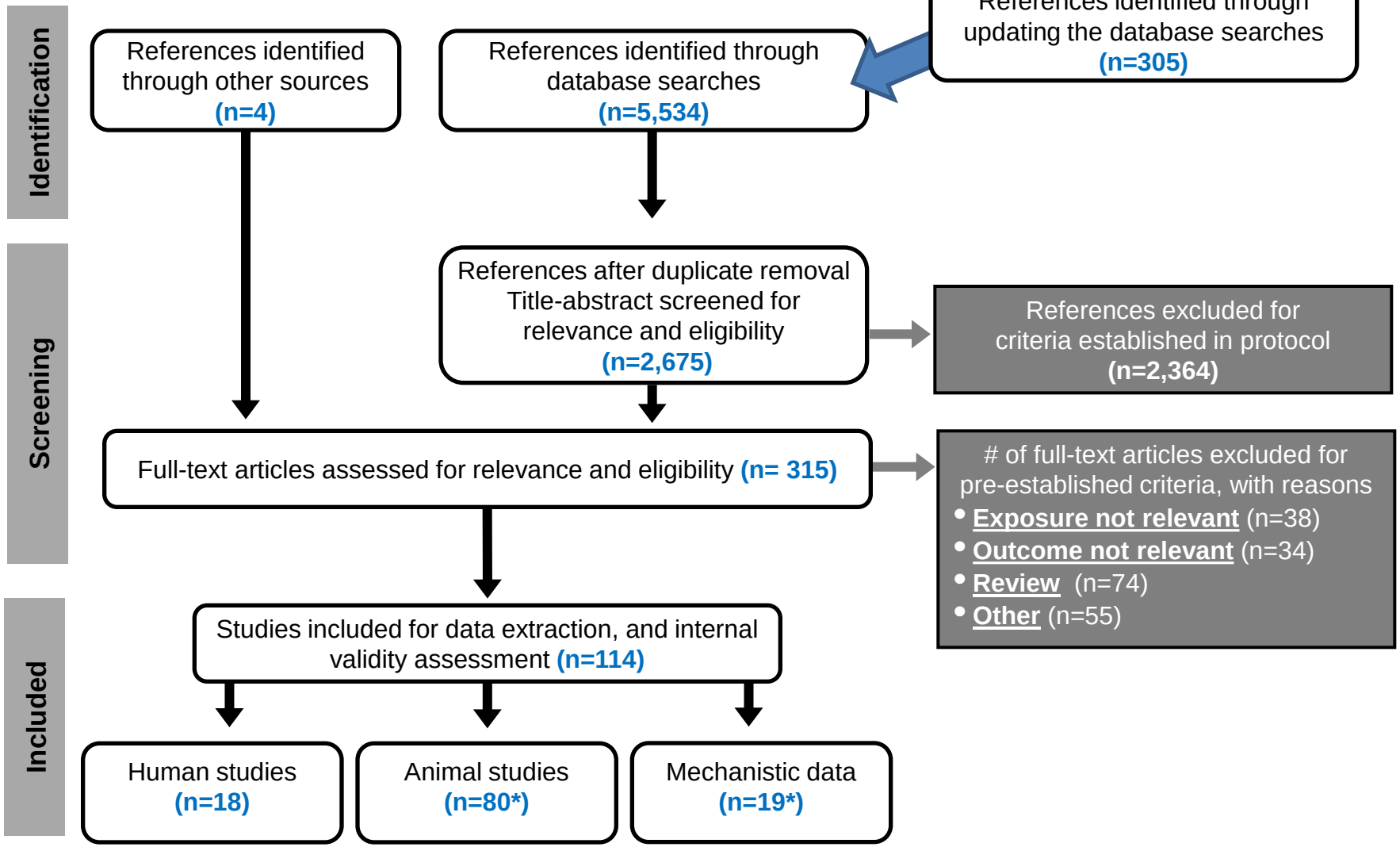
- Literature-based evaluation
  - OHAT Approach to systematic review and evidence integration



Preliminary Screening

2013 literature search

October 2014 Update



*3 studies with both animal and mechanistic data

Significance

- Anticipated to reach hazard ID conclusions for PFOA and PFOS-associated immunotoxicity
  - Apply systematic review methods to evaluate recent human functional immune evidence in context of animal and mechanistic data
  - Outputs shared with public and other agencies
    - Individual study quality / internal validity assessment
    - Data extraction files
- Leverage case study work
- Potential “next steps”
  - Consider the use of PFOA and PFOS data to explore immune and inflammation-related endpoints in the Tox21 data
  - Consider methods of using the relatively well studied PFOA and PFOS data along with mechanistic or *in vitro* data on other perfluoroalkyl acids to evaluate the potential immunotoxicity of data poor chemicals

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Charge

- To review and comment on the draft OHAT concept and determine whether the evaluation is an appropriate use of NTP resources.
- An evaluation concept is a brief document outlining the rationale, significance, approach, and expected outcome of a proposed evaluation.

Review Questions

1) Comment on the merit of the proposed evaluation relative to the mission and goals of the NTP. *The NTP's stated goals are to: Provide information on potentially hazardous substances to all stakeholders; Develop and validate improved testing methods; Strengthen the science base in toxicology; Coordinate toxicology testing programs across DHHS (http://ntp.niehs.nih.gov/go/test).*

2) Comment on the clarity and validity of the rationale for the proposed evaluation as articulated in the NTP evaluation concept document.
   - Has the scope of the problem been adequately defined?
   - Have the relevant scientific issues been identified and clearly articulated?
   - Are you aware of other scientific issues that need to be considered?

3) Comment on the proposed approach for further developing and refining the evaluation.

4) Rate the overall significance and public health impact of this evaluation as low, moderate, or high.

5) Provide any other comments you feel NTP staff should consider in developing this evaluation.