

# NTP Monograph

## Immunotoxicity Associated with Exposure to Perfluorooctanoic Acid (PFOA) or Perfluorooctane Sulfonate (PFOS)

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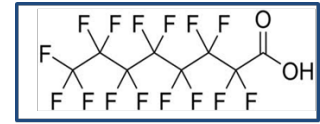
National Institute of Environmental Health Sciences





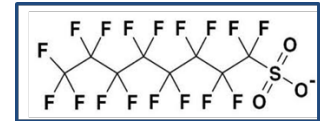
# Exposure to PFOA and PFOS

- **Perfluoroalkyl acids (PFAS) including PFOA and PFOS**
  - Extensive commercial/industrial use over last 50 years
- **PFOA and PFOS**
  - Use and emissions reduced in US and Europe
  - Not metabolized; not expected to degrade in environment
  - Slower human elimination rates
    - Half-lives 2-8 years in humans
    - Half-lives days or weeks in other animals



**PFOA**

Perfluorooctanoic Acid (PFOA)



**PFOS**

Perfluorooctane Sulfonate (PFOS)

Survey years	PFOA	PFOS
1999-2000	<b>5.21</b> (4.72-5.74)	<b>30.4</b> (27.1-33.9)
2005-2006	<b>3.92</b> (3.48-4.42)	<b>17.1</b> (16.0-18.2)
2011-2012	<b>2.08</b> (1.95-2.22)	<b>6.31</b> (5.84-6.82)
2015-2016	<b>1.56</b> (1.47-1.66)	<b>4.72</b> (4.40-5.07)

*Geometric mean serum concentrations [ $\mu\text{g/L}$  (95% CI)] US population*





# Why evaluate PFOA and PFOS immunotoxicity?

- Reports of potential PFOA /PFOS-associated changes in multiple immune measures

## – Experimental Animal Studies



Immunosuppression (reduced antibody response)



Hypersensitivity (increased IgE and airway hypersensitivity)



Autoimmunity: (no studies)

## – Reports in Humans



Immunosuppression (reduced antibody response to vaccines)



Hypersensitivity (increased incidence of asthma in children)



Autoimmunity (increased incidence of ulcerative colitis)



# National Toxicology Program (NTP)

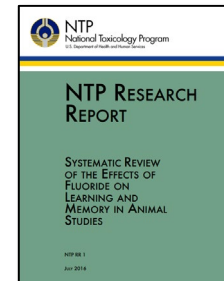
## Office of Health Assessment and Translation

- Conduct literature-based evaluations to assess the evidence that environmental exposures cause adverse health effects
- Evaluation format depends on purpose and extent of the evidence
  - Systematic evidence maps
  - Systematic reviews
- Communicated to public, government, scientific and medical communities as
  - Reports, Monographs, Journal articles

## NTP Monographs



## NTP Reports



## Workshops





# Systematic Review and Evidence Integration

## Systematic Review

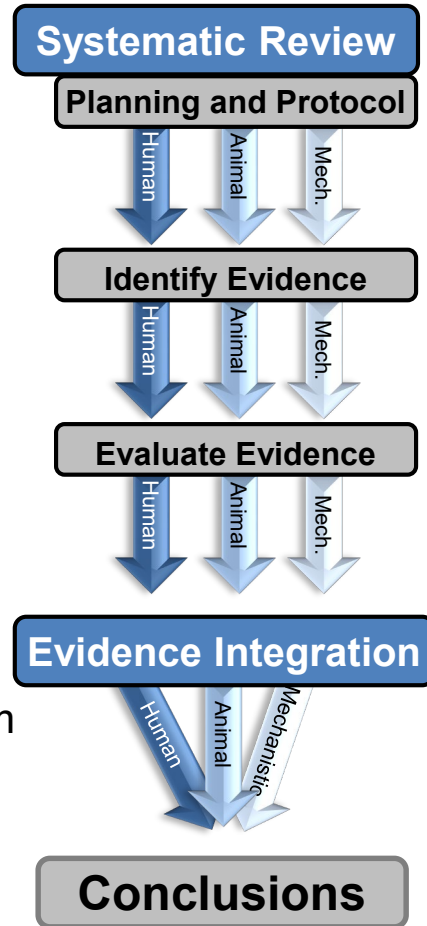
A predefined, multistep process to identify, select, critically assess, and synthesize data from published studies to answer a specific question

## Systematic Review Process

- Develop specific research question and protocol
- Perform comprehensive literature search
- Select relevant studies and extract data
- Assess individual study quality (risk of bias)

## Evidence Integration

A process for developing hazard conclusions by integrating evidence from human and experimental animal studies with consideration of the degree of support from mechanistic data





# PFOA and PFOS systematic review

## Objective

- To develop NTP hazard identification conclusions on the association between exposure to PFOA or PFOS and immunotoxicity
- Conclusions reached separately for each chemical

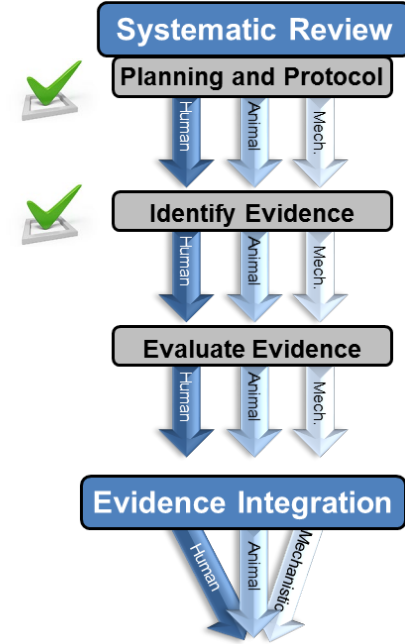
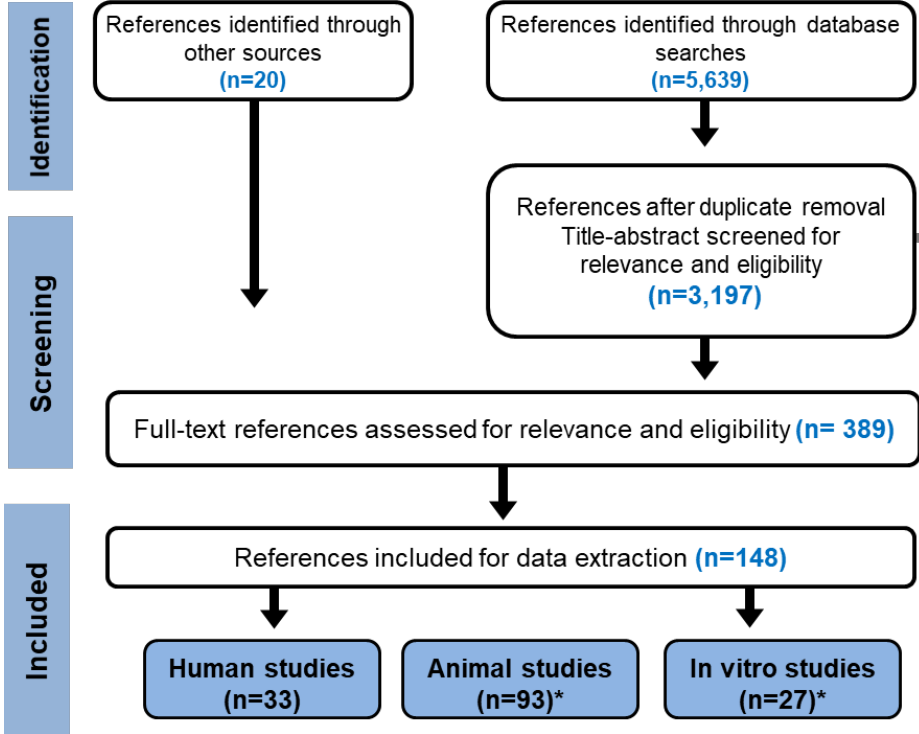
The screenshot shows the National Toxicology Program (NTP) website page for the systematic review on PFOA and PFOS. The page title is "Immunotoxicity Associated with Exposure to Perfluorooctanoic Acid (PFOA) or Perfluorooctane Sulfonate (PFOS)". The page includes a "Topic Overview" section with a small image of a white container and a red cap, and a "Background Information" section. The "Background Information" section states that PFOA and PFOS are extremely persistent chemicals that are widely distributed in the environment as a result of high chemical stability under normal environmental conditions and extensive use over the last 50 years in commercial and industrial applications including fluoropolymer manufacturing, food packaging, lubricants, water-resistant coating, and fire-fighting foams. PFOS was phased out of production and use in 2002, and U.S. manufacturers eliminated PFOA emissions and product content at the end of 2015. Although emissions have been dramatically reduced in the United States and Western Europe, it is not clear if global production has changed as there has been a shift in productions to Asia. Some published studies of PFOA and PFOS raised concerns about potential immune system health effects and NTP received nominations to conduct a review of immune effects for these chemicals. The "NTP conducted a systematic review to evaluate the evidence on exposure to PFOA or PFOS and immune-related health effects to determine whether exposure to either chemical is associated with immunotoxicity for humans. NTP concludes that both PFOA and PFOS are presumed to be an immune hazard to humans based on a high level of evidence from animal studies that PFOA and PFOS suppressed the antibody response and a moderate level of evidence from studies in humans. The evidence that these chemicals affect multiple aspects of the immune system supports the overall conclusion that both PFOA and PFOS alter immune functions in humans." The page also includes a "Documents" section and a "Back to Top" link.

<https://ntp.niehs.nih.gov/go/749926>



# PFOA and PFOS systematic review

## Identify evidence: Literature search and screening





# PFOA and PFOS systematic review

## Identify evidence: Extract data from studies

- Identifying Evidence

➡ Extract data into web-based project pages

Systematic Review

Planning and Protocol



Identify Evidence



Evaluate Evidence



Evidence Integration



### Bibliographic Details

Home / PFOA/PFOS Exposure and Immunotoxicity (2015) / DeWitt 2009

**DeWitt 2009**

Study type: Animal Bioassay

Full citation: DeWitt JC, Copeland CB, and Luebeck RW. 2009. Suppression of humoral immunity by perfluorooctanoic acid is independent of elevated serum corticosterone concentration in mice. *Toxicol Sci* 109(1): 106-112.

Abstract: The T-cell-dependent antibody response is suppressed in mice exposed to 3.75, 7.5, 15, and 30 mg PFOA (perfluorooctanoic acid)/kg body weight (bw) ...

Reference hyperlink: PubMed

COI reported: Not reported

Funding source: University of North Carolina, U.S. EPA Cooperative Training Agreement (CT829472)

Study identifier: (DeWitt, 2009 #342)

Author contacted?: ☑

Author contact details: Authors provided additional details in response to email in April - May 2015 for risk of bias clarification.

Summary and/or extraction comments: Data available: body weight; alkaline phosphatase (ALP); alanine aminotransferase (ALT); aspartate aminotransferase (AST); sorbitol dehydrogenase (SDH); blood urea nitrogen (BUN); creatinine; gamma-glutamyl transpeptidase...

### IgM antibody titer (SRBC)

#### Endpoint Details

Endpoint name	IgM antibody titer (SRBC)
System	Immune and lymphatic system
Effect	antibody (B cell) mediated immunity: function
Diagnostic description	ELISA
Observation time	15 days
Additional tags	antibody response immune system
Data reported?	<input checked="" type="checkbox"/>
Data extracted?	<input checked="" type="checkbox"/>
Values estimated?	<input checked="" type="checkbox"/>
Location in literature	Figure 3
NOEL	7.5 mg/kg-day ADD
LOEL	15 mg/kg-day ADD







# PFOA and PFOS systematic review

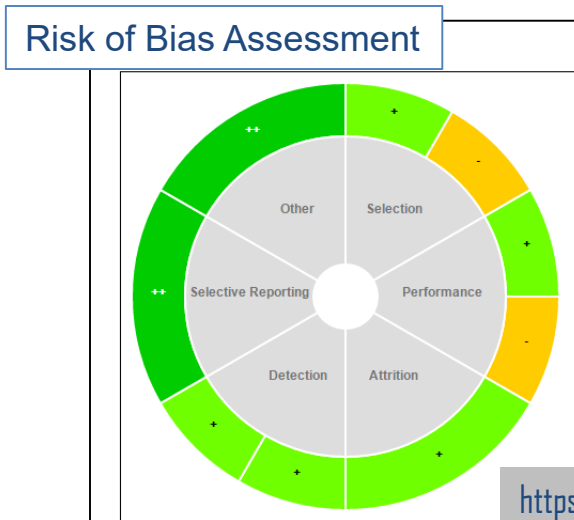
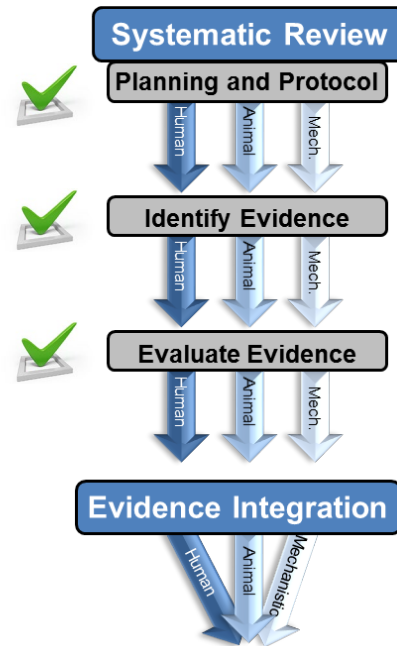
## Evaluate evidence: Assess individual studies

- Identifying Evidence

➔ Extract data into web-based project pages

- Evaluating Evidence

➔ Assess individual study quality or risk of bias

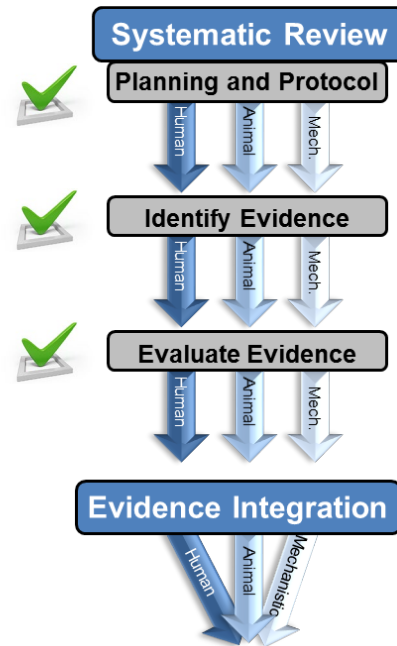




# PFOA and PFOS systematic review

## Develop bodies of evidence

- Results grouped on the same or similar outcomes
- **Main categories of immune response**
  - Immunosuppression
  - Hypersensitivity-related effects
  - Autoimmunity
- **Focus on primary outcomes**
  - Direct health outcomes or endpoints considered to have greater predictive value for overall immunotoxicity
    - Immune-related diseases or disease resistance assays
    - Measures of immune function

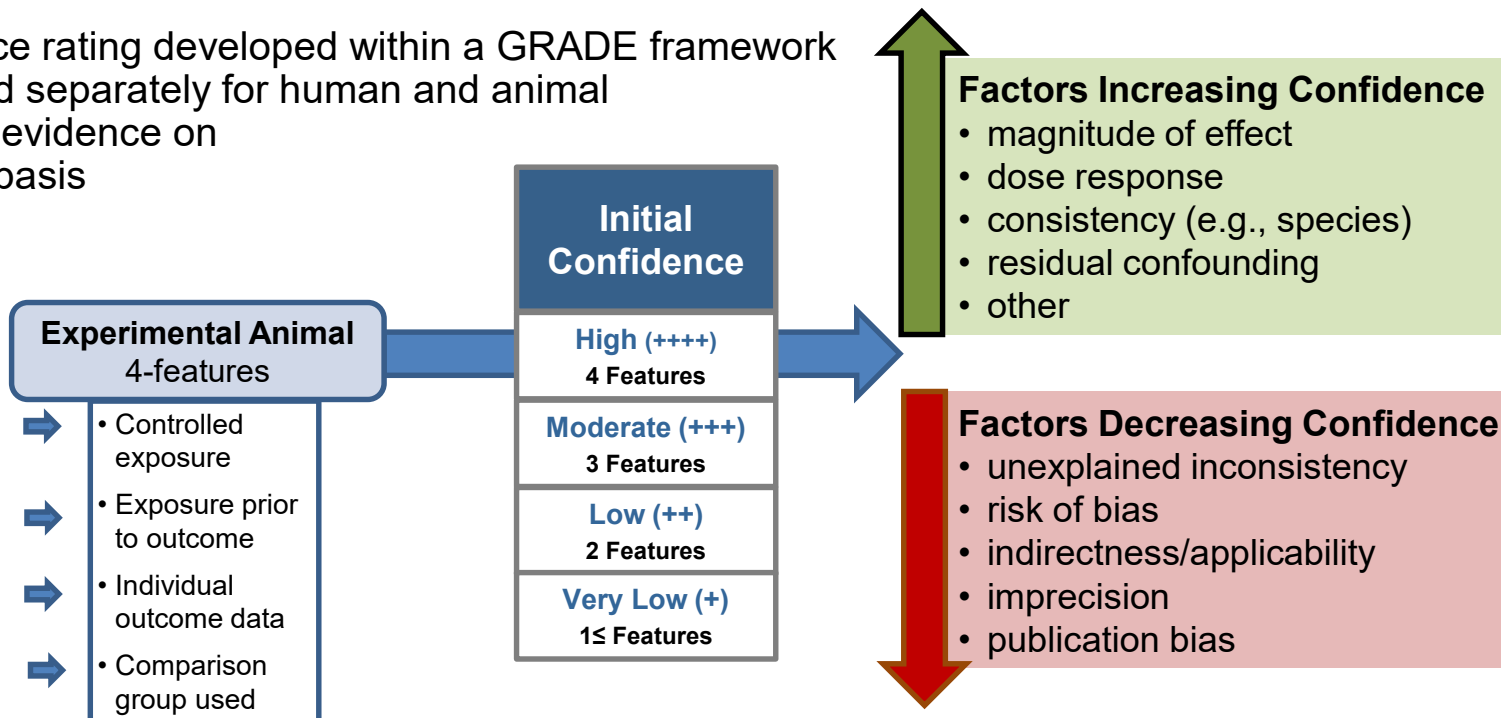




# PFOA and PFOS systematic review

## Evidence integration: Rating confidence in the bodies of evidence

- Rating is a measure of how confident you are that findings from a group of studies reflect the true relationship between exposure to a substance and effect
- Confidence rating developed within a GRADE framework  
Performed separately for human and animal bodies of evidence on outcome basis





# Example: PFOA antibody response data

## Animal body of evidence

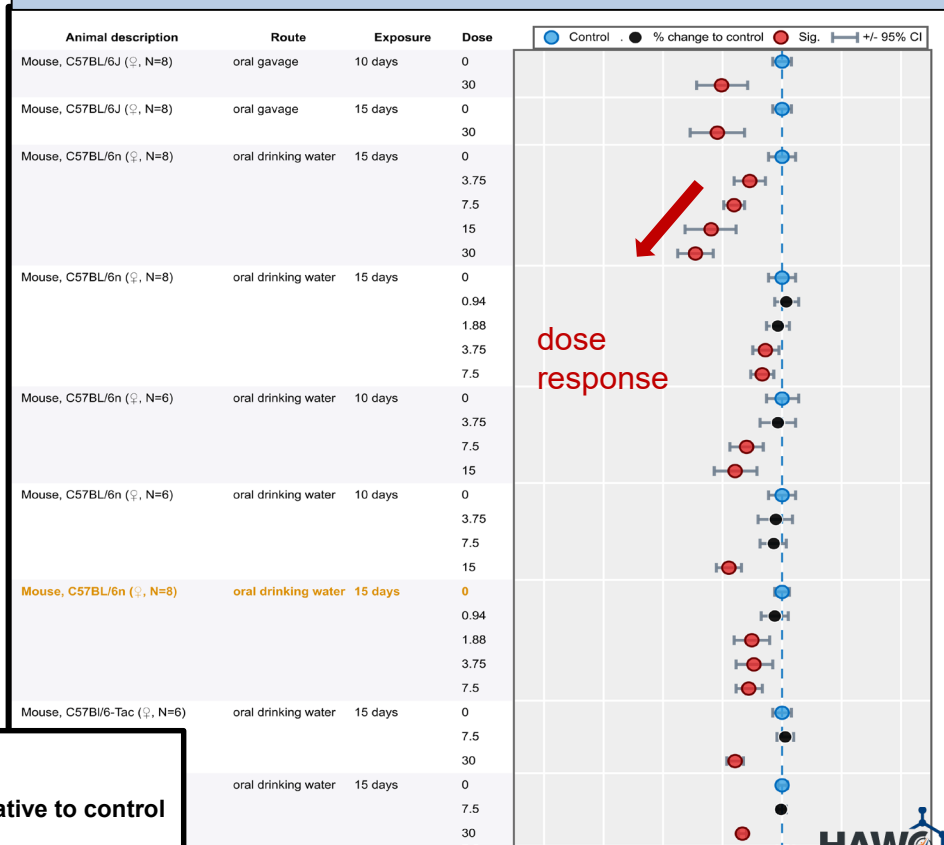
### • Studies

- 7 experimental studies in mammals
- Consistent suppression of primary antibody response (IgM) in mice
- Downgrade for risk of bias concerns
- Upgrade for evidence of dose response

### • High confidence

### • High level of evidence

Figure D6. Antigen-specific IgM antibody response in experimental animals - PFOA



- Control
- % change relative to control
- Significantly different



# Example: PFOA antibody response data

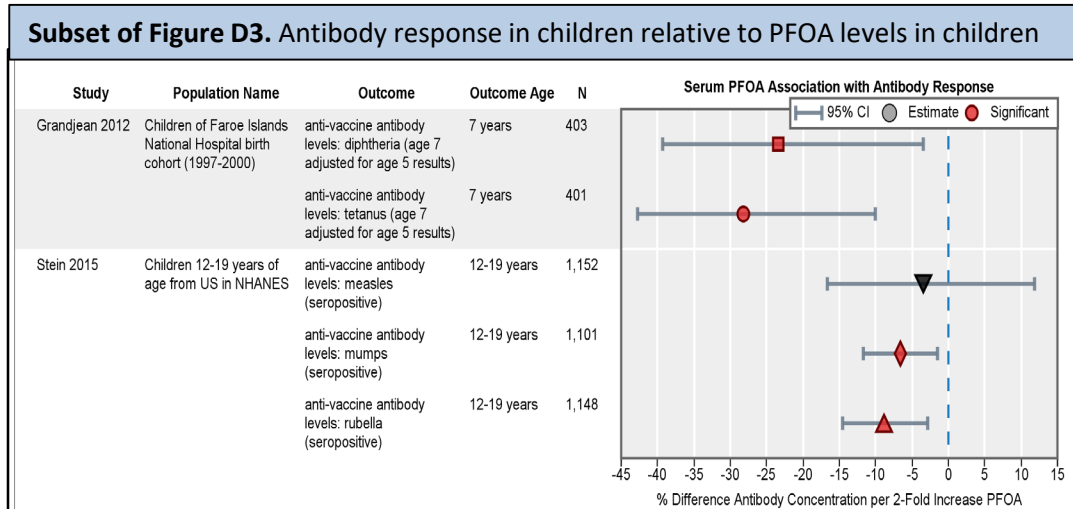
## Human body of evidence

### • Studies

- 4 prospective and 2 cross-sectional studies
- Suppression in one or more measure of anti-vaccine antibody response associated with prenatal, childhood, and adult exposures
- No upgrades or downgrades for factors that may influence confidence

### • Moderate confidence

### • Moderate level of evidence



■\* Significantly different

#### Anti-vaccine antibodies

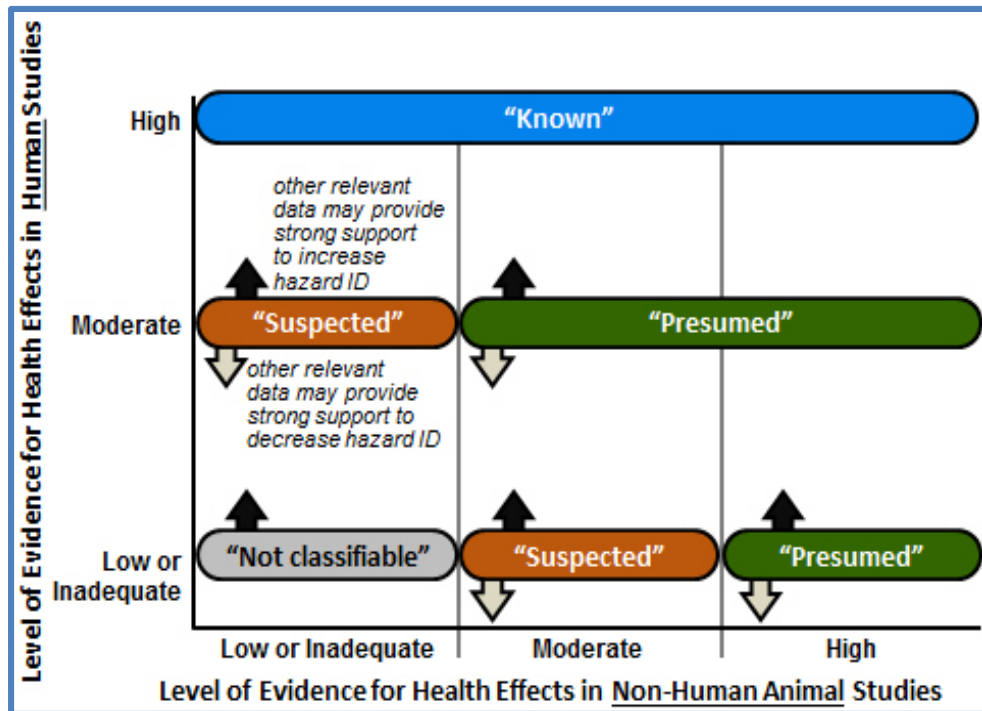
- diphtheria
- ▼ measles
- ◆ mumps
- ▲ rubella
- tetanus



# PFOA and PFOS systematic review

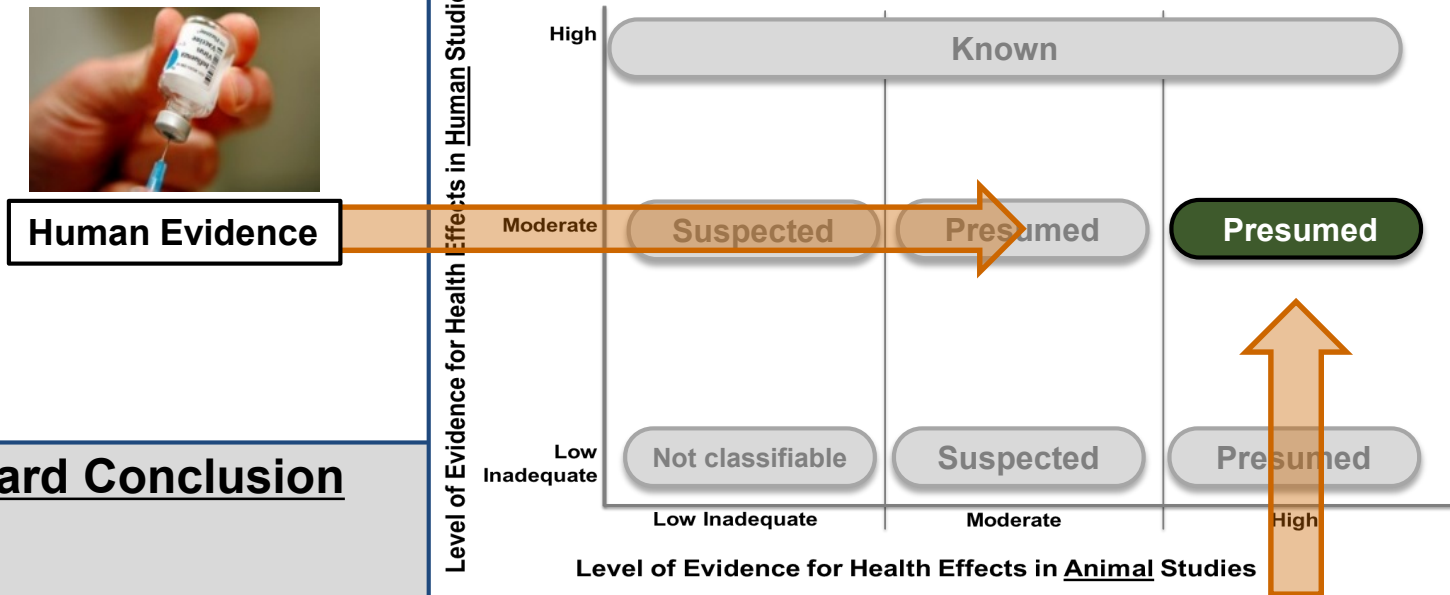
## Evidence integration: Combine evidence streams to develop conclusions

- **Initial Hazard Conclusion**  
Consider human and animal evidence together
- **Final Hazard Conclusion**  
Consider impact of mechanistic data and biological plausibility for the effect
  - Strong support to increase
  - Strong opposition to decrease





# Evidence integration: develop hazard conclusions



Human Evidence

## 1) Initial Hazard Conclusion

- Presumed

## 2) Consider Biological Plausibility

- Are there data showing PFOA-associated disruption of early events in the process leading to the antibody response?
- Were changes at same or lower concentrations as the observed effect?
- **Examples:** Key cell populations, cell signaling, activation



Animal



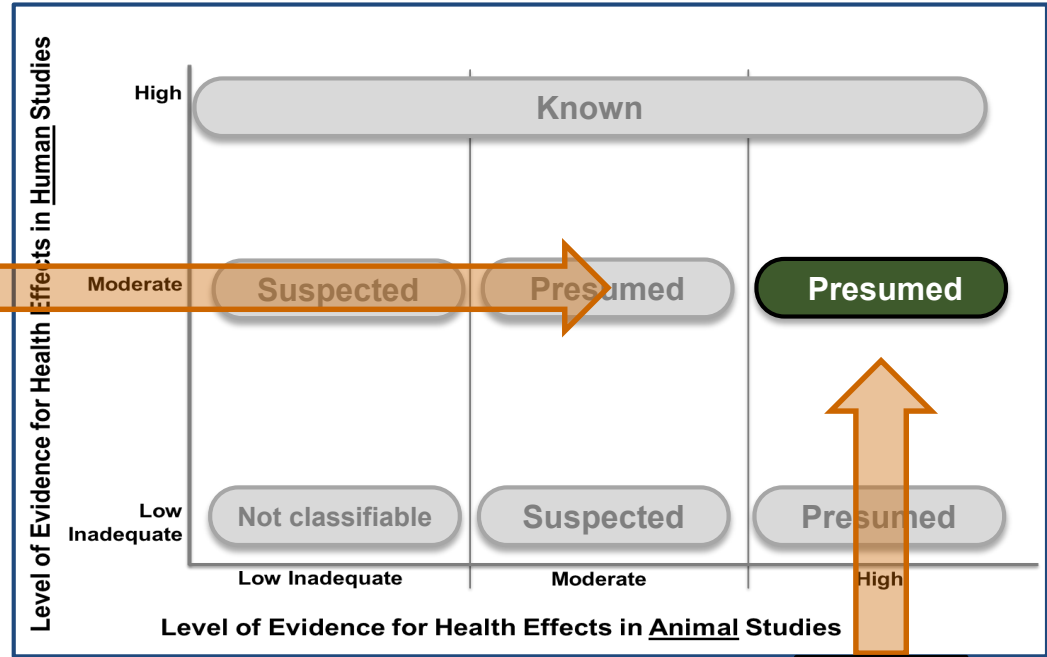
# Evidence integration: develop hazard conclusions



Human Evidence

## Suppression of the antibody response

- Similar bodies of evidence for PFOA and PFOS
- Most epidemiological studies examined both



Animal



**FINAL CONCLUSION:** Presumed to be an immune hazard to humans





## Human body of evidence

- **Studies**

- 6 prospective cohort studies [birth to age 9] (mostly no effect or decrease endpoints such as asthma, wheeze, eczema, Immunoglobulin E [IgE], or total allergic disease)
- 5 cross-sectional or case-control studies in children [age 10 to 19]
  - PFOA – increased asthma, total IgE, rhinitis
  - PFOS – Inconsistent results (increased or decreased) asthma, wheeze, IgE

- **PFOA**

- **Low confidence / low level of evidence**

## Animal body of evidence

- **PFOA**

- 2 mice studies; increased airway hypersensitivity
- **Moderate confidence and level of evidence**

### Hypersensitivity

- PFOA: *Low level of evidence* from human studies and *Moderate level of evidence* from animal studies
- PFOS: *Inadequate* evidence to support conclusions; inconsistent human animal results



## Human body of evidence

- **Studies**

- Two studies from the same population in Ohio valley (C8 study) reported PFOA-associated increases in ulcerative colitis an autoimmune disease in the colon/rectum
- Mixed results for rheumatoid arthritis and no evidence for other autoimmune diseases
  - First analysis: workers + residents; Second analysis: workers only (Steenland 2013, 2015)

- **Low confidence**

- No data on other populations, potential co-exposures to workers

- **Low level of evidence**

## Animal body of evidence

- No studies

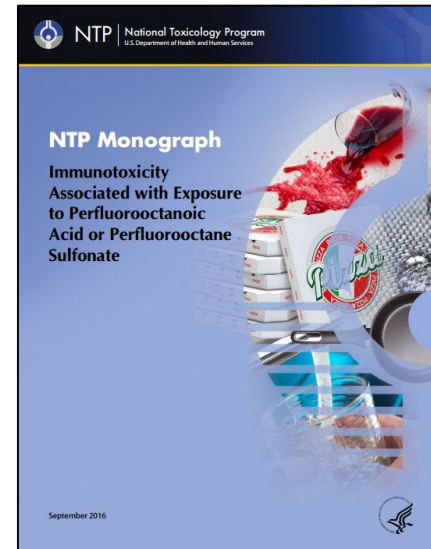
### Autoimmunity

- PFOA: *Low level of evidence* from human studies; *No* animal studies
- PFOS: *No studies*



## PFOA

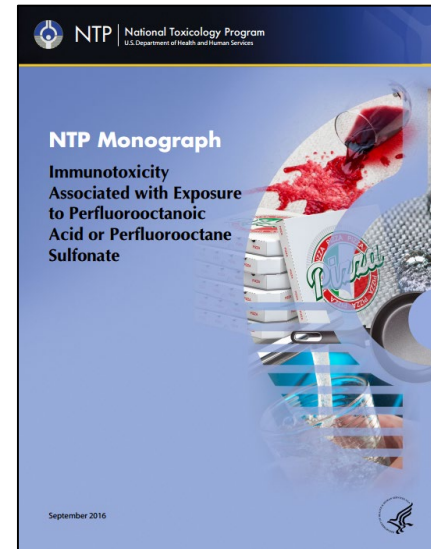
- Is *presumed to be an immune hazard to humans* based on
  - high level of evidence that PFOA suppressed the antibody response from animal studies
  - and a moderate level of evidence from studies in humans
- Supported by additional but weaker evidence, primarily from epidemiological studies that PFOA
  - increased hypersensitivity-related outcomes
  - increased autoimmune disease incidence
  - and reduced infectious disease resistance
- Evidence that multiple aspects of the immune system supports the overall conclusion that PFOA alters immune function in humans





## PFOS

- Is *presumed to be an immune hazard to humans* based on
  - high level of evidence that PFOS suppressed the antibody response from animal studies
  - and a moderate level of evidence from studies in humans
- Supported by additional but weaker evidence, primarily from experimental animal studies that PFOS
  - suppressed disease resistance, and
  - suppressed natural killer (NK) cell activity
- Evidence that multiple aspects of the immune system supports the overall conclusion that PFOS alters immune function in humans





Thank you

Questions?