



National Toxicology Program

U.S. Department of Health and Human Services

LITERATURE SEARCH RESULTS

FOR THE SYSTEMATIC REVIEW OF IMMUNOTOXICITY ASSOCIATED WITH EXPOSURE TO PERFLUOROOCTANOIC ACID (PFOA) OR PERFLUOROOCTANE SULFONATE (PFOS)

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(updated for results of literature search from May 18, 2016)

Office of Health Assessment and Translation
Division of the National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

LITERATURE SEARCH RESULTS

Literature Search

Search terms were developed to identify all relevant published evidence on immunotoxicity or immune-related health effects potentially associated with exposure to PFOA or PFOS by (1) reviewing Medical Subject Headings for relevant and appropriate immune terms, (2) extracting key immune health effects and immunotoxicity terminology from reviews and a sample of relevant primary data studies, (3) use of the chemical-specific search terms for PFOA from a draft systematic review of developmental PFOA exposure and fetal growth¹, and adaptation of the chemical-specific PFOA search strategy to generate search terms for PFOS. A combination of relevant subject headings and keywords were subsequently identified. A test set of relevant studies was used to ensure the search terms retrieve 100% of the test set. The following 9 electronic databases were searched using a search strategy tailored for each database (specific search terms used for the PubMed search presented in [Appendix 1](#); the search strategy for other databases are available in the protocol <http://ntp.niehs.nih.gov/go/749926>). No language restrictions or publication year limits were imposed, and the databases were searched on October 28, 2014 and October 22, 2015, with a final updated search on May 18, 2016.

Databases Searched

- Cochrane Library
- EMBASE
- PubChem
- PubMed
- Scopus
- Toxline
- Web of Science

Searching Other Resources

The reference lists of all included studies, relevant reviews, finalized or recent draft federal hazard assessments^{2,3,4,5,6}, commentaries, and other non-research articles were manually searched for

¹ Johnson P, Sutton P, Atchley D, Koustas E, Lam J, Robinson K, Sen S, Axelrad D, Woodruff T. 2013. Applying the Navigation Guide: Case Study #1. The Impact of Developmental Exposure to Perfluorooctanoic Acid (PFOA) On Fetal Growth. A Systematic Review of the Human Evidence - Protocol.

² ATSDR (Agency for Toxic Substances and Disease Registry). 2009. *Draft Toxicological Profile for Perfluoroalkyls*. Atlanta, GA: Division of Toxicology and Environmental Medicine/Applied Toxicology Branch. US Department of Health and Human Services: 404. Available: <http://www.atsdr.cdc.gov/toxprofiles/tp200.pdf>.

³ ATSDR (Agency for Toxic Substances and Disease Registry). 2015. *Draft Toxicological Profile for Perfluoroalkyls*. Atlanta, GA: Division of Toxicology and Environmental Medicine/Applied Toxicology Branch. US Department of Health and Human Services: 574. Available: <http://www.atsdr.cdc.gov/toxprofiles/tp200.pdf>.

⁴ US EPA (US Environmental Protection Agency). 2005. *Draft risk assessment of the potential human health effects associated with exposure to perfluorooctanoic acid and its salts*. Washington, DC: Office of Pollution Prevention and Toxics. US Environmental Protection Agency. Available: <http://www.epa.gov/opptintr/pfoa/pubs/pfoarisk.pdf>.

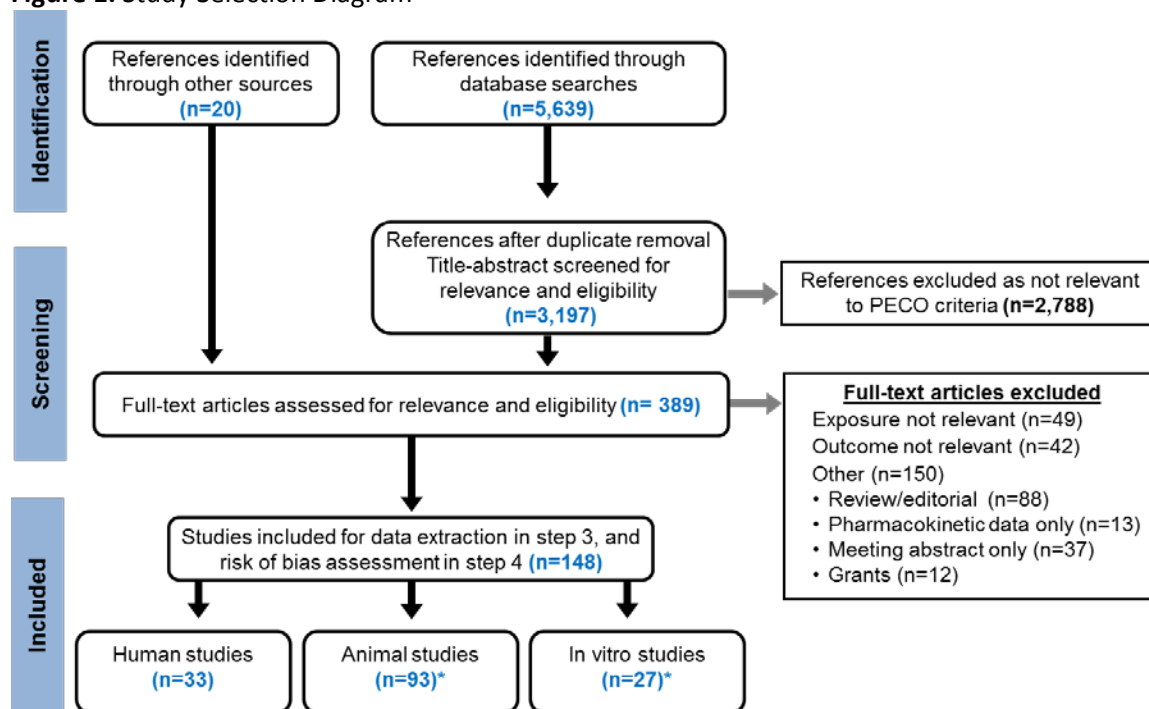
⁵ US EPA (US Environmental Protection Agency,). 2014. *Draft Health Effects Document for Perfluorooctane acid (PFOA)*. Office of Water. Available: [https://peerreview.versar.com/epa/pfoa/pdf/Health-Effects-Document-for-Perfluorooctanoic-Acid-\(PFOA\).pdf](https://peerreview.versar.com/epa/pfoa/pdf/Health-Effects-Document-for-Perfluorooctanoic-Acid-(PFOA).pdf).

additional relevant publications. NTP published a Request for Information about ongoing studies or upcoming publications on immune-related health effects of PFOA or PFOS in the Federal Register [80 FR 48886 (August 14, 2015)]. Studies identified by the public in response to the 2015 request for information or after posting of the protocol and initial list of included studies were also included.

Literature Search Results

The electronic database searches retrieved 3197 individual references, and 20 additional references were identified by technical advisors or from reviewing reference lists in published reviews and included studies. From the total references retrieved, 2788 were excluded during the title and abstract screening and 241 were excluded during the full text review. The screening results are outlined in a study selection diagram with reasons for exclusion documented at the full text review stage (Figure 1). The 148 included studies are listed below in the section for “list of included studies”; there are 33 human studies, 93* animal studies, and 27* in vitro/mechanistic studies.

Figure 1. Study Selection Diagram



* Five publications contained data relevant to both experimental animal studies and *in-vitro* studies

⁶ US EPA (US Environmental Protection Agency,). 2014. *Draft Health Effects Document for Perfluorooctane sulfonate (PFOS)*. Office of Water. Available: [https://peerreview.versar.com/epa/pfoa/pdf/Health-Effects-Document-for-Perfluorooctane-Sulfonate-\(PFOS\).pdf](https://peerreview.versar.com/epa/pfoa/pdf/Health-Effects-Document-for-Perfluorooctane-Sulfonate-(PFOS).pdf).

REFERENCES INCLUDED AFTER FULL-TEXT REVIEW

List of Included Studies

*studies identified in the updated literature search May 2016

Studies in humans

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Literature Search Results for Systematic Review of Immunotoxicity Associated with Exposure to PFOA or PFOS

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APPENDIX

Appendix 1. Literature Search Strategy

The strategy for this search is broad for the consideration of immune-related endpoints and comprehensive for PFOA or PFOS as an exposure or treatment in order to ensure inclusion of relevant papers. The search terms for PubMed are provided below. The specific search strategies for other databases are available in the protocol (<http://ntp.niehs.nih.gov/go/749926>).

Database	Search Terms
PUBMED	perfluoroalkyl*[tiab] OR perfluorocaprylic[tiab] OR perfluorocarbon*[tiab] OR perfluorocarboxyl*[tiab] OR perfluorochemical*[tiab] OR (perfluorinated[tiab] AND (C8[tiab] OR carboxylic[tiab] OR chemical*[tiab] OR compound*[tiab] OR octanoic[tiab])) OR PFAA*[tiab] OR "fluorinated polymer"[tiab] OR "fluorinated polymers"[tiab] OR (fluorinated[tiab] AND (polymer[tiab] OR polymers[tiab])) OR (fluorocarbon[tiab] AND (polymer[tiab] OR polymers[tiab])) OR Fluoropolymer*[tiab] OR (fluorinated[tiab] AND telomer*[tiab]) OR fluorotelomer*[tiab] OR fluoro-telomer*[tiab] OR fluorosurfactant*[tiab] OR "FC 143"[tiab] OR FC143[tiab] OR 335-67-1 [rn] OR Pentadecafluorooctanoate*[tiab] OR Pentadecafluorooctanoate*[tiab] OR pentadecafluorooctanoic[tiab] OR pentadecafluorooctanoic[tiab] OR "pentadecafluoro-1-octanoic"[tiab] OR "pentadecafluoro-n-octanoic"[tiab] OR "perfluoro-1-heptanecarboxylic"[tiab] OR perfluorocaprylic[tiab] OR perfluoroheptanecarboxylic[tiab] OR perfluorooctanoate[tiab] OR perfluorooctanoate[tiab] OR "perfluoro octanoate"[tiab] OR "perfluorooctanoic acid"[nm] OR

Database	Search Terms (continued)
	<p>perfluorooctanoic[tiab] OR perfluorooctanoic[tiab] OR "perfluoro octanoic"[tiab] OR "perfluoro-n-octanoic"[tiab] OR "perfluorooctanoyl chloride"[tiab] OR PFOA[tiab] OR APFO[tiab] OR 1763-23-1[rn] OR 307-35-7[rn] OR "1-octanesulfonic acid"[tiab] OR "1-perfluorooctanesulfonic"[tiab] OR "1-perfluorooctanesulfonic"[tiab] OR "heptadecafluoro-1-octanesulfonic"[tiab] OR "heptadecafluoro-1-octane sulfonic"[tiab] OR "heptadecafluorooctanesulfonic"[tiab] OR "heptadecafluorooctane sulfonic"[tiab] OR "heptadecafluorooctane sulfonic"[tiab] OR "perfluoroalkyl sulphonate"[tiab] OR perfluorooctanesulfonate[tiab] OR perfluorooctanesulfonate[tiab] OR "perfluorooctane sulfonate"[tiab] OR "perfluorooctane sulfonate"[tiab] OR "perfluoro-n-octanesulfonic"[tiab] OR perfluorooctanesulfonic[tiab] OR perfluorooctanesulfonic[tiab] OR "perfluorooctane sulfonic acid"[nm] OR "perfluorooctane sulfonic"[tiab] OR "perfluorooctane sulfonic"[tiab] OR perfluorooctanesulphonic[tiab] OR perfluorooctanesulphonic[tiab] OR "perfluorooctane sulphonic"[tiab] OR "perfluorooctane sulphonic"[tiab] OR perfluoroctylsulfonic[tiab] OR PFOS [tiab]</p> <p>AND</p> <p>immunology[sh] OR immune[tiab] OR immunocomp*[tiab] OR immunogen*[tiab] OR immunolog*[tiab] OR immunotox*[tiab] OR immunotoxins[mh] OR immunity[tiab] OR autoimmun*[tiab] OR "host resistance"[tiab] OR immunocompetence[mh] OR "immune system"[mh] OR spleen[tiab] OR splenic[tiab] OR splenocyt*[tiab] OR thymus[tiab] OR thymic[tiab] OR thymocyt*[tiab] OR leukocyt*[tiab] OR granulocyt*[tiab] OR basophil*[tiab] OR eosinophil*[tiab] OR neutrophil*[tiab] OR lymph[tiab] OR lymphoid*[tiab] OR lymphocyt*[tiab] OR "b-lymphocyte"[tiab] OR "b-lymphocytes"[tiab] OR "t-lymphocyte"[tiab] OR "t-lymphocytes"[tiab] OR "killer cell"[tiab] OR "killer cells"[tiab] OR "NK cell"[tiab] OR "NK-cell"[tiab] OR "NK-cells"[tiab] OR macrophag*[tiab] OR "mast cell"[tiab] OR "mast cells"[tiab] OR monocy*[tiab] OR phagocyt*[tiab] OR dendrit*[tiab] OR "t-cell"[tiab] OR "t cell"[tiab] OR "t cells"[tiab] OR "t-cells"[tiab] OR "T helper"[tiab] OR "T-helper"[tiab] OR "b-cell"[tiab] OR "b cell"[tiab] OR "b cells"[tiab] OR "b-cells"[tiab] OR antibod*[tiab] OR histamine*[tiab] OR histocompatib*[tiab] OR immunoglobulins[mh] OR immunoglobulin*[tiab] OR "immunoglobulin A"[tiab] OR IgA[tiab] OR "immunoglobulin D"[tiab] OR IgD[tiab] OR "immunoglobulin E"[tiab] OR IgE[tiab] OR "immunoglobulin G"[tiab] OR IgG[tiab] OR "immunoglobulin M"[tiab] OR IgM[tiab] OR "antigens, CD"[mh] OR CD3 [tiab] OR CD4 [tiab] OR CD8 [tiab] OR CD25 [tiab] OR CD27 [tiab] OR CD28 [tiab] OR CD29 [tiab] OR CD45*[tiab] OR cytokines[mh] OR cytokine*[tiab] OR chemokine*[tiab] OR interfeon*[tiab] OR interleukin*[tiab] OR "IL-6"[tiab] OR "IL-8"[tiab] OR lymphokine*[tiab] OR monokine*[tiab] OR ("tumor necrosis"[tiab] AND (factor[tiab] OR factors[tiab])) OR "TNF alpha"[tiab] OR "TNFalpha"[tiab] OR "immune system diseases"[mh] OR autoimmun*[tiab] OR addison[tiab] OR rheumatoid[tiab] OR glomerulonephritis[tiab] OR diabetes[tiab] OR graves[tiab] OR lupus[tiab] OR thyroiditis[tiab] OR hypersensitiv*[tiab] OR sensitization OR hyperresponsiv*[tiab] OR allergy[mh] OR allerg*[tiab] OR atopy[tiab] OR atopic[tiab] OR dermatitis[tiab] OR eczema[tiab] OR otitis[tiab] OR "ear infection"[tiab] OR "ear inflammation"[tiab] OR Respiratory tract infections[mh] OR (respiratory[tiab] AND infection*[tiab]) OR asthma[tiab] OR bronchitis[tiab] OR pneumonia[tiab] OR bronchiolitis[tiab] OR rhinitis[tiab] OR sinusitis[tiab] OR wheez*[tiab] OR crackle*[tiab] OR cough[mh] OR cough*[tiab] OR dyspnea[tiab] OR gastroenteritis[tiab] OR inflammation[mh] OR inflammat*[tiab] OR pro-inflammat*[tiab] OR anti-inflamm*[tiab] OR "inflammation mediators"[mh] OR autacoid*[tiab] OR eicosanoid*[tiab] OR prostaglandin*[tiab] OR immunomodulation[mh] OR immunomodul*[tiab] OR immunotherap*[tiab] OR vaccin*[tiab] OR immuniz*[tiab] OR immunosuppress*[tiab] OR desensitiz*[tiab] OR immunoproteins[mh] OR immunoprotein*[tiab] OR "c-reactive protein"[tiab] OR CRP[tiab] OR "complement component" [tiab] OR (complement[tiab] AND (C1 OR C2 OR C3 OR C4 OR C5 OR C6 OR C7 OR C8 OR C9))</p>