



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)

May 2016

(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>.

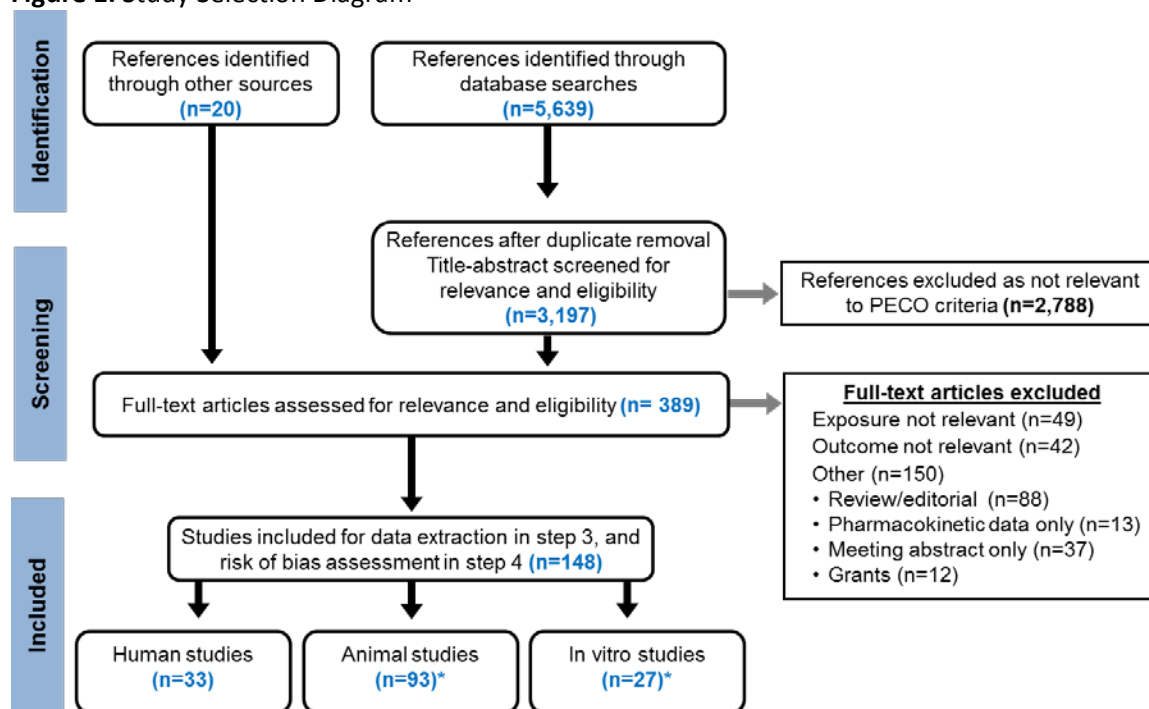
⁵ US EPA (US Environmental Protection Agency,). 2014. *Draft Health Effects Document for Perfluorooctane acid (PFOA)*. Office of Water. Available: [https://peerreview.versar.com/epa/pfoa/pdf/Health-Effects-Document-for-Perfluorooctanoic-Acid-\(PFOA\).pdf](https://peerreview.versar.com/epa/pfoa/pdf/Health-Effects-Document-for-Perfluorooctanoic-Acid-(PFOA).pdf).

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

- Amano K, Leung PSC, Rieger R, Quan C, Wang X, Marik J, Suen YF, Kurth MJ, Nantz MH, Ansari AA, Lam KS, Zeniya M, Matsuura E, Coppel RL, Gershwin ME. 2005. Chemical xenobiotics and mitochondrial autoantigens in primary biliary cirrhosis: Identification of antibodies against a common environmental, cosmetic, and food additive, 2-octynoic acid. *J Immunol* 174(9): 5874-5883.
- Anderson-Mahoney P, Kotlerman J, Takhar H, Gray D, Dahlgren J. 2008. Self-reported health effects among community residents exposed to perfluorooctanoate. *New Solut* 18(2): 129-143.
- Ashley-Martin J, Dodds L, Levy AR, Platt RW, Marshall JS, Arbuckle TE. 2015. Prenatal exposure to phthalates, bisphenol A and perfluoroalkyl substances and cord blood levels of IgE, TSLP and IL-33. *Environ Res* 140: 360-368.
- *Buser MC, Scinicariello F. 2016. Perfluoroalkyl substances and food allergies in adolescents. *Environ Int* 88: 74-79.
- Costa G, Sartori S, Consonni D. 2009. Thirty years of medical surveillance in perfluorooctanoic acid production workers. *J Occup Environ Med* 51(3): 364-372.
- Dong GH, Tung KY, Tsai CH, Liu MM, Wang D, Liu W, Jin YH, Hsieh WS, Lee YL, Chen PC. 2013. Serum polyfluoroalkyl concentrations, asthma outcomes, and immunological markers in a case-control study of Taiwanese children. *Environ Health Perspect* 121(4): 507-513, 513e501-508.
- Emmett EA, Zhang H, Shofer FS, Freeman D, Rodway NV, Desai C, Shaw LM. 2006. Community exposure to perfluorooctanoate: Relationships between serum levels and certain health parameters. *J Occup Environ Med* 48(8): 771-779.
- Fei C, McLaughlin JK, Lipworth L, Olsen J. 2010. Prenatal exposure to PFOA and PFOS and risk of hospitalization for infectious diseases in early childhood. *Environ Res* 110(8): 773-777.
- Genser B, Teles CA, Barreto ML, Fischer JE. 2015. Within- and between-group regression for improving the robustness of causal claims in cross-sectional analysis. *Environ Health* 14: 60.
- Grandjean P, Andersen EW, Budtz-Jorgensen E, Nielsen F, Molbak K, Weihe P, Heilmann C. 2012. Serum vaccine antibody concentrations in children exposed to perfluorinated compounds. *J Am Med Assoc* 307(4): 391-397.
- Granum B, Haug LS, Namork E, Stolevik SB, Thomsen C, Aaberge IS, van Loveren H, Lovik M, Nygaard UC. 2013. Prenatal exposure to perfluoroalkyl substances may be associated with altered vaccine antibody levels and immune-related health outcomes in early childhood. *J Immunotox* 10(4): 373-379.
- Humblet O, Diaz-Ramirez LG, Balmes JR, Pinney SM, Hiatt RA. 2014. Perfluoroalkyl Chemicals and Asthma among Children 12-19 Years of Age: NHANES (1999-2008). *Environ Health Perspect* 122(10): 1129-1133.
- Innes KE, Ducatman AM, Luster MI, Shankar A. 2011. Association of osteoarthritis with serum levels of the environmental contaminants perfluorooctanoate and perfluorooctane sulfonate in a large Appalachian population. *Am J Epidemiol* 174(4): 440-450.
- Jiang W, Zhang Y, Zhu L, Deng J. 2014. Serum levels of perfluoroalkyl acids (PFAAs) with isomer analysis and their associations with medical parameters in Chinese pregnant women. *Environ Int* 64: 40-47.

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

- Kielsen K, Shamim Z, Ryder LP, Nielsen F, Grandjean P, Budtz-Jorgensen E, Heilmann C. 2016. Antibody response to booster vaccination with tetanus and diphtheria in adults exposed to perfluorinated alkylates. *J Immunotoxicol*: 13(2):270-3.
- Leonard RC, Kreckmann KH, Sakr CJ, Symons JM. 2008. Retrospective cohort mortality study of workers in a polymer production plant including a reference population of regional workers. *Ann Epidemiol* 18(1): 15-22.
- Lin CY, Wen LL, Lin LY, Wen TW, Lien GW, Chen CY, Hsu SH, Chien KL, Sung FC, Chen PC, Su TC. 2011. Associations between levels of serum perfluorinated chemicals and adiponectin in a young hypertension cohort in Taiwan. *Environ Sci Technol* 45(24): 10691-10698.
- Looker C, Luster MI, Calafat AM, Johnson VJ, Burleson GR, Burleson FG, Fletcher T. 2014. Influenza vaccine response in adults exposed to perfluorooctanoate and perfluorooctanesulfonate. *Toxicol Sci* 138(1): 76-88.
- Mogensen UB, Grandjean P, Heilmann C, Nielsen F, Weihe P, Budtz-Jorgensen E. 2015. Structural equation modeling of immunotoxicity associated with exposure to perfluorinated alkylates. *Environ Health* 14: 47.
- Okada E, Sasaki S, Saijo Y, Washino N, Miyashita C, Kobayashi S, Konishi K, Ito YM, Ito R, Nakata A, Iwasaki Y, Saito K, Nakazawa H, Kishi R. 2012. Prenatal exposure to perfluorinated chemicals and relationship with allergies and infectious diseases in infants. *Environ Res* 112: 118-125.
- Okada E, Sasaki S, Kashino I, Matsuura H, Miyashita C, Kobayashi S, Itoh K, Ikeno T, Tamakoshi A, Kishi R. 2014. Prenatal exposure to perfluoroalkyl acids and allergic diseases in early childhood. *Environ Int* 65: 127-134.
- Osuna CE, Grandjean P, Weihe P, El-Fawal HA. 2014. Autoantibodies Associated with Prenatal and Childhood Exposure to Environmental Chemicals in Faroese Children. *Toxicol Sci*. 142(1): 158-66.
- Pennings JL, Jennen DG, Nygaard UC, Namork E, Haug LS, van Loveren H, Granum B. 2016. Cord blood gene expression supports that prenatal exposure to perfluoroalkyl substances causes depressed immune functionality in early childhood. *J Immunotoxicol* 13(2): 173-180.
- Predieri B, Iughetti L. 2015. High Levels of Perfluorooctane Sulfonate in Children at the Onset of Diabetes. 2015: 234358.
- Smit LA, Lenters V, Hoyer BB, Lindh CH, Pedersen HS, Liermontova I, Jonsson BA, Piersma AH, Bonde JP, Toft G, Vermeulen R, Heederik D. 2015. Prenatal exposure to environmental chemical contaminants and asthma and eczema in school-age children. *Allergy* 70(6): 653-660.
- Steenland K, Zhao L, Winquist A, Parks C. 2013. Ulcerative colitis and perfluorooctanoic acid (PFOA) in a highly exposed population of community residents and workers in the mid-Ohio valley. *Environ Health Perspect* 121(8): 900-905.
- Steenland K, Zhao L, Winquist A. 2015. A cohort incidence study of workers exposed to perfluorooctanoic acid (PFOA). *Occup Environ Med* 72(5): 373-380.
- Stein CR, McGovern KJ, Pajak AM, Maglione PJ, Wolff MS. 2016. Perfluoroalkyl and Polyfluoroalkyl Substances and Indicators of Immune Function in Children Aged 12 - 19 years: National Health and Nutrition Examination Survey. *Pediatr Res* 79(2): 348-357.
- Uhl SA, James-Todd T, Bell ML. 2013. Association of osteoarthritis with perfluorooctanoate and perfluorooctane sulfonate in NHANES 2003-2008. *Environ Health Perspect* 121(4): 447-452, 452e441-443.
- Wang IJ, Hsieh WS, Chen CY, Fletcher T, Lien GW, Chiang HL, Chiang CF, Wu TN, Chen PC. 2011. The effect of prenatal perfluorinated chemicals exposures on pediatric atopy. *Environ Res* 111(6): 785-791.
- Weber KE, Fischl AF, Murray PJ, Conway BN. 2014. Effect of BMI on cardiovascular and metabolic syndrome risk factors in an Appalachian pediatric population. *Diabetes Metab Syndr* 7: 445-453.

White SS, Fenton SE, Hines EP. 2011. Endocrine disrupting properties of perfluorooctanoic acid. *J Steroid Biochem Mol Biol* 127(1-2): 16-26.

*Zhu Y, Qin XD, Zeng XW, Paul G, Morawska L, Su MW, Tsai CH, Wang SQ, Lee YL, Dong GH. 2016. Associations of serum perfluoroalkyl acid levels with T-helper cell-specific cytokines in children: By gender and asthma status. *Sci Total Environ* 559: 166-173.

Studies in non-human animals

Adinehzadeh M, Reo NV. 1998. Effects of peroxisome proliferators on rat liver phospholipids: sphingomyelin degradation may be involved in hepatotoxic mechanism of perfluorodecanoic acid. *Chem Res Toxicol* 11(5): 428-440.

Alsarra IA, Brockmann WG, Cunningham ML, Badr MZ. 2006. Hepatocellular proliferation in response to agonists of peroxisome proliferator-activated receptor alpha: a role for Kupffer cells? *J Carcinog* 5: 26.

Arukwe A, Cangialosi MV, Letcher RJ, Rocha E, Mortensen AS. 2013. Changes in morphometry and association between whole-body fatty acids and steroid hormone profiles in relation to bioaccumulation patterns in salmon larvae exposed to perfluorooctane sulfonic or perfluorooctane carboxylic acids. *Aquat Toxicol* 130-131: 219-230.

Bilbao E, Raingard D, de Cerio OD, Ortiz-Zarragoitia M, Ruiz P, Izagirre U, Orbea A, Marigomez I, Cajaraville MP, Cancio I. 2010. Effects of exposure to Prestige-like heavy fuel oil and to perfluorooctane sulfonate on conventional biomarkers and target gene transcription in the thicklip grey mullet *Chelon labrosus*. *Aquat Toxicol* 98(3): 282-296.

Botelho SC, Saghafian M, Pavlova S, Hassan M, DePierre JW, Abedi-Valugerdi M. 2015. Complement activation is involved in the hepatic injury caused by high-dose exposure of mice to perfluorooctanoic acid. *Chemosphere* 129: 225-231.

Butenhoff J, Costa G, Elcombe C, Farrar D, Hansen K, Iwai H, Jung R, Kennedy G, Jr., Lieder P, Olsen G, Thomford P. 2002. Toxicity of ammonium perfluorooctanoate in male cynomolgus monkeys after oral dosing for 6 months. *Toxicol Sci* 69(1): 244-257.

Butenhoff JL, Kennedy Jr GL, Frame SR, O'Connor JC, York RG. 2004. The reproductive toxicology of ammonium perfluorooctanoate (APFO) in the rat. *Toxicology* 196(1-2): 95-116.

Butenhoff JL, Bjork JA, Chang SC, Ehresman DJ, Parker GA, Das K, Lau C, Lieder PH, van Otterdijk FM, Wallace KB. 2012. Toxicological evaluation of ammonium perfluorobutyrate in rats: Twenty-eight-day and ninety-day oral gavage studies. *Reprod Toxicol* 33(4): 513-530.

Cui L, Zhou QF, Liao CY, Fu JJ, Jiang GB. 2009. Studies on the toxicological effects of PFOA and PFOS on rats using histological observation and chemical analysis. *Arch Environ Contam Toxicol* 56(2): 338-349.

Dewitt JC, Copeland CB, Strynar MJ, Luebke RW. 2008. Perfluorooctanoic acid-induced immunomodulation in adult C57BL/6J or C57BL/6N female mice. *Environ Health Perspect* 116(5): 644-650.

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

DeWitt JC, Williams WC, Creech NJ, Luebke RW. 2016. Suppression of antigen-specific antibody responses in mice exposed to perfluorooctanoic acid: Role of PPARalpha and T- and B-cell targeting. *J Immunotoxicol* 13(1): 38-45.

Dong G, Zheng L, Jin Y, Lu X, Liu J, He Q. 2009. Effect of oral exposure to Perfluorooctane Sulfonate (PFOS) on spleen T cell subsets CD4+/CD8+ of C57BL/6 mice. *Huanjing Kexue Xuebao / Acta Scientiae Circumstantiae* 29(1): 181-185.

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

- Dong GH, Zhang YH, Zheng L, Liu W, Jin YH, He QC. 2009. Chronic effects of perfluorooctanesulfonate exposure on immunotoxicity in adult male C57BL/6 mice. *Arch Toxicol* 83(9): 805-815.
- Dong GH, Liu MM, Wang D, Zheng L, Liang ZF, Jin YH. 2011. Sub-chronic effect of perfluorooctanesulfonate (PFOS) on the balance of type 1 and type 2 cytokine in adult C57BL/6 mice. *Arch Toxicol* 85(10): 1235-1244.
- Dong GH, Wang J, Zhang YH, Liu MM, Wang D, Zheng L, Jin YH. 2012. Induction of p53-mediated apoptosis in splenocytes and thymocytes of C57BL/6 mice exposed to perfluorooctane sulfonate (PFOS). *Toxicol Appl Pharmacol* 264(2): 292-299.
- Dong GH, Zhang YH, Zheng L, Liang ZF, Jin YH, He QC. 2012. Subchronic effects of perfluorooctanesulfonate exposure on inflammation in adult male C57BL/6 mice. *Environ Toxicol* 27(5): 285-296.
- Fair PA, Driscoll E, Mollenhauer MA, Bradshaw SG, Yun SH, Kannan K, Bossart GD, Keil DE, Peden-Adams MM. 2011. Effects of environmentally-relevant levels of perfluorooctane sulfonate on clinical parameters and immunological functions in B6C3F1 mice. *J Immunotoxicol* 8(1): 17-29.
- Fair PA, Romano T, Schaefer AM, Reif JS, Bossart GD, Houde M, Muir D, Adams J, Rice C, Hulseley TC, Peden-Adams M. 2013. Associations between perfluoroalkyl compounds and immune and clinical chemistry parameters in highly exposed bottlenose dolphins (*Tursiops truncatus*). *Environ Toxicol Chem* 32(4): 736-746.
- Fairley KJ, Purdy R, Kearns S, Anderson SE, Meade B. 2007. Exposure to the immunosuppressant, perfluorooctanoic acid, enhances the murine IgE and airway hyperreactivity response to ovalbumin. *Toxicol Sci* 97(2): 375-383.
- Fang C, Huang Q, Ye T, Chen Y, Liu L, Kang M, Lin Y, Shen H, Dong S. 2013. Embryonic exposure to PFOS induces immunosuppression in the fish larvae of marine medaka. *Ecotoxicol Environ Saf* 92: 104-111.
- Griffith FD, Long JE. 1980. Animal toxicity studies with ammonium perfluorooctanoate. *Am Ind Hyg Assoc J* 41(8): 576-583.
- Guruge KS, Hikono H, Shimada N, Murakami K, Hasegawa J, Yeung LW, Yamanaka N, Yamashita N. 2009. Effect of perfluorooctane sulfonate (PFOS) on influenza A virus-induced mortality in female B6C3F1 mice. *J Toxicol Sci* 34(6): 687-691.
- Hines EP, White SS, Stanko JP, Gibbs-Flournoy EA, Lau C, Fenton SE. 2009. Phenotypic dichotomy following developmental exposure to perfluorooctanoic acid (PFOA) in female CD-1 mice: Low doses induce elevated serum leptin and insulin, and overweight in mid-life. *Mol Cell Endocrinol* 304(1-2): 97-105.
- Houde M, Giraudo M, Douville M, Bougas B, Couture P, De Silva AO, Spencer C, Lair S, Verreault J, Bernatchez L, Gagnon C. 2014. A multi-level biological approach to evaluate impacts of a major municipal effluent in wild St. Lawrence River yellow perch (*Perca flavescens*). *Sci Total Environ* 497-498: 307-318.
- Hu Q, Strynar MJ, DeWitt JC. 2010. Are developmentally exposed C57BL/6 mice insensitive to suppression of TDAR by PFOA? *J Immunotoxicol* 7(4): 344-349.
- Hu Q, Franklin JN, Bryan I, Morris E, Wood A, DeWitt JC. 2012. Does developmental exposure to perfluorooctanoic acid (PFOA) induce immunopathologies commonly observed in neurodevelopmental disorders? *Neurotox* 33(6): 1491-1498.
- Huang Q, Chen Y, Chi Y, Lin Y, Zhang H, Fang C, Dong S. 2015. Immunotoxic effects of perfluorooctane sulfonate and di(2-ethylhexyl) phthalate on the marine fish *Oryzias melastigma*. *Fish & shellfish immunology* 44(1): 302-306.
- IRDC (International Research and Development Corporation). 1978. *Ninety day subacute rat toxicity study*. Sponsor: 3M. U.S. Environmental Protection Agency Administrative Record 226-0441: 53.
- Iwai H, Yamashita K. 2006. A fourteen-day repeated dose oral toxicity study of APFO in rats. *Drug Chem Toxicol* 29(3): 323-332.

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

- Jacobson T, Holmstrom K, Yang G, Ford AT, Berger U, Sundelin B. 2010. Perfluorooctane sulfonate accumulation and parasite infestation in a field population of the amphipod *Monoporeia affinis* after microcosm exposure. *Aquat Toxicol* 98(1): 99-106.
- Kannan K, Perrotta E, Thomas NJ. 2006. Association between perfluorinated compounds and pathological conditions in southern sea otters. *Environ Sci Technol* 40(16): 4943-4948.
- Kannan K, Yun SH, Rudd RJ, Behr M. 2010. High concentrations of persistent organic pollutants including PCBs, DDT, PBDEs and PFOS in little brown bats with white-nose syndrome in New York, USA. *Chemosphere* 80(6): 613-618.
- Keil DE, Mehlmann T, Butterworth L, Peden-Adams MM. 2008. Gestational exposure to perfluorooctane sulfonate suppresses immune function in B6C3F1 mice. *Toxicol Sci* 103(1): 77-85.
- Lefebvre DE, Curran I, Armstrong C, Coady L, Parenteau M, Liston V, Barker M, Aziz S, Rutherford K, Bellon-Gagnon P, Shenton J, Mehta R, Bondy G. 2008. Immunomodulatory effects of dietary potassium perfluorooctane sulfonate (PFOS) exposure in adult Sprague-Dawley rats. *J Toxicol Environ Health A* 71(23): 1516-1525.
- *Liu W, Xu C, Sun X, Kuang H, Kuang X, Zou W, Yang B, Wu L, Liu F, Zou T, Zhang D. 2016. Grape seed proanthocyanidin extract protects against perfluorooctanoic acid-induced hepatotoxicity by attenuating inflammatory response, oxidative stress and apoptosis in mice. *Toxicology Research* 5(1): 224-234.
- Loveless SE, Hoban D, Sykes G, Frame SR, Everds NE. 2008. Evaluation of the immune system in rats and mice administered linear ammonium perfluorooctanoate. *Toxicol Sci* 105(1): 86-96.
- Lu Y, Luo B, Li J, Dai J. 2016. Perfluorooctanoic acid disrupts the blood-testis barrier and activates the TNFalpha/p38 MAPK signaling pathway in vivo and in vitro. *Arch Toxicol* 90(4): 971-983.
- *Lunardi D, Abelli L, Panti C, Marsili L, Fossi MC, Mancina A. 2016. Transcriptomic analysis of bottlenose dolphin (*Tursiops truncatus*) skin biopsies to assess the effects of emerging contaminants. *Mar Environ Res* 114: 74-79.
- Lv QY, Wan B, Guo LH, Yang Y, Ren XM, Zhang H. 2015. In vivo immunotoxicity of perfluorooctane sulfonate in BALB/c mice: Identification of T-cell receptor and calcium-mediated signaling pathway disruption through gene expression profiling of the spleen. *Chem Biol Interact* 240: 84-93.
- Minata M, Harada KH, Karrman A, Hitomi T, Hirosawa M, Murata M, Gonzalez FJ, Koizumi A. 2010. Role of peroxisome proliferator-activated receptor-alpha in hepatobiliary injury induced by ammonium perfluorooctanoate in mouse liver. *Ind Health* 48(1): 96-107.
- Mollenhauer MA, Bradshaw SG, Fair PA, McGuinn WD, Peden-Adams MM. 2011. Effects of perfluorooctane sulfonate (PFOS) exposure on markers of inflammation in female B6C3F1 mice. *J Environ Sci Health A Tox Hazard Subst Environ Eng* 46(2): 97-108.
- Nakagawa T, Ramdhan DH, Tanaka N, Naito H, Tamada H, Ito Y, Li Y, Hayashi Y, Yamagishi N, Yanagiba Y, Aoyama T, Gonzalez FJ, Nakajima T. 2012. Modulation of ammonium perfluorooctanoate-induced hepatic damage by genetically different PPARalpha in mice. *Arch Toxicol* 86(1): 63-74.
- Oh JH, Moon HB, Choe ES. 2013. Alterations in differentially expressed genes after repeated exposure to perfluorooctanoate and perfluorooctanesulfonate in liver of *Oryzias latipes*. *Arch Environ Contam Toxicol* 64(3): 475-483.
- Peden-Adams MM, Keller JM, Eudaly JG, Berger J, Gilkeson GS, Keil DE. 2008. Suppression of humoral immunity in mice following exposure to perfluorooctane sulfonate. *Toxicol Sci* 104(1): 144-154.
- Peden-Adams MM, Stuckey JE, Gaworecki KM, Berger-Ritchie J, Bryant K, Jodice PG, Scott TR, Ferrario JB, Guan B, Vigo C, Boone JS, McGuinn WD, DeWitt JC, Keil DE. 2009. Developmental toxicity in white leghorn chickens following in ovo exposure to perfluorooctane sulfonate (PFOS). *Reprod Toxicol* 27(3-4): 307-318.

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

- Qazi MR, Bogdanska J, Butenhoff JL, Nelson BD, DePierre JW, Abedi-Valugerdi M. 2009. High-dose, short-term exposure of mice to perfluorooctanesulfonate (PFOS) or perfluorooctanoate (PFOA) affects the number of circulating neutrophils differently, but enhances the inflammatory responses of macrophages to lipopolysaccharide (LPS) in a similar fashion. *Toxicology* 262(3): 207-214.
- Qazi MR, Xia Z, Bogdanska J, Chang SC, Ehresman DJ, Butenhoff JL, Nelson BD, DePierre JW, Abedi-Valugerdi M. 2009. The atrophy and changes in the cellular compositions of the thymus and spleen observed in mice subjected to short-term exposure to perfluorooctanesulfonate are high-dose phenomena mediated in part by peroxisome proliferator-activated receptor-alpha (PPARalpha). *Toxicology* 260(1-3): 68-76.
- Qazi MR, Abedi MR, Nelson BD, DePierre JW, Abedi-Valugerdi M. 2010. Dietary exposure to perfluorooctanoate or perfluorooctane sulfonate induces hypertrophy in centrilobular hepatocytes and alters the hepatic immune status in mice. *Int Immunopharmacol* 10(11): 1420-1427.
- Qazi MR, Nelson BD, Depierre JW, Abedi-Valugerdi M. 2010. 28-Day dietary exposure of mice to a low total dose (7 mg/kg) of perfluorooctanesulfonate (PFOS) alters neither the cellular compositions of the thymus and spleen nor humoral immune responses: does the route of administration play a pivotal role in PFOS-induced immunotoxicity? *Toxicology* 267(1-3): 132-139.
- Qazi MR, Nelson BD, DePierre JW, Abedi-Valugerdi M. 2012. High-dose dietary exposure of mice to perfluorooctanoate or perfluorooctane sulfonate exerts toxic effects on myeloid and B-lymphoid cells in the bone marrow and these effects are partially dependent on reduced food consumption. *Food Chem Toxicol* 50(9): 2955-2963.
- Qazi MR, Hassan M, Nelson BD, Depierre JW, Abedi-Valugerdi M. 2013. Sub-acute, moderate-dose, but not short-term, low-dose dietary pre-exposure of mice to perfluorooctanoate aggravates concanavalin A-induced hepatitis. *Toxicol Lett* 219(1): 1-7.
- Qazi MR, Hassan M, Nelson BD, DePierre JW, Abedi-Valugerdi M. 2013. Both sub-acute, moderate-dose and short-term, low-dose dietary exposure of mice to perfluorooctane sulfonate exacerbates concanavalin A-induced hepatitis. *Toxicol Lett* 217(1): 67-74.
- Riker Laboratories. 1987. *Two year oral (diet) toxicity/carcinogenicity study of FC-143 in rats*. U.S. Environmental Protection Agency Administrative Records 226-0437, 226-0438, 226-0439, and 226-440.
- Rosen MB, Thibodeaux JR, Wood CR, Zehr RD, Schmid JE, Lau C. 2007. Gene expression profiling in the lung and liver of PFOA-exposed mouse fetuses. *Toxicology* 239(1-2): 15-33.
- Rosen MB, Abbott BD, Wolf DC, Corton JC, Wood CR, Schmid JE, Das KP, Zehr RD, Blair ET, Lau C. 2008. Gene profiling in the livers of wild-type and PPARalpha-null mice exposed to perfluorooctanoic acid. *Toxicol Pathol* 36(4): 592-607.
- Rosen MB, Lee JS, Ren H, Vallanat B, Liu J, Waalkes MP, Abbott BD, Lau C, Corton JC. 2008. Toxicogenomic dissection of the perfluorooctanoic acid transcript profile in mouse liver: Evidence for the involvement of nuclear receptors PPAR(alpha) and CAR. *Toxicol Sci* 103(1): 46-56.
- Rosen MB, Schmid JR, Corton JC, Zehr RD, Das KP, Abbott BD, Lau C. 2010. Gene Expression Profiling in Wild-Type and PPARalpha-Null Mice Exposed to Perfluorooctane Sulfonate Reveals PPARalpha-Independent Effects. *PPAR Res* 2010.
- Ryu MH, Jha A, Ojo OO, Mahood TH, Basu S, Detillieux KA, Nikoobakht N, Wong CS, Loewen M, Becker AB, Halayko AJ. 2014. Chronic exposure to perfluorinated compounds: impact on airway hyperresponsiveness and inflammation. *Am J Physiol Lung Cell Mol Physiol* 307(10): L765-74.
- Seacat AM, Thomford PJ, Hansen KJ, Olsen GW, Case MT, Butenhoff JL. 2002. Subchronic toxicity studies on perfluorooctanesulfonate potassium salt in cynomolgus monkeys. *Toxicol Sci* 68(1): 249-264.
- Seacat AM, Thomford PJ, Hansen KJ, Clemen LA, Eldridge SR, Elcombe CR, Butenhoff JL. 2003. Sub-chronic dietary toxicity of potassium perfluorooctanesulfonate in rats. *Toxicology* 183(1-3): 117-131.

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

- Singh TS, Lee S, Kim HH, Choi JK, Kim SH. 2012. Perfluorooctanoic acid induces mast cell-mediated allergic inflammation by the release of histamine and inflammatory mediators. *Toxicol Lett* 210(1): 64-70.
- Sletten S, Bourgeon S, Bardsen BJ, Herzke D, Criscuolo F, Massemin S, Zahn S, Johnsen TV, Bustnes JO. 2016. Organohalogenated contaminants in white-tailed eagle (*Haliaeetus albicilla*) nestlings: An assessment of relationships to immunoglobulin levels, telomeres and oxidative stress. *Sci Total Environ* 539: 337-349.
- Smits JE, Nain S. 2013. Immunomodulation and hormonal disruption without compromised disease resistance in perfluorooctanoic acid (PFOA) exposed Japanese quail. *Environ Pollut* 179: 13-18.
- Son HY, Lee S, Tak EN, Cho HS, Shin HI, Kim SH, Yang JH. 2009. Perfluorooctanoic acid alters T lymphocyte phenotypes and cytokine expression in mice. *Environ Toxicol* 24(6): 580-588.
- Tan X, Xie G, Sun X, Li Q, Zhong W, Qiao P, Sun X, Jia W, Zhou Z. 2013. High fat diet feeding exaggerates perfluorooctanoic acid-induced liver injury in mice via modulating multiple metabolic pathways. *PLoS ONE* 8(4): e61409.
- Taylor BK, Dadia N, Yang CB, Krishnan S, Badr M. 2002. Peroxisome proliferator-activated receptor agonists inhibit inflammatory edema and hyperalgesia. *Inflammation* 26(3): 121-127.
- Taylor BK, Kriedt C, Nagalingam S, Dadia N, Badr M. 2005. Central administration of perfluorooctanoic acid inhibits cutaneous inflammation. *Inflamm Res* 54(6): 235-242.
- Thomford PJ. 2001. 4-Week capsule toxicity study with ammonium perfluorooctanoate (APFO) in *Cynomolgus* monkeys. Sponsor: APME Ad-Hoc APFO toxicology working group. 159.
- Thomford PJ. 2002. 4-week capsule toxicity study with perfluorooctane sulfonic acid potassium salt (PFOS; T-6295) in *Cynomolgus* monkeys. Sponsor: 3M. 235.
- Thomford PJ. 2002. 104-Week dietary chronic toxicity and carcinogenicity study with perfluorooctane sulfonic acid potassium salt (PFOS; T-6295) in rats. Prepared for: 3M. 216.
- Vetvicka V, Vetvickova J. 2013. Reversal of perfluorooctanesulfonate-induced immunotoxicity by a glucan-resveratrol-vitamin C combination. *Oriental Pharmacy and Experimental Medicine* 13(1): 77-84.
- Wan YJ, Badr MZ. 2006. Inhibition of Carrageenan-Induced Cutaneous Inflammation by PPAR Agonists Is Dependent on Hepatocyte-Specific Retinoid X Receptor Alpha. *PPAR Res* 2006: 96341.
- Wang Y, Wang L, Liang Y, Qiu W, Zhang J, Zhou Q, Jiang G. 2011. Modulation of dietary fat on the toxicological effects in thymus and spleen in BALB/c mice exposed to perfluorooctane sulfonate. *Toxicol Lett* 204(2-3): 174-182.
- Wang Y, Wang L, Li J, Liang Y, Ji H, Zhang J, Zhou Q, Jiang G. 2014. The mechanism of immunosuppression by perfluorooctanoic acid in BALB/c mice. *Toxicology Research* 3(3): 205-213.
- Watanabe MX, Kunisue T, Tao L, Kannan K, Subramanian A, Tanabe S, Iwata H. 2010. Dioxin-like and perfluorinated compounds in pigs in an Indian open waste dumping site: toxicokinetics and effects on hepatic cytochrome P450 and blood plasma hormones. *Environ Toxicol Chem* 29(7): 1551-1560.
- Wei Y, Liu Y, Wang J, Tao Y, Dai J. 2008. Toxicogenomic analysis of the hepatic effects of perfluorooctanoic acid on rare minnows (*Gobiocypris rarus*). *Toxicol Appl Pharmacol* 226(3): 285-297.
- Xie Y, Yang Q, Nelson BD, DePierre JW. 2002. Characterization of the adipose tissue atrophy induced by peroxisome proliferators in mice. *Lipids* 37(2): 139-146.
- *Xing J, Wang G, Zhao J, Wang E, Yin B, Fang D, Zhao J, Zhang H, Chen YQ, Chen W. 2016. Toxicity assessment of perfluorooctane sulfonate using acute and subchronic male C57BL/6J mouse models. *Environ Pollut* 210: 388-396.
- Yang Q, Xie Y, Depierre JW. 2000. Effects of peroxisome proliferators on the thymus and spleen of mice. *Clin Exp Immunol* 122(2): 219-226.

- Yang Q, Xie Y, Eriksson AM, Nelson BD, DePierre JW. 2001. Further evidence for the involvement of inhibition of cell proliferation and development in thymic and splenic atrophy induced by the peroxisome proliferator perfluorooctanoic acid in mice. *Biochem Pharmacol* 62(8): 1133-1140.
- Yang Q, Abedi-Valugerdi M, Xie Y, Zhao XY, Moller G, Nelson BD, DePierre JW. 2002. Potent suppression of the adaptive immune response in mice upon dietary exposure to the potent peroxisome proliferator, perfluorooctanoic acid. *Int Immunopharmacol* 2(2-3): 389-397.
- Yang Q, Xie Y, Alexson SE, Nelson BD, DePierre JW. 2002. Involvement of the peroxisome proliferator-activated receptor alpha in the immunomodulation caused by peroxisome proliferators in mice. *Biochem Pharmacol* 63(10): 1893-1900.
- Yang J, Li A, Yang Q, Li X. 2006. [Effects of peroxisome proliferators PFOA on immune system of mice]. *Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi* 22(2): 157-160.
- Yang JH. 2010. Perfluorooctanoic acid induces peroxisomal fatty acid oxidation and cytokine expression in the liver of male Japanese medaka (*Oryzias latipes*). *Chemosphere* 81(4): 548-552.
- Yang B, Zou WY, Hu ZZ, Liu FM, Zhou L, Yang SL, Kuang HB, Wu L, Wei J, Wang JL, Zou T, Zhang DL. 2014. Involvement of Oxidative Stress and Inflammation in Liver Injury Caused by Perfluorooctanoic Acid Exposure in Mice. *Biomed Res. Int.*: 7.
- Zeng HC, Zhang L, Li YY, Wang YJ, Xia W, Lin Y, Wei J, Xu SQ. 2011. Inflammation-like glial response in rat brain induced by prenatal PFOS exposure. *Neurotox* 32(1): 130-139.
- Zhang YH, Wang J, Dong GH, Liu MM, Wang D, Zheng L, Jin YH. 2013. Mechanism of perfluorooctanesulfonate (PFOS)-induced apoptosis in the immunocyte. *J Immunotoxicol* 10(1): 49-58.
- Zhang H, Fang W, Wang D, Gao N, Ding Y, Chen C. 2014. The role of interleukin family in perfluorooctanoic acid (PFOA)-induced immunotoxicity. *J Hazard Mater* 280: 552-560.
- Zhang F, Wei J, Li Q, Jiang R, Yu N, Qin J, Chen L. 2015. Effects of perfluorooctane sulfonate on the immune responses and expression of immune-related genes in Chinese mitten-handed crab *Eriocheir sinensis*. *Comp Biochem Physiol C Toxicol Pharmacol* 172-173: 13-18.
- Zheng L, Dong GH, Jin YH, He QC. 2009. Immunotoxic changes associated with a 7-day oral exposure to perfluorooctanesulfonate (PFOS) in adult male C57BL/6 mice. *Arch Toxicol* 83(7): 679-689.
- Zheng L, Dong GH, Zhang YH, Liang ZF, Jin YH, He QC. 2011. Type 1 and Type 2 cytokines imbalance in adult male C57BL/6 mice following a 7-day oral exposure to perfluorooctanesulfonate (PFOS). *J Immunotoxicol* 8(1): 30-38.
- Zou W, Liu W, Yang B, Wu L, Yang J, Zou T, Liu F, Xia L, Zhang D. 2015. Quercetin protects against perfluorooctanoic acid-induced liver injury by attenuating oxidative stress and inflammatory response in mice. *Int Immunopharmacol* 28(1): 129-135.

In vitro experimental studies

- Ahuja V, Eisenblatter M, Ignatius R, Stahlmann R. 2009. Ammonium perfluorooctanoate substantially alters phenotype and cytokine secretion of human monocyte-derived dendritic cells in vitro. *Immunopharm Immunot* 31(4): 641-646.
- Botelho SC, Saghafian M, Pavlova S, Hassan M, DePierre JW, Abedi-Valugerdi M. 2015. Complement activation is involved in the hepatic injury caused by high-dose exposure of mice to perfluorooctanoic acid. *Chemosphere* 129: 225-231.
- Brieger A, Bienefeld N, Hasan R, Goerlich R, Haase H. 2011. Impact of perfluorooctanesulfonate and perfluorooctanoic acid on human peripheral leukocytes. *Toxicol In Vitro* 25(4): 960-968.

- Corsini E, Avogadro A, Galbiati V, dell'Agli M, Marinovich M, Galli CL, Germolec DR. 2011. In vitro evaluation of the immunotoxic potential of perfluorinated compounds (PFCs). *Toxicol Appl Pharmacol* 250(2): 108-116.
- Corsini E, Sangiovanni E, Avogadro A, Galbiati V, Viviani B, Marinovich M, Galli CL, Dell'Agli M, Germolec DR. 2012. In vitro characterization of the immunotoxic potential of several perfluorinated compounds (PFCs). *Toxicol Appl Pharmacol* 258(2): 248-255.
- Gimenez-Bastida JA, Surma M, Zielinski H. 2015. In vitro evaluation of the cytotoxicity and modulation of mechanisms associated with inflammation induced by perfluorooctanesulfonate and perfluorooctanoic acid in human colon myofibroblasts CCD-18Co. *Toxicol In Vitro* 29(7): 1683-1691.
- Han Z, Liu Y, Wu D, Zhu Z, Lü C. 2012. Immunotoxicity and hepatotoxicity of PFOS and PFOA in tilapia (*Oreochromis niloticus*). *Chinese Journal of Geochemistry* 31(4): 424-430.
- Lee SW, Son HY, Yoon WK, Jung JY, Park BK, Cho ES, Park SJ, Kim TH, Ryu SY. 2010. Effect of Atrazine, Perfluorooctanoic Acid and Zearalenone on IFN gamma, TNF alpha, and IL-5 mRNA Expression in Jurkat Cells. *Biomolecules & Therapeutics* 18(3): 286-293.
- Levitt D, Liss A. 1986. Toxicity of perfluorinated fatty acids for human and murine B cell lines. *Toxicol Appl Pharmacol* 86(1): 1-11.
- Levitt D, Liss A. 1987. Perfluorinated fatty acids alter merocyanine 540 dye binding to plasma membranes. *J Toxicol Environ Health* 20(3): 303-316.
- Liao Y, Wang J, Huang QS, Fang C, Kiyama R, Shen H, Dong S. 2012. Evaluation of cellular response to perfluorooctane sulfonate in human umbilical vein endothelial cells. *Toxicol In Vitro* 26(3): 421-428.
- Liao Y, Dong S, Kiyama R, Cai P, Liu L, Shen H. 2013. Flos *Ionicerae* extracts and chlorogenic acid protect human umbilical vein endothelial cells from the toxic damage of perfluorooctane sulphonate. *Inflammation* 36(3): 767-779.
- Lu Y, Luo B, Li J, Dai J. 2015. Perfluorooctanoic acid disrupts the blood-testis barrier and activates the TNFalpha/p38 MAPK signaling pathway in vivo and in vitro. *Arch Toxicol*.
- Messina PV, Prieto G, Sabín J, Blanco E, Varela C, Doderó V, Ruso JM, Sarmiento F. 2007. A potentiometric and spectroscopic study on the interaction between human immunoglobulin G and sodium perfluorooctanoate in aqueous solution. *Macromol Symp* 251: 103-111.
- Messina PV, Prieto G, Salgado F, Varela C, Nogueira M, Doderó V, Ruso JM, Sarmiento F. 2007. The influence of sodium perfluorooctanoate on the conformational transitions of human immunoglobulin. *J Phys Chem B* 111(28): 8045-8052.
- Midgett K, Peden-Adams MM, Gilkeson GS, Kamen DL. 2015. In vitro evaluation of the effects of perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) on IL-2 production in human T-cells. *J Appl Toxicol* 35(5): 459-465.
- Miyano Y, Tsukuda S, Sakimoto I, Takeuchi R, Shimura S, Takahashi N, Kusayanagi T, Takakusagi Y, Okado M, Matsumoto Y, Takakusagi K, Takeuchi T, Kamisuki S, Nakazaki A, Ohta K, Miura M, Kuramochi K, Mizushima Y, Kobayashi S, Sugawara F, Sakaguchi K. 2012. Exploration of the binding proteins of perfluorooctane sulfonate by a T7 phage display screen. *Bioorg Med Chem* 20(13): 3985-3990.
- Singh TS, Lee S, Kim HH, Choi JK, Kim SH. 2012. Perfluorooctanoic acid induces mast cell-mediated allergic inflammation by the release of histamine and inflammatory mediators. *Toxicol Lett* 210(1): 64-70.
- Wang C, Nie X, Zhang Y, Li T, Mao J, Liu X, Gu Y, Shi J, Xiao J, Wan C, Wu Q. 2015. Reactive oxygen species mediate nitric oxide production through ERK/JNK MAPK signaling in HAPI microglia after PFOS exposure. *Toxicol Appl Pharmacol* 288(2): 143-151.
- Wei Y, Shi X, Zhang H, Wang J, Zhou B, Dai J. 2009. Combined effects of polyfluorinated and perfluorinated compounds on primary cultured hepatocytes from rare minnow (*Gobiocypris rarus*) using toxicogenomic analysis. *Aquat Toxicol* 95(1): 27-36.

- Wens B, De Boever P, Verbeke M, Hollanders K, Schoeters G. 2013. Cultured human peripheral blood mononuclear cells alter their gene expression when challenged with endocrine-disrupting chemicals. *Toxicology* 303: 17-24.
- Wirth JR, Peden-Adams MM, White ND, Bossart GD, Fair PA. 2014. In vitro PFOS exposure on immune endpoints in bottlenose dolphins (*Tursiops truncatus*) and mice. *J Appl Toxicol* 34(6): 658-666.
- Yamaki K, Yoshino S. 2010. Enhancement of Fc ϵ RI-mediated degranulation response in the rat basophilic leukemia cell line RBL2H3 by the fluorosurfactants perfluorooctanoic acid and perfluorooctane sulfonate. *Environ Toxicol Pharmacol* 29(2): 183-189.
- Yang Q, Xie Y, Depierre JW. 2000. Effects of peroxisome proliferators on the thymus and spleen of mice. *Clin Exp Immunol* 122(2): 219-226.
- Yang Q, Abedi-Valugerdi M, Xie Y, Zhao XY, Moller G, Nelson BD, DePierre JW. 2002. Potent suppression of the adaptive immune response in mice upon dietary exposure to the potent peroxisome proliferator, perfluorooctanoic acid. *Int Immunopharmacol* 2(2-3): 389-397.
- Yang J, Wang C, Nie X, Shi S, Xiao J, Ma X, Dong X, Zhang Y, Han J, Li T, Mao J, Liu X, Zhao J, Wu Q. 2015. Perfluorooctane sulfonate mediates microglial activation and secretion of TNF- α through Ca²⁺-dependent PKC-NF- κ B signaling. *Int Immunopharmacol* 28(1): 52-60.
- Zhu J, Qian W, Wang Y, Gao R, Wang J, Xiao H. 2015. Involvement of mitogen-activated protein kinase and NF- κ B signaling pathways in perfluorooctane sulfonic acid-induced inflammatory reaction in BV2 microglial cells. *J Appl Toxicol*.

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>