Supplemental materials

Literature search methods

The causal question of interest for this review is whether PFOA and PFOS are causally related to adverse immunological health conditions in humans. The search for relevant literature was designed and conducted according to recommended best practices (Rhomberg et al., 2013). Articles eligible for inclusion were original epidemiologic research studies that reported associations between exposure specifically to PFOA and/or PFOS and any health outcome primarily affecting the immune system, including immune cell and biomarker levels, atopic conditions, infectious diseases, autoimmune disorders, inflammatory conditions, and any other health conditions considered by the authors to be directly related to immune system function or origin. Non-human studies, studies that did not measure or estimate exposure specifically to PFOA or PFOS, clinical intervention studies, risk assessments, reviews, meta-analyses, commentaries, letters to the editor, case reports, news articles, unpublished reports, and abstracts were excluded, although the reference lists of some review articles were examined to identify additional relevant articles.

To identify relevant published epidemiologic studies of the associations of PFOA and PFOS with immunological conditions, we conducted searches of Scopus and MEDLINE (accessed via PubMed) through September 1, 2015, using keywords and keyword roots including PFOA, APFO, PFOS, PSOF, perfluoroocatan*, perfluor*, perfluorinate*, fluorochemical*, perfluoroalkyl*, allerg*, allergi*, allergy*, asthma*, atop*, autoimmun*, cytokine*, immun*, immune*, immunol*, immunologic*, infect*, infection*, infectious*, inflammat*, leukocyt*, lymphocyt*, ulcerative, and vaccin*, and the Medical Subject Heading (MeSH) keywords fluorocarbons, autoimmune diseases, hypersensitivity, immune system, immune system diseases, immune system phenomena, immune system processes, immunity – active, immunity – cellular, immunity – humoral, immunity – innate, immunity – mucosal, immunologic factors, infection, and inflammation. We examined titles and abstracts to identify potentially relevant articles for full-text review, and we checked bibliographies of reviewed articles and the C8 Science Panel Probable Link Reports (http://www.c8sciencepanel.org/prob_link.html) for additional relevant articles. If relevant unpublished materials were identified from these additional sources, they
were reviewed (if obtainable) but not considered for inclusion because of the non-systematic nature of the search for these materials.

The literature search was intentionally inclusive to avoid omission of relevant studies; however, the broad search criteria resulted in the initial identification of numerous irrelevant articles. Of 1,382 citations identified using these search criteria, the vast majority were either non-human studies or not relevant to PFASs, and were therefore excluded based on a review of titles and abstracts. Of 34 full-text articles reviewed, 3 were excluded because they did not evaluate immunological health conditions, 1 was excluded because it did not pertain specifically to PFOA or PFOS, 5 were excluded because they were non-human studies, and 1 was excluded because it did not estimate associations with any health outcomes. All investigators agreed on the final list of 24 included articles (Anderson-Mahoney et al., 2008; Ashley-Martin et al., 2015; Costa et al., 2009; Dong et al., 2013; Emmett et al., 2006; Fei et al., 2010; Grandjean et al., 2012; Granum et al., 2013; Humblet et al., 2014; Innes et al., 2011; Kielsen et al., 2015; Leonard et al., 2008; Lin et al., 2011; Looker et al., 2014; Okada et al., 2014; Okada et al., 2012; Olsen et al., 2003; Osuna et al., 2014; Pennings et al., 2015; Smit et al., 2015; Steenland et al., 2015; Steenland et al., 2013; Uhl et al., 2013; Wang et al., 2011).
### Supplemental Table 1. Design of epidemiologic studies of the association between exposure to perfluorooctanoic acid (PFOA) and/or perfluorooctanesulfonate (PFOS) and immunological health conditions. Columns show first author and year of study reference, location of study, type of study design, number and characteristics of study subjects, type of comparison population for estimates of association, methods of exposure and outcome assessment, funding sources, and additional comments.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Location</th>
<th>Design</th>
<th>Subjects</th>
<th>Comparison group</th>
<th>Exposure assessment</th>
<th>Outcome assessment</th>
<th>Funding</th>
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<tbody>
<tr>
<td>Deoan et al. 2003</td>
<td>Belgium and Decatur, Alabama, United States</td>
<td>Cross-sectional</td>
<td>518 workers at two fluorochromic manufacturing facilities (255 from Antwerp facility, mean age = 37 years; 263 from Decatur facility, mean age = 43 years) who voluntarily participated in a fluorochromic medical surveillance program (participation rate = 75% at Antwerp facility, 52% at Decatur facility)</td>
<td>Internal comparison</td>
<td>Surveillance program conducted in 2000</td>
<td>PFCA and PFOA measured in serum by HPLC-MS/MS</td>
<td>Antwerp geometric mean serum PFOA = 0.33 ppm (95% CI = 0.27–0.40)</td>
<td>NCI assume 3M Company</td>
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<td>Emmett et al. 2006</td>
<td>Little Hocking Water Association, Ohio, United States</td>
<td>Cross-sectional</td>
<td>371 residents from a stratified random sample of persons from households residing in the Little Hocking water district for 22 years, with high potential for PFOA exposure from water and air or water only (n = 317; participation rate = 41.2–48.7%) in areas with water and air exposure, 35.7–36.8% in areas with water only or from a lottery-selected group of volunteers with same eligibility criteria (n = 54), including 18 with substantial occupational PFOA exposure from analysis; median age = 50 years (range = 2.5–88.9), including 43 children &lt;18 years</td>
<td>Internal comparison</td>
<td>Study conducted in 2004–2005</td>
<td>PFOS measured in non-fasting serum by HPLC-MS/MS</td>
<td>Median serum PFOS: Overall (n = 371): 354 ng/mL (IQR = 184–571) Occupationally exposed subjects (n = 18): 775 ng/mL (IQR = 422–999) Community members with water and air exposure (n = 122): 298 ng/mL (IQR = 155–556) Community members with only water exposure (n = 238): 361 ng/mL (IQR = 186–555)</td>
<td>Environme ntal Justice Program and National Institute of Environmental Health Sciences</td>
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<td>Anderson-Mahoney et al. 2008</td>
<td>Mid-Ohio River Valley, Ohio and West Virginia, United States</td>
<td>Cross-sectional</td>
<td>560 white adult volunteers (mean age = 40.0 years, SD = 14.4) residing for ≥1 year near a Teflon manufacturing plant, including 65% from Lubec Public Service District in West Virginia or Little Hocking Water Association in Ohio, recruited through public invitation via TV, radio, and newspaper advertisements (participation rate = 2.5% from target population of ~70,010)</td>
<td>Study</td>
<td>Study conducted over 3 days in 2003</td>
<td>Residence along Ohio River near Teflon manufacturing plant in Wood County, West Virginia</td>
<td>Demographics, occupational, and health information assessed by questionnaire</td>
<td>Asthma and other chronic health outcomes assessed by questionnaire administered in person to groups of 30–40 participants or by telephone to individuals; excluded health outcomes diagnosed prior to time of residence in study area</td>
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<td>Leonard et al. 2008</td>
<td>1948-2002</td>
<td>Mean follow-up ± SD = 18 ± 15 years (range = &lt;1–49) for males, 16 ± 10 years (range = &lt;1–49) for females</td>
<td>Ever employment at the Parkersburg polymer manufacturing plant</td>
<td>Follow-up from 1948–2002</td>
<td>Mean employment duration ± SD = 19 ± 13 years (range = &lt;1–49) for males, 10 ± 11 years (range = &lt;1–44) for females</td>
<td>Mortality from infectious and parasitic diseases, asthma, or influenza and pneumonia ascertainment through linkage to the Social Security Administration (for vital status) and the DuPont Epidemiology Registry and National Death Index (for cause of death)</td>
<td>NR; assume E. I. du Pont de Nemours and Company (DuPont)</td>
<td>Results for mortality from asthma were calculated by subtracting observed and expected counts of deaths from bronchitis and emphysema from counts of deaths for bronchitis, emphysema, and asthma combined; 95% CIs for asthma SMRs were calculated using Fisher’s exact approach</td>
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<td>Costa et al. 2009</td>
<td>Trissino, Italy</td>
<td>Cross-sectional</td>
<td>53 male workers in the PFOA production department (37 currently exposed, 16 formerly exposed) at a chemical plant with annual medical exams; mean age 41.6 years (SD = 8.3) for currently exposed workers, 52.0 (SD = 8.7) for formerly exposed workers</td>
<td>Comparison 1: 34 currently exposed vs. 34 matched non-exposed workers</td>
<td>Workers classified as currently, formerly, or never occupationally exposed to PFOA</td>
<td>Median serum PFOA measured by HPLC-MS/MS in 2007 = 5.71 µg/mL (range = 0.20–47.94) in currently exposed workers, 4.43 µg/mL (range = 0.53–18.66) in formerly exposed workers; range in 2006 = 0.05–0.181 µg/mL in non-exposed workers; highest level recorded = 91.9 µg/mL in 2002</td>
<td>Medical exams conducted in 1978–2007 and PFOA measured in 2000–2007, but analyzed at single time point</td>
<td>NR</td>
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<td>Fei et al. 2010</td>
<td>Denmark</td>
<td>Prospective cohort</td>
<td>1,400 mother-child pairs including singleton live-born infants without congenital malformation, randomly selected from 43,045 eligible mothers in the Danish National Birth Cohort who completed two telephone interviews before birth and two telephone interviews after birth, and provided a blood sample at the first antenatal visit; ~50% of all general practitioners in Denmark participated in recruitment and ~60% of invited women participated in cohort; mean age of children at end of follow-up = 8.2 years (range = 5.8–10.7)</td>
<td>Internal comparison Follow-up from birth (1996–2002) through date of death, emigration, or December 31, 2008, whichever occurred first</td>
<td>PFPOA and PFOS measured blindly in maternal plasma by HPLC-MS/MS (except for 12 whole blood samples, which were multiplied by 2 for comparability to plasma) collected at first antenatal care visit (gestational weeks 4–14, median = 8 weeks)</td>
<td>Mean plasma PFOA = 5.6 ng/mL (range = &lt;1.0–41.5) Mean plasma PFOS = 35.3 ng/mL (range = 6.4–106.7)</td>
<td>Sociodemographic, reproductive, lifestyle, environmental, familial, and other information assessed via telephone interview at ~12 and 30 weeks of gestation and ~6 and 18 months after birth</td>
<td>Hospitalization due to infection in early childhood, ascertained by NR linkage to Danish National Hospital Register; excluded all hospitalizations within the week following an admission</td>
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| Innes et al. 2011 | Mid-Ohio River Valley, Ohio and West Virginia, United States | Cross-sectional     | 3,731 adults with osteoarthritis enrolled in the C8 Health Project (participation rate = 81% of all adult residents of 6 targeted Ohio Valley water districts), excluding those with a physician diagnosis of rheumatoid arthritis and those with missing data on PFOA, PFOS, or other covariates of interest; mean age of cases = 60.50 years (SD = 12.60) 45,701 adults without osteoarthritis from the same eligible study group; mean age of non-cases = 45.12 years (SD = 14.93) | Study conducted in 2005–2006 | PFPOA and PFOS measured in serum by HPLC-MS/MS | Median serum PFOA = 28.2 ng/mL (range = <0.5–22.412 ng/mL) Median serum PFOS = 20.5 ng/mL (range = <0.5–729.2 ng/mL) | Physician diagnosis of osteoarthritis and other medical conditions assessed via self-administered questionnaire | Demographic, lifestyle, and anthropometric characteristics assessed via self-administered questionnaire | 69,030 C8 Health Project participants 53,428 eligible adults aged 271 years 51,426 without physician diagnosis of rheumatoid arthritis 51,093 with data on serum PFOA and PFOS Endowments 49,432 with data on covariates of interest Fund; National Center for Complementary and Alternative Medicine and Office of Research on Women's Health 51,093 with data on serum PFOA and PFOS Endowments 49,432 with data on covariates of interest Fund; National Center for Complementary and Alternative Medicine and Office of Research on Women's Health
Standard childhood immunization schedule: diphtheria and tetanus, pertussis, polio, and Haemophilus type b at age 3 months, repeated at ages 5 and 12 months, with booster vaccination against diphtheria and tetanus at age 5 years; booster vaccine also included pertussis antigen as of 9/2003 and polio antigen as of 7/2004.

464 children (71%) participating at age 7 years did not differ significantly from nonparticipants in terms of sex, maternal perfluorinated compound levels, or antibody concentration at age 5 years.

Pearson's ρ between PFOA and PFOS at National Institute of Environmental Health Sciences; U.S. Environmental Protection Agency; Danish Council for Strategic Research; and Danish Environmental Protection Agency.

Serum concentrations of antibodies against tetanus toxoid measured using ELISA in child serum at ages 5 years (before and after the diphtheria and tetanus booster) and 7 years.

Total IgE in cord serum and serum at age 2 years measured using standard Vero cell-based neutralization assay in child serum at ages 5 and 7 years.

Serum concentrations of antibodies against tetanus toxoid measured using a commercially available kit.

High-sensitivity b-reactive protein measured in fasting serum using a commercially available kit.

Total IgE in cord serum and serum at age 2 years measured using a commercially available kit; values >100 KU/L = "increased", values <0.35 KU/L = "undetectable".

Internal comparison Follow-up from 201 children without atopic dermatitis from the same eligible study group.

Birth year, parental sociodemographics, parental medical and behavioral history, and childhood environment assessed by at-home interview; birth health information obtained from medical records; postnatal exposures (e.g., breastfeeding, early diet, birth order, home environment) assessed by International Study of Asthma and Allergies in Childhood questionnaire completed at age 2 years.

Serum concentrations of antibodies against tetanus toxoid measured using standard Vero cell-based neutralization assay in child serum at ages 5 and 7 years.

Clinically protective antibody concentration defined as >0.1 IU/mL.

Clinical sensitivity and specificity determined by a dermatologist based on a subgroup of participants.

National Health Research Institute of Taiwan and National Science Council of Taiwan.

Spearman's p between PFOA and PFOS = 0.09; correlations between other PFAS = 0.05–0.62.

Prospective cohort 483 children with cord blood specimens 328 with sufficient serum volume 244 with complete data and follow-up.

"There was no significant difference between those who lost to follow-up and those who completed the follow-up."
Supplemental Table 1, continued

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<tr>
<td>Okada et al. 2012</td>
<td>Sapporo, Japan</td>
<td>Prospective cohort</td>
<td>344 mother-child pairs (251 with cord serum IgE results) based on pregnant Japanese women (mean age = 31.3 years, SD = 4.4) enrolled at 23–35 weeks of gestation from a single obstetrics and gynecology hospital (participation rate = 28.6%), paired with their live-born infants</td>
<td>Internal comparison</td>
<td>Follow-up from 23–35 weeks of gestation (2002–2005) to age 18 months</td>
<td>PFDA and PFOS measured by HPLC-MS/MS in maternal serum obtained after second trimester of pregnancy or, in case of anemia, after delivery (proportion not specified)</td>
<td>Total IgE measured using ELISA in cord serum samples collected at delivery</td>
<td>Japanese Ministry of Health, Labor, and Welfare and Japanese Ministry of Education, Culture, Sports, Science, and Technolog y</td>
<td>1,796 women invited to participate 514 accepted 504 without miscarriage, stillbirth, relocation, or voluntary study withdrawal before delivery 491 without infant death, relocation, or voluntary study withdrawal after delivery 343 included with PFPA and PFOS in maternal serum and information on infant allergies and infectious diseases 231 included with total IgE in cord serum (excluding two considered to be contaminated by maternal blood)</td>
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<td>Dong et al. 2013</td>
<td>Northern Taiwan</td>
<td>Case-control</td>
<td>231 children aged 10–15 years with asthma diagnosed by a physician in the previous year at one of two hospitals; mean age = 13.6 years (SD = 0.7)</td>
<td>Study conducted in 2005–2010</td>
<td>PFDA and PFOS measured by HPLC-MS/MS in fasting serum drawn after study enrollment</td>
<td>Asthma diagnosed in the previous year by a physician at one of two participating hospitals</td>
<td>Japan Science Council in Taiwan</td>
<td>Spearman’s ρ between PFOA and PFOS = 0.64; correlations between other PFAS = 0.02–0.79</td>
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<td>Granum et al. 2013</td>
<td>Norway</td>
<td>Prospective cohort</td>
<td>99 pregnant women with singleton births already enrolled in the Norwegian Mother and Child Cohort Study (108,000 pregnancies between 1999 and 2008) and scheduled to give birth in Oslo or Akershus (participation rate = 25%), with maternal blood collected at delivery, excluding women with autoimmune diseases or use of steroidal, anti-inflammatory, or epileptic drugs during pregnancy; for analyses of serological outcomes at age 3 years (mean age = 35 months, range = 31–38 months), limited to 56 subjects with paired mother-child serum samples</td>
<td>Internal comparison</td>
<td>Follow-up from birth (2007–2008) to age 3 years</td>
<td>PFDA and PFOS measured by HPLC-MS/MS in maternal plasma collected 0–3 days after delivery</td>
<td>IgG antibody titers against tetanus toxoid, Haemophilus influenza type b, measles virus, and rubella measured using ELISA in serum at age 3 years</td>
<td>European Union Integrated Project NewGeneris; 6th Framework Program e; and Norwegian Institute of Public Health</td>
<td>Norwegian Childhood Vaccination Program includes tetanus and Haemophilus influenza type b vaccines at ages 1, 5, and 12 months, and measles and rubella at age 15 months; vaccination coverage ~93–94%, 4 children not following the standard program were excluded from analyses of vaccination responses 99 participants 93 with questionnaire at 1 year 89 with questionnaire at 2 years 85 with questionnaire at 3 years 76 with questionnaire at all 3 years 56 with paired mother-child blood</td>
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Correlation coefficients for 4 PFAS = 0.26–0.60 (P ≤ 0.011)
15,562 adults aged 20–84 years in NHANES 2003–4,562 with PFOA and PFOS data
4,102 with osteoarthritis data (including 365 [8.9%] with osteoarthritis)
3,809 with covariate data
Baseline survey
74% of adults consented to follow-up
32,712 participated in follow-up survey
6,027 past and current plant workers in earlier study
4,391 participated in baseline survey
3,713 participated in follow-up survey
(includes 1,890 participants in C8 Health Project)
Combined total = 32,254 with estimated historical PFOA serum concentrations (exclusions not specified)
C8 Class
Spearman’s \( \rho \) predictions and PFOA measurements
Obtained in 2005–2006 from 45,276
Family Foundation; Robert & Patricia Switzer Foundation; Carpenter/Sperry Fund; and Yale School of Forestry & Environmental Studies
Osteoarthritis assessed by self-administered questionnaire
based on question “Has a doctor or other health professional ever told you that you had arthritis?” and, if so, “Which ... it?” (excluded if type not specified; classified as non-case if type specified as rheumatoid or other non-osteoarthritis)
Internal comparison Study
PFOA and PFOS measured by HPLC/MS-MS in serum
Ever diagnosis with an autoimmune disease (lupus, multiple sclerosis, myasthenia gravis, Sjogren’s syndrome, vasculitis, Addison’s disease, or other specified), inflammatory bowel disease (ulcerative colitis or Crohn’s disease; excluding irritable bowel syndrome), arthritis (rheumatoid arthritis or osteoarthritis), or diabetes (type 1 or type 2; excluding pregnancy-induced) by a doctor or other health professional
Medical history assessed by self-administered questionnaire; for subjects who reported having had any chronic disease of interest, consent was requested for medical records review and health care provider contact; consent was granted by ~75%, and a relevant medical record was found for 92% of those who consented
% validated self-reports: 25% of 595 ulcerative colitis, 53% of 178 Crohn’s disease, 27% of 1,292 rheumatoid arthritis, 47% of 342 type 1 or insulin-dependent diabetes, 39% of 187 lupus, and 66% of 150 multiple sclerosis = 34% of autoimmune disorders combined
Analysis restricted to validated cases, with unvalidated self-reported cases excluded from analysis of each outcome
Cumulative PFOA exposure since 1952 (approximate first year of PFOA emissions from the plant) estimated based on historical annual serum PFOA estimates, developed from estimated intake of PFOA-contaminated drinking water, including information on amount of PFOA released from the polymer manufacturing plant, wind patterns, river flow, groundwater flow, and residential address history
For workers, past annual serum PFOA levels were estimated for each job
Median serum PFOA measured in 2005–2006 = 24 ng/mL (IQR = 10–59) for community members, 113 ng/mL (IQR = 56–256) for workers
Median serum PFOA in cases = 24.57 ng/mL (95% CI = 21.49–27.65); Median serum PFOA in non-cases = 21.23 ng/mL (95% CI = 20.06–22.59)
Median serum PFOS in children ever with asthma = 17.0 ng/mL (IQR = 10.8–25.8)
Median serum PFOS in children never with asthma = 16.8 ng/mL (IQR = 10.8–26.2)
Study conducted in 2003–2008
Internal comparison
Study conducted in 1999–2008
Uhl et al. 2013
United States
Cross-sectional
3,809 adults aged 20–84 years who lived, worked, or attended school in any of six water districts contaminated with PFOA from a nearby polymer manufacturing plant, were enrolled in the C8 Health Project in 2005–2006 (~85% participation by adults), and completed a follow-up survey (61% participation, based on 74% consented and 82% interviewed) in 2008–2010 and/or 2010–2011 by phone (63%) or online (37%), including 4% next-of-kin surveys for deceased subjects
Total: n = 28,841 community members and 3,713 workers; median year of birth = 1958 for community members, 1951 for workers
Study conducted in 2003–2008
Internal comparison
Study conducted in 1999–2008
Humblet et al. 2014
United States
Cross-sectional
1,877 children aged 12–19 years who participated between 1999 and 2008 in NHANES, which uses multistage probability sampling to select ~5,000 representative study participants annually from the civilian, noninstitutionalized U.S. population
PFOA and PFOS measured by HPLC/MS-MS in serum from a random sample of one-third of NHANES participants aged ≥12 years
Weighted mean PFOA in cases = 5.39 ng/mL (95% CI = 4.91–5.87)
Weighted mean PFOS in non-cases = 4.87 ng/mL (95% CI = 4.59–5.15)
Weighted mean PFOS in cases = 24.57 ng/mL (95% CI = 21.49–27.65)
Weighted mean PFOS in non-cases = 21.23 ng/mL (95% CI = 20.06–22.59)
Sociodemographic, dietary, medical, lifestyle, reproductive, and other information assessed by self-administered questionnaire
PFOS and PFOS measured by HPLC/MS-MS in serum from a random sample of one-third of NHANES participants aged ≥12 years from 1999–2000 and 2003–2008
Median serum PFOA in children ever with asthma = 4.3 ng/mL (IQR = 3.1–5.7)
Median serum PFOA in children never with asthma = 4.0 ng/mL (IQR = 2.8–5.4)
Sociodemographic, lifestyle, and other information assessed by self-administered questionnaire
Median serum PFOS in children ever with asthma = 17.0 ng/mL (IQR = 10.8–25.8)
Median serum PFOS in children never with asthma = 16.8 ng/mL (IQR = 10.8–26.2)
Osteoarthritis assessed by self-administered questionnaire based on question “Has a doctor or other health professional ever told you that you had arthritis?” and, if so, “Which type of arthritis was it?” (excluded if type not specified; classified as non-case if type specified as rheumatoid or other non-osteoarthritis)
Jubitz Family Foundation
Robert & Patricia Switzer Foundation
Cross-sectional
3,809 adults aged 20–84 years who lived, worked, or attended school in any of six water districts contaminated with PFOA from a nearby polymer manufacturing plant, were enrolled in the C8 Health Project in 2005–2006 (~85% participation by adults), and completed a follow-up survey (61% participation, based on 74% consented and 82% interviewed) in 2008–2010 and/or 2010–2011 by phone (63%) or online (37%), including 4% next-of-kin surveys for deceased subjects
Total: n = 28,841 community members and 3,713 workers; median year of birth = 1958 for community members, 1951 for workers
Study conducted in 2003–2008
Internal comparison
Study conducted in 1999–2008
Humblet et al. 2013
Mid-Ohio River Valley, Ohio and West Virginia, United States
Retrospective cohort
30,411 adults aged ≥20 years who lived, worked, or attended school in any of six water districts contaminated with PFOA from a nearby polymer manufacturing plant, were enrolled in the C8 Health Project in 2005–2006 (~85% participation by adults), and completed a follow-up survey (61% participation, based on 74% consented and 82% interviewed) in 2008–2010 and/or 2010–2011 by phone (63%) or online (37%), including 4% next-of-kin surveys for deceased subjects
1,823 additional current and former workers at the plant between 1948 and 2002 who were previously studied for mortality and were not enrolled in the C8 Health Project, but completed the same surveys (84% participation)
Total: n = 28,841 community members and 3,713 workers; median year of birth = 1958 for community members, 1951 for workers
Study conducted in 2003–2008
Internal comparison
Study conducted in 1999–2008
Uhl et al. 2013
United States
Cross-sectional
3,809 adults aged 20–84 years who lived, worked, or attended school in any of six water districts contaminated with PFOA from a nearby polymer manufacturing plant, were enrolled in the C8 Health Project in 2005–2006 (~85% participation by adults), and completed a follow-up survey (61% participation, based on 74% consented and 82% interviewed) in 2008–2010 and/or 2010–2011 by phone (63%) or online (37%), including 4% next-of-kin surveys for deceased subjects
1,823 additional current and former workers at the plant between 1948 and 2002 who were previously studied for mortality and were not enrolled in the C8 Health Project, but completed the same surveys (84% participation)
Total: n = 28,841 community members and 3,713 workers; median year of birth = 1958 for community members, 1951 for workers
Okada et al. 2014 Hokkaido, Japan Prospective cohort 2,062 mother-child pairs based on pregnant indigenous Japanese women (mean age = 30.4 ± 4.5 years) enrolled during their first trimester of pregnancy from one of 37 participating hospitals (participation rate = 53.3%), paired with their live-born, singleton infants without congenital malformation

Osuna et al. 2014 Tórshavn, Faroe Islands Prospective cohort 38 children born at a single national hospital who also provided a blood sample at age 7 years

Looker et al. 2014 Mid-Ohio River Valley, Ohio and West Virginia, United States Cross-sectional 33,500 eligible women

Internal comparison

Follow-up from first trimester of pregnancy (2003–2009) to age 24 months

Follow-up from birth (1988–1987) to age 7 years

Study conducted in 2010–2011

Internal comparison

Follow-up from a second interview and blood study, respectively, based on modified International Study of Asthma and Allergies in Childhood phase 3 questionnaire, including three questions on asthma (chronic cough or wheezing that woke the child at night), one question on wheezing (wheezing or whistling in chest), and two questions on allergic rhinoconjunctivitis symptoms (running or itchy nose or blocked nose and itchy, watery eyes without cold or flu). Total allergic diseases = at least one of asthma, wheezing, and allergic rhinoconjunctivitis symptoms
Genes correlated with 2 or more PFAS included those associated with plasma membrane or adhesion, immunological pathways (including regulation of T-cell receptor signaling pathway, and thymic T-cell selection), nucleotide metabolism, translation, signaling, and development.

Genes correlated with common cold episodes included those associated with membrane and adhesion, immunology (including NF-κB binding, NF-κB signaling pathway, and Th1/T2 cytokine signaling).

Internal comparison Follow-up from first trimester (2008–2011) to birth
PFDA and PFOS measured by HPLC-MS/MS in maternal first-trimester plasma
Geometric mean maternal plasma PFOA = 1.7 ng/mL (SD = 1.8)
Geometric mean maternal plasma PFOS = 4.6 ng/mL (SD = 1.8)
Also measured perfluorohexane sulfonate, 11 phthalate metabolites, and bisphenol A in first-trimester maternal spot urine

Immunglobulin E (IgE), B lymph cell, intracellular, lymph node, and positive regulation of IgG isotypes, signaling, development, and membrane and adhesion.
| Reference | Location          | Design                      | Subjects                                                                 | Comparison group                  | Dates                                                                 | Exposure assessment                                                                 | Outcome assessment                                                                 | Funding Comments                                                                 | Comments |
|-----------|-------------------|-----------------------------|--------------------------------------------------------------------------|-----------------------------------|----------------------------------------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------|
| Smit et al. 2015 | Greenland and Kharkiv, Ukraine | Prospective cohort          | 1,024 mother-child pairs (532 from Greenland, 492 from Ukraine) enrolled during routine antenatal care visits (participation rate = 85% in Greenland, 25% in Ukraine), followed until ages 5-9 years (mean age = 8.2 ± 0.6 years in Greenland, 7.1 ± 0.4 years in Ukraine; follow-up rate = 89% in Greenland, 80% in Ukraine) | Follow-up from pregnancy to age 5–9 years | PFOS and PFOS measured by HPLC-MS/MS in maternal serum (mean = 25 weeks in Greenland, 24 weeks in Ukraine) | Geometric mean maternal serum PFOS = 1.79 ng/mL (95th-99th percentiles = 0.80-3.66) in Greenland, 0.97 ng/mL (0.45-2.34) in Ukraine | Ever or current eczema, ever or current wheeze, and ever asthma assessed based on questions from the standardized International Study of Asthma and Allergies in Childhood, in interviews conducted by a medical doctor assisted by local health workers in Greenland and by pediatricians in Ukraine | European Union 5th and 7th Framework Programmes | Pearson’s $\rho$ between PFOS and PFOA = 0.51; $\rho$ between other pairs of PFAS ranged from 0.02 to 0.75; $\rho$ between PFOA or PFOS and phthalate metabolites ranged from -0.07 to 0.13 |
| Steenland et al. 2015 | Parkersburg, West Virginia, United States | Retrospective and prospective cohort | 3,713 workers (or next of kin for 6%) ever employed at a polymer production plant, with next of kin for deceased workers identified from death certificates; mean and median year of birth = 1951, SD = 14 (participation rate = 73%, including 79% among living workers and 48% among next of kin of deceased workers; further excluded 15% lacking occupational exposure estimates or with insufficient residential history information) | Follow-up from age 20 years or 1951 (whichever was later) until date of diagnosis or last interview (2008–2011) | Past annual PFOS serum levels from occupational exposure estimated using a job-exposure matrix based on >2,000 serum samples from workers in 1979-2004 | Past annual PFOS serum levels from residential exposure since 1951 estimated using an environmental fate and transport model based on historical emission estimates, physicochemical properties of PFOS, local geographic and meteorological data, combined with information on residential history, drinking water sources, and water consumption rates, and using a pharmacokinetic model based on each person's yearly intake rate estimates, demographic information, self-reported body weight, estimated background exposures, and PFOS half-life estimates | Ever diagnosis with an autoimmune disease, asthma with reported current medication, or osteoarthritis with reported current medication | CB Class Action Settlement Agreement | Comparing 3,713 included workers with 2,313 excluded workers, those included were less likely to be known to have died by the end of the study, more likely to be female, and younger |
|          |                   |                             | 166 workers with round 1 interview only, 549 with round 2 interview only, 2,998 with both interviews |                      | Annual serum estimates from occupational exposure model were used during years working at the plant if higher than residential estimates (true for ~82% of workers) | Mean measured serum PFOS in 2005-2006 (n = 1,881) = 325 ng/mL, SD = 300, median = 113 | Mean predicted serum PFOS in 2005-2006 (n = 1,881) = 218 ng/mL, SD = 358, median = 94 |                      | Cumulative serum PFOS quartile cut-offs for lagged analyses were 0.3, 0.6, and 11.42 µg/mL-year |
Supplemental Table 2. 10 warning signs of primary immunodeficiency*

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th></th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Four or more new ear infections within 1 year</td>
<td></td>
<td>Two or more new ear infections within 1 year</td>
</tr>
<tr>
<td>2</td>
<td>Two or more serious sinus infections within 1 year</td>
<td></td>
<td>Two or more new sinus infections within 1 year, in the absence of allergy</td>
</tr>
<tr>
<td>3</td>
<td>Two or more months on antibiotics with little effect</td>
<td></td>
<td>One pneumonia per year for more than 1 year</td>
</tr>
<tr>
<td>4</td>
<td>Two or more pneumonias within 1 year</td>
<td></td>
<td>Chronic diarrhea with weight loss</td>
</tr>
<tr>
<td>5</td>
<td>Failure of an infant to gain weight or grow normally</td>
<td></td>
<td>Recurrent viral infections (colds, herpes, warts, condyloma)</td>
</tr>
<tr>
<td>6</td>
<td>Recurrent, deep skin or organ abscesses</td>
<td></td>
<td>Recurrent need for intravenous antibiotics to clear infections</td>
</tr>
<tr>
<td>7</td>
<td>Persistent thrush in mouth or fungal infection on skin</td>
<td></td>
<td>Recurrent, deep abscesses of the skin or internal organs</td>
</tr>
<tr>
<td>8</td>
<td>Need for intravenous antibiotics to clear infections</td>
<td></td>
<td>Persistent thrush or fungal infection on skin or elsewhere</td>
</tr>
<tr>
<td>9</td>
<td>Two or more deep-seated infections including septicemia</td>
<td></td>
<td>Infection with normally harmless tuberculosis-like bacteria</td>
</tr>
<tr>
<td>10</td>
<td>A family history of primary immunodeficiency</td>
<td></td>
<td>A family history of primary immunodeficiency</td>
</tr>
</tbody>
</table>

*Adapted from Jeffrey Modell Foundation (2013)

References


