## Appendix F – Summary of Immune Effects

The following table summarizes the findings of previous epidemiological studies of PFAS and immune-related effects – specifically hospitalization due to infectious diseases, risk of respiratory tract infections, and decreased vaccine response. These studies include occupational exposure studies, studies of communities living near a PFOA manufacturing facility with high levels of PFOA in the drinking water, and studies of populations exposed to background levels of perfluoroalkyls (referred to as general population studies). This summary reflects the available literature as of 12/01/2020.

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| **Compound** | **Acronym** | **CAS Registry Number** |
| Perfluorooctanoic acid | PFOA | 335-67-1 |
| Perfluorononanoic acid | PFNA | 375-95-1 |
| Perfluorodecanoic acid | PFDA | 335-76-2 |
| Perfluoroundecanoic acid | PFUnA | 2058-94-8 |
| Perfluorododecanoic acid | PFDoDA | 375-73-5 |
| Perfluorohexane sulfonic acid | PFHxS | 1763-23-1 |
| Perfluorooctane sulfonic acid | PFOS | 754-91-6 |
| N-Methylperfluorooctane sulfonamidoacetic acid | MeFOSAA | 2355-31-9 |

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| Study Overview | Serum PFAS Levels | Outcome | Results |
| **Ait Bamai et al. 2020**Prospective cohort study of 2,689 children enrolled in the Hokkaido Study from 2003-2012; children were monitored for physician-diagnosed infectious disease up to 7 years of age. | Median maternal serum PFAS levels PFOA: 1.94 ng/mLPFNA: 1.14 ng/mLPFDA: 0.51 ng/mLPFUnA: 1.43 ng/mLPFDoDA: 0.17 ng/mLPFTrDA: 0.33 ng/mLPFHxS: 0.30 ng/mLPFOS: 5.12 ng/mL | Risk of infectious diseases in early life, based on mothers’ self-administered questionnaire: ChickenpoxOtitis mediaPneumoniaRSV | PFOA: OR (95% CI)Pneumonia: 1.17 (1.01, 1.37)PFDoDA: OR (95% CI)Chicken Pox: 0.85 (0.72, 1.00)No other significant associations were observed between maternal PFAS levels and any of the infectious diseases.  |
| **Dalsager et al. 2016**Prospective cohort study of 359 children (aged 1–4 years) participating in the Odense Child Cohort in Denmark (women enrolled 2010-2012); parents responded to texts every other week regarding the child’s symptoms of infection. | Median maternal serum PFAS level (measured at gestational age 10-16 weeks)PFOA: 1.68 ng/mLPFOS: 8.07 ng/mLPFHxS: 0.32 ng/mLPFNA: 0.70 ng/mLPFDA: 0.27 ng/mL | The following outcomes were evaluated both as odds of number of days above median and number of days (incidence rate):Fever (>101.3°F)CoughNasal DischargeDiarrheaVomiting  | Odds of number of days above median, Fever:PFOA: OR 1.97 (1.07–3.62), 3rd tertilePFOS: OR 2.35 (1.34–4.11), 3rd tertileRate of number of days, Fever:PFOS: IRR 1.65 (1.24–2.18), 3rd tertileOdds of number of days above median, Nasal Discharge:PFNA: OR 0.53 (0.31–0.92), 2nd tertile; OR 0.55 (0.31–0.97), 3rd tertileNo significant associations (p>0.05) between maternal serum levels of PFAS and any other outcomes. |
| **Dalsager et al. 2021**Prospective cohort study of 1,503 mother-child pairs (aged 1–5 years) participating in the Odense Child Cohort in Denmark (women enrolled 2010-2012); admission to hospital with an ICD-10 code for infection was collected through end of August 2015. | Median maternal serum PFAS level (measured at gestational age 10-16 weeks)PFOA: 1.68 ng/mLPFOS: 7.52 ng/mLPFHxS: 0.36 ng/mLPFNA: 0.64 ng/mLPFDA: 0.29 ng/mL | Risk of hospitalizations for infectious disease categorized as:Upper respiratory tract infections (URTI)Lower respiratory tract infections (LRTI)Gastrointestinal infections (GI)Other infections  | Hazard ratios (95% CI) for hospitalization per doubling of maternal PFAS concentrationsAny infectionPFOS: 1.23 (1.05, 1.44)LRTIPFOA: 1.27 (1.01, 1.59) PFOS: 1.54 (1.11, 2.15)No significant associations (p>0.05) between maternal serum levels of PFAS and any other outcomes. |
| **Fei et al. 2010**Prospective cohort study of 1,400 pregnant women participating in the Danish National Birth cohort study; offspring were monitored for hospitalization due to infections in early childhood (average age 8.2 years). | Mean maternal serum PFAS level (measured at gestation week 12)PFOA: 5.6 ng/mLPFOS: 35.3 ng/mL | Rate of hospitalization for infectious disease in young children | PFOA:IRR 0.96 (0.87–1.06) for trendIRR 1.21 (1.04–1.42) for trend, girlsIRR 0.83 (0.73–0.95) for trend, boysPFOS:IRR 1.00 (0.91–1.09) for trendIRR 1.18 (1.03–1.36) for trend, girlsIRR 0.90 (0.80–1.12) for trend, boys |
| **Goudarzi et al. 2017**Prospective cohort study of 1,558 participants in the Hokkaido Study on Environmental and Children’s Health; children were monitored for physician-diagnosed infectious disease up to 4 years of age. | Mean maternal serum PFAS level (measured at 28-32 weeks of gestation)PFOA: 2.71 ng/mLPFOS: 5.46 ng/mLPFHxS: 0.32 ng/mLPFNA: 1.40 ng/mLPFDA: 0.58 ng/mLPFUnA: 1.53 ng/mLPFDoDA: 0.19 ng/mL | Risk of “total infectious diseases” in early life, based on mothers’ self-administered questionnaire. “Total infectious diseases” was defined as at least one of these four common infectious diseases:Otitis mediaPneumoniaVaricellaRSV | PFOA: p=0.39 for trend, OR (95% CI)4th quartile: 1.11 (0.806–1.54) PFOS: p=0.008 for trend, OR (95% CI):2nd quartile: 1.44 (1.06–1.96)3rd quartile: 1.28 (0.949–1.73)4th quartile: 1.61 (1.18–2.21)PFHxS: p=0.93 for trend, OR (95% CI)4th quartile: 0.96 (0.73–1.41)PFNA: p=0.92 for trend, OR (95% CI)4th quartile: 0.92 (0.67–1.25)PFDA: p=0.11 for trend, OR (95% CI)4th quartile: 0.80 (0.59–1.08)PFUnA: p=0.79 for trend, OR (95% CI)4th quartile: 1.03 (0.76–1.40)PFDoDA: p=0.50 for trend, OR (95% CI)4th quartile: 1.07 (0.79–1.46) |
| **Grandjean et al. 2012**Prospective cohort study of children living in the Faroe Islands; children were examined prior to receiving vaccine boosters (5 years of age, n=532) for tetanus and diphtheria, 4 weeks after receiving the 5-year vaccine booster (n=456), and at age 7 (n=464). | Geometric mean maternal serum PFAS levelsPFOA: 3.20 ng/mLPFOS: 27.3 ng/mLPFHxS: 4.41 ng/mLPFNA: 0.60 ng/mLPFDA: 0.28 ng/mLMedian serum PFAS levels at age 5PFOA: 4.1 ng/mLPFOS: 17.3 ng/mLPFHxS: 0.6 ng/mLPFNA: 1.00 ng/mLPFDA: 0.28 ng/mLMedian serum PFAS levels at age 7PFOA: 4.4 ng/mLPFOS: 15.5 ng/mLPFHxS: 0.5 ng/mLPFNA: 1.1 ng/mLPFDA: 0.4 ng/mL | Tetanus and Diphtheria antibody levels at ages 5 and 7  | Changes in antibodies were assessed per two-fold increases in PFAS level. Tetanus antibody at age 5, βPFOS (age 5): -28.5% (-45.4, -6.1)PFHxS (age 5): -19.0% (-29.8, -6.6)PFDA (age 5): -19.9% (-33.1, -3.9)Tetanus antibody at age 7, βPFOA (age 5): -35.8% (-51.9, -14.2)PFHxS (age 5): -19.7% (-31.6, -5.7)PFHxS (age 7): -22.3% (-36.3, -5.2)PFDA (age 5): -22.3% (-35.8, -5.8)Diphtheria antibody at age 5, βPFNA (age 5): -16.1% (-28.8, -1.0)Diphtheria antibody at age 7, βPFOA (age 5): -25.2% (-42.9, -2.0)PFOA (age 7): -25.4% (-40.9, -5.8)PFOS (age 5): -27.6% (-45.8, -3.3)PFOS (age 7): -30.3% (-47.3, -7.8)No other significant associations were noted between maternal or child (ages 5 or 7 years) PFAS levels and antibody levels |
| **Grandjean et al. 2017**Prospective study of 516 children living in the Faroe Islands; serum antibodies to diphtheria and tetanus were measured at age 13 and compared to serum perfluoroalkyl levels at age 7 and 13. | Median serum PFAS levels at age 7PFOA: 4.4 ng/mLPFOS: 15.3 ng/mLPFHxS: 0.5 ng/mLPFNA: 1.1 ng/mLPFDA: 0.4 ng/mLMedian serum PFAS levels at age 13PFOA: 2.0 ng/mLPFOS: 6.7 ng/mLPFHxS: 0.4 ng/mLPFNA: 0.7 ng/mLPFDA: 0.3 ng/mL | Tetanus and Diphtheria antibody levels at ages 7 and 13  | Significant association between serum PFDA and antibodies for tetanus at age 7 (p=0.022), but not at age 13 (p=0.258). No other significant associations reported between any serum PFAS levels at ages 7 or 13 and diphtheria or tetanus antibody levels.  |
| **Granum et al. 2013**Prospective birth cohort study, subcohort of the Norwegian Mother and Child Cohort study, 56 children examined annually to age 3 years; exclusion criteria included maternal use of steroids or anti-inflammatory drugs during pregnancy, as well as maternal autoimmune disease. | Maternal median serum PFAS levels (measured at delivery)PFOA: 1.1 ng/mLPFOS: 5.5 ng/mLPFHxS: 0.3 ng/mLPFNA: 0.3 ng/mL | Rubella antibody levels*Hemophilus influenza* type B antibody levelsTetanus antibody levelsNumber of episodes of common cold (3-year period)Wheezing | Rubella antibody levels, βPFOA: -0.40 (-0.64, -0.17)PFOS: -0.08 (-0.14, -0.02)PFHxS: -0.38 (-0.66, -0.11)PFNA: -1.38 (-2.35, -0.40)Number of episodes of common cold, βPFOA: 0.42 (0.21, 0.62)PFNA: 0.74 (0.05, 1.43)No other significant associations were reported between any PFAS and outcome |
| **Huang et al. 2020**Prospective birth cohort, Shanghai Prenatal Cohort; mothers were enrolled at 29-41 weeks of gestation and children were followed-up at 5 years of age (n=344). | Median cord blood PFAS levelsPFOA: 6.68 ng/mLPFOS: 2.44 ng/mLPFHxS: 0.16 ng/mLPFNA: 0.63 ng/mLPFDA: 0.35 ng/mLPFUnA: 0.39 ng/mLPFDoDA: 0.09 ng/mL | Respiratory tract infections (RTIs) (both lower and upper) in the first 5 years of life. Assessed through self-report from parents, review of medical records, and IgG and IgE levels as biomarkers of humoral immunity  | There were no significant associations between any PFAS and total number of RTIs, nor were there any significant associations between PFAS levels and incidence of recurrent respiratory tract infections. There were no associations between PFAS and IgG or IgE concentrations.  |
| **Impinen et al. 2018**Prospective study of 641 infants participating in the Environment and Childhood Asthma study in Norway; health outcomes were evaluated at 2 and 10 years of age. | Mean cord PFAS levels:PFOA: 1.8 ng/mLPFOS: 5.6 ng/mLPFHxS: 0.3 ng/mLPFNA: 0.2 ng/mLPFUnA: 0.1 ng/mL | Number of common colds (0-2 years of age)Number of lower respiratory infections (0-10 years of age) | Common Cold, βPFUnA: 0.11 (0.08, 0.14)LRTI, βPFOA: 0.28 (0.22, 0.35)PFOS: 0.50 (0.42, 0.57)PFNA: 0.09 (0.03, 0.14)PFUnA: 0.18 (0.13, 0.23) |
| **Impinen et al. 2019**Prospective birth cohort, subcohort of the Norwegian Mother and Child Cohort Study enrolled between 1999-2008. Children were followed-up at 3 years (n=1,270) and 7 years (n=972). | Median maternal serum PFAS levels (collected mid-pregnancy)PFOA: 2.54 ng/mLPFOS: 12.87 ng/mLPFHxS: 0.65 ng/mLPFNA: 0.45 ng/mLPFUnA: 0.20 ng/mL | Parent-reported number of episodes of infections from 0-3 years of age and from 6-7 years of age. Infections included common cold (3 years only) and bronchitis/RS-virus/pneumonia (3 and 7 years) | Common cold, RR (95% CI)PFOA: 0.96 (0.94, 0.99)PFOS: 0.94 (0.92, 0.97)Bronchitis/pneumonia at 3 years of age, RR (95% CI)PFOA: 1.27 (1.12, 1.43)PFOS: 1.20 (1.07, 1.34)PFHxS: 1.15 (1.06, 1.24)No other associations were found for PFAS and episodes of infection.  |
| **Kvalem et al. 2020**Prospective birth cohort, the Environment and Childhood Asthma (ECA) study; PFAS exposure measured at age 10 and health outcomes collected at age 16 for 378 children. | Mean serum PFAS levels at 10 years of agePFOA: 4.62 ng/mLPFOS: 20.9 ng/mLPFHxS: 3.33 ng/mLPFNA: 0.63 ng/mLPFDA: 0.19 ng/mLPFUnA: 0.18 ng/mL  | Parent reported number of episodes of common cold and number of episodes of bronchitis and pneumonia between 10-16 years of age and in last 12 months  | Number of common colds in last 12 months at age 16, OR (95% CI) per IQR increase in PFAS from multinomial logistic regression models≥3 vs. 0 colds, PFOS: 0.67 (0.47, 0.96)≥3 vs. 0 colds, PFNA: 0.63 (0.44, 0.91)≥3 vs. 0 colds, PFDA: 0.56 (0.37, 0.84)≥3 vs. 0 colds, PFUnA: 0.64 (0.44, 0.92)LRTI between 10-16 years of age, RR (95% CI) per IQR increase in PFASPFOA: 1.10 (1.02, 1.19)PFOS: 1.34 (1.17, 1.55)No other significant associations found between PFAS and common cold or LRTI |
| **Kielsen et al. 2016**Prospective study of 12 adults in Denmark administered a booster vaccine for tetanus and diphtheria; antibody concentrations were measured 4- and 10-days post-vaccination. | Median serum PFAS levelsPFOA: 1.69 ng/mLPFOS: 9.52 ng/mLPFHxS: 0.37 ng/mLPFNA: 0.66 ng/mLPFDA: 0.30 ng/mLPFUnA: 0.21 ng/mLPFDoDA: 0.039 ng/mL | Tetanus and diphtheria antibody levels | DiphtheriaPFOS: inverse association (p=0.044), unadjustedPFNA: Inverse association (p=0.004), unadjustedPFDA: Inverse association (p=0.009), unadjustedPFUnA: Inverse association (p=0.036), unadjustedPFDoDA: Inverse association (p=0.038), unadjustedTetanusPFUnA: Inverse association (p=0.039), unadjustedPFDoDA: Inverse association (p=0.038), unadjusted |
| **Looker et al. 2014**Cross-sectional study of 411 adults participating in a follow-up study to the C8 Health Project; all participants received an influenza vaccine and were examined prior to vaccination and 21 days post vaccination; 755 adults in the follow-up study participated in a survey evaluating self-reported colds and influenza episodes. | Geometric mean serum PFOA: 33.74 ng/mL* 1st quartile: 0.25–13.7 ng/mL
* 2nd quartile: 13.8–31.5 ng/mL
* 3rd quartile: 31.6–90 ng/mL
* 4th quartile: 90.4–2,140 ng/mL

Geometric mean serum PFOS: 8.32 ng/mL | Seroprotection from influenza A H3N2 virusSeroprotection from influenza A H1N1 virusSeroprotection from influenza type B virusCold or flu infectionFrequency of colds | Influenza A H3N2 virus seroprotection, OR (95% CI)PFOA Q2: 0.34 (0.14, 0.83)PFOA Q3: 0.28 (0.11, 0.70)PFOA Q4: 0.39 (0.15, 0.99)No other significant associations were reported for PFAS levels (continuous or categorical) and the outcomes of interest. |
| **Manzano-Salgado et al. 2019**Prospective cohort – Spanish INMA birth cohort study (2003-2008) – of children with follow-ups at 1.5 years (n=1,188), 4 years (n=1,188) and 7 years (n-1,071). | Mean maternal serum PFAS levels (collected during first trimester)PFOA: 2.67 ng/mLPFOS: 6.41 ng/mLPFHxS: 0.67 ng/mLPFNA: 0.74 ng/mL | Mother-reported occurrence of LRTI at 1.5, 4, and 7 years of age (defined as occurrence of bronchitis, bronchiolitis, or pneumonia) | There were no associations between LRTIs and log-transformed PFAS levels.  |
| **Okada et al. 2012**Prospective cohort study of 343 pregnant women in Japan; cord blood samples collected at delivery to measure total IgE levels; infant allergies and infectious disease information collected during first 18 months of age. | Median maternal serum PFAS (measured after second trimester)PFOA: 1.3 ng/mLPFOS: 5.2 ng/mL | Infectious disease during the first 18 months of life | There were no statistically significant associations between maternal serum PFAS levels and infectious diseases during the first 18 months of life.  |
| **Pilkerton et al. 2018**Cross-sectional study of participants (≥ 12 years of age) from NHANES 1999-2000 and 2003-2004 data (n=581 women and 621 men adults [19-49 years], and 1012 youth [12-18 years]). | Mean serum PFASPFOAMen: 6.0 ng/mLWomen: 4.3 ng/mLYouth: 4.8 ng/mLPFOSMen: 28.1 ng/mLWomen: 22.1 ng/mLYouth: 25.1 ng/mL | Rubella IgG titers (log titers in analyses) | Adults, βMen PFOA Q3: -0.55 (-0.81, -0.28)PFOA Q4: -0.45 (-0.84, -0.05)No significant associations with Rubella titers for PFOA or PFOS in youth or in adult women. No associations between PFOS and Rubella titers in adult men.  |
| **Stein et al. 2016a**Cross-sectional study of 78 healthy adults in New York city vaccinated during the 2010–2011 season with the intranasal FluMist influenza vaccine. | Geometric mean serum PFASPFOA: 2.28 ng/mLPFOS: 5.22 ng/mLPFHxS: 1.1 ng/mLPFNA: 0.77 | Serum cytokines (IFN-α2, IFN-γ, TNF-α, IP 10) and chemokines (MCP-1, MIP1a) were measured pre-vaccination and 3- and 30-days post vaccination; nasal cytokine (IP-10), chemokine (MCP-1), and nasal mucosal IgA were measured 3- and 30-days post vaccination | Significant associations between serum PFHxS and changes in the serum cytokines IFN-γ (p=0.05) and TNF-α (p=0.04). No other associations between serum PFAS and seroconversion as measured by hemagglutinin inhibition or immunohistochemistry. No other associations between serum PFAS and changes in serum cytokine or chemokine levels or nasal cytokine, chemokine, or IgA levels.  |
| **Stein et al. 2016b**Cross-sectional study of adolescents (12–19 years of age) utilizing NHANES 1999–2000 and 2003–2004 data (n=1,191). | Geometric mean serum PFASPFOA: 4.13 ng/mLPFOS: 20.8 ng/mLPFHxS: 2.47 ng/mLPFNA: 0.765 ng/mL | Antibody titers for measles, mumps, and rubella in whole cohort as well as in seropositive subcohort  | Full Cohort, β per 2-fold increase in PFAS*Mumps*PFOS: -7.4% (-12.8, -1.7)Seropositive subcohort, β per 2-fold increase in PFAS*Mumps*PFOA: -6.6% (-11.7, -1.5)PFOS: -5.9% (-9.9, -1.6)*Rubella*PFOA: -8.9% (-14.6, -2.9)PFOS: -13.3% (-19.9, -6.2)PFHxS: -6.0% (-9.6, -2.2)No other significant associations were observed in the full cohort or subcohort. |
| **Timmermann et al. 2020**Subset analysis of RCT of early measles vaccination conducted in Guinea-Bissau from 2012-2015 (n=237). Intervention (n=135) included two doses of measles vaccine (at 4-7 months and at 9 months); control (n=102) included the usual single vaccination (at 9 months). | Median serum PFAS levels collected from children at baseline (4-7 months of age)PFOA: 0.68 ng/mLPFOS: 0.77 ng/mLPFHxS: 0.10 ng/mLPFNA: 0.21 ng/mLPFDA: 0.19 ng/mLPFUnA: 0.12 ng/mL | Measles antibody titers at baseline (no measles vaccination), 9-month visit (1 measles vaccination in intervention vs. none in controls), and at 2 years of age (2 measles vaccinations in intervention vs. 1 measles vaccination in control) with a doubling of serum PFAS at inclusion.Presence of fever, coughing, diarrhea, and any morbidity at inclusion and at 9-month visit with doubling of serum PFAS concentrations at baseline  | 9-month visit, control, βPFOS: -27% (-44, -4)9-month visit, intervention, βPFOS: -20% (-35, -1)PFDA: -25% (-42, -4)No other significant associations between percentage difference in measles antibody concentrations for any PFAS at any time points. Coughing, OR (95% CI)PFOA: 1.87 (1.02, 3.45)PFHxS: 2.15 (1.17, 3.97)Any Morbidity, OR (95% CI)PFOA: 2.02 (1.20, 3.41)PFHxS: 1.82 (1.06, 3.11) |

OR=odds ratio, IRR=incidence rate ratio, IQR=interquartile range