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.

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

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/mL PFNA: 1.14 ng/mL PFDA: 0.51 ng/mL PFUnA: 1.43 ng/mL PFDoDA: 0.17 ng/mL PFTrDA: 0.33 ng/mL PFHxS: 0.30 ng/mL PFOS: 5.12 ng/mL	Risk of infectious diseases in early life, based on mothers' self-administered questionnaire: Chickenpox Otitis media Pneumonia RSV	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	Median maternal serum PFAS level (measured at gestational	The following outcomes were evaluated both as odds of	Odds of number of days above median, Fever:

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.	age 10-16 weeks) PFOA: 1.68 ng/mL PFOS: 8.07 ng/mL PFHxS: 0.32 ng/mL PFNA: 0.70 ng/mL PFDA: 0.27 ng/mL	number of days above median and number of days (incidence rate): Fever (>101.3°F) Cough Nasal Discharge Diarrhea Vomiting	PFOA: OR 1.97 (1.07–3.62), 3rd tertile PFOS: OR 2.35 (1.34–4.11), 3rd tertile Rate of number of days, Fever: PFOS: IRR 1.65 (1.24–2.18), 3rd tertile Odds 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 tertile No 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/mL PFOS: 7.52 ng/mL PFHxS: 0.36 ng/mL PFNA: 0.64 ng/mL PFDA: 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 concentrations Any infection PFOS: 1.23 (1.05, 1.44) LRTI PFOA: 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;	Mean maternal serum PFAS level (measured at gestation week 12) PFOA: 5.6 ng/mL PFOS: 35.3 ng/mL	Rate of hospitalization for infectious disease in young children	PFOA: IRR 0.96 (0.87–1.06) for trend IRR 1.21 (1.04–1.42) for trend, girls IRR 0.83 (0.73–0.95) for trend, boys PFOS:

offspring were monitored for hospitalization due to infections in early childhood (average age 8.2 years).			IRR 1.00 (0.91–1.09) for trend IRR 1.18 (1.03–1.36) for trend, girls IRR 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/mL PFOS: 5.46 ng/mL PFHxS: 0.32 ng/mL PFNA: 1.40 ng/mL PFDA: 0.58 ng/mL PFUnA: 1.53 ng/mL PFDoDA: 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 media Pneumonia Varicella RSV	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	Geometric mean maternal serum PFAS levels PFOA: 3.20 ng/mL PFOS: 27.3 ng/mL PFHxS: 4.41 ng/mL PFNA: 0.60 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, β PFOS (age 5): -28.5% (-45.4, -6.1) PFHxS (age 5): -19.0% (-29.8, -6.6)

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).	PFDA: 0.28 ng/mL Median serum PFAS levels at age 5 PFOA: 4.1 ng/mL PFOS: 17.3 ng/mL PFHxS: 0.6 ng/mL PFNA: 1.00 ng/mL PFDA: 0.28 ng/mL Median serum PFAS levels at age 7 PFOA: 4.4 ng/mL PFOS: 15.5 ng/mL PFHxS: 0.5 ng/mL PFNA: 1.1 ng/mL PFDA: 0.4 ng/mL		PFDA (age 5): -19.9% (-33.1, -3.9) <u>Tetanus antibody at age 7, β</u> PFOA (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) <u>Diphtheria antibody at age 5, β</u> PFNA (age 5): -16.1% (-28.8, -1.0) <u>Diphtheria antibody at age 7, β</u> PFOA (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 7 PFOA: 4.4 ng/mL PFOS: 15.3 ng/mL PFHxS: 0.5 ng/mL PFNA: 1.1 ng/mL PFDA: 0.4 ng/mL Median serum PFAS levels at age 13 PFOA: 2.0 ng/mL PFOS: 6.7 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.

	PFHxS: 0.4 ng/mL PFNA: 0.7 ng/mL PFDA: 0.3 ng/mL		
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/mL PFOS: 5.5 ng/mL PFHxS: 0.3 ng/mL PFNA: 0.3 ng/mL	Rubella antibody levels *Hemophilus influenza* type B antibody levels Tetanus antibody levels Number of episodes of common cold (3-year period) Wheezing	<u>Rubella antibody levels, β</u> PFOA: -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) <u>Number of episodes of common cold, β</u> PFOA: 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 levels PFOA: 6.68 ng/mL PFOS: 2.44 ng/mL PFHxS: 0.16 ng/mL PFNA: 0.63 ng/mL PFDA: 0.35 ng/mL PFUnA: 0.39 ng/mL PFDoDA: 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/mL PFOS: 5.6 ng/mL PFHxS: 0.3 ng/mL PFNA: 0.2 ng/mL PFUnA: 0.1 ng/mL	Number of common colds (0-2 years of age) Number of lower respiratory infections (0-10 years of age)	<u>Common Cold, β</u> PFUnA: 0.11 (0.08, 0.14) <u>LRTI, β</u> PFOA: 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/mL PFOS: 12.87 ng/mL PFHxS: 0.65 ng/mL PFNA: 0.45 ng/mL PFUnA: 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)	<u>Common cold, RR (95% CI)</u> PFOA: 0.96 (0.94, 0.99) PFOS: 0.94 (0.92, 0.97) <u>Bronchitis/pneumonia at 3 years of age, RR (95% CI)</u> 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 age PFOA: 4.62 ng/mL PFOS: 20.9 ng/mL PFHxS: 3.33 ng/mL PFNA: 0.63 ng/mL PFDA: 0.19 ng/mL PFUnA: 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	<u>Number of common colds in last 12 months at age 16, OR (95% CI) per IQR increase in PFAS from multinomial logistic regression models</u> ≥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) <u>LRTI between 10-16 years of age, RR (95% CI) per IQR increase in PFAS</u> PFOA: 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	Median serum PFAS levels PFOA: 1.69 ng/mL PFOS: 9.52 ng/mL	Tetanus and diphtheria antibody levels	<u>Diphtheria</u> PFOS: inverse association (p=0.044), unadjusted

in Denmark administered a booster vaccine for tetanus and diphtheria; antibody concentrations were measured 4- and 10-days post-vaccination.	PFHxS: 0.37 ng/mL PFNA: 0.66 ng/mL PFDA: 0.30 ng/mL PFUnA: 0.21 ng/mL PFDoDA: 0.039 ng/mL		PFNA: Inverse association (p=0.004), unadjusted PFDA: Inverse association (p=0.009), unadjusted PFUnA: Inverse association (p=0.036), unadjusted PFDoDA: Inverse association (p=0.038), unadjusted <u>Tetanus</u> PFUnA: Inverse association (p=0.039), unadjusted PFDoDA: 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 virus Seroprotection from influenza A H1N1 virus Seroprotection from influenza type B virus Cold or flu infection Frequency of colds	<u>Influenza A H3N2 virus seroprotection, OR (95% CI)</u> 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	Mean maternal serum PFAS levels (collected during first trimester) PFOA: 2.67 ng/mL PFOS: 6.41 ng/mL PFHxS: 0.67 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.

years (n=1,188) and 7 years (n-1,071).	PFNA: 0.74 ng/mL		
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/mL PFOS: 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 PFAS PFOA Men: 6.0 ng/mL Women: 4.3 ng/mL Youth: 4.8 ng/mL PFOS Men: 28.1 ng/mL Women: 22.1 ng/mL Youth: 25.1 ng/mL	Rubella IgG titers (log titers in analyses)	<u>Adults, β</u> Men 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 PFAS PFOA: 2.28 ng/mL PFOS: 5.22 ng/mL PFHxS: 1.1 ng/mL PFNA: 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 PFAS PFOA: 4.13 ng/mL PFOS: 20.8 ng/mL PFHxS: 2.47 ng/mL PFNA: 0.765 ng/mL	Antibody titers for measles, mumps, and rubella in whole cohort as well as in seropositive subcohort	<u>Full Cohort, β per 2-fold increase in PFAS</u> *Mumps* PFOS: -7.4% (-12.8, -1.7) <u>Seropositive subcohort, β per 2-fold increase in PFAS</u> *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/mL PFOS: 0.77 ng/mL PFHxS: 0.10 ng/mL PFNA: 0.21 ng/mL PFDA: 0.19 ng/mL PFUnA: 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	<u>9-month visit, control, β</u> PFOS: -27% (-44, -4) <u>9-month visit, intervention, β</u> PFOS: -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. <u>Coughing, OR (95% CI)</u> PFOA: 1.87 (1.02, 3.45)

		inclusion and at 9-month visit with doubling of serum PFAS concentrations at baseline	PFHxS: 2.15 (1.17, 3.97) <u>Any Morbidity, OR (95% CI)</u> PFOA: 2.02 (1.20, 3.41) PFHxS: 1.82 (1.06, 3.11)

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