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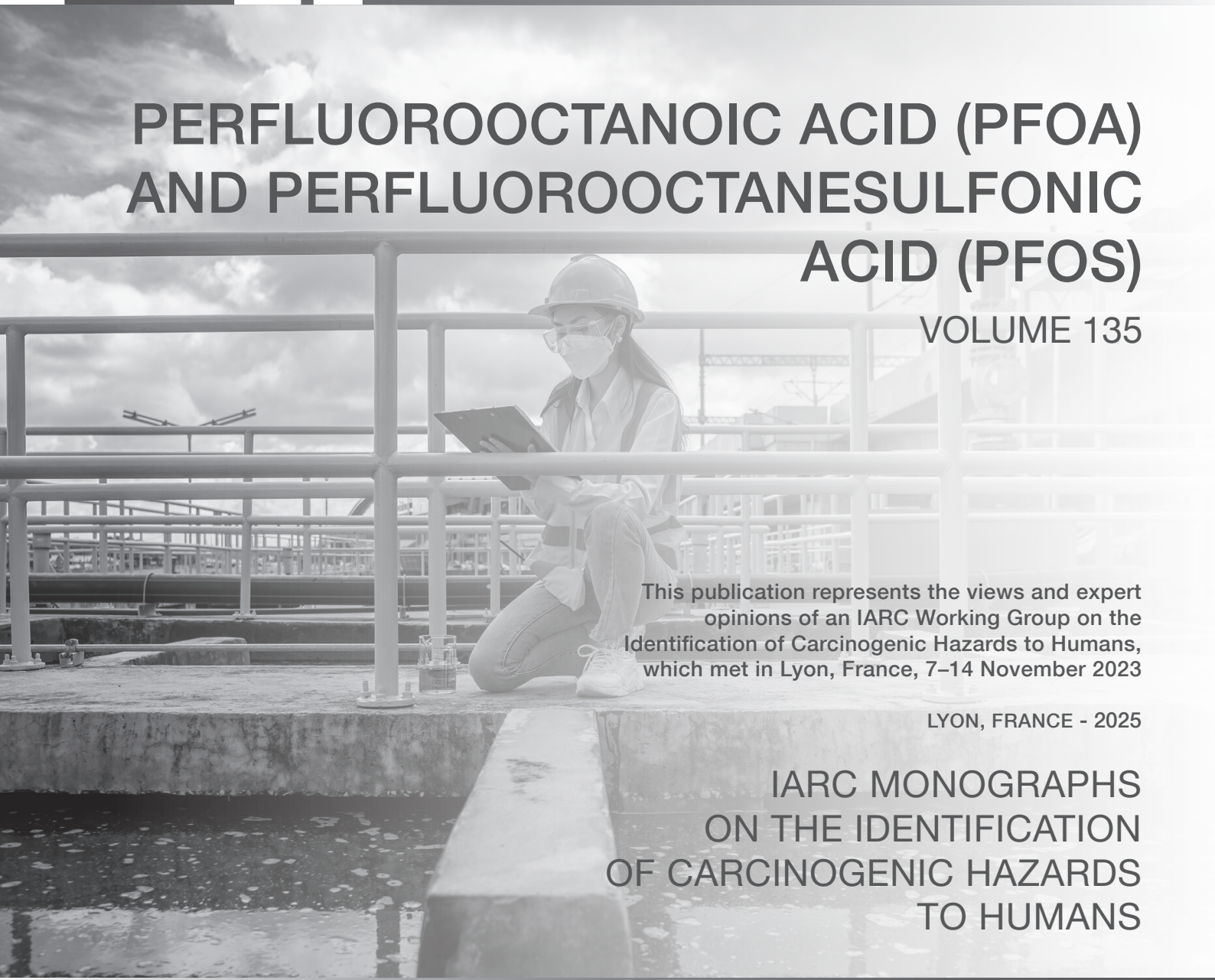

PERFLUOROOCTANOIC ACID (PFOA) AND PERFLUOROOCTANESULFONIC ACID (PFOS)

VOLUME 135

This publication represents the views and expert opinions of an IARC Working Group on the Identification of Carcinogenic Hazards to Humans, which met in Lyon, France, 7–14 November 2023

LYON, FRANCE - 2025

IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

International Agency for Research on Cancer

World Health Organization

Table S1.23 Exposure assessment review and critique for mechanistic studies on cancer and exposure to PFOA and PFOS

Reference and outcome	What was the study design?	What methods were used for the exposure assessment? (include data source, measured or modelled concentrations in environmental and biological media)	What was the exposure context? Specify time period and/or lifestage over which exposure data gathered, and how historical exposures were accounted for (if relevant)	What PFAS were measured? Were they correlated?	Which general category of exposure is relevant?	What exposure metrics were derived for use in analyses (e.g. single point measurement, average exposure over time, exposure duration, cumulative exposure etc.)?	Analytical method and LOD or LOQ for each PFAS and% subjects < LOD or LOQ if available	Was there potential for co-exposures to other agents that could impact the end-point being assessed? Which ones were measured?	Was there potential for differential exposure misclassification? Was there potential for non-differential exposure misclassification? (Likely/unlikely)
Abraham et al. (2020) Vaccine antibodies against *Haemophilus influenza* type b (Hib), tetanus, diphtheria KC7 – immunosuppressive in exposed humans (PFOA, PFOS)	Cross-sectional German one-year old children born in late 1990s (*n* = 101; breastfed, *n* = 80; formula-fed, *n* = 21) General population level PFAS exposure	Plasma PFAS were measured in one-year old children who had been vaccinated two or three times for Hib, tetanus, and diphtheria.	PFAS exposure and the outcomes were assessed at the same timepoint. Previous exposures considered by analysis to determine the influence of previous exclusive breastfeeding on outcome.	PFOA, PFOS, PFHxS, PFNA, PFBS, PFHxA, PFDA, PFDoDA, and ADONA were measured. Isomers are not mentioned. Correlations provided for PFOA, PFOS, PFHxS, PFNA. All were positively correlated with Spearman coefficients of 0.42–0.86.	One-year old children from general population; 27 of 101 subjects were from a “dioxin hotspot.”	Exposure metric was plasma PFAS (ng/mL) measured at a single timepoint at age one year. The outcome was measured at the same timepoint.	Analytical method was online extraction coupled with liquid chromatography coupled with tandem mass spectrometry. PFAS analysis was performed in 2019 in plasma samples that were collected in 1997–1999 and continuously frozen at −80 °C. LOQ was 0.25 ng/mL. Values < LOQ were assumed to be 50% of LOQ. PFOA and PFOS were detected in all 101 plasma samples. PFHxS was < LOQ in 1/101 samples; PFNA was < LOQ in 28/101 samples. PFBS, PFHxA, PFDA, PFDoDA, ADONA were < LOQ in most or all samples.	Other contaminants measured were 2378-substituted PCDDs and PCDFs, non-dioxin-like PCBs; mono-ortho-PCBs, coplanar PCBs, DDT and its metabolites, hexachlorobenzene, β-hexachlorocyclohexane, lead, cadmium, and mercury. PFAS were positively correlated with the other organic contaminants, with the highest Spearman coefficients for PFOA and total TEQs (PCDD, PCDFs, and dioxin-like PCBs) – 0.67, and PFOA and non-dioxin-like PCBs – 0.72. Analyses were performed to evaluate other contaminants as potential confounders of the association between PFAS and the outcomes.	Differential exposure misclassification is unlikely. Non-differential exposure misclassification is unlikely because plasma concentrations, although measured at a single time point, represent exposure over a relatively long period of time.
Aimuzi et al. (2020) Modulates receptor-mediated effects (KC8) – Thyroid hormones homeostasis	Cross-sectional (*n* = 1885) Shanghai Birth Cohort Study	Exposure was measured in maternal serum for correlation with free thyroxine (FT4), free triiodothyronine (FT3), thyroid stimulating hormone (TSH) and thyroid peroxidase antibody (TPOAb)	Maternal serum was collected before 16 weeks of gestation, Serum PFAS and outcome were measured in the same serum samples.	PFBS, PFOA, PFHpA, PFOS, PFHxS, PFNA, PFUA, PFDA, PFDoA, PFOSA. Isomers are not mentioned. Some PFAS were highly correlated, with the Spearman correlation coefficient ranged from 0.015 to 0.934	General population sources	Exposure metric was serum PFAS (ng/mL) measured in the same blood sample in which the outcome was evaluated.	Analytical method was high performance liquid chromatography-tandem mass spectrometry. PFOA: 0.02 PFOS: 0.1 PFHxS: 0.02 PFNA: 0.1 PFDA: 0.2 PFUnDA: 0.02 PFBS: 0.1 PFHxA: 0.1 Percent of samples in which PFAS were not detected is not stated.	Information collected on fish consumption, smoking, and alcohol consumption. Fish consumption (≤ once per week versus > once per week) was included in the analysis.	Differential or non-differential exposure misclassification is unlikely. Non-differential exposure misclassification is unlikely because serum concentrations, although measured at a single time point, represent exposure over a relatively long period of time.
Blake et al. (2018) Thyroid function (TSH; T4); kidney function (eGFR); body composition (BMI). KC8 -Modulates receptor-mediated effects (PFOA, PFOS)	Longitudinal, repeated measures study Subset of Fernald Community Cohort (FCC) living in zip codes bordering Ohio River and identified at high risk for PFAS/PFOA	Serum PFAS were measured in blood samples taken at enrolment and/or one or two follow up examinations in 1991–2008.	Serum PFAS and the outcomes were assessed at the same timepoint(s) and/or different timepoint(s) in each subject using linear mixed models to evaluate both the overall association with PFAS exposure as well as latent response to exposure. Several statistical analyses were performed including	PFOA, PFOS, PFNA, PFHxS, PFDA, perfluorooctane sulfonamide (PFOSA), 2-(*N*-methyl perfluorooctane sulfonamide) acetic acid (MePFOSA), 2-(*N*-ethyl perfluorooctane sulfonamide) acetic acid (EtPFOSA). All PFOS were positively correlated (Spearman	Participants were selected from the FCC based on identification as at high risk for exposure to PFAS (PFOA) based on living in zip codes bordering the Ohio River, which was contaminated with PFAS (PFOA). Serum PFAS levels in participants were compared to general	Exposure metric was serum PFAS in µg/L (ng/mL). Analysis was based on repeated measurements of serum PFAS and outcomes measured at the same timepoint for each subject, first serum PFAS measurement and all outcome measurements (including outcome	Analytical method was solid phase extraction high performance liquid chromatography tandem mass spectroscopy. Isomers were not mentioned. LODs (ng/mL): All PFAS except PFOS – 0.1PFOS – 0.2	No information on smoking, alcohol consumption, or exposure other carcinogens was reported.	Differential exposure misclassification is unlikely. Non-differential exposure assessment is unlikely because serum concentrations represent exposure over a relatively long period of time, and serum PFAS were measured multiple times in almost all subject (2 times – 44%; 3 times – 51%).

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	exposure. FCC consists of residents near a uranium processing site, but this subset was unlikely to have uranium exposure above background. Total number of participants was 210 adults (M – 81; F-129). n was less than 210 for some end-points and statistical analyses.		modelling the relationship between repeated serum PFAS and repeated outcome measurements from the same time point, the relationship between the first serum PFAS measurement and all outcome measurements (including outcomes measured before the first PFAS measurement), and the first serum PFAS measurement and outcomes subsequent to that measurement.	coefficients of 0.03–0.72), with the strongest correlation for PFNA and PFDA. The correlation coefficient for PFOA and PFOS was 0.36.	population (US. NHANES) serum PFAS data from approximately the same time period. Serum PFOA levels in subjects in 1999 were ~3x higher than in NHANES in 2000–2001. Serum PFHxS levels were ~1.4× higher in subjects than in NHANES throughout study period. Concentrations of serum PFOS and other PFAS were similar in study participants and NHANES.	measurements before and after first serum PFAS measurement), and first serum PFAS measurement and outcome measurements after first serum PFAS measurement.	% < LOD: PFOA – 0% PFOS – 0% PFNA – 0% PFHxS – 0% PFDA – 28% PFOSA – 22% MePFOSA – 0% EtPFOSA – 2% Values < LODs were replaced with the LOD divided by the square root of 2. At the time of the first serum measurement for each participant (n = 210), all compounds were detected in 100% of samples except for PFOSA (22% < LOD), PFDeA (28% < LOD), and Et-PFOSA (2% < LOD)		
Cheng et al. (2022) DNA methylation in leukocytes; serum lipids KC4 – induces epigenetic alterations (PFOA, PFOS)	Cross-sectional Adults (n = 94 [M-23, F-71] for PFAS and DNA methylation) undergoing elective surgery for benign condition or cosmetic reasons at hospital in Hubei Province, China General population	PFAS were measured in maternal serum samples taken during first trimester of pregnancy.	Plasma PFAS and outcomes (WBC DNA methylation; serum lipids) were measured in the same blood samples.	PFOA and PFOS were measured and were correlated with a Spearman rank correlation of 0.59. Other PFAS that were not measured including PFNA and PFHxS were likely also present.	General population	Exposure metric was plasma PFAS measured at same timepoint that outcomes were evaluated.	High-performance liquid chromatography – tandem triple quadrupole mass spectrometry. Isomers? LOD was 0.01 ng/mL for PFOA and PFOS. Plasma PFOA and PFOS > LOD in all samples.	Information on use of hypolipidemic drugs was collected. No information on smoking, alcohol consumption, or exposure other carcinogens is reported.	Differential exposure misclassification is unlikely. Non-differential exposure misclassification is unlikely because plasma concentrations, although measured at a single time point, represent exposure over a relatively long period of time.
Clarity et al. (2021) Telomere length in peripheral WBC KC9	Cross-sectional Study population was 176 female adults, including firefighters (n = 84) on active duty and with ≥ 5 years of service and office workers (n = 63) in San Francisco, California, USA.	PFAS were measured in serum samples.	Serum PFAS and outcome were measured in same serum samples.	PFOA, PFOS, PFBA, PFHxA, PFHpA, PFNA, PFDA, PFUnDA, PFDoA, PFBS, PFHxS, perfluorooctane sulfonamide (PFOSA) were measured. Isomers are not mentioned. Many, but not all, of the PFAS that were detected were positively correlated, based on log PFAS concentrations.	Firefighters in study group had potential occupational exposure to PFAS	Exposure metric was serum PFAS (ng/mL) measured in the same blood sample in which the outcome was evaluated.	Analytical method was solid phase extraction coupled with liquid chromatography-tandem mass spectrometry. LOQs were stated to be 0.05–0.1 ng/mL. However, use of the term “LOQ” appears to be an error, since LODs, rather than LOQs, are mentioned elsewhere in the paper and in Trowbridge et al. (2020), which is cited as	Metabolites of six organophosphate flame retardants and four brominated flame retardants were also measured in urine. Potential occupational exposure of firefighters to numerous additional contaminants. Those mentioned by the authors include benzene, PAHs, formaldehyde, dioxins, and PBDEs.	Differential exposure misclassification is unlikely. Non-differential exposure misclassification is unlikely because serum concentrations, although measured at a single time point, represent exposure over a relatively long period of time.

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Reference and outcome	What was the study design?	What methods were used for the exposure assessment? (include data source, measured or modelled concentrations in environmental and biological media)	What was the exposure context? Specify time period and/or lifestage over which exposure data gathered, and how historical exposures were accounted for (if relevant)	What PFAS were measured? Were they correlated?	Which general category of exposure is relevant?	What exposure metrics were derived for use in analyses (e.g. single point measurement, average exposure over time, exposure duration, cumulative exposure etc.)?	Analytical method and LOD or LOQ for each PFAS and% subjects < LOD or LOQ if available	Was there potential for co-exposures to other agents that could impact the end-point being assessed? Which ones were measured?	Was there potential for differential exposure misclassification? Was there potential for non-differential exposure misclassification? (Likely/unlikely)
	Occupational study						providing greater detail for the PFAS analysis of the samples for this study. For the seven PFAS detected in > 70% of samples, LODs provided in Trowbridge et al. (2020) were 0.02 ng/mL for PFHxS, PFOA, PFOS, PFNA, PFUnDA, and PFBS; 0.05 ng/mL for PFNA. Values < LODs were replaced with the LOD divided by the square root of 2. PFOA, PFOS, PFNA, and PFHxS were detected in 100% of samples. Detection frequencies for other PFAS that were detected were PFBS – 73%, PFDA – 99%, PFUnDA – 80%, PFDoA – < 70%. PFBA, PFHxA, PFHpA, and PFOSA were not detected.	Frequency of consumption of eggs and dairy products was considered in the analysis.	
Dalsager et al. (2021) Hospital admissions for infectious disease. KC7 – Immunosuppressive in exposed humans (PFOA, PFOS)	Prospective birth cohort Subset of Odense (Denmark) Child Cohort 1503 mother-child pairs from the general population Exposure based on maternal PFAS exposure measured during pregnancy.	PFAS were measured in maternal serum samples taken during first trimester of pregnancy.	Serum PFAS were assessed in maternal blood during first trimester of pregnancy and outcome was assessed in children from birth to 4 years of age.	PFOA, PFOS, PFNA, PFHxS, PFDA were measured. The highest correlations (Pearson's coefficient based on log transformed PFAS) were for PFOS and PFOA (0.6), PFOS and PFNA (0.6), PFOA and PFNA (0.7), and PFNA and PFDA (0.7). Coefficients for other PFAS were between 0.1 and 0.5.	Pregnant women from the general population.	Exposure metric was serum PFAS (ng/mL) measured at a single timepoint in the first trimester of pregnancy.	High-performance liquid chromatography – triple quadrupole mass spectrometry. Isomers were not mentioned. LOD was 0.03 ng/mL for PFOA and PFOS. All PFAS except PFHxS > LOD in all samples. PFHxS < LOD in 6 subjects. Values < LOD were replaced with the LOD divided by the square root of 2. Samples were collected at enrolment in 2010–2012 and were analysed for PFAS at different time points. (2011–199; 2013–330; 2014–191; 2019–979). Within batch and between batch coefficients of variation were < 3% and < 10.5%, respectively.	Information on smoking during pregnancy (yes/no) was collected.	Differential exposure misclassification is unlikely. Non-differential exposure misclassification is unlikely because plasma concentrations, although measured at a single time point, represent exposure over a relatively long period of time. Although samples were analysed at different time points over a period of years, the between batch coefficient of variation was relatively low.

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Di Nisio et al. (2020) Hormonal endometrial regulation MC – Multiple characteristics	Cross-sectional study [*n* = 1226, exposed (*n* = 146) and controls (*n* = 1080)]	Exposure was measured in serum for correlation with age of menarche and menstrual cycle	Serum samples were taken between June 2018 and March 2019. Outcome were measured in same serum samples.	PFOS and PFOA were measured No information on correlations in this Study	Exposure Group: A highly exposed area in the Veneto region of Italy, known as the red zone, is the area with the highest levels of PFAS, in particular PFOA is the most representative chemical in the region. Control group: low exposure area around it	Exposure metric was PFOA and PFOS (ng/mL) measured in serum sample at a single timepoint.	Analytical method was LC-MS/MS. Isomers were not mentioned. LOD/LOQ was not reported % of subjects in which PFAS were detected was not reported.	Smoking status and alcohol intake were considered in the analyses.	Differential exposure misclassification is unlikely. Misclassification is unlikely because serum concentrations, although measured at a single time point, represent exposure over a relatively long period of time.
Fletcher et al. (2013) Modulates receptor-mediated effects (KC8) – expression of genes involved with cholesterol metabolism, mobilization, or transport	Cross-sectional (*n* = 290 adults) C8 Health Project Elevated exposures to PFOA from contaminated drinking-water; general population level exposures to PFOS	Exposure was measured in serum for correlation with genes involved in cholesterol metabolism, mobilization, or transport	Serum samples were taken in September and- October 2010	PFOA, PFOS. Cited analytical method (Flaherty et al., 2005) appears to measure branched and linear PFOA, but these are not reported separately. There was no description of the correlation between PFOA and PFOS Other PFAS such as PFHxS, PFNA, PFHpA, PFDA likely present in serum from at least some of the subjects but were not measured	Exposure to PFOA from contaminated drinking-water General population level exposure to PFOS	Exposure metric was serum PFAS (ng/mL) measured in the same blood sample in which the outcome was evaluated.	Analytical method was solid phase extraction coupled with high performance liquid chromatography-tandem mass spectrometry. LOD: 0.5 ng/mL Values < LOD were assigned a value of 0.25 ng/mL Percent of samples in which PFAS were not detected is not stated.	Smoking ≥ 100 cigarettes over a lifetime was considered in the analysis	Differential exposure misclassification is unlikely. Non-differential exposure misclassification is unlikely because serum concentrations, although measured at a single time point, represent exposure over a relatively long period of time.
Goudarzi et al. (2017) KC7 Immunotoxic for the immune system in offspring KC4 – Induces epigenetic effects in exposed humans -	Prospective birth cohort study Hokkaido Study on Environment and Children's Health (*n* = 1558 mother-child pairs)	PFAS were measured in maternal plasma for correlation with common infectious diseases up to 4 years in offspring,	11 PFAS were measured in maternal plasma taken at 28–32 weeks of gestation. Outcome: Physicians' diagnosis of common infectious diseases including otitis media, pneumonia, respiratory syncytial virus infection, and varicella up to 4 years were extracted from the mother-reported questionnaires.	PFHxS, PFOS, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTrDA, and PFTeDA were measured. No information on correlations of PFASs in Hokkaido Study on Environment and Children's Health.	Pregnant women from the general population	Exposure metric was maternal plasma PFAS (ng/mL) measured at a single timepoint at 28–32 weeks of gestation.	Ultra-performance liquid chromatography coupled to triple quadrupole tandem mass spectrometry instrumentation MDL (mg/mL): PFHxS = 0.2 PFOS = 0.3PFHxA = 0.1 PFHpA = 0.1 PFOA = 0.2 PFNA = 0.3PFDA = 0.1 PFUnDA = 0.1 PFDoDA = 0.1 PFTrDA = 0.1 PFTeDA = 0.1 Concentrations < LOD were replaced with half the LOD PFHxA, PFHpA, and PFTeDA were excluded from data analysis because of low detection rates. The detection rates of the other PFAS, including PFOA and PFOS were > 97%, except for PFDoDa (90.6%) and PFHxS (82.6%).	During the first trimester of pregnancy, alcohol consumption and smoking during pregnancy, and maternal smoking status in the third trimester. At 4 years post-delivery, smoking status of parents, parental history of allergic diseases, having pets, cooling/heating system in homes, environmental tobacco smoke exposure	Differential exposure misclassification is unlikely evaluations based on prenatal exposure (maternal plasma PFAS measurements.)

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Grandjean et al. (2012) Decreased antibody response to tetanus and diphtheria vaccines in children KC7 – Immunosuppressive in exposed humans (PFOA, PFOS)	Prospective birth cohort followed until age 7 Study population was 587 children (309 boys, 278 girls) from general population in Faroe Islands	PFAS were measured in serum of mothers at week 32 of pregnancy and in children at age 5 (pre-booster)	Exposure was measured in mothers at week 32 of pregnancy (3rd trimester) and in children at age 5 (pre-booster). Outcomes (antibody response) were measured in children at age 5 (pre-booster and post-booster) and age 7.	PFOA, PFOS (branched and linear), PFHxS, PFNA, and PFDA were measured in serum. Correlations (Pearson coefficients) were reported for PFAS during pregnancy and in the child at age 5, and between different PFAS at age 5. Correlation coefficients for the same PFAS during pregnancy and in the child at age 5 ranged from 0.11 – 0.32. Correlations between different PFAS during pregnancy vs age 5 ranged from −0.06 – 0.28; most values were positive. Correlations between PFAS at age 5 were from 0.22 – 0.78, with the strongest correlation for PFNA and PFDA.	General population level exposure to pregnant women and children	Associations of maternal and age 5 serum PFAS (ng/mL) with antibody response to vaccines at age 5 and age 7 were evaluated.	PFOA, PFOS, PFNA, PFHxS, and PFDA were analysed using high pressure chromatography tandem mass spectrometry. PFOS was quantified by integration of 2 adjacent peaks representing the branched isomers and the linear isomer. LODs and percent of samples < LOD were not provided. Interquartile ranges are provided. Associations of outcomes with branched and linear PFOS are presented, but data on serum levels of PFOS isomers is not presented.	PCBs were measured in serum. Information on maternal smoking was collected.	Differential exposure misclassification is unlikely. Non-differential exposure misclassification is unlikely because plasma concentrations, although measured at a single time point, represent exposure over a relatively long period of time. For the analyses based on serum PFAS levels at age 5, breastfeeding may potentially impact both postnatal PFAS exposure and the outcomes evaluated in this study.
Kim et al. (2016) Insulin resistance (IR) and oxidative stress in humans KC5 – Induces oxidative stress in humans -	Longitudinal (Clinical trial) The vitamin C intervention study in the elderly (*n* = 141, aged 60 or over) in the Republic of Korea without a history of serious cardiovascular complications such as ischaemic heart diseases or stroke for community-based randomized crossover clinical trial) One group (vitamin C–placebo group, *n* = 71), vitamin C and placebo were supplemented sequentially, each for 4 weeks, and	PFAS were measured in serum samples for correlation with insulin resistance (IR) and oxidative stress	PFASwere measured for three times in medical examinations (first visit for baseline measurement and second and third crossover visits after placebo or vitamin C treatment). Outcome were measured for three times in medical examinations, same time as PFAS: Urinary oxidative stress biomarkers: malondialdehyde (MDA) and 8-hydroxy-2′-deoxyguanosine (8-OHdG) IR markers: Fasting glucose and insulin levels	PFBS, PFHxS, PFOS, PFDS, PFBA, PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTrDA and PFTeDA were measured. Isomers are not mentioned. 8 PFCs (PFHxS, PFOS, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, and PFTrDA) were found to be strongly correlated with each other (all, $P < 0.001$)	General population sources	Exposure metric was serum PFAS (ng/mL) measured in the same blood sample in which the outcome was evaluated.	Analytical method was high-performance liquid chromatography- triple–quadruple mass spectrometry. Of 15 PFCs, PFPeA and PFHxA were not detected in serum of any participants. Only eight PFCs (PFHxS, PFOS, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, and PFTrDA) among 15 PFCs showed a detection rate above 90% LODs were not reported in the paper. Concentrations < LOD were replaced with the LOD divided by the square root of 2	Air pollution (PM_{10}, O_3, and NO_2) concentrations and meteorological factors (outdoor temperature and dew point), urinary cotinine levels and urinary creatinine levels were measured	Differential exposure misclassification is unlikely. Non-differential exposure misclassification is unlikely because serum concentrations, although measured at a single time point, represent exposure over a relatively long period of time.

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	there was a 2-week non-treatment period (determined based on 6–8 hours of half-life for vitamin C) between vitamin C and placebo supplementation to flush out the effect of the first treatment (total of 10 weeks—4 + 2 + 4). The sequence of supplementation was reversed for the other group (placebo–vitamin C group, *n* = 70)								
Kim et al. (2020) Serum TSH at age 2, 4, and 6 years; free thyroxine (fT4), triiodothyronine (T3) at age 6 years, and subclinical and clinical thyroid disease at age 2, 4, and 6 years	Longitudinal Environment and Development of Children (EDC) study (Republic of Korea) Children in EDC study who were examined at age 2, 4, and/or 6 (*n* = 660; including 381 at age 2 [M-200; F-181], 569 at age 4 [M-299, F-270], 511 at age 6 [M-268, F-243]) General population level PFAS exposure	Serum PFAS were measured at 2, 4, and/or 6 years of age.	PFAS exposure and TSH were assessed at the same time points at ages 2, 4, and 6 years. The analysis of the association of TSH and serum PFAS considered TSH and serum PFAS data from all 3 time points. The analysis of the association of fT4, T3, and subclinical hypothyroidism at age 6 years considered with serum PFAS considered serum PFAS data from all 3 time points.	14 PFAS were measured (PFOA, PFOS, PFPeA, PFHxA, PFHpA, PFNA, PFDA, PFUnA, PFDoDA, PFTrDA, PFTeDA, PFBS, PFHxS, PFDS). PFAS detected in > 90% of samples at all 3 time points were included in the analysis (PFOA, PFOS, PFNA, PFDA, PFHxS). Information on correlations is not provided.	General population (children)	The analyses used models that considered serum (ng/mL) at all 3 time points (2, 4, and 6 years of age).	Analytical method was high pressure liquid chromatography-triple quadrupole mass spectrometry. LODs (ng/mL): PFPeA-0.076 PFHxA-0.180 PFHpA-0.157 PFOA-0.078 PFNA-0.050 PFDA-0.059 PFUnDA-0.078 PFDoDA-0.052 PFTrDA-0.146 PFTeDA-0.095 PFBS-0.2227 PFHxS-0.160 PFOS-0.113 PFDS-0.104 Concentrations < LOD were replaced with the LOD divided by the square root of 2	Information on maternal smoking during pregnancy was collected	Differential exposure misclassification is unlikely. Non-differential exposure misclassification is unlikely because serum PFAS concentrations, were measured at 1 to 3 time points and represent exposure over a relatively long period of time.

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Reference and outcome	What was the study design?	What methods were used for the exposure assessment? (include data source, measured or modelled concentrations in environmental and biological media)	What was the exposure context? Specify time period and/or lifestage over which exposure data gathered, and how historical exposures were accounted for (if relevant)	What PFAS were measured? Were they correlated?	Which general category of exposure is relevant?	What exposure metrics were derived for use in analyses (e.g. single point measurement, average exposure over time, exposure duration, cumulative exposure etc.)?	Analytical method and LOD or LOQ for each PFAS and% subjects < LOD or LOQ if available	Was there potential for co-exposures to other agents that could impact the end-point being assessed? Which ones were measured?	Was there potential for differential exposure misclassification? Was there potential for non-differential exposure misclassification? (Likely/unlikely)
							PFOS, PFOA, PFHxS, and PFNA were detected in > 95% of samples, and PFDA was detected in > 90% of samples.		
Knox et al. (2011) Serum estradiol, onset of menopause KC8 –Modulates receptor-mediated effects in exposed humans (PFOA, PFOS)	Cross-sectional Women, 18–65 years of age, (*n* = 25 957) from C8 Health Project study. Exposed to PFOA in drinking-water. Workers at industrial facility that used PFOA were excluded.	Serum PFOA and PFOS were measured in blood samples taken at enrolment in the study.	Serum estradiol was assessed at same time point as serum PFAS. Onset of menopause either occurred before, or would occur subsequent to, serum PFAS measurement.	PFOA and PFOS were evaluated in this study. Other PFAS measured in the C8 Health Study but not discussed in Knox et al., 2011 (Frisbee et al., 2009, which is cited in Knox et al., 2011) were PFNA, PFHxS, PFPeA, PFHxA, PFHpA, PFDA, PFUnA, PFDoA. Information on correlations of PFAS in the study group for this study was not provided.	PFOA – elevated exposure from drinking-water. PFOS – general population level exposure	Exposure metric was serum PFAS (ng/mL) measured at one timepoint.	Solid phase extraction coupled to high-performance liquid chromatography- mass spectrometry. From Frisbee et al. (2009), which is cited in Knox et al. (2011): LOD for all PFAS: 0.5 ng/mL PFOA detected in 100% of samples. PFOS in almost all samples. Values < LOD were replaced with the LOD	Other PFAS were measured (Frisbee et al., 2009) but not discussed in the paper. Information on smoking and alcohol consumption (yest/no) was collected. Individuals who were taking hormone medications (oral contraceptives, hormone replacement therapy, any other hormones, selective estrogen receptor modulators, fertility agents) were excluded from the study.	Differential exposure classification is unlikely. The potential for non-differential exposure misclassification is decreased because serum PFAS concentrations, although measured at a single time point, represent exposure over a relatively long period of time. However, the authors discuss that exposure to PFOA increased over time with increasing exposure from the industrial facility, and that serum PFOA increased with duration of residence in the impacted water districts.
Kvalem et al. (2020) Airways infections, allergy and asthma related health outcomes KC6 – Induces chronic inflammation and	Cross-sectional study Data from the 10- and 16-year follow-up investigations for the prospective, birth cohort Environment and Child Asthma (ECA) Study in Oslo (*n* = 378)	Exposure was measured in serum for correlation with airways infections, allergy and asthma related health outcomes	Participants with PFAS measurements at age 10 years Outcome data were obtained at ages 10 years.	PFBA, PFPeA, PFHxA, PFDoDa, PFTrDA, PFTeDa, PFBS, PFDS, MeFOSA, EtFOSA, PFOSA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFHxS, PFHpS and PFOS were measured. The inter-correlations for PFASs ranged from no correlation to strong correlation (correlation coefficients: 0–0.73	General population sources	Exposure metric was PFAS (ng/mL) measured in serum sample at a single timepoint.	Analytical method was LC-MS/MS LOQ was 0.050 ng/mL for all PFASs The Pearson correlations coefficients among PFASs ranged from 0–0.73. For PFOA and other PFAS, they ranged from 0.27–0.58, and for PFOS, they ranged from 021–0.68. The coefficient for PFOA and PFOS was 0.58. PFOA, PFOS, PFNA, PFHxS, PFHpA, PFDA, PFUnDA, PFHxS, and PFHpS were detected above the LOQ in ≥ 70% of samples Values < LODs were replaced with the LOD divided by the square root of 2	Co-exposure to other contaminants was not measured. Information on smoking and alcohol use was not collected.	Differential exposure misclassification is unlikely. Misclassification is unlikely because serum concentrations, although measured at a single time point, represent exposure over a relatively long period of time.
Lin et al. (2016) Endothelial cell damage and	Cross-sectional study	Exposure was measured in serum for correlation with oxidative stress, circulating endothelial	Serum samples were taken in 2006 to 2008.	PFOA, PFOS, PFNA and PFUA were measured. Isomers are not mentioned.	General population sources	Exposure metric was serum PFAS (ng/mL) measured in the same blood sample in	Analytical method was solid phase extraction coupled with high performance liquid	Smoking status and alcohol intake were considered in the analyses.	Differential exposure misclassification is unlikely.

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Reference and outcome	What was the study design?	What methods were used for the exposure assessment? (include data source, measured or modelled concentrations in environmental and biological media)	What was the exposure context? Specify time period and/or lifestage over which exposure data gathered, and how historical exposures were accounted for (if relevant)	What PFAS were measured? Were they correlated?	Which general category of exposure is relevant?	What exposure metrics were derived for use in analyses (e.g. single point measurement, average exposure over time, exposure duration, cumulative exposure etc.)?	Analytical method and LOD or LOQ for each PFAS and% subjects < LOD or LOQ if available	Was there potential for co-exposures to other agents that could impact the end-point being assessed? Which ones were measured?	Was there potential for differential exposure misclassification? Was there potential for non-differential exposure misclassification? (Likely/unlikely)
Atherosclerosis KC5 – Induces oxidative stress in humans -	(*n* = 848, children and adolescents) General population level PFAS exposure	microparticles (EMPs) and platelet microparticles (PMPs)	Outcome were measured in same serum samples (8-OHdG was measured in urine samples).	No information on correlations in this Study		which the outcome was evaluated.	chromatography-tandem mass spectrometry. LOQs (ng/mL): PFOA (1.5), PFOS (0.22), PFNA (0.75), PFUA (1.5)		Misclassification is unlikely because serum concentrations, although measured at a single time point, represent exposure over a relatively long period of time.
Lin et al. (2020) Urinary 8-hydroxy-2-deoxyxguanosine – marker of oxidative stress. Also: 8-nitroguanine – marker of nitrative stress, and serum lipid profile KC5 – induces oxidative stress in exposed humans (PFOA, PFOS)	Cross-sectional Study population was 597 adults (M-519 M, F-78) from control group of Taiwan, China, case–control study of cardiovascular disease. General population	Isomers of PFOA and PFOS were measured in serum samples	Serum samples for PFAS measurement and urine samples for 8-hydroxy-2-deoxyxguanosine measurement were taken at the same timepoint.	Linear and branched isomers of PFOA and PFOS were measured. PFAS measured were linear PFOA; branched PFOA (sum of perfluoro-5-methylheptanoic acid, perfluoro-6-methylheptanoic acid, perfluoro-4,4-dimethylhexanoic acid, perfluoro-5,5-dimethylhexanoic acid; two other PFOA isomers were not detectable), and linear PFOS; branched PFOS (sum of perfluoro-3,5-dimethylhexanesulfonate, perfluoro-4,5-dimethylhexanesulfonate, perfluoro-5,5-dimethylhexanesulfonate, perfluoro-4,5-dimethylhexanesulfonate; three other PFOS isomers were not detectable). Other PFAS that are commonly detectable in serum such as PFNA and PFHxS were not measured. Information on PFAS correlations not provided.	General population	Exposure metric was serum PFAS (ng/mL) measured at same timepoint that outcomes were evaluated.	Analytical method was solid phase extraction coupled with liquid chromatography-tandem mass spectrometry. LODs were 0.002–0.150 ng/mL. Values < LODs were replaced with the LOD divided by the square root of 2. Information on number of samples below LODs was not provided. It was stated that two PFOA isomers and three PFOS isomers were not detected in any sample.	Smoking status and alcohol intake were considered in the analyses.	Differential exposure misclassification is unlikely. Non-differential exposure misclassification is unlikely because serum concentrations, although measured at a single time point, represent exposure over a relatively long period of time.
Liu et al. (2018) KC9 Leukocyte telomere length in newborns	Cross-sectional component of prospective birth cohort study (*n* = 581 mother-child pairs)	Exposure was measured in cord plasma concentrations of 10 PFASs for correlation with leukocyte telomere length in newborns. Concentrations of ROS in cord serum of all the newborns have also been measured.	Cord blood samples were taken in 2012 to 2013. Outcome assessed in same cord blood at birth.	PFOA, PFOS, PFNA, PFDA, PFUA, PFDoA, PFOSA, PFHpA, PFHxS and PFBS were measured. Concentrations of PFOS, PFDA, PFNA, PFUA and PFDoA were strongly positive correlated.	General population sources	Exposure metric was cord plasma PFAS (ng/mL) measured in the same cord blood sample in which the outcome was evaluated.	Analytical method was HPLC-MS/MS. LODs (ng/mL): PFOA (0.09), PFOS (0.09), PFNA (0.02), PFDA (0.02), PFUA (0.02), PFDoA (0.05), PFOSA (0.12), PFHpA (0.03), PFHxS (0.02) PFBS (0.009)	Co-exposure to other contaminants was not measured. Information on smoking and alcohol use was not collected.	Differential exposure misclassification is unlikely. Differential exposure misclassification is unlikely evaluations based on prenatal exposure (cord plasma PFAS measurements.)

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							All PFAS were detected in 97.9–100% of samples except PFDoA – 89.8% Values < LOD were replaced with one-half the LOD		
Liu et al. (2022) DNA methylation in cord blood at birth and peripheral leukocytes at age 12 years. KC4 – Induces epigenetic effects in exposed humans (PFOA, PFOS)	Prospective birth cohort Health Outcomes and Measures of the Environment (HOME) Study (Cincinnati, OH, USA) and Project Viva (eastern MS, USA) Mother-child pairs from general population. DNA methylation assessed in cord blood (HOME study, *n* = 226; Project Viva, *n* = 371); leukocytes in children (HOME study – age 12 years, *n* = 160; Project Viva – age 7 years, *n* = 342). Exposure based on maternal serum PFAS during pregnancy.	Maternal serum PFAS measured during pregnancy (HOMES Study – 10.4–30.3 weeks; Project Viva – 30.9–42.6 weeks)	Maternal exposure assessed during pregnancy and outcome assessed in cord blood at birth and in child at age 12 (HOME Study – 1st, 2nd, or 3rd trimester) or age 7 (Project Viva – 3rd trimester).	PFOA, PFOS, PFNA, PFHxS were measured in HOME Study and Project Viva. Measurement of isomers is not mentioned. All PFAS were correlated in HOME Study (Pearson coefficient 0.29–0.63) with highest correlation for PFOA and PFOS, and PFHxS and PFOS. No information on correlations in Project Viva.	Pregnant women from the general population	Exposure metric was maternal serum PFAS (ng/mL) measured at a single timepoint in first, second, or third trimester of pregnancy.	Same analytical method used for HOME Study and Project Viva. Online solid phase extraction coupled to high-performance liquid chromatography-isotope dilution tandem mass spectrometry. LODs (ng/mL): PFOA, PFHxS – 0.1 PFOS – 0.2 PFNA – 0.082 Results < LOD replaced by LOD divided by square root of 2. No information on percent of results < LOD	Maternal smoking during pregnancy was assessed by serum cotinine.	There is a potential for exposure misclassification because serum PFAS were measured in different trimesters in different subjects. Health outcomes were assessed in children up to age 12 years. Regarding postnatal PFAS exposure, breastfeeding may impact both postnatal PFAS exposure and the risk of the outcomes evaluated in this study. Also, non-differential overall (not prenatal) exposure misclassification to PFAS may result from varying postnatal exposures through diet and other sources.
Lopez-Espinosa et al. (2016) Levels of estrogen, total testosterone, and insulin-like growth factor-1 (IGF-1) in children 6–9 years of age KC8 – Modulates receptor-mediated effects in exposed humans (PFOA, PFOS)	Cross-sectional Children 6–9 years of age from C8 Health Project (*n* = 2292; M −1120, F-1075) Elevated exposures to PFOA from contaminated drinking-water; general population level exposures to	PFOA, PFOS, and 8 other PFAS were measured in serum samples	PFAS and estradiol, total testosterone, and IGF-1 were measured in the same serum sample.	Ten PFAS were analysed (listed in Frisbee et al., 2009, which is cited): PFOA, PFOS, PFNA, PFHxS, PFPeA, PFHxA, PFHpA, PFDA, PFUnA, PFDoA. Information on correlations was provided for PFOA, PFOS, PFNA, PFHxS. They were low (Pearson coefficient (based on ln PFAS) of −0.08 to 0.33, except for PFOS and	Children from communities with elevated exposure to PFOA from drinking-water. General population level exposure to PFOS and other PFAS.	Exposure metric was serum PFAS (ng/mL) measured at the same timepoint that outcomes were evaluated.	Solid phase extraction coupled to high-performance liquid chromatography- mass spectrometry. LOD for all PFAS: 0.5 ng/mL PFOA detected in 100% of samples. PFOS, PFNA, PFHxS detected in ≥ 99.4% of samples. Values < LOD were replaced with the LOD divided by the square root of 2.	No information on co-exposure to other agents was collected.	Differential exposure misclassification is unlikely. Non-differential exposure misclassification is unlikely because serum concentrations, although measured at a single time point, represent exposure over a relatively long period of time.

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Reference and outcome	What was the study design?	What methods were used for the exposure assessment? (include data source, measured or modelled concentrations in environmental and biological media)	What was the exposure context? Specify time period and/or lifestage over which exposure data gathered, and how historical exposures were accounted for (if relevant)	What PFAS were measured? Were they correlated?	Which general category of exposure is relevant?	What exposure metrics were derived for use in analyses (e.g. single point measurement, average exposure over time, exposure duration, cumulative exposure etc.)?	Analytical method and LOD or LOQ for each PFAS and% subjects < LOD or LOQ if available	Was there potential for co-exposures to other agents that could impact the end-point being assessed? Which ones were measured?	Was there potential for differential exposure misclassification? Was there potential for non-differential exposure misclassification? (Likely/unlikely)
	PFOS and other PFAS			PFHxS (0.56 in boys, 0.61 in girls) Associations with outcomes were assessed only for PFOA, PFOS, PFNA, PFHxS.					
Lopez-Espinosa et al. (2021) White blood cell types cell counts and percentages (2005–2006 and 2010). Lymphocyte subsets cell count and percentages (2010) KC7 – immunosuppressive in exposed humans (PFOA, PFOS)	Cross-sectional (two separate surveys at different timepoints) C8 Health Project (42 782 adults who had consumed water contaminated with PFOA for at least one year; 2005–2006) Follow-up of subgroup of C8 Health Project (526 adults who lived in one of the contaminated water districts; 2010) Elevated exposures to PFOA from contaminated drinking-water; general population level exposures to PFOS	Serum PFAS measured in blood samples taken at enrolment (2005–2006) and at follow-up (2010)	Serum PFAS and outcome (White blood cell types) were evaluated in blood samples taken in 2005–2006. Serum PFAS and outcomes (white blood cell types, lymphocyte subtypes) were evaluated in blood samples taken in 2010. Serum PFOA was higher in 2005–2006 than in 2010, likely because all 2010 subjects lived in a contaminated water district. Serum PFOS was lower in 2010 than in 2005–2006, consistent with decreases in the US in general, likely due to ending the production of PFOS in the US during this time period.	Serum PFOA, PFOS, PFNA, and PFHxS were measured. Cited analytical method (Flaherty et al., 2005) appears to measure branched and linear PFOA, but these are not reported separately. Positive correlations between all PFAS ($P < 0.001$ in all cases), r range: 0.32–0.57 (2005–2006); 0.44–0.77 (2010). Other PFAS such as PFHpA and PFDA likely present in serum from at least some of the subjects but were not measured	Exposure to PFOA from contaminated drinking-water General population level exposure to PFOS	Exposure metric was serum PFAS (ng/mL) measured at the same timepoint that white blood cell parameters were evaluated.	Analysis with solid phase extraction coupled with reverse-phase high performance liquid chromatography-tandem mass spectrometry as described in Frisbee et al. (2009) for 2005–2006 samples and Kato et al. (2011) for 2010 samples. LODs (ng/mL): PFOA, PFOS, PFNA, PFHxS – 0.5 (2005–2006) PFOA – 0.5; PFOS – 0.2; PFNA, PFHxS – 0.1 (2010). Percent of samples ≤ LOD ranged from < 0.1% for PFOA to 2.6% for PFHxS. Values below LOD set at 50% of LOD.	Tobacco consumption; alcohol intake; regular use of paracetamol, aspirin, or other anti-inflammatory medications during the previous 4 years were considered in the analyses.	Differential exposure misclassification is unlikely Non-differential exposure misclassification is unlikely because serum concentrations, although measured at a single time point, represent exposure over a relatively long period of time.
Manzano-Salgado et al. (2019) Lower respiratory tract infections, asthma, eczema, and lung function in children KC6 – Induces chronic inflammation in exposed humans (PFOA, PFOS)	Prospective birth cohort Spanish INMA Birth Cohort 1214 mother-child pairs from the general population included in analysis; 29 pairs excluded due to incomplete information. Exposure based on maternal PFAS exposure measured during pregnancy.	Plasma PFAS measured in blood samples taken during first trimester of pregnancy (mean 12.3 weeks). Outcomes assessed in children at 1.5, 4, and 7 years of age.	Maternal PFAS were measured in first trimester of pregnancy. Immune and respiratory outcomes were assessed in children at ages 1.5, 4, and 7 years.	PFOA, PFOS, PFNA, and PFHxS were measured. Isomers are not mentioned. Positive correlations between all PFAS (Spearman coefficients of 0.43–0.68). PFOA and PFNA most highly correlated (Spearman coefficient of 0.68).	General population	Exposure metric was maternal plasma PFAS (ng/mL) measured at a single timepoint in first trimester of pregnancy.	Analysis with by column switching high performance liquid chromatography- tandem mass spectrometry using a modified protocol from Kato et al. (2011). LOQs were 0.20 ng/mL for PFOA, PFOS, and PFHxS and 0.10 ng/mL for PFNA. The percent of samples < LOQ were: PFOA-0%; PFOS-0%; PFNA-0.64%; PFHxS-3.7%. Values below LOQ were assumed to be 50% of LOQ.	Co-exposure to other agents was not measured. Information on smoking during pregnancy and diet was collected. Models were adjusted for smoking during pregnancy and for fish consumption during pregnancy, stated to be source of other environmental pollutants and "nutrients which can interfere with PFAS metabolism."	Differential exposure misclassification is unlikely evaluations based on prenatal exposure (maternal plasma PFAS measurements.) Health outcomes were assessed in children up to age 7 years. Regarding postnatal PFAS exposure, breastfeeding may impact both postnatal PFAS exposure and the risk of the outcomes evaluated in this study. Also, non-differential overall (not prenatal) exposure misclassification to PFAS may result from varying postnatal exposures through diet and other sources.

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Reference and outcome	What was the study design?	What methods were used for the exposure assessment? (include data source, measured or modelled concentrations in environmental and biological media)	What was the exposure context? Specify time period and/or lifestage over which exposure data gathered, and how historical exposures were accounted for (if relevant)	What PFAS were measured? Were they correlated?	Which general category of exposure is relevant?	What exposure metrics were derived for use in analyses (e.g. single point measurement, average exposure over time, exposure duration, cumulative exposure etc.)?	Analytical method and LOD or LOQ for each PFAS and% subjects < LOD or LOQ if available	Was there potential for co-exposures to other agents that could impact the end-point being assessed? Which ones were measured?	Was there potential for differential exposure misclassification? Was there potential for non-differential exposure misclassification? (Likely/unlikely)
Miura et al. (2018) DNA methylation in cord blood samples KC4 – Induces epigenetic effects in exposed humans (PFOA, PFOS)	Prospective birth cohort Sapporo cohort of the Hokkaido (Japan) study (190 mother-child pairs from the general population; discovery cohort) Taiwan, China Maternal and Infant Cohort Study (37 mother-child pairs from the general population; replication cohort) Exposure based on maternal serum PFAS exposure measured during pregnancy.	Discovery cohort: Maternal serum PFAS in samples taken at 24 to 41 weeks of pregnancy (2nd or 3rd trimester). Confirmation cohort: Maternal serum PFAS in samples taken at 28 to 36 weeks of pregnancy (3rd trimester). Outcome assessed in cord blood at birth.	Exposure assessed in 2nd or 3rd trimester of pregnancy and outcome assessed in cord blood at birth.	PFOA and PFOS were measured. Isomers are not mentioned. Serum PFOA and PFOS data for replication cohort are not provided. Information on the correlation of PFOA and PFOS is not provided. Other PFAS including PFNA and PFHxS are likely present but were not measured.	Pregnant women from the general population	Exposure metric was maternal serum PFAS (ng/mL) measured at a single timepoint in second or third trimester of pregnancy.	Column-switching liquid chromatography-tandem mass spectrometry (LC-MS/MS) as described in Okada et al. (2012); Washino et al. (2009). LOD: 0.5 ng/mL, values below LOD were assigned half the LOD (0.25 ng/mL)	Co-exposure to other contaminants was not measured. Information on smoking and alcohol use was not collected.	There is a potential for exposure misclassification because serum PFAS were measured in different trimesters in different subjects
Omoike et al. (2021) Lymphocyte count, absolute neutrophil count, c-reactive protein, albumin, serum iron, alkaline phosphatase, bilirubin KC5 – induces oxidative stress in exposed humans (PFOA, PFOS) KC6 – Induces chronic inflammation in exposed humans (PFOA, PFOS)	Cross-sectional US National Health and Nutrition Examination Survey (NHANES) 2005–2006, 2007–2008, 2009–2010, 2011–2012 cycles, subjects ≥ 20 years of age (*n* = 6652) General population	PFAS were measured in serum samples	Serum PFAS and outcomes were measured in same serum samples.	Associations with outcomes were evaluated for the five PFAS detected in > 82% of serum samples – PFOA, PFOS, PFNA, PFHxS, PFDA. PFOA and PFOS were reported as total PFOA or PFOS for 2005–2006, 2007–2008, and 2009–2010 cycles and as sum of branched and linear isomers for 2011–2012 cycle (CDC, 2022). Other PFAS were measured in NHANES. Although not reported in this study, some of these were detected in some samples. Information on correlations among PFAS not provided	General population	Exposure metric was serum PFAS (ng/mL) measured in the same blood sample in which outcomes were evaluated.	Analytical method was solid phase extraction coupled with high performance liquid chromatography-turbo ion spray ionization-tandem mass spectrometry. LODs varied in different NHANES cycles. Values < LOD were replaced with the LOD divided by the square root of 2. Associations with outcomes were evaluated for the 5 PFAS detected in > 82% of samples (PFOA −99.6%; PFOS-99.7%; PFNA-99.3%; PFHxS-98.3%; PFDA-82.6%)	Other contaminants measured in NHANES were not included in the analysis. Exposure to second-hand smoke and smoking status assessed by serum cotinine level. Information on alcohol use was not collected.	Differential exposure misclassification is unlikely. Non-differential exposure misclassification is unlikely because serum concentrations, although measured at a single time point, represent exposure over a relatively long period of time.
Pan et al. (2019) Genotoxicity (KC2) – Semen Quality	Cross-sectional (*n* = 646) Male partners of couples recruited at their first visit (regardless of	PFAS were measured in semen sample, after abstinence period of 2 days, and serum sample taken at the same time	Semen PFAS and outcomes (semen quality parameters) were assessed in the same sample. Serum PFAS was assessed at the same timepoint.	PFBA, PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTriDA, PFTeDA, PFBS, PFHxS, PFOS,6:2 and 8:2	General population	Exposure metrics were semen and serum PFAS (ng/mL) measured at same timepoint that outcomes were evaluated.	Ion-pair extraction followed by ultraperformance liquid chromatography-triple quadrupole mass spectrometry.	Co-exposure to other contaminants was not evaluated. Smoking and alcohol consumption during the past 3 months were considered	Differential exposure misclassification based on semen and serum PFAS is unlikely. Non-differential exposure misclassification based on

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	purpose for fertility assessment) to reproductive medical centre in Nanjing, China			Cl^-PFESAs. Isomers are not mentioned. Moderate-to-high correlations between individual PFAS levels in the two matrices. Serum: semen PFAS ratios vary among PFAS.			LOQ: 0.01–0.20 ng/mL for serum and 0.002–0.10 ng/mL for semen PFOA, PFNA, PFDA, PFUnDA PFTriDA, PFHxS, PFOS, 6:2 Cl^-PFESA detected in > 99% of serum samples; PPFDoDA, PFBS, 8:2 Cl^-PFESA detected in 80.3–96.5% of serum samples; PFHpA, PFTeDA detected in 23.6–37.0% of serum samples. PFOA, 6:2 Cl^-PFESA detected in 100% of semen samples; PFNA, PFDA, PFUnDA, PFTriDA, PFOS detected in 76.5–96.1% of semen samples; PFHpA, PFDoDA, PFTeDA, PFBS, PFHxS, 8:2 Cl^-PFESA detected in 2.6–30.7% of semen samples. Values < LOQ imputed using data on subject's age and body mass index (BMI) and BMI^2		semen and serum concentration is unlikely because semen and serum concentrations, although measured at a single time point, represent exposure over a relatively long period of time.
Wang et al. (2023) Induces epigenetic alterations (KC4) – DNA methylation in placenta. Birth size metrics also evaluated.	Cross-sectional (n = 180) Subset of participants in cohort study of pregnant women in Hebei Province, China, 2013–2014	Exposure was measured in sample of placenta obtained at delivery consisting of equal amounts of tissue from fetal and uterine sides of the placenta.	Placental PFAS and outcomes were measured in same placenta samples.	PFOS, PFOA, PFNA, PFHpS, PFHxA, PFDA, PFUdA, PFDoA, PFHxS, PFBS, PFHpA. Isomers are not mentioned. The PFASs in placenta were positively correlated with each other with correlation co-efficients between 0.174 and 0.727	Pregnant women from the general population	Exposure metric was placental PFAS (ng/g) measured in the same placenta sample in which outcomes were evaluated.	Ultraperformance liquid chromatography-tandem mass spectrometry. PFOS: 0.02 PFOA: 0.03 PFHxS: 0.01 PFUnDA: 0.04 PFNA: 0.03 PFDA: 0.05 PFDoDA: 0.03 PFHpS: 0.03 PFBS: 0.02 PFHxA: 0.06 PFHpA: 0.08 Detection rates: PFOA, PFOS – 100%; PFunDA, PFNA, PFDA – 82.2–96.7%; PFDoDA, PFHpS, PFBS – 21.1–59.4%; PFHxA, PFHpA – 2.8–3.3%. Values < LOQ were replaced with the LOD divided by the square root of 2	Co-exposure to other contaminants was not evaluated. Whether or not the subject's husband smoked was considered in the analysis. Information on alcohol use was not collected.	Differential exposure misclassification based on placental PFAS is unlikely. Non-differential exposure misclassification based on placental concentration is unlikely because placental concentrations, although measured at a single time point, represent exposure over a relatively long period of time

Table S1.23 Exposure assessment review and critique for mechanistic studies on cancer and exposure to PFOA and PFOS

Reference and outcome	What was the study design?	What methods were used for the exposure assessment? (include data source, measured or modelled concentrations in environmental and biological media)	What was the exposure context? Specify time period and/or lifestage over which exposure data gathered, and how historical exposures were accounted for (if relevant)	What PFAS were measured? Were they correlated?	Which general category of exposure is relevant?	What exposure metrics were derived for use in analyses (e.g. single point measurement, average exposure over time, exposure duration, cumulative exposure etc.)?	Analytical method and LOD or LOQ for each PFAS and% subjects < LOD or LOQ if available	Was there potential for co-exposures to other agents that could impact the end-point being assessed? Which ones were measured?	Was there potential for differential exposure misclassification? Was there potential for non-differential exposure misclassification? (Likely/unlikely)
Watkins et al. (2014) LINE-1 DNA methylation KC4 – Induces epigenetic effects in exposed humans (PFOA, PFOS)	Cross-sectional Subset of adults (M-322; F-363) from C8 Health Project Elevated exposures to PFOA from contaminated drinking-water; general population level exposures to PFOS	Serum PFAS measured in blood samples taken at enrolment (2005–2006) and at follow-up (2010). Mean of values at both timepoints also presented.	LINE-1 DNA methylation was evaluated in blood samples taken at follow-up in 2010. Serum PFOA decreased by 59% between enrolment (2005–2006) and follow-up (2010), likely due to reduced exposure to PFOA from contaminated water starting in 2007. Serum PFOS decreased by 55% between the two sampling events, consistent with decreases in the USA in general, likely due to ending the production of PFOS in the USA during this time period.	Evaluations based on serum PFOA, PFOS, PFNA, and PFHxS are reported in the study. These are the four PFAS detected in the blood serum of almost all US residents. One of the cited analytical methods (Flaherty et al., 2005) appears to measure branched and linear PFOA, but these are not reported separately. Information on whether the PFAS were correlated is not provided. The enrolment serum PFAS data are a subset of the enrolment data for the larger C8 Health Project study group reported in Frisbee et al. (2009). In the larger study group, 10 PFAS were measured. The four PFAS evaluated by Watkins et al. (2014) were detected in ≥ 97.7% of subjects. PFHxA, PFHpA, PFDA (not evaluated by Watkins et al. 2104) were detected in 37.5–53.2% of subjects, and PFDoA was detected in 0.7–8.7%. This information is not available for the follow-up samples.	Drinking-water – PFOA General population – PFOS, PFNA, PFHxS	The exposure metric for the data presented on associations with LINE-1 methylation was the mean of the serum PFAS (ng/mL) measurements at enrolment (2005–2006) and follow-up (2010). Analyses of associations of LINE-1 DNA methylation and serum PFAS at enrolment or at follow-up were stated to not to differ substantially from the main analysis, but the data are not shown.	Analysis with solid phase extraction coupled with solid phase extraction coupled to reverse-phase high performance liquid chromatography- tandem mass spectrometry as described in Frisbee et al. (2009) for enrolment samples and Kato et al. (2011) for follow-up samples. LOD/LOQ information is not provided in Watkins et al. (2014), but it is provided for the larger study group in Frisbee et al. (2009) and in the method presented by Kato et al. (2011). In Frisbee et al. 2009 (source of the enrolment serum PFAS [2005–2006]), the LOD was 0.5 ng/mL and samples with non-detectable PFOA, PFOS, PFNA, or PFHxS were assumed to have 50% of the LOD (0.25 ng/mL). The percent of samples < LOD in Frisbee et al. (2009) were: PFOA-0.1%; PFOS-0.5%; PFNA-2.3%; PFHxS-2.1%. In the study that is cited for the method used for analysis of the follow-up samples (Kato et al., 2011), LOD/LOQ values for the samples analysed were stated to be: PFOA, PFNA, PFHxS – 0.1/0.3 ng/mL; PFOS – 0.2/0.5 ng/mL. Kato et al. 2011 used the LOD/√2 for concentrations below the LOD. However, the LOD/LOQ values and the way concentrations < LOD were handled for the follow-up samples analysis are not provided by Watkins et al. (2014).	Co-exposure to other agents was not measured. Models were adjusted for smoking status (never/ever) and current alcohol consumption (yes/no)	Differential exposure misclassification is unlikely. Non-differential exposure misclassification is unlikely because serum concentrations, although measured at a single time point, represent exposure over a relatively long period of time.
Xie et al. (2023) Alters cell proliferation, death or nutrient supply (KC10) – Glioma	Case–control (137 glioma and 40 non-glioma brain tissue) from glioma patients age 2–77	PFAS were measured in glioma and non-glioma tissue Information on the area of the brain that was	Patients with glioma, 2–77 years old, were recruited at hospital.	PFOS, PFBS, PFHxS, PFCAs, FOSA, 6:2 Cl^- PFESA, 8:2 Cl^-PFESA. Isomers are not mentioned.	Glioma patients from the general population	Exposure metric was PFAS (ng/g) is glioma or non-glioma tissue at a single timepoint	Ultraperformance liquid chromatography – tandem mass spectrometry Reporting limit (RL): 0.05 ng/g	Co-exposure to other contaminants was not evaluated. Smoking and alcohol consumption were considered in the analysis.	Exposure classification was based on PFAS concentrations in gliomas of different grades and non-glioma tissue taken from different parts of the brain.

Table S1.23 Exposure assessment review and critique for mechanistic studies on cancer and exposure to PFOA and PFOS

Reference and outcome	What was the study design?	What methods were used for the exposure assessment? (include data source, measured or modelled concentrations in environmental and biological media)	What was the exposure context? Specify time period and/or lifestage over which exposure data gathered, and how historical exposures were accounted for (if relevant)	What PFAS were measured? Were they correlated?	Which general category of exposure is relevant?	What exposure metrics were derived for use in analyses (e.g. single point measurement, average exposure over time, exposure duration, cumulative exposure etc.)?	Analytical method and LOD or LOQ for each PFAS and% subjects < LOD or LOQ if available	Was there potential for co-exposures to other agents that could impact the end-point being assessed? Which ones were measured?	Was there potential for differential exposure misclassification? Was there potential for non-differential exposure misclassification? (Likely/unlikely)
	years in Guangzhou, China.	sampled was not provided.	A total of 137 glioma tissue and 40 non-glioma tissue samples were collected Paired samples from 18 patients; remainder were not paired samples (i.e. either glioma or non-glioma tissue, not both, from the glioma patient).	Statistically positive correlations (r2 = 0.54–0.92) were found between the concentrations of legacy and alternative PFASs			Values < RL considered to be zero when calculating total PFAS concentrations and ½ RL in multiple regression model analysis. At least one PFAS detected in all samples. PFOA, PFOS, PFHxA, FOSA, 6:2 Cl^-PFESA detected in 65–82% of glioma samples and 63–78% of non-glioma samples. Other PFAS detected in 6–51% of glioma samples and 5–43% of non-glioma samples.		There is potential for exposure misclassification because it is not known how the grade of the glioma or the area of the brain from which the tissue was taken impacts uptake of PFAS into the brain tissue.
Zhang et al. (2022) Common cold KC7 – immunosuppressive in exposed humans (PFOA, PFOS)	Cross-sectional US National Health and Nutrition Examination Survey (NHANES). Children age 3–11 from 2013–2014 cycle (*n* = 517). Adolescents age 12 = 19 from 2002–2016 cycles (*n* = 2732) Children and adolescents from general population	PFAS were measured in serum samples. In 2003–04 to 2011–12 cycles, PFOA and PFOS were measured as total PFOA or PFOS. In 2013–14 and 2015–16 cycles, isomers of PFOA and PFOS, including linear PFOA, sum of branched isomers of PFOA, linear PFOS, and the sum of monomethyl branched isomers of PFOS were measured. For these two cycles, concentrations of PFOA and PFOS were calculated as the sum concentration of the linear and branched isomers that were measured.	Outcome assessment based on response to question about cold(s) starting within past 30 days. Question was asked at same time that blood sample for PFAS analysis was taken.	Evaluation was based on PFOA, PFOS, PFNA, PFHxS, the most frequently detected PFAS in blood serum. Serum PFAS were positively correlated with Spearman coefficients of 0.28–0.63 in children, 0.30–0.80 in adolescents. Other PFAS were measured in NHANES. Although not reported in this publication, some of these were detected in some samples.	Children and adolescents from general population	Exposure metric was PFAS (ng/mL) measured in serum sample at a single timepoint.	Analytical method was solid phase extraction coupled to high performance liquid chromatography-isotope dilution-tandem mass spectrometry. LODs(ng/mL): PFOA – 0.1 (2003–2016, including for isomer-specific analysis in 2013–2016) PFOS – 0.4 (2003–2004); 0.2 (2005–2012); 0.1 for isomer-specific analysis (2013–2016) PFNA – 0.1 (2003–2006; 2013–2016) PFHxS – 0.3 (2003–2004); 0.1 (2005–2016). Values < LOD were replaced with the LOD divided by the square root of 2. All PFAS were detected in 99.1–100% of children and adolescent samples except for total branched isomers of PFOA (children – 24.18%; adolescents – 13.99%)	Other contaminants measured in NHANES were not included in the analysis. Exposure to tobacco smoke was evaluated by serum cotinine. Information on use of alcohol was not collected.	Differential exposure misclassification is unlikely. Non-differential exposure misclassification is unlikely because serum concentrations, although measured at a single time point, represent exposure over a relatively long period of time. .

ADONA, 3*H*-perfluoro-3-[(3-methoxy-propoxy)propanoic acid]; BMI, body mass index; DDT, dichlorodiphenyltrichloroethane; eGFR, estimated glomerular filtration rate; EMP, endothelial microparticle; EtPFOSA, 2-(*N*-methyl perfluorooctane sulfonamide) acetic acid; F, female; FCC, Fernald Community Cohort; HOME, Health Outcomes and Measures of the Environment; HPLC, high-performance liquid chromatography; INMA, INfancia y Medio Ambiente (Environment and Childhood); IR, insulin resistance; LC, liquid chromatography; LOD, limit of detection; LOQ, limit of quantification; M, male; MDA, malondialdehyde; MePFOSA, 2-(*N*-methyl perfluorooctane sulfonamide) acetic acid; MS/MS, tandem mass spectrometry; NHANES, National Health and Nutrition Examination Survey; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; OH, Ohio; PBDE, polybrominated diphenyl ether; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzodioxin; PCDF, polychlorinated dibenzofuran; PFAS, poly- and perfluoroalkyl substances; PFBA, perfluorobutanoic acid; PFBS, perfluorobutanesulfonic acid; PFC, polyfluorinated compound; PFDA, perfluorodecanoic acid; PFDoA, perfluorododecanoic acid; PFDoDA, perfluorododecanoic acid; PFDoDA, perfluorododecanoic acid; PFESA polyfluorinated ether sulfonate; PFHxA, perfluorohexanoic acid; PFHxS, perfluorohexanesulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; PFOSA, perfluorooctanesulfonylamide; PFPeA perfluoro-*n*-pentanoic acid; PFTeDA, perfluorotetradecanoic acid; PFTrDA, perfluorotridecanoic acid; PFTriDA, perfluorotridecanoic acid; PFUA, perfluoroundecanoic; PFUdA, perfluoroundecanoic; PFUnDA, perfluoroundecanoic acid; PMP, platelet microparticles; RL, reporting limit; ROS, reactive oxygen species; TEQ, toxic equivalent; TSH, thyroid-stimulating hormone; USA, United States of America.

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