

Table 4.1 PFNA: Epidemiologic studies of male reproductive toxicity (Revised November 5, 2021)<sup>2</sup>.

Reference; study location, period, design, sample	Exposure matrix and concentration (ng/mL)	Outcomes	Results	Covariates, other PFASs analyzed	Comments
Lind et al., 2017 Denmark 2010-2012 Prospective cohort N=299 Odense Child Cohort: sons of mothers who were >16 years old, of Western origin, had no communication barriers, delivered in a reference hospital, and did not use reproductive assistance.	Maternal serum collected at gestational week 5-12 (median 10 weeks) Median (IQR) 0.7 (0.5-0.9)	AGD <sub>AS</sub> & AGD <sub>AP</sub> and penile width at 3 months, measured three times by trained study technicians	<u>AGD<sub>AS</sub></u> $\beta$ (95% CI) per unit increase in ln(PFNA): <b>1.4 (0.02, 2.9) mm</b> No association when 2 <sup>nd</sup> , 3 <sup>rd</sup> , 4 <sup>th</sup> quartiles of PFNA were compared to 1 <sup>st</sup> <u>AGD<sub>AP</sub>, penile width</u> : no associations	Adjusted for "post-conceptual age" (sum of GA at birth and age of child at the AGD measurement, in days), z-score for weight at 3 months, parity, maternal smoking, and pre-pregnancy body mass index (BMI) Other PFASs: perfluorohexane sulfonic acid (PFHxS), PFOS, PFDA	Correlations among PFASs not reported. Women who gave birth in 2010 had higher PFOA, PFOS, and PFNA concentrations than women who gave birth in 2011-2012. Women who participated in this study were better educated, smoked less, and were more likely to be of Danish origin than nonparticipants.

<sup>2</sup> Studies are ordered by outcomes (AGD, male reproductive function, prostate cancer), and within outcomes, by publication date. Statistically significant results are in **bold** type. This table has been revised to include an additional study, Lopez-Espinosa et al. (2016), see page 25 below. The text of the hazard identification document (available here: <https://oehha.ca.gov/media/downloads/cnr/pfnapfdahid100121.pdf>) has not been updated to include discussion of Lopez-Espinosa et al. (2016).

Reference; study location, period, design, sample	Exposure matrix and concentration (ng/mL)	Outcomes	Results	Covariates, other PFASs analyzed	Comments
Tian et al., 2019 Shanghai, China 2012 Prospective cohort N=500 male singletons born to women who were recruited at gestational weeks 12-16 from one hospital	Maternal plasma (fasting) collected at 12-16 weeks gestation  Median (5, 25, 75, 95 percentiles): 1.75 (0.73, 1.30, 2.47, 3.99)  Geometric mean (GA; standard deviation or SD): 1.8 (1.68)	AGD [AGD <sub>AS</sub> & AGD <sub>AP</sub> ] at birth, 6 months, and 12 months  Measured by trained examiners with no knowledge of maternal PFAS concentrations	$\beta$ (95% CI) for unit change in ln(PFNA) (mm)  <u>AGD<sub>AS</sub></u> Birth: -0.51 (-1.19, 0.17) 6 months: -1.83 (-4.12, 0.45) 12 months: no association  <u>AGD<sub>AP</sub></u> Birth: -0.34 (-1.14, 0.46) 6 months: -0.87 (-3.17, 1.44) 12 months: no association  In longitudinal analyses, no associations with AGD	Selected <i>a priori</i> and adjusted for: maternal age, education, parity, and pre-pregnancy BMI; GA at birth; age at examination (days), infant size (weight at birth, weight-for-length z-score at 6 and 12 months of age)  Stratified by breastfeeding duration for AGD at 6 and 12 months  8 PFASs detected in $\geq 80\%$ of participants: PFHxS, PFOA, PFOS, PFNA, PFDA, PFUnDA, PFDoA, PFTrDA	Pearson correlation coefficient for ln-transformed PFNA and: PFOS r = 0.64 PFOA r = 0.39 PFDA r = 0.79 PFUnDA r = 0.796 PFDoA r = 0.47 PFTrDA r = 0.31  75% of mothers had university-level education or higher
Joensen et al., 2009 Denmark 2003 Cross-sectional* N=105 Healthy young men from the general population reporting for the military draft, median age 19 years. *Men with highest and lowest T levels were selected. Group 1, n=53, median 31.8 nmol/L Group 2, n=52, median 14.0 nmol/L	Serum Median (5 <sup>th</sup> , 95 <sup>th</sup> percentiles) All 0.8 (0.4, 1.8) High T 0.8 (0.4, 2.0) Low T 0.8 (0.4, 2.0)	Serum reproductive hormones and related proteins: T, E2, sex hormone-binding globulin (SHBG), LH, follicle-stimulating hormone (FSH), inhibin B, free androgen index (FAI)  Semen quality: semen volume; sperm concentration, count, % motile, morphology	No associations with T Due to low concentration, PFNA was not included in further analyses	PFNA was included only in bivariate analyses (no adjustments)  Other PFASs: PFHxS, PFPA, PFOA, PFOS, PFOSA, PFDA, PFUnDa, PFDoA, PFTrA	

Reference; study location, period, design, sample	Exposure matrix and concentration (ng/mL)	Outcomes	Results	Covariates, other PFASs analyzed	Comments
<p>Specht et al., 2012</p> <p>Kharkiv, Ukraine; Greenland; Warsaw, Poland</p> <p>2002-2004</p> <p>Cross-sectional</p> <p>N=604</p> <p>Men who provided semen and blood samples and completed questionnaires, and were partners of pregnant women enrolled in the INUENDO fertility cohort</p>	<p>Serum</p> <p>Median (range)</p> <p>Ukraine 1.0 (0.2, 4)</p> <p>Greenland 1.4 (0.5, 12)</p> <p>Poland 1.2 (0.5, 6)</p>	<p>Percentage of sperm with detectable DNA fragmentation by SCSA</p> <p>DNA fragmentation by in situ TUNEL assay</p> <p>Pro- (Fas) and anti-apoptotic (Bcl-xL) markers on sperm</p> <p>Serum: FSH, LH, E2, T, SHBG</p> <p>Inhibin B</p>	<p>No associations with sperm DNA fragmentation (SCSA and TUNEL assays) (data not reported).</p> <p>No consistent associations with apoptotic markers across study locations or models within locations (data not reported).</p> <p>No consistent relationship with SHBG.</p> <p>Associations with T, E2, and the gonadotropins FSH and LH were not consistent across locations (data not reported).</p> <p>Results for inhibin-B were not reported</p>	<p>Analyses were stratified by study location and adjusted for sexual abstinence period, age, BMI, caffeine consumption, serum cotinine, recent fever, self-reported genital infections, testicular disorders, and semen spillage.</p> <p>Alcohol use was not included due to frequency of missing data.</p> <p>Other PFASs: PFHxS, PFOA, PFOS</p> <p>Spearman's rank correlations among PFASs ranged from r=0.4 to r=0.9, though correlations with PFNA were not reported.</p>	<p>All men had pregnant partners, thus sterile and highly subfertile men are underrepresented.</p> <p>Men were asked to collect semen after <math>\geq 2</math> days of abstinence</p> <p>High frequency of missing data for Bcl-xL and Fas due to samples lost during shipment and insufficient number of cells for analysis.</p> <p>Many reproductive hormone samples were missing for Greenland (32%) and Poland (41%).</p>
<p>Toft et al., 2012</p> <p>Kharkiv, Ukraine; Greenland; Warsaw, Poland</p> <p>2002-2004</p> <p>Cross-sectional</p> <p>N=588</p> <p>Men who provided semen and blood samples and completed questionnaires, and were partners of pregnant women enrolled in the INUENDO fertility cohort</p>	<p>Serum median (33<sup>rd</sup>, 67<sup>th</sup> percentiles)</p> <p>All 1.2 (1.0, 1.5)</p> <p>Ukraine 1.0 (0.8, 1.2)</p> <p>Greenland 1.7 (1.3, 2.4)</p> <p>Poland 1.2 (1.0, 1.3)</p>	<p>Semen quality: sperm concentration, volume, total count, % morphologically normal sperm, % motile sperm</p>	<p>No associations with sperm concentration, volume, total count, % motile sperm (data not reported)</p> <p>NS association with lower % of normal sperm when PFNA was analyzed as a continuous variable (data not reported)</p>	<p>Selected <i>a priori</i> and adjusted for: age, abstinence time, semen spillage, current smoking, history of urogenital infections, BMI, country (combined analyses)</p> <p>Sperm motility analyses were restricted to samples analyzed within 1 hour of collection</p> <p>Other PFASs: PFHxS, PFOA, PFOS</p>	<p>Participation rates:</p> <p>Kharkiv 36%</p> <p>Greenland 79%</p> <p>Warsaw 29%</p> <p>All men had pregnant partners, thus sterile and highly subfertile men are underrepresented.</p> <p>Men were asked to collect semen after <math>\geq 2</math> days of abstinence</p> <p>Volume and total sperm count analyses were restricted to samples with no reported semen spillage</p>

Reference; study location, period, design, sample	Exposure matrix and concentration (ng/mL)	Outcomes	Results	Covariates, other PFASs analyzed	Comments
<p>Joensen et al., 2013</p> <p>Denmark</p> <p>2008-2009</p> <p>Cross-sectional</p> <p>N=247</p> <p>Healthy young men randomly selected from the general population, median age 19 years</p>	<p>Serum</p> <p>Median (IQR) 1.07 (0.88, 1.41)</p> <p>Mean <math>\pm</math> SD 1.23 <math>\pm</math> 0.63</p>	<p>Serum reproductive hormones and related proteins: total T, free T, E2, inhibin B, FAl; T<math>\times</math>100/SHBG), FSH, LH, SHBG</p> <p>Semen quality: volume; sperm count, concentration, motility, morphology, total normal sperm</p> <p>Testicular volume</p>	<p><math>\beta</math> (CI) per ng/mL increase in PFNA</p> <p><u>Hormones</u> (ln-transformed)</p> <p>Total T <math>\beta</math> = -0.059 (-0.118, 0.001) nmol/L</p> <p>Free T <math>\beta</math> = -0.052 (-0.114, 0.010) nmol/L</p> <p><b>E2 <math>\beta</math> = -0.075 (-0.013, -0.019) pmol/L</b></p> <p>No associations with other reproductive hormones or SHBG</p> <p><u>Semen quality and testicular volume</u>: no associations</p>	<p>Analyses with hormones and SHBG were adjusted for BMI and smoking</p> <p>Semen volume, concentration, and total count were adjusted for abstinence time</p> <p>% morphologically normal sperm was unadjusted</p> <p>Progressively motile % was adjusted for time to semen analysis</p> <p>Considered but not included: time of day of blood sample, ethnicity, recent alcohol use, prenatal exposure to tobacco smoke, previous or current diseases, recent fever, recent medication use, season, interaction with cigarette smoking</p> <p>Other PFASs: PFHxS, PFHpS, PFOA, PFOS, PFDA</p>	<p>Participation rate was ~30%, which is "higher than other population-based semen quality studies".</p> <p>Participants were recruited at a compulsory medical examination for consideration for military service</p> <p>Men were asked to abstain for 48 hours; median abstinence period was 62 hours.</p> <p>Analyses were blinded</p>

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Leter et al., 2014 Kharkiv, Ukraine; Greenland; Warsaw, Poland 2002-2004 Cross-sectional N = 262 from 607 male partners of pregnant women enrolled in the INUENDO fertility cohort (312 samples were randomly selected from those with sufficient semen. Further sample loss is due to "random unpredictable cell loss occurring during the processing of some samples."	Serum Mean ± SE: Kharkiv 1.1 ± 0.1 Greenland 2.2 ± 0.2 Warsaw 1.4 ± 0.1 Combined 1.6 ± 0.1	Sperm DNA global methylation levels, indicated by a) average DNA methylation in repetitive DNA sequences (Alu, LINE-1, Sata) and b) flow cytometric (FCM) immunodetection of 5-methyl-cytosines using the FCM Sperm DNA Global Methylation (DGML) Assay, performed by blinded investigators	Results were inconsistent across study location β (CI) per unit ln(PFNA): <u>Alu</u> For each study location, the association was negative but ns <u>LINE-1</u> Kharkiv β = 5.7 (1.4, 10.1) % No associations for other study locations <u>Sata</u> Kharkiv β = 9.3 (1.5, 17.1) % No associations for other study locations <u>FCM DGML</u> Warsaw β = -99.6 (-152.5, -46.8) units No associations for other study locations	Adjusted for age, smoking (selected <i>a priori</i> ), study location combined analyses) Other PFASs and correlations: PFHxS r=0.556 PFOA r=0.417 PFOS r=0.571 PFDA*, PFUnDA*, PFDODA* *excluded due to low detection rate	All men had pregnant partners, thus sterile and highly subfertile men are underrepresented. Men were asked to collect semen after ≥2 days of abstinence
Lewis et al., 2015 United States 2011-2012 Cross-sectional N = 857 males, 12-80 years Subset of the NHANES with data on serum PFASs, T, and thyroid hormones	Serum Median (IQR) by age group: 12 to <20 years: 0.78 (0.56, 1.19) 20 to <40 years: 0.98 (0.67, 1.31) 40 to <60 years: 1.00 (0.67, 1.57) 60 to 80 years: 1.07 (0.77, 1.58)	Serum total T, thyroid stimulating hormone (TSH), and free and total T and free and total thyroxine (T4)	Percent change (95% CI) in hormone concentrations per doubling of PFNA: No associations with T <u>12 to &lt;20-year-olds:</u> <b>TSH 16.3 (4.0, 30.2), p &lt; 0.05</b> <u>40 to 60-year-olds:</u> Total T4: -2.5 (-5.2, 0.2), p < 0.1. No other associations with thyroid hormones	Adjusted for age, body mass index (BMI), poverty income ratio, race/ethnicity, serum cotinine Other PFAS: PFHxS, PFOA, PFOS Correlations among PFASs were not reported	The largest association of any PFAS and thyroid hormones was that of PFNA with TSH in 12-20 year olds. Significant reduction in geometric mean levels of the included PFASs compared to previous NHANES studies

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<p>Louis et al., 2015</p> <p>Michigan and Texas</p> <p>2005-2009</p> <p>Cross-sectional</p> <p>N=462</p> <p>Population-based sample of couples planning pregnancy, recruited from a marketing database in Michigan and a fishing/hunting license registry in Texas.</p>	<p>Serum</p> <p>Median (IQR); geometric mean (95% CI)</p> <p>Michigan: 1.0 (0.75, 1.35); 0.96 (0.84, 1.11)</p> <p>Texas: 1.65 (1.2, 2.2); 1.68 (1.61, 1.76)</p>	<p>Semen quality:</p> <p>Volume, straw distance, sperm concentration, total count, hypo-osmotic swollen,</p> <p>8 motility measures,</p> <p>6 sperm head measures,</p> <p>12 individual and 2 summary morphology measures,</p> <p>2 sperm chromatin stability measures</p>	<p>Associations with 1-unit increase in ln(PFNA):</p> <p>No significant differences in semen volume; sperm viability, count, or concentration.</p> <p><b>% normal sperm, strict criteria, <math>\beta = 3.897</math> (0.564, 7.231)</b></p> <p><b>% of sperm with coiled tail, <math>\beta = -4.030</math> (-7.766, -0.293)</b></p> <p>No significant associations with other semen parameters</p>	<p>Adjusted for age, BMI, serum cotinine, abstinence, sample age, research site (Texas/Michigan)</p> <p>Other PFASs: PFOA, PFOS, PFOSA, Et- PFOSA-AcOH, Me-PFOSA-AcOH, PFDA</p>	<p>Semen was collected after <math>\geq 2</math> days' abstinence</p> <p>A 2<sup>nd</sup> sample collected approximately 1 month later was used to corroborate azoospermia observed in the 1<sup>st</sup> sample.</p> <p>Semen analysis was performed one day after collection.</p> <p>PFOA, PFOSA, and Me-PFOSA-AcOH were most often associated with semen parameters.</p>

Reference; study location, period, design, sample	Exposure matrix and concentration (ng/mL)	Outcomes	Results	Covariates, other PFASs analyzed	Comments
<p>Lopez-Espinosa et al., 2016<sup>3</sup></p> <p>Mid-Ohio Valley</p> <p>2005 to 2006</p> <p>Cross-sectional</p> <p>N = 1,169 6-9 year-old boys with PFAS and outcome measurements. Boys who had reached puberty (based on T &gt; 50 ng/dL) were excluded.</p> <p>Sample from the C8 Study; participants had consumed water from contaminated water districts or private wells near a fluoropolymer manufacturing plant in Parkersburg, West Virginia for at least one year up to 2004.</p>	<p>Serum</p> <p>Median 1.7</p> <p>Concentrations by quartiles:</p> <p>1<sup>st</sup>: &lt;LOD-1.3</p> <p>2<sup>nd</sup>: 1.4-1.7</p> <p>3<sup>rd</sup>: 1.8-2.3</p> <p>4<sup>th</sup>: 2.4-12.0</p>	<p>Serum</p> <p>Free T, total T, E2</p>	<p><u>Ln(total T)</u></p> <p>% difference (95% CI) in sex hormones associated with unit change in ln(PFNA)</p> <p>Main analysis: -2.1 (-5.5, 1.3)</p> <p>Adjusted for other PFAS: -0.9 (-4.5, 2.8)</p> <p>Adjusted for height: -1.7 (-5.1, 1.8)</p> <p>Adjusted for BMI: -1.9 (-5.2, 1.5)</p> <p>By PFNA quartile (compared to lowest quartile)</p> <p>2<sup>nd</sup>: -7.3 (-14.3, 0.3)</p> <p>3<sup>rd</sup>: <b>-8.1 (-15.1, -0.4)</b></p> <p>4<sup>th</sup>: -3.5 (-11.1, 4.8)</p> <p>p-trend=0.822</p> <p><u>Ln(E2)</u></p> <p>% difference (95% CI) in sex hormones associated with unit change in ln(PFNA)</p> <p>Main analysis: -2.5 (-6.2, 1.4)</p> <p>Adjusted for other PFAS: -0.9 (-4.8, 3.2)</p> <p>Adjusted for height: -2.2 (-5.9, 1.7)</p> <p>Adjusted for BMI: -2.4 (-6.1, 1.4)</p> <p>By PFNA quartile (compared to lowest quartile)</p> <p>2<sup>nd</sup>: 0.0 (-8.3, 9.1)</p> <p>3<sup>rd</sup>: 1.7 (-6.9, 11.0)</p> <p>4<sup>th</sup>: -6.2 (-14.4, 2.7)</p> <p>p-trend=0.120</p> <p>Free T was not included in multivariate analyses due to low proportion &gt; LOD</p>	<p>All models adjusted for age and sampling month; total T models were also adjusted for time of day of sampling</p> <p>Some models adjusted additionally for other PFASs, height, or BMI</p> <p>Considered but not included: race/ethnicity, household income</p> <p>Other PFASs: PFHxS, PFOA, PFOS</p>	<p>Correlations between PFNA and other measured PFASs were low (r = -0.09 to r=0.25)</p> <p>PFNA was inversely associated with insulin-like growth factor-1</p>

<sup>3</sup> Newly added to this table. Full citation: Lopez-Espinosa MJ, Mondal D, Armstrong BG, Eskenazi B, Fletcher T. 2016. Perfluoroalkyl substances, sex hormones, and insulin-like growth factor-1 at 6-9 years of age: A cross-sectional analysis within the C8 health project. Environ Health Perspect 124:1269-1275.

Reference; study location, period, design, sample	Exposure matrix and concentration (ng/mL)	Outcomes	Results	Covariates, other PFASs analyzed	Comments
Zhou et al., 2016 Taipei, Taiwan 2009-2010 Cross-sectional N=102 healthy 13-15-year-old boys from 7 public schools From the control cohort of the Genetics and Biomarkers study for Childhood Asthma	Serum sampled after 8-hour fast Median (IQR) 0.8 (0.6, 1.0)	Serum T and E2 (average of 2 values)	$\beta$ (95% CI) per ng/mL increase in PFNA: Ln(T) <b>-0.4233 (-0.6998, -0.1467) mmol/L</b> Ln(E2) 0.1252 (-0.0758, 0.3263) mmol/L	Adjusted for: age, parental education, BMI, environmental tobacco smoke exposure, regular exercise, month of survey  Other PFASs: PFBS, PFHxA, PFHxS, PFOA, PFOS, PFDA, PFDoA, PFTA	More associations between individual PFAS levels and hormone levels were reported in boys than in girls
Petersen et al., 2018 Faroe Islands 2007-2009 Cross-sectional N=263 Entire population of 24-26 year old men were invited	Serum Median (range) 0.49 (0.61, 18.10)	Serum reproductive hormones and related proteins: FSH, LH, T, free T, E2, SHBG, T/LH, free T/LH, T/E2, FT/E2), inhibin B, inhibin B/FSH Semen quality: Sperm conc., total sperm count, semen volume, % motile sperm	Specific results for PFNA were not reported. Authors state there were no associations between semen quality and any PFASs.  Associations with reproductive hormones were not mentioned for PFNA.	Reproductive hormones (except FSH, LH) were adjusted for BMI, smoking, age, time of day of blood sampling. Sperm conc., total sperm count, and semen volume were adjusted for abstinence (hours). % motile sperm was adjusted for interval between ejaculation and assessment.  Other PFASs: PFHxS, PFOA, PFOS, PFDA	49% of those reached by phone (24% of all young men invited by mail) participated.



Reference; study location, period, design, sample	Exposure matrix and concentration (ng/mL)	Outcomes	Results	Covariates, other PFASs analyzed	Comments
<p>Pan et al., 2019 Nanjing, China 2015-2016 Cross-sectional N=664 males from couples who visited a reproductive medical center. Some men had fecundity issues and some were partners of women with female factor infertility Exclusions: reproductive tract disease, medication for fertility, insufficient semen volume for analysis</p>	<p>Semen (after 2-day abstinence) Median (IQR) 0.024 (0.013, 0.042) Serum (same day as semen): median (IQR) 1.466 (1.011, 2.216)</p>	<p>Semen quality: semen volume, sperm conc., sperm count, progressively motile (%), VCL, VSL, morphologically normal (%), DNA fragmentation index (DFI), HDS Concentration and motility were measured by CASA</p>	<p>P-values were adjusted for false discovery rate/multiple comparisons Change (95% CI) per unit increase in: <u>Ln(semen PFNA):</u> <b>Progressively motile (%) <math>\beta=-1.999</math> (-3.284, -0.714) <math>p=0.02</math></b> <b>VCL (<math>\mu\text{m/s}</math>): <math>\beta=-0.792</math> (-1.542, -0.042) <math>p=0.1</math></b> <b>VSL (<math>\mu\text{m/s}</math>) <math>\beta=-0.686</math> (-1.315, -0.058) <math>p=0.1</math></b> <b>DFI (%) <math>\beta=0.106</math> (0.047, 0.165) <math>p=0.01</math></b> <b>HDS (%) <math>\beta=0.044</math> (0.002, 0.086) <math>p=0.1</math></b> No associations with other semen parameters <u>Ln(serum PFNA):</u> Morphologically normal (%) <math>\beta=-0.262</math> (-0.545, 0.020) <math>p=0.2</math> <b>HDS (%) <math>\beta=0.119</math> (0.063, 0.176) <math>p=0.01</math></b> No associations with other semen parameters.</p>	<p>Adjusted for: Age, BMI, BMI<sup>2</sup>, smoking status, alcohol use, abstinence time Also considered: having fathered a pregnancy, occupational hazards, medical history Analyses of associations with semen parameters focused on the most abundant PFASs in serum and semen and those detected in at least 80% of semen samples: PFOA, PFOS, 6:2 Cl-PFESA, PFNA, PFDA, PFUnDA</p>	<p>Correlation between serum and semen PFNA: <math>r=0.72</math> Correlations between serum PFNA and other PFASs: PFHxS <math>r=0.361</math> PFOA <math>r=0.570</math> PFOS <math>r=0.740</math> 6:2 Cl-PFESA <math>r=0.752</math> 8:2 Cl-PFESA <math>r=0.665</math> PFDA <math>r=0.825</math> PFUnDA <math>r=0.910</math> PFDoA <math>r=0.821</math> PFTrDA <math>r=0.810</math> Associations of PFNA with semen parameters were similar to those of other PFASs.</p>
<p>Cui et al., 2020 Nanjing, China 2015-2016 Cross-sectional N=651 (see Pan et al., 2019) Additional exclusion: missing reproductive hormone data</p>	<p>Serum Median (IQR) 1.47 (1.03, 2.23) Mean (range) 1.82 (0.27, 17.30) Semen sampled after 2-day abstinence: Median (IQR) 0.02 (0.01, 0.04) Mean (range) 0.03 (&lt;LOQ, 0.36)</p>	<p>Serum reproductive hormones and related proteins: total T, free T, E2, FSH, LH, T/LH as an indicator of Leydig cell function SHBG, FAI</p>	<p>% change (95% CI) in hormone level per unit change in <u>Ln(serum PFNA)</u>, for all men and men &lt; 30 years, with p-trend for analyses by PFNA quartiles: <b>Total T -3.99 (-7.01, -0.87), p-trend = 0.013</b> &lt; 30 years: <b>-5.54 (-9.09, -1.84), p-trend=0.004</b> <b>Free T -2.77 (-5.69, 0.25), p-trend = 0.072</b> &lt; 30 years: <b>-4.54 (-8.90, 0.02), p-trend=0.016</b> <b>E2 -2.08 (-7.56, 3.73), p-trend=0.475</b> &lt; 30 years: <b>-5.32 (-11.40, 1.19), p-trend=0.107</b> <b>SHBG -4.32 (-8.12, -0.37), p-trend = 0.033</b> &lt; 30 years: <b>-4.50 (-8.00, -0.87), p-trend=0.051</b> Total T/LH ratio <b>-3.4 (-7.92, 1.34), p-trend = 0.157</b> &lt; 30 years: <b>-1.65 (-7.18, 4.21), p-trend=0.573</b></p>	<p>Adjusted for: age, BMI, smoking status, time of blood sampling, fasting status Also considered: abstinence time, alcohol use, having fathered a pregnancy Focused on the most abundant PFASs (those that accounted for 70% and 73% % of PFASs in serum and semen samples, respectively): PFOA, PFOS, 6:2 Cl-PFESA, PFNA</p>	<p>No statistical adjustment for multiple tests Spearman correlation between serum and semen PFNA <math>r=0.716</math> Associations were stronger in younger men. No SS associations among men &gt;30 years. P-values for associations with serum PFAS were greater than for semen PFAS. Authors note that most toxicological studies demonstrate that PFAS</p>

Reference; study location, period, design, sample	Exposure matrix and concentration (ng/mL)	Outcomes	Results	Covariates, other PFASs analyzed	Comments
			FAI, FSH, LH: no associations <u>Ln(semen PFNA):</u> <b>Total T -5.27 (-8.27, -2.18), p-trend = 0.001</b> < 30 years: -7.18 (-10.97, -3.24), p-trend=0.001 Free T -2.76 (-5.71, 0.29), p-trend=0.075 < 30 years: -8.45 (-12.96, 3.71), p-trend=0.062 E2 -2.97 (-8.45, 2.84), p=0.308 < 30 years: -6.49 (-13.02, 0.54), p-trend=0.069 <b>SHBG -6.44 (-10.17, -2.55), p-trend=0.001</b> < 30 years: -3.82 (-7.67, 0.19), p-trend=0.001 <b>Total T/LH ratio -6.19 (-10.61, -1.56), p-trend=0.009</b> < 30 years: -6.32 (-12.02, -0.24), p-trend=0.042 FAI, FSH, LH: no associations		(including PFNA) exposure reduces T secretion. Effect sizes were greater but less likely to reach statistical significance in analyses restricted to men who had fasted.

Reference; study location, period, design, sample	Exposure matrix and concentration (ng/mL)	Outcomes	Results	Covariates, other PFASs analyzed	Comments
<p>Ma et al., 2021 Hangzhou, Zhejiang, China 2017</p> <p>Prospective cohort (IVF outcomes) and cross-sectional (hormones and semen quality outcomes)</p> <p>N=96 couples undergoing IVF treatment due to tubal factor infertility</p> <p>Men with severe male-factor infertility were excluded</p>	<p>Plasma</p> <p>Median (IQR) [range] 2.3 (1.7,3.9) [0.7, 16.7]</p> <p>Concentrations by tertiles: 1<sup>st</sup>: 0.7-1.8 2<sup>nd</sup>: 1.8-3.4 3<sup>rd</sup>: 3.4-16.7</p>	<p>Plasma reproductive hormones: FSH, LH, E2, T</p> <p>Semen quality: volume; sperm motility, concentration, motility, morphology</p> <p>IVF outcomes</p>	<p>Compared to 1<sup>st</sup> tertile of PFNA:</p> <p><u>Hormones</u></p> <p>No associations with FSH, LH, E2, or T</p> <p><u>Semen quality</u></p> <p><b>Sperm concentration ↓ in 2<sup>nd</sup> and 3<sup>rd</sup> (25% reduction) tertiles p-trend = 0.031</b></p> <p>Sperm count ns ↓ in 2<sup>nd</sup> and 3<sup>rd</sup> tertiles, p-trend = 0.050</p> <p>% sperm with normal morphology ns ↓ in 2<sup>nd</sup> and 3<sup>rd</sup> tertiles, p-trend = 0.109</p> <p>Progressive motility no association</p> <p><u>IVF outcomes</u></p> <p><b>2<sup>nd</sup> tertile exposure was associated with more fertilization, p-trend = 0.667</b></p> <p>No associations with number of good quality embryos at day 3, implantation, clinical pregnancy, or live births</p>	<p>Adjusted for age, BMI, smoking status</p> <p>Other PFASs: PFBA, PFHxS, PFHpA, PFOA, PFOS, PFOSA, PFNA, PFUnDA, PFDoA</p>	<p>Each couple contributed one cycle of IVF treatment to the study.</p> <p>Male and female partners' PFNA levels were highly correlated, r=0.74.</p> <p>PFNA was strongly correlated with:</p> <p>PFDA r = 0.881*</p> <p>PFOS r = 0.736*</p> <p>PFUnDA r = 0.870*</p> <p>*p&lt; 0.05</p> <p>2<sup>nd</sup> and 3<sup>rd</sup> tertile PFUnDA was associated with ↑ T</p>
<p>Hardell et al., 2014 Sweden, 2007-2011</p> <p>Case-control</p> <p>N=200 cases of newly diagnosed prostate cancer from one hospital</p> <p>N=186 population-based, matched controls with no history of cancer</p>	<p>Whole blood drawn after diagnosis but before treatment with radiation or chemotherapy.</p> <p>Mean, median (range)</p> <p>Cases 0.679, 0.612 (0.0500, 4.6)</p> <p>Controls 0.631, 0.572 (0.0850, 2.1)</p>	<p>Prostate cancer</p> <p>Medical records</p>	<p>OR = 1.2, 95% CI (0.8, 1.8) for exposure above control median</p> <p>Authors state that using 75<sup>th</sup> percentile exposure cutoff resulted in somewhat higher ORs, but did not show results.</p>	<p>Adjusted for age, BMI, year of sample.</p> <p>Matched on age and geographic area.</p> <p>Other PFASs: PFHxA, PFHxS, PFOA, PFOS, PFDA, PFUnDA, PFDoDA</p>	<p>Participation rates were 60% for controls and 79% for cases.</p> <p>Gleason score, prostate-specific antigen, and a combination of both were not associated with PFASs.</p> <p>Serum was sampled after cancer diagnosis.</p>

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<p>Ducatman et al., 2015 Mid-Ohio Valley 2005 – 2006 Cross-sectional N = 12,988 males over 20 years of age with measured PSA. Sample from the C8 Study, which initially included those who lived, worked, or went to school in one of the six water districts contaminated with PFOA from a chemical facility; an estimated 81% of eligible residents participated</p>	<p>Serum Mean ± SD 1.47 ± 1.63</p>	<p>Serum PSA concentration PSA ≥ 4.0 was considered clinically significant</p>	<p>Ratio of adjusted geometric mean ln(PFNA) concentrations for PSA ≥ 4.0 vs PSA &lt; 4.0, by age group: 20-49 years: 0.85 (0.69, 1.06) 50-69 years: 1.04 (0.95, 1.13) No relationship with PSA (continuous) in either age group</p>	<p>Stratified by age 20–49 years vs. 50–69 years and adjusted for geometric mean age within age strata (35 or 60 years), smoking status, alcohol intake, and BMI. Other PFASs: PFHxS, PFOA, PFOS</p>	<p>Sample size in analysis is approximately half of original sample. Other than exclusion of men ≥70 years, reasons for the reduced sample size are not stated. Unclear whether stratification and adjustment were appropriate and adequate for addressing confounding by age</p>