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REVIEW ARTICLE

Perfluoroalkyl and polyfluoroalkyl substances and measures of human fertility: a systematic review

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ABSTRACT

Perfluoroalkyl and polyfluoroalkyl substances (PFASs) are found widespread in the environment and humans. The relation of PFASs to fertility has now been examined in a relatively large number of epidemiologic studies and a synthesis is in order. The aim of this study was to assess the current human epidemiologic evidence on the association between exposure to PFASs and measures of human fertility, with particular emphasis on perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA). Systematic literature searches were initially conducted in MEDLINE and EMBASE and subsequently in references and citations of included papers. Studies were included if they assessed exposure to PFASs in biological samples in relation to reproductive hormones, semen characteristics, or time to pregnancy (TTP). Study characteristics and results were abstracted to predefined forms, and the studies were assessed for the risk of bias and confounding. Sixteen studies investigated the association between PFAS exposure in men and semen parameters, reproductive hormone levels, or TTP. There was a lack of consistent results among the numerous investigated exposure-outcome combinations. However, subtle associations between higher PFOS and lower testosterone or abnormal semen morphology cannot be excluded. Eleven studies assessed the association between PFAS exposure in women and TTP or reproductive hormones levels. Four of eight studies found prolonged TTP with higher PFOS or PFOA, but only one study found an association when restricting to nulliparous women. In men, there is little evidence of an association between PFAS exposure and semen quality or levels of reproductive hormones. For PFOS and PFOA, the literature indicates an association with female fecundability in parous women, which is most likely not causal.

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Introduction

Exposure to perfluoroalkyl and polyfluoroalkyl substances (PFASs) is ubiquitous, raising concern about potential adverse effects in humans. PFASs are a group of environmental toxicants that have been produced

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Supplemental data for this article can be accessed here.

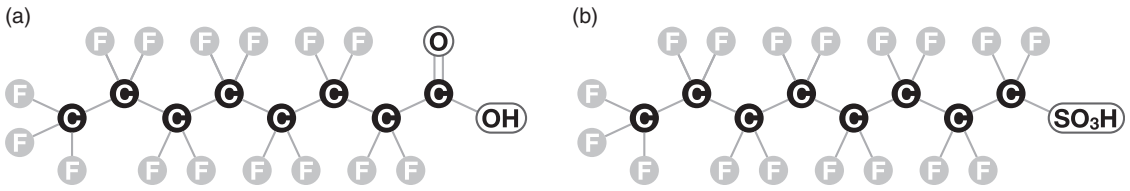

Figure 1. The chemical structure of PFOA (a) and PFOS (b).

since the 1950s and are used in various products due to their water- and oil repelling properties. Human exposure routes include ingestion, inhalation, and dermal absorption, and examples of exposure sources count food packaging material, food items such as fish, nonstick cookware, as well as textiles including clothes, footwear and carpets (Butenhoff et al. 2006; Kantiani et al. 2010). PFASs have been detected in humans all over the world and have long half-lives [approximately 5 years for perfluorooctane sulfonate (PFOS) and 3.5 years for perfluorooctanoate (PFOA)] (Lau et al. 2007; Olsen et al. 2007). The chemical structure of PFOS and PFOA is shown in Figure 1. PFASs are persistent in the environment and thus, exposure remains present even though the production of specific compounds such as PFOS and PFOA has been gradually eliminated in several countries since the year 2000.

PFASs may possess endocrine disrupting properties even though their chemical structure is dissimilar to the chemical structure of reproductive hormones. Some animal studies have shown changes in the synthesis of sex hormones associated with PFAS exposure. For instance, PFOA has been demonstrated to be associated with decreases in serum testosterone levels and increases in estradiol levels in male rats (Lau et al. 2007). PFOS exposure has been associated not only with decreases in serum concentrations of testosterone in both rats and mice (Biegel et al. 1995; Wan et al. 2011), but also with decreases in serum estradiol in male monkeys (Seacat et al. 2002). PFOA, PFOS, perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA) and perfluoroundecanoic acid (PFUnA) have been shown to influence the expression of estrogen-responsive genes in rainbow trout and rare minnows (Wei et al. 2007; Tilton et al. 2008; Benninghoff et al. 2011). *In vitro*, changes in estrogen biosynthesis with exposure to PFOA and PFOS have been reported (Kraugerud et al. 2011; Du et al. 2013). Furthermore, PFOA, PFNA, PFDA, PFOS and perfluorohexane sulfonate (PFHxS) have been shown to interfere with the estrogen receptor in human *in vitro* studies (Benninghoff et al. 2011; Henry & Fair 2013; Kjeldsen & Bonefeld-Jørgensen 2013). One study demonstrated that PFOS affects the number of implantation sites in female rats, but found no effect on mating, estrous cycling or fertility (Luebker et al. 2005). Estrous cyclicity was however affected by PFOS in another rat study (Austin et al. 2003). Furthermore, more spontaneous abortions occurred in rabbits exposed to PFOS compared to unexposed controls (Case et al. 2001). Mating and fertility, including semen parameters, were not affected by PFOA exposure in two studies on rats (Butenhoff et al. 2004; York et al. 2010), while the sperm count was lower in mice exposed to PFOS (Wan et al. 2011). Overall, the evidence from rodent studies to some extent supports an association between PFAS exposure and impaired fertility, however, the mechanisms behind potential reproductive effects of PFASs are not well established. In both males and females, endocrine disruption may be a possible mechanism as suggested in animal studies, but the current evidence from human *in vivo* studies is very limited (Barrett et al. 2015; Lewis et al. 2015; Tsai et al. 2015). In adult rats, López-Doval et al. (2014) demonstrated that PFOS had several potential effects on the hypothalamic-pituitary-testicular axis, including both gonadotropin releasing hormone, LH, FSH and testosterone. Thus, potential effects on testosterone may be caused by changes in LH secretion, changes of the hypothalamic noradrenaline concentration, modification of the activity of the direct neural pathway between the brain and the testis, or a direct effect of PFOS in the testis (López-Doval et al. 2014). In general, doses used in animal studies were orders of magnitude higher than what background-exposed humans experience, and effective dose ranges and no-adverse-effects-exposure-levels differed between studies and according to the studied outcomes. López-Doval et al. (2014) observed changes of the FSH gene expression in male rats at the lowest administered dose of 0.5 mg PFOS/kg/day, while Henry and Fair (2013) observed positive estrogenic responses for PFOA at concentrations of 0.03–30 μg/mL and for PFOS only at 30 μg/mL as well as anti-estrogenic activity for both PFOA and PFOS at 0.03–30 μg/mL. Du et al. (2013) reported changes in estrogen production in an assay using PFOA concentrations of 1×10^{-8}–3×10^{-7} M, but not at lower concentrations.

Associations between PFAS exposure and measures of female as well as male fertility have been addressed in a number of epidemiological studies. Commonly used male outcomes include semen parameters and

reproductive hormone levels. Time to pregnancy (TTP) has been used to assess couple fecundability (i.e., the probability of conception in a menstrual cycle, during which a couple has regular intercourse and neither use contraception) in relation to both male and female exposures. To our knowledge, the existing evidence on the association between PFAS exposure and human reproduction has not been systematically evaluated. We conducted a systematic review to evaluate the existing evidence while considering potential information and selection bias as well as confounding. The main objective of this systematic review was to assess the evidence of an association between human exposure to PFASs and reproductive outcomes, in particular TTP, semen parameters and levels of reproductive hormones. We mainly focused on exposure to PFOS and PFOA, as these compounds are usually detected with the highest human serum concentrations and are the most widely studied compounds.

Methods

Literature search

We performed searches of original peer-reviewed literature in the MEDLINE and EMBASE databases using the search terms ''perfluorooctane sulfonic acid'', ''perfluorooctanoic acid'', ''fluorocarbons'', ''perfluorinated'', ''polyfluorinated'', ''polyfluoroalkyl'', ''perfluoroalkyl'','' perfluorochemicals'','' perfluoro compound'', ''PFOS'', ''PFOA'', ''PFNA'', ''PFDA'', ''PFHxS'', ''PFUnA'', ''PFOSA'' and ''PFDeA'' in combination with ''Infertility'', ''Fertility'', ''Time-to-Pregnancy'', ''Reproduction'', ''Semen Analysis'' and ''Gonadal Steroid Hormones''. The items were listed as Medical Subject (MeSH) and Emtree headings as well as text and keyword terms. Only studies published in English were included and otherwise no other restrictions were applied. The latest searches were conducted on 12 October 2015. Two of the authors performed the search and selection process independently. Disagreements were resolved by consensus. In order to retrieve all relevant articles, we checked reference lists as well as citations by use of the Scopus database.

Study selection criteria

Selection criteria were based on the PICOS (Participants, Intervention/exposure, Comparisons, Outcomes, Study designs) criteria (Liberati et al. 2009) and included: *Participants:* Women and men. *Intervention/exposure:* PFASs measured in biological samples (e.g., blood) in adulthood. Studies were excluded if they estimated exposure indirectly (e.g., from residence or other proxy exposure markers). All PFASs were eligible. *Comparisons:* Studies comparing individuals based on their levels of PFASs, i.e., comparing groups categorized according to PFAS exposure levels (e.g., dichotomized or divided into tertiles or quartiles), or studies reporting outcomes according to differences in PFAS exposure levels on a continuous scale (including linear, log-transformed, or standardized PFAS levels). *Outcomes:* TTP (men and women), reproductive hormone levels (men and women) and semen parameters (men). These outcomes were chosen based on consensus in the author group. *Study designs:* Original human studies providing measures of association between PFAS levels and human reproductive outcomes, regardless of epidemiological design. Animal studies, case reports, editorials, comments, review articles and meta-analyses were excluded as well as abstracts and unpublished studies.

Data extraction and the risk of bias and confounding

Two of the authors (CCB and AV) abstracted data in duplicate to pre-defined forms concerning study characteristics (Tables 1 and 2) and results. Regarding studies on PFOS or PFOA and male reproduction, for exposure-outcome combinations reported in three studies or more, the results are summarized in Tables 3 and 4. All results from the studies on female exposure to PFOS or PFOA and TTP as well as infertility are summarized in Tables 5 and 6. The risk of selection and information bias as well as confounding was assessed. We defined selection bias as any bias due to participation depending on both the levels of PFASs and the outcomes under study. The risk of potential differential and non-differential measurement error and misclassification of exposures and outcomes were evaluated. We defined confounders as common causes of exposures and outcomes. Covariates adjusted for in the individual studies are shown in the Supplementary Material, Tables S1–S3.

We reported estimates and 95% CIs or *p* values if no CIs were stated, evaluating the magnitude and direction of point estimates and the wideness of confidence intervals. Reporting was done in accordance with the PRISMA checklist (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Moher et al. 2009), see Supplementary Material.

Results

Study selection

We identified 445 studies in MEDLINE and 685 articles in EMBASE. After removal of duplicates, a total of 864 articles were screened by title and 54 records were selected for abstract screening. Eighteen studies fulfilled

Table 1. Characteristics of studies concerning PFAS exposure and male reproduction.

Study	Location and setting	Period	N and participation rates	Study design	Exposure assessment and timing of blood sampling	Exposure level and categorization of PFOS and PFOA	Outcome ascertainment	Outcome definition
Olsen et al. (1998)	USA. General medical surveillance at PFOA production plant	1993 and 1995	111 and 80 –	Cross-sectional	Serum PFOA	Average exposure level not stated. Range 0.00–114.10 ppm. Stratified analyses: Quartiles of PFOA exposure. Regression models: PFOA continuous.	Hormones in serum	Free and total testosterone, DHEAS, estradiol, FSH, LH, SHBG
Sakr et al. (2007)	USA. Active workers with potential PFOA exposure at the Washington Works site	2004	782 55%	Cross-sectional	Serum PFOA	Mean PFOA 0.4 ppm (SD =0.9). Continuous levels	Hormones in blood	Testosterone, estradiol
Costa et al. (2009)	Italy. Men currently or former working at chemical plant	2000–2007	56 –	Cross-sectional	Serum PFOA	Current workers: median PFOA 13.6 μg/mL in 2002 and 7.1 μg/mL in 2007 Continuous levels	Hormones in blood	Testosterone, estradiol
Joensen et al. (2009)	Denmark. Young men considered for military service. Half selected from men with highest and half from men with lowest testosterone	2003	105 –	Cross-sectional	Serum levels of 10 PFAS. PFOA and PFOS were included in the analyses	Median PFOS: 24.5 ng/mL and PFOA: 4.9 ng/mL. Tertiles of individual as well as combined PFOA and PFOS exposure	Hormones in serum Semen sample	Testosterone, estradiol, SHBG, LH, FSH, Inhibin B, FAI, testosterone/LH, FAI/LH, estradiol/testosterone, Inhibin B/FSH Semen volume, concentration, total sperm count, motile sperm, morphologically normal, total morphologically normal sperm
Raymer et al. (2012)	USA. Male partners of infertile couples at the Duke Fertility Center	2002–2005	256 –	Cross-sectional	Plasma and semen PFOS and PFOA	Median PFOS: plasma 32.3 ng/mL; semen 0.6 ng/mL Median PFOA: plasma 9.2 ng/mL; semen <1.2 ng/mL. Continuous levels	Hormones in serum Semen sample	Estradiol, prolactin, follicle-stimulating hormone, free and total testosterone, LH Semen volume, pH, sperm concentration, white blood cell concentration, percent motile, initial total motile, percent swim-up overnight motility, swim-up concentration, percent swim-up motility, swim-up total motile, liquefaction, viscosity, volume, sperm concentration, directional motility

(continued)

Table 1. Continued

Study	Location and setting	Period	N and participation rates	Study design	Exposure assessment and timing of blood sampling	Exposure level and categorization of PFOS and PFOA	Outcome ascertainment	Outcome definition
Specht et al. (2012)	Greenland, Poland and Ukraine. Male partners of pregnant women enrolled during antenatal visits. INUENDO cohort	2002–2004	548 (Greenland: 198 (90%), Poland: 143 (68%), Ukraine: 207 (26%))	Cross-sectional	Serum PFOS, PFOA, PFHxS, PFNA	Median PFOS: Greenland 44.7 ng/mL; Poland 18.5 ng/mL; Ukraine 7.6 ng/mL Median PFOA: Greenland 4.5 ng/mL; Poland 4.8 ng/mL; Ukraine 1.3 ng/mL Tertiles	Semen sample Hormones in blood	DNA fragmentation index (sperm chromatin structure assay (SCSA)), DNA fragmentation (*in situ* terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) assay), and sperm Fas and Bcl-xL positivity by flow cytometry. Testosterone, Estradiol, FSH, LH, Inhibin B, SHBG
Toft et al. (2012)	INUENDO cohort (see Specht et al. 2012)	2002–2004	588; Greenland: 196 (79%), Poland: 189 (29%), Ukraine: 203 (36%)	Cross-sectional	Serum PFOS, PFOA, PFHxS, PFNA	Median PFOS: 18.4 ng/mL and PFOA: 3.8 ng/mL Tertiles	Semen sample	Sperm concentration, total sperm count, semen volume, percentage motile spermatozoa, percentage normal cells
Joensen et al. (2013)	Denmark. Young men randomly selected from those considered for military service	2008–2009	247 30%	Cross-sectional	Serum levels of 14 PFASs. PFOS, PFOA, PFHxS, PFHpS, PFNA and PFDA were included in the analyses	Median PFOS: 7.8 ng/mL and PFOA: 3.0 ng/mL Continuous PFAS levels	Hormones in blood Semen sample	Testosterone (T), FAI, Free testosterone (FT), FT/LH, FAI/LH, T/LH, T/Estradiol, Estradiol, SHBG, LH, FSH, Inhibin B, Inhibin B/FSH. All reproductive hormone outcome constellations were ln-transformed Semen volume (ln), concentration (cubic root), total sperm count (cubic root), progressively motile (sq), morphologically normal (sq rt), total normal count (cubic root)
Leter et al. (2014)	INUENDO cohort (see Specht et al. 2012)	2002–2004	262; Greenland: 112, Poland: 100, Ukraine: 100 –	Cross-sectional	Serum PFOS, PFOA, PFHxS, PFNA	Mean PFOS 27.2 ng/mL and PFOA 4.0 ng/mL Ln-transformed PFAS levels	Semen sample	Sperm DNA global methylation analysis (Alu, LINE-1, and Satα methylation by pyrosequencing; The flow-cytometric (FCM) sperm DNA global methylation (DGML) assay)
Governini et al. (2015)	Italy. Male patients attending the Center for Couple Sterility, Obstetrics and Gynecology Unit, University Hospital of Siena	1 year (not stated)	59 –	Cross-sectional	Whole blood and seminal plasma PFOS and PFOA	Whole blood PFOS: 7.07 ng/gf.w. and PFOA: 8.03 ng/gf.w	Semen sample	Sperm aneuploidy and diploidy for chromosomes 18, X and Y (FISH) Sperm DNA fragmentation (terminal deoxynucleotyl transferase-mediated dUTP nick end-labeling coupled with flow cytometry)

(continued)

Table 1. Continued

Study	Location and setting	Period	N and participation rates	Study design	Exposure assessment and timing of blood sampling	Exposure level and categorization of PFOS and PFOA	Outcome ascertainment	Outcome definition
Buck Louis et al. (2015)	Michigan & Texas, USA. Male partners of couples intending to become pregnant, recruited using marketing database and fishing/hunting license registry (LIFE study)	2005–2009	501 42% of telephone screened subset of eligible population	Cohort	Serum Et-PFOSA-AcOH, Me-PFOSA-AcOH, PFDA, PFNA, PFOSA, PFOS and PFOA	Median PFOS 19.15–21.6 ng/mL and PFOA 4.6–5.3 ng/mL	Two semen samples 1 month apart – sample 1 mainly used, sample 2 for validation	35 semen quality endpoints including semen volume, total sperm count, sperm concentration as well as measures of sperm motility, sperm head characteristics, straw distance, sperm morphology and sperm chromatin stability
Lewis et al. (2015)	USA. National survey (NHANES)	2011–2012	857 –	Cross-sectional	Serum PFOA, PFOS, PFHxS and PFNA	Median PFOS 4.60–11.1 ng/mL and PFOA 1.85–2.48 ng/mL	Serum hormones	Total testosterone
Tsai et al. (2015)	Taiwan. Urine screening population, 1–12 grades recruited 1992–2000	2006–2008	210 –	Cross-sectional	Serum levels of PFOA, PFOS, PFNA and PFUnA	Geometric mean PFOS 8.97 ng/mL and PFOA 2.75 ng/mL	Serum hormones	Estradiol, FSH, LH, SHBG, free and total testosterone
Den Hond et al. (2015)	Belgium. Male patients from four academic fertility clinics	Not stated	120 (case control) 163 (hormone analysis) –	Case-control	Serum levels of PFOS and PFOA	Geometric mean (case/control) PFOS 10.4/8.7 μg/mL and PFOA 2.8/2.4 μg/mL	Two semen samples Serum hormones	Subfertility = total motile count (TMC) < 20 million Sperm concentration, motility and morphology Total and free testosterone, LH, FSH, SHBG, total and free estradiol, inhibin B

The studies concerning time to pregnancy are listed in Table 2. See PFAS and reproductive hormone abbreviations in text. Regarding participation rates, – indicates that the paper did not provide information on this. Regarding the timing of blood sampling, all cross-sectional studies measured exposures simultaneously with the outcomes.

Table 2. Characteristics of studies concerning PFAS exposure and female reproduction.

Study	Location and setting	Period	*N* and participation rate (%)	Design	Exposure assessment	Exposure level and categorization of PFOS and PFOA	Outcome ascertainment	Outcome definition
Fei et al. (2009)	Denmark. Pregnant women recruited nationwide (Danish National Birth Cohort)	1996–2002	1240 30%	Cross-sectional	Plasma PFOS and PFOA. Sample taken between 4 and 14 gestational weeks	Median PFOS 33.7 ng/mL and PFOA 5.3 ng/mL Quartiles	TTP reported by interview at 12 weeks of gestation	Infertility = TTP >12 months or infertility treatment. Fecundity OR
Vestergaard et al. (2012)	Denmark. Nulliparous Trade union members intending to become pregnant. Followed 6 cycles	1992–1995	222 16%	Cohort	Serum PFOS, PFOA, PFHxS, PFNA, PFDA, Me-PFOSA-AcOH, PFDA, PFOSA at enrollment	Median PFOS 36.3 ng/mL and PFOA 5.6 ng/mL Dichotomized at median level. Also used as a log-transformed variable	TTP calculated by cycles from enrollment to conception. Pregnancy determined clinically or by pregnancy test.	Subfecundability = TTP >6 cycles. Fecundability ratio
Whitworth et al. (2012)	Norway. Pregnant women recruited nationwide, population based (Norwegian Mother and Child Cohort Study)	2003–2004	910 39%	Case-control	Plasma PFOS and PFOA at gestational week 17	Median PFOS 13.0 ng/mL and PFOA 2.2 ng/mL Quartiles	TTP reported by interview at 17 weeks of gestation	Subfecundity = TTP >12 months
Buck Louis et al. (2013)	Michigan; Texas, USA. Couples intending to become pregnant recruited using marketing database and fishing/hunting license registry (LIFE study)	2005–2007	401 (100 withdrew) 42% of telephone screened subset of eligible population	Cohort	Serum Et-PFOSA-AcOH, Me-PFOSA-AcOH, PFDA, PFNA, PFOSA, PFOS and PFOA at enrollment	Geometric mean PFOS 11.8 ng/mL and PFOA 3.1 ng/mL Log-transformed and divided by the SD	TTP calculated by cycles from enrollment to conception. Pregnancy determined by pregnancy test	Fecundability ORs
Jørgensen et al. (2014)	Greenland, Poland, and Ukraine. Pregnant women and their partners enrolled during antenatal visits	2002–2004	938 (448 from Greenland (90%); 203 from Poland (68%); 287 from Ukraine (26%))	Cross-sectional	Serum PFOS, PFOA, PFHxS, PFNA. Blood sample taken at various gestational weeks during pregnancy	Median PFOS 10.60 ng/mL and PFOA 1.65 ng/mL Continuous log-transformed exposure levels	TTP reported by interview at antenatal visit	Subfecundity = TTP >12 months. Fecundability ratios
Vélez et al. (2015)	Ten cities across Canada (MIREC study). Pregnant women	2008–2011	1743 39%	Cross-sectional	Plasma PFOA, PFOS and PFHxS measured in first trimester	Geometric mean PFOS 4.59 ng/mL and PFOA 1.66 ng/mL Log-transformed and divided by the SD	TTP reported during first trimester using a questionnaire	Infertility = TTP >12 months or infertility treatment for index pregnancy. Fecundability ORs
Bach et al. (2015a)	Denmark. Pregnant women recruited nationwide (Danish National Birth Cohort)	1996–2002	440 30%	Cross-sectional	Plasma PFOS and PFOA measured during pregnancy	Median PFOS 27.9 ng/mL and PFOA 4.0 ng/mL Quartiles as well as log-transformed continuous	TTP reported by interview at 12 weeks of gestation	Infertility = TTP >12 months or infertility treatment. Fecundability OR
Bach et al. (2015b)	Denmark. Pregnant women recruited at Aarhus University Hospital (Aarhus Birth Cohort)	2008–2013	1372 –	Cross-sectional	Serum levels of 16 PFAAs measured before 20 gestational weeks; included 7 compounds with >50% above LOQ	Median PFOS 8.3 ng/mL and PFOA 2.0 ng/mL Quartiles and per 0.1 ng/mL (continuous)	TTP reported by questionnaire in early pregnancy	Infertility = TTP >12 months or infertility treatment. Fecundability OR
Barrett et al. (2015)	Tromsø, Norway. Women aged 25–35 years old with regular menstrual cycles and no use of hormonal contraceptives (EBBA-I)	2000–2002	178 –	Cross-sectional	Serum PFHxS, PFOS, PFOSA, PFOA, PFNA, PFDA, PFUnA	Median (nulliparous/parous): PFOS 14.78/12.65 ng/mL, PFOA 3.36/2.03 ng/mL	Salivary estradiol and progesterone	Mean follicular estradiol; mean luteal progesterone

(continued)

Table 2. Continued

Study	Location and setting	Period	*N* and participation rate (%)	Design	Exposure assessment	Exposure level and categorization of PFOS and PFOA	Outcome ascertainment	Outcome definition
Lewis et al. (2015)	USA. National survey (NHANES)	2011–2012	825 –	Cross-sectional	Serum PFOA, PFOS, PFHxS and PFNA	Median PFOS 3.76–9.50 ng/mL and PFOA 1.49–2.55 ng/mL	Serum hormones	Total testosterone
Tsai et al. (2015)	Taiwan. Urine screening population 1–12 grades 1992–2000 followed up 2006–2008	2006–2008	330 –	Cross-sectional	Serum PFOA, PFOS, PFNA and PFUnA	Geometric mean PFOS 7.11 ng/mL and PFOA 2.73 ng/mL	Serum hormones	E2, FSH, LH, SHBG, free and total testosterone

See text for PFAS and outcome abbreviations. Regarding participation rate, – indicates that this was not stated in the paper.

the inclusion criteria, and after screening of reference lists and checking citations, we identified five additional articles. Hence, the total number of articles eligible for the review was 23 of which some provided results for both men and women. The full selection process is illustrated in the Supplementary Material, Figure S1.

Studies in men

Study characteristics

Sixteen studies investigated the association between PFAS exposure and male reproductive outcomes (Table 1). Thirteen studies were cross-sectional (Olsen et al. 1998; Sakr et al. 2007; Costa et al. 2009; Joensen et al. 2009; Raymer et al. 2012; Specht et al. 2012; Toft et al. 2012; Joensen et al. 2013; Jørgensen et al. 2014; Leter et al. 2014; Governini et al. 2015; Lewis et al. 2015; Tsai et al. 2015), two were from a pregnancy planner cohort (Buck Louis et al. 2013; Buck Louis et al. 2015) and one was a case-control study (Den Hond et al. 2015). Three studies were occupational (Olsen et al. 1998; Sakr et al. 2007; Costa et al. 2009) while the remaining studies studied non-occupationally exposed populations. Nine reported on semen characteristics (Joensen et al. 2009; Raymer et al. 2012; Specht et al. 2012; Toft et al. 2012; Joensen et al. 2013; Leter et al. 2014; Buck Louis et al. 2015; Den Hond et al. 2015; Governini et al. 2015) and 10 studies reported on the associations between PFASs and reproductive hormone levels (Olsen et al. 1998; Sakr et al. 2007; Costa et al. 2009; Joensen et al. 2009; Raymer et al. 2012; Specht et al. 2012; Joensen et al. 2013; Den Hond et al. 2015; Lewis et al. 2015; Tsai et al. 2015). Two studies reported on TTP (Buck Louis et al. 2013; Jørgensen et al. 2014). The studies measured exposures as well as outcomes once, besides from the study by Den Hond et al. (2015), which used two semen samples taken at least one week apart, and the study by Buck Louis et al. (2013), which evaluated whether a pregnancy was obtained each cycle. Sample sizes varied from 56 to 857, and study periods ranged from 1993 to 2012. Average exposure levels in the non-occupational studies ranged between 4.6 and 44.7 ng/mL for PFOS and 1.3 and 9.2 ng/mL for PFOA.

Reproductive hormones and related outcomes included testosterone (total or free), dehydroepiandrosterone (DHEAS), free androgen index (FAI), luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol, inhibin B and sex hormone binding globulin (SHBG). Semen parameters included semen volume, sperm concentration, sperm count, motility and morphology, as well as semen pH, white blood cell concentration,

liquefaction, viscosity, sperm DNA damage as well as apoptotic markers in semen.

Semen characteristics

For semen volume, total sperm count and sperm concentration, none of the studies found consistent associations with exposure to any PFASs (PFOA, PFOS, PFHxS, PFHpS, PFNA, PFDA, PFOSA, Et-PFOSA-AcOH, Me-PFOSA-AcOH), and there were no tendencies for the estimates to point in the same direction (Joensen et al. 2009; Raymer et al. 2012; Toft et al. 2012; Joensen et al. 2013; Barrett et al. 2015; Buck Louis et al. 2015; Den Hond et al. 2015) (see Table 3).

PFOA exposure was associated with a higher percentage of motile sperm in the study by Toft et al. (2012). However, among the other studies that investigated this association, no consistent associations were present (Joensen et al. 2009; Raymer et al. 2012; Joensen et al. 2013; Buck Louis et al. 2015). Joensen et al. (2013) found a lower percentage of progressively motile sperm with exposure to perfluoroheptane sulfonate (PFHpS). This association was not investigated in other studies. For PFOS, PFNA, PFDA, perfluorooctane sulfonamide (PFOSA) and PFHxS, no consistent associations were observed with motility parameters (Joensen et al. 2009; Raymer et al. 2012; Toft et al. 2012; Joensen et al. 2013; Buck Louis et al. 2015).

Two studies found serum levels of PFASs to be associated with sperm morphology (Joensen et al. 2009; Toft et al. 2012). In the study by Joensen et al. (2009), men with the highest combined PFOA and PFOS quartile had a reduced percentage and number of morphologically normal sperm cells compared with men in the lowest quartile. However, associations were attenuated when PFOA and PFOS exposures were analyzed separately (see Table 3). Toft et al. (2012) found a lower percentage of morphologically normal sperm with higher exposure to PFOS and PFHxS. These findings, however, were not replicated by Joensen et al. (2013), Buck Louis et al. (2015) or Den Hond et al. (2015). Levels of PFNA, PFDA, PFHpS, PFOSA and PFOA were not consistently associated with overall sperm morphology (Joensen et al. 2009; Toft et al. 2012; Joensen et al. 2013; Buck Louis et al. 2015; Den Hond et al. 2015). Buck Louis et al. (2015) found that PFOSA was associated with a higher percentage of bicephalic and immature sperm, while PFDA, PFNA, PFOA and PFOS were associated with a lower percentage of sperm with coiled tails.

A few studies reported on the possible associations between PFAS exposure and sperm DNA integrity and apoptotic markers (Specht et al. 2012; Leter et al. 2014; Buck Louis et al. 2015; Governini et al. 2015). PFOA, PFHxS, PFOS and PFNA were not consistently associated with sperm DNA integrity or fragmentation, or apoptotic markers in the study by Specht et al. (2012). Overall, the study by Leter et al. (2014) demonstrated no associations between PFOS, PFOA, PFNA, or PFHxS and sperm DNA global methylation. The study by Buck Louis et al. (2015) found a lower percentage of sperm with high DNA stainability with higher PFOSA, but no consistent associations for the other PFASs they investigated (Et-PFOSA-AcOH, Me-PFOSA-AcOH, PFDA, PFNA, PFOS and PFOA), and none of the PFASs were associated with DNA fragmentation index. Governini et al. (2015) found that men with the highest combined PFOA and PFOS levels had a higher DNA fragmentation index and higher rates of sperm aneuploidy, however this study included only 59 men.

Reproductive hormones and related outcomes

In an occupationally exposed population, Sakr et al. (2007) found higher testosterone with higher PFOA. However, the nine other studies that investigated the association between testosterone and PFOA had inconsistent results (see Table 4). Three studies found tendencies towards lower testosterone with higher exposure to PFOS (Joensen et al. 2009; Raymer et al. 2012), while four studies found no support for such an association (Specht et al. 2012; Lewis et al. 2015; Tsai et al. 2015; Den Hond et al. 2015). For PFHxS, PFNA, PFDA, PFUnA and PFHpS, there was no consistency regarding an association with testosterone levels (Specht et al. 2012; Joensen et al. 2013; Lewis et al. 2015; Tsai et al. 2015).

We report the outcomes free testosterone (measured or calculated) and FAI together. FAI is defined as the ratio between the testosterone and SHBG levels. Raymer et al. (2012) found that higher levels of PFOA were associated with higher levels of free testosterone. Tendencies towards higher FAI or free testosterone with higher PFOA were also observed in the studies by Joensen et al. (2013) and Olsen et al. (1998). Joensen et al. (2009), however, found a tendency towards lower FAI with higher PFOA exposure, and Den Hond et al. (2015) found no association between PFOA and free testosterone. Joensen et al. (2013) found lower FAI and free testosterone with higher PFOS exposure, and two other studies found similar tendencies (Joensen et al. 2009; Raymer et al. 2012), while Den Hond et al. (2015) found no association. Only one study reported on PFHxS, PFNA, PFDA and PFHpS in relation to these outcomes and found no consistent associations (Joensen et al. 2013).

Table 3. Results of studies on exposure to PFOA and PFOS in men and semen characteristics.

Outcome	Study	Outcome scale (unit)	Exposure scale	Measure of association	PFOA estimate	PFOS estimate
Semen volume	Joensen et al. (2009)	Ln (mL)	ng/mL	Regression coefficient (95% CI)	−0.00 (−0.07; 0.07)	0.00 (−0.01; 0.01)
	Toft et al. (2012)	Linear (mL)	Tertiles	Regression coefficient (95% CI)	3 (−16; 22)	8 (−9; 25)
					10 (−10; 29)	0 (−24; 25)
	Raymer et al. (2012)	Linear (mL)	ng/mL	Regression coefficient (95% CI)	0.01 (−0.02; 0.05)	0.00 (−0.01; 0.01)
	Joensen et al. (2013)	Ln (mL)	ng/mL	Regression coefficient (95% CI)	−0.01 (−0.04; 0.02)	0.02 (−0.001; 0.03)
	Buck Louis et al. (2015)	Linear (mL)	Ln	Regression coefficient (95% CI)	−0.09 (−0.46; 0.27)	0.06 (−0.20; 0.31)
Sperm concentration	Joensen et al. (2009)	Ln (10^6/mL)	ng/mL	Regression coefficient (95% CI)	−0.08 (−0.23; 0.07)	−0.02 (−0.04; 0.01)
	Toft et al. (2012)	Linear (10^6/mL)	Tertiles	Regression coefficient (95% CI)	4 (−27; 36)	14 (−15; 43)
					15 (−17; 48)	22 (−21; 64)
	Raymer et al. (2012)	Linear (10^6/mL)	ng/mL	Regression coefficient (95% CI)	0.14 (−1.24; 1.51)	0.16 (−0.23; 0.54)
	Joensen et al. (2013)	Cubit root (10^6/mL)	ng/mL	Regression coefficient (95% CI)	0.03 (−0.05; 0.11)	0.01 (−0.03; 0.05)
	Den Hond et al. (2015)	Linear (10^6/mL)	(μg/L) – ln-PFOS, untransformed PFOA	Regression coefficient (*p* value)	0.22 (0.31)	0.50 (0.34)
	Buck Louis et al. (2015)	Linear (10^6/mL)	Ln	Regression coefficient (95% CI)	0.39 (−12.58; 13.36)	0.03 (−9.02; 9.07)
Total sperm count	Joensen et al. (2009)	Ln (10^6)	ng/mL	Regression coefficient (95% CI)	−0.07 (−0.23; 0.09)	−0.02 (−0.05; 0.01)
	Toft et al. (2012)	Linear ($10^{6)}$	Tertiles	Regression coefficient (95% CI)	4 (−34; 42)	23 (−11; 57)
					22 (−17; 62)	18 (−32; 67)
	Joensen et al. (2013)	Cubic root (10^6)	ng/mL	Regression coefficient (95% CI)	0.03 (−0.08; 0.13)	0.05 (−0.01; 0.10)
	Buck Louis et al. (2015)	Linear (Concentration * 10^6/mL)	Ln	Regression coefficient (95% CI)	0.68 (−42.30; 43.66)	9.74 (−20.24; 39.72)
Motility	Joensen et al. (2009)	Ln (% motile)	ng/mL	Regression coefficient (95% CI)	−0.03 (−0.11; 0.05)	−0.01 (−0.02; 0.01)
	Toft et al. (2012)	Linear (% motile)	Tertiles	Regression coefficient (95% CI)	3 (−15; 21)	1 (−16; 18)
					19 (1; 39)	−1 (−26; 25)
	Raymer et al. (2012)	Linear (% motile)	ng/mL	Regression coefficient (95% CI)	0.27 (−0.13; 0.67)	0.04 (−0.07; 0.16)
	Joensen et al. (2013)	Squared progressively motile (%)	ng/mL	Regression coefficient (95% CI)	−4.43 (−109; 100)	−37.2 (−93.1; 18.7)
	Den Hond et al. (2015)	Linear (% motile)	(μg/L) – ln-PFOS, untransformed PFOA	Regression coefficient (*p* value)	2.4 (0.46)	14.0 (0.7)
	Buck Louis et al. (2015)	Linear (% motile)	Ln	Regression coefficient (95% CI)	1.44 (−1.32; 4.19)	1.56 (−0.36; 3.47)
Morphology	Joensen et al. (2009)	Morphology (not stated)	ng/mL	Regression coefficient (95% CI)	−0.54 (−1.20; 0.11)	−0.09 (−0.20; 0.03)
	Toft et al. (2012)	Linear (%)	Tertiles	Regression coefficient (95% CI)	−5 (−28; 18)	−22 (−44; −1)
					10 (−13; 34)	−35 (−66; −4)
	Joensen et al. (2013)	Square root of morphologically normal (%)	ng/mL	Regression coefficient (95% CI)	−0.01 (−0.07; 0.05)	0.002 (−0.03; 0.04)
		Cubic root of total normal count ($10^{6)}$			0.01 (−0.06; 0.07)	0.02 (−0.01; 0.06)
	Den Hond et al. (2015)	Linear (% normal)	(μg/L) – ln-PFOS, untransformed PFOA	Regression coefficient (*p* value)	0.24 (0.35)	0.56 (0.28)
	Buck Louis et al. (2015)	Linear (% normal)	Ln	Regression coefficient (95% CI)	1.73 (−1.35; 4.80)	1.84 (−0.31; 3.98)

For the study by Toft et al. (2012) the first estimate represents the difference between the second and first tertile, and the second estimate indicates the difference between the third and the first tertile. Estimates reported with more than two decimals were rounded to two decimals.

Table 4. Results of studies on exposure to PFOA and PFOS in men and reproductive hormones.

Outcome	Study	Outcome scale (unit)	Exposure scale	Measure of association	PFOA	PFOS
Testosterone	Olsen et al. (1998)	Linear (ng/dL)	ppm	Pearson correlation coefficient	1993: 0.01 1995: 0.02	–
	Sakr et al. (2007)	–	ppm	Regression coefficient (*p* value)	0.6 (0.03)	–
	Joensen et al. (2009)	Linear (nmol/L)	ng/mL	Regression coefficient (95% CI)	−0.98 (−2.33; 0.37)	−0.09 (−0.32; 0.15)
	Costa et al. (2009)	Linear (ng/mL)	µg/mL	Regression coefficient (*p* value)	−0.01 (−0.02; 0.01)	–
	Raymer et al. (2012)	Linear (ng/mL)	ng/mL	Spearman correlation coefficient (*p* value)	0.05 (0.4)	−0.01 (0.8)
	Joensen et al. (2013)	Ln (nmol/L)	ng/mL	Regression coefficient (95% CI)	−0.002 (−0.02; 0.02)	−0.01 (−0.02; 0.00)
	Tsai et al. (2015)	Ln (ng/dL)	Four categories	Mean (SD)	Lowest vs. highest: 12–17 years: 6.23 (0.23) vs. 6.48 (0.30) 18–30 years: 6.32 (0.05) vs. 6.28 (0.09)	Lowest vs. highest: 12–17 years: 6.11 (0.23) vs. 6.34 (0.31) 18–30 years: 6.33 (0.06) vs. 6.33 (0.05)
	Den Hond et al. (2015)	Linear (ng/dL)	(µg/L)	Regression coefficient (*p* value)	0.01 (0.80)	−0.07 (0.17)
	Lewis et al. (2015)	Linear (ng/dL)	100% increase	Regression coefficient	−1.4 to 17.3 depending on age	−2.7 to 7.9 depending on age
Free androgen index or free testosterone	Olsen et al. (1998)	Linear free testosterone (ng/dL)	ppm	Pearson correlation coefficient	1993: 0.09 1995: 0.01	–
	Joensen et al. (2009)	Ln free androgen index (ratio)	ng/mL	Regression coefficient (95% CI)	−0.04 (−0.09; 0.01)	−0.01 (−0.02; 0.00)
	Raymer et al. (2012)	Linear free testosterone (pg/mL)	ng/mL	Spearman correlation coefficient (*p* value)	0.16 (0.02)	−0.01 (0.8)
	Joensen et al. (2013)	Ln free androgen index (ratio) Ln free testosterone (nmol/mL)	ng/mL	Regression coefficient (95% CI)	0.01 (−0.01; 0.04) 0.00 (−0.02; 0.02)	−0.02 (−0.03; −0.01) −0.02 (−0.03; −0.01)
	Den Hond et al. (2015)	ng/dL	(µg/L)	Regression coefficient (*p* value)	0.06 (0.21)	0.04 (0.69)
Estradiol	Olsen et al. (1998)	Linear (pg/mL)	ppm	Pearson correlation coefficient	1993: 0.12 1995: 0.15	–
	Sakr et al. (2007)	–	ppm	Regression coefficient (*p* value)	22.3 (0.02)	–
	Joensen et al. (2009)	Ln (pmol/L)	ng/mL	Regression coefficient (95% CI)	−0.01 (−0.05; 0.03)	−0.001 (−0.01; 0.01)
	Costa et al. (2009)	–	µg/mL	Regression coefficient (*p* value)	−0.01 (−0.08; 0.06)	–
	Raymer et al. (2012)	Linear (pg/mL)	ng/mL	Spearman correlation coefficient (*p* value)	0.02 (0.8)	0.02 (0.8)
	Joensen et al. (2013)	Ln (pmol/L)	ng/mL	Regression coefficient (95% CI)	0.003 (−0.02; 0.02)	−0.01 (−0.02; 0.00)
	Den Hond et al. (2015)	Linear (pg/mL)	(µg/L)	Regression coefficient (*p* value)	0.01 (0.64)	−0.02 (0.70)
Sex hormone binding globuline	Olsen et al. (1998)	–	ppm	Pearson correlation coefficient	1993: −0.07 1995: 0.03	–
	Joensen et al. (2009)	Ln (nmol/L)	ng/mL	Regression coefficient (95% CI)	−0.01 (−0.07; 0.05)	0.002 (−0.01; 0.01)
	Joensen et al. (2013)	Ln (nmol/L)	ng/mL	Regression coefficient (95% CI)	−0.01 (−0.04; 0.01)	0.01 (−0.004; 0.02)
	Tsai et al. (2015)	Ln (nmol/L)	Four categories	Mean (SD)	Lowest vs. highest: 12–17 years: 3.24 (0.29) vs. 3.79 (0.39) 18–30 years: 3.14 (0.07) vs. 3.10 (0.14)	Lowest vs. highest: 12–17 years: 3.62 (0.29) vs. 3.46 (0.39) 18–30 years: 3.13 (0.10) vs. 3.16 (0.08)
	Den Hond et al. (2015)	Linear (nmol/L)	(µg/L)	Regression coefficient (*p* value)	−0.03 (0.34)	−0.03 (0.56)
Luteineizing hormone	Olsen et al. (1998)	–	ppm	Pearson correlation coefficient	1993: −0.06 1995: 0.13	–
	Joensen et al. (2009)	Ln (IU/L)	ng/mL	Regression coefficient (95% CI)	−0.01 (−0.08; 0.06)	0.000 (−0.01; 0.01)
	Raymer et al. (2012)	Linear (mIU/mL)	ng/mL	Spearman correlation coefficient (*p* value)	0.16 (0.01)	0.12 (0.06)
	Joensen et al. (2013)	Ln (IU/L)	ng/mL	Regression coefficient (95% CI)	0.01 (−0.02; 0.03)	0.01 (−0.01; 0.02)

(continued)

Table 4. Continued

Outcome	Study	Outcome scale (unit)	Exposure scale	Measure of association	PFOA	PFOS
	Den Hond et al. (2015)	Linear (mU/mL)	(µg/L)	Regression coefficient (*p* value)	−0.04 (0.24)	−0.05 (0.45)
Follicle stimulating hormone	Olsen et al. (1998)	–	ppm	Pearson correlation coefficient	1993: −0.12 1995: −0.13	–
	Joensen et al. (2009)	Ln (IU/L)	ng/mL	Regression coefficient (95% CI)	−0.04 (−0.14; 0.06)	0.004 (−0.13; 0.22)
	Raymer et al. (2012)	Linear (mIU/mL)	ng/mL	Spearman correlation coefficient (*p* value)	0.04 (0.6)	0.04 (0.6)
	Joensen et al. (2013)	Ln (IU/L)	ng/mL	Regression coefficient (95% CI)	0.02 (−0.01; 0.06)	0.01 (−0.01; 0.03)
	Tsai et al. (2015)	Ln (mIU/mL)	Four categories	Mean (SD)	Lowest vs. highest: 12–17 years: 1.29 (0.28) vs. 1.49 (0.36) 18–30 years: 1.29 (0.08) vs. 1.13 (0.15)	Lowest vs. highest: 12–17 years: 1.50 (0.22) vs. 0.76 (0.29) 18–30 years: 1.20 (0.11) vs. 1.26 (0.08)
	Den Hond et al. (2015)	Linear (mU/mL)	(µg/L)	Regression coefficient (*p* value)	−0.05 (0.23)	−0.13 (0.11)
Inhibin B	Joensen et al. (2009)	Ln (pg/mL)	ng/mL	Regression coefficient (95% CI)	0.01 (−0.08; 0.11)	−0.004 (−0.21; 0.12)
	Joensen et al. (2013)	Ln (pg/mL)	ng/mL	Regression coefficient (95% CI)	−0.01 (−0.03; 0.02)	0.003 (−0.01; 0.02)
	Den Hond et al. (2015)	Linear (pg/mL)	(µg/L)	Regression coefficient (*p* value)	0.07 (0.08)	0.12 (0.11)

Specht et al. (2012) performed general linear models but did not report any estimates for the association between exposure to PFOS or PFOA and testosterone, estradiol, SHBG, LH, FSH, and inhibin B. They stated to find higher PFOA and SHBG but no consistent associations in other exposure-outcome combinations. 1 ppm corresponds to approximately 1000 ng/mL. The studies by Olsen et al. (1998) and Costa et al. (2009) estimated associations by correlation coefficients. Estimates reported with more than two decimals were rounded to two decimals.

Two studies reported on the association between PFAS exposure and ratios of androgens (testosterone, free testosterone or FAI) and luteinising hormone (LH) (Joensen et al. 2009; Joensen et al. 2013). No associations were noted for any PFAS (PFOA, PFHxS, PFHpS, PFNA, PFDA) except for PFOS. Joensen et al. (2013) found lower free testosterone/LH, FAI/LH and testosterone/LH ratios with higher PFOS. Joensen et al. (2009) also found tendencies towards lower ratios.

Sakr et al. (2007) found higher estradiol with higher PFOA. However, results on the association between PFOA and estradiol pointed in different directions for the remaining six studies (see Table 4). Joensen et al. (2013) found lower estradiol with higher PFNA which was not replicated in the study by Specht et al. (2012). No consistent associations were reported for four other PFASs (PFOS, PFHxS, PFHpS, PFDA) and estradiol (Joensen et al. 2009; Raymer et al. 2012; Specht et al. 2012; Joensen et al. 2013; Den Hond et al. 2015) as well as for any PFAS (PFOS, PFOA, PFHxS, PFHpS, PFNA, PFDA, PFUnA) and the ratio between estradiol and testosterone or vice versa (Joensen et al. 2009; Joensen et al. 2013).

Regarding LH, Raymer et al. (2012) found higher LH with higher PFOA. Results from the remaining four studies pointed in different directions as they did for the other investigated PFAS (PFOS, PFHxS, PFHpS, PFNA, PFDA, PFUnA; see Table 4). For SHBG, FSH, inhibin B and the ratio between the latter two, no consistent associations were reported with any PFASs (PFOA, PFOS, PFHxS, PFHpS, PFNA, PFDA, PFUnA; see Table 4), except for the adolescents included in the study by Tsai et al. (2015) where higher PFOS and to some extent PFNA and PFUnA were associated with lower FSH.

Time to pregnancy

Buck Louis et al. (2013) found no associations between male levels of PFAS (PFOA, PFOS, PFOSA, PFNA, PFDA, 2-(N-ethyl-perfluorooctane sulfonamide)acetate (Et-PFOSA-AcOH) or 2-(N-methyl-perfluorooctane sulfonamido)acetate (Me-PFOSA-AcOH)) and TTP. Jørgensen et al. (2014) found tendencies towards longer TTP in couples when the male partner had higher levels of PFOS or PFNA, but not PFOA or PFHxS.

Studies in women

Study characteristics

We identified eight studies that investigated the association between female PFAS exposure and TTP (Fei et al. 2009; Vestergaard et al. 2012; Whitworth et al. 2012; Buck Louis et al. 2013; Jørgensen et al. 2014; Bach

et al. 2015a, 2015b; Vélez et al. 2015) and three studies that investigated PFAS exposure in relation to levels of estradiol and progesterone (Barrett et al. 2015; Lewis et al. 2015; Tsai et al. 2015) (Table 2). Five of the TTP studies were cross-sectional studies that measured PFAS levels and recorded the TTP after pregnancy was achieved (Fei et al. 2009; Jørgensen et al. 2014; Bach et al. 2015a, 2015b; Vélez et al. 2015). Two other studies were pregnancy planner studies and thus followed cohorts of women who intended to become pregnant. The women were followed for six months (Vestergaard et al. 2012) or 12 months (Buck Louis et al. 2013). These studies recorded PFAS exposure at inclusion and TTP was determined as the time elapsed from starting to try until pregnancy was achieved. Whitworth et al. (2012) carried out a nested case-control study. In this study, PFAS exposure and TTP were recorded after pregnancy was established. Study populations ranged from 222 to 1743 participants. Data were collected between 1992 and 2013. Average exposure levels ranged between 3.8 and 36.3 ng/mL for PFOS and 1.5 and 5.6 ng/mL for PFOA. The studies by Vestergaard et al. (2012) and Bach et al. (2015a) only included nulliparous women, while the other studies included parous women as well (Fei et al. 2009; Whitworth et al. 2012; Buck Louis et al. 2013; Jørgensen et al. 2014; Bach et al. 2015b; Vélez et al. 2015). Seven studies reported fecundity or fecundability odds ratios (FORs) defined as the odds of successful conception for women with higher levels of PFAS compared to women with reference PFAS levels in a given month or menstrual cycle (Fei et al. 2009; Vestergaard et al. 2012; Buck Louis et al. 2013; Jørgensen et al. 2014; Bach et al. 2015a, 2015b; Vélez et al. 2015). FORs below 1 thus indicate impaired fertility. Furthermore, some studies considered the odds ratios for infertility defined as a TTP longer than 12 months or the need for infertility treatment. Vestergaard et al (2012) defined subfecundability as a TTP above six menstrual cycles. Jørgensen et al. (2014) reported country-specific as well as pooled estimates; in this review we refer to the pooled estimates only. Bach et al. (2015b) included a new subpopulation from the Danish National Birth Cohort as well as the one investigated by Fei et al. (2009); in order to avoid duplicate reporting we only report the estimates from the new subpopulation in this review. Besides from the pregnancy planner studies (Vestergaard et al. 2012; Buck Louis et al. 2013) which evaluated the outcomes several times, the included studies only measured exposures and outcomes once.

The studies that investigated the association between exposure to PFASs and female reproductive hormones were cross-sectional and included between 178 and 825 women. One of the studies included both adolescents (12–18 years old) and adults (Tsai et al. 2015). These authors assessed the association between levels of PFASs and salivary estradiol and progesterone (Barrett et al. 2015) or serum testosterone (Lewis et al. 2015), estradiol, FSH, LH and SHBG (Tsai et al. 2015).

Fecundability odds ratios

Fei et al. (2009) found approximately 30% lower fecundability in women in the three highest PFOS quartiles compared to the lowest quartile (Table 5). There was no indication of a monotonic dose–response relationship. Estimates changed little with stratification by parity (Fei et al. 2012). Jørgensen et al. (2014) found a tendency towards lower fecundability odds with log-PFOS. With restriction to nulliparous women, this tendency disappeared. Vestergaard et al. (2012), Bach et al. (2015a), Buck Louis et al. (2013), Bach et al. (2015b) and Vélez et al. (2015) found no associations between exposure to PFOS and fecundability.

The study by Fei et al. (2009) suggested that PFOA exposure was associated with reduced fecundability (in the highest quartile, fecundability was approximately 40% lower than in the lowest quartile, see Table 6). Estimates changed little with stratification by parity. Jørgensen et al. (2014), Buck Louis et al. (2013), Vestergaard et al. (2012) and Bach et al. (2015a) found no indications of associations between PFOA and fecundability. The results from the studies by Vélez et al. (2015) and Bach et al. (2015b) indicated that higher PFOA was associated with lower fecundability, but in Bach et al. (2015b) this was not the case when the study was restricted to nulliparous women; Vélez et al. (2015) did not stratify any of their analyses by parity.

In the study by Buck Louis et al. (2013), PFOSA exposure was associated with 18% lower fecundability [FOR =0.82 (0.71; 0.95)] albeit only 10% of the samples had PFOSA levels above the limit of detection. Vestergaard et al. (2012) found no association regarding PFOSA. Jørgensen et al. (2014) found lower fecundability with higher levels of PFNA, but in nulliparous women only there was no association. Vestergaard et al. (2012) and Buck Louis et al. (2013) found no association regarding this compound. Also, the two latter studies found no associations for PFDA, Me-PFOSA-AcOH, or Et-PFOSA-AcOH. No associations were apparent for PFHxS in the studies by Vestergaard et al. (2012), Jørgensen et al. (2014) and Bach et al. (2015a) while Vélez et al. found lower fecundability with higher PFHxS. Bach et al. (2015a) found no associations regarding PFHpS, PFNA, PFDA and PFUnA.

Table 5. Results of studies on PFOS exposure in women and time to pregnancy as well as infertility.

		Fecundability OR (95% CI)			Infertility/subfecundability OR (95% CI)		
Study	Exposure scale (ng/mL)	All	Nulliparous	Parous	All	Nulliparous	Parous
Fei et al. (2009)	<26.1	1.00	–	–	1.00	–	–
	26.1–33.3	0.70 (0.56; 0.87)	0.79 (0.54; 1.16)	0.62 (0.46; 0.82)	1.70 (1.01; 2.86)	1.37 (0.61; 3.08)	2.07 (1.04; 4.11)
	33.4–43.2	0.67 (0.53; 0.84)	0.63 (0.43; 0.91)	0.64 (0.47; 0.87)	2.34 (1.40; 3.89)	2.50 (1.16; 5.37)	2.52 (1.24; 5.13)
	≥43.3	0.74 (0.58; 0.93)	0.60 (0.41; 0.87)	0.83 (0.61; 1.14)	1.77 (1.06; 2.95)	2.14 (1.00, 4.60)	1.59 (0.75, 3.37)
Vestergaard et al. (2012)	<36.28	–	1.00	–	–	1.00	–
	>36.28	–	1.03 (0.72; 1.47)	–	–	0.98 (0.54; 1.77)	–
Whitworth et al. (2012)	<10.34	–	–	–	1.0	–	–
	10.34–13.09	–	–	–	1.3 (0.9; 1.9)	0.8 (0.4; 1.6)	1.5 (0.9; 2.5)
	13.10–16.60	–	–	–	1.4 (1.0; 2.0)	0.8 (0.4; 1.4)	1.5 (0.9; 2.6)
	≥16.61	–	–	–	1.6 (1.1; 2.3)	0.7 (0.4, 1.3)	2.1 (1.2, 3.8)
Buck Louis et al. (2013)	Log-transformed and divided by SD	0.99 (0.85; 1.17)	–	–	–	–	–
Jørgensen et al. (2014)	Log	0.90 (0.76; 1.07)	1.09 (0.86; 1.37)	–	1.39 (0.93; 2.07)	0.91 (0.53; 1.55)	–
Vélez et al. (2015)	Log-transformed and divided by SD	0.96 (0.91; 1.02)	–	–	1.14 (0.98; 1.34)	–	–
Bach et al. (2015a)	<21.1	1.00	1.00	1.00	1.00	1.00	1.00
	21.1–27.8	1.08 (0.81; 1.44)	1.16 (0.77; 1.75)	1.04 (0.69; 1.55)	0.74 (0.31; 1.75)	0.64 (0.22; 1.87)	1.02 (0.25; 4.10)
	27.9–36.2	0.99 (0.73; 1.34)	1.01 (0.65; 1.57)	1.05 (0.69; 1.60)	1.01 (0.45; 2.28)	1.13 (0.41; 3.10)	0.88 (0.21; 3.73)
	≥36.3	0.99 (0.74; 1.33)	0.97 (0.62; 1.51)	1.04 (0.70; 1.55)	1.03 (0.46; 2.33)	1.23 (0.45; 3.39)	0.70 (0.16; 3.11)
	Log	0.96 (0.75; 1.24)	1.02 (0.72; 1.44)	0.91 (0.63; 1.30)	1.04 (0.54; 2.00)	1.15 (0.52; 2.54)	0.84 (0.28; 2.47)
Bach et al. (2015b)	<6.03	–	1.00	–	–	1.00	–
	6.03–8.32	–	0.98 (0.83; 1.16)	–	–	0.92 (0.62; 1.38)	–
	8.33–10.84	–	1.05 (0.89; 1.25)	–	–	0.77 (0.51; 1.17)	–
	≥10.85	–	1.09 (0.92; 1.29)	–	–	0.71 (0.47; 1.07)	–
	Per 0.1 ng/mL	–	1.00 (1.00; 1.00)	–	–	1.00 (0.99; 1.00)	–

Table 6. Result studies on exposure to PFOA in women and time to pregnancy as well as infertility.

		Fecundability OR (95% CI)			Infertility/subfecundability OR (95% CI)		
Study	Exposure scale (ng/mL)	All	Nulliparous	Parous	All	Nulliparous	Parous
Fei et al. (2009)	<3.91	1.00	–	–	1.00		
	3.91–5.20	0.72 (0.57; 0.90)	0.98 (0.59; 1.64)	0.61 (0.46; 0.80)	2.06(1.22; 3.51)	0.79 (0.30; 2.08)	3.39 (1.75; 6.53)
	5.21–6.96	0.73 (0.58; 0.92)	0.93 (0.56; 1.54)	0.62 (0.46; 0.83)	1.60 (0.93; 2.78)	0.55 (0.21; 1.43)	2.92 (1.44; 5.93)
	≥6.97	0.60 (0.47; 0.76)	0.63 (0.39; 1.04)	0.63 (0.44; 0.91)	2.54 (1.47; 4.39)	1.30 (0.52; 3.21)	2.99 (1.28; 6.98)
Vestergaard et al. (2012)	<5.60	–	1.00	–	–	1.00	–
	>5.60	–	0.92 (0.65; 1.31)		–	1.21 (0.67; 2.18)	–
Whitworth et al. (2012)	<1.66	–	–	–	1.0	–	–
	1.66–2.24	–	–	–	1.6 (1.1; 2.3)	0.6 (0.3; 1.5)	1.5 (0.9; 2.5)
	2.25–3.02	–	–	–	2.2(1.5; 3.2)	0.6 (0.3; 1.4)	2.4 (1.4; 4.1)
	≥3.03	–	–	–	2.0 (1.4; 3.0)	0.5 (0.2; 1.2)	2.1 (1.0; 4.4)
Buck Louis et al. (2013)	Log-transformed and divided by SD	0.95 (0.82; 1.11)	–	–	–	–	–
Jørgensen et al. (2014)	Log-transformed	1.04 (0.87; 1.25)	1.31 (1.03; 1.68)	–	1.11 (0.74; 1.66)	0.70 (0.40; 1.21)	–
Vélez et al. (2015)	Log-transformed and divided by SD	0.89 (0.83; 0.94)	–	–	1.31 (1.11; 1.53)	–	–
Bach et al. (2015a)	<3.1	1.00	1.00	1.00	1.00	1.00	1.00
	3.1–4.0	0.92 (0.69; 1.22)	0.82 (0.53; 1.26)	1.30 (0.86; 1.98)	1.30 (0.53; 3.19)	1.92 (0.67; 5.49)	0.39 (0.06; 2.40)
	4.1–5.5	0.94 (0.71; 1.26)	1.11 (0.73; 1.69)	0.96 (0.66; 1.41)	1.03 (0.41; 2.59)	1.22 (0.41; 3.67)	0.80 (0.18; 3.52)
	≥5.6	0.86 (0.63; 1.19)	0.99 (0.64; 1.54)	0.74 (0.48; 1.13)	1.67 (0.70; 4.00)	1.56 (0.55; 4.42)	1.74 (0.46; 6.55)
	Log	0.89 (0.68; 1.15)	1.26 (0.86; 1.85)	0.66 (0.46; 0.95)	1.18 (0.58; 2.39)	0.89 (0.36; 2.18)	2.12 (0.68; 6.64)
Bach et al. (2015b)	<1.54	–	1.00	–	–	1.00	–
	1.54–2.02	–	1.13 (0.95; 1.34)	–	–	0.73 (0.49; 1.10)	–
	2.03–2.65	–	1.16 (0.98; 1.37)	–	–	0.69 (0.46; 1.05)	–
	≥2.66	–	1.10 (0.93; 1.30)	–	–	0.71 (0.48; 1.07)	–
	Per 0.1 ng/mL	–	1.00 (0.99; 1.01)	–	–	1.00 (0.98; 1.01)	–

Infertility and subfecundability odds ratios

Fei et al. (2009) found at least 70% increased odds of infertility in the three higher quartiles of PFOS compared to the lowest quartile, but no monotonic dose–response relationship. Estimates did not differ markedly by parity. A dose–response relationship was shown in the study by Whitworth et al. (2012), but stratified by parity there was only an association in parous women. Vestergaard et al. (2012), Vélez et al. (2015) as well as Bach et al. (2015a, 2015b) found no association between PFOS exposure and subfecundability or infertility, while Jørgensen et al. (2014) found a tendency towards higher odds for infertility with log-PFOS which disappeared when the study was restricted to nulliparous women.

In the study by Fei et al. (2009), the odds for infertility were increased in the three higher quartiles of PFOA, but there was no monotonic dose–response relationship. With stratification by parity, associations were stronger in parous women and weaker in nulliparous women. Similar results were found in the study by Whitworth et al. (2012) who found twice the odds for infertility in the highest PFOA quartile compared to the reference. When stratified by parity, however, no association was apparent for nulliparous women. Vélez et al. (2015) found increased odds for infertility. In the study by Bach et al. (2015b) PFOA also tended to be associated with infertility. In the study by Vestergaard et al. (2012), Jørgensen et al. (2014) and Bach et al. (2015a) no association was found between PFOA exposure and subfecundability or infertility.

In the study by Jørgensen et al. (2014), the infertility odds were increased with exposure to PFNA, but not when the study was restricted to nulliparous women. Vestergaard et al. (2012) and Bach et al. (2015a) found no association for this compound. Jørgensen et al. (2014), Vestergaard et al. (2012) and Bach et al. (2015a) found no association between PFHxS and infertility while Vélez et al. (2015) found higher odds for infertility with exposure to this compound. Additionally, Vestergaard et al. (2012) found no associations between exposure to PFOSA, PFDA, Me-PFOSA-AcOH, or Et-PFOSA-AcOH, and subfecundability, and Bach et al. (2015a) demonstrated no associations between exposure to PFHpS, PFDA, or PFUnA and infertility.

Reproductive hormones

In nulliparous women Barrett et al. (2015) found that higher PFOS and to some extent PFOSA were associated with lower levels of estradiol and progesterone. PFOA, PFNA, PFDA, PFUnA and PFHxS were not clearly associated with either hormone, and the associations in parous women were inconsistent. In the study by Lewis et al. (2015) there were no consistent associations between any of the PFASs (PFOA, PFOS, PFHxS, PFNA) and testosterone levels. Regarding SHBG Tsai et al. (2015) found that higher PFOA was associated with lower SHBG in adolescents, but not adults. For the other PFASs (PFOS, PFNA, PFUnA) there were no clear associations with SHBG. Only PFUnA was associated with lower FSH in adolescents, but not in adults, and only PFOS was associated with lower testosterone in adolescents only as well.

Discussion

Evidence supporting an association between exposure to PFASs and male reproduction is sparse. A few studies demonstrated abnormal sperm morphology with exposure to some PFASs, but the overall evidence concerning PFAS exposure and sperm morphology is inconsistent. Other semen characteristics were not consistently associated with exposure to any PFASs. A couple of studies indicated that PFOS may be associated with lower levels of androgens, but several other studies did not replicate this finding. Associations between PFAS exposure and other reproductive hormone levels were inconsistent across studies. The studies with the highest exposure levels did not indicate stronger results than those with lower average exposure levels.

Regarding the association between PFOS or PFOA exposure and female fertility, four studies indicated impaired fecundability in relation to exposure to one or both compounds (Fei et al. 2009; Whitworth et al. 2012; Jørgensen et al. 2014; Vélez et al. 2015). However, four other studies did not support these findings (Vestergaard et al. 2012; Buck Louis et al. 2013; Bach et al. 2015a, 2015b), and with stratification by parity, associations were not replicated among nulliparous women in two of three studies that found an overall association with impaired fecundability. The results did not differ according to the average exposure levels in the studies. Based on the limited studies on PFASs other than PFOA and PFOS, the other PFASs were not clearly associated with female fecundability.

Different mechanisms may potentially explain why results differed according to parity. Serum levels of PFASs decrease during pregnancy, after childbirth and after lactation. After a nadir, levels slowly increase (Glynn et al. 2012; Brantsæter et al. 2013). If a parous woman attempts to become pregnant, the timing of exposure measurement is therefore crucial. In parous women, higher levels of PFASs measured during pregnancy may be due to a longer interpregnancy interval, allowing for more re-accumulation of PFASs, which is related to the

TTP. Women with longer interpregnancy intervals have more time to increase their body burden of PFASs after the last pregnancy compared to women with shorter interpregnancy intervals. This potential reverse causation mechanism has been discussed by several authors (Olsen et al. 2009; Vestergaard et al. 2012; Whitworth et al. 2012) and might have larger impact for PFOA than PFOS since PFOA is excreted more rapidly from the body during pregnancy and lactation (Glynn et al. 2012). Further, in parous women unmeasured confounding related to previous pregnancies and childbirths may be present (Bach et al. 2015a), representing yet another reason to restrict studies to nulliparous women.

The included outcomes are commonly used in epidemiological studies concerning reproduction. However, several limitations exist when TTP is used to study fecundability. The TTP reflects the couple fecundability and is also affected by family planning and behavioral patterns such as timing and frequency of intercourse and use of contraceptives. Some of these factors could potentially also be related to the levels of PFASs and thus potential confounders, but the studies were not able to control for such factors. Biologically sterile couples are not included in samples of pregnant women, and therefore exposures that cause sterility, as for instance infections causing complete obstruction of oviducts or vas deferens, are not represented in studies of TTP. The pregnancy planner studies followed couples for different amounts of time; for instance Vestergaard et al. followed couples for six months, which may have limited the ability to identify an association between PFAS exposure and TTP, whereas couples were followed for 12 cycles in the studies by Buck Louis et al.

Several studies suggest that sperm concentration is an important factor with respect to the probability of achieving pregnancy, but sperm motility and morphology have also been shown to be important indicators of fecundability independently of sperm concentration (Bonde et al. 1998; Guzick et al. 2001; Slama et al. 2002).

Measurement error and misclassification of the outcomes may be present in both male and female studies, but is not likely to depend on PFAS levels. Since levels of LH and FSH fluctuate throughout the day, a single measurement may not be representative for the average level in an individual. Non-differential misclassification and a potential bias towards the null may thus be present. Measurement error of TTP may play a role in studies of women who reported the TTP during pregnancy. However, previous studies indicate that women tend to recall TTP well even years after pregnancy (Joffe et al. 2005).

Most of the studies on male reproduction were cross-sectional and thus assessed exposures simultaneously with the outcomes. However, because of the long half-lives of PFAS exposures, samples are assumed to be representative for the time period where PFASs might have causally affected the semen production (several months back in time) or reproductive hormone homeostasis (Heller & Clermont 1963). Since the exposure assessment is likely to be independent of the outcomes, any misclassification would tend to be non-differential. However, for continuous exposures that are collapsed into categories (e.g., tertiles or quartiles), as used in several of the reviewed studies, non-differential measurement error can readily result in differential misclassification (Flegal et al. 1991), and further, non-differential misclassification does not always result in attenuation of study results (Jurek et al. 2005).

The quality of the exposure assessment is of concern in some of the studies considering female reproduction (Fei et al. 2009; Whitworth et al. 2012; Jørgensen et al. 2014; Bach et al. 2015a, 2015b; Vélez et al. 2015). These studies measured exposures during pregnancy rather than at the time of the first pregnancy attempt. Jørgensen et al. (2014) drew blood samples at different gestational weeks, but adjusted for this. In the studies by Whitworth et al. (2012), Fei et al. (2009) and Vélez et al. (2015) blood samples were drawn at approximately similar gestational weeks and thus, they did not adjust. Results did not change with restriction to women who gave a blood sample very early in gestation in the studies by Bach et al. (2015a, 2015b). Overall, the results of the studies concerning levels of PFASs and TTP in women did not differ according to the timing of blood sampling during pregnancy. In the two pregnancy planner studies (Vestergaard et al. 2012; Buck Louis et al. 2013) there was no reason to take gestational age at blood sampling into account since they measured exposure levels before pregnancy.

The external validity of a number of the included studies may be limited since they were based on highly selected populations, e.g., recruited at infertility clinics (Olsen et al. 1998; Sakr et al. 2007; Costa et al. 2009; Raymer et al. 2012; Vestergaard et al. 2012; Buck Louis et al. 2013; Buck Louis et al. 2015; Den Hond et al. 2015; Governini et al. 2015). The Polish cohort in the studies by Specht et al. (2012), Jørgensen et al. (2014), Toft et al. (2012) and Leter et al. (2014) as well as the study by Joensen et al. (2013) had participation rates below 30%. Participation rates were not reported in the studies by Raymer et al. (2012), Olsen et al. (1998) and Joensen et al. (2009). The study by Buck Louis et al. (2013) recruited participants from a selected source population, few of the invited individuals participated, and 20% dropped

out. Vestergaard et al. (2012) included a high proportion of couples with impaired fertility and furthermore had a low response rate (16%). For the studies where participation may have depended on the outcomes under study, it is unknown whether selection may also have been affected by PFAS levels, and therefore whether considerable selection bias may be present.

Confounding, i.e., unaccounted common causes of PFAS levels and the studied outcomes, might have affected the results of the included studies. In the studies of male reproduction, the potential confounders differ between reproductive hormones and semen parameters (Supplementary Material, Tables S1 and S2). Determinants for semen parameters, which are also likely causes of PFAS levels and therefore potential confounders, include age and BMI. These were taken into account in some but not all studies. In studies that did not adjust for these variables associations may have been biased towards lower semen quality with higher PFAS exposure, and thus lack of adjustment is unlikely to explain null results.

Important determinants for semen characteristics, but not potential confounders, include the time from ejaculation to analysis (when considering motility), abstinence period (when considering volume, total sperm count and sperm concentration) and spillage (when considering volume and total sperm count). Most studies adjusted for abstinence time while fewer took time from ejaculation to analysis or spillage into account. For the levels of reproductive hormones in males, the timing of blood sampling during the day may be considered an important determinant, but not a potential confounder.

For the levels of reproductive hormones in males, age may be considered one of the most important determinants. Age is also an important potential confounder for the association between PFAS exposure and testosterone since PFAS levels tend to increase with age while testosterone levels decrease with higher age. Lack of adjustment for age (Joensen et al. 2009, 2013; Raymer et al. 2012) could potentially cause bias towards an association between higher PFASs and lower testosterone levels. However, the impact of this potential confounder is probably negligible in the studies by Joensen et al. because all their participants were of similar age (18–25 years). BMI may also be an important confounder since testosterone tends to decrease with increasing BMI while the levels of PFASs may increase with higher BMI, potentially causing bias towards an association between higher PFASs and lower testosterone levels if not conditioned on. This was not addressed in the studies by Raymer et al. (2012) and Joensen et al. (2009).

All studies on female reproduction adjusted for maternal age and pre-pregnancy BMI. Both were variables we considered to be important potential confounders. Maternal socio-economic status or educational level was only included in the primary analyses by Fei et al. (2009) and Bach et al. (2015a, 2015b) as well as in a sensitivity analysis by Jørgensen et al. (2014). In our opinion, this could be an important confounder since it may be causally associated with both exposure and outcome, and lack of adjustment could potentially bias the investigated association. Several other covariates that we considered less important were included in a few of the studies (Supplementary Material, Tables S3).

An important question when addressing the association between PFAS exposure and human reproduction is whether both sexes could be affected, or whether any observed effects on couple fertility could derive from adverse effects in only one gender. Exposure sources are similar for couples that live together, and individual concentrations in couples may therefore be correlated (Jørgensen et al. 2014). An appropriate way to address this could be to investigate exposure levels in both males and females in relation to couple fecundity (Buck Louis et al. 2013; Jørgensen et al. 2014). Buck Louis et al. (2013) demonstrated no associations for PFAS exposures in men, but found female levels of PFOSA to be associated with TTP. However, the study by Jørgensen et al. (2014) found tendencies towards longer TTP with higher PFOS or PFNA in both men and women.

Regarding the association between female exposure to PFOS or PFNA and TTP Jørgensen et al. (2014) found no interaction between male and female exposure levels.

In relation to the reassuring results from the studies on PFASs and male reproduction it is not likely that any associations between female PFAS exposure and TTP is due to an association between male PFASs exposure and reproductive function.

Our comprehensive search strategy insured that we would identify the majority of the relevant published literature, but we did not include unpublished studies. Given the huge expenses for measuring PFASs publication bias may be less likely than for other topics, and further, the large amount of published studies with null results support that publication bias may be of little relevance for the associations between male and female reproduction and PFAS exposure. Our literature searches did not identify any potentially relevant studies using other reproductive outcomes than those included.

Future studies should focus on emerging PFASs that are substituting PFASs like PFOS and PFOA. Exposures in women should preferably be assessed at conception or otherwise during early pregnancy in biological samples

using state of the art laboratory techniques. Female studies should be restricted to nulliparous women or closely account for factors related to previous pregnancies in parous women. Levels of gonadotropins should be measured at a standardized time of the day. Finally, the mechanisms behind potential associations between PFAS exposures and reproduction should be further investigated in humans.

As suggested in a couple of recent studies, the fetal period or other critical periods during development of the reproductive system may be more sensitive to exposure of PFAS in both males and females (Kristensen et al. 2013; Vested et al. 2013), warranting further investigation.

Conclusions

In men, the evidence regarding an association between exposure to PFASs and semen characteristics as well as reproductive hormones is sparse despite the fact that a relatively large amount of studies have investigated the topic. Even though a few male studies suggested some associations, this was based on the examination of a large number of exposure-outcome combinations, and there was little consistency regarding results for specific exposures and outcomes across studies. With respect to male reproduction, high impact adverse exposures usually affect more than one aspect of the reproductive system (Lancranjan et al. 1975; Jurewicz et al. 2009). PFOS or other PFASs might be weakly associated with lower testosterone levels or impaired sperm morphology, but the lack of other consistent results regarding a large panel of outcomes limits the interpretation of this as causal.

Neither in the male nor female studies did the studies with the highest average exposure levels demonstrate stronger findings. For PFOS and PFOA, the literature indicates a possible association with female fecundability mainly among parous women, which is likely to be spurious. The lack of association in most studies in nulliparous women and from pregnancy planner studies failed to support a causal relationship between PFAS exposure and fertility in women. Knowledge on the influence of newly introduced PFASs is sparse and should be further investigated in future studies.

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Declaration of interest

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