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The Current Epidemiologic Evidence on Exposures to Poly- and Perfluoroalkyl Substances (PFASs) and Male Reproductive Health

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Abstract Environmental epidemiologists have given heightened research attention to the class of poly- and perfluoroalkyl substances, or PFASs, in recent years due to their ubiquity, persistence, and evidence of hormonal activity. Whereas prevalence studies have documented changes in serum levels over time among populations in the USA and elsewhere, few human reproductive health studies have been conducted. Given the weight of evidence demonstrating that hormonally active synthetic compounds can impact spermatogenesis, of interest is whether environmental exposures to PFASs are impacting sperm health and male fertility. We review the albeit scant empirical evidence to date to draw attention to this avenue of investigation and to highlight the types of studies that are needed to determine whether and how PFASs impact male reproduction.

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Introduction

Poly- and perfluoroalkyl substances, or PFASs, are human-made compounds that are favored by a variety of industries for their water and lipid resistant abilities [1, 2]. They are utilized in surfactants, oil repellants, and a variety of consumer products. Since the commercial introduction of PFASs more than 60 years ago, many studies have been conducted to evaluate the environmental and biological impacts of PFASs [3]. As a result, in 2009, under the Stockholm Convention, PFASs were listed as persistent organic pollutants due to their ubiquitous, persistent, bioaccumulative, and toxic nature [4, 5]. Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acids (PFOA), both long-chain PFASs, are the most commonly studied PFASs. In addition, fluorochemical residuals that biotransform into PFOS and PFOA, such as EtFOSAA and MeFOSAA, are included in most studies, but the metabolic mechanism and toxic effects in humans have not been well characterized [6–9, 10••]. In developed countries, long-chain PFASs have been recognized as persistent and toxic, and as such have been regulated or phased out by manufacturers, such as 3M, DuPont, Daikin, and Miteni in the USA, Japan, and Europe. However, production of long-chain PFASs continues in other regions of the world [5, 11]. Moreover, some manufacturers have now replaced PFOS and PFOA with short-chain PFASs, such as perfluorohexanoic acid (PFHxA) and perfluorobutane sulfonate (PFBS). It is acknowledged that the short-chain PFASs have shorter human half-lives, but recent publications [12–14, 15•] have expressed concerns that fluorinated replacements are similar to the long-chain

PFASs they replaced in terms of their hazardous potential for both the environment and humans [16].

Exposure Prevalence

The ubiquitous nature of PFASs has been documented throughout the world. In 2004, Kannan and colleagues examined the concentration levels of PFOS, PFHxS, PFOA, and PFOSA in 10 countries [17]. PFASs were found in all samples, with the USA and Poland reporting the highest exposure levels and India reporting the lowest levels [19]. Overall, concentrations of PFOS were much higher than any other poly- or perfluoro compounds, which have been corroborated by other studies [17–20]. However, a study from Sri Lanka found overall PFOA concentrations were higher than PFOS [21]. Although the levels of PFASs concentrations in the USA are generally higher than other countries, studies in the USA general population have reported a decline in the levels of exposure over time [20, 22, 23]. Globally, exposure to long-chain PFASs has been declining in the last decade, but increased levels of short-chained PFASs have been seen in several populations, including the USA [14, 15•, 20]. Table 1 summarizes several studies reporting the prevalence of PFASs exposure in the USA and other countries [17–23].

Impacts on Male Reproductive Health

Hormonally active properties of PFASs have been demonstrated in several experimental studies showing estrogenic, anti-estrogenic, and/or anti-androgenic activity [24, 25•]. Given that environmental endocrine disrupting chemicals have been associated with impaired male reproductive function [26, 27] and can impact sperm development [28], it is surprising that the impacts of PFASs on male reproductive health are not better understood. Table 2 summarizes key studies to date that have evaluated whether PFASs are associated with indicators of male fertility [2, 10, 29, 30••, 31••, 32–34, 35••, 36••].

PFASs and Sperm Parameters

Several studies have looked at associations between measured serum PFASs and sperm parameters such as concentration, motility, and morphology. Studies have found associations between increasing PFASs and fewer morphologically normal sperm cells, lower adjusted sperm concentration and total sperm count, smaller sperm heads, and higher proportions of immature sperm [30••, 31••, 32, 33]. These associations have largely been found for individual PFASs, but between studies, there have been conflicting findings for the same chemical. For example, in a study by Vested et al., early life exposure to PFOS was not associated with sperm parameters, including sperm concentration, total sperm count, motility, morphology, and semen volume [31••]. However, in a study by Toft et al., the group with the highest levels of PFOS exposure had 35 % fewer morphologically normal cells as compared to the least exposed individuals in a combined analysis of men from Poland, Greenland, and Ukraine [32]. A few studies have reported no associations between certain measured PFASs and sperm parameters [34, 35••]. With fewer than a dozen studies currently available, the body of evidence linking PFASs exposure to sperm parameters remains equivocal and more investigation is needed.

PFASs, Sperm DNA Outcomes, and Measures of Sperm Sex Ratio

There have been limited numbers of studies assessing PFASs in relation to sperm DNA outcomes, and findings have been inconsistent. It has been suggested that alterations in DNA methylation are linked to some developmental processes and molecular mechanisms, such as X chromosome inactivation, embryonic reprogramming, cellular differentiation, and some types of cancer [36••, 37, 38]. Leter et al. looked at associations between DNA methylation rates and PFAS serum levels and found inconsistent associations with sperm DNA global methylation in men from Ukraine, Poland, and Greenland [36••]. Sperm chromatin structure assay, in situ terminal deoxynucleotidyl transferase UTP nick-end labeling assay, and apoptotic markers were evaluated in relation to PFASs exposures [2]. Of the PFASs studied (PFOS, PFOA, PFNA, and PFHxS), consistent associations between PFASs exposure and sperm DNA fragmentation and apoptosis were not found [2]. Sperm sex chromosome ratios have been looked at in association with PFASs [29]. Kvist et al. found a negative association between PFOS and Y:X sex chromosome ratio in their Inuit population and a positive overall association in their combined analysis of men from Ukraine, Greenland, and Poland. No associations between PFOA and Y:X ratio were reported in this study [29]. Additionally, Bae et al. found that father's MeFOSAA and perfluorononanoic acid levels were significantly associated with more female as compared to male births in a secondary sex ratio study of 233 couples enrolled from community settings [10••].

Other Reproductive Health Outcomes

PFASs associations with reproductive hormone levels in human studies have been mixed [39]. Raymer et al. reported that among 256 men seen at a fertility clinic luteinizing hormone (LH) but not follicle stimulating hormone (FSH) was positively correlated with plasma PFOS and PFOA, and no significant associations were seen for total testosterone or estradiol [34]. Joensen et al. examined total testosterone, free testosterone, free androgen index (FAI), and other hormone ratios (i.e., testosterone/LH, free testosterone/LH, and FAI/LH) in a

Table 1 Prevalence of PFASs exposure

Authors	Title	Population	Outcome(s) of interest	Associations/findings
Calafat et al. (2007) [22]	Polyfluoroalkyl chemicals in the USA population: data from the National Health and Nutrition Examination Survey (NHANES) 2003–2004 and comparisons with NHANES 1999–2000	USA—2094 participants 12 years of age and older from NHANES 2003–2004	Measurable levels of PFASs and how they compare to 1999–2000 NHANES	PFNA, PFHxS, PFOS, and PFOA were found in most samples and changed according to two factors: race/ethnicity and sex. Compared to previous NHANES data, PFOS, PFOA, and PFHxS had significantly lower concentrations, while PFNA had higher concentrations.
Gribble et al. (2015) [18]	Longitudinal measures of perfluoroalkyl substances (PFAS) in serum of Gullah African Americans in South Carolina: 2003–2013	USA—71 Gullah African Americans participating in the SLEIGH study (81 % female)	Temporal changes in levels of PFASs in blood plasma from 2003 to 2013	Annual decreases of 9 % in PFOS concentrations were recorded in the years of study (2003–2013). Other PFASs compounds also declined.
Guruge et al. (2005) [21]	Perfluorinated organic compounds in human blood serum and seminal plasma: a study of urban and rural tea worker populations in Sri Lanka	Sri Lanka—30 men from Colombo (10), Talawakele (10) and Haldummulla (10)	Measurable levels of PFASs in blood and semen	PFOS, PFHS, PFUnA, PFDA, PFNA, and PFOA were detected in all blood samples, with PFOS and PFHS detected in all semen samples. PFOA was found in more than 70 % of semen samples.
Kannan et al. (2004) [17]	Perfluorooctanesulfonate and related fluorochemicals in human blood from several countries	Global—473 urban and suburban participants from USA (175), Colombia (56), Brazil (29), Belgium (20), Italy (50), Poland (25), India (45), Malaysia (23), Korea (50), and Japan (38)	Concentrations of PFOS, PFHxS, PFOA, and PFOSA	Of the four compounds, PFOS was found most often. For PFOS, USA and Poland reported the highest concentrations and India the lowest. No PFOS or PFOA concentration differences were found by gender or age.
Olsen et al. (2008) [23]	Perfluorooctanesulfonate and other polyfluoroalkyl chemicals in American Red Cross adult blood donors, 2000–2006	USA—600 American Red Cross Blood Donors	Levels of polyfluoroalkyls in serum compared to 645 samples from 2000 to 2001	Most of the PFBS, Me-PFOSA-AcOH, and Et-PFOSA-AcOH concentrations could not be reliably detected because they were lower than the limit of quantitation. Compared to 2000–2001 and controlling for sex and age, adjusted mean concentrations were lower in 2006.
Olsen et al. (2012) [20]	Temporal trends of perfluoroalkyl concentrations in American Red Cross adult blood donors, 2000–2010	USA—600 American Red Cross Blood Donors	Levels of PFASs in blood plasma compared to samples from 2000 to 2001 and 2006	PFOS and PFOA declined 76 and 48 %, respectively. PFHxS and PFHpA saw declines as well. Several alternatives, like PFNA, PFDA, and PFUnA, all had increases between 40 and 69 %.
Weihe et al. (2008) [19]	Serum concentrations of polyfluoroalkyl compounds in Faroese whale meat consumers	Faroes Island—103 children aged 7, 79 of those at age 14, and 12 pregnant women and their offspring 5 years later	Serum concentrations of PFASs including: PFOSA, Et-PFOSA-AcOH, Me-PFOSA-AcOH, PFHxS, PFOS, PFOA, PFNA, PFDeA, and PFDoA	8 of the 9 measured chemicals were frequently detected. PFOS mean concentrations were generally much higher than other PFASs.

Table 2 Studies investigating PFASs exposure effects on semen quality

Authors	Title	Population	Outcome(s) of interest	Associations and findings
Bae et al. (2015) [10••]	Maternal and paternal serum concentrations of perfluoroalkyl and polyfluoroalkyl substances and the secondary sex ratio	USA—233 couples	SSR—the ratio of male to female live births	More female births than males were significantly associated with the father's levels of MeFOSAA and perfluorononanoic acid. MeFOSAA had a dose response relationship with the father's concentrations.
Buck Louis et al. (2015) [30••]	Perfluorochemicals and human semen quality: The LIFE Study	USA—501 male partners of couples planning pregnancy	35 semen characteristics including general characteristics, motility, sperm head, morphology, and sperm chromatin stability	17 sperm measures were associated with 6 PFASs. PFDeA, PFNA, PFOA, and PFOS were shown to be associated with less coiled tail sperm. Lower DNA stainability, smaller sperm head area and perimeter, and higher bicephalic and immature sperm showed associations with PFOSA levels.
Kvist et al. (2012) [29]	Serum levels of perfluorinated compounds and sperm Y:X chromosome ratio in two European populations and in Inuit from Greenland	EU—607 men from Greenland (201), Poland (198), and Ukraine (208)	Sperm sex chromosome ratio (Y:X)	A positive association was found between overall PFOS concentrations and Y:X ratios. There was a negative association between PFOS in Inuit men only and Y:X ratio. No significant association was found between PFOA and Y:X ratio.
Joensen et al. (2009) [33]	Do perfluoroalkyl compounds impair human semen quality	Denmark—105 men	Semen quality and reproductive hormones	Fewer normal sperm cells were significantly associated with increasing PFAS levels. Concentration, total sperm count, and motility seemed low with increasing PFASs (not significant). No significant trend between reproductive hormones and PFASs (although nonsignificant trends were found)
Joensen et al. (2012) [35••]	PFOS (perfluorooctanesulfonate) in serum is negatively associated with testosterone levels, but not with semen quality, in healthy men	Denmark—247 men	Semen quality and levels of testosterone, estradiol, SHBG, LH, Inhibin-B, FSH from blood samples.	PFOS concentrations were negatively associated with a variety of hormonal measures, most importantly testosterone. PFOS was the only PFASs found at high concentrations and the only one to exhibit these effects. No associations were found between measured PFASs and semen quality with the exception of motility and PFHpS, which were negatively associated.

Table 2 (continued)

Authors	Title	Population	Outcome(s) of interest	Associations and findings
Leter et al. (2014) [36••]	Exposure to perfluoroalkyl substances and sperm DNA global methylation in Arctic and European populations	EU—312 fertile men from Greenland (112), Poland (100), and Ukraine (100)	Global DNA methylation rates in sperm	The methylation biomarkers were not consistently associated with PFASs concentrations. Associations were found within specific countries, but in aggregate analyses, the only significant association was for PFNA and global methylation levels.
Raymer et al. (2012) [34]	Concentrations of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) and their associations with human semen quality measurements	USA—256 men from the Duke University IVF Clinic	Semen quality and PFOA, PFOS, and reproductive hormones in blood samples	PFOS in blood or semen and PFOA levels in blood were not associated with semen quality. FSH was not shown to be impaired by these PFAS chemicals, whereas blood plasma levels of PFOA and PFOS showed positive correlations with luteinizing hormone.
Specht et al. (2012) [2]	Sperm DNA integrity in relation to exposure to environmental perfluoroalkyl substances—a study of spouses of pregnant women in three geographical regions	EU—604 men from Greenland (199), Poland (197), and Ukraine (208)	PFASs in serum and DNA damage in sperm cells	Findings for PFASs and sperm DNA fragmentation, apoptosis, and reproductive hormones were not consistent.
Toft et al. (2012) [32]	Exposure to perfluorinated compounds and human semen quality in arctic and European populations	EU—588 males Greenland (196), Poland (189), and Ukraine (203)	Serum PFASs levels and semen quality	PFHxS, PFOA, PFOS, and PFNA had non-consistent associations between total sperm count, semen volume, and sperm concentration. PFOS and PFHxS were associated with lower amounts of morphologically normal cells. High PFOA exposures were associated with higher motile spermatozoa.
Vested et al. (2013) [31••]	Associations of in utero exposure to perfluorinated alkyl acids with human semen quality and reproductive hormones in adult men	Denmark—169 male offspring of a pregnancy cohort	Semen parameters and reproductive hormone levels	Exposure to PFOA but not PFOS in utero appeared to alter sperm count and concentration negatively, while affecting luteinizing and follicle stimulating hormone positively.

cohort of healthy young Danish men and found that serum PFOS was negatively associated with these ratios [35••].

Other relevant studies include an investigation of cryptorchidism in a Danish and Finnish birth cohort that did not find an association with PFOA and PFOS measured in cord blood and risk for cryptorchidism [40]. In a Danish sample of pregnant women, Jensen et al. found no association between PFOS and PFOA and risk for miscarriage, whereas a significant association was seen between PFDA and PFNA and miscarriage risk [41]. We found one animal study particularly germane to this question, which evaluated ammonium perfluorooctanoate dosing and sperm parameters in two generations of rats. It did not find evidence of an impact on any of the reproductive health outcomes including mating and fertility, sperm parameters, and testis pathology [42].

Conclusion

Given the ubiquity of PFASs and increasing evidence of links between endocrine disrupting compounds and sperm health, the public health relevance of this problem is under-recognized. Epidemiologic research to date has been insufficient to adequately address the exposure contexts, the biotransformation processes, or the biomonitoring needs of an extensive class of compounds whose presence in the environment is rapidly changing. Most of the studies summarized here took advantage of existing biorepositories as opportunities to specifically examine PFASs. Few of the studies were initiated as a focused and comprehensive assessment of PFASs on male reproductive outcomes in adequately powered, population-based samples. What is needed is a concerted effort, akin to the recent research efforts seen in the USA and elsewhere, dedicated to elucidating the population health effects of bisphenol A (BPA). The impetus for targeted funding initiatives focusing on BPA in part emerged out of burgeoning animal evidence and a series of scattered yet suggestive human studies. Taken together, the current epidemiologic evidence base strongly suggests that PFASs are biologically active and persistent, are widely distributed in human populations, and their male reproductive impacts are biologically plausible, which is supported by suggestive yet equivocal findings to date in a paucity of studies. Funding and investigator leadership are needed now to launch a collaborative and coordinated research effort so that PFASs impacts on male reproductive health can be fully characterized.

Compliance with Ethical Standards

Conflict of Interest Melissa Perry, GiaLinh Nguyen, and Nicholas Porter declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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