What's in the Water? Lesson 5 Data Packet

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Introduction: Use the information in this packet to complete activities in Lesson 5: Health Impacts of PFAS Exposure. The majority of the data packet is a snapshot of health-related studies on PFAS, including work done on human, animal models, and wildlife. While this reference is not sufficient for achieving a complete understanding of the complex issues surrounding exposure to PFAS and potential health impacts linked to such exposure, it should provide a solid foundation. You may find it necessary to conduct more research in order to better understand specific issues discovered in this packet. Individual datasets and information are cited with the data as well as at the end of this packet.

As you work with the data provided in this packet, please remember:

- There are NO state or federal regulations on the PFAS family of chemicals. As you consider the data below, it may be helpful to know what the EPA has issued a non-enforceable, non-regulatory health advisory limit for PFAS at **70 parts per trillion (ppt)**. This limit is suggested in order to provide Americans with "a margin of protection from a lifetime of exposure to PFOA and PFOS from drinking water".
- This Data Packet provides a "snapshot" of the current knowledge on the topic. There are many, many more studies that will support and/or negate the findings shown here. The information provided here represents a range of information that has been gathered by numerous scientists around the world, but it is not exhaustive or conclusive.

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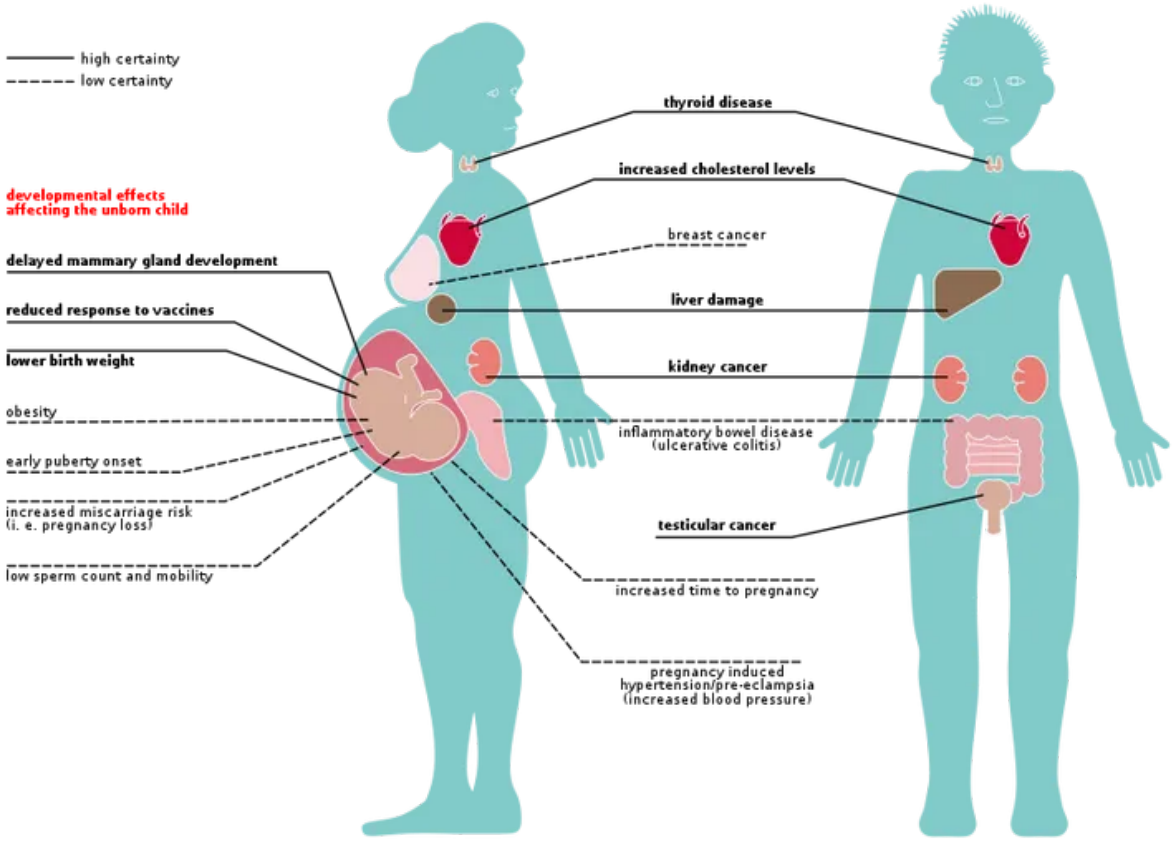
Health-Related Data

The data presented below covers both human, lab animal, and in-vitro studies on the interaction between PFAS exposure and adverse health outcomes

Source 8: Infographic from The European Environment Agency



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Source 9: Blood, Heart, and Circulation

Source 9.1: Bijland et al. *Toxicological Sciences* (2011)

Title: Perfluoroalkyl Sulfonates Cause Alkyl Chain Length–Dependent Hepatic Steatosis and Hypolipidemia Mainly by Impairing Lipoprotein Production in APOE*3-Leiden CETP Mice

Abstract: Perfluorobutane sulfonate (PFBS), perfluorohexane sulfonate (PFHxS), and perfluorooctane sulfonate (PFOS) are stable perfluoroalkyl sulfonate (PFAS) surfactants, and PFHxS and PFOS are frequently detected in human biomonitoring studies. Some epidemiological studies have shown modest positive correlations of serum PFOS with non-high-density lipoprotein (HDL)-cholesterol (C). This study investigated the mechanism underlying the effect of PFAS surfactants on lipoprotein metabolism. APOE*3-Leiden.CETP mice were fed a Western-type diet with PFBS, PFHxS, or PFOS (30, 6, and 3 mg/kg/day, respectively) for 4-6 weeks. Whereas PFBS modestly reduced only plasma triglycerides (TG), PFHxS and PFOS markedly reduced TG, non-HDL-C, and HDL-C. The decrease in very low-density lipoprotein (VLDL) was caused by enhanced lipoprotein lipase-mediated VLDL-TG clearance and by decreased production of VLDL-TG and VLDL-apolipoprotein B. Reduced HDL production, related to decreased apolipoprotein AI synthesis, resulted in decreased HDL. PFHxS and PFOS increased liver weight and hepatic TG content. Hepatic gene expression profiling data indicated that these effects were the combined result of peroxisome proliferator-activated receptor alpha and pregnane X receptor activation. In conclusion, the potency of PFAS to affect lipoprotein metabolism increased with increasing alkyl chain length. PFHxS and PFOS reduce plasma TG and total cholesterol mainly by impairing lipoprotein production, implying that the reported positive correlations of serum PFOS and non-HDL-C are associative rather than causal.

Also known as "bad" cholesterol

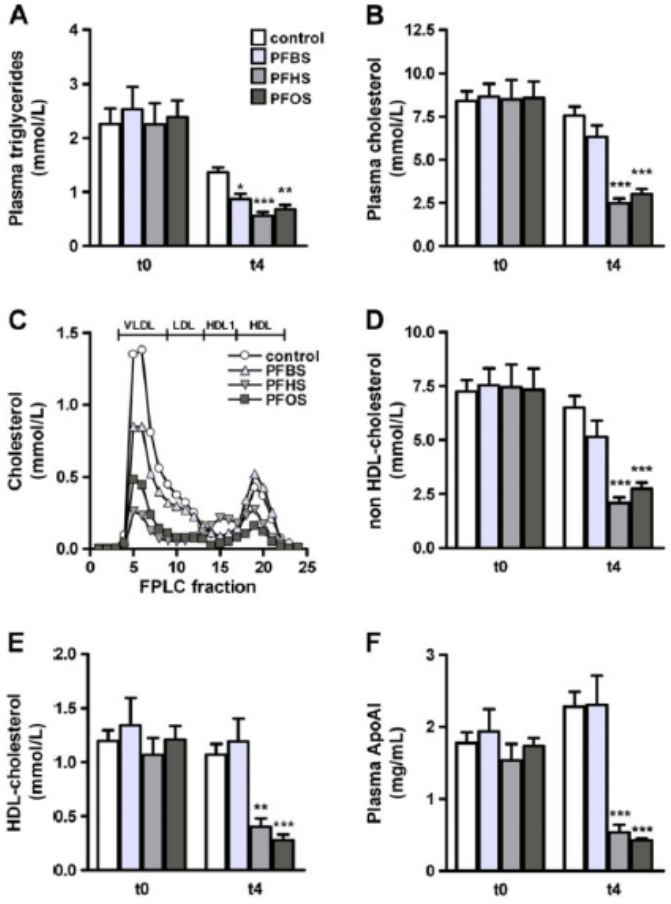

FIG. 1. Effect of PFAS on plasma TG, TC, HDL-C, and ApoAI. Mice received a Western-type diet without and with 0.03% PFBS, 0.006% PFHxS, or 0.003% PFOS for 4 weeks. At baseline (t0) and after 4 weeks of intervention (t4), 4-h fasted blood was taken and plasma was assayed for TG (A) and TC (B). After 4 weeks of intervention, cholesterol distribution over lipoproteins was determined (C). Plasma at t0 and t4 were also assayed for non-HDL-C (D), HDL-C (E), and apoAI (F). Data are means ± SEM ($n = 6$). *$p < 0.01$, **$p < 0.001$, and ***$p < 0.0001$ as compared with the control group.

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Source 9.2: Hagenaars and Knapen. Chemosphere (2011)

Title: Structure–activity relationship assessment of four perfluorinated chemicals using a prolonged zebrafish early life stage test

Abstract: Perfluorinated compounds (PFCs) are a group of anthropogenic chemicals containing diverse functional groups and chain lengths. They are known to be persistent and bioaccumulative explaining their worldwide environmental presence. The toxicological information on these chemicals is still incomplete and insufficient to assess their environmental impact and structure-activity relationship. In the present study, the developmental effects of PFOS (perfluorooctane sulfonate, C8), PFOA (perfluorooctanoic acid, C8), PFBS (perfluorobutane sulfonate, C4) and PFBA (perfluorobutanoic acid, C4) were evaluated in zebrafish embryos (*Danio rerio*). The different chain lengths and functional groups of the selected chemicals made it possible to determine the structure-activity relationship of these compounds. PFCs with longer chain lengths (C8) tend to be more toxic than PFCs with shorter chain lengths (C4). Comparison based on the functional groups of compounds with the same chain length indicates that PFCs with a sulfonate group have a larger toxic potential than the ones with a carboxyl group. Furthermore, exposure to the different PFCs resulted in some general effects, such as deformations of the tail and an uninflated swim bladder, as well as in more specific effects which might be related to the structure of the tested chemicals. Oedemas and effects on length could only be detected in 8-carbon PFCs while malformations of the head were a more specific action of the sulfonated PFCs. Effects on hatching rate and success were found in PFOA exposed embryos and heart rates were affected after exposure to PFOS, PFOA and PFBS.

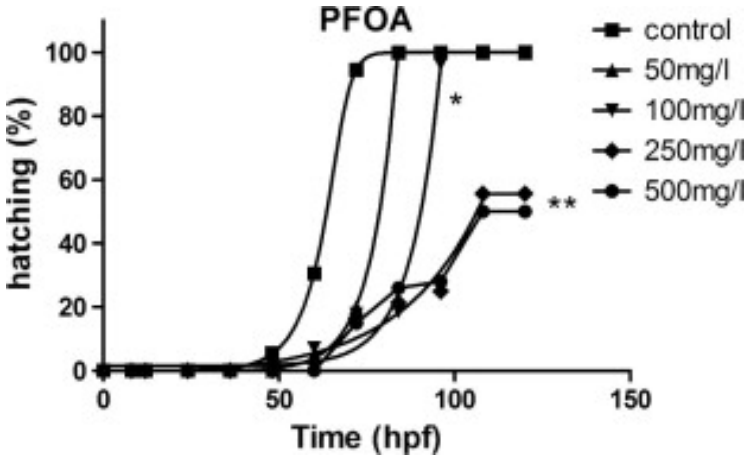

Fig. 2. Hatching rate PFOA. Hatching was significantly delayed after exposure to PFOA. The delayed hatching did not occur at concentrations lower than 50 mg L^{-1} and was only significant from the control at 100 mg L^{-1} ($*p < 0.05$), 250 mg L^{-1} and 500 mg L^{-1} PFOA ($**p < 0.01$).

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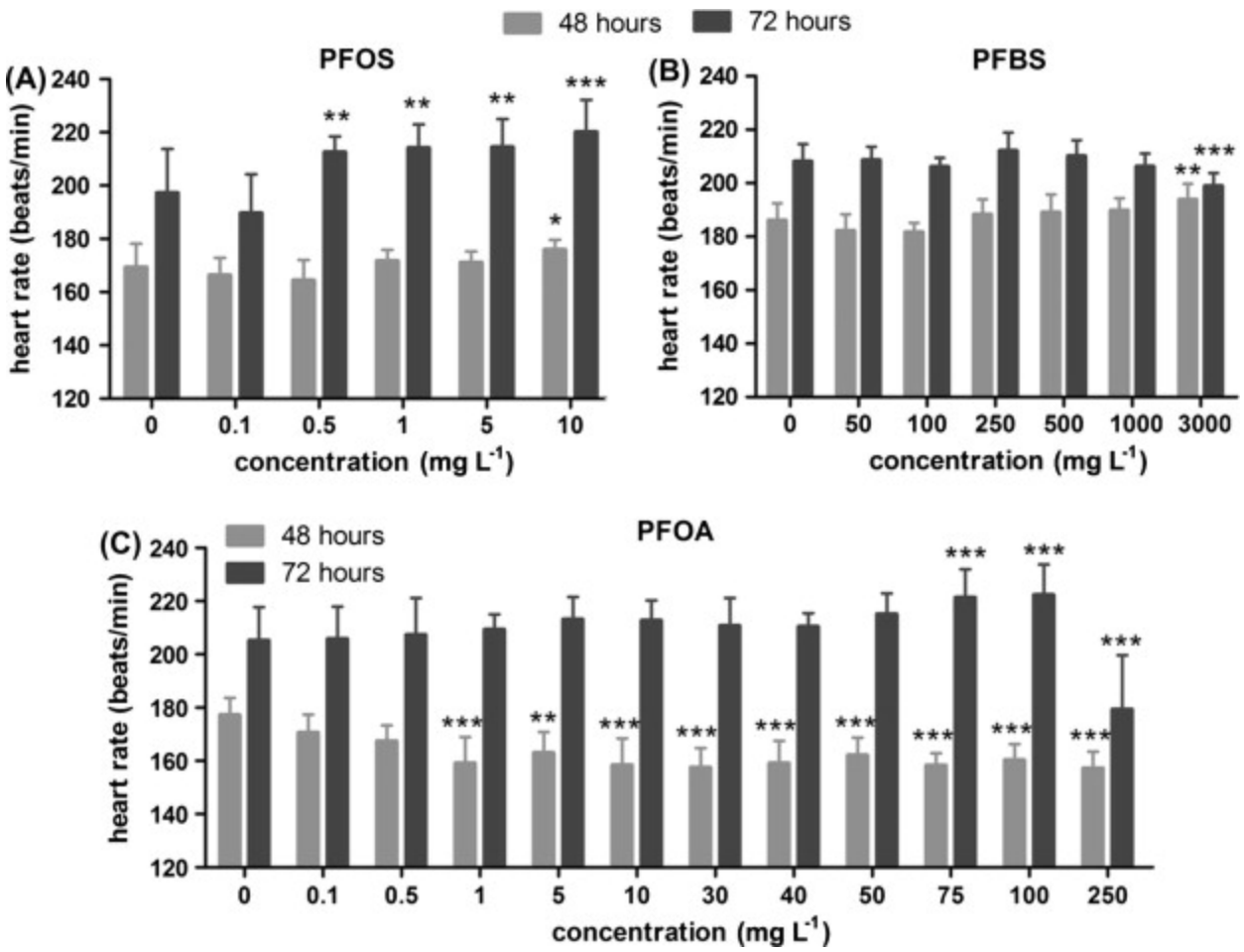

Fig. 3. Heart rate. Heart rate at 48 and 72 hpf {“post fertilization”} was altered in embryos exposed PFOS (A), PFBS (B) and PFOA (C). Values are represented as mean ± standard deviation. Values that were significantly different from the control are indicated by asterisks (∗p < 0.05, ∗∗p < 0.01, ∗∗∗p < 0.001).

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Source 9.3: Huang et al. Environment International (2018)

Title: Serum polyfluoroalkyl chemicals are associated with risk of cardiovascular diseases in national US population

Abstract:
Background: Perfluoroalkyl chemicals (PFCs) as possible cardiovascular disrupters are universally detected in humans. However, evidence from epidemiological studies appears insufficient and ambiguous.

Objectives: We aim to examine the serum PFCs levels and their associations with the prevalence of cardiovascular diseases (CVD) and related outcomes in general US population.

Methods: We investigated the serum levels of 12 major PFCs, including perfluorooctanoic acid (PFOA), per-fluorooctane sulfonic acid (PFOS), perfluorohexane sulfonic acid (PFHxS), 2-(N-ethyl-perfluorooctane sulfona-mido) acetate (EPAH), 2-(N-methyl-perfluorooctane sulfonamido) acetate (MPAH), perfluorodecanoic acid(PFDE), perfluorobutane sulfonate (PFBS), perfluoroheptanoic acid (PFHP), perfluorononanoic acid (PFNA),perfluorooctane sulfonamide (PFSA), perfluoroundecanoic acid (PFUA), and perfluorododecanoic acid (PFDO), in 10,859 participants from the National Health and Nutritional Examination Survey (NHANES) 1999–2014. Logistic regression models were used to estimate the associations between serum PFCs and 5 self-reported CVD outcomes, including congestive heart failure, coronary heart disease, angina pectoris, heart attack, and stroke. Linear regression analyses were used to estimate the PFCs and their associations with 8 traditional CVD risk factors like serum triglyceride and total cholesterol.

Results: In multivariable-adjusted models, total PFCs were positively associated with total CVD (p for trend = 0.0166), independent of traditional CVD risk factors, such as smoking status, diabetes, hypertension and serum cholesterol level. Compared with reference quartile of total PFCs levels, the multivariable adjusted odds ratios in increasing quartiles were 1.23 [95% confidence interval (CI): 0.91–1.66], 1.47 (95% CI: 1.14–1.89) and 1.45 (95% CI: 1.06–1.98) for total CVD. Similar positive associations were found if considering individual PFCs including PFOS, PFUA, MPAH, EPAH, PFDO, PFSA and PFBS. In addition, serum levels of MPAH and PFDO were positively associated with congestive heart failure; PFNA, PFDE, and PFUA were positively associated with coronary heart disease; PFUA and PFDO were positively associated with angina pectoris; and PFNA was posi-tively associated with heart attack.

Conclusions: Our findings suggested that exposure to PFCs was positively associated with risk of CVD. Further longitudinal studies are needed to increase our understanding about the role of PFCs exposure in the prevalence of CVD.

Table 5
Subgroup analyses between total PFCs and the presence of total CVD in NHANES 1999–2014[a].

Subgroups	Total PFCs [aOR (95% CI)]				p_{trend}	$p_{interaction}$
	Q1	Q2	Q3	Q4		
Age						
< 50 years	1.00	1.44 (0.66–3.16)	1.96 (0.68–5.61)	1.63 (0.39–6.89)	0.2500	
≥ 50 years	1.00	1.22 (0.87–1.72)	1.49 (1.13–1.96)	1.48 (1.05–2.08)	0.0151	0.1941
Sex						
Male	1.00	1.59 (1.05–2.40)	2.18 (1.38–3.45)	1.79 (1.14–2.83)	0.0276	
Female	1.00	1.04 (0.65–1.67)	1.06 (0.71–1.58)	1.28 (0.82–1.98)	0.2669	0.1048
Race						
Non-Hispanic white	1.00	1.21 (0.81–1.83)	1.55 (1.10–2.19)	1.50 (1.01–2.21)	0.0298	
Non-Hispanic black	1.00	1.10 (0.66–1.83)	0.94 (0.56–1.59)	0.93 (0.55–1.55)	0.6389	
Mexican American	1.00	1.35 (0.72–2.53)	1.12 (0.57–2.19)	1.51 (0.53–4.34)	0.5596	0.1613
Family PIR						
Low	1.00	1.27 (0.90–1.81)	1.41 (1.05–1.89)	1.48 (0.95–2.30)	0.0765	
High	1.00	1.30 (0.76–2.23)	1.95 (1.15–3.30)	1.77 (1.07–2.91)	0.0057	0.1169
Education levels						
≤ High school	1.00	1.30 (0.89–1.89)	1.49 (1.05–2.13)	1.54 (1.05–2.26)	0.0383	
> High school	1.00	1.12 (0.67–1.87)	1.35 (0.85–2.16)	1.32 (0.80–2.18)	0.1960	0.8617
Physical activity						
No regular activity	1.00	1.32 (0.97–1.80)	1.69 (1.23–2.34)	1.63 (1.12–2.37)	0.0110	
Regular low-to-vigorous	1.00	1.25 (0.69–2.28)	1.29 (0.69–2.44)	1.37 (0.70–2.69)	0.4077	0.9983
BMI						
< 25 kg/m^2	1.00	2.04 (1.09–3.84)	1.73 (0.97–3.07)	2.12 (1.17–3.85)	0.0519	
≥ 25 kg/m^2	1.00	1.02 (0.76–1.38)	1.41 (1.05–1.90)	1.28 (0.91–1.79)	0.0576	0.6931
Smoking status						
Never to moderate	1.00	1.26 (0.88–1.79)	1.54 (1.12–2.11)	1.47 (0.99–2.17)	0.0487	
Active	1.00	1.07 (0.62–1.86)	1.26 (0.63–2.52)	1.54 (0.80–2.94)	0.1619	0.5136
Alcohol						
Abstainer	1.00	1.19 (0.76–1.87)	1.20 (0.86–1.67)	1.29 (0.82–2.05)	0.3064	
Drinker	1.00	1.15 (0.71–1.85)	1.81 (1.18–2.78)	1.65 (1.02–2.67)	0.0111	0.3499
Hypertension						
Yes	1.00	1.15 (0.81–1.63)	1.33 (0.98–1.82)	1.36 (0.93–1.99)	0.0880	
No	1.00	1.46 (0.71–3.00)	1.97 (1.11–3.49)	1.79 (0.92–3.50)	0.0697	0.2938
Diabetes						
Yes	1.00	0.87 (0.56–1.34)	1.11 (0.67–1.85)	1.08 (0.65–1.78)	0.5494	
No	1.00	1.59 (1.08–2.34)	1.81 (1.23–2.66)	1.76 (1.17–2.64)	0.0158	0.1484
Family history of CVD						
Yes	1.00	1.02 (0.46–2.26)	1.06 (0.53–2.13)	1.20 (0.61–2.38)	0.5545	
No	1.00	1.29 (0.96–1.75)	1.59 (1.17–2.17)	1.58 (1.10–2.26)	0.0098	0.2826

[a] Adjusted covariates: age, sex, race/ethnicity, family PIR, education levels, physical activity levels, BMI, alcohol drinking status, smoking status, diabetes, hypertension, family history of CVD, total energy intake, log-transformed levels of serum cotinine, and log-transformed levels of serum total cholesterol. The total PFCs levels were used for quartiles in study population: < 12.11 ng/mL (quartile 1), 12.11–20.61 ng/mL (quartile 2), 20.61–33.63 ng/mL (quartile 3), and > 33.63 ng/mL (quartile 4). CI: confidence interval. aOR: adjusted odds ratio. p_{trend}, p for trend. $p_{interaction}$, p for interaction.

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Source 10: Pregnancy and Reproduction

Source 10.1: Huang et al. Environmental Health (2019)

Title: Prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances and the risk of hypertensive disorders of pregnancy

Abstract:
Background: Perfluoroalkyl and polyfluoroalkyl substances (PFAS) have been reported to disrupt endocrine system and reproduction. However, epidemiological evidence on the association between PFAS and preeclampsia is inconsistent. We aimed to investigate the association between prenatal PFAS exposure and hypertensive disorders of pregnancy (HDP) in humans.

Methods: PFAS were measured by liquid chromatography system coupled with tandem mass spectrometry in 687 umbilical cord plasma samples collected between 2011 and 2012 in Shanghai, China. Information on HDP including gestational hypertension and preeclampsia was abstracted from medical records. Multiple logistic regression was used to examine the association of each PFAS with gestational hypertension, preeclampsia, and overall HDP in separate models. Elastic net regression with logit link was used to identify independent associations between exposures and outcomes. Logistic regression was used to obtain the unpenalized estimates of the selected PFAS components for the associations with outcomes, adjusting for age, education level, pre-pregnancy BMI, parity, and mutual adjustment of selected PFAS.

Results: The risk of gestational hypertension and preeclampsia was 3.3% and 2.8% in our subjects, respectively. Perfluorobutane sulfonate (PFBS), perfluorohexane sulfonate (PFHxS), perfluoroundecanoic acid (PFUA) were associated with preeclampsia based on elastic net penalty regression. In the fully adjusted statistical model, women with a higher level of standardized ln-transformed PFBS had an increased odds of preeclampsia [adjusted odds ratio (AOR): 1.81, 95% confidence interval (CI): 1.03-3.17], and overall HDP (AOR: 1.64, 95% CI: 1.09-2.47).

Conclusions: Prenatal exposure to PFBS was positively associated with the risk of preeclampsia and overall HDP.

Table 5 Logistic regression models for the selected exposures and hypertensive disorders of pregnancy/preeclampsia

PFAS	Hypertensive disorders of pregnancy [a]AOR (95% CI)	Preeclampsia
PFBS		
[b]Standardized	1.64 (1.09–2.47)	1.81 (1.03–3.17)
T1 (≤0.0398)	1	1
T2 (0.0399–0.0554)	0.89 (0.39–2.44)	2.09 (0.51–8.53)
T3 (0.0556–0.4612)	2.26 (1.02–5.02)	3.51 (0.94–13.2)
P value for linear trend	0.03	0.05
PFHxS		
[b]Standardized	0.79 (0.55–1.13)	0.82 (0.49–1.37)
T1 (≤0.11402)	1	1
T2 (0.1403–0.1831)	0.94 (0.43–2.03)	1.14 (0.36–3.58)
T3 (0.1834–0.8465)	0.61 (0.26–1.41)	0.92 (0.27–3.11)
P value for linear trend	0.79	0.88
PFDoA		
[b]Standardized	0.76 (0.55–1.04)	
T1 (≤0.0775)	1	NA
T2 (0.0776–0.1118)	0.89 (0.42–1.88)	
T3 (0.112–1.1357)	0.54 (0.23–1.29)	
P value for linear trend	0.77	NA
PFUA		
[b]Standardized	NA	0.82 (0.53–1.27)
T1 (≤0.3276)		1
T2 (0.3277–0.4808)		0.83 (0.29–2.41)
T3 (0.4819–5.2653)		0.49 (0.13–1.75)
P value for linear trend	NA	0.28

Variance inflation variance (VIF) for exposures ranged from 1.01 to 1.1

[a]Adjusting for age, education, pre-pregnancy BMI, parity and mutual adjustment of PFAS including in the corresponding model

Abbreviations: *T1* tertile 1, *T2* tertile 2, *T3* tertile 3

[b]Standardized: PFAS concentration was subtracted by mean and then divided by its standard deviation

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Source 10.2: Groffen et al. Sci Total Environ. (2019)

Title: Limited reproductive impairment in a passerine bird species exposed along a perfluoroalkyl acid (PFAA) pollution gradient

Abstract: Although bird eggs have been used in biomonitoring studies on perfluoroalkyl acids (PFAAs), effects of environmental concentrations on reproduction remain largely unknown in wild birds. In the present study we examined the associations between the concentrations of 4 perfluoroalkyl sulfonic acids (PFSAs) and 11 perfluoroalkyl carboxylic acids (PFCAs) in the eggs of great tits (*Parus major*), collected along a distance gradient from a pollution source, and multiple reproductive parameters (including the start of egg laying, clutch size, hatching success, fledging success and total breeding success) along with egg shell thickness and body condition of the nestlings. The PFAA concentrations measured at the plant site were among the highest ever reported in wild bird eggs. PFAA concentrations decreased sharply with increasing distance (0-11 km) from the plant, but remained relatively elevated in the adjacent sites. PFAAs were grouped into principal components (PCs) to prevent collinearity. High concentrations of PFOS, PFDS, PFDoDA, PFTrDA and PFTeDA (grouped as PC1) were associated with a reduced hatching success of nests where at least one egg hatched, thinner egg shells and increased survival of the hatched chicks. High concentrations of PFDA (PC2) were associated with a reduced hatching success, especially in nests where no eggs hatched, an earlier start of egg laying and a reduction of total breeding success, mainly caused by the failure in hatching. Although the major manufacturer of PFAAs phased out the production of perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA) and related products in 2002, concentrations appear to have increased since previous measurements. Surprisingly, despite the very high concentrations close to the fluorochemical plant, there was no clear evidence for reproductive impairment as the observed associations between PFAA concentrations and reproductive parameters were rather limited compared to previous studies in songbirds. These findings also suggest potential differences in sensitivity between species. CAPSULE: Despite the very high PFAA concentrations at the perfluorochemical hotspot, correlations with reproductive parameters were limited.

Figure notes. Study graphs A-C only. PC stands for “Principle Component”, which is a statistical technique that allows researchers to combine multiple independent variables that have a similar effect on the dependent variable. PC1 was mainly influenced by PFOS, PFDS, PFDoDA, PFTrDA and PFTeDA and tominor extent by PFOA and PFNA; high concentrations of these com-pounds corresponded with high values of PC1. PC2 was mainly influ-enced by PFDA, therefore high values of PC2 mainly indicated highPFDA concentrations

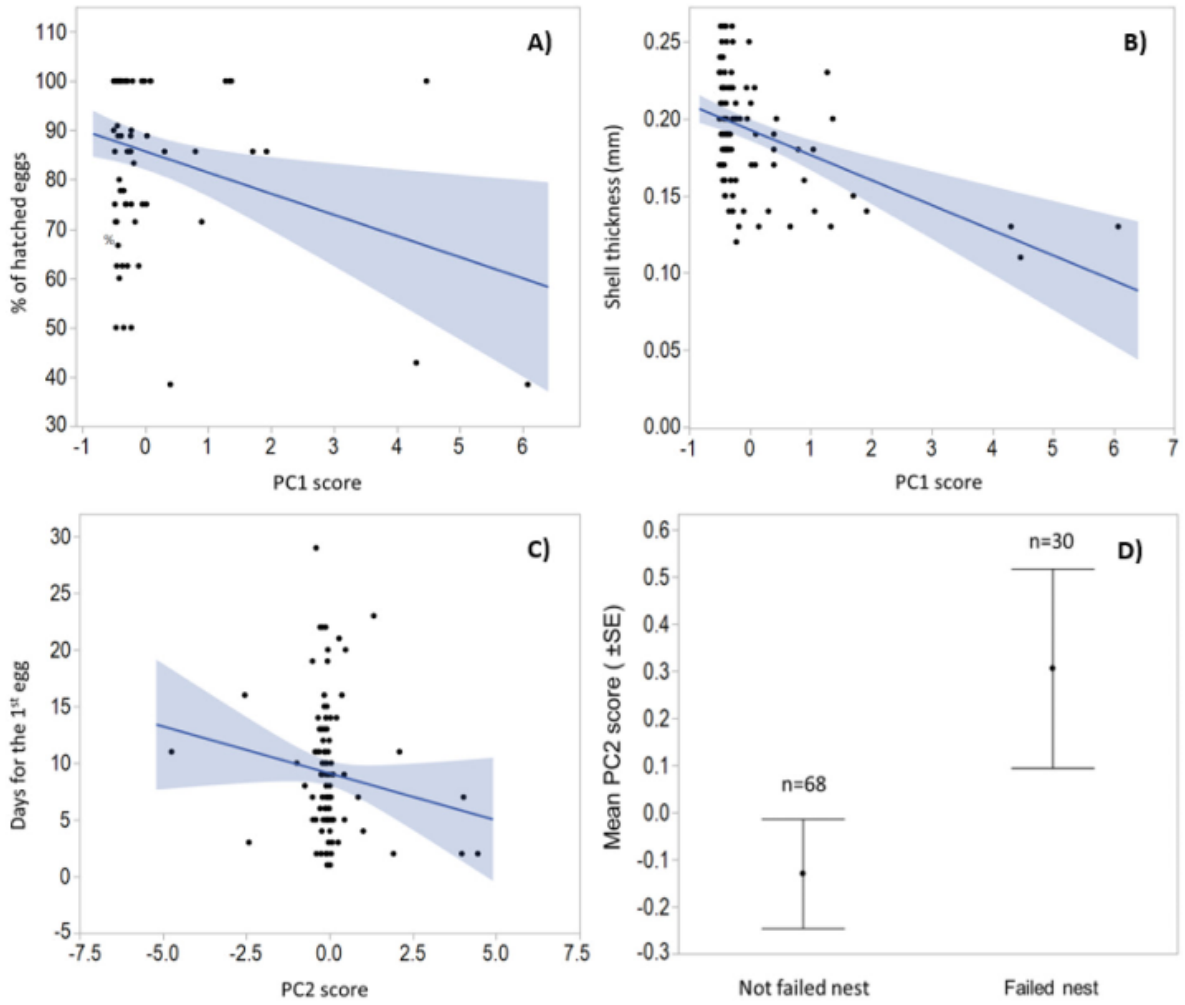

Fig. 4. Correlations between the Principal Components (PCs) and reproductive parameters. A) Negative correlation between PC1 factor scores and the percentage of hatched eggs in a nest. B) Negative correlation between PC1 factor scores and shell thickness (mm). C) Negative association between PC2 factor scores and the egg laying date. D) Effects of factor scores of PC2 on reproduction total failure. The blue band represents the 95% confidence intervals of the correlation coefficients.

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Source 10.3: Song et al Environ Int (2018)

Title: Biomonitoring PFAAs in blood and semen samples: Investigation of a potential link between PFAAs exposure and semen mobility in China

Abstract: Perfluoroalkyl acids (PFAAs) have been suspected to act as endocrine disruptors and adversely affect human reproductive health. We aimed to investigate the association between PFAAs in blood and semen, explore a potential link between PFAAs exposure and semen quality in the population of the Pearl River Delta (PRD) region in China, one of the "world factories". The monitoring results demonstrated that the population (103 male participants) from the PRD region in this study had higher PFAAs levels in blood and semen than some other areas in China. PFOS was found at the highest mean concentrations of 118.16 ng/mL in blood and 5.31 ng/mL in semen among the nine PFAAs. Significant associations were found between concentrations of several analytes in blood and semen, including Σ9 PFAAs ($r = 0.475$, $P < .01$), PFOA ($r = 0.215$, $P = .029$), PFHS ($r = 0.458$, $P < .01$) and PFOS ($r = 0.981$, $P < .01$). BMI was the most important factor to PFAAs, but there was no significant difference in PFAAs concentrations in blood and semen collected from participants with different smoking and drinking habits, education background and occupations. Negative correlations were significantly observed between sperm motility and PFBA, PFPeA, PFHxA, PFBS, PFOA, PFHS, PFOS and Σ9PFAAs in semen. Therefore, exposure to PFAAs may result in a decline in semen mobility in participants from the PRD region.

Table 6
Correlation between PFAAs in blood and semen and semen quality.

	Analytes in blood		Analytes in semen	
	Semen concentration	Progressive motility	Semen concentration	Progressive motility
PFBA	−0.026	0.248*	−0.005	−0.305**
PFPrA	−0.112	0.176	0.114	−0.180
PFPeA	−0.026	0.235*	0.008	−0.344**
PFHxA	−0.020	0.046	0.092	−0.349**
PFBS	−0.022	0.195*	0.044	−0.302**
PFHpA	−0.035	−0.052	0.073	−0.127
PFOA	−0.010	−0.212*	0.155	−0.312**
PFHS	0.017	−0.064	−0.057	−0.244*
PFOS	0.075	−0.231*	0.050	−0.200*
Σ_9PFAAs	0.077	−0.173	0.091	−0.519**

** P means that correlation is significant at the 0.01 level (2-tailed).

* P means that correlation is significant at the 0.05 level (2-tailed).

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Source 11: Endocrine System

Source 11.1: Lou et al Ectoxicology (2013)

Title: Effects of perfluorooctanesulfonate and perfluorobutanesulfonate on the growth and sexual development of *Xenopus laevis*

Abstract: Perfluorobutanesulfonate (PFBS), as a substitute for perfluorooctanesulfonate (PFOS), is widespread in the environment and biotic samples as well as PFOS. To investigate effects of PFOS and PFBS on the growth and sexual development of amphibians, we exposed Xenopus laevis tadpoles at a series of concentrations of PFOS and PFBS (0.1; 1; 100; 1,000 μg/l) as well as 17-beta-estradiol (E2, 100 ng/l) and 5 alpha-androstan-17-beta-ol-3-one (DHT, 100 ng/l) from stage 46/47 to 2 months post-metamorphosis. We found that neither PFOS nor PFBS had a significant effect on the survival and growth. However, they caused hepatohistological impairment at higher concentrations (100; 1,000 μg/l). Unlike E2, PFOS at all concentrations did not alter the sex ratio and induce intersex, but caused degeneration of spermatogonia in testes except for the lowest concentration. PFBS had no effect on the sex ratio and gonadal histology. PFOS and PFBS promoted expression of estrogen receptor (ER) and androgen receptor (AR), but not affected aromatase expression in the brain. The increase in expression of ER and AR suggests an increase in the responsiveness to the corresponding sex hormone and potential effects on sexual development. Our results show that PFBS as well as PFOS have adverse effects on hepatohistology and sexual development on X. laevis. Also, PFOS- and PFBS-induced increase in ER and AR expression highlights the need to further study effects of PFOS and PFBS on subsequently gonadal development, sexual dimorphism, and secondary sex characteristics in X. laevis. It is debatable that PFBS is widely used as a substitute of PFOS.

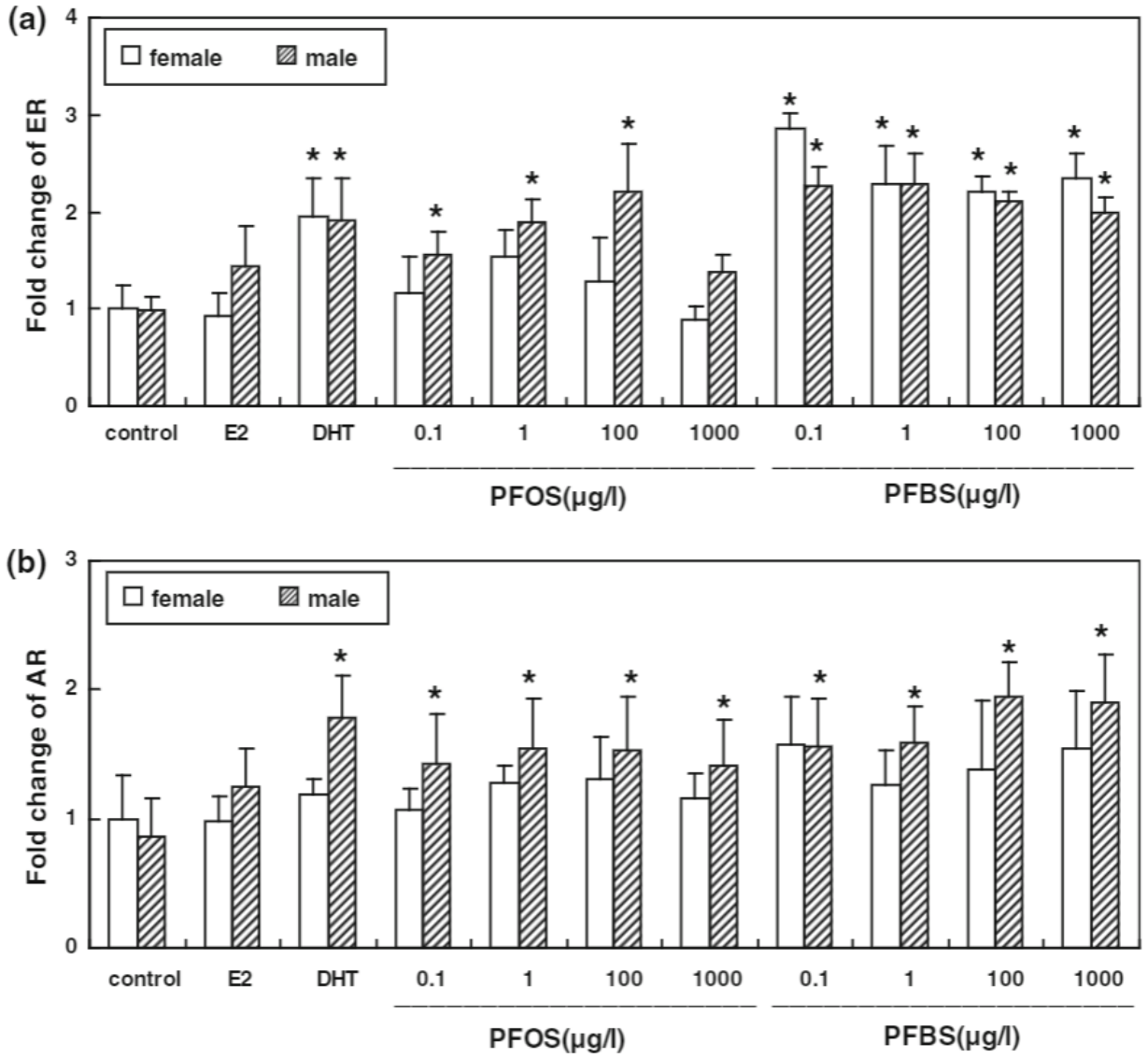

Fig. 4 mRNA expression of ER (**a**) and AR (**b**) in the brain of *Xenopus laevis* with exposure to PFOS and PFBS. Changes in expression level of ER and AR gene were quantified by normalizing to the abundance of corresponding gene in the female brain from control group. Data were showed as mean ± SD (n = 12). Significant differences between control and exposure groups are indicated by $^{*}P < 0.05$

Source 11.2: Kim et al Environ Sci Technol (2011)

Title: Trans-placental transfer of thirteen perfluorinated compounds and relations with fetal thyroid hormones.

Abstract: While the results of animal studies have shown that perfluorinated compounds (PFCs) can modulate concentrations of thyroid hormones in blood, limited information is available on relationships between concentrations of PFCs in human blood serum and fetal thyroid hormones. The relationship between concentrations of PFCs in blood and fetal thyroid hormone concentrations or birth weight, and ratios of major PFCs between maternal and fetal serum were determined. Concentrations of PFCs were measured in blood serum of pregnant women (n = 44), fetal cord blood serum (n = 43) and breast milk (n = 35). Total concentrations of thyroxin (T4), triiodothyronin (T3) and thyroid stimulating hormone (TSH) in blood serum were also quantified. The ratios of major PFCs in maternal versus fetal serum were 1:1.93, 1.02, 0.72, and 0.48 for perfluorotridecanoic acid (PFTrDA), perfluorooctanoic acid (PFOA), perfluorohexane sulfonate (PFHxS), and perfluorooctane sulfonate (PFOS), respectively. Fetal PFOS, PFOA, PFTrDA and maternal PFTrDA were correlated with fetal total T4 concentrations, but after adjusting for major covariates, most of the relationships were no longer statistically significant. However, the significant negative correlations between maternal PFOS and fetal T3, and maternal PFTrDA and fetal T4 and T3 remained. Since thyroid hormones are crucial in the early development of the fetus, its clinical implication should be evaluated. Given the observed trans-placental transfer of PFCs, efforts should be also made to elucidate the exposure sources among pregnant women.

Table 5. Correlations between PFC Concentrations (ng/mL) in Fetal Cord or Maternal Serum and Concentrations of Thyroid Hormones in Cord Blood Serum Samples[a]

thyroid hormones in fetal cord blood serum	PFCs in fetal cord blood serum						PFCs in maternal blood serum					
	N	PFHxS	PFOS	PFOA	PFTrDA	ΣPFCs	N	PFHxS	PFOS	PFOA	PFTrDA	ΣPFCs
T3												
not-adjusted	34	−0.228	−0.212	−0.276	−0.223	−0.285	32	−0.270	−0.422[b]	−0.202	−0.391[b]	−0.416[b]
adjusted[d]	34	−0.178	−0.157	−0.240	−0.190	−0.242	32	−0.261	−0.414[b]	−0.238	−0.380[b]	−0.413[b]
T4												
not-adjusted	35	−0.280	−0.344[b]	−0.297	−0.391[b]	−0.350[b]	33	−0.046	−0.293	0.058	−0.511[c]	−0.180
adjusted[e]	35	−0.111	−0.048	−0.157	−0.254	−0.128	33	0.030	−0.181	−0.071	−0.441[b]	−0.130
TSH												
not-adjusted	31	−0.185	−0.090	0.030	0.038	−0.106	29	−0.019	0.045	0.290	0.261	0.117
adjusted[e]	31	−0.069	−0.088	0.089	0.083	−0.051	29	0.091	0.109	0.443[b]	0.288	0.218

[a] Units in ng/dL for T3, μg/dl for T4 and μIU/mL for TSH. [b] $p < 0.05$. [c] $p < 0.01$. Pearson correlation tests were performed among the logarithms of fetal thyroid hormones and PFCs with- and without adjustment for influential covariates upon fetal thyroid hormones, which were selected from our preliminary analyses (multivariate model), as follows. [d] Maternal age and gestational age for T3. [e] Maternal age, gestational age and maternal BMI for T4 and TSH.

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Source 11.3: Zhou et al Environ Int (2016)

Title: Association of perfluoroalkyl substances exposure with reproductive hormone levels in adolescents: By sex status

Abstract: Polyfluoroalkyl substances (PFASs) are a group of common chemicals that ubiquitously exist in wildlife and humans. However, few studies have researched the effect of PFASs on reproductive hormones in adolescents. To provide information in this regard, we recruited 225 Taiwanese adolescents aged 13–15 years from 2009 to 2010 to investigate the relationship between serum PFASs (PFOS, PFOA, PFBS, PFDA, PFDoA, PFHxA, PFHxS, PFNA and PFTA) and reproductive hormone concentrations using a cross-sectional study design. Results showed PFOS and PFTA levels were highest among the PFASs, with a median concentrations of 29.9 (interquartile range: 13.0–43.8) ng/mL and 6.0 (0.6–25.9) ng/mL in males, and a median concentrations of 28.8 (14.8–42.6) ng/mL and 4.5 (0.3–18.4) ng/mL in females. After adjustment for confounding factors, nonsignificant associations between PFASs and reproductive hormone were found except for PFNA with ln(estradiol) (β = 0.2060, 95%CI: 0.0016, 0.4105). When stratified by sex, more significant associations were found in males than in females. Among males, PFASs were negatively associated with ln(testosterone) level for PFOS (β = − 0.0029, 95%CI: − 0.0055, − 0.0003), PFDA (β = − 0.2565, 95%CI: − 0.4135, − 0.0994), PFHxA (β = − 0.3095, 95%CI: − 0.5942, − 0.0248), and PFNA (β = − 0.4233, 95%CI: − 0.6998, − 0.1467). Furthermore, male participant ln(estradiol) levels were positively associated with PFOA (β = 0.0921, 95%CI: 0.0186, 0.1656), and PFHxS (β = 0.0462, 95%CI: 0.0020, 0.0905). Among females, a significant relationship was found only for PFDoA with ln(testosterone) (β = − 0.0119, 95%CI: − 0.0227, − 0.0010). In conclusion, this study showed higher levels of PFASs coincide with lower testosterone and higher estradiol levels, and more significant associations of PFASs with reproductive hormone were found in males than in females.

Table 2
Estimated coefficient (β) with 95% CI of natural log-transformed testosterone (nmol/L) per each 1 (ng/mL) increase in PFAS levels in multivariate linear regression models.

	Total coefficient (95% CI)[b]	Boys coefficient (95% CI)[c]	Girls coefficient (95% CI)[c]	*p*-Value for interaction[a]
PFOS	−0.0022 (−0.0076 to 0.0032)	**−0.0029 (−0.0055 to −0.0003)**	0.0005 (−0.0018 to 0.028)	0.060
PFOA	0.0642 (−0.0903 to 0.2186)	−0.0549 (−0.1186 to 0.0088)	−0.0697 (−0.1627 to 0.0233)	0.421
PFBS	−0.0391 (−0.6840 to 0.7622)	−0.0387 (−0.3261 to 0.2487)	0.1326 (−0.3576 to 0.6229)	0.457
PFDA	−0.1938 (−0.4842 to 0.0965)	**−0.2565 (−0.4135 to −0.0994)**	−0.0626 (−0.1730 to 0.0477)	0.103
PFDoA	−0.0016 (−0.0257 to 0.0225)	0.0056 (−0.0056 to 0.0168)	**−0.0119 (−0.0227 to −0.0010)**	0.119
PFHxA	−0.1817 (−0.7727 to 0.4092)	**−0.3095 (−0.5942 to −0.0248)**	−0.1896 (−0.4387 to 0.0595)	0.476
PFHxS	−0.0040 (−0.0732 to 0.0652)	0.0173 (−0.0211 to 0.0588)	−0.0182 (−0.0451 to 0.087)	0.699
PFNA	−0.3413 (−0.8036 to 0.1210)	**−0.4233 (−0.6998 to −0.1467)**	−0.1018 (−0.2684 to 0.0648)	0.042
PFTA	0.0006 (−0.0012 to 0.0024)	0.0009 (−0.0001 to 0.0019)	0.0003 (−0.0004 to 0.0009)	0.650

Coefficient represents the change in testosterone outcome for each 1 ng/mL increase in PFASs concentration.
[a] *p* from the interaction term between PFASs and sex in joint models.
[b] Models are adjusted for age, sex, BMI, ETS exposure, parental education, regular exercise, and month of survey.
[c] Models are adjusted for age, BMI, ETS exposure, parental education, regular exercise, and month of survey. Values with p ≤ 0.05 are indicated in bold, underlined text.

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Table 3
Estimated coefficient (β) with 95%CI of natural log-transformed estradiol (pmol/L) per each 1 (ng/mL) increase in PFAS levels in multivariate linear regression models.

	Total coefficient (95% CI)[b]	Boys coefficient (95% CI)[c]	Girls coefficient (95% CI)[c]	*p*-Value for interaction[a]
PFOS	0.0018 (−0.0006 to 0.0042)	0.0024 (−0.0007 to0.0055)	0.0005 (−0.0023 to 0.0033)	0.256
PFOA	0.0570 (−0.0112 to 0.1253)	**0.0921 (0.0186 to 0.1656)**	0.1015 (−0.0103 to 0.2134)	0.475
PFBS	0.0447 (−0.2763 to 0.3656)	0.0149 (−0.3216 to 0.3513)	0.3129 (−0.2771 to 0.9028)	0.316
PFDA	0.0537 (−0.0756 to 0.1829)	0.0734 (−0.1189 to 0.2657)	0.0131 (−0.1208 to 0.1469)	0.615
PFDoA	0.0037 (−0.0070 to 0.0144)	−0.0007 (−0.0139 to 0.0124)	0.0106 (−0.0026 to 0.0238)	0.221
PFHxA	−0.0529 (−0.3154 to 0.2096)	0.0600 (−0.2803 to 0.4003)	−0.1492 (−0.4515 to 0.1531)	0.307
PFHxS	0.0249 (−0.0056 to 0.0555)	**0.0462 (0.0020 to 0.0905)**	0.0171 (−0.0154 to 0.0496)	0.570
PFNA	**0.2060 (0.0016 to 0.4105)**	0.3204 (−0.0115 to 0.6522)	0.1252 (−0.0758 to 0.3263)	0.478
PFTA	0.0003 (−0.0005 to 0.0011)	−0.0003 (−0.0014 to 0.0009)	0.0007 (−0.0001 to 0.0014)	0.215

Coefficient represents the change in estradiol outcome for each 1 ng/mL increase in PFASs concentration.
[a] *p* from the interaction term between PFASs and sex in joint models.
[b] Models are adjusted for age, sex, BMI, ETS exposure, parental education, regular exercise, and month of survey.
[c] Models are adjusted for age, BMI, ETS exposure, parental education, regular exercise, and month of survey. Values with $p \leq 0.05$ are indicated in bold, underlined text.

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