Supplementary Material

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

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Search strategy

MEDLINE: ("perfluorooctane sulfonic acid"[Supplementary Concept] OR "perfluorooctane sulfonic acid"[All fields] OR "perfluorooctanoic acid"[Supplementary Concept] OR "perfluorooctanoic acid"[All fields] OR "fluorocarbons"[Mesh] OR "fluorocarbons"[All fields] OR "perfluorinated"[All Fields] OR “polyfluorinated" [All Fields] OR "polyfluoroalkyl"[All Fields] OR "perfluoroalkyl"[All Fields] OR ”perfluorochemicals"[All Fields] OR ”perfluoro compound"[All Fields] OR "PFOS"[All Fields] OR "PFOA"[All Fields] OR "PFNA"[All Fields] OR "PFDA"[All Fields] OR "PFHxS"[All Fields] OR "PFUnA"[All Fields] OR "PFOSA"[All Fields] OR "PFDeA"[All Fields]) AND ("Infertility"[Mesh] OR "Infertility"[All fields] OR "Fertility"[Mesh] OR "Fertility"[All fields] OR "Time-to-Pregnancy"[Mesh] OR "Time-to-Pregnancy"[All fields] OR "Reproduction"[Mesh] OR "Reproduction"[All fields] OR "Semen Analysis"[Mesh] OR "Semen Analysis"[All fields] OR "Gonadal Steroid Hormones"[Mesh] OR "Gonadal Steroid Hormones"[All fields])

EMBASE: ('fluorocarbon'/exp OR 'fluorocarbon' OR 'perfluoro compound'/exp OR 'perfluoro compound' OR 'perfluorooctanesulfonic acid'/exp OR 'perfluorooctanesulfonic acid' OR 'perfluorooctanoic acid'/exp OR 'perfluorooctanoic acid' OR polyfluoroalkyl OR perfluoroalkyl OR perfluorochemicals OR perfluorinated OR polyfluorinated OR pfos OR pfoa OR pfna OR pfda OR pfhxs OR pfuna OR pfosa OR pfdea) AND ('fertility'/exp OR 'fertility' OR 'infertility'/exp OR 'infertility' OR 'time to pregnancy'/exp OR 'time to pregnancy' OR 'reproduction'/exp OR 'reproduction' OR 'semen analysis'/exp OR 'semen analysis' OR 'sex hormone'/exp OR 'sex hormone')

Figure S1. Flowchart illustrating the study selection process

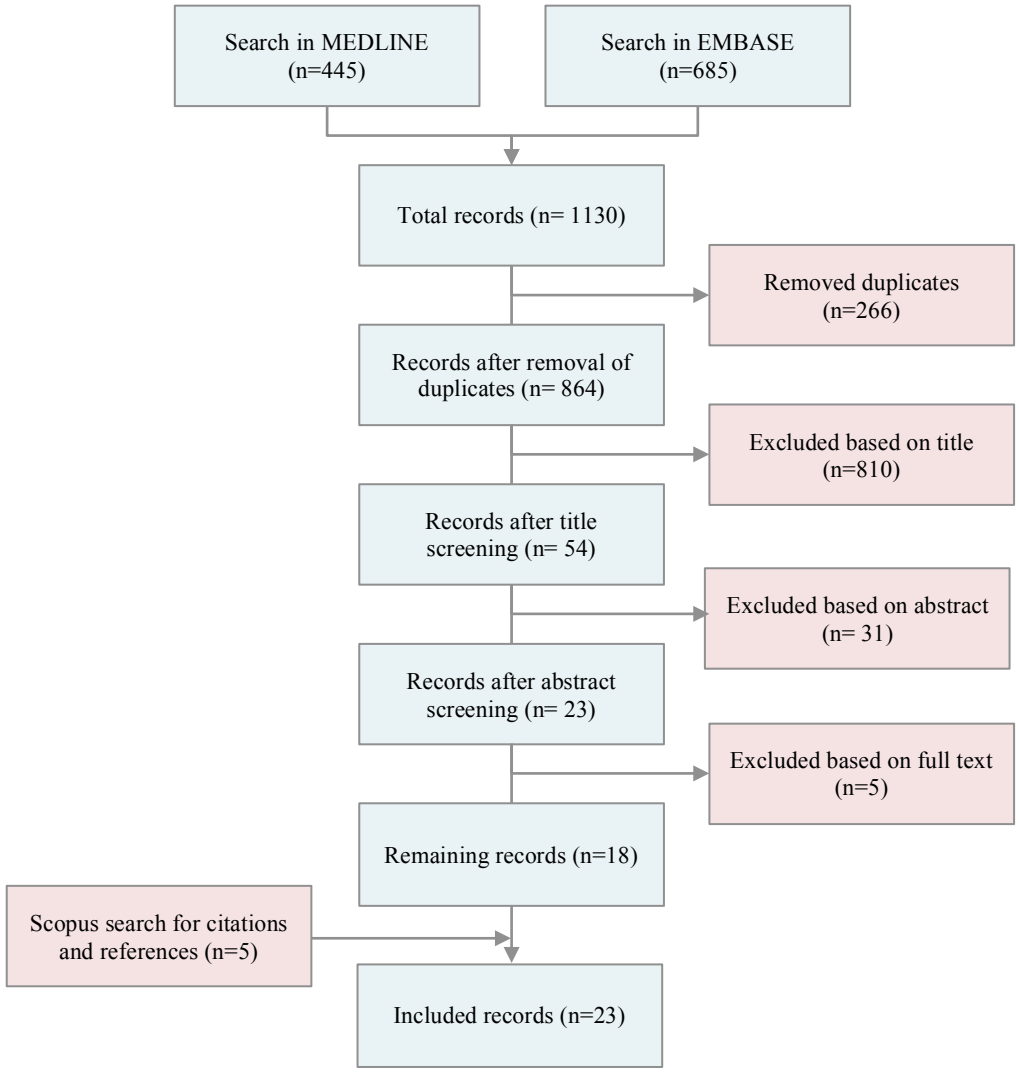

Table S1. Covariates included in studies of exposure to perfluoroalkyl and polyfluoroalkyl substances in men and reproductive hormones

	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	Lewis et al. 2015	Tsai et al. 2015	Den Hond et al. 2015
Body mass index	X	X	X			X	X	X	X	X
Smoking	X						X			X
Study site						X*				
Abstinence time						X				
Age	X	X	X			X		X	X	X
Alcohol consumption	X	X	X							
Caffeine						X				
Cotinine						X		X		
Fever past 3 months						X				
Ever urogenital or genital infections						X				
Testicular disorder						X				
Spillage						X				
Job seniority			X							
Years of observation			X							
Hour of blood sampling										
Socio-economic status, education, or income								X		X
Race/ethnicity								X		
High fat diet intake									X	
Environmental tobacco smoke										X

* Stratification

Table S2. Covariates included in studies of exposure to perfluoroalkyl and polyfluoroalkyl substances in men and semen quality

	Joensen et al. 2009	Raymer et al. 2012	Specht et al. 2012	Toft et al. 2012	Joensen et al. 2013	Leter et al. 2015	Governini et al. 2015	Buck Louis et al. 2015	Den Hond et al. 2015
Time to semen analysis	X*			X¶	X§			X	
Abstinence time	X†	X	X	X	X‖			X	
Spillage			X	X					
Age		X	X	X		X		X	X
Cotinine			X					X	
Smoking		X		X		X		X	X
Ever urogenital /genital infections			X	X					
BMI			X	X				X	X
Study site			X‡	X				X	
caffeine			X						
Fever past 3 months			X						
Testicular disorders			X						
Educational level									X
Environmental tobacco smoke									X

* Only motility
† Volume, concentration, and total sperm count
‡ Stratified
¶ Motility was restricted to samples analyzed within 1 hour
§ Only progressively motile parameter
‖ Only volume, concentration, total normal count and total count
In the study by Joensen et al. 2013, morphologically normal sperm was unadjusted. In the study by Joensen et al. 2009, morphology was unadjusted.

Table S3. Covariates included in analyses in studies of exposure to perfluoroalkyl and polyfluoroalkyl substances in women and reproductive outcomes

	Fei et al. 2009	Vestergaard et al. 2012	Whitworth et al. 2012	Buck Louis et al. 2013	Jørgensen et al. 2014	Vélez et al. 2015	Bach et al. 2015a	Bach et al. 2015b	Barret et al. 2015	Lewis et al. 2015	Tsai et al. 2015
Age	X	X	X	X	X	X	X	X	X	X	X
Pre-pregnancyBMI	X	X	X	X	X	X	X	X	X	X	X
Alcohol			X[†]						X		
Smoking		X			X				X		
Length of menstrual cycle		X									
Diseases affecting fecundability		X									
Oligospermia		X									
Maternal socio-economic status, educational level, or income	X						X	X		X	
Maternal alcohol consumption before pregnancy	X										
Paternal age	X										
Paternal education	X										
Sum of PFCs				X							
Serum cotinine				X						X	
Study site				X	X						
Gestational week at blood sampling		X[*]		X[c]	X						
Marital status									X		
Physical activity									X		
History of use of oral contraceptives									X		
Race/ethnicity										X	
High fat diet intake											X

[*] All samples were taken before pregnancy

[†] Only PFOA

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7-9
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8-9
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary material p. 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10, Supplementary material p. 3
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	21-25
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables 3-6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	26
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21-26
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	26-27
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	28

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097