

Perfluorinated Chemicals as Emerging Environmental Threats to Kidney Health: A Scoping Review

Supplemental Appendix: Study Protocol

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Protocol was developed in December 2017 by John W. Stanifer and Sarah Cantrell. The protocol is not registered with International Prospective Register of Systematic Reviews (PROSPERO) as they do not accept Scoping Reviews.

Introduction

1. Perfluoroalkyl and polyfluoroalkyl substances (PFASs) are a broad group of manufactured organic compounds that have been detected in soil, air, and water from all regions of the world, making them nearly ubiquitous as a pollutant (1).
2. Detectable levels of PFASs are found in most humans with nearly all adults in the United States demonstrating some level of exposure occurring through ingestion of contaminated soil, dust, food and food products, water or inhalation of contaminated air (2-6).
3. Increasing evidence has linked PFASs to carcinogenesis, endocrine, metabolic, and immunologic dyshomeostasis, and reproductive and developmental toxicity (7-12).
4. Despite increased recognition of their adverse human health effects, the role of PFASs on kidney health is not well understood.

Scoping Review Objective

To summarize and identify gaps in published evidence on the epidemiologic, pharmacokinetic, and toxicological impact of PFAS exposure on kidney health.

Methods

The objectives will be met by systematically searching PubMed, EMBASE, EBSCO Global Health, World Health Organization (WHO) Global Index Medicus (which includes regional indices, WHO Library Information System [WHOLIS], and Scientific Electronic Library Online [SciELO]), and Web of Science databases. We will collaborate with a specialized medical librarian to ensure the rigorous, transparent, and comprehensive search strategies.

Search Strategy

Concept 1: Perfluorinated Chemicals

- *Keywords—to be joined with “OR” and searched as text words*
 - PFAS
 - GenX
 - Perfluro*
 - Truncation will allow us to capture things like:
 - Perfluorinated
 - Perfluorochemicals
 - Perfluoroalkyl
 - Perfluorinated alkyl acids
 - Perfluoroalkyl sulfonate
 - Perfluoroalkyl carboxylate
 - Perfluorocarboxylic acid
 - Perfluorooctanoic acid
 - Perfluorooctane sulfonate
 - Perfluorooctane sulfonic acid

- Perfluorooctanesulfonic acid
 - Perfluorooctanesulfonamide
 - Perfluorooctanoate
 - Perfluorocaprylic acid
 - Perfluorohexane sulfonate
 - Perfluorohexanoic acid
 - Perfluorobutane sulfonate
 - Perfluorononanoic acid
 - Perfluorodecanoic acid
 - Perfluorooctyl
 - Perfluoroethers
 - Perfluoroalcohols
 - Perfluorooctanesulfonate
 - Perfluoroamines
 - Perfluorotripentylamine
 - Perfluoroketones
 - Perfluorosulfonic acids
 - Perfluorobutanesulfonic acid
- Polyfluoro*
 - Truncation will allow us to capture things like:
 - Polyfluorinated
 - Polyfluorochemicals
 - Polyfluoroalkyl
 - Polyfluoroalkyl compounds
 - Polyfluoroalkyl chemicals
 - Polyfluoroalkyl substances
 - mono polyfluoroalkyl phosphates
 - di-substituted polyfluoroalkyl phosphates
- Fluorotelomer alcohol
 - Teflon
 - Polytetrafluoroethylene
 - PFC
 - PFCs
 - PFOA
 - PFOS
 - PFAA
 - PENA
 - PFHxS
 - PFHxA
 - PFOSA
 - PFNA
 - PFDA
 - PFBS
 - PFTE

Concept 2: Kidney Function

- *Keywords—*

- Kidney
 - Renal
 - Glomerular filtration rate
 - GFR (title/abstract)
 - Blood urea nitrogen
 - BUN
 - AKI
 - CKD
 - ESRD
 - Nephropath*
 - Proteinuria
 - Albuminuria
 - Microalbuminuria
 - Macroalbuminuria
- Mesh:
 - “Kidney”[mh]
 - “Kidney Function Tests”[Mh]
 - “Kidney Diseases”[mh]
 - “Proteinuria”[Mh]

Search Limits:

- Study designs: All
- Search dates: 1990-present
- Population: Any—including animals
- Languages: Any

Databases to search:

- MEDLINE/PubMed
- EMBASE
- Web of Science
- Global Index Medicus from WHO
- Global Health from CABI

Search Strings

PubMed

- **Date: 2/22/2018**
- **Sort by: Publication Date**

#1	(perfluoro*[tw] OR polyfluoro*[tw] OR genx[tw] OR fluorotelomer alcohol[tw] OR teflon[tw] OR polytetrafluoroethylene[tw] OR PFAS[tiab] OR PFC[ti] OR PFCs[ti] OR	27,743
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	PFOA[ti] OR PFOS[ti] OR PFAA[ti] OR PENA[ti] OR PFHxS[ti] OR PFHxA[ti] OR PFOSA[ti] OR PFNA[ti] OR PFDA[ti] OR PFBS[ti] OR PFTE[ti])	
#2	("Kidney"[Mesh] OR "Kidney Diseases"[Mesh] OR "Kidney Function Tests"[Mesh] OR "Proteinuria"[Mesh] OR kidney[tw] OR renal[tw] OR glomerular filtration rate[tw] OR GFR[tiab] OR blood urea nitrogen[tw] OR BUN[tiab] OR AKI[tiab] OR CKD[tiab] OR ESRD[tiab] OR nephropath*[tw] OR proteinuria[tw] OR albuminuria[tw] OR microalbuminuria[tw] OR macroalbuminuria[tw])	1,076,066
	#1 AND #2	1,639

- **Date: 2/22/2018**
- **Sort by: Publication Date**

#1	(perfluoro*[tiab] OR polyfluoro*[tiab] OR genx[tiab] OR fluorotelomer alcohol[tiab] OR teflon[tiab] OR PFAS[tiab])	14,931
#2	("Kidney"[Mesh] OR "Kidney Diseases"[Mesh] OR "Kidney Function Tests"[Mesh] OR "Proteinuria"[Mesh] OR kidney[tiab] OR renal[tiab] OR glomerular filtration rate[tiab] OR blood urea nitrogen[tiab] OR nephropath*[tiab] OR proteinuria[tiab] OR albuminuria[tiab] OR microalbuminuria[tiab] OR macroalbuminuria[tiab])	1,035,684
#3	(metabolome OR metabolomics)	
	#1 AND #2	394
	Limit to 1990-present (Publication date from 1990/01/01)	295
	#1 AND #3	48

ADDITIONAL SEARCH PARAMETERS

#1	(perfluoro*[tiab] OR polyfluoro*[tiab] OR genx[tiab] OR fluorotelomer alcohol[tiab] OR teflon[tiab] OR PFAS[tiab])	
#2	(metabolome OR metabolomics)	
	#1 AND #2	
	Limit to 1990-present (Publication date from 1990/01/01)	48

EMBASE

- **Date: 2/22/2018**
- **Sort by: Publication Year**

#1	(perfluoro*:ab,ti OR polyfluoro*:ab,ti OR genx:ab,ti OR 'fluorotelomer alcohol':ab,ti OR teflon:ab,ti OR polytetrafluoroethylene:ab,ti OR pfas:ti OR pfc:ti OR pfc:ti OR pfoa:ti OR pfos:ti OR pfaa:ti OR pena:ti OR pfhxs:ti OR pfhxa:ti OR pfosa:ti OR pfna:ti OR pfda:ti OR pfbs:ti OR pfte:ti)	17,665
#2	('kidney'/exp OR 'kidney disease'/exp OR 'kidney function test'/exp OR 'proteinuria'/exp OR aki:ab,ti OR albuminuria:ab,ti OR 'blood urea nitrogen':ab,ti OR ckd:ab,ti OR esrd:ab,ti OR gfr:ab,ti OR 'glomerular filtration rate':ab,ti OR 'kidney'/exp OR 'kidney disease'/exp OR 'kidney function test'/exp OR 'proteinuria'/exp OR kidney:ab,ti OR macroalbuminuria:ab,ti OR microalbuminuria:ab,ti OR nephropath*:ab,ti OR	1,535,923

	proteinuria:ab,ti OR renal:ab,ti OR 'urea nitrogen blood level':ab,ti)	
	#1 AND #2	928

- **Date: 2/22/2018**
- **Sort by: Date**

#1	(perfluoro*:ab,ti OR polyfluoro*:ab,ti OR genx:ab,ti OR 'fluorotelomer alcohol':ab,ti OR teflon:ab,ti OR pfas:ti)	20,702
#2	('kidney'/exp OR 'kidney disease'/exp OR 'kidney function test'/exp OR 'proteinuria'/exp OR albuminuria:ab,ti OR 'blood urea nitrogen':ab,ti OR 'glomerular filtration rate':ab,ti OR kidney:ab,ti OR macroalbuminuria:ab,ti OR microalbuminuria:ab,ti OR nephropath*:ab,ti OR proteinuria:ab,ti OR renal:ab,ti OR 'urea nitrogen blood level':ab,ti)	1,532,794
	#1 AND #2	640
	Limit Publication Year 1990 to present	454

Global Health (on EBSCOhost)

- **Date of search: 2/22/2018**

#1	(perfluoro* OR polyfluoro* OR genx OR fluorotelomer alcohol OR teflon OR polytetrafluoroethylene OR PFAS OR PFC OR PFCs OR PFOA OR PFOS OR PFAA OR PENA OR PFHxS OR PFHxA OR PFOSA OR PFNA OR PFDA OR PFBS OR PFTE)	5,724
#2	(kidney OR renal OR glomerular filtration rate OR GFR OR blood urea nitrogen OR AKI OR CKD OR ESRD OR nephropath* OR proteinuria OR albuminuria OR microalbuminuria OR macroalbuminuria)	93,838
	#1 AND #2	139

- **Date of search: 2/22/2018**

#1	(perfluoro* OR polyfluoro* OR genx OR fluorotelomer alcohol OR teflon)	1,405
#2	(kidney OR renal OR glomerular filtration rate OR blood urea nitrogen OR nephropath* OR proteinuria OR albuminuria OR microalbuminuria OR macroalbuminuria)	87,824
	#1 AND #2	43
	Limit Publication Year 1990 to present	41

Global Index Medicus (WHO):

- Date searched: **2/22/2018**

	(tw:((perfluoro* OR polyfluoro* OR genx OR fluorotelomer alcohol OR teflon OR polytetrafluoroethylene OR PFAS OR PFC OR PFCs OR PFOA OR PFOS OR PFAA OR PENA OR PFHxS OR PFHxA OR PFOSA OR PFNA OR PFDA OR PFBS OR PFTE))) AND (tw:((kidney OR renal OR glomerular filtration rate OR GFR OR blood urea nitrogen OR AKI OR CKD OR ESRD OR nephropath* OR proteinuria OR albuminuria OR microalbuminuria OR macroalbuminuria)))	96
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- Date searched: **2/22/2018**

	(tw:((perfluoro* OR polyfluoro* OR genx OR fluorotelomer alcohol OR teflon))) AND (tw:((kidney OR renal OR glomerular filtration rate OR blood urea nitrogen OR nephropath* OR proteinuria OR albuminuria OR microalbuminuria OR macroalbuminuria)))	95
	Limit 1990 to present	23

Web of Science

- Date searched: **2/22/2018**

#1	(perfluoro* OR polyfluoro* OR genx OR fluorotelomer alcohol OR teflon OR polytetrafluoroethylene OR PFAS OR PFC OR PFCs OR PFOA OR PFOS OR PFAA OR PENA OR PFHxS OR PFHxA OR PFOSA OR PFNA OR PFDA OR PFBS OR PFTE)	74,186
#2	(kidney OR renal OR glomerular filtration rate OR GFR OR blood urea nitrogen OR AKI OR CKD OR ESRD OR nephropath* OR proteinuria OR albuminuria OR microalbuminuria OR macroalbuminuria)	890,885
	#1 AND #2	947

- Date searched: **2/22/2018**

#1	(perfluoro* OR polyfluoro* OR genx OR "fluorotelomer alcohol" OR teflon)	45,605
#2	(kidney OR renal OR glomerular filtration rate OR blood urea nitrogen OR nephropath* OR proteinuria OR albuminuria OR microalbuminuria OR macroalbuminuria)	886,253
	#1 AND #2	450
	Limit to 1990 to present	425

Eligibility of Studies and Study Selection

Studies will be selected in a two-stage process. First, reviewers will scan the titles and abstracts using the following inclusion criteria:

1. The study investigates the toxicology of PFASs in animal or humans; or
2. The study evaluates the epidemiology of PFASs in humans, with an exposure and outcome reported; or
3. The study evaluates the pharmacokinetics of PFASs in humans

Review articles, editorials, case reports, and studies only reporting methodology for chemical laboratory analyses or identification will be excluded. However, the works cited of review articles will be manually reviewed for additional studies to include in the full-text review. Studies meeting any one of the inclusion criteria will be included for full-text review. Reviewers will conduct a full-text review using the following inclusion criteria for pharmacokinetics, toxicology, and epidemiology studies of PFASs:

1. Pharmacokinetic studies must be conducted in humans and must report an outcome related to the pharmacokinetic role of the kidneys in metabolism, tissue distribution, or clearance and elimination of PFASs in humans.
2. Epidemiological studies must be conducted in humans and must report a measure of exposure to PFASs and report a kidney-related outcome (e.g. prevalence of kidney disease, changes in kidney function, mortality related to kidney diseases).
3. Toxicological studies can be conducted in animals or humans. They must report a PFAS-related kidney outcome including clinical outcome (e.g. prevalence of kidney disease, changes in kidney function, mortality related to kidney diseases), histological outcome (e.g. pathological evidence of alterations in kidney tissue), molecular outcome (e.g. disturbances in cellular pathways of kidney cell lines or tissue), or metabolic outcome (e.g. alterations of metabolic pathways with direct or indirect links to kidney function or kidney diseases).

Data Extraction

After identifying studies for final inclusion, reviewers will independently extract data into standard forms to facilitate data-charting, data synthesis, and results reporting. The standard data form will be composed of study's investigators, years of conduct, design, setting, population, study size, PFASs studied, variables for measuring PFAS exposure, kidney-related outcomes, major findings, and major limitations. In cases of missing or incomplete data, authors will be contacted for additional information. Errors in data extraction will be resolved by joint review of the original articles.

References

1. Giesy JP, Kannan K. Global distribution of perfluorooctane sulfonate in wildlife. *Environ Sci Technol.* 2001;35(7):1339-42.
2. Buck RC, Franklin J, Berger U, Conder JM, Cousins IT, de Voogt P, et al. Perfluoroalkyl and polyfluoroalkyl substances in the environment: terminology, classification, and origins. *Integr Environ Assess Manag.* 2011;7(4):513-41.
3. Perez F, Nadal M, Navarro-Ortega A, Fabrega F, Domingo JL, Barcelo D, et al. Accumulation of perfluoroalkyl substances in human tissues. *Environ Int.* 2013;59:354-62.
4. Calafat AM, Wong LY, Kuklennyik Z, Reidy JA, Needham LL. Polyfluoroalkyl chemicals in the U.S. population: data from the National Health and Nutrition Examination Survey (NHANES) 2003-2004 and comparisons with NHANES 1999-2000. *Environ Health Perspect.* 2007;115(11):1596-602.
5. Kannan K, Corsolini S, Falandysz J, Fillmann G, Kumar KS, Loganathan BG, et al. Perfluorooctanesulfonate and related fluorochemicals in human blood from several countries. *Environ Sci Technol.* 2004;38(17):4489-95.
6. Lewis RC, Johns LE, Meeker JD. Serum Biomarkers of Exposure to Perfluoroalkyl Substances in Relation to Serum Testosterone and Measures of Thyroid Function among Adults and Adolescents from NHANES 2011-2012. *Int J Environ Res Public Health.* 2015;12(6):6098-114.
7. Butenhoff JL. Translating toxicological information on perfluoroalkyls for human risk assessment. *Reprod Toxicol.* 2012;33(4):594-5.
8. Jensen AA, Leffers H. Emerging endocrine disruptors: perfluoroalkylated substances. *Int J Androl.* 2008;31(2):161-9.
9. Kudo N, Kawashima Y. Toxicity and toxicokinetics of perfluorooctanoic acid in humans and animals. *J Toxicol Sci.* 2003;28(2):49-57.
10. Li K, Gao P, Xiang P, Zhang X, Cui X, Ma LQ. Molecular mechanisms of PFOA-induced toxicity in animals and humans: Implications for health risks. *Environ Int.* 2017;99:43-54.
11. Steenland K, Fletcher T, Savitz DA. Epidemiologic evidence on the health effects of perfluorooctanoic acid (PFOA). *Environ Health Perspect.* 2010;118(8):1100-8.
12. Das KP, Wood CR, Lin MT, Starkov AA, Lau C, Wallace KB, et al. Perfluoroalkyl acids-induced liver steatosis: Effects on genes controlling lipid homeostasis. *Toxicology.* 2017;378:37-52.