

Perfluorinated Chemicals as Emerging Environmental Threats to Kidney Health

A Scoping Review

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Abstract

Background and objectives Per- and polyfluoroalkyl substances (PFASs) are a large group of manufactured nonbiodegradable compounds. Despite increasing awareness as global pollutants, the impact of PFAS exposure on human health is not well understood, and there are growing concerns for adverse effects on kidney function. Therefore, we conducted a scoping review to summarize and identify gaps in the understanding between PFAS exposure and kidney health.

Design, setting, participants, & measurements We systematically searched PubMed, EMBASE, EBSCO Global Health, World Health Organization Global Index, and Web of Science for studies published from 1990 to 2018. We included studies on the epidemiology, pharmacokinetics, or toxicology of PFAS exposure and kidney-related health, including clinical, histologic, molecular, and metabolic outcomes related to kidney disease, or outcomes related to the pharmacokinetic role of the kidneys.

Results We identified 74 studies, including 21 epidemiologic, 13 pharmacokinetic, and 40 toxicological studies. Three population-based epidemiologic studies demonstrated associations between PFAS exposure and lower kidney function. Along with toxicology studies ($n=10$) showing tubular histologic and cellular changes from PFAS exposure, pharmacokinetic studies ($n=5$) demonstrated the kidneys were major routes of elimination, with active proximal tubule transport. In several studies ($n=17$), PFAS exposure altered several pathways linked to kidney disease, including oxidative stress pathways, peroxisome proliferators-activated receptor pathways, NF-E2-related factor 2 pathways, partial epithelial mesenchymal transition, and enhanced endothelial permeability through actin filament modeling.

Conclusions A growing body of evidence portends PFASs are emerging environmental threats to kidney health; yet several important gaps in our understanding still exist.

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Introduction

Per- and polyfluoroalkyl substances (PFASs) are a large group of >3000 compounds used to provide stain- and grease-repelling properties to consumer products, including textiles, papers, and food packaging (1). PFASs are also used in aqueous fire-fighting foams used for distinguishing fires near airports and military bases (1). PFASs have been detected in soil, air, and water from all regions of the world, with bioaccumulation across entire ecological food chains. As such, PFASs are now recognized as globally ubiquitous pollutants.

Humans are exposed to PFASs through ingestion of contaminated soil, food, and water, and inhalation of contaminated air (1,2). Detectable levels are found in most humans, and in the United States, nearly all adults have demonstrated some level of PFAS exposure (2). Even with efforts to reduce or eliminate production, the drinking water for >6 million United States residents still exceeds the lifetime health advisory for both perfluorooctane sulfonate (PFOS) and

perfluorooctanoic acid (PFOA) (3). Likewise, because of an increase in large-scale production in countries such as China, human exposure remains high worldwide (4). Furthermore, pressure to phase out some PFASs, such as PFOS and PFOA, has led to precipitous increases in the production of unstudied and unregulated novel replacement compounds such as perfluoroether carboxylic acids (*e.g.*, GenX, Adona), chlorinated polyfluoroether sulfonates (*e.g.*, F-53B), and fluorotelomer alcohols (*e.g.*, Novec 1230).

Despite widespread exposure, the impact of PFASs on human health is only recently gaining awareness. As organic isomers with charged functional groups, such as sulfonic acids, carboxylic acids, and phosphonic acids (Figure 1), PFASs are increasingly linked to carcinogenesis; disruption of endocrine, metabolic, and immunologic pathways; and reproductive and developmental toxicity (5). Most notably, the C8 Health Project—a study convened as part of a legal settlement against a Mid-Ohio Valley manufacturer to

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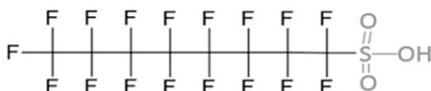
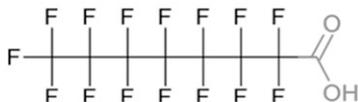
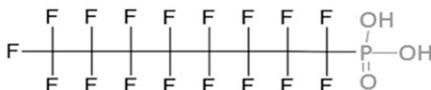
Perfluorooctane sulfonic acid (PFOS)**Perfluorooctanoic acid (PFOA)****Perfluorooctyl phosphonic acid (C8-PFPA)**

Figure 1. | Molecular structure for PFASs with sulfonic acid (PFOS), carboxylic acid (PFOA), and phosphonic acid (PFPA) moieties.

investigate the human health effects of PFAS exposure—demonstrated evidence linking PFOA exposure with testicular and genitourinary cancers, hyperlipidemia, thyroid diseases, ulcerative colitis, and gestational hypertension (6). Given their chemical properties and biologic effects, plausible concerns about PFAS exposure causing adverse kidney consequences are growing; yet, the relationship between PFAS exposure and kidney function is not well understood. Therefore, we conducted a scoping review to summarize existing knowledge and identify gaps in the epidemiologic, pharmacokinetic, and toxicological data on PFAS exposure and kidney-related health.

Materials and Methods

Search Strategy

With the assistance of a specialized medical librarian, we iteratively developed a comprehensive search strategy for the PubMed, EMBASE, EBSCO Global Health, World Health Organization (WHO) Global Index Medicus (which includes regional indices, WHO Library Information System, and Scientific Electronic Library Online), and Web of Science databases. We used Boolean logic with search terms including a combination of relevant subject headings and text words for kidney disease (*e.g.*, kidney diseases, renal, albuminuria, *etc.*) and PFASs (*e.g.*, perfluoro, polyfluoro, PFAS, *etc.*). We used controlled vocabularies (*e.g.*, medical subject heading terms) to identify synonyms. We applied no language or study design restrictions, and we included both human and animal studies. We searched for studies published from January 1 1990 to February 22, 2018. We supplemented the searches by manually reviewing the reference lists from review articles. The detailed search parameters are available in the study protocol (Supplemental Appendix). The study protocol was developed in December 2017; it is not registered in the International Prospective Register of Systematic Reviews as scoping reviews are not eligible for inclusion.

Study Selection

We screened the title and abstract for all identified studies. To be included for full-text review, each study had

to: (1) investigate the toxicology of PFASs in animals or humans, or (2) evaluate the epidemiology or pharmacokinetics of PFASs in humans. Review articles, editorials, case reports, and studies only reporting methodology for chemical analyses and identification were excluded. Studies were included in the final scoping review if full-text review demonstrated they investigated the pharmacokinetics, toxicology, or epidemiology of PFASs and reported a kidney-related outcome, including clinical outcomes (*e.g.*, prevalence of kidney disease, changes in kidney function, mortality related to kidney diseases), histologic outcomes (*e.g.*, pathologic evidence of alterations in kidney tissue), molecular outcomes (*e.g.*, disturbances in cellular pathways of kidney cell lines or tissue), or metabolic outcomes (*e.g.*, alterations of metabolic pathways with known links to kidney function or kidney diseases), or outcomes related to the pharmacokinetic role of the kidneys in metabolism, tissue distribution, or clearance and elimination of PFASs in humans.

Data Extraction

Two investigators independently reviewed and extracted data into standard forms to facilitate data-charting, data synthesis, and results reporting. Errors in data extraction were resolved by joint review of the original articles. In instances where insufficient data were presented in the article (*e.g.*, abstracts), we contacted the authors for additional information. For epidemiologic studies, we extracted each study's investigators, years of conduct, design, setting, population, study size, PFASs studied, methods for assessing PFAS exposure, kidney-related outcomes, and major findings. For pharmacokinetic studies, we extracted each study's investigators, year of publication, PFASs studied, pharmacokinetic parameters investigated, and major findings. For toxicology studies, we extracted each study's investigators, year of publication, design and animal model or cell line, PFASs studied, and major findings. We classified toxicology studies into mechanistic domains (clinical, histologic, cellular, or metabolic) on the basis of the major findings.

Results

We sought to identify epidemiologic, pharmacokinetic, or toxicological studies on PFAS exposure and kidney-related health. We identified 210 studies published between 1991 and 2018 meeting inclusion criteria for full-text review (Figure 2). We excluded 136 studies that were pharmacokinetic studies conducted only in animals or not describing the pharmacokinetic role of the kidneys ($n=84$; 61%), did not report a kidney-related outcome ($n=27$; 20%), or did not investigate PFAS exposure ($n=25$; 18%). After full-text review, we included 74 studies, of which 21 (28%) were epidemiologic, 13 (18%) were pharmacokinetic, and 40 (54%) were toxicological studies.

Human Epidemiologic Studies

We identified 21 epidemiologic studies, all published between 2003 and 2017, investigating PFAS exposure and kidney-related health, with 11 studies directly assessing exposure through serum concentrations and ten studies indirectly estimating exposure (Table 1). All of the studies

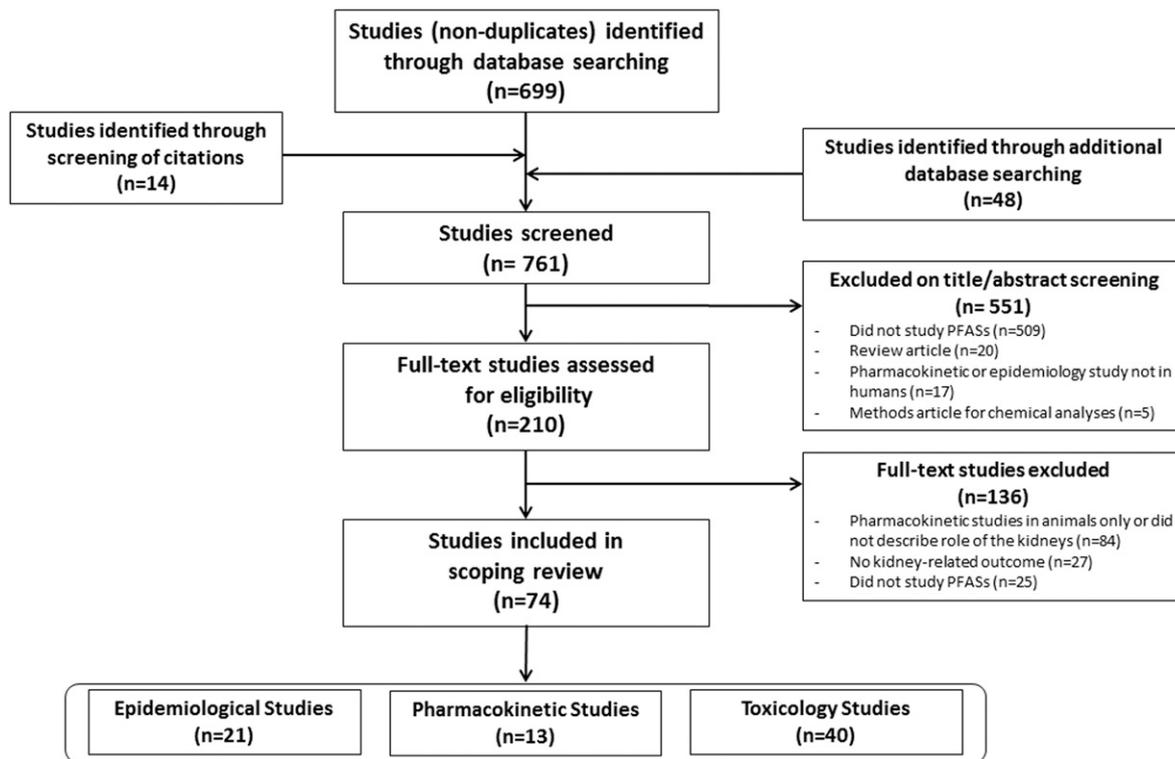


Figure 2. | Flow diagram of study selection.

investigated PFOA and/or PFOS; a few studies additionally investigated perfluorohexane sulfonate ($n=4$) or perfluorononanoic acid (PFNA) ($n=2$). All but two studies were conducted in the United States (17,21), and all but one were cross-sectional, retrospective cohort, or ecological studies (25). In six studies, PFAS exposure was associated with increased mortality from kidney-related cancers (18–22,24); however, the strength of the association varied, with standardized mortality ratios ranging from 1.07 to 12.8 (Figure 3).

We identified 14 studies investigating PFAS exposure and kidney function, of which three (21%) used indirect exposure assessments and 11 (79%) used directly measured PFAS serum concentrations, with two additionally using indirect model-based estimates. None of the studies using indirect exposure estimates demonstrated associations with CKD prevalence or kidney function, including a 30-year prospective study of only 53 adults finding no association with serum creatinine (7,11,25–27). We identified no studies investigating proteinuria outcomes.

Of the studies using direct measures of exposure, five reported significant associations between PFAS exposure and lower eGFR or greater CKD prevalence (7–11), including three population-based studies from the National Health and Nutrition Examination Survey (NHANES) (8–10). In a cross-sectional study of >4500 adults from NHANES, significant inverse associations between serum concentrations of PFOA and PFOS and eGFR were observed, with the highest quartile of exposure associated with a 5.7 and 6.7 ml/min per 1.73 m² lower eGFR for PFOA and PFOS exposure, respectively (9). Likewise, in a

cross-sectional study of 6305 adults from NHANES, serum PFOS concentrations were associated with increased odds (odds ratio, 1.15; 95% confidence interval, 1.07 to 1.25) of prevalent CKD (10). Although children have greater PFAS exposure compared with adults, we identified only two epidemiologic studies investigating kidney-related health among children (8,11). In a cross-sectional study of 1960 children from NHANES, a significant inverse association between serum concentrations of PFOA and PFOS and eGFR was observed, with the highest quartile of exposure associated with a 6.61 and 9.47 ml/min per 1.73 m² lower eGFR for PFOA and PFOS exposure, respectively (8).

Human Pharmacokinetic Studies

We identified 13 pharmacokinetic studies, published between 2005 and 2018, investigating the role of the kidneys in metabolism, tissue distribution, or elimination of PFASs in humans (Table 2). All of the studies ($n=13$) investigated PFOA or PFOS; a few studies additionally investigated perfluorohexanoic acid ($n=4$) and perfluorobutane sulfonate ($n=2$). Several studies ($n=5$) demonstrated variation in pharmacokinetic parameters on the basis of carbon-chain length, functional group, and isomer forms (28,30,33,37,40). Three studies demonstrated that after absorption PFASs distribute widely to the serum, liver, and kidneys as well as placenta and cord serum (29,34,35), with one showing perfluorobutyrate, perfluorododecanoic acid, and perfluorodecanoic acid highly concentrated in the kidneys (35).

Likewise, elimination varied on the basis of carbon-chain length, functional group, and isomer forms. Many studies

Table 1. Human epidemiologic studies (1990–2018) investigating per- and polyfluoroalkyl substances exposure and kidney health

Authors	Study Years	Study Design	Setting	Population	Sample Size	Exposure	Kidney Outcome	Major Findings	Summary Notes
Direct exposure assessments (n=11)									
Dhingra <i>et al.</i> (7)	1952–2012	Cross-sectional	Community surrounding manufacturer	Adults living in eligible area	29,499	PFOA ^a	eGFR	Association present	Negative trend in eGFR across measured serum PFOA quintiles ($\beta = -0.64$ to -1.03 ; $P = 0.01$)
Kataria <i>et al.</i> (8)	2003–2010	Cross-sectional	NHANES	Children 12–19 yr old	1960	PFOS, PFOA, PFHxS, PFNA	eGFR	Association present	Increased odds (OR, 2.0; 95% CI, 1.4 to 2.9) for lower eGFR with increasing exposure levels for PFOS and PFOA
Shankar <i>et al.</i> (9)	1999–2008	Cross-sectional	NHANES	Adults >20 yr old	4587	PFOA, PFOS	eGFR, prevalent CKD	Association present	eGFR: 5.7 and 6.7 ml/min per 1.73 m ² lower with increasing exposure Prevalent CKD: OR, 1.7 (95% CI, 1.0 to 2.9) and 1.8 (95% CI, 1.0 to 3.3) for PFOA and PFOS
Vearrier <i>et al.</i> (10)	2003–2008	Cross-sectional	NHANES	Adults	6305	PFOA	Prevalent CKD, incident ESKD	Association present	Prevalent CKD: OR, 1.2 (95% CI, 1.1 to 1.3); incident ESKD: OR, 1.9 (95% CI, 1.2 to 3.0)
Watkins <i>et al.</i> (11)	1989–2006	Retrospective cohort	Community surrounding manufacturer	Children (1–18 yr old) living in eligible area	9660	PFOA, PFOS, PFHxS, PFNA ^a	eGFR	Association present	Negative trend in eGFR (-0.73 to -1.34 ml/min per 1.73 m ²) with increasing exposure to each PFAS
Conway <i>et al.</i> (12)	2017	Cross-sectional	Community surrounding manufacturer	Adults living in eligible area	53,650	PFOA, PFOS, PFHxS, PFNA	eGFR	No observed association	No association with any PFAS
Emmett <i>et al.</i> (13)	2003–2005	Cross-sectional	Community surrounding manufacturer	Adults and children living in eligible areas	371	PFOA	Serum creatinine	No observed association	–
Olsen <i>et al.</i> (14)	2003	Cross-sectional	Occupational	Adult employees	518	PFOS	Serum creatinine	No observed association	–
Olsen <i>et al.</i> (15)	2012	Cross-sectional	Occupational	Male employees	506	PFOA, PFOA	eGFR, prevalent CKD	No observed association	No association with eGFR or prevalent CKD
Steenland <i>et al.</i> (16)	2005–2006	Cross-sectional	Community surrounding manufacturer	Adults living in the eligible area	54,951	PFOA, PFOS	Serum creatinine	No observed association	No observed association for PFOA or PFOS
Zhou <i>et al.</i> (17)	2013	Cross-sectional	Community surrounding manufacturer (China)	Manufacturer employees living in eligible area	39	PFOA, PFOS, PFHxS	Serum creatinine	No observed association	No observed association for PFOA, PFOS, or PFHxS
Indirect exposure assessments (n=10)									
Alexander <i>et al.</i> (18)	1961–1997	Retrospective cohort	Occupational	Adult employees	2083	PFOS	Genitourinary and kidney cancer	Association present	Genitourinary and kidney cancer: SMR, 12.8 (95% CI, 2.6 to 37.4)

Table 1. (Continued)

Authors	Study Years	Study Design	Setting	Population	Sample Size	Exposure	Kidney Outcome	Major Findings	Summary Notes
Barry <i>et al.</i> (19)	1952–2011	Retrospective cohort	Community surrounding manufacturer	Adults living in eligible area	32,254	PFOA	Kidney cancer	Association present	Kidney cancer: HR, 1.1 (95% CI, 1.0 to 1.2) per each unit increase in PFOA
Consonni <i>et al.</i> (20)	1950–2008	Retrospective cohort	Community surrounding manufacturer	Male employees	5879	PFOA	Mortality from kidney cancer	Association present	Kidney cancer: SMR, 1.7 (95% CI, 0.8 to 3.1)
Mastrantonio <i>et al.</i> (21)	1980–2013	Retrospective cohort (ecological)	Community surrounding manufacturer	High-risk districts	24 districts	PFOA, PFOS	Mortality from kidney cancer	Association present	Kidney cancer: SMR, 1.1 (95% CI, 0.9 to 1.2)
Steenland <i>et al.</i> (22)	1979–2004	Retrospective cohort	Occupational	Adult employees	5791	PFOA ^a	Mortality from kidney cancer	Association present	Kidney cancer: SMR, 1.3 (95% CI, 0.7 to 2.2)
Vieira <i>et al.</i> (23)	1996–2005	Retrospective cohort (ecological)	Community surrounding manufacturer	High-risk districts, counties	Six water districts, 13 counties	PFOA	Incident kidney cancer	Association present	Kidney cancer: OR, 2.0 (95% CI, 1.0 to 3.9)
Leonard <i>et al.</i> (24)	1948–2002	Retrospective cohort	Occupational	Adult employees	6027	PFAS, not specified	Mortality from kidney cancer, nephritis, or nephrosis	Association present (kidney cancer) No observed association (nephritis or nephrosis)	Kidney cancer: SMR, 1.5 (95% CI, 0.8 to 2.7)
Costa <i>et al.</i> (25)	1978–2007	Prospective cohort	Occupational	Male employees	53	PFOA	Serum creatinine	No observed association	–
Dhingra <i>et al.</i> (26)	1952–2011	Retrospective cohort	Community surrounding manufacturer	Adults living in eligible area	28,240	PFOA ^a	Prevalent CKD	No observed association	–
Raleigh <i>et al.</i> (27)	1947–2002	Retrospective cohort	Occupational	Adult employees	9027	Ammonium PFOA, PFOA	Mortality from kidney cancer, CKD	No observed association	No observed associations for ammonium PFOA or PFOA

PFOA, perfluorooctanoic acid; NHANES, The National Health and Nutrition Examination Survey; PFOS, perfluorooctane sulfonate; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoic acid; OR, odds ratio; 95% CI, 95% confidence interval; PFAS, per- and polyfluoroalkyl substances; SMR, standardized mortality ratio; HR, hazard ratio.

^aStudy used model-predicted cumulative serum concentrations as measure of exposure.

($n=5$) demonstrated the kidneys were major routes of elimination, especially for PFASs with short carbon-chain lengths (fewer than eight carbon atoms), carboxylic acid function groups, or branched isomer forms (33,36–38,40). $t_{1/2}$ ranged from 1.7 to 14.7 years, with kidney elimination affected by active secretion and reabsorption in the proximal tubules (37–40). Three studies demonstrated the basolateral and apical uptake of PFASs substances into proximal tubules was mediated by transporters of the solute-carrier protein family, particularly organic anion transporter (OAT)1 and OAT3 on the basolateral side, and OAT4 and urate transporter 1 (URAT1) on the apical side (38–40). Unlike other species, although men demonstrate longer $t_{1/2}$ compared with women, it remains unclear the extent to which the proximal tubule handling of PFASs is regulated through sex hormones (32,36).

Toxicology Studies

We identified 40 toxicology studies, published between 1991 and 2017, investigating PFAS exposure and kidney-related outcomes (Table 3). Among the 40 studies, 17 (40%) investigated clinical and/or histologic outcomes, 13 (33%) investigated cellular and/or histologic outcomes, and ten (25%) investigated metabolic outcomes. Most were experimental or observational animal studies, either alone ($n=32$)

or with *in vitro* models ($n=2$). A few studies used *in vitro* models alone ($n=5$). One study conducted metabolomic profiling among humans (77). Most of the studies investigated PFOA ($n=15$), PFOS ($n=21$), or both, but several ($n=14$) also studied perfluorobutane sulfonate, PFNA, perfluorododecanoic acid, perfluorohepanoic acid, perfluorohexanoic acid, perfluoroundecanoic acid, and fluorotelomer precursors.

Clinical and Histologic Findings

Several experimental animal studies ($n=8$) reported short-term clinical effects related to PFAS exposure, with most studies showing small changes in BUN and/or creatinine concentrations across a wide range of exposure doses (42,43,45,47,48,59,79,80). However, the short-term clinical effects were variable, with some animal studies ($n=3$) showing no changes in BUN or creatinine at exposure doses as high as 600 mg/kg for PFOA (41,44,46), and others showing increased concentrations of both BUN and creatinine at exposure doses as low as 0.05–1.00 mg/kg for perfluoroundecanoic acid and perfluorododecanoic acid (47).

Histologically, experimental studies ($n=12$) demonstrated several changes across a range of doses related to short- and long-term PFAS exposure. The most frequently observed abnormalities were tubular epithelial

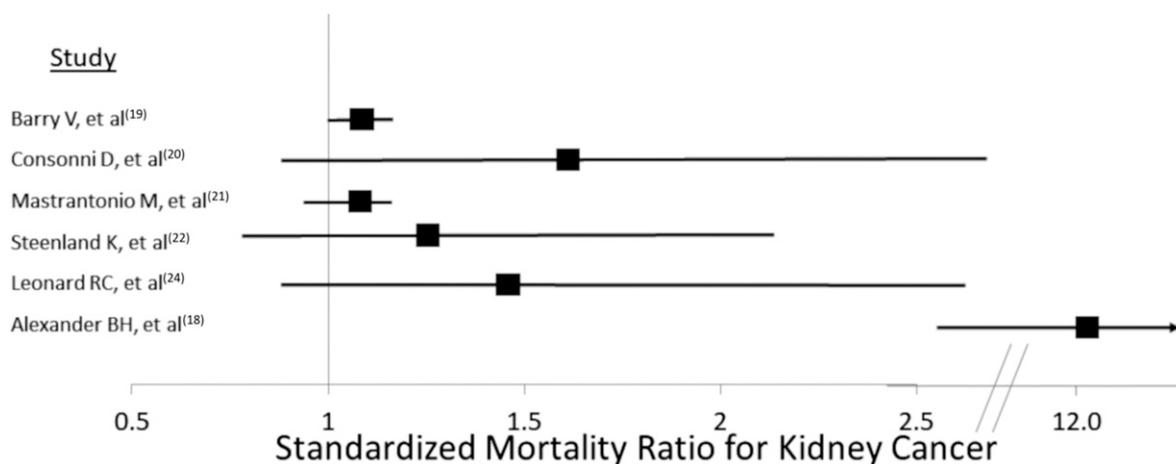


Figure 3. | Forest plot of studies demonstrating standardized mortality ratios associated with PFAS exposure.

hypertrophy or hyperplasia accompanied by increased kidney weights (50,51,53,55). Cytosolic changes of tubular epithelial cells, cortical and medullary congestion, with and without interstitial inflammation, focal papillary edema, fibrosis with increased collagen deposition, increased apoptotic cell death, and signs of tubular regeneration were also observed with PFAS exposure, particularly PFOS (44,52,58,59). Four studies showed high-dose exposure resulted in acute kidney toxicity, including early death from kidney failure, moderate to severe papillary necrosis, and glomerular changes with anasarca (44,48–50). One experimental study demonstrated that maternal exposure to PFOS and PFNA led to fewer nephrons and early-life hypertension among rat offspring (57), a finding consistent with human epidemiologic studies linking *in utero* exposure with lower birth weights (81–83). Five studies, three of which were conducted by manufacturers and included low-dose exposure, demonstrated no histologic changes in the kidneys (43,45,46,51,56).

Cellular Findings

Several studies linked PFAS exposure to increased oxidative stress in the kidneys, including enhanced expression of mitochondrial transport chain proteins (63,70,79), DNA damage (66), reduced cellular proliferation (66), and/or apoptosis (58,59,62). In six studies, a key pathway involved oxidative stress *via* the disruptive effects on peroxisome proliferators-activated receptors (PPAR) and their downstream functions (58–61,63,64). Two studies demonstrated that in the kidneys, exposure to PFOA dysregulated PPAR α and PPAR γ (60,61), key nuclear receptor hormones highly expressed in the proximal tubules and involved in adipogenesis, lipid metabolism, glucose homeostasis, and cell growth and differentiation. Three *in vitro* studies demonstrated kidney tubular epithelial (KTE) cells exposed to PFOS had sharp increases in apoptosis accompanied by fibrosis *via* a Sirt1-mediated PPAR γ deacetylation (58,59,61).

Other pathogenic pathways included PFASs' ability to induce dedifferentiation of KTE cells with partial epithelial mesenchymal transition (EMT), their role in upregulating antioxidant transcription factor NF-E2-related factor 2

(Nrf2), and their disrupting effects on epithelial cell junctions and permeability. Although debate exists as to the role of EMT in kidney fibrogenesis *in vivo*, two *in vitro* studies of KTE cells showed PFOS exposure induced EMT and cell migrations *via* Sirt1-mediated mechanisms, a finding consistent with prior studies linking Sirt1 to EMT programs and kidney fibrosis (58). Likewise, other studies reported significant upregulation of Nrf2 and its target gene expression in response to oxidative stress caused by PFOS exposure, with the zebrafish models demonstrating that sulforaphane, a Nrf2 inducer, attenuated the reactive oxygen species accumulation and gene expression changes (84). Although Nrf2 induction is a key defense for combating oxidative damage from chemical toxicity in the kidneys, few studies investigated the link between PFAS exposure and Nrf2 pathways. PFASs were also shown to interrupt KTE intercellular communication at gap junctions, and enhance endothelial permeability in human microvascular endothelial cells through actin filament remodeling, both of which are key features of podocyte injury (67,68).

Metabolic Findings

We identified ten studies ($n=10$) profiling numerous nascent metabolic changes related to PFAS exposure (71–80). Animal studies demonstrated that PFAS exposure led to derangements in lipid metabolism (73,74,78,80), glucose and mitochondrial energy metabolism (71–74,78,79), fatty acid metabolism and antioxidant (75,80), sex hormone homeostasis, and amino acid metabolism (71,72,76,78–80). In the only human study, metabolomic profiling on 181 Chinese men demonstrated lipid and amino acid metabolism, xenobiotic detoxifying, and metabolic pathways directly linked to CKD pathogenesis, including glutathione metabolism and nitric oxide generation, were disrupted by PFAS exposure (77).

Discussion

PFASs are globally pervasive environmental pollutants with widespread human exposure, and a growing body of evidence indicates PFAS exposure has adverse kidney consequences. Studies demonstrated many adverse

Table 2. Studies (1990–2018) investigating the pharmacokinetic role of the kidneys in metabolism, tissue distribution, or clearance and elimination of per- and polyfluoroalkyl substances in humans

Authors	Year	Exposure	Pharmacokinetic Properties	Major Findings
Beesoon <i>et al.</i> (28)	2015	PFOA, PFOS	Protein-binding; elimination	Key differences in protein-binding, volume of distribution, and kidney clearance related to different PFAS isomeric forms
Fàbrega <i>et al.</i> (29)	2013	PFOA, PFOS	Volume of distribution; tissue concentrations	Tissue concentration varied by organ (liver > plasma > kidney) Model-based predictions underestimate actual kidney concentrations
Fu <i>et al.</i> (30)	2016	PFOA, PFOS, PFHxA	Elimination	Highlighted possible nonkidney elimination pathways; $t_{1/2}$ (by daily clearance rates) ranged from 4.1 to 14.7 yr; $t_{1/2}$ (by annualized decline rates) ranged from 1.7 to 3.6 yr
Harada <i>et al.</i> (31)	2005	PFOA, PFOS	Elimination	Kidney clearance one fifth of the total clearance No observed sex differences in rate of clearance
Ingelido <i>et al.</i> (32)	2018	PFBA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUdA, PFDoA, PFBS, PFHxS, PFOS	Elimination	Elimination not mediated by OATP1A2 proximal tubule transporter
Olsen <i>et al.</i> (33)	2007	PFOA, PFOS, PFHxS	Elimination	$t_{1/2}$ ranged from 3.8 to 8.5 yr Kidney clearance effected by isomeric forms
Pan <i>et al.</i> (34)	2017	24 target PFASs, including Cl-PFESA	Protein-binding; volume of distribution	Placental transfer with high cord sera concentrations Higher placental transfer efficiencies associated with lower eGFR
Pérez <i>et al.</i> (35)	2013	PFOA, PFOS, PFBS, PFHxA	Volume of distribution; tissue concentrations	Tissue concentration varied by organ, with PFBS, PFDoDA, and PFDA demonstrating highest concentrations in the kidneys
Russell <i>et al.</i> (36)	2015	PFOA	Elimination	$t_{1/2}$ was 2.4 yr, slightly longer for men compared with women Elimination occurred almost exclusively by the kidneys
Shi <i>et al.</i> (37)	2016	Cl-PFESA	Elimination	Suggest Cl-PFESA is most bio-persistent known PFAS in humans, with median $t_{1/2}$ for kidney clearance of 280 yr and total body elimination of 15.3 yr
Worley <i>et al.</i> (38)	2017	PFOA	Metabolism; elimination	Glomerular filtration and active reabsorption and secretion by the proximal tubules <i>via</i> basolateral (<i>via</i> OAT1 and OAT3) and apical (<i>via</i> OAT4 and URAT1) uptake transporters
Yang <i>et al.</i> (39)	2010	PFOA	Elimination	Active reabsorption and secretion by the proximal tubules <i>via</i> apical OAT4 and URAT1; proximal tubular handling affected by extracellular pH and isomeric forms
Zhang <i>et al.</i> (40)	2013	PFOA, PFOS	Elimination	Key differences in kidney clearance related to different isomeric forms, including chain length, branched versus linear, and functional groups

PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; PFAS, per- and polyfluoroalkyl substances; PFHxA, perfluorohexanoic acid; PFBA, perfluorobutyrate; PFHpA, perfluoroheptanoic acid; PFNA, perfluorononanoic acid; PFDA, perfluorodecanoic acid; PFUdA, perfluoroundecanoic acid; PFDoA, perfluorododecanoic acid; PFBS, perfluorobutane sulfonate; PFHxS, perfluorohexane sulfonate; OATP1A2, organic anion transporting polypeptide 1A2; Cl-PFESA, chlorinated polyfluoroalkyl ether sulfonic acid; PFDoDA, perfluorododecanoic acid; OAT1, organic anion transporter 1; OAT3, organic anion transporter 3; OAT4, organic anion transporter 4; URAT1, urate transporter 1.

outcomes linked to PFAS exposure, including reduced kidney function, histologic and cellular derangements in the proximal tubules, and dysregulated metabolic pathways linked to kidney disease. Nonetheless, several important gaps still exist.

We observed consistent epidemiologic associations between PFAS exposure and reduced kidney function and/or kidney cancers, including a study from the C8 Health Project with >32,000 participants (19). Despite reduced exposure to putative, traditional risk factors (*e.g.*, cigarette

Table 3. Studies (1990–2018) investigating the toxicology of per- and polyfluoroalkyl substances in animals or humans

Study	Year	Study Design	Model/Cell Line	Exposure	Mechanistic Domain	Major Findings
Chang <i>et al.</i> (41)	2017	Animal	Monkeys	PFOS	Clinical	No observed association: Serum creatinine BUN
Fair <i>et al.</i> (42)	2013	Animal	Dolphins	PFOS, PFOA, PFDA	Clinical	Association present: ↑ Serum creatinine ↑ BUN
Butenhoff <i>et al.</i> (43)	2012	Animal	Rats	PFOS	Clinical Histologic	Association present: ↑ BUN (male and female) No observed kidney histologic changes
Lieder <i>et al.</i> (44)	2008	Animal	Rats	PFBS	Clinical Histologic	No observed association: Body weight Serum creatinine BUN Effects observed: Medullary and papillary tubular epithelial hyperplasia Interstitial infiltration with tubular basophilia and papillary edema Papillary necrosis ↑ BUN
Seacat <i>et al.</i> (45)	2003	Animal	Rats	PFOS	Clinical Histologic	Association present: No observed kidney histologic changes ↑ BUN
Son <i>et al.</i> (46)	2007	Animal	Mouse (male)	PFOA	Clinical Histologic	No observed association: Serum creatinine BUN Kidney weights No observed kidney histologic changes
Takahasi <i>et al.</i> (47)	2014	Animal	Rats	PFOA	Clinical	Association present: ↑ BUN
Xing <i>et al.</i> (48)	2016	Animal	Mouse (male)	PFOS	Clinical Histologic	Effects observed: Association present: Kidney tubular regeneration Acute toxicity, glomerular changes with peripheral edema ↑ mortality Chronic toxicity, ↓ body weight and kidney mass No observed kidney histologic changes
Klaunig <i>et al.</i> (49)	2015	Animal	Rats	PFHxA	Clinical Histologic	Association present: Effects observed: Dose-dependent decrease in survival (females) Papillary necrosis (females) Mild to moderate tubular atrophy ↑ mortality
Serex <i>et al.</i> (50)	2014	Animal	Rats	Fluoro-telomers	Clinical Histologic	Association present: Effects observed: Dose-dependent increase in kidney weights Kidney degeneration and necrosis, leading to death
Butenhoff <i>et al.</i> (51)	2004	Animal	Rats	aPFOA	Histologic	Effects observed: ↑ kidney weights (parents and offspring) ↓ body weights
Cui <i>et al.</i> (52)	2009	Animal	Rats	PFOA, PFOS	Histologic	Effects observed: Cortical and medullary congestion with enhanced acidophilia and tumefaction of proximal tubule cells
Curran <i>et al.</i> (53)	2008	Animal	Rats	PFOS	Histologic	Effects observed: ↑ kidney weights (male and female) Tubular epithelial hyperplasia
Kim <i>et al.</i> (54)	2011	Animal	Rats	PFOS	Histologic	Effects observed: Enhanced proximal tubular basophilia
Ladies <i>et al.</i> (55)	2005	Animal	Rats	Fluoro-telomers	Histologic	Effects observed: ↑ kidney weights (males) Tubular hypertrophy
Newsted <i>et al.</i> (56)	2008	Animal	Quail	PFBS	Histologic	No observed kidney histologic changes

Table 3. (Continued)

Study	Year	Study Design	Model/Cell Line	Exposure	Mechanistic Domain	Major Findings
Rogers <i>et al.</i> (57)	2013	Animal	Rats	PFOS, PFNA	Histologic	Effects observed: Fewer nephrons and elevated BP in offspring of maternal rats exposed during pregnancy
Chou <i>et al.</i> (58)	2017	Animal	Mouse	PFOS	Histologic	Effects observed: Kidney tubular inflammation and apoptosis Enhanced tubular fibrosis and cytosolic changes
		<i>In vitro</i>	RTE		Cellular	Effects observed: Epithelial mesenchymal transition induction and cell migration <i>via</i> PPAR γ deacetylation and Sirt1 sequestration
Wen <i>et al.</i> (59)	2016	Animal	RTE (rats)	PFOS	Histologic	Effects observed: Loss of epithelial cells Granular cytoplasmic changes in proximal tubules
		<i>In vitro</i>			Cellular	Effects observed: Dose-dependent reduction in cell proliferation Increased apoptosis Enhanced oxidative stress (<i>via</i> NFAT3, PPAR α , β , γ and SIRT1)
Abbott <i>et al.</i> (60)	2012	Animal	Mouse	PFOA	Cellular	Effects observed: Increased PPAR α , β , γ mRNA expression in kidney tissue Upregulation of Cyp4a14 gene expressing PPAR
Arukwe <i>et al.</i> (61)	2011	Animal	Salmon	PFOA, PFOS	Cellular	Effects observed: PFOA: increased PPAR α , γ mRNA, ACOX1, CAT expression PFOS: decreased PPAR α , γ mRNA expression in kidney tissue and increased expression of PPAR β , ACOX1, CAT
Chung (62)	2015	<i>In vitro</i>	RTE	PFOS	Cellular	Effects observed: Enhanced expression of fibrotic and oxidative stress markers accompanied by apoptosis of RTE cells
Diaz <i>et al.</i> (63)	1994	Animal	Rats (male)	PFOA	Cellular	Effects observed: Enhanced peroxisome proliferation Induction of p450 in kidneys Increased β oxidation of fatty acids
Eldasher <i>et al.</i> (64)	2013	Animal	Rats (male)	PFOA	Cellular	Effects observed: Enhanced expression of Cyp4a14 in kidneys
Eroğlu <i>et al.</i> (65)	2011	Animal	Rats	PFOS	Cellular	Effects observed: Enhanced markers for oxidative stress (MDA, SOD, and catalase)
Gorrochategui <i>et al.</i> (66)	2016	<i>In vitro</i>	RTE (<i>Xenopus laevis</i>)	PFBS, PFOS, PFOA, PFNA	Cellular	Effects observed: Reduced cellular proliferation Spectral alterations of DNA/RNA structures, protein structures, and fatty acids
Hu <i>et al.</i> (67)	2003	<i>In Vitro</i>	RTE (dolphin)	PFOS, PFHA, PFBS	Cellular	Effects observed: Carbon-chain length inhibition of intercellular communication at the gap junctions (PFOS and PFHA)
Qian <i>et al.</i> (68)	2010	<i>In vitro</i>	Microvascular endothelial cells	PFOS	Cellular	Effects observed: Induced reactive oxygen species leading to increased vascular permeability and actin filament re-modeling, with disruption of cell junction and cell adhesions
Takagi <i>et al.</i> (69)	1991	Animal	Rats (male)	PFOA, PFDA, PFBA	Cellular	No observed effects: Marker of oxidative stress and DNA damage (8-hydroxydeoxyguanosine)
Witzman <i>et al.</i> (70)	1996	Animal	Rats (male)	PFOA, PFDA	Cellular	Effects observed: \uparrow markers for oxidative stress, including mitochondrial markers
Kariuki <i>et al.</i> (71)	2017	Animal	Crustacean (<i>Daphnia magna</i>)	PFOS	Metabolic	Effects observed: Disrupted several energy metabolism pathways Enhanced protein degradation
Lankadurai <i>et al.</i> (72)	2012	Animal	Earthworm	PFOS	Metabolic	Effects observed: Increased fatty acid oxidation Disrupted glucose and energy metabolism, specifically glutamate and TCA cycle metabolites

Table 3. (Continued)

Study	Year	Study Design	Model/Cell Line	Exposure	Mechanistic Domain	Major Findings
Peng <i>et al.</i> (73)	2013	<i>In vitro</i>	Human hepatocytes	PFOA	Metabolic	Effects observed: Disrupted carnitine metabolism Disrupted cholesterol biosynthesis and lipid metabolism Disrupted amino acid metabolism
Skov <i>et al.</i> (74)	2015	Animal	Rats (male)	PFNA	Metabolic	Effects observed: Disrupted lipid metabolism
Tan <i>et al.</i> (75)	2013	Animal	Mice	PFOA	Metabolic	Effects observed: Disrupted fatty acid metabolism
Wagner <i>et al.</i> (76)	2017	Animal	Crustacean (<i>Daphnia magna</i>)	PFOS	Metabolic	Effects observed: Disrupted amino acid metabolism
Wang <i>et al.</i> (77)	2017	Human	Human	PFOA, PFOS	Metabolic	Effects observed: Disrupted lipid and fatty acid metabolism Disrupted energy metabolism, including TCA cycle and glutathione pathways Disrupted xenobiotic detoxifying, anti-oxidation, and nitric oxide signal pathways
Yu <i>et al.</i> (78)	2016	Animal	Mouse	PFOA	Metabolic	Effects observed: Disrupted amino acid metabolism Disrupted lipid metabolism Altered energy metabolism Increased β oxidation of fatty acids
Zhang <i>et al.</i> (79)	2011	Animal	Rats (male)	PFDoA	Metabolic	Effects observed: Disrupted kidney amino acid metabolism Altered glucose and energy metabolism
Ding <i>et al.</i> (80)	2009	Animal	Rats (male)	PFDoA	Metabolic	Effects observed: Disrupted lipid metabolism Disrupted fatty acid metabolism Disrupted amino acid metabolism
					Clinical	Association present: Serum creatinine BUN

PFOS, perfluorooctane sulfonate; PFOA, perfluorooctanoic acid; PFDA, perfluorodecanoic acid; PFBS, perfluorobutane sulfonate; PFUA, perfluoroundecanoic acid; PFHxA, perfluorohexanoic acid; aPFOA, ammonium perfluorooctanoic acid; PFNA, perfluorononanoic acid; RTE, kidney tubular epithelial; PPAR, peroxisome proliferator receptor; Sirt1, sirtuin 1; NFAT3, nuclear factor of activated T-cells 3; Cyp4a14, cytochrome p450 4A14; ACOX1, Acyl-CoA oxidase 1; CAT, catalase; P450, cytochrome P450; MDA, malondialdehyde; SOD, superoxide dismutase; PFHA, perfluoroheptanoic acid; PFBA, perfluorobutyrate; TCA, tricarboxylic acid; PFDoA, perfluorododecanoic acid.

smoke) in countries such as the United States, the incidence of genitourinary and/or kidney cancers continues to rise, and the potential increased risk for these cancers stemming from PFAS exposure may be of particular public health importance (85). For noncancer related kidney outcomes, a handful of studies comparing model-based PFAS exposure estimates with measured serum concentrations suggested the epidemiologic associations between PFAs exposure and reduced kidney function may be a phenomenon of reverse causation, *i.e.*, serum concentrations of PFASs accumulate as kidney function declines (7,11,16,26). Additionally, several of the epidemiologic studies are susceptible to exposure misclassification because of indirect exposure measurements (*e.g.*, cumulative occupational work-years), and longitudinal epidemiologic studies using direct serum PFAS measurements are needed to further characterize the epidemiologic risk of PFAS exposure.

Several toxicology studies demonstrated unequivocal histologic, cellular, and metabolic kidney-related outcomes related to PFAS exposure, including increased oxidative

stress with upregulated Sirt1 and Nrf2 gene expression, enhanced apoptosis and fibrosis with tubular epithelial histologic changes, induced EMT and cell migrations, and enhanced microvascular endothelial permeability through actin filament remodeling (58,59,84). Furthermore, the relationship between kidney function and steady-state PFAS serum concentrations appears to be more complex than previous pharmacokinetic models have reported, with the limited pharmacokinetic data in humans demonstrating key differences from other species. Studies have demonstrated that humans actively transport PFASs in the proximal tubules, with greater tubular reabsorption likely responsible for the longer $t_{1/2}$ in humans (33,39). Further, human proximal tubule handling of PFAS compounds differs on the basis of the carbon-chain length or functional group of the PFAS compound or the age, sex, or ethnicity of the individual, and such differences in the proximal tubular OAT-mediated transport of PFASs may be particularly salient given their putative importance in mediating other drug-induced nephrotoxicities, including

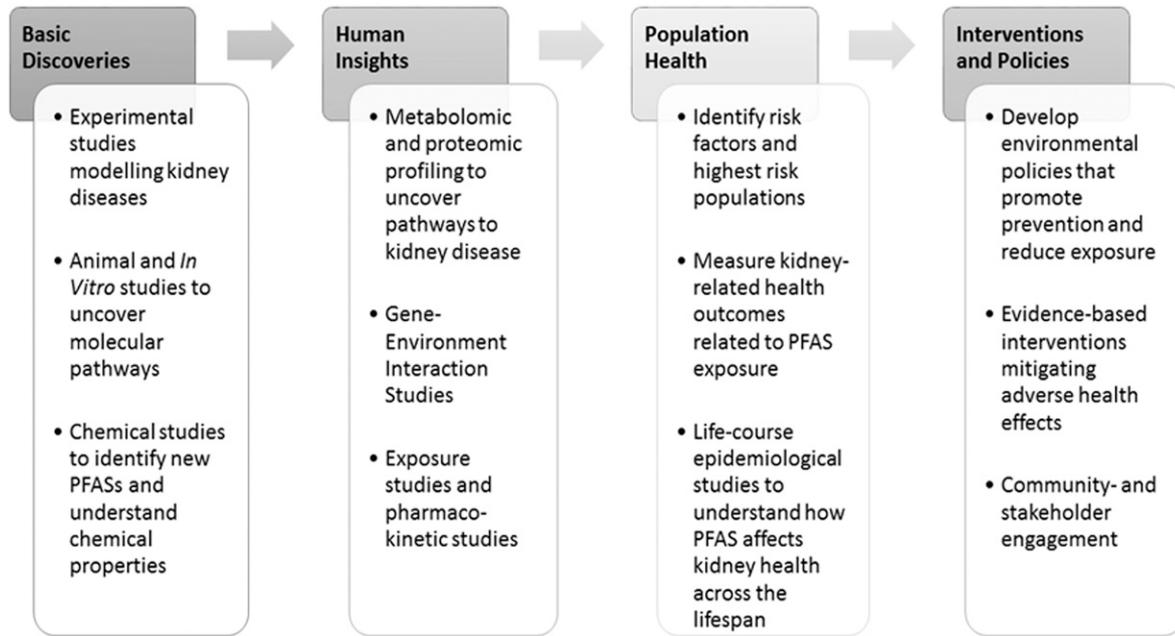


Figure 4. | Research across the translational spectrum is needed to better elucidate the potential link between PFAS exposure and adverse kidney health and eliminate potential disparities.

aristolochic acid, cephalosporin antibiotics, and tenofovir (86). Key differences in proximal tubule transporter activity across human populations may portend different risk profiles even at similar exposure levels (87), and studies investigating the potential role of proximal tubule transporter blockade (*e.g.*, URAT1) may facilitate a greater understanding of the risk to kidney health posed by PFAS compounds. Finally, children and adolescents may have adverse cardiovascular and kidney consequences related to increased PFAS exposure, and life-course studies will be critical to understand the long-term health impact (8,11,88,89).

The emerging recognition of PFASs as environmental threats to human health reflects a broader understanding of the complex determinants of human health and health disparities. Environmental risk factors contribute to the development and perpetuation of health disparities around the globe, with contaminants now linked to increased burdens of chronic diseases and cancers, maternal and neonatal mortality, and developmental toxicity. In the context of kidney disease, contaminants appear to play key roles in causing CKD of unknown etiology, accelerating diabetic nephropathy, contributing to AKI, and serving as “second hits” to genetic risk factors (*e.g.*, *APOL1*) (90). Nonetheless, how environmental toxins such as PFASs drive differences in kidney diseases across diverse population remains poorly understood. To understand the role environmental exposure to PFASs play in driving disparities in kidney disease, translational studies ranging from experimental models, metabolic profiling, to longitudinal life-course epidemiology will be needed (Figure 4). Furthermore, disparities in kidney disease arise from a complex interaction of factors, and studies explicating the effects of PFAS exposure with genetic, biologic, lifestyle, and other environmental risk factors (including PFAS–PFAS interactions) will be critical.

We note some limitations to our study. Although we included abstracts and scientific conference proceedings in our search strategy and several studies we included demonstrate negative findings, publication biases may still be present and further studies are needed. Additionally, given the paucity of data on alternative fluorinated compounds, we did not include them as a primary focus of our scoping review. However, many PFASs are being phased out of production and are being replaced by alternative PFAS compounds, which are increasingly being detected in the environment. For example, perfluoroether carboxylic acids, such as the commercial compound GenX, were very recently identified in urban municipal drinking water in North Carolina, and chlorinated polyfluorinated ether sulfonates, such as the commercial compound F-53B used in metal-plating industries, were recently detected in humans from China (34). Although these replacement compounds were manufactured as ostensibly safer alternatives to PFASs, they have chemical properties (*e.g.*, etherification, chlorination) that prompt serious concern, and studies such as the GenX Exposure Study are only just now beginning to investigate outcomes associated with exposure to these replacement compounds. Limited data demonstrate placental transfer (34), greater binding affinities to human liver fatty acid protein, extremely long $t_{1/2}$ in humans (37), and dose-dependent kidney tubular dilation and mineralization, papillary necrosis, and chronic progressive nephropathy in animal models (91). Further, many of the alternatives are themselves precursors to PFASs such as PFOA and PFOS, which through chemical breakdown or biotransformation can lead to persistent PFAS exposure despite phase-out efforts (92). Even more challenging is that hundreds of undiscovered PFAS compounds exist and their health effects are unknown, but

proprietary aegis impedes development of detection methods or authentication standards to facilitate their study.

In conclusion, a growing body of evidence portends PFASs are emerging environmental threats to kidney health; yet several important gaps in our understanding still exist. Given the drastic increased production of novel replacement PFAS compounds, studies investigating the relationship between PFAS exposure and kidney disease are urgently needed.

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Disclosures

None.

References

- Buck RC, Franklin J, Berger U, Conder JM, Cousins IT, de Voogt P, Jensen AA, Kannan K, Mabury SA, van Leeuwen SP: Perfluoroalkyl and polyfluoroalkyl substances in the environment: Terminology, classification, and origins. *Integr Environ Assess Manag* 7: 513–541, 2011
- Calafat AM, Wong LY, Kuklenyik 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* 115: 1596–1602, 2007
- Hu XC, Andrews DQ, Lindstrom AB, Bruton TA, Schaidler LA, Grandjean P, Lohmann R, Carignan CC, Blum A, Balan SA, Higgins CP, Sunderland EM: Detection of Poly- and Perfluoroalkyl Substances (PFASs) in U.S. drinking water linked to industrial sites, military fire training areas, and wastewater treatment plants. *Environ Sci Technol* 3: 344–350, 2016
- Environmental Protection Agency: *Long-Chain Perfluorinated Chemical (PFCs): Action Plan*, Washington, DC, United States Environmental Protection Agency, 2009
- 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* 99: 43–54, 2017
- Steenland K, Fletcher T, Savitz DA: Epidemiologic evidence on the health effects of perfluorooctanoic acid (PFOA). *Environ Health Perspect* 118: 1100–1108, 2010
- Dhingra R, Winquist A, Darrow LA, Klein M, Steenland K: A study of reverse causation: Examining the associations of perfluorooctanoic acid serum levels with two outcomes. *Environ Health Perspect* 125: 416–421, 2017
- Kataria A, Trachtman H, Malaga-Dieguez L, Trasande L: Association between perfluoroalkyl acids and kidney function in a cross-sectional study of adolescents. *Environ Health* 14: 89, 2015
- Shankar A, Xiao J, Ducatman A: Perfluoroalkyl chemicals and chronic kidney disease in US adults. *Am J Epidemiol* 174: 893–900, 2011
- Vearrier D, Jacobs D, Greenberg MI: Serum perfluorooctanoic acid concentration is associated with clinical renal disease but not clinical cardiovascular disease. *Clin Toxicol (Phila)* 51: 326, 2013
- Watkins DJ, Josson J, Elston B, Bartell SM, Shin HM, Vieira VM, Savitz DA, Fletcher T, Wellelius GA: Exposure to perfluoroalkyl acids and markers of kidney function among children and adolescents living near a chemical plant. *Environ Health Perspect* 121: 625–630, 2013
- Conway BN, Innes K, Costacou T, Arthur J: Perfluoroalkyl substances and kidney function in chronic kidney disease, anemia, and diabetes. *Diabetes* 66: A143, 2017
- Emmett EA, Zhang H, Shofer FS, Freeman D, Rodway NV, Desai C, Shaw LM: Community exposure to perfluorooctanoate: Relationships between serum levels and certain health parameters. *J Occup Environ Med* 48: 771–779, 2006
- Olsen GW, Burris JM, Burlew MM, Mandel JH: Epidemiologic assessment of worker serum perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) concentrations and medical surveillance examinations. *J Occup Environ Med* 45: 260–270, 2003
- Olsen G, Butenhoff J, Zobel L: PFOA, PFOS, and chronic kidney disease: Clearance comes before causation. *Epidemiology* 23: S610, 2012
- Steenland K, Tinker S, Shankar A, Ducatman A: Association of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) with uric acid among adults with elevated community exposure to PFOA. *Environ Health Perspect* 118: 229–233, 2010
- Zhou Z, Shi Y, Vestergren R, Wang T, Liang Y, Cai Y: Highly elevated serum concentrations of perfluoroalkyl substances in fishery employees from Tangxun lake, china. *Environ Sci Technol* 48: 3864–3874, 2014
- Alexander BH, Olsen GW, Burris JM, Mandel JH, Mandel JS: Mortality of employees of a perfluorooctanesulphonyl fluoride manufacturing facility. *Occup Environ Med* 60: 722–729, 2003
- Barry V, Winquist A, Steenland K: Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. *Environ Health Perspect* 121: 1313–1318, 2013
- Consonni D, Straif K, Symons JM, Tomenson JA, van Amelsvoort LG, Smeuwenhoek A, Cherrie JW, Bonetti P, Colombo I, Farrar DG, Bertazzi PA: Cancer risk among tetrafluoroethylene synthesis and polymerization workers. *Am J Epidemiol* 178: 350–358, 2013
- Mastrantonio M, Bai E, Uccelli R, Cordiano V, Screpanti A, Crosignani P: Drinking water contamination from perfluoroalkyl substances (PFAS): An ecological mortality study in the Veneto Region, Italy. *Eur J Public Health* 28: 180–185, 2017
- Steenland K, Woskie S: Cohort mortality study of workers exposed to perfluorooctanoic acid. *Am J Epidemiol* 176: 909–917, 2012
- Vieira VM, Hoffman K, Shin HM, Weinberg JM, Webster TF, Fletcher T: Perfluorooctanoic acid exposure and cancer outcomes in a contaminated community: A geographic analysis. *Environ Health Perspect* 121: 318–323, 2013
- Leonard RC, Kreckmann KH, Sakr CJ, Symons JM: Retrospective cohort mortality study of workers in a polymer production plant including a reference population of regional workers. *Ann Epidemiol* 18: 15–22, 2008
- Costa G, Sartori S, Consonni D: Thirty years of medical surveillance in perfluorooctanoic acid production workers. *J Occup Environ Med* 51: 364–372, 2009
- Dhingra R, Lally C, Darrow LA, Klein M, Winquist A, Steenland K: Perfluorooctanoic acid and chronic kidney disease: Longitudinal analysis of a Mid-Ohio Valley community. *Environ Res* 145: 85–92, 2016
- Raleigh KK, Alexander BH, Olsen GW, Ramachandran G, Morey SZ, Church TR, Logan PW, Scott LL, Allen EM: Mortality and cancer incidence in ammonium perfluorooctanoate production workers. *Occup Environ Med* 71: 500–506, 2014
- Beeson S, Martin JW: Isomer-specific binding affinity of perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) to serum proteins. *Environ Sci Technol* 49: 5722–5731, 2015
- Fàbrega F, Kumar V, Schuhmacher M, Domingo JL, Nadal M: PBPK modeling for PFOS and PFOA: Validation with human experimental data. *Toxicol Lett* 230: 244–251, 2014
- Fu J, Gao Y, Cui L, Wang T, Liang Y, Qu G, Yuan B, Wang Y, Zhang A, Jiang G: Occurrence, temporal trends, and half-lives of perfluoroalkyl acids (PFAAs) in occupational workers in China. *Sci Rep* 6: 38039, 2016
- Harada K, Inoue K, Morikawa A, Yoshinaga T, Saito N, Koizumi A: Renal clearance of perfluorooctane sulfonate and perfluorooctanoate in humans and their species-specific excretion. *Environ Res* 99: 253–261, 2005
- Ingelido AM, Abballe A, Gemma S, Dellatte E, Iacovella N, De Angelis G, Zampaglioni F, Marra V, Miniero R, Valentini S, Russo F,

- Vazzoler M, Testai E, De Felip E: Biomonitoring of perfluorinated compounds in adults exposed to contaminated drinking water in the Veneto Region, Italy. *Environ Int* 110: 149–159, 2018
33. Olsen GW, Burris JM, Ehresman DJ, Froehlich JW, Seacat AM, Butenhoff JL, Zobel LR: Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorocarbon production workers. *Environ Health Perspect* 115: 1298–1305, 2007
 34. Pan Y, Zhu Y, Zheng T, Cui Q, Buka SL, Zhang B, Guo Y, Xia W, Yeung LW, Li Y, Zhou A, Qiu L, Liu H, Jiang M, Wu C, Xu S, Dai J: Novel chlorinated polyfluorinated ether sulfonates and legacy per-/polyfluoroalkyl substances: Placental transfer and relationship with serum albumin and glomerular filtration rate. *Environ Sci Technol* 51: 634–644, 2017
 35. Pérez F, Nadal M, Navarro-Ortega A, Fàbrega F, Domingo JL, Barceló D, Farré M: Accumulation of perfluoroalkyl substances in human tissues. *Environ Int* 59: 354–362, 2013
 36. Russell MH, Waterland RL, Wong F: Calculation of chemical elimination half-life from blood with an ongoing exposure source: The example of perfluorooctanoic acid (PFOA). *Chemosphere* 129: 210–216, 2015
 37. Shi Y, Vestergren R, Xu L, Zhou Z, Li C, Liang Y, Cai Y: Human exposure and elimination kinetics of chlorinated polyfluoroalkyl ether sulfonic acids (Cl-PFESAs). *Environ Sci Technol* 50: 2396–2404, 2016
 38. Worley RR, Yang X, Fisher J: Physiologically based pharmacokinetic modeling of human exposure to perfluorooctanoic acid suggests historical non drinking-water exposures are important for predicting current serum concentrations. *Toxicol Appl Pharmacol* 330: 9–21, 2017
 39. Yang CH, Glover KP, Han X: Characterization of cellular uptake of perfluorooctanoate via organic anion-transporting polypeptide 1A2, organic anion transporter 4, and urate transporter 1 for their potential roles in mediating human renal reabsorption of perfluorocarboxylates. *Toxicol Sci* 117: 294–302, 2010
 40. Zhang Y, Beesoon S, Zhu L, Martin JW: Biomonitoring of perfluoroalkyl acids in human urine and estimates of biological half-life. *Environ Sci Technol* 47: 10619–10627, 2013
 41. Chang S, Allen BC, Andres KL, Ehresman DJ, Falvo R, Provencher A, Olsen GW, Butenhoff JL: Evaluation of serum lipid, thyroid, and hepatic clinical chemistries in association with serum perfluorooctanesulfonate (PFOS) in cynomolgus monkeys after oral dosing with potassium PFOS. *Toxicol Sci* 156: 387–401, 2017
 42. Fair PA, Romano T, Schaefer AM, Reif JS, Bossart GD, Houde M, Muir D, Adams J, Rice C, Hulsey TC, Peden-Adams M: Associations between perfluoroalkyl compounds and immune and clinical chemistry parameters in highly exposed bottlenose dolphins (*Tursiops truncatus*). *Environ Toxicol Chem* 32: 736–746, 2013
 43. Butenhoff JL, Chang SC, Olsen GW, Thomford PJ: Chronic dietary toxicity and carcinogenicity study with potassium perfluorooctanesulfonate in Sprague Dawley rats. *Toxicology* 293: 1–15, 2012
 44. Lieder PH, Chang SC, York RG, Butenhoff JL: Toxicological evaluation of potassium perfluorobutanesulfonate in a 90-day oral gavage study with Sprague-Dawley rats. *Toxicology* 255: 45–52, 2009
 45. Seacat AM, Thomford PJ, Hansen KJ, Clemen LA, Eldridge SR, Elcombe CR, Butenhoff JL: Sub-chronic dietary toxicity of potassium perfluorooctanesulfonate in rats. *Toxicology* 183: 117–131, 2003
 46. Son HY, Kim SH, Shin HI, Bae HI, Yang JH: Perfluorooctanoic acid-induced hepatic toxicity following 21-day oral exposure in mice. *Arch Toxicol* 82: 239–246, 2008
 47. Takahashi M, Ishida S, Hirata-Koizumi M, Ono A, Hirose A: Repeated dose and reproductive/developmental toxicity of perfluoroundecanoic acid in rats. *J Toxicol Sci* 39: 97–108, 2014
 48. Xing J, Wang G, Zhao J, Wang E, Yin B, Fang D, Zhao J, Zhang H, Chen YQ, Chen W: Toxicity assessment of perfluorooctane sulfonate using acute and subchronic male C57BL/6J mouse models. *Environ Pollut* 210: 388–396, 2016
 49. Klaunig JE, Shinohara M, Iwai H, Chengelis CP, Kirkpatrick JB, Wang Z, Bruner RH: Evaluation of the chronic toxicity and carcinogenicity of perfluorohexanoic acid (PFHxA) in Sprague-Dawley rats. *Toxicol Pathol* 43: 209–220, 2015
 50. Serex T, Anand S, Munley S, Donner EM, Frame SR, Buck RC, Loveless SE: Toxicological evaluation of 6:2 fluorotelomer alcohol. *Toxicology* 319: 1–9, 2014
 51. Butenhoff JL, Kennedy GL Jr., Frame SR, O'Connor JC, York RG: The reproductive toxicology of ammonium perfluorooctanoate (APFO) in the rat. *Toxicology* 196: 95–116, 2004
 52. Cui L, Zhou QF, Liao CY, Fu JJ, Jiang GB: Studies on the toxicological effects of PFOA and PFOS on rats using histological observation and chemical analysis. *Arch Environ Contam Toxicol* 56: 338–349, 2009
 53. Curran I, Hierlihy SL, Liston V, Pantazopoulos P, Nunnikhoven A, Tittlemier S, Barker M, Trick K, Bondy G: Altered fatty acid homeostasis and related toxicologic sequelae in rats exposed to dietary potassium perfluorooctanesulfonate (PFOS). *J Toxicol Environ Health A* 71: 1526–1541, 2008
 54. Kim HS, Jun Kwack S, Sik Han E, Seok Kang T, Hee Kim S, Young Han S: Induction of apoptosis and CYP4A1 expression in Sprague-Dawley rats exposed to low doses of perfluorooctane sulfonate. *J Toxicol Sci* 36: 201–210, 2011
 55. Ladics GS, Stadler JC, Makovec GT, Everds NE, Buck RC: Sub-chronic toxicity of a fluoroalkylethanol mixture in rats. *Drug Chem Toxicol* 28: 135–158, 2005
 56. Newsted JL, Beach SA, Gallagher SP, Giesy JP: Acute and chronic effects of perfluorobutane sulfonate (PFBS) on the mallard and northern bobwhite quail. *Arch Environ Contam Toxicol* 54: 535–545, 2008
 57. Rogers JM, Ellis-Hutchings RG, Grey BE, Zucker RM, Norwood J Jr., Grace CE, Gordon CJ, Lau C: Elevated blood pressure in offspring of rats exposed to diverse chemicals during pregnancy. *Toxicol Sci* 137: 436–446, 2014
 58. Chou HC, Wen LL, Chang CC, Lin CY, Jin L, Juan SH: From the cover: L-carnitine via PPAR γ - and Sirt1-dependent mechanisms attenuates epithelial-mesenchymal transition and renal fibrosis caused by perfluorooctanesulfonate. *Toxicol Sci* 160: 217–229, 2017
 59. Wen LL, Lin CY, Chou HC, Chang CC, Lo HY, Juan SH: Perfluorooctanesulfonate mediates renal tubular cell apoptosis through PPAR γ inactivation. *PLoS One* 11: e0155190, 2016
 60. Abbott BD, Wood CR, Watkins AM, Tatum-Gibbs K, Das KP, Lau C: Effects of perfluorooctanoic acid (PFOA) on expression of peroxisome proliferator-activated receptors (PPAR) and nuclear receptor-regulated genes in fetal and postnatal CD-1 mouse tissues. *Reprod Toxicol* 33: 491–505, 2012
 61. Arukwe A, Mortensen AS: Lipid peroxidation and oxidative stress responses of salmon fed a diet containing perfluorooctane sulfonic- or perfluorooctane carboxylic acids. *Comp Biochem Physiol C Toxicol Pharmacol* 154: 288–295, 2011
 62. Chung ACK: Perfluorooctane sulfonate (PFOS) promotes renal injury under diabetic condition *in vitro*. *Hong Kong J Nephrol* 17: S3–S4, 2015
 63. Diaz MJ, Chinje E, Kentish P, Jarnot B, George M, Gibson G: Induction of cytochrome P4504A by the peroxisome proliferator perfluoro-n-octanoic acid. *Toxicology* 86: 109–122, 1994
 64. Eldasher LM, Wen X, Little MS, Bircsak KM, Yacovino LL, Aleksunes LM: Hepatic and renal Bcrp transporter expression in mice treated with perfluorooctanoic acid. *Toxicology* 306: 108–113, 2013
 65. Eroglu P, Deniz M, Eke D, Çömelekoğlu U, Çelik A, Berköz M, et al.: Projective effect of curcumin against oxidative damage in rat kidney. *Turkish J Biochem* 36, 317–321, 2011
 66. Gorrochategui E, Lacorte S, Tauler R, Martin FL: Perfluoroalkylated substance effects in xenopus laevis A6 kidney epithelial cells determined by ATR-FTIR spectroscopy and chemometric analysis. *Chem Res Toxicol* 29: 924–932, 2016
 67. Hu W, Jones PD, Upham BL, Trosko JE, Lau C, Giesy JP: Inhibition of gap junctional intercellular communication by perfluorinated compounds in rat liver and dolphin kidney epithelial cell lines *in vitro* and Sprague-Dawley rats *in vivo*. *Toxicol Sci* 68: 429–436, 2002
 68. Qian Y, Ducatman A, Ward R, Leonard S, Bukowski V, Lan Guo N, Shi X, Vallyathan V, Castranova V: Perfluorooctane sulfonate (PFOS) induces reactive oxygen species (ROS) production in human microvascular endothelial cells: Role in endothelial permeability. *J Toxicol Environ Health A* 73: 819–836, 2010

69. Takagi A, Sai K, Umemura T, Hasegawa R, Kurokawa Y: Short-term exposure to the peroxisome proliferators, perfluorooctanoic acid and perfluorodecanoic acid, causes significant increase of 8-hydroxydeoxyguanosine in liver DNA of rats. *Cancer Lett* 57: 55–60, 1991
70. Witzmann FA, Fultz CD, Lipscomb JC: Toxicant-induced alterations in two-dimensional electrophoretic patterns of hepatic and renal stress proteins. *Electrophoresis* 17: 198–202, 1996
71. Kariuki MN, Nagato EG, Lankadurai BP, Simpson AJ, Simpson MJ: Analysis of sub-lethal toxicity of perfluorooctane sulfonate (PFOS) to daphnia magna Using ¹H nuclear magnetic resonance-based metabolomics. *Metabolites* 7: E15, 2017
72. Lankadurai BP, Simpson AJ, Simpson MJ: H-1 NMR metabolomics of *Eisenia fetida* responses after sub-lethal exposure to perfluorooctanoic acid and perfluorooctane sulfonate. *Environ Chem* 9: 502–511, 2012
73. Peng S, Yan L, Zhang J, Wang Z, Tian M, Shen H: An integrated metabolomics and transcriptomics approach to understanding metabolic pathway disturbance induced by perfluorooctanoic acid. *J Pharm Biomed Anal* 86: 56–64, 2013
74. Skov K, Kongsbak K, Hadrup N, Frandsen HL, Svingen T, Smedsgaard J, et al: Exposure to perfluorononanoic acid combined with a low-dose mixture of 14 human-relevant compounds disturbs energy/lipid homeostasis in rats. *Metabolomics* 11: 1451–1464, 2015
75. Tan X, Xie G, Sun X, Li Q, Zhong W, Qiao P, Sun X, Jia W, Zhou Z: High fat diet feeding exaggerates perfluorooctanoic acid-induced liver injury in mice via modulating multiple metabolic pathways. *PLoS One* 8: e61409, 2013
76. Wagner ND, Simpson AJ, Simpson MJ: Metabolomic responses to sublethal contaminant exposure in neonate and adult *Daphnia magna*. *Environ Toxicol Chem* 36: 938–946, 2017
77. Wang X, Liu L, Zhang W, Zhang J, Du X, Huang Q, Tian M, Shen H: Serum metabolome biomarkers associate low-level environmental perfluorinated compound exposure with oxidative/nitrosative stress in humans. *Environ Pollut* 229: 168–176, 2017
78. Yu N, Wei S, Li M, Yang J, Li K, Jin L, Xie Y, Giesy JP, Zhang X, Yu H: Effects of perfluorooctanoic acid on metabolic profiles in brain and liver of mouse revealed by a high-throughput targeted metabolomics approach. *Sci Rep* 6: 23963, 2016
79. Zhang H, Ding L, Fang X, Shi Z, Zhang Y, Chen H, Yan X, Dai J: Biological responses to perfluorododecanoic acid exposure in rat kidneys as determined by integrated proteomic and metabolomic studies. *PLoS One* 6: e20862, 2011
80. Ding L, Hao F, Shi Z, Wang Y, Zhang H, Tang H, Dai J: Systems biological responses to chronic perfluorododecanoic acid exposure by integrated metabolomic and transcriptomic studies. *J Proteome Res* 8: 2882–2891, 2009
81. Kishi R, Nakajima T, Goudarzi H, Kobayashi S, Sasaki S, Okada E, Miyashita C, Itoh S, Araki A, Ikeno T, Iwasaki Y, Nakazawa H: The association of prenatal exposure to perfluorinated chemicals with maternal essential and longchain polyunsaturated fatty acids during pregnancy and the birth weight of their offspring: The hokkaido study. *Environ Health Perspect* 123: 1038–1045, 2015
82. Chen MH, Ha EH, Wen TW, Su YN, Lien GW, Chen CY, Chen PC, Hsieh WS: Perfluorinated compounds in umbilical cord blood and adverse birth outcomes. *PLoS One* 7: e42474, 2012
83. Whitworth KW, Haug LS, Baird DD, Becher G, Hoppin JA, Skjaerven R, Thomsen C, Eggesbo M, Travlos G, Wilson R, Cupul-Uicab LA, Brantsaeter AL, Longnecker MP: Perfluorinated compounds in relation to birth weight in the Norwegian Mother and Child Cohort Study. *Am J Epidemiol* 175: 1209–1216, 2012
84. Shi X, Zhou B: The role of Nrf2 and MAPK pathways in PFOS-induced oxidative stress in zebrafish embryos. *Toxicol Sci* 115: 391–400, 2010
85. King SC, Pollack LA, Li J, King JB, Master VA: Continued increase in incidence of renal cell carcinoma, especially in young patients and high grade disease: United States 2001 to 2010. *J Urol* 191: 1665–1670, 2014
86. Hagos Y, Wolff NA: Assessment of the role of renal organic anion transporters in drug-induced nephrotoxicity. *Toxins (Basel)* 2: 2055–2082, 2010
87. Nigam SK, Bush KT, Martovetsky G, Ahn SY, Liu HC, Richard E, Bhatnagar V, Wu W: The organic anion transporter (OAT) family: A systems biology perspective. *Physiol Rev* 95: 83–123, 2015
88. Lin CY, Lin LY, Wen TW, Lien GW, Chien KL, Hsu SH, Liao CC, Sung FC, Chen PC, Su TC: Association between levels of serum perfluorooctane sulfate and carotid artery intima-media thickness in adolescents and young adults. *Int J Cardiol* 168: 3309–3316, 2013
89. Qin XD, Qian Z, Vaughn MG, Huang J, Ward P, Zeng XW, Zhou Y, Zhu Y, Yuan P, Li M, Bai Z, Paul G, Hao YT, Chen W, Chen PC, Dong GH, Lee YL: Positive associations of serum perfluoroalkyl substances with uric acid and hyperuricemia in children from Taiwan. *Environ Pollut* 212: 519–524, 2016
90. Stanifer JW, Muir A, Jafar TH, Patel UD: Chronic kidney disease in low- and middle-income countries. *Nephrol Dial Transplant* 31: 868–874, 2016
91. Caverly Rae JM, Craig L, Slone TW, Frame SR, Buxton LW, Kennedy GL: Evaluation of chronic toxicity and carcinogenicity of ammonium 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propanoate in Sprague-Dawley rats. *Toxicol Rep* 2: 939–949, 2015
92. Wang Z, Cousins IT, Scheringer M, Hungerbühler K: Fluorinated alternatives to long-chain perfluoroalkyl carboxylic acids (PFCA), perfluoroalkane sulfonic acids (PFSA) and their potential precursors. *Environ Int* 60: 242–248, 2013

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