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A State-of-the-Science Review of Interactions of Per- and Polyfluoroalkyl Substances (PFAS) with Renal Transporters in Health and Disease: Implications for Population Variability in PFAS Toxicokinetics

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Background: Per- and polyfluoroalkyl substances (PFAS) are ubiquitous in the environment and have been shown to cause various adverse health impacts. In animals, sex- and species-specific differences in PFAS elimination half-lives have been linked to the activity of kidney transporters. However, PFAS molecular interactions with kidney transporters are still not fully understood. Moreover, the impact of kidney disease on PFAS elimination remains unclear.

Objectives: This state-of-the-science review integrated current knowledge to assess how changes in kidney function and transporter expression from health to disease could affect PFAS toxicokinetics and identified priority research gaps that should be addressed to advance knowledge.

Methods: We searched for studies that measured PFAS uptake by kidney transporters, quantified transporter-level changes associated with kidney disease status, and developed PFAS pharmacokinetic models. We then used two databases to identify untested kidney transporters that have the potential for PFAS transport based on their endogenous substrates. Finally, we used an existing pharmacokinetic model for perfluorooctanoic acid (PFOA) in male rats to explore the influence of transporter expression levels, glomerular filtration rate (GFR), and serum albumin on serum half-lives.

Results: The literature search identified nine human and eight rat kidney transporters that were previously investigated for their ability to transport PFAS, as well as seven human and three rat transporters that were confirmed to transport specific PFAS. We proposed a candidate list of seven untested kidney transporters with the potential for PFAS transport. Model results indicated PFOA toxicokinetics were more influenced by changes in GFR than in transporter expression.

Discussion: Studies on additional transporters, particularly efflux transporters, and on more PFAS, especially current-use PFAS, are needed to better cover the role of transporters across the PFAS class. Remaining research gaps in transporter expression changes in specific kidney disease states could limit the effectiveness of risk assessment and prevent identification of vulnerable populations. https://doi.org/10.1289/EHP11885

Introduction

Per- and polyfluoroalkyl substances (PFAS), a class of thousands of manufactured chemicals with at least one perfluorinated carbon atom, have been ubiquitously detected in the environment,[1,2] humans,[3–5] and wildlife[5] worldwide. Of concern, identified health outcomes in humans and animals associated with specific PFAS exposures include altered immune function,[6] liver injury,[7,8] kidney disease,[9] and adverse reproductive and developmental outcomes.[10] In humans and animals, absorbed PFAS were shown to undergo key physiological processes, such as enterohepatic circulation, including secretion into bile and eventual reabsorption into the cell by the intestine,[11,12] as well as kidney reabsorption and secretion.[13] PFAS can be excreted from the body through urine and feces.[14] Previous studies have shown that PFAS bioaccumulation is related to their binding to serum albumin[15–17] and to fatty acid-binding proteins (FABPs)[18] and cell membrane transport[19–22] in various organs and tissues, including the liver, gut, kidney, and brain. High binding affinities to serum albumin[23] and FABPs[24] were observed for long-chain PFAS (e.g., C6–C11) compared with short-chain PFAS (e.g., $C < 6$).

For cell membrane transport, passive diffusion and protein-facilitated transport have been considered primary mechanisms for cellular uptake or secretion of PFAS.[13,25–27] Studies have identified a number of transport proteins located at the surface of endothelial cells responsible for PFAS cellular transport in humans[25,27] and rats.[13,25–27] Throughout this review, transporters are named using all capital letters for human transporters or using one capital letter followed by lowercase letters for animal transporters.[28] Known PFAS transporters include organic anion transporters (OATs/Oats)[25–27,29] and organic anion-transporting polypeptides (OATPs/Oatps).[27,29] PFAS can bind to these transporters and achieve transmembrane transport (e.g., uptake into the cell or secretion from the cell) through the conformational changes of transporters.[29] Studies have shown that the contribution of passive diffusion to the total PFAS uptake in cells varies between ~5% and 60%,[21,22,25–27,30,31] indicating that transporter-facilitated uptake is an important and often dominant component of PFAS transport regardless of cell type.

In animals, sex- and species-specific differences in elimination half-lives of PFAS have been linked to renal elimination, particularly the activity of kidney transport proteins and polypeptides for organic anions.[20] Renal elimination of PFAS includes one passive diffusion process, namely glomerular filtration, and two active pathways, namely tubular secretion and reabsorption (Figure 1).[20] Secretion and reabsorption of PFAS in the kidney are mediated via renal transporters expressed on the basolateral (facing the blood) and the apical (facing the urine) membranes of the proximal tubular cells.[20] Renal transporters can facilitate either uptake or efflux, or both under certain conditions.[25–27,30] An inverted U-shaped distribution has been reported between human serum PFAS concentrations and declining estimated glomerular filtration rates (eGFR), as eGFR changes from healthy kidney function through the advancing stages of kidney disease.[32] This inverted U-shaped pattern differs by sex.[32] One possible reason for this observed pattern may relate to the retained activities, during progressive kidney failure, of renal transporters that actively

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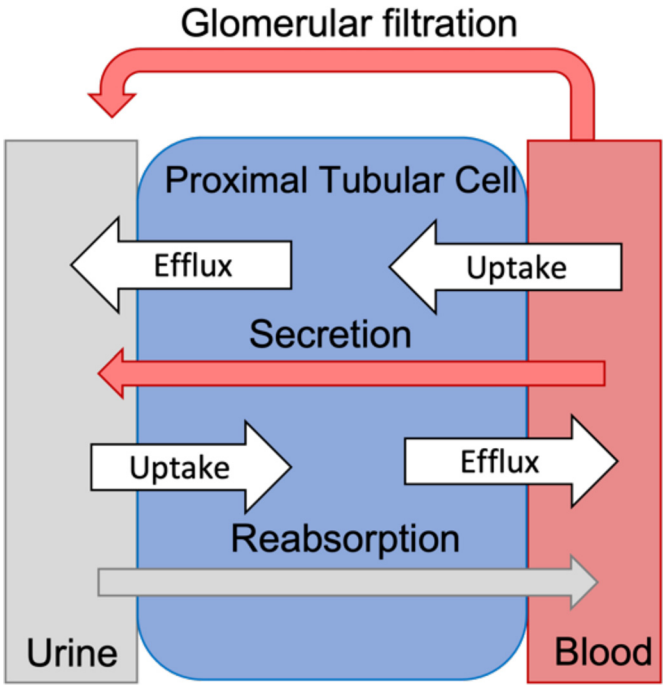

Figure 1. Conceptual diagram of processes in renal PFAS clearance. Renal clearance of PFAS comprises glomerular filtration, tubular secretion, and tubular reabsorption. Note: PFAS, per- and polyfluoroalkyl substances.

mediate PFAS secretion and reabsorption.[33] Another possible explanation is that early subclinical kidney damage can manifest initially as glomerular hyperfiltration as an adaptive response to nephron injury or loss, which may precede clinical functional decline.[34,35] The inverted U-shaped pattern could also be due to a combination of kidney disease causation due to PFAS (high PFAS concentration leading to progression of the kidney disease[36]) followed by enhanced excretion due to transporter failure in presence of albuminuria or moderate-to-severe declines in glomerular filtration.[32]

Previous studies have confirmed the role of renal transporters in facilitating PFAS transport in rats[21,26,30,31,37,38] and humans.[22,25,27,38] For example, Weaver et al. reported that Oat1 and Oat3 were involved in rat renal secretion of perfluoroheptanoic acid (PFHpA), perfluorooctanoic acid (PFOA), and perfluorononanoic acid (PFNA), whereas rat renal Oatp1a1 reportedly could contribute to the reabsorption of PFOA, PFNA, and perfluorodecanoic acid (PFDA).[26] Nakagawa et al. concluded that both human and rat renal OAT1/Oat1 and OAT3/Oat3 facilitated PFOA transport to similar degrees, whereas neither human nor rat renal OAT2/Oat2 facilitated PFOA transport, indicating the difference between the PFOA half-lives in humans and rats is not likely attributable to differences in the affinities of these three renal transporters.[38] In contrast, OAT4 and urate transporter 1 (URAT1) were identified as key transporters in kidney reabsorption of PFOA in humans and, as a result, may contribute significantly to the long half-life of PFOA in humans.[27] However, these are a small subset of kidney transporters, considering the large number of kidney transporter superfamilies that exist[39] [i.e., the solute carrier (*SLC*) and the adenosine triphosphate (ATP)-binding cassette (*ABC*) gene families].

In addition, expression levels and functions of renal transporters can be altered in various kidney disease states, with disease-specific outcomes.[40–42] For example, expression levels of Oat1 were significantly decreased 24 h after ischemia/reperfusion–induced acute kidney injury (AKI) in rats, but returned to normal after 72 h.[43] Conversely, expression levels of Oat1 were not significantly changed during the first 2 wk following 5/6 nephrectomy (removal of one kidney first followed by two poles of the remaining kidney 1 wk later[41]) in rats[44] but were significantly decreased after 6 wk.[45] To the best of our knowledge, no previous studies have investigated the influence of altered renal transporter expression by kidney disease status on the renal elimination of PFAS.

Previous observational studies have shown long half-lives of long-chain PFAS (i.e., $C \geq 6$) in humans; for instance, mean human serum half-lives for PFOA (C_8), perfluorooctane sulfonate (PFOS; C_8), and perfluorohexane sulfonate (PFHxS; C_6) ranged from ~ 2 to 3, ~ 3 to 4, and ~ 5 to 7 y, respectively.[46–51] In contrast, shorter human serum half-lives were observed for short-chain PFAS (e.g., $C < 6$), with a mean half-life for perfluorobutane sulfonic acid (PFBS; C_4) of 44 d, and for perfluoropentane sulfonic acid (PFPeS; C_5) of 230 d.[52] Notably, an observational study by Li et al.[50] reported PFHxS half-lives were widely variable among 106 individuals, and the reason is still unknown. Sex differences were observed, with more rapid elimination in women for PFHxS and PFOS, but comparable elimination for PFOA.[50] Uncertainties in PFAS half-lives may exist because they are based on observations in groups with differing exposure patterns, such as retired fluorochemical workers and residents of contaminated communities with serum levels investigated after exposure via drinking water. These half-lives should be expected to differ from steady-state exposures, or even from declining PFAS background exposure, such as from food.[50] Physiologically based pharmacokinetic (PBPK) modeling can be ideal to address these questions and examine how renal transporter expression and changes in kidney function between healthy and diseased states could impact estimations of PFAS half-lives representing accumulation and elimination over time. Indeed, even in the case where PFAS exposure itself may instigate kidney disease,[9,32,53] if the impact of that disease on transporters is known, it can also be integrated into the PBPK modeling of changes in PFAS toxicokinetics.

This review aimed to address how kidney function and the related expression of key transporters could affect PFAS toxicokinetics by facilitating their elimination and reabsorption. We first surveyed studies related to kidney transporters that mediate PFAS transport to summarize current knowledge. We then conducted a broader survey of other kidney transporters that could have the potential for molecular interactions with PFAS based on the similarity between PFAS and the transporters' endogenous ligands. Additional literature was reviewed to provide existing knowledge about kidney transport proteins or mRNA expression levels based on known changes in characteristic disease states. Finally, we reviewed studies that developed PBPK models for PFAS and used the model developed by Cheng and Ng[13] to illustrate how changes in renal transporter expression levels, GFR, and serum albumin in specific kidney disease states could impact PFAS toxicokinetics. We highlighted key insights into population and interindividual variability in contaminant toxicokinetics that are critical to identifying particularly sensitive populations for public health interventions.

Methods

Literature Search

We performed a literature review using the Web of Science, Scopus, and PubMed databases to locate studies focusing on PFAS, renal transporters, and PBPK models. We searched articles through 15 April 2023 with no lower limit on publication date, using the following search terms: *a*) for PFAS interactions with renal transporters, the search terms were ("PFAS" OR "perfluoro" OR "PFOA" OR "PFOS" AND "renal transporters"

Table 1. Tissue distributions, sex and species differences of tested human, rat, and zebrafish renal transporters for PFAS.

Gene name	Protein name	Tissue distribution[a]	Sex difference[b]	Species difference between human and rat[b]
Human (source for tissue distribution: https://www.proteinatlas.org)				
SLC22A6	OAT1	Kidney, brain,[c] endocrine tissue,[c] and GI tract[c]	—	N/N
SLC22A7	OAT2	Broad distribution[d] except for lung, proximal digestive tract, pancreas, placenta, ovary (liver, kidney, and adipose have protein expression)	—	Y/N
SLC22A8	OAT3	Kidney, brain,[c] endocrine tissues,[c] and GI tract[c]	—	N/N
SLC51A/B	OST α/β	Broad distribution[d] (GI tract and kidney have protein expression)	—	/
SLC22A11	OAT4	Kidney, placenta, epididymis, endocrine tissue,[c] GI tract,[c] liver,[c] and pancreas[c]	—	Y/Y
SLC22A12	URAT1	Kidney, brain,[c] GI tract,[c] liver,[c] and adipose[c]	—	N/Y
SLCO1A2	OATP1A2	Broad distribution except for adipose (all tissues have only mRNA expression according to the database)	—	N/N
SLCO2B1	OATP2B1	Broad distribution (kidney, eye, adipose, and skin have only mRNA expression according to the database)	—	/
SLC10A2	ASBT	GI tract, kidney,[c] brain,[c] lung,[c] liver,[c] muscle,[c] skin,[c] and bone[c]	—	N/Y
Rat (source for tissue distribution: https://www.solvobiotech.com/knowledge-center/transporters-a-z)				Human ortholog[54]
SLC22A6	Oat1	Kidney	—	OAT1
SLC22A7	Oat2	Liver and kidney	Y/N	OAT2
SLC22A8	Oat3	Kidney	—	OAT3
ABCC2	Mrp2	Liver, kidney, and GI tract	—	MRP2
SLCO1A1	Oatp1a1/Oatp1	Liver and kidney	Y/Y	OATP1A2
SLC34A1	Npt2	Kidney	—	NPT2
SLC22A12	Urat1	Kidney	—	URAT1
SLC10A2	Asbt	Kidney, bladder, and GI tract	—	ASBT
Zebrafish (source for tissue distribution[55])				
SLCO1D1	Oatp1d1	Intestine, liver, brain, gills, muscle, kidney, and ovary	—	OATP1A

Note: —, no information available; ABC, adenosine triphosphate (ATP)-binding cassette gene family; ASBT/Asbt, apical sodium-dependent bile acid transporter; GI, gastrointestinal; MRP/Mrp, multidrug resistance proteins; NPT/Npt, sodium–phosphate transporters; OAT/Oat, organic anion transporters; OATP/Oatp, organic anion-transporting polypeptides; OST, organic solute transporter; PFAS, per- and polyfluoroalkyl substances; SLC, solute carrier gene family; URAT/Urat, urate transporter.

[a]Tissues with higher transporter expression levels are listed before others.

[b]In these column, the first Y or N stands for yes or no for differences in physiology, and the second Y or N means yes or no for differences in PFAS toxicokinetics.

[c]Transporter only has mRNA expression in that tissue according to the database.

[d]"Broad distribution": found in brain, eye, endocrine tissues, lung, proximal digestive tract, GI tract, liver and gallbladder, pancreas, kidney and urinary bladder, reproductive tissues, muscle, adipose, skin, and bone.[24,36]

OR "kidney" OR "drug transporters"); *b*) for expression-level changes of renal transporters in kidney disease, the search terms were ("renal transporters" OR "drug transporters" and "kidney disease" OR "kidney failure" OR "AKI" OR "CKD"); and *c*) for PFAS-related PBPK models, the search terms were ("PFAS" OR "perfluoro" OR "PFOA" OR "PFOS" AND "PBPK models"). Four terms for PFAS (i.e., PFAS, perfluoro, PFOA, and PFOS) and three terms for renal transporter (i.e., renal transporter, kidney, and drug transporter) were included to reduce the possibility of missing a potential study that fulfilled our inclusion criteria. We also used the Research Rabbit application (version 32.2.0), a citation-based literature mapping tool, for an additional search. Specifically, we imported the articles identified from Web of Science, Scopus, and PubMed databases and used Research Rabbit to identify other relevant articles; we then reviewed these articles to identify further publications related to our research questions.

We conducted a search to create a candidate list of untested renal transporters with the potential to transport PFAS. Specifically, we first used a website-based transporter database included in the Guide to PHARMACOLOGY database[39] (https://www.guidetopharmacology.org; last accessed 12 April 2023) to identify transporters known to have fatty acids, bile acids, and phospholipids as substrates. We then conducted a literature search via Web of Science, Scopus, and PubMed for articles reporting transporters in tissues other than kidney that transport PFAS using the search terms ("PFAS" OR "perfluoro" OR "PFOA" OR "PFOS" AND "transporters" OR "transporting polypeptide" OR "drug transporters"). We excluded transporters already identified to transport PFAS in the kidney, as summarized in Table 1. After selecting the potential transporters, we used the Human Protein Atlas database[56] (https://www.proteinatlas.org; last accessed 12 April 2023) to confirm their expression in the kidney. Given that resources for animal transporters were relatively limited, we included only human transporters in the candidate list.

Study Selection

All articles underwent an identical screening process with specified inclusion and exclusion criteria. The inclusion criteria were established based on the research question of interest, which focused on how renal transporter expression and changes in health and disease state could impact PFAS half-life estimates. Regardless of the type (e.g., human observational studies or *in vivo, ex vivo, in vitro* studies), studies were included if they *a*) assessed the direct interaction between transporters and PFAS, *b*) quantified the expression and changes of renal transporters in kidney diseases, or *c*) developed PBPK models for PFAS. The exclusion criteria were that the studies *a*) indirectly assessed the influence of renal transporters on PFAS (e.g., renal transporters inhibited by certain PFAS), *b*) did not quantify the changes in renal transporter expression levels during kidney diseases, or *c*) developed PBPK models for chemicals other than PFAS.

Titles and abstracts of identified studies were scanned for eligibility by two reviewers, with any discrepancies resolved by a third reviewer. All full texts in English were then reviewed by two reviewers for final inclusion in the qualitative summary using the same inclusion and exclusion criteria, with a third reviewer again resolving discrepancies. The literature was complemented by identifying additional articles by analyzing the reference lists in various review articles.

Data Extraction

The following contents were extracted from the identified articles: *a*) for PFAS interaction with renal transporters, renal transporter characteristics (type, localization, and function), PFAS (specific compounds tested), uptake pattern, and information on the methods used; *b*) for expression-level changes of renal transporters as a result of kidney disease, renal transporter characteristics (type, localization, and function), changes in expression levels, the type of kidney disease, and information on the methods (e.g., *in vivo*, *ex vivo*, *in vitro*, or clinical); *c*) for PFAS transporters expressed in tissues other than kidney, transporter characteristics (type, localization, and function); and *d*) for PFAS-PBPK models, information on whether the models included transporter-specific mechanisms.

Using an Existing Model to Explore the Influence of Kidney Disease on PFOA Toxicokinetics

We used a PFOA-PBPK model for male rats, developed by Cheng and Ng[13] in Python (version 3.10.8) to explore the influence of changes in transporter expression levels, GFR, and serum albumin concentration on PFOA toxicokinetics. Details on the model development can be found in Cheng and Ng[13]; an overview of the model is provided here. The Cheng and Ng model is a permeability-limited PBPK model that includes four kidney transporters [i.e., Oat 1, Oat 3, Oatp1a1, and organic solute transporter-alpha/beta (Ost α/β)], glomerular filtration using a parameter for GFR, and binding to serum albumin as mechanisms for PFOA toxicokinetics.[13] To model changes in the toxicokinetics in response to kidney disease, we reviewed reported changes from other published studies. Schneider et al.[43] reported that GFR was decreased to 5%, 15%, and 33% of levels in sham-operated rats in 6, 24, and 72 h, respectively, after ischemia/reperfusion–induced AKI.

To model the potential impacts of kidney disease, we made the following adjustments to the Cheng and Ng model parameterization described in the original paper, we set *a*) the clearance rate constant for Oat1 and Oat3 to 20% of the original model default value to simulate how changes in transporter levels during kidney disease could affect PFOA toxicokinetics in the male rat, *b*) GFR to 33% and 5% of the original model default to simulate how changes in GFR during kidney disease could affect PFOA toxicokinetics, and *c*) albumin concentration to 70% of the original model default value to simulate the influence of albumin decrease owing to albuminuria. For transporter levels, the changes of Oat1 and Oat3 expression at 6 wk in Figure 4A were used to represent the worst-case scenario.

Results

Current Knowledge of Renal Transporters for PFAS Transport

We identified 508 papers based on our search terms and procedures. After exclusion of 498 papers because they did not report PFAS transport by renal transporters, 10 studies that directly assessed the uptake of PFAS by renal transporters were included in this review (Excel Table S1).

Perfluoroalkyl acids (PFAAs) were the most commonly investigated PFAS for their interaction with renal transporters.[21,26,30,31,37,38] Given that PFAAs are ionic compounds that are negatively charged when in aqueous environments (e.g., human fluids), renal transporters that have the ability to transport organic anions, such as OATs/Oats and URAT1/Urat1 from the *SLC*22 gene family and OATP1A1/Oatp1a1 from the *SLCO* gene family, were among the first to be investigated for their potential PFAS transport. To the best of our knowledge, the first-reported direct investigation of PFAS transport by renal transporters was by Katakura et al., who confirmed that rat renal Oat3 (an uptake transporter located at the basolateral membrane facing blood) and Oatp1a1 (an uptake transporter located at the apical membrane facing urine) facilitated PFOA transport, whereas Npt2 (type II sodium-dependent phosphate transporter, an uptake transporter located at the apical membrane facing urine) did not.[30] An earlier study by Kudo et al.[37] provided indirect evidence for renal Oats (Oat2 and Oat3) facilitating PFOA transport by multiple regression analysis between plasma PFOA concentrations and Oats mRNA levels in rats. Subsequent studies of PFAS transport by renal transporters have accumulated, with 10 additional original research studies published since 2007.[21,22,25–27,30,31,38,57,58] Four gene families other than *SLC22*[25,26,30,38,57] and *SLCO*[22,27,30,31] were investigated for their role in PFAS transport, including *SLC*10 (sodium–bile acid cotransporters),[21] *SLC*34 (sodium–phosphate cotransporters),[30] *SLC*51 (steroid-derived molecule transporters),[21] and *ABCC* (one of the five families in the ABC superfamily).[30]

A review by Han et al.[20] summarized the knowledge of renal transporters for PFAS transport prior to 2011. In this subsection, we update that knowledge with four additionally identified renal transporters, specify the PFAS investigated to date, and expand information on the distribution of these transporters in other tissues, as well as whether the transporter could be responsible for sex or species differences (Figure 2 and Table 1) by reviewing identified studies (Table 2). In this review, the renal transporters investigated in previous studies were classified according to their expression localizations [i.e., basolateral (facing the blood) or apical membrane (facing the urine) of the proximal tubular cells] and their cellular transport roles (i.e., cellular uptake or cellular efflux). This grouping deliberately oversimplifies the complex processes of renal elimination; however, it helps summarize the mechanisms of PFAS renal transport. Specifically, the uptake role of transporters at the basolateral membrane and the efflux role of transporters at the apical membrane contribute to PFAS secretion (i.e., negative contribution to PFAS reabsorption). In contrast, the uptake role of transporters at the apical membrane and the efflux role of transporters at the basolateral membrane have negative contribution to PFAS secretion (i.e., positive contribution to PFAS reabsorption).

So far, nine human renal uptake transporters have been investigated for their potential importance to PFAS transport (Figure 2A). These are: OAT1,[25,38] OAT2,[38] OAT3,[25,38] OAT4,[25,27] URAT1,[27] OATP1A2,[27] OATP2B1,[22] apical sodium-dependent bile acid transporter (ASBT),[21] and OST α/β.[21] The expression of most of these nine transporters (except for OATP2B1) in kidney was indicated by protein expression, whereas, to the best of our knowledge, at the time of this review only mRNA expression in kidney had been demonstrated for OATP2B1,[56] suggesting expression of OATP2B1 protein in kidney needs to be confirmed. OAT2[38] and OATP1A2[27] are the two transporters that did not exhibit significant activity in PFOA transport. To date, five transporters (namely OAT1, OAT3, OAT4, URAT1, and OATP2B1) have been confirmed to transport PFOA. In addition, ASBT and OST α/β reportedly mediated transport of PFOS, and OST α/β also facilitated PFBS and PFHxS transport, but ASBT did not; to the best of our knowledge, the role of ASBT and OST α/β has not been tested in PFOA transport. OATP2B1 and OST α/β have been shown to transport multiple PFAS (Figure 2A) and longer-chain PFAS showed higher affinities for both transporters (order of affinity: PFOS > PFHxS > PFBS).[21,22] This trend aligns with observations of longer half-lives for longer-chain PFAS in humans.[52] Among the confirmed PFAS renal uptake transporters, OAT1 and OAT3 reside in the basolateral membrane of the proximal tubular cells and therefore participate in PFAS renal secretion.[20] In contrast, OAT4, URAT1, and OATP2B1 are involved in PFAS renal

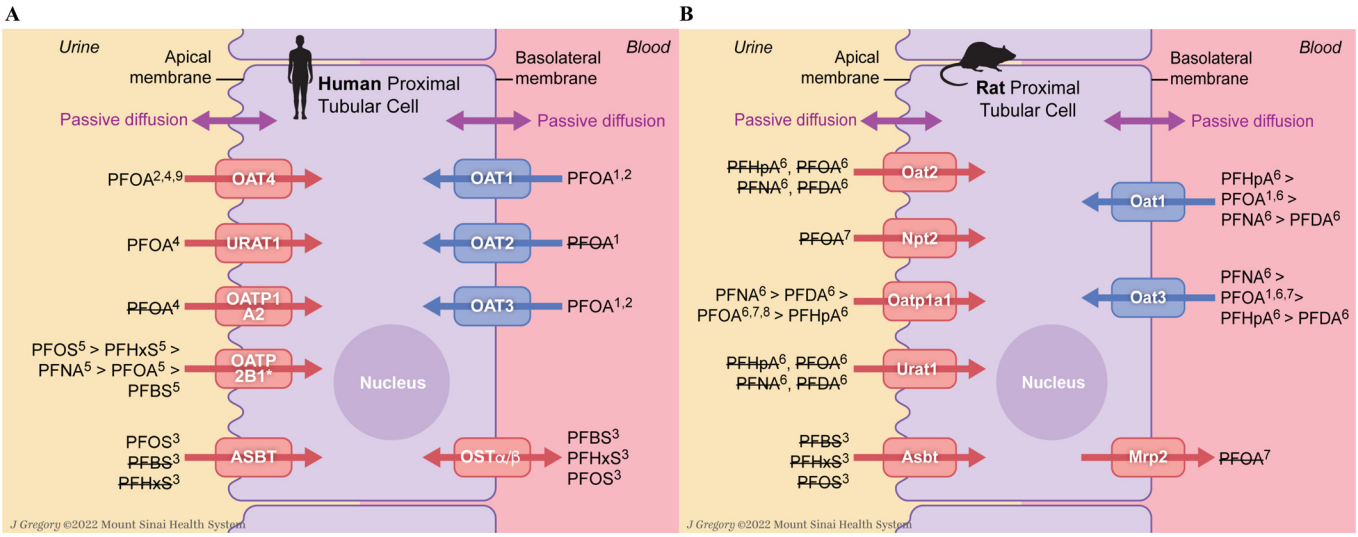

Figure 2. (A) Human and (B) rat renal transporters that have been tested for PFAS transport summarized from previous studies using *in vitro* methods. *OATP2B1 was identified only by mRNA expression in kidney according to the Human Protein Atlas database.[56] Transporter-facilitated uptake was often the dominant component of PFAS transport given that contribution of passive diffusion to the total PFAS uptake in cells varies between 5% and 60%.[21,22,25–27,30,31] PFAS denoted by strikethrough text indicates that compound was evaluated but reported to not be transported by the transporter. PFAS superscripts denote literature sources, and details are provided in Table 2. Note: PFAS, per- and polyfluoroalkyl substances; PFBS, perfluorobutane sulfonic acid; PFDA, perfluorodecanoic acid; PFHpA, perfluoroheptanoic acid; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate.

reabsorption because they are expressed in the apical membrane of proximal tubular cells.[20] To the best of our knowledge, OST α/β, expressed in the basolateral membrane (Figure 2A), was the only human renal efflux transporter that was tested and shown to transport PFBS, PFHxS, and PFOS,[21] indicating it was involved in renal reabsorption of these PFAS. Moreover, OST α/β was shown to transport bidirectionally, depending on the concentration gradient of PFAS.[21]

In the rat, eight renal uptake transporters have been studied for their potential role in PFAS transport; five of those did not transport PFAS (Figure 2B). Specifically, rat renal Oat2 and Urat1 did not demonstrate the capability to transport PFHpA, PFOA, PFNA or PFDA,[26] Npt2 was not involved in PFOA transport,[30] Asbt did not transport PFBS, PFHxS, or PFOS,[21] and multidrug resistance protein 2 (Mrp2) did not facilitate PFOA transport.[30] In contrast, rat renal Oat1[26,38] and Oatp1a1 (also referred to as Oatp1)[26,30] were considered to facilitate transport for PFHpA, PFOA, PFNA, and PFDA with compound-specific activities, and Oat3 was reported to transport PFOA.[26,30,38] The affinities of PFAS with renal transporters showed transporter-specific patterns. For example, PFHpA and PFOA had the highest affinities for rat Oat1 and Oat3, but the transport efficiencies of PFHpA, PFOA, and PFNA by both Oat1 and Oat 3 were similar.[26] In contrast, PFNA and PFDA had higher affinities and efficiencies for Oatp1a1 compared with PFOA.[26] This trend also aligned with observations of longer half-lives for longer-chain PFAS in rats. In addition, rat renal uptake transporters Oat1 and Oat3 are expressed at the basolateral membrane, indicating that they positively contribute to PFAS renal secretion, whereas Oatp1a1 resides in the apical membrane, suggesting it is involved in PFAS renal reabsorption.[20] To the best of our knowledge, Mrp2 is the only renal efflux transporter in rats that has been investigated for PFAS uptake, and a single previous study showed that Mrp2 did not play a role in PFOA renal elimination.[30] To date, one zebrafish renal transporter, Oatp1d1 (considered functionally similar to mammalian OATP1A/Oatp1a and OAT1B/Oatp1b), was investigated for its potential for PFAS transport mediation and showed the ability to mediate transport of PFOS but not PFOA.[59]

OAT4 is a human-specific transporter[60] that was previously demonstrated to transport PFOA[25,27]; thus, it may be one of the transporters responsible for species-specific differences in PFAS toxicokinetics. Human renal ASBT is another recently identified transporter that was considered responsible for species-specific

Table 2. Literature sources for studies that directly assessed the uptake of PFAS by renal transporters.

Reference number in Figure 2	Reference and year of publication	Study type	Cell line	Investigated transporters	Investigated PFAS
1	Nakagawa et al. 2008[38]	*In vitro*	HEK293	OAT1/Oat1; OAT2/Oat2; OAT3/Oat3	PFOA
2	Nakagawa et al. 2009[25]	*In vitro*	HEK293	OAT4	PFOA
3	Zhao et al. 2015[21]	*In vitro*	HEK293; CHO	ASBT/Asbt	PFBS; PFHxS; PFOS
4	Yang et al. 2010[27]	*In vitro*	HEK293; CHO	OATP1A2; OAT4; URAT1	PFCAs (C4–C12)
5	Zhao et al. 2017[22]	*In vitro*	CHO; HEK293	OATPs/Oatps	PFBS; PFHxS; PFOS
6	Weaver et al. 2010[26]	*In vitro*	CHO; HEK293	Oat1; Oat2; Oat3; Oatp1a1; Urat1	PFCAs (C2–C18)
7	Katakura et al. 2007[30]	*In vitro*	NA	Oatp1; Oat3; Npt2; Mrp2	PFOA
8	Yang et al. 2009[31]	*In vitro*	CHO	Oatp1a1	PFOA
9	Louisse et al. 2023[57]	*In vitro*	HEK293	OAT4	PFCAs (C7–C10); PFBS; PFHxS; PFOS

Note: See Table 1 for the protein names. ASBT/Asbt, apical sodium-dependent bile acid transporter; C, carbon; CHO, Chinese hamster ovarian; HEK293, human embryonic kidney 293; MRP/Mrp, multidrug resistance proteins; NA, not available; NPT/Npt, sodium–phosphate transporters; OAT/Oat, organic anion transporters; OATP/Oatp, organic anion-transporting polypeptides; PFAS, per- and polyfluoroalkyl substances; PFBS, perfluorobutane sulfonic acid; PFCAs, perfluoroalkyl carboxylic acids; PFHxS, perfluorohexane sulfonic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; URAT/Urat, urate transporter.

differences in PFAS toxicokinetics based on findings by Zhao et al.[21] that human ASBT transported PFOS, whereas rat Asbt did not. Although the expression of human renal OAT2 and rat renal Oat2 are at the opposite sides of the proximal tubular cell, these transporters have not been identified as related to species-specific differences in PFAS toxicokinetics given that they have not demonstrated the ability to facilitate PFAS secretion/reabsorption. Human and rat OAT1/Oat1 and OAT3/Oat3 are considered to play a limited role in species-specific differences given that they have shown comparable uptake ability for PFAS in laboratory studies.[26] However, inferential human population evidence has suggested that OAT1 and OAT3 may operate differently in humans compared with rats. Inhibition of transporters (e.g., Oat1, Oat3) by probenecid had a marked and sex-differential effect on PFOA elimination in rats.[61] In contrast, probenecid had no discernible effect on PFOA or PFOS excretion in a human population.[62] The authors concluded that OAT1 and OAT3 were "lazy" PFAS excreters (having lower capability for PFAS excretion) in humans compared with rats.[62] However, another possible reason causing the difference in probenecid effects on rats and humans could be the species-specific mechanisms of reabsorption of PFOA. Probenecid is a known inhibitor of not only OATs/Oats,[63] but also OATPs/Oatps,[63] MRPs/MRPs,[63] and URAT1/Urat1.[64] OAT4 and URAT1 are responsible for PFOA reabsorption in humans, but rats do not have an Oat4 and rat Urat1 does not transport PFOA[27] (Figure 2). This suggests the reabsorption of PFOA could be inhibited by probenecid in humans but not in the rat and that URAT1 could also be responsible for species differences in PFOA elimination. Although sex differences in PFHxS and PFOS (but not PFOA) elimination were observed in humans,[56] to the best of our knowledge, no human renal transporters to date have been specifically identified as responsible. Sex differences in PFAS half-lives could be partially or mostly attributed to nonrenal causes, including menstruation, breast-feeding, and transplacental transport of PFAS from mother to fetus in humans.[65,66]

Currently known PFAS renal transporters are also distributed in other tissues. For example, the human uptake transporter OAT4 is also expressed in the placenta,[67] indicating this transporter could play an important role in PFAS transfer from mother to fetus. OAT1 and OAT3 are also expressed in the brain, endocrine tissues, and gastrointestinal tract[56] (https://www.proteinatlas.org; Table 1), indicating they may play multiple roles in PFAS distribution in the human body. OATPs are expressed in the brain, liver, lungs, kidney, testes, and intestines.[68] OATP2B1 is present in a variety of tissues, especially gut and liver, and including proximal tubules and basolateral epithelial cells of the kidney.[69] *In vitro* evidence from the human colon cancer–derived Caco-2 cell line has suggested that OATP2B1 could be a contributor to the long human half-lives of several PFAS.[70] OST α/β, the efflux transporter studied among the human renal transporters, also resides in the liver, gallbladder, and ileum, suggesting it may play a significant role in PFAS elimination through enterohepatic circulation. In addition, Oatp1d1 is also expressed in zebrafish liver, brain, intestine, gill, ovary, and muscle tissues.[55] Overall, more information is available on tissue distribution of human transporters compared with rat and zebrafish, complicating comparisons of species differences.

Other Renal Transporters with the Potential for PFAS Transport

The currently known PFAS renal transporters are members of two transporter families: the SLC and ABC superfamilies.[20] The SLC superfamily is the second largest family of membrane proteins after G protein–coupled receptors.[39] SLC transporters do not rely on ATP hydrolysis and are largely, but not exclusively, uptake transporters; that is, they generally facilitate cellular uptake of molecules (e.g., endogenous metabolites, drugs, toxicants).[68,71–73] ABC transporters are ubiquitous membrane proteins that use ATP hydrolysis and mostly function as efflux transporters.[74,75] A total of 48 families in the SLC superfamily and 5 families in the ABC superfamily have been identified based on sequence similarities; details about the families and transporters can be found in the Guide to PHARMACOLOGY database.[39] Notably, many transporters have overlaps in terms of their substrates; this happens among transporters in the same superfamily and also among those across the SLC and ABC superfamilies.[74]

Kidney transporters with substrates that have similar molecular structures as PFAS or that have expression levels that were shown to positively correlate with PFAS concentrations were considered to have the potential for PFAS transport for this review. Fatty acids, which are endogenous substrates of FABPs, have similar structures as PFAS, especially perfluoroalkyl carboxylic acids.[76] A significant positive association was identified in humans between plasma PFOA and PFOS concentrations and bile acid levels.[12] In addition, phospholipid levels were significantly associated with long-chain PFAS concentrations in North Atlantic pilot whale tissues.[77] Based on our literature analysis, we proposed seven human renal transporters that may have the potential for PFAS transport (Table 3), suggesting these should be prioritized for further experimental evaluation. Specifically, OATP4A1, an uptake transporter at the basolateral membrane, was considered because of its ability to transport bile acids. MRP1, an efflux transporter at the basolateral membrane and MDR1/P-glycoprotein (MDR1/P-gp), an efflux transporter at the apical membrane, were also included because of their ability to transport phospholipids. Another efflux transporter at the apical membrane, breast cancer resistance protein (BCRP, also known as ABCP), was proposed because it has been shown to transport PFOA across the blood–testis barrier.[84] Three additional ABC transporters, namely, adrenoleukodystrophy protein (ALDP), ALD-related gene (ALDR), and peroxisomal membrane protein (PMP70) were included because they have been shown to transport very-long-chain fatty acids, monounsaturated very-long-chain fatty acids, branched-chain fatty acids and bile acids.[39] Unfortunately, to the best of our knowledge, information on the localization and mechanisms (uptake or efflux) is not currently available for these three transporters.

Levels and Patterns of Renal Transporter Expression in Kidney Disease

We identified 2,773 papers from the search for transporter expression-level changes in kidney disease (Excel Table S2). After exclusion of 2,749 papers, a total of 24 studies that quantified the changes of renal transporter expression during kidney disease were identified. Among these 24 publications, 12 studies used animal models to investigate renal transporter-level changes during AKI, 8 studies used animal models to investigate renal transporter changes during CKD, 3 used animal models to investigate renal transporter changes during diabetic nephropathy, and 1 assessed renal transporter changes in clinical patients with renal diseases (Excel Table S2).

Given the important role of relevant renal transporters in PFAS elimination, changes in expression levels and patterns of these transporters with kidney disease could substantially influence PFAS biological half-lives for specific populations. Kidney diseases can be acute or chronic, and both types can cause changes in transporter expressions and GFR. AKI is defined as acute renal dysfunction with mild-to-severe changes in renal function.[85,86] Chronic kidney disease (CKD) is defined as GFR <60 mL/min per 1.73 m^2 of functioning nephrons or markers of kidney damage (e.g., nephrotic syndrome, urinary tract symptoms), or both, of at least 3-months

Table 3. Candidate list of human renal transporters that have not been tested but may have potential for PFAS transport.

Gene name	Protein name	Function	Reference for transporter localization and function	Other tissue distribution	Evidence for the potential to transport PFAS	Reference for the evidence
Basolateral membrane (blood side)						
SLCO4A1	OATP4A1	Uptake	[78]	Broad distribution (eye)	Bile acid transporter	Database[a]
ABCC1	MRP1	Efflux	[79,80]	Broad distribution (eye, proximal digestive tract, and muscle)	Phospholipid transporter	
Apical membrane (urine side)						
ABCB1	MDR1/P-gp	Efflux	[81,82]	Broad distribution (eye, lung, proximal digestive tract, pancreas, testis, muscle, adipose, skin, and bone)	Phospholipid transporter	Database
ABCG2	ABCP/BCRP	Efflux	[83]	Broad distribution (eye, proximal digestive tract, liver, skin, adipose, and pancreas)	Transporting PFOA when expressing in blood–testis barrier	[84]
Unknown localization						
ABCD1	ALDP	Unknown	—	Broad distribution (eye)	Transporting long-chain fatty acid	Database
ABCD2	ALDR	Unknown	—	Broad distribution with only mRNA expression according to the database		
ABCD3	PMP70	Unknown	—	Broad distribution (eye)	Transporting long-chain fatty acid and bile acid	

Note: Source for tissue distribution: https://www.proteinatlas.org. See Table 1 for other protein names. —, No information available; ABC, adenosine triphosphate (ATP)-binding cassette gene family; ABCP/BCRP, breast cancer resistance protein; ASBT/Asbt, apical sodium-dependent bile acid transporter; ALDP, adrenoleukodystrophy protein; ALDR, ALD-related gene; MDR/MRP, multidrug resistance protein; OATP/Oatp, organic anion-transporting polypeptides; PFAS, per- and polyfluoroalkyl substances; PFOA, perfluorooctanoic acid; P-gp, P-glycoprotein; PMP, peroxisomal membrane protein; SLC, solute carrier gene family.
[a]Website-based Guide to PHARMACOLOGY database[39] (https://www.guidetopharmacology.org).

duration.[87] CKD is classified into five stages based on GFR. Stages 1 and 2 are defined as normal and mild kidney damage, respectively, stages 3 to 4 are defined as moderate and severe kidney damage, and stage 5 (GFR <15 mL/min per 1.73 m^2) is defined as kidney failure, also referred to as end-stage renal disease.[88] Although the causes of CKD vary globally, diabetes and hypertension are the main causes of CKD in all high- and middle-income counties, as well as in many low-income countries, whereas glomerulonephritis is another important cause of CKD, especially in Asia and sub-Saharan Africa.[87] Environmental exposures to metals and organic compounds have also been implicated in CKD epidemics,[87,89,90] and epidemiologic relationships have been identified between toxic metals, such as lead, and organic compounds, such as PFAS, with CKD.[9,91] In addition, albuminuria is an indicator of CKD and could also be a pathway of PFAS excretion given that many PFAS have been shown to bind to serum albumin.[15–17] The impact of albuminuria on PFAS toxicokinetics is discussed in the subsequent PBPK modeling section.

Previous studies have demonstrated that renal transporter expression levels were altered by the presence of kidney disease, with transporter- and disease-specific outcomes in rats,[45,92–97] and humans.[98,99] On the other hand, changes in renal transporter expression levels and function could also lead to kidney disease progression.[100–103] The changes that may occur in renal transporters because of different kidney disease pathologies or over the development of disease are not fully understood owing to the complexity of kidney diseases and the fact that they often occur alongside other comorbidities, such as diabetes, high blood pressure, and cardiovascular disease.[104–107] Nevertheless, we summarized the current knowledge on changes in the expression levels of renal transporters that have the ability or the potential for PFAS transport according to reported specified kidney diseases.

Most of the available information was derived from animal models and *in vitro* approaches. Human evidence (Figure 3A) included significantly lower BCRP expression levels in patients with glomerulonephritis secondary to small vessel vasculitis (SVV) and in P-gp expression levels in patients with glomerulonephritis secondary to systemic lupus erythematosus (SLE).[108] Nonsignificant differences were observed for other transporters (i.e., OATP1A2 and MRP2) in different patient groups (i.e., SVV, SVV-control, SLE, and SLE-control, Figure 3A).[108] An *ex vivo* study found that expression levels of P-gp in Sprague-Dawley female rats were $\sim 260\%$ and $\sim 160\%$ higher compared with levels in control rats 4 wk after uninephrectomy and 2 wk after uninephrectomy and diabetes, respectively (Figure 3B).[42] Six research articles were selected for reporting the time-dependent expression-level differences in renal transporter expression in rats with experimental drug (e.g., lycopene, cisplatin)–induced AKI or ischemia/reperfusion–induced AKI.[40,43,109–112] After compiling the data for each transporter from different articles (articles 1–11 in Table 4), we found a U-shaped distribution for Oat1 and Oat3 expression levels as a function of time, with either lower expression or no difference in expression compared with the levels of controls (Figure 3C). Oatp1a1 expression levels were 20% of control levels in 96 h after cisplatin-induced AKI (Figure 3C),[114] whereas Mrp2 expression levels were 220% and 280% of control levels in 96 h[114] and 240 h,[109] respectively, after cisplatin-induced AKI (Figure 3D). Expression levels of Mrp1 and P-gp also were higher—180% and 600% of control levels in 96 h after cisplatin-induced AKI.[114] More renal transporters were investigated in experimental CKD than AKI using rat models. Similar to the distribution in AKI, Oat1 and Oat3 expression levels in rats showed a U-shaped pattern with time after 5/6 nephrectomy (Figure 4A) based on data compiled from literature (articles 12–19 in Table 4).[41,44,45,117] In addition, expression levels of all targeted SLC transporters (i.e., Oat2, Urat1, Oatp1A1, Asbt, Ost α/β, Npt1, and Npt4) and Bcrp (ABC transporter) were lower in rats with CKD, whereas expression levels of Mrp2 (ABC transporter) were higher and diminished with time after 5/6 nephrectomy (Figure 4A,B).[94,118–120]

PBPK Modeling in Populations with Kidney Disease

We identified 258 papers from the search for PFAS-related PBPK models. After exclusion of 221 papers that did not develop PBPK models for PFAS, 37 studies that reported on PFAS-specific PBPK models were included in this review (Excel Table S3). Among these 37 studies, 9 did not consider renal reabsorption

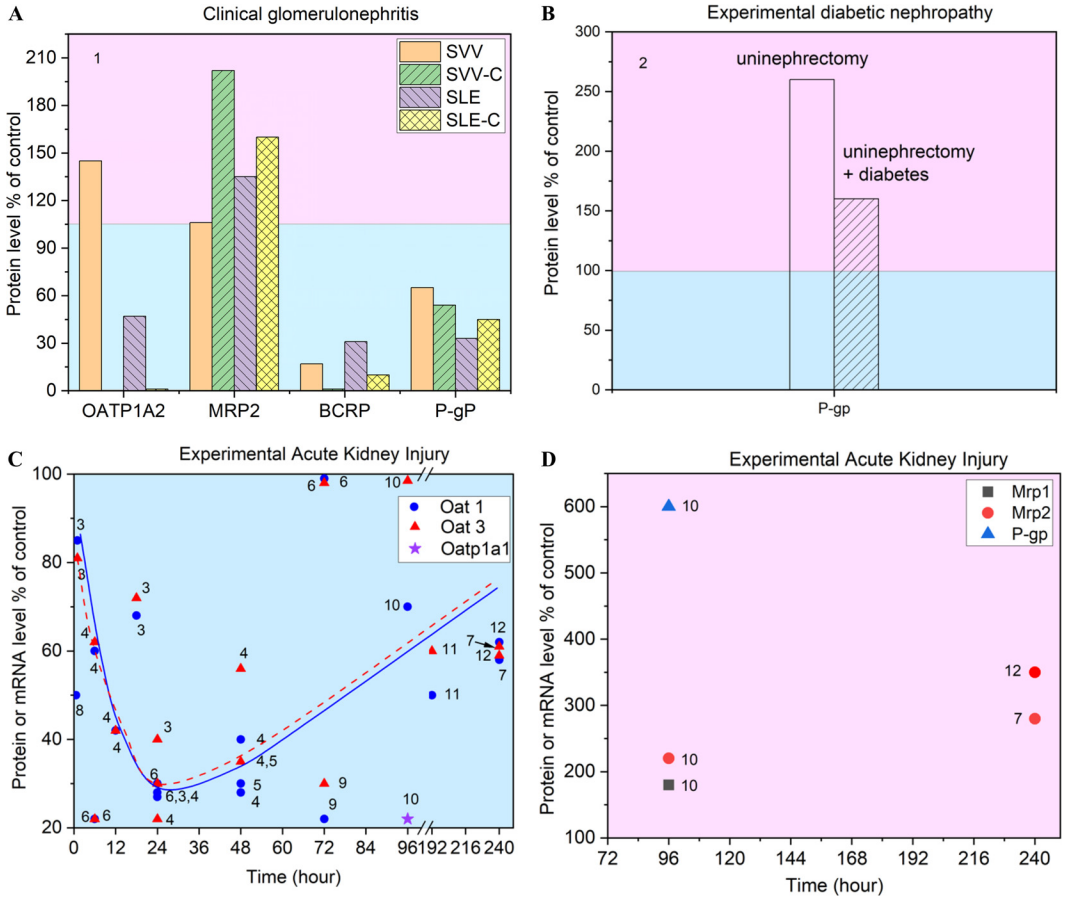

Figure 3. Renal transporter expression levels (percentage of control) in (A) human clinical glomerulonephritis, (B) experimental diabetic nephropathy in rats, and (C,D) experimental acute kidney injury in rats summarized from previous studies. In (A,B), the light blue shading below the horizontal line at 100 indicates value $<100\%$ and light purple shading above the horizontal line at 100 indicates value $>100\%$. All data used to construct the figures were extracted from the literature (see Table 4 and Excel Table S4 for references). Numbers in the figure are ordered according to Table 4 references. The numbers of people or animals included in the reviewed studies are provided in Table 4. Note: BCRP, breast cancer resistance protein; MRP/Mrp, multidrug resistance proteins; OAT/Oat, organic anion transporters; OATP/Oatp, organic anion-transporting polypeptides; P-gp, P-glycoprotein; SLE, glomerulonephritis secondary to systemic lupus erythematosus; SLE-C, SLE-control; SVV, glomerulonephritis secondary to small vessel vasculitis; SVV-C, SVV-control.

in their PBPK models,[121–129] and 24 of them considered renal reabsorption using a transporter maximum (T_m, representing transporter saturation) and an affinity constant (k_t, representing transporter uptake), but none of them were transporter-specific.[130–153] Four publications included transporter-specific pathways, with 2 for PFAS in fish,[154,155] and 2 for PFAS in male rats.[13,156]

PBPK models are useful tools to simulate the processes of absorption, distribution, metabolism, and excretion (ADME) of chemicals in different organs and tissues in animals and humans.[157] In addition, PBPK models provide a link between external exposure and internal toxicokinetics and can be used in two different frameworks. First, these models can help characterize the relationship between exposure dose and the effects on the chemical concentrations in the target organs.[158] Second, PBPK models can predict the external exposure using human biomonitoring data, such as chemical levels in blood or urine.[159] This inverse prediction can also be used in estimating the reference dose in support of risk assessment.[160] Previous studies have revealed that PFOA strongly binds to serum albumin, resulting in a long half-life in human blood[161] and that active renal reabsorption contributes to sex- and species-specific differences in PFAS half-lives.[20]

The permeability-limited PFOA-PBPK model for male rat developed by Cheng and Ng included four kidney transporters (i.e., Oat 1, Oat 3, Oatp1a1, and Ost α/β).[13] Although three of the four transporters (but not Ost α/β) showed significant changes in expression levels during experimentally simulated kidney diseases in previous studies,[103] only Oat1 and Oat3 had significant changes at the same time points (Figures 3 and 4). In addition, the Cheng and Ng model[13] included glomerular filtration as a pathway for PFAS excretion using a parameter for GFR, which might change significantly during the development of kidney disease. In this section, we describe using the Cheng and Ng model to simulate changes in transporter expression levels (by setting the clearance rate constant of Oat1 and Oat3 to 20% of the model default), in GFR (by setting GFR to 33%[43] and 5%[43] of the model default), and in albumin concentrations (by setting albumin concentration to 70% of the model default) to explore how such changes during kidney disease could affect PFOA toxicokinetics in the male rat. For transporter levels, the changes of Oat1 and Oat3 expression at 6 wk in Figure 4A were used to represent the worst-case scenario.

Serum PFOA toxicokinetics modeled using the modified Cheng and Ng PBPK model (Figure 5) showed biphasic patterns with fast initial clearance, during which the serum half-life (also called the apparent half-life) was short, and slow terminal clearance during which the half-life (also called the terminal half-life, $t_{1/2\infty}$) was long. The $t_{1/2\infty}$ reflected the rate and extent of elimination after the chemical or drug was accumulated, distributed, and reached pseudo-equilibrium. The serum PFOA $t_{1/2\infty}$ was longer in rats with decreased levels of Oat 1 and Oat 3 and GFR compared with healthy rats (Figure 5A,B) with normal levels. In addition,

Table 4. Literature sources for expression-level changes in putative PFAS renal transporters in various kidney disease conditions.

Reference number in Figures 3 and 4	Reference	Investigated transporters (PFAS-related)	Disease type	People (n) or animals (N)
1	108	P-gp; BCRP; MRP2; OATP1A2	Clinical glomerulonephritis	SVV: $n = 35$; SLE: $n = 36$
2	42	P-gp	Experimental diabetic nephropathy with rat	$N = 10$
Ex vivo Experimental AKI				
3	40	Oat1; Oat3	AKI with male rat	$N = 4$
4	111	Oat1; Oat3	AKI with male rat	$N = 3$
5	112	Oat1; Oat3	AKI with male rat	$N = 8$
6	43	Oat1; Oat3	AKI with female rat	$N = 3$–24
7	109	Oat1; Oat3; Mrp2	AKI with rat	$N = 7$
8	110	Oat1	AKI with rat	$N = 2$–5
9	113	Oat1; Oat3	AKI with rat	$N = 3$–5
10	114	Oat1; Oat3; Oatp1a1; Mrp1; Mrp2; P-gp	AKI with rat	$N = 6$
11	115	Oat1; Oat3	AKI with rat	$N = 4$
12	116	Oat1; Oat3; Mrp2	AKI with rat	$N = 3$
Ex vivo Experimental CKD				
13	44	Oat1; Oat3	CKD with male rat	$N = 6$–7
14	117	Oat1; Oat3	CKD with male rat	$N = 7$–10
15	45	Oat1; Oat2; Oat3; Urat1; Oatp1a1	CKD with male rat	$N = 12$
16	41	Oat1; Oat3	CKD with male rat	$N = 4$
17	118	Urat1; Bcrp	CKD with male rat	$N = 3$–7
18	119	Oatp1a1; Asbt; Ost α/β	CKD with male rat	$N = 8$
19	120	Bcrp; Mrp1; Mrp2	CKD with male and female rat	$N = 6$–7
20	94	Mrp2; P-gp	CKD with male rat	$N = 8$

Note: AKI, acute kidney injury; ASBT/Asbt, apical sodium-dependent bile acid transporter; BCRP/bcrp, breast cancer resistance protein; CKD, chronic kidney disease; MRP/Mrp, multidrug resistance proteins; OAT/Oat, organic anion transporters; OATP/Oatp, organic anion-transporting polypeptides; OST, organic solute transporter; PFAS, per- and polyfluoroalkyl substances; P-gp, P-glycoprotein; SLE, systemic lupus erythematosus; SVV, small vessel vasculitis; URAT/Urat, urate transporter.

both the decrease of transporter expression levels (i.e., Oat1 and Oat3) and GFR resulted in higher PFOA concentrations in plasma than those in healthy rats. PFOA toxicokinetics were more influenced by changes in GFR than in transporter expression levels, whereas serum PFOA $t_{1/2\infty}$ was more influenced by changes in transporter expression levels than GFR (Figure 5A,B). However, it is noteworthy that the modeled PFOA toxicokinetics ignored the influence of reabsorption transporter (Oatp1a1) changes in disease owing to a lack of data for this polypeptide (at the same time points as Oat1 and Oat3). Serum PFOA $t_{1/2\infty}$ were comparable between rats with 70% decreased albumin concentrations and healthy rats; however, the half-life at the initial phase was shorter in rats with decreased serum albumin concentration (Figure 5C), indicating a faster PFOA elimination due to the decrease of albumin. Lower serum PFAS measured in humans with albuminuria provides inferential evidence that this elimination difference also pertains to humans.[162] It should be noted that the model results were based on a single simulated exposure; in the real world, humans have continuous exposures, primarily by ingestion and inhalation, as well as complex patterns of excretion in progressive stages of kidney disease. This means, in the real world, the human body burden of PFAS may be elevated compared with the simulated scenario, particularly in populations with specific kidney diseases, although human populations with any albuminuria could have lower PFAS concentrations in serum than those with normal or mildly impaired renal function.

Discussion

Research Gaps and Promising Directions for PFAS Interactions with Renal Transporters

As knowledge around PFAS renal elimination has progressed to the molecular and cellular levels, a number of human and rat renal

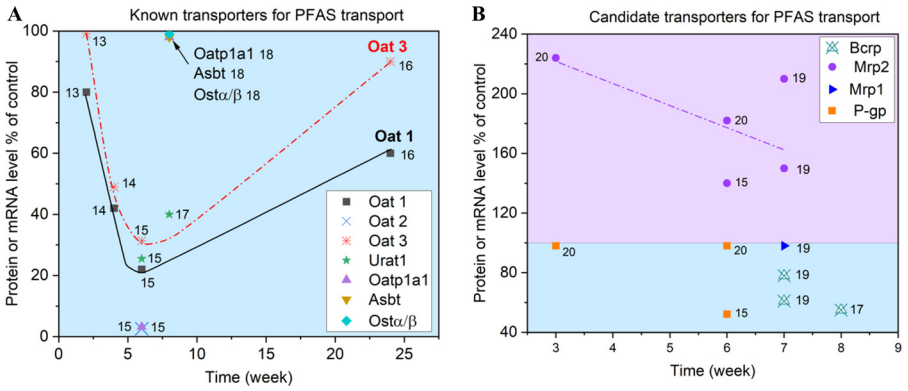

Figure 4. Expression levels of (A) current known renal transporters for PFAS transport and (B) candidate renal transporters for PFAS transport as a percentage of control in experimental chronic kidney failure in rats, summarized from reviewed studies. Light blue shading below the horizontal line at 100 indicates value $< 100\%$ and light purple shading above the horizontal line at 100 indicates value $> 100\%$. All data used to construct the figures were extracted from *ex vivo* studies from the literature (see Table 4 and Excel Table S4 for references). Numbers in the figure are ordered according to Table 4 references. Numbers of animals in the reviewed studies are provided in Table 4. Note: ASBT/Asbt, apical sodium-dependent bile acid transporter; BCRP/Bcrp, breast cancer resistance protein; MRP/Mrp, multidrug resistance proteins; OAT/Oat, organic anion transporters; OST, organic solute transporter; P-gp, P-glycoprotein; PFAS, per- and polyfluoroalkyl substances; URAT/Urat, urate transporter.

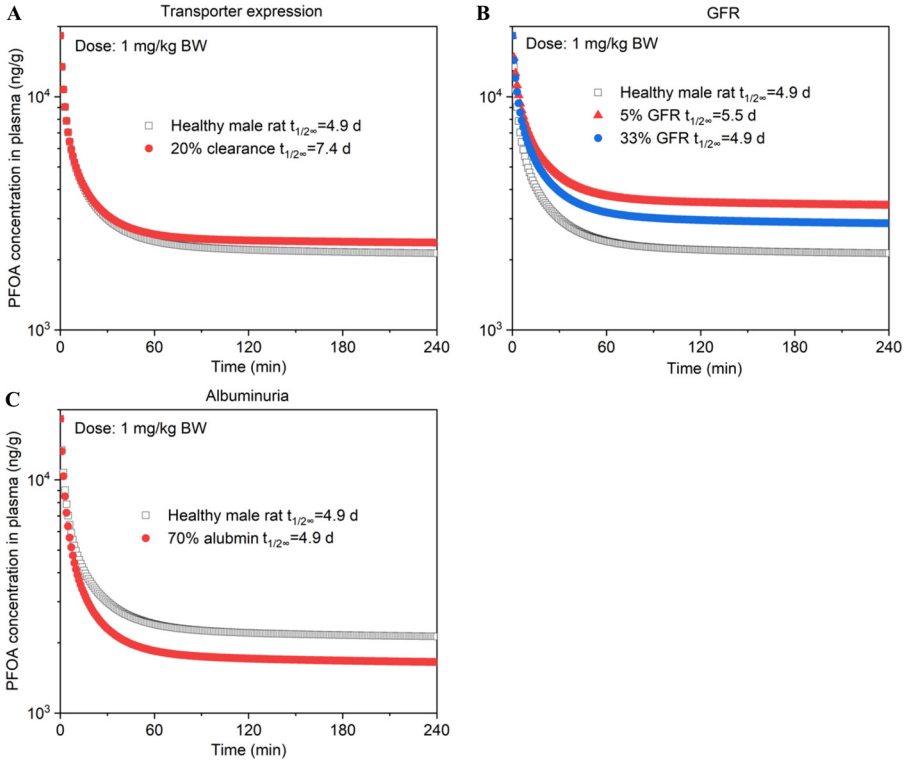

Figure 5. Simulations of PFOA toxicokinetics using the Cheng and Ng model[13] for male rats. (A) Effect of decreased expression levels of Oat1 and Oat3 (the clearance rate constants for Oat1 and Oat3 were set to 20% of the original model default value, and the transporter expression changes were obtained from Figure 4A) on PFOA half-life. (B) Effect of decreased GFR (by setting GFR to 33%[43] and 5%[43] of the model default) on serum PFOA half-life. (C) Effect of decreased albumin concentration mimicking albuminuria (by setting albumin concentration to 70% of the model default) on PFOA half-life. All data used to construct the figures are provided in Excel Table S5. Note: GFR, glomerular filtration rate; OAT/Oat, organic anion transporters; PFOA, perfluorooctanoic acid.

transporters located at the basolateral and apical membranes of proximal tubular cells have been investigated for their interactions and affinities with PFAS molecules.[22,26,27] Several human and rat renal transporters, such as OATs/Oats,[38] OST α/β,[21] and ASBT[21] have been shown to facilitate PFAS transport with medium-to-high affinities, and these affinities were also related to PFAS structures. To date, more renal uptake transporters (e.g., most SLC transporters) than efflux transporters (e.g., ABC transporters) have been studied in human and rat systems (Figure 2), based on interest in the renal reabsorption pathway extending PFAS half-lives. As a result, knowledge on the interactions between renal efflux transporters and PFAS remains incomplete. Some branched isomers of PFAS (e.g., of PFOS and PFOA) have been shown to have longer or much shorter half-lives than corresponding linear isomers in humans[163]; however, to the best of our knowledge, no related studies have been done in terms of renal transporters. In addition, the huge PFAS family includes not only the anionic PFAAs that are the ones studied until now, but also polyfluorinated substances and PFAS that are cationic or zwitterionic at environmental pH values.[164] Renal organic cation transporters (OCTs, from the *SLC*22 gene family) and multidrug and toxicant extrusion proteins (MATEs, from the *SLC*47 gene family) could be involved in cationic and zwitterionic PFAS transport.

Selection of an appropriate experimental model is an important consideration for studies of PFAS toxicokinetics and toxicodynamics and to understand the relevance for human and wildlife risk assessments. For example, in zebrafish, PFOA renal elimination is probably mediated by transporters other than Oatp1d1.[67] Although the endocrine system has been reported to be very similar in teleost fish and mammals, the role of the Oatp1 transporter in transporting PFAS differed substantially between zebrafish and mammals, and the substrate-binding sites of Oatp1d1 and mammalian OATP1 differed to some extent.[67] Therefore, zebrafish cannot be directly used as a model to study mammalian OAT/Oat transport systems with respect to PFAS transport and disposition.[67] Only a handful of PFAS, most notably PFOA, have been studied in terms of their interactions with renal transporters. Studies of more PFAS, especially the current-use PFAS (including shorter-chain PFAS and replacements, such as GenX) are also needed for better coverage of the role of transporters across the structurally diverse PFAS family.

This review has focused on direct PFAS transport by kidney transporters. Although we did not include the topic of transporter inhibition by PFAS, PFOA has been shown to induce Bcrp expression in mice and may inhibit the human BCRP transporter function at concentrations that exceed levels observed in humans.[165] In addition, nanomolar levels of GenX inhibited P-gp and Bcrp but not Mrp2 transporter activities in male and female rats, and GenX reduced P-gp and BCRP transporter activity in human cells.[166] Inhibition of transporter activity by a specific PFAS does not necessarily mean that the transporter can transport that specific PFAS. However, the inhibition of a transporter could influence its ability to transport other substrates (e.g., endogenous ligands or other PFAS). Adding to the complexity, different PFAS may compete with each other for binding to transporters.[167] Therefore, future work should also consider the inhibitory effect of PFAS on transporters and competitive binding, which are important considerations in the context of PFAS mixtures.

More Work Needed regarding Renal Transporters in Health and Disease

We have proposed a candidate list of renal transporters that have the potential for PFAS transport as a result of this review (Table 3).

This list will lengthen as the knowledge of PFAS-biomarker relationships, as well as information on the endogenous substrates of proteins, progresses. Animal experimental work addresses one aspect of the role of expression-level changes in renal transporters altered by kidney disease state. Overall, expression levels of SLC transporters (e.g., Oat1, Oat3, Oatp1a1), which are mainly uptake transporters, initially decreased and sometimes fully or partially returned to normal as the recovery progressed in surgically induced AKI and CKD, whereas expression levels of ABC transporters (e.g., Mrp 1, Bcrp, P-gp), which are mainly efflux transporters, had specific outcomes. For example, expression levels of BCRP and P-gp in humans with clinical glomerulonephritis was $\sim 70\%$ and $\sim 40\%$ lower, respectively,[108] whereas levels of P-gp in experimental rats with diabetic nephropathy was 50% higher.[42] Currently, clinical evidence for transporter changes in kidney diseases is scarce. PFAS-transporter roles and changes as a function of disease or developmental stages, as well as interaction with and modifications by other toxicants and medications, are poorly understood. In addition, specific changes in GFR, along with transporter expression changing during kidney disease, are also important for predicting PFAS toxicokinetics. Menstrual blood loss, breast-feeding, and childbirth are sex-specific excretion routes for PFAS[65,168] that could contribute to sex differences, but sex differences in the changes in expression levels of renal transporters may also play a role. These major research gaps are critical to understanding the interindividual variabilities in PFAS toxicokinetics and identifying particularly sensitive populations.

More Work Needed to Advance PBPK Models

PFOA toxicokinetics have been studied in patients with advanced cancer by Convertino et al., and they posited that the previously published half-lives of PFOA in healthy humans (i.e., 2–3 y[52]) were significantly longer than actual half-lives.[52] However, a limitation of that study was that they did not consider the influence of disease on PFOA elimination by the human body. This could be important because the renal transporter protein levels and GFR could be significantly altered in humans with kidney disease,[169] which will further strongly influence PFAS elimination from the human body. In addition, the fundamental limitation reported in the conclusions by Convertino et al.[124] concerning the PFOA half-life was the use of acute chemotherapeutic PFOA doses, which are orders of magnitude greater than chronic environmental exposures. To the degree that Convertino et al.[124] half-life data in terminally ill cancer patients can be interpreted, the apparently shorter half-lives most likely reflect a limit of reabsorption kinetics and binding capacity that operates at some point in the large exposure difference between the highest chronic environmental and the acute chemotherapeutic doses. More accurate, quantitative, and comprehensive characterization of renal tubular secretion and reabsorption pathways in both health and disease is required to further advance PFAS-PBPK models, especially for understanding the impacts of kidney disease on PFAS toxicokinetics. Appropriate exposure doses are also critical to toxicokinetic studies.

Fenton et al.[170] showed that GFR had sex- and age-dependent patterns, with significantly higher GFR in human males than females (92.0 vs. 88.1 mL/min per 1.73 m^2), in a healthy population from 20 to 80 years of age. In addition, GFR was ~ 100 mL/min per 1.73 m^2 until 35 years of age, followed by linear decreases along age increases, with a faster decline in females compared with males, and the major proportion of the healthy population >60 years of age had a GFR <60 mL/min per 1.73 m^2.[170] Variability in GFR in healthy populations could result in variability in PFAS toxicokinetics. According to Figure 5B, using a lower GFR in the model resulted in slower PFAS elimination (i.e., longer half-lives) and higher plasma PFAS concentrations in male rats compared with healthy male rats. Similarly, in humans, senior groups could have slower PFAS elimination (i.e., longer half-lives) and higher PFAS concentrations accumulated in blood compared with people <35 years of age. In addition, males have slightly faster PFAS elimination than females via the glomerular filtration pathway; however, transporter-facilitated pathways also contribute to sex differences in PFAS renal elimination.[20] There is limited information on the variability in transporter expression levels in humans. Moreover, to the best of our knowledge, there are no transporter-specific PFAS-PBPK models for humans so far. In this review, we used an existing PFOA-PBPK model for male rats to investigate the influence of changes in transporter levels, GFR, and serum albumin on PFOA toxicokinetics. However, translating these conclusions across species can be difficult owing to species differences. Therefore, more work is needed to understand the impacts of variability in transporter expression changes on the variability in PFAS toxicokinetics in humans.

Conclusion

Research on PFAS transport by renal transporters is increasing, yet the diversity of investigated PFAS and transporter types remains limited. Evidence supports that renal reabsorption is responsible for some sex- and species-specific differences in PFAS half-lives. Therefore, renal transporters that facilitate reabsorption have received more attention compared with those that facilitate excretion. Further studies are needed to explore additional renal transporters to fully understand the renal elimination mechanisms and to include more PFAS compounds, particularly the current-use PFAS, such as shorter-chain PFAS, to advance knowledge of their renal transport processes. In this review, we have identified seven potential PFAS transporters that should be prioritized for experimental evaluation. Kidney disease status can alter renal transporter expression levels and, therefore, influence the renal PFAS elimination; however, very limited work has been conducted investigating how various kidney diseases impact PFAS toxicokinetics. Moreover, research gaps exist in understanding the expression changes of renal transporters as a function of developmental stages at different life stages. PBPK models are useful tools for simulating PFAS toxicokinetics; however, they require PFAS-specific data and complex parameters describing ADME mechanisms. Unfortunately, most of the data and parameters specific to PFAS are not currently available. Alternatively, *in silico* and *in vitro* methods could aid in PBPK parameterization. Progress on more mechanisms of toxicokinetics for the broad PFAS class in kidney health and disease status is critically needed to comprehensively assess human health risk and identify vulnerable populations.

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