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Article

PFAS Depuration in Humans: Toxicokinetics, Elimination Strategies, and Clinical Challenges

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Abstract

Per- and polyfluoroalkyl substances (PFAS) are a class of persistent synthetic chemicals that bioaccumulate in humans, with measurable body burdens in nearly all individuals. Their persistence arises from metabolic inertness and efficient renal and enterohepatic recirculation, resulting in biological half-lives of several years. Epidemiological studies increasingly associate chronic PFAS exposure with adverse outcomes, including endocrine disruption, cardiovascular disease, immunotoxicity, and male reproductive effects. While reducing environmental sources remains critical, there is an urgent need for strategies that accelerate elimination in individuals with elevated burdens. This review synthesizes current research on human PFAS depuration, highlighting toxicokinetic mechanisms underlying their persistence, including serum protein binding and transporter-mediated recirculation. Clinical interventions are critically assessed, with particular focus on pharmaceutical agents that disrupt recirculation pathways. Notably, bile acid sequestrants such as cholestyramine have demonstrated significant efficacy in recent trials. Emerging lifestyle-based approaches, including dietary fiber supplementation and physical activity, are also considered for their potential to enhance elimination and counteract metabolic disturbances. The most pressing research gap is the lack of long-term clinical studies that directly link reductions in PFAS body burden to demonstrable health improvements, and integrating depuration strategies with broad public health measures will therefore be essential to address this global challenge.

Keywords: PFAS, Toxicokinetics, Bioaccumulation, Elimination, Biological half-lives, Recirculation, Bile acid sequestrants, Cholestyramine, Plasmapheresis, Dietary Fiber

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Abbreviations: Per and polyfluoroalkyl substances (PFAS), Cardiovascular Disease (CVD), Human Serum Albumin (HSA), Perfluoroalkyl Acids (PFAAs), Organic Anion Transporters (OATs), Organic Anion Transporting Polypeptides (OATPs), Sodium Taurocholate Cotransporting Polypeptide (NTCP), Multidrug Resistance Associated Protein 2 (MRP2), Multidrug Resistance Associated Protein 4 (MRP4), Breast Cancer Resistance Protein (BCRP), Uric Acid Transporter 1 (URAT1), Firefighter Collaborative Research Project (FCRP), Apical Sodium Dependent Bile Acid Transporter (ASBT), Diabetes Prevention Program (DPP), Solute Carrier Transporters (SLC), ATP Binding Cassette (ABC)

1. Introduction

Per- and polyfluoroalkyl substances (PFAS) are a large group of synthetic chemicals characterized by carbon-fluorine bonds, which are among the strongest in organic chemistry. These bonds confer exceptional stability [1], but this resilience also makes them environmentally persistent "forever chemicals" that resist degradation [2]. Their widespread use in industrial applications and consumer products has led to ubiquitous environmental

contamination, making human exposure a global reality, primarily through drinking water and food [3]. Consequently, nearly all individuals have a detectable body burden [4]. This persistent internal body burden is a significant public health concern, as a growing body of epidemiological evidence links chronic exposure to a spectrum of adverse health outcomes [5]. Mounting evidence suggests that PFAS act as endocrine-disrupting chemicals, with studies linking exposure to an increased risk of obesity, unfavorable cardiometabolic profiles [6], and metabolic disruption [7]. The cardiovascular system appears particularly vulnerable, with extensive evidence suggesting that accumulated serum levels contribute to an increased risk of cardiovascular disease (CVD) [8]. Furthermore, PFAS exposure is negatively associated with male reproductive health, including testicular dysfunction and reduced semen quality [9].

The remarkable bioaccumulation of these compounds is driven by their unique toxicokinetic properties, leading to biological half-lives that can span many years [10]. This persistence is governed by mechanisms that include metabolic inertness, high affinity for serum protein binding, and highly efficient transporter-mediated renal and enterohepatic recirculation, which form the basis for all removal strategies [11]. These processes effectively prevent the natural elimination of PFAS from the body.

Although most of PFAS research has focused on environmental detection and remediation, relatively little attention has been paid to strategies that actively reduce the body burden of PFAS in humans [12]. Given their long biological half-lives and potential for chronic harm, there is a critical need for effective strategies to accelerate the elimination of these chemicals in individuals with high body burdens [13]. This review narrows this gap by synthesizing the current state of research on human PFAS depuration. The sections that follow progress from foundational concepts in PFAS chemistry and toxicokinetics to evidence on natural human elimination rates, physiological and lifestyle modifiers [14], and pharmacological interventions, such as the use of bile acid sequestrants like cholestyramine, which has shown significant efficacy [15]. The interplay between environmental exposure reduction and body burden is also examined, and challenges, methodological limitations, and future research directions are discussed, emphasizing the most critical research gap: the necessity for long-term clinical trials to conclusively associate a reduction in the PFAS body burden with measurable improvements in health outcomes. This will be crucial for validating future therapeutic interventions.

2. The Toxicokinetic Basis of PFAS Persistence and Bioaccumulation

The remarkable persistence of per and polyfluoroalkyl substances (PFAS) in the human body is not a passive process but an active one, dictated by a specific set of physicochemical properties and their interactions with biological systems [16]. Comprehending the toxicokinetic processes of absorption, distribution, metabolism, and excretion is essential for developing effective strategies to facilitate PFAS elimination and for accurately evaluating their associated health risks [17].

2.1. Chemical Properties and Exposure Pathways

PFAS are synthetic compounds characterized by a carbon fluorine (C-F) bond, one of the strongest bonds in organic chemistry, which makes them resistant to metabolic breakdown [18]. Most PFAS are amphiphilic, possessing a water repelling (hydrophobic) fluorinated tail and a water attracting (hydrophilic) head. Figure 1 illustrates this general molecular structure, highlighting the common functional head groups (e.g., carboxylate or sulfonate) and the stable perfluorinated tail. This structure drives them to bind with proteins rather than accumulating in fatty tissues, which is a key difference from many other persistent pollutants [19]. These structural characteristics, including carbon chain length and functional groups, significantly influence their environmental mobility and bioaccumulation potential [20].

Human exposure occurs via multiple pathways. The most common routes for the general population are the ingestion of contaminated drinking water and food [21]. Dietary intake can result from bioaccumulation in food chains and migration from food packaging materials. Inhalation of contaminated indoor dust from consumer products, such as stain repellent carpets and textiles, is another significant source of exposure [22]. Occupational exposure can be significant for workers in industries that manufacture or use PFAS containing products. Dermal absorption may occur through contact with contaminated soil, water, or consumer goods treated with PFAS [23]. Additionally, prenatal exposure can occur through placental transfer, potentially impacting fetal development and posing risks to newborns [24].

2.2. Absorption, Distribution, and Protein Binding

Once ingested, PFAS are readily absorbed into the bloodstream, with bioavailability often exceeding 90% for legacy compounds. In circulation, they bind strongly to serum proteins, primarily human serum albumin (HSA) and globulins [25,26]. This protein binding is a critical determinant of their toxicokinetics. Recent research has shown that this binding preference depends on the length of

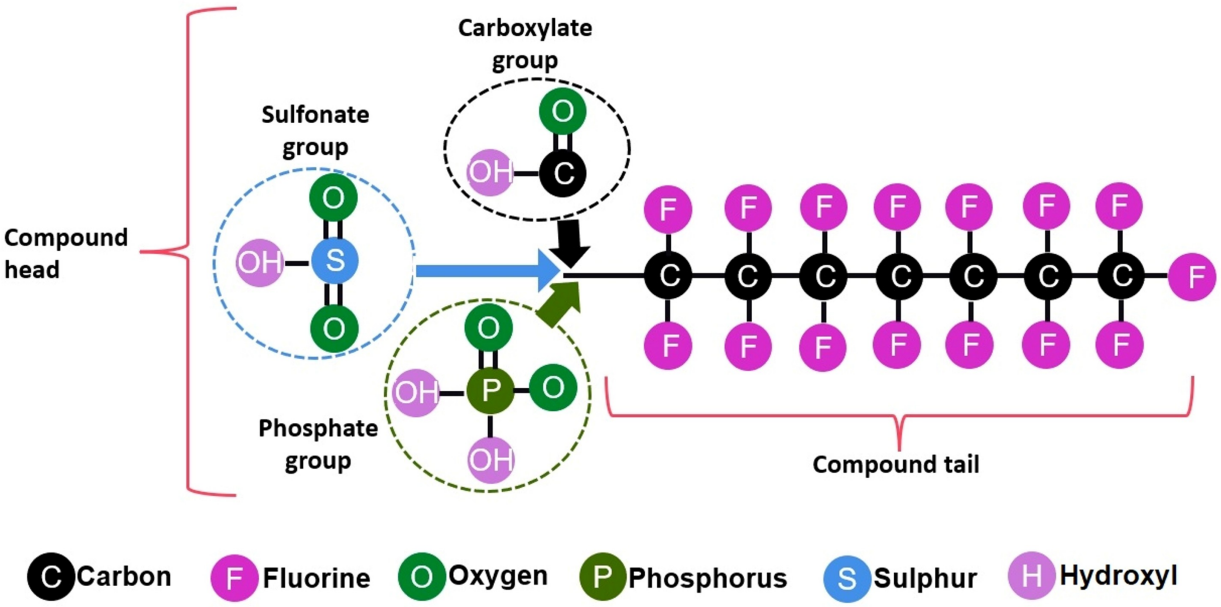

Figure 1. Generalized chemical structure of a per and polyfluoroalkyl substance (PFAS). The structure consists of a hydrophilic functional head (e.g., sulfonate, carboxylate, or phosphate group) and a hydrophobic, perfluorinated carbon chain tail.

the perfluorinated carbon chain (ηpfc); shorter chain PFAS ($\eta pfc<7$) bind preferentially to HSA, whereas longer chain congeners ($\eta pfc\geq 7$) show an increasing affinity for globulins [27]. This strong protein binding sequesters the vast majority of PFAS within the circulatory system, restricting their elimination via filtration in the kidneys and dictating their distribution to protein rich tissues, such as the liver and kidneys [28]. Isomer specific differences also influence the distribution, with linear isomers showing different partitioning between plasma and blood cells compared to their branched counterparts [29]. Beyond the blood and liver, recent evidence suggests that bone may be an additional long term storage site [30,31]. Furthermore, PFAS can cross the placenta and are transferred via human milk, leading to exposure during critical developmental windows [32,33].

2.3. The Recirculation Bottleneck and Biological Half Life

Perfluoroalkyl acids (PFAAs), a major subclass of PFAS, are metabolically inert. Their elimination is therefore entirely dependent on physical excretion, which is severely limited by two active physiological loops that create a "recirculation bottleneck":

Renal Reabsorption: In the kidney, a small fraction of PFAS filtered from the blood is efficiently reabsorbed into circulation by organic anion transporters (OATs) and organic anion transporting polypeptides (OATPs) [30,31].

Enterohepatic Recirculation: In the gastrointestinal system, PFAS excreted from the liver into bile are reabsorbed from the intestine back into the blood [34,35].

Computational modeling suggests that the binding affinity of PFAS to key transporters in this pathway is a critical predictor of their human half lives [27,36]. These highly efficient recirculation mechanisms are the primary reason for the exceptionally long biological half lives of many PFAS, which can range from several years to over a decade for compounds such as perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), and perfluorohexane sulfonate (PFHxS). Excretion of PFAS also occurs to a lesser extent through the hair and nails [37]. A conceptual schematic of human PFAS exposure, hepatic handling (including enterohepatic recirculation), and renal secretion and reabsorption leading to urinary excretion is presented in Figure 2.

2.4. Congener Specific Differences

The toxicokinetic behavior of PFAS varies significantly based on their chemical structures.

Long chain PFAS (e.g., PFOA, PFOS, and PFHxS): These compounds have half lives measured in years. Their persistence is driven by the recirculation mechanisms described above [38]. PFOA elimination is primarily limited by renal reabsorption, whereas PFOS persistence is significantly influenced by a highly efficient enterohepatic loop. PFHxS has one of the longest half lives, often exceeding a decade, suggesting that it is subject to extremely efficient reabsorption in both the kidneys and the gut [39,40].

Short Chain PFAS (e.g., PFBS, PFBA): In contrast, shorter chain alternatives have biological half lives on the order of days to weeks. Their shorter fluorinated tails lead to

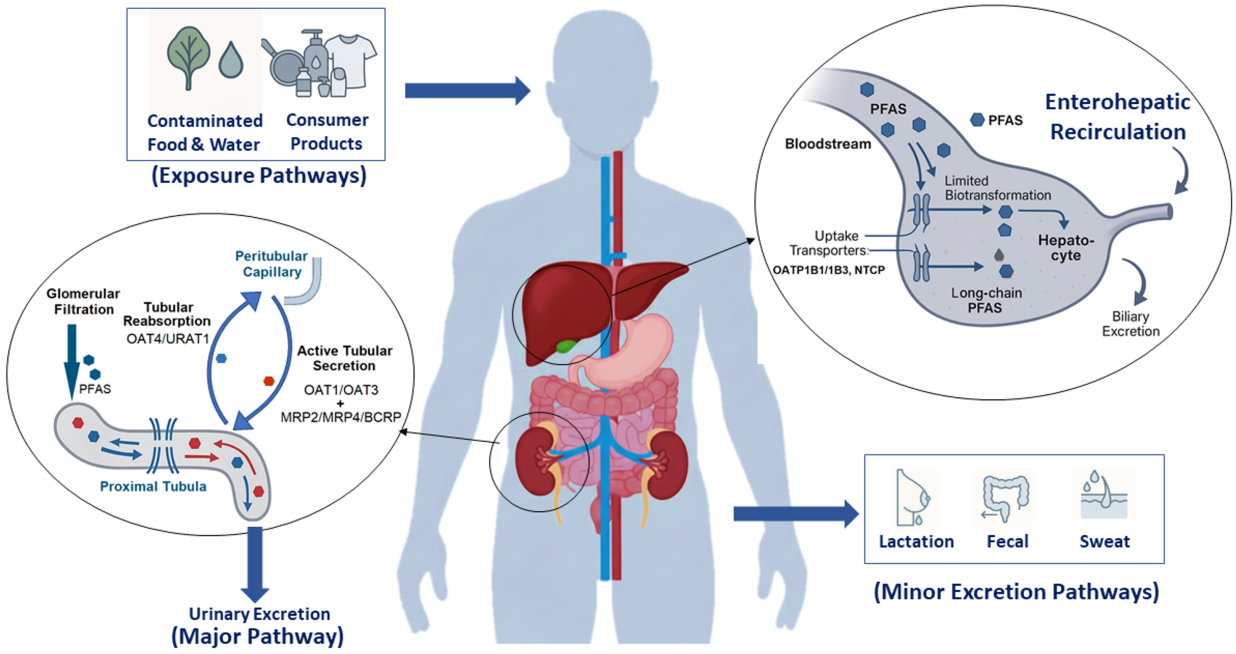

Figure 2. Human exposure, disposition, and clearance of PFAS. Exposure occurs primarily through contaminated food, water, and consumer products. After absorption into the blood, PFAS undergo hepatic uptake into hepatocytes via OATP1B1/1B3 and NTCP, with limited biotransformation, biliary excretion, and enterohepatic recirculation that prolong their persistence in the body. In the kidney, PFAS are filtered at the glomerulus, actively secreted by basolateral OAT1/OAT3 with apical efflux (MRP2/MRP4/BCRP), and reabsorbed from the tubular lumen via OAT4/URAT1; net urinary excretion is the major elimination pathway. Minor excretion pathways include fecal elimination (from bile) and lactational transfer.

weaker interactions with reabsorptive transporters, resulting in more efficient urinary excretion. Consequently, they do not bioaccumulate to the same extent as their long chain counterparts [41].

This differential behavior underscores the need for any effective strategy for risk assessment or removal to be tailored to the specific profile of the PFAS congeners present [42].

3. Clinically Investigated Interventions for Accelerating PFAS Elimination

Given the long biological half lives of many PFAS, research has shifted from observation to intervention, exploring strategies to accelerate their removal from the human body. The primary focus has been on repurposing existing drugs and procedures to interrupt the physiological pathways responsible for PFAS retention [43,44].

3.1. Pharmaceutical Approaches: Bile Acid Sequestrants

The most compelling evidence for a human depuration strategy comes from the use of bile acid sequestrants such as cholestyramine. These are non-absorbable anion exchange resins that bind to bile acids in the intestine. This action prevents the reabsorption of bile acids, thereby interrupting the enterohepatic circulation loop [34]. Because certain PFAS, particularly long chain sulfonates like PFOS, are excreted from the liver into the bile, they can also be bound by the resin in the gut. This sequestration prevents their reabsorption back into the bloodstream and shunts them toward permanent elimination in the feces [39,40]. A landmark randomized, placebo controlled, crossover clinical trial demonstrated the profound efficacy of this approach in 45 adults with high occupational PFAS exposure. Treatment with cholestyramine (three times daily) for 12 weeks resulted in a mean 60% decrease in serum PFOS levels. The intervention also produced significant reductions for other legacy PFAS, including PFHxS, PFOA, PFNA, and PFDA [15]. This trial builds on earlier, smaller scale work which first suggested the potential of this approach. An initial interventional study and a subsequent case series documented increased fecal excretion and decreases in serum PFAS concentrations following cholestyramine therapy, although the uncontrolled designs of these early studies limited definitive conclusions [45,46]. Despite its proven efficacy, the use of cholestyramine is limited due to its side effect profile. Adverse effects are predominantly gastrointestinal, including constipation, bloating, and abdominal discomfort, which can negatively impact long term patient adherence. As a non-specific binding agent, cholestyramine can also interfere with the absorption of fat soluble vitamins (A, D, E, K) and other medications, necessitating careful clinical management. Therefore, it is not considered suitable for widespread use in the general population without further research in larger, more diverse cohorts [15].

3.2. Extracorporeal Removal Methods: Targeting the Circulatory Reservoir

An alternative approach to accelerating PFAS elimination involves the direct physical removal of these compounds from the body. Extracorporeal methods leverage the toxicokinetic fact that the vast majority of the body's PFAS burden resides in the bloodstream, tightly bound to serum proteins like albumin and globulins [27]. Therefore, removing PFAS laden blood components can directly deplete the total body load. This can be achieved through phlebotomy (whole blood donation) or, more efficiently, through plasmapheresis (plasma donation), which selectively removes the plasma component where PFAS are most concentrated [47,48]. The most robust evidence for this strategy comes from a landmark randomized clinical trial involving 285 Australian firefighters with occupational PFAS exposure [49]. Participants were randomized to donate plasma every 6 weeks, donate whole blood every 12 weeks, or serve as an observation only control group for one year. The results were unequivocal: both interventions significantly reduced serum PFAS levels compared to the control group. Plasma donation was the most effective method, reducing mean serum PFOS levels by approximately 30% (2.9 ng/mL). Whole blood donation also produced a significant, though smaller, reduction of about 11% (1.1 ng/mL) [49]. Notably, plasma donation was also effective at reducing levels of the highly persistent PFHxS, whereas blood donation was not. Both blood and plasma donation are well established, routine medical procedures with a well understood safety profile. However, the critical unanswered question is whether the observed reductions in PFAS levels translate into tangible improvements in long term health outcomes [49]. To address this critical gap, follow up studies are now underway. The Firefighter Collaborative Research Project (FCRP) in the United States is a large scale randomized controlled trial designed not only to replicate the findings of the Australian study but also to investigate the impact of PFAS reduction on key clinical endpoints, including cardiovascular health and cancer risk biomarkers [50]. While more invasive and costly procedures like therapeutic plasma exchange could theoretically remove PFAS more rapidly, they are not considered practical or justifiable interventions for otherwise healthy individuals due to the associated risks and resource requirements [51,52].

3.3. Other Investigated and Conceptual Pharmaceutical Approaches

In order to enhance PFAS elimination, researchers have also explored other pharmaceutical avenues, primarily by targeting the renal reabsorption pathway. The most notable example involves uricosuric agents, such as probenecid, a drug used to treat gout. The therapeutic hypothesis was that since probenecid inhibits organic anion transporters (OATs) to increase the excretion of uric acid, it might also block the OAT mediated reabsorption of PFAS in the kidney tubules, thereby increasing their urinary clearance [53]. However, this mechanism, while plausible, has not been successfully translated from animal models to humans. An observational study analyzing data from the large scale C8 Health Project found no evidence of benefit. Participants taking probenecid did not have lower serum PFAS levels; in fact, their concentrations were modestly, though not statistically significantly, higher than non users [45]. This discrepancy highlights significant interspecies differences in transporter function and underscores that the specific transporters dominant in human PFAS reabsorption, such as OAT4 and URAT1, are evidently not effectively inhibited by probenecid at clinical doses [54]. Given the lack of efficacy, probenecid is not a recommended strategy for PFAS removal. While specific drug repurposing has been unsuccessful, several conceptual pharmaceutical strategies remain areas of future interest. One theoretical approach involves the use of albumin binding disruptors. Given that PFAS bind strongly to serum albumin, a drug could theoretically displace PFAS from their binding sites, which would increase the unbound fraction of PFAS in the blood available for glomerular filtration and subsequent renal excretion [27]. However, this carries significant potential risks, including transiently increasing the concentration of free, biologically active PFAS, which could lead to redistribution into sensitive tissues and acute toxicity. No PFAS specific clinical evidence exists for this approach, and the concept is extrapolated from general studies of xenobiotic albumin interactions [19,55,56]. A more precise future direction may lie in the development of highly specific transporter targeted drugs. Rather than using broad spectrum inhibitors like probenecid, a more sophisticated strategy would involve designing molecules that can selectively inhibit the key human transporters responsible for PFAS recapture in both the renal and enterohepatic loops. These include OATPs (e.g., OATP1B1, OATP1B3) in the liver and the apical sodium dependent bile acid transporter (ASBT) in the intestine [34,57]. Pharmacological competition for these specific transporters could theoretically be used to modulate PFAS kinetics and enhance their excretion, representing a more targeted and potentially more effective avenue for future pharmaceutical intervention [58].

4. Modifiable Lifestyle Factors and Their Potential Role in PFAS Elimination

Beyond clinical and pharmaceutical interventions, research is beginning to explore less invasive, lifestyle based strategies that may help modulate the body's endogenous excretion pathways or mitigate the adverse health effects associated with PFAS accumulation [59]. These approaches,

which include dietary changes, physical activity, and induced perspiration, are appealing due to their high safety profile and accessibility. However, the evidence base for these strategies is largely preliminary and, in some cases, contradictory, highlighting a critical need for more rigorous investigation [60].

4.1. Dietary Interventions and Nutritional Factors

An emerging non-invasive approach to promoting the elimination of per and polyfluoroalkyl substances (PFAS) involves dietary interventions, most notably increasing the intake of specific types of dietary fiber [61]. Gel forming soluble fibers, such as oat β glucan and psyllium, have the ability to form viscous matrices in the small intestine, which can physically entrap PFAS that are excreted into the intestinal tract via bile. This mechanism disrupts the enterohepatic recirculation of PFAS and promotes their fecal elimination, a process analogous to that of bile acid sequestrants such as cholestyramine [62]. Support for this approach is provided by epidemiological studies, which have consistently reported inverse associations between dietary fiber consumption and serum concentrations of PFAS in the general population [62,63]. Notably, higher intake of dietary fiber, fruits, and vegetables is linked to lower serum levels of several major PFAS, including PFOA and PFOS. Building on these observations, a recent Canadian pilot clinical trial demonstrated that supplementation with a soluble fiber product, specifically oat β glucan, for four weeks resulted in modest but statistically significant reductions in serum levels of PFOS and PFOA. However, the trial's limited sample size and short duration highlight the need for larger and longer term randomized controlled trials to determine the optimal types and doses of fiber, and to confirm these results [61]. Overall, these findings suggest that dietary fiber supplementation may represent a promising, accessible, and low cost strategy to enhance the elimination of PFAS from the human body.

4.2. Physical Activity and Metabolic Health

While physical activity and dietary interventions may not directly enhance the elimination of PFAS from the human body, accumulating evidence suggests they play a crucial role in mitigating the adverse metabolic effects associated with PFAS exposure [7]. Epidemiological studies have consistently linked PFAS exposure to metabolic disruption, weight gain, and altered body composition, particularly affecting individuals with higher risk profiles for metabolic disorders [14,64]. The landmark Diabetes Prevention Program (DPP) study provided compelling evidence for this relationship by following 957 adults at high risk of type 2 diabetes for approximately 15 years. In this pivotal prospective cohort study, participants with higher plasma PFAS concentrations demonstrated significant increases in weight and hip girth over the extended follow up period. Specifically, each doubling in total PFAS concentration was associated with a 1.80 kg increase in body weight from baseline to 9 years post randomization among participants in the placebo group. However, the most significant finding was that these obesogenic effects were completely attenuated in participants who received a structured lifestyle intervention consisting of training in diet, physical activity, and behavior modification [14]. In the lifestyle intervention group, the same doubling in PFAS concentrations was associated with a non significant weight change of -0.59 kg, effectively nullifying the weight promoting effects observed in the control group. Recent research has expanded on these findings, suggesting that the protective effects of physical activity extend beyond weight management to other metabolic parameters. Studies examining physical activity as a modifier of PFAS toxicity have reported that individuals meeting physical activity guidelines show reduced associations between PFAS exposure and adverse liver function biomarkers compared to sedentary individuals [65]. Additionally, emerging evidence indicates that physical activity may influence PFAS elimination through enhanced metabolic processes, including biotransformation and excretion pathways, although direct evidence for increased PFAS clearance through exercise remains limited [66]. While the direct impact of exercise on PFAS elimination rates requires further investigation, these findings collectively suggest that maintaining metabolic health through lifestyle interventions represents a practical and accessible approach to counteract some of the negative health consequences associated with ubiquitous PFAS exposure.

4.3. The Role of Induced Perspiration

Induced sweating through exercise or sauna use has been investigated as a potential excretion pathway for various persistent toxicants. Studies have successfully demonstrated that some organochlorine pesticides and heavy metals can be eliminated through sweat, sometimes at concentrations higher than those found in urine or blood [67,68]. This has led to the hypothesis that perspiration could serve as a minor, non-invasive route for PFAS clearance. However, direct evidence for this pathway is lacking and contradictory. A study that specifically measured legacy PFAS in the blood, urine, and sweat of participants found that perfluorohexane sulfonate (PFHxS), PFOS, and PFOA did not appear to be excreted efficiently into perspiration [45,69]. While sweating is a plausible route for some xenobiotics, current evidence does not support it as a significant elimination pathway for the most common and persistent PFAS congeners.

5. Discussion: Challenges, Clinical Considerations, and Future Directions

The field of human PFAS depuration has rapidly evolved from toxicological observation to active clinical investigation. These compounds exhibit unique toxicokinetics characterized by metabolic inertness, strong protein binding, and highly efficient renal and enterohepatic recirculation. Such features reveal physiological vulnerabilities that can be exploited for therapeutic benefit. As demonstrated, interventions such as bile acid sequestrants and plasma donation have proven effective at significantly reducing serum concentrations of legacy PFAS [15,49]. However, despite this progress, the path toward establishing safe, effective, and widely applicable depuration therapies faces significant challenges and critical knowledge gaps. Current interventions are limited in both scope and clinical validation. Many of the available strategies are adapted from environmental water treatment technologies, such as anion exchange resins and activated carbon. However, these approaches have not yet been robustly translated or optimized for use in human clinical settings [70–73]. The inherent chemical stability and long biological half lives of legacy PFAS make them exceptionally resistant to removal from the human body [74]. Consequently, clinical trials evaluating depuration therapies are few, often underpowered, and typically focus on highly exposed or special populations, which limits the generalizability of their findings [75]. The most profound limitation of the current research is the gap in clinical outcomes. To date, no intervention has demonstrated that lowering an individual's PFAS body burden translates to a tangible improvement in long term health outcomes or a reduced risk of PFAS associated diseases [76]. This necessitates careful risk benefit analysis for any proposed therapy. Interventions like cholestyramine, while effective, are limited by gastrointestinal side effects and potential interference with nutrient absorption [75]. Medical device assisted interventions are resource intensive and carry inherent procedural risks. The ethical imperative, therefore, is to weigh these risks against an unquantified clinical benefit, underscoring that primary prevention through exposure reduction remains the most critical public health strategy [74]. Furthermore, existing evidence is largely confined to a few legacy long chain PFAS, leaving a significant knowledge gap regarding the thousands of other compounds, including emerging short chain alternatives [70,71]. Looking forward, the future of PFAS depuration likely lies in the development of novel, targeted, and more accessible technologies. One promising frontier is the translation of advanced adsorbent materials and nanotechnology from environmental remediation to safe oral therapeutics. However, significant challenges related to biocompatibility, toxicity, and regulatory approval must be overcome before clinical application [77,78]. A more sophisticated pharmaceutical approach involves the rational design of molecules that can directly target the biological pathways of PFAS retention. Advances in identifying the specific solute carrier (SLC) and ATP binding cassette (ABC) transporters that drive PFAS recirculation provide a molecular blueprint for these agents, though translating these findings into safe and effective human therapies remains in its infancy [77,78]. To advance the field, future research must prioritize several key areas. First and foremost is the need for well powered, long term clinical trials that move beyond surrogate endpoints to evaluate the impact of PFAS reduction on validated clinical health outcomes [71,75]. Second, research must expand to include a wider array of PFAS compounds and more diverse human populations. Finally, investment is needed to bridge the translational gap for emerging technologies, from developing safe in vivo adsorbents to designing transporter targeted drugs. By addressing these priorities, the scientific and medical communities can move from simply demonstrating the possibility of PFAS removal to establishing evidence based clinical strategies that can meaningfully reduce the health burden of these "forever chemicals" [76,79].

6. Conclusion

This review consolidates the current understanding of human PFAS depuration, underscoring a field that has progressed from foundational toxicokinetics to successful clinical interventions. The extraordinary persistence of these "forever chemicals" is not merely a passive trait but the result of active, highly efficient physiological recapture mechanisms, including renal and enterohepatic recirculation. The success of interventions like cholestyramine and plasma donation validates these pathways as viable therapeutic targets and confirms that the multi year half lives of legacy PFAS can be significantly shortened. Similarly, emerging lifestyle strategies, such as dietary fiber supplementation, offer promising, accessible avenues for enhancing elimination, though they require more rigorous clinical validation. Despite these advances, the most critical gap in the current body of research remains the lack of evidence linking a reduction in PFAS body burden to tangible improvements in clinical health outcomes. While lowering serum PFAS concentrations is now an achievable endpoint, its ultimate benefit in mitigating the risk of associated diseases is unknown. Therefore, future research must prioritize well designed, long term clinical trials that can bridge this gap. Concurrently, the development of next generation therapies, including novel oral sorbents and precisely targeted pharmaceutical agents, holds the potential to provide safer and more effective solutions. Ultimately, integrating these therapeutic strategies with robust public health measures

to reduce ongoing environmental exposure will be essential to meaningfully address the global health challenge posed by PFAS.

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