

Understanding PFAS Interactions with Kidney Function in Health and Disease

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Motivation

Per and polyfluoroalkyl substances (PFAS) are ubiquitous environmental contaminants, many of which have long half-lives in human (2-5 years). Those PFAS with the longest half-lives have also been identified as bioaccumulative and toxic, and thus clearance is seen as one key metric for PFAS hazard. Renal elimination is the most critical process in determining total body clearance of PFAS.¹ Sex- and species-specific differences in PFAS elimination have been linked to the activity of renal transporters.¹ However, the interactions between PFAS and renal transporters are still not fully understood, which complicates our ability to conduct hazard and risk assessment for the thousands of PFAS that exist.

Moreover, kidney disease alters the expression of renal transporters², which will further influence PFAS renal elimination. However, little is known about the influence of kidney disease on PFAS toxicokinetics.

Project Description

In this study, we will 1) characterize five human renal transporters relevant to renal elimination and reabsorption of PFAS through literature review, and 2) investigate the uptake rates of PFAS by renal transporters in health and disease using *in vitro* cell-based assays. In this project, we will focus on two legacy PFAS (perfluorooctanoic acid, PFOA and perfluorooctane sulfonate, PFOS) for validation and two emerging PFAS (GenX and F53B) to address ongoing exposure concerns (Figure 1).

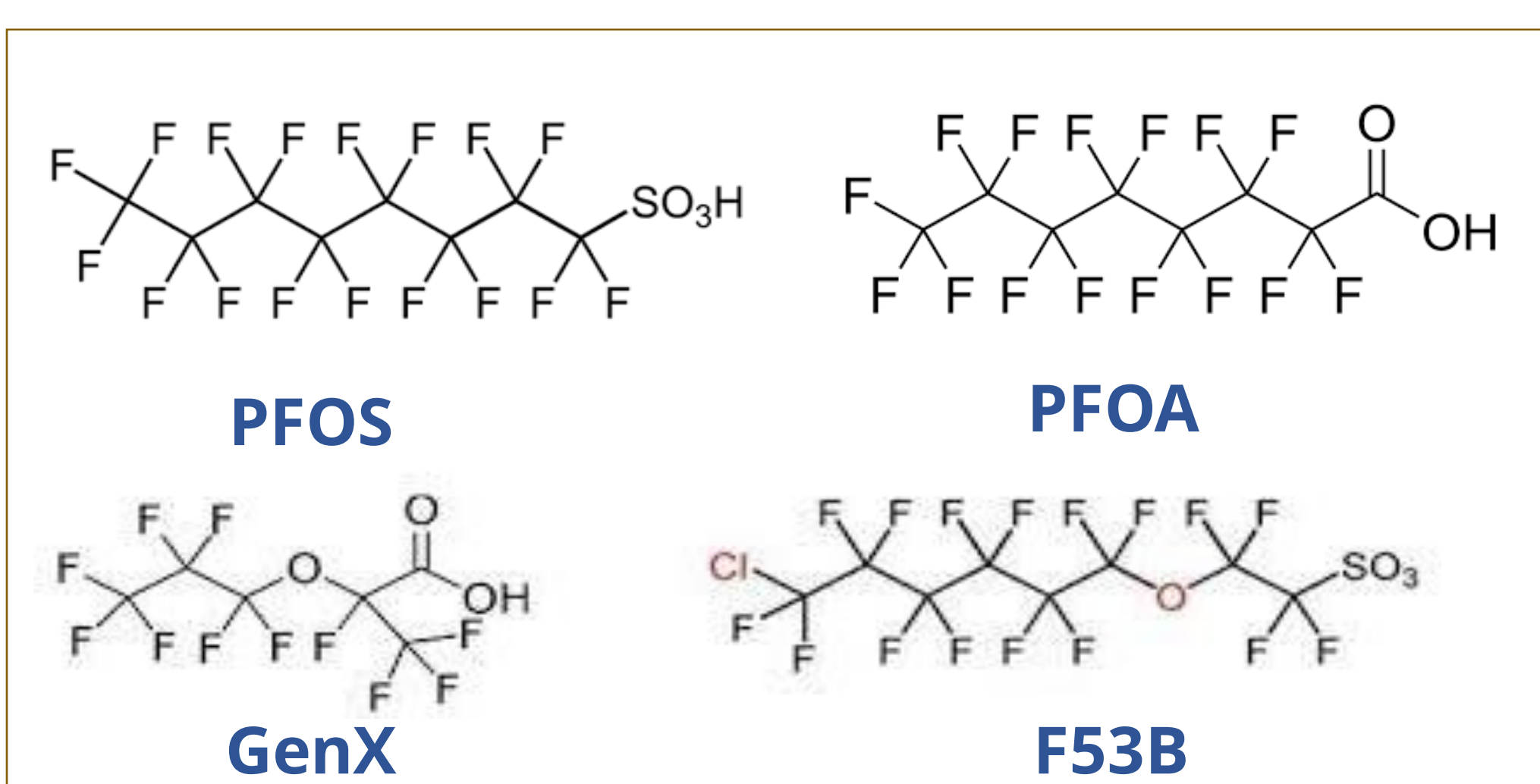


Figure 1. Structures of PFOS, PFOA, GenX, and F53B.

We will evaluate how differences in renal transporter expression in health and disease could impact PFAS renal elimination in humans.

Approach and Innovation:

- State of the art *in vitro* approaches will be used to investigate two emerging PFAS for the first time for their interactions with renal transporters.
- As these represent only a small subset of both renal transporters and PFAS, this pilot will be a first step in work needed to more comprehensively understand PFAS renal elimination

Project Deliverables

- We anticipate two high-quality peer-reviewed publications.
- Results and outputs generated by this project will be used to apply for external funding (NIH R01 or similar).
- The mid-term milestones are (1) identification of transporters to be tested and (2) pilot *in vitro* experiments.
- The final milestones are (1) characterization of transport rate of test PFAS by target transporters, (2) publication submissions, and (3) proposal submission.

Potential Impact

This work will collect pilot data of PFAS uptake rates by renal transporters in health and disease, providing critical data to inform research and policy.

This work will also provide up-to-date knowledge of how kidney function affects both legacy and emerging PFAS elimination. This knowledge is critical to setting evidence-based health advisory limits for these ubiquitous chemicals and for identifying particularly sensitive populations.

References

1. Han X, Nabb DL, Russell MH, et al. 2012. Renal Elimination of Perfluorocarboxylates (PFCAs). *Chem Res Toxicol* 25: 35–46.
2. Joy MS, Roberts BV, Wang J, et al. 2014. A pilot study of leukocyte expression patterns for drug metabolizing enzyme and transporter transcripts in autoimmune glomerulonephritis. *Int J Clin Pharmacol Ther* 52:303–313

