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Article

Estimation of the Half-Lives of Recently Detected Per- and Polyfluorinated Alkyl Ethers in an Exposed Community

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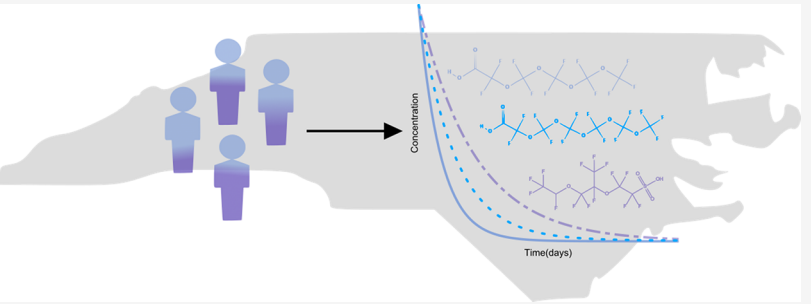

ABSTRACT: To estimate half-lives for novel fluoroethers, the GenX Exposure Study obtained two serum measurements for per- and polyfluoroalkyl substances (PFAS) for 44 participants of age 12−86 years from North Carolina, collected 5 and 11 months after fluoroether discharges into the drinking water source were controlled. The estimated half-lives for these compounds were 127 days (95% confidence interval (95% CI) = 86, 243 days) for perfluorotetraoxadecanoic acid (PFO4DA), 296 days for Nafion byproduct 2 (95% CI = 176, 924 days), and 379 days (95% CI = 199, 3870 days) for perfluoro-3,5,7,9,11-pentaoxadodecanoic acid (PFO5DoA). Using these estimates and the literature values, a model was built that predicted PFAS half-lives using structural properties. Three chemical properties predicted 55% of the variance of PFAS half-lives based on 15 PFAS. A model with only molecular weight predicted 69% of the variance. Some properties can predict the half-lives of PFAS, but a deeper understanding is needed. These fluoroethers had biological half-lives longer than published half-lives for PFHxA and PFHpA (30−60 days) but shorter than those for PFOA and PFOS (800−1200 days). These are the first and possibly only estimates of human elimination half-lives of these fluoroethers.

KEYWORDS: *exposure, PFAS, water, humans, environment, toxicokinetic modeling*

INTRODUCTION

Per- and polyfluoroalkyl substances (PFAS) are a class of compounds that contain at least one fully fluorinated methylene (−CF_2−) or methyl (−CF_3) group.[1,2] Production of PFAS began in the 1930s, and they have since become ubiquitous in natural and human impacted environments due to their use in hundreds of different applications—including stain, oil, and water repellant coatings in food containers, textiles, pharmaceutical packaging, apparel, and personal care products such as floss.[1,3−6] As part of chemical production, novel PFAS can be created as byproducts and can be discharged to air and surface water. PFAS are often not removed via conventional drinking water treatment methods and have therefore been found in relatively high concentrations in drinking water of communities where water is impacted by facilities that produce PFAS directly or use them in abundance for production of other products.[7−9]

The vast majority of PFAS tend to be persistent in the environment or breakdown into more persistent transformation products. Longer chain perfluoroalkyl acids (PFAAs) such as perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) are highly persistent (or slowly excreted) in the human body.[10−15] According to the 2021 toxicological profile by the Agency for Toxic Substances and Disease Registry (ATSDR) estimates of the human half-lives of PFOA, PFOS, and perfluorohexanesulfonic acid (PFHxS), three of the most well-studied long chain PFAAs have fallen between 2.1 and 10.1 years,[2,16,17] 3.1−27 years,[2,12,16] and 4.7−35 years,[2,12,16] respectively. Studies have also shown that PFAS generally demonstrate first-order elimination kinetics.[11,12] A thorough understanding of the toxicokinetic implications of a

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chemical structure and specifically how a compound's chemical structure may impact its elimination half-life is useful in the design of exposure and health effects studies. While the absorption and distribution of many perfluoroalkyl acids is similar, their excretion rates can differ greatly.[18] One important factor that may explain the long half-lives of some PFAAs in humans is their interaction with renal resorption transporters, which may play an important role in perfluoroalkyl acid's long half-lives.[18] Due to this, hormone mediated transporter differences across sexes in animal studies have been shown to cause differences in the excretion of some PFAS in rats and mice.[12,19] Although sex differences resulting from differences in hormone mediated transporters have not been directly observed in humans, sex differences—possibly due to other causes such as menstruation—have been observed in human studies.[12,19] In the literature, differences in structure across PFAS congeners and isomers lead to differences in excretion half-lives.[10,16,20] PFAS, unlike many other organic contaminants, such as pesticides and phthalates, are not metabolized, which influences the complexities of the study of their elimination. Some properties of these compounds that could affect half-life include head group, branching, number of carbons, ether oxygens, electrostatic surface potential, and protein binding affinity.[21−31] Among other things, these factors may influence the routes of excretion by which PFAS are excreted. Examples from the literature in both humans and animals have shown that sulfonated PFAS are often more bioaccumulative than PFAS with carboxylic acid head groups; branching affects solubility through changes in intermolecular interactions; number of carbons in a PFAS chain affects clearance rates in animal models; and the inclusion of ether oxygens generally shortens PFAS half-lives.[22,23,28,30,32]

In North Carolina, the Fayetteville Works fluorochemical manufacturing plant has discharged wastewater containing a variety of PFAS into the Cape Fear River since 1980.[33] Several understudied and novel PFAS, including hexafluoropropylene oxide dimer acid (HFPO−DA or GenX), PFO4DA, PFO5DoA, and perfluoro-2-{[perfluoro-3-(perfluoroethoxy)-2-propanyl]oxy}ethanesulfonic acid (Nafion byproduct 2), have been detected downstream of this facility in the Cape Fear River.[34−39] These PFAS fall into a class of PFAS known as fluoroethers due to the presence of one or more ether oxygen atoms interspersed in the fluorinated alkyl chain.[34,37−41] In June 2017, this discharge was revealed to downstream residents who worked with state and federal agencies to stop discharge to the river by July 2017.[34,38−40] Since then, measured levels of novel PFAS in water samples, including those uniquely discovered in the Cape Fear River, decreased by several orders of magnitude and/or became undetectable. Contemporaneously, many of the residents switched to bottled drinking water before the point source was controlled.[34,39] To address community concerns about the impact of PFAS-contaminated drinking water, in November 2017, the GenX Exposure Study collected blood from residents of New Hanover County, NC, to investigate community exposure to these novel fluoroethers.[42]

Fluoroether chemistry was introduced as a PFOA replacement, but little is known about the toxicokinetic properties of these novel PFAS, particularly for the species formed as byproducts of production. Therefore, it is important to obtain putative toxicokinetic information about novel fluoroethers to improve studies of these compounds and fluoroethers as a class. The importance of this information supersedes the limitations of this study, namely, that there were only two separate samples six months apart in a study of a relatively small sample size. In this study, we used data from the GenX Exposure Study to calculate human half-lives for three fluoroethers Nafion byproduct 2, perfluoro-3,5,7,9-tetraoxadecanoic acid (PFO4DA), and perfluoro-3,5,7,9,11-pentaoxadodecanoic acid (PFO5DoA); these structures can be seen in Figure 1. Then, the resulting estimates were combined with reference data from the literature to build a model assessing the relationship between chemical properties of PFAS and their elimination half-lives.

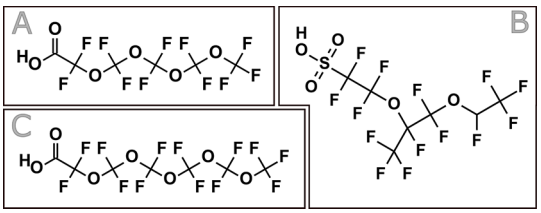

Figure 1. Chemical structures of (A) PFO4DA, (B) Nafion byproduct 2, and (C) PFO5DoA.

METHODS

Cohort. Serum PFAS measurement data were drawn from the GenX Exposure Study, a community-based cohort created to assess exposure to novel PFAS from drinking water. A detailed account of the process of recruitment, consenting, and sample collection can be found in Kotlarz et al.[42] In November 2017, individuals from New Hanover County, North Carolina, whose drinking water was provided by the Cape Fear Public Utility Authority were recruited for the GenX Exposure Study; individuals provided a serum sample at that time, five months after the cessation of point-source fluoroether discharge to the Cape Fear River. In May 2018, 44 participants provided the second serum sample; 11 months after discharge stopped. Study participants provided written informed consent, and the study complied with the North Carolina State University Institutional Review Board.

Chemical Analysis of Blood. Blood serum from participants was analyzed for 20 different PFAS, 10 fluoroethers, and 10 long-chain perfluoroalkyl acids, using liquid chromatography high-resolution mass spectrometry (LC HMRS).[42,43] Analytical standards were acquired from Wellington Laboratories [hexafluoropropylene oxide dimer acid (HFPO−DA/GenX), perfluorobutanoic acid (PFBA), perfluoropentanoic acid (PFPeA), perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), PFOA, perfluorononanoic acid (PFNA), perfluorobutanesulfonic acid (PFBS), PFHxS, PFOS, and 6:2 fluorotelomer sulfonate (6:2 FTS)] or the Chemours company [perfluoro-2-methoxyacetic acid (PFMOAA), perfluoro-2-methoxypropanoic acid, 2,3,3,3-tetrafluoro-2-(pentafluoroethoxy)propanoic acid, perfluoro-2-ethoxypropanoic acid (PEPA), perfluoro-3,5,7-trioxaoctanoic acid (PFO4DA), perfluoro-3,5,7,9,11-pentaoxadodecanoic acid (PFO5DoA), 1,1,2,2-tetrafluoro-2-(1,2,2,2-tetrafluoroethoxy)-ethanesulfonic acid (NVHOS), perfluoro-3,6-dioxa-4-methyl-7-octene-1-sulfonic acid (Nafion byproduct 1), and Nafion byproduct 2]. Analyzed PFAS were chosen based on PFAS previously reported in the lower Cape Fear River and the available standards at the time.[42,43]

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Half-Life Estimation. To estimate half-lives of the fluoroethers, we modeled each PFAS as a simple elimination process using noncompartmental first-order rate kinetics. This represented an estimate of the amount of chemicals eliminated from the body per day. A simplified elimination model is appropriate as ongoing exposure has effectively ceased.[34,39]

The model is thus the first-order decay process of the form: eq 1.

$$\ln C = \beta_0 + X_1\beta_1 + \text{age}\ \beta_2 + \text{gender}\ \beta_3 + \epsilon \quad (1)$$

C is the concentration of a given PFAS for an individual, X_1 is the time in days from the first sampling session, β_1 is the estimate of how much the concentration of a given chemical in the blood decreases per day in ng/mL/day. β_2 represents the effect of age on concentration in ng/mL/each year older a participant is, and β_3 represents the effect of gender on concentration. ϵ is error. Gender and age were chosen as covariates because they may have a significant effect on the rate of PFAS excretion.[20,44] Weight and body mass index were considered but not included because they were not recorded at the second sampling session.

Using β_1 as the elimination coefficient, k_e (ng/mL/day), we estimated the rate of removal for a chemical compound using first-rate laws (eq 2) and use the estimated k_e to find the half-life (eq 3).

First-order rate equation:

$$C_p = C_0 e^{k_e t} \quad (2)$$

Elimination half-life from elimination coefficient:

$$\frac{\ln 2}{k_e} = t_{1/2} \quad (3)$$

Half-Life Predictions. With these new half-life estimates for these three chemicals along with the literature values for 12 other PFAS, we built two different linear models for the prediction of PFAS half-life using lm() in base R version 3.6.3.[45] Forward stepwise selection was used to identify the most effective model for predicting PFAS half-life using the regsubsets command from the leaps package in R.[46] The full model considered the number of carbons in the chain, head group (1 = sulfonic acid, 0 = carboxylic acid), the number of oxygens in the chain, and presence or absence of branches (1 or 0). The properties K_{ow}, K_{oa}, and water solubility were considered but not included because they are generally considered unreliable for PFAS.[47] The first model included three predictor variables based on chemical structure: the number of carbons in the chain, head group (1 = sulfonic acid, 0 = carboxylic acid), and presence or absence of branches (1 or 0).[45] This model assumes that PFAS which are not explicitly labeled as branched are in their linear form. A simplified second model was also tested for comparison using molecular weight (MW) as the only structural predictor. MW provides some information about the molecule but lacks specific chemical moieties that can influence the PFAS behavior in biological systems. MW was not included in the first model as it is directly correlated with the sum of carbon and oxygen contents and did not improve model predictions. The repeatedcv method from the caret package was used to do repeated four-fold cross validation with 100 repeats to assess the models.[48] Code for all analyses is included in the Supporting Information.

RESULTS AND DISCUSSION

A total of 44 participants, ranging in age from 12 to 86 years and comprising 64% female and 36% males, provided blood samples approximately 177 days apart (Table 1). Five long-chain PFAAs PFAS and five fluoroethers were detected in the blood serum of participants (Table 2). Fluoroether concentrations were higher in the November 2017 samples than in May 2018, consistent with biological elimination. Nafion byproduct 2, PFO5DoA, and PFO4DA were measured in nearly every participant at both time points, whereas PFO3OA and NVHOS were found only in the first sampling. This result may suggest a half-life shorter than that of our six-month sampling interval. In addition, GenX was not detected in any participants' blood serum in the initial sampling five months after point source reduction was reported. Recently, the European Chemicals Agency (ECHA) estimated the half-life of GenX in workers at 81 h.[49] This estimate falls well below half-life estimates of the additional fluoroethers reported here (Table 3) and could explain the lack of detection of GenX in participants in this study.

Table 1. Demographic Characteristics of the 44 Individuals Who Provided Two Serum Samples Six Months Apart[a]

characteristic	% of participants
age group	
12−18	5
18−35	11
35−55	36
55−70	30
70−86	18
gender	
male	36
female	64

[a]GenX Exposure Study, New Hanover County, NC, 2017−2018.

Following cessation of discharge to the Cape Fear River, novel PFAS levels in the Cape Fear River had decreased by several orders of magnitude.[35] Additionally, many participants in the GenX Exposure Study had switched to bottled drinking water at the time of this study.[34,39] As a result, we assumed that any further novel PFAS exposure was negligible and was not enough to violate the assumptions of the first-order elimination model.

We focused on the three fluoroethers detected at both time points, Nafion byproduct 2, PFO4DA, and PFO5DoA. The first parameter estimated was the excretion coefficients. The excretion coefficients were −0.00234 ng/mL/day for Nafion byproduct 2, −0.00546 ng/mL/day for PFO4DA, and −0.00183 ng/mL/day for PFO5DoA (Table 3). Using these excretion coefficients, the estimated half-lives for the three fluoroethers were calculated (Table 3). Nafion byproduct 2 has an estimated half-life of 296 days with a 95% confidence interval (CI) of 176−924 days. PFO4DA has an estimated half-life of 127 ays (95% CI 176−924 days). PFO5DoA has an estimated half-life of 379 days (95% CI, 199−3870 days). These fluoroethers all had shorter half-lives than long-chain PFAAs such as PFOA and PFOS, but longer half-lives than those for other PFAAs with much shorter half-lives such as PFHxA (32 days) and PFHpA (62 days).[20,44] The half-lives of PFO3OA and NVHOS could not be estimated because they could not be detected in most of the samples after 177 days.

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Table 2. Novel Fluoroethers Detected in Blood Serum Samples at Two Sample Collection Times in 44 Participants, Each Sampled Twice, from the GenX Exposure Study in New Hanover County, NC, 2017−2018

compound	median concentration November 2017 (ng/mL)	median concentration May 2018 (ng/mL)	number > MRL at both measurements	detection limits (ng/mL)
Nafion byproduct 2	4.14	2.47	44	0.1−0.123
PFO5DoA	12.41	8.91	43	0.5
PFO4DA	5.60	1.16	40	0.1−0.111
PFO3OA	1.02	NA	1	0.1−1.281
NVHOS	1.14	NA	1	0.1−0.234

Table 3. Estimated Values for Half-Lives, Excretion Coefficients for Three Novel Fluoroethers, and the 95% Confidence Interval of Those Estimates[a]

compound	half-life (days)	half-life 95% CI (days)	excretion coefficient (ng/mL/day)	excretion coefficient 95% CI (ng/mL/day)	effect of age on concentration (ng/mL/year)	effect of gender concentration (ng/mL) in males
PFO4DA	127	86, 243	−0.00546*	−0.00806, −0.00285	0.0129	0.376
Nafion byproduct 2	296	176, 924	−0.00234*	−0.00393, −0.000750	0.017*	0.34*
PFO5DoA	379	199, 3870	−0.00183*	−0.00348, −0.000179	0.0160*	0.298

[a]* indicates significant values ($p < 0.05$).

Table 4. Chemical and Physical Properties for 15 PFAS That May Influence the Biological Half-Life

compound	carbons (in chain)	molecular weight	ether oxygens	head group	branched?	log K_{ow}	half-life (days)
GenX	6	330.053	1	carboxylic acid	Yes	5.13[a]	3.375[f]
PFHxA	6	314.045	0	carboxylic acid	No	2.8[a]	32[g]
NVHOS	4	298.1	1	sulfonic acid	No	2.58[a]	NA
PFO3DOA	5	312.044	3	carboxylic acid	No	6.07[a]	NA
PFHpA	7	364.062	0	carboxylic acid	No	2.05[b]	464[i]
PFO4DA	6	378.05	4	carboxylic acid	No	8.53[a]	127[c]
Nafion byproduct 2	7	464.13	2	sulfonic acid	Yes	5.98[a]	296[c]
PFHpS	7	450.12	0	sulfonic acid	No	4.85[a]	533[e]
PFOA	8	414.07	0	carboxylic acid	No	3.1[b]	902[e]
PFOS	8	500.13	0	sulfonic acid	No	5.61[b]	1241[d]
PFNA	9	464.078	0	carboxylic acid	No	3.54[b]	1417[i]
PFHxS	6	400.11	0	sulfonic acid	No	3.48[a]	1661[e]
PFDA	10	514.086	0	carboxylic acid	No	4.15[b]	3743[i]
PFUnA	11	564.093	0	carboxylic acid	No	4.00[b]	3743[i]
PFPeS	5	350.1	0	sulfonic acid	No	3.38[a]	343[e]
PFBS	4	300.09	0	sulfonic acid	No	2.76[b]	26[h]
PFO5DoA	7	44.057	5	carboxylic acid	No	10.4	379[c]

[a]Predicted values from EPA Chemistry Dashboard.[53] [b]Experimental values from EPA Chemistry Dashboard.[53] [c]Estimates from the model. [d]Li et al.[12] [e]Li et al.[19] [f]Values from ECHA report.[49] [g]Russel et al.[52] NA, no data to estimate. [h]Value from Olsen et al.[54] [i]Weighted average from Zhang et al.[16]

Sex has been noted as an important factor in elimination speed—although the mechanism is unclear in humans and may differ between species—for some long-chain PFAAs in animal models as well as in humans.[12,16,19,20] PFAS have been shown to interact with renal resorption transporters.[18] Hormone mediated differences across renal transporters between sexes in animal studies cause excretion differences.[12,19] While renal transporters also apply to human PFAS excretion, there is currently no evidence that they cause the observed sex differences.[12,18,19] Those could be due to other causes such as menstruation.[12,19] As menstruation can influence the excretion of PFAS, the association of age and gender with the PFAS excretion rate may be different in postmenopausal people. Using eq 1, we not only estimated excretion coefficients, but we also estimated the impact of gender and age on fluoroether elimination (Table 3). In our elimination models, female gender was associated with significantly lower concentrations of Nafion byproduct 2. It also appeared to be important for the other compounds, but we lacked statistical power to assess this difference. Age can influence the excretion rate of chemicals because of the changes in organs and regulatory systems that affect pharmacokinetics as age increases.[50] For example, there is a marked reduction in renal and hepatic clearance as age increases.[50] In the equation to predict excretion coefficients, age was associated with significantly higher serum levels of Nafion byproduct 2 and PFO5DoA, suggesting that older people may have a slower elimination of these compounds. As age increased, the concentrations of these PFAS in the serum also increased. These concentration differences could be caused by several factors, including, but not limited to, excretion rates. Other factors include differences in intake rate of PFAS contaminated water or differences in exposure to other sources of PFAS contamination.

After estimating the half-lives of the fluoroethers, we built models to explore what chemical and physical properties of all PFAS influence their half-lives. Table 4 lists structural and

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chemical properties for 12 PFAS, including five fluoroethers. These features were selected because they have been shown to affect the half-lives of the well-studied PFAS or commonly affect the toxicokinetics of other compounds. Features we considered include: the number of carbons in the chain, branching of the molecule, type of head group, MW, number of ether oxygens, and octanol and water partition coefficient (K_{ow}). The number of carbons in the chain of the PFAS approximates the chain length without the complexity of branching. Compound head group (carboxylic or sulfonic) has shown significant effects on elimination rates based on comparison of compounds with similar chain length (e.g., PFHxS vs PFHxA[51,52]), with sulfonic acids having longer half-lives. In the same way that PFAS excretion can differ between the sexes due to differences in renal transporters, these features could affect how they interact with renal transporters, changing the rate at which they are excreted from the body.[12,18,19] Using variable selection, the number of carbons within the chain, the head group, and the presence or absence of branching were all found to have meaningful predictive power when trying to predict the half-lives of PFAS with an R_2 value of 0.69. Cross-validation of the model gave R_2 = 0.66 with a standard deviation of 0.27. The predictive equation was ln(half-life) = 0.1460 + (1.2651 × HG) + (0.7857 × C) + (−2.4321 × B), where HG is the presence of a sulfonic acid, 1 for yes and 0 for no; C is the number of carbons in the chain; and B is the presence of branching in the compound, 1 if there is at least one branch and 0 if there is not. This model (Model 1) suggests that longer chain PFAS with sulfonic head groups and no branching have longer half-lives shorter chain PFAS with some combination of branching and carboxylic head group. Model predictions are listed in Table 5.

A simpler model was also built using just MW as the predictor of half-life. This model was built separately as MW was considered an important property of these compounds, which contained important information on their chemical properties, but did not improve the more complex model according to stepwise selection and cross-validation. The predictive equation was ln(half-life) = −2.51357 + (0.02006 × MW). Table 5 shows the results of the MW model (Model 2). Cross validation found that this model has an R_2 = 0.72 with a standard deviation of 0.25. This simpler model shows promise in predicting half-lives and generalizability although the increased R_2 and decreased standard deviation are probably due to the reduction in variables in the model. One important thing that this model points to is the importance and predictive value of the MW for half-life though MW was not important in models that included more chemical specific information.

The results of these predictive models help to explain some results in this study. The presence of branching could explain some of the very short half-life of GenX (~3 days) and consequent lack of detection in this study, while its MW alone would not be able to explain a half-life so much shorter than the other novel PFAS. The more complex model predicts the half-life of NVHOS to be between 22 and 395 days; the longer value is probably an overestimate because most people had no detectable NVHOS less than a year after exposure stopped. The model predicted the half-life of PFO3OA to be between 17 and 190 days.

PFAS are complex chemicals both chemically and biologically. More experimental data are needed to estimate coefficients which may inform half-life estimates; for example, protein−water distribution coefficients (Dpw), membrane-water distribution coefficients (Dmw), and experimentally derived Koa values could prove useful for predicting half-lives as human data are limited for most PFAS, unfortunately these are not currently available for PFAS. These models were imperfect in predicting PFAS half-lives with these relatively simplistic parameters. They were, nonetheless, able to predict many of the half-lives of these compounds, which demonstrated both the importance of these parameters and the knowledge gap in our understanding of PFAS properties. For the chemicals evaluated here, these may be the only available human exposure data. While these models perform well in terms of high adjusted R_2, the variation in estimates over cross-validation sets was high. This is not surprising, given the relatively small number of PFAS with well understood toxicokinetics. While the specific parameters of the models built on this small data set are unlikely to generalize to other PFAS outside of this chemical set very well, they provide empirical support for these properties as important in predicting half-lives in combination with additional properties needed to understand differences across PFAS. For example, one study showed that electrostatic surface potential can affect how PFAS partition in the body.[31] Molecular docking experiments have shown that protein binding affinity and tissue partitioning can be used to predict the toxicokinetic properties of PFAS as well.[27] Physiologically based pharmacokinetic modeling is also an important tool for investigating the kinetics of poorly understood compounds. These models could be used to develop a more complex understanding of PFAS excretion, as well, given the correct parameters. These properties, going beyond simple estimates based on structure,

Table 5. Combined Results of the Modeled Half-Lives from Both Models with Elements of PFAS That Were Determined To Be Important Using Variable Selection[a]

compound	literature half-life (days)	Model 1 predicted half-life 95% CI (days)	Model 2 predicted half-life 95% CI (days)
PFHxS	1661[d]	145, 1420	122, 490
PFNA	1417[h]	530, 3440	396, 1980
PFOS	1241[c]	630, 7700	663, 5050
PFOA	902[c]	280, 13508	164, 639
PFHpS	533[d]	320, 3130	318, 1410
Nafion byproduct 2	296[b]	13.9, 5603	397, 1980
PFO4DA	116[b]	48.1, 3274	72.9, 340
PFHpA	464.0[h]	124, 616	320, 1410
PFHxA	32.0[f]	48.1, 327	13.7, 136
PFDA	3743[h]	918, 9660	797, 7370
PFUnA	3743[h]	1510, 28600	1490, 29600
PFPeS	343[d]	17.0, 190	36.0, 220
PFBS	26[g]	21.9, 395	9.30, 114
PFO5DoA	379[b]	124, 616	287, 1220
GenX	3.38[e]	1.74, 69.8	21.1, 168
NVHOS	NA	21.9, 395	8.80, 111
PFO3OA	NA	17.0, 190	13, 133

[a]The results for the model that included structural features of the modeled half-lives are shown on the left (Model 1). The results for the model that included molecular weight (Model 2) are on the right. These predicted values are listed alongside estimated half-lives for the novel PFAS or the literature reported serum half-lives for long-chain PFAAs. These models were used to predict intervals for NVHOS and PFO3OA that do not have known half-lives. [b]Estimates from the model. [c]Li et al.[12] [d]Li et al.[19] [e]Values from ECHA report.[49] [f]Russel et al.[52] [g]Olsen et al.[54] [h]Weighted average from Zhang et al.[16]

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should be investigated to better understand the toxicokinetic properties, of these compounds to improve the predictive power and generalizability of models like this and expand the knowledgebase of PFAS toxicokinetic properties. The study was limited by its small sample size with only 44 individuals and only two repeat measurements per person. However, these estimates are the first and possibly only empirical toxicokinetic estimates in humans for these novel fluoroether PFAS. These estimates of toxicokinetic parameters provide important and timely properties for future studies of these compounds. Continued exposure to novel PFAS in the Cape Fear River has been reduced by several orders of magnitude, so there may be no future ability to estimate half-lives and elimination rates for these compounds in an exposed human population, except occupationally exposed workers or other exposure events. Knowledge of these constants will help in the design and implementation of research that can elucidate possible health effects and further describe the toxicokinetic properties of novel PFAS.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.est.2c08241.

R code used for analysis and modeling as described in the manuscript (PDF)

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N.K., D.R.U.K., D.N.C., D.J.W., C.S.L., J.C.D., and J.A.H. contributed to sample collection. N.K., D.R.U.K., D.N.C., M.S., and J.M. contributed to sample processing and analysis. D.J.W. conducted the statistical analysis and drafted the manuscript. D.R. helped to plan all analyses. J.A.H. oversaw the project. All authors contributed significantly to shaping, editing, and providing critical feedback on the manuscript.

Notes

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■ ABBREVIATIONS

PFAS, per- and polyfluoroalkyl substances; PFOS, perfluorooctanesulfonic acid; PFOA, perfluorooctanoic acid; PFHxS, perfluorohexane sulfonic acid; PFO4DA, perfluoro-3,5,7,9-tetraoxadecanoic acid; PFBA, perfluorobutanoic acid; PFHxA, perfluorohexanoic acid; HFPO−DA, hexafluoropropylene oxide dimer acid; PFHpA, perfluoroheptanoic acid; Nafion byproduct 2, perfluoro-2-{[perfluoro-3-(perfluoroethoxy)-2-propanyl]oxy}ethanesulfonic acid; PFBS, perfluorobutane sulfonic acid; PFNA, perfluorononanoic acid; 6:2 FTS, 6:2 fluorotelomer sulfonate; PFMOAA, perfluoro-2-methoxyacetic acid; PEPA, perfluoro-2-ethoxypropanoic acid; PFO2HxA, perfluoro-3,5-dioxahexanoic acid; PFO3OA, perfluoro-3,5,7-trioxaoctanoic acid; PFO4DA, perfluoro-3,5,7,9-tetraoxadecanoic acid; PFO5DoA, perfluoro-3,5,7,9,11-pentaoxadodecanoic acid; NVHOS, 1,1,2,2-tetrafluoro-2-(1,2,2,2-tetrafluoroethoxy)ethanesulfonic acid; Nafion byproduct 1, perfluoro-3,6-dioxa-4-methyl-7-octene-1-sulfonic acid; ECHA, European Chemicals Agency

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