Environmental Science & Technology

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Identification of Per- and Polyfluoroalkyl Substances in the Cape Fear River by High Resolution Mass Spectrometry and Nontargeted Screening

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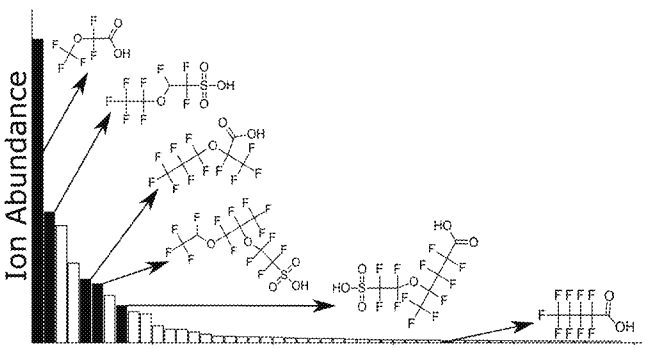
Supporting Information

ABSTRACT: Ongoing chemical development in response to regulation of historical perfluorinated compounds, (i.e., perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS)) has resulted in a proliferation of novel per- and polyfluorinated species. Screening and monitoring for these emerging chemicals benefit from a nontargeted approach due to a lack of necessary standards and a paucity of information about the replacement chemistries. In this paper, we apply nontargeted screening to the Cape Fear River of North Carolina, a fluorochemically impacted watershed. The continued presence of perfluorinated ether acids was confirmed, with a total of 37 unique chemical formulas comprising 58 isomers detected. Structural determination was carried out by LC-MS/MS to determine isomeric structures where possible. Novel structures determined included perfluorinated ether acid species containing two acidic sites, polyfluorinated ether acids containing a single hydrogenation, and previously unreported perfluorinated ether acids. Compounds identified by an initial nontargeted screen were monitored over repeated sampling to track long-term reductions in PFAS content during emission source control. Hierarchical clustering of the time course data was used to associate groups of chemicals based on their trends over time. Six clusters were identified and showed some similarity in chemical class; they are believed to represent the byproducts of different fluorochemical production lines.



INTRODUCTION

Fluorinated polymers and fluorosurfactants are constantly evolving due to in-demand consumer and industrial products with a long and complicated history of environmental impacts.[1] A consequence of the ubiquity of per- and polyfluoroalkyl substances (PFASs) in industry is their extensive environmental infiltration due to their use as manufacturing aids, production as waste, and release as degradations and side-products of manufactured products. PFASs possess exemplary thermochemical inertness, and fluorinated carbons are resistant to biological breakdown,[2] which is the cause of their persistent nature in the environment[3] and was the driving rationale for the erroneous assumption of biological inertness for over 25 years.[4]

The most historically dominant PFAS species, perfluorooctanesulfonate (PFOS) and perfluorooctanoic acid (PFOA), were used extensively before triggering domestic and international action due to concerns about their negative toxicological effects and bioaccumulation potential.[5−7] Long-term toxicological studies demonstrated that these species have broad spectrum influence and require exposure controls.[8,9] Coinciding with the environmental studies in the previous decade, domestic manufacturing began phasing out PFOA and PFOS,[10,11] but the chemical qualities of fluorochemicals are difficult, or impossible, to replicate using nonfluorinated species.[12,13] Consequently, industries developed fluorinated alternatives, including short-chain PFASs and perfluoroalkyl ether acids, to replace legacy long-chain PFASs.[14,15]

A chief difficulty with chemical phase-out is the assurance that replacement chemicals from the same class demonstrate improved environmental and human health profiles. Historically, reliance on chemicals within a single chemical class has not markedly overcome fundamental issues presented by the original compounds (e.g., the replacement of polychlorinated biphenyls with short-chain chlorinated paraffins or the

Received: October 25, 2018
Revised: February 25, 2019
Accepted: March 14, 2019

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DOI: 10.1021/acs.est.8b06017
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

ED_002541B_00000541-00001

emerging replacements for brominated flame retardants).[16,17] Due to the aforementioned uniqueness of fluorinated compounds, there may be challenges to the prospect of alleviating the toxicological effects associated with PFOA/PFOS or legacy PFASs by using related chemistries.[13,18] One company has introduced a new line of "short-chain" PFOS replacements which exhibit nearly identical structures but potentially better biological clearance rates.[19] Others have introduced branched polymeric surfactants with "low-bioaccumulation potential".[20] Still, more manufacturers have created species with interspersed ether-oxygen linkages[21] or partial hydrogenation.[22] The net result is a proliferation of product chemicals, precursors, and degradation products with limited publicly available toxicological and physical data due to the proprietary nature of these compounds. Monitoring this vast new chemical landscape requires the development of new analytical methodologies.

High-resolution mass spectrometry (HRMS) has a proven track record in compound elucidation and environmental screening that is well suited to the task of identifying and monitoring emerging pollutants through accurate chemical prediction and structural elucidation.[23−28] HRMS approaches have been applied to numerous environmental samples collected around fluorochemical point sources to identify new unregulated compounds. For example, new structures were resolved in water located around Chinese manufacturing facilities[28] and in river water from domestic sites.[29] Potential structures were assigned to numerous PFASs in Alabama[26] and previously in the Cape Fear River of North Carolina.[29,30] In each case, spatial and/or temporal sampling was used to compare impacted and baseline water samples, while identifying molecular features associated with the fluorochemical waste stream.

In North Carolina, discovery of the chemical hexafluoropropylene oxide dimer acid (HFPO-DA) sparked intense scrutiny of its long-term effects, resulting in the establishment of a preliminary NC state drinking water health goal.[31] Since initial reporting by media outlets,[32] the "chemical" GenX has been used as a public synonym for HFPO-DA. While GenX has occupied the center of the debate regarding fluorochemical contamination in the Cape Fear River, the presence of other fluorinated chemicals of related classes is also of interest. We combine the previously demonstrated nontargeted approach with techniques for structural assignment by tandem mass spectrometry (MS/MS) to identify the additional fluorochemical species affecting the Cape Fear watershed.

■ METHODS

Sample Collection. Surface water grab samples were collected in May 2017 from the main flow of the Cape Fear River and its tributaries at the William O. Huske Lock and Dam. An "upstream" sample was collected approximately 2 miles upstream of the dam, representative of the background contents of the river. A "downstream" sample was collected immediately above the dam, representative of the impacts of nearby (<1 mile) manufacturing outfall (Supporting Information Figure S1). Longitudinal grab samples of the manufacturing outfall were collected weekly by the North Carolina Department of Environmental Quality (NCDEQ) throughout the summer of 2017,[33] and follow-up samples were collected at the original sampling locations in February 2018. At each site, water was collected in a precleaned one liter high-density polyethyelene (HDPE) Nalgene bottle according to an established procedure.[34]

The collected water was processed as previously described, after stabilization with the addition of 5 mL 35% nitric acid.[26] In brief, one liter of water was measured in an HDPE graduated cylinder, and the sample bottle was washed with 10 mL of methanol to desorb analytes adhered to the interior of the bottle. The water and methanol were pooled in the bottle and filtered using a Whatman GF/A glass fiber filter. From this filtered sample, 500 mL of liquid was concentrated using a SPC10-P Sep-Pak concentrator onto an Oasis WAX Plus SPE cartridge (225 mg sorbent, 60 μm particle size) that had been preconditioned with methanol (MeOH) and water per manufacturer instructions. SPE cartridges were washed with 4 mL of pH 4 acetate buffer, followed by 4 mL of neutral methanol, and then compounds were eluted in 4 mL of 0.1% NH_4OH in MeOH. The methanol wash fraction could have contained nonacidic PFAS, but preliminary experiments did not detect these in samples from the Cape Fear, so they were discarded in the work for this manuscript. The eluent was evaporated under a nitrogen stream at 40 °C to a final volume of 1 mL and diluted 4-fold with 2.5 mM ammonium formate. A method blank was prepared in parallel using laboratory deionized water.

Sample Analysis and Data Processing. Initial mass spectrometry (MS) analysis on the collected water samples was carried out by liquid chromatography coupled to time-of-flight (TOF) in a fashion previously described;[29] instrument details are located in the Supporting Information. MS sample data was postprocessed using a software workflow of Agilent ProFinder, MassHunter, and Mass Profiler. Samples were subjected to batch recursive molecular feature extraction (MFE) in ProFinder using previously determined thresholds for this instrument and separation gradient (Supporting Information Table S3). A molecular feature, as defined by the software, consists of a specific isotopic distribution with a distinct extracted ion chromatogram peak abundance and is assigned a monoisotopic mass and retention time. Molecular features identified in the method blank were removed from the sample data, and the remaining values were exported for comparison in Mass Profiler. Samples collected downstream of the known fluorochemical point source were compared to upstream samples, which should be free of species introduced by the intervening facility. Pairwise comparison was used to identify features unique to the downstream samples as well as species which were significantly increased (>3-fold increase in integrated peak area). The list of the top 100 most abundant unique and statistically significant species was exported and prepared as an inclusion list for further MS/MS investigation.

Structural investigation of the molecular features was performed using an Agilent 1260 Infinity UPLC coupled to an Agilent 6530 quadrupole time-of-flight (QTOF). Parameters for LC separation were the same as the initial TOF analysis, but MS settings were adjusted to allow collection of MS/MS fragmentation spectra of the targeted inclusion list from the TOF analysis. Modifications to the MS collection are detailed in the Supporting Information.

The raw data collected from QTOF MS/MS experiments was processed using ProFinder, followed by filtering to isolate features for closer inspection. Comparison of precursor and fragment masses allowed a maximum 5 ppm precursor and 20 ppm fragment mass error; average mass error was ~1 ppm, consistent with the performance specifications of the instru-

DOI: 10.1021/acs.est.8b06017
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

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ment. Features were individually examined to determine structures where possible. For each mass-to-charge (m/z) identified at the formula level or better (Confidence 4+), an ±10 ppm extracted ion chromatogram of the theoretical precursor mass was generated to determine retention times (Supporting Information Figures 1−83). Composite MS/MS spectra consisting of multiple averaged MS/MS scans at collision induced dissociation (CID) energies of 10 and 25 V; spectrawere generated for individual isomers of each precursor, where possible.

The list of molecular features was sorted by integrated peak area and the isotopic distributions for each of the molecular features; a putative empirical formula was assigned using MassHunter's formula generator tool. This assignment is a score obtained by matching the feature's accurate mass and isotopic distribution with theoretical values calculated using known isotopic distributions of a potential formula's constituent elements (i.e., 1.1% ^{13}C, 0.4% ^{15}N, etc.). Allowed atoms included C, H, N, O, S, F, Cl, Br, and P. For compounds with only poorly scoring isotopic matches (e.g., <70%), background subtraction of the precursor spectrum was carried out against a background of the 0.2 min regions immediately preceding and following the chromatographic peak, and a second attempt at formula assignment was made.

The MS/MS spectra collected for each molecular feature were manually examined to ascertain the accuracy of the precursor formula and attempt to resolve molecular structures. Emphasis was placed on chemicals demonstrating a negative mass defect—the difference between the exact and nominal mass of the compound, a common signature of halogenation.[22] It is worth noting that this is only a rough proxy for the inclusion of critical atoms of interest (i.e F, Cl, Br) in small molecules and significant supporting data is necessary to classify an unknown as a PFAS.[35] Fragment ions were assigned partial empirical formulas based on exact monoisotopic mass using a similar process to the precursor mass but using the precursor formula as the list of allowed atoms. Potential formulas were compared against the existing EPA's Comptox Chemicals Dashboard,[36] an internally maintained PFAS database, and extant literature, including publications, patents, and the CAS registry, to obtain known potential structures. Potential structures were also generated *de novo* based on observed fragments and related chemicals. A degree-of-confidence assessment for each chemical feature was assigned based on the Schymanski classification.[37] Briefly, where verified standards existed for a proposed structure, comparison with the retention time and MS/MS structure of the standard was carried out; matches were assigned a confidence level of 1. In the absence of a confirmed standard, fragment ions were compared to available standards with similar substructures and empirical or *in silico* library spectra; probable structures were assigned a confidence level of 2. Where structures could not be completely resolved by MS/MS, partial elucidation of chemical class/structure was based on diagnostic fragments and relationship to identified compounds; tentative candidates were assigned a confidence level of 3. In absence of quality MS/MS spectra or where incompatible tentative candidates could not be resolved, only a molecular formula was determined; molecular formula level assignments were given a confidence level of 4. Features with lower confidence were not reported here.

Clustering of Non-Targeted Chemical Features by Time Trend. The samples collected in May 2017 and February 2018 bracketed significant changes to the Cape Fear River as the result of regulatory actions by NCDEQ against the Chemours company.[33] As part of their ongoing monitoring, the state collected water samples proximate to the waste outfall into the Cape Fear River over several months during the summer of 2017. These samples were acquired from NCDEQ, analyzed by TOF-MS as described, and the ion abundances for the species were monitored over the sampling time points. Abundance measurements for each chemical were normalized to the highest abundance for the feature across all sampling points for that chemical. Time trends of chemical features were hierarchical clustered for similarity with *hclust* in R (3.4.4) using Euclidean distance and the "Ward.D2" clustering criterion;[38] cluster p-values were calculated using *pvclust*[39] with 10000 bootstrap iterations and filtered to $p < 0.05$.

RESULTS AND DISCUSSION

Feature extraction from surface water collected upstream of a fluorochemical manufacturing site yielded ~120 distinct molecular features. Features with PFAS-like MS signatures were all from the legacy perfluorinated acids (PFBA, PFPeA, PFHxA, PFHpA, PFHxS, PFOA, and PFOS). No additional PFAS species were detected in the samples. The existence of these fluorinated compounds in the surface water is expected, because of their persistent nature and ubiquitous use in preceding years, and has been previously reported.[40−44]

Feature extraction from the sample immediately downstream from the fluorochemical manufacturer yielded a significantly larger amount of ~260 distinct molecular features of which nearly 200 possess the negative mass defect marker indicative of potential halogenation (Supporting Information Table 1). A comparison of the total signal intensity of species with a negative mass defect in the upstream and downstream samples indicates that while ~15% of the total ion current for the upstream sample is resultant from perfluorinated acids above, the downstream sample is, by total ion intensity, >90% composed of species with a negative mass defect. Further, the ambient PFASs detected upstream make up <1% of the total ion intensity in the downstream sample. Clearly, wastewater discharge from the fluorochemical manufacture introduces a significant number of compounds to the river besides the legacy perfluorinated acids detailed in EPA 537[45] (Supporting Information Table 1).

Manual curation of detected chemical features yielded 58 distinct chromatographically resolved PFAS peaks, corresponding to 38 unique molecular formulas. Recent efforts have been made to identify novel contaminant species in fluorochemically impacted water supplies by the US EPA and other groups.[26,46−49] Cross-referencing literature lists of expected monoisotopic masses and their hypothetical structures against the molecular features observed in this study accounts for roughly half of the unique features, with the remainder being unidentified based on literature comparison.

The features were individually examined to determine novel structures as described in the Methods section (Supporting Information Table 2). For each mass-to-charge (m/z) identified at the formula level or better, an extracted ion chromatogram of the precursor mass was generated to determine retention times (Supporting Information Figures 1−83). Composite MS/MS spectra consisting of multiple averaged MS/MS scans at 10 and 25 CID settings were

DOI: 10.1021/acs.est.8b06017
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

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Table 1. Identified Perfluorinated Ether Acids

ID	Conf	Formula	Theoretical [M]	ppm error	Isomers	CAS	Ref
1	1	$C_3HF_5O_3$	179.9846	1.68	1	674-13-5	29
2	1	$C_4HF_7O_3$	229.9814	2.18	2	13140-29-9, 377-73-1	29
3	1/2b	$C_4HF_7O_4$	245.9763	0.41	1	39492-88-1	29
4	2b	$C_5HF_9O_3$	279.9782	1.43	1	267239-61-2	29
5	3	$C_5HF_9O_4$	295.9731	2.71	1		
6	1	$C_5HF_9O_5$	311.968	0.96	1	39492-89-2	29
7	1	$C_6HF_{11}O_3$	329.975	1.22	1	13252-13-6	29
8	3	$C_6HF_{11}O_4$	345.9699	0.58	1		
9	3	$C_6HF_{11}O_5$	361.9648	0.83	1		
10	1	$C_6HF_{11}O_6$	377.9597	1.59	1		29
11	4	$C_8HF_{13}O_4$	407.9667	0.25	1		
12	3	$C_7HF_{13}O_5$	411.9616	1.46	1		
13	1	$C_7HF_{13}O_7$	443.9515	0.90	1		29
14	2b	$C_4HF_9O_4S$	315.94518	1.97	1	113507-82-7	29
15	3	$C_5HF_{11}O_4S$	365.94199	0.85	1		
16	1	$C_7HF_{13}O_5S$	443.93371	0.20	1	29311-67-9	29
17	3	$C_8HF_{15}O_5S$	493.93052	0.04	1		

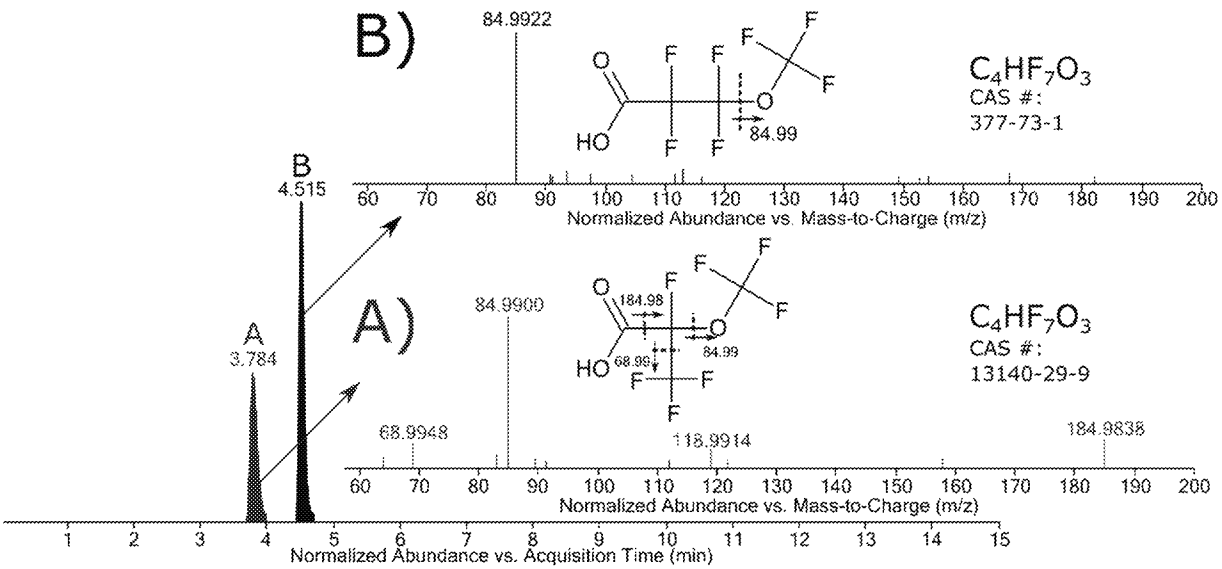

Figure 1. Determination of isomeric branching of perfluorinated ether compounds based on MS/MS fragmentation patterns. Compound 2A elutes at 3.8 min and has multiple major mass fragments. Compound 2B elutes later at 4.5 min and fragments only at the terminal ether linkage.

generated for individual isomers of each precursor, where possible (Supporting Information Figures 1−83).

Group A: Perfluorinated Ether Acids. A frequently observed PFAS class is that of fluoroether acids (here Group A), which exist with a general formula $CF_3(CF_2)_n(CF_2O)_m(R_1)$, where the headgroup, R_1, is an acidic moiety such as −COOH or $-SO_3H$.[29,30] These were expected to be the primary contaminants identified in the survey, given that nearby production includes perfluorinated polyvinyl ethers, empirical formula $(CF_2)_n(CF_2O)_m$. The production of the ammonium salt of 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy) propanoic acid,[21] where $n = 3$, $m = 1$, R1 = COOH is shown in the above scheme, and "Nafion", a copolymer of tetrafluoroethylene and perfluoro(4-methyl-3,6-dioxaoct-7-ene)sulfonic acid, a monomer where $n = 3$, $m = 2$, $R_1 = SO_3H$ is shown as above.[50] Numerous molecules in this series were found during this sampling event (Table 1).

Compound 2 was identified previously in historical sampling in the river basin;[29] however, the UPLC separation resolved two isomeric structures with different MS/MS fragmentation patterns (Figure 1), which was not observed for other Group A species. The more abundant isomer of compound 2 (2B) is available as a standard, and its MS/MS fragmentation pattern and retention were confirmed to match the tentative assignment. The additional isomer is currently not commercially available and was assigned on the basis of MS/MS fragmentation and the shift in reverse phase retention time, indicative of increased branching (Schymanski Level 2b).[51]

The primary fragments for perfluorinated ether carboxylic acids are typically decarboxylation (neutral loss of 43.9898 Da) and production of the terminal ether fragment (here CF_3O^-, 84.99067 Da). Sulfonated acids produce a sulfonate (SO_3^-, 79.9568 Da) fragment instead of a decarboxylation, but the primary structural fragment remains the terminal ether. These patterns were observed across all Group A compounds, but the lack of significant internal fragmentation makes it difficult to assign complete linkage isomerization of longer perfluorinated

DOI: 10.1021/acs.est.8b06017
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

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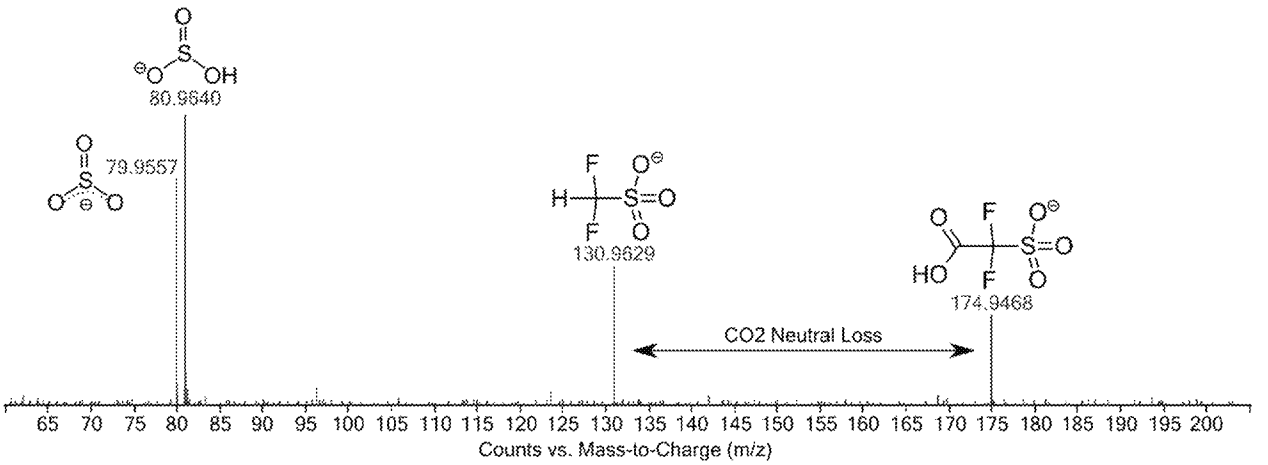


Figure 2. Annotated MS/MS spectrum of precursor m/z 174.9496 (compound 18), assigned the molecular formula $C_2H_2F_2O_5S$.

Table 2. Identified Perfluorinated Ether Acids with Multiple Acidic Sites

ID	Conf	Formula	Theoretical [M]	ppm error	Isomers	CAS	Ref
18	2b	$C_2H_2F_2O_5S$	175.9591	0.57	1	422-67-3	55
19	2b/3	$C_5H_2F_8O_6S$	341.9444	2.35	2	790642-73-8	55
20	3	$C_6H_2F_{10}O_5$	343.9743	2.33	1	919005-07-5	56
21	4	$C_7H_3F_{11}O_7S$	439.9424	0.68	2		
22	2b/3	$C_7H_2F_{12}O_6S$	441.938	0.23	2	852157-01-8	57
23	2b/3	$C_8H_2F_{14}O_7S$	507.9298	1.18	2	1235024-21-1	57
24	2b/3	$C_7H_3F_{13}O_8S_2$	525.9062	0.19	2	916340-65-3	58

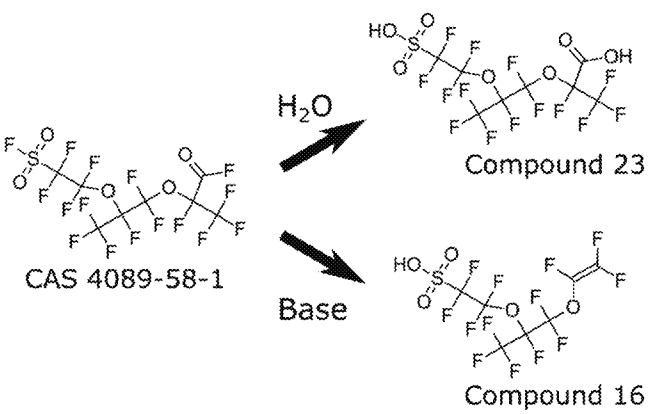
ethers based on MS/MS alone, and many compounds remain level 3 identifications.

The initial patent description of the polyvinyl ether process refers to the creation of multiple competing side reactions and low molecular weight polyfluoro-ether byproducts,[52,53] which have been used as reactants and starting materials in more complicated copolymer production schemes.[54] Without further information about manufacturing processes, it is not immediately clear which reactions and waste streams yield the perfluoroether compounds detected and whether they are primary or secondary waste products. Further, broader nontargeted efforts would be necessary to determine whether they are contained in finished products directly impacting consumers or only in the nearby environment; however, the spatial and temporal correlation of detected species is highly suggestive of the point source (i.e., manufacturing outfall).

Group B: Multi-Headed Perfluoroether Species. Perfluoroether species previously described can be thought of in a more general sense as compounds with the form R_1-$(CF_2)_n(CF_2O)_m$-R_2, where R_1 and R_2 are both variable head groups. While R_1 is CF_3 for the Group A perfluorinated acids previously discussed, some compounds were observed with multiple acidic groups (R_1, R_2 = −COOH or $-SO_3H$). This group of compounds was identified in both −1 and −2 charge states and had initial predicted formulas suggesting an overabundance of oxygens which could only be structurally supported by multiple acidic sites on the perfluorinated backbone. Further, diagnostic ions for CO_2 and/or SO_3 were observed (Figure 2). We grouped these species as Group B, multiply sulfonated and/or carboxylated perfluorinated ether acids (Table 2).

While these species have not been previously reported in environmental media, to the best of our knowledge, the literature of fluorochemical manufacturers proposes a few possible structures in this group, primarily as side products in fluoropolymer production and degradation.[55−57] The formation of short chain fluorosulfonyl ($-SO_2F$) and acyl fluoride (−COF) fluoroethers formed as byproducts or intermediate steps in fluoropolymer synthesis is the likely source of precursor compounds that degrade into the observed compounds.[52] Aqueous hydrolysis of the acid fluoride intermediates during production or water treatment yields the familiar carboxylic acid (−COOH) and sulfonic acid moieties ($-SO_3H$), while more basic conditions (e.g., KOH, Na_2CO_3, etc.) yield further hydrolysis products (Scheme 1). These full and partial hydrolysis reactions are well-known steps in fluoropolymer production and in the abatement of fluoroether salts.[59−61]

Scheme 1. Transformation of a Fluorosulfonyl/Acyl Fluoride Fluoroether to Sulfonate End Products by Hydroloysis



DOI: 10.1021/acs.est.8b06017
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

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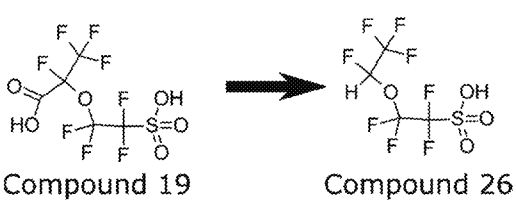
Table 3. Identified Polyfluorinated Ether Acids with a Single Hydrogen Substitution

ID	Conf	Formula	Theoretical [M]	ppm error	Isomers	CAS	Ref
25	2b/3	$C_3H_2F_6O_4S$	247.9578	1.62	3	905363-45-3	58
26	1	$C_4H_2F_8O_4S$	297.9546	1.35	1	905363-44-2	58
27	2b/3	$C_5H_2F_{10}O_4S$	347.9514	1.15	3	935443-55-3	58
28	3	$C_6H_2F_{12}O_4S$	397.9482	1.51	2		
29	3	$C_8H_2F_{14}O_4S$	459.9450	0.00	3		
30	2b/3	$C_5H_2F_8O_3$	261.9876	1.15	3	919005-00-8, 919005-13-3	56
31	2b/3	$C_6H_2F_{10}O_3$	311.9844	1.61	3	919005-19-9	56
32	3	$C_7H_2F_{12}O_3$	361.9812	3.05	1	919005-26-8	56
33	3	$C_6H_2F_{12}O_5S$	413.9431	0.00	2		
34	1	$C_7H_2F_{14}O_5S$	463.9399	1.30	2	749836-20-2	29
35	4	$C_9H_2F_{16}O_6S$	541.9317	0.00	1		
36	1	$C_8H_2F_{14}O_4$	427.9730	2.11	1	773804-62-9	
37	4	$C_8H_2F_{14}O_7$	475.9577	4.42	2		

Group C: Single-H Containing Polyfluorinated Acids. Another subset of fluorinated compounds, Group C, was identified with molecular formulas containing a single F → H substitution compared to that in the Group A perfluorinated ether compounds (Table 3). For example, compound 14 ($C_4HO_4SF_9$) and compound 26 ($C_4H_2O_4SF_8$) differ by the substitution of a hydrogen for a fluorine. These compounds are highly isomerized, and MS/MS fragmentation is frequently insufficient to unequivocally assign the structure; the structures presented in the Supporting Information (Table S-2) are representative of a single observed isomer.

The production of polyfluorosulfonic acid ethers of the form R-OCFH−CF_2−SO_3 was described in early patent filings,[58] and their use as fluoropolymer surfactants was mentioned in a follow up.[62] The use and production of these chemicals as part of Nafion manufacturing is assumed to be responsible for at least some of the observed species. In contrast to the previously mentioned literature structures, MS/MS fragmentation of some polyether sulfonate isomers indicates that the single hydrogen substitution occurs on the tail ether rather than adjacent to the head; for example, the fragment C_2HF_4O− (116.9969 Da) from one isomer of compound 30 (Supporting Information Figure 64) is derived from a two carbon polyfluorinated ether unit (Supporting Information Table S-4). These species are assumed to be products of the fluorosulfonyl and/or acyl fluoride species which produced Group B but further decomposed. The complete loss of a headgroup (e.g., decarboxylation) during production, waste treatment, or naturally in surface water would yield a compound with a single hydrogen in that site (Scheme 2). Thermally decarboxylated perfluoroether species are noted as potentially undesirable byproducts of fluoropolymer production in the patent literature of fluoropolymer production,[60] and partially decarboxylated species are noted as possible products from multiply acidic species such as Group B chemicals.[63]

Scheme 2. Transformation by Decarboxylation of Sulfonated Carboxylic Acid Perfluoroether to Yield the Polyfluorosulfonic Acid



Presence and Prevalence of Novel Species. The lack of authentic standards limits the potential for quantitative measurements of novel compounds; relative abundance and semiquantitative estimates of emerging compounds are all that are available. However, this information remains useful for targeting individual chemicals for follow-up study and for monitoring environmental changes in response to systemic actions. Our examination of the May 2017 downstream sample could assign 35 of the top 50 most abundant features, corresponding to ~90% of the total ion current in the sample (Figure 3). While ion abundances are sensitive to many aspects of the sample matrix and molecules, the structural similarity of the fluoroethers would suggest some similarity in instrument response, and that species can be roughly compared. At least one species of each of the three major chemical groups outlined (groups A, B, and C) exhibited a higher ion abundance than the HFPO-DA species with a targeted health goal. Further, of the targeted compounds detailed in EPA 537,[45] only perfluoropentanoic acid (PFPeA) is present in the top 50; thus, the fluorochemical load in the system would be greatly underestimated by traditional targeted approaches. Additionally, including the compounds previously detailed in studies of the Cape Fear River[29,30] accounts for only ~50% of the total ion intensity in the initial sample, suggesting that even single-time-point nontargeted survey can fail to sufficiently capture the chemical complexity of a location.

An advantage of nontargeted analysis is the historical data banking of samples and the ability to perform relative quantification across disparate sample sets. The comparison of chemical species abundance over the time period from May 2017 to February 2018 revealed several distinct abundance patterns from simple visual inspection (Figure 4). Many fluoroether species exhibited exponential decline in concentration (Figure 4, left) while others showed lagging or even temporarily increased abundances (Figure 4, center and right).

Matrices of the weekly relative ion abundance of each of the identified chemical features over the eight sampling points were clustered for similarity using Ward's clustering criterion implemented in R *hclust*;[38] *p*-value calculations for clusters were performed using multiscale bootstrap resampling implemented in the *pvclust* package. Clustering of the time-trend data yielded six distinct chemical clusters (Figure 5, Supporting Information Figures 84−89).

DOI: 10.1021/acs.est.8b06017
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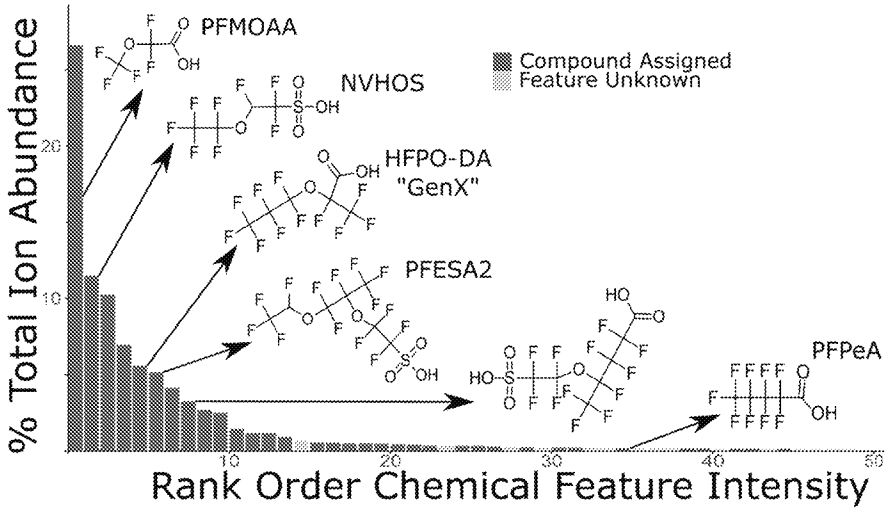

Figure 3. Total ion abundance as a percentage of the sum of all chemical features for compounds identified in a May 2017 sample of the Cape Fear River downstream of a fluorochemical manufacturer. Selected highly abundant compounds confirmed by standards obtained from and labeled by Chemours include: compounds 1 (PFMOAA), 26 (NVHOS), 7 (HFPO-DA), 34 (PFESA2), 22 (PFESA4), and perfluoropentanoic acid (PFPeA).

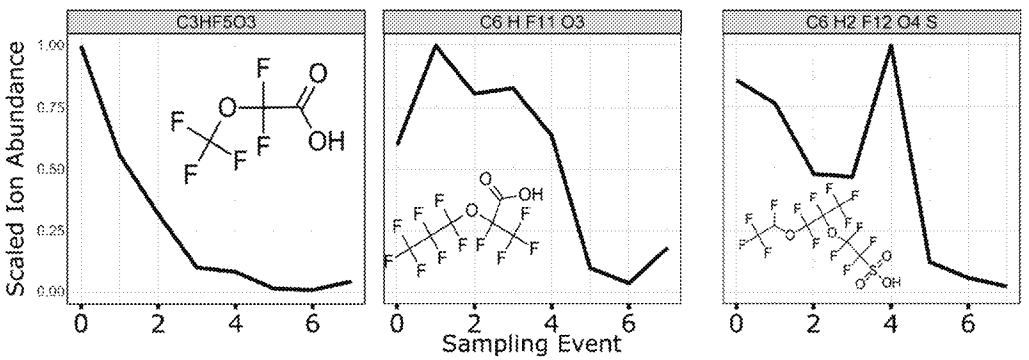

Figure 4. Scaled ion abundance of three chemical features confirmed by standard and detected in the Cape Fear River over a time course sample. Time points one to six were taken weekly beginning June 19, 2017 with time points zero and seven being collected in May 2017 and February 2018, respectively.

These clusters support the hypothesis that multiple production processes generate distinct groups of the chemicals observed in the Cape Fear River, as the compound abundances are correlated over time and are chemically similar based on naive classification. For example, the cluster at branch 16 (Figure 5) contains the H-substituted sulfonic acid ethers from Group C. These compounds abruptly and almost uniformly vanish following the initial sampling event (Supporting Information Figure 86), while the clusters at branches 13 and 18 contain the perfluoroether carboxylic acids and their associated H substituted versions; both classes exponentially and smoothly decrease from the early sampling events (Supporting Information Figures 84,87). Other clusters contain more chemical variation, as well as more complex time-trend patterns, that may be reflective of species with multiple sources or processes involving multiple PFAS classes.

It is worth noting that the chemical assignment provided to each feature is not required for clustering. Application of the clustering approach reveals chemical feature relationships that could be used to target unidentified species for follow-up analysis based on their close association with compounds of interest (e.g., HFPO-DA), and occurs before the assignment of formulas or structures.

Environmental Impact. The phase-out of PFOA/PFOS and longer-chain PFAS materials has led to an increased prevalence of replacement chemicals. The chemical groups detailed here are derived from processes and procedures that are over 20 years old within the fluorochemical production industry but are only now becoming apparent due to increased scrutiny of environmental media and the proliferation of nontargeted methodologies. Fluorinated ethers such as those described here have been reported in the Cape Fear River previously.[29,30] Similar structures have been reported in numerous locations worldwide, indicating that emerging PFAS are every bit as ubiquitous as their PFOA/PFOS antecedents.[64,65] Physiochemical characteristics of similar perfluorinated ether compounds suggest that the fluoroether substances are of reduced health impact compared to similarly sized perfluorinated acids, but retain some degree of health risk.[66] Further, longer-chain perfluorinated ethers are not currently regulated similarly to long chain perfluorinated acids and exhibit similar bioaccumulation potential, as evidenced by the preliminary reporting in human blood in spite of their relative low abundance in surface water.[67] Efforts to determine reasonable health levels for these emerging compounds are ongoing. During the preparation of this manuscript, the state of North Carolina set a drinking water health goal for a single perfluorinated ether acid (PFECA) compound, HFPO-DA, at 140 ng/L, based on their assessment of human health risk from available data submitted in the European Union.[31,68,69]

DOI: 10.1021/acs.est.8b06017
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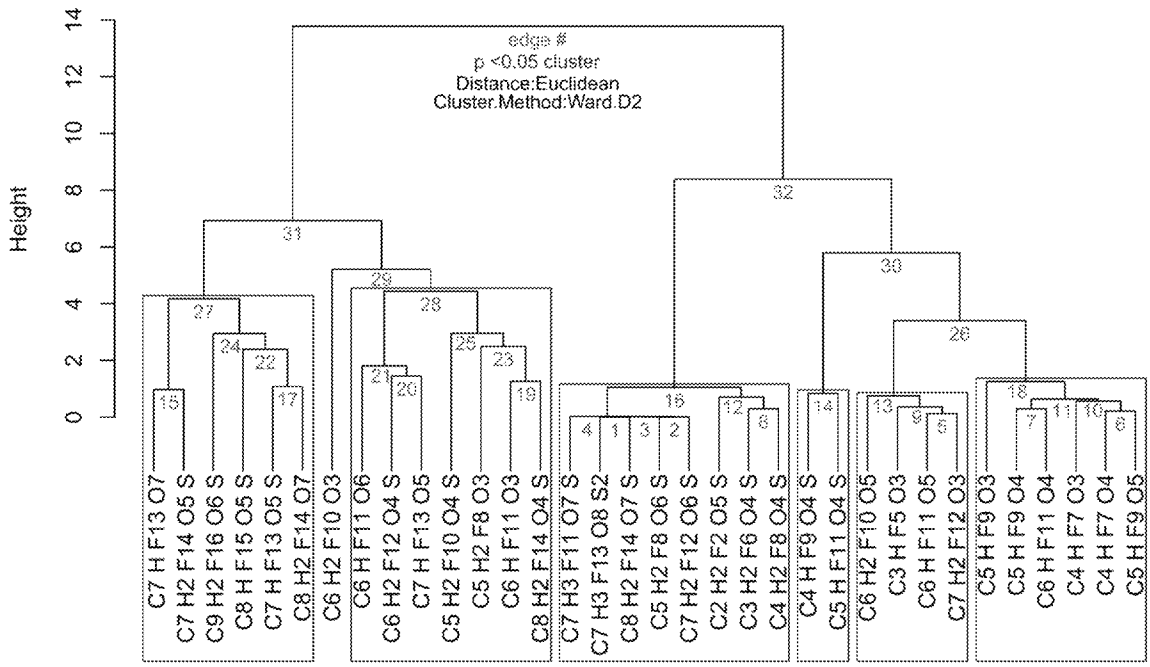

Figure 5. Clustering of identified chemical features from scaled ion-abundance of features detected in the Cape Fear River in eight sampling events between May 2017 and February 2018.

Sulfonated ether substances in this measurement series are primarily associated with sulfonated fluoropolymer production, specifically the Nafion polymer, and are of lesser widespread concern due to the limited manufacture of such polymers and their primary application being energy-related technologies, such as fuel cells.[50] Nevertheless, for locations that are exposed to such manufacturing waste streams, sulfonated fluorinated acids have shown higher accumulation potential and toxicological effects than equivalent carboxylic acids.[19] Further, other sulfonated ether acids, such as F-53B, have shown equivalent bioaccumulation potential as the regulated perfluorinated sulfonic acid PFOS.[70,71] Other sulfonated fluoroether species have begun to be detected by other groups, but they exhibit different structural elements and likely have different origins that need to be examined independently.[64,72] The continued appearance of new PFAS species necessitates an increase in the generation of toxicological profiling and monitoring efforts to assess human risk from exposure to these novel chemicals.

With regards to human exposure, it has been demonstrated that perfluoroether compounds are poorly cleared by water treatment processes, including activated carbon, and the most effective method of removal is through source control.[30,73] Long-term monitoring of impacted watersheds remains an important tool for both detecting new chemical species over multiyear time scales and for determining shorter-term changes in local chemical load. An application of this approach to other watersheds has been effective for other chemical classes, such as surfactants.[23,47] During the course of this study, our monitoring activities resulted in the cessation of discharge from the vinyl ether production at the source manufacturing location, which resulted in a concomitant decrease in PFECAs hypothesized to derive from that process, but not in the immediate reduction of the perfluorinated ether sulfonic acid (PFESAs) species since they derive from a different source than the PFECAs.[33] Targeted methods and single time-point nontargeted surveys can easily miss transient chemicals or underestimate chemical loads for exposure assessment; some species spiked as much as 5-fold during the sampling period (cluster branch 27, Supporting Information Figure S8), even as other compounds were declining. The proactive application of a nontargeted screening approach is capable of identifying and monitoring chemicals present in the water, even prior to complete structural elucidation or toxicological analysis and provides a useful tool toward those ends.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.8b06017.

All detected chemical features, assigned chemical species, software settings for molecular feature extraction, common MS/MS fragments of PFAS compounds, chromatographic traces for molecular ions of chemical features, composite MS/MS fragmentation spectra of chemical features, scaled abundance time trends for chemical features, statistical validation of chemical feature clustering, sampling map (PDF)

Cape Fear upstream and downstream data (XLSX)

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.est.8b06017
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

ED_002541B_00000541-00008

ACKNOWLEDGMENTS

The U.S. Environmental Protection Agency, through its Office of Research and Development, funded and managed the research described here. This document has been reviewed by the U.S. Environmental Protection Agency, Office of Research and Development, and approved for publication. The views expressed in this article are those of the authors and do not necessarily represent the views or policies of the U.S. Environmental Protection Agency. This research was supported in part by an appointment to the Postdoctoral Research Program at the National Exposure Research Laboratory administered by the Oak Ridge Institute for Science and Education through Interagency Agreement DW89992431601 between the U.S. Department of Energy and the U.S. Environmental Protection Agency.

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