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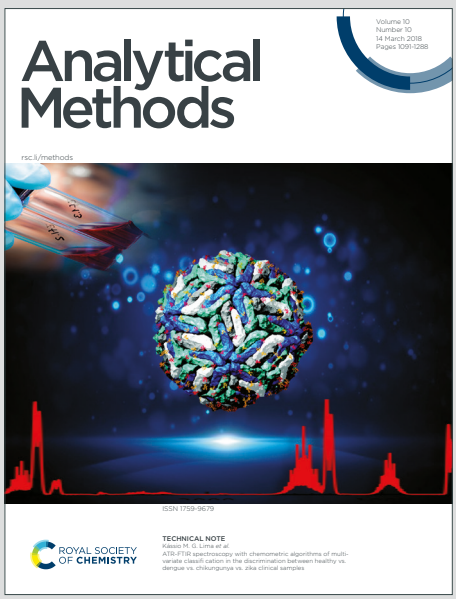

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Direct-inject suppressed ion chromatography-mass spectrometry method with online preconcentration for short- and ultra short-chain perfluoroalkyl carboxylic acids in fresh water

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ABSTRACT

This work developed a novel analytical method to detect short- and ultra-short chain perfluoroalkyl carboxylic acids (PFCAs) in freshwater samples by direct injection using ion chromatography mass spectrometry (IC-MS). Ultra-short chain PFCAs, including trifluoroacetic acid (TFA), are often present in aqueous environments at higher concentrations than the longer chain PFCAs, however there are currently a limited number of methods that can analyze them. Detection limits ranged between 1.3 – 2.8 ng/L (ppt) of the PFCAs (C2 – C6) analyzed and were comparable to other LC-MS and GC-MS methods. The precision of this method ranged from 0.4 – 7.6% for all the PFCAs (C2 – C6). An advantage of this method is small samples sizes under 1 mL can be used. This method was applied to real freshwater samples which included tap water, precipitation, lake water, and river water. TFA was detectable in most of the samples with online pre-concentration and no other additional pretreatment sample preparation,

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though method performance was decreased in samples with high conductivity. A new unidentified isobaric interferent for TFA was present in most of the freshwater samples.

INTRODUCTION

Per-and polyfluoroalkyl substances (PFAS) are a widely used man-made class of organofluorinated compounds containing over 4700 chemicals.[1] Perfluoroalkyl acids (PFAA) are a subset of PFAS that are widely used in many consumer and industrial products including stain repellents, non-stick food paper or pans, and firefighting foams.[2,3] Perfluoroalkyl carboxylic acids (PFCA, $C_nF_{2n+1}COOH$), a major class of PFAAs, are highly polar, stable in the environment, resistant to photolysis, and are miscible and highly soluble in water. They have large acid dissociation constants, low Henry's law constants, and low octanol-water partitioning coefficients.[4] Long chain (≥ 8 carbons) PFCAs are toxic in the environment, bioaccumulate, and magnify in food chains.[5,6] While short chain (≤ 7 carbons) PFCAs do not bioaccumulate in the conventional sense they are present in humans[7] and also accumulate in plants and are phytotoxic.[8,9] The high persistence of all PFCAs leads to their accumulation in the environment.[8,10–12] Ultra-short-chain (2–4 carbons) PFCAs are often present in much higher concentrations in the environment, especially aqueous environments, in comparison to other PFCAs.[13,14] In particular, trifluoroacetic acid (TFA), the shortest PFCA with a pK_a of 0.23–0.47,[15,16] is frequently found at much higher abundance than other PFAS.[13,17] Ultra-short-chain PFCAs are highly water soluble and mobile in water, resulting in their rapid entry into the water cycle, while their very persistent nature prevents many removal processes from reducing their burden in freshwater.[13,18]

One major source of ultra-short-chain PFCAs to the aquatic environment is atmospheric formation

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from several precursor gases. The Montreal Protocol is a global agreement to regulate and phase out chlorofluorocarbons (CFCs), commonly used as refrigerants, due to their role as stratospheric ozone-depleting substances. Montreal Protocol-mandated CFC replacements have degradation pathways known to produce ultra-short-chain PFCAs.[19–22] The most recent Kigali Amendment was added to further limit the production of CFCs and their prior replacements.[22] One major class of new replacements to satisfy the Kigali Amendment are hydrofluoroolefins (HFOs), which were selected due to their shorter atmospheric lifetimes as well as their lower global warming potentials in comparison to CFC and previous replacement compounds. However, some HFOs have a 100% degradation yield of TFA under atmospheric conditions.[8] The increased usage of HFOs under the Kigali Amendment to the Montreal Protocol is therefore expected to cause an increase in ultra-short-chain PFCA production and, as a result, concentrations in the environment.[23] Environmental increases of TFA and other ultra-short-chain PFCAs have already been attributed to the introduction of CFC replacements.[9,24] Another source of TFA to natural waters is photooxidation of molecules containing an aryl-CF_3 group, including pharmaceuticals and pesticides.[25–27] Additionally, biodegradation of PFAS,[28] as well as emissions from landfills, industry, and wastewater[25,29] are possible contributors to environmental burdens of ultra-short-chain PFCAs. The relative contributions of these sources to ultra-short-chain PFCA contamination in fresh waters are not yet well understood.

Quantitative measurements of ultra-short-chain PFCAs in fresh waters are increasingly important given the prevalence of these molecules and their expected accumulation in fresh and marine waters. The main instruments currently used to separate and quantify environmental PFCAs are liquid, and gas chromatographs fitted with mass spectrometers. Liquid chromatography (LC) has been the method of choice for separation of PFCAs without requiring derivatization, with a growing variety of stationary phases being reported fit for use including reverse phase (RP)[17], hydrophilic liquid interaction (HILIC)[30],

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ion exchange (IE)[25,31], and mixed-mode ion exchange within an RP column (MM).[24,30,32] A notable difference typically exists between instruments, where ion chromatography (IC) system components are made entirely of inert polymeric materials like polyether ether ketone (PEEK) instead of stainless steel in LC systems, to prevent analyte-surface interactions for ionic species. Here, we will combine the use of RP, HILIC, IE, and MM under the umbrella term of LC, unless specifics within one of these requires further delineation, and IC to denote the different instrumentation. With applications for longer chain PFCAs, LC tandem mass spectrometry (LC-MS/MS) has been used because they are surfactant molecules, water-soluble, and thus readily amenable to electrospray ionization (ESI). LC systems often contain fluoropolymer components, like polytetrafluorethylene (PTFE) and these materials leach ultrashort-chain PFAS creating a contamination source of PFCAs, including TFA.[33] To overcome PFCA contamination in LC systems, trap columns have been used to delay their elution and reduce backgrounds in the method to improve detection limits.[34] It is also difficult to impossible to retain short-chain PFCAs on traditional RP columns because they are too polar to partition into the stationary phase under most standard mobile phase solvent conditions. This has only recently been mitigated through the use of MM columns, where reasonable retention factors (k') have been obtained.[24,25] Gas chromatographs with mass spectrometers (GC-MS) have also been used because they are widely available, relatively inexpensive, contain no fluoropolymer parts, and produce excellent separation and resolution. The disadvantage of GC-MS is that PFCAs are non-volatile and therefore any environmental sample containing them must be derivatized. There are many different derivatization methods used when analyzing PFCAs, including 2,4-difluoroaniline,[35–38] benzyl bromide,[39] pentafluorophenyl diazoethane,[40,41] dimethyl sulfate,[42–44] Fischer esterification,[45] and diphenyl diazomethane[46]. Derivatization methods are time consuming, often requiring extensive sample preparation, in addition to the use of hazardous reagents. Few derivatization methods have been effectively applied to short-chain PFCAs[46] because they often produce extremely volatile

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products that are difficult to retain on a GC column.[42,47,48]

Previous analytical methods, whether LC- or GC-based, for ultra-short-chain PFCAs required cleanup steps to reduce matrix effects and/or to concentrate the PFCA concentrations from the initial samples, including "clean" samples like ice cores.[49]. Commonly used cleanup strategies included liquid-liquid extraction (LLE)[44,50] and solid phase extraction (SPE).[51,52] With ultra-short-chain PFCA pervasiveness in the environment, including within analytical laboratories, any sample handling could result in contamination.[46] Relatively high levels in environmental water samples, on the order of 20 ng L^{-1} to 3 µg L^{-1},[53,54] are above typical LC-MS/MS instrumental detection limits, which suggests that direct injection should be possible. However, ionisation suppression, caused by other matrix components of environmental samples (e.g., Cl^- and NO_3^- in groundwater samples) often necessitate cleanup steps. Methods that allow for the direct injection quantitation of PFCAs in aqueous environmental samples on LC and IC systems are developing and appearing on the market to fill this gap.[49,55–57] For TFA, LC-MS/MS direct-inject methods have been developed for water[25] and more complex matrices, such as wine[58] and urine.[59]

The objective of this work was to develop a direct injection method that exploits the fully ionized state of ultra-short-chain PFCAs as they are found in freshwater environmental samples using IC coupled to mass spectrometry (IC-MS), a subset of LC that separates ionic compounds based on their hydrated ionic radius. Herein, we show that ultra-short-chain PFCAs can be separated readily from environmental anions because of adsorption and ionic interactions with the column functional groups, reducing the likelihood of matrix effects from the on-column separation, while also determining detection limits, optimized separation parameters, and environmental concentrations.

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EXPERIMENTAL SECTION

Reagents and Materials. Nomenclature of the PFCAs can be found in the supplementary information (Table S1). Salts of PFCAs include sodium trifluoroacetate (TFA; C2; Aldrich Chemicals, 98%), sodium pentafluoropropionate (PFPrA; C3; Aldrich Chemicals, 99%), sodium perfluorobutanoate (PFBA; C4; Synquest Laboratories, 98%), sodium perfluoropentanoate (PFPeA; C5; Synquest Laboratories, 97-103%), and sodium perfluorohexanoate (PFHxA; C6; Synquest Laboratories, 98%). Mass-labeled $^{13}C_2$-TFA (>97%) was purchased from Toronto Research Chemicals (Toronto, ON, Canada). Inorganic anion stock solutions were prepared from a primary mixed anion standard concentrate (Dionex Seven Anion Standard II in deionized water, Thermo Scientific) which contained F^-, Cl^-, NO_2^-, Br^-, and NO_3^- as sodium salts, PO_4^{3-} as the monobasic potassium salt, and SO_4^{2-} as the dibasic sodium salt. Calibration standards and eluents were prepared with Milli-Q water (18.2 MΩ·cm at 25 ˚C) obtained from an in-house system (Direct 8; EMD Millipore). The mobile phase also contained methanol (MeOH; UHPLC Grade; Fisher Chemical, MA, US) and 100 mM sodium hydroxide (NaOH; prepared from 49-51% in water for IC eluent; Sigma Aldrich).

Ion Chromatograph-Mass Spectrometer. A Thermo Scientific (Waltham, Massachusetts, USA) ICS-6000 coupled to a single quadrupole ISQ-EC-MS was used to separate and analyze select perfluoroalkyl acids and inorganic and organic anions. A Thermo Scientific AS-AP autosampler delivers 750 µL of aqueous sample onto an anion exchange column (TAC-ULP1 5 x 23 mm) where its anionic contents are preconcentrated. Sample anions of C2-C6 PFCAs and seven inorganic anions are then separated with a gradient program for sodium hydroxide (NaOH) using an AG24 IonPac guard (2 x 50 mm) and AS24 IonPac microbore analytical anion-exchange column (2 x 250 mm, 11µm particle size, 55% Divinylbenzene (DVB) crosslinking, alkanol quarternary ammonium ion functional group). The

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separation method was optimized with a gradient elution program at a mobile phase flow rate of 0.35 mL min^{-1} conducted over 25 minutes. The starting condition was 10 mM NaOH held for 7 minutes, then linearly ramped up to 40 mM NaOH over 2 minutes and ramped up again to 52 mM NaOH for an additional 11 minutes. The conditions were held at 52 mM until 23 minutes, then returned stepwise to the initial conditions of 10 mM NaOH and held until 25 minutes to re-equilibrate, which was held constant as the next injection with the AS-AP was prepared (Figure S1).

The column effluent was passed through a suppressor (ADRS 600, 2 mm) in external water mode with an auxiliary (AXP) pump providing a flow through the regenerant ports at 1 mL min^{-1} and with an applied current of 87 mA. The eluent then passes through a conductivity cell, with measurements recorded at 5 Hz before a secondary AXP pump tees in 0.2 mL min^{-1} of methanol and the eluent is ionized under negative electrospray ionization conditions followed by detection in the MS operated in selective ion monitoring (SIM) mode for each analyte of interest listed in Table 1 as well as $^{13}C_2$ TFA (m/z 115). The vaporizer temperature was set to 450 ˚C, ion transfer temperature was at 250 ˚C, source voltage at -3000 V, and a nitrogen gas generator was used for the sheath gas pressure at 45 psig and auxiliary gas pressure at 5 psig. The chromatographic peaks and mass spectrum were analyzed using the Chromeleon™ 7 software package.

Calibration and QA-QC. A mixed PFCA standard was prepared with the internal standard $^{13}C_2$-TFA (250 ppt) and was used for the 7-point calibration curve to quantify the samples (5 – 500 ppt). $^{13}C_2$-TFA, an ultra-short PFCA, was the only internal standard used to normalize all the PFAS. Future work could add an additional isotopically labelled standard for the short chain PFCAs (C4-C6) to have higher certainty in their quantification while using external calibration. TFA and PFPrA were present as contaminants in the Milli-Q water ranging from <LOD – 86 ppt (TFA averaged 11 ppt; PFPrA averaged 44 ppt; n=13). Milli-Q water was therefore not suitable to be used as a sample blank; however, it was used

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to make all the standards. To account for TFA contamination in the standards, a reagent blank composed of Milli-Q water spiked with $^{13}C_2$-TFA was analyzed in triplicate for each calibration. The average of the TFA signal in this reagent blank was subtracted from the 6 remaining standards and used as a correction for the contamination. IC-MS systems use nonfluorinated components, which leach lower concentrations of PFAS, reducing contamination.[33] The standard deviation of the eluent background, which did not contain a TFA peak, was used as a method blank to determine range limits. This was done by running the instrument method in triplicate without injecting anything. Background levels of TFA from the IC-MS system components were negligible, especially in comparison to the fluctuating levels of lab contamination in the standards from the Milli-Q water. The standard deviation of the method blank was obtained similarly for all PFCAs at their retention time ranges and was used to divide by the peak heights (signal) of each standard point of the calibration curve to determine the signal to noise ratio. The signal to noise ratio was plotted against the concentration of the standards to determine the slope, then to calculate the limit of detection (LOD) 3 was divided by the slope, and 10 was divided by the slope to determine the limit of quantification (LOQ). The precision was calculated by determining the relative standard deviation from the 125 ppt mixed standard (n=6) using the internal standard $^{13}C_2$-TFA to normalize the peak area for all PFCAs.

Environmental and Drinking Water Samples. All drinking and surface water samples were collected into pre-cleaned (pre-rinsed 3x with Milli-Q water and final 1x rinse with MeOH)125 mL polypropylene bottles and stored at room temperature for 9 days. Eleven tap water samples were collected in March 2023 from homes across the Greater Toronto Area, ON, Canada and our laboratory (Figure S2). Lake and river samples were collected from shorelines in March 2023. Lake samples were collected from within 1 m of the shorelines of Lake Huron (43.232 N, 81.911 W), Lake Simcoe (44.547 N, 79.216 W), and Lake Ontario (43.635 N, 79.347 W). River samples were collected from the Ausable River Cut (43.222 N,

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81.865 W) and the West Don River (43.730 N, 79.375 W), and a single pond sample was collected from the Moccasin Trail Pond (43.7338 N, 79.332 W). For all of these samples, the collections began with at least three rinses of the sampling containers with the water of interest. The conductivity, chloride, and dissolved organic carbon (DOC) content of these water bodies, where available, are provided for context in Table S2. Precipitation was collected between June 16th and July 15th, 2021, and August 17th to September 16th, 2021, from the rooftop of the Petrie Science and Engineering Building at York University in Toronto, ON, Canada (43.774 N, 79.507 W). The precipitation was collected with our automated wet deposition collector[60] into 10 L polypropylene jerry cans, with a subsample transferred into pre-cleaned 1 L polypropylene bottles which were stored at room temperature. Our cleaning procedure for these samples has found that the method performs effectively.[61] Sampling blanks were not possible to include because of the TFA contamination in the Milli-Q water. Therefore, for direct sample injection, the instrument detection limits coupled with the use of an isotopically labeled internal standard sets the method detection limits, alongside rigorous lab and sampling practices.

RESULTS AND DISCUSSION

Method performance. PFCAs are present in environmental fresh waters at trace levels and are orders of magnitude lower than other anions. For example, short- and ultra-short chain PFCAs are present at sub-ppt to low-ppb levels, while anions such as chloride and nitrate are typically present at ppb to ppm levels.[62,63] The shorter the PFCA chain length, the more similar the properties of the PFCA to these matrix ions. For these PFCAs, selectivity of analysis can be improved by first separating them from other major environmental anions. Retention of the ultra-short-chain PFCAs, particularly TFA, is difficult with traditional LC stationary phases, such as C18. Using modern LC MM stationary phases, retention of ultra-short chain PFCAs is possible, but matrix effects remain problematic.[64] Here, we applied IE to explicitly separate C2 to C6 ionic PFCAs from major environmental ions using an aqueous hydroxide gradient and

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an alkanol quaternary ammonium ion based anion exchange column (Figure 1). The optimized method retained the PFCAs, with retention factors (k') ranging from 2.17 for TFA to 6.17 for the C6 PFCA (Table 1). The PFCAs were separated from their closest neighboring ion with resolution (R) ranging from 0.50 for TFA to 2.76 for the C6 PFCA (Figure 1, Table 1). The traditional conductivity detector used for ion exchange chromatography cannot detect PFCAs at environmental levels. Thus, we coupled a MS in SIM mode for the detection of these trace analytes as well as providing additional selectivity. Full peak resolution ($R \geq 1.5$) is not required when the anions can be further distinguished by their mass to charge ratios within the mass spectrometer. The precision was under 10% for all PFCAs, with the majority under 5% (Table 1). The method accuracy was previously determined and reported for precipitation samples (n=201) ranging from 0.34 – 23% percent relative error.[61] Particular attention was paid to ensuring the functionality of the suppressor was used to protect the instrument, without which the aqueous hydroxide eluent could precipitate within the ESI source and/or damage the MS. Shutdown sequences were written in Chromeleon to ensure that the MS would be shut down in the event of suppressor failure (see SI; Section S1). Use of this suppressed IC-MS method led to instrumental limits of detection (LODs) at the single digit ppt level. Our TFA LOD is comparable to other reported detection limits, though lower than most (Table 2). Our LODs are somewhat higher than those achieved for C4 and longer PFCAs by LC-MS/MS, which are in the sub-ppt range.[13,24,51] Considering that a single quadrupole is used here, these performance outcomes due to ion-selective retention are a promising new avenue for aqueous sample PFAS analysis, particularly the ultra-short-chain homologues. We expect that use of MS with higher resolving power or tandem MS could further improve method performance. The LOQs for this method were all under under 10 ppt (TFA: 7.0 ppt; PFPrA: 4.4 ppt; PFBA: 9.4 ppt; PFPeA: 6.3 ppt; PFHxA: 7.7 ppt).

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Previous methods for the quantitative determination of TFA and other short chain PFCAs have often relied upon sample preparation to minimize matrix effects (Table 2). The most common method to do this is solid phase extraction (SPE) with weak anion exchange resin. While the resins themselves have not, to our knowledge, demonstrated separation of TFA from matrix ions, it is possible to remove weak matrix acids (e.g., organic acids) by adjusting the solution pH.[46] Concentrating TFA in samples with SPE can create poor recoveries and difficulties for any subsequent analytical technique by also increasing the ion competition on the anion exchange sites from high concentration of other anions, like chloride in ocean water samples.[46] Sample handling, including extractions, is always cautioned to be undertaken with extreme care because avoiding contamination with ultra-short chain PFCAs is a challenge.[33,46] Methods that minimize sample handling are highly desirable, as a result, the option to do direct injection of aqueous samples is the most appealing. Tentative results of TFA were previously obtained by injecting and analyzing filtered water samples with supercritical fluid chromatography (SFC) tandem MS.[29] This was done by diluting the water samples with mass labeled PFBA and correcting with blank water injections because there was poor recovery (<5%) of TFA with SPE-WAX, so some sample preparation was still preformed for this direct injection method.[29] Methods for direct injection of TFA in water samples were previously developed using a hybrid of HILIC and non-suppressed IE columns with electrospray ionization coupled to tandem MS (LC-MS/MS).[25,32] Direct injection of environmental samples for quantitative determination of TFA and other ultra-short-chain PFCAs with our IC-MS method is expected to work, as the instrument and its components were developed for the analysis of major ions in aqueous environmental samples. With the addition of the low instrumental LODs and explicit separation from matrix ions, quantitative determinations ought to be possible on a wide variety of samples. A downside of direct injection using liquid chromatography is the inability to analyze other major anions alongside the PFAS in samples. The additional anion concentration information gives insight into sample sources,

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transportation and fate in the environment. The co-elution of these major anions present in environmental samples needs to be considered to prevent matrix suppression, regardless of using an LC or IC separation prior to detection and quantitation.[25]

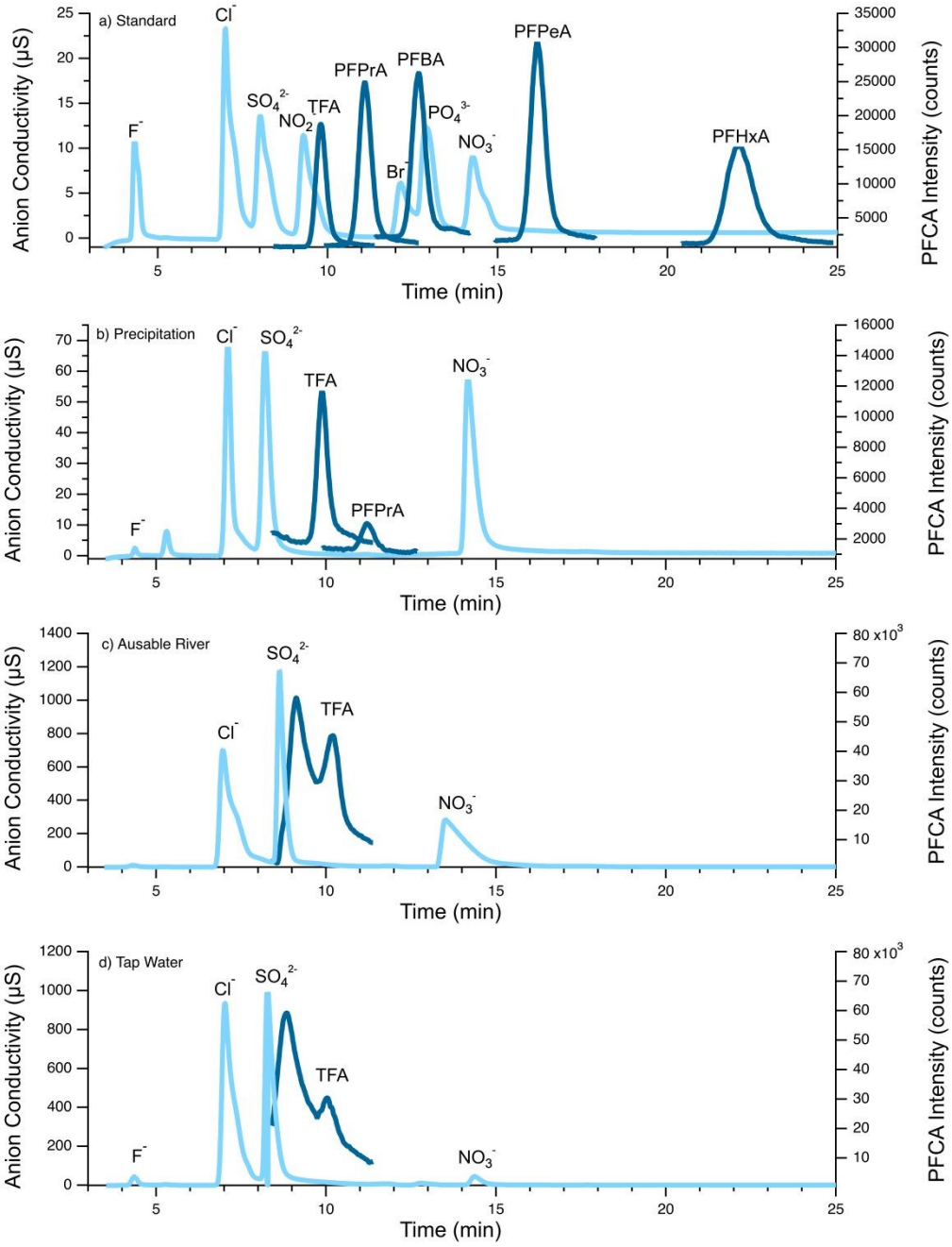

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Figure 1: IC-MS separation of (a) the major inorganic anions (light blue, conductivity, left axis) from C2-C6 PFCAs (dark blue, raw MS signal intensity, right axis) in an analytical standard containing trifluoroacetic acid (TFA, 500 ppt, m/z 113), perfluoroproionic acid (PFPrA, 500 ppt, m/z 163), perfluorobutanoic acid (PFBA, 500 ppt, m/z 213), perfluoropentanoic acid (PFPeA, 500 ppt, m/z 263), and perfluorohexanoic acid (PFHxA, 500 ppt, m/z 313) and fluoride (F^-, 20 ppb), chloride (Cl^-, 100 ppb), nitrite (NO_2^-, 100 ppb), sulfate (SO_4^{2-}, 100 ppb), bromide (Br^-, 100 ppb), phosphate (PO_4^{3-}, 200 ppb), and nitrate (NO_3^-, 100 ppb). The same separation performed on a real environmental samples is shown for precipitation (b), the Ausable River (c), and tap water (d). The separation of TFA and PFPrA from the prevalent anions (F^-, Cl^-, SO_4^{2-}, NO_3^-) is made visible with the selected ion counts from the mass. Note that there is an unlabeled peak corresponding to the known elution region of a mixture of organic acids present in the conductivity trace of panel (b).

Table 1. Separation parameters for PFCAs (C2-C6) to determine quality control of the IC-MS method performance using external calibration with the internal standard $^{13}C_2$-TFA, including the retention factor, resolution, precision, and the LOD. The calibration linearity r^2 ranged from 0.9909 – 0.9975 for the standards 5 ppt to 500 ppt[1].

Anions	Quantitation ion (m/z)	t_r (min)	Retention factor (k')	Closest-eluting ion	Resolution[2]	Precision[3] (%)	Instrumental detection limit (ppt)	Instrumental detection limit (pg)
TFA	113	9.8	2.17	NO_2^-	0.50	1.4	2.10	1.57
PFPrA	163	11.1	2.60	Br^-	0.74	7.6	1.33	1.00
PFBA	213	12.7	3.11	PO_4^{3-}	0.44	3.5	2.84	2.13
PFPeA	263	16.2	4.24	NO_3^-	1.38	1.0	1.89	1.41
PFHxA	313	22.1	6.17	PFPeA	2.76	0.4	2.30	1.73

[1]Calibration linearity starts to drop around 5 ppt when using a 1000 ppt standard as the upper limit standard

[2]Calculated from closest-eluting ion

[3]Calculated with 125 ppt mixed standard with $^{13}C_2$-TFA (n=6)

Table 2. Selected comparison to published analytical methods reporting performance criteria for trifluoroacetic acid (TFA) in environmental freshwater samples.

Study	Sample Volume	Sample Preparation	Separation	Method Limit of Detection (concentration)	Instrument Limit of Detection	Pre-Injection Concentration Factor
This work	750 µL	Online concentration	Suppressed IE	2.10 ppt	2.10 ppt	None
Zheng[31]	300 mL	SPE	Non-suppressed IE	27 ppt	NR	1500
Ye[46]	500 mL	SPE and derivatization	GC-phenyl methyl-polysiloxane	14.60 ppt	55 fg	500
Pickard[24]	100 mL	SPE	MM	0.151 ppt	NR	200
Liang[32]	10 µL	None	MM	3.5 – 5 ppt	NR	None
Scheurer[25]	100 µL	Centrifugation	Non-suppressed IE	16.7 ppt[1]	NR	None
Björnsdotter[29]	500 mL	Sonication, filtration, and dilution	SFC	34 ppt	NR	1000
Wang[30]	2 mL	Vortexed, filtered, and online SPE	MM	3.285 ppt	NR	None

NR: not reported.
IE: Ion Exchange.
MM: Mixed Mode.
SFC: Supercritical Fluid Chromatography.
[1]Converted from LOQ 50 pg/mL (Divided by 3)

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Sample preparation has frequently been used in the analysis of PFAS in environmental water samples. The most commonly used sample preparation technique used is SPE which requires large sample volumes (e.g., 500 mL) in comparison to direct injection methods.[24,29,46] Ultra-short chain PFCAs are difficult to analyze with LC methods and instead of the standard reverse phase columns newer methods using MM or IE columns are being developed to obtain the necessary retention of TFA to separate it from the large collection of poor or unretained matrix close to the system dead volume.[24,25,30,32] MM columns with such targeted selectivity still require sample cleanup steps to prevent the high concentrations of inorganic and organic acids in freshwater samples from introducing matrix effects that bias determinations of the trace levels of TFA.[24,30] To date, there is insufficient evidence to suggest that quantitative analysis and effective quality control are in place for direct injection to be used with a mixed mode analytical column for LC-MS/MS analysis. For example, in this prior work it was reported that there was a lack of signal for the internal standard, $^{13}C_2$-TFA, and recovery of 25 ppt of TFA across all samples was zero.[32] Using ion chromatography as an alternative method of analysis allows for separating the trace levels of PFAS from the major inorganic and organic anions in samples reducing the matrix suppression.

Mass Spectrometry Optimization. Organic modifiers can improve electrospray ionization by lowering surface tension, allowing for a more stable and reproducible Taylor cone, and producing smaller droplets, all of which improve ion formation and increase instrument sensitivity. Unfortunately, organic solvents are not compatible with suppressed IC, as they result in an accelerated degradation of the suppressor. Thus, our aqueous hydroxide separation method was designed to perform methanol addition after the conductivity detector and before the MS to allow the benefits of the addition of organic solvent without damaging the suppressor. Currently, methanol was the only organic modifier tested with this method. Methanol at 0.2 mL/min was combined with the suppressed outflow from the IC of 0.35 mL/min creating

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a total flow of 0.55 mL/min. Although the addition of methanol resulted in a 37% dilution of the analyte peaks, we found that its introduction increased the signal intensity of TFA by a factor of 2.5 (Figure 2).

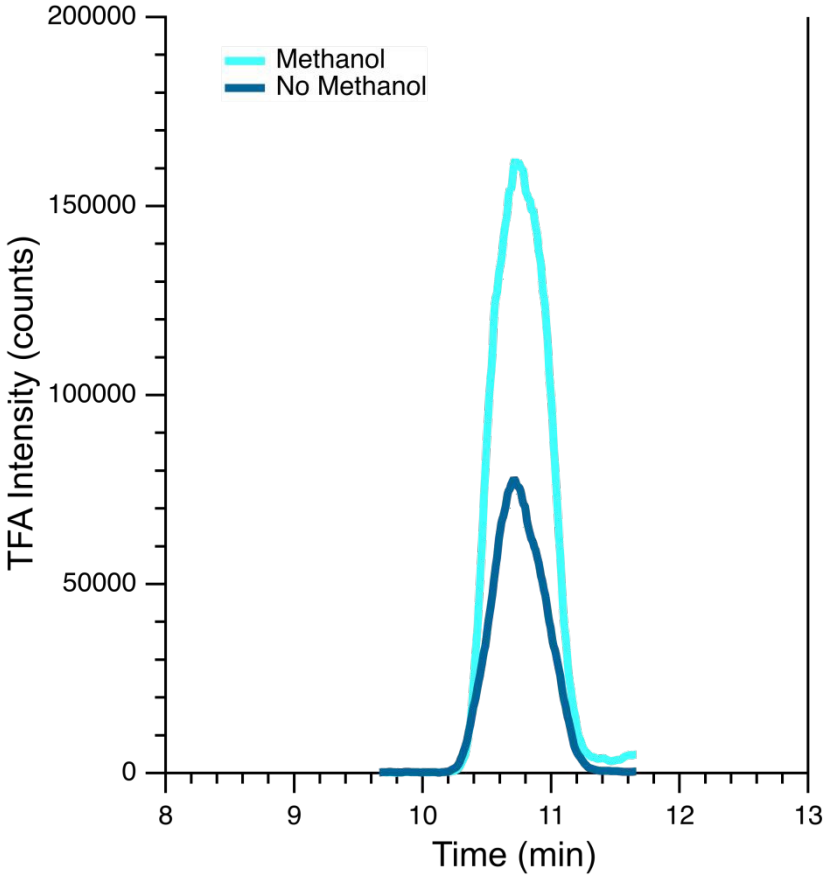

Figure 2. Chromatogram depicting TFA signal in the presence (light blue) and absence (dark blue) of methanol for injections of a 1 ppm standard of TFA.

Real Sample Analysis. Here we characterize the presence and variability of ultra-short-chain PFCAs—primarily TFA and PFPrA—in laboratory standards, tap water, precipitation, and regional freshwater systems across the Greater Toronto Area and Ontario. Results are interpreted in the context of known sources (e.g., laboratory contamination, atmospheric deposition, and agricultural runoff) and compared with previously reported concentrations to assess environmental relevance. Consistently detected levels of TFA and PFPrA were observed in Milli-Q water that was used to make standards and required

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subtraction during each analytical batch analysis. As a result, Milli-Q water was not useful toward obtaining field blanks. TFA was the only PFCA that was detectable with direct injection in tap water samples. Nine of the eleven tap water samples from across the Greater Toronto Area (GTA) were above the detection level for TFA. The TFA concentrations in tap water ranged widely from <2.10 – 673 ppt, with a median of 165 ppt (Figure 3). These concentrations are comparable to previously measured TFA levels in Toronto area drinking water in 2022 at 271 ppt[46] and Indiana, USA in 2020 at 79 ppt.[31] While most tap water in the GTA is from Lake Ontario, the samples here came from different water treatment facilities, which could impact TFA levels. Building or personal filtration systems,[32] which were not tracked in this study, could also play a role in the removal of TFA in water systems, which could explain the wide range of concentrations.

Two summertime precipitation samples that were analyzed had detectable levels of TFA (645 and 508 ppt) and PFPrA (104 and 144 ppt) (Figure 4). Concentrations in this study are higher than those reported from wintertime precipitation samples collected at the same location for both TFA and PFPrA of 150 and 62.3 ppt, respectively.[46] TFA was within the upper range of summertime precipitation concentrations collected in Ohio, USA in 2019 where the summed PFAS ranged from 50 – 850 ppt, with TFA accounting for around 90% of the measured PFAS (which did not include PFPrA).[65]

TFA was the only detectable PFCA by direct injection in all three lake samples (177 – 867 ppt) where Lake Ontario had the lowest concentration and Lake Simcoe had the highest concentration (Figure 4). Analyzed lake water contained similar levels of TFA as surface water measured in USA[54] and Sweden[66]. The concentrations of ultra-short-chain PFCAs present in the Great Lakes are much higher compared to previous measurements of long chain PFCAs made in 2006-2017. Lake Ontario TFA levels are approximately 10-fold higher than the sum of C4 – C12 PFCAs (19.4 ppt)[67] and the Lake Huron TFA concentrations were 67 times the sum of C4 – C12 PFCAs (7.2 ppt).[67] The highest amount of TFA (1636

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ppt) across all freshwater samples was measured in the Ausable River, which drains agricultural land and empties into Lake Huron. Agricultural runoff has previously been associated with elevated TFA in freshwater and has been attributed to transformations of pesticides containing an aryl CF_3 group.[25,66,68,69] Levels of NO_3^- were 15.5 times higher than Lake Ontario in the Ausable River sample, consistent with the endpoint of fertilizer ammonium nitrification and subsequent loss of the highly mobile NO_3^- anion to the aquatic environment.[70,71]

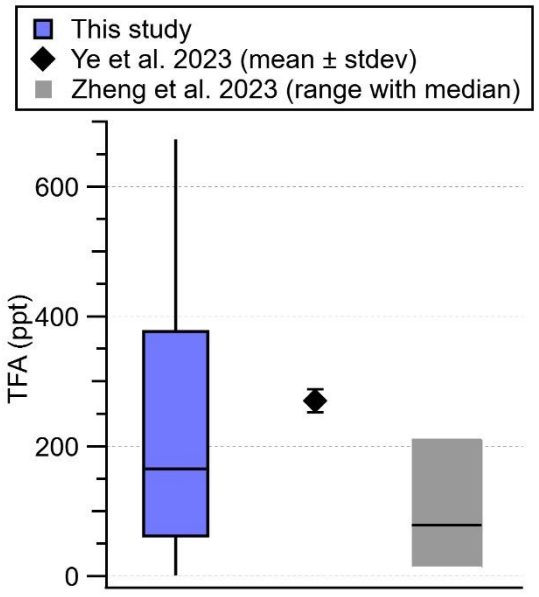

Figure 3. Boxplot of TFA in Greater Toronto Area tap water samples (n = 11) collected in March 2023, reported in ppt. Horizontal lines represent 25th, 50th (median), and 75th percentiles, while the vertical lines represent the full range of the measurements. Shown with TFA tap water measurements from North America from Ye et al.[46] (Toronto, n =1, mean ± standard deviation of 3 replicate extractions) and Zheng et al.[31] (Indiana, range shown with median, n = 81). Measurements below LOD were included as ½ LOD.

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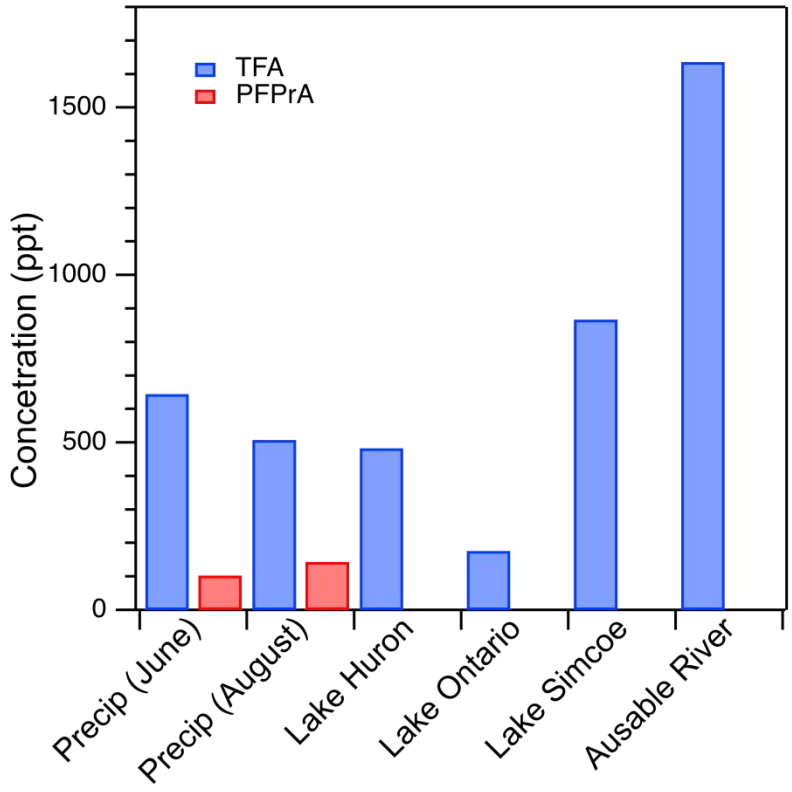

Figure 4. Measured TFA (blue) and PFPrA (red) concentrations (ppt) in freshwater samples collected around Ontario.

Matrix Impacts. This direct injection method was found to work with freshwater environmental samples only. The chloride content in ocean water was determined to have too much of a matrix effect in the conductivity to analyze without additional cleanup steps. The composition of the sample is always important to take into consideration for a quantitative method, as some of our freshwater samples were challenging to analyze by direct injection due to very high concentrations and conductivity of ionic constituents. For example, the Moccasin Trail Pond and Don Valley West River samples had extremely high matrix signals arising around a 6-minute retention time and leading to an overloaded asymmetric peak, alongside others (Figure S3) indicating the matrix was composed of high quantities of organic acids and/or chloride. The absolute water conductivity was not measured for these specific samples, though separate measurements of the Don River during the same time period reported >2000 µS/cm conductivity, which was 5 – 37 times higher compared to the Ausable River and Lakes Ontario and Huron (Table S2).

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Substantial chloride content was also found in the Don River, consistent with widespread use of salt to deice roads in this region during winter. Though we do not have measurements for Moccasin Trail Pond, its proximity to major roadways suggest it would also be highly contaminated with road salt. We were unable to quantify these samples without further cleanup steps due to the loss of the entire $^{13}C_2$-TFA internal standard counts in the mass spectrometer indicative of strong matrix suppression of TFA. This calls into question the validity of some previously published TFA direct injection methods using LC-MS/MS [32] which also reported that $^{13}C_2$-TFA did not generate a parallel signal in spiked samples.

Analytical interferences in this method can also arise from compounds that have similar retention times as the target analyte and yield negative ions at the same mass to charge ratio used for selected ion monitoring. This is a known analytical challenge in PFAS analysis using reverse phase and other separations. Multiple papers have retroactively determined that some PFAS measurements were false positives or artificially inflated.[72–74] Cis-acetylacrylic acid was previously identified as an isobaric interferent for TFA, however it was only found present in biological samples and is unlikely to be present in freshwater samples.[75] A similar issue was determined here, with an unknown isobaric interference measured at 113 m/z with a similar retention time as TFA. This was found in tap water, lake water, and river water samples, but was not present in the precipitation samples. Given the anion exchange separation method used, the unknown isobaric interference is likely an acid. Under the gradient eluent conditions of this method, it elutes about one minute before, and with a much larger peak area, than the TFA peak. This further confirms that cis-acetylacrylic acid is unlikely to be the interferent in our samples, as mono-organic acids elute earlier in the separation than TFA with retention times around 5-6 minutes. Organic acids present in our samples are represented by an unlabeled peak in Figures 1 and S3. Comparisons to the internal standard can help verify that the correct peak is being analyzed, as ion chromatography is well-known to experience shifts in retention time that depend on the concentration of the target analyte, but

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also other competing ions from the sample and its matrix that can undergo exchange on the analytical column. The internal standard is therefore especially useful in samples where the TFA peak area is below detection limits, allowing a retention time to be assigned correctly, and preventing the isobaric interference from potentially causing an artificially inflated PFAS measurement. In cases where there is a significant TFA signal, reducing the concentrations of both the contamination and the analyte by removing the on-line concentration step in the sample preparation results improved separation. By injecting with a 250 µL loop instead of 750 µL into the concentrator column, the resolution between TFA and the isobaric interference in the Ausable River sample improved from 1.03 to 1.87 (Figure 5) and allowed TFA detection in the Moccasin Trail Pond sample (Figure S6). We attempted to determine the identity of the isobaric interference. Using an expanded mass window, we determined that the m/z 113 signal corresponded to the M+2 isotope of a larger signal at m/z 111. The relative signal abundances were consistent with isotopes of sulfur (Table S3). We initially suspected that the signal corresponded to methyl sulfate. We compared the retention times of an authentic methyl sulfate standard to that of the unknown, including through standard addition. The retention times did not fully match across m/z 111–113 (Figure S4a–c). Moreover, standard addition of methyl sulfate to the sample resulted in the unknown peak splitting, indicating that methyl sulfate is not an exact match for the unknown present in the sample.

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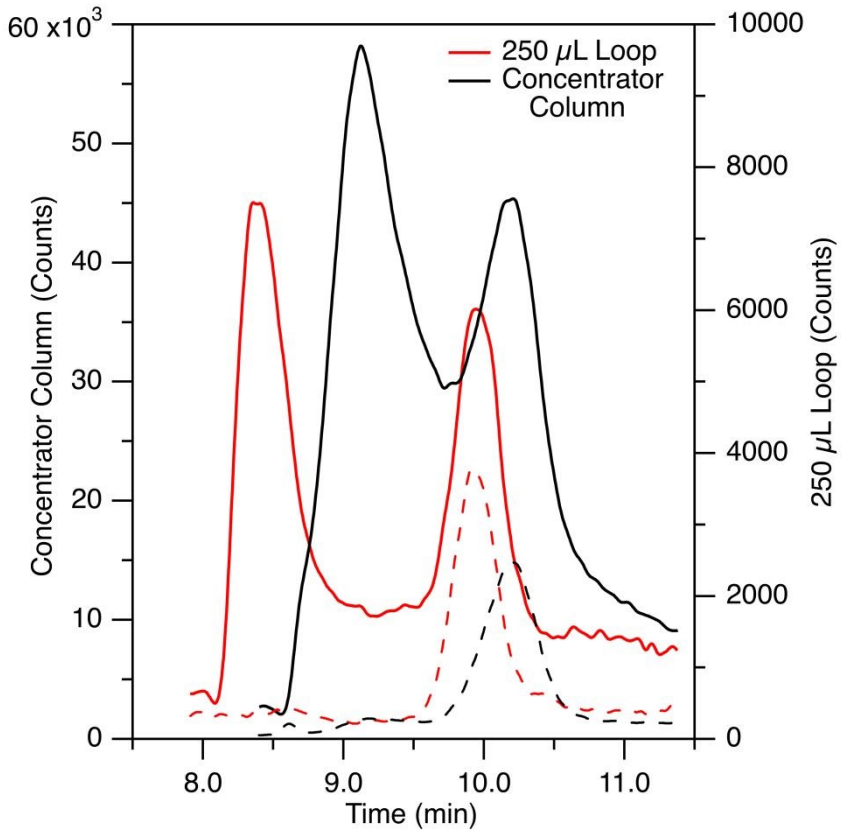

Figure 5. Chromatogram of TFA in the Ausable River sample at 113 m/z (solid lines) injected with a 250 µL loop (Red) and 750 µL to a concentrator column (Black) overlayed with dashed lines representing $^{13}C_2$ TFA at 115 m/z for each injection.

CONCLUSIONS AND IMPLICATIONS

Here, we demonstrated a suppressed ion chromatography method to physically separate PFCAs from major environmental anions to reduce the background matrix and improve the limit of detection. A single quad mass spectrometer is used to filter other acids in the sample to improve separation.

The sample type and method used are important in determining the amount of TFA in the environment. The matrix effects in different sample types can introduce inaccurate analysis of the TFA concentration if it is not taken into consideration. High conductivity signals indicating large amounts of chloride and a loss of the internal standard $^{13}C_2$-TFA signal show a suppression of TFA in some sample types, which limited the application of our method. When internal standard suppression is paired with isobaric acids that contain similar properties to TFA, precautions need to be taken when analyzing

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different sample types by both direct and solid phase extraction (SPE) methods to selectively only analyze TFA and not report inflated concentrations.

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Data availability statement

The data supporting this article have been included as part of the Supplementary Information.