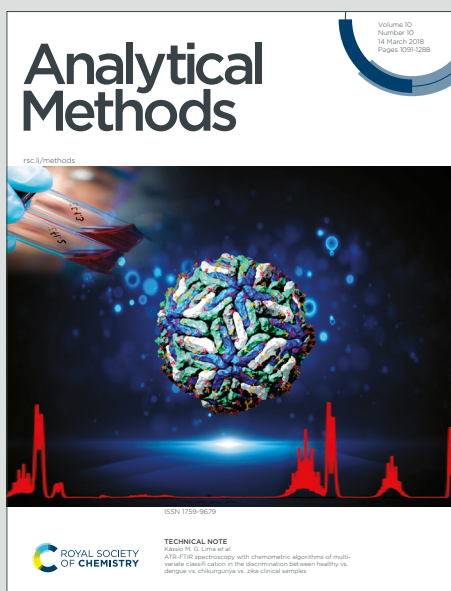


# Analytical Methods

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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,

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

## 21 INTRODUCTION

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

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



39 from several precursor gases. The Montreal Protocol is a global agreement to regulate and phase out  
40 chlorofluorocarbons (CFCs), commonly used as refrigerants, due to their role as stratospheric ozone-  
41 depleting substances. Montreal Protocol-mandated CFC replacements have degradation pathways known  
42 to produce ultra-short-chain PFCAs.<sup>19–22</sup> The most recent Kigali Amendment was added to further limit  
43 the production of CFCs and their prior replacements.<sup>22</sup> One major class of new replacements to satisfy the  
44 Kigali Amendment are hydrofluoroolefins (HFOs), which were selected due to their shorter atmospheric  
45 lifetimes as well as their lower global warming potentials in comparison to CFC and previous replacement  
46 compounds. However, some HFOs have a 100% degradation yield of TFA under atmospheric conditions.<sup>8</sup>  
47 The increased usage of HFOs under the Kigali Amendment to the Montreal Protocol is therefore expected  
48 to cause an increase in ultra-short-chain PFCA production and, as a result, concentrations in the  
49 environment.<sup>23</sup> Environmental increases of TFA and other ultra-short-chain PFCAs have already been  
50 attributed to the introduction of CFC replacements.<sup>9,24</sup> Another source of TFA to natural waters is  
51 photooxidation of molecules containing an aryl-CF<sub>3</sub> group, including pharmaceuticals and pesticides.<sup>25–27</sup>  
52 Additionally, biodegradation of PFAS,<sup>28</sup> as well as emissions from landfills, industry, and wastewater<sup>25,29</sup>  
53 are possible contributors to environmental burdens of ultra-short-chain PFCAs. The relative contributions  
54 of these sources to ultra-short-chain PFCA contamination in fresh waters are not yet well understood.

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

1 61 ion exchange (IE)<sup>25,31</sup>, and mixed-mode ion exchange within an RP column (MM).<sup>24,30,32</sup> A notable  
2  
3 62 difference typically exists between instruments, where ion chromatography (IC) system components are  
4  
5 63 made entirely of inert polymeric materials like polyether ether ketone (PEEK) instead of stainless steel in  
6  
7 64 LC systems, to prevent analyte-surface interactions for ionic species. Here, we will combine the use of  
8  
9 65 RP, HILIC, IE, and MM under the umbrella term of LC, unless specifics within one of these requires  
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11 66 further delineation, and IC to denote the different instrumentation. With applications for longer chain  
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13 67 PFCAs, LC tandem mass spectrometry (LC-MS/MS) has been used because they are surfactant molecules,  
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15 68 water-soluble, and thus readily amenable to electrospray ionization (ESI). LC systems often contain  
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17 69 fluoropolymer components, like polytetrafluorethylene (PTFE) and these materials leach ultrashort-chain  
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19 70 PFAS creating a contamination source of PFCAs, including TFA.<sup>33</sup> To overcome PFCA contamination in  
20  
21 71 LC systems, trap columns have been used to delay their elution and reduce backgrounds in the method to  
22  
23 72 improve detection limits.<sup>34</sup> It is also difficult to impossible to retain short-chain PFCAs on traditional RP  
24  
25 73 columns because they are too polar to partition into the stationary phase under most standard mobile phase  
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27 74 solvent conditions. This has only recently been mitigated through the use of MM columns, where  
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29 75 reasonable retention factors ( $k'$ ) have been obtained.<sup>24,25</sup> Gas chromatographs with mass spectrometers  
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31 76 (GC-MS) have also been used because they are widely available, relatively inexpensive, contain no  
32  
33 77 fluoropolymer parts, and produce excellent separation and resolution. The disadvantage of GC-MS is that  
34  
35 78 PFCAs are non-volatile and therefore any environmental sample containing them must be derivatized.  
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37 79 There are many different derivatization methods used when analyzing PFCAs, including 2,4-  
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39 80 difluoroaniline,<sup>35-38</sup> benzyl bromide,<sup>39</sup> pentafluorophenyl diazoethane,<sup>40,41</sup> dimethyl sulfate,<sup>42-44</sup> Fischer  
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41 81 esterification,<sup>45</sup> and diphenyl diazomethane<sup>46</sup>. Derivatization methods are time consuming, often requiring  
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43 82 extensive sample preparation, in addition to the use of hazardous reagents. Few derivatization methods  
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45 83 have been effectively applied to short-chain PFCAs<sup>46</sup> because they often produce extremely volatile  
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84 products that are difficult to retain on a GC column.<sup>42,47,48</sup>

85 Previous analytical methods, whether LC- or GC-based, for ultra-short-chain PFCAs required cleanup  
86 steps to reduce matrix effects and/or to concentrate the PFCAs concentrations from the initial samples,  
87 including “clean” samples like ice cores.<sup>49</sup> Commonly used cleanup strategies included liquid-liquid  
88 extraction (LLE)<sup>44,50</sup> and solid phase extraction (SPE).<sup>51,52</sup> With ultra-short-chain PFCAs pervasiveness in  
89 the environment, including within analytical laboratories, any sample handling could result in  
90 contamination.<sup>46</sup> Relatively high levels in environmental water samples, on the order of 20 ng L<sup>-1</sup> to 3 µg  
91 L<sup>-1</sup>,<sup>53,54</sup> are above typical LC-MS/MS instrumental detection limits, which suggests that direct injection  
92 should be possible. However, ionisation suppression, caused by other matrix components of  
93 environmental samples (e.g., Cl<sup>-</sup> and NO<sub>3</sub><sup>-</sup> in groundwater samples) often necessitate cleanup steps.  
94 Methods that allow for the direct injection quantitation of PFCAs in aqueous environmental samples on  
95 LC and IC systems are developing and appearing on the market to fill this gap.<sup>49,55–57</sup> For TFA, LC-MS/MS  
96 direct-inject methods have been developed for water<sup>25</sup> and more complex matrices, such as wine<sup>58</sup> and  
97 urine.<sup>59</sup>

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



## 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  $^{13}\text{C}_2$ -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  $\text{F}^-$ ,  $\text{Cl}^-$ ,  $\text{NO}_2^-$ ,  $\text{Br}^-$ , and  $\text{NO}_3^-$  as sodium salts,  $\text{PO}_4^{3-}$  as the monobasic potassium salt, and  $\text{SO}_4^{2-}$  as the dibasic sodium salt. Calibration standards and eluents were prepared with Milli-Q water (18.2  $\text{M}\Omega\cdot\text{cm}$  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  $\mu\text{L}$  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, 11 $\mu\text{m}$  particle size, 55% Divinylbenzene (DVB) crosslinking, alkanol quarternary ammonium ion functional group). The



1 127 separation method was optimized with a gradient elution program at a mobile phase flow rate of 0.35 mL  
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3 128 min<sup>-1</sup> conducted over 25 minutes. The starting condition was 10 mM NaOH held for 7 minutes, then  
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6 129 linearly ramped up to 40 mM NaOH over 2 minutes and ramped up again to 52 mM NaOH for an  
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8 130 additional 11 minutes. The conditions were held at 52 mM until 23 minutes, then returned stepwise to the  
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10 131 initial conditions of 10 mM NaOH and held until 25 minutes to re-equilibrate, which was held constant  
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12 132 as the next injection with the AS-AP was prepared (Figure S1).

13 133 The column effluent was passed through a suppressor (ADRS 600, 2 mm) in external water mode  
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15 134 with an auxiliary (AXP) pump providing a flow through the regenerant ports at 1 mL min<sup>-1</sup> and with an  
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17 135 applied current of 87 mA. The eluent then passes through a conductivity cell, with measurements recorded  
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19 136 at 5 Hz before a secondary AXP pump tees in 0.2 mL min<sup>-1</sup> of methanol and the eluent is ionized under  
20  
21 137 negative electrospray ionization conditions followed by detection in the MS operated in selective ion  
22  
23 138 monitoring (SIM) mode for each analyte of interest listed in Table 1 as well as <sup>13</sup>C<sub>2</sub> TFA (m/z 115). The  
24  
25 139 vaporizer temperature was set to 450 °C, ion transfer temperature was at 250 °C, source voltage at -3000  
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27 140 V, and a nitrogen gas generator was used for the sheath gas pressure at 45 psig and auxiliary gas pressure  
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29 141 at 5 psig. The chromatographic peaks and mass spectrum were analyzed using the Chromeleon™ 7  
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31 142 software package.

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34 143 **Calibration and QA-QC.** A mixed PFCA standard was prepared with the internal standard <sup>13</sup>C<sub>2</sub>-TFA  
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36 144 (250 ppt) and was used for the 7-point calibration curve to quantify the samples (5 – 500 ppt). <sup>13</sup>C<sub>2</sub>-TFA,  
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38 145 an ultra-short PFCA, was the only internal standard used to normalize all the PFAS. Future work could  
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40 146 add an additional isotopically labelled standard for the short chain PFCAs (C4-C6) to have higher  
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42 147 certainty in their quantification while using external calibration. TFA and PFPrA were present as  
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44 148 contaminants in the Milli-Q water ranging from <LOD – 86 ppt (TFA averaged 11 ppt; PFPrA averaged  
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46 149 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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1 150 to make all the standards. To account for TFA contamination in the standards, a reagent blank composed  
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3 151 of Milli-Q water spiked with  $^{13}\text{C}_2$ -TFA was analyzed in triplicate for each calibration. The average of the  
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5 152 TFA signal in this reagent blank was subtracted from the 6 remaining standards and used as a correction  
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7  
8 153 for the contamination. IC-MS systems use nonfluorinated components, which leach lower concentrations  
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11 154 of PFAS, reducing contamination.<sup>33</sup> The standard deviation of the eluent background, which did not  
12  
13 155 contain a TFA peak, was used as a method blank to determine range limits. This was done by running the  
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15 156 instrument method in triplicate without injecting anything. Background levels of TFA from the IC-MS  
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17 157 system components were negligible, especially in comparison to the fluctuating levels of lab  
18  
19 158 contamination in the standards from the Milli-Q water. The standard deviation of the method blank was  
20  
21 159 obtained similarly for all PFCAs at their retention time ranges and was used to divide by the peak heights  
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23 160 (signal) of each standard point of the calibration curve to determine the signal to noise ratio. The signal  
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25 161 to noise ratio was plotted against the concentration of the standards to determine the slope, then to  
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27 162 calculate the limit of detection (LOD) 3 was divided by the slope, and 10 was divided by the slope to  
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29 163 determine the limit of quantification (LOQ). The precision was calculated by determining the relative  
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31 164 standard deviation from the 125 ppt mixed standard (n=6) using the internal standard  $^{13}\text{C}_2$ -TFA to  
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33 165 normalize the peak area for all PFCAs.  
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42 166 **Environmental and Drinking Water Samples.** All drinking and surface water samples were collected into  
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45 167 pre-cleaned (pre-rinsed 3x with Milli-Q water and final 1x rinse with MeOH) 125 mL polypropylene  
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47 168 bottles and stored at room temperature for 9 days. Eleven tap water samples were collected in March 2023  
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50 169 from homes across the Greater Toronto Area, ON, Canada and our laboratory (Figure S2). Lake and river  
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52 170 samples were collected from shorelines in March 2023. Lake samples were collected from within 1 m of  
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55 171 the shorelines of Lake Huron (43.232 N, 81.911 W), Lake Simcoe (44.547 N, 79.216 W), and Lake  
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58 172 Ontario (43.635 N, 79.347 W). River samples were collected from the Ausable River Cut (43.222 N,  
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1 173 81.865 W) and the West Don River (43.730 N, 79.375 W), and a single pond sample was collected from  
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3 174 the Moccasin Trail Pond (43.7338 N, 79.332 W). For all of these samples, the collections began with at  
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5 175 least three rinses of the sampling containers with the water of interest. The conductivity, chloride, and  
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7 176 dissolved organic carbon (DOC) content of these water bodies, where available, are provided for context  
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9 177 in Table S2. Precipitation was collected between June 16<sup>th</sup> and July 15<sup>th</sup>, 2021, and August 17<sup>th</sup> to  
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11 178 September 16<sup>th</sup>, 2021, from the rooftop of the Petrie Science and Engineering Building at York University  
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13 179 in Toronto, ON, Canada (43.774 N, 79.507 W). The precipitation was collected with our automated wet  
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15 180 deposition collector<sup>60</sup> into 10 L polypropylene jerry cans, with a subsample transferred into pre-cleaned 1  
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17 181 L polypropylene bottles which were stored at room temperature. Our cleaning procedure for these samples  
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19 182 has found that the method performs effectively.<sup>61</sup> Sampling blanks were not possible to include because  
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21 183 of the TFA contamination in the Milli-Q water. Therefore, for direct sample injection, the instrument  
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23 184 detection limits coupled with the use of an isotopically labeled internal standard sets the method detection  
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25 185 limits, alongside rigorous lab and sampling practices.

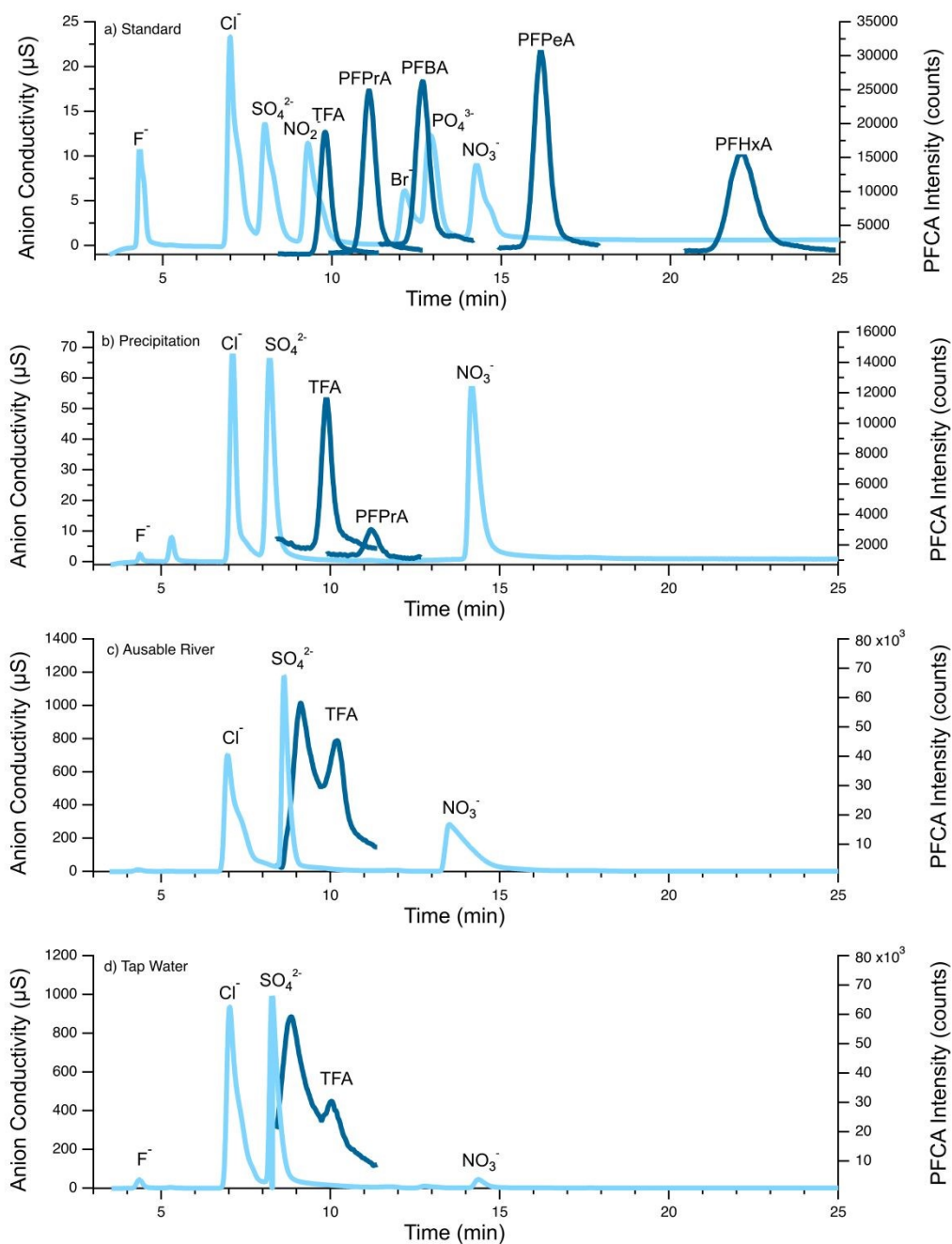
## 186 RESULTS AND DISCUSSION

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

1 196 an alkanol quaternary ammonium ion based anion exchange column (Figure 1). The optimized method  
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3 197 retained the PFCAs, with retention factors ( $k'$ ) ranging from 2.17 for TFA to 6.17 for the C6 PFCA (Table  
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5 198 1). The PFCAs were separated from their closest neighboring ion with resolution ( $R$ ) ranging from 0.50  
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7 199 for TFA to 2.76 for the C6 PFCA (Figure 1, Table 1). The traditional conductivity detector used for ion  
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9 200 exchange chromatography cannot detect PFCAs at environmental levels. Thus, we coupled a MS in SIM  
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11 201 mode for the detection of these trace analytes as well as providing additional selectivity. Full peak  
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13 202 resolution ( $R \geq 1.5$ ) is not required when the anions can be further distinguished by their mass to charge  
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15 203 ratios within the mass spectrometer. The precision was under 10% for all PFCAs, with the majority under  
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17 204 5% (Table 1). The method accuracy was previously determined and reported for precipitation samples  
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19 205 ( $n=201$ ) ranging from 0.34 – 23% percent relative error.<sup>61</sup> Particular attention was paid to ensuring the  
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21 206 functionality of the suppressor was used to protect the instrument, without which the aqueous hydroxide  
22  
23 207 eluent could precipitate within the ESI source and/or damage the MS. Shutdown sequences were written  
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25 208 in Chromeleon to ensure that the MS would be shut down in the event of suppressor failure (see SI;  
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27 209 Section S1). Use of this suppressed IC-MS method led to instrumental limits of detection (LODs) at the  
28  
29 210 single digit ppt level. Our TFA LOD is comparable to other reported detection limits, though lower than  
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31 211 most (Table 2). Our LODs are somewhat higher than those achieved for C4 and longer PFCAs by LC-  
32  
33 212 MS/MS, which are in the sub-ppt range.<sup>13,24,51</sup> Considering that a single quadrupole is used here, these  
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35 213 performance outcomes due to ion-selective retention are a promising new avenue for aqueous sample  
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37 214 PFAS analysis, particularly the ultra-short-chain homologues. We expect that use of MS with higher  
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39 215 resolving power or tandem MS could further improve method performance. The LOQs for this method  
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41 216 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  
42  
43 217 ppt).

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

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.<sup>25</sup>



**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<sup>-</sup>, 20 ppb), chloride (Cl<sup>-</sup>, 100 ppb), nitrite (NO<sub>2</sub><sup>-</sup>, 100 ppb), sulfate (SO<sub>4</sub><sup>2-</sup>, 100 ppb), bromide (Br<sup>-</sup>, 100 ppb), phosphate (PO<sub>4</sub><sup>3-</sup>, 200 ppb), and nitrate (NO<sub>3</sub><sup>-</sup>, 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<sup>-</sup>, Cl<sup>-</sup>, SO<sub>4</sub><sup>2-</sup>, NO<sub>3</sub><sup>-</sup>) 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  $^{13}\text{C}_2$ -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<sup>1</sup>.

Anions	Quantitation ion (m/z)	$t_r$ (min)	Retention factor (k')	Closest-eluting ion	Resolution <sup>2</sup>	Precision <sup>3</sup> (%)	Instrumental detection limit (ppt)	Instrumental detection limit (pg)
TFA	113	9.8	2.17	$\text{NO}_2^-$	0.50	1.4	2.10	1.57
PFPrA	163	11.1	2.60	$\text{Br}^-$	0.74	7.6	1.33	1.00
PFBA	213	12.7	3.11	$\text{PO}_4^{3-}$	0.44	3.5	2.84	2.13
PFPeA	263	16.2	4.24	$\text{NO}_3^-$	1.38	1.0	1.89	1.41
PFHxA	313	22.1	6.17	PFPeA	2.76	0.4	2.30	1.73

<sup>1</sup>Calibration linearity starts to drop around 5 ppt when using a 1000 ppt standard as the upper limit standard

<sup>2</sup>Calculated from closest-eluting ion

<sup>3</sup>Calculated with 125 ppt mixed standard with  $^{13}\text{C}_2$ -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 $\mu$ L	Online concentration	Suppressed IE	2.10 ppt	2.10 ppt	None
Zheng <sup>31</sup>	300 mL	SPE	Non-suppressed IE	27 ppt	NR	1500
Ye <sup>46</sup>	500 mL	SPE and derivatization	GC-phenyl methyl-polysiloxane	14.60 ppt	55 fg	500
Pickard <sup>24</sup>	100 mL	SPE	MM	0.151 ppt	NR	200
Liang <sup>32</sup>	10 $\mu$ L	None	MM	3.5 – 5 ppt	NR	None
Scheurer <sup>25</sup>	100 $\mu$ L	Centrifugation	Non-suppressed IE	16.7 ppt <sup>1</sup>	NR	None
Björnsdotter <sup>29</sup>	500 mL	Sonication, filtration, and dilution	SFC	34 ppt	NR	1000
Wang <sup>30</sup>	2 mL	Vortexed, filtered, and online SPE	MM	3.285 ppt	NR	None

NR: not reported.

IE: Ion Exchange.

MM: Mixed Mode.

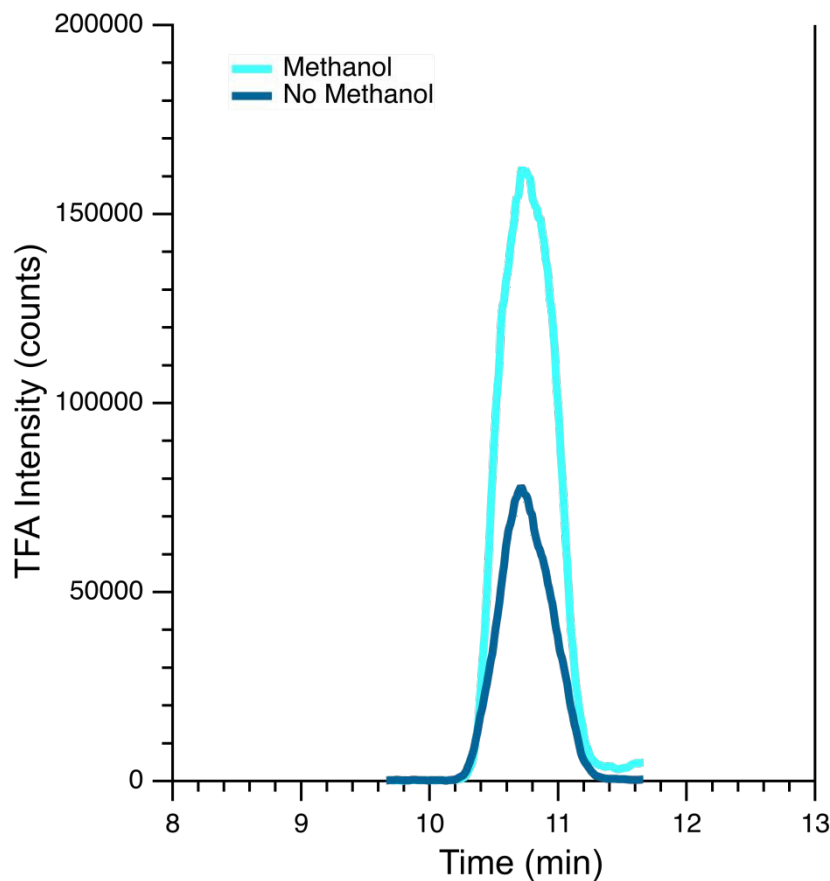
SFC: Supercritical Fluid Chromatography.

<sup>1</sup>Converted from LOQ 50 pg/mL (Divided by 3)

258  
259 Sample preparation has frequently been used in the analysis of PFAS in environmental water  
260 samples. The most commonly used sample preparation technique used is SPE which requires large sample  
261 volumes (e.g., 500 mL) in comparison to direct injection methods.<sup>24,29,46</sup> Ultra-short chain PFCAs are  
262 difficult to analyze with LC methods and instead of the standard reverse phase columns newer methods  
263 using MM or IE columns are being developed to obtain the necessary retention of TFA to separate it from  
264 the large collection of poor or unretained matrix close to the system dead volume.<sup>24,25,30,32</sup> MM columns  
265 with such targeted selectivity still require sample cleanup steps to prevent the high concentrations of  
266 inorganic and organic acids in freshwater samples from introducing matrix effects that bias determinations  
267 of the trace levels of TFA.<sup>24,30</sup> To date, there is insufficient evidence to suggest that quantitative analysis  
268 and effective quality control are in place for direct injection to be used with a mixed mode analytical  
269 column for LC-MS/MS analysis. For example, in this prior work it was reported that there was a lack of  
270 signal for the internal standard, <sup>13</sup>C<sub>2</sub>-TFA, and recovery of 25 ppt of TFA across all samples was zero.<sup>32</sup>  
271 Using ion chromatography as an alternative method of analysis allows for separating the trace levels of  
272 PFAS from the major inorganic and organic anions in samples reducing the matrix suppression.

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

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



84  
85 **Figure 2.** Chromatogram depicting TFA signal in the presence (light blue) and absence (dark blue) of  
86 methanol for injections of a 1 ppm standard of TFA.

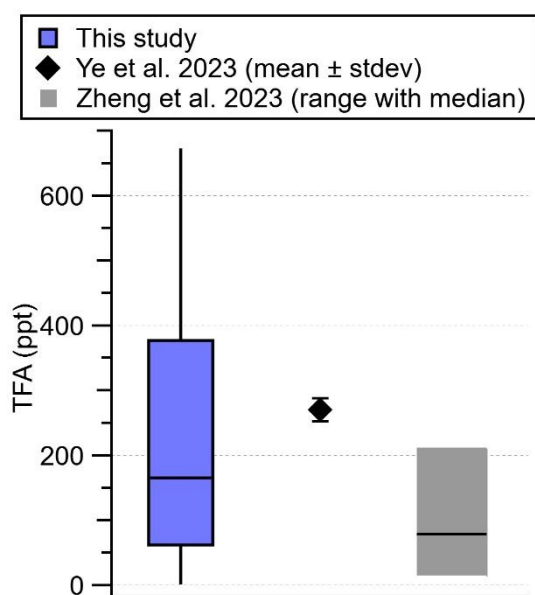
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89 **Real Sample Analysis.** Here we characterize the presence and variability of ultra-short-chain PFCAs—  
90 primarily TFA and PFPrA—in laboratory standards, tap water, precipitation, and regional freshwater  
91 systems across the Greater Toronto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

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

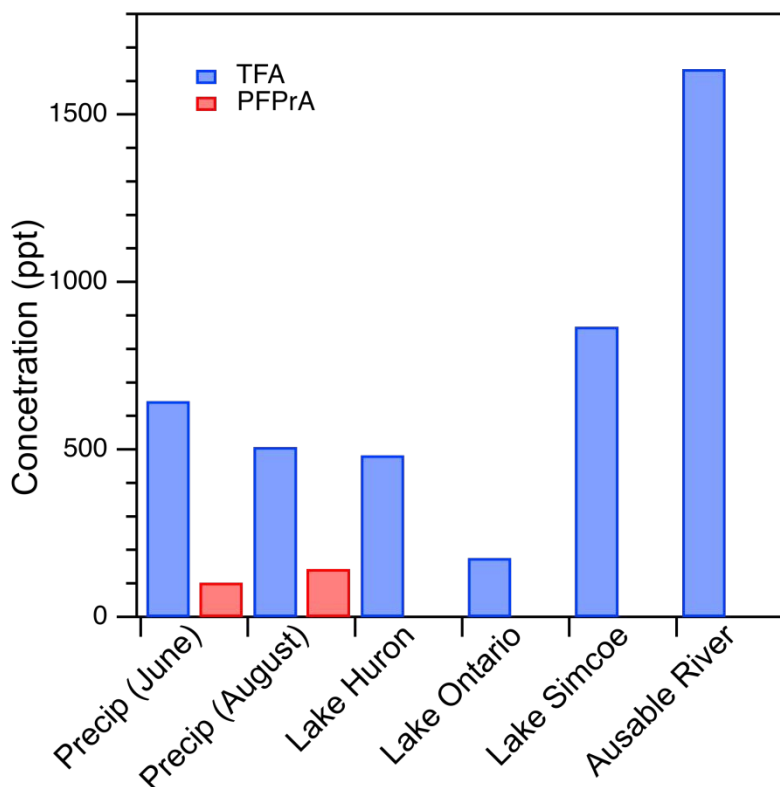
Two summertime precipitation samples that were analyzed had detectable levels of TFA (645 and  
508 ppt) and PFPrA (104 and 144 ppt) (Figure 4). Concentrations in this study are higher than those  
reported from wintertime precipitation samples collected at the same location for both TFA and PFPrA  
of 150 and 62.3 ppt, respectively.<sup>46</sup> 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).<sup>65</sup>

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<sup>54</sup> and  
Sweden<sup>66</sup>. 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)<sup>67</sup> and the Lake Huron TFA  
concentrations were 67 times the sum of C4 – C12 PFCAs (7.2 ppt).<sup>67</sup> The highest amount of TFA (1636

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  $\text{CF}_3$  group.<sup>25,66,68,69</sup> Levels of  $\text{NO}_3^-$  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  $\text{NO}_3^-$  anion to the aquatic environment.<sup>70,71</sup>



**Figure 3.** Boxplot of TFA in Greater Toronto Area tap water samples ( $n = 11$ ) collected in March 2023, reported in ppt. Horizontal lines represent 25<sup>th</sup>, 50<sup>th</sup> (median), and 75<sup>th</sup> 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.<sup>46</sup> (Toronto,  $n = 1$ , mean  $\pm$  standard deviation of 3 replicate extractions) and Zheng et al.<sup>31</sup> (Indiana, range shown with median,  $n = 81$ ). Measurements below LOD were included as  $\frac{1}{2}$  LOD.



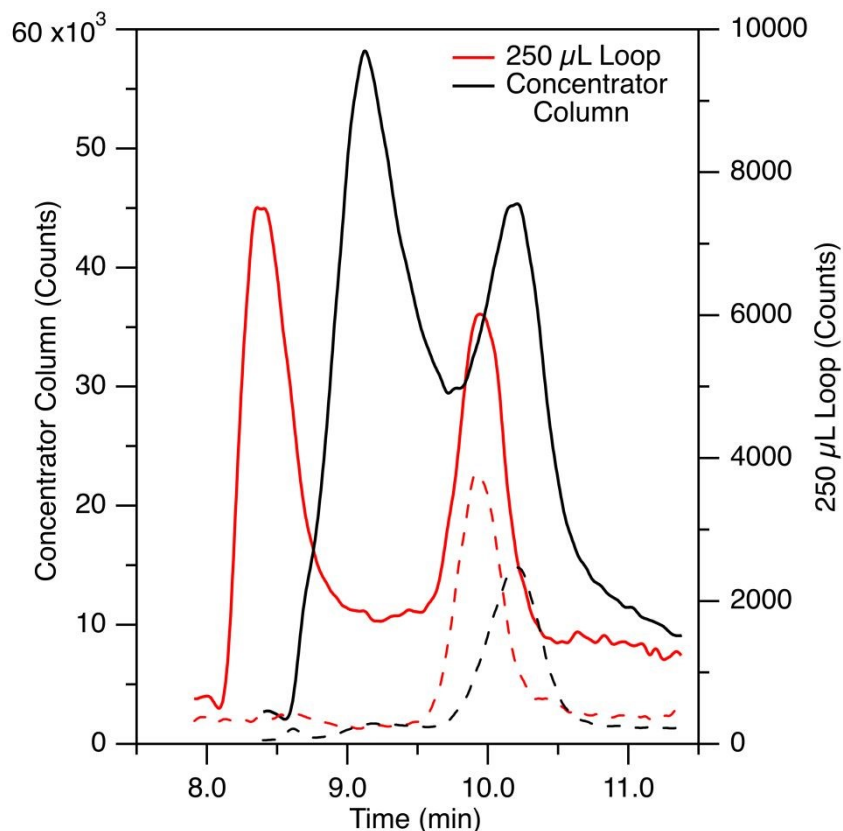
**Figure 4.** Measured TFA (blue) and PFPrA (red) concentrations (ppt) in freshwater samples collected around Ontario.

**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  $>2000 \mu\text{S}/\text{cm}$  conductivity, which was 5 – 37 times higher compared to the Ausable River and Lakes Ontario and Huron (Table S2).

346 Substantial chloride content was also found in the Don River, consistent with widespread use of salt to  
347 deice roads in this region during winter. Though we do not have measurements for Moccasin Trail Pond,  
348 its proximity to major roadways suggest it would also be highly contaminated with road salt. We were  
349 unable to quantify these samples without further cleanup steps due to the loss of the entire  $^{13}\text{C}_2$ -TFA  
350 internal standard counts in the mass spectrometer indicative of strong matrix suppression of TFA. This  
351 calls into question the validity of some previously published TFA direct injection methods using LC-  
352 MS/MS <sup>32</sup> which also reported that  $^{13}\text{C}_2$ -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.<sup>72-74</sup> 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.<sup>75</sup> 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

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  $\mu\text{L}$  loop instead of 750  $\mu\text{L}$  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.



**Figure 5.** Chromatogram of TFA in the Ausable River sample at 113 m/z (solid lines) injected with a 250  $\mu\text{L}$  loop (Red) and 750  $\mu\text{L}$  to a concentrator column (Black) overlaid with dashed lines representing  $^{13}\text{C}_2$  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  $^{13}\text{C}_2$ -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.

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