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Review

Trifluoroacetic Acid in Complex Matrices: A Critical Review of Analytical Strategies, Uncertainties, and Standardization Needs

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Abstract

Trifluoroacetic acid (TFA), the shortest perfluoroalkyl carboxylic acid, is the most prevalent ultra-short-chain PFAS in the environment. Its high polarity, strong acidity, water solubility, persistence, and mobility promote widespread occurrence across aquatic, terrestrial, agricultural, food, plant, and biological matrices. These same properties make reliable determination challenging because TFA shows poor reversed-phase retention, limited enrichment potential, few confirmatory ions, and frequent laboratory/background contamination. This review critically evaluates extraction and analytical strategies for TFA determination, including direct injection, dilute-and-shoot, SPE, solvent-based extraction, LC-MS/MS, IC-MS/MS, HILIC and mixed-mode LC-MS/MS, CE-MS/MS, HRMS, and fluorine-balance approaches. No single method is universally optimal: background contamination is often limited in low-concentration water samples, extraction efficiency dominates uncertainty in soils, plants, and foods, and ion suppression is critical in biological fluids. Direct injection is generally preferable for clean water and supports interlaboratory-validated methods, whereas complex matrices require matrix-specific extraction, with acetonitrile/water and isotope dilution among the most reliable options. Acidified methanol may cause esterification artifacts, and SPE methods adapted from long-chain PFAS are often unsuitable. The review proposes a matrix-specific extraction hierarchy and a minimum reporting checklist to improve harmonization and data comparability.

Keywords: trifluoroacetic acid; ultra-short-chain PFAS; analytical detection challenges; sample preparation; future perspectives

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1. Introduction

Environmental monitoring is essential for evaluating the occurrence, distribution, and long-term accumulation of persistent contaminants in both natural and engineered systems. Recently, significant attention has focused on highly mobile and persistent fluorinated compounds, which are transported via atmospheric, aquatic, and terrestrial pathways and ultimately enter drinking water resources, agricultural systems, and food chains [1,2].

Per- and polyfluoroalkyl substances (PFAS) represent a large and diverse class of fluorinated chemicals characterized by their exceptional chemical stability and environmental persistence [3]. Trifluoroacetic acid (TFA; CF_3COOH), which predominantly exists as trifluoroacetate (CF_3COO^-) in aqueous environmental systems, has become one of the most significant ultra-short-chain PFAS in both aquatic and terrestrial environments [4,5].

According to widely accepted PFAS definitions, TFA is generally classified within the PFAS family because it contains a fully fluorinated methyl group and thus represents the shortest perfluoroalkyl carboxylic acid (PFCA) [6]. In contrast to many long-chain PFAS, which are primarily discussed in the context of bioaccumulation and protein binding, TFA is of particular concern due to its high persistence, substantial environmental mobility, and potential for continuous accumulation in water resources, plants, food, and other exposure-relevant matrices [5].

The environmental burden of TFA arises from both direct and indirect anthropogenic sources. As illustrated in Figure 1, TFA may be released directly through industrial activities or generated as a terminal degradation product of fluorinated precursors, including fluorinated gases such as hydrofluorocarbons (HFCs) and hydrofluoroolefins (HFOs), agrochemicals, pharmaceuticals, and other industrial chemicals [4].

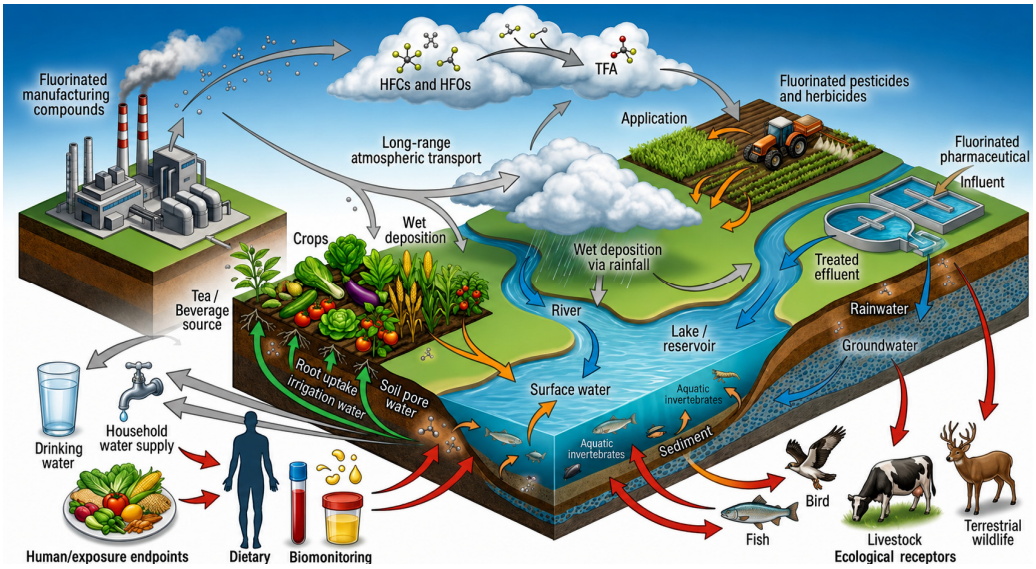


Figure 1. Conceptual diagram illustrating the environmental lifecycle, multimedia transport pathways, and exposure routes of trifluoroacetic acid (TFA) and other highly persistent fluorinated contaminants.

More broadly, fluorinated organic compounds containing at least one carbon-bound trifluoromethyl (C–CF_3) moiety may ultimately form TFA, particularly when this moiety is resistant to biochemical or photochemical degradation [5]. Atmospheric oxidation of volatile fluorinated compounds and the degradation of fluorinated pesticides are major contributors to environmental TFA contamination, particularly in water resources [7]. The stability of the trifluoromethyl group and the strength of the C–F bond render TFA highly persistent, enabling its accumulation across various environmental compartments [4,5]. The presence of TFA in drinking-water systems is particularly concerning, due to its high solubility and ionic nature, which hinders its removal by conventional treatment processes [8].

Additionally, the documented occurrence of TFA in beer and tea [9], a broad range of plant-origin foods [10], and wine [11] highlights potential dietary exposure pathways and underscores the need for analytical methods applicable not only to water but also to complex matrices such as plants, food, beverages, soil, and biological samples. Although the environmental and regulatory interest in TFA is increasing, its reliable determination remains analytically challenging.

The extreme polarity, strong acidity, and high mobility of TFA complicate extraction, enrichment, chromatographic retention, and mass spectrometric detection [6]. As a result, conventional PFAS methods designed for medium- and long-chain compounds often

provide inadequate retention, recovery, and selectivity for TFA, which can lead to underestimation and matrix-related biases [6,12]. Accurate TFA determination therefore depends not only on instrumental sensitivity but also on robust sample preparation, effective compensation for matrix effects, and method validation. Furthermore, as TFA data are increasingly compared across environmental compartments and monitoring programs, harmonized analytical protocols and standardized quality-assurance/quality-control (QA/QC) practices are necessary to ensure that reported concentrations reflect true environmental variability rather than methodological differences.

While previous reviews have addressed the sources, environmental occurrence, fate, exposure, toxicity, and broader analytical challenges of TFA and other ultra-short-chain PFAS [4,6], a comprehensive and critical assessment of extraction strategies, sample preparation, and matrix-specific analytical performance for TFA remains lacking. This gap is particularly important because TFA monitoring is increasingly applied to food, plants, soil, and biological samples, where matrix effects and extraction losses often contribute substantially to analytical uncertainty. This review critically evaluates extraction and sample preparation strategies for the reliable determination of TFA in environmental, food, plant, and biological matrices. Particular emphasis is placed on extraction efficiency, recovery, matrix effects, contamination control, and calibration strategy, which are considered central determinants of analytical data quality. The review focuses on direct injection, dilute-and-shoot approaches, solid-phase extraction (SPE), aqueous and organic solvent extraction, and protein precipitation, as well as chromatographic separation, mass spectrometric (MS)-based detection, method validation, and quality assurance. By comparing current workflows and identifying matrix-specific limitations, this review aims to provide practical recommendations that support the harmonization, validation, and implementation of fit-for-purpose analytical methods for TFA monitoring across diverse matrices.

2. Materials and Methods

2.1. Literature Search Strategy

The literature included in this review was identified through searches of Web of Science, Scopus, Google Scholar, and PubMed using combinations of the terms “trifluoroacetic acid”, “TFA”, and “ultra-short-chain PFAS”. Relevant peer-reviewed articles published in English, as well as analytical methods, technical reports, and regulatory documents published between 1998 and August 2026 were considered.

2.2. AI-Assisted Preparation of Visual Materials

Gemini 2.0 Flash (Google LLC, Mountain View, CA, USA) was used to generate and visually refine the Graphical Abstract, Figures 1 and 3. The authors provided the scientific content, terminology, conceptual relationships, and instructions for the intended organization of these visual materials. All generated outputs were reviewed for scientific accuracy, and their text, labels, arrangement, and graphical elements were corrected and finalized by the authors. Gemini was used only for figure preparation and was not used for data generation, data analysis, or formulation of scientific conclusions. The authors take full responsibility for the accuracy and final content of the visual materials.

3. Physicochemical Properties

The analytical behavior of TFA is determined by its small molecular size, strong acidity, high polarity, and high water solubility. These characteristics distinguish TFA from longer-chain PFAS and limit the applicability of conventional PFAS analytical methods. In contrast to hydrophobic PFAS, which are readily retained on reversed-phase (RP) columns and

SPE sorbents, TFA predominantly exists as a highly mobile anion, and therefore requires specialized extraction and chromatographic techniques [6] (Figure 2, Table 1).

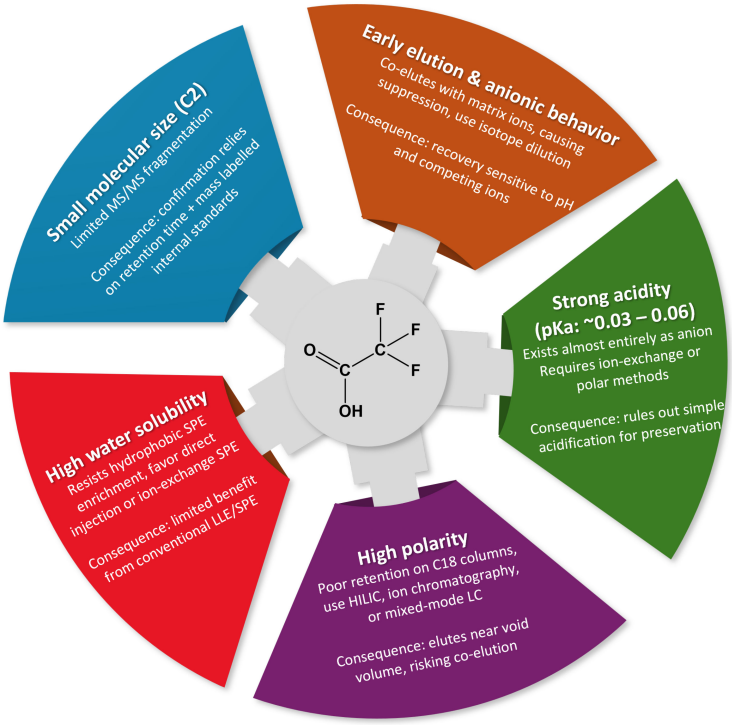


Figure 2. Physicochemical properties of TFA and the resulting analytical challenges.

TFA is the shortest PFCA and possesses a very low acid dissociation constant (pK_a) with reported values ranging from ~0.03 to 0.60 [13–16], resulting in its predominant existence as the trifluoroacetate anion (CF_3COO^-) under both environmental and analytical conditions [4,17,18]. Consequently, hydrophobic interactions with C18 stationary phases are minimal, whereas ion-exchange and polar interaction mechanisms play a significant role in chromatographic retention and enrichment.

The high polarity and water solubility of TFA present significant challenges for sample extraction and enrichment. Conventional liquid–liquid extraction (LLE) and hydrophobic SPE typically demonstrate poor performance. In contrast, direct injection, ion-exchange SPE, and ion chromatography (IC) are often more suitable, particularly for water samples [6]. In complex matrices such as soil, food, plants, and biological samples, TFA may co-extract with salts and other polar compounds, thereby increasing the risk of matrix effects [6].

Another major analytical limitation is the poor retention of TFA on conventional RP liquid chromatography (LC) columns. Studies have shown that TFA may elute near the void volume or may not be retained on certain C18 columns, resulting in co-elution with matrix components and increased ion suppression [18]. Therefore, IC, hydrophilic interaction chromatography (HILIC), and mixed-mode ion-exchange chromatography are often preferred for the analysis of ultra-short-chain PFAS [12].

TFA produces limited MS/MS fragmentation due to its small molecular size, which reduces the number of confirmatory product ions available. Quantification is typically based on the m/z 113→69 transition, while the fluoride ion (m/z 19) may serve as an additional qualifier ion. Alternatively, high-resolution mass spectrometry (HRMS) can provide confident identification through accurate-mass measurements. Consequently, reliable TFA identification relies on adequate chromatographic separation, retention-time matching, isotope-labelled internal standards (ISs), and rigorous quality-control procedures rather than MS/MS fragmentation alone [6].

Matrix effects represent a significant analytical challenge. Since TFA frequently elutes early and co-elutes with salts and other polar compounds, signal suppression or enhancement may occur during electrospray ionization. To enhance quantification accuracy, isotope dilution, matrix-matched calibration, or standard addition are commonly recommended [19].

In summary, the combination of strong acidity, high polarity, weak retention in RP columns, limited MS/MS fragmentation, and susceptibility to matrix effects makes TFA one of the most analytically challenging PFAS. These properties must be carefully considered when selecting appropriate extraction, separation, and detection strategies.

Table 1. Physicochemical properties of TFA and associated analytical implications.

Physicochemical Property	Analytical Consequence	Recommended Analytical Response	References
Very small molecular size	Limited MS/MS fragmentation	Use optimized MRM transitions and isotope-labelled standards	[6]
Strong acidity (low pK_a)	Exists mainly as an anion	Apply ion-exchange or polar chromatographic methods	[17]
High polarity	Poor retention on C_{18} columns	Use HILIC, IC, or mixed-mode LC	[12,18]
High water solubility	Difficult enrichment by hydrophobic SPE	Consider direct injection or ion-exchange SPE	[6]
Weak reversed-phase retention	Early elution and matrix interference	Improve chromatographic selectivity	[18]
Anionic behavior	Recovery affected by pH and competing ions	Optimize SPE and extraction conditions	[6,18]
Early LC elution	Increased ion suppression/enhancement	Use matrix-matched calibration or isotope dilution	[6,19]
High environmental mobility	Occurs in diverse matrices	Apply matrix-specific validation strategies	[6]

4. Sample Collection, Storage, and Contamination Control

In the analysis of TFA, analytical data quality is often determined before sample extraction begins. Environmental and food samples generally contain TFA at low µg/L or µg/kg concentrations, with regulatory limits established at similar levels. Consequently, errors during sampling, transport, or storage may contribute more to overall analytical uncertainty than those occurring during instrumental analysis. The EU Drinking Water Directive (Directive (EU) 2020/2184), establishes a 0.5 µg/L "PFAS Total" parametric value, with a compliance deadline of 12 January 2026 [20]. In contrast, TFA is excluded from the more stringent 0.1 µg/L "sum of 20 PFAS" parameter, as this list omits ultra-short-chain species [21]. For the protection of groundwater against pollution and deterioration, the European Parliament and the Council of the European Union set a relative potency factor (RPF) of 0.002 perfluorooctanoic acid (PFOA) equivalents for TFA and set a threshold of 0.0044 µg/L PFOA equivalents for the sum of 25 PFAS (now including TFA), expressed as the annual average value, in inland surface water in spring of 2026 [22].

These thresholds highlight the importance of strict procedural blank control, as even minor contamination, such as a few tens of ng/L, can represent a significant proportion of the regulatory limit. Therefore, rigorous blank control is a fundamental requirement for reliable TFA analysis.

TFA is unusual in that the primary pre-analytical risk is contamination rather than analyte loss. Due to its very low pK_a and high water solubility, TFA remains predominantly as anion and exhibits minimal binding to hydrophobic surfaces, making losses through container-wall sorption negligible compared with those of long-chain PFAS [6]. However,

TFA is frequently detected throughout the laboratory environment, including in ambient air, reagent water, chromatographic solvents, and through leaching from fluoropolymer components [6,23]. It is therefore advisable to replace any fluoropolymer materials, including polytetrafluoroethylene (PTFE) tubing, vial liners, and cap septa with polypropylene (PP) or high-density polyethylene (HDPE) alternatives where possible, and to verify reagent water and mobile phases for background TFA prior to use [24]. Because no laboratory material or reagent can be assumed to be free of TFA, contamination levels should be quantified rather than assumed or estimated. This requires the use of field blanks during sampling and transport, method blanks to monitor contamination introduced during sample preparation, and solvent or instrument blanks to assess carryover and mobile-phase background, with all blank levels reported transparently rather than subtracted without documentation.

Filtration is another critical pre-analytical step that warrants careful evaluation. The removal of particulates from water, soil leachates, or food homogenates is often essential; however, membrane filters may introduce interfering compounds and, in some cases, retain small amounts of the analyte [25]. This retention is generally less significant for highly polar substances such as TFA, the potential influence of filter material on analytical recovery should be verified experimentally. Filter composition, conditioning volume, and the timing of filtration relative to the addition of the IS should therefore be optimized and documented for each matrix.

Storage is comparatively less problematic because TFA is highly stable. Its environmental persistence ensures that it does not degrade significantly in refrigerated or frozen conditions [8], thereby minimizing concerns regarding analyte degradation. Instead, the primary considerations are contamination introduced through caps and headspace, as well as concentration changes due to solvent evaporation. Complex extracts from plant, food, and biological samples present an additional challenge: storage conditions must also maintain matrix stability, as alterations in the matrix can affect ionization efficiency during LC–MS/MS analysis [26]. For water, storage at 4 °C is adequate for short durations, while freezing at −20 °C, or −80 °C for biological samples, is recommended for extended storage or for solid and extracted materials [27]. Sampling and QA/QC considerations are listed in Table 2.

Table 2. Sampling and QA/QC considerations for trifluoroacetic acid (TFA) analysis across different matrices.

Matrix	Sampling Container	Storage	Potential Contamination Source	Recommended Blank/Control	References
Drinking, surface, groundwater, rain water	HDPE/PP bottles; avoid PTFE-lined caps	4 °C in the dark (short); −20 °C (long)	PTFE cap liners, reagent water, LC solvents, laboratory air	Field + reagent-water blank + procedural blank + solvent/instrument blank + isotope-labelled IS	[8,19,28]
Soil and sediment	HDPE/PP or glass jars with PP lids	−20 °C	Sampling equipment, deposition, extraction solvents (methanol esterification artefacts)	Full-workflow procedural blank + matrix spike + isotope-labelled IS	[29,30]
Plant and solid food	PP bags or HDPE containers; lyophilize if needed	−20 °C	Rinsing water, homogenizer equipment, solvents	Low-TFA matrix blank + procedural blank + isotope-labelled IS	[9,29]
Beverages, liquid food	Glass or HDPE	4 °C or −20 °C	Caps/septa, filtration materials, solvents	Solvent/dilution blank + procedural blank, + matrix spike + isotope-labelled IS	[9]
Biological (serum, plasma, urine)	PP tubes/vials; avoid fluoropolymer materials	−20 to −80 °C	Tube additives, precipitation solvents, consumables; competing ions (e.g., phosphate, chloride)	Low-TFA matrix blank + procedural blank + isotope-labelled IS	[31]

Considerations of pH and ionic strength are primarily relevant for post-sampling procedures. TFA remains fully deprotonated across the typical pH range encountered, so acidification, a common preservation step for many organic analytes, does not stabilize TFA and may adversely affect ion-exchange enrichment or IC if not carefully controlled [8]. In samples with high inorganic content, competing anions can disrupt both SPE retention and electrospray efficiency [26]. These matrix effects are most effectively addressed during extraction and calibration strategies (Sections 5 and 7) rather than during sampling. For solid foods and plants, the European Union Reference Laboratory for Single Residue Methods (EURL-SRM) reporting limit for TFA in fruit and vegetables, 0.04 mg/kg fresh weight, serves as a practical benchmark for required workflow cleanliness and analytical performance.

5. Extraction and Sample Preparation Strategies

Sample preparation is a critical determinant of TFA data quality [26]. The physicochemical behavior described in Section 3 undermines the hydrophobic-retention logic that underpins most established PFAS workflows [5]. Consequently, optimal preparation methods are highly matrix-dependent, and inappropriate choices may introduce greater analytical uncertainty than the analytical instrument itself. This section summarizes the principal approaches and evaluates, based on mechanistic considerations, their efficiency, associated risks, and areas lacking adequate validation. A cross-matrix ranking and assessment of routine suitability are addressed in Section 8.

5.1. Direct Injection and Dilute-and-Shoot Approaches

For clean aqueous samples, direct injection is generally considered the most reliable method [8,12,19,32,33]. The extreme polarity of these analytes, which complicates enrichment due to the lack of a hydrophobic moiety, also reduces the benefits of conventional extraction procedures. Additional sample preparation primarily increases the risk of analyte loss and contamination without enhancing selectivity. The standardized direct-injection method for TFA determination in water specifies a working range of 0.1–3.0 µg/L and was evaluated in an interlaboratory trial involving twelve laboratories, with relative reproducibility standard deviations of approximately 6–20% [19].

This approach is most suitable for drinking water, surface water, groundwater, rainwater, bottled water, diluted wastewater, and certain beverages. The dilute-and-shoot variant applies this principle to higher-matrix liquid samples; beverages and liquid foods are typically diluted tenfold in water prior to injection to decrease matrix complexity and viscosity [20]. Key advantages include minimal handling, reduced risk of analyte loss, low contamination risk, rapid processing, and suitability for routine monitoring. The main limitation is the lack of preconcentration, which means the achievable limit of detection (LOD) and limit of quantification (LOQ) depend on instrument sensitivity and require sensitive MS/MS or HRMS. Matrix effects from co-eluting salts and polar compounds persist and must be addressed through isotope dilution, matrix-matched calibration, or standard addition. Overall, for clean water samples, direct injection is generally preferable to SPE [26].

5.2. Solid-Phase Extraction (SPE)

SPE provides enrichment and cleanup; however, its application to TFA requires matrix-specific optimization and careful evaluation. Conventional PFAS SPE methods, such as RP or weak-anion-exchange (WAX) protocols exemplified by EPA 533/537, are designed for analytes with a perfluorinated tail, which TFA lacks [34]. Due to minimal nonpolar interactions, TFA retention relies almost exclusively on anion exchange, making it susceptible

to breakthrough and displacement by the high concentrations of inorganic anions (e.g., chloride, sulfate, bicarbonate) commonly found in environmental waters. Empirical studies demonstrate that, in systematic evaluations of adsorbable and extractable organic fluorine, ultra-short-chain perfluoroalkyl acids (PFAAs), including TFA, exhibit the lowest recovery rates among all chain lengths [35]. Early targeted research achieved quantitative recovery of TFA from most water matrices using an anion-exchange disc; however, saline samples necessitated an additional liquid–liquid cleanup step due to interference from competing anions [28].

Among available sorbent types, WAX is strongly pH-dependent and benefits from an organic wash that reduces matrix effects, but its capacity is significantly diminished in the presence of competing anions. Strong anion exchange (SAX/MAX) provides stronger retention but complicates the elution of tightly bound TFA [34]. Mixed-mode phases offer intermediate performance.

Online SPE represents a promising strategy for TFA enrichment. Large-volume injection with a WAX trap column, coupled to HILIC or ion-exchange separation, enables the capture of ultra-short-chain PFAS that are not retained by RP columns and achieves low nanogram per liter LOQs for TFA in surface water [36,37]. However, these configurations require specialized instrumentation and meticulous optimization. While SPE offers genuine advantages, including preconcentration, cleanup, lower LOQ, and suitability for complex or low-level water samples, it also presents notable limitations: breakthrough, incomplete retention, challenging elution, matrix-dependent recovery, and increased contamination risk of blanks. Therefore, SPE can be successfully applied to TFA only following TFA-specific optimization and validation; direct transfer of unmodified long-chain PFAS protocols is not recommended [38].

5.3. Aqueous Extraction for Soil and Sediment

Although TFA is highly mobile, its recovery from soil remains dependent on the specific matrix. Factors such as soil organic matter, clay content, ionic strength, and moisture can significantly influence the extraction efficiency [39,40]. Additionally, post-extraction processing steps, including centrifugation and filtration, may affect the final measured concentration. Comparative studies of extraction strategies for German grassland and farmland soils demonstrate that extraction behavior is determined by matrix interactions, extraction solvent conditions, and pH conditions. Since TFA predominantly partitions into the aqueous phase at pH values above approximately 1, aqueous or salt-assisted extraction methods are preferred [30].

Methanolic extraction under acidic conditions can esterify TFA to volatile methyl trifluoroacetate, resulting in analyte loss and providing a strong rationale against the use of acidified methanol for soil extraction. In the same study, acetonitrile/water extraction achieved nearly quantitative IS recovery in method blanks, whereas a methanol/sodium-sulfate salting-out approach resulted in recoveries of only approximately 63%. Furthermore, an evaporative up-concentration step further reduced recovery for methanolic methods. Previous headspace-gas chromatography (HS-GC) studies have demonstrated the feasibility of low-level soil analysis, with method detection limits (MDL) near 0.2 ng/g [29].

Regardless of whether shaking, sonication, or centrifugation-assisted extraction is employed, the consistent finding is that soil extraction methods require matrix-specific optimization and validation. Farmland soil, grassland soil, sediment, and sludge are not interchangeable, and acidic methanolic extraction presents a significant risk of esterification-related analyte loss.

5.4. Extraction Methods for Plant and Food Matrices

For plant-derived foods, the standard reference method is the Quick Polar Pesticides (QuPPe) protocol developed by the EURL-SRM. This method involves water adjustment, acidified-methanol extraction, centrifugation, filtration, and subsequent LC- or Ion chromatography (IC)-MS/MS analysis using IS. Polypropylene vials are employed to minimize adsorptive losses of highly polar analytes (EURL-SRM QuPPe-PO, the plant-origin adaptation of the method). The EURL-SRM reporting limit for TFA in fruits and vegetables is 0.04 mg/kg fresh weight [41].

In practical applications, extraction typically utilizes acidified methanol or acetonitrile/water systems [42], followed by homogenization, centrifugation, optional cleanup, and simple dilution for liquid foods and beverages. Major analytical challenges include matrix effects from sugars, organic acids, pigments, proteins, and salts [41,43]; variable recovery rates across crop types; and differences in plant water content that affect extraction efficiency [43]. Dispersive C_{18} or similar cleanup procedures can also reduce matrix effects but may also result in analyte loss [41]. The acidified methanolic step presents the same esterification-related loss mechanism previously identified for soil matrices [30].

Capillary electrophoresis (CE)–MS/MS has been validated for TFA and difluoroacetic acid in plant matrices as an alternative with reduced matrix effects [42]. Additionally, TFA transfer into beverages such as beer and tea infusions is a well-documented exposure pathway [9]. Overall, analytical methods for foods and plants require validation specific to each crop or matrix group, and methods validated for one commodity should not be assumed to be directly transferable to others.

5.5. Preparation of Biological Samples

Common procedures for preparing urine, serum, plasma, and tissue samples include dilution, protein precipitation using acetonitrile or methanol (often acidified), centrifugation, filtration or ultrafiltration, anion-exchange cleanup, and isotope dilution [44]. A validated IC method with suppressed-conductivity detection, requiring only ultrafiltration, has been demonstrated for the simultaneous determination of TFA and bromide in plasma and urine. However, this method is applicable only at the relatively high micromolar concentrations associated with anesthetic metabolism of fluorinated pharmaceutical products, rather than the lower concentrations relevant to environmental exposure [31].

For trace-level PFAS in serum and plasma, the standard approach involves methanol- or acetonitrile-based protein precipitation followed by isotope-dilution LC-MS/MS. Because TFA-free human serum is not available as a calibration matrix, surrogate-matrix calibration with ISs is necessary to ensure accuracy [45]. Although validated PFAS panels for serum and plasma generally exclude ultra-short-chain PFAS, a small number of peer-reviewed studies have reported TFA in human serum using methods that included matrix-specific recovery testing and analytical QA/QC [46–50]. However, these methods remain study-specific and heterogeneous, and no harmonized or interlaboratory-validated method for trace-level TFA determination in serum or plasma is currently available (see Section 9).

The primary challenges include strong ion suppression, low expected analyte concentrations, and interference from proteins and salts [26]. These factors require matrix-matched calibration and the use of ISs [38]. Thus, for biological matrices, extraction recovery alone is not a sufficient performance criterion; ion suppression, matrix effects, and calibration accuracy must also be systematically evaluated and reported.

6. Chromatographic Separation and Detection Methods

Following either the extraction and isolation of TFA or its direct injection, the selection of a separation and detection platform determines the selectivity, sensitivity, and confirmation power of the analysis. Given that TFA is a small, strongly acidic anion with weak hydrophobic character and limited fragmentation, no single analytical platform is optimal for all matrices. The relative advantages of each method must therefore be evaluated in the context of the physicochemical behavior of TFA described in Section 3. In addition to chromatographic performance and detection sensitivity, instrumental background contamination should be routinely assessed because TFA may be present in the LC-system, mobile phases, or solvent delivery components, resulting in background peaks that can compromise trace-level analysis. Instrumental blanks should therefore be analyzed regularly, and one effective strategy to minimize interference is the use of a trapping (delay) column installed upstream of the injector to retain background TFA originating from the LC system and separate the instrument-derived blank peak from the analyte signal [51]. This section first provides an overview of available columns, stationary phases, and instrument configurations (Section 6.1, Table 3), and subsequently evaluates each platform individually (Sections 6.2–6.7).

6.1. Columns, Stationary Phases, and Instrument Configurations

Column selection is the most critical factor in TFA analysis, as the analyte's properties (Section 3) limit the applicability of RP retention mechanisms commonly employed in most PFAS methods. On standard C18 phases, TFA elutes at or near the void volume; therefore, effective retention requires alternative separation mechanisms based on ionic and polar interactions. Polar-endcapped or mixed-mode RP/anion-exchange columns, such as the polar mixed-mode Raptor Polar X used for C1–C4 PFAS, combine weak hydrophobic and anion-exchange interactions, allowing the method to remain compatible with conventional LC-MS instrumentation. Additionally, a mixed-mode column forms the basis of the standardized direct-injection water method [12,19].

Taniyasu et al. [18] combined offline weak anion-exchange solid-phase extraction (WAX-SPE) with mixed-mode ion-exchange separation on an RSpak JJ-50 2D column (Shodex, Resonac Corporation, Tokyo, Japan) and MS/MS detection, achieving a TFA LOQ of 0.5 ng/L in precipitation samples.

HILIC and hybrid HILIC/ion-exchange phases represent intermediate approaches and are often combined with large-volume injection and an online WAX trapping to retain and concentrate TFA using conventional hardware [12]. In addition to liquid chromatography, CE enables the electrophoretic separation of TFA in a bare fused-silica capillary [42]. Supercritical fluid chromatography (SFC)–MS/MS provides a further separation option for TFA and other ultra-short-chain PFAS, as discussed in Section 6.8.

Detection is primarily performed using triple-quadrupole MS in negative electrospray mode, monitoring the single informative transition m/z 113→69, which corresponds to the loss of CO_2 and formation of the CF_3^- fragment ion. Due to the absence of a strong qualifier transition, confirmation depends on retention-time matching with a $^{13}C_2$-TFA IS [6]. The fluoride ion (m/z 19) generated during fragmentation may also be monitored as an alternative qualifier ion; however, its low specificity and potential contribution from other fluorinated species limit its use as a standalone confirmation transition. High-resolution instruments, such as Orbitrap and quadrupole time-of-flight (Q-TOF) systems, often coupled with online SPE, provide exact-mass confirmation and enable retrospective screening, although they share the same fragmentation limitation. The main column and instrument configurations are summarized in Table 3.

Table 3. Columns, stationary phases, and instrument configurations used for TFA determination.

Platform	Column/Stationary Phase	Instrument/Detector	Acquisition	Best-Suited Matrix	Key Limitation	References
RP/mixed-mode LC-MS/MS	Polar-endcapped or mixed-mode RP/anion-exchange (e.g., Raptor Polar X (Restek)	(–)ESI-MS/MS	Direct injection; MRM 113→69 and 113→19; $^{13}C_2$-TFA IS	Water, beverages, serum	Weak retention on conventional C_{18}; limited confirmatory transitions	[12,19,49]
Ion-exchange LC-MS/MS	Mixed-mode ion-exchange RSpak JJ-50 2D (Shodex); ammonium acetate/methanol eluent	(–)ESI-MS/MS	Offline WAX-SPE followed by LC-MS/MS; MRM 113→69 for TFA	Precipitation, water	Requires offline SPE preparation	[18]
IC–MS/MS	Anion-exchange IC column with eluent suppression	IC coupled to suppressed conductivity detection or (–)ESI-MS/MS	Hydroxide or carbonate eluent; MRM or selected-ion monitoring	Water, selected biological matrices (plasma/urine/serum)	Requires specialized IC systems; high inorganic ion concentrations may reduce retention and suppress ionization	[31,50]
HILIC/hybrid HILIC–IEX LC-MS/MS	HILIC or hybrid HILIC/ion-exchange, often with online WAX trapping and large-volume injection	(–)ESI-MS/MS or HRMS	High-organic injection solvent; online SPE enrichment	Trace-level water and complex aqueous matrices	Sensitive to injection-solvent composition and matrix-dependent retention behavior	[12]
CE-MS/MS	Bare fused-silica capillary using electrophoretic separation	CE–(–)ESI-MS/MS	Anionic separation by electrophoretic mobility	Plant, food	Limited routine availability; lower robustness and method transferability compared with LC-based approaches	[42]
HRMS (targeted + non-target screening)	Mixed-mode LC/HILIC, or online SPE	Orbitrap or Q-TOF	Exact mass; full-scan/data-dependent MS^2; non-target screening	Water, non-target screening	Limited fragmentation information; lower sensitivity for trace-level quantification compared with optimized triple-quadrupole MS/MS; requires appropriate reference standards	[6]

Table 3. *Cont.*

Platform	Column/Stationary Phase	Instrument/Detector	Acquisition	Best-Suited Matrix	Key Limitation	References
Sum-parameter/fluorine balance approaches	Combustion IC (EOF/AOF); ^{19}F-NMR	CI or NMR spectrometer	Total fluorine or extractable/adsorbable organic fluorine measurement; non-compound-specific analysis	All matrices for fluorine mass-balance assessment	Non-selective; potential underestimation of ultra-short-chain PFAS; high detection limits for ^{19}F-NMR	[52–54]
GC-MS(/MS)	Capillary GC column selected for the TFA derivative; e.g., HP-5MS	Mass spectrometer, including electron-capture negative-ionization MS (ECNI-MS)	Derivatization followed by selected-ion monitoring (SIM)	Water and atmospheric sample extracts	Requires derivatization; potential uncertainty from reaction yield, contamination, and analyte loss	[55–57]
SFC-MS/MS	Diol stationary phase; e.g., Torus DIOL (Waters)	(–)ESI-MS/MS	MRM; isotope-dilution quantification	Surface water, precipitation, wastewater effluent	Requires dedicated SFC instrumentation and matrix-specific validation	[58,59]

6.2. Liquid Chromatography–Mass Spectrometry

Liquid chromatography–tandem mass spectrometry (LC-MS/MS) is the most widely available analytical platform and, consequently, the most common choice for routine TFA analysis. The primary limitation of this technique is chromatographic: on conventional RP (C_{18}) columns, TFA exhibits poor retention and may elute at or near the void volume, co-eluting with salts and other polar matrix components, which may lead to ion suppression [37]. Sufficient retention requires the use of polar-endcapped, mixed-mode RP, or anion-exchange columns, or alternatively, a fundamentally different separation mechanism (see Sections 6.3 and 6.4). Direct-injection LC-MS/MS has been standardized for TFA determination in water; the working range and interlaboratory validation results are summarized in Section 5.1 [19].

Detection is typically performed using MS/MS in multiple reaction monitoring (MRM) mode. However, confirmation is constrained because the deprotonated precursor ion (m/z 113) produces only one major product ion (m/z 69, CF_3^-). Although the fragment ion m/z 19 (F^-) can be monitored as an additional qualifier, its limited specificity restricts its confirmatory value, resulting in greater reliance on chromatographic retention time and isotope-labelled ISs for reliable identification. As a result, identification relies heavily on retention-time matching, IS, and rigorous QA/QC procedures [6]. Quantification with $^{13}C_2$-TFA corrects for both recovery and ionization effects and is considered essential. With an appropriate column and a sensitive instrument, LC-MS/MS is well suited for routine laboratory analysis, although its confirmation capability for TFA remains intrinsically limited.

6.3. Ion Chromatography-Mass Spectrometry

TFA behaves as a small inorganic-like anion, a property exploited in early ion chromatographic work showing that trace TFA can be resolved from chloride, phosphate, and other background anions on anion-exchange columns with suppressed conductivity detection [60]. Accordingly, IC retains TFA through anion exchange interactions, whereas conventional RP chromatography provides limited retention. IC-MS/MS was included alongside HPLC-MS/MS in the interlaboratory validation of DIN 38407-53, which specifies a working range of 0.1–3.0 µg/L [19].

This method is particularly effective for water matrices, as it separates TFA from chloride, sulfate, and other common anions, thereby reducing charge competition and ionization suppression at the source. Previous studies have demonstrated the robustness of IC with suppressed-conductivity detection for TFA in plasma and urine, requiring only ultrafiltration [31]. The primary trade-offs are practical: coupling IC to MS requires suppression of the high-ionic-strength eluent and careful management of make-up flow [61]. High inorganic loads may still suppress signal if not adequately separated [62].

With careful optimization, IC-MS/MS represents one of the most reliable platforms for TFA analysis in aqueous matrices [6]. Its strength lies in the direct handling of highly polar, non-retained compounds without reliance on hydrophobic interactions, allowing robust separation based on ionic properties. The use of suppressor technology reduces eluent background and enhances MS compatibility, thereby enhancing sensitivity despite the inherently high ionic strength of IC eluents [63,64]. In addition, IC provides effective separation of TFA from inorganic anions such as chloride and acetate, which might otherwise contribute to ion suppression or analytical interference [60].

However, reliable performance depends on careful control of instrumental conditions, including suppressor efficiency, eluent composition, and make-up flow to stabilize electrospray ionization [63]. Matrix-derived inorganic ions may still affect signal intensity if chromatographic separation is insufficient, requiring method optimization tailored to sample composition [19]. When these factors are properly managed, IC-MS/MS offers

a robust and selective approach that is particularly well suited to clean and moderately complex aqueous matrices and can outperform conventional RP-LC-MS/MS methods [19].

6.4. HILIC and Mixed-Mode LC-MS/MS

HILIC and hybrid HILIC/ion-exchange phases provide an intermediate approach, enhancing retention of highly polar analytes while remaining compatible with conventional LC-MS instruments [12,65]. These columns are increasingly preferred for ultra-short-chain PFAS. An effective configuration combines large-volume injection and online WAX trapping with HILIC/ion-exchange separation, enabling the capture of TFA and related compounds that elute unretained from RP columns [5]. The primary limitation is operational: HILIC retention is highly sensitive to the composition of the injection solvent [66]. Consequently, aqueous-rich extracts must be diluted with a high-organic mobile phase or otherwise conditioned to prevent peak distortion. Although this approach improves chromatographic retention, it remains susceptible to matrix effects and high salt concentrations [6]. Method development is therefore demanding; however, for laboratories lacking IC capability, mixed-mode and HILIC columns provide the most practical LC-based solution for achieving adequate TFA retention [12].

6.5. High-Resolution Mass Spectrometry-Based Methods

HRMS provides high-resolution accurate-mass measurement, enabling targeted quantification, suspect and non-target screening, and retrospective interrogation of acquired data for additional ultra-short and short-chain PFAS [67,68]. Online-SPE coupled to LC–HRMS has been applied to TFA and related compounds in surface water [37], and Orbitrap platforms (Thermo Fisher Scientific, Bremen, Germany) are well established for broader PFAS panels. A related hybrid approach, IC coupled to Orbitrap HRMS (IC-HRMS), has also been used for suspect screening of PFCAs including TFA in drinking water, combining IC's mechanistic suitability for small anions with HRMS's capacity for retrospective and suspect analysis [69].

For TFA specifically, however, HRMS faces the same fundamental obstacles as tandem MS: the low molecular mass allows limited diagnostic fragmentation, so confirmation relies primarily on accurate mass, isotope pattern, and retention behavior, and comparison with authentic standards rather than on extensive product-ion spectra. Consequently, authentic reference standards remain essential for unequivocal identification and reliable quantification [6]. HRMS is therefore most valuable for placing TFA within the broader ultra-short-chain PFAS profile and identifying emerging fluorinated compounds, rather than for surpassing IC-MS/MS or LC-MS/MS for routine TFA analysis.

6.6. Capillary Electrophoresis-Mass Spectrometry

CE is known for its capability to analyze small and highly charged molecules because it separates ions according to their electrophoretic mobility rather than hydrophobic interactions. This separation mechanism makes CE especially attractive for TFA, offering high sensitivity while minimizing matrix-related interferences. A Good Laboratory Practice (GLP)-validated CE-MS/MS method for the determination of TFA and difluoroacetic acid in plant samples achieved the regulatory LOQ of 0.01 mg/kg across seven different products. Compared with a comparable LC-MS/MS approach, the CE–MS/MS method was at least ten times more sensitive on a column-loading basis and showed substantially lower matrix effects [42].

The advantages of CE are not restricted to mass spectrometric detection. Since TFA has no UV chromophore, a validated CE method coupled with capacitively coupled contactless conductivity detection (CE-C4D) has been developed achieving separation in less than one minute and reliable quantification in six different water types. The method demonstrated

good linearity and precision, providing a simple and cost-effective alternative when MS instrumentation is unavailable [70]. Moreover, CE-MS/MS has been successfully applied to biological samples. For example, Azab et al. (2020) reported a multisegment-injection nonaqueous CE-MS/MS platform for high-throughput biomonitoring of perfluoroalkyl substances in serum, highlighting the broader applicability of CE-MS/MS beyond environmental and food analysis [71].

Despite these strengths, several factors limit the routine adoption of CE-MS/MS. Compared with LC-MS/MS, CE-MS interfaces are less mature and remain less standardized. Ongoing developments in both sheath-liquid and sheathless interface designs aim to improve the trade-off between analytical sensitivity, operational robustness, and practical usability [72]. Furthermore, the inherently small injection volumes used in CE can restrict concentration sensitivity, and the technique is still uncommon in routine monitoring laboratories. Consequently, CE-MS/MS is best viewed as a powerful complementary analytical tool for specialized laboratories and difficult analytical applications rather than as a mainstream platform for routine monitoring.

6.7. Gas Chromatography-Mass Spectrometry

Gas chromatography coupled to mass spectrometry (GC–MS) provides an alternative approach for the TFA determination; however, due to its ionic and nonvolatile nature, conversion to a volatile derivative is required. Derivatization with 2,4-difluoroaniline has been used to determine gaseous and particulate TFA in atmospheric samples [56]. In a separate study on drinking water, derivatized TFA was measured by GC–MS, whereas other PFAS were analyzed using HILIC–MS/MS or reversed-phase LC–MS/MS [57].

GC-based analysis has also contributed to the broader characterization of TFA and other PFAS in environmental dust matrices [73]. In a recent study, rapid derivatization with diphenyldiazomethane enabled the quantitative GC-MS analysis of C_2-C_{14} PFCAs in aqueous matrices. The derivatization reaction was completed in less than one minute, and the method achieved detection limits within one order of magnitude of those obtained by conventional LC-MS/MS methods [55]. Although GC–MS provides effective retention and separation of TFA, derivatization introduces additional sources of uncertainty associated with reaction yield, contamination, and analyte loss.

6.8. Supercritical Fluid Chromatography-Mass Spectrometry

Supercritical fluid chromatography coupled to tandem mass spectrometry (SFC–MS/MS), including ultra-performance convergence chromatography, provides another alternative for separating TFA and other ultra-short-chain PFAS [58]. The approach was initially developed for simultaneous quantitative determination of ultra-short- to long-chain PFAS in rain and river water [58]. Subsequent quantitative applications included the analysis of waters associated with known or suspected contamination sources [74] and the determination of PFAA inputs and outputs for a freshwater-lake mass balance [59]. SFC–MS/MS has also been used for qualitative TFA determination in a fluorine mass-balance study of wastewater-treatment effluent and sludge [75]. In general, SFC offers rapid analysis and narrow chromatographic peaks; however, its broader application is restricted by the limited instrumentation availability and the need for matrix-specific validation.

6.9. Sum-Parameter and Fluorine-Balance Approaches

A distinct group of methods estimates total fluorine or total organofluorine rather than identifying individual compounds. These include total fluorine and total organic fluorine, the extractable and adsorbable organic fluorine fractions (EOF and AOF) measured by combining IC, fluorine-19 nuclear magnetic resonance spectroscopy (^{19}F-NMR), and the indirect total oxidizable precursor (TOP) assay [52].

Such methods are valuable for fluorine mass balance assessments and for evaluating the fraction of organofluorine not accounted for by targeted compound analysis. However, they are not suitable for the specific determination of TFA. Combustion IC is nonselective, and the extraction or adsorption steps that preceded it often fail to capture ultra-short-chain species, resulting in frequent loss of TFA and potential overestimation of treatment efficiency or degradation in fluorine-balanced studies [53]. The TOP assay has similar limitations because it involves an oxidation step followed by targeted LC analysis, which commonly relies on RP-LC that provides inadequate retention of short-chain oxidation products. Moreover, TFA itself is a terminal oxidation product and therefore cannot be further converted through the TOP process [76]. ^{19}F-NMR avoids matrix and preparation bias by quantifying the terminal –CF_3 resonance directly, but its detection limit (approximately 50 µg/L) is too high for environmental TFA [77]. Overall, sum-parameter and fluorine-balance methods complement, but cannot replace, targeted TFA quantification. When ultra-short-chain PFAS are of concern, TFA should be quantified using dedicated analytical methods and reported separately.

7. Method Validation and Analytical Performance

Validation practices for TFA are highly variable across matrices, and the distinction between reporting a detection and demonstrating a reliable, defensible measurement represents a defining challenge in the current literature (Table 4). For water matrices, validation efforts have advanced sufficiently to establish formal interlaboratory assessment and method standardization. In contrast, for soil, food, and particularly biological matrices, many published methods still report performance data that are either incomplete or do not clearly distinguish between different sources of analytical uncertainty.

7.1. Calibration and Quantification Strategy

The most consequential choice is how quantification compensates for matrix effects and analytical losses. Isotope dilution with $^{13}C_2$-TFA has become the de facto standard and is considered essential for complex matrices, because it corrects simultaneously for ionization suppression and for losses occurring after the isotopically labelled standard is introduced [6]. Where an IS is unavailable or a surrogate (for example $^{13}C_3$-perfluorobutanoic acid (PFBA)) is used, the correction efficiency is reduced, since a structurally different surrogate may not accurately represent TFA-specific extraction, retention, and ionization behavior. Matrix-matched calibration and standard addition remain valuable alternatives, particularly for matrices where a true blank matrix is unavailable. For serum, where PFAS-free human matrix cannot be obtained, a charcoal-stripped surrogate matrix combined with a labelled TFA surrogate is used precisely because conventional calibration would be biassed. The recurring limitation in the literature is the assumption that isotope correction is sufficient without independent evaluation of its performance within the specific matrix.

7.2. Sensitivity and Linearity

Reported detection limits vary widely, ranging from sub-ng/L using online-SPE–HRMS in surface water to micromolar-level methods for anesthetic-metabolite monitoring [31]. The critical consideration is not the lowest achievable LOQ, but whether it is fit for purpose relative to applicable regulatory values and analytical reporting requirements. Relevant benchmarks include the EU "PFAS Total" parametric value of 0.50 µg/L [20], the matrix-dependent working range of 0.10–3.0 µg/L specified in DIN 38407-53 for direct-injection analysis of water [19], and the EURL-SRM quantitative reporting limit of 0.04 mg/kg fresh weight for TFA in fruits and vegetables [10]. While linearity is gener-

ally well characterized, linear ranges are frequently reported without verification at low concentrations, which is essential when sample concentrations are near the LOQ.

7.3. Trueness, Extraction Efficiency, and Matrix Effect

The most frequent reporting deficiency concerns the inappropriate combination of distinct analytical performance parameters into a single recovery value. Many studies report a "recovery" value near 100% that reflects isotope-corrected apparent recovery, without separately quantifying absolute extraction efficiency or the magnitude of the matrix effect [26,38]. Extraction efficiency refers to the proportion of native analyte released from the matrix, while the matrix effect denotes changes in ionization response. Isotope-corrected recovery combines both factors and can mask poor extraction if the labelled standard is added only after extraction [78]. For example, in soil analysis, acetonitrile/water extraction achieved nearly quantitative IS recovery, whereas a methanol/sodium-sulfate approach yielded only about 63%, and acidic methanolic conditions risked esterification loss [30]. Reporting extraction efficiency, matrix effect, and isotope-corrected recovery as separate values provides greater interpretability than presenting a single combined recovery figure.

7.4. Precision and Interlaboratory Comparability

Intra- and inter-day precision are commonly reported and, for well-developed methods, typically exhibit relative standard deviations below 10%. However, true interlaboratory reproducibility has been demonstrated almost exclusively for water [19], with reproducibility relative standard deviations (RSDs) of 6–20% across 12 laboratories. By contrast, interlaboratory comparisons in other matrices show substantially poorer agreement. EOF measurements yielded coefficients of variation of 67% in groundwater and 20% in eel tissue [79], and serum PFAS biomonitoring under the EU-wide HBM4EU quality assurance program achieved RSDs of only 13–22% even after iterative improvement across four rounds [80]. For TFA, the water-method validation summarized in Section 5.1 provides evidence of interlaboratory reproducibility [19]. Currently, no equivalent interlaboratory evidence exists for soil, food, or biological TFA measurements, which remains the primary barrier to comparing concentrations across studies and monitoring programs.

7.5. Contamination Controls and Stability

Carryover and blank correction are critical components of method validation for an analyte as susceptible to background interference as TFA (Section 4) [51]. Blank levels should be systematically characterized and reported relative to the LOQ, rather than subtracted without documentation. Carryover must be explicitly assessed, particularly given the use of high-concentration calibration ranges [81]. In contrast, storage stability is rarely a limiting factor due to TFA's resistance to degradation. The more relevant stability concern is whether complex extracts maintain consistent ionization behavior throughout the analytical sequence, a factor that is rarely evaluated [82].

Overall, TFA is increasingly reported across environmental and biological matrices, whereas comprehensive validation of the underlying analytical methods remains limited. Analytical methods for water now achieve a high standard, including interlaboratory agreement. In contrast, methods for soil, food, and biological matrices often omit absolute extraction efficiency, only partially characterize matrix effects, and lack interlaboratory benchmarks. Improving data comparability requires separate reporting of extraction efficiency and matrix effects, verified application of isotope dilution, transparent contamination-control procedures, and expansion of interlaboratory validation efforts beyond water matrices.

Table 4. Validation parameters reported in representative TFA analytical methods.

Matrix	Extraction/Prep	Instrument	LOD/LOQ	Recovery	Matrix Effect	IS	Major Limitation	Reference
Drinking, surface, groundwater, precipitation	Direct injection	LC-MS/MS	LOQ: 0.1 µg/L (range up to 3.0)	NA	corrected by IS; reproducibility RSD ~6–20%	$^{13}C_2$-TFA	Limited to aqueous matrices; no preconcentration	[19]
Precipitation, water	Offline WAX-SPE	Ion-exchange LC–MS/MS; RSpak JJ-50 2D	TFA LOQ: 0.5 ng/L	TFA: 99% in SPE tests; 76% in rainwater matrix spikes	NA	isotope-labelled IS	Requires offline SPE preparation	[18]
Plant, soil, water	Acidic methanol derivatization followed by headspace analysis	HS-GC-MS/ electron capture detector (ECD)	MDL: 34 ng/g (plant); 0.2 ng/g (soil); 6.5 ng/L (water)	87–121%	NA	none (spike recovery)	Derivatization required; no isotope-labelled IS	[29]
Grass, farmland soil	Acetonitrile/water vs. methanol salting-out extraction	LC-MS/MS	NA	IS recovery ~100% (acetonitrile/water) vs. ~63% (methanol)	Addressed via IS	$^{13}C_2$-TFA	Strong matrix dependent; esterification risk under acidic methanol conditions	[30]
Fruit, grain, vegetables	Acetonitrile/water	CE-MS/MS	LOQ: 0.01 mg/kg	GLP-validated performance	Lower matrix effects than LC-MS/MS	isotope-labelled IS	Limited availability in routine laboratories	[42]
Beverages, water	Dilute-and-shoot (~10-fold dilution)	LC-MS/MS	validated water range: 0.10–2.02 µg/L	validated	Matrix effects reduced by dilution	$^{13}C_3$-PFBA (surrogate)	Surrogate does not fully mimic TFA behaviour	[83]
Plasma, urine	Ultrafiltration	IC with suppressed conductivity detection	linear range: 10–250 µM	NA	NA	External calibration	Applicable mainly to high concentrations; limited relevance for environmental exposure levels	[31]

NA: not available.

8. Critical Comparison of Extraction Efficiency

Comparing extraction methods for TFA does not support the identification of a universally optimal approach, as the predominant source of analytical error varies substantially among matrices. In clean aqueous samples, recovery is seldom problematic; instead, background contamination and blank control are the primary analytical challenges. For solids such as soil and plant material, the limiting factor is absolute extraction efficiency, defined as the fraction of native analyte released from the matrix. In biological fluids, ionization suppression rather than extraction recovery is typically the dominant source of uncertainty. Therefore, ranking methods solely by their reported recovery figure is misleading, since an isotope-corrected recovery near 100% may mask poor absolute extraction efficiency or substantial matrix effects (Section 7). A more meaningful criterion is whether a method effectively controls the dominant error source associated with the target matrix. Figure 3 summarizes this matrix-specific decision framework, illustrating the relationship between sample type, dominant analytical uncertainty, and the most appropriate extraction and detection strategy for achieving reliable TFA quantification.

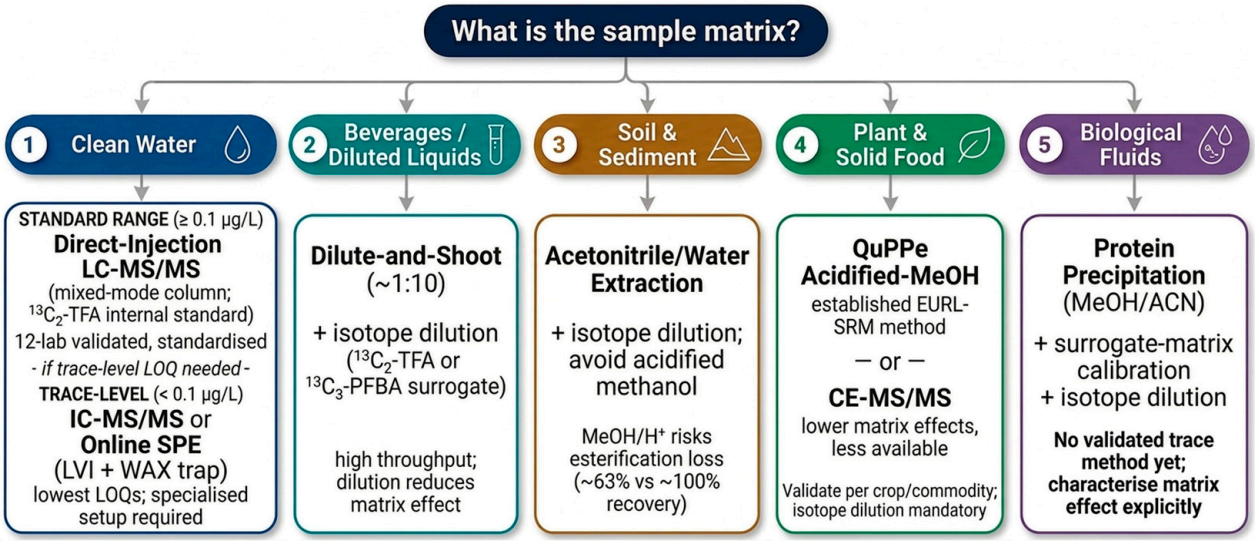


Figure 3. Matrix-specific method selection for TFA analysis, summarizing the recommended extraction and detection approach for each sample type. LIV: large volume injection.

For clean water matrices, this approach supports minimal sample manipulation. Direct injection avoids extraction losses and minimizes contamination risks, and it now forms the basis of a standardized, interlaboratory-validated method for drinking water [19]. Its primary limitation is the lack of preconcentration, which only becomes significant when the required LOQ is lower than what the instrument can achieve with a neat sample. In such cases, the analytical challenge is to enrich an analyte that is inherently resistant to enrichment. Conventional sorbent SPE is a less effective solution: WAX phases are susceptible to breakthrough and displacement by the high background of inorganic anions in environmental water [16], and ultra-short-chain PFAS exhibit the poorest recovery on these phases (Section 5.2). A more robust solution is online SPE combined with large-volume injections, which can achieve low-ng/L limits when appropriately optimized, although it requires dedicated instrumentation and has limited applicability for routine monitoring laboratories.

For solid and complex food samples, extraction efficiency is the primary determinant of analytical performance, and the choice of method has significant consequences. Aqueous and salt-assisted extraction methods leverage TFA mobility, but their effectiveness varies with matrix composition, whereas acetonitrile/water extraction generally provides more consistent performance and IS recovery, in line with established multi-residue extraction principles [84]. In contrast, acidified methanol poses a specific risk of esterification loss and performed substantially worse in direct comparisons [30].

From a quantitative perspective, the key challenge is not recovery alone but the combined contribution of extraction efficiency and matrix effects. As demonstrated in foundational LC–MS/MS studies, absolute recovery, matrix effects, and overall process efficiency must be evaluated separately to avoid misinterpretation of method performance [26,38]. Accordingly, a systematic approach is recommended: apply acetonitrile/water extraction where feasible, use isotope dilution for quantification, and report absolute extraction efficiency independently of matrix-effect-corrected recovery (Figure 3).

For biological fluids, no extraction strategy fully resolves the dominant issue of ion suppression, which is inherent to electrospray ionization in complex matrices [85,86]. Protein precipitation can serve as a pragmatic clean-up step but is insufficient as a standalone solution. Reliable quantification therefore requires isotope dilution in combination with matrix-matched or surrogate-matrix calibration, and method validation must explicitly demonstrate control of matrix effects rather than relying on recovery metrics alone, consistent with current bioanalytical validation guidance [87].

Table 5 compares sample-preparation strategies in terms of recovery reliability, routine applicability, relative time requirements, consumable costs, and operational complexity to support matrix-specific method selection in routine monitoring laboratories. The major conclusion is that the optimal method is highly matrix-dependent: for clean water, direct injection is generally preferable to any extraction; for trace water, online SPE offers the most effective enrichment; and for soil, food, and biological samples, extraction efficiency and matrix effects, rather than instrumental sensitivity, are the primary determinants of data quality.

Table 5. Comparative assessment of extraction efficiency and suitability of sample-preparation strategies for TFA.

Method	Suitable Matrix	Recovery Reliability	Routine Applicability	Relative Time Requirement *	Relative Consumable Cost *	Sample-Preparation Complexity *	Recommendation	References
Direct injection	Clean water	High	High	Fast	Low	Low	First choice for water; standardized	[8,19]
Dilute-and-shoot	Beverages, urine, diluted wastewater	Medium–high	High	Fast	Low	Low	Useful with sensitive MS + isotope dilution	[6,9]
WAX-SPE	Water (enrichment/ cleanup)	Variable (often low)	Medium	Slow	High	Moderate	Only after TFA-specific validation	[28,54]
SAX/MAX-SPE	Water, extracts	Variable	Low–medium	Slow	High	Moderate	Promising but matrix-dependent; validate elution	[6,28]
Online SPE (large-volume injection + WAX trapping)	Trace-level water	High if optimized	Low (specialized)	Fast (once established)	Low	Moderate	Best enrichment route for trace water	[12]
Aqueous/salt-assisted extraction	Soil, sediment	Matrix-dependent	Medium	Moderate	Moderate	Moderate	Validate by soil type; avoid acidic methanol	[29,30]
Acetonitrile/water extraction	Food, plants, soil	Matrix-dependent (good with isotope dilution)	Medium–high	Moderate	Low	Low	Recommended with isotope dilution; report extraction efficiency separately	[30,42]
Acidified methanol (QuPPe)	Food, plants	Medium (needs isotope dilution)	High (established)	Moderate	Low	Low	Use with isotope dilution; watch esterification	[88]
Protein precipitation with cold acetonitrile, followed by supernatant dilution	Human serum	Method-dependent; requires TFA-specific recovery and matrix-effect assessment	Medium; requires matrix-specific validation	Short preparation; 5 min centrifugation step	Low	Low	Validate TFA recovery, matrix effects, and interferences; isotope dilution and surrogate-matrix calibration used in the cited study	[49]
Ultrafiltration	Plasma, urine	Medium	Medium	Moderate	Moderate	Moderate	Suitable only where concentrations are relatively high	[31]

* Ratings are qualitative. Recovery reliability: High = reproducible; Medium = condition-dependent; Low = inconsistent. Routine applicability: High = readily implemented; Medium = requires optimization or expertise; Low = substantial operational demands. Time, consumable cost, and complexity refer to sample preparation and depend on matrix, batch size, automation, and analytical platform. Consumable costs exclude instrumentation, maintenance, and personnel. Instrument configurations and limitations are summarized in Table 3.

9. Analytical Gaps and Future Directions

The preceding sections demonstrate that the field is advancing unevenly: while water analysis is well established and increasingly harmonized, and supported by interlaboratory validation, monitoring in other matrices remains fragmented. The following gaps are presented not as criticisms of individual studies, but as priority areas for methodological improvement required to achieve comparable and reliable TFA datasets across laboratories, matrices, and monitoring programs.

For water, a standardized, interlaboratory-validated method is now available [19], and comparable official methods have been developed in other regions (Table 6). However, no equivalent standardization exists for soil, food, plant, or biological matrices, where methods remain laboratory-specific and are difficult to compare. Addressing this gap requires extending harmonized protocols beyond water and, importantly, organizing interlaboratory comparison exercises for solid and biological matrices. Single-laboratory validation alone cannot establish the reproducibility that has been demonstrated for water methods.

A related deficiency is the limited availability of certified reference materials (CRMs). In the absence of matrix-matched CRMs for soil, plant tissue, food, and serum, laboratories are unable to independently verify trueness, and apparent agreement between methods may reflect shared bias rather than analytical accuracy [89]. Investment in developing such CRMs would be the most effective step toward improving comparability and addressing multiple sources of uncertainty simultaneously. Reporting practices represent another area for improvement. As outlined in Section 7, extraction efficiency and matrix effects are often combined into a single isotope-corrected recovery value, which obscures whether uncertainty arises primarily from incomplete analyte ionization suppression [26,38]. Future studies should report absolute extraction efficiency, matrix effects, and isotope-corrected recovery as separate performance parameters, and should explicitly characterize matrix effects rather than presuming their elimination through isotope dilution [90].

The limited comparability of SPE methods is partly attributable to insufficient reporting of critical performance parameters. Enrichment recoveries for highly polar acids are matrix-dependent and sensitive to competing anions (Section 5.2); however, breakthrough behavior, competing-ion effects, and elution performance are rarely reported in sufficient detail to evaluate method transferability [91].

Online SPE combined with large-volume injection (LVI) offers a promising route to automated enrichment of TFA and other ultra-short-chain PFAS in water. Wang et al. demonstrated online SPE–HPLC–HRMS using a 2 mL sample loading volume [37,92]. Jacob and Helbling also demonstrated online SPE coupled to HPLC–MS/MS for the simultaneous determination of short- and ultra-short-chain PFAS in water and wastewater samples [93]. Such workflows may reduce manual handling and opportunities for contamination associated with offline extraction. However, larger loading volumes do not necessarily improve TFA sensitivity: breakthrough and losses during washing must be evaluated alongside matrix effects [37]. Future studies should assess method transferability, carryover, sorbent lifetime, solvent consumption, and cost per sample to establish the practical benefits for routine monitoring.

Ion mobility spectrometry–mass spectrometry (IMS–MS) provides an additional separation dimension and collision cross-section information that can strengthen PFAS identification and suspect screening [94]. However, its application to TFA requires specific optimization. In a recent LC–IMS–MS study of human serum, TFA eluted near the column void volume and exhibited pronounced clustering in the ion mobility dimension, preventing reliable quantification under the investigated conditions [95]. Future studies should evaluate in order to improve chromatographic retention and control of ion clustering to enable reliable TFA measurements and better discrimination from matrix interferences.

Such evaluations should establish sensitivity at environmentally relevant concentrations and the reproducibility of mobility measurements.

Table 6. Current analytical gaps and recommendations.

Gap	Why It Matters	Affected Matrices	Recommended Action	References
Harmonization limited to water	Methods for non-water matrices remain laboratory-specific, limiting comparability	Soil, food, plant, biological	Extend standardized protocols to non-water matrices and establish interlaboratory validation	[19]
Limited interlaboratory validation beyond water	Method reproducibility remains unverified beyond single-laboratory studies	Soil, food, plant, biological	Organize matrix-specific interlaboratory comparison studies	[6,19]
Lack of CRMs	Trueness cannot be independently verified, increasing the risk of systematic bias	All non-water matrices	Develop matrix-matched CRMs (soil, plant, food, serum)	[6]
Incomplete reporting of extraction performance	Isotope-corrected recovery may mask poor extraction efficiency	Soil, food, plant, biological	Report extraction efficiency, matrix effect, and corrected recovery as separate parameters	[6,30]
Insufficient characterization of matrix effects	Ion suppression or enhancement compromises quantification accuracy	Food, plant, biological, complex water	Quantify matrix effects explicitly and apply matrix-matched calibration or standard addition where appropriate	[6,19]
Limited biomonitoring methods	No validated trace-level methods are available for human biomonitoring	Serum, plasma, urine	Develop and validate low-level biomonitoring methods using isotope dilution and surrogate-matrix calibration	[31,45]
Limited validation across food and plant matrices	Recovery and method performance vary substantially among commodities	Fruits, cereals, vegetables, beverages	Validate methods by matrix group and assess cross-commodity applicability	[42,88]
Limited comparability of SPE methods	Recovery depends strongly on competing ions and sample matrix	Water	Report breakthrough, competing-ion effects, and elution efficiency; validate SPE specifically for TFA	[28,54]
Limited availability of isotope-labelled standards	Simultaneous isotope-dilution quantification of ultra-short-chain PFAS remains restricted	All matrices (ultra-short-chain PFAS)	Develop labelled analogues for other ultra-short-chain PFAS and incorporate them into CRMs	[6,19]
Limited integration with complementary techniques	Targeted TFA analysis alone does not capture total organofluorine or unidentified fluorinated compounds	All matrices	Combine targeted TFA analysis with HRMS and fluorine mass balance, acknowledging the under-recovery of ultra-short-chain PFAS in sum-parameter methods	[52,54]

Biological monitoring of TFA remains less harmonized than water analysis. Peer-reviewed studies have reported TFA in human serum, including an LC-MS/MS method employing acetonitrile protein precipitation, isotope-labelled internal standards, and surrogate-matrix calibration [49]. However, further work is needed to establish comparability across laboratories and performance at low exposure concentrations. Priorities include matrix-specific validation, assessment of analytical interferences, appropriate calibration strategies, and interlaboratory comparison exercises.

While food and plant matrices benefit from the QuPPe framework and dedicated methods [42,88], validation remains largely commodity-specific and inconsistent, and few studies demonstrate transferability across different crop groups and food categories.

In addition to $^{13}C_2$-TFA, isotopically labelled analogues are commercially available for other ultra-short-chain PFAS, including perfluoropropanoic acid (PFPrA), trifluoromethanesulfonic acid (TFMS), perfluoroethanesulfonic acid (PFEtS), and perfluoropropanesulfonic acid (PFPrS), as summarized in Table 7. Their incorporation into validated analytical workflows can support simultaneous isotope-dilution quantification of these compounds. Future work should evaluate their performance across different matrices and sample-preparation procedures. The development of matrix-matched reference materials remains a complementary priority [89].

Table 7. Examples of commercially listed isotope-labelled standards for selected ultra-short-chain PFAS.

Target Analyte	Isotopically Labelled Analogue	Supplier and Example Catalogue Number
TFA	$^{13}C_2$-TFA	[96–98]
PFPrA	$^{13}C_3$-PFPrA	[96,99]
TFMS	^{13}C-TFMS	[96]
PFEtS	$^{13}C_2$-PFEtS	[96]
PFPrS	$^{13}C_3$-PFPrS	[96]

Additionally, targeted TFA quantification should be integrated with complementary analytical techniques rather than considered independently. Although fluorine mass-balance approaches and HRMS each have specific limitations for TFA determination (Sections 6.5 and 6.6), their use alongside targeted analysis can provide a more comprehensive understanding of ultra-short-chain PFAS occurrence and total organofluorine burdens, provided that the well-documented under-recovery of ultra-short-chain species in sum-parameter methods is acknowledged [54].

10. Proposed Minimum Reporting Checklist for TFA Methods

A persistent challenge in comparing TFA data arises not from the inability of studies to detect the analyte, but from incomplete reporting of critical analytical details required to evaluate measurement reliability. This lack of detail prevents readers from determining whether measured concentrations represent true environmental levels or contributions from procedural artefacts and analytical bias. The proposed checklist presented in Table 8 is designed to address this issue directly. It is structured around the specific challenges associated with TFA analysis, including ubiquitous background contamination, weak analyte retention, reliance on single-product-ion detection, and matrix-dependent extraction, rather than serving as a generic validation list. Adoption of this checklist would improve transparency, facilitate interlaboratory comparison, and enhance confidence in reported TFA concentrations across laboratories and sample matrices. Several checklist items warrant particular emphasis due to their frequent omission. Blank assessment and contamination control are essential for TFA due to its widespread presence in laboratory air, solvents, and consumables; blank levels should therefore be reported relative to the LOQ, rather than subtracted without disclosure (Section 4). Extraction efficiency and matrix effects should be reported as independent parameters alongside isotope-corrected recovery, as combining these metrics obscures the primary source of uncertainty (Section 7). Confirmation criteria require explicit description because TFA generates often only one major diagnostic product ion (m/z 113→69). Although the transition to m/z 19 (F^-) can be monitored

as a qualifier, its low specificity limits its confirmatory value, precluding the standard two-transition identification approach [6,27]. Authors should specify the alternative confirmation methods employed, such as analysis on an alternative chromatographic column, retention-time matching with an isotope-labelled standard, IC-based separation, or HRMS confirmation. Reporting units and measurement basis must be clearly defined (e.g., fresh weight versus dry weight for plant and food matrices), and each reported concentration should be accompanied by an assessment of measurement uncertainty, given the wide range of interlaboratory reproducibility for TFA, even in standardized water methods [19]. Collectively, these requirements distinguish between mere detection and a scientifically defensible measurement.

Table 8. Minimum reporting checklist for analytical studies determining TFA concentrations.

Checklist Item	What to Report	Why It Matters for TFA
Sample matrix description	Matrix type, subcategory, water content, relevant composition characteristics	Recovery and matrix effects are strongly matrix- and commodity-specific
Sampling container and storage	Container material (avoid fluoropolymers), storage temperature, holding time, and preservation conditions	Background contamination is the primary pre-analytical concern
Blank strategy	Field, procedural, solvent, and instrument blanks; blank levels reported vs. LOQ	TFA is ubiquitous in laboratory air, reagents, solvents, and consumables
Extraction/sample preparation method	Solvent(s), solvent ratios, workflow, evaporation steps, acid conditions	Recovery depends strongly on extraction conditions; acidified methanol may cause esterification losses
Extraction efficiency (absolute)	Absolute extraction efficiency determined independently of IS correction	Poor extraction can be masked by IS correction
Matrix effects	Ion suppression or enhancement (e.g., post-extraction spike experiments or post-column infusion)	Early eluting TFA frequently co-elutes with salts and other polar matrix constituents; suppression is common
IS	Identity ($^{13}C_2$-TFA preferred) and point of addition within the analytical workflow	Appropriate isotope dilution is essential for correcting recovery losses and matrix effects
Calibration strategy	Isotope dilution, matrix-matched calibration, or standard addition; calibration range and weighting	True blank matrices are often unavailable (e.g., serum)
LOD and LOQ	Values, calculation approach, and suitability for the intended application or regulatory threshold	Method sensitivity should be appropriate for expected concentrations and regulatory limits
Carryover assessment	Carryover after high-concentration standards or samples and corrective measures	Instrumental background and carryover may bias low-level TFA measurements
Stability test	Stability of samples and extracts during storage and throughout analytical sequence	TFA is persistent, but extract composition and ionization efficiency may change over time
Confirmation criteria	Product-ion transitions, retention-time criteria, qualifier ions (e.g., m/z 113→19), and alternative confirmation approaches (e.g., alternative chromatographic column, IC, or HRMS)	TFA generates often only one major diagnostic product ion (113→69), limiting conventional two-transition confirmation
QC samples	QC materials, analysis frequency, acceptance criteria, and corrective actions	Demonstrates method performance and analytical control for a contamination-prone analyte
Control charts	Use of control charts for blanks, QC samples, IS responses, and recoveries	Monitors analytical stability and detects contamination, drift, or recovery changes over time
Reporting units	Units, fresh vs. dry weight, normalization procedure (if applicable)	Enables comparison across matrices and studies
Measurement uncertainty	Estimated measurement uncertainty or confidence interval accompanying reported concentrations	Supports interpretation and comparison of analytical results across laboratories

11. Conclusions and Perspectives

TFA poses a distinct analytical challenge within PFAS analysis due to its small size, strong acidity, extreme polarity, and high mobility. These properties undermine conventional hydrophobic retention-based methods, leading to poor enrichment, weak chromatographic retention, and limited MS/MS fragmentation. As a result, analytical accuracy depends more on rigorous control of pre-analytical factors, particularly sample preparation, contamination, and matrix effects, than on instrumental sensitivity alone. No universally optimal method exists, as the dominant source of analytical error varies by matrix. Contamination is the primary concern in clean water, extraction efficiency in soils and plants, and ionization suppression in biological matrices. Method selection should therefore target the main matrix-specific uncertainty rather than rely solely on recovery values.

Direct injection is generally the preferred approach for clean water, minimizing sample handling, reducing contamination risk, and has been supported by interlaboratory validation. More complex matrices require extraction, with acetonitrile/water-based extraction combined with isotope dilution currently representing the most robust general approach. In contrast, acidified methanol should be avoided due to esterification risks, while SPE remains matrix-dependent and requires specific validation for TFA.

A key limitation in the current literature is the conflation of extraction efficiency, matrix effects, and isotope-corrected recovery into a single metric, thereby obscuring analytical uncertainty and limiting comparability. While water analysis has reached a relatively high level of harmonization, methods for soils, food, plants, and especially biological matrices remain less standardized, with limited interlaboratory validation and a lack of matrix-matched certified reference materials.

Addressing these gaps requires the development of harmonized, matrix-specific methods, expanded interlaboratory validation, improved reference materials, and broader availability of matching ISs for ultra-short-chain PFAS. The matrix-specific recommendations, critical method comparison, minimum reporting checklist, and future research priorities presented in this review are intended to support the development of more robust, transparent, and comparable analytical workflows for TFA.

Future research should evaluate online SPE combined with large-volume injection for automated enrichment and IMS-MS for improved selectivity in short-chain PFAS analysis, with particular attention to demonstrating their sensitivity and quantitative reliability for TFA.

More broadly, TFA shifts the main analytical challenge from detection to ensuring sample integrity and measurement quality. Future efforts should therefore focus on validated, matrix-specific workflows that explicitly assess extraction efficiency, matrix effects, and uncertainty. As regulatory attention toward TFA and other ultra-short-chain PFAS continues to increase, analytical methods specifically designed for highly polar compounds, together with greater harmonization of analytical practices and closer integration of monitoring data with environmental and regulatory frameworks, will be essential for producing reliable data and enabling meaningful exposure and risk assessment.

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