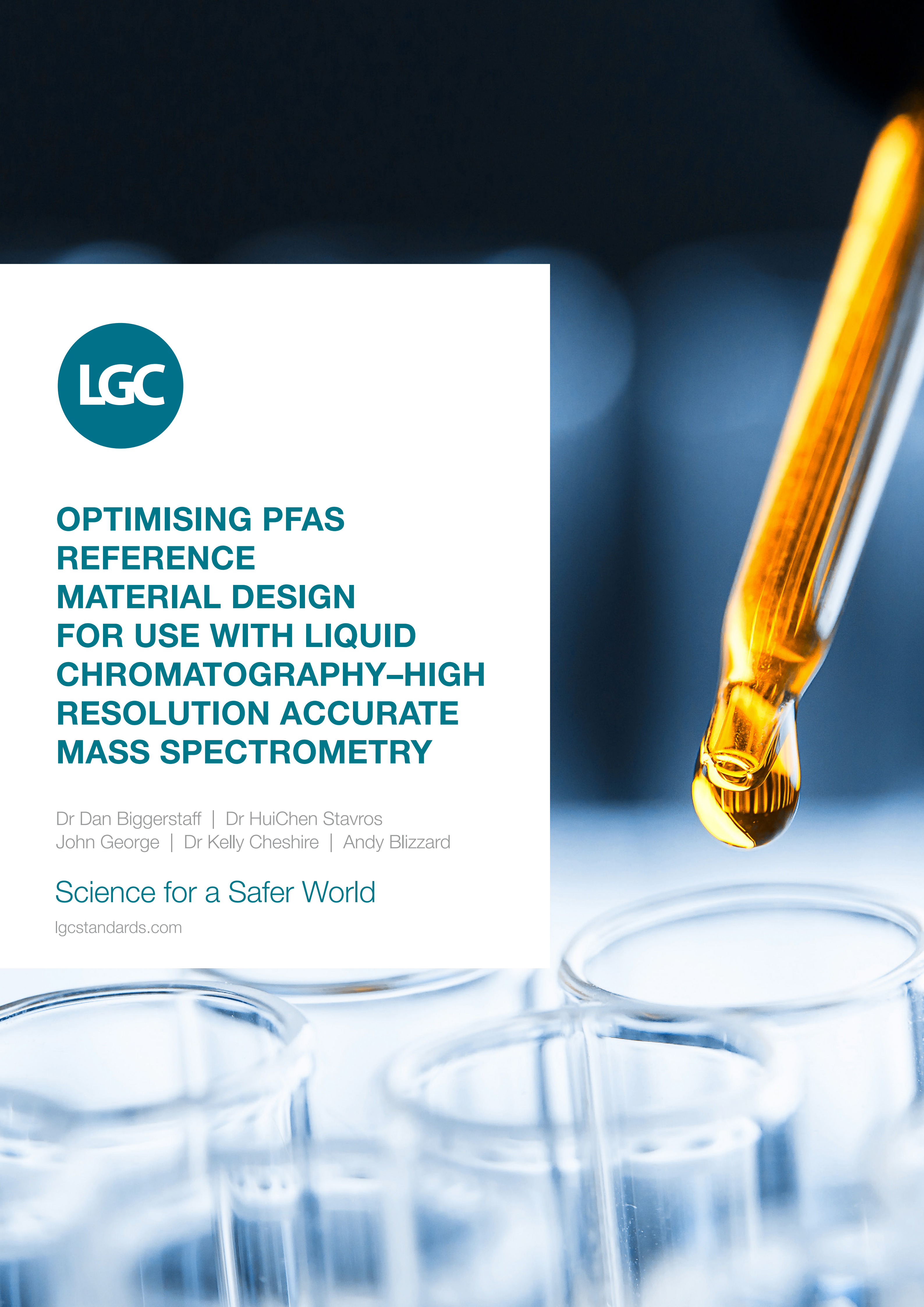

# OPTIMISING PFAS REFERENCE MATERIAL DESIGN FOR USE WITH LIQUID CHROMATOGRAPHY–HIGH RESOLUTION ACCURATE MASS SPECTROMETRY

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# Introduction: what are PFAS and where are they found?

Per- and Polyfluoroalkylated Substances (PFAS) are a diverse group of synthetic chemicals, widely used in various industrial applications and consumer products due to their unique properties. These substances are characterised by their strong carbon-fluorine bonds, which provide exceptional resistance to heat, water, and oil. As a result, PFAS have been employed in many industrial practices, including the production of non-stick cookware, water-repellent clothing, firefighting foams, food packaging materials, pesticides and more[1].

The widespread use of PFAS, coupled with their environmental persistence and resistance to degradation, has led to significant environmental and public health concerns. These chemicals find their way into the environment through manufacturing processes, during use and waste disposal, and via wastewater (see Figure 1). They are then known to persist in the environment and bioaccumulate in living organisms over time, earning them the name “forever chemicals”[2].

## FIGURE 1 How PFAS may enter our environment

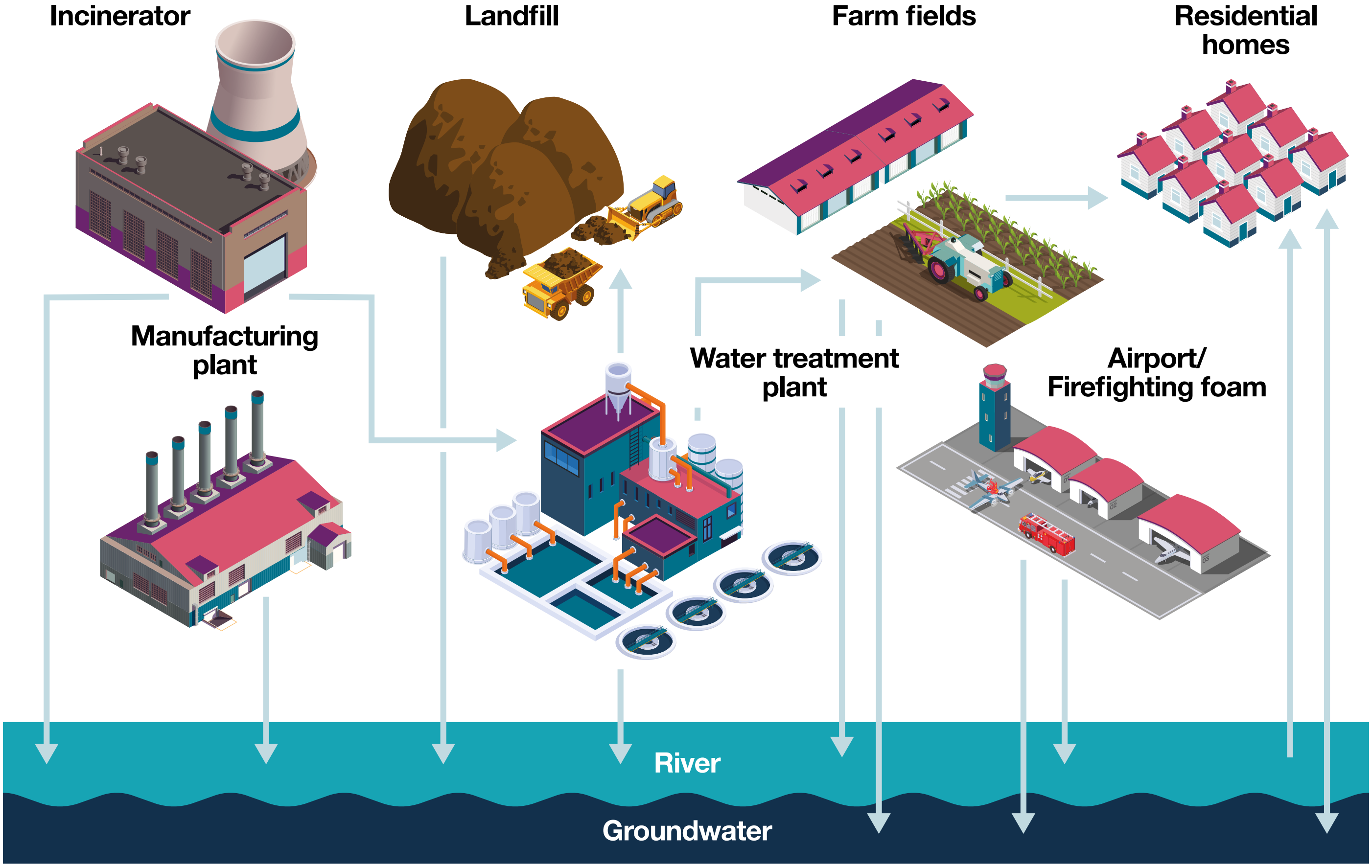


FIGURE 1: Adapted from GAO *2021* and coastalreview.org *2023*

PFAS have been detected globally, and in various environmental matrices that indicate widespread exposure – including water, soil, and air, as well as human blood samples[3-6]. Exposure to PFAS has also been associated with a range of adverse health effects: epidemiological studies linking it to liver damage, thyroid disease, decreased fertility, increased cholesterol levels, and a higher risk of certain cancers[7-8].

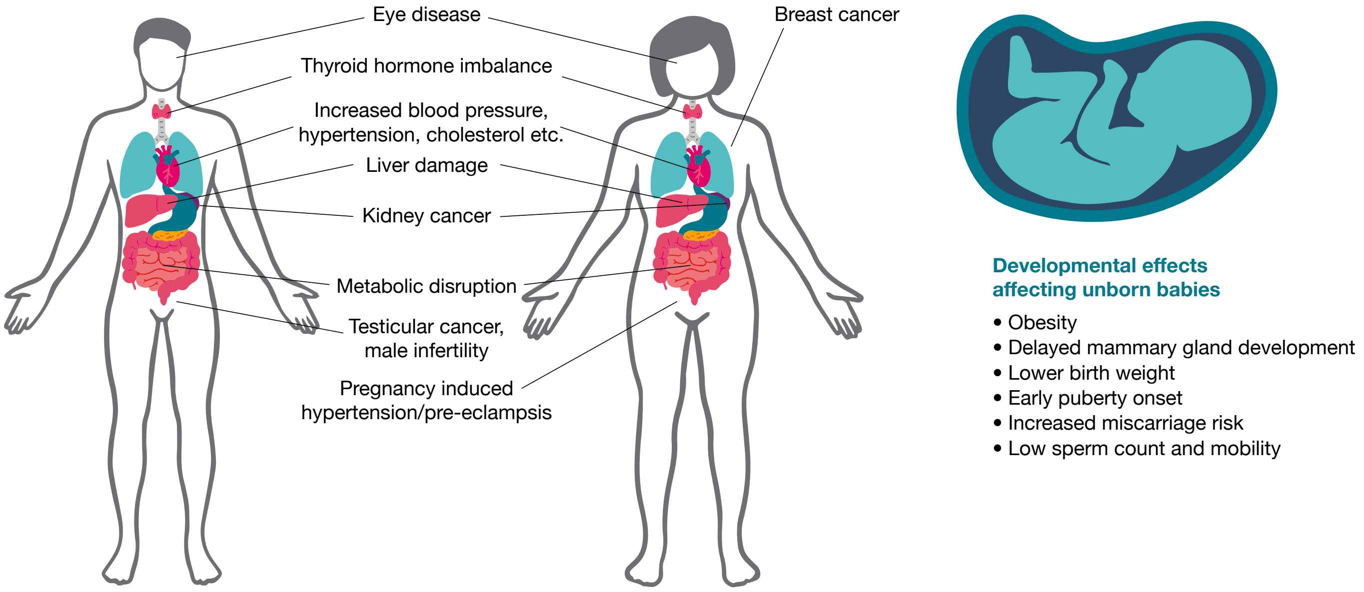
Given these potential health risks, there has been a growing interest in:

- understanding the behaviour of PFAS in the environment,
- tracking their pathways of human exposure,
- developing advanced analytical techniques for detecting PFAS at trace levels,
- exploring alternative materials to replace PFAS in industrial and consumer products,
- devising effective methods for their removal and remediation, and
- controlling their use to minimise further negative environmental and human health impacts[3-10].

The findings from these and other studies are helping to improve our understanding of these compounds, and inform the development of regulations.

## FIGURE 2

## Diseases and disorders associated with exposure to PFAS



**Developmental effects affecting unborn babies**

- Obesity
- Delayed mammary gland development
- Lower birth weight
- Early puberty onset
- Increased miscarriage risk
- Low sperm count and mobility

FIGURE 2: Adapted from Chukwuebuka *et al* 2024

# Global regulation

In response to the emerging concerns about PFAS, regulatory agencies worldwide have begun to establish guidelines and regulations to limit PFAS emissions and reduce exposure[11-13]. However, the regulatory landscape is vast, and subject to regional nuances which can be complicated to navigate. Back in 2019, the International Standards Organisation (ISO) released standard ISO 21675:2019 in an effort to standardise the approach to assessing PFAS in water by solid particulate material (SPM) using Liquid Chromatography-Tandem Mass Spectrometry (LC MS/MS)[14]. In the US, agencies such as ASTM International (ASTM), AOAC International (AOAC), the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Department of Agriculture (USDA) and the Environmental Protection Agency (US EPA) have all developed test methods and guidelines for monitoring PFAS in several food, environmental and biological matrices[15-18]. In 2021, the US EPA outlined its strategic roadmap to safeguard the environment and public health, as well as to hold polluters accountable[19], and has released a variety of methods – such as 533, 537, 537.1, UCMR5, 8237, 1633, OTM-45, and OTM-50 – to support targeted analysis (TA) of PFAS[20-27].

> ***The regulatory landscape is vast, and subject to regional nuances which can be complicated to navigate.***

Most recently Maximum Contaminant Levels (MCLs) were finalised and enforced for multiple PFAS compounds in drinking water[28], and efforts are now being made to also understand the impact of compounds not currently regulated through Non-Targeted Analysis (NTA)[18]. NTA looks to quantify PFAS present in samples by two different means: Total Oxidisable Precursor (TOP) and Extractable Organic Fluorine (EOF). With TOP, a sample is typically treated with sodium bisulphate and heat to break down long chain PFAS into known perfluorosulfonated compounds that are on the targeted list, giving an indication of all the non-targeted PFAS present in the sample. For EOF, samples are run through a carbon cartridge to trap organofluorine compounds, combustion is then performed to convert this to Hydrogen Fluoride (HF), and then Ion Chromatography (IC) is performed to give an indication of total PFAS load in a sample. Then, the ratio of targeted to non-targeted PFAS is measured to understand the full amount of PFAS present in the sample[29-33]. The US EPA is looking to establish NTA methods for the determination of PFAS, and currently EPA Method 1621 outlines how to facilitate the aggregate concentration of organofluorines in wastewater where PFAS are the primary sources of organofluorines present.

In Europe, several PFAS compounds listed under the Stockholm Convention on Persistent Organic Pollutants (POPs) have come under scrutiny, including Perfluorooctanoic Acid (PFOA), Perfluorooctane Sulfonic Acid (PFOS), Perfluorooctane Sulfonyl Fluoride (PFOSF), Perfluorohexane Sulfonic Acid (PFHxS), associated salts and other related compounds[34]. There are also PFAS restrictions under the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals regulation (REACH), which include C9-C14 linear and/or branched Perfluorocarboxylic Acids (C9-C14 PFCAs), their salts and C9-C14 PFCA-related substances, and which also address PFAS candidates registered as substances of very high concern (SVHC)[35-36]. The European Chemicals Agency (ECHA) is meanwhile engaged in educating the public and manufacturers on the dangers these chemicals pose. In 2020, a series of restrictions were implemented, including the introduction of a limit for combined exposure to PFOA, PFOS and two other PFAS compounds – Perfluorononanoic Acid (PFNA) and PFHxS – in food[37]. Since then, testing requirements have evolved further with the EU Drinking Water Directive (which specifies a maximum limit of 0.5 µg/l for all 20 PFAS listed), and the EU Groundwater Directive (which sets testing requirements for 24 PFAS compounds)[38-39]. Most recent activity includes Germany, Denmark, Netherlands, Norway and Sweden seeking action to restrict the manufacture, placement on the market and use of PFAS, due to their persistence in the environment, the dangers they pose, and the difficulty of removing them from the environment once present [40]. Data and information gathering is currently ongoing here for the multiple industries that this proposed restriction would impact – ranging from food and pharmaceuticals to textiles, as well as the petroleum and mining industries[41].

Following Brexit, the UK REACH program was established in 2021 to safeguard human health and the environment within the UK, and to set out guidelines for the Health and Safety Executive (HSE), along with the Environment Agency, to deliver regulatory activities. A major focus for these groups is the restriction of PFAS, and the monitoring of candidate PFAS substances of very high concern[42]. In addition, the UK Drinking Water Inspectorate (DWI) has provided guidance to water companies in England and Wales for monitoring PFAS in drinking water. These guidelines outline a tiered approach for 48 PFAS compounds, with an upper limit of 0.1 micrograms per litre of water, the equivalent of 0.1 parts per billion (ppb)[43].

In other areas of the world, some preliminary restrictions have been put in place to minimise further PFAS contamination, but work is still underway to understand the full extent to which the contamination is present so that the appropriate actions can be taken. The New Zealand Environmental Protection Authority (EPA NZ) has set restrictions on firefighting foams, imposed a complete ban on PFAS in cosmetics, and has also been gathering data on the prevalence of PFAS in groundwater[44-46]. Meanwhile, Australia's PFAS Taskforce has been established in order to focus on human health, contamination of the environment and consumer goods[47], with further work in development in collaboration with the EPA NZ for a National Environmental Management Plan on PFAS[48]. In 2021, Health Canada also declared its intention to address PFAS in order to protect Canadian citizens and the environment. This led to the prohibition through regulation of PFOS, PFOA, and long-chain perfluorocarboxylic acids (LC-PFCAs), together with their associated salts and precursors. Regulators have also signalled their intention to initiate data gathering to help inform future actions[49].

Some of the highest levels of PFAS contamination have already been found in surface water in Asia, and further contamination seems inevitable as their use continues to rise[50, 51]. At present, most PFAS are considered uncontrolled, although some regions are adopting Stockholm Convention rules on PFOS, and implementing their own frameworks in order to monitor PFAS contamination to learn more[52]. PFOS and PFOA first came under restriction in 2011 in China, which subsequently announced its intent to ban the manufacture, import and export of PFOS, its salts, and PFOSF in 2014[53]. Most recently, China has set limits of 40 ng/L and 80 ng/L for PFOS and PFOA in drinking water under GB5749-2022. In Japan, PFOA, Perfluorohexanoic Acid (PFHxA), PFHxS, and PFOS are partially regulated with a 50 ng/l limit set for PFOS and PFOA combined. Meanwhile, Thailand has banned the manufacture, import and use of PFOA and its salts, and in South Korea, national guidelines have been put in place with regard to Food Contact Materials[52].

# Problems and mitigation strategies in PFAS testing

Testing is required to prove adherence to global regulations, and for ongoing monitoring of PFAS in the environment. However, it is not without its challenges. There are many factors that can complicate and impact the reliability of analyses performed – including matrix effects, co-elution of similar compounds, concentration, ionisability of compounds, peak resolution, adsorption, identifying new emerging PFAS compounds, and more[54-55].

> ***There are many factors that can complicate and impact the reliability of analyses performed – including matrix effects, co-elution of similar compounds, concentration, ionisability of compounds, peak resolution, adsorption, identifying new emerging PFAS compounds, and more[54-55].***

Many PFAS can undergo environmental and biological transformations, leading to the formation of new compounds that need to be identified and quantified. The limited availability of analytical standards for these emerging PFAS complicates their identification and quantification, necessitating the development of non-targeted analytical approaches that need to be run in addition to the targeted analyses performed for regulated compounds[55-56]. High Resolution Mass Spectrometry (HRMS) has shown great promise in NTA, enabling the detection of unknown PFAS by their accurate mass and characteristic fragmentation patterns[55, 57-59].

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# Matrix effects

The difficulty of assessing known and unknown PFAS is further exacerbated by matrix effects. Contamination is widespread due to PFAS' extensive use and persistent nature, and they are therefore found commonly in a variety of matrices – including water, soil, sediment, air, biota, food, consumer products, and human tissues[60-62]. Components within these matrices, such as organic matter or coextracted substances, then interact with PFAS, complicating identification and quantification of the PFAS present within a sample, and therefore compromising the reliability of results. These matrix effects are then further exacerbated by the diversity in chemical structures, varying physicochemical properties, and ultra-trace concentrations that PFAS are often found at, and required to be tested for in regulations[60]. Solvents used during sample preparation and in reference materials used to calibrate instruments can also impact analytical performance by interacting with PFAS compounds[61].

Fortunately, there are many strategies to mitigate such effects, including matrix-matched calibration or sample preparation techniques such as Solid Phase Extraction (SPE)[61-62]. However, the use of stable isotopically labelled internal standards coupled with advanced instrumentation, such as High Resolution Accurate Mass Spectrometry (HRAMS), demonstrate the most promise in facilitating the correction of variations in sample recovery and instrument response, as well as the differentiation of PFAS signals from matrix interference[60, 61, 63-67].

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# Adsorption

It is well known that PFAS compounds adsorb onto different surfaces – a factor that is increasingly being studied as a potential means of water remediation[68-69], with some work also examining the impact of adsorption on analytical results[70-73]. PFAS adsorb to surfaces to varying degrees depending on the matrix, type of surface, and PFAS chain length. This can introduce a high degree of bias in sample results – especially when PFAS compounds are being measured at very low concentrations in the environment. In EPA Method 1633, this issue is addressed by having to matrix match the working standards with the final sample preparation matrix, and to use the same type of sample vial. This minimises bias in the data, since the working standard behaves similarly to the final sample[73].

Little work has been done on exploring the surface adsorption effects of the reference material to see if bias is being introduced there as well. For most other types of analytes, the reference materials are typically at relatively high concentration – so even if there is some surface adsorption, it is a very small percentage. With PFAS, some reference materials are manufactured at part per billion concentrations in order to minimise the number of intermediate dilutions needed to calibrate in the part per trillion concentration range required by analytical methods[20-27, 34, 38, 39, 43]. Therefore, in order to ensure that analyses are reliable, it is crucial to understand if there could be enough surface adsorption to bias results.

Despite all these challenges, laboratories are still required to identify and confirm the presence of PFAS compounds quickly – particularly if PFAS levels are found to exceed MCLs set so that appropriate measures can be taken to safeguard human and environmental health. There are many published studies which focus on instrumentation and method development as a means of improving analytical accuracy and efficiency[74-79], but few factoring in the role that reference material design plays in allowing laboratories to be as efficient as possible. Not all analytes respond the same – and therefore having all analytes at the same concentration in a reference material may not be the most efficient design for calibration in laboratories. To make the issue more complex, different LC/MS instruments can have significantly different Electrospray Ionisation (ESI) characteristics, which can necessitate additional calibration points to get the required number within the linear range[25].

Reference materials are essential for enhancing analytical accuracy by calibrating instruments, developing and validating methods, spiking samples, and serving as internal standards for quality control and assurance[60, 62, 80-83]. To ensure their reliability, it is crucial to address factors that might affect the integrity of these standards, such as matrix effects or adsorption. Additionally, understanding the response factors of various instruments and column performance can help optimise the design of reference materials for efficient use across different instruments, without compromising quality. With the US EPA setting legally enforceable MCLs for several PFAS compounds in drinking water at low ng/L concentrations[27], it is important to understand how different PFAS analytes in reference materials interact with solvents and surfaces, as well as response factors, to ensure that results are accurate and regulatory limits are met effectively.

This study focuses on two key aspects: stability and efficiency. Firstly, we have explored the parameters that could impact data integrity with the analytes in EPA Method 1633, UCMR5 and EU Drinking Water Directive regulatory standards. Secondly, response factors and concentration ratios have been evaluated in order to design the most efficient calibration solution.

# Experimental design

***Stability:***

In a previous pilot study[84], four variables were examined to see if they had an impact on the stability of a long chain perfluorocarboxylic acid reference material:

- concentration (1000 µg/mL and 100 ng/mL)
- solvent (methanol:water 96:4, isopropanol:water 96:4 and acetonitrile:water 96:4)
- modifier (with and without sodium hydroxide)
- container surface (untreated and silanised).

Analyses were performed using the Thermo Scientific Vanquish HPLC with Orbitrap Exploris 120 mass spectrometer, coupled with Advanced Material Technology's HALO 90 Å PFAS 2.7µm x 2.1mm x 100mm LC column. The gradient parameters are outlined in Table 1, and stability conditions in Table 2.

## TABLE 1 Gradient Conditions

| Time (minutes) | Mobile Phase* | |
|---|---|---|
| | %A | %B |
| 0.0 | 95 | 5 |
| 5.0 | 55 | 45 |
| 24.0 | 5 | 95 |
| 27.0 | 5 | 95 |
| 27.3 | 95 | 5 |

**Mobile Phase A = water w/5 mM Ammonium acetate; Mobile Phase B = Methanol*

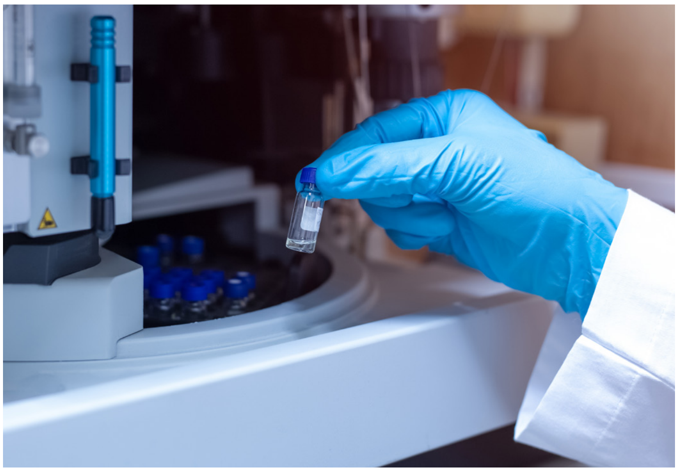
## TABLE 2 Stability Conditions

| Solvent / Vessel | Normal Autosampler Vial | Silanised Autosampler Vial |
|---|---|---|
| Methanol:Water 96:4 w/ NaOH | ✓ | ✓ |
| Methanol:Water 96:4 w/o NaOH | ✓ | ✓ |
| Isopropanol:Water 96:4 w/o NaOH | ✓ | ✓ |
| Acetonitrile:Water 96:4 w/o NaOH | ✓ | ✓ |

To expand on the previous study, a solution of all 40 of the EPA Method 1633 analytes was sealed at 10µg/mL in Methanol:Water 96:4 w/NaOH. On day one, an ampoule of the 1633 solution was diluted to 100 ng/mL into each of the eight combinations (Table 2). The original 100 ng/mL samples were analysed for 11 weeks. For the results shown at week 11, a new 10 µg/mL ampoule was pulled from storage, diluted to 100 ng/mL in an untreated vial and analysed as the reference point. The results are presented in Table 3.

***Response factors:***

Another important feature in the design of a reference material is optimisation of the concentration ratios to provide the user with the most efficient solution for calibration and quality control. This allows the laboratory to reduce the time spent on calibration and validation, which provides more time for billable samples. Figure 3 shows a chromatogram of the 40 EPA Method 1633 analytes all at the same concentration. The large difference in analyte response is clear.



In LC/ESI-MS analysis, three variables that affect an analyte's overall response are:

- the analyte's native ability for ionisation. This is primarily a characteristic of the functional groups contained in the analyte.
- the design of the source: individual instrument manufacturers optimise their ESI source performance differently, which impacts the ionisation efficiency of different analytes.
- source optimisation based on method conditions.

Table 4 shows the response or concentration ratio of the various analytes in EPA Method 1633, for four different instrument manufacturers.

# Results

## TABLE 3

## Stability Results for EPA Method 1633 analytes

| EPA 1633 Analytes % Recovery at Week 11 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | M w/ OH | | M w/o OH | | I w/o OH | | A w/o OH | |
| **Abbreviation** | **Unsilanised** | **Silanised** | **Unsilanised** | **Silanised** | **Unsilanised** | **Silanised** | **Unsilanised** | **Silanised** |
| **PFPeA** | 109% | 113% | 102% | 100% | 101% | 99% | 98% | 92% |
| **PFBA** | 108% | 112% | 99% | 97% | 98% | 97% | 96% | 92% |
| **PFOS** | 84% | 86% | 74% | 77% | 79% | 78% | 78% | 73% |
| **PFOA** | 113% | 119% | 107% | 107% | 109% | 107% | 106% | 102% |
| **PFBS** | 108% | 113% | 101% | 104% | 100% | 99% | 97% | 93% |
| **PFDA** | 104% | 109% | 99% | 98% | 98% | 98% | 98% | 91% |
| **PFHpA** | 107% | 112% | 102% | 100% | 101% | 99% | 97% | 93% |
| **PFHxA** | 108% | 112% | 101% | 99% | 101% | 98% | 97% | 91% |
| **PFNA** | 103% | 107% | 97% | 98% | 99% | 97% | 97% | 91% |
| **PFTeDA** | 106% | 108% | 104% | 103% | 93% | 94% | 93% | 88% |
| **PFDoA** | 107% | 110% | 100% | 98% | 98% | 96% | 94% | 88% |
| **PFTrDA** | 108% | 109% | 101% | 97% | 95% | 95% | 94% | 88% |
| **PFUnDA** | 105% | 109% | 98% | 96% | 96% | 97% | 95% | 90% |
| **NEtFSOA** | 105% | 107% | 96% | 95% | 93% | 94% | 90% | 82% |
| **PFOSA** | 104% | 108% | 97% | 94% | 97% | 96% | 95% | 88% |
| **6:2FTS** | 105% | 108% | 97% | 96% | 99% | 97% | 97% | 90% |
| **NMeFOSE** | 102% | 104% | 91% | 90% | 80% | 91% | 88% | 85% |
| **NEtFOSE** | 104% | 102% | 93% | 90% | 65% | 65% | 89% | 85% |
| **NMeFSOA** | 102% | 106% | 96% | 93% | 95% | 96% | 90% | 77% |
| **8:2FTS** | 106% | 109% | 99% | 97% | 99% | 98% | 98% | 91% |
| **PFDS** | 105% | 109% | 98% | 97% | 99% | 99% | 96% | 91% |
| **NMeFSOAA** | 104% | 108% | 103% | 102% | 98% | 95% | 93% | 88% |
| **NEtFSOAA** | 103% | 107% | 103% | 102% | 97% | 95% | 92% | 87% |
| **7:3FTCA** | 103% | 107% | 96% | 97% | 100% | 97% | 94% | 88% |
| **HFPO-DA** | 109% | 111% | 100% | 99% | 100% | 98% | 33% | 30% |
| **PFHpS** | 105% | 108% | 98% | 97% | 99% | 97% | 98% | 93% |
| **PFNS** | 105% | 108% | 97% | 96% | 98% | 98% | 98% | 91% |
| **4:2FTS** | 108% | 113% | 103% | 99% | 101% | 98% | 98% | 92% |
| **PFHxS** | 108% | 110% | 100% | 98% | 99% | 96% | 96% | 90% |
| **NFDHA** | 109% | 112% | 99% | 99% | 100% | 97% | 96% | 91% |
| **ADONA** | 107% | 113% | 101% | 101% | 100% | 97% | 98% | 91% |
| **11ClPF3OUdS** | 105% | 109% | 98% | 96% | 98% | 97% | 97% | 90% |
| **9ClPF3ONS** | 104% | 108% | 98% | 96% | 98% | 97% | 97% | 92% |
| **PFEESA** | 108% | 112% | 100% | 99% | 99% | 97% | 96% | 91% |
| **PFMPA** | 108% | 109% | 99% | 99% | 100% | 98% | 95% | 91% |
| **PFMBA** | 108% | 112% | 102% | 100% | 101% | 98% | 97% | 93% |
| **PFPeS** | 109% | 113% | 103% | 100% | 102% | 99% | 98% | 94% |
| **3:3FTCA** | 109% | 112% | 101% | 97% | 102% | 98% | 98% | 92% |
| **3:5FTCA** | 107% | 114% | 102% | 100% | 100% | 97% | 99% | 91% |
| **PFDoS** | 104% | 108% | 98% | 95% | 96% | 97% | 95% | 89% |

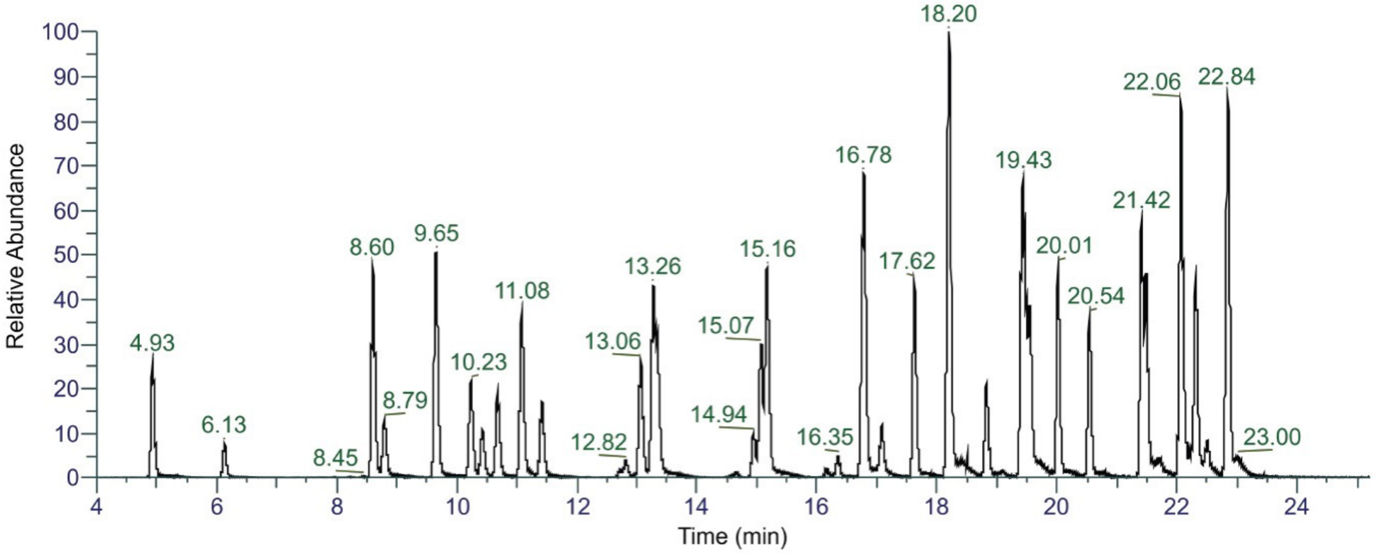
*M w/ OH – Methanol:Water 96:4 with 4 mmol NaOH*
*M w/o OH – Methanol:Water 96:4 without NaOH*
*I w/o OH – Isopropanol:Water 96:4 without NaOH*
*A w/o OH – Acetonitrile:Water 96:4 without NaOH*

**TABLE 4**

**Relative Response/Concentration Ratios for EPA Method 1633 analytes on instruments from four different manufacturers**

| | Relative Response/Concentration Ratio | | | |
|---|---|---|---|---|
| Abbreviation | Instrument Manufacturer 1 | Instrument Manufacturer 2 | Instrument Manufacturer 3 | Instrument Manufacturer 4 |
| PFPeA | 6 | 2 | 2 | 2 |
| PFBA | 5 | 4 | 3 | 4 |
| PFOS | 3 | 11 | 1 | 1 |
| PFOA | 3 | 1 | 2 | 1 |
| PFBS | 3 | 9 | 1 | 1 |
| PFDA | 4 | 2 | 3 | 1 |
| PFHpA | 3 | 2 | 2 | 1 |
| PFHxA | 4 | 1 | 2 | 1 |
| PFNA | 2 | 2 | 3 | 1 |
| PFTeDA | 4 | 1 | 3 | 1 |
| PFDoA | 3 | 1 | 3 | 1 |
| PFTrDA | 4 | 1 | 3 | 1 |
| PFUnDA | 4 | 1 | 3 | 1 |
| NEtFSOA | 4 | 9 | 1 | 1 |
| PFOSA | 2 | 5 | 2 | 1 |
| 6:2FTS | 12 | 11 | 10 | 4 |
| NMeFOSE | 3 | 10 | 4 | 10 |
| NEtFOSE | 3 | 9 | 6 | 10 |
| NMeFSOA | 5 | 14 | 1 | 1 |
| 8:2FTS | 15 | 10 | 10 | 4 |
| PFDS | 3 | 11 | 2 | 1 |
| NMeFSOAA | 7 | 7 | 6 | 1 |
| NEtFSOAA | 8 | 2 | 7 | 1 |
| 7:3FTCA | 34 | 69 | 8 | 10 |
| HFPO-DA | 4 | 3 | 3 | 4 |
| PFHpS | 3 | 10 | 2 | 1 |
| PFNS | 3 | 13 | 2 | 1 |
| 4:2FTS | 16 | 10 | 8 | 4 |
| PFHxS | 3 | 19 | 1 | 1 |
| NFDHA | 9 | 7 | 2 | 2 |
| ADONA | 2 | 1 | 2 | 4 |
| 11ClPF3OUdS | 3 | 2 | 2 | 4 |
| 9ClPF3ONS | 2 | 2 | 2 | 4 |
| PFEESA | 1 | 2 | 1 | 2 |
| PFMPA | 13 | 2 | 4 | 2 |
| PFMBA | 4 | 3 | 4 | 2 |
| PFPeS | 3 | 9 | 1 | 1 |
| 3:3FTCA | 71 | 7 | 26 | 5 |
| 3:5FTCA | 16 | 9 | 13 | 10 |
| PFDoS | 4 | 15 | 1 | 1 |

**FIGURE 3** Chromatogram showing EPA Method 1633 PFAS Analytes on Advanced Material Technology's HALO 90 Å PFAS 2.7µm x 2.1mm x 100mm LC column



## Discussion

***Stability:***

In a previous pilot study[84], the effect of stability on a single analyte solution of perfluorotridecanoic acid was evaluated and it was found that, for the 1000 µg/mL solution, the modifier appears to have the greatest impact on stability. All variations with NaOH demonstrated good recovery over the five weeks at this concentration. For the 100 ng/mL solution, all solutions showed a trend of decreasing recovery, which could indicate that perfluorotridecanoic acid is adsorbing on the wall of the vial, with potential to bias the results of a sample high. This could have significant consequences on how intermediate working solutions are prepared and stored when diluting from the higher concentration reference material. An approximate 20% decrease was observed across the various conditions. This could indicate that approximately 20 ng of the perfluorotridecanoic acid adsorbed onto the surface of the vial regardless of solvent, modifier, or vial surface treatment.

This study focused on the impact of analyte stability when multiple PFAS compounds are combined to form one mixture (with the data presented in Table 3). For the solution with all 40 of the EPA 1633 analytes at 100 ng/mL, good recovery was observed on both the silanised and unsilanised vials in all solvents used. No noticeable loss of the long chain compounds was observed. If the surface adsorption is related to a discrete surface attribute such that approximately 20 ng of material is absorbed, then for larger component mixtures with a higher mass loading, the loss would be spread out over many compounds and not be significant for any single component.

***Response factors:***

Table 4 shows the response factors for the 40 analytes in EPA Method 1633. The lower the number, the higher the response for that analyte. An analyte with a response ratio of 10 would need 10 times the concentration to give the same response. Also, the ratios are only compared within the instrument, not between. The data do not make any indication as to specific instrument sensitivity.

There are nine different types of functional groups represented in that set of analytes; Perfluoroalkyl Carboxylic Acids (PFCAs), Perfluoroalkyl Sulfonic Acids (PFSAs), Fluorotelomer Sulfonic Acids (FTSAs), Perfluorooctane Sulfonamides (PFOSAs), Perfluorooctane Sulfonoacetic Acids (FPSAAs), Perfluorooctane Sulfonamide Ethanols (PFOSEs), Per- and Polyfluoroether Carboxylic Acids (PFECAs), Per- and Polyfluoroether Sulfonic Acids (PFESA) and Fluorotelomer Carboxylic Acids (FTCAs). In looking at the data set as a whole, it is easy to see the influence of the functional group. For the most part, the PFCAs and PFSAs show the best response ratio (lowest numbers) across all instruments, and the FTCAs show higher response ratios. The difference in the response ratios across the instruments indicates a combination of source design and method optimisation. These data illustrate that a single solution will not provide the most efficient analytical efficiency for all labs. This is where being able to optimise the concentration for various instruments can improve a laboratory's efficiency and sample throughput.

## Conclusion

With the promulgation of legally enforceable MCLs by the US EPA, it is important to understand the factors that can cause bias in reference materials used for PFAS analysis, so that results are as accurate as possible. Our stability study results indicate that, while higher concentration reference material solutions purchased from an accredited supplier are well studied, making lower concentration intermediate working solutions in the laboratory may result in stability issues that could introduce bias if they are kept for too long. Laboratories making intermediate working solutions should validate their stability to determine the appropriate hold times.

We have also demonstrated that, to optimise a laboratory's calibration and verification efficiency, it must be borne in mind that the best concentration ratio is different for individual instrument manufacturers. Moreover, having this data available allows reference material manufacturers to design solutions that will maximise the number of billable samples that a laboratory can process.

## Acknowledgements

The authors wish to express their gratitude to HALO Columns for their generous contribution of the HALO 90 Å PFAS 2.7µm x 2.1mm x 100mm column, which significantly supported our analyses. The provision of this high-quality LC column played a crucial role in enabling the successful completion of our research. We are thankful for their support and partnership in advancing scientific inquiry into PFAS analysis.

## The need for high quality reference standards and proficiency testing

To help ensure the safety of our environment, and to align with rapidly evolving PFAS regulations, laboratories must be able to constantly amend their analytical procedures. LGC Standards' portfolio of **~500 high-quality PFAS products**, **including >70 SILS**, is designed precisely to help you adapt to such regulatory and scientific developments. Our portfolio offers **130+ Dr Ehrenstorfer PFAS reference materials certificated to ISO 17034 or ISO 17025** – including the groundbreaking **PFASiMix kit**, which improves your laboratory's efficiency with its mixture of 27 PFAS analytes, designed for maximum stability. To further support your PFAS analysis, we provide ready-to-use mixtures created specifically to address key regulations, such as the **EU Drinking Water Directive**, **EU Groundwater Directive**, **UK DWI**, **UCMR5 and EPA Methods 533 and 537.1**, as well as **EPA Method 1633**. In tandem with our reference materials offering, AXIO Proficiency Testing provides three schemes designed to help you assess and improve **your laboratory's analysis of PFAS in soil, potable water, surface water and groundwater**

Meanwhile, **our extensive TRC range of PFAS analytical standards and research chemicals** facilitate wide-ranging analysis, including research into their potential harmful effects. Lastly, should you require **a custom molecule**, we have more than 40 years' experience working through some of the most complex synthetic pathways to deliver you high quality research chemicals.

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