Guidance Document on Analytical Parameters for the Determination of Per- and Polyfluoroalkyl Substances (PFAS) in Food and Feed

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Authorship

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ANNEX: Example of Methodology for the Determination of Per- and Polyfluoroalkyl substances (PFAS) in Food and Feed

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1. GENERAL

1.1. Field of application

This document on analytical parameters for the determination of selected per- and polyfluoroalkyl substances (PFAS) in food and feed was developed within the network of the European Union Reference Laboratory (EURL) for halogenated POPs in Feed and Food, the respective National Reference Laboratories (NRLs) of EU member states and international experts in the field of persistent organic pollutants (POPs) analysis. The guidance in this document is intended for laboratories involved in the official control of contaminants in food and feed and focuses on the determination of these substances in the laboratory. It is intended as general guidance for laboratories and particularly for those that do not have an existing method. It provides useful key elements in a set of analytical parameters contributing to further harmonization in the field of PFAS analysis in food and feed as part of the EURL's official mandate and scope of work.

1.2. Abbreviations

Abbreviation	Definition
br-PFOS	Branched perfluorooctane sulfonic acid
CWG	Core Working Group
EC	European Commission
ECF	Electrochemical fluorination process
EFSA	European Food Safety Authority
EURL	European Union Reference Laboratory
HDPE	High density polyethylene
HRMS	High resolution mass spectrometry
IARC	International Agency for Research on Cancer
ILIS	Isotope-labelled internal standard
IS	Internal standard
ISO	International Standardisation Organisation
IUPAC	International Union of Pure and Applied Chemistry
LDPE	Low density polyethylene
L-PFOS	Linear perfluorooctane sulfonic acid
LOD	Limit of detection
LOQ	Limit of quantification
LRMS	Low resolution mass spectrometry
ME	Matrix effect
ML	Maximum level
MRM	Multiple reaction monitoring
NRL	National Reference Laboratory
OFL	Official Laboratory
PEEK	Polyether ether ketone

PFAS	Per- and polyfluoroalkyl substances
PFCA	Perfluoroalkyl carboxylic acids
PFHxA	Perfluorohexanoic acid
PFHxS	Perfluorohexane sulfonic acid
PFNA	Perfluorononaoic acid
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctane sulfonic acid
PFSA	Perfluoroalkyl sulfonic acids
POPs	Persistent organic pollutants
PTFE	Polytetrafluoroethylene
PVDF	Polyvinylidene fluoride
QC	Quality control
RS	Recovery standard
RT	Retention time
SANTE	Directorate-General for Health and Food Safety, European Commission
S/N	Signal to noise ratio
SRM	Selected reaction monitoring
TDCA	Taurodeoxycholic acid
(U)HPLC	(Ultra) High performance liquid chromatography
w.w.	Wet weight

1.3. Introduction

NOTE: All recommendations given in this document should be considered as "Guidance for reliable analyses".

Information on sampling is not given in this document. The reader is referred to the Commission Implementing Regulation laying down methods of sampling and analysis for the control of perfluoroalkyl substances in certain foodstuffs which is currently in preparation [1]. In addition, Commission Directive (EC) No 2002/63 [2] for pesticide residues in and on products of plant and animal origin and Commission Regulations (EC) No 333/2007 [3] for lead, cadmium, mercury, inorganic tin, 3-MCPD and benzo(a)pyrene in foodstuffs, and (EC) No 2017/644 [4] and (EC) No 152/2009 [5] for PCDD/Fs and PCBs in feed/food can be used as the directions given therein are expected to be similar for PFAS. Additionally, all procedures used for sampling should avoid the use of equipment containing polytetrafluoroethylene (PTFE) or other fluoropolymers in order to minimize the risk of contamination.

1.4. Background

Per- and polyfluoroalkyl substances (PFAS) are a group of man-made organic compounds consisting of a hydrophobic fluorinated alkyl chain and a hydrophilic functional group. This class of compounds includes a large number of substances, namely all that contain the perfluoroalkyl moiety (C_nF_{2n+1}−) [6]. In polyfluorinated substances, one or more CF_2 moieties are replaced by the corresponding number of CH_2 groups.

PFAS have been used since the 1950s. Due to the stability of the C-F bond, many PFAS are resistant to biological, chemical and physical transformation. Some PFAS – often called 'precursors' - may undergo biological, chemical and physical transformation to a stable PFAS. PFAS are widely used as monomeric or polymeric substances in direct or indirect uses and subsequently have been found in the environment (water, air, soil, sediments, and biota) but also in food, wildlife and humans.

Two of the most frequently used PFAS have been listed in the annexes of the Stockholm Convention on Persistent Organic Pollutants (POPs) [7] – perfluorooctane sulfonic acid (PFOS) in 2009 and perfluorooctanoic acid (PFOA) in 2019 – with the aim of elimination of production and uses. Perfluorohexane sulfonic acid (PFHxS) is considered for listing in the Stockholm Convention. In the most recent scientific opinion by the European Food Safety Authority (EFSA), four PFAS have been assessed, namely, PFOS, PFOA, PFHxS and perfluorononaoic acid (PFNA) [8].

The International Agency for Research on Cancer (IARC) has not classified PFOS as to its carcinogenicity to humans (status: November 2021). PFOA was classified by IARC as possibly carcinogenic to humans (Group 2B) [9]. In the EU, PFOA has a harmonised classification as a suspected carcinogen and presumed human reproductive toxicant [10].

PFOS and related substances have been produced by the electrochemical fluorination process (ECF) mainly; and thus, usually occur as a mixture of linear (L-PFOS) and branched (br-PFOS) isomers. PFOA has been produced by either the ECF process to generate linear and branched isomers or the telomerisation process from pentafluoroethyl iodide (in the case of PFOA), which results in linear products. For PFHxS, there are currently no known direct uses. PFNA is used as a surfactant in the production of the fluoropolymer polyvinylidene fluoride (PVDF). In addition, PFNA is a by-product of the synthesis of PFOA and short-chain perfluoroalkyl carboxylic acids (PFCA) such as perfluorohexanoic acid (PFHxA).

In 2018, the European Commission, Directorate-General for Health and Food Safety (SANTE), asked the European Reference Laboratory (EURL) for halogenated POPs in Feed and Food to develop the analytical parameters and conditions to reach low limits of quantification in the routine analysis of food laboratories to protect human health from adverse effects of PFAS from food consumption. Subsequently, under the coordination of the EURL, a core working group on perfluoroalkyl substances ("CWG PFAS" for short) was established.

1.5. Scope

The recommendations contained within this guidance document apply to PFAS, in particular to PFCA and perfluoroalkyl sulfonic acids (PFSA), FOSA, and selected substitutes in food and feed matrices. The recommendations may also be applied to other PFAS.

The recommendations are designed to allow the monitoring of PFAS concentrations in food and feed as part of studies on:

- the establishment of current maximum levels of these contaminants,
- the establishment or maintenance of databases that may be used to recommend action levels and maximum levels,
- the exposure assessment of populations through dietary intake and assessment of risk,
- enforcement (once limits are established).

Other purposes could include studies on time trends and patterns in order to identify the source(s) of possible contamination particularly during incidents involving such contamination.

1.6. Analytes of interest

The requirements given in this chapter will apply to the following PFAS (**Table 1**) in food and feed samples. PFCA und PFSA share similar physico-chemical properties, can be captured by one analytical method, and have been found to be of most concern in food and feed [8]. In addition, further emerging perfluoroalkyl substances may be considered, such as FOSA and PFAS substitutes (**Table 1**). The requirements may also be applicable to the analysis of other PFAS (e.g. PFCA/PFSA precursors) and matrices (such as human tissues, environmental samples and drinking water), but these are beyond the scope of this document.

Table 1: Analytes of interest

Acronym	Description	Remark
Perfluoroalkyl carboxylic acids (PFCA)		
PFBA	Perfluorobutanoic acid	
PFPeA	Perfluoropentanoic acid	
PFHxA	Perfluorohexanoic acid	
PFHpA	Perfluoroheptanoic acid	
PFOA	**Perfluorooctanoic acid**	**Main compound [8]**
PFNA	**Perfluorononanoic acid**	**Main compound [8]**
PFDA	Perfluorodecanoic acid	
PFUnDA	Perfluoroundecanoic acid	
PFDoDA	Perfluorododecanoic acid	
PFTrDA	Perfluorotridecanoic acid	
PFTeDA	Perfluorotetradecanoic acid	

Table 1 (continued)

Acronym	Description	Remark
Perfluoroalkyl sulfonic acids (PFSA)		
PFBS	Perfluorobutane sulfonic acid	
PFPeS	Perfluoropentanesulfonic acid	
PFHxS	**Perfluorohexane sulfonic acid**	**Main compound [8]**
PFHpS	Perfluoroheptane sulfonic acid	
PFOS	**Perfluorooctane sulfonic acid**	**Main compound [8]** (reported as "total PFOS" based on isomer quantification using linear PFOS)
PFNS	Perfluorononane sulfonic acid	
PFDS	Perfluorodecane sulfonic acid	
PFUnDS	Perfluroundecane sulfonic acid	
PFDoDS	Perfluorododecane sulfonic acid	
PFTrDS	Perfluorotridecane sulfonic acid	
Perfluoroalkane sulfonamides		
FOSA	Perfluorooctane sulfonamide	
PFAS substitutes		
DONA	2,2,3-Trifluoro-3-[1,1,2,2,3,3-hexafluor-3-(trifluoromethoxy)propoxy]-propionic acid	
GenX	2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)-propanoic acid	
F-53B	Potassium 9-chlorohexadecafluoro-3-oxanonane-1-sulfonate	
	Potassium 11-chloroeicosafluoro-3-oxaundecane-1-sulfonate (minor component of F-53B)	
Capstone A	1-Propanaminium, N,N-dimethyl-N-oxide-3-[[(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)sulfonyl]amino]-, hydroxide	
Capstone B	1-Propanaminium, N-(carboxymethyl)-N,N-dimethyl-3-[[(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)sulfonyl]amino]-, hydroxide	

1.7. Terms and definitions

For purposes of this guidance document, the following terms and definitions apply:

Accuracy: Closeness of agreement between a test result and the accepted reference value [11]. It is determined by determining trueness and precision [12].

Apparent recovery: Observed value derived from an analytical procedure by means of a calibration graph, *expressed as percentage [13]. E.g. when using isotope-labelled internal standards the recovery is corrected for extraction/clean-up losses and matrix-effects and is about 100 %.*

Batch *also referred to as 'lot'*: A quantity of material which is known or assumed to be produced under uniform conditions [14].

Bias: Difference between the estimated value of the test result and an accepted reference value [12,11].

Blanks:

- **Calibration blank***:* A calibration standard that does not contain the analyte(s) of interest at a detectable level [15].
- **Reagent blank** *also referred to as 'procedural blank':* Sample that does not contain the matrix that is brought through the entire measurement procedure and analysed in the same manner as a test sample [16].
- **Sample blank** *also referred to as 'matrix blank':* Matrix with no analyte present [15].
- **Solvent blank:** A solution which is made up from the solvent(s) contained in the solution presented to the instrument [15].

Fortified or fortification: Addition of analyte for the purpose of recovery determination [17].

Interference: A systematic error in the measure of a signal caused by the presence of concomitants in a sample [14]**.**

Interlaboratory study: The organisation, performance and evaluation of tests on the same sample by two or more laboratories in accordance with predetermined conditions to determine testing performance. According to the purpose the study can be classified as collaborative study or proficiency study [12].

Internal standard (IS): A substance not contained in the sample with physical-chemical properties as similar as possible to those of the analyte that has to be identified and which is added to each sample as well as to each calibration standard [18]. *Respective isotope-labelled internal standards are used as the basis for quantification of the analytes.*

Limit of quantification (LOQ): lowest content of the analyte which can be measured with reasonable statistical certainty [4], i.e. the lowest concentration or mass of the analyte that has been validated with acceptable accuracy by applying the complete analytical method and identification criteria [17].

Lower bound: Concept which requires using zero for the contribution of each non-quantified congener or substance to a sum parameter [4].

Matrix: The material making up the sample.

Matrix effect (ME): The combined effect of all components of the sample other than the analyte on the measurement of the quantity. If a specific component can be identified as causing an effect then this is referred to as interference [14]. *The matrix effect (ME) is typically expressed in % and can be calculated according to equation 1 below [19].*

$$ME\ (\%) = \left(\frac{\bar{A}_{[matrix]}}{\bar{A}_{[solvent]}} - 1\right) \times 100 \qquad \textbf{(Eq. 1)}$$

with:

ME = Matrix effect
A_{matrix} = peak area of the analyte fortified to a blank sample extract before injection
$A_{solvent}$ = peak area of the analyte in solvent standard at same concentration
ME < 0 Suppression of the ion signal
ME > 0 Enhancement of the ion signal

Measurement uncertainty: A parameter, associated with the results of a measurement, that characterizes the dispersion of the values that could reasonably be attributed to the measurand (the quantity being measured) [14].

Precision*:* Closeness of agreement between independent test/measurement results obtained under stipulated (predetermined) conditions. The measure of precision usually is expressed in terms of imprecision and computed as standard deviation of the test result. Less precision is determined by a larger standard deviation. [12,11]

Recovery *also referred to as 'extraction recovery', 'absolute recovery', or 'recovery factor':* Yield of a preconcentration or extraction stage of an analytical process for an analyte divided by amount of analyte in the original sample, *expressed as percentage [13].*

Recovery standard (RS) also referred to as '*syringe/injection/volumetric standard'*: a compound of known chemical purity that is not contained in the sample and is added to every sample, blank or standard at a known concentration, after sample processing and prior to instrument analysis. Recovery standards can be used for quantification of the IS.

Repeatability: Precision under repeatability conditions, i.e. conditions where independent test results are obtained with the same method on identical test items in the same laboratory by the same operator using the same equipment within short intervals of time [11,12]. *E.g. three replicates, same method and sample material, same operator and instruments, within a short interval of time (one day/sequence).*

Selectivity (qualitative): The extent to which other substances interfere with the determination of a substance according to a given procedure [14].

Trueness: Closeness of agreement between the average value obtained from a large series of test results and an accepted reference value [11,12]. Trueness is usually expressed as bias [20].

Validation: Provision of objective evidence that a given item fulfils specified requirements, where the specified requirements are adequate for an intended use [21].

Within-laboratory reproducibility *also referred to as 'intermediate precision'*: Precision obtained in the same laboratory under a set of within-laboratory conditions [12], i.e. conditions where test results are obtained with the same method, the same test sample, under some different operating conditions. *E.g. different operators, different instruments, three replicates, three concentrations across three days/sequences in a specific laboratory.*

NOTE: "Method" as used in this document can be considered synonymous with the term "procedure".

1.8. Guidance for analytical quality assurance

1.8.1. Recommendations for laboratories

Laboratories should be accredited by a recognised body operating in accordance with ISO/IEC 17011 [22] to ensure that they are applying analytical quality assurance. Methods shall be accredited following the ISO/IEC 17025 [21] standard.

Laboratories should demonstrate proficiency in the analysis of PFAS at the concentrations of interest (i.e. between the LOQ and e.g. 100 times the LOQ and/or the range of legal limits) by validation, ongoing internal quality control and continuous successful participation in inter-laboratory studies conducted by accredited bodies according to EN ISO/IEC 17043 [23], e.g. the EURL.

1.8.2. General aspects regarding sample pre-treatment and storage

The samples must be stored and transported in containers that can be demonstrated to be free from the relevant PFAS (e.g. polypropylene/polyethylene containers) while preserving the integrity of the sample.

Sample quantity used for the extraction should be sufficient to fulfil the requirements with respect to a sufficiently low working range including the concentrations at the suggested LOQs.

The specific sample preparation procedures used for the products under consideration shall follow legal documents, e.g. Commission Regulations (EC) No 152/2009 [5] and (EU) 2017/644 [4].

1.8.3. General aspects to avoid contamination / high blank levels

Measures must be taken to avoid cross-contamination at each stage of the sampling and analysis procedure in the laboratory.

In the course of sampling and the preparation of the samples, precautions shall be taken to avoid any changes which would affect the content of PFAS, adversely affect the analytical determination or make the aggregate samples unrepresentative.

The person responsible for sampling should take the following precautions into account: do not wear clothing or gloves that contain fluoropolymer linings or that are treated with PFAS to improve water and stain repellence; do not use PFAS containing moisturizers, cosmetics, hand cream, sunscreens and related products at the sampling day.

Materials used during sampling, sample storage and sample transmission should be free of PFAS. Specifically, avoid the sample to be in contact with any fluoropolymer materials (e.g. PTFE, PVDF and others), such as fluoropolymer cutting boards, sampling containers, linings of caps of sampling containers. Avoid contact with other PFAS containing materials.

The analyst shall ensure that samples do not become contaminated during sample preparation by following the precautions described above. Furthermore wherever possible, the apparatus and equipment coming into contact with the sample shall not contain PFAS and shall be replaced by e.g. stainless steel, high density polyethylene (HDPE) or polypropylene parts. These should be cleaned with PFAS-free water and/or PFAS-free solvents and detergents to minimise the risk of contamination [1].

The following (not exhaustive) list gives an overview of materials/consumables that may cause cross-contamination in the laboratory:

- PTFE products (e.g. PTFE lined vial caps)
- Aluminium foil
- Teflon™ and other fluoropolymer-containing materials
- Low density polyethylene (LDPE)
- Decon 90
- Gore-Tex®
- Lubricants during instrument maintenance

Reagents and other equipment used for analysis and sampling should be controlled to avoid possible introduction or loss of PFAS.

A reagent blank analysis should be performed by carrying out the entire analytical procedure replacing the sample matrix by water. The levels in the reagent blanks should be monitored in each sequence of samples. Further blanks (e.g. solvent blank, calibration blank) can optionally be monitored. They may help to check for potential contamination at different stages of the analysis.

1.8.4. General quality control measures

Regular reagent blanks, and fortification experiments or analysis of control samples (preferably, using (certified) reference materials or in the absence of these, materials from successful and accredited PT exercises) should be performed as internal quality control measures. Quality control (QC) charts [24] for reagent blanks, fortification experiments or analysis of control samples should be recorded and checked to make sure that the analytical performance is in accordance with the requirements.

1.9. Validation parameters

For routine analysis of PFAS in food and feed samples, laboratories should demonstrate the performance of the methodology during the validation procedure and/or during routine analysis. Performance should be demonstrated in a range from 1 x the LOQ to e.g. 100 x the LOQ and should cover legal limits (if available).

Table 2 provides recommendation of selected parameters for validation studies that should be carried out before routine analysis. Definitions can be found in section 1.7.

Table 2: Recommendations for validation studies and routine quality control measures

Grouping of matrices	▪ Use of a single food or feed matrix to represent a matrix group if the matrices in the group share similar physico-chemical properties. ▪ Examples for matrix groups are given in Annex A of document No SANTE/12682/2019 for pesticides: e.g. milk and dairy products; meat (muscle) and seafood; etc. [17] ▪ Further sub-grouping might be necessary for analytes and/or methods if significant matrix effects are observed.
Selectivity of the analytical procedure	▪ Similarly, analytical methods should demonstrate the ability to reliably and consistently separate the analytes of interest from other co-extracted and possibly interfering compounds that may be present.
Trueness	▪ The measurement process used must provide a valid estimate of the true concentration in a sample. ▪ This is necessary to avoid rejection of a sample on the basis of poor reliability of the determined concentration. ▪ Trueness can be estimated from regular analysis of certified reference materials, fortification experiments or participation in inter-laboratory studies.
Precision	▪ Precision can be calculated from results generated under repeatability and within-laboratory reproducibility conditions.
Limit of quantification	▪ Specific required LOQs are given in section 2.1.4. ▪ Required LOQs may be revised in the future according to evaluations resulting from new toxicological studies and hazard assessments.

1.10. Instrumentation

(Ultra) High performance liquid chromatography ((U)HPLC) coupled to low resolution or high resolution mass spectrometry (LRMS or HRMS) is recommended for analysis of PFCA and PFSA.

1.10.1. LC-System

The LC system must provide consistent sample injection volumes and be capable of performing binary linear gradients at a constant flow rate. PFAS may build up in PTFE transfer lines when the system is idle for more than one day. To prevent long delays in purging high levels of PFAS from the LC solvent lines, it may be useful to replace PTFE tubing with polyether ether ketone (PEEK) tubing and the PTFE solvent frits with stainless steel frits. In addition a delay column can be installed before the injection valve to reduce the co-elution of PFAS originating from sources prior to the sample loop (e.g. mobile phase, fittings, tubes). Thorough rinse of the LC-needle can reduce the co-elution of PFAS accumulated in sample loop and valves.

1.10.2. Analytical column

The laboratory may select the LC column. Based on previous experience a C18 liquid chromatography column packed with solid phase particles is recommended (see Annex).

1.10.3. Mass spectrometer

The mass spectrometer must be capable of electrospray ionization in the negative ion mode. The system must be capable of producing specific product ions for the method analytes within specified retention time segments.

2. SPECIFIC REQUIREMENTS

2.1. Analytical performance criteria

Analytical performance criteria are an important element of quality assurance. These parameters provide information about the suitability of a method and the quality of the results. Common criteria are the basis for the comparability of results and methods between laboratories.

However, different control purposes require different performance criteria; i.e. substance/matrix combinations for which maximum levels (ML) are legally prescribed require more stringent criteria than substance/matrix combinations without existing maximum levels. **Table 3** defines the criteria for the methods for PFAS analysis that shall be verified. Further explanation of each parameter is given in the following sections.

Table 3: Typical validation parameters and performance characteristics for PFAS analysed in samples for compliance testing of maximum levels or monitoring purposes

Parameter	Compliance testing of maximum levels[a)]	Monitoring purposes[b)]
Trueness[c)]	± 20 %	± 35 %
Within-laboratory reproducibility (intermediate precision)	≤ 20 %	≤ 25 %
LOQ	See section 2.1.4, **Table 4** and **Table 5**	

a) only for substance/matrix combinations with legally required maximum levels
b) for substance/matrix combinations without legally required maximum levels and for substance/matrix combinations with legally required maximum levels in order to achieve the LOQs in Table 4 and Table 5 for collecting occurrence data
c) or expressed as apparent recovery (80-120% for compliance testing and 65-135% for monitoring purposes)

2.1.1. Trueness

Trueness can be estimated from regular analysis of certified reference materials, fortification experiments or participation in inter-laboratory studies and should be between -20 % and +20 % for compliance testing of maximum levels and between -35 % and +35 % for monitoring purposes (**Table 3**).

2.1.2. (Apparent) Recovery

The control of analytical recovery is essential for reliable analysis.

QC samples should frequently be analysed as internal QC measures. The apparent recovery of PFAS in QC samples should be in the range of 80-120 % (compliance testing) and 65-135 % (monitoring purposes). Higher deviations for individual results might be accepted, if the criterion for trueness can be fulfilled.

The recovery of the added IS may conveniently be measured, relative to the RS or QC samples. For PFAS, the recoveries of the individual IS should be in the range of 30-140 %, reflecting what is currently achieved.

2.1.3. Precision

Precision can be calculated from results generated under repeatability and within-laboratory reproducibility conditions, e.g. derived from routine QC samples. Within-laboratory reproducibility should be ≤ 20 % for analysis of PFAS for compliance testing of maximum levels and ≤ 25 % for monitoring purposes (**Table 3**).

2.1.4. Limit of quantification

Approaches for the estimation of LOQs are described in the addendum to the "Guidance Document on the Estimation of LOD and LOQ for Measurements in the Field of Contaminants in Feed and Food". For the LOQ estimation in PFAS determinations, the lowest validated level approach is recommended. [25] This means that the LOQ is the lowest successfully validated level of an analyte, for which it has been demonstrated that the respective criteria for identification (see section 2.4.3), trueness and precision (see section 2.1.1 and 2.1.3) are met.

The following LOQs for the four individual PFAS (PFOS, PFOA, PFNA, PFHxS) are the maximum LOQs to be achieved in routine analysis in order to gather further occurrence data (**Table 4**).

However, given that some foods show concentrations even below these levels, targeted LOQs in the range of 0.001 – 0.040 µg/kg w.w. for the four individual PFAS (PFOS, PFOA, PFNA, PFHxS) are desirable (**Table 5**).

NOTE: Specific aims of the analytical method (as defined under 1.5) may call for even lower LOQs, particularly for exposure assessment.

Table 4: Required limits of quantification (LOQ) in µg/kg w.w. for the four individual PFAS (PFOS, PFOA, PFNA, PFHxS) [26]

Matrix	PFOS	PFOA	PFNA	PFHxS	other PFAS[d)]
Eggs, crustaceans and molluscs	≤ 0.30	≤ 0.30	≤ 0.30	≤ 0.30	
Fish meat and meat of terrestrial animals	≤ 0.10	≤ 0.10	≤ 0.10	≤ 0.10	
Edible offal of terrestrial animals	≤ 0.50	≤ 0.50	≤ 0.50	≤ 0.50	
Fish oil	≤ 0.50	≤ 0.50	≤ 0.50	≤ 0.50	
Fruits	≤ 0.010	≤ 0.010	≤ 0.005	≤ 0.015	
Vegetables (except wild fungi)	≤ 0.010	≤ 0.010	≤ 0.005	≤ 0.015	
Wild fungi	≤ 1.5	≤ 0.010	≤ 0.005	≤ 0.015	
Food for infants and young children sold as ready to eat	≤ 0.010	≤ 0.010	≤ 0.005	≤ 0.015	
Milk	≤ 0.020	≤ 0.010	≤ 0.050	≤ 0.060	
Feed[d)]					

[d)] Will be specified when regulations/decisions on elevated levels are established.

Table 5: Targeted limits of quantification (LOQ) in µg/kg w.w. for the four individual PFAS (PFOS, PFOA, PFNA, PFHxS) [26]

Matrix	PFOS	PFOA	PFNA	PFHxS	other PFAS[d)]
Fruits	≤ 0.002	≤ 0.001	≤ 0.001	≤ 0.004	
Vegetables	≤ 0.002	≤ 0.001	≤ 0.001	≤ 0.004	
Food for infants and young children sold as ready to eat	≤ 0.002	≤ 0.001	≤ 0.001	≤ 0.004	
Milk	≤ 0.010	≤ 0.010	≤ 0.020	≤ 0.040	
Feed[d)]					

[d)] Will be specified when regulations/decisions on elevated levels are established.

The estimation of LOQs requires consideration of the reagent blanks as follows:

- Contribution of blank levels should be ≤ 30% of the levels in samples analysed in the accompanying batch
- Higher contribution requires the inclusion of blank levels in the estimation of LOQs
- Subtraction of blank concentrations may be performed

2.2. Method validation

As described in section 1.9, prior to routine analysis of PFAS in food and feed samples, laboratories should demonstrate the performance of their methodology during the validation procedure. Within-laboratory method validation is essential to provide evidence that the method is fit for the intended purpose. **Table 6** summarizes the parameters and criteria which shall be verified during method validation. An example of a practical approach to the validation procedure (minimum requirements) is given below.

Table 6: Validation parameters and criteria

Parameter	Description	Criterion	Cross ref.
Linearity	Linearity check from five calibration levels	Deviation of back-calculated concentration from true concentration ≤ 20 %	-
Trueness	Average apparent recovery for each fortification level tested; expressed as 'bias'	**Table 3**	Section 2.1
Precision	Within-laboratory reproducibility for each fortification level tested	**Table 3**	Section 2.1
LOQ	Lowest fortification level meeting the identification requirements and analytical performance criteria for recovery and precision	-	Section 2.1.4
Ion ratio, retention time	Check compliance with identification requirements for MS techniques	**Table 9**	Section 2.4.3

Example approach:

Validation needs to be performed for all analytes within the scope of the method and for at least one representative matrix group (within the scope of the method).

General overview:

- Duration: ≥ 2 days
- Operator: 1 technician (preferably more)
- Matrix: 1 matrix (e.g. pork meat) with 5 different batches **or** 5 different matrices of one matrix group (see **Table *2*** in section 1.9)
- Sample set **per batch or matrix** (if validation is performed for a matrix group):
    - 1 reagent blank
    - 1 sample blank
    - 2 fortified samples at 1 x the targeted LOQ
    - 2 fortified samples at one other higher level e.g. in the range 2-50 x the targeted LOQ
    - 2 fortified samples at one other higher level e.g. in the range 50-100 x the targeted LOQ
    - Additional samples and fortification levels optional

    NOTE: The range of fortification levels should cover achievable LOQs and, if available MLs, of all analytes within the scope of the method.

Specific overview of sample set:

- Prepare a set of samples of specified test material, i.e. 5 different batches of e.g. pork meat (if validation is performed for one matrix) **or** 1 batch of e.g. pork meat, lamb meat, salmon muscle, plaice muscle, and bovine meat each (if validation is performed for one matrix group) (see **Table 7** and **Table 8**).
- Fortify two or three of the test material batches with the analytes at **1x the targeted LOQ** and at least **two other higher levels** e.g. in the range of 2-100x the targeted LOQ (Table 7 and 8).
- Perform the analysis at each concentration level for at least **two replicates** (**Table 7** and **Table 8**).
- Analyse the samples.
- Calculate the concentration detected in each sample.
- Repeat these steps on at least **one other day** with the rest of test material batches, different operators (if possible) and as many different environmental conditions as possible, e.g. different batches of reagents, solvents or a variation of other parameters (**Table 7** and **Table 8**).
- Determine the mean concentration, standard deviation and the coefficient of variation (%) of the fortfied samples for each fortification level tested.
- Evaluate the parameters from **Table 6** and verify them against the criteria.

Table 7: Example of a validation sample set if validation is performed for one matrix (e.g. pork meat)

	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
Test material	Pork meat 1	Pork meat 2	Pork meat 3	Pork meat 4	Pork meat 5
Operator	Technician A	Technician A	Technician A (or B)	Technician A (or B)	Technician A (or B)
Day	1	1	1 or 2	2	2
Fortification levels	1x targeted LOQ	1x targeted LOQ	1x targeted LOQ	1x targeted LOQ	1x targeted LOQ
	E.g. 5x targeted LOQ	E.g. 5x targeted LOQ	E.g. 5x targeted LOQ	E.g. 5x targeted LOQ	E.g. 5x targeted LOQ
	E.g. 50x targeted LOQ	E.g. 50x targeted LOQ	E.g. 50x targeted LOQ	E.g. 50x targeted LOQ	E.g. 50x targeted LOQ
Number of replicates per fortification level	2	2	2	2	2
Number of sample blanks	1	1	1	1	1
Number of reagent blanks	1	1	1	1	1

NOTE: Additional batches of test material, replicates, days, operators and fortification levels optional.

Table 8: Example of a validation sample set if validation is performed for a matrix group (e.g. meat (muscle) and seafood)

	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
Test material	Pork meat	Lamb meat	Salmon muscle	Plaice muscle	Bovine meat
Operator	Technician A	Technician A	Technician A (or B)	Technician A (or B)	Technician A (or B)
Day	1	1	1 or 2	2	2
Fortification levels	1x targeted LOQ	1x targeted LOQ	1x targeted LOQ	1x targeted LOQ	1x targeted LOQ
	E.g. 5x targeted LOQ	E.g. 5x targeted LOQ	E.g. 5x targeted LOQ	E.g. 5x targeted LOQ	E.g. 5x targeted LOQ
	E.g. 50x targeted LOQ	E.g. 50x targeted LOQ	E.g. 50x targeted LOQ	E.g. 50x targeted LOQ	E.g. 50x targeted LOQ
Number of replicates per fortification level	2	2	2	2	2
Number of sample blanks	1	1	1	1	1
Number of reagent blanks	1	1	1	1	1

NOTE: Additional batches of test material, replicates, days, operators and fortification levels optional.

Instrumental sample sequence:

- Calibration standards
- Reagent blank
- Sample blank
- Fortified samples
- Calibration standards

2.3. Quantification

In order to validate the complete analytical procedure the addition of IS should be carried out at the very beginning of the analytical method e.g. prior to extraction.

It is preferable that isotope-labelled IS (ILIS) of at least the four main compounds (**Table 1**) should be used as this would improve the reliability of the quantitation.

If additional PFAS (for which no ILIS are available) are being simultaneously determined, relative response factors shall be determined using appropriate[1] isotope-labelled PFAS and the validity of these can be confirmed either by using appropriate calibration solutions or by reference materials.

Quantification of PFOS should include L-PFOS and br-PFOS (**Figure 1**) with br-PFOS being quantified using the linear standard (native and ILIS). This quantification procedure is regarded by the authors as the most pragmatic approach in view of challenges in method development. Identification and quantification of chromatographically separated br-PFOS (monomethyl-substituted branched isomers (2/3/4/5/6-PFOS)) should be based on mass transitions for which the best responses were obtained (e.g. *m/z* 499 > 80, 499 > 99, 499 > 169). 1-PFOS often co-elutes with L-PFOS on C18 columns and contributes only 1% to the technical PFOS standard. In addition, the concentration of di-methyl-substituted branched isomers is believed to be negligible low. For identification of the retention time of br-PFOS it is recommended to measure a native technical PFOS standard[2] with each sequence.

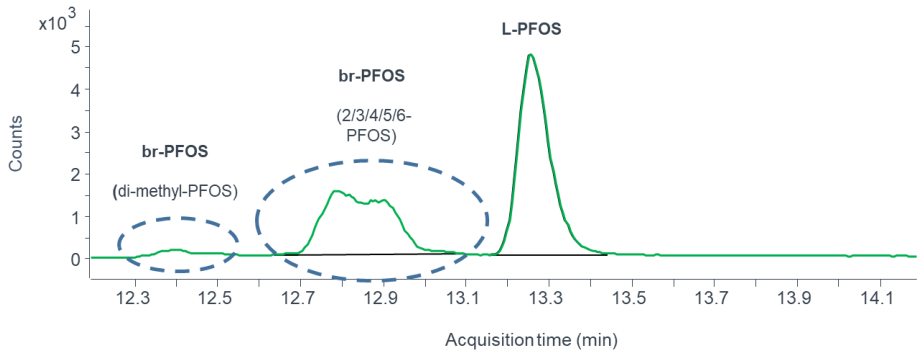

Figure 1: Extracted-ion chromatogram (mass transition *m/z* 499 → 80) of linear PFOS (L-PFOS) and its branched isomers (br-PFOS) of a technical PFOS standard.

[1] e.g. the chromatographically closest available ILIS
[2] perfluorooctanesulfonate (technical grade), CAS-number not available

2.4. Measurement

2.4.1. Exclusion of interfering substances

Separation of PFAS from interfering (e.g. taurodeoxycholic acid) or other possible coeluting interfering substances should be carried out by suitable sample preparation methods and/or chromatography/mass spectrometry techniques.

NOTE: Taurodeoxycholic acid (TDCA) is an endogenous compound which is formed in liver cells and normally found in matrices of animal origin (mainly eggs and offal). Under typically C18 LC column separation conditions it eluates at the same retention time and shares the same mass transition as PFOS (499 > 80). This may lead to false positive identification or over-reporting of the PFOS concentration. Therefore, TDCA should be removed by suitable sample preparation methods using ENVI-Carb or suitable LC separation methods (e.g. FluoroSep RP Octyl column). [27,28] Alternatively, the interference-free 499 > 99 mass transition can be used for quantification of PFOS. This mass transition is, however, less sensitive than the 499 > 80 transition and thus leading to a decrease in PFOS LOQs [28].

2.4.2. Analytical calibration curve

The lower range of the calibration curve is indicated by the LOQ (or targeted LOQ) for PFAS. This should extend to between 5.0 and 10 µg/kg at the higher end of range, reflecting the concentrations for PFAS that are reported in the current literature. At least five calibration concentrations are required to prepare the initial calibration curve spanning a 1000-fold concentration range. If the calibration curve spans several orders of magnitude the use of weighting factors (e.g. 1/x) is recommended.

2.4.3. Identification requirements

In **Table 9**, mass spectrometric performance and peak identification criteria for reliable analysis of PFAS are listed. Further identification and confirmation criteria are described in internationally standardized methods for e.g. PFAS in drinking water [29] and pesticides [17].

Table 9: Mass spectrometric performance and peak identification criteria for different LC-MS techniques

(U)HPLC-LRMS	Unit mass resolution
Typical systems (examples)	MS/MS triple quadrupole, ion trap, Q-trap, Q-TOF, Q-Orbitrap
Acquisition	Selected or multiple reaction monitoring (SRM, MRM)
Minimum number of ions	2 product ions
Ion ratio	Ion ratio from sample extracts should be within ± 30 % (relative) of average of calibration standards from same sequence [e)].
Signal to noise (S/N) ratio	≥ 3
Retention time (RT)	The ratio of the chromatographic RT of the analyte to that of the IS (i.e. relative RT of the analyte) shall correspond to that of the calibration standard with a maximum deviation of 1 %.
Other	Analyte peaks from both product ions in the extracted ion chromatograms must fully overlap.

Table 9 (continued)

(U)HPLC-HRMS	Accurate mass resolution
Typical systems (examples)	High resolution MS: (Q-)TOF, (Q-)Orbitrap
Mass resolution	≥ 10 000 at 10 % valley (for the entire mass range)
Acquisition	Full scan, all ion fragmentation (AIF)/MS^E, (variable) data-independent acquisition (vDIA)
Minimum number of ions	2 ions with mass accuracy ≤ 5 ppm [f), g)]
Signal to noise (S/N) ratio	≥ 3
Retention time (RT)	The ratio of the chromatographic RT of the analyte to that of the IS (i.e. relative RT of the analyte) shall correspond to that of the calibration standard with a maximum deviation of 1 %.
Other	Analyte peaks from precursor and/or product ion(s) in the extracted ion chromatograms must fully overlap.

e) applying identical MS/MS conditions, in particular collision energy and collision gas pressure, for each transition of an analyte

f) preferably including the molecular ion, (de)protonated molecule or adduct ion and at least one fragment ion

g) <1 mDa for m/z <200

NOTE: PFAS with only one specific MS/MS transition (e.g. PFBA, PFPeA) should be verified using a second chromatographic separation method (i.e. the use of a secondary LC elution on a different analytical column and eluent) or another MS method (e.g. the use of high resolution MS).

2.5. Reporting of results

The concentrations determined in test samples shall be expressed in units of µg/kg wet weight for food or in µg/kg product for feed (optionally, relative to a feed with a moisture content of 12 %). Results shall be reported as anions[3] or neutral compounds[4], respectively, and to two significant figures (2.5.1).

The uncertainty of measurement (2.5.2) should also be included as an aid to the interpretation of the data. The analytical results shall be reported as x ± U whereby x is the analytical result and U is the expanded measurement uncertainty using a coverage factor of 2 which gives a level of confidence of approximately 95 %.

PFOS should be reported as “total PFOS” and additionally as L-PFOS and br-PFOS, if possible.

All target analytes should be reported as individual concentrations and PFOA, PFOS, PFNA and PFHxS additionally as lower bound summed concentration (∑PFOA, PFNA, PFOS, PFHxS).

[3] if they exist as anions (e.g. PFCA, PFSA)
[4] if they do not exist as anions (e.g. FOSA)

NOTE: Only concentrations of PFAS, which have been confirmed by at least two MS/MS transitions should be reported. Otherwise a different chromatographic method or another MS method should be used to confirm the result (see 2.4.3). If this is not possible, the information that the result is not sufficiently confirmed must be included in the reporting format[5].

Additional information that should (optionally) be included in the report:

- Information on the methods used for extraction and purification for PFAS should be included – this information can be basic, e.g. mention of the techniques used in the analysis.
- As an aid to the evaluation of the reported data, the recoveries of the individual internal standards should be included. Data for feed may also additionally be reported as µg/kg product relative to a feed with a moisture content of 12 % along with the determined moisture content.

2.5.1. Rounding of results

Results shall be rounded to two significant figures.

The following general rules are proposed for rounding the result:

a) If the digit following the digit to be rounded is less than 5 (0, 1, 2, 3, 4), the previous digit will not change.
b) If the digit following the digit to be rounded is 5 or more (5, 6, 7, 8, 9), round the previous digit up by one unit.
c) The measurement uncertainty will be estimated by using the primary result (not final (rounded) result).
d) The measurement uncertainty will be rounded by using the same rules and should be given with the same number of decimals as the final (rounded) result.

Example:

1. Primary result = 0.5678 µg/kg
2. Primary value for the measurement uncertainty (MU e.g. 30 %) = 0.5678 x 0.3 = 0.17034 µg/kg
3. **Rounded value of the measurement uncertainty = 0.17 µg/kg (two significant figures)**
4. **Final (rounded) result = 0.57 µg/kg (two significant figures)**
5. **Reported result = 0.57 µg/kg ± 0.17 µg/kg (k = 2; 95 %)**

[5] For reporting the level of identification confirmation, the open text within the variable 'anmethText' can be used to report additional information regarding the analytical method or analysis.

2.5.2. Measurement uncertainty

As a first estimation for the combined uncertainty u the within-laboratory reproducibility standard deviation may be used. However, if possible, the uncertainty of the bias (after correction for a constant laboratory bias) should be included in the measurement uncertainty estimation, which can be derived from a) analysis of certified reference materials, b) participation in proficiency tests or c) fortification experiments.

The reporting of sum parameters and the possible comparison with legal limits requires the additional estimation of an expanded measurement uncertainty for theses sum parameters. For PFAS this is the case for the sum of PFOS, PFOA, PFNA and PFHxS and for total PFOS, if calculated as the sum of linear and branched PFOS.

In these cases the calculation of the combined uncertainty u of the sum parameter is calculated as the square root of the sum of squares of the individual combined uncertainties. For these calculations the rounded results and uncertainties of the individual substances can be used. Further rounding is then performed according to 2.5.1.

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