IUPAC Technical Report

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Analytical chemistry of engineered nanomaterials: Part 2. analysis in complex samples (IUPAC Technical Report)

https://doi.org/10.1515/pac-2022-0401
Received April 25, 2022; accepted July 12, 2023

Abstract: Recently, the scope, regulation, legislation, and metrology of the analytical chemistry of engineered nanomaterials (ENMs) have been reviewed in the Part 1 of the IUPAC Technical Report. Chemical analysis of nanomaterials in complex sample matrices presents a substantial challenge for analytical science and regulatory agencies. The purpose of the present Part 2 is to discuss the detection, characterization, and quantification of nanomaterials in samples of complex matrices including methods for sample preparation and fitness for purpose. Analytical methods applied to analysis in matrices of environmental samples, food, cosmetics, and biological samples as well as those used to monitor the fate of ENMs in the environment and biological systems are reported. Tables of numerous recently published works on analyses of typical ENMs with detailed protocols and conclusive comments are presented. There is a rapid development in the field mostly in the stage of accumulation of factual material. The single-particle inductively coupled plasma mass spectrometry is already widely used at the chemical analysis of metal-containing nanoparticles.

Keywords: Analytical chemistry; biological matrices; complex sample matrices; cosmetics; engineered nanomaterials; environment; fate of nanomaterials; food; real-world samples; sample preparation.

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Article note: This document was prepared in the framework of IUPAC Project 2017-005-3-500.
Sponsoring bodies: The Analytical Chemistry Division, Chemistry and Human Health Division and the Chemistry and the Environment Division: see more details on p. xx.

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1 Introduction

The rapid increase in the fabrication of engineered nanomaterials (ENMs) and their use in food, cosmetics, textiles, consumer products, and medical diagnostics and treatment to provide specific functionalities require analytical methods that can be applied to the detection and characterization of ENMs in the complex matrices of nano-enabled products. The widespread preparation and use of these products provides numerous routes for the entry of ENMs into the environment and potential harm to humans, necessitating reliable risk assessment strategies [1, 2]. Chemical analysis of nanomaterials in environmental and biological matrices as well as monitoring their fate in these complex matrices presents a substantial challenge for analytical chemistry and regulatory agencies. This challenge is related to the inherent difficulties of detection and analysis of nanoscale materials in such matrices in comparison to bulk materials or even to pristine ENMs. Moreover, the different strengths and limitations of analytical techniques complicate the choice of the most suitable method, and often a multi-method characterization approach is needed.

Part 1 of this IUPAC Technical Report, “Scope, regulation, legislation, and metrology” [3], provides an overview of ENM definitions and classification, analytical scenarios encountered with the analysis of both pristine nanomaterials and nanomaterials in complex matrices, evaluation of the current status regarding nanomaterial identification and characterization for regulatory purposes and legislation, and a large and critical overview of the metrology of nanomaterials. An engineered nanomaterial is defined by the International Organization for Standardization (ISO) as a nanomaterial designed for a specific purpose or function, while a nanomaterial generally is “a material with any external dimension on the nanoscale (nano-object) or having an internal or surface structure in the nanoscale (nanostructured material)” [4].

In this second part, we provide approaches to fitness for purpose, methods for sample preparation, and lists of techniques with references for the detection, characterization, and quantification of nanomaterials in complex matrices. Methods of analysis in matrices of environmental samples, food, cosmetics, and biological samples as well as those used to monitor the fate of ENMs in the environment and biological systems are covered and documented by tables with recently published examples.

2 Methods, techniques, and approaches

2.1 Methods for sample preparation

Ideally, the analysis of ENMs in complex matrices such as food, cosmetics, consumer products, and environmental or biological samples should be performed in situ, at the typically low concentrations found in the original sample. Unfortunately, sample preparation is routinely necessary to concentrate the nanomaterial, to extract or isolate nanomaterials from complex matrices, or to remove or reduce matrix effects [5, 6]. The recent IUPAC recommendations provide a glossary of methods and terms for extraction for analytical scale sample preparation [7] and separation methods [8]. In environmental samples specifically, sample matrices typically contain natural particles that are often similar in composition and size to ENMs but may be present in amounts a few orders of magnitude higher. For all sample preparation techniques, sample manipulation should be minimized as far as possible to ensure analytical accuracy. The same is true for the sample storage conditions and the time between sample preparation and analysis. Reproducibility of the sample preparation step is crucial for the comparability of number-weighted size distributions. Regardless of the sample preparation protocol applied, the size distribution needs to remain unaltered and an adequate number of particles must be analyzed to minimize the sampling error for the particle size distribution [9]. Of special concern for nanoparticles (a class of ENMs, abbreviated as NPs) is the selective loss of some particle size fractions or modification of the particle's agglomeration state. Given that the bioavailability of ENMs is affected by their dissolution, the extraction and/or sample preparation method should be able to isolate dissolved forms or maintain the ratio between particle and dissolved forms. The two most common scenarios are either to immobilize the ionic species, e.g., by ion exchange resins [10], or to capture the particles by low molecular cutoff filters and wash out the ions [11].

Sample preparation strategies should be selected in accordance with the sample matrix, the target nanoparticles, and the available analytical techniques since the employed strategy will have an impact on the sample and the information provided by the technique. Similarly, the state of the sample (e.g., solid, liquid, and gaseous samples) requires consideration. A summary of procedures for different types of samples and techniques is presented in Table 1. Sample preparation has been classified according to the sample requirements for the selected technique, the instrument configuration, and the objective of analysis [12]:

- **Total elemental content** of the nanoparticles is typically measured by inductively coupled plasma mass spectrometry (ICP-MS) or optical emission spectroscopy (ICP-OES) and related methods. In many cases, samples are prepared by acid and/or microwave digestion, and some samples may require a dry ashing pretreatment. Direct examination of a solid sample or laser ablation can also be used to prepare samples for electrothermal atomic absorption spectrometry (ETAAS) and mass spectrometry (MS), respectively.
- Determination of **size, concentration, composition, and speciation** requires liquid dispersions that maintain the intact nanoparticles. The corresponding approaches include chromatographic separation and field-flow fractionation methods; both separation techniques can be coupled to a range of detection systems, including elemental detectors, light scattering, refractive index, and ultraviolet–visible or fluorescence detectors. Very few samples can be examined directly; most will require dispersion and removal of interfering components by filtration, centrifugation, oxidation, and extraction or sedimentation.
- **Characterization of the shape, size, and composition** using electron microscopy, atomic force microscopy, and related methods requires deposition of a thin sample layer on a solid support, either directly from the solid state or, more typically, by depositing a dispersion and drying the sample. Depending on the sample type, it may be necessary to remove some matrix components using methods similar to those noted above for the preparation of dispersions. Electron microscopy often requires coating or staining of the sample and biological samples may require fixation.

Table 1: Sample preparation procedures for inorganic nanomaterials organized according to the type of sample and analysis method; adapted from [12].

1) Total elemental content [typically determined with electrothermal atomic absorption spectrometry (ETAAS), inductively coupled plasma mass spectrometry (ICP-MS), inductively coupled plasma optical emission spectroscopy (ICP-OES)].	
Cosmetics and personal care products	Acid digestion; microwave-assisted digestion (MAD); alkaline fusion; laser ablation
Food and beverages	Acid digestion; MAD; dry ashing; dry ashing and acid digestion
Other consumer products (fabrics, sprays, paints, adhesives, packaging)	Acid digestion; MAD; dry ashing; dry ashing and acid digestion
Biological tissues (animal and vegetable)	Acid digestion; MAD; direct solid sampling; acid digestions and MAD; laser ablation
Environmental samples (water, soils, sediments)	Acid digestion; MAD; laser ablation, extraction
(2) Size, concentration, composition, and speciation analysis (analyzed by continuous separation methods coupled to various detectors, selected electrochemical methods).	
Cosmetics and personal care products	Dispersion (water, bovine serum albumin (BSA), 2-[4-(2,4,4-trimethylpentan-2-yl)phenoxy] ethanol (Triton X-100), ethanol, methanol); dispersion and filtration/centrifugation; dispersion and defatting; defatting and dispersion; oxidation with H_2O_2
Food and beverages	Direct analysis; dilution; dissolution, dispersion, suspension; defatting with hexane; centrifugation, filtration; suspension in BSA; centrifugal ultrafiltration; acid, enzymatic, or in vitro extraction/digestion
Other consumer products (fabrics, sprays, paints, adhesives, packaging)	Direct analysis, dilution, dissolution, suspension; collection of aerosol; leaching studies; abrasion; aqueous extraction and cloud-point extraction (CPE); oxidation with H_2O_2
Biological tissues (animal and vegetable)	Direct analysis; dilution; CPE; settling, centrifugation; filtration, centrifugal ultrafiltration, serial filtration; evaporation; dilution, direct analysis
Environmental samples (water, soils, sediments)	Direct analysis; dilution; CPE; settling, centrifugation; filtration, centrifugal ultrafiltration, serial filtration; evaporation; dilution, direct analysis, extraction
(3) Size, shape, and composition analysis (e.g., transmission electron microscopy [TEM], scanning electron microscopy [SEM], atomic force microscopy [AFM], X-ray diffraction [XRD]).	
Cosmetics and personal care products	Direct sample application; dispersion and sample application; dilution and sample application; resin embedding
Food and beverages	Direct sample application; resin embedding; dissolution, dispersion and centrifugation and sample application; thin sectioning; water extraction and sample application; chemical fixation, post-fixation, staining, dehydration, resin embedding, thin sectioning
Other consumer products (fabrics, sprays, paints, adhesives, packaging)	Direct sample application; dilution and sample application; dry ashing and application of ashes; resin embedding, thin sections; CPE; centrifugation; fixation
Biological tissues (animal and vegetable)	Direct sample application; suspension and sample application; high pressure freezing, cryosubstitution, ultrathin sections; fixation and postfixation; thin section; centrifugation
Environmental samples (water, soils, sediments)	Direct sample application; chemical fixation, post-fixation, staining, chemical dehydration; resin embedding and thin sections; CPE; ligand-assisted extraction

2.1.1 Sample preparation from liquid samples

One of the most common methods used for the pre-fractionation and pre-concentration of nanomaterials prior to characterization is **membrane filtration** which will remove particles larger than the membrane pore size [13]. However, when nanomaterial size is near the pore size of the membrane, only a fraction of the nanomaterial will be filtered. This partial filtration is caused by the variability of the membrane pore size, the non-spherical shape of the nanomaterials, particularly those present in environmental samples, and possible interactions such as electrostatic repulsion. **Centrifugation** and particularly ultracentrifugation is a second common approach that is used to separate or pre-concentrate nanomaterials in suspensions according to particle size and density.

Cloud-point extraction (CPE) has also been employed for pre-concentrating nanomaterials. Surfactant is added to an aqueous suspension at a concentration above the critical micelle concentration, and the sample is heated to the cloud point temperature [13]. Above this temperature, the surfactant separates from the liquid phase, and the nanomaterial is concentrated in the surfactant phase which can be separated by centrifugation. This method has been used in a number of studies as a key tool to enrich and extract nanoparticles from complex environmental matrices, prior to analysis and to preserve the colloidal status of unstable environmental samples [14]. Indeed, many different CPE protocols have been applied to the extraction and/or pre-concentration of metal ions, nanoparticles, or organic substances, and the speciation of metals and some other elements. Remarkably, the opportunity to combine state-of-the-art multi-element analyses using ICP-MS with CPE is still largely unexploited. Furthermore, the specificity of CPE and a detailed comparison with filtration and centrifugation methods have yet to be established. The dispersion of samples containing nanomaterials frequently uses **sonication** to break up particle agglomerates. The addition of energy to a colloidal system can result in unexpected or unwanted effects; therefore, sonication parameters (intensity, duration, temperature) must be optimized.

Extraction is a general technique often used for separation/preconcentration and speciation analysis. Various types of extraction in connection with atomic absorption spectrometry (AAS), ICP-OES, and ICP-MS have been applied for metallic nanoparticles, particularly in environmental water samples (see Tables in Section 3). A solid-phase extraction (SPE) can be coupled with sequential elution. The magnetic solid-phase extraction (MSPE) procedures have shown excellent performance with a low limit of detection (LOD), high extraction factors (EF), high recoveries, and acceptable precision [15–17]. It is important to ensure that the extraction process does not have an impact on the particle size distribution or agglomeration state, which underlines the importance of well-planned particle extraction procedures. To isolate nanoparticles from biological matrices, **tissue degradation** under acid or basic conditions is used. However, digestions are likely to lead to particle dissolution or aggregation, or nanoparticle surface alterations, which will provide false information about the physical state of the particles [18]. Therefore, except for resistant nanoparticles such as TiO_2, acid solubilization of biological tissues is generally not recommended. Alkali and enzymatic solubilizations have been used with success, although published results indicate that numerous factors may affect the efficiency of these methods.

2.1.2 Sample preparation from solid matrices

Direct solid sampling and slurry sampling have helped significantly to decrease the number of preliminary operations in the analytical process for the handling of solid samples. Slurries are solid dispersions in a liquid phase that can be transported as solutions, enabling the direct determination of an analyte, reducing the time required for analysis, and minimizing the risks of contamination by circumventing sample decomposition with wet or dry oxidation procedures. Some examples of the slurry sampling technique have provided interesting results. Direct slurry sampling with graphite furnace AAS (GFAAS) was used for the detection and sizing of metal nanoparticles in chicken meat matrix reference material [19]. Slurry sampling was also used for the determination of TiO_2 nanoparticles in river water by ICP-MS and ICP-OES [20], assessment of composition of surface-modified TiO_2 nanoparticle catalyst by laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS) [21], chemical analysis of size-tailored magnetic colloids of nickel and cobalt nanoferrites by ICP-OES [22], accurate sizing of CeO_2 nanoparticles by the analysis of the optical forward-scattered field [23] and for many other purposes. Nonetheless, several problems including calibration, weighing errors, sample inhomogeneity, etc., may become important, unless experiments are carefully optimized [24].

The selection of sample preparation technique for analysis of nanoparticles is determined by the sample matrix and objective of the analysis. Nanoparticles in liquid samples are usually subjected to preconcentration with varying degree of success using membrane filtration and centrifugation. On the other hand, the potential of cloud point extraction seems to be still largely unexploited and future research focus could bring this technique into forefront. The extraction of nanoparticles from solid samples is still dominated by sample/tissue degradation with alkali and enzymatic dissolution being the most used, however, direct analysis solid and slurry samples is on the rise.

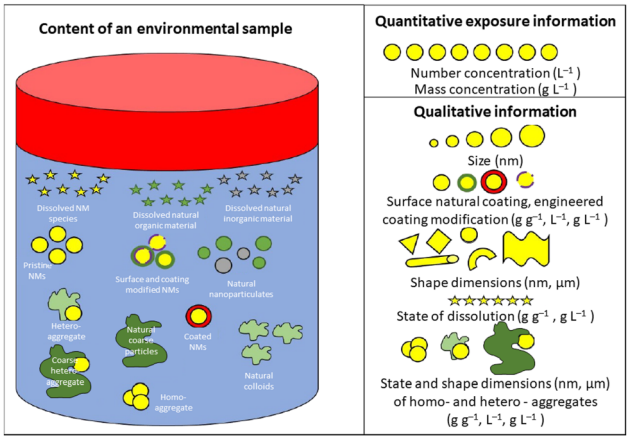

Fig. 1: Nanomaterials and natural matrix components in environmental samples; adapted from [26].

2.2 Analytical approaches: Fitness for purpose

The main challenge in analyzing nanomaterials is the requirement for obtaining a range of qualitative and quantitative information in order to distinguish between materials with similar composition but different physical properties. Conventional analytes only require the identification and mass quantification of the chemical species, whereas the analysis of ENMs requires compositional analysis as well as information on particle numbers, shape, size distributions, and surface chemistry and charge. Analytical measurements are also strongly influenced by the complexity of sample matrices and by dynamic physicochemical processes that alter the state of the ENMs such as dissolution, agglomeration, redox chemistry. Whereas some of these issues may arise in analyses of bulk materials as well (e.g., similarity in chemical composition), the others are specific for nanomaterials (e.g., size, shape, surface properties).

The analysis of pristine ENMs in industrial or research laboratories is reasonably straightforward, despite the relatively large number of properties that must be assessed. This is primarily due to the fact that the synthesis and characterization procedures and the sample history are well-known [13]. Although analysis of ENMs in food, cosmetics, and other consumer products is more complex, the initial matrix is clearly defined. However, environmental, or biological samples are typically exposed to a very large number of additional components, not all of which are identified. This substantially increases the complexity of the analysis. Analysis of environmental soil and water samples is further complicated by the potentially high background of naturally occurring nanoparticles, which may be similar in size, shape, and/or chemical composition to their engineered analogues, as illustrated in Fig. 1.

To date, the vast majority of data on ENMs concentrations in the environment have come from modeling studies, however, these studies have systematically noted a very large uncertainty due to the poor quality of input data and the use of a large number of simplifying assumptions [5, 25]. Very few analytical methods are currently available to detect and characterize nanoparticles under real-world conditions. For risk evaluation, analytical measurements are required to validate the models that are currently used. Analytical methods are also required to evaluate the persistence or aging (fate) of nanomaterials in environmental and biological matrices.

2.3 Techniques for characterization and determination of nanomaterials

As noted above, the complete characterization of nanomaterials requires the assessment of a range of properties that depend on the nanomaterial composition and its intended application. Important aspects of the topic of chemical analysis have been discussed recently [3, 27, 28]. Many reviews summarizing the principles, capabilities, advantages, and limitations of the various methods are available covering mainly the characterization of pristine ENMs as prepared, rather than detection and characterization in a complex matrix [2, 29–32]. Other reviews

Table 2: Parameters that are typically characterized for nanomaterials and the corresponding methods that can be used.

Properties	Techniques
Physical	
Size[a] (equivalent spherical diameter; for particles displaying a regular geometry, dimension of one or several axes of the particle)	TEM, HRTEM, SEM, DLS, MALS, NTA, SAXS, SEM, AFM, STM, DCS, spICP-MS, UV–Vis, TRPS, EPLS, FFF, SEC, HDC, AUC[b], VIP
Particle size distribution[a] (cumulative distribution of particle concentration as a function of particle size)	TEM, SEM, AFM, STM, DCS, DLS, SAXS, NTA, spICP-MS, TRPS, FFF, SEC, HDC, AUC, CLS[b]
Shape (external geometric form of a particle)	TEM, SEM, HRTEM, AFM, STM, EPLS, 3D-tomography, MALS, SAXS
Agglomeration (collection of weakly or medium strongly bound particles where the resulting external surface area is similar to the sum of the surface areas of the individual components)	DLS, DCS, UV–Vis, SEM, TEM, AFM, STM, FFF, SEC, HDC, AUC, CPS
Specific surface area (total surface area of the powder particles per unit of mass, $m^2\ g^{-1}$)	BET, liquid NMR, adsorption from solution
Surface charge (electrical charge on a surface; frequently measured as "zeta potential")	EPM (optical or acoustic)
Density	DCS, RMM-MEMS
Dispersion/dispersibility (uniform distribution of particles in matrix; maximum concentration of the dispersed particles per mass or volume of the dispersing medium under specified conditions)	SEM, AFM, TEM DLS, MALS, NTA
Optical properties	UV–Vis, NIR, PL, EELS-STEM
Magnetic properties	SQUID, VSM, Mössbauer, MFM, FMR, XMCD, magnetic susceptibility
Chemical	
Elemental/molecular composition (number of elements alone or in molecules, including oxidation state of the elements and molecular structure)	XRD, XPS, ICP-MS, ICP-OES, AAS, TEM-EDX, TEM-EELS, SEM-EDS, NMR, MFM, LEIS, XAS, FT-IR, Raman, NMR, MS
Concentration (mass, amount, or particle number of ENM per mass or volume of a sample matrix)	spICP-MS, UV–Vis, MALS, PTA, DCS, TRPS, SAXS, VIP, PCC
Solubility (maximum concentration of solute per a unit mass or volume of solvent at specified or standard temperature and pressure)	AAS, ICP-OES, ICP-MS (after separation of particles by filtration, dialysis, centrifugation), spICP-MS
Crystal structure/amorphous content (crystalline phase, defects, core–shell structure)	XRD, EXAFS, HRTEM, TEM + electron diffraction (SAED or CBED)
Surface chemistry (ligands, coatings, covalent modifications) (Number of molecules per specific surface area or mass of material)	TGA, XPS, SIMS, TEM-EDS, NMR, FTIR, optical probes, extraction + MS or chromatography

[a]Methods for measuring size and size distribution include particle counting methods (such as microscopy and NTA), ensemble methods (such as DLS and SAXS), and separation or fractionation methods (such as FFF and DCS). [b]FFF, DCS, filtration, and chromatographic methods can be used with various detectors. [c]Methods (except for spICP-MS) require initial separation of particles from supernatant containing ions.

summarize techniques that are used for applications in the areas of electronics and computing and food, environmental, biological, pharmaceutical, and agricultural analysis [33–35]. Table 2 summarizes the properties that may require assessment and the methods that are typically employed. In most cases, multiple methods are used, and their choice depends on the specific material, the information required and the equipment, and expertise available.

The properties in Table 2 are divided into physical and chemical categories. Among the physical properties, size/size distribution and shape are almost always necessary and a variety of particle counting methods (such as microscopy or particle tracking) and ensemble methods that interrogate the entire sample (such as small-angle

X-ray scattering (SAXS) and light scattering) are available. Separation methods that couple a fractionation technique such as field-flow fractionation (FFF), chromatography, or sedimentation with an appropriate detector are also widely used. To date, electron microscopy is considered as the method of choice for obtaining detailed particle size distributions over a wide size range for most nanomaterials [36]. However, spICP-MS is rapidly developing and has the capability to generate number-based particle size distributions as well as to provide particle number concentrations and compositional information; its use and range of applicability are expected to continue increasing. Note that light scattering techniques such as dynamic light scattering (DLS), multi-angle light scattering (MALS), and particle tracking analysis in complex matrices generate data that are difficult to interpret. This is due to the presence of multiple types of particles and the requirement for information on matrix properties such as viscosity or refractive index which may not be available. Other important physical properties include surface area, surface charge, and agglomeration.

This report will focus primarily on methods for chemical analysis and their application to ENMs in complex matrices. Important chemical properties include elemental or molecular composition, structure, concentration, and surface chemistry. Some points concerning the main techniques employed for the chemical analysis of nanomaterials/nanoparticles are discussed in the following subsections. Two recent IUPAC recommendations summarize metrological and quality concepts for analytical chemistry [37] and provide a glossary of methods and terms for analytical spectroscopy [38].

2.3.1 Microscopy and spectroscopy

Electron microscopy (EM) is able to visualize nanoparticles at the single-particle level, and hence provides information about their physical size, shape, or aggregation state. As with other particle counting methods, it is essential to analyze a large number of particles to ensure counting statistics that are representative of the original sample. The number of particles that must be counted is larger for ENMs with high polydispersity. Except for three-dimensional tomographic methods, EM provides a two-dimensional representation of the particles. Most EM techniques function under a vacuum, potentially affecting the aggregation state and observed size of the particles. Environmental scanning electron microscopes (ESEM) have an inferior resolution (tens of nanometers), but they can be used under less strict vacuum conditions and even in liquid, which is useful for reducing artefacts due to agglomeration. Despite this advantage, the lower resolution is problematic for small particles sizes. Cryogenic preparation techniques or the embedding of samples in hydrophilic resins have also been used to conserve colloidal samples; however, the techniques are still not widespread for use with nanoparticles. As an example, ESEM has been employed to study nanoparticle uptake and translocation in plants [39].

The power of microscopy for chemical analysis is in its combination with spectroscopic tools to provide information on elemental composition when coupled with **energy dispersive X-ray spectroscopy** (EDS) and chemical structure when coupled with electron energy-loss spectroscopy (EELS) [18]. The techniques of EDS and EELS are complementary, covering measurements of both light and heavy elements.

Transmission electron microscopy (TEM) is generally the most useful EM technique for characterizing nanoparticles in complex matrices, as well as some nanoparticle coatings [33]. It is able to provide a spatial resolution below 1 nm, which can be matched by scanning electron microscopes (SEM) fitted with a field-emission electron gun. For instance, nanoparticles could be well characterized through the use of high-resolution field-emission gun scanning electron microscopy in combination with X-ray analysis (FEG-SEM/EDS) [40]. In this case, the chemical composition of nanoparticles was identified in earthworm tissue after exposure to contaminated soil.

High-resolution TEM is able to provide images with a subatomic level resolution which are useful for obtaining information on the crystal structure of nanomaterials. Selected-area electron diffraction (SAED) and convergent-beam electron diffraction (CBED) are complementary in that they can be used in combination with conventional TEM to further identify the crystal structures. These microscopy spectroscopies could be applied to any characterization scenario; however, both matrix complexity and concentration levels can practically limit their application [29, 33]. High-resolution scanning transmission electron microscopy (HRSTEM) has a unique ability to image local cellular environments adjacent to a nanoparticle at near atomic resolution and can be used

in combination with EDS and EELS. These tools can be used to analyze particle location, translocation and potential reformation, ion dispersion, and the in vivo synthesis of second-generation nanoparticles. Such analyses can provide an in-depth understanding of tissue–particle interactions and insight into the effects that are caused by the nanoparticles [41].

Although optical microscopy has a much lower resolution than EM and often requires covalently attached fluorophore on nanoparticles, the recent combination of enhanced dark-field microscopy with hyperspectral imaging (EDF-HSI) has been successfully used to analyze ENMs in complex matrices. The analysis is performed under atmospheric pressure in the original sample matrix, and the results provide both spectral and spatial information. This technique enables fast and quantitative insights into the interactions between nanomaterials and organisms at the cellular or invertebrate level [42]. The utilization of EDF-HSI for the analysis of ENMs in biological matrices has been reviewed [43, 44].

2.3.2 Continuous separation techniques

The use of hyphenated techniques, such as continuous separation techniques coupled to elemental, light scattering, or spectroscopy detectors, is increasing due to their ability to simultaneously obtain particle size and multi-elemental information. These techniques were initially developed to reduce polydispersity and complexity of the sample prior to analysis. **Field flow fractionation** (FFF) is a separation technique that fractionates ENMs in a laminar flow in a narrow channel under the application of an external perpendicular field [45–47]. This method provides size information over a range of 1 nm to 100 mm, depending on the separation mode, allows one to maintain the native conditions of the dispersed sample and is compatible with coupling to a range of online detectors (e.g., ICP-OES, ICP-MS, UV–Vis, dynamic light scattering) and off-line collection of fractions for microscopy or other analyses.

While commonly-used FFF detectors, including UV, light-scattering, and fluorescence, do not provide nanoparticle compositional information and do not respond directly to the mass concentration of nanoparticles, ICP-OES and ICP-MS coupled to FFF can possess both nanoparticle sizing and compositional analysis at the $\mu g\ L^{-1}$ level with a detection level at least 10 to 100-fold lower than DLS or UV-FFF techniques [48]. Numerous variations of the FFF technique are continuously being developed including asymmetric flow FFF (AF4), sedimentation, thermal, magnetic, and electrical FFF. Excellent recoveries of nearly 90 % have been observed for Ag nanoparticles when the various flows were properly optimized [49]. Thus, FFF combined with elemental and sizing detectors has emerged as a tool with great potential for analysis of samples in complex matrices, including environmental and biological samples and consumer products [50].

The chromatographic separation of nanoparticles can be performed using **hydrodynamic chromatography** (HDC) and **size exclusion chromatography** (SEC). The main disadvantage of these techniques is the long analysis time per sample (around 30 min) and/or low sample injection volume (generally 20 µL), resulting in particle number concentration for environmentally relevant nanoparticles that fall below instrumental detection limits [18]. Whereas SEC has a limited size separation range, HDC has a low separation power with respect to either SEC or FFF [49]. **Gel electrophoresis** (GE) and **capillary electrophoresis** (CE) with UV–Vis or fluorescence detection are the most used techniques for the separation and characterization of nanoparticles based on their size, shape, and surface functionalization. The advantage of CE is the high resolution that is attainable in addition to its capacity to analyze both ionic species and nanoparticles. Although the potential of these two techniques has been examined, especially with respect to the gels (GE) and buffers (CE), they have rarely been applied to real world-samples. In both GE and CE, the addition of ionic surfactants plays a critical role in the separation of nanoparticles. The CE separations of bioconjugated quantum dots serve as examples [51]. The separation techniques have also been extensively used in the detection of nanoparticles in complex matrices and thus these techniques are discussed further in Section 3.

2.3.3 Atomic spectrometric techniques

Conventional atomic spectrometric techniques like ETAAS and ICP-OES can provide total elemental concentrations for a variety of samples. However, they are only able to provide information about the physicochemical form of the element (whether present as dissolved species or particles), when used together with size fractionation techniques (e.g., filtration, centrifugation) or when used online as an element-specific detector for a size fractionation method (e.g., FFF, HDC, SEC, EC).

Among different versions of ICP-MS available on the market, mass analyzers such as quadrupole (ICP-Q-MS), scanning sector field (SF-ICP-MS), static sector field with multi-collector detector (MCICP-MS), and time of flight (ICP-TOF-MS) are the most commonly used, each having several advantages and disadvantages [18, 52]. The quadrupole ICP-MS instruments are most appropriate for the detection of mono-elemental ENMs only. Triple quadrupole ICP-MS (ICP-QQQ-MS) offers an improved detection, e.g., for SiO_2 and for TiO_2 nanoparticles in complex matrices. Analysis of nanocomposites, naturally formed or unknown ENMs requires the simultaneous detection of all of the elements present in the single particle, which can be achieved by ICP-TOF-MS [52]. The enhanced capability of ICP-TOF-MS is reflected by its significantly higher cost.

Today, the **single-particle ICP-MS** (spICP-MS) is widely used for the analysis of metal-containing nanoparticles [53–56]. It is exploited to give:

(i) Qualitative information about the presence of particulate and/or dissolved forms of specific elements.
(ii) Characterization of the mass of a given element per particle. This information can be converted into particle size as long as information about the composition, shape, and density of the particles is known or assumed.
(iii) Quantitative information about particle number concentrations and mass concentrations of the dissolved and/or particulate forms of the inorganic nanoparticles [57].

This technique utilizes a standard ICP-MS setup and makes use of ultrafast, time-resolved detection to probe nanoparticles that are introduced into diluted suspensions, (ideally) one by one. The technique can be used down to parts per trillion particle number concentration levels. Quantification can be performed using nanoparticle standards of the same elemental composition or dissolved standard solutions, after taking into account the nebulization efficiency, to obtain particle size and size distributions. A comprehensive and systematic study of the accuracy, precision, and robustness of spICP-MS, using a rigorously characterized reference material issued by the National Institute of Standards and Technology (NIST), has been performed as well as necessary advancement toward full validation and adoption of spICP-MS by the broader research community [58]. Signal drift correction and flicker correction have been solved as well [59, 60]. Limitations of spICP-MS for the determination of nanoparticle size distributions and dissolution have been presented, demonstrating an impact of the ICP-MS sample introduction system [61].

Recent instrumental developments of spICP-MS, from the sample introduction system to the detector to coupling of spICP-MS to separation and fractionation techniques have been reviewed, along with some of the remaining challenges [62]. Among the important challenges are the sample preparation, the attainment of high transport efficiency, and the optimization of experimental conditions to ensure that nanoparticles enter the ICP fully vaporized, atomized, and ionized, regardless of their elemental composition, size, and sample matrix. The attainment of mass resolutions that provide isotopic information, the simultaneous multielement detection of nanoparticle signals (of the order of hundreds of microseconds), and the lack of appropriate reference materials for calibration are also challenges. Innovations and advances in the field of spICP-MS are represented by the coupling of spICP-MS to separation techniques such as capillary electrophoresis (CE), electrospray-differential mobility analysis (ES-DMA), AF4, flow injection (FI), isotope dilution, laser desorption and ablation, and time-of-flight (TOF) [62, 63].

Recently, a multi-mode determination of nanoparticle metal mass fraction and number concentration has been achieved based on a dual inlet system consisting of a pneumatic nebulizer and a microdroplet generator [64]. This setup provided seamless and robust operation in a total of three analysis modes. Each analysis mode is based on a different calibration principle, thus constituting an independent way to determine metal mass

fractions and nanoparticle number concentrations and improving the validation capabilities of spICP-MS for nanoparticle analysis [64].

X-ray absorption spectroscopy (XAS) at both the near-edge X-ray absorption spectroscopy (XANES) region and the extended X-ray absorption fine structure (EXAFS) region, have proven to be invaluable tools for in situ structural characterization of ENMs [33, 65, 66]. The XANES spectra provide information about the oxidation state, fractional d-electron density, and the electronic environment of the absorbing atom, while the EXAFS spectra yield information about the element coordination such as the number, type, and distance of the backscattering atoms surrounding the central absorbing atom. Due to limitations in sensitivity (mg kg^{-1} range), synchrotrons are usually needed to acquire the XAS spectra, so this technique is neither routine nor readily available [30].

2.3.4 Electroanalytical techniques

Electrochemistry is also considered as an efficient and cost-effective method able to detect, characterize and quantify various nanomaterials. Concerning the analysis of ENMs, two electroanalytical techniques have been particularly well developed – **voltammetry of immobilized particles** (VIP) and **particle collision coulometry** (PCC) – complementary techniques which can be used in combination. The VIP technique involves the immobilization of the nanoparticles on the electrode surface, which means that nanoparticles are separated from the media in which they are suspended, typically using a drop and dry approach, electrostatic interactions, or chemical deposition [67]. Various electrode materials, including chemically modified ones, have been developed for this purpose. If the surface coverage of the electrode is low enough, the peak potential can be directly related to the diameter of the nanoparticle; the peak potential and the area under the voltammetric peak can then be used to get qualitative and quantitative information, respectively. A molar-ratio method was applied to the determination of the stoichiometry and apparent binding constant of gold nanoparticle-organic capping complexes using voltammetric data [68].

For PCC, a modification of the baseline of a chronoamperogram (current vs. time plot) is evaluated when a metal or metal oxide nanoparticles randomly impacts the surface of a microelectrode held at a fixed potential, due to the oxidation/reduction of the nanoparticle. The charge involved in the process is related to the mass of the electroactive species [69]. Sensitivity can be increased via electrocatalysis, mass transfer, or using magnetic fields. Using electrochemical impedance spectroscopy and electrochemical scanning microscopy silver species present in linear low-density polyethylene (LLDPE) films with different Ag(I)/Ag(0) ratios and silver nanoparticle features usable as food contact polymers were characterized [70].

There is a large number of techniques available for determination and characterization of nanoparticles, and the selection of the technique really depends on the objective of the analysis. No single technique can be used as a universal tool to answer all analytical challenges and thus combining the advantages of individual techniques is necessary. Microscopic and spectroscopic analysis provide superior spatial resolution; however, they are not techniques of choice for particle number concentration. Continuous separation techniques are great tools for analysis of nanoparticles in complex matrices, but lack resolution when samples containing particles of similar size are analyzed. Atomic spectrometric techniques currently dominate the field of nanoparticles analysis because they are able to provide information about (i) the presence of particulate and/or dissolved forms of the analyte, (ii) mass of the analyte per particle, and (iii) particle number concentration. However, majority of spectrometric instruments used have quadrupole detector, and thus can monitor only one element at a time. Electrochemical analysis and X-ray absorption spectroscopy are very useful in chemical speciation of nanoparticles.

3 Analysis in samples with complex composition of matrix

Large segments of the current research are focused on the detection and quantification of nanomaterials in complex, real-world matrices. In this section, this topic is summarized in detail, organized by the matrix type.

3.1 Environmental systems

Engineered nanomaterials incorporated in various consumer products are released into the environment. Unfortunately, rather few analytical techniques are available that allow the detection of ENMs in complex environmental matrices. The major limitations of existing techniques are their relatively high detection limits and the difficulty to distinguish engineered ENMs from other chemical forms (e.g., dissolved ions) or natural colloids at the low concentrations expected in environmental matrices [71]. Despite the limitations of existing analytical tools, it is possible to use modeling to estimate the concentration of ENMs in environmental compartments while some methods can characterize the materials, even if the determination of their concentration is challenging. A combination of these two approaches has the potential to improve our understanding of the behavior of ENMs in complex environmental samples and to be particularly useful for risk assessment purposes [72].

In this section we note that a different type of nanomaterial, denoted as nanoplastics, must be considered as they have become, together with plastics, an environmental pollution issue. The **nanoplastics as engineered nanoparticles** are delivered through their commercial sources such as beauty and hygiene products, abrasive cleaning supplies, air-blasting mechanisms, and plastic powders used to make larger plastics. Over commercial products, nanoplastics can occur in the environment as the plastic debris of mechanical fragmentation and degradation of macro- and microplastics which complicate the detection and quantification [73, 74]. Engineered or primary nanoplastics identified in personal care products, biomedical applications, and laboratory use are defined as less than 100 nm in a single dimension [75], although the size range from 1 to 1000 nm was also considered [76].

Nanoplastics may occur as homoaggregates and heteroaggregates in which polymers are associated with heteroatoms or metal oxides [77]. State-of-art methodologies for pretreatment, separation, identification, and quantification of nanoplastics have been published recently with Raman spectroscopy and py-GC-MS as the most popular analytical methods [78]. Nanoplastics doped with metal particles are characterized by techniques such as DLS, Raman spectroscopy, TEM, and hyperspectral microscopy [79]. A hyphenated AF4 with total organic carbon (TOC) detection for polystyrene nanoplastics in the presence of dissolved organic matter and clay colloids has been developed as a more robust method of size-resolved quantification of the nanoplastics compared to other AF4 detection modes [80].

3.1.1 Engineered nanomaterials (ENMs) in waters

Many environmental ENM analyses involve water samples and spiked waters (surface, river, lake, sea, waste ones as blank material with known quantity values of ENMs added), which are analyzed directly or after a suitable dilution. As thermodynamic equilibrium does not exist for nanomaterials in water, physicochemical and chemical properties of nanomaterials in water depend on the surrounding media and may change during any handling/preparation process. Moreover, several artifacts may occur during sample transport, storage, and preparation, such as nanomaterial loss due to attachment to vials, contamination, and transformation. Therefore, it is essential to test the effect of transport, storage, and preparation on the nanomaterial by conducting control experiments with known quantities of well-defined particles [13]. For instance, filtration is often used because it removes microbial contamination and suspended particles in addition to aggregates. A recent filtration study has compared six different membrane filters for Ag and CeO_2 nanoparticles in aqueous samples analyzed by the emerging technique of spICP-MS. The highest recoveries were obtained for Milli-Q, rainwater, and river water samples with filtration over a polypropylene membrane [81].

Aside from traditional techniques for the determination of metal-containing nanoparticles in environmental waters, less conventional approaches for sample pretreatment, preconcentration, on- and offline detection, size characterization and quantification of metal-containing nanoparticles in environmental samples have also been used. Among them, cloud-point and solid-phase extractions provide high preconcentration factors and recoveries, and electrothermal AAS provides possibilities for the still challenging distinction between dissolved ions and nanoparticles should be mentioned. The combination of separation and detection, such as FFF and HDC with

Table 3: Examples of recent studies on the analysis of ENMs (mostly nanoparticles, abbreviated as NPs) in environmental samples.

Target nanoobject	Matrix[a]	Sample preparation	Detection/quantification method	Comments	Reference
Ag and Au NPs (citrate-coated Ag NPs and tannic acid-coated Au NPs)	Spiked ultrapure, natural, and waste waters	Filtration study with different membranes	spICP-MS, TEM	Dissolution of Ag NPs while Au NPs were stable for10 days	[94]
Ag NPs	Wastewater influents and effluents, river water		HDC coupled with ICP-MS and spICP-MS	LOD of 0.03 μg L^{-1} for HDC ICP-MS and 0.1 μg L^{-1} for HDC spICP-MS (80 nm Ag NPs)	[71]
Ag NPs	Environmental and waste waters	Centrifugation	HDC, AF4, spICP-MS, DLS, TEM	HDC and sp-ICP-MS recommended for NP size and concentration	[84]
Ag NPs aggregates (two sizes of citrate-coated Ag NPs and polyvinyl pyrrolidone (PVP) coated Ag NPs)	Aqueous suspension of environmentally relevant concentration in $NaNO_3$	Dilution with deionized water	DLS, TEM, spICP-MS,	Citrate-coated Ag NPs aggregated with increasing ionic strength, whereas PVP-coated Ag NPs were sterically stable, the collision frequency is predominant in the aggregation	[95]
Ag NPs coated with polyvinyl pyrrolidone (PVP), citrate, and polyvinyl alcohol (PVA)	River, lake, and waste waters	SPE with reusable magnetic chitosan microspheres	ICP-MS	Good species selectivity and reusability for extraction of Ag NPs in the presence of Ag^{+}	[96]
Ag NPs	Environmental waters	Ligand – assisted magnetic SPE	GFAAS	Speciation of Ag NPs and Ag ions	[97]
Ag, CeO_2, Fe_2O_3	Spiked soft and natural river waters	Extraction	AF4-ICP-MS, spICP-MS	Effect of extractants, elemental ratio approach to ENMs quantification	[98]
Ag and CeO_2 NPs	Natural waters (rain and rivers)	Membrane filtration	spICP-MS	Six membranes are evaluated with the highest recoveries in case of polypropylene	[81]
Cu NPs	Spiked natural soil extracts	Samples wet-sieved, centrifugation, microwave digestion, spiking with Cu NPs	spICP-MS	Discrimination between the background, dissolved, and particulate signal	[99]
Au NPs	Spiked soil extracts	CPE, acid digestion	AF4, spICP-MS	Pre-concentration of manufactured NPs	[88]
Au NPs of various concentrations and surface coatings	Spiked soil extracts using NIST SRMs	Centrifugal separation	AF4 coupled with UV–Vis, MALS, spICP-MS	Complementary techniques used to interrogate and quantify complex interactions	[89]
TiO_2 NPs (anatase and rutile)	Spiked river water	Microwave-assisted digestion	spICP-MS (^{47}Ti isotope monitored), TEM, DLS	LOD for NP diameter 37 nm and Ti concentration (0.058 pg mL^{-1} for anatase, 3.69 pg mL^{-1} for rutile)	[100]
TiO_2 NPs	Surface water		spICP-MS, spICP-TOF-MS, TEM, autoSEM, bulk elemental analysis	Discrimination between natural and engineered NPs	[86]
ZnO NPs	Spiked natural waters	A column with strong metal binding resin of 1,1′-iminodi(1,1-ethanediol) (Chelex 100)	spICP-MS	Solution of the problem when the dissolution of ZnO increases background levels of Zn	[101]
ZnO NPs	Environmental water		AF4 coupled to UV–Vis	Polystyrene NPs as a size standard, in agreement with DLS	[102]
ZnO NPs and Zn colloids	Spiked natural waters	Ion-exchange	Ion-exchange column coupled to spICP-MS (IEC-spICP-MS)	Size LOD of 8.2 nm in Milli-Q water, 4.3 nm in river water, 17.7 nm in rainwater, LOD of NPs 450 mL^{-1} for rainwater	[103]

Table 3: (continued)

Target nanoobject	Matrix[a]	Sample preparation	Detection/quantification method	Comments	Reference
ZnO NPs	Wastewater, tap water, lake water, river water	CPE with the addition of β-mercaptoethylamine to reduce Zn^{2+} interference	ICP-MS	Satisfactory extraction efficiency	[104]
Rare earth oxides (La_2O_3) NPs	Environmental water	Ion-exchange	spICP-MS coupled to ion-exchange resin	Impact of the storage container composition and ICP-MS sample introduction system, NP size distributions	[61]
CeO_2 NPs	Natural waters (rainwater and river waters)		spICE-MS as sector field ICP-MS with 50 µs dwell times	Lowering size detection limit of NPs to below 4.0 nm, conc of $(1.6 \pm 0.3) \times 10^9$ L^{-1} in the river	[105]
Carbon nanotubes, nanoplastics	Simulated natural surface water		AF4/MALS	Method to fraction natural organic matter (NOM)-coated carbon nanotubes (CNT) (sized 0.75×3000 nm) and nanoplastics (sized 60, 200, and 300 nm)	[106]
Polystyrene (PS) and poly(methyl methacrylate) (PMMA) nanoplastics	Environmental waters	2-[4-(2,4,4-trimethylpentan-2-yl)phenoxy] ethanol (Triton X-45) based CPE, thermal treatment at 190 °C for 3 h	Py-GC-MS	Detection limits of 11.5 and 2.5 fmol L^{-1} for PS and PMMA, resp	[107]
Polystyrene nanoplastics (100 nm)	Pure water and seawater	Ag colloid as the active substrate for SERS, NaCl as the aggregating agent	SERS, TEM, DLS	Detection down to 40 µg mL^{-1}	[108]
Polyvinylchloride nanoplastics	Recycled PVC powders (RPP)	Washing and filtering through a 1 µm poly(ether sulfone) filter	Correlative RISE	Direct chemical identification and morphological characterization of individual NPs on RPP surface	[109]
Polystyrene nanoplastics (50 nm)	River water	Ag NPs and $MgSO_4$ placed on a silicon wafer	SERS	Limitations due to the uneven distribution of nanoplastics on a silicon wafer and SERS spectra may overlap at multicomponent nanoplastics	[110]
Polystyrene nanoplastics (50, 100, 200, and 500 nm)	Natural waters with clay colloids and humic acid		AF4 with TOC detection	Efficient separation and robust, size-resolved quantification of nanoplastics	[80]
Polystyrene nanoplastics (50, 100, 200, and 500 nm)	Spiked lake water	KI added to Ag NPs as a coagulant and cleaner to remove surface impurities	SERS	Detection limit of 6.25 µg mL^{-1} for 100 nm PS nanoplastics	[111]
CeO_2 NPs	Soil		spICP-TOF-MS	Distinguished engineered CeO_2 NPs from natural NPs	[91]
Fullerenes	Suspended matter in sewage water	Filtration with mesh sizes of 8.0, 0.7, and 0.45 µm	LC HR-MS using atmospheric pressure photoionization, 100 % toluene isocratic mobile phase	Effective tool for qualifying the presence of fullerenes	[112]

[a]Spiked matrix means a blank material with known quantity values of ENMs added.

ICP-MS, UV–Vis, light scattering, and fluorescence detectors, is proved useful for the analysis of metal and metal oxides nanoparticles in waters containing organic matter, natural waters, and municipal wastewaters. Some recent studies are indicated in Table 3.

The technique of spICP-MS represents today the routine technique for the analysis of nanoparticles in natural waters and spiked waters [57]. The explosive growth and improvement in spICP-MS including the development of various sample introduction systems helps to analyze and understand nanoparticle behavior in complex matrices. In combination with size separation techniques, such as HDC or electrospray-differential mobility analysis, it is highly promising for the assessment of the shape and structure-related information on nanoparticles and their aggregates [82]. In that case, HDC provides information about the hydrodynamic diameter and spICP-MS gives information on the nanoparticle core which can help to distinguish between spherical and non-spherical particles as well as between pristine and surface-modified nanoparticles [83]. In a comparison with several methods including AF4, DLS, and TEM, the combination of HDC and spICP-MS is recommended for particle size and concentrations determination in waters with high recoveries [84]. Particle coincidence and dissolved analyte interferences, matrix effects, data acquisition and processing, the influence of instrument components, and other factors should be considered [54, 56, 62, 85]. Detection and quantification of ENMs requires their distinction from natural nanoparticles with similar intrinsic properties such as composition, size, surface chemistry, and other. Application of multi-element analysis to individual particles using spICP-TOF-MS revealed that specific metal elements are often present in natural nanoparticles but no specific multi-element signatures were detected for ENMs [86].

Many nanoplastics are retained in wastewater even after the wastewater treatment plant and others end up in the sludge. Nanoplastics have not been adequately researched and are thus difficult to characterize [87]. Some but not all quantification techniques require complex sample pretreatment or total removal of the organic-rich matrix or biofilms present. Regarding characterization and quantification, together with the FTIR and Raman spectroscopy as the most common techniques for analysis of plastic functional groups, other destructive methods, such as pyrolysis gas chromatography mass spectrometry (Py-GC-MS) and thermal extraction desorption gas chromatography mass spectrometry (TED-GC-MS), may be desirable.

3.1.2 ENMs in soil and sediments

The introduction of ENMs from anthropogenic contributions to soils and sediments occurs through industrial activities, wastewater sludge, consumer, and agricultural products. The isolation and pre-concentration of metal nanoparticles is an important component in the preparation of soil samples. Conventional extraction methods involve the use of dialysis, centrifugation, filtration, liquid–liquid extraction, or liquid–solid extractions, which can affect the physicochemical properties of the nanoparticles [88]. The principal methods used to detect and characterize ENMs in soils and sediments include TEM, HDC, AF4, and DLS. Both HDC and AF4 are typically coupled to specific detectors, such as DLS, ICP-MS, or fluorescence. The approach based on the combination of in situ complementary and hyphenated analytical techniques can effectively be used to interrogate and quantify these complex interactions involving natural matrices [89]. As in water matrices, at low concentrations of ENMs, most conventional analytical techniques are not able to take advantage of inherent differences (e.g. in terms of composition, isotopic signatures, element ratios, structure, shape, or surface characteristics) to distinguish between naturally occurring nanoparticles and ENMs of similar composition [90]. However, spICP-TOF-MS has been shown to distinguish between such nanoparticles and ENMs in soil by simultaneously detecting multiple elements or isotopes on an individual particle level [91].

For the detection, speciation, and quantification of micro- and nanoplastics in alpine snow, new highly sensitive method based on thermal desorption–proton transfer reaction–mass spectrometry (TD-PTR-MS) could be of interest closing the methodological gap of chemical characterization and quantification at a nanogram scale [92].

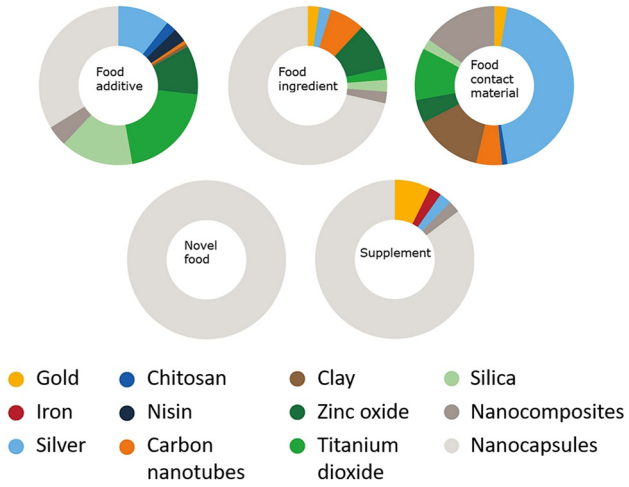

Fig. 2: The most frequently used types of nanomaterials found in food and food contact materials; adapted from [115].

3.1.3 Nanoparticles in air and aerosols

Aerosols are very complex in structure and can contain a great number of different chemical compounds even within a single particle. They should be analyzed for both size and chemical composition, in real-time or off-line applications. Characterization of aerosol nanoparticles is critical to the advancement of science and practical nanotechnologies. Key areas cover, among others, rapid aerosol nanoparticle measurements, detection, characterization, and behavior of low nanometer particles, nanoparticle size distribution measurements, and particle standards for size, concentration, morphology, and structure.

Single-particle aerosol mass spectroscopy (SPAMS) is employed for the determination of aerosol particles, thus including emissions and distribution patterns of atmospheric nanoparticles. In comparison to filter-based analytical techniques and traditional individual particle measurements, SPAMS is advantageous due to its continuous real-time detection of single particles [93].

Among challenges on the novel field of nanoplastics and other pollutants in environmental samples such as snow, natural and drinking water, and air there are their low concentrations, consequences of non-existent standards, losses during sample preparation, weathering and oxidation changes, as well as degradation. The amount of organic matter in the soil matrix, the discrimination and identification of large aggregates are also challenging, and can be solved by coupling size fractionation to molecular analysis [113].

3.2 Food, beverages, nutraceuticals, and food contact materials

The current use of nanomaterials in food primarily concerns three areas: food structure (taste, flavor, texture, consistency), food additives, and food packaging [6]. For example, Ag and ZnO NPs are found in dietary supplements and color additives, and nanoscale structures of silica are used as a taste intensifier in dietetic beverages and preservatives. Other examples include nano-encapsulates for delivery of lipophilic vitamins and nutrients, nanosilver with antimicrobial properties, non-metallic NMs in food packaging materials or other surfaces in contact with food, and TiO_2 in food containers for UV protection [114]. The distribution of nanomaterials found in food products is shown in Fig. 2.

The complexity of food matrices represents a potential problem in all areas of food analysis and is a particular issue when attempting to identify and characterize ENMs in food products. The matrix components such as surfactants, proteins, carbohydrates, and salts can affect the physical characteristics and behavior of ENMs and thus alter the measured parameter. Typically, particle size distribution in both the pristine NPs and

those extracted from food products is characterized. Moreover, it is necessary to distinguish between intentionally added ENMs and naturally occurring and incidental/contaminating materials which fit the nanomaterial definition and interfere with ENMs as the analytes [116, 117].

Relevant analytical strategies for the detection, identification, and characterization of nanoparticles in food products have been frequently investigated, including special attention to the crucial role of sample preparation strategies [6]. The sample preparation, in principle, does not differ from that required for conventional analytes in food and beverages. One important point is the minimum size of the sample that should be processed to be representative of the whole sample. Typical steps include homogenization, extraction of ENMs from the matrix, preconcentration or dilution of the sample/extract, and finally (in difference from some other analytes) stabilization of the nanomaterial suspension. To remove matrix materials, filtration and centrifugation are the conventional techniques for co-suspended particles larger than ENMs of interest together with dialysis to remove dissolved substances. Among the effective approaches for food sample homogenization and separation of ENMs from the matrix are (i) dissolution of the matrix in an aqueous solvent, (ii) chemical digestion if the ENM is not affected by the dissolving reagent, (iii) in the opposite case, enzymatic digestion as means to break down the matrix while leaving the ENMs intact, (iv) liquid/liquid partitioning, (v) cloud-point extraction of ENMs from liquid matrices as known for environmental waters. The microwave-assisted acid digestion with nitric acid and hydrogen peroxide was investigated for the removal of the organic matrix, and the efficiency of sample preparation was evaluated. The application of the generic sample preparation procedure and its quality criteria requires knowledge about the target nanoparticles [118].

The techniques of HDC, LC, CE, and mainly FFF or AF4 were used to separate ENMs from food matrices containing suspended solids of limited size (e.g., through filters with a pore size of 450 nm) [119]. In many cases, it may be necessary to rely on multiple sample preparation methods to adequately isolate ENMs for their analysis [116]. Sonication plays an important role in this regard and could alter the agglomeration state of the particles and consequently have an impact on particle size distributions for techniques that do not selectively measure the constituent particles [120].

Previously, to analyze the ENMs in a foodstuff, particularly metal-based materials, electron microscopies have been recognized as standard methods and were recommended by the EFSA for the size and morphology characterization in food [121] whilst spectrometric techniques such as atomic absorption spectrometry AAS, optical emission spectrometry OES, inductively coupled plasma mass spectrometry (ICP-MS), and particle-induced X-ray emission have been considered for the determination of total elemental content [117]. Both spICP-MS and matrix-assisted laser desorption/ionization-time of flight MS (MALDI-TOF-MS) are often coupled online to HDC [85, 122] while ICP-MS is combined with FFF (AF4) [119]. Examples of application of these and some other approaches (ELISA, SPR) are indicated in Table 4.

Validation protocols for the detection and quantification of nanoparticles in food samples require information about the chemical identity, particle size, and mass or particle number concentration. Among other factors, selectivity against matrix constituents and other nanoparticles, but also application of methods to particles from different suppliers should be tested [9]. To date, as no single analytical method can provide all of the necessary information regarding ENMs in food, a combination of several methods and approaches is strongly recommended [123]. Research priorities in this area include: (i) systematic research into how variations in sample preparation strategies influence detection and characterization data for currently available analytical methods; (ii) expansion of the data for detection of ENMs (both inorganic and organic) in food systems by most frequently used methods; (iii) targeted development of new analytical toolsets (or expansion of the capabilities of existing toolsets) that require minimal sample preparation (direct measurement) and are inexpensive, rapid, and less labor- or expertise-intensive to use; (iv) development of model systems (especially reference materials) to better understand how ENMs behave in various food matrices over time [116]. The absence of alternative standardized procedures for the sizing and quantification of (engineered) nanoparticles in food matrices also needs more intensive activities [120].

Table 4: Examples of recent studies on the analysis of ENMs (mostly nanoparticles, abbreviated as NPs) in food matrices.

Target nanoobject	Matrix[a]	Sample preparation[a]	Detection/quantification method	Comments	Reference
Ag NPs	Chicken meat	Homogenized chicken meat sample spiked with Ag NPs, enzymolysis by Proteinase K	TEM and AF4/spICP-MS	No detectable dissolution of Ag NPs during the sample preparation	[124]
Ag NPs (candidate reference material Nanolyse 14)	Chicken meat	In vitro model that included saliva, gastric and intestinal digestions	spICP-MS	Relevance of using physiological conditions for accurate risk assessment	[125]
Ag NPs	Chicken meat (matrix reference material "NanoLyse13" as chicken meat homogenate spiked with PVP-Ag NPs	Direct slurry sampling	GFAAS	Good agreement with the reference size by TEM	[19]
Ag NPs (PEG-coated NPs)	Food simulants (10 %, 20 %, or 50 % ethanol, 3 % acetic acid, olive oil) and low fat cow milk under migration conditions	Incubation for 4 h or 10 days at 40 °C	spICP-MS	Particle mass and number concentrations, ionic concentration, and particle size distributions	[126]
Ag NPs	Plastic food containers (baby bottle and food box), food simulants extracts	Food box digestion in microwave system, baby bottle calcinated in a muffle furnace	SEM-EDX, spICP-MS	Speciation of dissolved silver and Ag NPs	[127]
Ag NPs (nanosilver impregnated containers and coated films food packaging)	Apples, bread, carrots, soft cheese, meat, milk powder, orange juice, water	Samples stored in sealed containers at 40 °C, carbonized using a Bunsen burner, digestion with conc. HNO_3	ICP-MS, AAS, TEM, SEM-EDS, TEM-EDS,	Insignificant release of Ag NPs from containers, higher levels of migration from coated films found	[128]
Ag NPs (10, 20, and 60 nm)	Orange juice and mussels	Dispersive μSPE technique with sulfonated nanocellulose	CE with photometry	Highly selective absorption of Ag NPs irrespective of size and coating, simple cleanup to remove interferences, LOD of 20 g L^{-1}	[129]
Au NPs	Mustard and lettuce plants	Digestion with macerozyme R-10 enzyme	spICP-MS	Extraction without obvious aggregation or dissolution	[130]
TiO_2 NPs (food additive E171 in EU)	Chewing gum products	Cell treatment with different concentrations (25–400 μg mL^{-1}) of TiO_2	TEM-EDS, XRD	Intracellular oxidative stress in human lung fibroblast cells assessed	[131]
TiO_2 NPs	Candy products (chewing gum)	Simple extraction of chewing gum samples using an ultrasonic bath	Triple quadrupole spICP-MS	Superior sensitivity due to the more efficient removal of spectral interferences, CeO_2 particles as an internal standard for the determination of the particle number concentration	[132]
TiO_2 nanosized particles	Food products (coffee cream, yogurt snacks, hard candy, chewy candy)	Acid digestion	ICP-MS, Raman spectroscopy	Raman allows analysis of anatase >100 ppb TiO_2 in food products	[133]

Table 4: (continued)

Target nanoobject	Matrix[a]	Sample preparation[a]	Detection/quantification method	Comments	Reference
TiO_2 (food grade additive E171 in EU)	Custard cream, candies, white and yellow sugar pearls, confectionery masses	Dispersion in water, sonification	Raman spectroscopy, TEM, TEM/EDX, spICP-MS, CLS	Size distribution, impact of the extraction process and instrumentation	[134]
TiO_2 (food additive E171 in EU)	Pristine materials	Six sample preparation protocols with probe dispersion, sonication, centrifugation	TEM, spICP-MS	Variation in particle size and shape distribution and, physicochemical form	[135]
TiO_2 pristine food grade and food additive E171 in EU	Confectioneries (chocolate candies, white chewing gum dragées)	Sonification	CLS, spICP-MS, TEM,	Number-based particle size distribution, and particle concentration, interlaboratory testing by 7 experienced European food control and food research laboratories,	[120]
TiO_2 (food additive E171 in EU)	Chewing gum, chocolate candy, cake decoration, spiked milk	Extraction	Triple-quadrupole and high-resolution spICP-MS	Combination of spICP-MS with microscopy and TiO_2 recovery allowed the identification of aggregated/agglomerated particles	[136]
TiO_2 (food additive E171 in EU)	Food additives, pharmaceuticals		spICP-MS	Optimized Excel spreadsheet, use of reference material	[137]
SiO_2 NPs (food additive E551 in EU)	Tomato soup	Acid digestion and colloidal extraction	AF4/MALS and ICP-MS	Stepwise sample preparation by the introduction of quantitative quality criteria	[118]
Synthetic amorphous SiO_2 NPs (food additive E551 in EU)	Different food-grade samples	Dispersion and filtration of food-grade synthetic amorphous silica samples	DLS, AF4/MALS-ICPMS, TEM	Information from each type of analytical technique and implications related to current EC regulation 1169/2011	[138]
Synthetic amorphous SiO_2 NPs (food additive E551 in EU)	Tomato sauce	Microwave-assisted acid digestion	AF4/MALS, ICP-MS	Digestion partially dissolves silica NPs, low pH value leads to strong agglomeration	[139]
SiO_2 NPs (food additive E551 in EU)	Commercial high-fat coffee creamer	Extraction after cleanup with hexane in a two-phase (hexane vs. water) aqueous environment	AF4/ICP-MS	Size characterization, mass quantification, practical for routine analysis of polydisperse SiO_2 NPs	[140]
Pb NPs	Game meat	A modified version of the enzymatic digestion method	spICP-MS	Mass and particle number concentrations, size LOD strongly depended on the level of dissolved lead	[141]
Iron oxides NPs (food additive E172 in EU)	Pigments		TEM, SAXS (also DLS, ICP-MS, XRD, AF4)	Comparable results from both methods	[142]

Table 4: (continued)

Target nanoobject	Matrix[a]	Sample preparation[a]	Detection/quantification method	Comments	Reference
Liposome NPs	Beverage matrix	To remove insoluble components in the orange-flavoured beverage Acrodisc syringe filters (diameter 25 mm; Pall, Ann Arbor, MI, USA) of different pore size To remove insoluble components in the orange-flavoured beverage Acrodisc syringe filters (diameter 25 mm; Pall, Ann Arbor, MI, USA) of different pore size To remove insoluble components in the orange-flavoured beverage Acrodisc syringe filters (diameter 25 mm; Pall, Ann Arbor, MI, USA) of different pore size filtration using syringe filters	HDC, MALDI-TOF MS	LOQ 1 mg mL^{-1}, good linearity, repeatability, and reproducibility	[122]
ZnO NPs	Orange juice, chicken breast with NPs migrated from two widely employed food packaging materials	Extraction with Tris (hydroxymethyl) aminomethane hydrochloride (Tris HCl)	spICP-MS, TEM	NP size below LOD prevented characterization in juice using spICP-MS	[143]
Polystyrene nanoplastics	Spiked fish sample	Homogenization, acid digestion, enzymatic digestion	AF4/MALS	Acid digestion resulted in large aggregates/agglomerates >1 µm	[144]

[a]Spiked matrix means a blank material with known quantity values of ENMs added.

3.3 Cosmetics, personal care, and other consumer products

Cosmetics, cosmeceuticals, sunscreens, and personal care products use several nanomaterials such as metals (Au, Ag, Cu, Pt, etc.), metal oxides (TiO_2, ZnO, etc.), liposomes, nanocapsules, solid lipid nanoparticles, nanocrystals, dendrimers, cubosomes, niosomes, and fullerenes in their formulations. These nanomaterials improve cosmetics properties, including better skin penetration, specific targeting into cells, active ingredient release, transparency, unique texture, color, solubility, and enhanced UV protection [145–148]. Novel nanocosmeceuticals such as liposomes, niosomes, nanoemulsions, solid lipid nanoparticles, nanostructured lipid carriers, and nanospheres are used as nanocarriers and have replaced conventional delivery systems, although, additional health hazards due to increased use of nanoparticles in cosmeceuticals have also been signaled [149]. Plastic from consumer goods can break down into microplastics and nanoplastics complicating the detection and quantification.

Currently, there are gaps between the commercialization of nanomaterials in cosmetic and personal care products, and the regulatory frameworks needed to assess these products in the USA, Europe, Japan, and Latin America prior to and after commercialization [150]. According to the EC regulation on cosmetics [151, 152], any ingredient present as a nanomaterial should be indicated on the ingredient list. There is thus an urgent need for analytical methods able to determine the size of the relevant ingredients to assess if they meet the nanomaterial definition. Analytical techniques of sample preparation and methods of the determination and characterization of engineered nanomaterials in individual types of cosmetics are indicated by examples in Table 5. They represent a spectrum of techniques generally applied to samples of complex matrices.

3.4 Biological sample matrices

For ENMs exposed to biological matrices, similarly to previous sample systems, changes in pH, ionic strength, redox conditions, relative humidity, or ligand composition can result in enhanced or reduced dissolution, aggregation, surface reconstruction, or surface ligand adsorption. Some of these consequences are mentioned in Section 3.5. Because of these transformations, the physicochemical characterization of pristine ENMs may be irrelevant after their interaction with biological systems. More, together with metallic nanoparticles, the nanoplastics are available from the main human consumption sources – seafood. Using currently available analytical technology, it is challenging to quantitatively analyze distribution and physical properties of engineered nanoparticles in the body/biological tissues. Fate of pristine nanomaterials like dissolution is also detected. For such studies, biological tissues with added engineered nanoparticles as a model (spiked matrices) or uptake of such nanoparticles by plants are typically used (Table 6).

Several analytical strategies used for the characterization, detection, and quantification of nanoparticles, with a focus on biological matrices, are shown in Fig. 3. The spICP-MS method is a rapidly evolving technique for the analysis of ENMs also in biological matrices. This technique provides information about the number concentration of ENMs in solution, their elemental composition, size, and size distribution in addition to the amount of the dissolved analyte present in the sample. The LOD is strongly related to the background contribution of the dissolved analyte, but generally low tens of nm are reported. Several hyphenated techniques have been developed for the separation of dissolved matrix constituents from the ENMs to reduce matrix interferences or improve the abilities of the detectors, but their applicability to biological matrices is generally limited. Generally, poor resolution and dependence of retention time on the ENMs surface coating make this technique less suitable for the analysis of complex matrices. From the FFF techniques, only AF4 and sedimentation FFF (SdFFF) are commonly used for the analysis of ENMs in biological matrices. The former FFF type applies a perpendicular cross fluid flow, while the latter uses a centrifugal force. Hyphynated technique of FFF with multi-elemental detectors, such as ICP-MS, expanded its applicability (e.g., see Table 6).

Light scattering detectors such as dynamic light scattering (DLS) and multi-angle light scattering (MALS) have limited applications in the analysis of ENMs in biological matrices. **Mass cytometry** (Cy-TOF) is a version of flow cytometry in which the fluorescence detector has been replaced by ICP-TOF-MS and represents an emerging technique for ENM analysis. Initially, this instrument was designed to improve cell phenotype analysis; however,

Table 5: Examples of recent studies for the analysis of ENMs (mostly nanoparticles, abbreviated as NPs) in cosmetics and other consumer products.

Target nanoobject	Matrix	Sample preparation	Detection/quantification method	Comments	Reference
Ag NPs	Toothbrushes	Chemical digestion with nitric acid, dilution with water	ICP-MS for the total amount, spICP-MS and TEM for NPs characterization	Ag release in levels of ng L^{-1} indicates close to negligible human and environmental exposure	[153]
Ag NPs	Liquid silver-based consumer products, environ-mental water samples	Centrifugation for the separation of Ag NPs from dissolved Ag in consumer products	spICP-MS, TEM	Good repeatability and an overall acceptable bias for positive screening test	[154]
Ag, Au, and TiO_2 NPs	Cosmetic inventories, skin layers in vitro, albino hairless mouse model in vivo	Exposure in Franz diffusion cell system	EDF-HIS, SAM	Sufficient sensitivity for detection of very low levels of NPs	[155]
TiO_2 NPs	Sunscreens	Acid digestion, dispersion in 2-[4-(2,4,4-trimethylpentan-2-yl)phenoxy] ethanol (Triton X-100), dilution	spICP-MS	Mass content determined by standard addition	[156]
TiO_2 and Au NPs, elemental impurities (al, Fe, ti, and si)	Shampoo, sunscreen, antiwrinkle cream, day cream, night cream, toothpaste, and lip balm	1st acid digestion for elemental impurities; 2nd suspension in SDS and 3rd defatting with hexane and re-suspension in water	DLS, spICP-MS, ICP-MS, ICP-OES	spICP-MS was the best technique for routine analysis, prohibited elements according to the European Commission regulation No 1223/2009 were not found	[157]
Al_2O_3, TiO_2, and SiO_2 NPs	Toothpaste	Chemical digestion, dilution in water or water/SDS, chemical oxidation	AF4, spICP-MS	Determination and confirmation of the number-based particle size distribution	[158]
TiO_2 NPs	Sunscreen, coating of chocolate candies	Sunscreen defatting with hexane and filtration; coating extraction with water, sonication, and filtration	spICP-MS, AF4-MALS-sp-ICP-MS, DLS	Methodological comparison	[159]
TiO_2 NPs (pristine TiO_2 NPs and TiO_2 NPs dispersed in a sunscreen matrix as internal references)	Commercial sunscreens	Ultracentrifugation and hexane washing, thermal destruction of the matrix, surfactant-assisted particle extraction	AF4/MALS, AF4/ICP-MS	Surfactant-assisted particle extraction revealed TiO_2 NPs, recoveries of above 90 %, no increase in particle size due to sample preparation	[160]
TiO_2 NPs	Sunscreens with commercial nano-TiO_2 UV filters		2D X-ray absorption (2D-XRA) imaging, (Cryo-STEM)	in situ determination of aggregation state, Characterization of dispersion state	[161]
TiO_2 and ZnO NPs	Sunscreens	Sample dilution for TEM	AFM, LCSM, XRD, TEM	Dilution can alter NPs; a combination of XRD and TEM was suitable for analyzing commercial sunscreens	[162]
TiO_2 and ZnO NPs	Sunscreen powder	Dispersed in 2-[4-(2,4,4-trimethylpentan-2-yl)phenoxy]ethanol (Triton X-100), vortexed and sonicated 30 min, diluted with water	XRD, TEM, spICP-MS	spICP-MS as the best candidate in NPs, TEM, and XRD can verify the data	[163]

Table 5: (continued)

Target nanoobject	Matrix	Sample preparation	Detection/quantification method	Comments	Reference
TiO_2 and ZnO NPs	Cream and spray sunscreens	Dilution using 2-[4-(2,4,4-trimethylpentan-2-yl)phenoxy]ethanol (Triton X-100) aqueous solution and sonication for 20 min	spICP-MS, AF4/ICP-MS	Particle size distribution and determination by standard addition	[164]
TiO_2 NPs	Textiles: Table placemats, wet wipes, microfiber cloths, baby bodysuits with Ti content of 2.63 to 1448 $\mu g g^{-1}$.	Leaching test	ICP-MS, spICP-MS), in conjunction with TEM	TiO_2 release by mass and particle number, as well as size distribution, total Ti release	[153]
Fullerenes	Antiaging serum and facial mask	Toluene extraction, centrifugation, separation of the organic phase, evaporation to dryness, and reconstitution with aqueous SDS	MECC, CZE, AF4; TEM	SDS micelles revealed particles with different degrees of aggregation	[165]
Polyethylene nanoplastics	Facial scrubs containing polyethylene microbeads (0.2 mm diameter)	Fractionation by sequential filtration to isolate particles of the size <100 nm	SEM, XPS, FTIR	Polyethylene (FT IR) and elemental (XPS) identification	[166]
Nylon and polyethylene terephthalate nanoplastics	Plastic teabags	Plastic teabags steeped in reverse osmosis water for 5 min at 95 °C	SEM, XPS, FTIR	A single plastic teabag at brewing temperature (95 °C) releases approximately 11.6 billion microplastics and 3.1 billion nanoplastics into a single cup of the beverage	[167]

Table 6: Examples of recent studies for the analysis of ENMs (mostly nanoparticles, abbreviated as NPs) in biological samples.

Target nanoobject	Matrix[a]	Sample preparation	Detection/quantification method	Comments[a]	Reference
Ag NPs	Plants (*Arabidopsis thaliana*)	Enzymatic digestion with Macerozyme R-10	spICP-MS, TEM	No change in the size of Ag NPs after extraction, size distribution determination	[174]
Ag NPs	Plasma and blood of burn patients		HDC coupled spICP-MS	Simultaneous characterization of Ag NPs and determination of dissolved Ag	[175]
Ag NPs	Ex vivo human placenta perfusion model		spICP-MS	Impact of Ag NPs surface modifications on placental transfer	[176]
Ag NPs	Mouse blood and liver	Various pretreatments (sodium hydroxide, tetramethylammonium hydroxide, nitric acid, hydrochloric acid, and proteinase K)	spICP-MS	Distribution study	[177]
Ag NPs	Rainbow trout (*Oncorhynchus mykiss*)		TEM in combination with EDX	Characterization of Ag NPs in plankton and Ag found in fish using Ag NPs spiked tap water	[178]
Ag and Au NPs	Human whole blood	Minimal sample preparation	spICP-MS	nanogram per liter range, validation	[179]
Ag and Au NPs	Human urine, blood, and serum		spICP-MS and AF4-FFF-MALS-UV-ICP-MS	Concentration limits for spICP-MS in pg mL^{-1}, AF4-FFF-ICP-MS in ng mL^{-1}, AF4-FFF-ICP-MS could detect smaller sized NPs	[180]
Au NPs	Tomato plant tissues	Digestion with Macerozyme R-10	spICP-MS	LOD size 20 nm and Au NPs number concentration 1000 mL^{-1}	[181]
Au NPs	Liver and spleen of wistar rat	Alkaline and enzymatic (proteinase K) digestions	HPLC coupled to ICP-MS	Degradation process found of Au NPs intraperitoneally injected into Wistar rats	[182]
Au NPs	In vitro exposure to human breast cancer cell lines	Alkaline digestion of cells	spICP-MS	Analysis to qualify and quantify intracellular Au NPs content, confirmed validity of spICP-MS for quantification and size distribution	[183]
Au NPs	Mouse blood		spICP-MS	Detection of dynamic changes in size and concentration	[184]
Au, CuO, ZnO NPs	Plant materials (lettuce, corn, and kale)	Enzyme-based extraction and new methanol-based extraction	spICP-MS	MeOH extraction gave a reproducible particle size distribution without major alteration caused by the extraction	[185]
SiO_2 NPs	Biological serum	No chemical sample pretreatment	AF4 with NTA detector	Size- and number-based concentration in good agreement with MALS and ICP-MS	[186]
SiO_2 and TiO_2 NPs	Postmortem tissues (liver, spleen, kidney, intestinal, jejunum, ileum)	Validated sample digestion	spICP-HRMS, SEM with EDS	Detection of primary particles, aggregates, and agglomerates	[187]
TiO_2 NPs	Rice plant (*Oryza sativa* L.)	Acid digestion, enzymatic digestion	EM, spICP-MS, ICP-OES	Agreement of the results, size distribution information	[188]

Table 6: (continued)

Target nanoobject	Matrix[a]	Sample preparation	Detection/quantification method	Comments[a]	Reference
TiO_2 NPs, Ag NPs	Human urine	Samples diluted (1:5 to 1:10) with 10 cL L^{-1} glycerol	spICP-MS	Validation of the overall procedure	[189]
TiO_2 NPs	Radish plant (*Raphanus sativus* L.)	Enzymatic digestion	spICP-QQQ-MS, spICP-MS	Reduction in background level with a significant increase in the sensitivity	[190]
TiO_2 NPs	Spiked urine and blood	Dispersion media (polyvinylpyrrolidone and polyethylene glycol), sonication	DLS, spICP-MS	Sample preparation scheme development, use of SRM NIST 1898 NP	[191]
TiO_2 NPs	Edible mussels bred in polluted artificial seawater		ICP-MS, spICP-MS, TEM	Potential nanoparticle formation in vivo	[192]
CeO_2 NPs	Plants (cucumber, tomato, soybean, and pumpkin)	Enzymatic digestion with Macerozyme R-10 enzyme	spICP-MS	Size and size distribution, particle concentration, and dissolved cerium detection	[193]
CeO_2 NPs	Urine, plasma	Enzymatic digestion	spICP-MS, ICP-MS	Internal standardization in correcting the matrix effect in the spICP-MS analysis	[194]
Fe_3O_4 NPs (Ferumoxytol)	Spiking into rat blood plasma and cell fractions		AF4 coupled with UV–Vis, MALS, and ICP-MS, spICP-MS, TEM,	Increase in NPs diameter in plasma	[195]
Pt NPs	Uptake by plants (*Lepidium sativum* and *Sinapis alba*)	Enzymatic digestion	spICP-MS	Digestion without changing Pt NPs oxidation or aggregation state	[196]
Metal NPs	Shellfish seafood (clams and oysters)	Alkaline digestion	spICP-MS and ICP-MS	Determination and size distribution for Y, La, ce, pr, and Gd	[197]
Carbon nanoplastics and nanotubes	Eggshells	Extraction	AF4 coupled to MALS	Particle size distribution	[106]
Polystyrene (PS) and poly(methyl methacrylate) (PMMA) nanoplastics	Tissue of aquatic animals	Alkaline digestion and protein precipitation	Py GC-MS	A sensitive and robust method for chemical composition, mass concentration, and size distribution of nanoplastics, LOD of 0.03 μg g^{-1} for PS and 0.09 μg g^{-1} for PMMA	[198]
Polyvinylchloride (PVC), polyethylene terephthalate, polyethylene (PE), polystyrene (PS, 100 nm) nanoplastics	Oyster and fish tissues	Combination of common extraction, enzymatic digestion, sequential membrane filtration, centrifugal concentration, and purification (dialysis and sodium dodecylsulfate (SDS) incubation)	NTA, TEM, Raman spectra	Treatment with corolase enzyme complex and subsequently with lipase achieved the highest digestion efficiencies (88–89 %) without change of the morphology or structure of NPs	[199]

[a]Spiked matrix means a blank material with known quantity values of ENMs added.

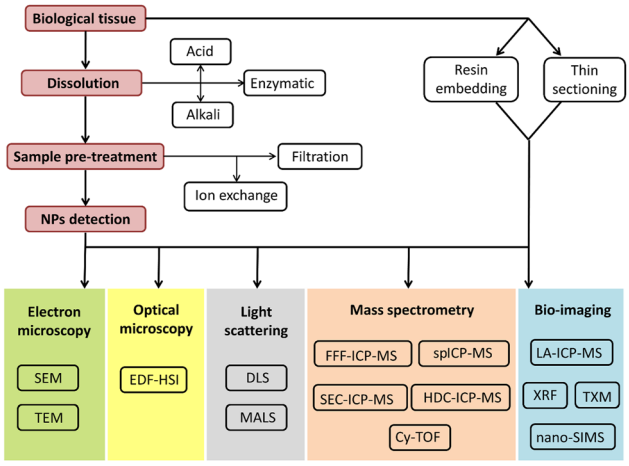

Fig. 3: Schematic illustration of individual sample preparation and analysis methods for detection, characterization, and quantification of nanoparticles in biological samples; adapted from [18].

it has found application in several studies of the cellular uptake of ENMs. Unlike in traditional spICP-MS where only *m/z* of the studied particle is acquired, Cy-TOF can collect a large number of *m/z* data simultaneously, which can be used to identify whether the detected particles are within the cell if the particle signal coincides with e.g., a nuclear marker. This instrument has been used, for instance, to quantitatively analyze and distinguish between intracellular Ag and cell-associated Ag after exposure of human T-lymphocytes cell line to Ag nanoparticles [168], for absolute quantification of Ag nanoparticles in a single cell [169], and for in vivo studies of the uptake of Au nanoparticles by lung cells following inhalation [170]. More recently, several studies have examined the heterogeneous nature of cell–nanoparticles interactions and investigated dose and/or size response effects for several metal nanoparticles [171–173].

In summary, when selecting the extraction protocol for analysis of ENMs present in the matrix, their physiochemical and chemical properties should be considered as they have a crucial impact on the accuracy of the reported results. While artifact formation is often discussed during the sample preparation steps, sample transportation and storage may also have a significant contribution. During the sample preparation it is absolutely critical to set an adequate minimum sample size that would be representative of the whole sample. Typical steps include homogenization, extraction, preconcentration or dilution, and stabilization of the ENMs in the suspension. Considering the number of steps taken prior to sample analysis, robust validation protocols need to be in place.

3.5 Fate of nanomaterials in environmental and biological matrices

3.5.1 Fate of engineered nanomaterials (ENMs) in environmental samples

The quantification and characterization of ENMs are crucial for the assessment of their environmental fate, transport behavior, and health risks. At the same time, ENMs are not static entities, and their characterization studies must also include information about the dynamics of the interfacial region between the nanomaterial surface and the surrounding medium. Thus, the identification and accurate characterization of engineered and naturally occurring nanoparticles is a difficult task. Biological interactions and environmental fate of engineered nanoparticles are affected by colloidal stability and aggregation. The fate of ENMs refers to both the chemical and physical changes (transformations) occurring to the particles while in natural systems, also to their mobility and localization in a specific environment. The physicochemical properties of the nanomaterial and the environmental conditions (e.g., pH, ionic strength, organic matter, and oxygen concentration) determine which transformation processes are relevant. The transformation processes may occur simultaneously or interfere with each other. Especially important is the fact that the pristine and transformed forms of nanoparticles may differ in uptake and toxicity (Fig. 4).

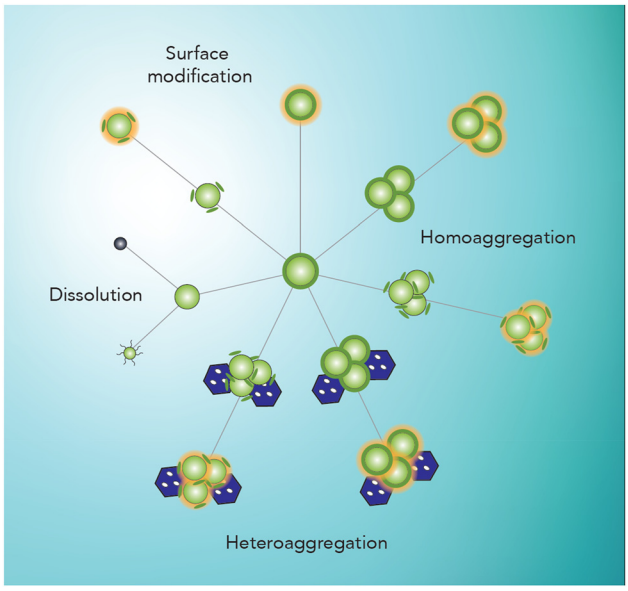

Fig. 4: Schematic overview of the processes determining the forms/species in which nanomaterials may occur in the natural environment; adapted from [57].

For instance, Ag nanoparticles adsorb dissolved organic matter (DOM), preferentially short-chained DOM compared to long-chain and aromatic ones, thus inhibiting aggregation at higher Ag nanoparticles concentrations [200]. The surface composition of TiO_2 (5 nm) and α-Fe_2O_3 (2 nm) nanoparticles was shown to be controlled by the adsorption of biological components (proteins and amino acids), inorganic oxyanions (phosphates and carbonates), and environmental ligands (humic acid). The extent of surface adsorption depends on the solution phase composition and the affinity of different components to adsorb to the nanoparticle surface with a range of possible surface interactions, adsorption energetics, and adsorption modes including reversible adsorption, irreversible adsorption, and co-adsorption [201]. The Ag nanoparticles released into the environment are mostly transformed into silver sulfide (Ag_2S) nanoparticles, and corresponding speciation analysis (Ag_2S, Ag, and AgCl nanoparticles in the presence of Ag^+ ions) by selective extraction and sequential elution is of importance for understanding environmental processes [202]. Fates of ZnO and CeO_2 nanoparticles during the typical drinking water treatment process investigated by spICP-MS confirmed that particle concentrations were reduced by a minimum of 60 % and most were reduced by more than 95 % from source water to final drinking water [203].

The major transformations of ENMs include:

- **Dissolution**. A transformation process is referred to as dissolution if it breaks the solid nanoscale (below 100 nm) form of the material down into ionic or molecular dispersions due to interactions with water or other solvents. Dissolution only affects inorganic nanomaterials (metal or metalloid). Organic and carbon-based inorganic nanomaterials, such as fullerenes and carbon nanotubes, do not dissolve, at least not in the same manner as metals or other chemical elements.
- **Attachment and aggregation** with natural particles (heteroaggregation). Nanomaterials are prone to form agglomerates with the natural suspended matter, natural colloids, and aerosols or attach to the surfaces of larger natural particles such as soil and sediment grains.
- **Sorption of natural organic matter**. Natural organic matter can be sorbed by particles in aqueous media to form a coating around the surface of the nanomaterial, also described as an eco-corona. The presence of a natural organic matter (NOM) coating is known to interfere with dissolution and heteroaggregation. Depending on the type of NOM, heteroaggregation is reduced by NOM that provides additional stability to nanomaterials by replacing the original coatings, resulting in electrostatic and steric repulsion between particles [204, 205].

The different properties of ENMs result in significant differences in the fate, transformation, antimicrobial activities, and effects on biological wastewater treatment [206]. Understanding the behavior of nanoparticles in the environment, such as their permeability into biological tissues, becomes key to understanding their toxicological effects. Analytical monitoring of the size distribution of the nanoparticles over time is a useful indication of their stability, which will influence other biological (including toxicity) and chemical reactions [56]. The fate of nanoparticles in the environment can be monitored by numerous analytical techniques mentioned above (Section 2). Most techniques used for nanoparticle aggregation analysis are limited to ensemble measurements or require harsh sample preparation that may introduce artifacts. An ideal method would analyze aggregate size in situ with single nanoparticle resolution. The spICP-MS method was established as a high-throughput analytical technique to quantify nanoparticle size distributions and aggregation in situ [207]. In addition, the novel coupled methods (called hyphenation techniques which typically represent the combination of a separation technique with spectroscopic detection technology) like **electrospray-differential mobility analysis with single-particle inductively coupled plasma mass spectrometry** (ES-DMA-spICP-MS) should have the capacity for real-time size, mass, and concentration measurement of nanoparticles on a particle-to-particle basis. The feasibility of this technique was validated through both concentration and mass calibration using NIST gold nanoparticle reference materials. The independent and simultaneous quantification of nanoparticle size and mass can provide detailed information on nanoparticle aggregation states, differentiating aggregated nanoparticles and nonaggregated states based on the "apparent density" derived from both DMA size and spICP-MS mass [208]. Using a combination of X-ray based spectroscopic image analysis with near edge X-ray absorption fine spectra (NEXAFS) possessed necessary analytical chemical information on nanoplastics particles [209].

Material flow models indicate that a variety of ENMs may accumulate in waste streams, generating nanowaste following the disposal of end-of-life ENMs and nano-enabled products. Challenges in nanowaste characterization and appropriate analytical techniques include: *separation techniques coupled to spectrometry-based methods* as promising tools to detect nanowaste and determine particle size distributions in liquid waste samples; *standardized leaching protocols* that can be applied to generate soluble fractions stemming from solid wastes, while microfiltration and ultrafiltration can be used to enrich nanoparticulate species; *imaging techniques combined with X-ray-based methods* as powerful tools for determining particle size, morphology, and screening elemental composition. Nonetheless, the quantification of nanowaste is currently hampered due mainly to difficulties in differentiating engineered from naturally occurring nanoparticles. A promising approach to deal with these challenges might be the application of nanotracers with unique optical properties, or elemental or isotopic fingerprints [210]. For analytical monitoring of fate of nanoplastics in municipal waste water treatment plants, the use of nanoparticles labeled with a rare metal like Pd or In is proposed [211].

3.5.2 Fate of engineered nanomaterials (ENMs) in biological systems and biodistribution

The biotransformation of nanoparticles involves different processes, including aggregation/agglomeration, and reactions with biomolecules that affect metabolism and are reflected in their toxicity [212]. Exposure of biological systems to ENMs can happen via different routes including ingestion of food or medicines, intravenous injection, inhalation, and skin contact (e.g., by body care products or textiles). Moreover, some nanoparticles are studied and used as drug carriers, radiosensitizers, and imaging agents. Their biodistribution is essential for evaluating their efficacy and safety [170]. The biodistribution of ENMs is affected by their chemical/elemental composition, size and size distribution, shape, coatings, surface properties, and their stability. For instance, cellular uptake of Ag nanoparticles is size-, dose- and coating-dependent [213]. The results of biodistribution studies give qualitative and often quantitative insights into the organs and tissues in which ENMs accumulate, and consequently, allow the determination of the actual dosage of ENMs at the site of toxicity as well as the organs that are at risk for suffering adverse effects from the ENMs [214]. Biodistribution studies are often carried out as in vivo studies for which test animals (often rats and mice) are commonly used, or, in some dedicated cases, humans [215]. Commonly, different parameters of interest are varied and tested, including ENM concentration, size, and shape as well as the duration of exposure, which is often up to 90 days.

From an analytical point of view, the reliable detection and quantification of the tissue distribution of ENMs is not trivial and requires well-developed methods and **multi-instrumental approaches**. All steps of the analysis must be properly addressed, including sample collection, sub-sampling, sample storage, sample preparation, and final instrumental analysis. For the dissolution of tissues and particle-containing body fluids, acid digestion in open or closed systems (generally with nitric acid in combination with hydrochloric acid, hydrofluoric acid, and hydrogen peroxide), enzymatic digestion or soft dissolutions and extractions are often used [214]. A variety of imaging and analytical methods have been developed to study nanoparticles in cells with benefits and limitations associated with each method. Here, HRSTEM should be mentioned with its unique ability to image the local environment of a nanoparticle at near-atomic resolution and apply analytical tools to these environments such as EDS and EELS [216]. The combination of ICP-MS and EM has been shown to be a valuable tool to identify which organs or tissues contain the most ENMs. Various types of ICP-MS and spICP-MS and related combined techniques together with XANES spectroscopy were used in the development of methylmercury detoxification mechanism via in vivo formation of HgSe nanoparticles [11].

The spICP-MS method was used to observe a size decrease for CeO_2 nanoparticles in lung and liver tissue over time [217], to detect Au nanoparticles in biological fluids [218], and to monitor the absorption and distribution of Ag nanoparticles into deeper skin layers in the ionized form [219]. In combination with DLS and UV–Vis, spICP-MS was also employed to evaluate changes in size, aggregation, chemical composition, and silver speciation of four different sizes of Ag nanoparticles exposed to four different formulations of artificial sweat [220]. To identify single nanoparticles of metals and metal oxides in biological tissues spICP-MS combined with FFF was used [214]. Complementary techniques (spICP-MS, TEM, and HPLC-ICP-MS) revealed the degradation of 40 nm citrate-stabilized Au nanoparticles in rat liver to smaller particles and low-molecular weight Au species [221]. Inductively coupled plasma mass spectrometry, X-ray fluorescence, and X-ray absorption spectroscopy helped to demonstrate the whole-body biodistribution of administrated SiO_2-Fe_3O_4 core–shell nanoparticles [222]. The application of μ-XANES showed the biotransformation of 25 nm CuO and $CuSO_4$ into $Cu_3(PO_4)_2$ (acute assays), whereas 40 and 80 nm CuO remained as CuO (chronic assays) [223]. Mass cytometry techniques have been developed for single-cell analyses and used to quantify the cellular association of inorganic nanoparticles [171], and the heterogeneous interaction between nanoparticles and human immune cells at a single-cell level [172].

Analytical methods for the determination of **nanoliposomes** and their associated fate in vivo include fluorescence labeling, radiolabeling, magnetic resonance imaging (MRI), MS, and computed tomography, each with its applicability and limitations [224]. **Nanoplastics** are potentially more hazardous than microplastics because of their small size, allowing them to penetrate cell membranes, induce toxicological impact on their environment, and cause possible risk to humans [225]. The mutual interrelationship between vascular plants and micro- and nanoplastics began to attract attention considering both the effect of vascular plants on the fate of these plastics and the effect of plastics on vascular plants [226]. Fluorescence confocal microscopy (LSCM) and SEM have been used to observe the internalization and specific locations of nanoplastics after absorption on plants [227].

4 Summary and future challenges

Engineered nanomaterials important today and in future in many technology areas, including advanced manufacturing, healthcare, and food safety, need reliable and economical methods for their detection and monitoring. Physical characterization and chemical analysis of ENMs require measurement of size and shape, analysis of chemical composition and surface coatings, significantly exceeds the requirements for conventional chemical analytes. Moreover, there is a difference between pristine ENMs which have clearly defined chemical composition of their core, specific surface coatings, and monodisperse size distributions, and the same nanomaterials in complex, real-world matrices where they typically undergo different transformations. This results in difficulties with the identification, characterization, and quantification of these materials and requires much more complex analytical approaches. Hence, the analysis of ENMs is not feasible with a single analytical technique but rather requires a combination of multiple sophisticated procedures and instrumentation.

In this report, the achievements of existing modern and powerful methods for chemical analysis of ENMs in complex matrices have been reviewed, and progress toward their further improvement has been demonstrated. These advances in scientific and practical analytical work require the development of sample preparation and sample storage techniques that introduce minimal artifacts to the analysis. The analytical techniques must differentiate between manufactured ENMs and nanomaterials that occur naturally in environmental and biological matrices in which they can undergo possible transformations resulting in different fate.

Since a large number of ENMs are of inorganic nature, the ICP-MS method in its classical and single-particle modes (spICP-MS), often coupled with separation methods within hyphenated techniques, represents one of the most intensively developed and applied chemical analytical approaches. Particle number concentration measurement by spICP-MS was found to agree well with several other techniques, many of which are much more established. Thus, the unique combination of extremely rapid analysis and trueness makes spICP-MS a practical technique, but the metrological infrastructure needed for its full application in the real world is inadequately developed.

In conclusion, it can be stated that the field of chemical analysis of ENMs is new, still in the stage of accumulation of new factual material, and will continuously expand and develop. The required analytical data are both imperative for understanding the behavior of ENM in complex matrices and challenging for current analytical methodologies. Validation of methods is required and should be based on standardized (reference) materials and the organization of interlaboratory comparison studies at the international level.

List of abbreviations

AAS	atomic absorption spectrometry
AFM	atomic force microscopy
AF4	asymmetric flow field-flow fractionation (FFF)
AUC	analytical ultracentrifugation
BSA	bovine serum albumin
BET	Brunauer–Emmett–Teller specific surface area analysis
CBED	convergent-beam electron diffraction
CE	capillary electrophoresis
CL	chemiluminiscence
CLS	centrifugal liquid sedimentation
CPE	cloud-point extraction
Cy-TOF	mass cytometry
DLS	dynamic light scattering
DCS	differential centrifugal sedimentation
DLS	diameter laser scattering
DOM	dissolved organic matter
DSPE	dispersive solid-phase extraction (SPE)
EDF-HSI	enhanced dark-field microscopy with hyperspectral imaging
EDS	energy dispersive X-ray spectroscopy
EDX	energy-dispersive X-ray analysis
EELS	electron energy-loss spectroscopy
EF	extraction factor
EM	electron microscopy
ENM	engineered nanomaterial
EPLS	elliptically polarized light scattering
EPM	electrophoretic mobility
ES-DMA-spICP-MS	electrospray-differential mobility analysis with single particle inductively coupled plasma mass spectrometry (spICP-MS)
ESEM	environmental scanning electron microscopy
ETAAS	electrothermal atomic absorption spectrometry (AAS)
EXAFS	extended X-ray absorption fine structure

FAAS	flame atomic absorption spectrometry (AAS)
FEG-SEM/EDS	field-emission gun scanning electron microscopy/energy dispersive X-ray spectroscopy (SEM/EDS)
FFF	field-flow fractionation
Fl	fluorescence
FlFFF	flow field-flow fractionation (also flow FFF, F4)
FMR	functional magnetic resonance
FT-IR	Fourier transform infrared spectroscopy
GC-MS	gas chromatography-mass spectrometry (MS)
GE	gel electrophoresis
GFAAS	graphite furnace atomic absorption spectrometry (AAS)
HDC	hydrodynamic chromatography
HFSLME	hollow fiber supported liquid membrane extraction
HGAFS	hydride generation atomic fluorescent spectrometry
HPLC	high performance liquid chromatography (LC)
HRTEM	high resolution transmission electron microscopy (TEM)
ICP-MS	inductively coupled plasma mass spectrometry (MS)
ICP-OES	inductively coupled plasma optical emission spectrometry
ICP-Q-MS	inductively coupled plasma quadrupole mass spectrometry (MS)
ICP-TOF-MS	inductively coupled plasma time-of-flight mass spectrometry (MS)
LA-ICP-MS	laser ablation inductively coupled plasma mass spectrometry (ICP-MS)
LC	liquid chromatography
LC-HRMS	liquid chromatography high resolution mass spectrometry (MS)
LSCM	laser scanning confocal microscopy
LC UV	liquid chromatography with UV detection
LEIS	low-energy ion scattering
LOD	limit of detection
MAD	microwave-assisted digestion
MALS	multi-angle light-scattering
MECC	electrokinetic capillary chromatography
MFM	magnetic force microscopy
MS	mass spectrometry
nano-SIMS	nanoscale secondary ion mass spectrometry
NOM	natural organic matter
NMR	nuclear magnetic resonance
NP	nanoparticle
NTA	nanoparticle tracking analysis
PCC	particle collision coulometry
PL	photoluminescence spectroscopy
PTA	particle tracking analysis
Py-GC-MS	pyrolysis gas chromatography-mass spectrometry (GC MS)
RISE	Raman imaging and scanning electron microscopy
RMM-MEMS	resonant mass measurement microelectromechanical system
SAED	selected-area electron diffraction
SAXS	small-angle X-ray scattering
SDS	sodium dodecyl sulfate
SEC	size exclusion chromatography
SEM	scanning electron microscopy
SERS	surface-enhanced Raman spectroscopy
SME	solvent microextraction
SPAMS	single-particle aerosol mass spectrometry (MS)
SPE	solid-phase extraction
spICP-MS	single particle inductively coupled plasma mass spectrometry (ICP-MS)
STEM	scanning transmission electron microscopy (TEM)
STM	scanning tunneling microscopy
SQUID	superconducting quantum interference device (also scanning SQUID microscopy)
TED-GC-MS	thermal extraction desorption gas chromatography-mass spectrometry (GC-MS)
TEM	transmission electron microscopy
TOC	total organic carbon
TRPS	tunable resistive pulse sensing

TXM	transition X-ray microscopy
UV–Vis	Ultraviolet–visible spectrometry
VIP	voltammetry of immobilized particles
VPSEM	variable-pressure scanning electron microscopy (SEM)
VSM	vibrating sample magnetometry
XANES	near-edge X-ray absorption spectroscopy
XAS	X-ray absorption spectrometry
XMCD	X-ray magnetic circular dichroism
XPS	X-ray photoelectron spectrometry
XRF	X-ray fluorescence
XRD	X-ray diffraction

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Research funding: This document was prepared in the framework of IUPAC Project 2017-005-3-500. Sponsoring bodies: The Analytical Chemistry Division, Chemistry and Human Health Division and the Chemistry and the Environment Division: see more details on p. xx.

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