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Critical Review

Current Methods and Prospects for Analysis and Characterization of Nanomaterials in the Environment

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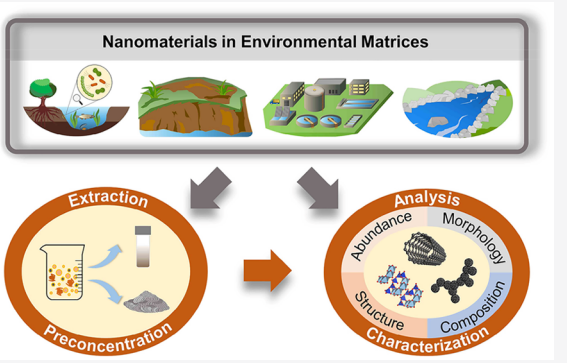
ABSTRACT: Analysis and characterization of naturally occurring and engineered nanomaterials in the environment are critical for understanding their environmental behaviors and defining real exposure scenarios for environmental risk assessment. However, this is challenging primarily due to the low concentration, structural heterogeneity, and dynamic transformation of nanomaterials in complex environmental matrices. In this critical review, we first summarize sample pretreatment methods developed for separation and preconcentration of nanomaterials from environmental samples, including natural waters, wastewater, soils, sediments, and biological media. Then, we review the state-of-the-art microscopic, spectroscopic, mass spectrometric, electrochemical, and size-fractionation methods for determination of mass and number abundance, as well as the morphological, compositional, and structural properties of nanomaterials, with discussion on their advantages and limitations. Despite recent advances in detecting and characterizing nanomaterials in the environment, challenges remain to improve the analytical sensitivity and resolution and to expand the method applications. It is important to develop methods for simultaneous determination of multifaceted nanomaterial properties for *in situ* analysis and characterization of nanomaterials under dynamic environmental conditions and for detection of nanoscale contaminants of emerging concern (e.g., nanoplastics and biological nanoparticles), which will greatly facilitate the standardization of nanomaterial analysis and characterization methods for environmental samples.



KEYWORDS: *Natural nanomaterials, engineered nanomaterials, environmental samples, sample pretreatment, abundance, morphology, composition, structure*

INTRODUCTION

Nanomaterials originated from both natural and anthropogenic sources are ubiquitous on Earth's surface.[1] Naturally occurring nanomaterials with various compositions, such as nanoscale metal oxides, sulfides, and carbonaceous materials, have abundantly existed in the atmosphere, hydrosphere, lithosphere, and biosphere for billions of years.[2,3] Furthermore, the rapid development of nanotechnology in the past few decades has led to the vast production of engineered nanomaterials (ENMs) with specific functions in almost all aspects of modern life,[4] and these nanomaterials are inevitably released to different environmental media during material production, utilization, and disposal.[5,6] Therefore, millions of tons of ENMs enter the environment as a result of accidental and incidental releases.[1]

Owing to the large specific surface area and high surface energy, nanomaterials may play critical roles in biogeochemical cycling of their constitutive elements.[1,7] In particular, nanomaterials often possess unique surface properties, and thus, the reactivity and bioavailability of nanomaterials in environmental processes tend to deviate from their bulk-scale counterparts.[8,9] The extent to which nanomaterials may be beneficial or detrimental to the natural environment and human health may not be accurately predicted based on the existing knowledge of the dissolved or bulk species with the same elemental composition.[10,11] To understand the environmental behavior, fate, and effects of nanomaterials, it is important to obtain information regarding their occurrence and evolving characteristics, including mass and number abundances, as well as their morphological, compositional, electronic, and structural properties.

To address this need, an array of microscopic, spectroscopic, mass spectrometric, electrochemical, and light scattering-based techniques have been made available for the analysis and characterization of nanomaterials from relatively simple samples (e.g., pure materials or liquid suspensions).[12] However, in

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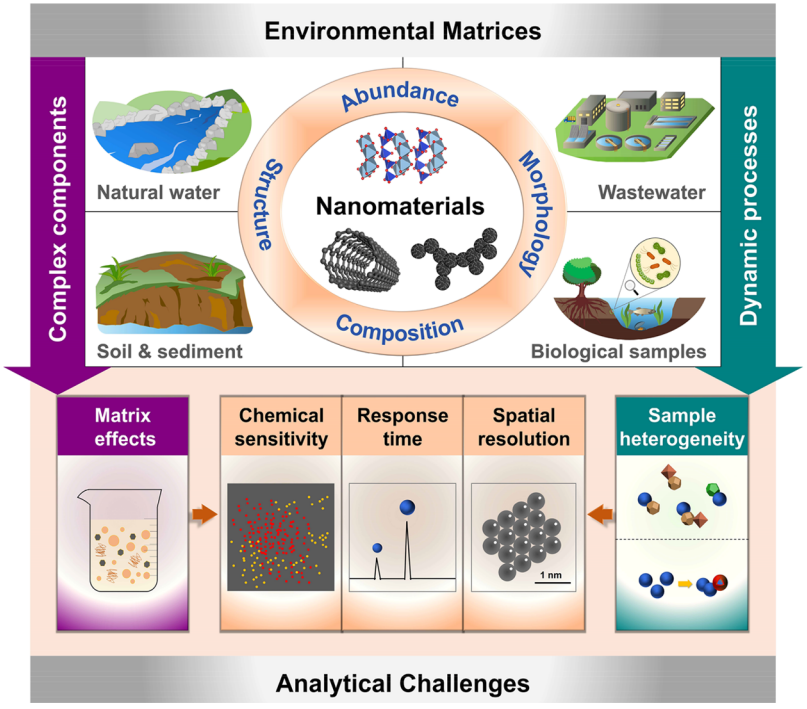

Figure 1. Challenges for the analysis and characterization of nanomaterials in various environmental matrices, such as natural waters, wastewater, soils, and sediments, as well as biological samples. These challenges arise primarily from the matrix effects and sample heterogeneity induced by the complex environmental components and dynamic environmental processes, which call for improved chemical sensitivity, response time, and spatial resolution to obtain accurate information on the abundance, morphology, composition, and structure of nanomaterials in the environment.

complex real-world environmental matrices, analyzing nanomaterials with sufficient spatial and chemical resolutions remains rather challenging (Figure 1). This challenge is magnified by the coexistence of various nanomaterials of diverse chemical compositions (and different morphologies and structures) in the environment (Figure 2). On one hand, natural nanomaterials (NNMs) and environmentally weathered ENMs tend to be extremely complex in elemental composition, crystalline phases, or functional groups.[13−15] The overall properties and behaviors of these nanomaterials may not be appropriately represented by summation of the coexisting components. Thus, appropriate chemical and spatial resolutions are essential for analyzing these nanomaterials, particularly when the minor fractions may dictate the nanoscale reactions. On the other hand, the concentrations of ENMs in environmental samples are often low,[16,17] and hence, analyses of these nanomaterials are hindered by matrix effects induced by high-abundance environmental substances (e.g., soil minerals, macromolecules, living organisms, dissolved ions, and complexes).[16] In most cases, sample pretreatment procedures, such as extraction and preconcentration, are needed to enhance the analytical detection limits.[18,19]

In this critical review, we summarize the state-of-the-art methods for analyzing and characterizing nanomaterials in complex environmental matrices, including natural waters, wastewater, soils/sediments, and biological samples (e.g., animals, plants, and microorganisms). Measurement and characterization of airborne nanoscale particulate matter is a research hotspot in atmospheric environmental studies and has been comprehensively reviewed elsewhere;[20,21] herein, it is only sporadically discussed when pertinent to a technique with versatile applications. In the following sections, we first review recent advances in methodology for extracting and preconcentrating nanomaterials from environmental matrices and then

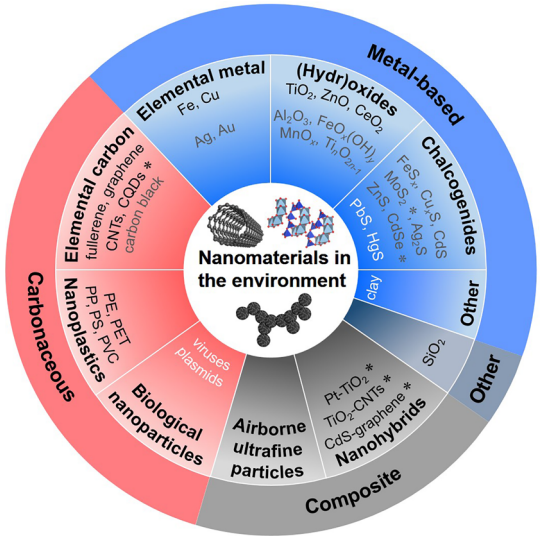

Figure 2. Category of nanomaterials of various compositions (metal-based, carbonaceous, composite, and other nanomaterials) in the environment.[1,5,7,16,22] These nanomaterials have different abundances and degrees of compositional/structural complexity, which pose different challenges for their analysis and characterization. Specific nanomaterials with predominantly anthropogenic, predominantly natural, or both anthropogenic and natural sources are denoted with black, white, and gray fonts, respectively. Nanomaterials with expected environmental release but no documented detection in the environment are denoted by asterisks. Abbreviations: CNTs, carbon nanotubes; CQDs, carbon quantum dots; PE, polyethylene; PET, polyethylene terephthalate; PP, polypropylene; PS, polystyrene; PVC, polyvinyl chloride.

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discuss the applicability and limitations of current and emerging techniques to identify, characterize, and quantify nanomaterials. Finally, we offer perspectives on future research needs for the development of analytical and characterization methods for environmental nanotechnology and nanogeoscience studies.

SAMPLE PRETREATMENT FOR ANALYSIS AND CHARACTERIZATION OF NANOMATERIALS IN ENVIRONMENTAL MATRICES

Nanomaterials in environmental matrices (e.g., waters, soils/sediments, and organisms) typically need to be separated from the matrix prior to analysis and characterization. The concentrations of ENMs in aquatic environments are normally lower than the detection limits of most currently available analytical techniques for nanomaterials. Moreover, the ions and natural colloids abundantly present in environmental matrices tend to interfere with the analysis of ENMs. Thus, an extraction process is often needed to preconcentrate the nanomaterials while removing the interfering constituents. Nanomaterials in soils/sediments and biological samples are usually first extracted into a liquid matrix, which can be analyzed with or without further treatment. In this section, we summarize the applicability and limitations of current methods for extraction and preconcentration of nanomaterials from complex environmental matrices to obtain samples in a form suitable for downstream analysis and characterization (Figure 3).

Preconcentration of Nanomaterials from Aqueous Samples. The low concentrations of ENMs in typical aquatic environments (normally ranging from 10^{-2} to 10 μg/L in surface waters and from 10 to 10^2 μg/L in municipal wastewater)[16] are major factors preventing their detection and characterization by techniques commonly used for characterizing nanoparticle (NP) suspensions at higher concentrations (>0.1 mg/L), such as dynamic light scattering (DLS), nanoparticle tracking analysis (NTA), and differential centrifugal sedimentation (DCS).[23,24] In addition to conventional NP separation and preconcentration methods (e.g., ultracentrifugation, ultrafiltration, and dialysis),[25] extraction methods including solid-phase extraction (SPE), liquid-phase extraction (LPE), and cloud point extraction (CPE), have been developed to separate and preconcentrate nanomaterials from aqueous media for subsequent analysis.[18,19]

A variety of solid materials and devices have been used for extracting nanomaterials from aqueous matrices, including ion-exchange resin, C-18-based SPE columns, membranes, and magnetic adsorbent materials. In early studies, commercial ion-exchange resin[26] or C-18 columns[27] were used as adsorbents. Recently, capillary column-based solid-phase microextraction (SPME) techniques, including hydrophilic polymer monolithic capillary microextraction[28−30] and in-tube SPME,[31] have been used to extract metallic (e.g., Au and Ag)[28,29,31] and insoluble metal oxide (e.g., TiO_2)[30] NPs from aqueous matrices. Membrane materials (e.g., polyvinylidene fluoride micropore membrane) have also been tested for SPE of nanomaterials and achieved high enrichment factors.[32,33] Alternatively, magnetic solid-phase extraction employing Fe_3O_4-based adsorbents[34−37] has proved to be a facile method for extracting nanomaterials from environmental waters, and the NP-loaded adsorbents can be collected by simply applying a magnetic field.[35,36] Notably, most of these SPE methods have been used to extract nanomaterials with relatively high chemical stability and minimal water solubility. Whether these SPE methods work for more labile and soluble nanomaterials, such as ZnO and CuO NPs, remains to be validated.

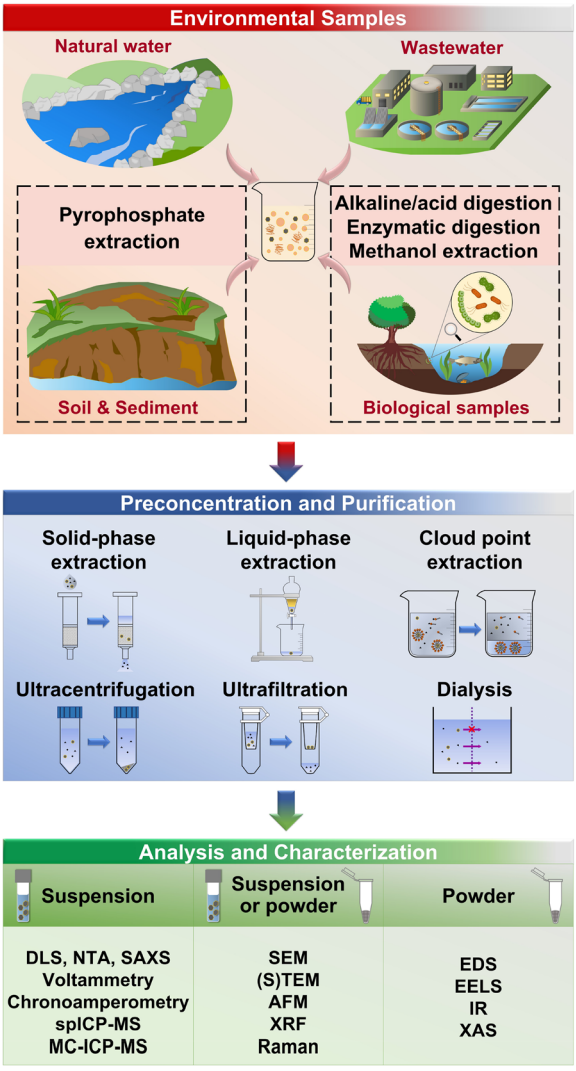

Figure 3. Methods for extracting and preconcentrating nanomaterials from complex environmental matrices to obtain liquid suspension or solid powder samples prior to analysis and characterization. (Acronyms for the analysis and characterization methods are given in the List of Acronyms.)

Regarding LPE methods, nanomaterials in aqueous samples are extracted into water-immiscible ionic liquids[38,39] or organic solvents (e.g., hexane and cyclohexane)[40,41] after surface modification of the nanomaterials with surfactants. Quantitative transfer of nanomaterials from the aqueous phase into the ionic liquids can be facilitated by the addition of cationic surfactants,[38,39] whereas that into organic solvents entails hydrophobization of nanomaterial surface.[40,41] In either case, the surface properties of the nanomaterials, and possibly their aggregation states, are drastically changed, which has limited the application of LPE.

The CPE methods usually involve using a trace level of Triton X-114 (TX-114), a nonionic surfactant with a lower critical solution temperature (LCST) of 23−25 °C, and salts (e.g., NaCl and $NaNO_3$) to promote phase separation. When the surfactant-added sample is heated to a temperature above the LCST of TX-114, micelles are formed, and a variety of metal-based and carbonaceous nanomaterials can be extracted into the surfactant-rich phase, achieving enrichment factors on the order of 10^2.[42,43] The TX-114-based CPE has proved to be a

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robust method against matrix interferences (e.g., salts, organic matter, and inorganic colloids)[44] and has been successfully used to extract Ag,[43,45] ZnO,[46] CuO,[47] Ag_2S,[48] and ZnS[48] NPs spiked in environmental waters for subsequent inductively coupled plasma mass spectrometry (ICP-MS) quantification, with limit of detection (LOD) ranging from 6 to 50 ng/L. The extracted nanomaterials in the surfactant-rich phase can also be directly analyzed by electrothermal atomic absorption spectrometry, which could improve the LOD by 1 order of magnitude, for example, 0.7 ng/L for Ag NPs.[49] To minimize the interference of dissolved metal ions (e.g., Ag^+, Zn^{2+}, and Cu^{2+}), a complexing agent, such as thiosulfate,[43] ethylenediaminetetraacetate,[46−49] or thiocyanate,[50] can be added to prevent the coextraction of dissolved species. The CPE methods are also capable of extracting nanomaterials with different surface coatings (with the exception of bovine serum albumin)[44,47] or a mixture of different NPs (e.g., Ag, Au, and Fe_3O_4).[51]

Extraction of Nanomaterials from Soil and Sediment Samples. Nanomaterials in solid-containing environmental matrices such as soils, sediments, and sludge usually need to be extracted from the matrices prior to analysis and characterization, although in some cases the sample may be analyzed/characterized *in situ* (e.g., with electron microscopy). The extracts, which contain coextracted soil components, are usually further treated to preconcentrate/fractionate nanomaterials to minimize interferences from the abundant colloidal particles extracted along with the target nanomaterials.[52−54] Extraction methods for nanomaterials in soils and sediments have been intensively studied in the past few years, aiming to achieve high and consistent recoveries while preserving the intrinsic properties of nanomaterials. Standard leaching tests have been used to extract nanomaterials from soils and sediments.[55] However, these methods suffer from inconsistent recoveries and interferences from chemical species other than nanomaterials, such as dissolved ionic metals, which hamper accurate quantification and characterization of the nanomaterials.

Modified extraction methods have recently been developed to improve NP recoveries and achieve speciation analysis in soils or sediments. Notably, sodium pyrophosphate, an established reagent for extracting organic and inorganic colloids,[56,57] including NNMs,[57,58] from soils and sediments, has recently been demonstrated to be efficient for extracting various ENMs with enhanced recoveries. A recent study evaluated the efficiency of various extractants, including sodium pyrophosphate, in extracting nanoparticulate Ag from a field soil amended with biosolids containing Ag NPs and reported that pyrophosphate, among the tested reagents, showed the highest recoveries of nanoparticulate Ag while inhibiting its dissolution.[59] After optimization, the pyrophosphate-based method could efficiently extract Ag NPs at low concentrations (on the order of 0.1 μg/g soil).[60] In organic-rich soils, the recovery of nanomaterials may be improved by UV digestion, which could effectively degrade soil organic matter and release nanomaterials.[61] Most recently, pyrophosphate-based sequential extraction methods have been developed to distinguish between metallic (e.g., Au and Ag) nanoparticles and the respective metal ions in soils and sediments.[62,63]

Although pyrophosphate-based reagents are by far the most commonly used extractants for separating nanomaterials from soils/sediments, their applications have been limited to extracting nanomaterials with low water solubility (e.g., Au, Ag, TiO_2, and CeO_2),[59−65] for which dissolution during extraction causes only negligible artifacts. To extract moderately soluble nanomaterials, such as CuO NPs, from soils/sediments, a multistep method was recently developed. This approach uses a mixture extractant that contains a dispersing agent, a metal ion chelating agent, and an alkaline pH buffer.[66] The extraction was followed by CPE to separate CuO NPs from dissolved copper(II) species. However, the extraction efficiency was relatively low (i.e., 46% after three cycles) under optimized conditions,[66] and this method remains to be validated for the extraction of nanomaterials with greater solubility.

Extraction of Nanomaterials from Biological Samples. Different from soil and sediment samples, in which nanomaterials are often associated with the surface of mineral particles, nanomaterials may be assimilated by organisms and reside within tissues or cells in biological samples. Hence, extraction of nanomaterials from biological matrices, such as animal and plant tissues and microbial cells, is more challenging and requires methods capable of effectively digesting the biological tissues while causing minimal alteration to the properties of nanomaterials. However, traditional digestion methods for biological samples (e.g., acid digestion) are not applicable for extracting labile metal-based nanomaterials (e.g., Ag, ZnO, and CuO NPs) from biological matrices due to potential dissolution of these nanomaterials during digestion. In contrast, digestion of biological tissues with enzymes or organic bases has been used to extract labile metal-based nanomaterials, as these digestion methods cause minimal alteration to nanomaterials and yield an extract compatible for various downstream analysis.[67,68]

Enzymatic and alkaline digestion are commonly used to extract metal-based nanomaterials from animal tissues. Enzymatic digestion using proteinase K enabled the extraction of metallic[67,68] and insoluble metal oxide (e.g., TiO_2) NPs[69] from mammalian tissues, but subsequent single particle ICP-MS (spICP-MS) analysis yielded low recoveries (e.g., 68%),[67] possibly because tissue residues after enzymatic digestion could deteriorate the transport efficiency of nanomaterials in the spICP-MS analysis.[68] Efforts have been made to improve the recovery of enzymatic digestion. For instance, the addition of hydrogen peroxide after enzymatic digestion with proteinase K improved the recoveries for CeO_2 NPs from zebrafish tissues.[70] Ultrasound-assisted enzymatic digestion using a mixture of pancreatin and lipase recently has been developed to extract engineered (e.g., TiO_2)[71] NPs spiked in bivalve mollusks with high recoveries and successfully used for the analysis of various metal-containing nanomaterials in marine bivalve mollusks.[72] Compared to enzymatic digestion, alkaline digestion using tetramethylammonium hydroxide (TMAH) yielded higher recoveries for Au and Ag NPs in mammalian tissues,[73] as well as in a variety of commonly used model organisms for environmental studies.[73−75] However, alkaline digestion with relatively high TMAH concentrations (e.g., ≥5%, v/v) over an extended period of time led to dissolution of Ag NPs,[59,76,77] and thus, alkaline digestion procedures should be pretested and optimized to avoid artifacts. Meanwhile, it was recently demonstrated that TMAH used in alkaline digestion of rainbow trout liver tissue caused precipitation of Ag^+, which could interfere with the spICP-MS analysis, and this challenge may be tackled by the use of $CaCl_2$ during digestion.[78]

For plant tissues, although acid digestion has been used to extract carbon-based nanomaterials (e.g., multiwalled carbon nanotubes)[79] and insoluble metal oxide (e.g., TiO_2) NPs,[80] more labile metal-containing nanomaterials are commonly extracted by enzymatic digestion, mainly with Macerozyme R-10, a macerating enzyme from *Rhizopus* sp. This method has

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Environ. Sci. Technol. 2022, 56, 7426−7447

Table 1. Applicability of Techniques for Analyzing and Characterizing the Abundance, Morphology, Composition, and Structure of Nanomaterials in Environmental Samples[a]

Category	Technique	Abundance	Morphology	Composition	Structure
Microscopic techniques	SEM	number conc. (sq.)	shape and size of primary particles, resolution: down to 1 nm[98]	N/A	N/A
	(S)TEM (with SAED)	number conc. (sq.)	shape and size of primary particles, resolution: down to 0.1 nm[98]	chemical components (requiring supplementary information)	crystal phase, crystallinity, defects
	AFM	presence of nanoscale particles (ql.)	shape and size of primary particles and aggregates; longitudinal resolution: 0.1 nm; lateral resolution: down to 0.1 nm[99]	N/A	N/A
Spectroscopic techniques	EDS	mass conc. (sq.)	shape and size, resolution: down to 1 nm[100] (when coupled with STEM)	elements	N/A
	EELS	N/A	shape and size, resolution: down to 0.4 nm[101]	elements, oxidation states	chemical bonding
	XRF (μ-, nano-)	mass conc. (sq.)	size, resolution: down to 50 nm[100,102]	elements	N/A
	IR	mass conc. (qn.), LOD down to 1 μg/L or 1 μg/g level (for NIRF)[103,104]	N/A	functional groups	N/A
	Raman	mass conc. (qn.), LOD down to μg/L level with pretreatment (for SERS)[105,106]	N/A	chemical components	chemical bonding, defects
	XAS	N/A	N/A	elements	chemical bonding, defects
Mass spectrometric techniques	spICP-MS	number and mass conc. (qn.), with LOD on the order of 10^4/L to 10^6/L for number conc. and < ng/L for mass conc.[107−109]	size (requiring information on NP shape), detection limit: 3−180 nm (element-specific)[110]	elements/isotopes	N/A
	LA-ICP-MS	mass conc. (qn.), with ng/g LOD[100]	N/A	elements/isotopes	N/A
	nanoSIMS	N/A	size, resolution: down to 50 nm[111]	elements/isotopes	N/A
	MC-ICP-MS	N/A	N/A	elements/isotopes (with relatively high precision of isotope ratios)[112]	N/A
Light scattering-based techniques	DLS	number conc. (sq.)	size (hydrodynamic diameter) of aggregates	N/A	N/A
	NTA	number conc. (qn.) with 10^{10}/L LOD[113]	size (hydrodynamic diameter; 30−1000 nm)[114,115] of aggregates	N/A	N/A
	SAXS	number conc. (sq.)	size of primary particles and aggregates	N/A	N/A
Electrochemical techniques	Voltammetry	number and mass conc. (qn.), with 10^{10}/L to 10^{11}/L LOD for number conc. and correspondingly μg/L LOD for mass conc.[116,117]	N/A	N/A	N/A
	Chronoamperometry	number conc. (qn.), ng/L LOD; time resolution: 1 min[118]	size of primary particles and aggregates	chemical components (requiring supplementary information)	crystallinity

[a]Abbreviations: conc., concentration; LOD, limit of detection; N/A, not applicable; ql., qualitative; qn., quantitative; sq., semiquantitative. Acronyms for the analysis and characterization methods are given in the List of Acronyms.

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Environ. Sci. Technol. 2022, 56, 7426−7447

been used to investigate the uptake and bioaccumulation of various nanomaterials, including metallic (e.g., Au, Ag, and Pt),[81−85] insoluble metal oxide (e.g., CeO_2 and TiO_2),[80,84,86] and metal sulfide (e.g., Ag_2S)[87] NPs in plants. Recently, this method was used to extract CuO NPs, a moderately soluble metal oxide nanomaterial, from plant tissues, but the recovery was not reported.[88] Alternatively, a methanol-based protocol was recently developed for extracting both insoluble (e.g., Au) and moderately water-soluble (e.g., CuO and ZnO) NPs from leaf tissues of plants prior to spICP-MS analysis, which yielded recoveries as high as 100%, 81%−99%, and 69%−95%, respectively, for Au, CuO, and ZnO NPs, and limited artifacts in particle size measurement.[89]

Unlike animal and plant tissues, unicellular microorganism samples require minimal sample preparation prior to analysis. The small sizes and simple physiologies of microbial cells allow for direct analysis of these samples using single-cell ICP-MS[90,91] and optical microscopy[92] for assessing cellular uptake of metal- and carbon-based nanomaterials. While nanomaterials in microorganisms (e.g., yeast cells) can be extracted using enzymatic digestion,[77,93] analysis of nanomaterials in unicellular microorganisms can also be achieved more facilely after mechanical lysis of the cells.[94−96] For instance, a simple procedure involving sonication in deionized water was used to lyse marine microbial cells for subsequent spICP-MS analysis of Ag NPs.[94] More recently, a glass microbead-assisted sonication method was developed for more efficient lysis of yeast[95] and bacteria[96] cells for analysis of metal-based nanomaterials.

METHODS TO IDENTIFY, CHARACTERIZE, AND QUANTIFY NANOMATERIALS IN ENVIRONMENTAL SAMPLES

In this section, we discuss the capabilities and limitations of currently available and emerging techniques for obtaining the morphological, compositional, and structural properties of nanomaterials in the environment, including electron microscopic, spectroscopic, mass spectrometric, and electrochemical techniques (Table 1), along with size fractionation techniques. Many of the listed methods can be used to (semi)quantitatively determine the abundance of nanomaterials in different environmental matrices, with varying LODs, among which spICP-MS and chronoamperometry stand out for their high sensitivity. The morphologies (i.e., shapes and sizes) of nanomaterials can be characterized by various microscopic and spectroscopic techniques with different spatial resolutions. Many techniques can also provide information on the chemical, elemental, and even isotopic composition of nanomaterials, including the type of functional groups and the oxidation state of elements, whereas fewer techniques can be used to characterize the crystal structure of nanomaterials, providing information such as crystallinity, crystal phase, type of chemical bonding, and the presence of defects. Light scattering-based techniques such as DLS, NTA, and small-angle X-ray scattering (SAXS) are useful tools for characterizing the sizes and aggregation states of nanomaterials in aqueous suspension. However, these techniques require relatively high particle concentrations.[23,24,97] The principles and practical considerations of the light scattering-based techniques have been summarized in recent reviews[12,24,97] and thus are not discussed herein.

Electron Microscopy-Based Methods. Electron microscopy techniques, such as scanning electron microscopy (SEM), transmission electron microscopy (TEM), and scanning TEM (STEM), are commonly used to determine the size and morphology of nanomaterials. However, definitive identification of nanomaterials in environmental samples using electron microscopy may be hampered by artifacts due to the presence of nanoscale objects inherent in the matrix (e.g., cellular structures in biological samples) or introduced during sample preparation.[119,120] Such artifacts can be avoided by coupling with elemental and structural analysis, such as energy-dispersive X-ray spectroscopy (EDS) and selected area electron diffraction (SAED), and electron microscopy-based technologies have been widely used for the identification and characterization of low-concentration nanomaterials in complex matrices, including airborne particulate matter,[121] sewage sludge,[122] wastewater,[123] surface waters,[124] and plant tissues.[80] In addition to SAED,[121,122,125] information on the crystal structure of crystalline nanomaterials can be obtained by analyzing lattice fringes observed by high-resolution TEM.[121−123] Furthermore, the latest spherical aberration-corrected high angle annular dark field STEM can achieve atomic-level spatial resolution (below 0.1 nm), allowing for unambiguous identification of the crystal structure as well as the presence of crystal defects.[126−129]

The high vacuum condition in the electron microscope instruments requires that the samples should be in a dehydrated state, and artifacts due to aggregation of nanomaterials and precipitation of salts may occur during sample preparation, which typically involves drop deposition (and subsequent solvent evaporation), adsorption deposition, or ultracentrifugation harvesting.[25] In contrast, some electron microscopy techniques have enabled the observation of samples in hydrated forms. Environmental SEM (ESEM), or atmospheric SEM, which operates under relatively low vacuum (on the order of 10^2 to 10^3 Pa), allows characterization of nanomaterials in hydrated samples (e.g., wet soil),[130,131] and the latest modifications of ESEM, namely, "Wet-SEM" or "Wet-STEM", allow observation of nanomaterials in liquid suspension.[132,133] Due to the low vacuum condition entailed in this technique, the spatial resolution of ESEM is relatively low compared to conventional SEM and STEM. In contrast to the "open cell" approach used in ESEM and its modifications, a "closed cell" approach has enabled *in situ* TEM characterization of liquid samples. In the liquid-cell TEM (or liquid-phase TEM) analysis, a thin layer of the liquid sample is enclosed in a vacuum-tight sample cell with thin windows consisting of an electron-transparent material (most commonly silicon nitride).[134] Alternatively, cryogenic TEM (cryo-TEM) with subnanometer resolution, which was originally developed for determining the structures of biomolecules,[135] allows *in situ* characterization of NP suspension in a frozen, hydrated state.[136] These sophisticated electron microscopy techniques, which have been widely used in materials science and life science research, may serve as powerful tools for *in situ* analysis of nanomaterials in the environment.

The ESEM and cryo-TEM methods require specialized sample preparation; even for conventional SEM and (S)TEM, certain types of samples (e.g., NP-containing biological samples) need multistep treatment prior to analysis.[137] In addition to the sophisticated sample preparation, a major limitation with electron microscopic analysis of ENMs in environmental samples is the small field of view at high magnification. Due to their low concentrations in environmental matrices, it is rather difficult to locate ENMs during electron microscopy analysis.

Spectroscopic Methods. A variety of spectroscopic methods can be used to characterize the elemental compositions and chemical structures of nanomaterials. Nevertheless, only a few of these techniques with sufficiently high spatial resolution

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and low detection limits are suitable for analyzing low levels of nanomaterials in complex environmental matrices. In this section, we discuss the capabilities and limitations of commonly used as well as emerging spectroscopic techniques for analysis and characterization of nanomaterials in the environment, including EDS, electron energy loss spectroscopy (EELS), and X-ray fluorescence (XRF) spectrometry for elemental analysis as well as infrared (IR) spectroscopy, Raman spectroscopy, and X-ray absorption spectroscopy (XAS) for structural analysis.

Elemental analysis of NP samples following microscopic examination calls for spatial resolution down to the nanometer range. Therefore, regular EDS attached to SEM with spatial resolution in the submicrometer range is unsuitable for analyzing nanomaterials in environmental samples.[100] Conversely, EDS coupled with STEM has spatial resolutions down to a few nanometers and can be operated in line-scanning and mapping modes,[100,125,129] which has proven to be a useful tool for identifying the composition of nanomaterials in complex environmental matrices.[121,124] EELS coupled with STEM is another spectroscopic tool for determining the elemental composition of nanomaterials in complex matrices.[126,127,138] Notably, EELS has atomic-level spatial resolution,[101] and EELS-based elemental mapping (also called energy-filtered TEM) has been used to identify the chemical composition of nanomaterials in airborne particulate matter,[121] as well as the macromolecular corona of nanomaterials as thin as approximately 1 nm.[126] Moreover, EELS can determine the oxidation state of elements comprising the nanomaterials,[127,138] and its high spatial resolution makes EELS superior to X-ray photoelectron spectroscopy with micrometer-level lateral resolution in determining the oxidation state of nanomaterials in complex environmental matrices.[126,127]

XRF spectrometry is a nondestructive *in situ* elemental analysis technique requiring minimal sample preparation. It was mainly applied for analysis of bulk materials or pure nanomaterials, due to its relatively low spatial resolution and high detection limit. Recently, synchrotron radiation-based microscopic and nanoscopic XRFs (μ-XRF and nano-XRF, respectively) with improved spatial resolution have facilitated NP analysis in complex environmental samples. For instance, a spatial resolution down to 50 nm was reported for the latest synchrotron-based nano-XRF.[102] Elemental mapping by μ-XRF has been used, alone or in combination with mass spectrometry-based imaging techniques (to be discussed later), to characterize the distribution of nanomaterials in plant[139,140] and animal tissues.[102,141−143] Note that EDS and EELS are static techniques generating elemental information on samples fixed on sample holders, whereas *in situ* XRF analysis with high temporal resolution can provide dynamic information on nanomaterial properties. In fact, spatially resolved XRF microscopy with sub-100 nm spatial resolution was recently applied to acquire quasi-real-time elemental maps of ZnO nanorods in simulated wastewater.[144] Given further improvements in spatial resolutions and detection limits, XRF can potentially be used for characterization of nanomaterials in environment matrices.

Infrared and Raman spectroscopies can yield extensive information on chemical structures of materials, and these methods are particularly useful for identifying carbonaceous nanomaterials such as carbon nanotubes (CNTs)[145] and graphene-family nanomaterials[146] in environmental matrices. However, their relatively low spatial resolutions (1−10 μm and 10^2 nm, respectively)[147] are often insufficient for spatially resolved analysis or characterization of nanomaterials in environmental matrices. The coupling of IR or Raman spectroscopy to the tip of an atomic force microscope (AFM) or scanning tunneling microscope has enabled nanoscale chemical analysis with sub-50 nm resolutions.[147] Notably, tip-enhanced Raman spectroscopy can achieve subnanometer resolution and are well suited to analyze liquid samples,[147,148] thus showing great potential for analyzing and characterizing nanomaterials in environmental samples. Infrared and Raman spectroscopy-based methods have also shown capability for quantification of carbonaceous and metal-based nanomaterials in the environment. For example, near-infrared fluorescence (NIRF) spectroscopy can quantitatively determine concentrations of single-walled CNTs in various environmental samples, including wastewater,[103] fish tissues,[149] and sediments.[103,104] Furthermore, surface-enhanced Raman spectroscopy (SERS) was recently explored for analyzing nanomaterials (mainly NPs of noble metals, Ag and Au) in environmental matrices, such as plant tissues[106] and surface waters,[105,150] after extraction and preconcentration. Although the detection limit of SERS for nanomaterials in aqueous matrices is on the mg/L level, the extraction and preconcentration pretreatment enables detection of nanomaterials on the μg/L level.[105,106]

Synchrotron-based XAS, including extended X-ray absorption fine structure (EXAFS) and X-ray absorption near edge structure (XANES) spectroscopy, provides information on the atomic coordination environment (e.g., coordination number, bond length) of solid materials and can yield structural information on nanomaterials in environmental matrices, such as biological samples[139,151] and soils/sludge.[152,153] One limitation of the XAS techniques for analyzing nanomaterials in environmental matrices is their low sensitivity. Typically, to obtain reliable EXAFS or XANES spectra, the total content of the target element in the sample needs to be above 1 mg/kg.[153] This constraint may be overcome by coupling microprobe-based XAS with other techniques capable of identifying nanomaterials with localized high concentration. For instance, μ-EXAFS spectroscopy was used to confirm the presence of metallic copper NPs in the rhizosphere of wetland plants under copper stress, and, prior to μ-EXAFS analysis, elemental mapping by μ-XRF was used to identify the "points-of-interest" in the sample, where particulate copper species may exist.[154]

Mass Spectrometric Methods. A variety of mass spectrometric methods have demonstrated capabilities for analyzing and characterizing nanomaterials in complex matrices and to provide multifaceted information such as the concentrations, sizes, and elemental compositions of nanomaterials, as well as their distributions within solid samples (e.g., biological tissue).[155] In this section, we highlight recent advances in three categories of mass spectrometric methods for analysis and characterization of nanomaterials in the environment, namely, spICP-MS, mass spectrometry-enabled nanomaterial imaging, and isotopic fingerprinting.

Single Particle ICP-MS. ICP-MS operated in the time-resolved analysis mode is a powerful technique for analyzing trace levels (at ng/L) of metal- and metalloid-based nanomaterials in aqueous matrices, including natural waters, wastewater, and NP suspensions extracted from soils/sediments or biological tissues.[109,156−158] ICP-MS analysis in the single particle mode can give information on the number concentration of the nanomaterials and the mass of individual particles, as well as particle size and size distribution, which can be calculated by assuming a specific shape (e.g., sphere) and composition (e.g., mass fraction of the constituent metal) of the nanomateri-

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Environ. Sci. Technol. 2022, 56, 7426−7447

als.[107,159] Recently, the spectrum of information that can be obtained by spICP-MS was expanded to other properties of nanomaterials, such as the presence of pores within a particle.[160] The sensitivity of spICP-MS analysis is higher than that of other nanoparticle sizing techniques, such as DLS, NTA, and DCS with a detection limit above 0.1 mg/L,[23,24,161] as well as field-flow fractionation (FFF) coupled to ICP-MS with a detection limit on the order from 0.1 to 1 μg/L.[162−164] Moreover, it was recently demonstrated in an interlaboratory study that sizes and particle number concentrations of Au NPs measured by spICP-MS were highly consistent with those measured by SEM, whereas other sizing techniques such as DLS and NTA yielded larger particle sizes, broader size distributions, and lower particle number concentrations.[165]

A key feature of spICP-MS analysis is its ability to distinguish between nanoparticulate and dissolved metal species based on the particle-related peak signals versus the baseline, although the presence of dissolved metal species has been a major barrier to achieving high analysis sensitivity by spICP-MS.[166] The smallest size of a nanoparticle that can be detected (i.e., the size detection limit, D_{min}) by spICP-MS varies for different metal elements constituting the nanomaterials[167] and depends on the instrument sensitivity for the element, density of nanoparticles, and background noise primarily arising from dissolved species.[110,167,168]

Among the commonly investigated nanomaterials, high sensitivity may be readily achieved for Ce-, Au-, and Ag-based NPs, while analyses of Si-, Ti-, Fe-, and Zn-based NPs are rather challenging,[110,167] mainly due to isobaric or polyatomic interferences and the presence of high background metal concentrations. For instance, the difficulty to analyze Si-containing NPs arises from the high abundance of Si in natural waters and polyatomic interference of ^{28}Si from dinitrogen ions, and the analytical sensitivity can be improved by using microsecond dwell time.[169] The spICP-MS analysis of Ti-containing NPs (e.g., TiO_2 NPs) in environmental waters is also challenging in terms of analytical sensitivity,[170] due to isobaric and polyatomic interferences with ^{48}Ti measurement on a standard quadrupole ICP-MS with 1 atomic mass unit resolution.[171] This challenge may be solved by targeting alternative isotopes (e.g., ^{47}Ti and ^{49}Ti)[170,172] less prone to isobaric/polyatomic interferences or by employing high-resolution ICP-MS with mass resolution at or better than 0.01 atomic mass unit.[173] In the analysis of Fe-containing NPs, monitoring the most abundant Fe isotope (i.e., ^{56}Fe) is also prone to polyatomic interference (e.g., from $^{40}Ar^{16}O^+$, $^{40}Ca^{16}O^+$), which may be suppressed by using H_2 or NH_3 as the reaction gas.[174−176] The fast dissolution and relatively high water solubility of ZnO NPs make it particularly challenging to analyze low levels of ZnO NPs dispersed in pure water.[177] Online coupling of an ion-exchange resin column prior to spICP-MS analysis can effectively reduce dissolved zinc concentration and improve the detectability of ZnO NPs;[178] this strategy can also improve the sensitivity for the analysis of Ag NPs, which can undergo fast dissolution under certain conditions.[179]

Although most spICP-MS studies have been performed using instruments with a quadrupole mass analyzer,[158] it was recently found that instruments with a magnetic sector field mass analyzer can significantly improve the sensitivity in single particle analysis.[180,181] For instance, the D_{min} values of Ag, TiO_2, and Fe_3O_4 NPs as measured by the sector-field ICP-MS were as low as 3, 12, and 19 nm, respectively.[182,183] Most recently, a sector-field ICP-MS with the latest microdroplet generation sample introduction system achieved D_{min} values below 10 nm for a variety of metal oxide NPs, including TiO_2, Al_2O_3, Fe_3O_4, and CuO NPs.[184]

Single particle analysis on a quadrupole-based instrument has largely been operated in a way that only one isotope is detected at a time. Yet, the latest models operated at microsecond dwell times (e.g., 20−100 μs) have enabled the analysis of dual isotopes and have been used to analyze bimetallic Au−Ag NPs with either homogeneous alloy or core−shell structures[185−187] and to explore the possibility of differentiating between engineered and natural nanomaterials.[185] Most recently, a state-of-the-art quadrupole-based ICP-MS instrument capable of detecting up to 16 elements in a single run has been used for multi-element analysis of nanomaterials in wastewater and biosolids.[188] Alternatively, ICP-MS with a time-of-flight (TOF) mass analyzer that is capable of quasi-simultaneous multi-element analysis on a particle-by-particle basis has been applied for the analysis of NPs in aqueous samples.[189,190] Single particle multi-element fingerprinting analysis enabled by ICP-MS with a TOF mass analyzer has also been used to differentiate engineered CeO_2 NPs from natural Ce-containing NPs in colloids extracted from soils,[191] as well as to detect and quantify TiO_2 NPs in surface waters with high background Ti levels.[192,193] Despite the potential of this technique for source apportionment of nanomaterials in complex matrices, several barriers must be overcome before it becomes a routine analytical tool, including insufficient sensitivity for some elements (high D_{min}) and complex data analysis.[194,195]

Mass Spectrometry for Nanomaterial Imaging. Apart from electron microscopy and associated spectroscopic methods (e.g., EDS and EELS) and synchrotron-based μ-/nano-XRF, mass spectrometric techniques can be used to visualize the distribution of nanomaterials within solid matrices (e.g., biological tissue), including laser ablation ICP-MS (LA-ICP-MS) and secondary ion mass spectrometry (SIMS).

LA-ICP-MS is a technique for *in situ* elemental analysis of solid samples with micrometer-level spatial resolution (on the order from 1 to 10 μm).[100] In LA-ICP-MS analysis, a solid material is ablated with high-power laser, and a certain volume (typically with a lateral area from 10 to 10^5 μm^2 and a depth from 1 to 10 μm) of the material is removed from the surface after each laser shot to form aerosols, which are introduced to the ICP-MS instrument for elemental analysis. LA-ICP-MS has been used to investigate the uptakes and spatial distributions of metallic[141,142,196] and metal oxide[140,196] NPs in terrestrial and aquatic organisms. However, due to the micrometer-level spatial resolution, elemental distribution images obtained by LA-ICP-MS (with pixel sizes typically above 1 μm) cannot provide direct evidence for the presence of nanomaterials within the biological tissues. Moreover, conventional LA-ICP-MS cannot distinguish between nanoparticulate and dissolved forms of metals, and complementary techniques, such as XANES, were used to analyze the speciation of metals detected in the biological tissues.[141,142] Recently, novel approaches were developed for single particle analysis in biological matrices[197−199] and soils[200] by LA-ICP-MS. For instance, by optimizing the laser ablation and spICP-MS conditions, not only the spatial distribution of Au NPs but also the particle number concentration and size at a particular location of a biological sample could be obtained.[197] Note that sophisticated data analysis is required for transforming the large raw data sets into spatially resolved particle size and concentration data.[198,199] Apart from metal-based nanomateri-

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als, LA-ICP-MS has also been explored for quantification, tracking, and imaging of graphene and potentially other carbonaceous nanomaterials in plants by using inherent residual metals (e.g., Ni and Mn), which are widely and stably present in graphene materials, as fingerprints.[201] Given that potential interferences from abundant background metals may be present, the indicative metals need to be carefully selected when using this method to analyze carbonaceous nanomaterials in more complex matrices (e.g., soils).

SIMS is a high-sensitivity surface analysis technique capable of determining the chemical composition of the top few atom layers of a solid sample, enabling two-dimensional elemental mapping as well as depth profiling and three-dimensional imaging. During SIMS analysis, a sample placed under an ultrahigh vacuum is bombarded with an accelerated primary ion beam, and the secondary ions ejected from the surface of the sample are analyzed by a mass spectrometer. SIMS with a TOF mass analyzer (TOF-SIMS), which is the most common type of SIMS, has been used to identify and determine the two- or three-dimensional spatial distribution of inorganic NPs (e.g., CeO_2 and TiO_2)[143,202] in biological materials such as rat lung tissues[143] and algal (*Chlorella vulgaris*) biofilms.[202] The lateral resolution of conventional TOF-SIMS analysis is typically above 100 nm, and it was recently improved to below 50 nm.[111] This so-called nanoscale SIMS (or nanoSIMS) holds great potential for quantitative elemental imaging of biomaterials on the subcellular or suborganelle level.[102,111,203,204] For instance, TOF-SIMS with a lateral resolution of approximately 80 nm was used to study the uptake and distribution of aggregated Ag and CeO_2 NPs in plant root tissues.[84] It is expected that the lateral resolution of nanoSIMS can be further improved, enabling the detection of individually dispersed NPs. As with conventional electron microscopy, the samples need to be chemically or cryogenically fixed prior to SIMS analysis,[102] and thus, alteration to NP properties may occur.

Isotope-Based Techniques. Labeling nanomaterials with radioactive and stable isotopes has enabled the detection and quantification of these isotopically labeled nanomaterials with high sensitivities and selectivities against interferences from natural background;[205] radiolabeling enables very low detection limits (in the range from pg/L to ng/L), whereas stable isotope labeling yields detection limits on the order from 1 to 10 ng/L (or ng/kg).[206,207] However, these isotopic tracer techniques cannot be used for analyzing nanomaterials without such deliberate labels, which is the case for the majority of natural and engineered nanomaterials already present in or being released into the environment, except for nanomaterials with known inherent isotope ratios (e.g., CNTs).[208]

In contrast, the recently developed isotopic fingerprinting technique based on multicollector ICP-MS (MC-ICP-MS) analysis of stable isotope ratios shows great promise for identification, quantification, and source tracing of nanomaterials. For instance, isotope fractionation occurs during the dissolution and formation of Ag NPs in the aquatic environments, and the variation in the $^{109}Ag/^{107}Ag$ ratio can be potentially used to distinguish between engineered and naturally formed Ag NPs.[209] Si and O dual isotopic fingerprinting assisted by machine learning has enabled differentiation of natural SiO_2 NPs (e.g., quartz and diatomite) from engineered SiO_2 NPs synthesized with different methods.[210] Furthermore, Si isotopic fingerprinting methods were recently successfully applied in source apportionment of fine particulate matter, a large fraction of which falls in the nanoscale size range, in polluted urban air. Si isotopic composition analysis enabled the direct tracing of primary sources of fine particulate matter,[211] whereas a combination of Si abundance and isotopic composition analysis (i.e., two-dimensional Si fingerprints) was recently shown to be a viable tool for estimating contributions from both primary and secondary sources.[212] Most recently, a chemical multifingerprinting approach integrating elemental fingerprints, high-resolution structural fingerprints, and/or stable isotopic fingerprints demonstrated its capability to identify the sources of ultrafine particles (with sizes <100 nm) in human serum and pleural effusion,[213] as well as airborne magnetite NPs in the urban atmosphere.[214]

Electrochemical Methods. Electrochemical techniques, such as voltammetry and particle−electrode collision-based chronoamperometry, have shown great potential for *in situ* detection and characterization of nanomaterials in aqueous environments.[215] The electrochemical measurement can be performed on portable instruments, making them particularly suitable for on-site environmental analysis.

In voltammetry measurements, metal-based nanoparticles produce electrochemical signals at different electrode potentials than corresponding dissolved metal species, which can be translated to the presence and concentration of nanomaterials. Voltammetric techniques, such as anodic stripping voltammetry and adsorptive cathodic stripping voltammetry, have been explored to detect a variety of nanomaterials, including metal chalcogenides (e.g., Cu_xS,[216] FeS,[217,218] and HgSe)[116] and metallic (e.g., Au[117] and Ag)[219,220] NPs, in artificial and natural aqueous matrices. However, the voltammetric signal is highly dependent on the composition of the aqueous matrix, including the type and composition of the electrolyte as well as the presence of electroactive dissolved metals, inorganic ligands (e.g., sulfide ions), and natural organic matter (NOM).[217,218] Moreover, the analyte selectivity of voltammetric measurement is relatively low. For instance, nanoparticles of different metal sulfides can produce an electrochemical signal at similar redox potentials, which prevents their unambiguous identification.[221] The voltammetric response of NPs also depends on their other properties, for example, size,[220] surface coating,[222] and aggregation status.[219] Thus, it remains challenging to use voltammetry to analyze nanoparticles in complex environmental samples.

Particle−electrode collision-based chronoamperometric techniques have shown potential for quantitative analysis of nanomaterials in aqueous matrices on a single particle basis.[223] In a chronoamperometric measurement, the electrode potential is held constant, and the electric current intensity as a function of time (i.e., a chronoamperometric profile) is recorded. Typically, multiple spikes (current transients) can be observed in a chronoamperometric profile, each corresponding to a particle−electrode collision event followed by electrooxidation of the particle. The frequencies and charges of the current transients are further translated into the concentrations and sizes of NPs. Particle collision-based chronoamperometry via the electrooxidation mechanism, i.e., anodic particle coulometry (also called particle impact chronoamperometry or the "nano-impact" method), recently evolved into a relatively mature technique for nanoparticle analysis and characterization.[118,223−225] In addition to measuring number concentrations and particle sizes, this technique has demonstrated capabilities to determine the morphologies of nanomaterials[226] and to assess aggregation states (e.g., irreversible or reversible aggregation).[227,228] Despite these capabilities, the performance of the "nano-impact" method

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Environ. Sci. Technol. 2022, 56, 7426−7447

in complex environmental matrices is yet to be validated, particularly considering the potential influences of electroactive constituents, such as NOM.

Size Fractionation Methods. Nanomaterials in the environment are polydisperse in size, and it is critical to accurately determine the particle size distributions of nanomaterials. Some of the methods discussed above (e.g., spICP-MS and particle impact chronoamperometry) have shown capability or potential to determine the size distributions of NPs in complex aqueous matrices. It is also desirable to separate NPs with different sizes prior to downstream analysis and characterization. Sequential filtration and (ultra)centrifugation have been used as fractionation methods to separate colloids/NPs with different sizes.[175,229] Moreover, a variety of chromatography-based and chromatography-like techniques have been developed for more accurate size fractionation of NPs, including hydrodynamic chromatography (HDC), size exclusion chromatography (SEC), FFF, capillary electrophoresis (CE), and electrospray-differential mobility analysis (ES-DMA).

HDC is a facile technique for separating particles and macromolecules based on their sizes. The most commonly used HDC columns are columns packed with nonporous microbeads (as compared to porous microbeads in SEC columns), although columns in other forms (e.g., open-tubular capillary[230] and microchip)[231] are also available. Particles with different sizes (and correspondingly different hydrodynamic diameters) are separated as they flow through a packed bed column, due to velocity gradients that develop within the capillaries between microbeads. Larger particles elute faster because they spend less time near the edges of the capillaries, where the linear velocity is slower.[232] HDC may be coupled to a range of analysis tools, including DLS, multi-angle laser light scattering, UV−vis, and fluorescence detectors.[233−235] In particular, HDC coupled to ICP-MS, either in the conventional or single particle mode, has demonstrated great potential for separating and sizing NPs in aqueous samples at relatively low concentrations (e.g., with LOD values below 0.1 μg/L).[232,236,237]

In SEC, NPs with different sizes and dissolved metal ions/complexes are separated after passing a liquid chromatography column packed with porous micrometer-sized particles. The largest NPs are eluted first, followed by smaller particles, and the dissolved species are eluted last.[238,239] The SEC method coupled to ICP-MS has been successfully used to separate and quantify metallic (e.g., Ag and Au),[240,241] metal oxide (e.g., NiO and CeO_2),[242] and metal sulfide (e.g., Ag_2S)[243] NPs and their corresponding metal ions in environmental water samples, as well as Au and Ag NP in biological matrices, such as algae[244] and bacteria,[77] after alkaline digestion or lysis. Note that SEC has so far only been used for separating NPs with known sizes spiked in aqueous samples or exposed to organisms. The capability of this technique for analyzing samples with unknown sizes is yet to be demonstrated.

FFF is a family of techniques widely used for the separation and sizing of biomolecules, natural colloids, and ENMs.[245] In contrast to chromatography methods, fractionation in FFF takes place in a thin, elongated channel without a stationary phase under the action of an external field (e.g., centrifugal force or a flow) perpendicularly applied to a laminar flow, in which the analytes diffuse.[25,246] Among different types of FFF techniques, flow FFF (FlFFF), and particularly asymmetric FlFFF (AF4), is the most commonly used one for separating and analyzing NPs with different sizes. FlFFF can be coupled to a range of analysis techniques, such as UV−vis, fluorescence, DLS, TEM, AFM, and ICP-MS,[247,248] and FlFFF coupled to ICP-MS has become a powerful and popular tool for analyzing μg/L level nanomaterials in environmental matrices,[246,247] such as wastewater[163] and river water.[164] These sequential analytical methods combined the advantages of FlFFF, such as the high size resolution over a wide size range and minimal alteration to NP properties, and the advantages of ICP-MS, such as high sensitivity and elemental selectivity. As an alternative to AF4, hollow fiber FlFFF, which uses a low-cost, disposable hollow fiber as the focusing/relaxation channel, has been online coupled to ICP-MS and achieved the separation and detection of Ag NPs in surface waters with sizes down to 1.4 nm.[249] In addition, sedimentation/centrifugal FFF (SdFFF), which involves sedimentation of particles due to centrifugal force, is the other type of FFF that can be coupled to ICP-MS, and this technique is more suitable for separating and analyzing NPs with larger densities and sizes.[246] Recently, the coupling of FlFFF and/or SdFFF to spICP-MS enabled characterization of nanocomposite particles, such as Ag@SiO_2[250] and Au@Ag[186] core−shell NPs, as well as Au NPs contained in nanoplastic colloids.[251] The FFF methods may be utilized for fractionating NPs over a broad size range (from one nanometer up to a few micrometers), and yet the loss of NPs during the fractionation process is a problem that remains to be addressed.

Capillary electrophoresis can separate NPs with different sizes and surface charge properties. When suspended in aqueous media, a variety of nanoparticles (e.g., metal oxide NPs, surface-functionalized metallic and carbon-based nanomaterials) carry surface charges. The charged NPs migrate driven by electroosmotic flow under the action of an external electric field and exhibit electrophoretic mobilities that are proportional to the charge-to-size ratios of spherical NPs, which enable their fractionation by electrophoretic methods, including gel electrophoresis and CE.[252] Compared to gel electrophoresis, CE typically leads to more reproducible migration time and higher size resolution,[18] although run-to-run variation in migration time possibly occurs in CE operation.[253] Early studies on electrophoretic separation of nanomaterials employed TEM, hyperspectral imaging, UV−vis, and fluorescence spectroscopy to analyze the nanomaterials.[25] However, these analysis methods typically work for nanomaterials at relatively high concentrations, which makes corresponding electrophoretic methods unsuitable for analyzing environmental samples. Recently, CE was coupled to ICP-MS for the separation and size characterization of Ag and Au NPs in complex matrices, including river water and wastewater with LODs at the submicrogram per liter level.[254,255] Moreover, CE has been coupled to spICP-MS to analyze Ag NPs with different sizes[256] and surface coatings.[257] However, the lack of matrix-matched NP standards is currently a major factor limiting the application of CE-based methods for analysis of nanomaterials in environmental matrices.

The combination of electrospray with differential mobility analysis, a common aerosol measurement technique,[258,259] has long been used for high-resolution size fractionations and measurements of NPs in liquid suspensions.[260−262] However, the ES-DMA techniques, commonly equipped with a condensation particle counter as detector, are usually used to analyze nanomaterials at relatively high concentrations (e.g., >0.1 mg/L),[260] and the presence of nonvolatile salts or organic compounds may cause analytical artifacts.[262] Coupling ES-DMA to ICP-MS can differentiate target nanomaterials (e.g., Au NPs) from salt particles artificially produced during electrospray, and

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Environ. Sci. Technol. 2022, 56, 7426−7447

yet the detection limit is not significantly improved compared to conventional ES-DMA with a condensation particle counter detector.[263] Recently, ES-DMA coupled to spICP-MS has enabled accurate sizing and concentration determination of Au NPs at environmentally relevant levels,[264] as well as differentiation of NPs with different morphologies (e.g., nanorods versus nanospheres).[265] Moreover, the independent determination of particle size by differential mobility analysis and particle mass by spICP-MS allows the calculation of "apparent density", which can be used to differentiate between NP mixtures versus aggregates.[264]

■ ENDURING CHALLENGES AND FUTURE PERSPECTIVES

Recent methodological advances for the determination of the abundance, morphology, composition, and structure of nanomaterials have focused on improving the analytical speed, throughput, spatial resolution, and chemical sensitivity, mitigating matrix effects in complex matrices and tracing the sources and processes, as well as simultaneously providing multifaceted information. These improvements have facilitated research on identifying sources, environmental transformations, and ecological/health effects of naturally occurring and engineered nanomaterials. However, challenges remain to further improve the performance and expand the applications of the current methods. Emerging techniques may also be tailored to future needs in the analysis and characterization of nanomaterials to enhance a wide variety of environmental applications.

(1) Quantitatively assessing the mass and number concentrations of nanoscale particles is an essential prerequisite for accurate estimation of environmental behaviors and risks of nanomaterials. Nevertheless, information regarding abundance and morphology are often obtained from different sample aliquots analyzed by different methods, which may not be comparable due to the heterogeneous nature of environmental samples. Only a few methods simultaneously provide mass/number concentrations together with size estimates and yet rarely achieve satisfactory sensitivities for both parameters. For instance, although the mass detection limit of spICP-MS is as low as sub-ng/L (corresponding to the particle number detection limit on the level of 10^4 to 10^6 particles per liter) for many elements,[107−109] high size resolution cannot be facilely attained for routine analysis of environmental samples. It is particularly challenging to analyze nanomaterials that tend to occur as small monomers and aggregates in natural environments. Mineral nanoparticles containing Hg and S often exhibit primary particle sizes below 10 nm,[9,266−268] whereas size detection limits for these elements of environmental significance are well above 10 nm even with the latest instruments under optimized conditions,[110] making spICP-MS unsuitable for analyzing these NPs in the environment. On the other hand, microscopic and spectroscopic techniques with high spatial resolution (Table 1) generally do not have the capability to accurately quantify the concentrations of nanoparticles in environmental samples. It is desirable that future advances in instrumental hardware and data processing will allow assessments of both abundances and morphologies of nanomaterials and nanoconjugates in a single run with improved chemical sensitivity and spatial resolution. Toward this end, efforts are needed to develop integrated platforms comprising online coupled high-sensitivity quantification techniques and high-resolution characterization (e.g., nanoSIMS).

(2) Despite the continuous development of the pretreatment methods of complex environmental samples, a number of nanomaterial properties, such as aggregation status and surface composition, are inevitably altered during extraction and preconcentration processes of nanomaterials, which likely lead to inaccurate estimation of the characteristics and subsequent environmental behaviors and impacts of nanomaterials. Therefore, *in situ* characterization techniques of nanomaterials in complex matrices are needed. Notably, nanomaterials in environmental samples are typically enveloped in "coronas", which are composed of adsorbed macromolecules (e.g., humic substances, extracellular polymeric substances, and proteins) and can significantly affect the environmental fate and ecological effects of nanomaterials.[269] In biological matrices, nanomaterials are coated with a variety of proteins and metabolites,[270] and these biomolecular coronas largely influence the behaviors, fate, and biological effects of the nanomaterials.[271,272] The chemical composition and structure of the environmental and biomolecular coronas are dynamic, and it is desirable to develop *in situ* characterization techniques (at least, pretreatment methods capable of maintaining nanomaterial integrity) to advance understanding of pertinent structure−activity relationships. In particular, there is a great need to develop techniques for *in situ* and real-time analysis and characterization of nanomaterials in living organisms (i.e., *in vivo* analysis), including the dynamic composition and structure of environmental/biomolecule corona on the surface of the nanomaterials. Current methods for *in situ* corona analysis (e.g., fluorescence correlation spectroscopy, isothermal titration calorimetry, circular dichroism, and Raman spectroscopy) are not sufficiently sensitive for environmental samples with low nanomaterial concentrations.[273] Advanced mass spectrometric techniques capable of *ex situ* analysis of NOM and protein coronas (such as TOF-SIMS, electrospray ionization ICP-MS, and Fourier transform ion cyclotron resonance mass spectrometry)[155,269,273] may be adopted for *in situ* analysis of nanomaterials with coronas, when properly interfaced to single particle analysis tools with tailored sample introduction systems.

(3) Current studies have largely focused on metal-based and elemental carbon-based nanomaterials (Figure 2), but there recently have been increasing interests in the environmental occurrence of other nanoscale materials, including nanoplastics[274,275] and biological nanoparticles (e.g., viruses[276,277] and plasmids).[278,279] These emerging nanoscale contaminants exhibit distinct environmental behaviors and effects due to their unique physicochemical properties. Moreover, some biological nanoparticles play important roles in the transmittance of pathogenic[276] or antibiotic resistance genes,[278,279] warranting fast and accurate detection and characterization of these nanoscale biological particles at low concentrations in the environment. Thus, there is a huge need for developing methods to analyze and characterize these emerging nanoscale contaminants in the environment. The analysis of

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Environ. Sci. Technol. 2022, 56, 7426−7447

nanoplastics in environmental matrices is a research hotspot, but only a limited number of studies have dealt with real environmental samples.[275,280] So far, most reported methods for separating, detecting, and characterizing nanoplastics are adopted from the analyses of microplastics and inorganic nanomaterials, and these methods typically have size detection limits above 100 nm,[275] although the latest Raman tweezers technique with spatial resolution down to 50 nm has the potential to lower this size detection limit.[281,282] As with the analysis of inorganic nanomaterials, only a limited number of methods can simultaneously quantify the abundance and characterize the composition or morphology of nanoplastics in environmental matrices.[280,283] Moreover, their smaller size than microplastics and higher heterogeneity than engineered nanoparticles makes nanoplastics more challenging to analyze and characterize in environmental samples.[284] Hence, future research efforts on developing analysis and characterization methods specific to the structural and surface properties of nanoplastics are warranted. Viruses and plasmids in the environment have been detected by high-throughput nucleic acid sequencing tests, but the current analysis methods usually suffered from low recoveries.[285−287] Moreover, while providing (semi)quantitative information on the abundance of viruses and plasmids, these sequencing-based analysis methods give no clue on the physicochemical properties of the biological nanoparticles, and it is desirable to develop methods to directly characterize the key properties dictating their environmental fate, for example, their propensity to adhere to environmental surfaces.[288]

(4) The sustainable development and safe application of nanotechnology require standardized methods for characterizing the physicochemical properties, evaluating the performances, and assessing the environmental risks of nanomaterials.[289] While standardized methods are available for measuring the concentration and characterizing the size, shape, composition, structure, and surface chemistry of nanomaterials, few are designed for environmental samples; for instance, among the suite of standards developed so far by the International Organization for Standardization (ISO) toward the analysis and characterization of nanomaterials, only two deal with nanomaterials in complex environmental matrices,[290,291] which largely focus on sampling, pretreatment, and detection of nanomaterials. Ongoing and future efforts in this field should place more emphasis on standard protocols tailored to the characterization of nanomaterials with low abundance and structural heterogeneity in the environmental matrices with high degrees of complexity. Notably, different types of environmental samples containing nanomaterials pose different analytical challenges. Hence, standardized protocols of sample pretreatment ought to be tailored according to specific environmental matrices, and the standardized methods of nanomaterial analysis and characterization ought to be established with full consideration of the type and properties of diverse nanomaterials. Such standards are expected to effectively supplement existing standard methods for reliable prediction of the environmental risks of nanomaterials.

Overall, the biggest challenge for analysis and characterization of nanomaterials in the environment arises from the dynamic changes of nanomaterial properties in complex environmental matrices. Artifacts associated with almost all current extraction and preconcentration methods highlight the need for developing methods capable of *in situ*, direct, and quantitative analysis and characterization. This goal calls for improvement in chemical sensitivity, response time, and spatial resolution of current techniques. Moreover, integrated platforms enabled by online coupling of *in situ* analysis and characterization techniques that provide multifaceted information are essential for accurate evaluation of the environmental behaviors and impacts of nanomaterials. An adage commonly attributed to Peter Drucker, an influential author in management theory and practice, says that "we can only improve what we actually measure". Accordingly, emerging opportunities to improve nanomaterial quantification and characterization methods are likely to contribute to the beneficial impact and sustainability of the growing nanotechnology industry.

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Environ. Sci. Technol. 2022, 56, 7426−7447

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■ LIST OF ACRONYMS

AF4 = asymmetric FlFFF
AFM = atomic force microscope
CE = capillary electrophoresis
CNTs = carbon nanotubes
CPE = cloud point extraction
cryo-TEM = cryogenic TEM
DCS = differential centrifugal sedimentation
DLS = dynamic light scattering
D_{min} = size detection limit
EDS = dispersive X-ray spectroscopy
EELS = electron energy loss spectroscopy
ENMs = engineered nanomaterials
ES-DMA = electrospray-differential mobility analysis
ESEM = environmental SEM
EXAFS = extended X-ray absorption fine structure
FFF = field-flow fractionation
FlFFF = flow FFF
HDC = hydrodynamic chromatography
ICP-MS = inductively coupled plasma mass spectrometry
IR = infrared
LA-ICP-MS = laser ablation ICP-MS
LCST = lower critical solution temperature
LOD = limit of detection
LPE = liquid-phase extraction
MC-ICP-MS = multicollector ICP-MS
nanoSIMS = nanoscale SIMS
NNMs = natural nanomaterials
NOM = natural organic matter
NP = nanoparticle
NIRF = near-infrared fluorescence
NTA = nanoparticle tracking analysis
SAED = selected area electron diffraction
SAXS = small-angle X-ray scattering
SdFFF = sedimentation/centrifugal FFF
SEC = size exclusion chromatography
SEM = scanning electron microscopy
SERS = surface-enhanced Raman spectroscopy
SIMS = secondary ion mass spectrometry
SPE = solid-phase extraction
spICP-MS = single particle ICP-MS
SPME = solid-phase microextraction
STEM = scanning TEM
TEM = transmission electron microscopy
TMAH = tetramethylammonium hydroxide
TOF = time-of-flight
TOF-SIMS = SIMS with a TOF mass analyzer
TX-114 = Triton X-114
XANES = X-ray absorption near edge structure
XAS = X-ray absorption spectroscopy
XRF = X-ray fluorescence

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