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Review

Advances in Methodological Evolution and Integration of Single-Particle Analysis for Nanoparticles in Environmental Matrices

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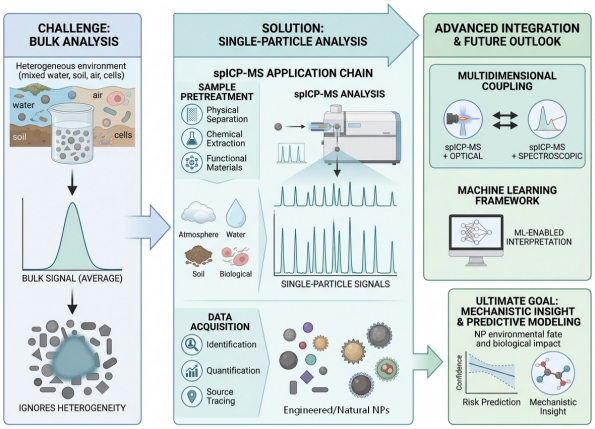
Highlights

- Systematic summary of separation and extraction of nanoparticles from environmental samples
- Identification and quantification of engineered and natural nanoparticles across atmospheric, aquatic, and terrestrial systems
- Future application of single-particle mass spectrometry coupled with optical and spectroscopic techniques
- Enhanced data interpretation for nanoparticle classification, toxicity mechanism elucidation and risk prediction with machine learning

Abstract: Environmental heterogeneity significantly influences the transport, transformation, and ecological risks of nanoparticles (NPs). Traditional bulk-scale analytical approaches often overlook inter-particle heterogeneity, thereby limiting a nuanced understanding of nanoparticle behavior and associated risks. Since single-particle analysis can enable high-throughput and highly sensitive detection of NPs in complex environmental matrices, this review emphasizes that characterizing NPs at the single-particle level is therefore crucial for accurately assessing their environmental fate and biological impacts. This review traces the evolution of single-particle Inductively Coupled Plasma Mass Spectrometry (spICP-MS) from its quadrupole foundations to time-of-flight configurations, and summarizes their applications across environmental matrix. The optimization and integration of strategies such as physical separation, chemical extraction, and functionalized material pretreatment laid the methodological foundation for single-particle analysis. The applications of spICP-MS are demonstrated in the identification, quantification, and source tracing of metallic NPs in atmospheric, aquatic, soil, and biological samples. Special attention is given to its multidimensional coupling with optical and spectroscopic techniques, as well as emerging machine learning-enabled frameworks for intelligent data interpretation and risk prediction. Ultimately, this work highlights the pivotal role of multidisciplinary technological integration and data-driven strategies in advancing environmental nanoscience toward an era focused on mechanistic insight and predictive modeling.



1. Introduction

Heterogeneity refers to the diversity and unevenness of specific characteristics within a system. Environmental heterogeneity refers to the diversity and complexity of physical, chemical, and biological characteristics across the particle size, which influences environmental processes, including migration, transformation, and biological effects [1]. In particular, nanoparticles (NPs) play a crucial role in these complex environmental processes. As the size of NPs decreases, their specific surface area and surface energy increase sharply, directly altering their physicochemical properties [2]. The increase in specific surface area leads to a sharp rise in the number of surface atoms and an insufficient number of coordinated atoms, resulting in surface defects and significantly enhancing their activity [3]. For example, the NPs such as nano-size iron are widely used in the remediation of soil and groundwater pollution due to their highly efficient reactive and adsorptive-reductive properties [4]. The diversity in the biological world, such as microbial communities and the plant rhizosphere, interacts with environmental NPs in complex ways [5]. For example, the influence of *Escherichia coli* on nano plastics and nano-size iron particles in porous media will lead to their different migration and retention behaviors [6,7]. During the absorption process by plant roots, iron oxide NPs cause oxidative stress responses in plants, affecting their growth and development [8].

Single-particle characteristics are of great significance for understanding their environmental processes, which requires the high-precision analytical techniques. In 2003, Degueldre et al. firstly demonstrated quantitative individual particle detection, introducing the concept of single-particle Inductively Coupled Plasma Mass Spectrometry (spICP-MS) [9]. This technique represents a fundamental departure from conventional bulk analysis: while bulk ICP-MS quantifies the total elemental concentration averaged across all dissolved and particulate species, spICP-MS resolves discrete nanoparticles as individual signal events, thereby preserving information on particle number concentration, size distribution, and elemental composition at the single-particle level [10]. The most widely deployed variant, quadrupole-based spICP-MS, operates by monitoring a single mass-to-charge ratio per measurement interval, with transient signal pulses generated when individual particles are atomized and ionized in the plasma [11]. Its key advantages are widespread commercial availability, mature protocols, and demonstrated robustness across diverse environmental matrices. However, its principal limitation is the inherently single-element detection capability that only one element can be monitored per particle event, precluding the simultaneous acquisition of multi-element fingerprints essential for source apportionment in complex environmental samples. A transformative advancement arrived with the development of single-particle Inductively Coupled Plasma Time-of-Flight Mass Spectrometry (spICP-TOF-MS), which employs a time-of-flight mass analyzer to extract and accelerate all ions simultaneously, enabling the quasi-simultaneous detection of virtually all elements across the mass range for each individual particle event [12]. This full-spectrum capability generates genuine multi-element fingerprints per particle, providing the data foundation for source discrimination between engineered nanoparticles (ENPs) and natural NPs [13]. The development of spICP-TOF-MS is not a replacement but a complementary extension of the quadrupole platform, which established the operational foundation, including sample introduction protocols, signal calibration, and the relationship between signal intensity and particle mass, upon which TOF-based systems have built. The choice between the two platforms depends on analytical objectives: quadrupole instruments remain the practical choice for targeted single-element quantification, while TOF-MS is essential for multi-element fingerprinting in source-unknown complex matrices [14].

Currently, single-particle characterization techniques are undergoing a paradigm shift from traditional ensemble-averaged analysis toward the elucidation of individual particle behaviors. Driven by advances in instrument sensitivity [9], the capability for simultaneous multi-element detection via TOF-MS [15,16], spICP-MS has enabled the direct quantification and source identification of ENPs and natural NPs across diverse environmental media, unveiling nano-scale processes that remain undetectable by conventional bulk analytical methods [17]. Two emerging directions are further expanding its analytical frontiers: the hyphenation with optical and spectroscopic techniques, which overcomes the intrinsic limitation of single-element analysis by enabling simultaneous characterization of chemical composition and molecular identity at the single-particle level [18]; and the deep integration with machine learning algorithms, which has established automated pipelines for identifying particle origins and evolutionary patterns from massive single-particle datasets, laying a robust foundation for predictive environmental risk models [19].

This review systematically synthesizes advancements in the field. The discourse commences with sample pretreatment, elucidating that high-efficiency separation techniques serve as a prerequisite for single-particle analysis. It subsequently demonstrates the quantitative and source-tracking applications of these techniques across diverse environmental media, including the atmosphere, water bodies, soils, and biota. Emphasis is then placed on the cutting-edge integration with optical/spectroscopic methods, enabling multi-dimensional characterization spanning "elemental-molecular" properties. The discussion further explores an emerging paradigm of machine learning-empowered

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intelligent data interpretation and risk prediction. Structured along the logical progression of pretreatment, detection, integration, and intelligent analysis, the review systematically traces the holistic development of the technological chain.

2. Extraction of Nanoparticles from Environmental Samples

Prerequisite to the analysis of NPs in environmental samples lies in their efficient and intact separation and extraction. It is important to recognize that physical separation and chemical extraction are complementary rather than alternative strategies in a complete sample preparation workflow. Physical separation methods, such as centrifugation and filtration, typically serve as the initial step, removing large interfering particles, reducing matrix load, and concentrating the nanoparticle fraction. Chemical extraction approaches, including cloud-point extraction and enzymatic digestion, are subsequently employed to release NPs from the matrix, disrupt binding associations with organic matter or mineral phases, or improve recovery from complex solid matrices such as sludge, sediment, or biological tissue. Surface modification and functionalized material strategies, exemplified by magnetic adsorption and biorecognition mechanisms, offer a third dimension: they enable the selective capture of specific nanoparticle populations through tailored interfacial interactions, achieving high recovery rates and superior selectivity that physical and chemical methods alone may not provide. The current trend is advancing toward hyphenated online and automated technologies, such as online extraction coupled with spICP-MS. These integrated systems not only improve analytical efficiency but also preserve particle integrity to the greatest extent, thereby establishing a robust foundation for subsequent single-particle analysis and environmental behavior studies.

2.1. Physical Centrifugation and Filtration

Physical separation methods mainly rely on the differences in physical properties between NPs and matrix components to achieve separation, with the aim of maintaining the original state of the particles to the greatest extent. Centrifugation is one of the most widely used physical separation methods. Ultracentrifugation achieves rapid sedimentation through high centrifugal force (typically > 100,000× *g*). It is particularly suitable for the enrichment of metallic NPs in plant tissues and water samples [20–22]. Density gradient centrifugation further enhances the resolution of separation and enables the classification and separation of particles based on the differences in their sedimentation rates at different densities. However, the centrifugation method faces two major challenges: one is that high centrifugal force may cause particle deformation or aggregation, the other is that for NPs with densities close to those of the matrix components (such as certain polymer NPs), the separation efficiency is limited [23], as shown in Figure 1a.

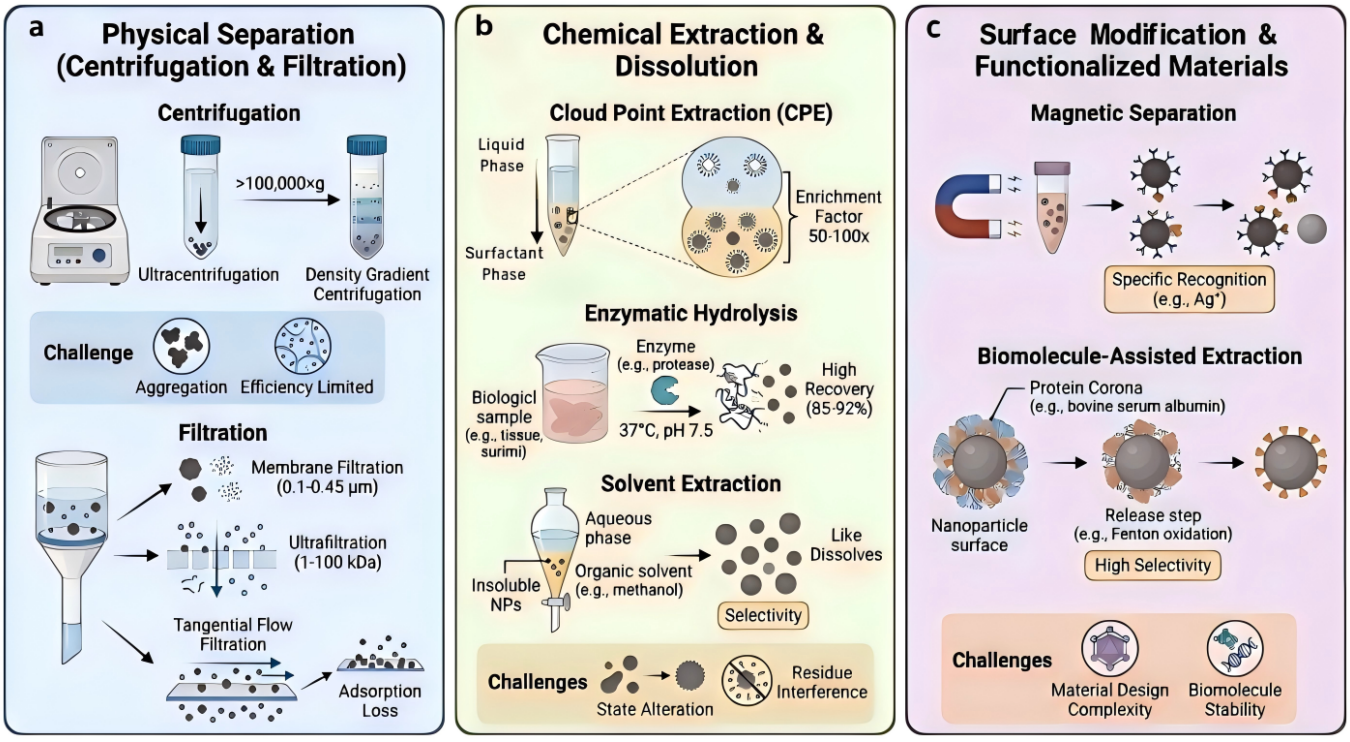

Figure 1. Principal strategies for the separation and extraction of nanoparticles from complex matrices including (**a**) physical separation, (**b**) chemical extraction, and (**c**) surface modification.

Filtration methods encompass membrane filtration, ultrafiltration, and related methods. Conventional membrane filtration (with pore sizes of 0.1–0.45 μm) is suitable for removing large particle interference, but has a low retention efficiency for NPs. Ultrafiltration employs membranes with smaller pore sizes (1–100 kDa), enabling molecular-level separation and is particularly suitable for distinguishing dissolved from particulate metals [24]. The hollow fiber ultrafiltration (HFUF) coupled with spICP-MS can improve size detection limit of metallic NPs by removing metal ions from suspensions [25].

Tangential flow filtration reduces membrane fouling through flow parallel to the membrane surface, enhancing its applicability in processing complex environmental samples [26]. It is worth noting that the adsorption loss during the filtration process is the main limitation of this method, especially in the analysis of low-concentration samples where its impact is significant.

2.2. Chemical Extraction and Dissolution

Chemical extraction methods achieve separation by altering the surface properties of NPs or the chemical environment of the surrounding medium. As shown in Figure 1b, they usually have higher selectivity but may change the original state of the particles. Cloud point extraction (CPE), as a green and efficient preconcentration technique, has received extensive attention in recent years [27–31]. This method takes advantage of the phase transition behavior of surfactants at a specific temperature (cloud point temperature) to transfer hydrophobic NPs from the aqueous phase to the surfactant-enriched phase, with an enrichment factor of up to 50–100 times. The advantages of CPE lie in its simple operation and low consumption of organic solvents, but it has a relatively low extraction efficiency for hydrophilic NPs, and the residual surfactant may interfere with subsequent analysis.

Enzymatic hydrolysis demonstrates unique advantages in the processing of biological samples. Taboada-Lupez et al. developed an enzymatic hydrolysis extraction method for TiO_2 NPs in surimi samples. They used protease to degrade the protein matrix under mild conditions (37 °C, pH 7.5), achieving a nanoparticle recovery rate of 85–92% while maintaining the original particle size distribution almost intact [32]. Gao et al. developed a mechanical-assisted alkaline extraction method, combining vortex oscillation and alkaline conditions (pH 10–11), which significantly enhanced the extraction efficiency of NPs from plant tissues (>90%) [33]. The limitations of enzymatic hydrolysis lie in its relatively high cost, long processing time (usually 12–24 h), and the potential introduction of metal contamination.

The solvent extraction method is designed based on the principle of "like dissolves like". Laughton et al. developed a methanol-based extraction method, which achieved a recovery rate of over 75% for insoluble and slightly water-soluble NPs (such as CeO_2 and TiO_2) in plant tissues [34]. The key point to this method lies in choosing the appropriate solvent polarity, which should fully extract the target particles while minimizing the co-extraction of interfering substances. Espada-Bernabé et al. developed a rapid and low-cost water-based extraction protocol suitable for the simultaneous extraction of SiO_2 and TiO_2 NPs from food, but strict control of pH and ionic strength is necessary to prevent particle aggregation [35].

When facing complex environmental samples, a single extraction method often hardly meets the requirements, and the combined application of multiple methods has become a development trend. For instance, Torrent et al. combined CPE with centrifugation. Firstly, CPE was used to enrich silver NPs in soil leachate, and then the samples were purified by centrifugation, reducing the detection limit to 0.1 μg L^{-1} [29]. Bland et al. established a method combining CPE, centrifugation and ultrasonic disruption to achieve quantitative characterization of soluble CuO NPs in soil [27]. The assessment of particle integrity is receiving increasing attention. Paton et al. systematically compared the effects of different pretreatment strategies on the size distribution of natural single particles and found that mild enzymatic treatment had the least impact on particle size (change < 5%), while strong acid digestion led to significant changes in particle dissolution and size distribution [23].

2.3. Surface Modification with Functionalized Materials

Specific separation methods achieve highly selective separation of target NPs by designing materials with specific recognition capabilities, as shown in Figure 1c. Magnetic separation technology has attracted much attention due to its simple operation and rapid separation characteristics. Zhang et al. developed silver ion-imprinted magnetic adsorbents, which specifically recognize Ag^+ and AgNPs through surface imprinted cavities. Combined with spICP-MS analysis, they achieved the separation and determination of dissolved silver and nano-silver in antibacterial gel samples, with a selectivity coefficient of 15.3 [36]. Ch'ng et al. reported a semi-automated screening platform based on magnetic NPs, which significantly increased the processing throughput through the specific binding of functionalized magnetic beads to target particles [37]. The challenge of magnetic separation lies in the design and synthesis of functionalized materials, which requires a balance between binding capacity, selectivity and stability.

The assisted extraction by biomolecules represents a new development direction. Li et al. proposed a protein corona-induced extraction method. This method takes advantage of the selective adsorption of bovine serum albumin on the surface of Ag_2S NPs to form a protein

corona, and then releases the particles through Fenton oxidation. The recovery rate of Ag_2S NPs in natural water bodies by this method is 89–94%, and it is almost not interfered by other metal sulfides [31]. The advantages of bio-molecule-assisted extraction lie in its high selectivity and environmental friendliness, but the stability of bio-molecules and their long-term impact on particle surfaces still need in-depth research.

2.4. Automatic Separation toward Efficiency and Standardization

Table 1 summarizes the extraction efficiency, advantages, and limitations of the principal methods discussed above. The risk of physical and chemical property changes such as agglomeration, dissolution or surface modification of NPs during the extraction process are still challenges. Therefore, it is necessary to develop milder and more selective extraction reagents to minimize the impact on the original state of the particles. By coupling online separation techniques, particles can be separated and purified according to their physicochemical properties before entering spICP-MS, thereby significantly reducing matrix interference and enhancing the accuracy of particle size determination. Online coupling technology demonstrates the advantages of automated analysis. Tou et al. developed a direct microwave-assisted extraction with spICP-MS, which enabled the automatic analysis of Ti, Zn, Ag, and Au NPs in sediment samples. The analysis time for a single sample was reduced to 15 min, and the risk of sample contamination and particle loss was also minimized [38]. Capillary Electrophoresis coupled with spICP-MS (CE-spICP-MS) achieves separation based on the surface charge of particles, offering distinctive insights for analyzing functionalized NPs or investigating alterations in particle surface chemistry [39].

Table 1. Comparison of extraction and preconcentration methods for environmental nanoparticle analysis.

Method	Efficiency/Enrichment factor	Advantages	Limitations	Refs.
Cloud point extraction (CPE)	Enrichment factor: 50–100×	Green, low organic solvent, high enrichment.	Lower efficiency for hydrophilic NPs; Surfactant residue may interfere.	[31]
Hollow fiber ultrafiltration (HFUF)	Removes >95% dissolved ions	Effective removal of dissolved metal interference; Improved size detection limit for metal-containing NPs.	Membrane adsorption losses for low-concentration samples.	[25]
Membrane filtration (0.1–0.45 μm)	-	Effective for removing large particle interference (>450 nm).	Adsorption losses on membrane surface.	[24]
Ultracentrifugation (>100,000× *g*)	Recovery varies by particle density and matrix composition	Rapid sedimentation.	High centrifugal force may cause particle deformation or aggregation; Limited for NPs with density close to matrix.	[20–23]
Tangential flow filtration (TFF)	-	Flow parallel to membrane surface reduces fouling.	Adsorption losses on membrane surface.	[26]
Enzymatic hydrolysis	Recovery: 85–92%	Preservation of particle size distribution under mild conditions.	Processing time (12–24 h); Potential introduction of metal contamination from enzymes.	[32]
Mechanical-assisted alkaline extraction	Recovery: >90%	Enhanced extraction efficiency for NPs from plant tissues	Alkaline conditions alter particle surface properties.	[33]
Methanol-based extraction	Recovery: >75% for insoluble and slightly water-soluble NPs	-	Solvent polarity need be optimized per particle type.	[34]
Protein corona-induced extraction	Recovery: 89–94%	High selectivity; Non-destructive to particle morphology.	Potential instability of bio-molecules and their effects on particle surface	[31]
Ion-imprinted magnetic adsorption	Selectivity coefficient: 15.3 (imprinted vs. non-imprinted)	Selective recognition of target species via surface imprinted cavities	Material synthesis requires optimization of binding capacity, selectivity, and stability	[36]

While not yet integrated with spICP-MS, certain separation techniques have demonstrated promising particle isolation capabilities. These separation and purification based on the physicochemical properties of particles significantly reduce matrix interference and enhance the accuracy of particle size determination. Asymmetrical Flow Field-Flow Fractionation Coupled with ICP-MS (AF4-ICP-MS) performs gentle separation based on the hydrodynamic diameter of particles and is widely employed for the size characterization and quantification of NPs in food matrices [40–42], environmental water systems [43], and biological media [44]. Hydrodynamic chromatography coupled with ICP-MS (HDC-ICP-MS) provides accelerated size separation capabilities, making it suitable for studying the aggregation kinetics of NPs [45]. The implementation of these combinatorial strategies not only achieves the "separation prior to analysis" approach, thereby enhancing the selectivity of targeted particle

detection, but also enables systematic investigation into particle aggregation states and colloidal stability [46,47].

In the future, it is necessary to establish standardized reference methods and develop corresponding certified reference materials. With the advancement of analytical techniques such as spICP-TOF-MS and the integration of interdisciplinary fields, the methodology for extracting NPs will provide a solid technical support for a comprehensive understanding of the environmental behavior and ecological risks of nanomaterials.

3. Identification and Quantification of Single Nanoparticle

This section first examines the inherent methodological limitations of spICP-MS, encompassing both quadrupole and time-of-flight configurations, with regard to size detection limits, matrix effects, and quantitative accuracy. Building upon this foundation, it systematically details the applications of spICP-MS across four environmental domains. For atmospheric particulates, spICP-MS enables high-throughput quantification of metal nanoparticle number concentrations and size distributions from air filters, facilitating source apportionment from office printing, industrial activities, and natural events. In aquatic environments, the technique is pivotal for detecting ENPs, tracking their transformations in complex matrices (wastewater, leachate) with advanced pretreatment methods. The analysis of soil and sediment presents significant challenges, with core achievements centered on developing extraction protocols to quantify both ENPs and incidental NPs from sources such as road runoff and sewage sludge, despite ongoing issues with method standardization. In biological samples, spICP-MS quantifies NP uptake and distribution in plants, animals, and humans; recent instrumental advances extending to single-cell analysis are also highlighted. Table 2 summarizes the nanoparticle species, environmental matrices, extraction methods, and detection approaches covered in this section.

Table 2. Summary of nanoparticle species, environmental matrices, analytical bottlenecks, robust methodologies, and representative references.

NPs	Medium	Bottleneck	Methodology	Refs.
CeO_2	Soil	Soil's complex nature, aging effects during extraction.	Tetrasodium pyrophosphate extraction + spICP-MS	[21]
	Plant	Simultaneous detection of particulate Ce, dissolved Ce in plant.	Ultra-centrifugation + enzymatic digestion + spICP-MS	[20,22]
Ag_2S	Waters	Selective extraction of Ag_2S-NPs from real waters without morphological change.	Protein corona–induced extraction + spICP-MS	[31]
			CPE + spICP-MS	[28]
	Plant tissues	Quantification of Ag_2S-NPs with unchanged morphology	Enzymatic extraction + spICP-MS	[48]
TiO_2	Food	Isolation of TiO_2 NPs from protein-rich solid matrix without particle dissolution	Enzymatic extraction + spICP-MS	[32,49]
	Human breast milk & infant formula	Low concentration in lipid/protein-rich fluid	Enzymatic/aqueous extraction + spICP-MS	[50]
Ti, Zn, Ag, Au	Sediment	Simultaneous extraction of multiple NP types from heterogeneous solid matrix; High TOC interference.	Ultrasonication + Sedimentation + spICP-MS	[38]
Ag	Soil leachates	Interference of great amounts of Ag(I)	CPE + Centrifugation + spICP-MS	[29]
	Antibacterial gel extracts		Ion-imprinted magnetic adsorption + spICP-MS	[36]
	Plant tissues	Discriminating particulate uptake from dissolved ion uptake	Enzymatic/alkaline extraction + spICP-MS	[51]
	Shewanella oneidensis cells	Distinguishing intracellular between extracellular formation	Cell lysis + Mild extraction + spICP-MS	[52]
	Animal tissues (liver, organs)	Simultaneous extraction of both particulate and ionic silver in original forms from lipid-rich tissue.	Alkaline digestion + spICP-MS	[53]
	Infant oral mucosa	Low NP dose penetrating small tissues	Acid digestion + Microwave + spICP-MS	[54]
Au	Tomato	Measurement of AuNP size and concentration without particle dissolution	Enzymatic extraction + spICP-MS	[55]
	Animal tissues (liver, organs)	Preservation of particle integrity	Alkaline digestion + spICP-MS	[53]
Fe, Zn, Cu, Pb	Road runoff sediment	Extraction of diverse incidental NPs (<300 nm) from complex traffic-related solid matrix	Surfactant-assisted extraction + spICP-MS	[56]
Ag, Ti, Zn, Fe	Sewage sludge	Co-extraction of high dissolved ion background	Tetrasodium Pyrophosphate / BCR extraction + spICP-MS	[57,58]
Se	Plant tissues	Foliar uptake quantification at low dose	Enzymatic digestion + spICP-MS	[59]
Pt	Plant tissues	Size-dependent bioavailability below 10 nm	Acid digestion + spICP-MS	[60]
Multi-elements (Hg-associated)	Soil & Sediment	Distinguishing Hg-bearing NPs from background mineral particles	CPE + Centrifugation + spICP-TOF-MS	[61]

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3.1. Inherent Methodological Limitations of spICP-MS System

The application of spICP-MS must acknowledge inherent methodological limitations that affect both quadrupole and time-of-flight platforms. The smallest nanoparticle that can be reliably distinguished from the background signal is element-specific and governed by instrument sensitivity, the dissolved ion baseline, and spectral interferences. A comprehensive study of size detection limits for 40 elements demonstrated that for many analytes, particles must be at least 10–20 nm in diameter to be detected, with lighter or interference-prone elements exhibiting substantially larger thresholds [62]. In quadrupole-based spICP-MS, the single-element monitoring mode requires prior knowledge of the target element; in spICP-TOF-MS, the division of the available ion budget across the full mass spectrum can result in per-element sensitivity somewhat lower than that of an optimized quadrupole instrument, potentially elevating size detection limits for elements present at trace levels [14].

The introduction of complex environmental samples into the plasma can produce both spectral and non-spectral interferences that compromise analytical performance. Spectral interferences, such as polyatomic species (e.g., ArO^+ on ^{56}Fe, $ArCl^+$ on ^{75}As), are common to both platforms and can elevate background signals, effectively degrading size detection limits unless mitigated by collision/reaction cell technology [63]. Non-spectral matrix effects arise from high concentrations of dissolved salts or organic matter, which can suppress or enhance analyte sensitivity and alter sample transport efficiency. These effects introduce biases in both particle size and number concentration if not corrected through matrix-matched calibration or standard addition approaches. TOF analyzers render spICP-TOF-MS particularly susceptible to polyatomic interferences, as the interference cannot be physically resolved from the analyte signal.

The conversion of raw signal intensities into particle mass and number concentration depends critically on the determination of transport efficiency, the fraction of nebulized sample that reaches the plasma. Recognized discrepancies between the available calibration methods remain a significant source of uncertainty [64]. Furthermore, the calculation of particle diameter from elemental mass assumes spherical geometry and requires a priori knowledge of particle composition and density. These assumptions are often unrealistic for environmentally aged, heterogeneous, or multi-phase particles, and their inaccuracies directly propagate into size distribution errors. For spICP-TOF-MS, the substantially larger data volume introduces additional challenges for quality control and reproducible data processing.

3.2. Atmospheric Particulates and Dusts

The application of spICP-MS has emerged as a pivotal analytical technique for precise source apportionment and characterization of atmospheric particulate matter, particularly metallic/metallic oxide NPs. This technique enables direct analysis of particulate matter collected on air filters, achieving high-throughput quantification of both number concentration and size distribution of atmospheric particles, thereby introducing a novel dimension to ambient air quality monitoring [65].

The application of spICP-MS has enhanced our understanding of the release characteristics of atmospheric NPs from anthropogenic and natural sources, thereby advancing the traceability and risk assessment. Regarding anthropogenic sources, this technology precisely elucidates the physicochemical properties of submicron metallic particles emitted during office printing and nanoscale metal-containing particles generated during paper shredding, thereby establishing a direct correlation between routine activities and the compositional variation of atmospheric particulate matter [66]. In the domain of occupational exposure, Through the simultaneous analysis of airborne particulates from welding workplaces and biological samples (such as exhaled breath condensate), spICP-MS has enabled, for the first time, the quantitative tracking of metal oxide NPs (e.g., Cr_2O_3) from environmental exposure to internal accumulation in the human body. This advancement provides critical data support for establishing nanoparticle-based exposure-response relationships [67]. In the domain of natural and episodic sources, spICP-MS was not only employed for the first time to delineate the nano-species distribution of metallic elements (adsorbed forms and discrete nano-phases) in volcanic ash, but also revealed the contribution of natural processes to the chemical speciation diversity of atmospheric NPs [68], and identified the unique Cr-rich nanoparticle clusters emitted from wildfires burning tires, which indicates how such abrupt events substantially alter particle concentrations and environmental mobility [69]. As shown in Figure 2a, these research findings highlight the indispensable role of spICP-MS in elucidating the environmental behaviors of multi-scale and multi-source atmospheric NPs. The technical advantage of spICP-MS lies in its high sensitivity and statistical reliability. Compared to bulk analysis, spICP-MS provides particle-number-based distribution information, enabling more sensitive detection of variations in pollution sources and effectively distinguishing background levels from contamination events.

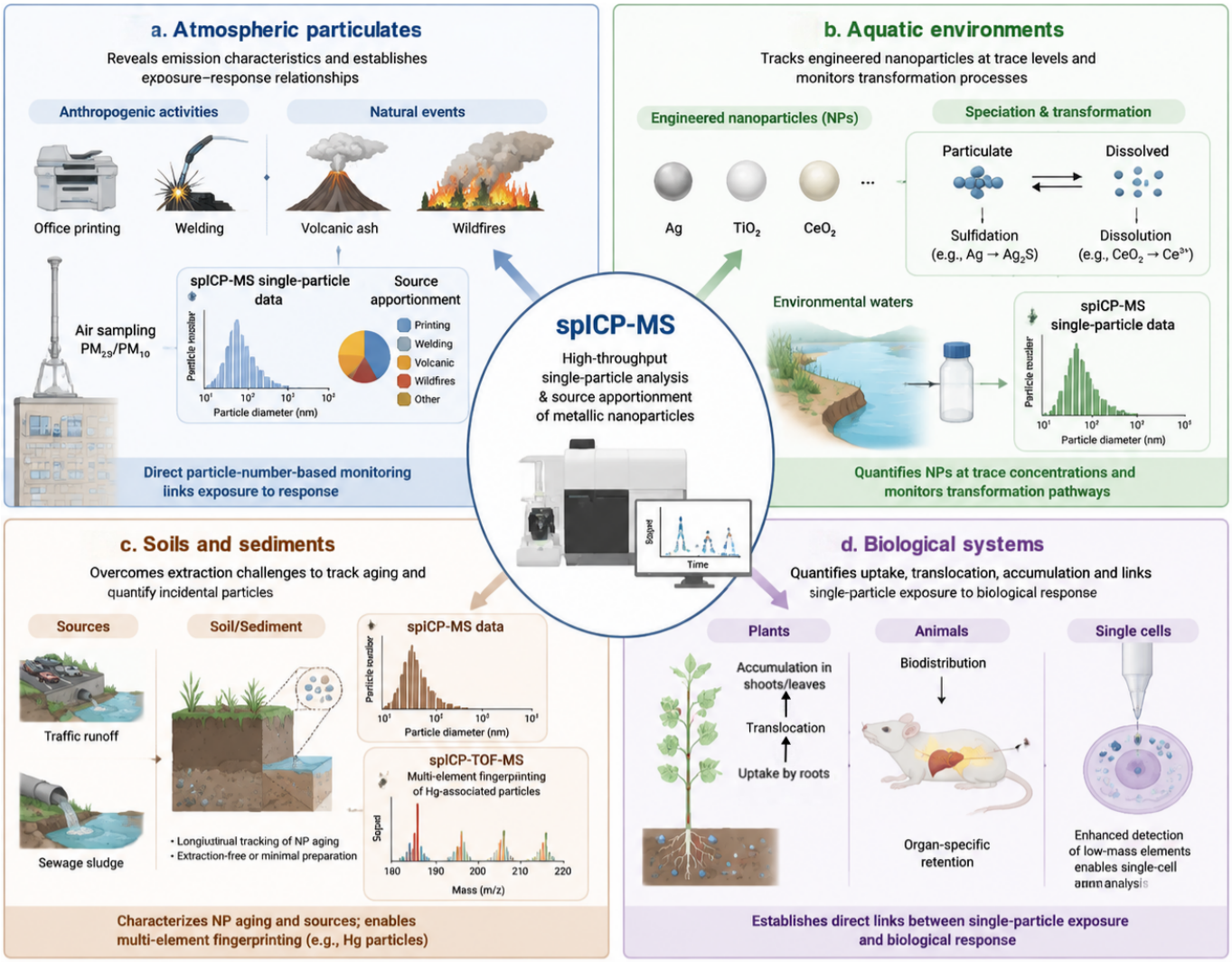

Figure 2. Identification and source attribution of nanoparticles by spICP-MS across environmental compartments, such as (**a**) atmospheric, (**b**) aquatic, (**c**) terrestrial, and (**d**) biological system.

3.3. Nano-Scale Particulates in Aquatic Environments

Water bodies serve as critical environments for the transport and transformation of ENPs and natural NPs, and spICP-MS is the most widely applied technique in this field, primarily focusing on detection, occurrence, and transformation. In the realm of detection and occurrence analysis, spICP-MS has been successfully implemented across diverse water bodies worldwide. ENPs such as silver, titanium dioxide, and cerium dioxide have been detected in recreational waters [70,71], rivers [72], lakes [73,74], and even marine environments [75], with confirmed number concentrations and particle sizes typically ranging from tens to hundreds of nanometers. In the ultra-trace concentration scenarios, analytical methodologies integrating CPE [29] and anion exchange as pretreatment techniques with spICP-MS have been developed [76]. These approaches substantially enhance the analytical sensitivity and matrix interference resistance for NPs in complex aqueous matrices, such as wastewater [77] and landfill leachate [78].

In the field of transformation and fate studies, spICP-MS has demonstrated distinct advantages. The spICP-MS analysis enables the simultaneous determination of particulate and dissolved metal species, thereby facilitating real-time tracking of the transformation processes of NPs, as shown in Figure 2b. For example, studies have revealed that Ag NPs undergo rapid sulfidation in natural water bodies to form Ag_2S NPs [79,80], while the presence of microplastics significantly influences the photochemical transformation processes of Ag^+ [81]. The size and numbers of neodymium (Nd) in the form of colloids are influenced by natural organic matters [82]. Furthermore, research on wastewater treatment plants demonstrates that a significant proportion of metallic NPs can be effectively removed and accumulated in sludge [83]. However, a fraction of NPs may bypass treatment processes and enter receiving water bodies [84], underscoring the dual role of wastewater treatment plants as both sinks and sources of NPs.

3.4. Particles in the Nanophase of Soil and Sediment

Soil and sediment are one of the ultimate sinks for NPs, yet their complex matrices pose substantial analytical challenges. As discussed in the preceding chapter, a key achievement of spICP-MS in this field lies in the development of a suite of targeted pretreatment methods, enabling a breakthrough from non-detectable to quantifiable levels. The application of spICP-MS enables the longitudinal tracking of ENPs after their introduction into soil systems. Liu et al. investigated the behavior of CeO_2 NPs during soil aging processes employing an optimized extraction protocol integrated with spICP-MS [21]. They observed that although the particle number concentration varied over time, the particle size distribution remained relatively stable, indicating no significant dissolution or pronounced aggregation of the NPs during the test period. This provides direct evidence for assessing the persistence of certain ENPs in soil. Similarly, research on zero-valent iron NPs in soil elucidates their interaction mechanism with cadmium ions in wastewater [85].

The incidental NPs, referring to unintentionally produced particles originating from processes such as friction, corrosion, and combustion, are attracting attention due to their ubiquity and potential risks in the environment. A key advantage of spICP-MS lies in its capacity to detect and quantify analytes based on elemental signals, even without prior knowledge of their precise chemical speciation. As shown in Figure 2c, Baur et al. employed surfactant-assisted extraction to successfully liberate and quantify various metallic NPs such as Fe, Zn, Cu, and Pb from road runoff sediments, thereby highlighting traffic-related activities as a significant source of metallic NPs in urban environment [56]. In-depth research on sewage sludge [57,58] and landfill leachate [78] has revealed the presence of considerable concentrations of diverse metallic NPs, including Ag, Ti, Zn, Fe, among others. Xu et al. revealed the coexisting of Hg with Al, Fe, Mg, Ti, Si, and Ce on individual particles in soils and subaquatic sediments upon the fast and simultaneous multi-element detection capabilities of spICP-TOF-MS [61]. These NPs, once introduced into the environment through agricultural application of sludge or leakage of leachate, may pose long-term risks. It is also employed to assess the stability of iron oxide NPs generated during soil remediation processes [86].

Despite the substantial progress achieved, this field continues to face formidable challenges. The foremost consideration lies in achieving an equilibrium between extraction efficiency and data authenticity. Efficient extraction may alter the surface properties of NPs or induce dissolution, whereas gentle extraction could result in suboptimal recovery rates. Evaluating and calibrating extraction efficiency thus presents a critical challenge. The pronounced heterogeneity of soil matrices poses considerable challenges in establishing standardized and universally accepted Standard Operating Procedures (SOPs) and reference materials [87]. The detection limit for ultrafine particles requires further enhancement. Atypically high concentrations of dissolved ions in soil extracts may interfere with the identification of signal signatures from extremely fine NPs.

3.5. Nanoparticle Analysis in Biological Systems

In contrast to the abiotic matrices discussed above, advent of spICP-MS in the biological sciences has fundamentally transformed the understanding of NPs absorption, transport, accumulation, and toxicity mechanisms, thereby enabling an unprecedented transition from the tissue level to the single-cell level, as shown in Figure 2d. This technique accurately quantifies the process of metallic NPs uptake from roots and their subsequent translocation to above ground plant tissues. Researches have demonstrated that plants are capable of absorbing [51] and translocating Au NPs [55]. Additionally, studies indicate that wheat leaves can uptake Se NPs, thereby influencing physiological processes [59]. The SiO_2-coated ZnO NPs are almost translocated to upper leaves and the stem in the form of particulate in foliar application [88]. Furthermore, the absorption of Pt NPs in rice exhibits a size-dependent behavior [60]. The translocation of larger SiO_2 NPs than well-known size exclusion limits (50 nm) were founded in plant tissues [89]. The study has also demonstrated that plants can uptake sparingly soluble Ag_2S NPs and induce morphological transformations within their tissues [48]. The potential formation of Ag NPs inside the *Shewanella oneidensis* cell had been further confirmed using spICP-MS [52].

The application of spICP-MS has been increasingly advanced in studies on NPs exposure in animals and humans, of which the concentration of NPs in biological tissues (e.g., liver) [53], bodily fluids, and even single cells [90] are qualified. The studies indicate that orally administered CeO_2 NPs exhibit broad bio-distribution and potential long-term retention in murine models [91], while Ag NPs demonstrate the capability to penetrate the infant oral mucosa [54]. TiO_2 particles have been detected in human breast milk and infant formula [50], and dietary exposure to TiO_2 NPs has been assessed in populations consuming seafood [49]. The spICP-MS analysis provides direct experimental data for a comprehensive assessment of the human health risks associated with NPs. Furthermore, this technology has been extensively applied in studies concerning the accumulation of and response to NPs in aquatic organisms, such as bivalves [92–94], fish cells [95], and zooplankton [96], thereby establishing dose-response relationships from environmental concentrations to biological effects and providing a methodological foundation for ecological risk assessment.

The analytical scope of spICP-MS in biological systems has been further broadened by instrumental advances enabling the sensitive detection of low-mass elements such as carbon and phosphorus [97]. By extending the single-particle analytical concept to the cellular domain, single-cell ICP-MS has emerged as a powerful approach that enables the simultaneous monitoring of metal-containing NPs and the biological cells with which they interact [90]. This capability allows researchers to quantify the elemental composition of individual cells via their intrinsic elemental signals such as phosphorus, magnesium, sulfur, and iron, while concurrently determining the number and elemental content of associated metal nanoparticles [64]. The ability to differentiate individual metal nanoparticles, single cells, and their aggregates at the single-particle level opens new avenues for investigating the mechanisms of nanoparticle uptake, intracellular processing, and toxicological effects, establishing a direct link between exposure at the single-particle level and biological response at the single-cell level.

4. Hyphenated Techniques for Multidimensional Single-Particle Characterization

The preceding chapters have established spICP-MS as a powerful analytical platform for quantifying nanoparticle number concentrations, size distributions, and elemental compositions across diverse environmental matrices. However, spICP-MS variants are inherently atom-centered techniques that cannot distinguish chemical speciation, molecular identity, or crystalline phase among particles of identical elemental composition. This chapter examines how the hyphenation of spICP-MS with complementary optical and spectroscopic techniques overcomes this constraint, enabling a transition from single-dimensional elemental analysis to multidimensional characterization spanning the elemental-molecular continuum. The discussion begins with the rationale for hyphenation and an overview of the principal strategies currently employed, followed by an in-depth examination of the OF2i-Raman-spICP-TOF-MS platform as the most advanced realization of integrated in-situ multimodal characterization, with particular focus on its capability to distinguish anatase from rutile TiO_2 at the single-particle level. The chapter then extends to applications in toxicology and environmental fate studies, and concludes with perspectives on future technological development.

4.1. Rationale and Strategies for Hyphenating spICP-MS with Spectroscopic Techniques

The spICP-MS analysis enables precise quantification of particle number concentration, size distribution, and elemental composition by individually introducing suspended particles into the plasma and detecting their transient ionic cloud signals. However, their analytical perspective is essentially atom-centered, and there are fundamental limitations. The estimation of ENPs density is even needed supporting information about surface area conducted by BET measurement [98]. Crucially, spICP-MS alone is incapable of distinguishing the chemical speciation of particles that share the same elemental composition. A quintessential example is titanium dioxide (TiO_2), which exists in nature and engineered products in multiple crystalline phases, most commonly anatase and rutile, that exhibit markedly different physicochemical properties, environmental behaviors, and toxicological profiles [99]. Particle size and mass calculation models typically assume particles to be spherical, homogeneous, and characterized by known elemental mass fractions [100,101]. However, these assumptions can introduce substantial errors when analyzing real-world particles that exhibit complex morphologies, heterogeneity, or aging effects.

To overcome these limitations, the analytical science community is actively exploring hyphenation of spICP-MS with complementary analytical techniques. Among these interdisciplinary integrations, the convergence with optical and spectroscopic techniques, such as Raman spectroscopy and optical trapping, stands out as one of the most promising advancements [102]. This prominence derives from their capacity to non-invasively and in situ furnish molecular fingerprints, crystallographic characteristics, and even dynamic behavioral data of particulate matter. This integrated approach aims to establish a multimodal analytical platform, enabling comprehensive characterization, from elemental composition (what elements are present) to chemical speciation (what substances exist) and further to interactions (morphological features and dynamic processes) at the single-particle level.

Groundbreaking methodological innovation that combines advantages of different instruments are following certain logical rules and underlying architecture [103]. At present, the integration of spICP-MS with optical/spectroscopic techniques predominantly follows three principal strategies: sequential analytical, integrated in situ, and enhanced complementary approaches. Sequential analysis involves conducting independent examinations on identical sample sets or localized sample regions using spectroscopic and mass spectrometric techniques, followed by data integration to derive comprehensive analytical insights. For instance, in the analysis of soil or sediment samples, micro-Raman spectroscopy can initially be employed to map the spatial distribution and identify the mineral phases of titanium-bearing particles through localization. Subsequently, laser ablation-inductively coupled plasma-mass spectrometry (LA-ICP-MS) can be utilized to perform imaging analysis on the identical region, thereby elucidating the multi-elemental associations and spatial distribution of metal contaminants coexisting with these particles [104–106].

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Although this offline mode is not strictly synchronized in terms of temporal and spatial dimensions, it provides robust evidence for investigating the formation of particle-pollutant complexes and the phase-dependent behavior of ENPs [106,107].

4.2. Integrated In-Situ Characterization: The OF2i-Raman-spICP-TOF-MS Platform and Phase Identification

Integrated in situ analysis represents the cutting-edge of current technological advancement, aiming to achieve continuous, real-time, and multidimensional characterization of individual particles. The most representative achievement is an innovative system integrating optofluidic induction (OF2i), Raman spectroscopy, and single-particle inductively coupled plasma time-of-flight mass spectrometry (OF2i-Raman-spICP-TOF-MS) [102,108]. The operational workflow and synergistic advantages of this platform are as follows (see Figure 3): (1) Optofluidic force induction (OF2i) is employed to counteract hydrodynamic forces within microfluidic channels by aligning a weakly focused vortex laser beam antiparallelly to the fluid flow. This configuration enables the stable optical trapping of individual particles at size- and refractive index-dependent equilibrium positions, thereby facilitating in situ size-based sorting and complete matrix elimination. (2) In-situ Raman spectroscopy enables direct spectral analysis of the individual optically trapped particles, thereby obtaining their molecular vibration fingerprints. This functionality is particularly critical for distinguishing polymorphic forms of the same compound. For TiO_2 NPs, the characteristic Raman bands of anatase and rutile provide unambiguous phase identification at the single-particle level. The experimental Raman spectra of individual trapped TiO_2 particles, when compared against reference spectra of both phases, enabled a clear identification of particles as anatase. This a priori molecular information is essential for correcting the key assumptions made by spICP-MS, where inaccurate estimates of particle density (e.g., 3.9 g/cm^3 for anatase vs. 4.24 g/cm^3 for rutile) or elemental mass fractions directly compromise the accuracy of mass and size distribution models [102]. (3) The optically characterized target particles are released from the capture site and transported to spICP-TOF-MS. The full-spectrum acquisition capability of spICP-TOF-MS enables simultaneous multi-elements and isotopic analysis during individual particle events. For example, following Raman-based phase identification, the TOF-MS can simultaneously determine the Ti content and potential impurity elements (such as Al, Fe, or Nb that may indicate natural versus engineered origin) within the same TiO_2 particle. This closed-loop design represents the first conceptual realization of seamless integration for size-selective sorting, molecular identification, and comprehensive elemental fingerprint analysis of the same single-particle population, epitomizing the highest level of multimodal characterization for individual particles.

The capability to unambiguously resolve anatase from rutile at the single-particle level has profound implications. Anatase TiO_2 exhibits significantly higher photocatalytic activity and reactive oxygen species generation capacity than rutile, directly influencing its environmental transformation kinetics and ecotoxicological effects. Conventional bulk-phase quantification can only report the ensemble-average phase composition, masking critical information on particle-to-particle heterogeneity. With the OF2i-Raman-spICP-TOF-MS platform, researchers can directly correlate the crystal structure of individual TiO_2 NPs with their elemental composition, size, and dissolution behavior, thereby enabling mechanistic understanding of how phase identity governs environmental fate and biological interactions.

4.3. From Toxicology to Environmental Fate: Applications and Perspectives of Multimodal Single-Particle Analysis

In toxicological research, the combined use of hyphenated techniques can elucidate the interaction between nanoparticles and biological systems at unprecedented resolution. OF2i-Raman-spICP-TOF-MS platform can be used to conduct correlation analysis on the crystal structure, such as Anatase vs. Rutile TiO_2 nanocrystal, and elemental dissolution behavior of particles before and after their exposure to cells, thereby elucidating their toxicity mechanisms at the molecular level [99]. By treating cells as complex “particles”, spICP-TOF-MS can quantify the number of nanoparticle uptakes and elemental contents within a single cell [109,110]. When this quantitative uptake data is correlated with Raman spectroscopy, which can provide a fingerprint of the cell’s metabolic states, a direct relationship between “nanoparticle uptake-cell biochemical response” is established. This approach transcends traditional toxicology, which is often limited to correlating “total exposure dose–observed effect,” by enabling dissection of the specific contributions of individual particle properties to biological outcomes.

In environmental transformation studies, hyphenated techniques similarly excel. The combination of spICP-MS with X-ray absorption spectroscopy has been employed to evaluate the release of colloidal arsenic from environmental samples, where the spectroscopic technique identifies the chemical speciation (e.g., As(III) vs. As(V)) while spICP-MS quantifies the size distribution and elemental association of the arsenic-bearing particles [106]. Similarly, spICP-MS was used to unravel the effect of different food types on the physicochemical properties and gastrointestinal stability of ZnO nanoparticles released from packaging materials, where coupling with complementary spectroscopic techniques

enabled characterization of both dissolution kinetics and the evolving particle speciation [107]. These examples illustrate the transformative potential of hyphenated approaches: they bridge the gap between the "elemental world" of mass spectrometry and the "molecular world" of spectroscopy, enabling a holistic understanding of nanoparticle identity, transformation, and biological interactions.

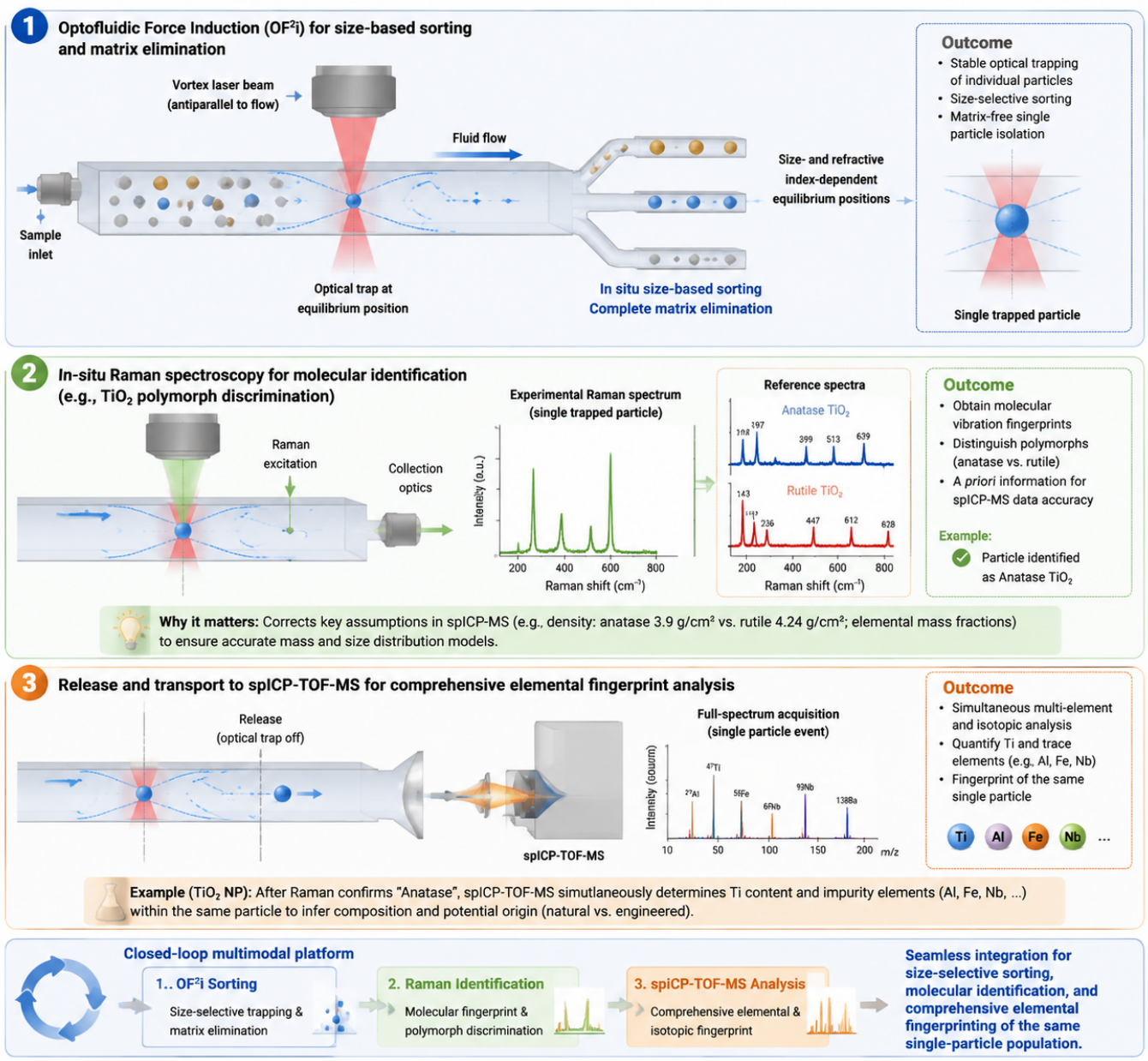

Figure 3. Operational workflow and synergistic advantages of integrating optofluidic induction (OF2i), Raman spectroscopy, and single-particle inductively coupled plasma time-of-flight mass spectrometry (OF2i-Raman-spICP-TOF-MS).

The integrated online analytical platform exemplified by OF2i-Raman-spICP-TOF-MS signifies a new milestone in multimodal characterization technology for single-particle analysis, expanding the analysis of particulate matter from a single "elemental world" to a new dimension of "element–molecule" binary synergy. This technology has the potential for further enhancement in terms of integration degree. More compact and user-friendly commercial integrated systems should be promoted to accelerate their application. Automated microfluidic technology can be employed to enhance the robustness and throughput of single-particle analysis, and may contribute to accelerating the data acquisition speed of spectroscopy. With the deepening of interdisciplinary collaborations and continuous technological innovations, "spectroscopy–mass spectrometry" hyphenation is poised to propel single-particle analysis into a new era characterized by more comprehensive information, deeper insights, and broader applications.

5. Analytical Improvement with Machine Learning

Machine learning (ML) plays a pivotal role in advancing spICP-MS for environmental nanoparticle research. In intelligent identification and source tracking, ML overcomes the limitations of conventional methods by analyzing multi-element fingerprint data at the single-particle level, enabling high-precision and interpretable classification of ENPs and natural NPs in complex environmental matrices. For elucidating toxicity mechanisms, the integration of ML with spICP-MS allows for identifying translocation pathway of NPs, organ-specific accumulation of NPs, and their associations with toxicological phenotypes from high-dimensional dynamic data, thereby shifting toxicity studies from "black-box" observations to mechanistic understanding. In risk assessment and prediction, ML leverages parameters related to particle dissolution, transformation, and stability provided by spICP-MS to develop quantitative models that incorporate environmental behavior and biological effects, supporting end-to-end regulation from "safe-by-design" strategies to risk early warning. Overall, as an intelligent analytical core, ML significantly enhances the capabilities of spICP-MS in nanoparticle identification, mechanistic interpretation, and risk prediction, driving the field toward a data-driven and model-integrated paradigm of precision science.

5.1. Intelligent Identification and Traceability of Nanoparticles

The sources of nano and submicron particles in the environment are increasingly complex, ranging from natural NPs generated by geological weathering and biological activities, to ENPs from industrial production and consumer products (see Figure 4a). Accurate identification and quantification of these particles, especially trace amounts of ENPs, is essential to assess their environmental fate and ecological risk. The spICP-MS analysis provides a comprehensive dataset of multi-elemental fingerprints from individual particles, thereby establishing a robust data foundation for the application of ML. To be specific, spICP-TOF-MS makes it possible to simultaneously obtain dozens of elements from thousands of single particles in a single analysis [101]. However, this technique also poses new challenges: instead of a few simple concentration values, it produces massive single-particle data sets that are highly dimensional, sparse, and contain complex patterns. Traditional data processing methods based on empirical threshold or simple ratio, such as the decision tree [101], face notable limitations that strong subjectivity, difficulty in handling nonlinear relationships, and an inability to fully exploit all information embedded in the data. Karkee and Gundlach-Graham systematically compared the performance of conventional decision tree classifiers relying on fixed elemental ratios (e.g., Ti/Fe, Ti/Al) against more advanced approaches, demonstrating that the latter can automatically learn complex multi-element association patterns without requiring pre-defined thresholds [101]. ML, as a collection of algorithms that can automatically learn patterns from data and make predictions, is a natural key to addressing this challenge. The introduction of ML is not a simple superposition of technologies, but an upgrade of analytical methodology, aiming to achieve a paradigm shift from "artificial rule judgment" to "intelligent identification of algorithmic models".

The spICP-TOF-MS outputs a set of quantitative elemental signals (mass or count) for each particle in a regular data format, which is very suitable as the input features of ML models. Particles from different sources have unique multi-element fingerprints, such as the "pure titanium" feature of engineered TiO_2 vs. characteristic element association patterns for natural minerals, which provide highly discriminative features for ML classification [111]. By analyzing suspensions of known pure substances, such as standard ENPs, pure minerals, high-quality, labeled training data can be obtained [112], creating conditions for the construction of supervised learning models. The instrument stability and data reproducibility of spICP-TOF-MS have been continuously improved. Online calibration methods, such as droplet calibration, ensure the quantitative accuracy of the data and provide quality assurance for the establishment of reliable ML models [113].

In complex substrates such as soil or sediments, the physicochemical properties of ENPs (e.g., TiO_2) and natural NPs (e.g., Ti minerals) may overlap and cannot be differentiated by size or single element alone. Bland et al. pioneered the systematic application of supervised learning, such as random forests, to this scenario. From a data preprocessing perspective, their workflow involved first setting elemental signal intensities below a threshold to zero, followed by a log-ratio transformation to address the compositional nature of the data, where a higher signal in one element necessarily reduces the proportional representation of others, and to mitigate the dominance of high-abundance elements in distance-based calculations. The choice of random forest was motivated by its robustness to outliers, its capacity to handle variables measured on different scales, and its intrinsic feature importance metrics. For validation, they constructed a synthetic dataset by spiking standard engineered TiO_2 nanoparticles into a well-characterized natural soil background, thereby generating labeled ground truth data for assessing classification performance. The model achieved accurate classification even when particle size distributions overlapped, outperforming traditional methods based on fixed elemental ratios. Importantly, the feature importance rankings provided by the random forest model identified the elements most diagnostic for distinguishing engineered TiO_2 from natural Ti minerals, offering interpretability

beyond prediction accuracy alone. This study demonstrated the ability of ML to utilize the full range of elemental information to achieve specific identification of ENPs in extremely challenging and complex environmental matrices, providing a key tool for assessing the accumulation of ENPs in the environment [112].

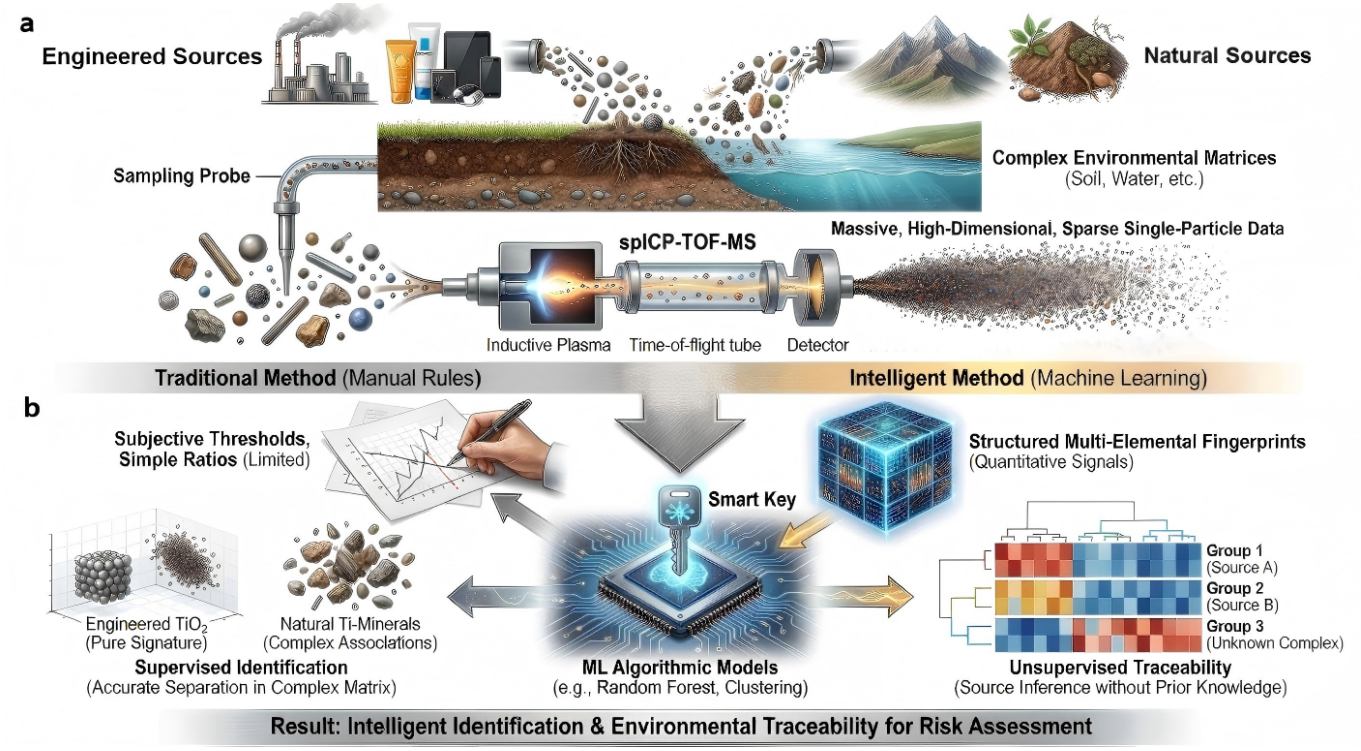

Figure 4. Application of machine learning at nanoparticle identification. (**a**) Environmental matrices introduced high-dimensional data by engineered and natural nanoparticles. (**b**) Conventional thresholds and machine learning algorithms decoded multi-elemental fingerprints of nanoparticles.

In environmental samples not appreciably contaminated or from diverse sources, the particle population composition is unknown, and the intrinsic grouping needs to be explored to infer the source. Baalousha et al. used cluster analysis to analyze spICP-TOF-MS data of NPs in natural water [114]. Their preprocessing pipeline began with filtering particle events from background noise using multi-element Poisson statistics thresholds, followed by normalization of elemental intensities to mitigate concentration effects. For model selection, they adopted a combined approach: principal component analysis (PCA) was applied first to reduce data dimensionality, and then hierarchical clustering was performed on the principal components to group particles with similar elemental fingerprints. The optimal number of clusters was determined using the elbow method in conjunction with geochemical domain knowledge. For interpretability, the centroid composition of each cluster was examined and interpreted as a prototypical multi-element profile, which could then be matched to known mineral types, organic–inorganic complexes, or particles from distinct geological units, thus revealing the diversity of natural NPs in the environment and their potential source associations. This exploratory analysis of unknown complex granular systems is realized without prior knowledge, and natural groupings in the data can be discovered (see Figure 4b).

The spICP-MS analysis opens the door to parse complex mixtures of environments at the single-particle level, and machine learning is the essential smart key to interpret the vast amount of data behind this door. The combination of the ML and spICP-MS is not only necessary and feasible, but also has achieved remarkable results in practical problems such as distinguishing engineering particles from natural particles and exploring particle community structure.

5.2. Novel Insight into Mechanism of Nanoparticles' Toxicity

Traditional toxicology studies often treat organisms as "black boxes" and only focus on initial exposure and final effects. The application of spICP-MS with the ML support can "illuminate" the inside of the black box to dynamically track and analyze the complex fate of NPs in vivo. The groundbreaking study by Zhang et al. is a model in this direction. As shown in Figure 5a, they used spICP-TOF-MS to analyze the organs of mice inhaling environmental magnetized NPs, and t-Distributed Stochastic Neighbor Embedding (t-SNE) algorithm was used to visualize the multi-element fingerprints of the particles [115]. In their data preprocessing workflow, the

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multi-element composition of each particle was first standardized to relative abundance, eliminating the confounding effect of particle size differences so that the analysis focused on compositional rather than mass variations. The choice of t-SNE over principal component analysis (PCA) was deliberate: while PCA prioritizes the preservation of global variance structure, t-SNE excels at preserving local neighborhood relationships, meaning that particles with similar multi-element fingerprints are positioned in close proximity in the low-dimensional projection. For interpretability, the relative positioning and degree of overlap between particle populations from different organs were directly interpreted as indicators of exposure pathway connectivity-particle populations from the brain and spleen that overlapped extensively with those from the lung were inferred to share a common source and translocation pathway. The results clearly showed that the particle populations in the brain and spleen were highly clustered with the source particles in the lung, while the particle populations in the liver were significantly separated. This data-driven pattern directly revealed that environmental magnetite NPs had clear exposure routes across the lung-blood barrier to the brain and through the immune system to the spleen, providing direct evidence for the understanding of the neurological and immunotoxin mechanisms of ultrafine particles.

Sometime, the toxicity can be attributable to specific particle subpopulations characterized by particular size ranges, surface chemistries, or aggregation states. As shown in Figure 5b, Laycock et al. integrated a gene knockout mouse model with spICP-MS to demonstrate that the absence of surfactant proteins SP-D and SP-A alters the aggregation state, rather than the overall clearance rate, of inhaled gold NPs within the lung [116]. From a validation perspective, this study illustrates a "biological validation" strategy, wherein the specificity of an observed effect is confirmed by comparing phenotypic differences between wild-type and genetically modified organisms. By comparing the spICP-MS-derived particle size distributions between wild-type and knockout mice under otherwise identical exposure conditions, the role of specific surfactant proteins in modulating particle aggregation could be isolated. This suggests that the in vivo aggregation state of particles is one of the key dosage metrics influencing their biological effects. ML can identify the characteristics of these "active subpopulations" and incorporate their quantity or surface area as the biologically effective dose into toxicity models.

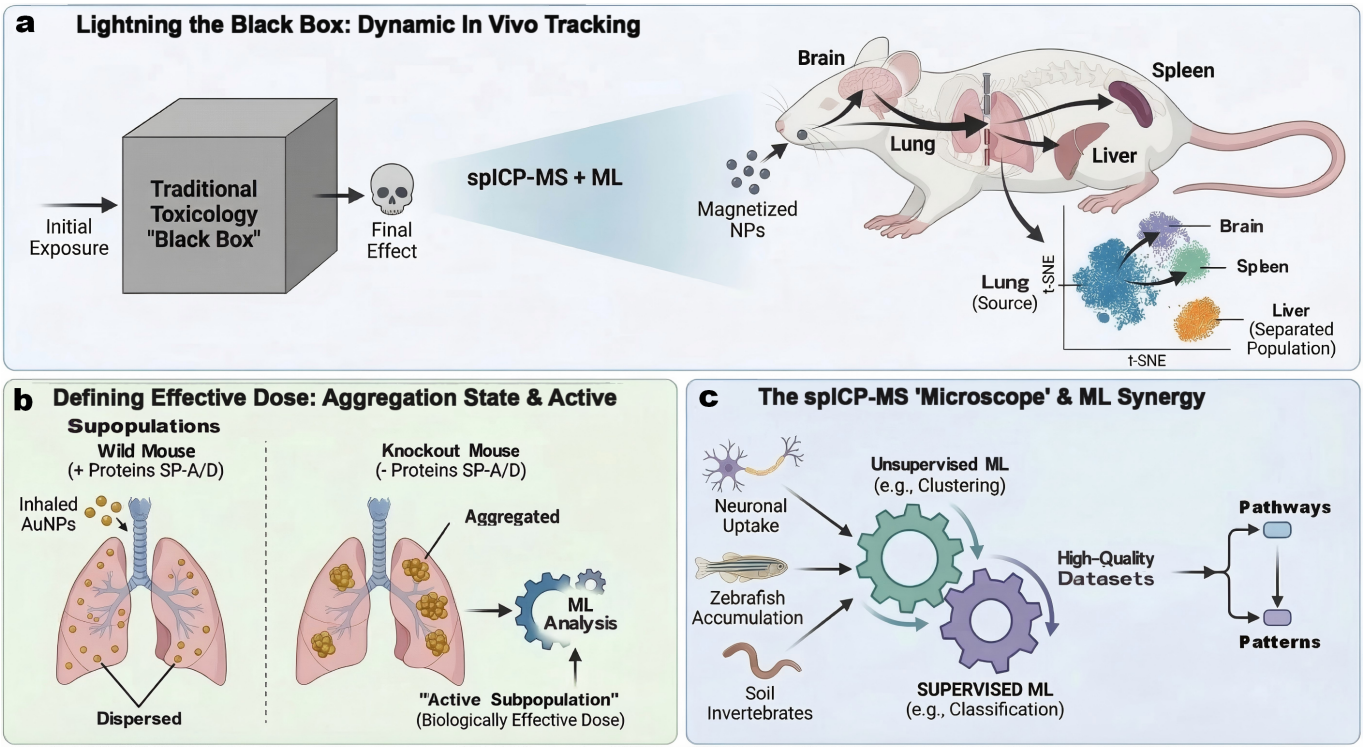

Figure 5. Application of machine learning at tracing nanoparticles. (**a**) Employing t-SNE clustering to trace the translocation of nanoparticles across organs. (**b**) Determining the biologically effective dose based on the aggregation state of gold nanoparticles in the mouse lung. (**c**) Revealing complex biological exposure pathways and latent patterns.

The spICP-MS analysis provides a "microscope" for observing the nanoscale world, as shown in Figure 5c. From elucidating the neuronal uptake pathways of magnetite nanoparticle [115] to quantifying accumulation patterns in zebrafish models [117] and further probing the toxicological thresholds in soil-dwelling invertebrates [118], these studies are progressively generating high-quality datasets and offering groundbreaking applications in deconvoluting intricate biological exposure pathways of NPs. ML, particularly its unsupervised (e.g., clustering,

dimensionality reduction) and supervised (e.g., classification, regression) algorithms, offers an ideal solution for uncovering latent patterns in high-dimensional single-particle data [115]. Combination of the two can dynamically track and analyze the complex fate of NPs within living organisms.

5.3. Predictive Models for Nanoparticles' Risk

The ML equips researchers with the "intelligent brain" necessary to interpret this vast and complex landscape, which is advancing through the development and application of increasingly sophisticated algorithms. For instance, data obtained by spICP-MS may provide foundation for constructing next-generation Quantitative Structure-Activity Relationship (QSAR) models [119]. Quantitatively acquired spICP-MS data complement spectroscopic data, establishing a comprehensive mapping of particle distribution and transformation from the sub-cellular to the organ level. A predictive model hinges upon precise input parameters. The spICP-MS analysis provides a novel dimension of data by resolving intricate details undetectable through conventional methodologies. Classical dissolution models (e.g., zero-order and first-order kinetics) employ a single rate constant. The applications of spICP-MS reveal that even within monodisperse Ag NPs populations, dissolution events exhibit spatiotemporal heterogeneity. For instance, in urban wastewater environments, a fraction of AgNPs dissolve rapidly, while others remain stable; furthermore, the dynamic process of dissolved silver re-nucleating to form secondary NPs was directly observed via simultaneous monitoring of both the particle size distribution and the dissolved Ag^+ concentration [120]. This finding has critical methodological implications for predictive model construction: a distribution function of dissolution rates, rather than a single average value, should serve as the model input to capture the true heterogeneity of nanoparticle behavior. The simultaneous acquisition of both particulate and dissolved metal signals by spICP-MS provides the data structure necessary to parameterize such distribution-based models.

Predictive models must incorporate the influence of environmental factors. The spICP-MS analysis enables precise quantification of how these factors alter particle stability. The ozonation treatment markedly alters the dissolution-agglomeration equilibrium of AgNPs. The spICP-MS analysis enables the quantitative analysis of dynamic variations in particle number concentration and dissolved ions under different ozone dosages, thereby providing quantitative coefficients for predicting their fate during water treatment processes [121]. Similarly, the size and morphological changes of AgNPs in bread during simulated digestion were precisely quantified, serving as critical kinetic data for assessing their dietary risk [122].

Predictive models are evolving from phenomenological descriptions toward mechanistic simulations. The spICP-MS application enables the discrimination and independent modeling of competitive processes. For instance, by simultaneously monitoring both the particle size distribution of ZnO NPs migrating from packaging into food simulants and the concentration of dissolved ions, distinct sub-models for "particle dissolution" and "particle aggregation/sedimentation" can be established and coupled. This integrated approach allows for more accurate prediction of the long-term stability and functional persistence of ZnO NPs within complex food matrices [106]. The ultimate risk of nanomaterials represents a composite outcome of their environmental transformation, bioaccumulation, and in vivo toxicity. The spICP-MS application enables the development of integrated chain models that delineate the nexus between environmental fate and biological effects. For instance, spICP-MS was employed to determine the transformation rate of CuO NPs in soil [123]. The resultant data can serve as a dynamic input for the bioavailable Cu concentration in ecotoxicological models, thereby enabling adaptive coupling between environmental chemical models and biological effect models. This metric demonstrates a stronger correlation with specific histopathological endpoints compared to traditional dosimetry based on total Ti mass, thereby laying the groundwork for constructing more mechanistically relevant dose-response prediction models [117].

The development of models capable of accurately predicting the reactivity and stability of nanomaterials in complex environments represents a cornerstone of the "safety-by-design" paradigm [124]. The spICP-MS application facilitates the transformation of "safety-by-design" into a computationally tractable and optimizable engineering problem by establishing a quantitative relationship framework encompassing "structure-kinetics-effect." Systematic investigations employing spICP-MS enable the identification of key designable attributes governing reaction and stability, along with quantitative assessment of their impacts. Rodrigues et al. provided a concrete demonstration of this approach through spICP-TOFMS analysis of ZnO nanoparticles with and without a zinc phosphate shell coating [125]. By quantitatively comparing the dissolution-agglomeration kinetic parameters between coated and uncoated particles under identical exposure conditions, a "stabilization efficiency" metric was extracted that directly quantifies the protective effect of the shell. Similarly, Xu et al. employed spICP-TOF-MS to investigate how arsenic binding to sulfidized nanoscale zerovalent iron (S-nZVI) altered particle reactivity at the single-particle level, extracting quantitative parameters for "reaction activity" that directly linked surface chemistry modifications to changes in dehalogenation performance [126]. These two studies exemplify how spICP-MS-derived kinetic parameters can

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serve as design inputs for material optimization. The data obtained by spICP-MS provide direct empirical evidence for optimizing core dimensions [117] and core-shell architectures [125] to enhance material longevity. A quantitative structure-activity relationship model correlating material properties with environmental kinetic parameters can be established. By integrating toxicological thresholds, the range of material property combinations that meet predetermined risk thresholds can be quantitatively determined. The spICP-MS application is transforming the prediction of reaction stability and risk management into a data-driven precision engineering discipline by serving as a "high-resolution tracer" for the behavior of nanomaterials in complex systems.

6. Conclusions and Outlook

This review has systematically examined spICP-MS and spICP-TOF-MS as analytical tools for environmental nanoparticle research, tracing their development from foundational principles through to cutting-edge applications. We have shown how these techniques are applied across atmospheric, aquatic, soil, and biological matrices, what extraction and pretreatment strategies render complex samples analyzable, how single-particle signals are translated into number concentrations and size distributions, and what inherent limitations in size detection limits, matrix effects, and quantitative accuracy must be navigated for robust data interpretation. The achievements enabled by this analytical capability are substantial: the direct quantification of ENPs against high natural backgrounds, the real-time tracking of particle transformation processes such as dissolution and sulfidation, the elucidation of NPs uptake and translocation pathways in plants and animals at the single-particle level, and the discrimination of sources through multi-element fingerprinting.

The technology continues to evolve along two principal trajectories. The first is multimodal hyphenation, exemplified by platforms such as OF2i-Raman-spICP-TOF-MS, which integrate optical trapping, molecular spectroscopy, and elemental mass spectrometry to simultaneously characterize the size, crystal phase, and chemical composition of individual particles that capabilities neither technique can achieve alone. The second is machine learning-assisted data analysis, where supervised and unsupervised algorithms are increasingly employed to classify particle populations, identify source signatures, and reveal latent patterns in high-dimensional single-particle datasets. Concrete progress has been made in establishing data preprocessing pipelines, validating model performance against synthetic ground-truth datasets, and extracting interpretable elemental fingerprints that link particles to their origins. The ongoing challenge is to move these methodological demonstrations toward standardized, reproducible workflows that can be adopted across laboratories.

Looking ahead, the maturation of single-particle analysis and its hyphenated derivatives position transformative tools for environmental nanoscience. By resolving the heterogeneity that bulk measurements obscure, these techniques provide the mechanistic insights needed to connect nanomaterial properties to environmental fate and biological effects. The integration of single-particle data into predictive models, from dissolution kinetics to dosimetry and risk assessment, offers a pathway toward the "safe-by-design" engineering of nanomaterials and evidence-based environmental risk governance. In this sense, spICP-MS and spICP-TOF-MS are not merely analytical techniques but platforms for more mechanistic, predictive, and ultimately more responsible environmental nanotechnology.

Author Contributions

C.Y.: Conceptualization, Investigation and Original Draft. C.M.: Investigation, Review and Editing. J.X.: Conceptualization, Supervision, Review & Editing, Funding acquisition. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

During the preparation of this work, the authors used ChatGPT for generation of some raw visual materials. ChatGPT-supported tool was used for language refinement. After using this tool, the authors extensively modified and adjusted the generated content, and take full

responsibility for the content presented in the published article.

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