Lab on a Chip

Devices and applications at the micro- and nanoscale

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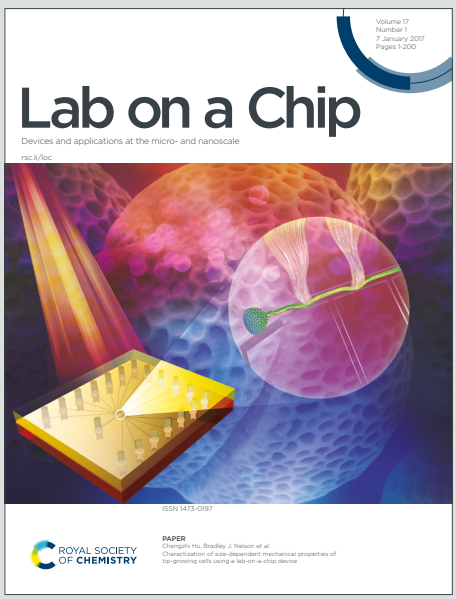

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Lab-on-a-Chip Systems for Microplastic and Nanoplastic Sampling, Detection, Characterization and Bioassessment

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Microplastics and nanoplastics are ubiquitous environmental contaminants, with growing evidence of their ecological and human health risks. However, a clear understanding of their impacts remains limited due to challenges in isolating MPs/NPs from complex environmental and biological matrices, insufficient sensitivity at the submicron scale, lack of standardized testing protocols, and inconsistent biological outcomes arising from variability in particle properties and cell models. Lab-on-a-chip (LoC) systems offer an integrated solution by combining automated sample handling, on-chip particle enrichment, multimodal characterization, and physiologically relevant culture models under controlled microenvironments. This review first examines current analytical techniques for MPs/NPs, followed by a detailed analysis of state-of-the-art LoC strategies for particle sampling, detection, characterization, and biological impact assessments. From filtration and density-based separation for sample preparation to advanced on-chip enrichment and detection techniques such as surface-enhanced Raman spectroscopy (SERS)-coupled microfluidic platforms, we evaluate the strengths and weaknesses of each approach, identify analytical bottlenecks, and provide directions for system integration to improve sensitivity, specificity, and throughput. For biological impact evaluation, we compare 2D monolayers, co-cultures, organoids, and organ-on-a-chip models, highlighting sources of experimental variation and providing guidelines for improved reproducibility and relevance. Ultimately, we aim to outline future directions for leveraging the advantages of LoC systems to enable high-throughput, standardized and meaningful ecological analysis of MPs/NPs, advancing their potential for long-term environmental monitoring of plastic pollution as well as human toxicity screening and health impact assessment.

1. From global contaminants to bioanalytical bottlenecks

Microplastics (MPs) and nanoplastics (NPs) have emerged as pervasive and persistent pollutants, infiltrating oceans, freshwater systems, soils, and even the human brain[1]. Despite mounting evidence of their ecological and human health impacts, accurately detecting and assessing these particles remains a significant challenge[2]. Conventional approaches, such as optical spectroscopy, electron microscopy, and chromatography have advanced our understanding, yet they are often time-consuming, labor-intensive, and reliant on expensive instrumentation[3]. Moreover, these techniques frequently lack *in situ* capability and fall short in sensitivity at environmentally relevant concentrations, and limited reproducibility across laboratories[4]. Similarly, traditional biological assays and cell models, while indispensable, often fail to capture the physical and dynamic interactions of MPs with tissues and barriers in a physiologically relevant manner[5]. The fundamental bottleneck in achieving standardized, reproducible, and biologically meaningful assessments for these particles arises from their broad size range, low concentrations in natural settings, complex heterogeneous physiochemical properties, and the absence of integrated systems capable of efficiently sampling, detecting, characterizing, and enriching them for downstream biological impact studies[6].

Lab-on-a-chip (LoC) systems have emerged as a promising solution to these challenges, employing microfabricated channels with customizable geometries and functional modules to manipulate fluids, particles, and cells. These systems are well suited for precise handling of MPs and NPs, while also enabling integrated analysis and biological testing[7,8]. Passive manipulation techniques, such as hydrodynamic and inertial focusing, offer simplicity comparable to filtration methods, while providing enhanced control over particle size, improved contamination control, and greater suitability for continuous and field applications[9]. In contrast, active techniques including acoustics, dielectrophoresis, and magnetophoresis enable selective trapping or sorting based on particle types or physicochemical properties[10], extend the size detection limit down to below 50 nm[11], and allow precise control over particle capture, release, and simultaneous inline characterization[12]. Recent advances in digital microfluidics, integrated with state-of-the-art artificial intelligence (AI) and emerging *in situ* material characterization methods, have greatly enhanced the detection and characterization of small-sized nanoparticles and pushed detection sensitivity to lower concentrations[13–16]. However, technical challenges remain. For example, polymer-based substrates (e.g., PDMS) may introduce analytical limitations at the submicron scale, including nonspecific adsorption and signal interference, which affect detection sensitivity and accuracy.

In addition, environmental matrix complexity continues to limit the feasibility and scalability of these techniques for field applications. Sensitivity and specificity for real-world MPs and NPs remain uncertain because of their low abundance and co-existence with other contaminants (eco-corona). These limitations also hinder biological impact studies, as real-world particles are difficult to consistently deliver to biological models using conventional tools[17]. As a result, most toxicological evaluations rely on pristine, commercially sourced particles and employ high-dose exposures, which lack environmental

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relevance and translational fidelity[18,19]. Targeted integration of LoC modules for particle enrichment and controlled delivery may help bridge this gap by enabling more consistent and physiologically relevant exposure of MPs and NPs in downstream biological studies.

Emerging organ-on-a-chip (OoC) platforms, such as gut-on-a-chip, lung-on-a-chip, and neurovascular models, offer highly physiologically relevant environments to study MPs/NPs transport, accumulation, and toxicity[20]. These systems recreate tissue-tissue interfaces, dynamic flow, and complex co-culture architectures, enabling more realistic assessments of how MPs and NPs interact with human physiology[21]. For example, Han et al. employed a gut-on-chip model integrated with inline, real-time sensing to investigate how peristaltic motion influences NP toxicity. They found that peristaltic motion reduced the inflammatory response triggered by nanoplastics[22]. An increasing number of studies now leverage these OoC platforms to examine MPs/NPs biological effects because they better reproduce key biological factors and often yield results comparable to animal studies[22–25]. In general, NPs exhibit higher toxicity than MPs, with toxicological outcomes strongly dependent on particle size, surface chemistry, and concentration[26,27]. Moreover, inflammatory and oxidative stress responses, genotoxicity, and potential endocrine-disrupting effects have been repeatedly observed, raising concerns about long-term human health impacts[28,29]. Nevertheless, challenges remain in standardizing these models, ensuring inter-laboratory reproducibility, and correlating *in vitro* outcomes with *in vivo* human health data. This dual challenge arises from difficulties in isolating and characterizing real-world particles, limited analytical confidence, and the inability to replicate physiologically relevant exposures *in vitro*. As a result, the link between environmentally sourced particles and downstream biological responses remains largely unexplored.

Taken together, these challenges underscore the urgent need for system-level approaches that integrate environmental sampling and detection, physicochemical characterization, and biological assessment of MPs and NPs within a streamlined platform. This review examines both conventional analytical pipelines and recent advances in LoC technologies across these domains, with particular focus on their strengths, limitations, and opportunities for modular integration. By analyzing key design principles and metrics, identifying persistent bottlenecks, and highlighting potential paths for convergence, we aim to provide a comprehensive perspective to support the development of more reproducible, reliable, and scalable integrated LoC solutions.

2. Comparison of Environmental MPs/NPs Sampling, Detection and Characterization Methods

Environmental MPs/NPs analysis relies on a diverse set of established sampling, detection, and characterization techniques, each with distinct strengths and limitations. This section reviews the workflow of conventional methods alongside LoC approaches, providing a parallel comparison of capabilities, performance metrics, and system design considerations for MPs/NPs analysis.

2.1. Conventional environmental MPs/NPs sampling, detection and characterization workflow

2.1.1. Sampling and Pretreatment

Conventional environmental MPs/NPs analysis follows a sequential workflow that begins with bulk sample processing and size-based fractionation, followed by matrix removal and preconcentration prior to downstream characterization[30]. Environmental samples are typically first subjected to sequential filtration to partition particles by size, using membrane filters such as polycarbonate or glass fibre arranged in series with decreasing pore sizes (commonly 5 μm, 0.45 μm, and 0.2 μm). Syringe filtration is commonly applied to small volumes, while vacuum-assisted systems are used for larger samples. Filtration efficiency is strongly influenced by sample composition; high organic loads often cause membrane clogging, compromised recovery, and reduced selectivity for NPs, motivating the use of improved membrane materials and surface modifications to enhance hydrophilicity to reduce fouling[31].

Following size fractionation, pretreatment is performed to remove organic matrices and further isolate plastic particles. Chemical digestion using oxidizing agents such as hydrogen peroxide (H_2O_2), Fenton's reagent, or sodium hypochlorite is widely employed, while enzymatic digestion with proteinase K, lipase, or cellulase provides a milder alternative when polymer preservation is critical[32]. Density-based separation is then used to isolate plastics from inorganic debris, particularly in sediments and sludge, by suspending samples in high-density salt solutions (e.g., NaCl, $ZnCl_2$, or NaI), often aided by centrifugation[33]. Additional steps such as flocculation or elutriation may be applied depending on sample type[34]. Because MPs and especially NPs are typically present at low environmental concentrations, the workflow concludes with preconcentration through large-volume filtration, evaporation, or centrifugation to reduce sample volume prior to analysis. For airborne MPs/NPs sampling, analogous workflows rely on high-volume air collectors with size-selective inlets and inert collection media, coupled with strict contamination controls[35].

2.1.2. Particle detection and characterization

Following isolation and pretreatment, conventional MPs/NPs analysis relies on a combination of spectroscopic, chromatographic, and microscopic techniques to characterize particle composition, size, and morphology. Spectroscopic methods are typically employed as the initial step for polymer identification, exploiting characteristic optical signatures of plastic materials[36]. FTIR spectroscopy is widely used for MPs larger than approximately 5 μm using attenuated total

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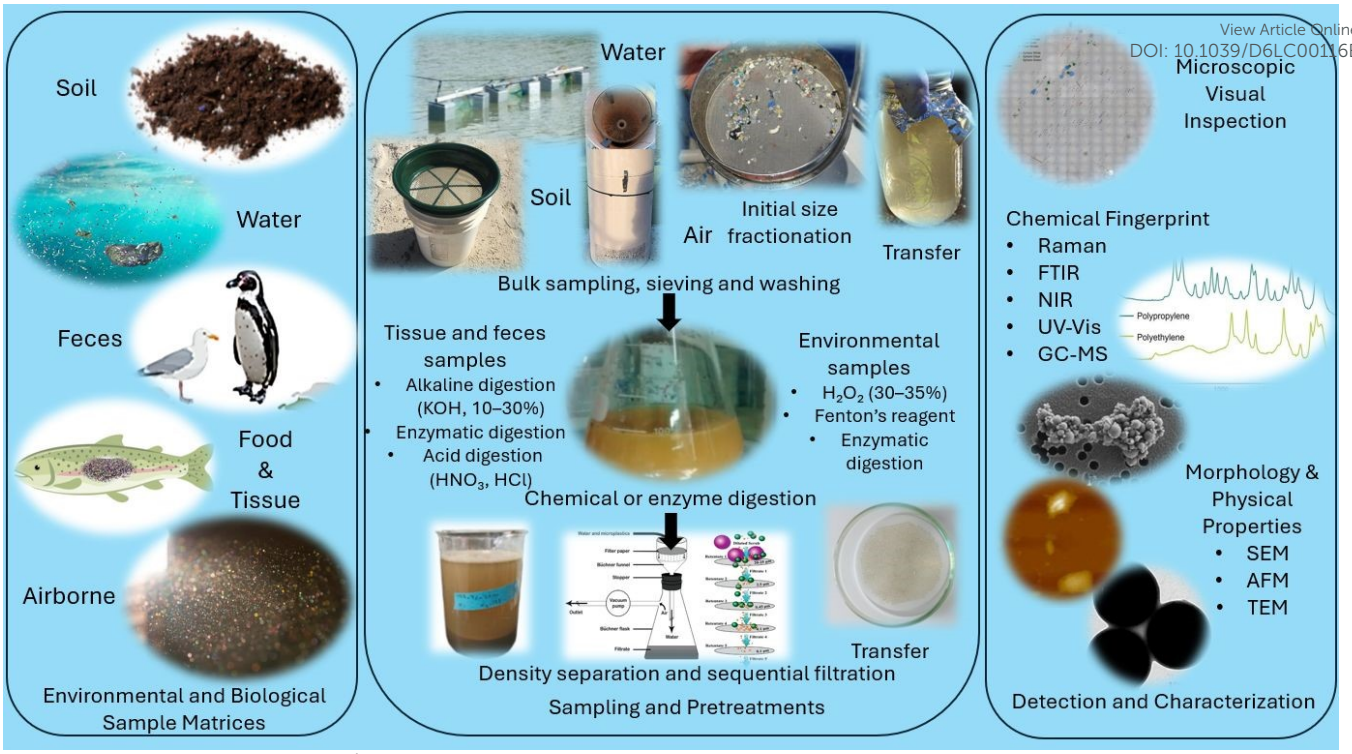

Fig. 1 Conventional worflow of MPs/NPs sampling, detection, and characterization. In general, initial sampling step relies on bulk samping, followed by size-based fractionation and collection into glass container transferred back to laboratory for further processing. Then, different types of samples utilize different digestion reagents followed by density based separation, the supernatant goes through sequential filtration and isolate particles of interests of variety of sizes, finally trapped on membrane filters for characterizations. Depends on the nature of downstream characterization techniques, further processing of the filter paper is required.

reflectance (ATR) or imaging modes, while Raman spectroscopy offers higher spatial resolution and can detect particles approaching the micron scale[37]. UV–Vis spectroscopy is primarily applied to labelled NPs or bulk absorbance monitoring but lacks molecular specificity for unlabelled environmental samples. In complex matrices, spectral interpretation is frequently challenged by fluorescence interference, water absorption, polymer weathering, and additives, often requiring manual validation or advanced spectral deconvolution.

To provide higher chemical specificity, chromatography- and thermally based techniques are commonly applied as confirmatory tools. Gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-mass spectrometry (LC-MS) enable sensitive detection of polymer degradation products, plasticizers, and additives, while pyrolysis-GC-MS (Py-GC-MS) is particularly effective for polymer type identification through thermal decomposition[38]. Thermal analysis methods, including differential scanning calorimetry (DSC) combined with thermogravimetric analysis (TGA), further support polymer identification based on distinct thermal transitions[39]. In parallel, microscopy-based approaches provide essential physical characterization, with scanning electron microscopy (SEM) and transmission electron microscopy (TEM) used to resolve particle size, morphology, and nanoscale features, often supplemented by elemental analysis[40]. Fluorescence microscopy, atomic force microscopy (AFM), and nanoparticle tracking analysis (NTA) offer additional size and surface information but frequently require labelling or specialized preparation[41]. While these techniques are powerful and complementary, they remain labour-intensive and are typically applied sequentially, limiting throughput and integration in conventional MP/NP characterization workflows. Fig. 1 shows examples of conventional workflow for MPs/NPs sampling and characterization.

2.2. LoC-based MPs/NPs detection and characterization methods

2.2.1. On-chip particle enrichment and manipulation

Microfluidic particle manipulation strategies can be broadly categorized into two classes: passive approaches, which rely on intrinsic hydrodynamic effects and channel geometry, and active approaches, which employ externally applied acoustic, electric, or electrokinetic fields to dynamically control particle trajectories. Both methods have been used for MPs/NPs analysis.

Common passive particle manipulation strategies include deterministic lateral displacement (DLD), centrifugal channel[42], and inertial focusing in spiral or serpentine channels, which enable membrane-free particle enrichment. These approaches have been widely applied to isolate MPs/NPs from environmental water matrices across broad size ranges, typically larger than 10 µm, while preserving particle integrity and surface chemistry[43,44]. A key advantage of passive microfluidic systems is their low power requirement, structural simplicity, and ease of integration into portable, field-deployable LoC platforms. Several studies have demonstrated on-site MPs sampling using passive LoC devices, offering advantages over traditional bulk filtration workflows by reducing sample handling, minimizing cross-contamination, and lowering the risk of losing small particles during transfer or off-chip processing[45]. However, passive techniques are intrinsically

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constrained by channel dimensions and hydrodynamic operating windows, often necessitating upstream prefiltration to remove large particulates and prevent clogging. While this requirement poses minimal challenges for relatively clean matrices such as drinking water or surface seawater, it becomes a significant limitation for on-site sampling of wastewater or highly organic-rich environmental samples. In such contexts, one can consider integrate with pulsatile flow[46], acoustic microbubble streaming[47], and multilayer channel design to avoid clogging[48]. Furthermore, acoustic streaming and mixing can potentially allow on-chip digestion to further minimize particle loss and streamline sampling process.

Active microfluidic techniques enable precise size separation and single-particle trapping, which are particularly valuable for NPs analysis, as downstream characterization methods such as SERS often require isolated particles to achieve maximum sensitivity. A typical particle size range for active manipulation methods is smaller than 10 µm, so it compensates for the passive methods well. Using Raman tweezer and microfluidic device, Shi et al., was able to enrich 30 nm polystyrene NPs in natural waters at above 80% recovery rate[49]. Acoustofluidic approaches, including standing surface acoustic waves (SSAW) and bulk acoustic waves (BAW), have demonstrated high-resolution and high-throughput NPs separation, for example, an Echogrid platform consists of surface displacement transducer (SDT) creates a grid of trapping nodes on a microfluidic device that can enrich MPs[50], and by adjusting acoustic wave propagation angle, the EchoTilt platform is able to enrich NPs down to 25 nm in drinking water[51]. DC electric field generated electrophoresis can also capture MPs typically within the range of 1 µm to 10 µm[52], however, it requires mixing with conductive solutions. By combining with Raman spectroscopy, both enrichment and detection can be done on chip at the same time[53]. For environmentally relevant MPs/NPs analysis, active LoC manipulation must account for eco-corona-coated particles that typically carry net negative surface charge. One can utilize this advantage to separate MPs/NPs from more positively charged mineral particles[54]. For a LoC design, this can be achieved by implementing a positively charged substrate or positive hot spots in the channel under tuneable flow rate. Dielectrophoretic methods offer material-dependent selectivity but perform poorly in high-salinity environmental samples, for example seawater. Acoustic approaches are robust to surface chemistry and scale with particle size, making them suitable for heterogeneous matrices; however, limited acoustic contrast and similar polymer densities constrain specificity. Therefore, activation and particle manipulation methods should be tailored to specific environment and particle types, which requires comprehensive understanding through blank sample analysis prior to system design.

Despite these strengths, active microfluidic techniques face inherent trade-offs that limit their applicability in real-world environmental sampling. High selectivity is often achieved at the expense of throughput, making it challenging to process the large sample volumes typically required for environmental MPs/NPs analysis. In contrast, passive microfluidic approaches generally rely on higher flow rates (often >100 µL min^{-1}) to generate inertial lift or Dean forces for particle manipulation[55]. Active microfluidic systems, however, usually operate at lower flow rates to allow externally applied fields to dominate particle transport. This operating regime is highly size-dependent: manipulation of NPs typically requires low flow rates (<10 µL min^{-1}) and small channel dimensions to ensure sufficient field–particle interaction. Consequently, scaling active microfluidic platforms for high-throughput processing of nanoscale particles remains challenging and necessitates further advances in device architecture, field coupling efficiency, and parallelization strategies. In addition, active systems generally require more complex fabrication, external power, and expert operation, which constrains scalability and field deployment. Finally, many active microfluidic studies focus on spherical or near-spherical particles, whereas environmental MPs/NPs often exhibit irregular, fibrous, or fragmented morphologies, highlighting the need for LoC designs that can robustly manipulate various particle shapes.

2.2.2 On-chip particle detection and characterization

Another key advantage of LoC platforms is their enclosed microfluidic architecture, which preserves the native physicochemical state of MPs/NPs and the surrounding sample environment while minimizing contamination introduced by manual handling. This controlled microenvironment improves the fidelity of particle identification and enables more reliable interpretation of particle-matrix interactions. In addition, active particle manipulation techniques that exploit physical properties, such as optical, acoustic, or electrical responses, allow real-time particle positioning and characterization within the same device[56]. The optical transparency of commonly used materials such as PDMS facilitates direct visualization of larger MPs and supports seamless integration with Raman spectroscopy and other optical microscopy techniques for label-free identification and allow for further downstream analysis. However, it can introduce analytical challenges, including intrinsic Raman background, autofluorescence, and nonspecific adsorption, which may interfere with signal detection, particularly for submicron particles. These limitations can be partially mitigated through surface modifications such as PEGylation or other antifouling coatings to reduce adsorption, as well as through material selection, surface treatment, or background-subtraction strategies to minimize optical interference[57]. Alternative materials such as glass or thermoplastics (e.g., PMMA) offer reduced background signals but may involve trade-offs in fabrication complexity. Overall, these systems still have limited suitability for field deployment because of their reliance on complex instrumentation, which constrains the broader application of LoC systems for on-site environmental analysis. In the future, integrating microfluidic chips with portable customized detection systems, such as handheld Raman devices and miniaturized near-infrared (NIR) spectrometers, may enable on-site MPs/NPs analysis[58].

2.3. Machine learning (ML)-enabled identification and characterization of MPs/NPs

As LoC platforms increasingly enable high-throughput enrichment, isolation, and spectroscopic interrogation of MPs/NPs, data volume and complexity have emerged as major bottlenecks in reliable particle identification and characterization. Spectral signatures acquired from Raman, SERS, infrared, or multimodal on-chip sensing often vary substantially due to particle size, morphology, surface weathering, polymer heterogeneity, and

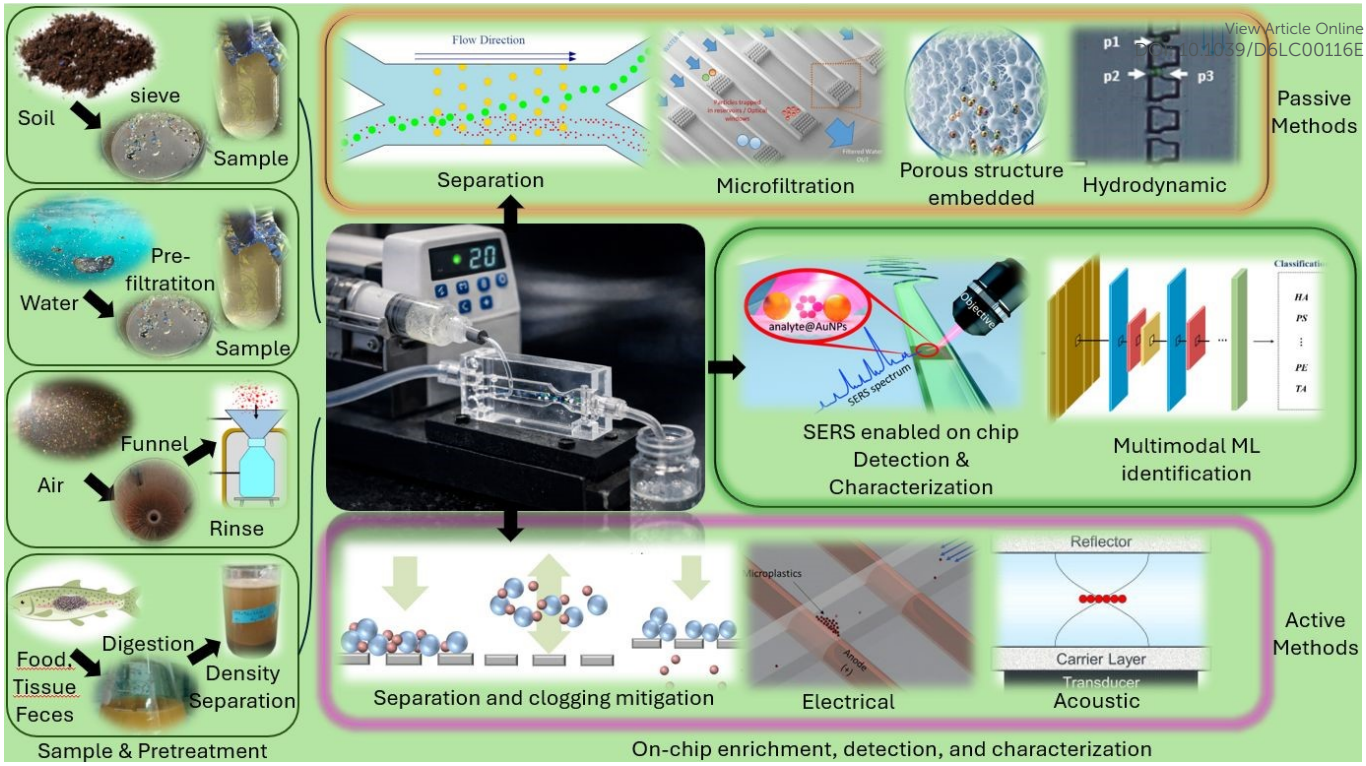

Fig. 2 LoC system workflow of MPs/NPs sampling, detection, and characterization. Different types of samples have different initial pretreament to reduce the complexity of the matrices, for example, digestion of organic matters in wastewater, feces, or food samples is required. Then, initial size filtration is also needed to isolate smaller sized particles. Final collected samples will go through syringe and LoC device of different channel configurations. MPs/NPs can be trapped on chip for downstream characterization, or collected from chip outlet and conduct off-chip characterization.

interference from coexisting complex environmental matrices[59], limiting the robustness of traditional rule-based or library-matching approaches, particularly for NPs and environmentally aged particles. Recent advances in ML address these challenges by enabling automated, data-driven interpretation of high-dimensional signals generated within LoC systems, with demonstrated improvements in polymer classification, signal denoising, interferent discrimination, and detection sensitivity at environmentally relevant concentrations[60,61]. In addition, ML-driven background correction can help mitigate substrate-induced signal interference arising from PDMS[62,63]. The controlled and reproducible microenvironments inherent to LoC platforms further facilitate seamless ML integration by generating consistent, information-rich datasets for automated analysis. Beyond particle identification, ML-augmented LoC systems can support digital device designs that capture and analyse MPs/NPs transport dynamics in real time. For example, a recent study demonstrated the use of ML algorithms for simultaneous MPs identification and velocity measurement within microfluidic channels[64]. Such advances extend the LoC-ML synergy beyond classification tasks, enabling quantitative investigation of MPs/NPs transport behaviour and interactions with complex environmental matrices. Furthermore, ML can be leveraged to predict particle location and spatial distribution within microfluidic channels, reducing the need for exhaustive scanning and significantly improving detection efficiency for low-abundance MPs/NPs[65]. In addition, ML-guided optimization of channel geometries and multiphysics flow profiles enables the design of tunable chip environments that enhance particle capture and enrichment under realistic conditions[66–68]. Looking forward, ML-driven closed-loop control represents a promising direction for enhancing in-line MPs/NPs detection, quantification, and targeted sampling under real-world environmental variability. Fig. 2 represents examples of LoC systems for MPs/NPs analysis.

2.4. LoC system design guidelines considering ecological study needs

Conventional MPs/NPs detection workflows remain constrained by limited sensitivity at the submicron scale, leading to systematic underrepresentation of nanoscale particles in environmental exposure assessments. This gap is particularly concerning because emerging evidence suggests that NPs exhibit higher bioavailability and surface reactivity, enhanced cellular uptake, and increased potential for trophic transfer compared to larger MPs[69]. Particles below ~1 µm are more likely to cross biological barriers, interact with microbial communities, and accumulate within tissues, yet are frequently lost during filtration and sample transfer steps in conventional workflows. As a result, current analytical approaches risk underestimating both NPs abundance and their associated ecological impacts. These limitations highlight the need for LoC systems designed not only for analytical sensitivity, but also for ecologically relevant exposure characterization[70,71]. For this aim, LoC platforms should prioritize (i) high-volume processing of environmentally relevant water samples, (ii) size-inclusive particle retention focusing on submicron to nanoscale ranges, and (iii) minimal particle loss between enrichment and characterization stages, (iv) allow continuous sampling and reusable for environmentally relevant low concentrations. Additionally, LOC

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Table 1 Comparisons between conventional and LoC methods

Performance metric	Conventional bulk methods	LoC-based approaches
Sampling size range	Above 10 µm most efficiently, can go down to 1 µm using vacuum filtration	MPs in submicron scale, NPs down to 50 nm
Detection limit	High sensitivity achievable for bulk polymer mass; limited for low-abundance NPs	High sensitivity for single-particle or localized detection when coupled with Raman/SERS; system-dependent
Enrichment factor	Moderate; relies on large-volume filtration or centrifugation	High local enrichment achievable via hydrodynamic, acoustic, or electrokinetic focusing
Throughput / sample volume	High total volume (L-m³ scale) but slow and labor-intensive	High particle processing rates but typically limited total volume (mL-100 mL); scalability needs improvements
Sorting / isolation resolution	Size-based fractionation only; limited selectivity for shape or material	High-resolution size- and property-based manipulation; single-particle trapping possible
Particle loss risk	High during multi-step transfer, filtration, and digestion	Low due to enclosed architecture and reduced handling, with minimal tubing.
Reproducibility	Operator- and protocol-dependent; batch variability common	High intra-device reproducibility: device-to-device variation remains high depending on fabrication
Compatibility with biological exposure models	Indirect; requires particle recovery and resuspension	Direct coupling is possible but needs to consider decontamination and sterilization.
Field deployable	Limited to bulk sampling; requires laboratory infrastructure,	Increasingly feasible with portable, integrated systems; power and robustness remain challenges

designs must aim to preserve particle physicochemical properties and enable direct meaningful coupling between environmental sampling and ecological exposure models.

Detection specificity represents a particular challenge, and urgent need meet for accurate MPs/NPs ecological impact assessments. Recent studies have reported high false-positive rates in MPs identification from complex environmental (e.g. eco-corona) and biological matrices (e.g. lipids) [72]. This suggests that, rather than focusing solely on lowering detection limits, future LoC designs should prioritize strategies that enhance characterization specificity, either through controlled selective particle isolation and interferent removal or by serving as enabling interfaces for established characterization techniques. For example, many practices use LoC systems to precisely position MPs/NPs onto microfabricated, SERS-optimized substrates, improving signal-to-noise and reducing ambiguity in polymer identification[73], however, it is recommended such experiments should include positive control group, which has known polymer types in the same environmental matrix, using dual identification system, and implementing multimodal ML identification algorithms that uses images and spectroscopic data.

Finally, broader adoption of LoC technologies requires alignment with environmental monitoring standards that emphasize sample representativeness, contamination control, QA/QC, and reporting consistency. Because many LoC demonstrations operate at volume below those specified in standard protocols[74], To address the inherent throughput limitations, designs should incorporate strategies such as massive parallelization or multi-layer architectures to increase processing capacity without substantially increasing system complexity or cost. Material selection, background suppression, and environmentally conscious design, such as reduced reagent use and reusable components will also be essential for translating LoC innovations into standardized, field-deployable MPs/NPs monitoring tools. **Table 1** summarizes comparisons between conventional and LoC approaches for MPs/NPs detection and characterization across key performance metrics relevant to ecological risk assessment.

3. MPs/NPs biological risk assessment models

MPs/NPs have attracted significant attention due to their potential impacts on human health; however, inconsistent findings persist because of the lack of standardized biological models. LoC-based systems have therefore emerged as promising platforms due to their ability to recapitulate key physiological features under controlled and reproducible conditions. In this section, we compare conventional *in vitro* models with LoC-based systems, highlight the unique advantages of LoC platforms, and discuss remaining challenges and opportunities for improvement to bridge translational gaps.

3.1. *In vitro* models for MPs/NPs biological impacts evaluation

3.1.1. 2D monolayer cultures. Two-dimensional (2D) monolayer cultures remain the most commonly used models for assessing MPs/NPs-induced toxicity due to their simplicity, scalability, and compatibility with standard readouts such as viability assays, permeability testing, toxicity measurements, and many others. For instance, monolayers of intestinal (Caco-2), pulmonary (A549), or endothelial (HUVEC) cells offer insight into barrier integrity and MPs/NPs uptake mechanisms[75,76].

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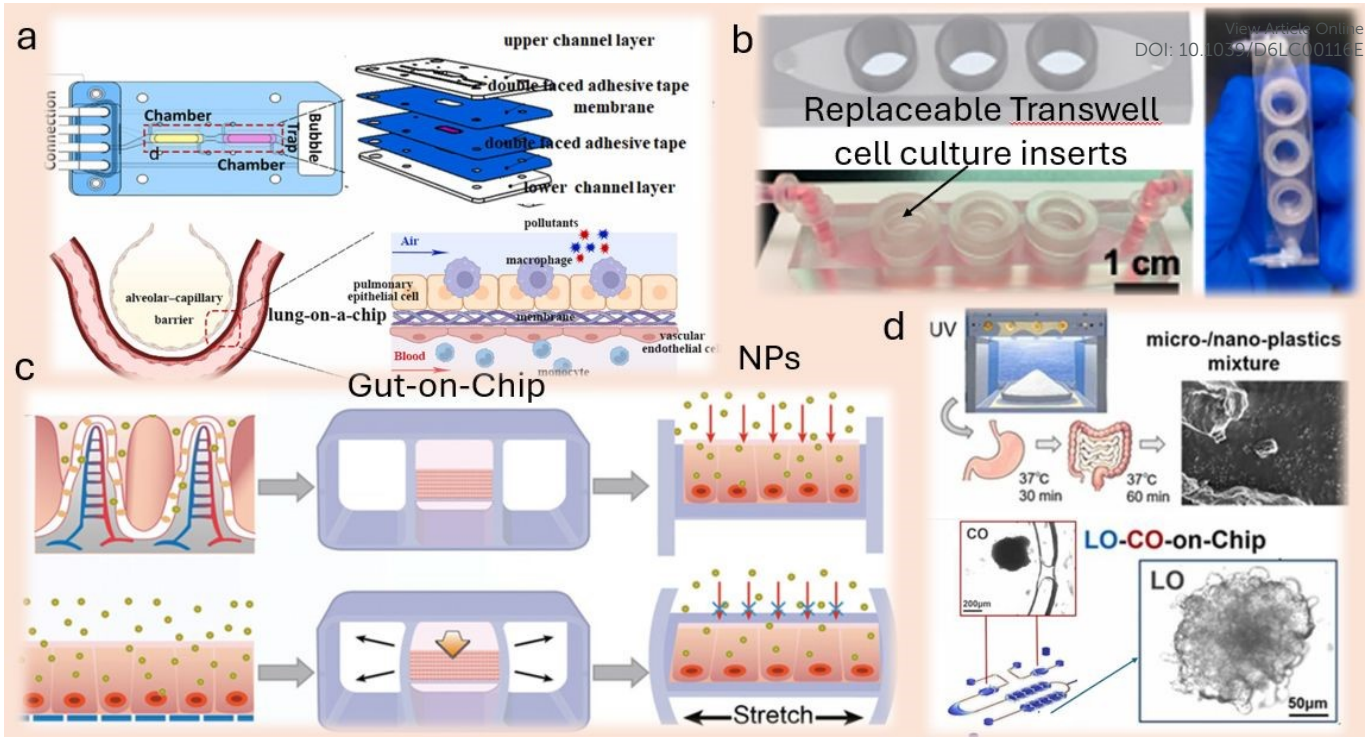

Figure 3 Representative organ-on-chip and organoid-on-chip models used to study MPs/NPs toxicity across multiple organ systems. (a) A dynamic air-blood barrier chip mimicking capillary shear stress distinguishes PET-MP-induced pulmonary damage better than static Transwells, (b) A cardiac organoid-on-chip under perfusion shows PS-NP-induced oxidative stress, mitochondrial dysfunction, calcium dysregulation, and fibrotic remodeling, (c) A gut-on-chip applying cyclic strain reveals strain-dependent modulation of NP-induced inflammation, (d) A hepatic-cardiac organoid-on-chip demonstrates low-dose MP/NP mixtures trigger reductive stress and cardiac hypertrophy via liver-heart crosstalk.

More advanced 2D systems incorporate co-cultures on Transwell inserts[77,78], such as epithelial-immune or epithelial-endothelial models, to better mimic tissue microenvironments and reveal crosstalk responses, such as cytokine signalling or immune modulation upon MPs/NPs exposure[77,79]. However, these models often lack physiological flow and three-dimensional architecture, which limits their relevance to *in vivo* exposure conditions.

3.1.2. 3D cell cultures. Three-dimensional (3D) spheroid and organoid models offer improved physiological relevance, mimicking tissue architecture, cell polarity, and extracellular matrix interactions. Intestinal organoids derived from primary, or stem cell sources have been used to evaluate MPs/NPs-induced oxidative stress, tight junction disruption, and cytokine release[80]. Likewise, tumor spheroids have demonstrated differential uptake of NPs and cancer progression comparing with 2D assays[81]. Incorporating human dermal fibroblast (HDF) cell lines derived spheroids, we can study NPs uptaken by human skin[82]. Yet these systems are typically static and requires long term culturing. While useful for characterizing toxicity, they present analytical challenges, for example, it is difficult to visualize or quantify particle penetration depth and systemic distribution due to the absence of vascularization.

3.1.3. Influence of environmental alterations and model limitations. Environmental transformations, including UV aging, microbial colonization, organic matter adsorption profoundly change MPs/NPs surface chemistry, size, aggregation, and thereby their interaction with cells[76,83]. While these alterations increase uptake, oxidative stress, and inflammatory responses *in vitro*, results vary widely due to inconsistent particle preparation, exposure conditions, and model systems. Crucially, most studies still use static monocultures that do not capture flows, barrier mechanics, or complex cell-cell interactions. This gap suggests that dynamic models (flow, co-cultures, organ-on-a-chip) could yield very different transport and toxicity profiles[83,84]. More realist, standardized platforms are urgently needed to link particle properties to biologically meaningful outcomes.

3.2. Animal *in vivo* models for toxicity evaluations

Animal models provide essential whole-organism context for MPs/NPs toxicity, enabling evaluation of biodistribution, accumulation, systemic inflammation, cognitive and behaviour affects, and long-term outcomes that cannot be captured *in vitro*. Rodent, porcine, and zebrafish models have been widely used to study oral, inhalation, and dermal exposure pathways, revealing MPs/NPs accumulation in the gut, liver, lung, brain, and reproductive organs, as well as impacts on metabolism, immune regulation, neurodevelopment, and reproduction[85–88]. Importantly, *in vivo* studies have demonstrated particle translocation across biological barriers and multiorgan effects at exposure levels comparable to environmental conditions[89]. However, animal models are limited by species-specific differences, ethical constraints, limited experimental throughput, and difficulty in isolating mechanistic pathways,

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Table 2 Comparative summary of *in vitro, in vivo*, and OoC models used to evaluate MPs/NPs toxicity in lung, intestine, and brain systems.

Model	Biological complexity	Exposure realism	Key observations	Key limitations
Lung-2D[90]	Single-cell type, or limited multicell	Static, high dose (>500 μg mL^{-1})	Dose-dependent cytotoxicity, oxidative stress, barrier loss	Overestimates toxicity, lacks flow, immune interaction, short term
Lung-3D[91]	Multi-cell, self-organized	Static, low dose (<100 μg mL^{-1})	Minimal acute toxicity; altered differentiation markers	No vascular interface; limited transport assessment, short term
Mice Lung[92]	Full organism	Realistic inhalation, chronic exposure	Inflammation, particle retention, immune activation	Species differences; limited mechanistic resolution, heterogeneous
Lung-LoC[93]	Epithelium–endothelium–immune	Dynamic flow, barrier transport	NP translocation, permeability increase, inflammation	Design complexity, operational expertise required
Intestine-2D[94]	Single-cell type, or limited multicell	Static exposure	Mild toxicity unless inflamed	No peristalsis or flow
Intestine-3D[95]	Tissue architecture	Static, low dose	Barrier dysfunction under stress	No mechanical cues or systemic coupling
Mice Intestine[96]	Whole gut system	Oral exposure	Accumulation, inflammation, microbiome effects	Difficult dose control; low temporal resolution, loss of tracebility
Intestine-LOC[20]	Multi-organ coupling	Flow + peristalsis	Transport modulated by mechanics; secondary organ effects	Limited immune representation
Brain-2D[97]	Neural or endothelial cells	Static, high dose	ROS, apoptosis, mitochondrial damage	Poor BBB relevance
Brain-3D[98]	Neurodevelopmental context	Long-term exposure	Developmental disruption, oxidative stress	No circulation or immune input
Rat brain[99]	Full BBB + CNS	Systemic exposure	NP brain accumulation, BBB impairment, ROS	Species-dependent BBB transport
Brain-LOC[100]	Endothelium-astrocyte-pericyte	Size-resolved transport	Size-dependent permeability; inflammation-amplified damage	Technical complexity

motivating the development of complementary *in vitro* and microphysiological systems.

3.3. LoC systems for assessments of MPs/NPs biological impacts

3.3.1. 2D culturing assays. Static OoC and insert systems offer simplified, well-controlled models for studying MPs/NPs impacts on epithelial and immune cells. Commonly used cell lines include Caco-2, HT29, and RAW 264.7, typically cultured on rigid or semi-rigid membranes such as glass, PET, or porous substrates, or on PDMS supports, and sometimes arranged like a Transwell system[101,102]. These setups enable measurement of cytotoxicity and barrier integrity, are relatively easy to standardize, and require minimal reagent use while allowing continuous perfusion[103] (Fig.3a-b). However, the cells in these systems often remain confined to 2D monolayers, which lack the complex three-dimensional architecture. Nevertheless, compared with conventional Transwell systems, their microscale configuration offers key advantages, including shorter diffusion distances, improved mass transport, and reduced reagent consumption, which collectively enable more efficient and higher-throughput analyses.

3.3.2. 3D culturing and organoids-on-chip. 3D culture and organoid-on-chip models are increasingly used to capture tissue-level complexity in MPs/NPs toxicity assessments. For example, a recent study showed that prolonged exposure of human iPSC-derived cerebral organoids to polypropylene NPs led to impaired neural development comparable with findings in mice[104]. Gut and lung organoid chip systems have also been widely applied to study MPs/NPs uptake, inflammation, and epithelial damage[105–108]. Zhang et al. used a cardiac organoid-on-chip under fluidic perfusion to show that PS NPs induced oxidative stress, mitochondrial dysfunction, calcium dysregulation, and ultimately fibrotic remodelling, with disease-model organoids exhibiting heightened vulnerability even at low exposures[109]. Chen et al. employed an endothelialized microfluidic thrombosis chip perfused with whole blood enriched with MPs, they found that MPs reduced fibrin-platelet binding, increased the risk of thrombus shedding under flows, and revealed cumulative vascular injury consistent with *in vivo* exposure[110]. Tumoroid-on-chip models are a cutting-edge approach to simulate tumor progression under physiologically relevant conditions. Researchers have begun employing this type of model to investigate the effects of NPs on cancer-related signalling pathways, opening new avenues for studying MP/NPs and advancing broader environmental toxicology research using such platforms[111,112].

3.3.3. Dynamic systems. By incorporating physiologically relevant dynamic cues, OoC platforms provide a superior means of mimicking native tissue microenvironments. Notably, gut- and lung-on-chip systems have revealed that biomechanical forces, including cyclic stretching, peristaltic motion, breathing-mimicking strain, and interstitial flow, significantly influence how cells interact with and respond to MPs/NPs[113]. For instance, a recent gut-on-chip study exposed intestinal epithelial cells to NPs under periodic strain mimicking peristalsis (Fig3c) and found that NPs exposure caused vacuolization, apoptosis, and tight junction protein loss; secretion of inflammatory cytokines IL-6 and TNF-α peaked at ~24 h. Intriguingly, raising the peristaltic strain from 5 % to 6.5 % reduced IL-6 and TNF-α secretion by ~2.7- and ~3.3-fold respectively, demonstrating that stronger mechanical motion can, counterintuitively, dampen NPs-induced inflammation[114]. Another lung-chip work used alveolar epithelial cells cultured on a stretchable electrochemical sensor under cyclic mechanical tension (mimicking respiration) and showed that cyclic stretch increases NPs uptake and enhances oxidative stress versus static culture and the amplitude of strain was a key variable[115]. In addition, microfluidic approaches enable precise spatial control and continuous perfusion over physiologically relevant shear stress across a wide range (~0.02-30 dyne/cm²), facilitating accurate modelling of tissue-specific flow conditions relevant to MPs/NPs transport and interaction[116]. For instance, Fu et al. developed a dynamic air-blood barrier (ABB) *in vitro* model that mimics capillary shear and blood flow (flow velocity ~0.5 mm/s, shear stress ranging from 0.15 to 0.35 dyne/cm²) to compare pulmonary damage from PET MPs against static Transwell ABB models, demonstrating that the dynamic ABB better distinguishes toxic effects and more closely parallels *in vivo* mouse outcomes[117]. Especially, there is a powerful rising application of multiorgan on chip or body-on-a-chip to study MPs/NPs transport in biological systems. For example, a gut-liver-on-a-chip used intestinal peristalsis and a dynamic hepatic flow environment to explore the translocation in the intestines and accumulation in the liver of MPs following oral ingestion[118]; a hepatic-cardiac organoids-on-a-chip showed that a low dose mixture of MPs/NPs triggers reductive stress and cardiac hypertrophy via liver-heart crosstalk, even when traditional toxicity markers are minimally elevated[119]. (Fig.3d)

3.3.4. Comparisons between models. Studies using similar MPs/NPs have reported divergent outcomes owing to differences in model design, cell type selection, and exposure regimens. Conversely, nearly identical chip or culture systems have produced varying results when challenged with particles of different size distributions, surface chemistries, or weathering degrees. Flow rate, culture time, and endpoint assays also differ widely between laboratories. Such inconsistencies make it difficult to extract generalized toxicity thresholds or to identify reproducible mechanistic pathways. Despite this heterogeneity, some common findings emerge. NPs consistently show greater cellular uptake and stronger cytotoxic or pro-inflammatory responses than larger MPs. Toxicity typically scales with dose, particle size, and exposure duration, with oxidative stress and cytokine release as recurrent endpoints. Yet no published work has examined environmentally sourced MPs/NPs in fully integrated, physiologically relevant LoC platforms under chronic exposure conditions. Table 3 compares model types for three major organs, the lung, intestine, and brain, highlighting cell lines, particle characteristics, exposure parameters, and observed biological outcomes to underscore the urgent need for standardized protocol.

3.4 LoC chip design for clinical and translational considerations

MPs/NPs have been found in human and animal tissues, although no specific clinical diagnostic tests or MPs/NPs-associated diseases have yet been established, growing evidence suggests that chronic, low-dose exposure and accumulation may contribute to long-term human health risks that are poorly captured by existing *in vitro* and animal models. Conventional *in vitro* systems lack physiological transport, tissue-tissue interactions, and chronic exposure capability, while *in vivo* animal studies are constrained by species-specific differences, ethical considerations, and limited mechanistic resolution. LoC platforms offer a unique translational advantage by enabling controlled, human-relevant microphysiological environments that bridge these gaps. In particular, body-on-chip and multi-organ chip designs allow investigation of MPs/NPs translocation, accumulation, and organ-organ crosstalk under defined flow and exposure conditions, without the confounding factors inherent to animal models. Importantly, the integration of patient-derived cells, including primary cells and induced pluripotent stem cells (iPSCs), enables personalized toxicity screening by capturing inter-individual variability and disease-specific responses, such as in asthma or inflammatory bowel disease[120,121]. By enabling long-term, low-dose exposure studies in human-relevant and patient-specific

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Figure 4 Conceptual Workflow of MPs/NPs sampling, characterization, and toxicity evaluation.

systems, LoC platforms provide a powerful framework to link MPs/NPs exposure profiles with emergent biological dysfunction and disease-relevant pathways, positioning them as a critical intermediate step toward future clinical risk assessment.

4. Roadmap to integrated LoC systems

To advance toward practical and translational applications, a systematic roadmap for the development of integrated LoC systems is needed. Integrated LoC platforms provide a promising path to address the intertwined challenges in sampling, detection, characterization, and biological assessment of MPs/NPs. Rather than operating as isolated analytical tools, next-generation LoC systems can be designed as fluidic networks, where each module, from sampling and pre-treatment to sensing and cell-based evaluation, acts as a tunable link in an interconnected workflow. By optimizing and coupling these links, a single platform could continuously collect, detect, characterize, and sort MPs/NPs (and other environmental particles) for downstream biological assessment, achieving an end-to-end analytical pipeline within a controlled microenvironment.

To enhance scalability and field readiness, modular LoC devices can employ parallelized or multiplexed flow channels and high-resolution 3D-printed manifolds (e.g., stereolithography (SLA), ~25-100 µm resolution, or two-photon polymerization, ~100 nm–1 µm resolution) to boost throughput while maintaining the micro- to nanoscale fidelity required for handling submicron particles; however, resin-based printing often introduces surface roughness (typically ~1-10 µm for SLA), which can promote nonspecific particle trapping and necessitates post-processing for reliable particle recovery[122]. Similarly, insufficiently cured PDMS and other system components (e.g., tubing and connectors) may introduce artifacts through material leaching or particle-surface interactions, affecting both particle recovery and downstream biological toxicity assessments; these effects can be mitigated through thorough curing, surface passivation, use of inert or low-adsorption materials, and controlled decontamination protocols (e.g., ethanol washing and UV exposure) to minimize background toxicity.

Beyond these considerations, system-level integration should minimize dead volume and uncontrolled particle loss during inter-module transport. Tubing-free or low-dead-volume fluidic interfaces, such as monolithic chip integration, direct chip-to-chip sealing, or valve-assisted routing, can reduce particle adsorption, sedimentation, and dispersion during transfer. Incorporating flow-controlled interfaces and recirculation strategies further enables precise delivery of low-abundance MPs/NPs from sampling and characterization modules to downstream OoC platforms, preserving particle integrity and improving exposure consistency.

To ensure widespread adoption, the manufacturability and cost of LoC devices must be considered from the outset. Low-cost rapid prototyping methods, such as laser cutting, should be prioritized during early-stage development for design iteration and accessibility, whereas scalable manufacturing approaches such as injection molding are better suited for high-volume production despite their high initial tooling costs. In parallel, detection modules should rely on minimal optics or portable readers to facilitate field deployment. Importantly, these systems should be designed for integration with digital

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workflows, including cloud-based data storage and ML-enabled high-throughput analysis, to enable real-time interpretation and knowledge sharing. Embedding microcontrollers and wireless modules can further support in situ monitoring, with data uploaded directly to shared databases or environmental dashboards.

The vision of fully integrated microfluidic systems that sample, sort, detect, and characterize particles in a continuous workflow has already materialized in other domains. For example, Chen et al. demonstrated a fully integrated microfluidic chip for multiplexed virus detection, seamlessly combining sample preparation, amplification, and optical readout within a single platform[123]. A similar trend toward system-level integration has emerged in the extracellular vesicle (EV) field, where on-chip separation, detection, and molecular profiling are now routinely implemented. However, unlike EVs, which can often be isolated using specific biological surface markers, environmental MPs/NPs rely primarily on physical and chemical properties, making the direct translation of EV-based microfluidic strategies to MPs/NPs chips uniquely challenging. Furthermore, linking particle processing directly to cellular evaluation, for instance, correlating exposure dynamics with biological response on the same chip, remains largely unexplored, yet represents a critical step toward true end-to-end automation. Importantly, real-world MPs/NPs are rarely pristine; they are typically associated with complex layers of adsorbed abiotic and biological contaminants (eco-corona or protein corona), which can significantly influence particle behavior, transport, and toxicity. Preserving these native particle characteristics within integrated microfluidic systems is therefore essential for maintaining environmental relevance and may enable the eco-corona to serve as a reservoir of biomarkers for toxicity assessment[124,125]. With the rapid advances in modular design, sensing technologies, and on-chip microphysiological modelling, we believe that integrated LoC systems capable of continuous MPs/NPs analysis and biological assessment will soon become a practical reality. Fig. 4 depicts the conceptual integrated MPs/NPs LoC system.

5. Future perspectives

Despite rapid progress, environmental MPs/NPs analysis remains limited by fragmentation across sampling, detection, and biological assessment workflows. Key technological bottlenecks include the lack of field-deployable systems that simultaneously offer sufficient throughput, sensitivity, and specificity; poor compatibility between bulk environmental sampling and nanoscale characterization; and limited ability to operate under complex, contamination-prone conditions. While LoC platforms have demonstrated powerful enrichment and manipulation capabilities, their small operating volumes, susceptibility to clogging, and sensitivity to matrix variability constrain large-scale deployment. Established platforms such as droplet microfluidics, alongside emerging AI-driven digital microfluidics approaches, offer complementary strategies to address these limitations[126]. By discretizing samples into isolated microreactors, droplet systems reduce flow-related constraints and enable high-throughput screening of heterogeneous particle populations, while digital microfluidics provides programmable, electrode-based manipulation of discrete droplets without continuous flow, offering flexible and contamination-resistant sample handling under complex environmental conditions.

Beyond technological integration, the future impact of LoC platforms for MPs/NPs analysis will depend on their alignment with regulatory, environmental, and translational requirements. To support large-scale environmental monitoring and risk assessment, LoC systems must evolve toward standardized performance metrics, including defined detection limits, size-resolved recovery efficiencies, reproducibility across laboratories, and traceable calibration strategies. Modular yet harmonized system architectures, coupled with reference materials, benchmark protocols, and interoperable data formats will be essential to enable cross-study comparability and regulatory acceptance. From a deployment perspective, future LoC designs should prioritize operational robustness, minimal user intervention, and compatibility with field sampling workflows, rather than maximal analytical complexity. This includes the development of hybrid bulk-microfluidic interfaces, as well as clog-resistant channel architectures such as multi-layer or parallelized designs to distribute flow and reduce blockage, and the incorporation of active mitigation strategies (e.g., acoustic streaming or flow perturbation) to prevent particle accumulation, alongside automated feedback control for flow stability and quality assurance.

A major unmet need across MPs/NPs toxicology is the lack of standardized exposure protocols that reflect environmentally realistic concentrations, particle aging states, and chronic exposure scenarios. Current *in vitro* and *in vivo* studies vary widely in particle preparation, dosing regimens, and biological endpoints, making cross-study comparisons difficult and limiting regulatory relevance. Integrated organ-on-a-chip and body-on-a-chip platforms offer a promising pathway toward standardization by enabling controlled, perfusion-based exposure, defined residence times, and reproducible tissue-level responses under human-relevant conditions. In addition, the integration of continuous, real-time, in situ biological state monitoring, such as transepithelial/transendothelial electrical resistance (TEER) and other embedded sensing modalities, enables dynamic assessment of barrier integrity and provides insight into MPs/NPs transport dynamics, including particle translocation across epithelial or endothelial layers during exposure[127]. By coupling LoC-based particle enrichment with downstream microphysiological models, future systems can systematically interrogate low-dose, long-term exposure effects, particle translocation, and organ-organ interactions, capabilities that are difficult to achieve with conventional static cultures or animal models alone.

Looking forward, the translation of LoC technologies into regulatory and environmental monitoring frameworks will depend on their ability to generate reproducible, interpretable, and comparable data across laboratories and deployment contexts. Rather than serving as standalone analytical replacements, LoC platforms are best positioned as modular, enabling interfaces that bridge environmental sampling, high-specificity detection, and mechanistic biological evaluation. Integration with machine learning-assisted spectral analysis, standardized reporting metrics, and interoperable data

pipelines will be essential for scaling MPs/NPs monitoring efforts and informing risk assessment. In this context, the authors envision integrated LoC systems as foundational tools for next-generation environmental surveillance, supporting hypothesis-driven toxicology, informing exposure-response relationships, and ultimately guiding evidence-based regulatory decisions on MPs/NPs pollution.

Conclusions

A critical barrier in the MPs/NPs field is the disconnect between environmental sampling and physiologically relevant biological assessment, which limits our ability to accurately evaluate their impacts on human health and ecosystems. LoC technologies offer a transformative path by integrating sampling, detection, characterization, and bioassessment within a single, controllable platform. Emerging advances in modular design, microphysiological modelling, and digital integration now make standardized, automated analysis increasingly feasible. Future efforts should focus on scalable fabrication, data harmonization, and linking particle analytics with cellular responses. With collaborative innovation, integrated LoC systems could evolve from proof-of-concept devices into validated, field-ready MPs/NPs analytical platforms that bridge environmental monitoring with human health risk assessment.

Author contributions

L. Gong: Conceptualization, Writing – original draft, Writing – review & editing, Visualization. E. Eskandari: Writing – review & editing. I. Khan: Writing – review & editing. L. Yang: Conceptualization, Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included, and no new data were generated or analysed as part of this review.

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Data availability

No primary research results, software or code have been included, and no new data were generated or analysed as part of this review.