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Highlight

- Infusion therapy identified as significant, overlooked microplastic exposure route
- Review emphasizes clinical relevance of particle properties beyond size
- Addresses limitations of current test methods and regulatory standards for microplastics
- Proposes functional classification of particles based on size for clinical relevance
- Calls for standardized, multi-method approach for microplastic detection and risk assessment

Microplastic Particles and Infusion Therapy — Evidence, Implications, and Unanswered Questions

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Keywords

Microplastic, Infusion, Medical Devices, Contamination, Testing

Abstract

The growing accumulation of plastic waste, including microscopic particles in the environment, is an alarming development. It has long been recognised that these particles can enter the human body. Recent studies focus on environmental sources of these particles. This article highlights a less frequently discussed, but significant, route of exposure: the infusion of particles via medical devices and pharmaceutical containers.

One possible reason for this is the assumption that infusion devices are inherently safe due to strict regulations and rigorous testing. Nonetheless, advances in clinical research and the development of specialised test methods have yet to be fully integrated into current industry standards.

This paper reviews the current understanding of microscopic plastic particles, with emphasis on their interaction with the human body, applied test methods and limitations. It further contrasts these insights with existing regulations. Finally, it identifies key areas for future interdisciplinary research in biomedicine, engineering, and public health.

1. Introduction

The need to detect and assess ubiquitous plastic particles in the environment, in organisms, in the food chain and in public water supplies has become a critical issue for science, politics and industry. Concerns range from the profound impact on technical systems to the accumulating threat these materials pose to the environment, with unpredictable consequences for nature. Most importantly, the presence of these particles poses possible health hazards to humans, underscoring the need for comprehensive action and scientific research. Plastic particles have been detected in human blood [1] and other body fluids, the liver, [2] placenta, [3] the lungs, [4] the brain, [5] and in various other organs and tissues. Clinical research on the physiological effects is ongoing. Data from in vitro studies, animal models, and observational research indicate associations between the presence of individual and aggregated particles and severe clinical health outcomes, including inflammatory reactions and plaque formation [6], causing embolisms [7] and even myocardial infarction and stroke. [8]

While the presence of microplastics in human bodies is well recognised and increasingly documented, many contributing factors and underlying mechanisms remain the subject of ongoing research. This review assesses single publications and other reviews to demonstrate the current level of scientific knowledge and addresses four major interdependent areas for future research and action (see Figure 1). A specific focus is on medical devices as a commonly underestimated source of particles in human bodies and how currently established test methods and regulatory requirements will have to be improved to cope with the concerns related to particulate contamination.

These four research areas are interlinked by the following relations:

- Relevant detection methods that intend to assess a risk for public health must be capable of measuring clinically relevant properties.
- Deficiencies in detection methods can lead to difficulties in particle source tracing, which in turn affects the clinical rationality of regulatory standards.
- A scientifically sound approach to regulate medical devices requires an assessment of clinical relevance, particle transportation, source tracing and suitable test methods that allow for standardization.

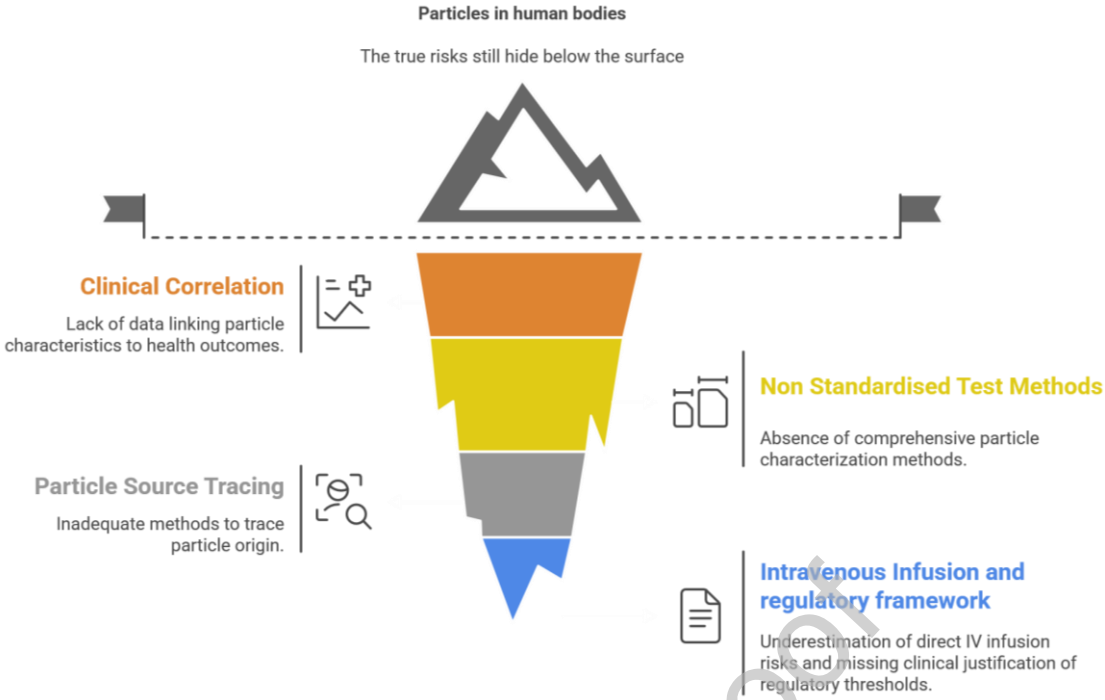

Figure 1 The four major focus areas of this review

2. Search strategy and selection criteria

The scope of this review combines areas of scientific interest that are connected but originate from very different fields, such as engineering, environmental and chemical research and medicine and health. Several literature search runs were conducted in Google Scholar and Elicit.org, which included papers published in PubMed and Web of Science. Additionally, the search functions of relevant scientific journals were used. Different keywords like “Particulate contamination“, „Particle Testing“, ”Microplastics” and “nanoplastics” were used isolated and in combination. Full search prompts were used such as “What influence do the morphology of contaminating particles (size, shape, surface) and the material have on the occurrence of complications in infusion medicine (e.g. systemic inflammatory reactions, pulmonary embolism, renal insufficiency)?“.

Inclusion criteria were:

- Relation to medical applications
- Relation to environmental sciences, specifically when also covering plastic materials

Exclusion criteria were:

- Publication date earlier than 2010
- Particles from irrelevant materials, unless the publication indicates a specific interesting other aspect
- Particles originating from aggregation of pharmaceutical or biomedical substances were not in scope of the review and only considered for delineation of the subject

Isolated Case Studies were included in the review to survey the applied test methods and potential limitations in the methods depending on the reported results.

A preliminary search yielded 133 records. All of these were screened for contributions to the research areas of interest and grouped accordingly.

- 61 records were further analysed for the reported applied test methods, the scope of the study and reported technical limitations.
- 20 records were further analysed for the discussion of clinical impacts of particulates in the human body; specifically to identify particles properties and the related risk profile.

Because the selection was not exhaustive, selection bias may be present; readers should interpret the synthesis as a selective overview rather than a comprehensive mapping of the evidence. The reported publications were selected because of their specific contribution to the description of the addressed topics. For the scope of this review, quantitative synthesis of search results is considered less relevant and could therefore be omitted without compromising scientific accuracy.

The selection process is summarized in figure 2:

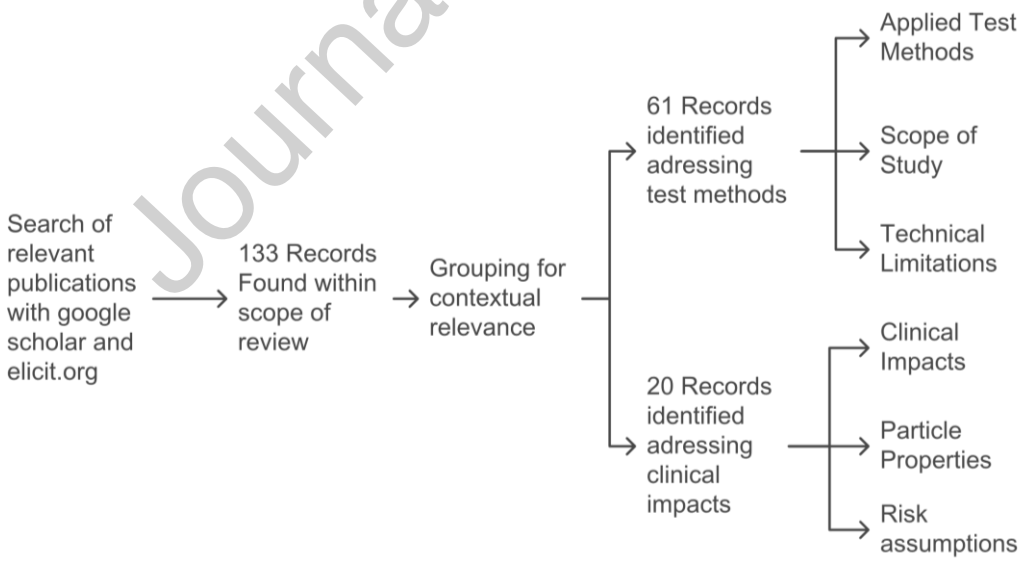

Figure 2: Research screening and analysis process

The applicable regulatory requirements and resources have not been identified via literature search. They have been derived from known industry standards, instead.

When the term microplastic is used in this review, it is meant to include nanoplastics. Combinations and abbreviations (MP, MNP, NP) of these terms are avoided as there is no common definition of these terms and the actual clinically relevant size categories are not necessarily following the conventions of SI units. Only where titles of references are cited, the terms are carried over to this review.

3. Clinical Correlation and expected health outcomes

The available literature about the clinical impact of microplastics in general is growing (such as the extensive collection of data reported from studies in humans and animals done by Ali and colleagues [9]). This development enables the critical review of currently established test methods and requirements for the assessment of risk profiles of medical devices and other sources of particulate matter. When trying to understand this risk profile for the public, the different properties of such matter, such as shape, dimensions or surface, must be assessed for their clinical relevance. The available literature has been reviewed to identify the reported assumed clinical relevance of certain particle properties. The findings of that review are presented in Table 1. Findings from different kinds of studies (observational, animal models, in and ex vivo) have been reviewed and examples for the clinical relevance have been quoted. In many cases, these examples are a matter of ongoing clinical research and associations with the particle characteristics may be derived from biological plausibility and theoretical assessment. Proving causality between the presence of particles and associated clinical outcomes is difficult, but is subject of current research. [10] However, the current level of knowledge and understanding allows the determination of the requirements profile for a more comprehensive assessment methodology.

Table 1: Reported clinical relevance of specific particle properties

	Characteristic	**Examples for Clinical Relevance**
Shape	• fibres, • spherical, • irregular	• "Spherical plastic particles were shown to cause oxidative stress in endothelial cell models" [6] • could cause inflammatory reactions, plaque formation and alter toxic effects [6, 11, 12, 13] • Non-spherical particles can have different interactions with endothelial cells which affects internalization and transportation [14, 15, 12, 16, 17]
Size	..	• Particles smaller than ~5µm are able to traverse capillaries allowing particles to be dispersed in the entire body [6, 11, 14] • Smaller particles correlate with greater induced toxicity and higher intracellular oxidative stress [18, 11, 12, 13, 19, 6] • Particles smaller than 10 to 12 µm can be consumed by macrophages, potentially altering cell activities [7] • Larger particles can occlude vessels, restrict microcirculation and cause embolism [7, 16, 14, 20, 21,] • Particles smaller than 100 nm have the potential to cross the blood brain barrier [14, 12, 5]

Surface	• surface area • Porosity • Sharp edged • Surface charge	• Adsorption of pharmaceutically active substances [22] • Triggering blood coagulation [23, 24,] • Narrowing of vessel lumen by causing numerous small injuries [6] • Toxicity pattern might depend on the surface charge of particles [12, 18, 15, 12, 19, 25, 6] • Degraded or weathered surfaces might augment cell toxicity [15] • Transportation and accumulation potential correlates with the charge of the particles [26, 17, 6, 5]
Material	• Plastic resins • Colorants • Adjuvants • Rigidity / Flexibility	• Adsorption of pharmaceutically active substances [27] • Adsorption and desorption of hormones [28] • Triggering blood coagulation [23] • Toxicology [29, 12, 25] • Higher potential to penetrate tissues for flexible particles [26]
Quantity	..	• Accumulation in organs [6, 5, 30, 3, 31] • Increased blood pressure by deposition in vessels and organs[6] • pathological effects such as mucus secretion, gut barrier dysfunction and inflammation in organs with an accumulation of MNP material [19]
unspecific	..	• haemolysis, oxidative stress, endothelial damage, and thrombus formation [6] • significantly higher risk of primary endpoint events, including myocardial infarction and stroke [8] • promoting the development of pericardial effusions, the inhibition of angiogenesis, and the induction of a prothrombotic status [8] • carrier for additional bioburden [16] • systemic and local inflammation [21, 18, 11, 15, 12, 13, 19, 16, 24, 32, 14, 5, 7, 25]

4. Particle Source Tracing – What do we know about the relevant Entry Routes

As elaborated in the previous section, the number of publications that discuss the microplastic material and the impact to human health grew significantly over the past years. A scoping review published in 2024 analysed 26 individual articles reporting the presence of plastic material in human organ systems and body fluids. [31] This review suggests “inhalation and ingestion through food and water” as potential entry routes. Other reviews also mention “penetration through the skin via cosmetics and clothes contact”. [25] Another review, intended to assess the human exposure to Microplastics through air, water and food, calculates an average daily intake of approximately 3 to 13500 particles per day by inhalation and approximately 1000 to 15500 particles per ingestion for an adult person (with a presumed body weight of 70 kg).[33] Although based on various modelling assumptions, these magnitudes can provide a benchmark for comparing with the relative contribution of a less frequently reported, yet substantial source of particle exposure: the direct infusion of pharmaceuticals and solutions.

One liter of an infusion solution may contain up to 2000 particles in the size range of 10-25 µm according to European Requirements. [34] The actual load might be higher and is further

increased by thousands to millions of particles by the Medical Devices that are used to prepare and administer the infusion solutions or drugs. [35, 36, 37]

In addition to the quantitative comparison of particle exposure, the routes of uptake within the human body are also of relevance. When ingested, microplastic particles are passed through the digestive tract and get mostly excreted. [9] Similarly inhaled particles are cleared from the lungs after inhalation. [9] Only a (currently not determined) fraction of particles can transverse into the cardiovascular system after inhalation and ingestion. Infused particles, on the contrary, are directly released into the bloodstream.

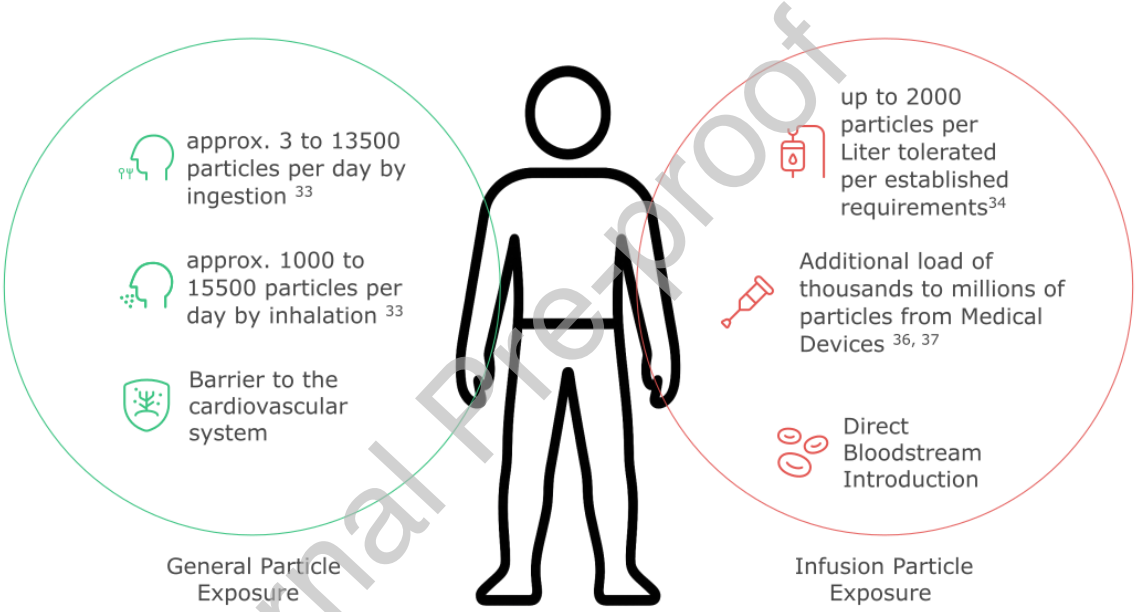

Figure 3: Comparing Particle Exposure Routes

Infusion therapy is widely used in both clinical and non-clinical settings. Common applications range from the administration of simple fluids for hydration and blood transfusions to the delivery of a wide variety of medications in hospitalised patients [38] and even the infusion of diverse supplements such as vitamins in a non-clinical setting or at alternative practitioners. [39,40]

Substantial evidence indicates that particulate contamination of medical devices can negatively impact patient health. While it is difficult to precisely predict the effect of a single particle of given properties, multiple studies have demonstrated that in-line filtration can reduce complications associated with infusion therapy. [41,42] Unfortunately, in-line filtration is

not the ultimate solution to manage particulate contamination as the adsorption of active ingredients of the infusate in those filters must be considered in clinical decision-making. [42] Despite the risks, awareness of particulate contamination remains low among healthcare professionals and patients. In a study exploring patients' perspectives on the quality and safety of intravenous infusions, [38] concerns were mainly related to technical aspects such as pump alarms or mobility restrictions, while issues related to infection or particulate contamination were notably absent.

Regulators and authorities have brought microscopic plastics on the political agenda, but their efforts have largely concentrated on environmental pollution. [43] Meanwhile, standard gravity-driven infusion sets remain classified under the lowest risk category according to the European Medical Device Regulation (MDR), a classification that does not require third-party certification before market approval.

Medical devices are widely regarded as highly regulated [44,45] potentially causing medical professionals to assume inherent safety in the design and use of those devices. This assumption is reinforced by the fact that many clinical studies do not identify intravenous infusion as a potential source of plastic particles found in patient tissues. However, regulatory frameworks necessarily reflect the scientific understanding and analytical capabilities available at the time of their formulation. In the field of microplastics, both fundamental knowledge and detection technologies have advanced considerably in recent years. These developments naturally open the door to a renewed examination of current detection and assessment approaches. Revisiting and refining regulatory requirements in light of this expanded knowledge base represents a logical and forward-looking step that supports continued progress in environmental engineering and medical device applications.

5. Scientific Justification of regulatory thresholds for intravenous infusion

As with any manufacturing process, the achievable level of cleanliness for a product has its limitations. Consequently, the presence of particulate matter in medical devices, and, in many cases, the unintentional administration of these particles into the patient's body is often an unavoidable circumstance. Taken measures to provide a product in a certain state of cleanliness depend on the criticality of the contamination, which requires awareness and risk assessment. This risk-based approach is required by medical device laws and regulations in many global jurisdictions (such as GSPR 4 of the EU MDR, § 820.30 of the US CFR 21, Chapter 2 of Japanese MHLW No 169), as well as international standards such as ISO 13485 or ISO 14971.

However, these general regulatory requirements must be translated into concrete methodologies, including specific product verification test methods and corresponding acceptance criteria. Developing these approaches requires a deeper understanding of the properties of particles and their potential effects on the human body. Not all particle characteristics are clinically relevant, and some may only be significant depending on the particle's origin or composition.

In the scientific literature, particles are commonly categorised based on their nature and source into three groups: **inherent**, **intrinsic**, and **extrinsic** particles. [45]

- **Inherent particles**, such as protein aggregates or other unavoidable or intended by-products of drug formulation [46]. These are outside the scope of this review.
- **Intrinsic particles** originate directly from the medical device or pharmaceutical container itself, arising during manufacturing or use.
- **Extrinsic particles** originate from external sources, such as the production environment (e.g., airborne dust, fibres from clothing, human hair), or may be introduced during transportation or handling. [47]

For the purposes of this review, the focus is on contaminant particles, specifically intrinsic and extrinsic, as these are directly related to the medical device or container or their manufacturing, transportation or use.

Currently, regulatory requirements for medical devices and pharmaceutical containers primarily focus on the quantification and size of particles. In the absence of comprehensive scientific models that incorporate additional risk factors, particle size remains the

predominant criterion for evaluation. While this approach simplifies assessment, it also introduces limitations, particularly given inconsistencies across regulatory standards.

For instance, the United States Pharmacopoeia (USP) [48] sets limits of 25 particles per mL (>10 µm) and 3 particles per mL (>25 µm) for containers holding more than 100 mL. The European Pharmacopoeia[34] allows for 12 particles per mL (≥10 µm) and 2 particles per mL (≥25 µm) for similar containers. These thresholds still allow for significant particulate loads; for example, under European requirements, a 1-liter infusion bag may legally contain up to 2,000 particles between 10–25 µm or as many as 12,000 particles smaller than 10 µm.

The international standard for infusion devices ISO 8536-4 [35] introduces three particle size categories: >100 µm, 51–100 µm, and 25–50 µm. Acceptable contamination levels are determined by multiplying particle counts with specific weighting factors per category. Likewise, the international standard for infusion containers limits contamination to no more than 25 particles/mL (>10 µm) and 3 particles/mL (>25 µm).

Across all standards, particle size remains the sole parameter for differentiation, and none provide a scientifically validated rationale linking particle counts to clinical outcomes or risk thresholds. Moreover, particle shape, another potentially critical factor, is not addressed. While ISO standards permit microscopic assessment that could reveal particle morphology, commonly used methods like light obscuration, as referenced in the USP, assume a spherical particle shape, reducing accuracy for irregular particles and limiting the ability to consider specific shapes in the assessment of the test results.

The reliance on arbitrary size categories, particularly the 25 µm cutoff between *visible* and *sub-visible* particles, lacks a clear correlation with clinical risk. It remains unclear how these categories translate to potential harm within the human body.

ISO/TR 8417 [49] attempts to address this shortcoming by advocating for a risk management approach that prioritizes the reduction of clinically significant risks over mere compliance with particle count thresholds. This technical report emphasizes the importance of measuring the actual particle load to determine both baseline contamination levels and the effectiveness of mitigation strategies. However, in the absence of a comprehensive, scientifically validated testing method, ISO/TR 8417 still references existing pharmacopoeias and technical standards as a baseline.

Until further research establishes the clinical relevance of different particle sizes, this paper proposes to classify particles into two functional categories: those larger and smaller than 5 to 10 µm. This size distinction is medically meaningful and allows researchers to estimate the potential physiological pathways and outcomes:

- **Embolic particles** (typically >10 µm) may obstruct microvasculature, potentially leading to embolism [7]
- **Sub- or micro-embolic particles** (<5–10 µm) may pass through the alveolar capillary network into the arterial circulation, reaching distal tissues [41, 10]

This size convention is crucial to draw conclusions about the potential intake route. As micro-embolic particles have the potential to transfer through the capillaries of the cardiovascular system. They may not only be infused as contaminants from medical devices or pharmaceutical containers but also inhaled or ingested. [12]

While the exact clinical implications of different particle sizes remain a subject for future research, adopting a consistent, size-aware framework is clearly of medical relevance and provides a solid foundation for refining testing strategies and regulatory oversight. However, as outlined earlier, particle size alone is not sufficient. The full profile of particle properties must be considered when selecting appropriate test methods, an area explored in recent publications and further reviewed in the following chapter.

6. Methods for Determining Particulate Contamination and missing standardisation

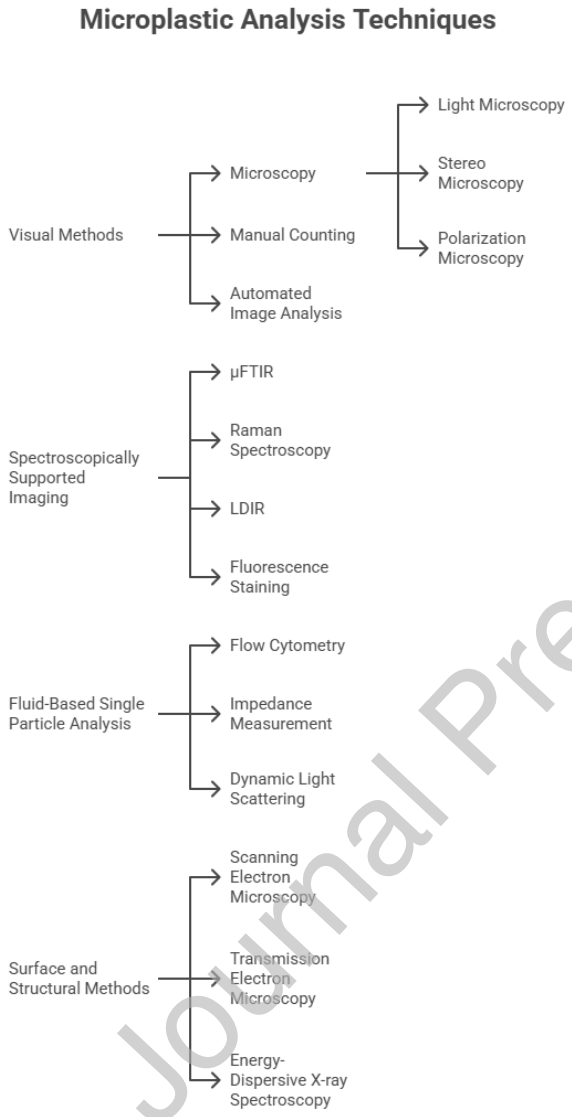

Figure 4 Overview of test methods that are applied to detect microplastics in tissues or other matrices.

(LDIR – Laser Direct Infrared

µFTIR - micro Fourier Transform Interferometer)

A wide variety of technical methods are currently available to identify and characterise particulate contamination. These range from optical microscopy to advanced chemical analyses. Researchers typically select methods based on their research focus, equipment availability, or familiarity with certain technologies.

Figure 4 summarises and categorises the most frequently applied methods in this field.

Other reviews have been published before, listing the applied methods for detecting particles in body tissues or liquids [50] or in biopharmaceutical research and development [51]. To evaluate the potential of these techniques for future standardisation, both in scientific and industrial contexts, this review goes further by identifying limitations reported in the literature for each method. Table 2: Applied test methods and reported limitations presents a summary of those findings.

Table 2: Applied test methods and reported limitations

	Applied for	**Reported limitations of test method**
Raman Spectroscopy (incl. Surface-Enhanced Raman Scattering SERS)	Detection of MP in pharmaceutical containers [22] Detection of MP in human thrombi [52] Detection of MNP in food and beverages - review [53] Machine Learning-Based MP Detection [54] Detection of PDMS residuals in syringes [36] Detection of MP in human placenta [55] Detection of MP in human breast milk [56] Detection of MP in human body fluids [57] Comparison of impacts of PS and SiO2 NP in rodents [58] Detection of Polystyrene NP in water [59] Detection of MNP in cirrhotic liver tissue [2] Detection of MP in human lung tissue [60]	Complex matrices can interfere with the measurement [53] Weak signals compared to background noise [36] Particle mass information is lacking [57] Lower limit of detection at ~4 µm [2] Time consuming assessment [52] Weathered particles can show an altered spectrum [60]
(Pyrolysis) Gas Chromatography–Mass Spectrometry (Py-) GC-MS and Liquid Chromatography–Mass Spectrometry LC-MS	Detection and quantification of plastic particles in human blood [1] and thrombi [61] Analysis of carotid plaque specimens for MNP [8] Quantitation of MNP in Human Blood [62] Detection of MNP in human arteries [63] Quantitation and identification of MP in human placental specimens [3] Detection and Analysis of MP in human cervical cancer patients [30] Identification and quantification in PP bottles [64] Quantifying polymers in human blood [65] Detection of MNP in placentas, meconium and breastmilk [66] Measuring plastic particles and pharmaceuticals in surface water samples [27] Detection of MP in stool samples of children [67]	Determination of the particle masses, but not the number of particles [1] No information on particle size, shape or presence of un-targeted material [68], [63] GC-MS was combined with electron microscopy for visual assessment [8] Py-GC-MS not suitable for PE and PVC in biological matrices [65] Py-GC/MS loses information on particle size, color, and shape [67]
(µ) FTIR	Characterisation of Microplastics in human blood [68] Detection and Analysis of MP in human cervical cancer patients [30] Detection of Microplastic in human placenta [69] Detection of Microplastic in meconium [70] Detection of Microplastics in human lung tissue [4] Detection of microplastics in human colon [71] Comparison of different infusion sets for their impact on protein particle formation [46]	Process of identifying and quantifying MPs is described as time- and cost-consuming [69] Lower detection limit at 5-10 µm with µFTIR [72]
Optical photothermal infrared (O-PTIR)	Detection of Plastic Particles from Infusion Sets and Containers [73]	-
LDIR	Identification of particles in infusion containers [74] Detection of MP in Patients undergoing cardiac surgery [75] Detection of MNP from plastic feeding and water bottles [76]	Lower Detection Limit at 20 µm [76,75]
Light Obscuration, Micro-Flow Imaging or Dynamic light scattering	Quantitation of Protein Particles in Parenteral Solutions [77] Comparison of different infusion sets for their impact on protein particle formation [46] Instrument Evaluation for sub-visible particle detection [78] Assessment of weathering effects on polystyrene beads [15]	Underestimation of (higher) particle concentrations [79] Measurement artefacts at higher particle numbers [78] Lower detection limit around 2 µm [78]
Scanning Electron Microscopy (SEM) and Energy Dispersive Spectroscopy (EDX)	Detection of MP in human placenta [80] Analysis of particles from infusion lines filtered by in-line filtration [81]	..
others	Tracing of particles in rodent models via PET scanning [82] Manual counting of particles from drug containers under optical microscope [83] Validation of PTA for MNP size determination [84] Flow-through quantification of microplastics using impedance spectroscopy [85,86]	..

The choice of the applied method for each of the studies might have been driven by availability at the point of assessment (such as laboratory research technologies versus clinical on-site detection technologies) or the experiences of the respective researchers with those technologies.

Notably, many test methods were not applied in isolation. Spectroscopic techniques were often combined with microscopy to assess particle size and, to a limited extent, shape. Some studies used integrated systems, [57] while others performed additional microscopic assessments separately. [36,71]

Chemical analysis methods such as GC-MS allow targeted identification of specific materials based on known spectra. These are suitable for confirming the presence of predefined plastic types but are less appropriate when assessing unknown or mixed-material contaminations. In such cases, other materials such as glass fragments from ampoules or metal shavings from production lines, may be present and pose equal or greater risks. [17] Another disadvantage of the method is its destructive nature, [87] which excludes the option to repeat assessments or conduct additional tests on analysed samples.

Another critical differentiator in method selection is the detection limit, particularly concerning particle size. For example, particles in the 5–10 µm range are already at or near the lower detection threshold of Raman and FTIR spectroscopy and fall below the reliable resolution of LDIR.

A recurring concern in the reviewed literature is the lack of standardised protocols, specifically regarding sensitivity, specificity, resolution, operational procedures, and auxiliary materials. This deficiency not only impedes comparability across studies but also undermines the reliability of these methods for regulatory pass/fail testing of medical devices. Even when basic detection is technically feasible, the absence of validated parameters for repeatability and comparability presents a significant barrier.

Importantly, there is a substantial distinction between material identification and continuous quantification of contamination. Most studies to date have focused on establishing the presence of microplastics in human tissues, the environment, and relevant products. While this presence is now undeniably confirmed, the remaining challenge is to establish a robust, cost-effective, reproducible testing methodology suitable for both research and commercial laboratory settings.

Developing such a methodology involves more than simply detecting particles. Several recent studies have demonstrated the presence of plastic materials in various sizes and shapes in pharmaceutical containers [64, 74] and in medical devices. [44, 36, 73] However, to enable manufacturers and regulators to trace contamination sources and implement targeted interventions, material identification is also essential.

While a variety of analytical techniques are available for detecting and characterizing particulate contamination, the practical application of these methods in clinical and industrial settings reveals several challenges. These challenges stem not only from the technical limitations of each method, but also from the lack of standardized protocols and the complexity of sample preparation.

7. Challenges and Current Limitations

While several of the test methods reviewed are well-suited for controlled scientific studies, many are not readily applicable in high-throughput processes. Recent research has produced significant advances in detecting and characterizing particles, particularly in the academic context. However, industrial applications require additional criteria, such as repeatability, efficiency, cost-effectiveness, standardisation, and potential for automation.

The test methods identified require distinct and often incompatible sample preparation procedures. The wide range of particle sizes from submicron particles (<5 µm) to visible fibres over 100 µm makes it unlikely that any single method can cover the full size spectrum. As a result, samples may need to be fractionated by particle size before testing, potentially introducing variability or loss.

Another critical factor is the sample volume. In devices such as infusion sets, particles are typically not accessible without prior extraction usually by flushing with a defined volume of liquid. For example, ISO 8536-4:2019 specifies flushing 10 devices with 500 mL each, resulting in a total test volume of 5 Liter.

To apply multiple analytical methods to such a volume, the sample must be subdivided into equal, representative portions. This introduces further complexity in ensuring that each portion reflects the overall particle distribution and concentration especially when dealing with heterogeneous or sparsely distributed contaminants.

Evidently, a solitary technology is inadequate of detecting all clinically relevant particle characteristics in a single analysis. Therefore, a combined multi-method approach is necessary. Such an approach must define a reasonable sequence of tests and, ideally, allow for automated sample handling to reduce manual processing errors and improve throughput.

Summary of Key Limitations:

- **No single method** detects all relevant particle characteristics.
- **Automation and standardisation** of combined methods are currently lacking.
- **Optical methods** struggle with translucent or transparent particles.
- **Sample preparation requirements vary widely** between methods.
- **Large sample volumes**, especially in flushed devices, require careful sub-sampling and handling.
- **No current framework** fully links detected particle properties to clinical significance.

These limitations underscore the need for further research and development in both analytical methodology and regulatory frameworks. Addressing these issues is essential for ensuring patient safety and for establishing robust standards in medical device testing.

8. Conclusion and Outlook

There is growing consensus that the intake and accumulation of plastic particles pose health risks to humans. Proper regulatory and political responses however are still in development and urgently needed to establish a clinically acceptable state of the art. This review has identified several avenues for future research that can collectively contribute to a more comprehensive and up-to-date framework for the detection and assessment of microplastic particles. The following offers a brief indication of these directions.

Clinically acceptable state of the art

Future academic research will need to integrate insights from health sciences, material science, manufacturing, and analytical technologies to establish repeatable, comprehensive, and scientifically validated procedures that can be integrated into international testing standards. A key objective will be to bridge clinical understanding of health impacts with analytical capabilities and develop a risk-proportionate assessment framework that aligns particle characteristics with their potential clinical relevance. This review draws connections between the clinically relevant particle characteristics and their detectability by currently available and established test methods. By bringing these two perspectives together, the foundation is laid to develop methods based on sound clinical scientific knowledge.

Comparing Exposure Pathways

Current data is limited in terms of quantifying and comparing exposure through direct medical applications, such as infusion therapies with environmental exposure (e.g., via air, water, or food). Large-scale, statistically sound studies quantifying patient exposure, such as the number and type of infusion devices and pharmaceutical containers used per therapy could help clarify the role of medical products as a distinct and significant route of plastic particle intake. This review indicates that a risk proportionate discussion of particulate matter requires a holistic approach, including all relevant entry routes and further investigation of reasonable transportation mechanisms inside the body. Particle properties can also be used to draw conclusions about their origins. As summarised in this review, particle sizes around 5 to 10 µm will allow particles to cross the capillary network or the intestinal wall and enter the blood stream. Bigger particles are more likely to have entered via different routes, potentially by direct infusion. Also, other properties (such as surface

properties or the grade of degradation) might be factors that help tracing the origins of plastics matter accumulation in patient's bodies.

Identifying Particle Sources

Another promising area of research involves comparing particle material profiles. Certain polymers, such as polyvinyl chloride (PVC), polyethylene PE, poly propylene PP, and polystyrene PS, are commonly used in infusion and medical devices, while others may be more indicative of environmental exposure. Comparing the composition of particles in human tissues to those typically found in environmental samples (e.g., water, air) may help trace particle origins more precisely.
In addition to chemical composition, other particle characteristics, such as morphology or degradation patterns may also help in source identification. For example, Raman spectroscopy has been shown to detect signs of weathering, which may suggest environmental exposure. [60]

Emerging technologies and machine learning

Most studies were conducted utilizing available and well-established testing technologies. Current developments in analytics and automation might allow to merge currently isolated particle property information and provide a more comprehensive view of the relevant sample characteristics. Systems like the LDIR allow to combine spectral and morphometrical analysis with the potential to further speed up and standardize sample assessment. [88]
Recent studies highlight the potential of machine learning and neural networks to assist in automated analysis and classification of large numbers of particles.
Such tools could significantly accelerate data processing and enhance pattern recognition across large datasets. The application of machine learning methods allows to use material properties and physical effects for alternative testing concepts, such as polarized light scattering [89] and integration into microfluidic sensors. [90]

The need for standardisation in the applied test methods

The ongoing scientific and industrial discourse on microplastic contamination and the health impact of microscopic microplastic particles underscores the urgent need for the development and standardisation of test methods. These methods must be capable of assessing all clinically relevant particle properties and must support consistent, reproducible comparisons by minimizing variability in particle detection, characterization, and risk evaluation.

Conclusions can only be deemed scientifically valid and broadly applicable if based on standardised approaches. The absence of such standards is of critical importance in the medical device sector due to implied health risks. Harmonised testing methodologies are essential for enabling manufacturers, regulators, and health authorities to accurately assess and compare the safety of devices and to ensure that patient risks are adequately controlled.

Furthermore, clinical, environmental and public health research areas would greatly benefit from such standardisation. This review identified the relevant input criteria in the development of a standardised methodology.

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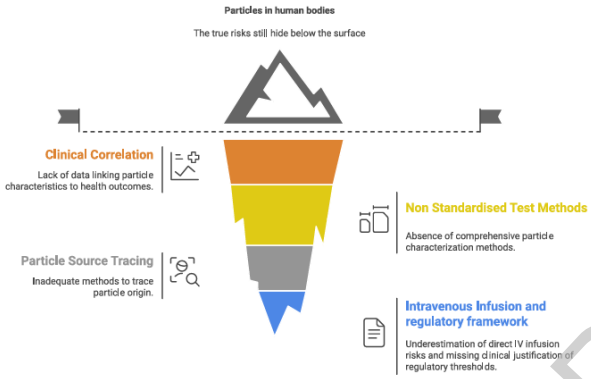
Graphical abstract



Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Marc von Pawlowski reports a relationship with TUV SUD Group that includes: employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.