

Research Paper

An integrated approach to assess exposure and early health effects in human populations exposed to micro- and nanoplastics

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ABSTRACT

Although cumulative evidence from in vitro and in vivo studies indicates that micro- and nanoplastics (MNPs) can induce toxic effects, and MNPs have been detected in several human fluids and tissues, the consequences of MNP exposure to human health still remain unknown. Human biomonitoring (HBM) studies allow assessing human exposure to MPs and associated adverse health effects, contributing to the risk assessment of these environmental pollutants. To date, reliable human exposure estimates are hindered by the lack of standardized processing and analytical methods to detect MNPs in human tissues, and limited evidence on the MNP-related adverse health effects exists. Occupational environments, where plastics are processed, may represent prioritized settings for such evaluations, as workers typically face higher exposure levels than the general population. Population sub-groups with potentially higher susceptibility, such as children and pregnant women, should also be considered. To develop effective preventive strategies, it is essential to identify and validate sensitive and specific biomarkers of exposure and early biological changes, which could result in adverse health effects. Standardized protocols integrating environmental exposure assessment with HBM, and sensitive methods for evaluating internal dose resulting from cumulative exposure to MNP particles and associated chemicals are needed. Based on the experience gathered by a multidisciplinary panel of experts belonging to the European Research Cluster to Understand the Health Impacts of MNPs (CUSP), this consensus paper describes the key elements that should be part of an integrated HBM approach for MNP exposure, emphasizing existing challenges and proposing solutions for future studies.

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1. Introduction

Environmental pollution caused by micro-/nanoplastics (MNPs) can pose a threat to human health (Winiarska et al., 2024). Microplastics (MPs, 1 μm – 5 mm) and nanoplastics (NPs, < 1 μm) (ECHA, 2020) can reach the environment as primary MNPs (i.e., pellets, or virgin plastics included in personal care products), or secondary MNPs, originating from abrasion during daily usage of plastic products, or degradation and fragmentation of larger plastic waste items (Yang et al., 2023a, 2023b). MNPs have been identified in all environmental compartments, where they can interact with living organisms (Choudhury et al., 2024).

Inhalation is, together with ingestion, the main exposure route of humans to MNPs (Domenech and Marcos, 2021). The presence of MNPs has been documented in indoor air, and Wieland et al. (Wieland et al., 2022) estimated that humans might be exposed to >48,000 airborne MP particles per day. Flooring, synthetic garments, textile and household furniture seem to be substantial sources for MNPs contaminating indoor air and the main source of exposure for the general population (Facciola et al., 2021). Moreover, in certain work environments, the potential for exposure to MNPs during the mechanical and environmental degradation of plastic materials, or through the intentional addition of MNPs as product ingredients is at elevated levels. However, to date, the occurrence and the emission sources of MNPs at workplaces have received little attention (Murashov et al., 2021; Ramsperger et al., 2023). Despite the existing evidence on plastic industry-associated diseases (Burkhardt et al., 1999; Prata, 2018; Wieland et al., 2022), plastic particles are still considered nuisance dust with an OSHA permissible exposure limit of 5 mg/m^3 for respirable dust (OSHA, 2025).

MNPs occurrence in human tissue and biological fluid samples has been demonstrated (Brits et al., 2024; Horvatits et al., 2022; Huang et al., 2022; Leslie et al., 2022; Nihart et al., 2025; Rotchell et al., 2023, 2024; Schwabl et al., 2019; Zhang et al., 2021; Zhu et al., 2023), although the lack of harmonized methods precludes comparisons among studies. Furthermore, evidence on the adverse health effects of MNP exposure in human populations has been poorly investigated, although their intrinsic toxic potential has been demonstrated through in vitro and in vivo studies (Dick Vethaak and Legler, 2021; Panizzolo et al., 2023; Sun and Wang, 2023). Moreover, their lifetime accumulation in tissues (Wu et al., 2022), raises concerns about long-term effects.

Although health risk assessment frameworks for environmental MNPs are already available, as the one recently proposed by Vogel and co-authors (Vogel et al., 2024), their implementation is currently limited by the fragmentation and incompleteness of exposure and effects data (Thompson et al., 2024). Human biomonitoring (HBM) is a recognized and important tool for assessing the internal exposure of humans resulting from aggregated exposure to chemicals (Jones, 2020; OECD, 2022), as well as effect biomarkers reflecting subclinical changes before the onset of disease. Hence, HBM studies allow anticipating the potential adverse effects of new and emerging chemicals and elucidating dose–effect and dose–response relationships. However, evidence on the adverse health effects related to MNP exposure in human populations is even sparser than that on the internal dose of MNPs (Zuri et al., 2023). Epidemiological studies following a proper design have never been carried out, and, to date, only small case-study reports are available.

Over the past four years, the European Research Cluster to Understand the Health Impacts of MNPs (CUSP) has performed HBM studies to assess MNP exposure both in occupationally exposed- and the general population. This paper presents our consensus view, based on the experience collected and insights gathered, on the key elements that should be part of an integrated approach to assess biomarkers of exposure and effects in biological samples of MNP-exposed human populations. First, we provide an overview of the environmental monitoring campaign that should complement HBM studies (section 2). Then, we propose a set of biomarkers of exposure and effects to be used (section 3), emphasizing their scientifically based relevance and the limitations of the proposed assays, as well as confounding factors to be considered

(section 4). The steps of the methodological approach are described in detail in section 5. Finally, section 6 highlights the challenges of implementing such approach, and suggests solutions to be adopted in future studies to overcome these limitations.

2. Environmental exposure assessment

Environmental monitoring reveals potential MNP exposure sources and concentrations and, hence, it complements HBM studies to achieve a robust MNP risk assessment (Bocca and Battistini, 2024; Ladeira and Viegas, 2016). In occupational studies, where inhalation is the main exposure route, a detailed characterization of the exposure scenarios can be performed using the classical tools of Industrial Hygiene implemented with high-precision equipment (as summarized in the Supplementary material S1), following the EN standards for assessment of workplace exposure to chemical and biological agents (BS EN 689:2018, 2019; EN 16966:2018, 2018; EN 17058:2018, 2018). However, specially adapted sampling equipment might be needed for MNP analytics. Particular emphasis should be placed on quality assessment/quality control (QA/QC) measures as cross-contamination with MNPs from equipment or the environment represents a permanent risk (Kernchen et al., 2022).

As the ingestion (oral) route of exposure is likely more relevant for the general population, direct assessment of exposure is complicated and not feasible. To address this issue, the risks of exposure to MNPs should be estimated using food logs and questionnaire data, such as the food frequency questionnaire (Harvard University, 2025), accompanied by validation using characterization and quantification of MNPs in stool samples. Since dietary habits vary significantly, food consumption data should be normalized (either by weight or serving portion) and ranked by levels of risk for exposure to MNPs and intrinsic characteristics of the food in question that may contribute to health risks (Food Safety Authority, 2016; WHO, 2022).

As it happens with engineered micro- and nano-sized particles, characterization methods should allow the analyses of the collected sample in terms of physico-chemical characteristics, i.e., polymer types, sizes and shapes of MNPs. However, in the case of MNP exposure, particles are highly heterogeneous for these parameters. Hence, a combination of different detection methods will be needed to identify the whole particle spectrum. Thermo-analytical methods, such as Pyrolysis Gas Chromatography Mass Spectrometry (Py-GC–MS) or Thermal Extraction/Desorption Gas Chromatography Mass Spectrometry (TED-GC–MS), give information about the MNP type of polymer and their mass concentration within a sample (García et al., 2024; Leslie et al., 2022; Marfella et al., 2024); however, no information on particle number, shape and size are recorded. Such information about the MNP properties is essential to understand the mechanisms underlying the potential adverse effects of MNPs on human health (Wieland et al., 2024).

Micro resolved Fourier transform infrared (μFTIR) spectroscopy is, together with confocal Raman microscopy (CRM), the most commonly used state-of-the-art analytical methods in microplastic research, enabling the identification of polymer types, their abundance, shape, and size (Vela et al., 2023; Venus et al., 2022). Focal plane array (FPA) based μFTIR spectroscopy allows the identification of particles in a size range from 10 to 500 μm , whereas particles exceeding 500 μm can be analysed by attenuated total reflectance (ATR)-FTIR spectroscopy (Möller et al., 2020). Particle sizes below 10 μm (down to ~ 300 nm depending on the instrument) can be measured with CRM. However, measuring the whole sample matrix with high resolution is very time demanding. Therefore, spectroscopy-based imaging techniques could be complemented with thermoanalytical methods, especially by thermogravimetric analysis, as the latter can have a higher sample throughput compared to the spectroscopic techniques, serving as a first screening for the presence and mass concentration of MNPs within an exposure scenario.

In the case of direct air sampling onto a suitable filter substrate for μ FTIR and CRM (i.e., silver membrane or aluminum oxide filter), sample processing might not be necessary, and the filters could be measured via the above-mentioned techniques as collected (i.e., see FTIR chemical imaging results in Fig. 1). If indirect air samples, such as deposition samples or dust, are taken sample processing might be necessary depending on the amount of background matrix.

Whatever the analytical technique used to detect MNPs, sample collection, processing and the identification of small MNPs capable of crossing biological barrier and being internalized ($< 5 \mu\text{m}$) are critical steps. Different sample processing protocols are currently used in literature, where many are not fully validated for being harmless for the analysed polymer types (Munno et al., 2023). The main challenge is to avoid sample contamination with MNP from the surrounding environment, and to ensure MNP particle integrity during sample purification as well as prevention of particle loss during treatment. Especially for small MPs and NPs, validated sample processing protocols following strict QA/QC measures and standardized analytical workflows combining different methods are still under development. The lack of a harmonized approach hampers the comparison of different studies and therefore final conclusions on the human exposure to small MPs and NPs.

3. Biomarkers

HBM studies aim to investigate whether MNP emissions may impact human health by measuring biomarkers of exposure and of early health effects in biological samples of exposed people in occupational scenarios or in the general population. An exposure biomarker is the concentration of a parent compound or its metabolites in biological matrices, whereas an effect biomarker is a measurable biochemical, physiological, and behavioural effect or other alterations within an organism that, depending on the magnitude, can be associated with an established or possible health impairment or disease (Zare Jeddi et al., 2021).

Biomarkers should ideally be measured in biological matrices collected non-invasively (or by minimally-invasive procedures) to enable a routine screening and monitoring of donors. Accordingly, the protocols adopted by CUSP Partners were mainly focusing on three biological matrices, namely exhaled breath condensate (EBC), blood and urine. Among them, EBC is considered a valuable biological matrix to monitor inhalation exposure as it allows analyses in tissues of first

contact such as the lung lining fluid (Scheepers and Cocker, 2019). This is especially relevant when assessing exposures to particulate materials that tend to accumulate at the entry sites (Forest et al., 2021; Forest and Pourchez, 2023; Marie-Desvergne et al., 2022). Moreover, for specific investigations, i.e., to assess a potential gut dysbiosis or characterize the microbiome and address the ingestion route of exposure, stool sampling should also be considered (Schwabl et al., 2019; Yan et al., 2022; Zhang et al., 2021). Fig. 2 provides an overview of the suggested biological matrices to be collected in HBM studies with MNPs, as well as the type of biomarkers that can be assessed from each of them, which are explained more in detail in the following sections.

3.1. Biomarkers of exposure

Human exposure to MNPs involves both the particulate plastic materials themselves but also a wide array of associated chemicals such as additives and contaminants. This complex mixture of particles and chemicals represents a multifaceted exposure scenario with potential implications for human health.

3.1.1. Detection of micro- and nanoplastics in biological fluids

When considering exposure to airborne MNPs, measuring particles in EBC could help giving an estimate of particle retention in the lungs. Its rationale is based on the assumption that insoluble particles may behave differently according to their physico-chemical parameters, mainly size which, in turn, can affect their aerodynamic behaviour (Oberdörster et al., 2005). Nanoparticle tracking analysis has been used for the quantification of particles in biological matrices, such as EBC, and can thus support the assessment of internal dose of particles (Guseva Canu et al., 2023; Panizzolo et al., 2024). However, this technique is limited by the lack of the spectroscopic identification and characterization of the chemical composition of particles. Therefore, it should be coupled with other methods.

The detection of MNPs in complex human biological matrices remains a challenging task, mostly because the strong endogenous background from human samples that overlaps with the signals of the particle, and aggravates reliable detection of MNPs. For such samples, a sample purification step prior to the concentration on the filter surface on which the analysis takes place is mostly necessary. Sample purification should ideally be plastic-conserving (Löder et al., 2017) and, as

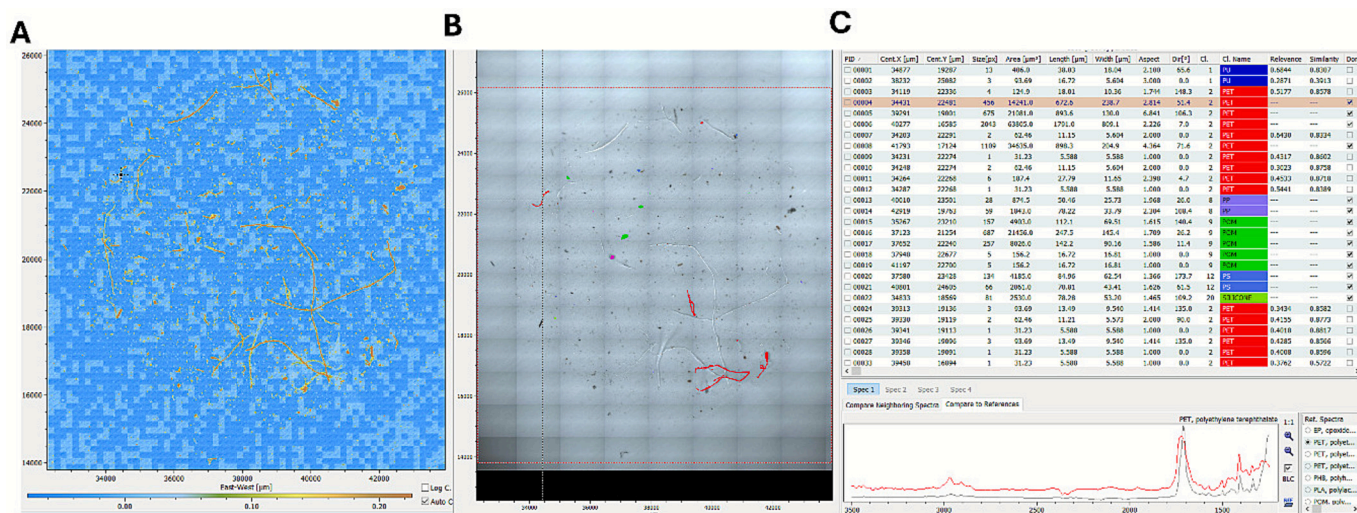


Fig. 1. Software-based automatic detection of microplastics (MPs) in an air sample collected via active air pumping on aluminum oxide filters using focal plane array Fourier transform infrared (FPA-FTIR). (A) Chemical image of the measured sample created from FPA-FTIR measurement, (B) Optical image of the same filter. The automatically identified MPs are polymer-specific colour coded, i.e., red-labelled particles and fibres are identified as polyethylene terephthalate (PET). (C) Respective fingerprint spectra of a PET fibre. Non-plastic particles and fibres collected on the filter are consequently not colour-coded. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

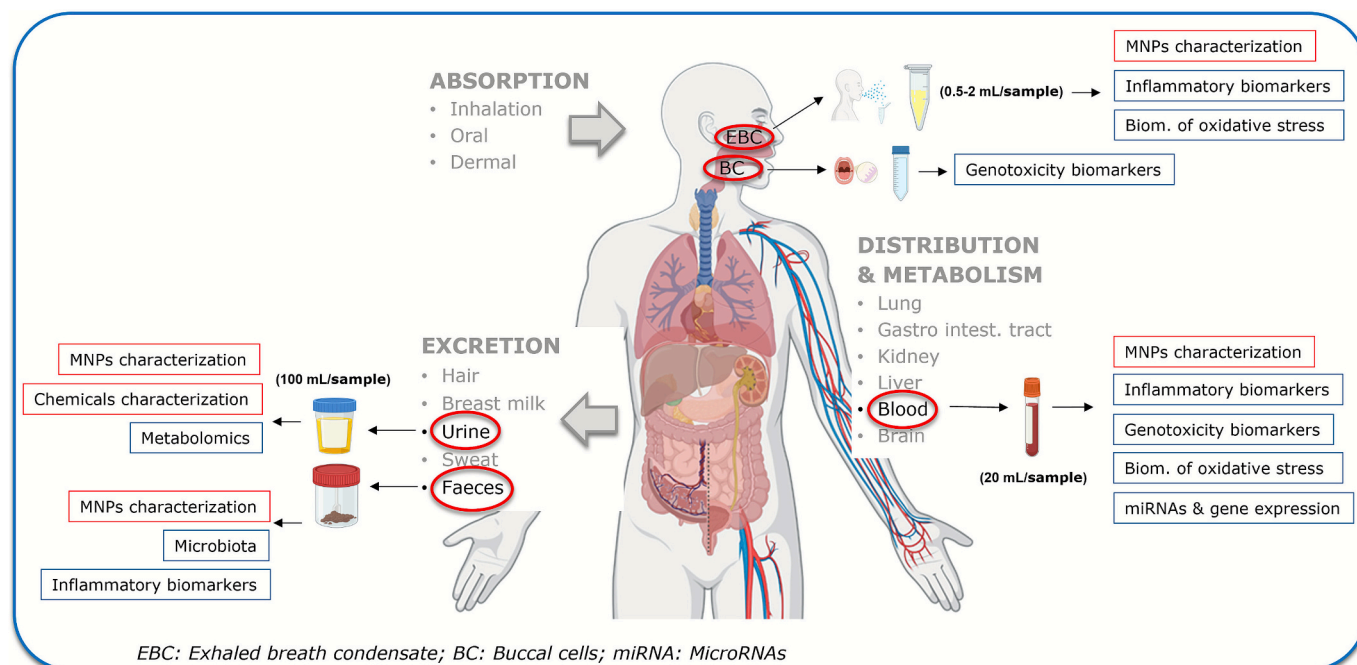


Fig. 2. Human samples collected in the different CUSP projects. Maximum amount per sample for exhaled breath condensate (EBC), blood and urine, as well as biomarkers of exposure (framed in red) and effects (framed in blue) that have been assessed from the different samples are indicated. *Partly created with BioRender™.* (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

stated in section 2, special care must be taken and QA/QC criteria fulfilled during sampling, sample processing and analytical pipeline to avoid contamination with MNPs for producing reliable data.

Molecular imaging techniques based on infrared and Raman spectroscopies – mainly CRM, μ FTIR and μ ATR-FTIR – are the only methods that allow the simultaneous chemical identification, visualization and characterization of MNPs. That includes the determination of the number concentration of the particles as well as size, shape distributions and surface properties of singular particles ranging from nano to micro size. There are still only a limited number of publications for characterization of MNPs in biological fluids and matrices by means of imaging tools. Analysis of urine (Rotchell et al., 2024), human blood (Leonard et al., 2024), faeces (Hartmann et al., 2024), vein tissues (Rotchell et al., 2023) and human lungs (Jenner et al., 2022) by means of μ FTIR showed very low levels of MPs ranging from 5 μ m up to 3000 μ m, with concentrations around 0.5–15 MP/g. To improve diffraction limited spatial resolution, Raman based spectroscopic methods were applied. Raman spectroscopy and Raman microspectroscopy detected MPs ranging from 2.1 to 26 μ m in thrombocytes, from 3 to 13 μ m in urine, as well as from 1.6 to 126 μ m in EBC (Geng et al., 2023; Massardo et al., 2024; Wu et al., 2023a). However, none of these studies was able to detect plastic particles of toxicological relevant sizes, which is assumed to be smaller than 5 μ m in diameter for the inhalation route (Champion et al., 2008; Yang et al., 2023b). This may be due to sample processing, depending on the mesh size used during the isolation step, and to the performance of the positioning stage and image processing.

Due to the lack of data on NPs and toxicological relevant MPs in human fluids, CRM has been developed and verified within the CUSP in terms of visualization, chemical identification and quantification of MNPs smaller than 5 μ m, down to 300 nm, in human blood, EBC and urine. Analysis by means of CRM involves coupling of CRM with particle searching algorithm to enable fast screening of large sample areas, followed by chemical imaging of a smaller region for a more detailed characterization of the nano-sized fraction (Fig. 3).

For method verification, blood, urine and EBC samples were spiked with known concentrations of nano-sized particles. The samples were digested using an adapted protocol by Löder and co-workers (Löder

et al., 2017) and subsequently filtrated on Anodisc filters (pore size 20 nm) to enrich and evenly distribute the sample in a defined area. Achieved recovery of mass and number concentrations ranged from 75 to 100 % depending on certain biological fluids. Limits of detection (LOD) and quantification (LOQ) were measured to be 15 ppb at the filtrated volume of 10 mL.

Accurate detection and chemical identification of MNPs in human samples are challenged due to the complexity of biological matrices, typically low particle concentrations, limited sensitivity for nanosized fractions (<1 μ m), and the lack of validated, standardized analytical protocols. To address these limitations, future strategies should integrate complementary analytical techniques with advanced data processing methods. Combining Raman imaging with high-quality bright-field stitched imaging and particle-search algorithms, supported by a precision-controlled positioning stage, offers a promising approach to enhance particle localization and spectroscopic accuracy. This integrated method improves visualization and targeting efficiency for subsequent Raman measurements, particularly for nanosized particles. Further advances in image processing and artificial intelligence (AI)-assisted particle recognition are expected to increase analytical reliability and reduce false positives. Establishing rigorous method validation and standardization will be essential to ensure reproducible detection and identification of toxicologically relevant MNPs, in particular those below 5 μ m.

3.1.2. Plastic-associated chemicals

MNP-associated chemicals are substances intentionally added during production processes (i.e., plasticizers, additives and stabilizers) that are not covalently bound to plastics and may leach from plastic products or from internalized particles (Prata, 2018). In addition, chemicals can be released during mechanical abrasion (i.e., wear from driving) or form part of an “eco- or bio-corona” composed of environmental pollutants, microbial components, or biological molecules that adsorb onto MNP surfaces (Dick Vethaak and Legler, 2021). A recent report from the PlastChem project (Monclús et al., 2025) has identified up to 16,000 chemicals that might be present in plastics. Some of them are well-known hazardous substances (i.e., bisphenols, phthalates), whereas

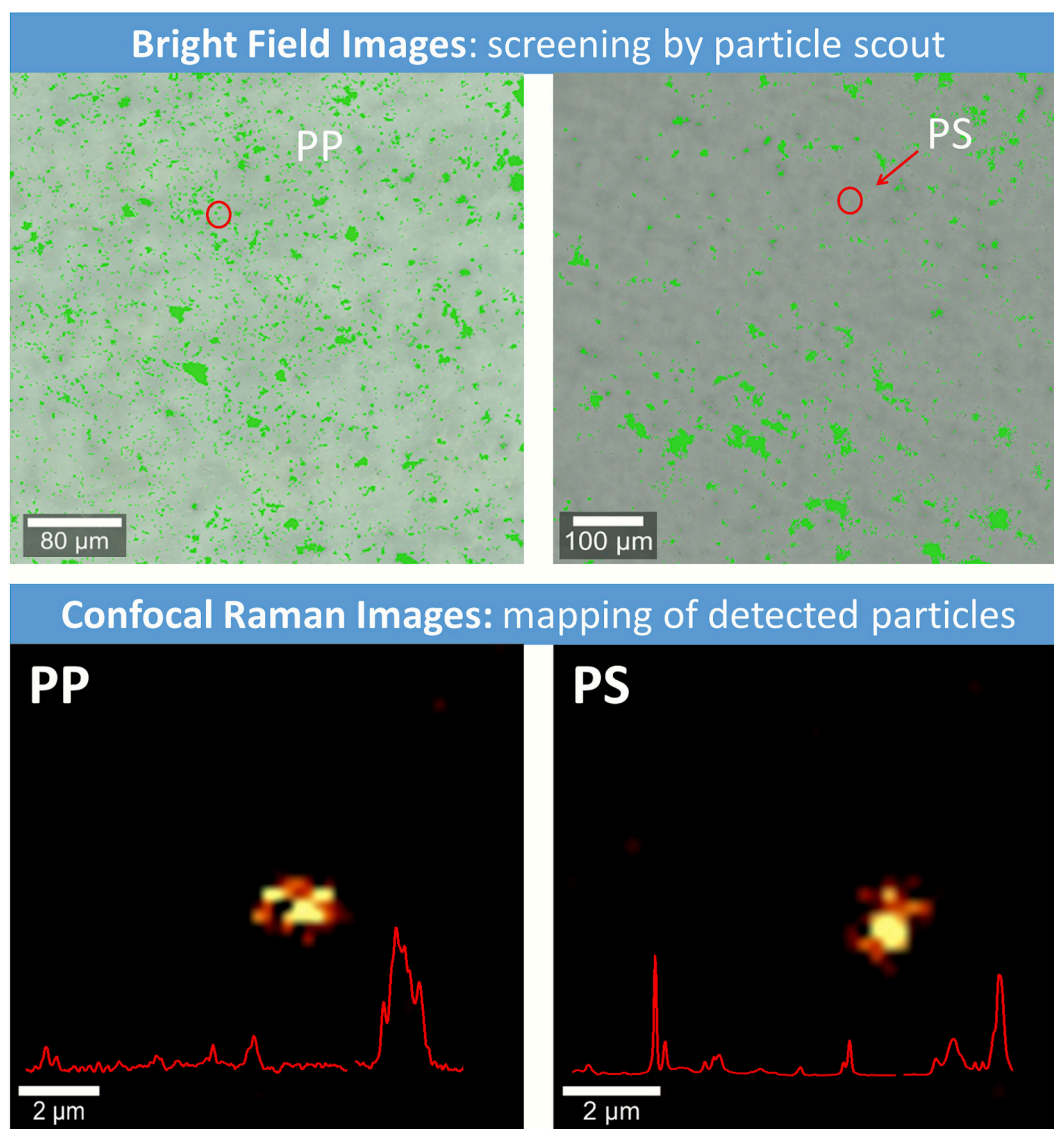


Fig. 3. Detection, identification, and characterization of micro- and nanoplastics in digested and filtrated whole blood sample from a textile industry worker. **Top panel:** High quality bright field image was used to localize particle positions (highlighted in green). Raman spectra were acquired at these positions using particle searching algorithm, enabling chemical identification of selected particles. **Bottom panel:** Confocal Raman microscopy images at locations marked with red circles provide detailed analysis of particle size and morphology of nanoscale plastics. The integrated Raman spectra (marked in red) from visualized particles reveal distinct molecular fingerprints of unambiguously identifying polypropylene (PP) and polystyrene (PS) nanoplastics. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the hazards of others are still unknown. Therefore, plastic-related chemicals and pollutants should also be considered in HBM studies dealing with MNPs. However, the background levels of most of these compounds in human samples are already high (Govarts et al., 2023) in comparison to the small increase generated through their release from MNPs, as exposure to these chemicals also occurs through several other sources (i.e., diet, water, and personal care products). Hence, a significant increase in their internal levels specifically related to MNP exposure would be difficult to detect, preventing the use of these chemicals as markers of exposure to MNPs.

3.2. Biomarkers of early health effects

Relying on the evidence of common pathways across the species, as well as on the evidence that MNPs share similar mechanisms of action with other foreign particulates, a panel of putative biomarkers reflecting long-term endpoints, such as chronic inflammation and fibrosis, cancer, as well as cardiovascular endpoints can be set up (Ghelli et al., 2022;

Hemmendinger et al., 2023; Panizzolo et al., 2023). Table 1 summarizes a core battery of effect biomarkers that have been assessed by the CUSP projects in different human matrices. The physiological/pathological meaning of each biomarker is also indicated to help the reader choose the most appropriate set of biomarkers according to the goal of the study and the availability of human samples. A more detailed explanation of each of these biomarkers is provided in the following sub-sections. As epidemiological studies investigating MNP exposure in humans are not available, the suitability of the different biomarkers for assessing MNP effects is supported by in vitro and in vivo studies, and by studies performed with nanomaterial workers.

3.2.1. Biomarkers of oxidative stress and inflammation

Oxidative stress (OS) is a central mechanism of action for both pulmonary and extra-pulmonary health effects of particulate matter (Mills et al., 2009), and several studies of exposure to particles in humans have applied biomarkers of oxidative damage in the blood compartment or in terms of products excreted in urine or EBC. Moreover, MNPs have been

Table 1

Suggested biological matrices and effect biomarkers to be assessed in human biomonitoring studies of micro- and nanoplastic exposure. EBC: Exhaled Breath Condensate.

Biomarker	Biological matrix	Physiological/ Pathological meaning	Reference
15-F2t-Isoprostane (8-isoprostane)	Urine/EBC	Oxidative stress (produced by the reaction of free radicals with arachidonic acid, including arachidonic esters in phospholipids)	(Romanazzi et al., 2013)
Malondialdehyde (MDA)	Urine/ EBC/blood	Oxidative stress (degradation of the unstable peroxides derived from polyunsaturated fatty acids)	(Donisi et al., 2024; Toto et al., 2022)
8-Oxo-2'-deoxyguanosine (8OH-dG)	Urine/EBC	Oxidative DNA damage	(Graille et al., 2020; Malinowska et al., 2022)
Total Antioxidant Power (TAP)	Urine	Non-enzymatic antioxidant capacity	(Hemmendinger et al., 2023; Malinowska et al., 2022)
Tumour necrosis factor (TNF- α), Interleukin 1 beta (IL-1 β), Interleukin 6 (IL-6)	EBC	Pro-inflammatory cytokines	(Ghelli et al., 2022; Hemmendinger et al., 2023; Lu et al., 2021; Xu et al., 2019)
Interleukin 10 (IL-10)	EBC	Immuno-suppressive cytokine	(Ghelli et al., 2022; Hemmendinger et al., 2023)
Interleukin 17 (IL-17 A)	EBC	Key cytokine that links T cell activation to neutrophil mobilization and activation	(Hemmendinger et al., 2023)
Krebs von den Lungen 6 (KL-6) glycoprotein	EBC/ plasma	Potential biomarkers of interstitial lung disease; activation of pro-fibrotic cascade in the lung	(Hemmendinger et al., 2023; Lu et al., 2022)
Surfactant protein-D (SPD)	EBC	Regulation of pulmonary host defence and inflammation; potential biomarkers of interstitial lung disease	(Xu et al., 2023)
C-Reactive Protein (Hs-CRP)	Blood/EBC	Low grade systemic inflammation	(Ghelli et al., 2022; Lee et al., 2024)
Vascular Cell Adhesion Molecule-1 (VCAM-1)	Blood	Cell adhesion molecules that help regulate inflammation-associated vascular adhesion and the transendothelial migration of leukocytes	(Kong et al., 2018; Sivakumar et al., 2025)
Plasminogen activator inhibitor-1 (PAI-1),	Blood	A protein mainly produced by the endothelium. Elevated PAI-1 is a risk factor for thrombosis and atherosclerosis.	(Dawson and Henney, 1992; Sivakumar et al., 2025)
SOD: superoxide dismutase	Blood /plasma	Antioxidant enzyme activity	(Deng et al., 2017; Vecchiotti et al., 2021)

Table 1 (continued)

Biomarker	Biological matrix	Physiological/ Pathological meaning	Reference
DNA strand breaks (Comet assay + FPG-ENDO III)	Blood	Basal and oxidatively damaged DNA	(Živković et al., 2024)
DNA (hypo/hyper) methylation microRNA (miRNAs)	Blood	Impaired expression of genes involved in DNA methylation reactions leading to global DNA methylation changes; gene-specific methylation of tumour suppressor, inflammatory, and DNA repair genes; potential cancer development. DNA hypermethylation might represent biomarker of both exposure and disease development (e.g., fibrosis, cancer).	(Meehan et al., 2018)
Micronucleus assay	Blood/ buccal cells	Chromosome breaks or losses	(Bolognesi and Fenech, 2019)
Metabolomics	Urine	Overall functional readout of the physiological state of a given biological system.	(De Rosa et al., 2025)
Microbiota disruption	Stool	Loss of microbial balance affects host metabolism and immunity.	(Jiménez-Arroyo et al., 2023)

shown to affect reactive oxygen species (ROS) production in both in vitro and in vivo models (Panizzolo et al., 2023). 8-Oxo-2'-deoxyguanosine (8OH-dG), 8-isoprostane (15-F2t-Isoprostane) and Malondialdehyde (MDA) are the most studied biomarkers, reflecting systemic OS (Graille et al., 2020; Toto et al., 2022). Increased levels of MDA were found in 10 out of 14 experimental studies dealing with MNPs (Panizzolo et al., 2023).

Endogenous defence systems, such as superoxide dismutase (SOD) and catalase, allow balancing an excess in ROS production. Several in vitro studies where human cell lines were exposed to varying concentrations of PS (from 25 to 1200 $\mu\text{g/mL}$) have shown an initial downward trend in SOD enzyme activity in the first few hours, with small increases after 48 h (Cheng et al., 2022; Vecchiotti et al., 2021).

Total antioxidant power (TAP) can be used to assess the cumulative effects of the antioxidants present in the matrices analysed (Hemmendinger et al., 2023; Malinowska et al., 2022). Studies in animal models showed a significant increase in TAP levels after 24 h following exposure to PET, and polyethylene (PE) (Xiao et al., 2021).

Inflammation is one of the main outcomes investigated following MNP exposure; hence, inflammatory biomarkers deserve a great importance for biomonitoring purposes. A key role is played by cytokines, protein-based chemical mediators produced by a broad range of cells, including the immune cells recruited at the inflammation site (Bianchi et al., 2025). Various cytokines such as interleukins 1-beta (IL-1 β), IL-6, IL-8 and IL-10, and Tumour Necrosis Factor alpha - TNF- α and Interferon-gamma - INF- γ have been used as biomarkers of inflammation in cell lines and animal studies. A recent review (Panizzolo et al., 2023) reported significant increases in cytokine levels in in vitro and in vivo models after exposure to PE and PS (5.0 to 0.1 μm).

TNF- α and IL-1 β are indicative of the recruitment and activation of pro-inflammatory Th1-lymphocytes; while interleukins 17 (IL-17) and IL-4 indicate macrophage recruitment and, via Th2-lymphocytes, they

favour the maturation of B-lymphocytes into plasma cells producing E-type antibodies (IgE). IL-10, on the other hand, is an immunosuppressive cytokine, which reduces the recruitment of effector T-lymphocytes and counteracts the effects of TNF- α and IL-1 β . Besides, IL-17 can mediate protective innate immunity to pathogens or contribute to the pathogenesis of inflammatory diseases (Zenobia and Hajishengallis, 2015).

3.2.2. Biomarkers of lung epithelial permeability, fibrosis and endothelial dysfunction

Although MPs have been found in human lung tissue and sputum, there is little information on the mechanisms by which MNPs affect lung integrity (Lu et al., 2022).

Surfactant proteins such as SP-A and SP-D are involved in the regulation of pulmonary host defence and inflammation and can be detectable in blood or in lung fluids (Tomonaga et al., 2021). A decrease in SP-D can be interpreted as the result of cell injury and/or decrease in number of type II alveolar epithelial cells caused by foreign particles. Moreover, clinical studies have suggested that the Krebs von den Lungen 6 (KL-6) glycoprotein determined in blood is a potential biomarker of interstitial lung disease (d'Alessandro et al., 2020). Recent occupational studies have also suggested that SP-D and KL-6 measured in EBC can be used as potential biomarkers of interstitial lung disease (Bergamaschi et al., 2022; Hemmendinger et al., 2023).

Plasminogen activator inhibitor-1 (PAI-1) – also known as endothelial plasminogen activator inhibitor – is a protein mainly produced by the endothelium (cells lining blood vessels), that in humans is encoded by the SERPINE1 gene. Elevated PAI-1 is a recognized risk factor for thrombosis and atherosclerosis (Dawson and Henney, 1992). Besides, vascular cell adhesion molecule-1 (VCAM-1) can also be implicated in cardiovascular outcomes associated with MNPs (Sivakumar et al., 2025). Although only pilot (unpublished) studies have determined the circulating levels of these biomarkers in workers exposed to MNP, finding of MPs in blood, thrombi, and atherosclerotic plaques, has raised concerns on its relationship with negative cardiovascular outcomes (Sivakumar et al., 2025).

3.2.3. Biomarkers of genotoxicity

Biomarkers of genotoxicity are classical effect biomarkers that have been extensively used in HBM studies as they are considered to be predictive for cancer risk (Rodríguez-Carrillo et al., 2023; Ladeira, 2024; Zare Jeddi et al., 2021). Most widely used matrices for early genetic effects are blood, nasal and buccal cells. The cytokinesis-block micronucleus (CBMN) assay in peripheral blood lymphocytes is the most used method to assess chromosome damage in biomonitoring studies (Bolognesi and Fenech, 2019; Ladeira, 2024). Moreover, flow-cytometric analysis of micronuclei (MN) in reticulocytes (MNRET) is a sensitive high-throughput method (Abramsson-Zetterberg, 2000) to detect systemic effects, too. On the other hand, the evaluation of MN in buccal cells provides a complementary method for assessing chromosome damage at the site of contact (i.e., ingested or inhaled MNPLs) (Malacarne et al., 2022; Pinto et al., 2025). In addition, assessment of DNA strand breaks through the comet assay in mononuclear blood cells, which does not require cell division, is currently recognized as one of the most sensitive biomarkers for detecting initial, still repairable, DNA damage (Živković et al., 2024).

Although there is not available literature on genotoxic effects assessed in MNP exposed human populations, recent in vivo studies have reported significantly increased DNA damage (evaluated by the comet assay) in rat peripheral blood cells (Farag et al., 2023) and mouse spleen cells (Nikolic et al., 2022) orally administrated with PE (4–6 μ m) for 35 d, and fluorescent PS (40 & 200 nm) for 5 w, respectively. DNA damage has also been reported in different cell lines after exposure to MNPs, mainly PS. The outcomes seem to be cell-line specific, depending on the differential uptake of particles and generation of ROS (Domenech et al., 2023). Similarly, increased MN levels were induced by PE (10–45 μ m) in

human blood lymphocytes (Çobanoğlu et al., 2021), which are the target cells assessed in the CBMN assay in humans. Hence, both types of genotoxic biomarkers seem to be adequate for HBM studies with MNPs.

3.3. Towards more specific biomarkers of micro- and nanoplastic exposure

3.3.1. Metabolomics

Metabolomics is a powerful tool for elucidating the biological effects of MNPs by analysing metabolic profile changes. It can reveal toxicity mechanisms, identify metabolite alterations, and help discover biomarkers of MNP exposure (Wu et al., 2023b). Although widely used in other fields, its application in MNP exposure studies remains limited to animal models. For example, PS MPs induced neurochemical dysregulation in zebrafish embryos altering the cholinergic agents, dopaminergic and GABAergic neurotransmission systems critical for normal brain function (Jeong et al., 2022). PS MPs also disrupt cardiac function through oxidative stress and metabolic unbalance in fish embryos (Dimitriadis et al., 2021), induced hepatic lipid accumulations (Chen et al., 2025) and impaired placental metabolism (Aghaei et al., 2022).

Despite the detection of MPs in various human tissues and body fluids, few studies have examined their metabolomic impacts in humans. Only one study assessed urine metabolites in workers potentially exposed to MNPs, revealing alterations in amino acid and Nicotinamide Adenine Dinucleotide (NAD) metabolisms (De Rosa et al., 2025). Given its non-invasive nature, urine metabolomics is suitable for assessing exposure-related changes. Future research should apply metabolomics to high-risk populations to better understand MNP-induced health effects.

3.3.2. Biomarkers of gut dysbiosis

The gut microbiota is a complex and dynamic community of microorganisms inhabiting the gastrointestinal tract, playing roles in digestion, vitamin synthesis, immune modulation, and maintaining intestinal integrity (Den Besten et al., 2013; Hou et al., 2022; Jandhyala et al., 2015). Dysbiosis, an imbalance in microbial composition, has been linked to a range of conditions, from metabolic disorders and inflammatory conditions to even neuropsychiatric disorders via the gut-brain axis (Weiss and Hennet, 2017).

Microbial biomarkers of gut dysbiosis focus on shifts in microbiota composition and diversity. Key metrics include alpha diversity (within-sample richness and evenness) and beta diversity (between-sample differences), both of which are altered in conditions like obesity and inflammatory bowel disease (Rodríguez et al., 2025; Zwezerijnen-Jiwa et al., 2023).

A commonly studied microbial biomarker is the Firmicutes/Bacteroidetes (F/B) ratio. These two dominant phyla are essential for producing short-chain fatty acids, which support gut health. In fact, an elevated F/B ratio has been associated with obesity, type 2 diabetes, and cardiovascular disease (Magne et al., 2020). Several studies have explored the impact of MNPLs on gut microbiota using animals (Gałęcka et al., 2025; Lu et al., 2018; Rocabert et al., 2025; Zhu et al., 2024). In addition, artificially digested PET microparticles have been reported to influence microbial communities in human gut microbiota cultures through in vitro exposure systems (Tamargo et al., 2022). Nevertheless, to the best of our knowledge, such dysbiosis has not yet been employed as a biomarker of MNP exposure in humans.

3.3.3. Circulating miRNAs as candidate biomarkers of MNP exposure

MicroRNAs (miRNAs) are a class of small (~22 nucleotides) non-coding RNAs that play a critical role in post-transcriptional regulation of gene expression (Bartel, 2004). Although miRNAs primarily function within cells, they can also be actively released into the extracellular space and detectable in various biofluids, including plasma (Arroyo et al., 2011; Chen et al., 2012). miRNA expression is frequently dysregulated in human diseases and can serve as a sensitive indicator of

environmental exposures (Condrat et al., 2020; Letelier et al., 2023). Owing to their remarkable stability in biofluids, these expression changes highlight the potential of miRNAs as reliable and non-invasive clinical biomarkers (Sandau et al., 2024), but no information related to MNPs exposure is available.

In this line, experiments have been conducted within CUSP using ex vivo spiked blood samples from healthy donors to identify circulating miRNAs through small RNA sequencing (RNA-seq) that could work as biomarkers of MNP exposure (Arribas Arranz et al., 2025). The subsequent phase should shift to quantify the expression levels of the identified circulating miRNAs in exposed human populations. Technically, this will require collecting peripheral blood from donors, followed by plasma separation, miRNA extraction, and quantification via quantitative polymerase chain reaction (qPCR).

3.3.4. Deregulated gene expression in white blood cells

Gene expression biomarkers are molecular indicators identified through high-throughput transcriptomic analyses, providing insights into cellular or tissue states. The development of such biomarkers generally follows a four-step pipeline: the collection of high-quality samples, large-scale transcriptomic analysis, computational identification of candidate biomarkers, and validation in independent cohorts (Stransky and de Souza, 2013; Winiarska et al., 2024).

In the context of environmental health, gene expression signatures associated with MNP exposure have been identified using ex vivo spiked blood samples from healthy donors, and being detected through cutting-edge scRNA-seq (Arribas Arranz et al., 2025). The subsequent phase should transition to quantify the newly defined gene expression signature in exposed donors. From a technical perspective, this process will necessitate the collection of peripheral blood from donors, followed by the extraction of white blood cells, and subsequent quantification using qPCR.

4. Individual risk factors and co-exposures

One important issue regarding biomarkers of early biological effects is the potential influence that confounding and mediating factors, related to socio-demographic and lifestyle factors, may have on them. Most effect biomarkers are not specific for one type of exposure. Hence, controlling the potential influence of exogenous or endogenous factors that may affect them is crucial for a correct interpretation of the results. For instance, gender, age, and alcohol consumption are well-known confounding variables affecting MN frequencies (Fenech et al., 2011; Tavares et al., 2022). A significant effect of the country of origin on this biomarker was also reported within the HBM4EU project (Tavares et al., 2022). The observed geographical variability was suggested to be related to i.e., dietary habits, which are expected to have an important influence when assessing the effects of MNP exposure as the presence of plastic particles have been reported in very different types of food and drinks (Ramsperger et al., 2023).

In order to reduce the likelihood of biased result interpretation when associating external exposure with individuals' biomarker levels, potentially confounding variables should be assessed in all volunteers. This will consist in documenting several life habit-, health- and occupational-related factors through answering a detailed questionnaire (as the one included in Supplementary material S2). The corresponding control groups should be chosen to match with the exposed groups at least in terms of country, gender, age and smoking status.

Finally, as EBC collection can be affected by respiratory health status, we recommend assessing participants' respiratory function through pulmonary function tests according to the recommendations of the American Thoracic Society and European Respiratory Society (Stanojevic et al., 2022).

5. A methodological approach for human biomonitoring campaigns

The procedures proposed in the following sub-sections basically follow the stepwise approach described in the OECD guidance document for occupational studies (Hopf et al., 2024; OECD, 2022). Nevertheless, the procedures are also applicable to other target groups and have been focused on the assessment of MNP exposure through the inhalation route. An overview of the proposed HBM approach is shown in Fig. 4.

An example of the detailed preparatory procedures and steps of a field campaign is provided in Supplementary material S3.

5.1. Study design and target population

As MNPs are ubiquitous environmental pollutants, the study design and approached target populations can vary according to the aim of the study, as well as the specificity and sensitivity of biomarkers, able to detect subtle changes linked to such exposure. For example, workers in plastic fabric manufacturing are likely to experience higher levels of MNP exposure as compared to the general population (Facciola et al., 2021; Murashov et al., 2021; Prata, 2018). However, any occupational exposure may overlap with the environmental background, making it challenging to attribute any observed effects specifically to MNPs rather than to other co-occurring pollutants (Boccia et al., 2024). Moreover, certain population groups are likely more susceptible to the potential health hazards of MNPs; i.e., pregnant women and children, due to intense physiological changes they undergo during pregnancy, growth and development (Amran et al., 2022; Jinesh and Aditi, 2025).

The possible population recruitment strategies that could be followed are detailed in Supplementary Material S3. Most CUSP studies addressing occupational populations used a cross-sectorial design that, although providing insights into the potential association between MNP exposure and some health effects, cannot lead to firm conclusions about the causal relationships over time (Capili, 2021). Furthermore, due to the problems for recruiting companies and volunteers, sample sizes were low. To solve these problems, multicenter prospective studies could be carried out instead of multiple cross-sectional studies, to ensure the assessment of long-term effects in cohorts with a defined MNP exposure, as it has been successfully implemented in the case of nanotechnology workers (Guseva Canu et al., 2023). In any case, to ensure robustness and generalizability, sample size calculations should be conducted for each study during the planning phase. An example of such type of calculations can be found in the Supplementary material S4.

5.2. Human subjects and data protection

Prior to enrolment in any biomonitoring study, participants will be thoroughly informed about the project, its objectives, and their rights. Written informed consent will subsequently be acquired from volunteers, workers and parents/caregivers of paediatric participants (Hopf et al., 2024). Processing of information will be based on the principles of correctness, lawfulness and transparency, and the protection of confidentiality and rights pursuant EU's General Data Protection Regulation (GDPR). It is recommended to involve a data protection officer and disclose his/her contact details to the research participants.

All data, in accordance with current legislation, will be processed in an aggregate and pseudo-anonymous way, so that individual subjects cannot be identified in any way. Participant's and company's confidentiality is also strictly guaranteed in the frame of any result publication in reports and scientific publications. Sharing of human data under FAIR principles (findability, accessibility, interoperability, and reusability) should also comply with the GDPR regulation (Zare Jeddi et al., 2025).

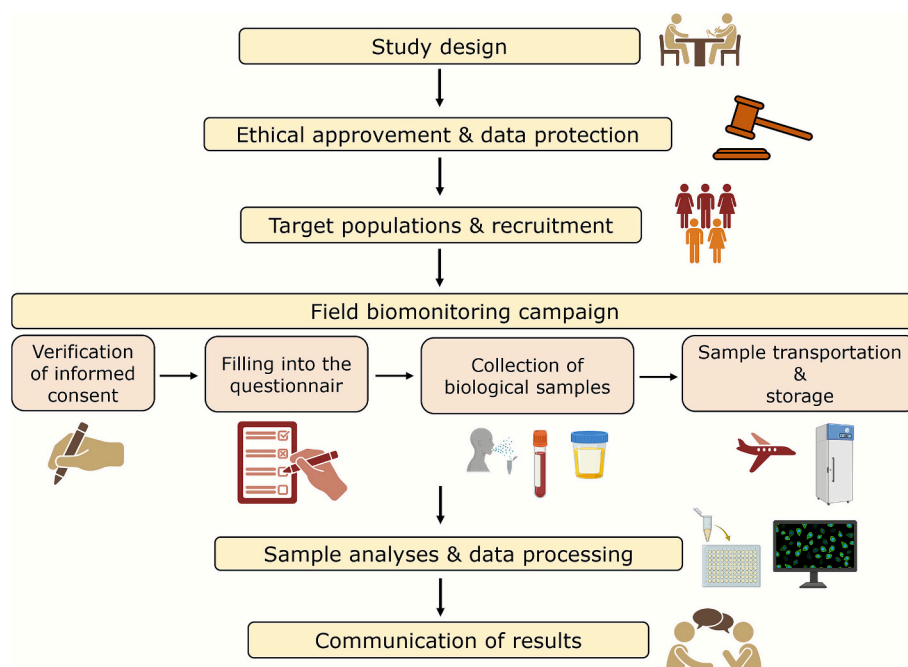


Fig. 4. Steps of the human biomonitoring approach proposed by the CUSP partners for assessing micro- and nanoplastic exposure in human populations. *Partly created with BioRender™.*

5.3. Collection of human samples and data analysis

Sampling of biological matrices also require a standardized approach and detailed procedures, which are described in Supplementary material S3. In addition, Supplementary material S5 provides a detailed description of the sample analyses performed for the biomarkers of effects listed in Table 1. Many biomarkers can suffer from temperature changes and, considering that many activities are not performed in equipped laboratories but at company's premises, this should be taken into account. Collected samples should be shipped and stored as soon as possible.

Selection of matrices to be sampled and tests to be performed will vary according to the aim of the study and the target population (i.e., occupational, susceptible groups, etc). In the case of occupational studies, biological sample collection must take place in a clean and separate room, to avoid as much as possible sample contamination from air or surface pollutants. In addition, all described procedures take place during working hours, and thus are not subject to any compensation or payments given to worker participants.

Despite the increasing number of studies reporting the presence of MNPs in human samples, only a few of them also investigated the associated health effects (Zuri et al., 2023). Whenever possible, both exposure and effect biomarkers should be assessed in the same study and from the same human samples to allow establishing a direct relationship between individuals' exposure levels and specific biological outcomes. Furthermore, environmental biomonitoring (i.e., air exposure assessment in occupational settings) should also be integrated with HBM studies to better understand exposure sources and concentrations by using toxicokinetics models (Ladeira and Viegas, 2016).

5.4. Results restitution to participants

Aggregated results (at group level) from the exposure and HBM campaigns are presented to each company or participants' group. Individual data of exposure biomarkers can be offered to the volunteers of the study. On the other hand, data on effect biomarkers, which are not diagnostic tests, but biological indicators of early and reversible effect, sensitive but not very specific, cannot only be offered as aggregated

results. In the case of occupational studies, recommendations and advice are provided to improve practices if required, and to improve occupational health and safety policies. These restitutions rely on European regulations, standardization and best practices. The advice should be given with their hierarchical weighting according to the nine prevention principles (International Labour Office, 2023).

6. Challenges of performing human biomonitoring studies with micro- and nanoplastics

As shown in the previous sections, HBM studies with MNPs share common challenges with other environmental pollutants as well as with nanomaterials. The ubiquitous nature of MNP contamination makes a true "unexposed" population unrealistic, which leads to the need of larger populations sizes with similar and contrasting exposures. However, one critical challenge faced by all the CUSP projects has been the problems for recruiting companies and volunteers. As a result, the size of the groups assessed till now was smaller than initially foreseen. Underrepresentation of either exposed or control groups due to lack of willingness to participate or donate biological specimens may hamper the generalizability of the results. International studies performed with multicenter prospective cohorts, as the one implemented with workers exposed to nanomaterials (Guseva Canu et al., 2023), could help reaching appropriate sample sizes at the same time that supporting the assessment of causal relationships over time. To achieve this goal, all relevant stakeholders related to the HBM studies should be involved from the early steps of study design to promote awareness of the potential MNP risks.

The potential toxic effects exerted by MNPs depend not only on the polymer composition but also on other physico-chemical properties (i.e., size, shape or surface chemical) (Jahedi et al., 2025). Hence, a thorough characterization of MNPs in human samples is needed both to provide accurate estimation of the internal doses, and to unequivocally identify the nature of the MNP exposure. Although analytical techniques have made possible the measurement of MNPs in biological and environmental media, the lack of harmonized and validated methods still represents an issue, especially for NPs. Interlaboratory comparisons, as the one recently published under the CUSP umbrella to identify MPs in a

water-soluble matrix (Ciornii et al., 2025), and an integrated approach that incorporates various state-of-the-art methods are urgently needed to set up standardized protocols for accurate measurements in human matrices. Moreover, the available volume of sample per collection (Fig. 2), especially in the case of EBC (1–2 mL) and blood samples (15–20 mL, even less in children), affects the sensitivity of MNP characterization methods in these samples.

An additional challenge linked to MNP assessment is the fact that plastic contamination during the collection of biological samples is difficult to avoid as most of the devices and materials used are plastic-made. For instance, flowing breath through a plastic tube when collecting EBC could favour leaching of plastic fragments. Furthermore, several effects biomarkers require collecting samples under aseptic conditions (i.e., assessment of MN in peripheral blood lymphocytes) using plastic-made tubes, for which non-plastic alternatives do not exist or are difficult to apply in field campaigns. Therefore, the plastic materials used in such devices or tubes should be carefully recorded (i.e., for EBC collection with TURBO-DECCS™, high density medical grade PP homopolymer is involved) and caution should be taken when interpreting results regarding these polymer types.

The approach presented here encourages the integration of external exposure assessment and HBM studies, where both reliable and sensitive exposure and effect biomarkers should be assessed at the same time from the same human samples. This implies a careful choice of the target population, samples to be taken and assessed biomarkers based on the goal of the study. Current available methods, especially those detecting plastic particles in human matrices as well as some well-established biomarkers of biological effects, require manual scoring, making the analyses extremely time-consuming. Furthermore, classical validated biomarkers of effects should be complemented with more specific biomarkers of MNP effects, which still need further standardization efforts. Therefore, standardized and high-throughput methods are urgently needed for regulatory biomonitoring of MNP.

In conclusion, although the importance of HBM as an approach to manage MNP hazards has been recognized and considered as a research priority for future research in MNP exposure, (Lozano-Paniagua, 2024; Ruggieri et al., 2025), the available human data are insufficient to provide a comprehensive understanding of the potential health risks associated with MNP exposures. The present paper presents an integrated and practical HBM approach that has been developed based on the studies carried out by the EU CUSP members. Despite the progress achieved, several challenges should still be overcome in future studies. These include the need of working with international multicenter prospective cohorts, whose members should be deeply involved in the design and execution of the study, allowing proper sample sizes and the assessment of causal relationships. Interlaboratory comparisons are required to standardize and validate protocols for both characterizing MNPs in human samples as well as assessing different effect biomarkers, resulting in robust protocols to obtain reliable data. Furthermore, high-throughput methods should be prioritized to speed up the generation of an information that is urgently needed to address this emerging environmental threat.

CRediT authorship contribution statement

Julia Catalán: Writing – original draft, Validation, Supervision, Conceptualization. **Anani K. Afanou:** Writing – original draft, Methodology. **Jéssica Arribas Arranz:** Writing – original draft. **Arantxa Ballesteros Ríaza:** Writing – original draft. **Ivana Banić:** Writing – original draft, Validation. **Hubert Dirven:** Writing – original draft, Validation, Methodology. **Irina Estrela-Lopis:** Writing – original draft, Validation. **Alba Hernández:** Writing – original draft, Validation. **Tomi Kanerva:** Writing – original draft, Validation, Supervision, Methodology. **Christian Laforsch:** Validation, Supervision. **Esther Lenssen:** Validation, Conceptualization. **Martin G.J. Löder:** Writing – original draft, Validation, Supervision. **Susana Pastor:** Writing – original draft,

Validation, Conceptualization. **Hanna Pulli:** Validation. **Anja F.R.M. Ramsperger:** Writing – original draft, Visualization, Validation. **Igor Snapkow:** Writing – original draft, Validation, Conceptualization. **Mirjana Turkalj:** Writing – original draft, Validation, Conceptualization. **Verónica Vela:** Validation. **Tom Venus:** Validation, Supervision. **Runyu Zou:** Writing – original draft, Validation, Conceptualization. **Enrico Bergamaschi:** Writing – original draft, Validation, Supervision, Conceptualization.

Declaration of competing interest

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.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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