Microplastics and Nanoplastics

REVIEW

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Impacts of micro- and nanoplastics on early-life health: a roadmap towards risk assessment

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Abstract

Micro- and nanoplastics (MNPs) are ubiquitous environmental pollutants representing a concern for human health. MNPs have been detected in human placentas, indicating that during pregnancy maternal exposure may lead to placental transfer and foetal exposure, with potential for adverse effects on early-life development. However, a comprehensive risk assessment (RA) framework, specific to early-life is lacking. Here, we propose a novel roadmap to assist the development of an early-life health RA of MNPs. This roadmap is designed based on established chemical, mixture, particle, and MNP assessment strategies aligned with standard RA components (problem formulation, hazard identification, hazard characterisation, exposure assessment, risk characterisation). We systematically work through these stages to identify what is needed to progress a RA for the early-life impacts of MNPs, including what information is missing, and what may be used in the interim. While challenges such as complex physicochemical properties of MNPs, limited toxicity data at relevant exposure levels, and uncertainties related to characterising complex exposures have been described elsewhere, our work discusses how these challenges specifically impact early-life stages such as the significance of MNP presence in biological samples and factors influencing bioaccumulation and placental transfer. Additionally, we introduce the development of new technology readiness levels for methods used in the detection of MNPs in complex matrices. Importantly, this review integrates a broad scope of relevant information into one comprehensive document, providing a unified resource. We highlight specific requirements and areas for targeted research, including the development of dose-response relationships specific to early-life stages and novel strategies for assessing bioaccumulation and placental transfer of MNPs. By addressing these gaps, our roadmap aims to advance the development of a robust framework, ultimately enhancing the understanding and mitigation of risks associated with early-life exposure to MNPs.

Keywords Microplastics, Nanoplastics, Human-health, Pregnancy, Risk-assessment, Early-life, Placenta, Hazard, Exposure, Reproductive toxicity

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Introduction

Micro- and nanoplastics (MNPs) are widespread environmental pollutants to which humans are unavoidably exposed through air, food and water [1]. Microplastics (MPs) can be defined as particles smaller than 5 mm and nanoplastics (NPs) less than 1 μm [2, 3], and can be further categorised as primary MNPs, purposefully manufactured, and secondary which result from environmental degradation of larger plastic debris [1, 4]. Although research on the effects of MNPs on human health is still in its infancy, there is emerging evidence that exposure to MNPs may pose a health risk [1, 5, 6]. Increasingly, there are concerns that maternal exposure to MNPs during pregnancy results in foetal exposure [2, 3], which holds significance as the developing foetus and children exhibit greater vulnerability than adults due to rapid growth and development [7]. MNPs have been detected in the human placenta [8–12], and in vivo and in vitro studies indicate that exposures may lead to placental dysfunction and foetal damage [2, 3, 13].

There has been extensive development in the field of human-health risk assessment (RA) of MNPs, including recent publications from the World Health Organization (WHO) addressing implications of dietary and inhalation exposure of humans to MNPs [1], as well as the identification of four clear paradigms that need to be addressed for adequate assessment of human health risks of MNPs [2]. However, there is an urgent need to specifically assess the potential health risks of MNP exposure for the developing foetus and resulting child (collectively referred to from here-on to as early-life), as it is believed that the lifelong health of a person can be critically affected through *in utero* exposures [14]. However due to limited hazard and exposure data, the impact of MNP exposure on early-life remain largely unexplored. We build upon the existing work on MNP RA to provide a roadmap to support development of a comprehensive RA framework specifically addressing early-life health, including outlining the factors which need to be considered for early-life RA and identifying knowledge gaps that need to be addressed. We have focused on reproductive toxicity, in particular developmental effects, of MNPs during early-life stages, and incorporated a structured methodological approach that systematically addresses all stages of a traditional RA, identifying specific research areas crucial for closing existing knowledge gaps. For pragmatic classification purposes and focus on early-life health, the development of the RA roadmap primarily uses examples of developmental toxicity. This is defined as adverse effects induced during pregnancy that may manifest, for example, as structural abnormalities, altered growth, and functional impairments in the developing foetus or resulting child [15]. Adverse impacts may be observed at cellular and molecular levels, and a comprehensive RA should try to integrate clinical, molecular, and inflammatory markers to evaluate potential effects on early-life health. Our approach builds upon established strategies used in RA for chemicals, plastics, mixtures, and particles in general, and MNPs specifically. The document is organised into sections covering the key components involved in developing the framework. The methods section outlines the development process for the roadmap; we then methodically work through the recognised stages of RA: problem formulation, hazard identification, hazard characterisation, exposure assessment and risk characterisation. Through the development of a roadmap to achieve a RA we outline key research areas crucial for closing knowledge gaps and ultimately establish a robust framework for the RA of MNPs affecting early-life health.

Methods

The development of the roadmap was facilitated by an evidence mapping exercise of the existing RA approaches to MNPs and included a literature review to identify the knowledge regarding exposure and hazards associated with MNPs, identify knowledge gaps and outline key research areas crucial for addressing and closing these. Existing standards and guidance for MNP-specific RA approaches were identified and screened. Based on this screening, missing elements required for development of the roadmap were identified. To fill these gaps general RA approaches for chemicals, mixtures, and nanomaterials (NMs) were identified and assessed for their potential to be adopted or adapted for MNPs. Key resources used can be found in Supplementary Materials (SM) Table S1.1.

PubMed [16] and Web of Science [17] were queried to identify the potentially relevant peer-reviewed literature. We searched review articles and primary research papers that identified MNP hazards and evidence of maternal exposure, respectively. No publishing date limit was used, and the searches were originally conducted between January and March 2022 to allow drafting of the RA strategy, with further supporting literature subsequently obtained during strategy development; an updated search was also performed in May 2024 to ensure most recent advances were accounted for. The search terms used are detailed in SM Tables S1.2-1.5. RA methods require reasonably robust datasets on exposure routes and concentrations to characterise risk. However, due to knowledge gaps associated with MNPs, current RAs provide insufficient guidance to inform exposure characterisation of MNPs at this stage. To identify information needed for exposure assessments of MNPs, an additional literature screening exercise was undertaken focused on identifying studies reporting evidence of MNPs in biological systems, factors influencing MNP exposure, and any useful data for exposure quantification. The search terms used for this are described in the SM.

Approach: a roadmap towards risk assessment

The methods undertaken enabled identification of data gaps regarding exposure and hazards associated with MNPs. This knowledge gap analysis then allowed formulation of a proposed framework for a RA strategy, extensively informed by the World Health Organisation (WHO) "Human Health Risk Assessment Toolkit: Chemical Hazards" [18] and the International Council of Chemical Associations (ICCA) "Guidance on Chemical Risk Assessment" [19]. The literature review provided contextual information to inform the subsequent sections. The proposed adaptable framework accounts for current data deficiencies while presenting a roadmap for advancing the MNP risk analysis as new evidence emerges.

Problem formulation

Problem formulation, as outlined by the WHO [18], defines the objectives, approach and scope of the HHRA, including the risk management goals and acceptable uncertainty that will drive the analysis (Fig. 1).

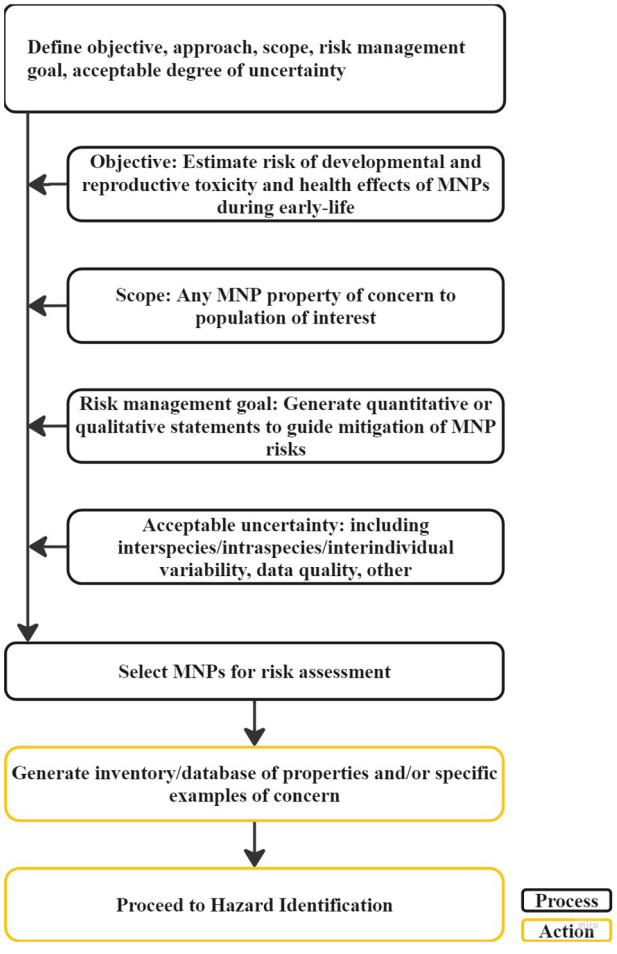

Fig. 1 Flowchart of Problem Formulation in the framework for RA of MNPs

Risk assessment objectives

The HHRA aims to estimate the risk of potential developmental and reproductive toxicity and health effects of MNPs during early-life.

Statement of the problem

MNPs have distinct properties when compared to chemicals, including morphology, small particle size, large surface area, and potential to act as vectors for microorganisms and environmental pollutants [20]. MNPs can also contain a variety of chemicals (see Sect. 3.2.1.3) and weathering processes (e.g., ultraviolet irradiation, mechanical or thermal stress) can further alter the properties and composition of MNPs over time [22].

This results in a wide array of potentially hazardous properties that should be analysed in RAs, and those with an early-life scope require exposure data specific to the placenta and developing foetus, rather than comprehensive environmental presence. However, only limited information is available due to ethical and practical constraints on obtaining such samples [23]. Additionally required, but currently insufficient data, are exposure routes, toxicokinetics, and full toxicity profiles for MNPs. This knowledge gap, compounded by the distinct and diverse properties of MNPs creates difficulties in evaluating potential risks. Potentially hazardous properties include the polymer type, additives, and non-intentionally added substances (NIAS) (e.g., impurities, by-products, and breakdown products), as well as particle-specific properties including size, morphology, surface charge, and hydrophobicity [5, 24, 25]. The absorption of unknown environmental chemicals, such as heavy metals, antibiotics, and persistent organic pollutants, pose a hazard [5, 26], which is heightened by an understanding that concomitant exposure of MNPs with adsorbed heavy metals via the gastrointestinal track (GIT), for example, can increase bioaccumulation of these heavy metals [27]. This issue is further complicated by the characteristics of microplastics, which influence their bioaccumulation and effects, and is highlighted as an area requiring improved research focus [28]. Additional factors such as weathering, protein coronas and microbial biofilms can further influence hazards [13, 24, 29, 30]. Specific details on identified hazards are provided in Hazard Identification (Sect. 3.2).

Risk management goals

Risk management goals of an RA may include informing policymakers and the plastic value chain (including suppliers, brands, etc.) on mitigating measures to reduce exposure to MNPs from currently underappreciated sources, such as unintended generation from the routine use of plastic food contact materials [31–33]. Beyond just raising awareness of these exposure sources,

policymakers could incentivise best practices aimed at reducing MNP generation; for example, by stipulating new technical standards to minimise abrasion from regular plastics usage. These goals are informed by qualitative statements and recommendations for risk management, through to quantitative guidance based on risk estimates. Common outputs from a human health hazard assessment are a Derived No Effect Level (DNEL) or a Derived Minimal Effect Level (DMEL) [34], which are then compared to actual or estimated human exposure levels. The quotient of effect level-to-exposure level, also known as risk characterisation ratio (RCR), provides quantitative information on risk, with values larger than 1 indicating the Margin of Safety, and values below 1, where exposures exceed effect levels, showing risk and the need for reducing exposure. However, in cases where a DNEL/DMEL cannot be established, a qualitative approach may be adopted, and risk characterisation is achieved through justification rather than calculating an RCR. A thorough qualitative assessment should determine the conditions necessary for the safe utilisation of MNPs by employing risk management measures (RMMs) that are suitable and proportional. A Weight of Evidence (WoE) approach [35] should also be considered, when multiple data sources of varying quality and related scientific uncertainty are available (see 3.5.1).

A quantitative approach is preferred for MNP RA; however, dose-response toxicity data are generally not available, and robust quantitative approaches typically require toxicity testing across multiple doses. This data scarcity necessitates the initial adoption of a qualitative approach for a MNP RA. In the future, as the evidence base expands, a semi-quantitative approach may be taken, where qualitative descriptors and quantitative estimates are combined to characterise risk in cases where a full quantitative assessment is not (yet) feasible. Ultimately, robust quantitative methods, utilising data from hazard and exposure assessments, should be used. A comparison of the three different approaches (qualitative, semi-quantitative, and quantitative) is provided in SM Table S2.1.

Acceptable degree of uncertainty

Existing RA approaches state [18, 19] that uncertainties and potential impacts on the derived risk should be identified and documented at each stage of the RA, aligning with the acceptable degree of uncertainty defined in the Problem Formulation [18, 36, 37]. This includes data quality uncertainties and variations in contact/exposure rates between species and populations, to ensure risk is not under or overestimated [36, 38]; concerns have already been raised regarding the quality and reliability of data available when attempts were made to assign a human health-based threshold value on MPs found in drinking water [39]. We identified two further key areas to reduce uncertainty in MNP RA: (1) aligning MNP exposures with mixture toxicity concepts, and (2) improving current methods to characterise and quantify MNPs in complex matrices.

Since MNPs contain mixtures of polymers, additives, impurities, and adsorbed pollutants [40], a mixtures RA approach is relevant. The Environmental Protection Agency (EPA) [41] identified that merging assumptions for chemical mixtures and individual chemicals can minimise uncertainty, a potentially valuable tool for MNPs. The European Food Safety Authority (EFSA) [37] suggests for RA of combined exposure to multiple chemicals using whole mixture approaches (WMAs) or component-based approaches (CBAs). In a WMA, substances are grouped as a single unit. This is useful when the composition is partially known, or characterisation is difficult. On the other hand, CBA requires defined mixtures with known exposures, making its use currently limited for MNP RA. EFSA also recommends basing the assessment on the most hazardous ingredient [37].

The Mixture Assessment Factor (MAF) approach, suggested as a tool to account for potential mixture risks during chemical RAs [42], could potentially be adapted for use in a MNP RA. The MAF is a generic factor applied to safe exposure levels determined for individual substances, lowering them to account for data gaps and additive effects between chemicals. Potential strategies for using the MAF include conducting chemical analysis to determine composition, estimating hazards through read-across or quantitative structure–activity relationships (QSARs), applying default conservative MAFs, separating by toxic modes of action, simplifying via multivariate statistics, empirically deriving MAFs from toxicity tests, and developing predictive interaction models [37, 43]. However, it is important to consider that MNPs involve complex interactions, including agonistic, additive, synergistic, and antagonistic effects. Therefore, the MAF approach may be overly simplistic to account for these nuances.

Grouping approaches to address the complex mixture of heterogeneous particles have been extensively developed and implemented in various regulatory and scientific contexts [44] . These methods are crucial for assessing risks from combined chemical exposures, particularly when components share common mechanisms or pathways. Criteria for grouping can include regulatory requirements, such as those in European pesticide regulations [44, 45], and scientific considerations like structural, physicochemical, metabolic, and toxicological factors [44] . EFSA employs a tiered approach that incorporates organ/system-level effects, phenomenological effects, modes of action (MOA), and mechanisms of action to enhance RA precision [37]. Starting with dose

addition and hazard index (HI) estimation, specific risk assessment options are applied sequentially or in parallel when unacceptable risks are identified. These include reference point index (RPI), modified RPI (mRPI), and MAF approaches, focusing on specific effects, uncertainty factors, and vulnerable populations [44]. Read-across methods can be used to predict toxicity based on structurally similar chemicals, filling data gaps and supporting comprehensive assessments [44, 45]. The implementation of these approaches is bolstered by ongoing developments in new approach methodologies (NAMs), integrated testing and assessment (IATA), and improved data sharing and RA tools, for chemicals [44, 45] and for nanomaterials [46]. A pressing issue related to uncertainty is the suitability of methods for characterising and quantifying MNPs in complex matrices. Documenting methodological advances through technology readiness levels (TRLs) could help to gain confidence in the methods used and therefore reduce uncertainty. TRLs provide a structured framework indicating a technology's maturity from initial concepts to fully operational systems, facilitating comparison and highlighting the progression and reliability of different methods [47, 48]. For example, a technique may be at high risk for false positives and false negatives, potentially leading to over- or underestimation of MNP abundance [49]. While TRLs are not a solution for all types of uncertainty, they could reduce uncertainties related to technological maturity and readiness.

A revised TRL strategy for MNP characterisation tools is proposed in Table 1, which adapts TRLs to identify, characterise, and quantify MNPs in human tissues, and a flowchart on how to assign TRLs is provided in Fig. 2; aligning with quantification in human tissues would allow for development of robust methods that provide empirical data to understand direct *in utero* exposure. However, for quantification of full maternal exposure, methods for quantification in all matrices would be required and linked to exposure modelling techniques, e.g. drinking water, air, food etc. Understanding method maturity as it relates to MNPs identification, characterisation, and quantification in human tissue supports a better understanding and reduction of data uncertainties as it allows accurate communication of method status, informs development of appropriate methods, and supports risk analysis. The specific application of the techniques can influence a TRL ranking; for example, fluorescence microscopy may be assigned a high TRL for studying model nanoparticle uptake and toxicity in exposure studies, yet have lower applicability for detecting real-world MNPs in human tissue. Similarly, electron microscopy (EM) could receive a high TRL for measuring particle size and size distribution, but a low TRL for chemical characterisation. Furthermore, some emerging analytical techniques that combine microscopy and spectroscopy to measure almost all the various physicochemical properties noted in the following section could currently receive low TRL scores, as they are not yet extensively tested in in vivo human studies, however, are promising for future development. Examples include correlated scanning electron microscopy (SEM)+Raman microscopy, or atomic force microscopy (AFM)+infrared (IR) spectroscopy (i.e. photo-induced force microscopy (PIFM)). A low TRL ranking does not imply these analytical techniques cannot properly assess MNPs, it solely indicates the level of broad development and adaptation to date. More information on promising techniques is outlined in the review by Mandemaker and Meirer [50]. The considerations presented here serve as a tool to evaluate the advancement of these promising MNP detection and microspectroscopy techniques in this relatively young research field. It is crucial to highlight that, beyond the analytical method itself, a fundamental factor is ensuring the plastic contamination-free preparation and concentration of the sample prior to MNP analysis.

Hazard identification

Hazard identification is used to determine whether exposure to a substance has the potential to cause adverse effects in a population of concern [18]. It informs subsequent hazard characterisation and exposure assessment, and the general steps are outlined in Fig. 3. If unknown, then data gathering is required to better identify the hazard. Concurrent hazard and exposure assessment are recommended due to interdependence [19]; hazard data informs toxicity drivers needing exposure evaluation, and predicted exposures influence RA priority tier allocation.

To assess early-life health risks associated with MNP exposure, the first step requires characterising properties and identifying which of these may cause adverse effects (Table 2). An additional complexity at this stage is that, as noted before, weathering of MNPs can influence all properties outlined here (polymer type excluded), as well as facilitating the release of MNP-associated chemicals [24].

Data on plastic-related chemicals from industrial, scientific, and regulatory data sources can aid hazard identification, such as PlasticMap [77], Plastic Health Map [78], databases of Chemicals associated with Plastic Packaging (CPPdb) [79, 80], European Chemicals Agency (ECHA) [81, 82], the Registry of Toxic Effects of Chemical Substances (RTECS) [83], the NORMAN network database [84], the Danish Environmental Protection Agency [85], as well as peer-reviewed literature containing in vitro and in vivo toxicity studies.

Existing RA strategies recommend a tiered approach to screen and prioritise substances for assessment (see Sect. 3.2.1) [18, 19]. The goal is to optimise screening while minimising resource usage. This information can also inform the risk characterisation stage (Sect. 3.5). For

Table 1 TRL scales for MNP methods, compared to existing European Commission (EC) considerations [47, 48, 51, 52]

TRL	Scale as used by Horizon 2020		TRL scales for MNP methods (as applied for the identification, characterisation and quantification of MNPs in human tissue)		
	Short description	Long description	Short description		Long description
1	Basic principles observed	Scientific research begins to be translated into applied research and development (R&D). Activities might include paper studies of a technology's basic properties.	Idea	Proposed hypothesis of using the method	**Proposed hypothesis of using the method**. Identification of opportunities. It is recognised that technology successfully used for other nano- or microsized material might be applied for identification, characterisation or quantification of MNPs in human tissue.
2	Technology concept formulated	Invention begins. Once basic principles observed, practical applications can be invented. Activities limited to analytic studies.	Technology concept and/or application formulated	Future R&D activities planned	**Future R&D activities planned.** Applications are speculative and may be no proof or detailed analysis to support assumptions. Examples still limited to analytic studies. Supporting information includes publications or other references that outline application being considered and provide analysis to support concept.
3	Experimental proof of concept	Active R&D is initiated. This includes analytical studies and/or laboratory studies. Activities might include components that are not yet integrated or representative.	Analytical and experimental critical function and/or characteristic proof of concept	Active R&D is initiated	**Active R&D is initiated.** Includes analytical and laboratory-scale studies to validate predictions of separate elements of the technology. Examples include components that are not yet integrated. Supporting information includes results of laboratory tests performed to measure parameters of interest and comparison to analytical predictions for critical subsystems. Work moved beyond paper phase to experimental work that verify the concept works as expected. Components of the technology are validated but not yet integrated into a complete system. Complementary modelling and simulation may be used.
4	Technology validated in lab	Basic technological components integrated to establish that they would work together. Activities include integration of "ad hoc" hardware in the laboratory.	Technology validated in laboratory	ex vivo animal studies	**Proven feasibility for ex vivo application in animals (non-human).** The separate elements of the technology can be shown to work together for application to animal tissue.
5	Technology validated in relevant environment	The basic technological components integrated for testing in a simulated environment. Activities include laboratory integration of components.	Laboratory scale, similar technology validation in simulated environment	in vivo animal studies	**Proven feasibility for in vivo application in animals (non-human)**. The separate elements of the technology can be shown to work together for application to animal tissue (including in vitro applications).
6	Technology demonstrated in relevant environment	A model or prototype that represents a near desired configuration. Activities include testing in a simulated operational environment or laboratory.	Laboratory scale, similar technology validation in relevant environment	ex vivo human studies	**Proven feasibility for ex vivo application to human tissue.** The separate elements of the technology shown to work together for application to human cells or tissues.
7	System prototype demonstration in operational environment	Prototype at planned operational level and ready for demonstration in operational environment. Activities include prototype field testing.	Demonstration in relevant environment (internal reproducibility confirmed)	in vivo human studies	**Proven feasibility for in vivo application in humans.** This includes validation and intra-group reproducibility and demonstrates that the technology is applicable for the targeted environment.
8	System complete and qualified	Technology proven to work in its final form and under expected conditions. Activities include developmental testing and evaluation of whether it will meet operational requirements.	Established as feasible in relevant environment (inter-laboratory reproducibility)	*in vivo* human studies	**Proven feasibility for *in vivo* application in humans (inter-group reproducibility).** This includes validation and inter-group reproducibility and demonstrates establishment of the technology for application in the targeted environment. Supporting material such as standard operating procedures (SOPs) of all elements and stages within elements are under-development or completed. Publications of its successful application are available.

Table 1 (continued)

TRL	Scale as used by Horizon 2020		TRL scales for MNP methods (as applied for the identification, characterisation and quantification of MNPs in human tissue)			
	Short description	Long description	Short description		Long description	
9	Actual system proven in operational environment	Actual application of the technology in its final form and under real-life conditions, such as those encountered in operational tests and evaluations. Activities include using the innovation under operational conditions.	Actual system proven in operational environment	Widespread application. Method established as gold standard.	The technology is in its final form, widely used and supporting material (e.g., SOPs) are available.	

MNPs, the proposed tier structure considers polymer, chemical, and particulate hazards, however, this can be adapted as new hazard data emerges.

Although it has been shown that detectable levels of harmful contaminants, such as BPA, can be found in up to 84% of microplastics extracted from seafood [86], it is important to note that focusing solely on contaminant exposure from MNPs does not account for other significant exposure routes unrelated to plastics. Based on consumption estimates from EFSA and assuming complete release from MPs, the contribution of MNPs to overall chemical exposure is relatively small compared to other sources [87, 88]. This could lead to incorrect assumptions that exposure to these contaminants is negligible when based only on MNP exposure. However, understanding MNP hazards associated with MNP exposure is still crucial for the regulation of plastics, as they can contribute to environmental chemical contamination, highlighting the necessity of comprehending their leaching potential and overall contribution to total exposure and associated risks.

Tier allocation of MNPs based on polymers, particles and chemicals of concern

Ideally, the proposed tiering framework would group MNPs based on known hazardous properties such as reproductive and developmental toxicity, mutagenicity, bioaccumulation, and physicochemical hazards. This framework aims to eventually assign point values to hazardous characteristics and exposure which can be used to generate a priority score, and can also be used to inform semi-quantitative RA (see Sect. 3.5.3). Points would be assigned based on the severity and relevance of each hazard. For instance, a human health hazard, such as known endocrine-disrupting activity, might be assigned more points than a hazard linked to concerns relating specifically to polymer physicochemical properties. However, due to significant data limitations and uncertainties, it is not yet feasible to develop a defined, hazard-weighted point allocation system. This system can be developed and evolve alongside future research and development. Figure 4 provides an example of how tiering may look, which will evolve with the addition of numerical values to specific hazards as more information becomes available.

To avoid overlooking potential risk, points should also be allocated to account for uncertainty and data gaps when hazard and exposure data is lacking, although currently this may allocate all MNPs to the highest tier. This highlights the need for further research to refine a point allocation system. The ICCA [19] guidance prioritisation utilises exposure potential, yet has limitations for MNPs as quantitative exposure and dose-toxicity data are lacking. While available data indicates high doses are required for toxicity [3, 89], with substantial data gaps

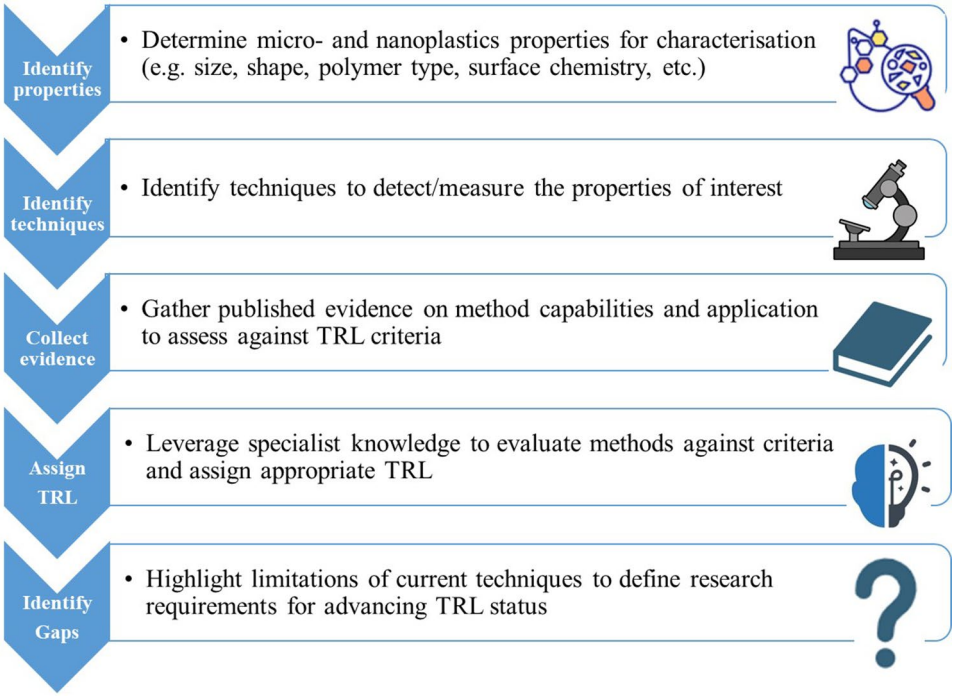

Fig. 2 Flowchart for using Technology Readiness Levels (TRLs) to assess method maturity

this cannot be assumed for all polymers. Thus, toxic effects from minimal exposures for unevaluated MNPs cannot be ruled out.

Another consideration within the tiering approach is whether detecting MNPs in the placenta should automatically assign them to a high priority tier. While placental presence indicates a potential for bioaccumulation, it may not prove to be an inherent hazard or risk without more data on toxicity and effects. Currently, research has identified polyethylene (PE), polystyrene (PS), polypropylene (PP), polyethylene terephthalate (PET) and polyvinyl chloride (PVC) in placental samples [9–12]. However, the argument could be made that MNPs of all polymer types of a certain size have the potential to cross the placental barrier, which would group all polymers into the highest tier. Therefore, a more balanced approach should also consider placental detection alongside factors such as polymer hazards, additives and particle morphology.

MNPs with the highest priority scores (≥5) based on available evidence would be allocated to Tier 1 and are the highest priority for assessment. Assignment to Tier 1 does not necessarily mean these MNPs present the absolute highest risk, as exposure levels also contribute to overall risk. However, allocating them to the top tier based on significant concern identified from the hazard evidence ensures these substances undergo a prioritised and comprehensive assessment. Certain identified hazards associated with reproductive and developmental toxicity should automatically allocate MNPs to the highest priority for RA; for example, if contains known endocrine disruptors, as maternal exposure is associated with negative impacts on foetal growth and neurological development [90]. While the level of chemical exposures specifically linked to MNPs needs to be contrasted with known exposures from other sources (as previously discussed), due to the potential for serious health impacts, the initial allocation to high priority is warranted. This priority status may be revisited if it is established that environmental exposures from other sources are already significantly high.

MNPs receiving a score of 3–4 would be allocated to Tier 2, indicating medium priority for assessment with less data requirements compared to Tier 1. Scores of 1–2 assign MNPs to Tier 3, designating low priority for assessment. A score of zero means no hazard or exposure has been identified, so RA may not currently be necessary. The tier system and MNPs should undergo periodic reviews to account for new information that may necessitate a new tier designation and ensure that the framework remains adaptive and responsive to emerging scientific data. Examples of information that can support hazard identification and tier allocation will be provided in the following sections.

Polymers as a hazard In defining hazards posed by polymer chemistry, it can be difficult to distinguish this with particle specific hazards, as polymer chemistry will affect particle properties, such as size, shape, surface chemistry etc. Conversely, there is potential for polymer-specific effects which may be relevant for a MNP RA. For exam-

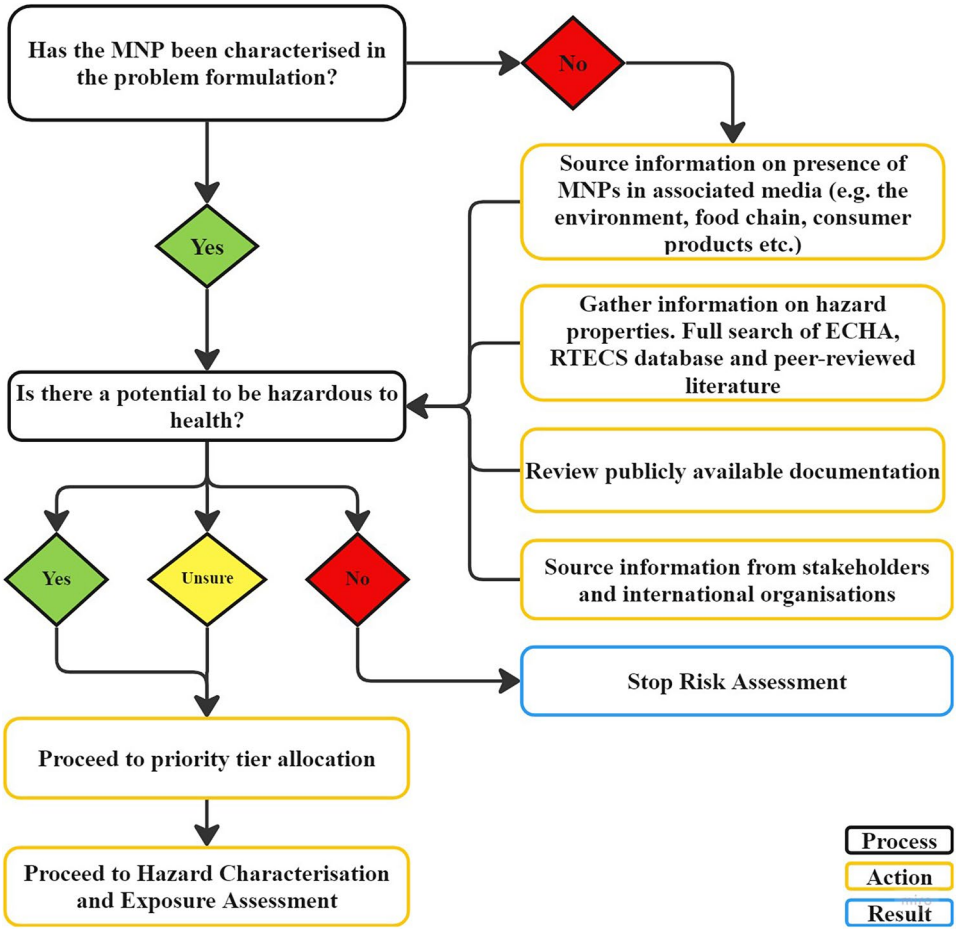

Fig. 3 Flowchart of Hazard Identification in the framework for RA of MNPs

ple, when linked to the adsorption of environmental pollutants, as different types of polymers, such as PE and PP, exhibit varying capacities to adsorb environmental pollutants, which could influence the overall toxicity of MNPs and potential health impacts following exposure [57]. Or that PVC and PU demonstrate higher toxicity in vitro compared to PET and HDPE [91]. It is suggested that there may be polymer-specific effects on placental functioning [24], and certain polymers are known to specifically release toxic monomers, such as from styrene [92–94] and from PUR, which utilises carcinogenic monomers and toxic additives, and PVC, which contains more hazardous additives compared to other plastics [95]. Therefore, there is potential to rank polymer hazards based on the presence of these toxic monomers [96]. However, MNPs in the environment, and those that humans are exposed to, have undergone various degrees of weathering and ageing. MNPs may follow different degradation pathways [97], with weathering seemingly affecting polymer composition [98]. A recent article explores the influence of environmental stressors on the degradation of plastic particles and other particles [99]. Thus, the toxicity of pure polymers is limited as a reliable indicator in hazard assessments, and an improved understanding of MNP ageing is necessary. Environmental prevalence of polymers should also be considered for tiering, for example there are certain polymers that make up the greatest proportion in sediment and the water column (marine and freshwater), such as PE, PET, PA, PP, PS, PVC, PVA and PU [91, 100], however the relevance of environmental prevalence will increase as dose-dependent toxicity data improves.

Given this, it would be pragmatic to explore existing and forthcoming mechanisms that may allow RA of these separately. For example, RA models are available for assessment of nanoparticles, albeit linked to occupational exposures [96], While for polymers, the European Commission (EC) plan to categorise polymers under REACH into 'polymers of low concern' (PLC) or 'Polymers Requiring Registration' (PRR), based on various polymer properties including molecular weight, reactive functional groups, and polymer surface activity [30]. However, only 5.5% of the estimated 200,000 polymers on the EU market will be classified as PRR under these criteria [101]. Moreover, The PRR criteria have key

Table 2 Properties of MNPs to consider during hazard identification

MNP characteristic	Considerations for hazard identification
Polymer type	MNPs are composed of various types of polymers with distinct physical and chemical properties that influence adsorption capacity [53], toxicity [54], and informs need for mixtures assessment [42].
Size	Influences toxicity [25, 55], adsorption capacity [56, 57], ability to cross biological barriers and enter maternal circulation/cross placental barrier [11, 24, 55, 58–60] and bioaccumulation [29, 61–63].
Morphology	Shape affects interaction with cells/tissues e.g. membrane crossing, cell adherence [25, 54], fragments and fibres show higher bioaccumulation [11].
Crystallinity/porosity	Can affect various properties, including density, mechanical strength, persistence to degradation, leaching and/or adsorption of contaminants [64].
Surface area/chemistry	Larger surface area increases reactivity [65] and adverse effect risk, polarity-related surface properties lead to adsorption of contaminants which may accumulate and causing toxicity by desorption processes [25, 66, 67].
Contaminants	Additives, dyes, non-intentionally added substances, impurities, reaction by-products can leach out causing toxicity [68–70]. MNPs can transport microorganisms [71–73], antibiotics, persistent organic pollutants and heavy metals [5, 26]. Protein coronas facilitate placental transfer of PS particles [74].
Swelling	Depending on polymerisation, polarity and solvents MNPs can swell to different extent resulting in the release of process chemicals as well as additives [75, 76].

gaps in assessing polymer hazards, they do not consider polymers' tendency to generate environmental MNPs, anionic and amphoteric polymers, impurities and stability additives, or high production and widespread use polymers that heavily contribute to plastic pollution. Additionally, the PRR does not address metal content or binding affinities, critical factors in determining toxicity and extent of contaminant accumulation. Fundamentally, polymers utilised in large quantities and contributing significantly to plastic pollution would not subject to registration requirements under the proposed scheme, despite their disproportionate impact. Furthermore, the exclusion of various polymer subclasses, such as polyesters and surface-active polymers, lacks sufficient justification [102].

Methods are under development that may aid polymer hazard tiering based on mechanical and physical properties. For example, the MicroPlastic Index [103] looks at theoretical particle size and energy required for MNP formation.

Particles of concern Particle characteristics such as size, shape, surface properties, and concentration can influence the toxicity of MNPs. Smaller MNPs demonstrate increased reactivity [65] and can bypass biological barriers including the placental barrier [104]. All current data on translocation is based on PS particles which indicate a size-dependent maternal-to-foetal translocation, where smaller particles are transferred more readily than bigger particles [3, 13, 24]. More information related to hazards specifically associated with size is needed, such as size-dependent toxicity data.

Shape-dependent toxicity occurs with NMs, such as carbon nanotubes and asbestos fibres [105], however, the effect of MNP shape on toxicity is understudied. Most MNP toxicity research uses PS spheres, yet fragments and fibres are reported to dominate in placental samples [11, 106]. Fibres also demonstrate increased accumulation and more severe intestinal toxicity in zebrafish models compared to spherical particles [63]. Until more information becomes available, hypothetical models, such as the high aspect ratio nanoparticle (HARN) model, which explores the shape-dependent toxicity of nanoparticles with a high ratio of length to width [107], may be applied to identify potential hazards of MNPs.

MNPs can undergo surface modifications due to biological processes, such as the attachment of microorganisms, which secrete biofilms or extracellular substances, and environmental factors, such as ultraviolet irradiation [29]. This creates uncertainty when assessing hazard, as surface properties influenced placental transport of MNPs in an ex vivo model; increased transport of carboxylated PS MNPs across the placental barrier and greater accumulation of amine modified PS MNPs in placental tissue were observed [84, 85] and serum proteins facilitated differential transplacental transport as well, preferentially transporting plain, then carboxylated, then amine modified MNPs [108, 109].

Concentration-dependent MNP toxicity has been observed in various testing models, although most use unrealistically high doses that may not correspond to real life exposures [29, 63, 110]. However, the durability and slow degradation of MNPs allows for bioaccumulation in organisms, increasing exposure over time [62]. Without definitive real-world exposure or bioaccumulation data, it is prudent to take a conservative approach and assume that higher internal concentrations in organisms, in particular in respective gastrointestinal tracts, are possible through gradual accumulation in the body.

MNP-associated chemicals of concern Plastics contain a complex mixture of intentionally added substances

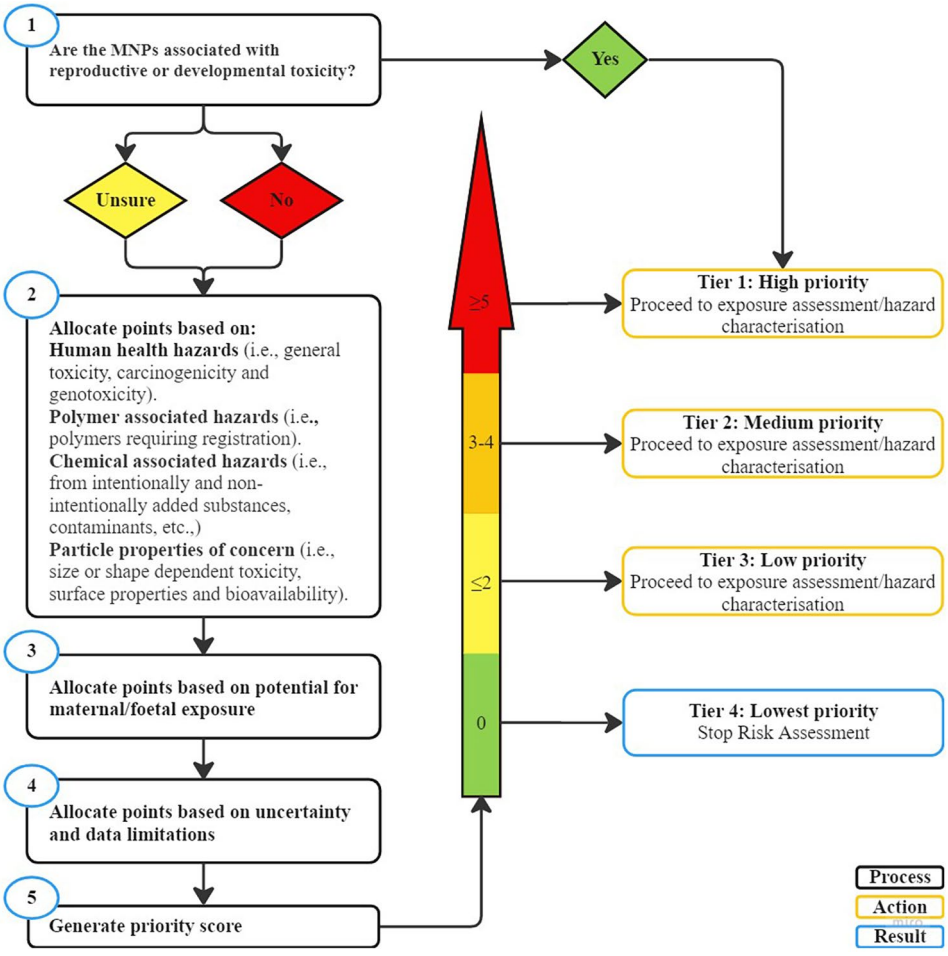

Fig. 4 Example of hazardous characteristics to consider for priority tier system

(IAS) such as plasticisers, stabilisers, antioxidants, flame-retardants, fillers, and colorants. The final product also contains non-intentionally added substances (NIAS) such as impurities, reaction by-products, and breakdown products of polymerisation and compounding [70]. Over 4,700 IASs have been identified in plastic food packaging [79] and over 13,000 chemicals are associated with plastics manufacturing worldwide [32]. Many of these chemicals are not covalently bound to the polymer matrix and can transfer into food or the environment, with up to 2,000 found to migrate or be extractable from food-contact plastics [111]. This results in continuous exposure to complex chemical mixtures [112].

A key issue is that many of these chemicals are hazardous; carcinogenic, mutagenic, toxic for development, persistent, bioaccumulative, or endocrine disrupting [113]. Over 3,200 have been identified as substances of potential concern, yet many have not been assessed for hazards, and most have received little regulatory attention [32]. Chemical profiling of MNPs has been used to assess the effects of these chemicals on gene expression in placental cells, data which can aid hazard characterisation [24]. MNPs also adsorb and accumulate contaminants when released into the environment, including Persistent Organic Pollutants (POPs), heavy metals and antibiotics, which can transfer to organisms [5, 26]. Numerous physical and chemical interactions influence contaminant sorption, which must be considered alongside environmental properties such as pH, temperature, and salinity contributing to research gaps that need to be addressed [28]. These factors add complexity to RA, as hazards of individual chemicals as well as their mixture toxicities are often unclear.

Hazard characterisation

Hazard characterisation, as outlined in chemical RAs [18, 19], describes the potential of the substance to cause adverse health outcomes following exposure. This involves linking available guidance values (see Sect. 3.4.5) to contact rates and exposure rates.

The WHO [18] define contact rates as the mass or volume of the medium in contact with the body, and exposure rate the concentration of a substance in an exposure medium multiplied by the rate at which a person inhales,

ingests or has dermal contact with that medium, divided by a representative body weight. Contact and exposure estimates require reference values to quantify risks relative to safe levels. As guidance values do not currently exist for MNPs, this limits progression to Risk Characterisation based on guidance from chemical RAs. Figure 5 outlines the information that can be utilised to progress through the RA.

In the absence of guidance values for MNPs, hazard testing is necessary to obtain dose-response data.

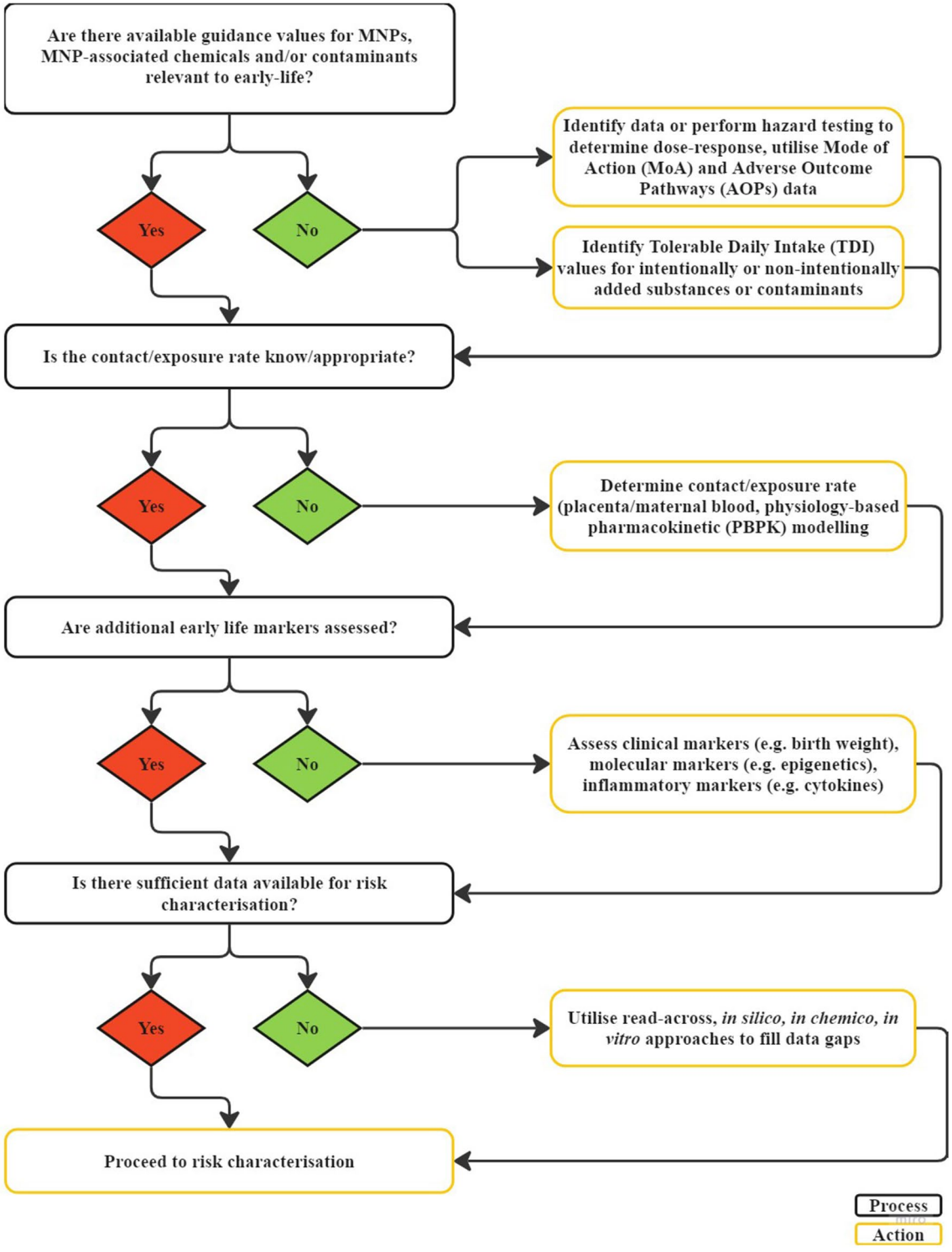

Fig. 5 Flowchart of Hazard Characterisation in the framework for RA of MNPs

Alternatively, a Mode of Action (MOA) approach could qualitatively or quantitatively assess the ability of MNPs to induce adverse effects from exposure [18, 19]. Adverse Outcome Pathways (AOPs) relevant to MNPs are being developed, for example, based on the toxicity mechanisms of chemical additives [114]. This is achieved using molecular in vivo and in vitro toxicity databases alongside deep learning models. These efforts aim to propose AOPs pertinent to MNP pollution, providing insights into the toxicity mechanisms, such as neurotoxicity, inflammation, lipid metabolism, and cancer pathways, of a broad range of environmental chemicals, such as plastic additives, helping to address previously identified research gaps [114]. However, due to the lack of data on the direct or indirect effects of MNPs on humans and limited information on molecular initiating events (MIEs) and key events required to derive an AOP or MOA for any specific type of MPs, these techniques are currently limited. For example, the physicochemical characteristics of the particle need to be considered, and it is difficult to identify a MIE and determine whether it is triggered by the biomolecular coating or polymer surface chemistry [115]. However, developments in these areas will help define MOA and allow for a better RA.

Existing guidance may be relevant for chemical additives and contaminants identified during Hazard Identification, especially for high priority substances. These values could be applicable, however must be carefully evaluated for relevance to early-life. For example, workplace exposure limits such as 8-hour time-weighted averages (TWAs), designed for healthy adult workers [116], may lack relevance for early-life RAs, which require consideration of continuous exposures and vulnerable developmental stages [117]. In contrast, Tolerable Daily Intake (TDI) values estimate the maximum safe daily exposure level over a lifetime based on toxicity data and uncertainty factors [118]. As such, TDIs like EFSA's 0.2 ng/kg bodyweight standard for Bisphenol A (BPA) could prove more useful in evaluating MNP risk [119].

For early-life effects, we must consider how guidance values translate to actual contact and exposure rates for the developing foetus. Although it may be preferential to monitor pregnant mothers (i.e., blood sampling), given this would provide a holistic picture, there would be increased uncertainty and dependence on fate modelling to estimate foetal exposure. For example, physiology-based pharmacokinetic (PBPK) modelling is a simulation technique that incorporates blood flow and tissue composition of organs to define pharmacokinetics, and is already used to predict foetal drug exposure during pregnancy [120]. Moreover, PBPK models originally developed for assessment of chemical distribution are now being adapted to MNPs [121], aiming to reduce uncertainty between external exposure and internal dosimetry, enhancing HHRA accuracy. Therefore PBPK modelling may be useful to predict foetal exposure rates to MNPs, and the potential transfer of chemicals to the foetus during pregnancy, based on the simulated maternal-foetal pharmacokinetics [81]. In comparison to maternal blood sampling, placental exposure monitoring may have both advantages and disadvantages. It can provide valuable information on bioaccumulation and placental transfer kinetics across the full pregnancy, rather than transient maternal blood levels. This can strengthen modelling of long-term foetal exposures. However, variability introduced through non-standardised sampling and storage may compromise data quality and limit reproducibility between studies [23]. Additionally, placental sampling only occurs at delivery, meaning opportunities for risk mitigation are reduced for that pregnancy, whereas maternal blood tests can be acted on during gestation. Along with barriers surrounding ethical approval and practical constraints around tissue collection [23], these factors highlight current limitations associated with placental sampling for high-volume exposure screening. Thus, maternal blood monitoring may present a more standardised and feasible approach for estimating exposure rates. An integrated strategy harnessing both methodologies could provide the most effective for hazard characterisation. To address limitations in studying reproductive effects in mammals, such as limited particle characterisation, and the use of single polymer types, standard guidelines such as OECD 421, 422, and 443 contain key points that should be included when studying reproductive effects in mammals, such as fertility and foetal effects [39]. This can enhance the reliability, relevance, and comparability of data on MNP's reproductive toxicity.

Various clinical, molecular, and inflammatory markers should also be integrated to gauge the potential impact on early-life; for example, birth weight, a fundamental clinical parameter, holds great significance in this assessment. Low birth weight (less than 2,500 g) is associated with increased neonatal mortality, developmental delays, and chronic health conditions, while high birth weight (above 4,000 g) may indicate maternal health issues like gestational diabetes, posing risks to both mother and child [122]. Beyond clinical measures, molecular markers like mitochondrial and telomere targets and epigenetic modifications can reveal genetic predispositions to conditions, such as preeclampsia, that can affect birth outcomes and future health [123]. Inflammatory markers like cytokines and C-reactive protein provide insights into maternal-foetal inflammation, which can trigger a cascade of events that may adversely affect birth outcomes. Elevated inflammatory markers may predict risks for conditions like preterm birth [124].

Structured testing strategies like the Grouping and Read-across of Nanomaterials and Nanoforms (GRACIOUS) framework for nanomaterials [46] and Organisation for Economic Cooperation and Development (OECD) guidance for chemical mixtures [36] are recommended to fill data gaps. These strategies utilise *in silico*, *in chemico*, and in vitro testing first to reduce in vivo needs and allow grouping by physicochemical properties or common mechanisms/adverse outcome pathways (AOPs). Incorporating early-life hazard assessment tools, such as in vitro and ex vivo placental models [3] facilitates implementation of a structured approach to evaluate the early-life health effects of MNPs.

Exposure assessment

The exposure assessment (Fig. 6) begins with how the population of concern (early-life) may come into contact with MNPs, the characteristics of MNPs the population is exposed to, and how much and how long exposure is likely to occur [18]. We have also considered factors associated with MNPs that may increase exposure, e.g., size of MNPs influencing barrier permeability. The following sections consider information that may inform each stage and exposure considerations are also presented in Fig. 7. When data on MNPs is missing, information from extensively studied particles may serve as a model for filling data gaps and defining relevant exposure metrics for an MNP RA.

To streamline the exposure assessment, prioritisation of data becomes crucial. While endpoints related to pregnant mothers can aid in determining contact and exposure rates for the placenta, they may not be indicative of contact and exposure rates in the developing foetus.

Maternal, placental and foetal routes of MNP exposure

Data indicates the presence of MNPs in human placenta samples [8–12], as well as in meconium and amniotic fluid [9, 10, 125], indicating that particles can pass through the placenta rather than being retained, and that foetal exposure is possible. However, other studies have failed to detect MNPs, or highlighted concerns that despite stringent controls, that sample contamination may occur [9, 126]. Overall, current evidence (see SM Table 3.1) only provides snapshot data at birth rather

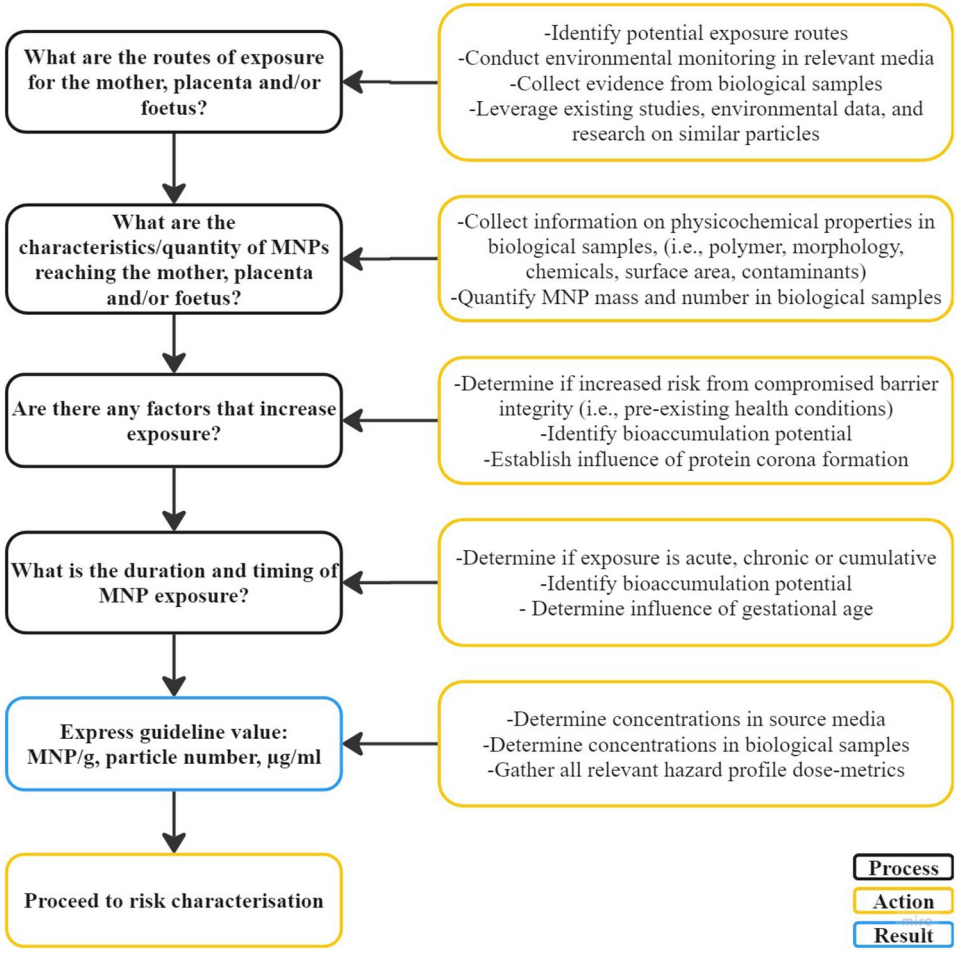

Fig. 6 Flowchart of Exposure Assessment in the framework for RA of MNPs

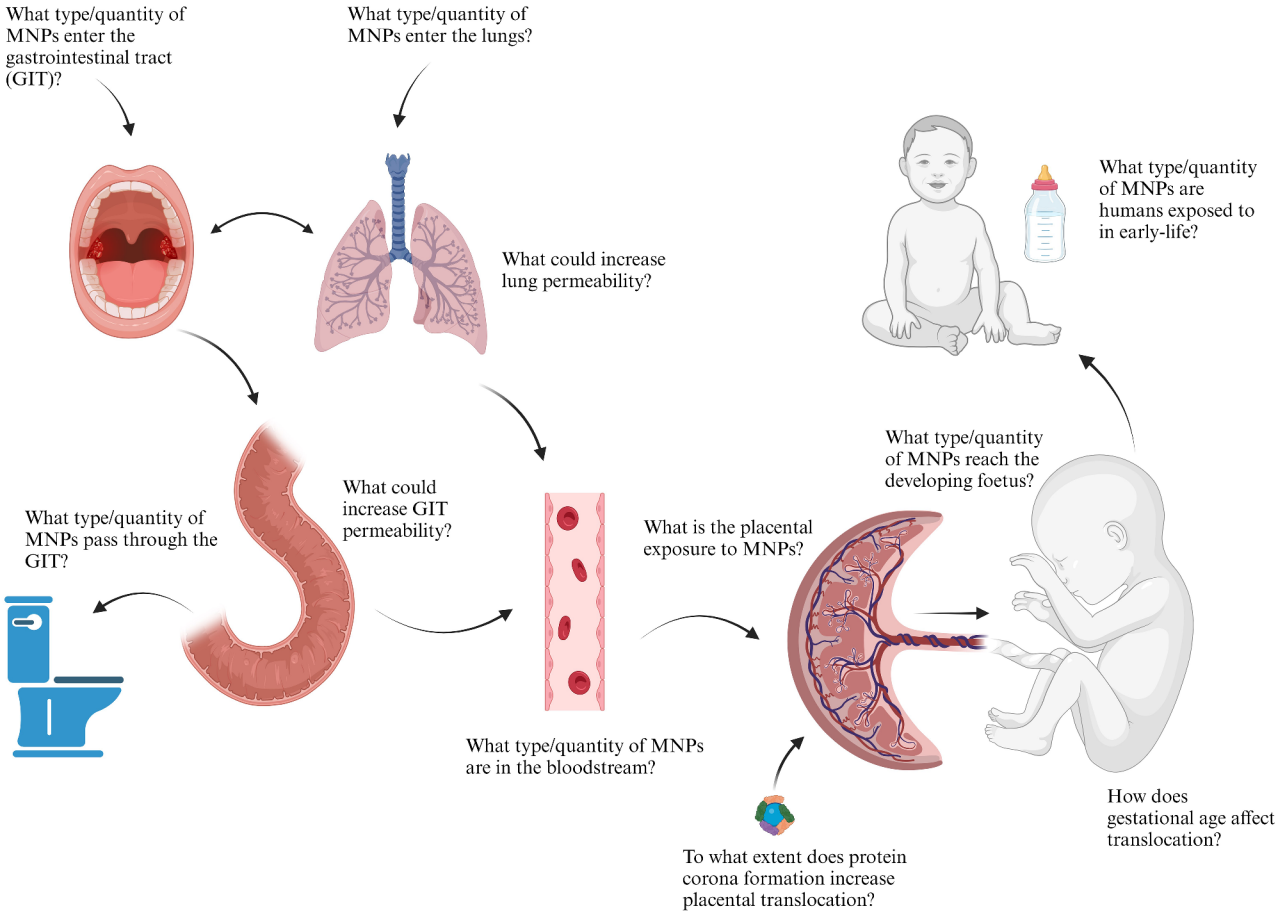

Fig. 7 Potential routes of early-life exposure to MNPs, and factors to consider that may influence exposure

than exposure throughout gestation. Understanding exposure pathways is essential to managing risks associated with MNPs. However, a lack of sampling and analysis methods, at a suitable level of sensitivity (refer to TRLs, Sect. 3.1.7) hinders assessing total (the absolute amount) and relative (exposure level in proportion to a reference value) exposures, present a major barrier to performing a RA. While the widespread presence of MNPs in the environment is acknowledged, what reaches the placenta and developing foetus is, at present, unknown.

Recent reviews [127–129] report on human exposure sources and pathways. They indicate a high prevalence of MNPs in indoor environments, particularly in settled dust and from synthetic textiles, and that outdoor air contains MNPs from tire abrasion, atmospheric fallout, and dust, with both indoor and outdoor air contributing to exposure through inhalation [127, 129]. While information on the effects of MNPs inhalation in humans is limited, MNPs have been detected in bronchoalveolar lavage fluid (BALF) [130] and sputum in adults [131]. MNPs in the lung have the potential to then enter the bloodstream, as observed with other particles [132–134] and animal models have demonstrated maternal lung to foetal translocation of MNPs [60]. Larger inhaled particles (above 5 µm diameter) are likely to become trapped within lung mucus and undergo mucociliary clearance [135], which may result in increased ingestion.

Ingestion is the most studied route to date, with MNPs reaching the gastrointestinal system through consumed food, drinks, food packaging and mucociliary clearance [127]. The presence of MNPs in human and animal faeces [136–138] provides evidence that intake has occurred, dermal exposure occurs through contact with dust, personal care products, textiles, and food contact materials [139]. However, dermal translocation/absorption capabilities are currently not known, but probable, considering data on NMs indicate that particles ≤ 4 nm in diameter can penetrate intact skin, which increases to 45 nm for damaged skin [140]. Therefore skin conditions such as eczema, of which 60% of cases appear within the first year of life, may also increase uptake as the skin barrier is compromised [141]. In addition, some personal care products, such as cosmetics, contain nanosized ingredients designed to increase dermal penetration and may also cause skin damage [142], both of which may increase dermal uptake of MNPs. However, here remains

considerable unknown factors regarding potential dermal exposure routes and consequent absorption kinetics of MNPs. Another consideration when estimating exposure is social determinants of health [143], as increased body burden of plasticisers has been observed in pregnant women in minority racial/ethnic groups, low-income areas and those with lower educational attainment [7].

Meconium-stained amniotic fluid (MSAF) occurs in up to 25% of pregnancies, more often in Black and South Asian populations [144]. Up to 10% of newborns experience meconium aspiration syndrome in which they inhale MSAF *in utero* or during delivery, with ethnicity potentially influencing exposure extent [145]; this creates a potential for additional inhalation exposure if MNPs are present in the amniotic fluid. MNPs have also been detected in breastmilk [146], and infant formula [147] indicating a postnatal route of early-life exposure. Quantifying this presents a unique challenge given differences in rates of breast feeding versus formula use, and the use of plastic baby-bottles and milk-storage bags [10]. Child-specific behaviours such as crawling, increased hand-to-mouth activity, mouthing on plastic toys and surfaces [148] can also raise early-life MNP exposures. The breathing zone is also closer to the ground for infants and children [148], increasing exposure to dust containing MNPs; additionally, greater relative ingestion and inhalation rates per unit body weight when compared to adults, and may lead to increased uptake [7, 149].

Characteristics and quantity of MNPs reaching the placenta and/or foetus

Accurate evaluation of MNP risks necessitates quantifying exposure concentrations and hazardous profiles of MNPs reaching the mother, placenta and foetus. The current methods used for MNP monitoring were designed for other materials, such as NMs, and have been adapted for MNPs with varying success. Advancing spectroscopic techniques is required to better characterise MNP exposures in terms of number, size and shape [104]. Also relevant are methods providing data on polymer type, mass, concentrations in source media (food, water, soil, air) [138], and identifying MNP forms in these media to predict relevant exposure characteristics and quantities.

Evaluating *in utero* exposure to MNPs and associated chemicals is critical. MNP and MNP-associated chemicals, including endocrine disruptors, have been detected in human amniotic fluid [125, 150]; this is of concern, as the continual ingestion and excretion of amniotic fluid by the foetus creates the potential for recurrent exposure [151]. It is also critical to recognise the potential for indirect foetal harm caused by placental damage resulting from the translocation or accumulation of particles, as is observed with NMs [152]. Quantifying MNP exposure levels in fluids surrounding the foetus during gestation is therefore critical to ascertain uptake potential and enhance risk prediction considering placental toxicity concerns that may manifest in the developing foetus.

As previously highlighted, maternal exposure may be used to estimate placental uptake and foetal exposure using PBPK modelling [24, 81]. While at present no research has quantified MNPs in maternal blood, data obtained from adult females [153] could fill this gap. Maternal exposure may also be estimated using environmental data with inhalation, and ingestion estimates. However, the OECD [36] highlights that measured exposure data is preferred over modelled exposure data. Underscoring the significance of this preference is the widely varying range of adult ingestion estimates, from 258 particles/day [154] to as much as 5 g per week [155]. The 5 g figure, though widely reported, was later found to have significant methodological errors in the analysis [156], with authors concluding that the calculations, which used data consolidated from different measurements, led to an overestimation of the mass of ingested MPs. The corrected analysis indicates that the actual ingestion rate is substantially lower, while also highlighting issues with using modelled data.

Characteristics of MNPs, such as size, may also influence MNP exposure. For example, it is understood that MNPs larger than 150 µm pass through the GIT to be excreted and EFSA [157] estimate up to 90% of ingested MNPs are excreted in faeces; indicating that the majority of MNPs humans are exposed to pass through the GIT. However, MNPs smaller than 150 µm may translocate across the gut epithelium [157] and MNPs up to 10 µm via immune cells into lymphatic tissue [67]. However, MNPs smaller than 1.5 µm may penetrate deeply into organs [157].

Examples of research that may be used to inform characteristic and quantity are summarised SM Table S3.1. However, it is important to note that variations in the sensitivity, selectivity, sample processing, instrumentation, and data analysis inherent to each detection technique can substantially influence the uncertainty around measured MNP concentrations and characterisation; it is hoped that monitoring technological advances of these systems via TRL assignment will help to reduce this uncertainty. Faecal excretion data from maternal stool samples and adult populations (see study details in SM Table S3.2) [4, 137, 158] may inform ingestion quantities and allow the characterisation of MNP properties that humans are exposed to. However, this would not factor in systematic absorption and accumulation. There are also multiple factors that could reduce excretion, which should be considered when determining exposure (see Sect. 3.4.3).

Intake estimations compared against excretion data may provide insights into quantities that persists within

Table 3 Factors that could alter barrier permeability and increase exposure to MNPs

Biological effect	Factor	Influence
Increased gastrointestinal track (GIT) permeability	Larger MNPs	MNPs > 150 µm trigger immune responses and inflammation when bound to intestinal lumen [166].
	Pre-existing health conditions	Conditions increasing permeability: Inflammatory Bowel Disease (IBD), Celiac disease, food allergies, irritable bowel syndrome, diabetes, mental illness, obesity [110, 167–170].
	Lifestyle factors	Alcohol use, western diet, some medications (e.g., non-steroidal anti-inflammatory drugs) [168, 171, 172].
	Dysbiosis	Caused by multiple factors including MNPs, lipopolysaccharide (LPS) from bacteria, lifestyle, IBD [173–175].
	Particulate matter (PM)	PM2.5 & PM10 activate inflammatory pathways damaging GIT lining [176].
	LPS	Activates inflammation, oxidative stress and injury [177, 178].
	Nanomaterials (NMs)	Titanium dioxide (TiO2) nanoparticles cause inflammation, impact intestinal barrier function, and alter gut microbiome, especially in those with intestinal diseases. Comparisons made to MNPs based on similar size and chemical inertness [179].
Increased lung permeability	MNPs	40 nm polystyrene (PS) NPs reduce epithelial resistance by depleting tight junction proteins [180].
	NMs	Silicon dioxide (SiO2) nanoparticles increase alveolar permeability in mice. TiO2 nanoparticles exacerbate LPS-dependent lung inflammation with size-dependent effects. Multi-walled carbon nanotubes increase lung inflammation, permeability, oedema, and eosinophilia in rats [181–183].
	LPS	Toll-like receptor activation inducing neutrophil alveolitis, proinflammatory factors and enhanced epithelial permeability in vivo [184].
Increased dermal permeability	Preterm born	Thinner stratum corneum with increased permeability [185].
	Atopic dermatitis	Barrier permeability dysfunction, decreased antimicrobial barrier function [141].
Improved translocation across barriers	Protein corona	Human plasma enabled 80 nm PS particle transfer in an ex vivo placenta model [74]. Protein coronas facilitated nanoparticle translocation in human digestion models [186]. Low-density lipoprotein and immunoglobulin G enhanced uptake of SiO2 nanoparticles in human lung epithelial cells [187].
	Eco-corona	Potential to increase NP bioreactivity following eco-corona formation in vitro [188] and increased uptake and decreased removal from the GIT in *Daphnia magna* [189].

the body. However, it is important to note that excretion of MNPs does not indicate that no hazard is present, as leaching of chemicals and/or contaminants prior to excretion must also be considered. It is possible to estimate leaching using *in chemico* approaches, according to literature available. This supports method selections, and decisions on choice of suitable biological simulant fluid, to address both exposure routes and biological compartments [159–165]. However, in context to this release it will be important to consider whether effects by different components can be antagonistic, additive or synergistic, as discussed earlier, with uncertainty consideration pertaining to mixture effects of known toxicants.

Factors that could increase exposure and how these may apply to MNPs

While the majority of MNPs are believed to pass through the GIT [157], there are factors which may decrease excretion rates, such as an increase in GIT permeability (leaky gut) due to compromised integrity of the intestinal barrier or improved translocation across biological barriers. This may allow substances to cross into the bloodstream that would otherwise be restricted, increasing contact and exposure rates. Some of these factors are outlined in Table 3, and include MNP and NM exposure, certain health conditions, and dysbiosis. Although assessing the effects of heightened barrier permeability presents difficulties, it remains crucial to consider these factors during exposure estimation. Neglecting to do so could lead to an underestimation of exposure.

Duration and timing of MNP exposure

Duration of exposure. The duration and frequency of exposure is critical to exposure assessment and should identify exposure as single, cumulative, short, medium or long-term [151]. MNPs detected in meconium indicate particles are excreted by the foetus, however bioaccumulation and gestational age may influence exposure levels [29, 190]. Recurrent foetal ingestion and exhalation of MNPs within amniotic fluid could also lead to chronic exposures [151].

Bioaccumulation. MNPs have been found to accumulate in tissues and organs in rats (21 nm) [60], mice (0.1 and 2 µm) [191], zebrafish (4–40 µm) [63] and marine organisms (10 µm −5 mm) [62]. PS nanoparticles (21 nm) accumulated in rat foetal tissues including the liver, lungs, heart, kidney, and brain following maternal respiratory exposure [60]. Probabilistic lifetime exposure models can provide estimations that MNPs can irreversibly accumulate in humans [190], however, the ability of MNPs to accumulate in the placenta and/or foetus needs attention for accurate exposures. The accumulation of MNPs in maternal organs allows for re-introduction into the circulatory system, as deposited particulates

may leach from tissues back into the bloodstream [67], increasing the potential for translocation across the placenta to foetal tissues.

Gestational age. The timing of exposure to environmental contaminants is extremely important in predicting foetal susceptibility and the risk associated with that exposure. Organogenesis may be affected by early embryonic exposures, while later embryonic exposures influence organ system maturation [192]. Major windows of vulnerability exist *in utero* and throughout early-life, when the human brain is uniquely susceptible to chemical toxicities [192]. The impact of certain drugs on the foetus also varies with gestational age, owing to organ development stages and vulnerability fluctuations throughout pregnancy [193], a factor also to consider when assessing MNP associated contaminants.

Currently, there is limited evidence on how gestational age influences MNP translocation. However, murine animal models indicate an increased early pregnancy exposure risk for some NMs, with reduced placental transfer as pregnancy progresses [194, 195]. However, distinct variations exist in placental anatomy and function when comparing mouse and human models [196], and caution should be taken when extrapolating data from mice to humans. Carbon black particles were found in the same abundance in term and prenatal human placentas, which is suggested to indicate a maximal transfer from maternal blood to the foetus, occurring in the first and second trimester [197], however, may also indicate continuous replacement. To understand MNPs exposure and identify critical pregnancy stages, it is important to comprehend how gestational age affects foetal exposure and potential hazard during windows of vulnerability.

Guideline values for MNP exposure

A further challenge in quantifying MNP exposure is dose metrics and the most suitable toxicological endpoints on which to base guidelines and evaluate the risks linked to exposure [67]. Spectroscopic techniques for monitoring MNP exposure from environmental samples often report concentrations per volume sampled (e.g., particles/m3), however, in vitro toxicological studies frequently express MNP doses as mass concentrations (μg/mL) [104], which does not provide information on MNP size or number, limiting comparison to environmental levels. Recently, the Barchiesi model has been proposed for MP characterisation that better aligns with the limitations in analytical detection methods used for characterising MNPs in bulk samples of mixed particles [198]. The model accounts for toxicologically-relevant metrics of particle volume and surface area and allows for assessment of microplastic mixtures without the calibration that is required by other similar models. Bridging dose metrics between environmental or source (e.g. within food) sampling and toxicological impact is essential to evaluate potential MNP risks, and is discussed by Koelmans and Redondo-Hasselerharm [199].

The usual metric for chemical exposure and expression of guideline values is mass-based, as per the previous example for BPA [119]. However, this has long been considered inappropriate for particle assessment [200], and overlooks the crucial consideration of polymer content. There is a need for a comprehensive assessment that incorporates other properties such as surface area or particle number or shape which may bear more relevance for MNP hazards and as such should be considered when guideline values are established. Given the multi-faceted hazard profile present in MNPs, with risks associated with chemical release and with particle properties, it is possible that multiple dose-metrics will be relevant.

Examining existing in vivo and in vitro studies, environmental data, and knowledge from other well-researched particles may provide educated interim judgments regarding exposures, with potential for read across. Complexity arises, as a robust assessment requires data on the physicochemical properties, for example, polymers found, whereas exposure data often groups MNPs, limiting polymer-specific understanding behaviours and associated hazards.

Risk characterisation

To characterise risk to early-life, associated with MNPs, hazard and exposure data are combined to justify appropriate RMMs. Depending on the goals established in Problem Formulation, Risk Characterisation will differ depending on the qualitative, semi-quantitative or quantitative approach adopted (Fig. 8). No matter the approach, expert judgment is required to accurately characterise risk, with transparency and appropriate justification for conclusions drawn [201]. As current evidence indicates that a quantitative approach is not yet feasible based on current data availability, this section will focus on using WoE with a qualitative or semi-qualitative approach to characterise risk. WoE consolidates varied evidence sources, making it most relevant for these approaches where conclusions or risk rankings need to be informed.

Weight of evidence

Determining the strength of evidence and overall weight to assign different data underlies the interpretation, judgment and conclusions made throughout the risk characterisation process. A WoE approach [35] is recommended for MNP RA as there are likely to be multiple sources of data available with varying quality. A comprehensive evaluation of these sources is required to reach an informed conclusion on risk, along with an acceptable level of uncertainty being defined during the Problem

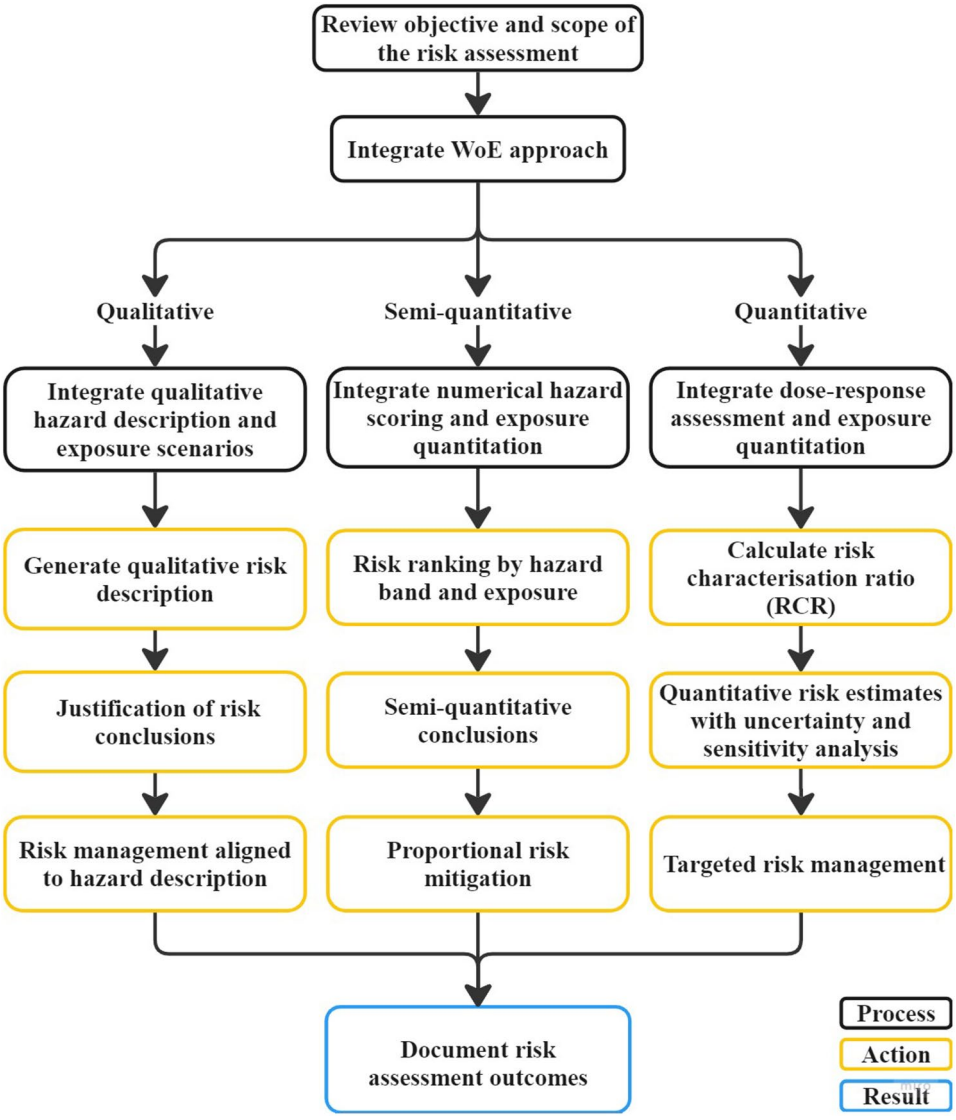

Fig. 8 Flowchart of Risk Characterisation in the framework for RA of MNPs

Formulation. Since current data on MNP hazards and exposures varies substantially, selectively synthesising the strongest evidence reduces the likelihood of over or underestimating the risks. The transparency and systematic documentation entailed in a WoE strategy also aligns with clearly defining the RA scope and objectives during problem formulation.

Qualitative WoE provides a framework to systematically assess the available evidence and strengthen risk conclusions. Semi-quantitative WoE can aid integrating scored hazard data with exposure estimations to support ranking. Used appropriately, WoE enables developing evidence-based risk conclusions from disparate data with known confidence levels. This approach can therefore strengthen MNP risk characterisation given present data constraints.

Qualitative approach

The ECHA Guidance on Information Requirements and Chemical Safety Assessment [201] note that for qualitative RAs, risk characterisation is completed in the absence of dose-response (DNEL/DMEL) data for the human health hazard endpoints. This is achieved using a systematic, documented approach for justification rather than calculating a RCR, which is the goal for a quantitative RA. In the absence of quantitative dose-response data for MNPs, risk characterisation would rely on a qualitative approach. This involves a systematic collection and analysis of available information on the environmental and health impacts of MNPs. Key considerations should include those highlighted here, such as their interaction with biological systems, persistence in different environmental contexts, and potential for bioaccumulation and toxicity, including their mechanism of action.

Expert judgement and studies on similar pollutants will be integral to this process, guiding the development of protective measures and the identification of priorities for further research [201].

Additionally, for chemicals with no dose-response data, ECHA [201] recommend the use of hazard control banding that reflect the severity of the hazard. For instance, MNPs could be grouped into high, moderate or low risk bands based on available toxicity data, considering physicochemical properties and exposure scenarios. MNPs demonstrating developmental, endocrine or carcinogenic effects would likely warrant placement in the high concern band, while those causing minimal toxicity, such as irritation, could be assigned to lower bands. With limited quantitative dose-response data currently, systematically grouping MNPs by severity of potential effects enables prioritisation of RMMs, with more stringent control measures required for higher risk bands. The absence of data should also be considered at this stage, as risk mitigation should involve improving research for such MNPs. An example of qualitative hazard banding is presented in Table 4.

Table 4 Example of qualitative hazard banding for Risk Characterisation of MNPs

Hazard Level	Description	Qualitative Risk Characterisation Statement	Recommended Risk Management Measures
High	Reproductive and/or developmental toxicity demonstrated at low doses relevant to exposure levels in toxicity studies. Of high concern for early-life health impacts.	High probability of risk to early-life based on qualitative exposure scenarios.	Implement strict measures to minimise exposure; lifestyle and dietary changes, awareness campaigns, stricter regulations, bans, enhanced environmental monitoring, clean-up efforts, and risk reduction strategies.
Moderate	Minor reproductive and/or developmental toxicity at doses unlikely to be encountered.	Potential for risk to early-life if exposure regularly exceeds those causing effects in toxicity studies.	Implement precautionary measure; increase monitoring, awareness, reduction of MNP exposure sources during pregnancy, including better waste management and reduced use of specific MNP-containing products.
Low	No evidence of reproductive and/or developmental toxicity up to highest doses tested.	Available data indicates low potential of risk to early-life under anticipated exposure levels.	General precautionary measures. No specific actions needed to protect early-life at this time. Monitor and minimise potential sources of MNPs to maintain low levels with basic precautions, such as correct waste disposal.
Unknown	No or extremely limited data for MNP hazard and exposure scenarios.	Further research required to accurately categorise risk.	

As the evidence base of MNP toxicity increases over time, this qualitative categorisation approach could transition towards semi-quantitative methods, then eventually to quantitative methods. However, it provides a reasonable interim risk mitigation plan given current data limitations. Uncertainty is greater with qualitative approaches, so clearly documenting the rationale behind risk band assignments and conclusions is essential, along with the WoE approach (Sect. 3.5.1). This allows a rational prioritisation and risk management aligned with hazard levels, which should be periodically reviewed and refined as more data becomes available.

Semi-quantitative approach

The semi-quantitative approach can expand upon the qualitative approach by assigning a numerical value that can help inform hazard banding, for example, using the tiering process outlined in Sect. 3.2.1 (Fig. 4), in which a priority score is calculated based on hazardous properties. Exposure potential should also be factored in, when possible, to assign risk scores, however as previously discussed, without dose-response data, the impact of exposure would likely remain qualitative. An example of hazard banding for semi-quantitative MNP risk characterisation is presented in Table 5.

Overall, this allows integration of available hazard data with exposure assessments to reach a semi-quantitative risk characterisation. Again, as data quality and availability improve, the assessment would shift towards more robust quantitative methods. However, this provides a feasible target to progress towards in the interim.

For a meaningful semi-qualitative approach, clear specification of terminology is critical; exposure potential ratings like high, medium or low require explicit thresholds. While insights from more characterised surrogate particles may be informative, directly generalising risks to MNPs is likely inappropriate given their high variability in properties and behaviours, ultimately necessitating dedicated research efforts. Additionally, criteria for what constitutes 'adequate' study of MNP hazards should be specified, with sufficiency thresholds for data volume to enable hazard classification at each banding level. Using unambiguous language and defining key terms supports consistent interpretation and application of the MNP RA framework.

Table 5 Hazard banding approach for semi-quantitative risk characterisation of MNPs. Adapted from ECHA [201]

Hazard band	Description	Priority score	Exposure	Recommended risk management measures
High	MNPs in this category pose a high risk to early-life, with substantial potential for adverse effects.	≥ 5	Detected in biological samples (i.e. placenta, cord blood etc.) at concentrations linked to reproductive/developmental toxicity. High environmental abundance. Size/shape/polymer preferential for placental transfer and bioaccumulation.	Implement strict measures to minimise exposure, such as lifestyle and dietary changes and awareness campaigns, stricter regulations, bans, and enhanced environmental monitoring, clean-up efforts, and risk reduction strategies.
Moderate	MNPs in this category pose a moderate risk to early-life, with potential for adverse effects to early-life under certain conditions.	1–4	Detected in biological samples (i.e. placenta, cord blood etc.) at concentrations not linked to significant reproductive/developmental toxicity. Medium environmental abundance. Limited evidence of preferential placental transfer and bioaccumulation based on size/shape/polymer.	Implement precautionary measure; Increase monitoring, awareness, and reduction of MNP exposure sources during pregnancy, including better waste management and reduced use of specific MNP-containing products.
Low	MNPs in this category pose minimal risk, with low potential for adverse effects to early-life.	0	Not detected or very limited detection in biological samples. No toxicity detected at levels detected in biological samples. Low environmental abundance. No evidence of preferential placental transfer and bioaccumulation based on size/shape/polymer.	General precautionary measures No specific actions needed to protect early-life at this time. Monitor and minimise potential sources of MNPs to maintain low levels with basic precautions, such as correct waste disposal.
Unknown	MNPs in this category have not been adequately studied or evaluated for potential hazards. MNP risk level remains uncertain.	N/A	No or extremely limited data for MNP exposure scenarios.	Further research needed to accurately classify risk

Table 6 Risk management measures recommended to control MNP emissions [202–204]

Approach	Description
Source-directed	Sustainable design and manufacturing of textiles, tires, and complementary products to minimise MNP generation; restriction of placing products containing intentionally added MNPs on the market.
Use-oriented	Best use practices and mitigation technologies to reduce preventable releases; labelling requirements.
End-of-life	Improved waste management to prevent leakage into environment.
End-of-pipe	Improved wastewater, storm water, and runoff management and treatment to retain emitted microplastics.

Hazard banding can be challenging when there are imbalances between the availability of hazard and exposure data. If robust hazard data is available but exposure data is lacking, conservative exposure estimates may be utilised to derive an initial risk ranking [19], such as information outlined in Sect. 3.4. Alternatively, if exposure estimates are adequate but hazard data is limited, read-across techniques and modelling methods may provide interim toxicity information by extrapolating from similar materials or predicting activity. Uncertainty factors should also be incorporated when either hazard or exposure data availability is limited [18, 19], and preliminary hazard bands adjusted iteratively as new data becomes available.

Risk management measures

Policymakers are beginning to address MNP emissions through various RMMs aimed to reduce preventable releases (Table 6), such as restricting MNPs intentionally added to products, improved labelling to allow consumers to make more informed choices, preventing environmental leakage, and capturing emitted MNPs before they reach water bodies [202–204]. However, there are limitations to control options due to the ubiquitous spread in the environment, making complete exposure elimination impossible. Therefore, high hazard banding and associated control measures may not always be actionable, particularly secondary sources like tyre and textile wear, which likely represent the majority share of environmental MNP pollution in OECD countries [202]. Effective risk reduction relies on improving the scientific ability to measure MNP emissions, prioritise major sources based on risk levels, and promote evidence-based solutions that address top priorities. As highlighted in Sect. 3.2.1.1, Methods such as the MicroPlastic Index may also be utilised for the reduction of MNP generation, aiding selection or redesign of polymers [103].

Document risk characterisation results

Documentation of risk characterisation need not vary from other clearly established RAs. The methodology

should be clearly described, justifying the qualitative or semi-qualitative approach adopted, based on data availability and acceptable uncertainty, as defined during the problem formulation. This should detail the steps achieved to identify of hazard and exposures, uncertainties, limitations and assumptions to provide transparency in the conclusions made. Documentation should also cover the information utilised, weighting decisions, calculations, models and integration methods to demonstrate scientific rigor and enable reproducibility. Suitable RMMs linked to the characterised risk levels need reporting. Recommendations for further data requirements and analyses to refine the assessment by reducing key uncertainties will facilitate iterative improvements. It should also explicitly state when the RA should be reviewed, if this is a set date, (i.e. annually), or when new data becomes available, or as testing methods improve [18, 40].

Future directions

Through the development of a roadmap to enable robust early-life MNP RA framework we have highlighted numerous research requirements that must be addressed. Key data gaps exist across all the assessment stages, as summarised in Table 7. Obtaining dose-response data is critical for establishing guideline values, requiring development of standardised reference MNPs and non-animal approaches. Exposure characterisation necessitates analytical techniques with greater sensitivity and specificity as well as fate modelling to address their variability. Identifying determinants of placental transfer and foetal bioaccumulation are needed, as well as associations between polymer characteristics and toxicity. Expanded absorption, distribution, metabolism, excretion (ADME) and toxicokinetic data through in vitro and *in silico* approaches can aid absorption and transformation predictions. Identification of early developmental effects and windows of heightened susceptibility are key.

Table 7 Current gaps in knowledge and information still required to develop a Human Health Risk Assessment (HHRA) framework, specifically addressing the impact of MNPs on early-life health

Research gap	Details
Quantitative approach	Data including contact rates, dose-response toxicity data, exposure data (incl. MNP type) and mechanisms of toxicity needed to enable a quantitative RA.
Semi-quantitative approach	Exposure data, clear definition of terminology for consistent interpretation and application of a semi-quantitative approach.
Mixtures approach	Improved understanding of MNP constituents, contaminants, exposures and hazardous components to allow mixtures-based assessment.
Polymer hazards	Improved polymer hazard data (beyond PS), specific to early-life effects.
Particle hazards	Particle associated hazards must be defined including shape, size, surface characterisation, concentrations associated hazards and effect of weathering.
Chemical hazards	Chemical hazards associated with MNPs needed to identify and prioritise greatest early-life risks, including IAS and NIAS as well as adsorption, leaching and accumulation potential.
Priority tier data	Improved MNP identification/characterisation and associated hazards needed before tier assignment is feasible.
Hazard values	None currently available for MNPs to enable guideline value development.
Reference materials	Needed for environmentally/biologically relevant MNPs and for standardisation of research, and therefore we first need to know what are relevant and accurate forms of MNPs.
Dose-responses	Lacking to identify placental/foetal health impacts at biologically relevant concentrations.
Non-animal testing	Increased and standardised models required for hazard characterisation given extensive data needs.
Use of existing paradigms	Improved research of the use of existing paradigms, used for NMs, that could be used for hazard insights; requires data like rigidity and biopersistence.
Sample contamination	Experimental contamination vs. true exposure creates difficulty in generating precise exposure estimates.
Standardised reporting	Standardised biological sample reporting (i.e. MNP/g, MNP per sample, µg/ml needed to enable study comparisons with environmental to biological relevance considered.
Significance of presence	Requires research e.g. fate following lung exposure, toxicity based on placental presence etc.
Characterising exposure	Ubiquitous nature of MNPs, multiple exposure routes and limitations of foetal detection methods inhibits exposure characterisation. Increased research to identify most relevant routes of exposure for early-life, including data on MNP characteristics, quantities, and life-stage related factors.
Excretion rates	Cautious use of excretion rates needed until better understood what is retained in body, and leaching potential of MNP associated chemicals that pass through the body.
Exposure duration	Implications of acute/cumulative/combined need elucidating, as well as impact of gestational age, maximal transfer etc.
Bioaccumulation	Unknown in placenta/foetus to estimate realistic exposure estimates.
Integrating factors	Complex, yet important to include social determinants of health including geography, race/ethnicity, health inequalities, general health, and lifestyle habits in hazard and exposure assessments.

Targeted, collaborative research initiatives focused on addressing current data gaps are essential to translating existing practices for assessing MNPs. Integrating perspectives across polymer science, nanotechnology, analytical chemistry, toxicology, and RA fields will facilitate a comprehensive characterisation of hazards and exposures. Advancing MNP RA tools can enable scientifically supported regulation and material innovation to mitigate risks to early-life.

Conclusions

This review outlines a proposed foundation for RA of MNPs relevant to early-life health. Leveraging established approaches for chemicals, particles, and mixtures, we present a framework aligned with existing RA components. Significant knowledge gaps and complexities related to the distinct properties of MNPs are highlighted, centred on exposure characterisation, hazard data, and early-life impacts. While current limitations preclude a comprehensive assessment, targeted research efforts focused on addressing key data needs hold promise for translating practices to evaluate MNPs. Cross-disciplinary engagement is required to generate the evidence base necessary for understanding and mitigating risks during early-life and advancement of a robust early-life MNP RA. Overall, this review calls attention to critical research directions needed to elucidate the impacts of MNPs on this highly vulnerable population.

Abbreviations

ADME	Absorption, Distribution, Metabolism, Excretion
AFM	Atomic Force Microscopy
AOP	Adverse Outcome Pathway
AURORA	Actionable eUropean ROadmap for early-life health Risk Assessment of micro- and nanoplastics
BALF	Bronchoalveolar Lavage Fluid
BPA	Bisphenol A
CBA	Component-Based Approach
DNEL	Derived No Effect Level
DMEL	Derived Minimal Effect Level
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EM	Electron Microscopy
EPA	Environmental Protection Agency
FTIR	Fourier-Transform Infrared [Microspectroscopy]
GIT	Gastrointestinal Tract
GRACIOUS	Grouping, Read-Across, Characterisation and Integrated Approaches for Environmental and Health Safety
HARN	High Aspect Ratio Nanoparticle
HDPE	High-density Polyethylene
HHRA	Human Health Risk Assessment
IAS	Intentionally Added Substances
IBD	Inflammatory Bowel Disease
ICCA	International Council of Chemical Associations
IR	Infrared
LDPE	Low-density Polyethylene
LPS	Lipopolysaccharide
MAF	Mixture Assessment Factor
MIE	Molecular Initiating Events
MNP	Micro- and Nanoplastics
MOA	Mode of Action
MP	Microplastics
MSAF	Meconium-Stained Amniotic Fluid
NM	Nanomaterial
NP	Nanoplastics
NIAS	Non-intentionally added substances
OECD	Organisation for Economic Cooperation and Development
PA	Polyamide
PBPK	Physiology Based Pharmacokinetics
PC	Polycarbonate
PCB	Polychlorinated biphenyl
PCP	Polychloroprene
PE	Polyethylene
PET	Polyethylene Terephthalate
PIFM	Photo-Induced Force Microscopy
PLC	Polymers of Low Concern
PM	Particulate Matter
POPs	Persistent Organic Pollutants
PP	Polypropylene
PTFE	Polytetrafluoroethylene
PRR	Polymers Requiring Registration
PS	Polystyrene
PBS	Polybutylene succinate
PU	Polyurethane
PVC	Polyvinyl Chloride
PMMA	Polymethyl methacrylate
QSAR	Quantitative structure–activity relationship
RA	Risk Assessment
RCR	Risk Characterisation Ratio
R&D	Research and Development
RMM	Risk Management Measures
RTECS	Registry of Toxic Effects of Chemical Substances
SEM	Scanning Electron Microscopy
SOP	Standard Operating Procedure
SiO2	Silicon dioxide
TDI	Tolerable Daily Intake
TiO2	Titanium dioxide
TRL	Technology Readiness Level
TWA	Time Weighted Average
WHO	World Health Organisation
WMA	Whole Mixture Approach
WoE	Weight of Evidence

Supplementary Information

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Supplementary Material 1

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Author contributions

MSPB, EAC, AD, LT, and YCdV: conceptualisation and design of study: EAC and MSPB: evaluation of literature, and drafting the manuscript; AD and YCdV: developed and conducted the evidence mapping of the existing RA approaches to MNPs; YCdV: developed the TRL scales for MNP methods, with additional contributions by LDBM, FM, BMW, BMSB, NDS and RZ; KSG, JvB HMC, HMD, JL, JM, LZ, NDS, BMSB, RZ and TSN contributed to review and editing of the final manuscript. All authors read and approved the final manuscript.

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