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Nano- and microplastic PBK modeling in the context of human exposure and risk assessment

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ABSTRACT

Insufficient data on nano- and microplastics (NMP) hinder robust evaluation of their potential health risks. Methodological disparities and the absence of established toxicity thresholds impede the comparability and practical application of research findings. The diverse attributes of NMP, such as variations in sizes, shapes, and compositions, complicate human health risk assessment. Although probability density functions (PDFs) show promise in capturing this diversity, their integration into risk assessment frameworks is limited. Physiologically based kinetic (PBK) models offer a potential solution to bridge the gap between external exposure and internal dosimetry for risk evaluation. However, the heterogeneity of NMP poses challenges for accurate biodistribution modeling.

A literature review, encompassing both experimental and modeling studies, was conducted to examine biodistribution studies of monodisperse micro- and nanoparticles. The literature search in PubMed and Scopus databases yielded 39 studies that met the inclusion criteria. Evaluation criteria were adapted from previous Quality Assurance and Quality Control (QA-QC) studies, best practice guidelines from WHO (2010), OECD guidance (2021), and additional criteria specific to NMP risk assessment. Subsequently, a conceptual framework for a comprehensive NMP-PBK model was developed, addressing the multidimensionality of NMP particles.

Parameters for an NMP-PBK model are presented. QA-QC evaluations revealed that most experimental studies scored relatively well (>0) in particle characterizations and environmental settings but fell short in criteria application for biodistribution modeling. The evaluation of modeling studies revealed that information regarding the model type and allometric scaling requires improvement. Three potential applications of PDFs in PBK modeling of NMP are identified: capturing the multidimensionality of the NMP continuum, quantifying the probabilistic definition of external exposure, and calculating the bio-accessibility fraction of NMP in the human body. A framework for an NMP-PBK model is proposed, integrating PDFs to enhance the assessment of NMP's impact on human health.

1. Introduction

Nano- (<1 μm) and microplastics (from 1 to 5000 μm) (NMP), (SAPEA, 2019) raise concerns about their adverse effects on living organisms, including humans. (Coffin et al., 2022; Noventa et al., 2021; WHO, 2022; Wright and Kelly, 2017; WHO, 2019) Over the past decade, there has been a surge in research focused on understanding NMP exposure pathways to humans. (WHO, 2022) However, the absence of standardized methods and measurement units across studies, coupled with analytical challenges pertaining to minimum particle size and automation, has significantly impeded both comparability and the effective utilization of research findings. (Noventa et al., 2021; Gimiliani and Izar, 2022; Koelmans et al., 2020) Various studies also detected NMP particles and/or plastic polymers in digested human samples,

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including blood (Leslie et al., 2022), gut (Jenner et al., 2022), lung (Jenner et al., 2022), and placenta (Ragusa et al., 2021). Despite these findings, the health risks they pose remain uncertain, (SAPEA, 2019; Coffin et al., 2022; WHO, 2022) since the benchmark dose for NMP in humans is still unknown. Establishing a benchmark dose and quantifying the internal concentration of NMP in different tissues is essential for comprehensive risk assessment. (Noventa et al., 2021) However, the complexity of NMP as a mixture with diverse characteristics, including sizes, shapes and polymer types, presents challenges in determining their risk potential. (Koelmans et al., 2022; Kooi et al., 2021) Therefore, it is crucial to develop alignment methods to translate and standardize NMP studies into a common measurement unit. (Koelmans et al., 2020)

Previous studies have demonstrated the efficacy of probability density functions (PDFs) for visualizing and capturing the diversity of NMP in a unified measurement unit, which facilitates fate modeling, exposure assessment, and effect studies. (Koelmans et al., 2020) However, the application of probabilistic approaches to NMP risk assessment, either in exposure assessment or effect studies on human health, remains limited. We are aware of only one study that correctly takes the diversity of NMP into account when estimating the external exposure of humans to NMP (Mohamed Nor et al., 2021) (reviewed by Pletz, 2022). This study used PDFs but did not yet address internal exposure, and could not yet include the most recent literature on the characteristics of NMP in the exposure routes relevant to humans.

Physiologically based kinetic (PBK) models are the effective tools needed to quantitatively translate external exposure to internal exposure, after which exposure at the tissue level can be compared with the benchmark dose for the same tissues. PBK models use mathematical equations to describe the biokinetics and biodistribution processes of small molecules, and their application has extended to include nanoparticle-based drugs. (Siccardi et al., 2018; Yuan et al., 2019) Given the transport barriers that exist in the human body, there is a consensus that only the smallest particles of the NMP continuum are relevant for exposure and risks of NMP to humans. (WHO, 2022; FAO, 2017) Because the sizes of the NMP particles are comparable to small molecules or engineered nanoparticles, it seems feasible to implement PBK models to estimate the internal exposure of NMP within the human body. (Prata, 2023) However, the heterogeneity of NMP poses a challenge because the biodistribution depends on the properties of the diverse particles, and because of the potential for multiple mechanisms of action that can occur simultaneously. (Koelmans et al., 2022) Due to the unique feature that NMP characteristics can vary over many orders of magnitude, modeling approaches such as those used for relatively monodisperse nanoparticles and engineered nanomaterials are not readily applicable. Previous reviews have focused on particle biodistribution in general, (Yuan et al., 2019; Li et al., 2010; Liu et al., 2016) and have suggested biodistribution modeling for NMP. (Noventa et al., 2021; Prata, 2023; Guan et al., 2023) However, there is no study which proposes a plausible approach that tries to do full justice to the NMPs' heterogeneity. There are no studies that aim to provide guidance on modeling human internal exposure to NMPs based on a literature synthesis and new insights.

The aim of this paper is fourfold. First, we aim to provide an overview of the development of PBK models for NMP risk assessment purposes. Secondly, our objective is to establish a quality control and quality assurance (QA-QC) framework tailored for NMP biodistribution studies, and to provide a practical guideline for building PBK models for NMP. Our third goal is to address the diversity of NMP by incorporating PDFs and rescaling methods into the risk assessment process. Lastly, we aim to propose a holistic human health risk assessment framework for NMP, grounded in the alignment of exposure and effects data.

2. Methods

A literature review was conducted to investigate both laboratory-based and *in silico* biodistribution studies of NMP within the human body (Figure S1). The inclusion criteria were designed to encompass studies that specifically examined the biodistribution of NMP, including polymeric nanoparticles due to mechanistic similarity. Studies investigating the dermal route of NMP distribution were not included due to the negligible probability of NMP particles penetrating the epithelial barrier via dermal exposure. (WHO, 2022; Prata, 2023) In addition, insights from rodent studies are also useful and were included in this study. Two scientific databases, PubMed and Scopus, were employed to conduct an extensive literature search for this study. Two distinct search strings were utilized: (1) "physiologically based" AND "pharmacokinetic" OR "kinetic" AND "modeling" AND "particles" OR "microplastics" OR "nanoplastics," and (2) "biodistribution" AND "modeling" AND "particles" OR "microplastics" OR "nanoplastics". Only English publications from the last ten years were included, with the search conducted until October 2023.

The review focused on assessing the adequacy of studies for future implementation in the biodistribution modeling of NMP. The evaluation criteria for experimental studies were derived and adapted from previous QA-QC studies. (De Ruijter et al., 2020; Gouin et al., 2022) These screening criteria were originally designed to assess the suitability of study outputs for risk assessment purposes. Therefore, a new criteria called "applicability for biodistribution modeling" was introduced to fit our study objectives (Table 1A). As for modeling studies, criteria were developed based on the best practice guidelines of PBK models in risk assessments, (IPCS, 2010) the OECD guidance on reporting PBK models, (OECD, 2021) as well as relevant studies on PBK modeling and simulations. (Zhuang and Lu, 2016; Abouir et al., 2021) These evaluation criteria were adapted to specifically address the context of NMP risk assessment for human health (Table 1B). Each evaluation criterion is

Table 1
List of QA-QC assessment criteria for biodistribution experimental and modeling studies.

A. Experimental studies*	B. Modeling studies**
Particle characterization	Scope and purpose of the model
Size	Objective
Shape	Particle type
Polymer type	Species
Source of particle	Dose simulated in the model
Chemical purity	Administration route
Surface characteristics	Settings of the model
Experimental study design	Model structure
In vivo:	Organ compartment
Dose/concentration	Type of model (Blood flow-limited or
Administration route	membrane-flow limited model)
Test species	*Type of model (Transient blood flow and*
Sample size	*membrane-limited flow model)*
Frequency/duration of	Simulation time
exposure	Model Equation
Test medium/delivery vehicle	*Mathematical equations represent NMPs diversities*
Controls	*using rescaling methods*
In vitro	PBPK Software (or other computational
Dose/concentration	software)
In vitro test system description	Model parameters
Sample size/replicate	Source of datasets
Test medium/delivery vehicle	Input parameters
Frequency/duration of	Estimated (fitted) parameters
exposure	Allometric scaling
Controls	Model outcomes and performances
Applicability for	Model outcome
biodistribution modeling	Model validation
Target tissue/organ	Model performance
Biokinetic parameter	Sensitivity and uncertainty analysis
Statistical analysis	
Longest time-point	
Biodistribution metric	
Biodistribution value	

* The criteria derived from previous studies are presented in normal text format, while the adjusted and new criteria for this study are presented in Italic style.
** While general criteria employed in other particle or pharmaceutical studies are indicated in normal text format, distinctive criteria pertinent to NMP are written in Italic style.

scored 0, 1 or 2, reflecting adherence, with higher scores indicating greater potential for biodistribution modeling of NMP. Detailed explanation of scoring for each criteria is provided as Supplementary Materials; **Table S1 and S2**.

The distribution of study characteristics was quantified through contingency table analysis. Visual representation of individual study assessments was presented as heatmaps for each category. The statistical analysis and visualization were performed using GraphPad Prism Software version 9.3.1 (GraphPad Software, San Diego, California, USA). The incorporation of NMP diversities into the development of PBK models is discussed. The practical guideline encompasses the data inputs, essential model parameters, and how to link these information with external exposure data. These findings were then incorporated into a comprehensive risk assessment framework for NMP and human health.

3. Results and discussion

3.1. Review of NMP biodistribution studies

3.1.1. A brief history of PBK modeling

The concept of Physiologically based pharmacokinetic (PBPK) modeling was introduced by Teorell in 1937 as a mathematical tool to simulate pharmacokinetic data by integrating biological and physiological components within a multi-compartment model. (Paini et al., 2019) In recent years, the application of PBPK modeling has expanded beyond the pharmaceutical industry, encompassing chemical risk assessment endeavors. (IPCS, 2010; Paini et al., 2019) Consequently, the terms "Physiologically Based Kinetic" (PBK) or "Physiologically Based Toxicokinetic" (PBTK) model have emerged to describe the utilization of this modeling approach in risk assessment and supporting regulatory decision-making for emerging chemical compounds. (IPCS, 2010; Paini et al., 2019) While the term PBPK is commonly used in the pharmaceutical field, PBK or PBTK terms are more prevalent in the field of ecotoxicology. (Schneckener et al., 2020) Nonetheless, both PBK and PBTK models offer valuable tools for understanding and predicting the absorption, distribution, metabolism, and excretion (ADME) of chemicals, thereby facilitating risk assessment efforts. (Siccardi et al., 2018; Sager et al., 2015.).

Several review studies have provided insights into the applications of PBK models. Some reviews have focused on case studies illustrating how PBK modeling and simulation can be employed throughout different stages of drug discovery and development, (Zhuang and Lu, 2016; Abouir et al., 2021) computational approaches, and software utilized in PBK modeling, (Wu et al., 2020) and the verification of PBK models. (Sager et al., 2015.) Other reviews have focused on the ADME processes of nanoparticles and the factors to be considered when developing PBK models for nanoparticles. (Yuan et al., 2019; Li et al., 2010) In the fields of toxicology and chemical risk assessment, reviews have explored how to construct PBK models in the absence of animal data to support the decision-making process. (Paini et al., 2019; Paini et al., 2017).

With the rising concern surrounding the impact of NMP on public health, the utilization of PBK models has been proposed to estimate internal exposure to NMP. (Coffin et al., 2022; Noventa et al., 2021) Despite this, a dedicated PBK model focusing on the tissue distribution of NMP in human systems has yet to be developed. Notably, Noventa *et al.* (Noventa et al., 2021) highlight the significance of considering inhalation exposure from indoor environments in addition to oral exposure in the formulation of the next NMP-oriented PBK model. Presently, there is limited knowledge concerning the translocation and internalization of NMP, particularly in relation to variations in size, shape, and composition. (Coffin et al., 2022) However, recent studies by Prata *et al.* (Prata, 2023) and Wu *et al.* (Wu et al., 2022) comprehensively reviewed the absorption, distribution, metabolism, and excretion (ADME) processes of NMP and have called for the development of a PBK model tailored to NMP.

3.1.2. PBK models: What is under the hood?

PBK models can be constructed either top-down or bottom-up. (Tylutki et al., 2016) In the top-down approach, the model primarily relies on observed clinical data, whereas the bottom-up approach entails building a mechanistic model based on knowledge about the human body, utilizing *in vitro* information as input data. Both approaches are commonly employed in drug development studies. However, when dealing with chemicals or emerging contaminants such as NMP, the bottom-up approach is more suitable due to the scarcity and uncertainties of *in vivo* data for such contaminants.

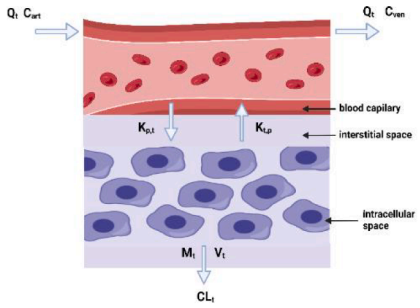
When developing PBK models for particles, researchers commonly utilize two principal frameworks: perfusion (blood flow-limited) and diffusion (membrane-limited) models. (Yuan et al., 2019; Li et al., 2010) In the context of perfusion-limited models, it is posited that molecules or particles within tissues swiftly attain distribution equilibrium with those present in the circulatory system. This implies that particles can readily traverse tissue cell membranes, with blood perfusion serving as a constraining factor. (Li et al., 2010) In contrast, diffusion-limited models perceive tissue cell membranes as barriers hindering particle movement. These membranes establish distinct intracellular and extracellular spaces within the tissue, thereby influencing particle behavior. (Yuan et al., 2019) Blood-flow limited models find application in the context of small molecules or drug compounds soluble in bodily fluids. Conversely, membrane-limited models are better suited for very small particle entities, such as nanoparticles, due to their limited ability to traverse vascular membranes. (Li et al., 2014) Given the extensive range of particle sizes inherent in NMP, we assume that smaller particle (NP) may conform to blood-flow limited behavior, while bigger particle (MP) could exhibit membrane-limited behavior (Fig. 1). However, when we consider the general properties of NMP, the membrane-limited (diffusion) PBK model might be the best option.

In addition, we present the physiological, physico-chemical, and ADME-related model parameters required for a NMP-PBK model, based on the most recent biodistribution studies focusing on NMP and other types of polymer particles (Figure S2). These parameters serve as crucial inputs for constructing either a minimum PBK model or a whole-body PBK model specific to NMP. It is important to emphasize that when additional data become available in the future, the number and specificity of the model parameters will inevitably increase, allowing for a more refined and accurate representation of NMP behavior within the human body.

3.1.3. Physiological parameters

Physiological parameters play a crucial role in PBK modeling and are typically used as direct inputs in the model to represent prior knowledge about anatomy and physiology. (Kuepfer et al., 2016) When employing specific PBK software such as GastroPlus or PK-Sim, this information is often included in the software's database. The values of physiological and anatomical parameters for a given species, such as body weight, organ volume, organ weight, and organ density, can be obtained from relevant scientific literature. (Brown et al., 1997) Furthermore, inter-individual variability in these parameters can be estimated using data from sources like the NHANES database (The National Health and Nutrition Examination Survey, 1995) or the International Commission on Radiological Protection (ICRP) database. (Alexaklrin Obninsk, et al., 2003).

Additionally, cardiac output (QCC) and regional blood flow (QC) are essential physiological parameters in PBK models. Cardiac output represents the total blood flow and is typically expressed in units of liters per minute (L/min). Regional blood flow, on the other hand, represents the relative blood flow for each compartment as a fraction of the cardiac output. The number of organ compartments included in the model may vary depending on the study objectives (as depicted in Fig. 2C). Consequently, the number of regional blood flow parameters will also differ for each study, reflecting the specific compartments included in the model.



Blood-flow limited (Perfusion)

$$\frac{dM_t}{dt} = \frac{Qt}{V_t} \cdot C_{art} - \frac{Qt}{V_t \cdot R_t} \cdot C_{ven} - ((K_{up} . M_t) - (K_{out} . M_{pc})) - K_{li} . M_t - CL_t . M_t$$

Membrane-flow limited (Diffusion)

$$\frac{dM_t}{dt} = K_{p,t} \cdot C_{art} - \frac{K_{t,p}}{R_t} \cdot C_t - ((K_{up} . M_t) - (K_{out} . M_{pc})) - K_{li} . M_t - CL_t . M_t$$

Fig. 1. Kinetic transport diagram ("Created with BioRender.com") and equations for blood-flow limited and membrane-flow limited model NMP, (adapted from Li et al. (Li et al., 2010) and Yuan et al. (Yuan et al., 2019); M is the particle number, C is concentration, CL is clearance, R is the tissue-to-plasma partition coefficient, Q is blood flow, V is volume, $K_{p,t}$ is a permeability coefficient (size-dependent), K_{up} and K_{out} are the uptake and desorption rates of phagocytosis. K_{li} is the transfer coefficient to the lymph node, For non-eliminating tissues (brain, gut and heart), the CL will be equal to zero.

When the inhalation route is involved in the exposure or is a route of elimination, it is necessary to consider the alveolar or pulmonary ventilation rate in the PBK model. (Rietjens et al., 2011; Campbell, 2016) This parameter accounts for the rate of air movement in and out of the lungs during respiration and is essential for accurately representing the absorption or elimination of inhaled substances. (Prata, 2023) It is crucial to underscore that all deposition mechanisms are profoundly influenced by the specific pattern of breathing. Notably, there are significant differences in breathing patterns during rest versus physical exertion, resulting in substantial disparities in the deposition of inhaled substances within the respiratory system.(WHO, 2022).

3.1.4. Physico-chemical (NMP-properties) parameters

Particle size and shape are key determinants of NMP interactions with biological systems. Research indicates that cellular uptake varies based on particle size; smaller particles like 1 μm and 4 μm are more readily absorbed than larger 10 μm particles. (Paul et al., 2022) Furthermore, particle shape contributes to toxicity, as irregularly shaped particles with rough surfaces induce pro-inflammatory cytokine release and haemolysis, while spherical particles exhibit reduced cytotoxicity. (Paul et al., 2022; Choi, 2021) Surface characteristics of NMP, such as surface chemistry, functional groups, and surface charge, also play a pivotal role in their toxic potential and interactions with biological systems. (Besseling et al., 2017) The pH and ionic strength of particles impact surface properties, affecting particle aggregation in both aquatic and airborne environments. Weathering introduces changes in surface charge, with weathered polyethylene NMP predominantly displaying negatively charged surfaces. (Mohamed Nor et al., 2021).

NMP often contain chemical additives such as phthalates, bisphenols, and per- and polyfluoroalkyl substances. However, research suggests that exposure to these additives from NMP is relatively small. (Mohamed Nor et al., 2021; EFSA, 2016) Modeling studies indicate a minor contribution of NMP leaching to total chemical intake (~2%). (Mohamed Nor et al., 2021) For instance, average exposure to bisphenol A from dietary and non-dietary sources results in limited overall intake (2–4 %). (EFSA, 2016) Therefore implications for risks on the tissue level also are small. Given the complex interplay of NMP characteristics and their potential effects, it is imperative to firstly focus on understanding the biodistribution of the particles. Thus, it is recommended to omit exposure to plastic associated chemicals in the model presently. (Mohamed Nor et al., 2021) While NMP have been implicated in various adverse effects, elucidating their internal dynamics provides crucial insights into their behavior within biological systems. This strategic focus is particularly relevant for developing a comprehensive risk assessment framework to assess the health implications of NMP and guide future research endeavors.

3.1.5. Absorption-related parameters

In PBPK modeling, absorption rates often rely on *in vitro* studies with specific cell lines. Common choices are cultured CaCo-2 cells (intestinal epithelial-like), HT29-MTX cells (intestinal goblet-like), THP-1 cells (macrophage-like), and Raji B lymphocytes (M cell-like). (EFSA, 2016; Stock et al., 2019) In the context of inhalation routes, human A549 cell lines are used. (Rietjens et al., 2011).

The absorption of NMP particles is size-dependent and influenced by specific physiological systems. Larger particles (100–150 μm) are primarily absorbed by the digestive system, (EFSA, 2016; Yuan et al., 2022; Hirt and Body-Malapel, 2020) while smaller particles (1–10 μm) are predominantly taken up by the respiratory system. (WHO, 2022; Prata, 2023) The translocation of circulating particles into interstitial tissue typically has a size limitation of around 20 μm (Prata et al., 2022). Within the gut, the primary site of uptake for micron-scale particles is suggested to be through the gut-associated lymphatic tissue (GALT), facilitated by the Microfold (M) cells located in the Peyer's patches. (Galloway, 2015) In mice, particles in Peyer's patches, such as polymethyl methacrylate and polystyrene, typically exhibit sizes $\leq$ 10 μm. (Prata, 2023) Among these, particles smaller than 5 μm are transported to the spleen or mesenteric lymph nodes within macrophages, while larger particles tend to be sequestered, impeding their migration. (Eldridge et al., 1990) Additionally, larger particles can enter the intestine through alternative mechanisms such as persorption or uptake by migratory phagocytes. (Prata, 2023; Wu et al., 2022).

Human *in vitro* studies have reported a range of intestinal absorption fractions (f_{abs}) for nano- and microscaled particles, approximately around 0.2–0.45 %. (Mohamed Nor et al., 2021) Regarding inhalation routes, the absorption rate is often divided into the deposition fraction in the lower (f_{rep_low}), middle (f_{rep_mid}) and upper (f_{rep_up}) respiratory tract. (Campbell, 2016) Large particles (5–10 μm aerodynamic size) tend to be deposited in the nasopharyngeal region with little absorption. (Cheng, 2014; Deng et al., 2019) Particles around 2.5–5 μm aerodynamic size can penetrate into the tracheobronchial region. (Cheng, 2014; Deng et al., 2019) Very small particles (<2.5 μm aerodynamic size) can penetrate deep into the alveolar sacs where they can deposit, and pulmonary macrophages in alveoli can scavenge and clear some insoluble particles into the lymphatic system. (Prata, 2023; Cheng, 2014; Deng et al., 2019) For instance, deposition fractions predicted for ultrafine particles range from 0.020 to 0.028 (for the upper fraction), from 0.18 to 0.28 (for the middle fraction), and from 0.04 to 0.16 (for the lower fraction). (Sturm, 2016).

3.1.6. Distribution-related parameters

The distribution of substances, including NMP, within tissues or organs is influenced by various factors related to both the physiology of the individual and the chemical properties of the substance. (Brochot, 2015) Physiological factors include epithelial cellular permeability,

vascular permeability, regional blood flow, cardiac output, and the tissue perfusion rate. Distribution of NMP in systemic circulation might depend on size, charge, and reactive groups on the surface. (Persiani, et al., 2023).

Upon traversing biological barriers and entering the bloodstream, NMP engage with red blood cells (RBCs) and various substantial molecules, including albumin and globulin, leading to the creation of conglomerated complexes that could potentially obstruct blood vessels. (Lee et al., 2021) Human umbilical vein endothelial cells (HUVEC) provide a valuable model for scrutinizing how vascular endothelium reacts to NMP. (Persiani, et al., 2023; Lee et al., 2021) The distribution of NMP via systemic circulation takes place subsequent to their uptake by macrophages, monocytes, granulocytes, or myeloid dendritic cells, contingent upon particle characteristics. While NPs larger than 0.2 μm can enter the cardiovascular system, smaller NPs (<0.1 μm) would remain in the blood. (Wu et al., 2022) Particles in the size range of 0.1 to 0.2 μm may continue to circulate in the bloodstream, undergo splenic filtration, or accumulate in certain tissues or organs. (Wu et al., 2022; Barlow et al., 2017) The behavior of particles in the bloodstream is complex and influenced by various factors, including size, shape, surface charge, and biological interactions. (Persiani et al., 2023) Unlike ingested NMP, NMP of a respirable aerodynamic size in the air have a high likelihood of depositing within the alveolar regions of human lungs from where they could subsequently traverse epithelial layers via the gas exchange between alveoli and capillaries. (Barlow et al., 2017).

The preferential uptake of NMP by antigen-presenting cells suggests that the mechanism of internalization into the cell cytoplasm might occur through phagocytosis as opposed to nonspecific cellular intake. (Persiani, et al., 2023) Thus, parameters governing the internalization process, such as maximum uptake rate constants and maximum release rate constants via phagocytosis or other potential mechanisms, are encompassed within distribution-related parameters. However, particles < 5 μm are efficiently transported by M cells to the lymphatic system rather than being retained within the Peyer's Patches for an extended period like larger particles. (Eldridge et al., 1990) This process helps remove smaller NMP particles from the gut tissue and facilitates their clearance from the body via the lymphatic system.

NMP present in the systemic circulation generally exhibit a short half-life (K_{50}). (Prata, 2023) For instance, within one hour of oral administration of 0.2–0.3 μm PS NMP in mice, they can be detected in various systems, including the digestive system (stomach, intestine, liver), circulatory system (heart, blood, lung capillaries), renal system (kidney, bladder), and even the brain. (Im et al., 2022) Notably, only particles larger than 1.5 μm are anticipated to be precluded from entering organ capillaries, thus evading penetration into organs. (Persiani, et al., 2023) In the respiratory system, NMP can be eliminated through mucociliary transport mechanisms or transported by macrophage into the lymph node. (Prata, 2023; Eldridge et al., 1990).

3.1.7. Metabolism-related parameters

In a comprehensive context, particle metabolism encompasses all processes that modify their physiochemical attributes. For polymeric particles, this includes the degradation of the polymer matrix. (Li et al., 2010) Understanding the metabolism processes of NMP is crucial in comprehending their potential harm to humans. These processes can occur through diverse mechanisms, including microbiological activities, inflammatory responses, generation of reactive oxygen species, and the release of enzymes. (Prata, 2023; Wu et al., 2022) NMP are known to be chemically inert, and so far there is no evidence that biodegradation occurs in the human body. (Wu et al., 2022) However, the recent discovery of a PET hydrolase enzyme from the human saliva metagenome suggests the potential interaction of NMPs with specific enzymes in the human body, although this is still an area of limited testing and research. (White and Wallace, 2023; Eiamthong et al., 2022).

Several important metabolism-related parameters have been reported in various studies, (Campbell, 2016; Gao et al., 2019; Li et al., 2022) namely maximum velocity (V_{max}), the Michaelis constant (K_m) and clearance rate (CL). V_{max} represents the maximum velocity of the metabolic reaction per kilogram of body weight. The Michaelis constant (K_m) is a parameter in the Michaelis-Menten equation used to describe the metabolism of contaminants. K_m represents the substrate concentration at which the reaction rate is half of V_{max} and is indicative of the affinity of the contaminant for enzymes. (Brochot, 2015) Lastly, clearance parameter (CL) refers to the rate at which a substance is eliminated or cleared from an organ or the body through metabolism. In a PBK model, the user needs to provide the clearance per kilogram of body weight, which is used in conjunction with the calculated body weight to compute the clearance. (Brochot, 2015).

3.1.8. Elimination-related parameters

Kidney excretion is a potential pathway for the elimination of NMP, despite the glomerular filtration barrier's natural limitation to particles below approximately 10 nm in size. (Pironti et al., 2023; Sun et al., 2022) However, several studies revealed that nanoparticles between 10 and 20 nm have been observed to traverse this barrier. (Feng et al., 2018; Wang et al., 2018) On the other hand, larger nanoparticles (20–100 nm) and particles exceeding 100 nm cannot penetrate the glomerular filtration barrier. Instead, they enter the renal tubule system before eventual excretion in urine. (Feng et al., 2018; Wyss et al., 2020; Wang et al., 2018) Mechanisms such as exocytosis and endocytosis in proximity to the tubular epithelial cells may be involved in this process. A recent study by Pironti et al. (2023) detected polyethylene vinyl acetate (PVA), polyvinyl chloride (PVC), polypropylene (PP), and polyethylene (PE) MP in human urine samples. In an *in vivo* mice study, the presence of NMP (3 μm and 100 nm) was also found in urine samples after 4 h following tail vein injection, gavage and pulmonary perfusion. (Sun et al., 2022) Other studies suggest that small nanoparticles (<10 nm) are more likely to be excreted by the kidneys, whereas larger nanoparticles (>200 nm) tend to aggregate in the liver with potential excretion via splenic filtration. (Zielińska et al., 2020; Zhao et al., 2019).

In PBK modeling, the renal excretion rate (K_{urine}) refers to to how quickly a particular substance is removed from the plasma by the kidney and excreted in urine. Human embryonic kidney (HEK 293) cells and human hepatocellular (Hep G2) liver cells have been deployed to scrutinize these mechanisms concerning NMP. (Goodman et al., 2022) The fecal elimination rate (K_{exc}) represents the clearance rate per unit of body weight. One study has revealed a wide range of NMP (0.8–41.6 items/gr) in stool samples. (Schwabl et al., 2019) In PBK modeling, fecal elimination is often modeled as a first-order reaction within each organ or compartment. Both of these excretion rates parameters are typically obtained from *in vivo* experiments. (Li et al., 2014).

3.2. Study characteristics

Out of the 39 studies included in this review, 23 were experimental studies, while only 16 were modeling studies (Fig. 2A). The experimental studies predominantly focused on NMP, while the modeling studies primarily examined other polymeric particles (see Fig. 2). This discrepancy highlights the need for biodistribution models specifically tailored to NMP, as there is a sufficient quantity of input data available for these particles. Among the included studies, only 9 employed human cell lines as their study subjects, while the majority used rodents such as rats or mice (Fig. 2B). This indicates that allometric scaling will be necessary to translate the findings from rodents to humans. Fig. 2C illustrates the distribution of organ compartments utilized in biodistribution studies of NMP and OPP ('Other polymeric particles'). In OPP studies, the liver and blood were most commonly studied organ compartment (17 studies). This observation is reasonable given that the liver plays a crucial role in the elimination process of polymer particles, and the distribution of particle in the organism can be assessed through blood analysis. In studies focusing on NMP, the gastrointestinal (GI) tract was the most frequently studied organ compartment (12 studies),

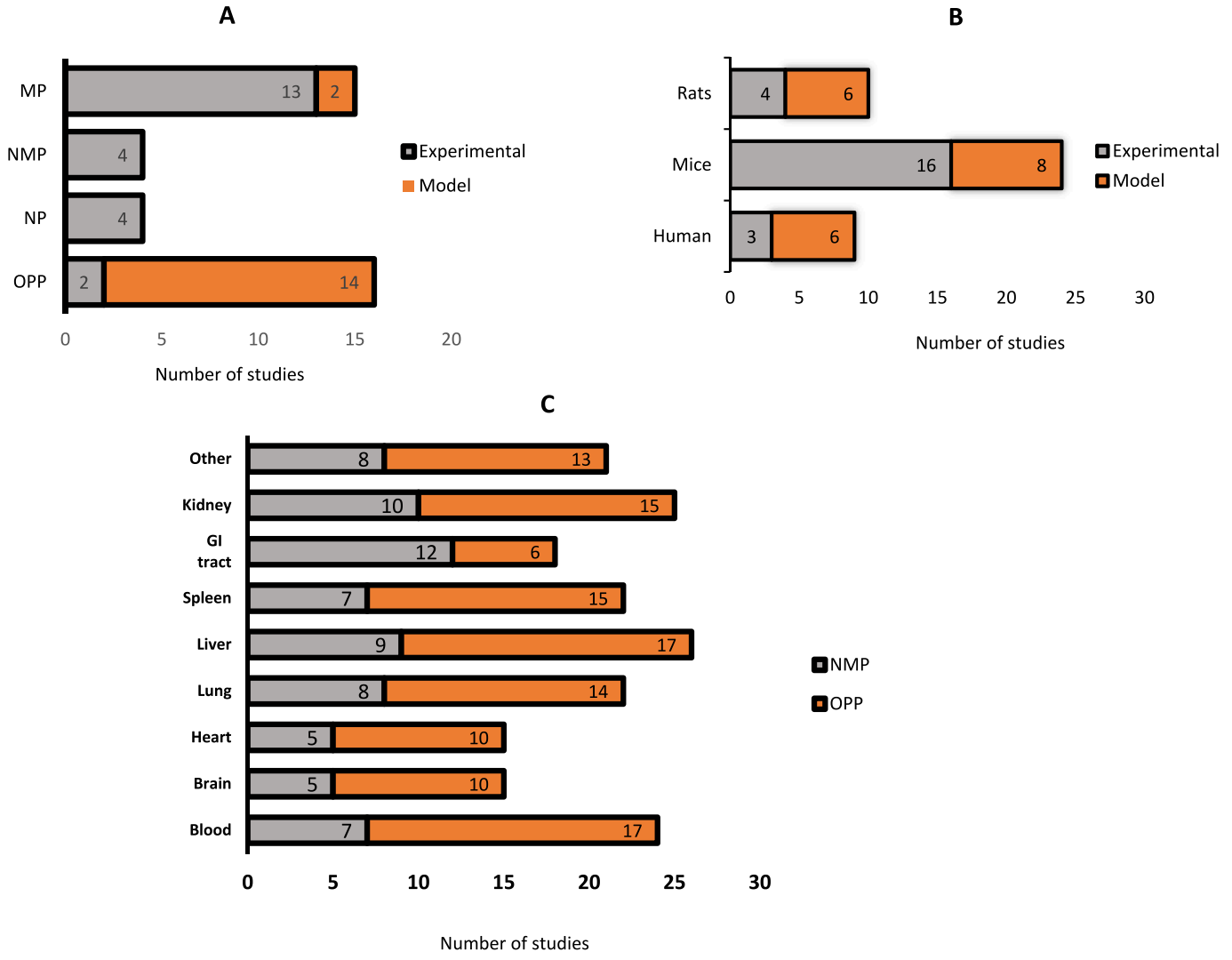


Fig. 2. (A) distribution of modeling and experimental studies based on the type of particle (MP = microplastics, NP = nanoplastics, NMP = nano- and microplastics, OPP = other polymeric particles (i.e PLGA, PEG, PLA, PCL, PAA, PCA, and polymeric radioactive particles) (B) distribution of studies based on the type of species (C) distribution of organ compartments used in biodistribution study of nano- and microplastics and other polymeric particles.

primarily due to the absorption of NMP via ingestion routes.

3.2.1. *Evaluation of experimental studies*

In this section, we discuss how the experimental studies from the literature scored on the QA-QC criteria in the different categories (Table 1). The first assessment criterion is particle characterization. Particle characterization is an essential component of experimental studies involving particles, encompassing particle size, shape, polymer type, particle source, chemical purity, and surface characteristics. The significance of providing clear explanations and thorough characterization in these aspects has been emphasized by previous studies. (Koelmans et al., 2022; Kooi et al., 2021; Gouin et al., 2022) The studies that employed NMP in their research achieved a higher score for the criteria on particle type (Fig. 3), owing to less adjustment required for the physico-chemical properties-related parameters in the PBK model compared to OPP. Several studies that fully reported particle characteristics received high scores for this criterion. (Paul et al., 2022; Wang et al., 2021; Lee et al., 2023) The study by Paul et al. (2022) demonstrated that 1 μm PS particles crossed the Caco-2 membrane epithelium more effectively, with a 66.4 % transfer rate, compared to 10 μm PS particles. Factors such as particle shape and polymer identity also influence the likelihood of NMP encountering and being ingested, thereby affecting their bioavailability. (De Ruijter et al., 2020) Kaplan et al. (2023) showed that spherical poly(lactic-co-glycolic acid (PLGA) nanoparticles released more encapsulated human serum albumin than either rod-shaped or elliptical disc shaped particles, suggesting that particle shape plays a significant role in the cellular uptake of these particles. However, certain studies that reported particle size, shape, and polymer type lacked analytical characterization, instead relying on information gleaned from material safety data sheets or size separation through sieves, resulting in lower scores. (Jiang et al., 2021; Keinänen et al., 2021; Stock et al., 2020) Further, studies with deficient scores in particle characterization necessitated additional verification concerning the chemical purity and surface characteristics of the particles they examined.

The second criterion for assessment is experimental settings. Several variables are crucial for input parameters in a PBK model, including exposure concentration (dose), administration route, and test species. In a study from Paul et al. (2022) the concentration unit used was particle surface area/mL, which is considered a toxicologically relevant metric. (Koelmans et al., 2022) Utilizing multiple doses, excluding the control, is also essential in risk assessment. In toxicity assessment, relying solely on a single-dose experiment makes it challenging to establish a benchmark dose. (Coffin et al., 2022; Noventa et al., 2021) Therefore, studies

A

Publication	Particle characterization						Experimental study design						Applicability for biodistribution modeling						Total score
	Size	Shape	Polymer type	Source	Chemical purity	Surface	Dose	in vitro system	Replicate	Medium/vehicle	Duration of exposure	Controls	Tissue/organ	Biokinetic parameter	Statistical analysis	Longest timepoint	Output indicator	Biodistribution value	
Paul, 2022	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	35
Shi, 2021	2	2	2	2	1	1	2	2	2	2	2	1	1	1	2	0	1	1	27
Stock, 2020	2	2	1	2	1	2	2	2	2	2	2	2	2	1	0	0	1	1	27
Merkley, 2022	1	0	2	2	0	0	1	2	0	0	2	0	1	1	2	1	1	1	17
Hou, 2021	1	2	2	2	2	0	2	2	2	2	2	1	1	1	2	0	1	1	26
Han, 2021	2	2	2	2	2	0	1	2	2	2	2	1	1	1	2	2	1	1	28

B

Publication	Particle characterization						Experimental study design							Applicability for biodistribution modeling						Total score
	Size	Shape	Polymer type	Source	Chemical purity	Surface	Dose	Administration	Test species	Sample size	Duration of exposure	Medium/vehicle	Controls	Tissue/organ	Biokinetic parameter	Statistical analysis	Longest timepoint	Output indicator	Biodistribution value	
Walczak, 2015	2	0	2	2	2	2	1	2	2	2	1	2	1	2	1	2	1	2	2	31
Navarro, 2014	2	2	1	0	2	2	1	2	2	1	2	2	1	2	2	2	2	2	2	32
Sun, 2021	2	2	2	2	0	0	2	2	2	2	2	2	1	1	0	2	0	1	1	26
Jiang, 2021	1	0	1	2	2	0	2	2	2	2	2	2	1	1	1	2	0	1	1	25
Keinanen, 2021	1	0	1	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	33
Lee, 2022	2	1	2	2	2	0	2	2	2	2	2	2	2	2	2	2	1	2	1	33
Schwarzfischer, 2022	2	2	2	2	2	0	1	2	2	2	2	2	2	2	1	2	0	1	1	30
Im, 2022	2	2	2	2	2	2	1	2	2	0	2	2	0	2	2	2	2	2	2	33
Ahmed, 2022	1	2	2	2	1	1	2	2	2	2	2	0	1	1	1	2	0	1	1	26
Deng, 2017	1	2	2	2	0	0	2	2	2	2	2	2	1	1	1	2	2	2	2	30
Lee, 2023	2	2	2	2	2	2	2	2	2	2	2	2	1	2	1	2	2	2	2	36
Liang, 2021	2	2	2	2	2	0	2	2	2	2	2	2	1	2	1	2	2	2	2	34

C

Publication	Particle characterization						Experimental study design in vivo							Experimental study design in vitro						Applicability for biodistribution modeling						Total score
	Size	Shape	Polymer type	Source	Chemical purity	Surface	Dose	Administration	Test species	Sample size	Duration of exposure	Medium/vehicle	Controls	Dose	in vitro system	Replicate	Medium/vehicle	Duration of exposure	Controls	Tissue/organ	Biokinetic parameter	Statistical analysis	Longest timepoint	Output indicator	Biodistribution value	
Kaplan, 2023	2	2	1	2	2	2	1	2	2	2	2	2	1	1	2	2	2	2	1	2	1	2	2	2	1	43
Tsukigawa, 2022	2	0	1	2	2	2	2	2	2	0	2	0	0	2	2	2	2	2	2	2	2	2	2	2	2	41
Sun, 2021	1	0	2	2	2	0	2	2	2	2	2	2	1	2	2	2	2	2	1	1	1	2	0	1	1	37
Wang, 2021	2	2	2	2	2	2	1	2	2	2	2	2	1	2	2	2	2	2	1	1	1	2	2	1	1	43
Stock, 2019	2	2	2	2	0	0	2	2	2	2	2	2	1	2	2	2	2	2	1	2	1	2	2	2	2	43

Fig. 3. Results of individual assessment from experimental studies: (A) *in vitro* (B) *in vivo* and (C) both *in vivo* and *in vitro*. Scores signify the following: 2 = reliable without restrictions, 1 = somewhat reliable but with restrictions, 0 = not reliable. Full literature references are provided in the Supporting Information.

incorporating multiple doses, e.g. (Lee et al., 2023; Lee et al., 2022; Liang et al., 2021) receive higher scores for this criterion. While most experimental studies in this review meet all the criteria for experimental settings, some lack clear explanations of the test medium or delivery vehicle and controls in their publications. (Im et al., 2022; Merkley et al., 2022; Tsukigawa et al., 2015) The delivered dose is also determined by the properties of the medium, which can results in formation of larger agglomerates. (WHO, 2022) The use of protein in the sample preparation to disperse NMP also may generate the reactive oxygen species, due to the potential of protein corona formation on the particle surface, which enhance cellular interaction. (Gouin et al., 2022; Fernández-Cruz et al., 2018) Additionally, the presence of positive or negative controls for both *in vitro* and *in vivo* studies allows for a comparison of relative performance. (Gouin et al., 2022) Overall, the experimental studies involved in this review largely fulfill the criteria for experimental settings (by 85 % in total), with a few exceptions regarding clarity in reporting test media, delivery vehicles, and controls.

The final criterion for experimental studies is the applicability for biodistribution modeling. Here we emphasize that studies may not have aimed to provide data specifically for biodistribution modelling. Our judgment therefore says nothing about the quality or legitimacy of a study, but only about whether a study is suitable for modelling, in hindsight. This applicability criterion encompasses several factors, including the target tissue or organ compartment, biokinetic parameters representing the ADME (absorption, distribution, metabolism, and excretion) process, statistical analysis, longest time-point, biodistribution metric, and biodistribution values. Studies that incorporate multiple organ compartments (Im et al., 2022; Kaplan et al., 2023; Keinänen et al., 2021; Liang et al., 2021; Navarro et al., 2014; Tsukigawa et al., 2015; Walczak et al., 2015) receive higher scores as they provide a more comprehensive representation of the biokinetic processes involved in the expected biodistribution model. Time-series data is also important

to identify the longest time-point measured in the experiment, which relates to the time taken to reach the maximum concentration (t_{max}) in the future biodistribution model. Some studies only perform statistical analysis to determine whether there is a significant toxicity effect on certain tissues or organs, while lacking this longest-timepoint criterion. (Ahmed et al., 2022; Hou et al., 2021; Shi et al., 2021; Stock et al., 2020; H. Sun et al., 2021; R. Sun et al., 2021) Certain studies excel in reporting biodistribution values and biodistribution metrics, (Im et al., 2022; Lee et al., 2023, Lee et al., 2022; Tsukigawa et al., 2015) utilizing terms like area under curve (AUC), %ID/gr of tissue, maximum plasma concentration (C_{max}), terminal half-life ($t_{1/2}$), total clearance (CL) or the benchmark dose (e.g NOAEL, LD_{50}, IC_{50}). These values are crucial for practical application in PBK models for NMP. While the abovementioned criteria are important for research reproducibility and quality assurance of findings, this last criterion holds utmost significance when considering the practicality of applying these values to PBK models for NMP. The assessment score for all studies for each criterion is available in **Table S2**.

Despite the shortcomings identified through the screening criteria developed in this study, there are several studies that received no zero scores in any category. (Paul et al., 2022; Wang et al., 2021; Kaplan et al., 2023; Lee et al., 2023) This implies that conducting an experimental study that fully aligns with these criteria is indeed feasible.

3.2.2. *Evaluation of modeling studies*

The first assessment criterion for modeling studies are the scope and purpose of the model (Table 1). This criterion considers the model's objective, particle type, species, dose, and administration routes. Most of the studies reviewed in this context fulfill these criteria, except for particle type (Fig. 4). Remarkably, the studies conducted by Mohamed Nor et al. (2021) and Yang et al. (2019) stand out with higher scores due to their inclusion of NMP within their respective models. It is necessary to explicitly mention the particle types and consider their relevant characteristics when conducting modeling studies, as most of the modeling studies in this review are based on polymers used for drug deliveries. For example, polyethylene glycol (PEG) can be modified to have a neutral charge and form a hydrophilic three-dimensional barrier that hinders cell interactions, thereby reducing internalization. (Zielińska et al., 2020) On the other hand, the potential hydrophobic nature of NMP makes them more easily engulfed by macrophages. (Larson et al., 2012) Moreover, the size difference between microparticle and nanoparticles influences their *in vivo* biodistribution. In the human body, Kupffer cells are responsible for the clearance of particles larger than 500 nm from the bloodstream, while the kidneys handle particles smaller than 10 nm, and particles exceeding 200 nm, are typically managed by the spleen. (Agarwal, 2003) Size is also a critical factor when considering the use of particles for drug delivery. Particles exceeding approximately 3 μm in diameter run the risk of obstructing the smallest blood capillaries, which are typically around 5 μm in size. This highlights the significance of selecting appropriately sized carrier particles. (Di et al., 2021) For efficient and sustained drug delivery, particles ranging from 10 to 200 nm are considered optimal as they can evade both kidney and spleen clearance. (Di et al., 2021) When targeting organs such as the liver, spleen, and immune cells, particles within the 200 nm to 1 μm range are favored. This size range is particularly relevant for scenarios involving intravenous administration. (Agarwal and Roy, 2013).

The second assessment criterion for modeling studies involves evaluating the settings of the model, including the model structure, organ compartments, model type, simulation time, model equations, and the software used (**Table S1**). Among the studies reviewed, four studies received a perfect score for this evaluation criterion (L. Deng et al., 2019; Li et al., 2014; Li et al., 2021; Lin et al., 2016) (Fig. 4). However, most studies received lower scores due to a lack of information regarding the model type, whether perfusion (blood-flow) limited or diffusion (membrane-flow) limited. This distinction is crucial as it affects the model equations and determines which process limits the particle kinetics within the body circulatory system. Another variable to consider is the software used in the study. Several papers received lower scores (0 or 1) because they either did not mention the software name or, if mentioned, did not provide the necessary information, such as links to scripts or codes. This information is critical, primarily when non-standard PBK software or general computational models like MATLAB, R Studio, or Python are utilized. The inclusion of such information is vital for ensuring the reproducibility of future research and to guarantee the quality of the model calculations.

Publication	Scope and purpose of the model					Settings of the model						Model parameters				Outcome and performances				Total score
	Objective	Particle type	Species	Dose	Administration	Structure	compartment	Type	Sim. time	Equatior	Software	Datasets	Inp. parameters	Opt. parameters	Allometric scale	Outcome	Validation	Performance	Sensitivity	
McSweeney, 2018	2	1	2	2	2	1	1	1	2	2	2	2	2	1	2	2	2	1	1	31
Lin, 2016	2	1	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	36
Gao, 2019	2	1	2	2	2	2	2	0	2	2	2	2	2	2	2	2	2	2	2	35
Shalgunov, 2017	2	1	2	2	2	2	2	2	2	2	0	2	2	2	0	2	2	1	0	30
Minnema, 2022	2	1	2	2	2	2	2	2	2	0	1	2	2	2	0	1	2	2	2	31
Mohamed Nor, 2021	2	2	2	2	2	2	1	0	2	2	2	2	2	2	1	1	2	2	2	33
Raza, 2022	2	1	2	2	2	0	1	1	2	0	2	2	2	2	0	2	2	2	0	27
Gilkey, 2015	2	1	2	2	2	1	1	0	2	2	1	2	2	2	0	2	2	1	2	29
Li, 2014	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	37
Li, 2013	2	1	2	2	2	2	2	2	2	0	1	1	2	2	2	2	1	2	2	32
Li, 2021	2	1	2	2	2	2	2	2	2	2	2	2	2	2	0	2	2	2	2	35
Deng, 2019	2	1	2	2	2	2	2	2	2	2	2	2	2	2	1	2	1	2	2	35
Carlander, 2016	2	1	2	2	2	2	2	1	2	0	1	2	2	2	0	2	2	2	2	31
Saffari, 2019	2	1	2	2	2	0	2	0	2	2	0	2	1	2	1	2	0	1	2	26
Tichacek, 2020	2	1	2	2	2	2	1	0	2	2	0	2	2	2	0	2	1	2	0	27
Yang, 2019	2	2	2	2	2	1	1	1	2	2	1	1	2	2	2	2	2	2	2	33

Fig. 4. Results of individual assessment for modeling studies. Scores signify the following: 2 = reliable without restrictions, 1 = somewhat reliable but with restrictions, 0 = not reliable. Full literature references are provided in the Supporting Information.

The third criterion for modeling studies involves evaluating the model parameters, including variables such as the source of datasets, availability of input parameters, optimization or estimation of model parameters, and the consideration of allometric scaling. Among the studies reviewed, two studies received perfect scores for clearly explaining these variables in their research (Li et al., 2014; Gao et al., 2019) (Fig. 4). However, most of the studies in this review lacked reporting on allometric scaling for their model parameters. A study from Gao et al. (2019) explicitly stated that their rat model was scaled up to humans by replacing physiological and pharmacokinetic parameters with human-specific values. The calculations for each parameter were well-explained, and relevant references were provided. Most PBK models discussed in this review were developed using a so-called bottom-up approach. Therefore, they predominantly depend on input parameters derived from *in vitro* studies conducted on rodents. Allometric scaling allows for the extrapolation of data from one species to another based on physiological and anatomical differences. It is crucial to clearly describe the methods used for allometric scaling to ensure transparency and accuracy in model parameter estimation for human applications.

The fourth and final criterion applied in the modeling studies focuses on model outcomes, model validation, model performance, and the presence of sensitivity or uncertainty analysis. Model validation was predominantly performed in the modeling studies included in this review, although not all model outputs met the predetermined validation criteria. In our QA/QC assessment tool, we have evaluated the quality of model validation in two ways: (a) by assessing whether simulations using the calibrated model were compared with empirical biodistribution datasets other than those used for calibration, i.e., independent datasets, and (b) by evaluating whether simulations in which parameter values were based on results from independent tests and experiments (i.e., first principles) are consistent with independent biodistribution datasets (Table S1). Most of the studies adhered to the recommended "good" model definition by WHO (IPCS, 2010) where the predicted values were expected to deviate by less than a two-fold difference from the experimental data. Studies that achieved this criterion received a score of 2 (Fig. 4). Alternatively, some studies used a benchmark of $R^2 > 0.75$ from linear regression analysis to assess the performance of their models Several studies that did not receive a perfect score (score of 2), provided explanations for the inadequate performance of their models, and thus were awarded a score of 1. Among the studies reviewed, the majority conducted local sensitivity analysis as part of their research, (L. Deng et al., 2019; Di et al., 2021; Gilkey et al., 2015; Li et al., 2014, 2021; Lin et al., 2016; McSweeney et al., 2018) However, only two studies (Mohamed Nor et al., 2021; Yang et al., 2019) conducted global sensitivity analysis, using Monte Carlo simulation for their model parameters. Additionally, some studies employed alternative methods, such as the propagation of errors approach (Saffari et al., 2019) and fourth order Runge-Kutta integration algorithm approach (Carlander et al., 2016). Notably, three studies (Raza et al., 2022; Shalgunov et al., 2017; Tichacek et al., 2020) did not include sensitivity analysis, and consequently, received lower scores in this regard. Overall, majority of the modeling studies reviewed demonstrated commendable reporting of model outcomes and performances, thereby satisfying the specified assessment criteria.

3.3. Addressing the diversity of NMP for the development of PBK models

Dietary and inhaled NMP consists of a heterogeneous mixture of polymers, sizes, and shapes, are associated with various chemicals found in plastic products. NMP undergoes biofouling, weathering, aging, and interacts with chemicals, organisms, and natural particles under variable environmental conditions. The polymer composition and density of NMP depend on the polymers used, emission levels, and environmental alteration processes. The most abundant NMP polymers are PE, PET, PA, PP, PS, PVA, and PVC. (SAPEA, 2019) NMP particles span a wide size range, from nano- to millimeter-scale, with smaller particles being more abundant. The shapes of NMP include fragments, fibers, and films, influenced by product or material categories. NMP characteristics follow a continuous distribution, and PDFs can be used to describe their diversity. (Koelmans et al., 2022).

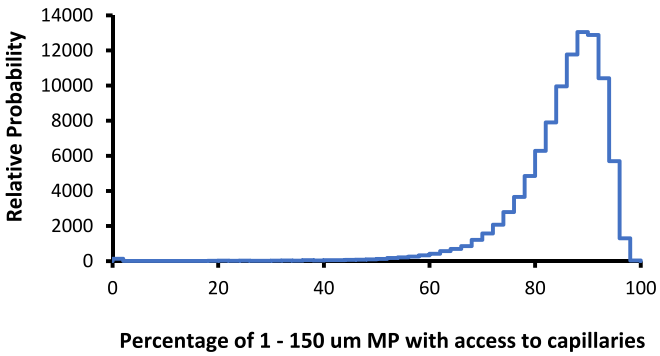


Fig. 5. Probability distribution of the fraction of NMP particles (1 to 150 μm) that theoretically have access to the capillaries of the human circulatory system, accounting for uncertainty and diversity of NMP and blood vessel dimensions.

A PDF is a mathematical function that accurately describes the distribution of a particular characteristic of NMP. (Kooi and Koelmans, 2019) This function is developed by fitting it to empirical data collected from a large number of datasets for NMP in a specific environmental area, or, likewise, in dietary components relevant for human exposure. For instance, three PDFs can capture the size, shape, and density, encompassing a total of twelve parameters that encompass the entire range of diversity in environmental NMP. (Kooi and Koelmans, 2019) On the other hand, when using bins or categories, the information within the bin is lost. (Hartmann et al., 2019; Bucci and Rochman, 2022; Rochman et al., 2019) The PDFs framework maintains the diversity of NMP mixtures in a lossless manner using continuous mathematical functions. (Koelmans et al., 2023) PDFs have several applications, including probabilistic quantification of MP in transport and fate modeling, scaling number concentrations from limited size ranges to the full 1 to 5000 μm MP size range, converting number concentrations to mass concentrations, assessing exposure, effects, and risks, and quantifying and visualizing the bioavailability of NMP (as shown in Fig. 5). (Koelmans et al., 2023) PDFs for environmental media have been calibrated using a *meta*-analysis of over 60,000 MP particles, with their characteristics measured using FTIR imaging. (Kooi et al., 2021) Similarly, PDFs have been developed to describe the diversity of NMP traits in components of the human diet. (Mohamed Nor et al., 2021) Such calibrations allow for the derivation of polymer- and exposure pathway-specific PDFs, which are useful for conducting external and internal exposure assessments.

So far, PDFs have often been expressed as power law equations of the form $Y = bX^{-\alpha}$, where X represents toxicologically relevant metrics (TRMs) like particle size, volume, or surface area. (Koelmans et al., 2022) These metrics are utilized to define the dose of organisms, such as humans, exposed to NMP. Using these equations as an example, we present three potential applications of PDFs in the PBK modeling of NMP.

3.3.1. Probabilistic modeling of the multidimensionality of the NMP continuum

Given the time scales relevant to human exposure to NMP particles, the characteristics of the particles can be considered as a continuum. As mentioned above, it is particularly interesting to model TRMs as a continuum, i.e. via PDFs, and that also applies to PBK models.

3.3.2. Probabilistic definition of external exposure

In section 3.4.2 we discuss external exposure, which serves as the starting point for quantifying internal exposure by establishing the

boundary conditions in PBK modeling. PDFs can be defined for all dietary components relevant to human exposure and for inhaled air, incorporating probabilistic treatment of model parameters to consider uncertainty and the diverse characteristics of particles.

3.3.3. Probabilities of transfer and accessibility dependent on NMP particle characteristics

Following external exposure, the absorption of particles from the gut involves processes like transcytosis, micropinocytosis, phagocytosis, receptor-mediated endocytosis, paracellular transport, persorption, or uptake by migratory phagocytes. (Wright and Kelly, 2017; Prata, 2023) This absorption is known to be size-dependent, with transfer probabilities varying based on the size and shape of particles. Similar size-dependent dynamics apply to other transfer processes within the body, such as the recirculation of NMP through the human circulatory system, crossing the blood–brain barrier to reach the brain, or excretion in the liver via phagocytosis or biliary excretion. Over time, both external and internal exposures at these transfer barriers can be best described as exposure to a continuum of particles and their characteristics, which can be effectively represented by continuous PDFs. Known size boundaries and probabilities of transfer within these boundaries are typically reported as distributions or probabilities, making them suitable for modeling using PDFs. As a proof-of-concept example, we present the theoretical bio-accessibility of NMP particles in the human circulatory system. Once these particles enter the circulatory system, larger particles (e.g., >5 μm) have the potential to become trapped in capillaries, while smaller particles (e.g., <5 μm) are eliminated by macrophages of the reticuloendothelial system. (Wright and Kelly, 2017; Prata, 2023; Yee et al., 2021) The occurrence and fraction of particles in the NMP continuum affected by these processes depend on the distribution of blood vessel dimensions and the particle dimensions present in the bloodstream. By assuming a common particle size power law slope of $\alpha = 2.5 \pm 0.25$ (Kooi et al., 2021), considering observed gut translocation for inert particles (e.g., starch granules) with sizes up to 150 ± 25 μm in humans (WHO, 2022; Prata, 2023; Yee et al., 2021), and utilizing empirical data on the distribution of blood vessel dimensions and interindividual variability (Camasão and Mantovani, 2021), we calculate the fraction of NMP particles residing in capillaries versus veins and arteries. The probabilistic calculation with 10^5 Monte Carlo iterations accounts for uncertainties in power law slope, translocatable size boundaries, and blood vessel dimensions. Our results indicate that a median of 85.4 % (with 67.5 – 93.5 % being the 5th to 95th percentile range of the distribution) of the particles would enter the capillaries, while the remaining fraction would be distributed among veins, venules, arteries, and arterioles due to size restrictions (Fig. 5). This approach provides a more accurate representation of the distribution processes occurring in the human body, encompassing various polydisperse fractions of the total NMP continuum. In addition, it is important to acknowledge that a continuum of size-dependent uptake exists. For instance, it is probable that very few particles measuring 150 μm in size can traverse the gut barrier (<0.002 % of ingested fraction) (Gardner et al., 1995), while this likelihood increases as particle size diminishes, reaching approximately 0.5 % for sub-micron particles. (Gardner et al., 1995) Consequently, the gut epithelium can be likened to a selective filter or sieve, and the initial external PDF undergoes alterations as particles traverse the epithelium in a manner regulated by both size and rate limitations. It is important to note that fully probabilistic PBK models can be computationally demanding. To reduce the number of iterations needed for representative sampling and to conserve computational memory for processing other model parameters, the implementation of Monte Carlo simulations with Latin Hypercube sampling is recommended.

3.4. Comprehensive risk assessment framework for NMP and human health

3.4.1. Probability density functions in the context of risk assessment

Above we described the use of PDFs in the context of external exposure assessment and internal exposure assessment, the latter through PBK (biodistribution) modeling. The next step is to link PDF-based PBK models to PDF-based effect assessments to obtain a PDF-based probabilistic risk assessment framework. The merits of such a probabilistic framework is that it enables us to do justice to all propagating diversities and uncertainties in the nature as well as in the abundance of the NMP materials that humans are exposed to, in media relevant for human exposure, as well as to the diversity in body characteristics relevant for fate, effects and thus risks in the human body.

Recently, a risk assessment framework has been developed that assures a consistent risk characterization for all NMP relevant to human exposure, maintaining the multidimensionality of the material. (Koelmans et al., 2022) The framework measures or models exposure (Fig. 6) so that the full NMP continuum is taken into account. In the case of modeling emission and exposure, concentrations and TRMs are captured in PDFs, which allow for the definition of size cut-offs so as to implement relevant bioavailability limitations for uptake and biodistribution in the human body. In the case of exposure assessment through empirical data, PDFs also are used to fill in data gaps due to different analytical methods targeting different fractions of the full NMP continuum. The resulting set of TRM concentrations is input in PBK models, through which lifetime internal exposure at the sensitive target site (e.g. tissues, organs, fluids) is assessed. This is informed by reference dose data from toxicity tests, which allow for the assessment of the most likely mechanisms of effect and their target sites. NMP in media relevant for human exposure differ from laboratory NMP used in experiments, and understanding its exposure and risks requires addressing this difference. Using PDFs can solve this challenge, because effect thresholds measured for the 'monotype' NMP typically used in effects tests can be translated into the same set of TRMs used for the exposure assessment. Consequently, this integrated approach facilitates more relevant and realistic comparisons of exposure and hazard data – often referred to as 'apple-to-apple' comparisons - in the risk characterization of NMP. In situations where data are inadequate to establish complete PDFs for all model parameters, incorporating provisional values, such as averages, maximums, or minimums is advisable. This strategy enables the performance of 'worst-case' assessments until more comprehensive data are available.

3.4.2. Linking external exposure to internal exposure

Humans are exposed to NMP from various sources, predominantly through two pathways: ingestion and inhalation. In recent research by Mohamed Nor et al. (2021) NMP occurrences were identified in nine intake media (fish, mollusc, crustacean, tap water, bottled water, salt, beer, milk and air) from existing literature then. As described in section 3.3, PDFs are recommended to define the heterogeneous NMP mixture in each intake media. (Mohamed Nor et al., 2021) However, the databases for these human intake media usually have several discrepancies due to varying definitions of NMP and analytical techniques. Hence, we also propose correction techniques such as size realignment (Koelmans et al., 2020) to correct for these inconsistencies in the databases before unifying the different datasets into one PDF for one intake media.

Although humans are exposed to the whole continuum of NMP, only a small fraction of NMP particles is bioaccessible. This bioaccessible fraction can likely be taken up in the intestine via several possible mechanisms identified, i.e., phagocytosis, endocytosis, persorption (Wright and Kelly, 2017; Prata, 2023). The fraction of particles absorbed in the intestines is a crucial parameter as it will determine the eventual internal exposure to other affected organs. As discussed in the earlier section (Section 3.1.5 under subsection Absorption-related parameters), particle uptake is limited by the size range and even then the likelihood decreases as particle sizes increases (see section 3.3 under subsection

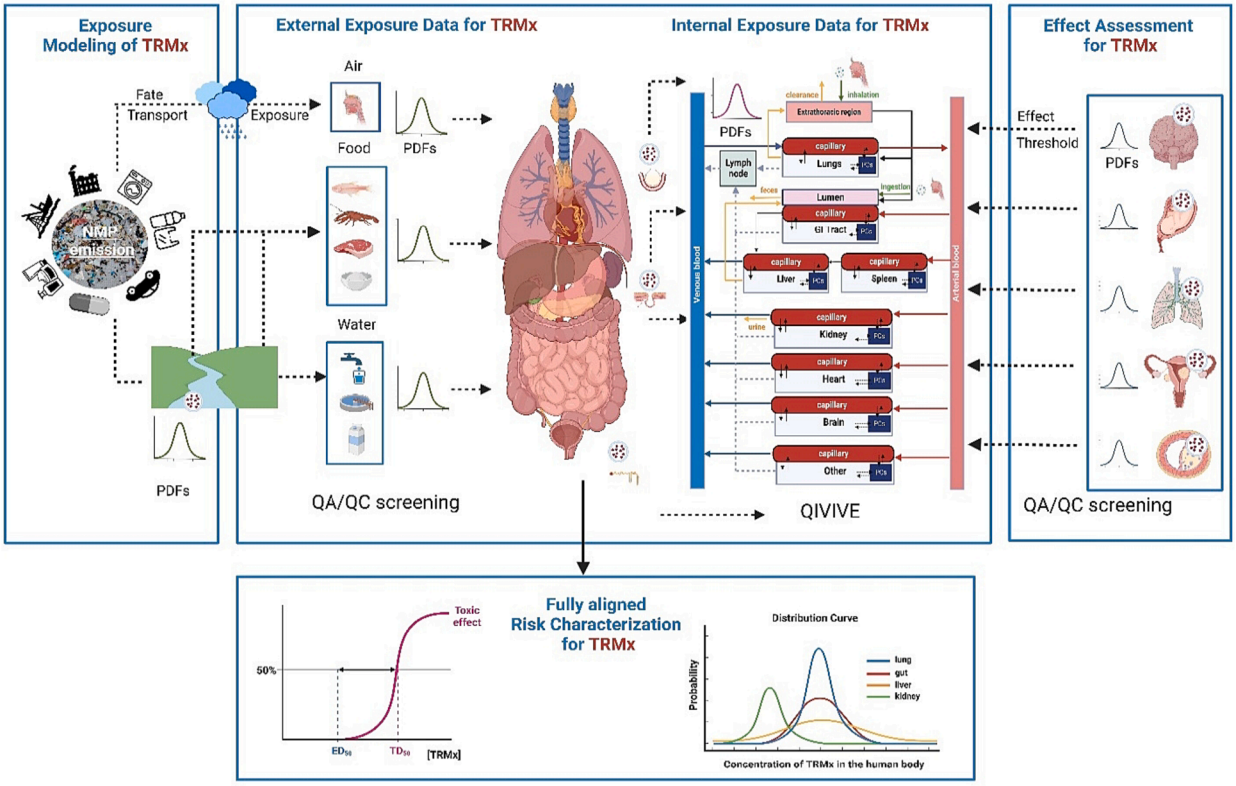


Fig. 6. A PDF-based risk assessment framework for NMP and human health ("Created with BioRender.com"). From left to right: exposure is modeled from emission models and fate models. These provide predicted concentrations in media relevant for human exposure, such as air, water, soils, crops, and biota. Alternatively, NMP can be directly measured in air and in components of the human diet. Both types of data can be converted into PDFs from which external exposure is modeled probabilistically. External exposure provides the boundary conditions for internal (PBK) exposure modeling where certain size fractions are available for translocation at a certain probability, both of which can be captured through PDFs. Biodistribution is modeled as transport via the circulatory system and absorption by various organs and tissues. The resulting concentrations and characteristics, which resemble only a small and specific fraction of the original suite of particles humans are exposed to, can be compared with empirical data on NMP concentrations in human samples, and with reference dose (in mg/kg bw/day) or reference concentration (mg/L or ppm). Model output is a set of probabilistic distributions of risk characterization ratios along the transport routes of NMP particles in the human body. A detailed presentation of the structure for the PBK model for internal exposure is provided as Figure S3.

'Probabilities of transfer and accessibility dependent on NMP particle characteristics'). A fraction of the total particles inhaled can be trapped in the upper airways and subsequently swallowed through the nasopharyngeal cavity. (Fry and Black, 1973) These swallowed particles from the air compartment may also likely be absorbed in the intestines.

Another important parameter linking external and internal exposure is the tissue removal excretion rate constant. Absorbed NMP particles can likely be removed from the circulatory system via phagocytosis or the biliary excretion pathway in the liver. (Mohamed Nor et al., 2021) However, little is known about the removal of NMP particles from the circulatory system in humans. Our previous study (Mohamed Nor et al., 2021) performed a scenario-based analysis with several possible biliary excretion rates estimated from three rat and mouse studies on nanoparticles. We propose that the tissue removal excretion pathway should be defined probabilistically to account for the uncertainties of this parameter.

Finally, the unabsorbed NMP in the gastrointestinal tract are lost via egestion. This parameter is defined as a loss rate constant based on stool frequencies which was applied by Mohamed Nor *et al.* (Mohamed Nor et al., 2021) The amount of NMP egested in stool can be used as one of the model outputs to calibrate and validate the PBK model against empirical data.

3.4.3. Tissue dosimetry

Determining the appropriate dose for *in vitro* studies is crucial for toxicological research. (Teeguarden et al., 2007) When reporting administered particle doses, the commonly used metrics of initial mass or number concentration may not accurately represent the actual dose delivered to cells over time. (WHO, 2022) To accurately assess the potential adverse effects of a substance, it is essential to consider factors such as the mass, surface area, volume, or the number of particles that come into direct contact with cells, as well as the area under the time-concentration curve. (WHO, 2022; Koelmans et al., 2022) These parameters provide a more accurate representation of the dose at the site of action by taking into account particle characteristics, medium properties, and exposure duration. (Fernández-Cruz et al., 2018) However, a standardized method for determining the equivalent *in vitro* dose corresponding to human exposure estimates is currently lacking, posing challenges for researchers in establishing relevant and comparable dose ranges. (WHO, 2022; Sohal et al., 2018).

In vitro models, such as cell monocultures or co-cultures, provide valuable data on the biokinetics of substances. (WHO, 2022) However, it is essential to note that these models differ from cells within an organ and may not fully replicate the physiological conditions of oral or inhalation exposure, which are more relevant for human exposure scenarios. (Fernández-Cruz et al., 2018; Teeguarden et al., 2007).

Applying PBK modeling for dose–response analysis offers a more accurate extrapolation to human exposure conditions by providing an analysis based on the target tissue or cellular dose. (IPCS, 2010) The correlation between the concentration of an active substance and its toxic effects on a specific tissue underscores the importance of understanding the mode of action (MOA) driving the adverse response. (Clewell et al., 2002) In a MOA-focused risk assessment, relevant scientific data encompassing anatomical, physiological, biochemical, and

physicochemical aspects can be integrated into PBK models. These models serve to represent dose metrics that are pertinent to biological reactions. (IPCS, 2010) In the context of NMP exposure, this approach can be termed as the toxicological relevance metrics (TRM) approach, where the specific MOA determines the selection of the TRM to be employed within the PBK model (Fig. 6). For instances, aspect ratio is a relevant TRM for an internal damage related to fibre toxicity, and surface area is a suitable TRM for oxidative stress. (Koelmans et al., 2022) Given that particles might be involved in multiple MOAs, (Koelmans et al., 2022) it becomes necessary to simultaneously incorporate diverse TRMs to comprehensively capture their potential effects.

In the context of NMP risk assessment, Quantitative *In Vitro* to *In Vivo* Extrapolation (QIVIVE) plays a crucial role in enhancing the accuracy of predictive PBK models. QIVIVE has two primary applications in NMP risk assessment. First, it acts as a valuable tool for deriving model parameters for PBK models by translating *in vitro* data from rodent studies into kinetic rate data for *in vivo* scenarios. Second, QIVIVE is essential in estimating the human equivalent dose using a reverse dosimetry approach, where the internal concentration determined by the PBK model informs the calculation of the human equivalent dose. Furthermore, the approach tackles the polydispersity of NMP particles for the relevant TRMs by using PDFs to characterize this polydispersity. This step includes rescaling data sets from monodisperse to polydisperse particles, accounting for variations in size, shape, and/or density, thus contributing to a more accurate and comprehensive risk assessment framework (Fig. 6).

3.4.4. Interspecies extrapolation

In the context of NMP and human health risk assessment, extrapolation methodologies from mice to humans have been proposed. These methodologies utilize toxicokinetic and toxicodynamic estimations along with risk assessment schemes. One approach involves multiplying animal doses at various times based on body weight and surface area ratios across species. (Schmid and Cassee, 2017) Another method applies an extrapolation algorithm to transform internal doses of mice into human equivalent doses. (Yang et al., 2019) For instance, in the assessment of polystyrene MP, the no-observed-adverse-effect-level (NOAEL) in mice, body weight ratios, and an allometric exponent were used to estimate human equivalent doses. (Yang et al., 2019) To establish more stringent standards, the NOAEL of mice was replaced with threshold doses of biomarkers estimated from the Weibull threshold model. Additionally, a default safety factor of 10 was applied to account for variabilities in biological processes and sensitivities between mice and humans. (IPCS, 2010).

These extrapolation approaches contribute to a comprehensive human health risk assessment of NMP, considering limited *in vivo* data. (Noventa et al., 2021; WHO, 2022) They help bridge the knowledge gap by providing estimations of threshold exposure concentrations in humans based on available information from animal studies. (Noventa et al., 2021) However, it is important to note that these extrapolations still involve uncertainties and assumptions due to the inherent differences between animal models and human systems.

4. Conclusion

This study explores the development of PBK models for calculating the biodistribution of chemicals in the human body, with a particular emphasis on addressing knowledge gaps in assessing internal exposure to NMP. The studies included in this research can serve as a foundational basis for the development and validation of NMP-specific PBK models. The outlined assessment criteria, applicable to both experimental and modeling studies, offer valuable guidance for selecting relevant data inputs for these models. It is important to note, that our QA-QC assessment revealed that neither modeling nor experimental biodistribution studies achieved a perfect score. However, several studies did receive a non-zero score for all criteria.

To accommodate the diverse nature of NMP, the PDFs approach is a powerful method that can be employed. A proof of concept has been demonstrated by integrating the concept of PDFs into the assessment of the bio-accessible fraction of NMP within the human body. Furthermore, we have established a robust framework that aligns NMP exposure data with potential health effects, forming a solid foundation for human health risk assessment. However, certain considerations should be taken into account. For example, caution should be exercised when extrapolating *in vitro* data to *in vivo* conditions, as well as when translating external exposure levels to the delivered dose in the body. These factors need to be carefully considered to ensure the accuracy and reliability of the PBK models and their application in assessing the potential risks associated with NMP on human health. The PDF-supported probabilistic calculation of error propagation based on all known uncertainties in parameters and variables used in PBK models is crucial to communicate the implications of NMP particles to policymakers and the public in a transparent and unbiased manner.

CRediT authorship contribution statement

Ira Wardani: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Nur Hazimah Mohamed Nor:** Data curation, Funding acquisition, Supervision, Writing – review & editing. **Stephanie L Wright:** Data curation, Formal analysis, Writing – review & editing. **Ingeborg M Kooter:** Writing – review & editing. **Albert A. Koelmans:** Conceptualization, Data curation, Formal analysis, Supervision, Validation, Visualization, Writing – review & editing.

Declaration of competing interest

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

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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