



## Nano- and microplastics: a comprehensive review on their exposure routes, translocation, and fate in humans

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### ABSTRACT

Contamination of the environment with nano- and microplastic particles (NMPs) and its putative adverse effects on organisms, ecosystems, and human health is gaining increasing scientific and public attention. Various studies show that NMPs occur abundantly within the environment, leading to a high likelihood of human exposure to NMPs. Here, different exposure scenarios can occur. The most notable exposure routes of NMPs into the human body are via the airways and gastrointestinal tract (GIT) through inhalation or ingestion, but also via the skin due to the use of personal care products (PCPs) containing NMPs. Once NMPs have entered the human body, it is possible that they are translocated from the exposed organ to other body compartments. In our review article, we combine the current knowledge on the (1) exposure routes of NMPs to humans with the basic understanding of the potential (2) translocation mechanisms into human tissues and, consequently, their (3) fate within the human body. Regarding the (1) exposure routes, we reviewed the current knowledge on the occurrence of NMPs in food, beverages, personal care products and the air (focusing on indoors and workplaces) and found that the studies suggest an abundant presence of MPs within the exposure scenarios. The overall abundance of MPs in exposure matrices relevant to humans highlights the importance of understanding whether NMPs have the potential for tissue translocation. Therefore, we describe the current knowledge on the potential (2) translocation pathways of NMPs from the skin, GIT and respiratory systems to other body compartments. Here, particular attention was paid to how likely NMPs can translocate from the primary exposed organs to secondary organs due to naturally occurring defence mechanisms against tissue translocation. Based on the current understanding, we conclude that a dermal translocation of NMPs is rather unlikely. In contrast, small MPs and NPs can generally translocate from the GIT and respiratory system to other tissues. Thus, we reviewed the existing literature on the (3) fate of

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NMPs within the human body. Based on the current knowledge of the contamination of human exposure routes and the potential translocation mechanisms, we critically discuss the size of the detected particles reported in the fate studies. In some cases, the particles detected in human tissue samples exceed the size of a particle to overcome biological barriers allowing particle translocation into tissues. Therefore, we emphasize the importance of critically reading and discussing the presented results of NMP in human tissue samples.

## 1. Introduction

The overall increase in single-use throw-away plastic products and packaging has led to a tenfold increase in plastics in municipal solid waste from 1960 until 2005 (Geyer et al., 2017; Jambeck et al., 2015; Lebreton and Andrady, 2019), and has even accelerated during the SARS-CoV-2 pandemic (Klemeš et al., 2020; Vanapalli et al., 2021). This increase in plastic waste is further accompanied by more plastic litter in the environment (GESAMP, 2016; Katare et al., 2022).

Once plastics enter the environment, the properties which make them useful turn into a threat to the environment. For instance, the longevity of plastics leads to plastic accumulation in the environment that is expected to persist for hundreds to thousands of years depending on the plastic type (Barnes et al., 2009). However, due to UV radiation, mechanical and biological degradation, larger plastic items can brittle into ever smaller particles (Barnes et al., 2009). Recently, it has been shown that degradation, for instance of polystyrene (PS), is a two-stage process where photooxidation at the near-surface layer is the first step followed by microcrack formation and particle rupturing, leading to the formation of a multitude of even smaller particles (Meides et al., 2021). Thompson et al., 2004 introduced the term microplastics (MPs), which has later been described as all plastic particles smaller than 5 mm in diameter (Arthur et al., 2009). Although there is no official lower size limit of MPs, 1  $\mu\text{m}$  is widely accepted nowadays, and particles smaller than 1  $\mu\text{m}$  are usually termed nanoplastics (NPs) (Gigault et al., 2018; Hartmann et al., 2019). Although MPs have been detected abundantly in the environment, detection and identification of NPs is still very challenging, mainly due to methodological and analytical limitations for detecting NMPs in environmental samples and biological matrices. This aspect has been comprehensively reviewed elsewhere (e.g., Chen et al., 2020; Möller et al., 2020; O'Connor et al., 2019; Schwaferts et al., 2019).

However, the number of NMPs occurring in nature increases with decreasing particle sizes (Hale et al., 2020). Yet, the overall occurrence of NMPs and their small sizes is a potential health risk for organisms. The risk of accidental ingestion or inhalation is much greater for smaller particles than larger particles. In addition, as particle size decreases, the surface area to mass ratio increases. Consequently, the reactivity and toxicity of particles increases, making subsequent interactions with biological barriers more likely (Buzea et al., 2007). Although NMPs have been present in the environment for several decades (Carpenter and Smith, 1972), they are regarded as a rather newly introduced environmental particulate stressors. Furthermore, as NMPs are a highly diverse group of contaminants with various physicochemical properties, overall conclusions on the potential adverse health effects of NMPs are challenging. However, first attempts to perform a risk assessment of NMPs for humans were conducted, which will be discussed later.

Studies on ingestion and subsequent translocation of NMPs in different organisms in nature (Barboza et al., 2020) and laboratory studies (Galloway et al., 2017; Yong et al., 2020) have raised concern about putative adverse effects of NMPs, even to humans (Prata et al., 2020; Wright and Kelly, 2017). Prata et al. (2020) highlighted that upon exposure and uptake, the potential toxicity of NMPs may result from oxidative stress and inflammation, which consequently could disrupt the immune and nervous system. NMPs from the environment may not solely be coated with an eco-corona which is known for enhancing the cellular uptake (Ramsperger et al., 2020) but also with potentially pathogenic microorganisms (Gkoutselis et al., 2021; Kettner et al., 2019; Kirstein et al., 2016; Weig et al., 2021). The accumulation of pathogens

on the surface of NMPs, exceeding the concentration of the surrounding media, may lead to a health threat upon uptake of an increased pathogen load on the particles by organisms.

The number of studies concerning the potential effects of NMPs on an environmental and organismal level steadily increases (Gabriel et al., 2015). In contrast, research on human exposure and toxicity is a relatively new field in NMP research. Nevertheless, there is a growing number of articles addressing the exposure of humans to NMP (Cox et al., 2019; Senathirajah et al., 2021) and their potential health risks (see, e.g. Prata et al., 2020; Rahman et al., 2021; Wright and Kelly, 2017). However, most review articles either focus on a specific exposure route (e.g., Chen et al., 2019; Danopoulos et al., 2020; Mercogliano et al., 2020; Peixoto et al., 2019; Yuan et al., 2022; Zhang et al., 2020) or the potential adverse health effects of NMP to humans upon exposure (Campanale et al., 2020; Danopoulos et al., 2021; Huang et al., 2021; Vethaak and Legler, 2021). In our review article, we combine the current knowledge on the contamination levels of the three major (1) exposure routes of NMPs to humans with the basic understanding of the potential (2) translocation mechanisms into human tissues and, consequently, their (3) fate within the human body. Regarding the (1) exposure scenarios, we reviewed the current knowledge on the occurrence of NMPs in food, beverages, personal care products (PCPs) and the air (focusing on indoors and workplaces). To avoid redundancies to other review articles describing the exposure levels of NMPs to humans, we focused on studies published after 2015. Furthermore, we describe the current knowledge on the potential (2) translocation pathways of NMPs from the primarily exposed organs (skin, gastrointestinal tract (GIT) and lung) into human tissues. Particular attention was paid to the mechanisms that allow particles to translocate into tissues and how likely the translocation from the primary exposed organs to secondary organs is. Based on the presented results of the NMP contamination in the different exposure scenarios and the current understanding of the potential translocation pathways, we critically discuss the significance of the described NMP in the (3) fate studies.

Since there is little to no data on the contamination of the environment and organisms with NPs, we mainly refer to MPs in our review article. We use the abbreviations MPs (5 mm – 1  $\mu\text{m}$ ) or NPs (<1  $\mu\text{m}$ ) to indicate the size class in the respective sections summarized and discussed. For more general statements, we use the abbreviation NMPs.

## 2. Methods of literature research

To avoid redundancy to other review articles, we only included studies from 2015 for the (1) exposure scenarios. To describe the potential (2) translocation mechanisms of NMPs from primary exposed organs (lung, GIT and skin) to other tissues and secondary organs, we did not set a threshold for the year of publication since the general understanding of the mechanisms requires fundamental literature. Since the topic of the (3) fate of NMPs in human tissue samples is a relatively new field of research, we included all studies published so far in the sense of NMPs.

We used *Google Scholar*, *ISI Web of Knowledge/Web of Science*, *Scopus*, *PubMed*, and *Embase* as databases. The common search terms for all chapters were: *microplastic\**, *nanoplastic\**, and *human exposure*. For the more specific chapters, we included the following search terms: *drinking water and beverages* for NMP in drinking water; *meat, fish, seafood, edible tissue, vegetables, milk, egg, roots and tubers, plants and herbs, confectionary, honey, sugar, salt, cereal, rice, maize, wheat, barky, spelt, rye, oat,*

sorghum, millet, teabag, oil, olive oil, vegetable oil, and palm oil for the NMP in food chapter; atmosphere, atmospheric, and air in the NMP inhalation chapter; and cosmetics, personal care products, contraceptive, eye, contact lenses, and ocular surface for the PCP chapter. We were using the additional search terms *human tissue* and *organs* in the fate chapter. No studies were excluded.

### 3. Human exposure to NMPs

Since MPs have been detected abundantly in the environment, the exposure of human beings to NMPs is highly likely (Prata et al., 2021). There are numerous routes of exposure through which humans can come into contact with NMPs. Here we summarize the current knowledge on the contamination with NMPs of drinking water and beverages, the most relevant food items, and indoor air. Furthermore, we address polymers intentionally added as ingredient in PCPs designed for direct application on the human body.

#### 3.1. Drinking water and beverages

Water is essential to sustain human life, and we consume water as plain drinking water as well as in other beverages and in food. Although there are guidelines for drinking water quality (WHO, 2017), contamination with NMPs has yet not been implemented. In the report on microplastics in drinking water by the World Health Organization (WHO) (Organization, 2019), it was described that MP should, in principle, be effectively removed since drinking water treatment is designed to remove particulate matter from drinking water sources. However, it is assumed that the contamination of drinking water with MPs could stem from the raw water used for its generation due to inefficient removal of the particles (Pivokonsky et al., 2018). Zhang et al. (2020) described that the efficiency of removing particles  $>50 \mu\text{m}$  ranges from 25–90%, depending on the treatment technologies of the respective drinking water treatment plants. Since many bottled water and other beverages contain filtered municipal tap water, the contamination with particles  $<50 \mu\text{m}$  could originate from the drinking water used to produce them. However, Mason et al. (2018) compared bottled water from the same brand available in glass or plastic bottles, and the contribution of the plastic bottle to the NMPs load is larger than that stemming from the water directly. Therefore, another potential source of the NMP contamination of bottled water may derive from the production processes, like packaging (Zhang et al., 2020). Furthermore, one potential reason for the higher contamination of plastic bottled water could be the repeated mechanical stress of opening and closing the bottles, increasing MPs release (Winkler et al., 2019).

Several studies investigated drinking water and beverages contamination with MPs, and other review articles have already summarized the current knowledge of MPs in drinking water (e.g. Danopoulos et al., 2020; Eerkes-Medrano et al., 2018; Koelmans et al., 2019). MPs were detected in drinking water, beverages like beer, refreshments, and wine across the globe (Kankanige and Babel, 2020; Makhdoumi et al., 2021; Mason et al., 2018; Shruti et al., 2021). Schymanski et al. (2018) describe that 80% of the detected particles have a size distribution of 5–20  $\mu\text{m}$  and Oßmann et al. (2018) highlighted that more than 90% of the detected particles in their study were even smaller than 5  $\mu\text{m}$ . Consequently, most MPs in drinking water and beverages are not visible to the naked eye.

However, there is a consensus on the occurrence of MPs in bottled drinking water and beverages produced for human consumption, although the actual amount of NMPs within drinking water is still to be evaluated. Based on 10 publications reviewed, Zhang et al. (2020) calculated a human microplastic intake of up to  $4.7 \times 10^3$  particles per person per year. Finally, it's worth of note that drinking water is not solely used for direct consumption but also for further food processing. Therefore, it could contribute to the NMP content in processed food items.

#### 3.2. Food

One of the main uptake routes of NMPs by humans is through food. To obtain a comprehensive picture of NMPs contamination in raw and processed food, we used food categories based on a technical report published by the European Food Safety Authority (EFSA) (EFSA CONTAM Panel, 2016; Food and Authority, 2011) and the classification and description system FoodEx2 (revision 2) (European Food Safety Authority, 2015, 2021) (see Table 1).

Amongst the major food commodities for humans are eggs, meat, milk, cereal and roots (FAO, 2013). Approximately 19% of the global population use seafood as their primary source of animal protein, which indicates how heavily reliant humans are on the oceans' life as protein source (Beaumont et al., 2019; Golden et al., 2016). Over the last 70 years, the global fishery capture production increased by a factor of  $\sim 5$  (1950: 19 million tons living weight; 2019: 94 million tons living weight), whereas the global aquaculture production increased by a factor of  $\sim 200$  (1950:  $6 \times 10^5$  tons living weight; 2019: 120 million tons living weight) (FAO, 2020; FishStatJ software v4.02.04, 2022), to meet the increase in protein needs caused by a growing world population. Therefore, we first summarize the current knowledge of NMPs contamination in 'blue meat', a term introduced by Naylor et al. (2021) defining aquatic foods captured from or cultivated in marine and freshwater ecosystems. It must be noted that within this review, we only consider studies focusing on NMPs content in edible parts of the animals, starting with the findings on species consumed as a whole organism.

Mussels are filter feeders and therefore inadvertently ingest NMPs with their food. As a protein source for humans, they thus represent a potential vector of NMPs (Gündoğdu et al., 2020; Nalbone et al., 2021; Ribeiro et al., 2020; Sparks et al., 2021; Kumar et al., 2021; Wakkaf et al., 2020). The contamination of mussels with MPs was mainly stated in MPs per gram of wet weight (MPs/g w.w.) of the mussels and ranged from  $0.040 \pm 0.003$  MPs/g w.w. up to  $0.9 \pm 0.1$  MPs/g w.w. (Gündoğdu et al., 2020; Nalbone et al., 2021; Ribeiro et al., 2020; Sparks et al., 2021; Kumar et al., 2021), whereas one study estimated a higher value of 2.4 MPs/g w.w. (Wakkaf et al., 2020). Different polymer types with different shapes and sizes were detected in mussel tissues (Table 2). Next to mussels, other species consumed in whole may be relevant vectors of NMPs to humans. Ribeiro et al. (2020) analyzed wild and farm seafood (i.e., prawns, squids, sardines) and highlighted a high variability of polymers depending on the studied species. Furthermore, the occurrence of MPs in other commercially relevant marine species was evaluated in edible tissue of crab (Akhbarizadeh et al., 2019; Daniel et al., 2020a; Ribeiro et al., 2020; Zhang et al., 2021), sea urchin (Feng et al., 2020), shrimp (Daniel et al., 2020b, 2021), prawn (Akhbarizadeh et al., 2019; Ribeiro et al., 2020) and squid (Daniel et al., 2021; Ribeiro et al., 2020). Most studies showed that the percentage of MPs in edible tissues is generally lower than in the inedible ones, like the organisms' digestive tract (Daniel et al., 2020a; Wakkaf et al., 2020; Zhang et al., 2021). This implements that animals that are eaten whole, including their digestive

**Table 1**  
Grouping of food categories used in the present chapter.

CATEGORY	subgroup
Cereals	A0EZF, A0EZV
Fruit and Vegetable	A07XJ, A0EZG, A0EZN, A0EZH
Oils	A015E
Roots and Tubers	A00ZS
Other plants and herbs	A010R, A0EZM
Terrestrial Meat	A0EZS, A0EZT
Marine Meat	A0EZR, A0EZQ
Milk	A0BXZ
Eggs	A031E
Confectionery	A04PE
Particular food	A03TD, A03PV, A03RR
Other	A03VA, A042N
isolated purified ingredients	A0BXX

**Table 2**

Overview of MPs found in selected animal food products. Cellulose Acetate (CA), Cellophane (CE), Ethylene Propylene diene monomer rubber (EPDM), Extruded PS (EPS), Ethylene-vinyl acetate (EVA), Polyamide (PA), Polyacrylamide (PAAm), Polyacrylonitrile (PAN), Polybutylene terephthalate (PBT), Polyethylene (PE), High-density PE (HDPE), Low-density PE (LDPE), Polyethylene terephthalate (PET), Polyethersulfone (PES), Poly(methyl methacrylate) (PMMA), Polypropylene (PP), Polystyrene (PS), Polysulfone (PSU), Polytetrafluoroethylene (PTFE), Polyurethane (PU), Polyvinyl acetate (PVA), Polyvinyl chloride (PVC). ATR-FTIR = Attenuated Total Reflection- Fourier-transform infrared spectroscopy, FPA = Focal Plane Array detector, FE-SEM = Field Emission- Scanning Electron Microscopy, EDX = Energy-dispersive X-ray spectroscopy, Py-GCMS = Pyrolysis-gas chromatography-mass spectrometry. Raw data rounded.

Food matrix	Polymer types found	NMP size	Detected concentrations	Analytical Method	Ref.
Mussel	- PET - Latex - PS-cotton - PVC - CA - EVA - HDPE - Nylon	500 $\mu\text{m}$ – 2000 $\mu\text{m}$	0.040 $\pm$ 0.003 MPs/g wet weight (w.w.) 87% of mussels contained MPs	Stereomicroscope sorting FTIR-ATR	Sparks et al., 2021
Mussel	- PE - PP - PET - PVC	~ 500–1500 $\mu\text{m}$	Fresh mussels: 0.20 $\pm$ 0.24 MPs/g w.w. Processed mussels: 0.9 $\pm$ 0.1 MPs/g w.w. 61 % of mussels contained MPs	Stereomicroscope sorting FTIR	Nalbone et al., 2021,
Mussel	- PE - PP - CE	not specified	0.7 $\pm$ 0.5 – 3.5 $\pm$ 0.3 MPs/g w.w. 97% of mussels contained MPs	Stereomicroscope sorting FTIR	Wakkaf et al., 2020
Mussel	- PE - PP - Nylon - EVA - PET - p-acrylic acid	mean 1.7 $\pm$ 0.1 mm	Mean 0.06 MPs/g w.w Range 0.03–0.09 MPs/g w.w. 92% of vendors sold mussels that contained MPs	Stereomicroscope sorting $\mu$ -Raman	Gündođdu et al. (2020)
Mussel	FTIR: - PP - PET - PAN - PE - PA - PU - PS - PBT Raman: - PA - PP - PE - PAN - PU - PET - PS - PMMA	3–60 $\mu\text{m}$ (Raman analysis) Mostly <100 $\mu\text{m}$ (FTIR analysis)	0.63 $\pm$ 0.59 MPs/g w.w.	FPA-based $\mu$ -FTIR $\mu$ -Raman	Kumar et al. (2021)
Mussel	- PVC	not specified	Range 0–24 $\mu\text{g/g}$	Py-GC/MS	Ribeiro et al. (2020)
Shrimp	Not detected			Stereomicroscope sorting FTIR	Daniel et al. (2021)
Shrimp	- PS - PA - PE - PP	150–1000 $\mu\text{m}$ (72% of total) <500 $\mu\text{m}$ (less than 25%)	0.04 $\pm$ 0.07 MPs/g w.w. 31% of the shrimps were contaminated with MPs	Stereomicroscope sorting FTIR	Daniel et al. (2020b)
Prawn	- PVC - PP - PMMA	not specified	PVC: 0–16 $\mu\text{g/g}$ PP: 0–15 $\mu\text{g/g}$	Py-GC/MS	Ribeiro et al. (2020)
Prawn	not identified	Mainly <50 $\mu\text{m}$ in muscle	0.36 MPs/g w.w. (muscle) 0.77 MPs/g w.w. (gill)	Stereomicroscope sorting FTIR	Akhbarizadeh et al. (2019)
Squid	- PP - PS - PE	~100–400 $\mu\text{m}$	0.008 $\pm$ 0.02 MPs/g w.w.	Stereomicroscope sorting FTIR	Daniel et al. (2021)
Squid	- PVC - PP	not specified	PVC: 0–11 $\mu\text{g/g}$ PP: 0–24 $\mu\text{g/g}$	Py-GC/MS	Ribeiro et al. (2020)
Crab	- PP - PS - PE	~100–400 $\mu\text{m}$	0.003 $\pm$ 0.01 MPs/g w.w. 13 % of edible tissue contained MPs	Stereomicroscope sorting FTIR	Daniel et al. (2021)
Crab	- CE - PET - PE - PP - PA	20–5000 $\mu\text{m}$	0.80 $\pm$ 1.1 – 23 $\pm$ 25 MPs/g w.w. No MPs were found in crab's muscles.	Stereomicroscope sorting $\mu$ -FTIR	Zhang et al. (2021)
Crab	- PS - PE	not specified	PS: 0.28–8.1 $\mu\text{g/g}$ PE: 0–40 $\mu\text{g/g}$	Py-GC/MS	Ribeiro et al. (2020)

(continued on next page)

Table 2 (continued)

Food matrix	Polymer types found	NMP size	Detected concentrations	Analytical Method	Ref.
Crab	- PVC - PP - PMMA not identified	Mainly <50 µm in muscle	PVC: 1.2–39 µg/g PP: 2.5–26 µg/g PMMA: 0–4.5 µg/g 0.26 MPs/g w.w. (muscle) 0.86 MPs/g w.w. (gill)	Stereomicroscope sorting Hot probe testing SEM-EDX	Akhbarizadeh et al. (2019)
Urchin	- CE - PET:PS - PE - PP - PP:PE - PA - ryon - PAN - PU - PVA:PE	7–1000 µm (60% of total) (range 30–4700 µm)	From 0.16 ± 0.09 MPs/g w.w to 2.3 ± 1.7 MPs/g w.w. ~90% of urchins contained MPs	Stereomicroscope sorting FTIR	Feng et al. (2020)
Fish	- PS - PE - PVC - PP - PMMA	not specified	PS: 0–100 µg/g PE: 0–2400 µg/g PVC: 0–10 µg/g PP: 0–60 µg/g PMMA: 0–30 µg/g	Py-GC/MS	Ribeiro et al. (2020)
Fish	- PE - PP - EPDM - PS	100–200 µm in edible tissue (range 115–210 µm) 200–400 µm in inedible tissue (range 136–4010 µm)	Edible: 0.005 ± 0.02 MPs/g w.w. 7% of fishes had MPs in edible parts. Inedible: 0.05 ± 0.01 MPs/g w.w. 41% of fishes had MPs in inedible parts.	Stereomicroscope sorting FTIR	Daniel et al. (2020a)
Fish	not identified	Mainly < 50 µm in muscle	0.16–0.28 MPs/g w.w. (muscle) 0.25 MPs/g w.w. (gill)	Stereomicroscope sorting Hot probe testing SEM-EDX	Akhbarizadeh et al. (2019)
Fish	- PP - PET - PE - PVC	mean: 1100 ± 940 µm (range 190–3800 µm)	Total 6 MPs found	Stereomicroscope sorting Raman FESEM-EDX	Karami et al. (2018)
Fish	- PP - PE - PS - PET - PA-6	not specified	29 MPs in eviscerated flesh and 7 MPs in organs	Stereomicroscope sorting Raman FESEM-EDX	Karami et al. (2017a)
Chicken	- PE - PS	1–10 mm	Gizzard: mean 46 ± 43 MPs/gizzard Crop: mean 11 ± 15 MPs/crop	Stereomicroscope	Lwanga et al. (2017)
Chicken meat	- EPS - Fibers (not specified)	130–450 µm	4–19 MPs/kg packaged meat	Stereomicroscope sorting ATR-FTIR	Kedzierski et al. (2020)
Milk	- PES - PSU	Fibers and fragments of <500 µm – 5 mm	3–11 MPs/L milk	Stereomicroscope SEM-EDS µ-Raman	Kutralam-Muniasamy et al. (2020)
Milk	- PP - HDPE - LDPE - PAAm	Fibers: 30 – 6740 µm Fragments: 2–180 µm	Fibers: 30–250 MPs/L milk Fragments: 100–280 MPs/L milk	Stereomicroscope sorting FTIR	Diaz-Basantes et al. (2020)
Milk	- PP - PE - PES - PS - PTFE - PU - PSU - PVA	69–99% <50 µm <sup>2</sup>	Samples ranged from 800–9700 MPs/L milk	µ-Raman SEM-EDX	Costa Filho et al. (2021)

tract, are a potentially larger vector for NMPs than when only parts of the animals are consumed. For instance, larger fish are usually not eaten whole, but mainly the fillet is consumed by humans. Here, the translocation of MPs from the digestive tract into edible tissues like fish fillet has already been shown in a laboratory study (Zeytin et al., 2020) and also in fish captured in nature for human consumption (Daniel et al., 2020a; Gabriel et al., 2015; Karami et al., 2017a). Therefore, both marine animals eaten as a whole, and saltwater fish fillet consumption can serve as a vector for human consumption of NMPs. However, 12.5% of the total share of captured fish derives from inland freshwater ecosystems (FAO, 2020). Although there are no studies demonstrating NMPs in the fillet of freshwater fish for human consumption, it has been

described that freshwater fish also ingest MPs (Galafassi et al., 2021; Parker et al., 2021). Consequently, fillet of freshwater fish might be an additional vector of NMPs to humans.

The total protein requirement of humans is not only met by blue meat but also by a high proportion of meat. Poultry consumption, in particular, has increased over the last 60 years, even overtaking beef consumption (Naylor et al., 2021). However, only little information on MPs levels in meat have been published. First attempts were made to analyze the MPs content in chicken (Huerta Lwanga et al., 2017; Kedzierski et al., 2020). Both studies showed that MPs were attached to chicken tissues. Kedzierski et al. (2020) highlighted that the MPs associated with the washed chicken meat mainly derived from the packaging



itself. [Huerta Lwanga et al. \(2017\)](#) found MPs >1 mm in size in the gizzard of dissected chickens. The authors state that even a thorough washing of the gizzard would not guarantee the complete removal of MPs and calculated possible annual ingestion of 840 MPs per person per year in Mexico. However, to our best knowledge, MPs were not detected within the meat fillet mainly used for human consumption. This lack of knowledge may depend on time- and cost-consuming approaches like enzymatic digestion ([Löder et al., 2017](#)) that would be needed prior to analysis of the meat. Recently, [Huang et al. \(2020\)](#) used a non-disruptive method, namely mid-infrared spectroscopy, to detect MPs within chicken meat without destroying the meat matrix. However, the method's sensitivity for detecting MPs is very low (between 1% and 10% (w/w)) and needs to be improved to apply it to real samples.

Another important source of nutrients for humans are milk and dairy products. Milk is not solely used as a raw product but also for many processed food items, like butter, cheese, cream, and ready-made products.

A few studies have already investigated the contamination of MPs in milk (Table 2). For example, [Kutralam-Muniasamy et al. \(2020\)](#) detected MPs in branded milk from Mexico, reporting 3-11 MPs/L, and [Diaz-Basantes et al. \(2020\)](#) reported higher levels of average 40 MPs/L in milk from Ecuador. However, [Costa Filho et al. \(2021\)](#) reported much higher contamination levels, with 88 MPs/L in raw milk and 694 MPs/L in powdered milk. Therefore, although it is premature to conclude on MPs levels in milk, the results of [Costa Filho et al. \(2021\)](#) suggest that MPs' presence increases with milk processing.

In addition, humans consume and also need carbohydrates, with cereals accounting for the largest proportion. The FAO estimates that cereals are mainly produced for direct human consumption (41%) and animal feed (45%), the remaining percentages for industrial applications (brewing, biofuels, etc.). Cereals contribute 55-70% of the total diets of developing countries, with 2/3 represented by corn and wheat. Corn, oats, barley, wheat and sorghum are the main grains used in animal feeding globally ([Kleih et al., 2006](#); [World Trade Organization, 2019](#)). Therefore, MP- containing cereals may serve as a direct vector when consumed by humans or indirectly by consuming animal products containing NMPs. There is growing evidence for the contamination of the terrestrial environment, with increasing attention drawn on agricultural soils for food production. However, if this leads to the contamination of cereals is not known to date. Possible transfer of NMPs to cereals may stem from agricultural soils ([Harms et al., 2021](#); [Rillig et al., 2017](#); [Steinmetz et al., 2016](#); [Wang et al., 2021](#)), irrigation of cereal crops with contaminated waters ([Domenech and Marcos, 2021](#)), and fertilization with sewage sludge and polymer-coated fertilizer ([Corradini et al., 2019](#); [Lian et al., 2021](#); [van den Berg et al., 2020](#); [Weithmann et al., 2018](#)). It is not known whether NMPs can enter the crop plant tissue grown on agricultural fields. However, in laboratory studies, it was shown that vascular plants could act as sinks for model NMPs as their surfaces can adsorb them ([Taylor et al., 2020](#)) or even be

taken up into the plant's tissues ([Austen et al., 2022](#); [Bosker et al., 2019](#); [Dong et al., 2021](#); [Li et al., 2021](#); [Lian et al., 2021](#); [Yin et al., 2021](#); [Zhou et al., 2021](#)). Nevertheless, most studies have focused on the potential effects of NMPs on plant physiology ([Dong et al., 2020](#); [Pehlivan and Gedik, 2021](#); [Urbina et al., 2020](#); [Wu et al., 2022](#)).

Furthermore, industrial processing and packaging may lead to NMPs contamination of cereals ([Dessi et al., 2021](#)). Despite the high proportion of human consumption of cereals, very little data on their contamination by NMPs exists. We observed only one study investigating the MPs contamination of rice produced for human consumption (Table 3). [Dessi et al. \(2021\)](#) investigated the mass concentration of MPs in store-bought rice and found 45-322 µg/g dry weight. The authors found no difference between paper and plastic packaging of the rice. However, washing the rice before further processing reduced the mass of MPs within the samples. Noteworthy, pre-cooked rice contained a fourfold higher concentration of MPs, suggesting that industrial processes may be the primary source of MPs contamination.

Next to cereals, fruits and vegetables contribute to the overall consumption of carbohydrates. There is little information about NMPs' presence in commercial vegetables and fruits produced for human consumption. To our best knowledge, only [Oliveri Conti et al. \(2020\)](#) quantified MPs in several Italian fruits and vegetables produced for human consumption of different contamination levels, with fruit samples being generally more contaminated than vegetables (Table 3). However, the accumulation of NMPs has been described in edible tissues of radish ([Tympa et al., 2021](#)) or cucumber ([Li et al., 2021](#)) in plants grown under laboratory conditions.

Furthermore, the usual diet of humans also contains processed foods, reported in our used classification system (Table 1) as oil, confectionary, teabags, honey & sugar and salt (Table 4). To date, no studies are available reporting NMPs in confectionary or oil. However, some studies were published investigating NMPs in other processed foods. For instance, [Li et al. \(2020\)](#) detected MPs in packed Nori seaweed, and other edible macroalgae were discussed to be potential vectors for NMPs to humans ([Yang et al., 2021](#)). Some studies documented the presence of MPs and other fibers in honey ([Diaz-Basantes et al., 2020](#); [Liebezeit and Liebezeit, 2013, 2015](#); [Mühlschlegel et al., 2017](#)) and sugar ([Liebezeit and Liebezeit, 2013, 2015](#)) and several studies detected MPs in salt samples ([Fadare et al., 2021](#); [Fischer et al., 2019](#); [Gündoğdu, 2018](#); [Iñiguez et al., 2017](#); [Karami et al., 2017b](#); [Kim et al., 2018](#); [Kosuth et al., 2018](#); [Lee et al., 2019](#); [Nithin et al., 2021](#); [Renzi et al., 2019](#); [Renzi and Blašković, 2018](#); [Seth and Shrivastav, 2018](#); [Tahir et al., 2019](#); [Yang et al., 2015](#)) (Table 4). Furthermore, two studies detected the release of MPs from commercial teabags during a typical steeping process ([Hernandez et al., 2019](#); [Xu et al., 2021](#)). These results indicate that raw and processed food items may potentially contribute to human exposure to NMPs via ingestion.

**Table 3**

Overview of MPs found in rice, vegetables and fruits. Cellulose Acetate (CA), Cellophane (CE), Ethylene Propylene diene monomer rubber (EPDM), Extruded PS (EPS), Ethylene-vinyl acetate (EVA), Polyamide (PA), Polyacrylamide (PAAm), Polyacrylonitrile (PAN), Polybutylene terephthalate (PBT), Polyethylene (PE), High-density PE (HDPE), Low-density PE (LDPE), Polyethylene terephthalate (PET), Polyethersulfone (PES), Poly(methyl methacrylate) (PMMA), Polypropylene (PP), Polystyrene (PS), Polysulfone (PSU), Polytetrafluoroethylene (PTFE), Polyurethane (PU), Polyvinyl acetate (PVA), Polyvinyl chloride (PVC). SEM= Scanning Electron Microscopy, EDX= Energy-dispersive X-ray spectroscopy, Py-GCMS= Pyrolysis-gas chromatography-mass spectrometry. Raw data rounded.

Food matrix	Polymer types found	NMP size	Reported concentrations	Analytical methods	Ref.
Rice	- PE - PP - PET	Not determined	Dry rice: 67 ± 26 µg/g dry weight (d.w.) Washed rice: 52 ± 5 µg/g dw Dry instant rice: 280 ± 50 µg/g dw Washed instant rice: 170 ± 41 µg/g dw	Py-GC/MS	<a href="#">Dessi et al. (2021)</a>
Fruit and vegetable	not specified	1.5–2.5 µm	Apples 1.96 × 10 <sup>5</sup> ± 1.3 × 10 <sup>5</sup> MPs/g Pears 1.90 × 10 <sup>5</sup> ± 1.1 × 10 <sup>5</sup> MPs/g Broccoli 1.26 × 10 <sup>5</sup> ± 8.0 × 10 <sup>4</sup> MPs/g Lettuce 5.10 × 10 <sup>4</sup> ± 2.5 × 10 <sup>4</sup> MPs/g Carrot: 1.02 × 10 <sup>5</sup> ± 4.4 × 10 <sup>4</sup> MPs/g	SEM-EDX	<a href="#">Oliveri Conti et al. (2020)</a>

**Table 4**

Overview of MPs found in processed foods. Cellulose Acetate (CA), Cellophane (CE), Ethylene Propylene diene monomer rubber (EPDM), Extruded PS (EPS), Ethylene-vinyl acetate (EVA), Isobutyl Vinyl Ether (IBVE), Polyamide (PA), Polyacrylamide (PAAm), Polyacrylonitrile (PAN), Poly(butyl methacrylate) (PBMA), Polybutylene terephthalate (PBT), Polyethylene (PE), High-density PE (HDPE), Low-density PE (LDPE), Polyetherimide (PEI), Polyethylene terephthalate (PET), Polyethersulfone (PES), Poly(methyl methacrylate) (PMMA), Polyoxymethylene (POM), Polypropylene (PP), Polystyrene (PS), Polysulfone (PSU), Polytetrafluoroethylene (PTFE), Polyurethane (PU), Polyvinyl acetate (PVA), Polyvinyl chloride (PVC). ATR-FTIR = Attenuated Total Reflection- Fourier-transform infrared spectroscopy, FPA= Focal Plane Array detector, FE-SEM = Field Emission- Scanning Electron Microscopy, EDX = Energy-dispersive X-ray spectroscopy, Py-GCMS = Pyrolysis-gas chromatography-mass spectrometry, XPS = X-Ray Photoelectron Spectroscopy, NTA = Nanoparticle Tracking Analysis, NIR = Near-Infrared spectroscopy. Raw data rounded.

Food matrix	Polymer types found	NMP size	Reported concentrations	Analytical method	Ref.
Nori seaweed	- not specified	not specified	0.9–3 MPs/g	Stereomicroscope μ-FTIR	Li et al. (2020)
Honey, Sugar	- not specified	not specified	Honey, fibers 170 ± 150 MPs/kg, fragments 9 ± 9 MPs/kg Sugar, fibers 220 ± 120 MPs/kg, fragments 32 ± 7 MPs/kg Unrefined sugar, fibers 560 MPs/kg, fragments 540 MPs/kg	Stereomicroscope	Liebezeit and Liebezeit (2013)
Honey	- not specified	not specified	Fibers 10–340 MPs/kg, fragments 2–82 MPs/kg.	Stereomicroscope	Liebezeit and Liebezeit (2015)
Honey	- PET	>30 μm	0–8.3 MPs/kg (mean 3.8 MPs/kg)	Raman FTIR-ATR	Mühlschlegel et al. (2017)
Honey	- PP - HDPE/LDPE - PAAm	Fibers 67–2700 μm, fragments 5–230 μm	Fibers 20–180 MPs/L, fragments 190–830 MPs/L.	Stereomicroscope sorting FTIR	Diaz-Basantes et al. (2020)
Salt	- not specified	4–4600 μm	1600–3 × 10 <sup>4</sup> MPs/kg	Stereomicroscope sorting μ-FTIR	Renzi and Blašković (2018)
Salt	- not specified	100–5000 μm	47–800 MPs/kg (mean 210 MPs/kg)	Stereomicroscope	Kosuth et al. (2018)
Salt	- PVA - PP - PE	4–4700 μm	0.67 ± 1.2–3.4 ± 4.9 MPs/kg	Stereomicroscope sorting FTIR	Fadare et al. (2021)
Salt	- Nylon - LDPE - PP - PET	not specified	470 ± 120–1600 ± 150 MPs/kg	FTIR	Nithin et al. (2021)
Salt	- PP - PE - PS - PEI - PET - POM	90–1500 μm	9.8 MPs/kg	Stereomicroscope sorting FTIR	Lee et al. (2019)
Salt	- PET - PVC - PA6 - PE - PS - IBVE - PA - PC - PP - PBMA - PU - Viscose	10–150 μm	170–320 MPs/kg (IT); 70–220 MPs/kg (CRO)	FTIR ATR	Renzi et al. (2019)
Salt	- PVA - PE - PS	390–9400 μm	6.7 - 53 MPs/kg	FTIR	Tahir et al. (2019)
Salt	- PES - PS - PA - PE - PET	80% of fragments and fibers were smaller than 500 and 2000 μm resp.	103±39 - 56±49 MPs/kg; 64 μg/kg	Stereomicroscope sorting μ-FTIR	Seth and Shrivastav (2018)
Lake salt, Rock salt, Sea salt	Lake salt: - PP - PE - Teflon - PET Rock salt: - PET - PE - PP Sea salt: - PE - PP - PET	100–5000 μm	Lake salt: 28–460 MPs/kg (mean 250 ± 310 part/kg) Rock salt: 0–150 MPs/kg (mean 38 ± 55 MPs/kg) Sea salt: 0–1700 MPs/kg (mean 680 ± 2600 MPs/kg)	Stereomicroscope sorting FTIR	Kim et al. (2018)
Sea salt, well salt		30–3500 μm	Sea salt: 50–280 MPs/kg Well salt: 120–190 MPs/kg		Iñiguez et al. (2017)

(continued on next page)

Table 4 (continued)

Food matrix	Polymer types found	NMP size	Reported concentrations	Analytical method	Ref.
Lake salt, Rock salt, Sea salt	-PET -PP -PE -PET -PES -PE -PB -PP -CE	45–4300 µm	Lake salt: 43–360 MPs/kg Rock salt: 7–200 MPs/kg Sea salt: 550–680 MPs/kg.	Stereomicroscope sorting FTIR Stereomicroscope sorting µ-FTIR	Yang et al. (2015)
Lake salt, Rock salt, Sea salt	Lake salt: -PE -PP -PU -PET -PMMA -PVC -PA-6 Rock salt: -PP Sea salt: -PU -PET -PP -PE -PVC -PA-6	not specified	Lake salt: 8–100 MPs/kg (mean 38 ± 14 MPs/kg) Rock salt: 9–16 MPs/kg (mean 12 ± 1.2 MPs/kg) Sea salt: 16–84 MPs/kg (mean 46 ± 13 MPs/kg).	Stereomicroscope sorting µ-Raman	Gündoğdu (2018)
Salt	-PP -PE -PET -polyisoprene: PS (copolymer) -PAN -PA-6	160–980 µm	10 MPs/kg	Stereomicroscope sorting Raman	Karami et al. (2017b)
Salt	-PP -PET -PE -PS -PVC -PUR -PA -PMMA -PC	-	140–2000 µg/kg	Py-GC/MS	Fischer et al. (2019)
Teabags	-PET -nylon	50–100 µm and 10–400 nm 1–50 µm and 50–600 nm	Estimation of 2.3 million micron-sized and 14.7 billion submicron particles per cup of tea	SEM XPS FTIR NTA	Hernandez et al. (2019)
Teabags	-nylon	500 nm to 100 µm.	Not stated	NIR FTIR	Xu et al. (2021)

### 3.3. Inhalation

Several comprehensive review articles on the contamination of the atmosphere and breathable ambient air with NMPs already exist (Amato-Lourenço et al., 2020; Bianco and Passananti, 2020; Chen et al., 2019; Wieland et al., 2022; Zhang et al., 2020). A recent study extrapolated wet and dry deposition data to the whole area of the River Weser catchment and reported a total MPs deposition of 232 tons. Furthermore the authors report a MP concentration of 500 MPs per m<sup>3</sup> even in outdoor environments (Kernchen et al., 2021). Although these numbers already seem to be relatively high, most studies indicate that exposure to indoor air seems to comprise a higher likelihood of inhaling NMPs than that of outdoor air (Dris et al., 2017; Liu et al., 2019; Wieland et al., 2022). Interestingly, Liao et al. (2021) reported that the mean values of MPs in indoor air samples were an order of magnitude higher than in outdoor samples. The United States Environmental Protection Agency (EPA) described the concentration of chemicals in indoor environments as 2 to 5 times higher than outdoor concentrations (EPA, 1987). Although the current data suggest that this seems to apply to the concentration of NMP, this needs further investigation. However, since the

EPA and the WHO estimate that European citizens usually spend approximately 90 % of their time indoors (Sarigiannis, 2014; US Environmental Protection Agency, 1986), in this review, we focus on the contamination of indoor environments with NMPs.

First attempts to estimate the inhalation of NMPs from indoor air were made using different methods (Table 5). One way to assess the contamination with airborne NMPs is by directly filtering the ambient air (Dris et al., 2017; Liao et al., 2021) or using a breathing mannikin (Vianello et al., 2019). In addition, passive sampling is another approach to assess the contamination with NMPs, for instance, via microparticle sedimentation into openly placed glass wear (Jenner et al., 2021; Soltani et al., 2021) or collecting dust samples (Dris et al., 2017; Zhang et al., 2020). To date, there is no doubt of the presence of NMPs in indoor air, and Wieland et al. (2022) estimated that humans might inhale more than 48,000 MPs per day.

The abundance of NMPs in indoor environments is likely influenced by the use of plastics in diverse human activities. Flooring, synthetic garments, textile and household furniture seem to be the significant determinants for NMPs contamination of the air as reviewed by Facciola et al. (Facciola et al., 2021). The highest concentrations of indoor



**Table 5**

Overview of airborne MPs in indoor environments. Polyamide (PA), Polyacrylonitrile (PAN), Polyethylene (PE), Polyethylene terephthalate (PET), Poly(methyl methacrylate) (PMMA), Polypropylene (PP), Polyvinyl (PV). ATR-FTIR = Attenuated Total Reflection- Fourier-transform infrared spectroscopy, FPA = Focal Plane Array detector, HPLC = High-performance liquid chromatography Raw data rounded.

Indoor sample	Polymer types found	NMP size	Reported concentrations	Analytical method	Ref.
Filtering, passive sampling & dust samples from a vacuum cleaner	- PP - PA-cotton mixture	Dust samples: 4700–4900 $\mu\text{m}$ Indoor air: <3300 $\mu\text{m}$	Filtering: range 0.4–59 fibers/ $\text{m}^3$ with a median value of 5.4 fibers/ $\text{m}^3$ Passive sampling: range 2.7 to 20 fibers/day, corresponding to a deposition rate between 1600 and 11,000 fibers/day/ $\text{m}^2$ Collected bags of vacuum cleaners: ranged 190 and 670 fibers/mg dust samples. Mean concentration: 1600 $\pm$ 1200 MPs/ $\text{m}^3$	Stereomicroscope sorting FTIR-ATR	Dris et al. (2017)
Filtering & passive sampling	- PE - PA - PP	Fibers: 60 $\pm$ 2.7%: 5–30 $\mu\text{m}$ 29 $\pm$ 2.3%: 30–100 $\mu\text{m}$ 11%: >100 $\mu\text{m}$	Total number of inhaled MPs: 270 MPs The average number of inhaled MPs per unit volume: 9.3 $\pm$ 5.8 MP/ $\text{m}^3$	Stereomicroscope sorting $\mu$ -FTIR	Liao et al. (2021)
Filtering	- PE - PET - nylon - PP	Fibers: 13% Fragments 87% Size distribution 37–240 $\mu\text{m}$ with a $D_{50}$ of 21–36 $\mu\text{m}$	Total number of inhaled MPs: 270 MPs The average number of inhaled MPs per unit volume: 9.3 $\pm$ 5.8 MP/ $\text{m}^3$	FPA- $\mu$ FTIR-	Vianello et al. (2019)
Passive sampling	- PET - PC	-	PET concentrations in the range of 29–1.1 $\times 10^5$ $\mu\text{g/g}$ dust sample PC concentrations in the range of <0.11–1700 $\mu\text{g/g}$ dust sample	HPLC	Zhang et al. (2020)
Passive sampling	- PET - PA - acrylates - PP - co-polymer blends - PAN - PE - PMMA	Fibers (90%) Fragments (8%) Film (1%) Sphere (1%) Foam (<1%) Size not stated	Mean MPs concentration: 1400 $\pm$ 1000 MPs/ $\text{m}^2$ per day	$\mu$ -FTIR	Jenner et al. (2021)
Passive sampling	- PE - PE:PET - PA - PV	Fibers: - 50–200 $\mu\text{m}$ (5%) - 200–400 $\mu\text{m}$ (19%) - 400–600 $\mu\text{m}$ (17%) Fragments: - 686 $\mu\text{m}$ (average) Films: - 100 $\mu\text{m}$ (average)	In total, 7400 fibers, 64 fragments and 18 films were collected. The deposition rate of fibrous MPs ranged from 22 to 6200 fibers/ $\text{m}^2$ per day with an average of 3100 fibers/ $\text{m}^2$ per day	Stereomicroscope sorting FTIR	Soltani et al. (2021)

airborne MPs (1600  $\pm$  1200 MPs/ $\text{m}^3$ ) were reported by Liao et al. (2021) by active air filtering. They reported that 2/3 of the number of all particles collected were smaller than 30  $\mu\text{m}$  (Liao et al., 2021). Therefore, we can speculate that smaller particles dominate airborne MPs, which is plausible considering that smaller particles remain suspended in the air longer than larger particles. However, to date, there are no data on the occurrence and prevalence of MPs smaller than 5  $\mu\text{m}$  in private indoor environments. Therefore, reliable statements regarding the potential exposure to small MPs or NPs cannot be made.

In some working environments, the potential of being exposed to NMPs generated during mechanical and environmental degradation of plastic goods or by NMPs being added as ingredients to, for example, printer inks, spray paints, injection mouldings, and abrasive may be enhanced (Murashov et al., 2020, <https://blogs.cdc.gov/niosh-science-blog/2020/02/19/microplastics/>; Bitounis et al., 2022; Getzlaff et al., 2019). However, to date, the occurrence and emission sources of NMPs at workplaces have received little attention. Wieland et al. (2022) compared workplace concentrations of different airborne microparticles and associated occupational diseases. As for many particles and fibers, the physicochemical properties like size, shape,  $\zeta$ -potential, adsorbed molecules and pathogens, and the MPs' bio-persistence should be regarded as possible drivers of MPs' toxicity (Ramsperger et al., 2020, 2021; Wieland et al., 2022). The US National Institute for Occupational Safety and Health (NIOSH) has defined exposure limits for workers for

other airborne particles, such as asbestos or silica dust (Wieland et al., 2022; NIOSH 2020, <https://blogs.cdc.gov/niosh-science-blog/2020/02/19/microplastics/>). To date, NMPs are considered nuisance dust with a permissible exposure limit (PEL) of 5 mg/ $\text{m}^3$  for respirable dust (Bartley and Feldman, 1984, guideline 0600 Issue 3). However, NMP-associated diseases in occupational settings have already been described and summarized (Burkhart et al., 1999; Prata, 2018; Wieland et al., 2022). For instance, the exposure of workers to vinyl chloride monomers used for the production of PVC induce DNA damage in lymphocytes of plastic industry workers (Awara et al., 1998). In addition to the production of the plastic material itself the processing industry may pose a potential hazard to workers. Burkhart et al. (1999) analyzed the workers' particulate exposure during nylon flocking (applying short fibers to adhesive-coated surfaces) and found an average respirable particulate matter of 2.2 mg/ $\text{m}^3$ . Although this value is below the NIOSH PEL set for nuisance dust, cases of interstitial lung disease were suggested to be linked to the detected respirable particles (Burkhart et al., 1999).

NMPs may be generated via flocking or degradation and from a bottom-up production mechanism during high energy or high heat processes. One example is 3D printing, which is becoming popular in offices and at home, and releases potentially harmful volatile organic compounds and ultrafine particles into the air (Du Preez et al., 2018). Some studies compared the particulate release of 3D printers with PLA

and Acrylonitrile-Butadiene-Styrol-Copolymer (ABS) filaments (Stephens et al., 2013; Vance et al., 2017; Zhang et al., 2019). Zhang et al. (2019) suggested that particles released from PLA filament 3D printers were mainly composed of PLA bulk material, whereas particles from ABS 3D printers differed from the bulk material. In all reported studies investigating the emission of NMPs during 3D printing, several million particles were described to be released. For instance, Stephens et al. (2013) estimated that approximately  $2.0 \times 10^{10}$  and  $1.9 \times 10^{11}$  particles, mainly consisting of particles in the fine to ultrafine range ( $<0.2$ – $0.1 \mu\text{m}$ ), are released every minute for a 3D printer utilizing a PLA and ABS feedstock, respectively. Although it is currently unclear whether the particles consist purely of the bulk material of the filament, these numbers are alarming, especially given the duration of the printing processes. Next to 3D printers, laser toner printers are known to emit high numbers of nanoparticles, including NP (Bello et al., 2021; Getzlaff et al., 2019). As most of the printing devices are currently sold as stand-alone devices without any exhaust ventilation or filtering accessories, the results suggest that caution should be taken when operating in inadequately ventilated or unfiltered indoor environments. Especially because the emitted particles are so small that they can deposit in the deep alveolar region of the lungs upon inhalation (Stephens et al., 2013) and were discussed to be a severe health threat (Bello et al., 2021; Bitounis et al., 2022).

### 3.4. Personal care products (PCPs)

The term PCPs is often used synonymously for cosmetics, although there is a slight but essential difference. The European Commission defined cosmetics as follows: “Any substance or preparation intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition or correcting body odours.” (European Commission, 2013). However, the term PCPs is not defined by law, but most PCPs are regulated as cosmetics, although some PCPs can be regulated as drugs. For instance, the Food & Drug Administration (FDA) listed PCP drugs as “(...) skin protectants (such as lip balms and diaper ointments), mouthwashes marketed with therapeutic claims, antiperspirants, and treatments for dandruff or acne.” (FDA, 2016). Since both PCPs cosmetics and PCPs drugs are intentionally applied onto the human body, we decided to not separate them further concerning NMPs.

The European Commission initiated a restriction procedure on MPs in cosmetics in January 2018. Although an adopted restriction (if agreed by the member states) for the European Union is expected by 2022 (Anagnosti et al., 2021; [https://www.europarl.europa.eu/doceo/document/E-9-2021-003388\\_EN.html](https://www.europarl.europa.eu/doceo/document/E-9-2021-003388_EN.html)), several European countries have already banned the intentional use of MPs in PCPs (Kentin and Kaarto, 2018). However, one of the main difficulties in proposing a general restriction of MPs in PCPs is the lack of a definition of the size range of MPs (Kentin and Kaarto, 2018). In the initiated proposal, the size of MPs was set to be lower than 5 mm in size without a lower threshold (ECHA 2021, [https://www.europarl.europa.eu/doceo/document/E-9-2021-003388\\_EN.html](https://www.europarl.europa.eu/doceo/document/E-9-2021-003388_EN.html)). Although the industry has already responded to the pressure from non-governmental organizations and the concerned public by excluding MPs from several products (Anagnosti et al., 2021), the use of MPs is neither restricted in the European Union nor worldwide. Therefore, PCPs can still contain NMPs.

MPs are intentionally added to PCPs for different functions like viscosity regulators, emulsifiers, glitters, skin conditioning, exfoliants, abrasives, and many more (UNEP, 2015; Yurtsever, 2019). Depending on the desired function of the added MPs to PCPs, different polymer types, shapes, and sizes are used. The most often used polymer type is PE in various shapes and sizes (Gouin and Brunning, 2015; UNEP, 2015). Interestingly, the information on the main size ranges found in the

literature is highly heterogeneous and depends on the intended function of the added polymer. For example, Gouin and Brunning (2015) summarized that particles smaller than  $60 \mu\text{m}$  are ineffective as abrasion and exfoliation and the optimum size is around  $450 \mu\text{m}$ . However, Sun et al. (2020) propose that the diameters of MPs added to PCPs range from  $24 \mu\text{m}$  to  $2 \text{mm}$ , with more than 95% smaller than  $350 \mu\text{m}$ . The United Nations Environment Programme (UNEP, 2015) highlighted that the primary size of MPs in PCPs lays in between  $1$  and  $50 \mu\text{m}$ . The size of the added MPs seems to depend on the product type (Sun et al., 2020). For example, in toothpaste, the reported sizes range from  $4$ – $20 \mu\text{m}$  (Ustabasi and Baysal, 2019) and  $3$ – $145 \mu\text{m}$  (Praveena et al., 2018). In facial scrubs, sizes were reported between  $10$ – $178 \mu\text{m}$  (Praveena et al., 2018) and  $313 \pm 130 \mu\text{m}$  (Lei et al., 2017) and in shower gels of about  $422 \pm 185 \mu\text{m}$  (Lei et al., 2017).

Next to the variations in size, MP concentrations are also highly different in PCPs. Variations from less than  $1 \%$  (Ustabasi and Baysal, 2019) up to  $90 \%$  were reported (UNEP, 2015). Sun et al. (2020) described the concentrations of MPs in PCPs and found the documented concentrations ranging from  $2.15$  particles per gram up to  $3.11 \times 10^6$  particles per gram.

Besides the fact that MPs intentionally added to PCPs contribute to overall environmental pollution (Gouin and Brunning, 2015; Praveena et al., 2018), when washed off the body, the direct exposure of humans to the particles is a potential pathway of MPs entering the human body. Especially MPs in toothpaste and other cosmetics applied on mucosa may potentially translocate directly into the human body. For example, swallowing or incomplete rinsing of the mouth after tooth brushing leads to a transfer of MPs into the GIT. Another vulnerable area where PCPs contact the human body is the eye. The skin is relatively thin, and the mucous membrane interacts directly with the environment when the eye is open. Potential contact of the eye’s mucous membrane with NMPs can occur through eye shadow and other cosmetic products, contact lenses, and NMPs in the air. As the global PCPs market and the use of contact lenses continue to increase, it is essential to investigate eye and eye care products as a potential gateway for NMPs into our bodies and the environment (<https://www.statista.com/statistics/297070/growth-rate-of-the-global-cosmetics-market/>; <https://www.statista.com/study/48868/contact-lenses-report/>). Contact lenses could release NMPs themselves when worn, as they are often made of hydrogel polymers, on the other hand, NMPs from the air could stick to the contact lenses and thus be taken up by ocular surface epithelial cells through prolonged contact time (Burgener and Bhamla, 2021). In addition, glitter, commonly used in eye shadow, can be identified as a primary source of MPs entering the environment and possibly the human body. Glitter, usually in hexagonal form, consists of a core polymer of PET coated with colored aluminum and a transparent polymer, which produces the typical sparkle (Tagg and Ivar do Sul, 2019; Yurtsever, 2019). There are no studies examining the uptake of NMPs by ocular epithelial cells, nor are there any studies showing the presence or accumulation of NMPs in ocular tissues. Hence the relevance of this translocation pathway is unclear.

Other PCPs used by a large part of society are contraceptives and period products. For instance, condoms are a relatively safe, effective, user-controlled contraceptive method that is easy to use and relatively inexpensive. Although the highest share of condom material used on the market are latex, condoms made of polyurethane (PU) or elastomers have already been introduced to the market in the early 1990s (Gallo et al., 2006). Furthermore, Munoz et al. (2022) recently showed that 12 of 24 period products directly in contact with the vaginal wall contained plastic. These products released fibers during *in vitro* tests and fragmented to release up to 17 billion NPs per tampon. A relatively high number of condoms (Lambert et al., 2013) and period products are disposed of down the toilet entering waste water treatment plants or are released to the environments via improper waste disposal, where they may release a substantial number of NMPs. Besides their contribution to environmental pollution with NMPs, it has not been shown whether

condoms made of plastic or plastic containing period products release NMPs during usage and whether potentially released particles may interact with the respective tissues.

#### 4. Translocation of NMPs into human tissues

The translocation of NMPs to our body compartments may occur after applying NMPs-containing PCPs to the skin or after ingestion and inhalation. The potential translocation pathways for the respective primarily exposed organs are described in the following. Since the translocation mechanisms of particulate matter through the human skin is distinct from those within the GUT and lung, we decided to describe the mechanisms separately.

##### 4.1. Human skin

Applying PCPs-containing NMPs onto our skin can directly facilitate the particles translocating from the skin into deeper tissue layers. However, the translocation of particulate matter into the skin is complex (Schneider et al., 2009). The human skin comprises four layers: the stratum corneum, the viable dermis, the dermis and the subcutaneous connective tissue (Desai et al., 2010). The stratum corneum is the outermost layer and provides an effective defensive barrier against particulate matter and pathogens in a healthy status. Schneider et al. (2009) comprehensively reviewed the reported translocation of nanoparticles through the human skin. One potential pathway to how particulate matter could be transported through the skin barrier is via the transappendageal pathway across hair follicles, sebaceous glands, and sweat glands (Desai et al., 2010; Schneider et al., 2009). Vogt et al. (2006) detected a high density of Langerhans cells (dendritic cells) around hair follicles, capable of internalizing nanoparticles of various sizes, whereas the transport across the epidermis was restricted to 40 nm particles in their experimental setup. However, it has to be noted that the transappendageal pathway is restricted to a relatively small area since the total amount of openings amounts between 0.1 and 1.3% of the entire skin (Bos and Meinardi, 2000; Schneider et al., 2009). Nevertheless, keeping in mind the very high concentration of NMPs in some PCPs described above, the translocation of NMPs via the transappendageal pathway might be relevant to consider.

Bos and Meinardi (2000) proposed the 500 Dalton rule by investigating the molecular weight of common contact allergens and topical drugs. They conclude that a molecular weight increasing over 500 Dalton leads to a rapid decline in human skin absorption. Assuming a spherical PS particle with a density of 1.05 g/cm<sup>3</sup>, it should not exceed a size of 1.15 nm to be absorbed directly by the skin. However, Schneider et al. (2009) proposed that next to the size, the particles' properties and skin's health status are important factors for translocation. Kohli and Alpar (2004) tested differently charged PS particles of different sizes (50, 100, 200 and 500 nm, positive, negative and neutral charge). They showed that only 50 and 500 nm negatively charged particles penetrated the investigated pigskin. They assume that the density of the negative charges of the 50 and 500 nm particles is higher (50 nm because of the high surface ratio and 500 nm because of a higher number of functional groups) compared to the 100 and 200 nm particles, enabling the interaction and translocation through the skin (Kohli and Alpar, 2004). However, the skin was mechanically stressed, which could impede the barrier function and allow the particles' translocation. Furthermore, the human skin has unique properties, and translocation studies performed in animal models are of limited use for understanding the human skin barrier (Bos and Meinardi, 2000). Laresse Filon et al. (2015) comprehensively reviewed the size-dependent translocation of nanoparticles across the human skin. They conclude that nanoparticles can cross the intact skin if their sizes do not exceed 4 nm, nanoparticles between 4–20 nm can potentially cross intact and damaged skin, nanoparticles between 21 and 45 nm can cross only damaged skin, and nanoparticles with sizes >45 nm cannot translocate through the human

skin. However, they also highlighted that the material properties (metal or non-metal nanoparticles) are important factors (Laresse Filon et al., 2015). No studies are reporting the translocation of NMPs through the human skin to our best knowledge.

##### 4.2. Gastrointestinal tract

NMPs entering the human body via ingestion will encounter different defense mechanisms against tissue translocation. The first line of defense a particle would experience after entering the GIT is the mucus layer produced by the enterocytes in the form of membrane-bound mucins and the goblet cells in the form of secretory mucins. The mucus layer coats the interior surface of the digestive tract and is essential in the maintenance of intestinal homeostasis (Herath et al., 2020). In a healthy GIT, the mucus layer serves as a permeable barrier allowing the absorption of nutrients but limiting the transport of pathogens and microorganisms to the gut epithelial cells (Rackaityte and Lynch, 2020; Vancamelbeke and Vermeire, 2018). However, *in vivo* experiments with mice showed that due to oral exposure to NMPs, the intestinal microbiome's composition can be altered, leading to dysbiosis (Lu et al., 2018). Dysbiosis can change the thickness of the mucus layer and could result in abnormal mucus invasion and epithelial adherence of pathogens (Herath et al., 2020) or may even allow NMPs to interact with the epithelial layer directly. Moreover, the intestinal microbiota is considered a metabolic organ that may contribute to the metabolic health of the human host and, when imbalanced, to the pathogenesis of different disorders. Tamargo et al. (2022) evaluated the effects of the digestion of MPs on the human gut microbiota using feces from healthy donors and the internationally validated Dynamic Gastrointestinal Simulator simgi® model that represents the main functional sections of the digestive tract. The feeding with MPs altered human microbial colonic community composition, promoting the formation of biofilms and MPs biodegradation through digestion by intestinal bacteria (Tamargo et al., 2022).

##### 4.3. Lung

The defense mechanisms associated with the ingestion of NMPs do not seem to depend as closely on particle sizes, as is the case for NMPs inhalation, the first line of defense depends on the particle sizes. The exposure to airborne particles is usually classified by the particles' aerodynamic diameter, with PM<sub>10</sub> (coarse particles ≤ 10 μm), PM<sub>2.5</sub> (fine particles ≤ 2.5 μm) and PM<sub>0.1</sub> (ultrafine particles ≤ 0.1 μm). The occurrence of atmospheric MPs of PM<sub>10</sub> have already been reported (Kernchen et al., 2021) and the inhalation of NMP is therefore generally possible. PM<sub>10</sub> are usually trapped in the nasopharyngeal area by hair and mucus, whereas PM<sub>2.5</sub> can reach the bronchioles and alveoli. PM<sub>0.1</sub> can directly translocate transcellularly across the alveolar epithelium (Cooper and Loxham, 2019; Schraufnagel, 2020). However, defensive mechanisms against PM<sub>2.5-0.1</sub> also occur within the respiratory system. The epithelial layer contains, similar to the GIT, goblet cells contributing to a mucus layer entrapping inhaled particles. By ciliary beating (the so-called mucociliary escalator mechanism), even PM<sub>0.1</sub> can be transported within the mucus towards the mouth, where the mucus can be expelled or swallowed (Schraufnagel, 2020).

##### 4.4. Transport of NMP across the biological barriers of the GIT and lung

When entrapped within the mucus of the respiratory system or the GIT, a particle can also be transported towards the epithelial layer (Hussain et al., 2001). Here, two potential pathways for the transport from one side of the epithelium to the other can occur. In epithelial cells, small particles (<100 nm) are more easily transported transcellularly through the epithelium by endocytosis than larger particles (in the lower micrometer range), which are transported paracellularly (Boland et al., 1999; Volkheimer, 1975, 1977; Zeytin et al., 2020). The paracellular

transport is mainly regulated through the presence of junctional complexes, like tight junctions, adherence junctions and desmosomes. Tight junctions are the apical-most adhesive complexes sealing the intercellular space (Vancamelbeke and Vermeire, 2018) and make the paracellular transport of particles challenging. However, goblet cells interrupt the network of tight junctions, loosening the tight junctions between epithelial and neighboring goblet cells, consequently allowing the transport of particulate matter in a paracellular manner (Volkheimer, 1977). Within the GIT, the transcellular pathway is also involved in internalizing larger molecules, pathogens and microorganisms (Vancamelbeke and Vermeire, 2018). Once NMPs may have crossed the epithelial layer of the lung, gastrointestinal tract or skin, there is another line of defense. Underneath the dermis of the skin, the interstitium of the lung or the lamina propria in the GIT, i.e. all corresponding tissues directly under the epithelial layer, there are various immune cells such as macrophages, dendritic cells, T and B lymphocytes, eosinophils and mast cells.

The lamina propria of the entire GIT is richly populated with diffusely distributed immune cells of different type. Furthermore, it additionally contains situated solitary lymphoid follicles, covered by the so-called follicle-associated epithelium (FAE). Whole aggregates of lymphoid follicles, mainly found in the wall of the ileum and appendix vermiformis, are called aggregated lymph follicles or Peyer's patches. The surface of each follicle is domed by propria tissue and covered with FAE (so-called dome epithelium). Intestinal villi and crypts are missing here, there are no goblet cells, and the mucus is very thin or missing. Instead, M-cells (M = microfold, this cell type is named after its' physiological appearance as the cells have no microvilli but only short microplacae. M-cells can amount 10-15% of the cells in the FAE) are firmly anchored within the epithelium in between enterocytes and can internalize particulate matter, even the size of bacteria (Foged et al., 2005; Hussain et al., 2001; Owen, 1999). M cells transport molecules and particulate matter into pockets, in which migrating lymphocytes, macrophages, and dendritic cells are found (Owen, 1999). With the initiation of an immune response activated B-lymphocytes differentiate into plasma cell precursors on site or in neighboring mesentery lymph nodes where the immune response is further set in motion. The plasma cell precursors differentiate to mature Immunoglobulin A-producing plasma cells that produce an antibody directed against the initial antigen. In addition, dendritic cells push - outside the FAE regions - long projections between the enterocytes into the intestinal lumen to further sense for pathogens or release cytokines (Scott et al., 2005). Furthermore, dendritic cells are in principle capable of internalizing PS particles up to 15  $\mu\text{m}$  in size (Foged et al., 2005).

If, for example, microorganisms or NMP penetrate the mucus and epithelial layer of the GIT, they may be phagocytosed by macrophages in the lamina propria (Grainger et al., 2017). These are ideally positioned to ingest and eliminate any bacteria that have passed through (Bain and Schridde, 2018). In principle, macrophages in the lamina propria can trigger the described inflammatory responses, but usually show a silent response to the invader in a healthy organism (Bain and Schridde, 2018; Grainger et al., 2017). However, if specific antigens are perceived or there is increased invasion with pathogens, the immune cells (especially macrophages and dendritic cells) can trigger an inflammatory process by releasing cytokines or migrating into the mesenteric lymph nodes and initiating an immune response. After initiation of the immune response, cells reach the blood circulation via the lymph vessels, lymph nodes and finally the thoracic duct, to be distributed throughout the whole organism (Hampton and Chtanova, 2019; Owen, 1999).

The actual transport of NMPs across biological barriers that may trigger inflammatory responses has not yet been demonstrated. However, *in vitro* experiments showed that macrophages are in principle able to internalize MPs (Ramsperger et al., 2021; Stock et al., 2021), which is even enhanced in the case of environmentally exposed particles coated with an eco-corona (Ramsperger et al., 2020). After particle interaction, NMPs have been shown to trigger inflammatory responses in epithelial

cells (Wu et al., 2020) and macrophages (Völkl et al., 2022). The transport of NMPs across more realistic biological barrier models was shown by using single cell culture approaches (Xu et al., 2019) and co-culture of cell lines representing small intestinal barrier models (Stock et al., 2021, DeLoid et al., 2021; Hesler et al., 2019). Furthermore, first attempts were made to estimate the uptake and potential effects of MP on organoid structures of the lung (Song et al., 2022) and intestine (Hou et al., 2022). Here, although MP fibers showed no adverse effects on mature organoids the development of lung organoids was hampered by the presence of MP fibers. The authors state, that the development of lung tissue of young children may be affected by airborne NMP, however, this needs further investigations (Song et al., 2022). The exposure of NP to intestinal organoids resulted in an accumulation of NP mainly in goblet, Paneth and endocrine cells, which consequently induced apoptosis and inflammatory responses (Hou et al., 2022).

Furthermore, *in vivo* studies using mouse model systems revealed the translocation of model nanoparticles from the lungs to the systemic circulation (Campagnolo et al., 2017; Miller et al., 2017; Raftis and Miller, 2019; Stapleton et al., 2012). Miller et al. (2017) and Raftis and Miller (2019) exposed healthy human volunteers to 5 nm gold nanoparticles via inhalation and detected the particles in the blood even three months after exposure. This retention indicates that for small NPs, translocation from the respiratory system in healthy human beings into the blood circulation may be possible. Interestingly, Burkhardt et al. (1999) linked the workers' exposure to plastic products with interstitial lung diseases, suggesting that the transport of NMPs and the subsequent inflammatory response are generally possible in human.

To our best knowledge, no empirical *in vivo* studies with volunteer human beings exposed to NMPs either via inhalation, ingestion or dermal exposure were conducted. Therefore, we reviewed the fate of NMPs in different human tissue samples to estimate the amount of NMP present in human tissues and their overall translocation within the human body.

## 5. The fate of NMPs within the human body

There is a lack of scientific literature documenting the occurrence of NMPs in humans. However, already more than twenty years ago, Pauly et al. (1998) described the presence of fibers in cancerous and non-pathologic human lung tissues. They found fibers in 87% of human lung specimens and discussed that some fibers were made of plastic due to their shape and structure. Since the aim of the study was not to primarily distinguish between natural and plastic fibers, the polymeric composition was not investigated spectroscopically (Pauly et al., 1998). In a more recent study, applying Raman spectroscopy on 20 routine coroner autopsy samples from individuals living in São Paulo, polymeric particles and fibers were detected in 13 samples (Amato-Lourenço et al., 2021). In total, 31 MPs were detected, of which 88% were fragments (mean size:  $3.9 \pm 0.7 \mu\text{m}$ ) and 13% fibers (mean fiber length:  $11 \pm 2 \mu\text{m}$ ). Although  $\text{PM}_{10}$  is usually trapped in the nasopharyngeal region (Cooper and Loxham, 2019; Schraufnagel, 2020), smaller particles may potentially be inhaled, entering deeper lung regions. However, a recent study found MP much larger than  $\text{PM}_{10}$  in different regions of the human lung (mean particle length:  $105.22 \pm 92.82 \mu\text{m}$ , mean particle width:  $34.44 \pm 22.61 \mu\text{m}$ ) (Jenner et al., 2022). Furthermore, Huang et al. (2022) indirectly measured the contamination of the human lung with NMPs using sputum samples of 22 volunteers. They found different polymer types mainly smaller than  $500 \mu\text{m}$  (median:  $75.43 \mu\text{m}$ ). To monitor potential procedural contamination, they conducted one blank sample. Subsequently, the authors corrected the sputum samples with the blank sample value and found a median number of 39.5 MPs/10 mL sputum.

Two pilot studies on the contamination of the human placenta with NMPs were conducted (Braun et al., 2021; Ragusa et al., 2021). Both studies showed the contamination of human placenta samples from vaginal (Ragusa et al., 2021) and cesarean delivery (Braun et al., 2021).



Furthermore, one study investigated MPs in human colon tissue samples (Ibrahim et al., 2021). They found a mean of 28 MPs/g colon sample, with 96% of all MPs being fibers of approximately 1 mm length. Interestingly, the authors found mainly fibers in their samples, whereas in human stool samples, mainly fragment- and film-shaped MPs were detected (Schwabi et al., 2019). A second study confirmed the presence of MPs in human stool samples but unfortunately no information regarding the shape of the MPs were given (N. Zhang et al., 2021). Therefore, we can only speculate that the differences in the observed shapes from colon and stool samples could either derive from differences in the sample collection, procedure, and subsequent measurements or by the fact that fibers are more likely to stick to the colon tissues than fragments and films that are more easily released. However, this is highly speculative and needs further investigation. Just recently, Horvatsits et al. (2022) described the presence of MPs in human liver, spleen and kidney samples. Out of 17 tissue samples, the authors found six MPs ranging from 4–30  $\mu\text{m}$  in size. Another study investigated NMPs in human blood samples (Leslie et al., 2022). The authors found a mean NMPs concentration of 1.6  $\mu\text{g}/\text{mL}$  of blood by using Py-GCMS. It has to be noted that the particle size distribution is defined by the opening of the venipuncture (0.5 mm, upper limit) and the filter mesh size (700 nm, lower limit). The authors aimed to detect five different polymer types (PET, PE, PS, PMMA and PP). All polymer types were detected except for PP.

At this point, we would like to emphasise that in both the exposure studies and the fate studies different sampling procedures and analytical techniques have been applied while quality assurance and quality control (QA/QC) measures are often lacking. A few studies investigated the quality and reliability of data and whether a proper risk assessment can be performed based on current knowledge. For instance, Koelmans et al. (2019) determined the reliability of studies using nine quality control criteria in a systematic review, including 50 publications on NMPs in freshwater, wastewater and drinking water. They concluded that out of the 50 publications, only 4 scored positive in all criteria and can be considered reliable data. Furthermore, Coffin et al. (2022) aimed to develop and evaluate the feasibility and confidence in deriving a human health-based threshold value for MPs in drinking water. The authors scored the quality of the reviewed publications and concluded that currently, the uncertainties in the data are too high to develop a human health-based threshold for drinking water quality. The conclusion of Coffin et al. (2022) is in great agreement with the WHO report (2022), indicating that "(...) the available data are of only very limited use for assessing the risk of NMP to human health".

Therefore, we would like to highlight that the comparability between studies is challenging and the interpretation of the presented results above should be taken with caution.

## 6. Reasons why reported studies should be interpreted critically

In our review article, we described the current knowledge of the NMP contamination of the most relevant (1) exposure routes to humans, the potential (2) translocation mechanisms of NMP across biological barriers and summarized the studies of the (3) fate of NMP in human tissues and fluids. Although our review article did not aim to compare contamination levels of NMP in the different studies investigating exposure scenarios and the fate of NMP in human tissues, it is essential to keep several aspects in mind. Other review articles have already addressed the analytical challenges for assessing NMPs in matrices relevant to human exposure and described the crucial steps during sample collection and processing (Alexy et al., 2020; Koelmans et al., 2020; Noventa et al., 2021; Van Raamsdonk et al., 2020; Toussaint et al., 2019; Wright and Kelly, 2017). Especially sufficient QA/QC in NMP analysis are essential. Considering that NMPs are usually found everywhere in the laboratory environment, the possible contamination of a sample (exposure template or human tissues and fluids) should be kept in mind. In brief, using procedural blank samples in every step is critical

to monitor potential contamination during sampling and sample processing. Further information on how to sufficiently perform QA/QC in NMP research can be found elsewhere (Brander et al., 2020; Enders et al., 2020; Möller et al., 2020). However, even if QA/QC measures have been addressed, studies must be critically viewed. For instance, in Ragusa et al. (2021), the authors state that they performed procedural blanks and corrected the samples with the blank values; however, the numbers of particles found in the blanks are not stated and therefore, it is hard to interpret the data. Furthermore, they state that they have excluded fibers from their analysis as they could not use laminar airflow cabinets during sample processing. However, NMP fragments also occur in the ambient air and may contribute to the potential airborne contamination of the samples. Another example is the Study of Ibrahim et al. (2021). The authors followed several steps to prevent airborne plastic contamination: E.g. cotton lab wear was worn, liquid reagents were prefiltered before usage (although no mesh sizes were stated), test devices were pre-cleaned, and the use of plastic items for sample processing was kept to a minimum. Here it must be noted that although the authors used blank samples during microscopy, they did not describe the use of blanks during sample collection but have pre-checked the formalin fixative and filters for plastic contamination (Ibrahim et al., 2021).

Given the limitations of state-of-the-art analytical methods, particle numbers and sizes found in exposure matrices and in human tissues and fluids may not reflect accurate numbers. Möller et al. (2020) summarized the advantages and disadvantages of the different techniques used in NMP identification. In brief, visual sorting or hot needle tests are highly error-prone and not recommended. In contrast, vibrational spectroscopy and chromatographic techniques are state-of-the-art and suitable MP identification techniques. Vibrational techniques include Raman or Fourier transform infrared (FTIR) spectroscopy and allow the precise identification of different polymer types. However, it must be noted that a particle's detection limit is at  $\sim 1 \mu\text{m}$  for Raman and  $\sim 10 \mu\text{m}$  for FTIR (depending on the instrument); therefore, smaller MP and NP cannot be detected.

On the other hand, chromatographic techniques such as pyrolysis-gas chromatography-mass spectrometry (py-GCMS) or thermal extraction desorption GCMS (TED-GCMS) can identify MP and even NP within a non-treated sample. However, both methods can only measure relatively small sample sizes and are destructive. Therefore, no information can be given about the number of particles, size and shape (Möller et al., 2020). However, by comparing different particulate contaminants, Wieland et al. (2022) concluded that the size, shape and surface properties play a decisive role in particle toxicity and should be considered. In principle, to determine the size of NMP, the samples could be filtered and therefore grouped in different size classes and subsequently analyzed with py- or TED-GCMS. However, due to the pre-processing of the sample, the decisive advantage that no sample preparation is necessary for chromatographic methods is lost, and the prior processing of the samples create the risk of sample contamination or loss of particles.

Another commonly used method in the presented studies is scanning electron microscopy coupled with energy dispersive X-ray spectroscopy (SEM-EDS) emission detection. However, an accurate interpretation of the spectra is only possible for flat-polished samples or thin films with irrelevant topography (Girão, 2020). Therefore, due to the different limitations of the various methods as well as the potential contamination of a sample, both the numbers and the polymer types should be critically viewed in the reported studies.

If one considers the translocation mechanisms described earlier in our review article, the size of the particles seems to be one of the driving factors for tissue translocation. For instance, the translocation of particles in healthy human skin is determined by their size, which should not exceed the lower nanometer size range. For the GI and lung, the particles should not exceed sizes of the lower micrometre size range, namely  $< 10 \mu\text{m}$  or even smaller, with an increasing translocation potential with



decreasing particle sizes. Particulate matter's size-related transport across biological barriers was investigated *in vitro* and *in vivo*. In rodent models, it was shown *in vivo* that radioactive-labelled NPs are more likely to be translocated within the GIT mucosa than MPs. The smaller NPs (50 and 100 nm) showed a higher adsorption rate than 1  $\mu\text{m}$  MP particles (33, 26 and 4.5%, respectively) (Jani et al., 1990). Furthermore, after intratracheal exposure of mice to 20 nm rhodamine-labelled polystyrene NPs the particles could be detected in maternal and fetal tissues (Fournier et al., 2020). However, it has to be noted that it cannot entirely be ruled out that the labelling of the used particles may have leached, and it was not the particles per se being detected. Furthermore, using an *in vitro* model of the small intestinal epithelium, DeLoid et al. (2021) showed significantly higher uptake of small NPs (25 nm carboxylated PS spheres) than larger particles. However, Stock et al. (2019), using a similar epithelial model, demonstrated that the uptake of MP (1, 4 and 10  $\mu\text{m}$ ) is generally possible.

Keeping the potential for tissue translocation in mind, most particle sizes detected in the exposure matrices are much larger than the described particle sizes for translocation mechanisms. For instance, the smallest NMP sizes described in the exposure scenario studies presented in this review are in the lower micrometre size range: 1–50  $\mu\text{m}$  (Hernandez et al., 2019), 1.5–2.5  $\mu\text{m}$  (Oliveri Conti et al., 2020), 2–180  $\mu\text{m}$  (Diaz-Basantes et al., 2020), 3–60  $\mu\text{m}$  (Kumar et al., 2021), 3–145  $\mu\text{m}$  (Praveena et al., 2018), 4–20  $\mu\text{m}$  (Ustabasi et al., 2019), <5  $\mu\text{m}$  (Oßmann et al., 2018) and 5–20  $\mu\text{m}$  (Schymanski et al., 2018). However, not all studies present clear evidence that the small fraction of the reported NMP in the exposure matrices are indeed plastic particles. For instance, Praveena et al. (2018) performed FTIR analysis only on the larger fraction of isolated NMPs. Ustabasi and Baysal (2019) did not perform FTIR analysis on single particles but measured a film consisting of particle aggregates. Diaz-Basantes et al. (2020) used FTIR to identify the polymeric composition of 10 particles per sample. The particles must be larger than the instrument's detection limits; therefore, the authors cannot conclude the presence of small NMPs.

In the fate studies, very small MPs (<3  $\mu\text{m}$ ) or NPs were also not reported or insufficiently identified. The smallest particles found in human tissues were 2  $\mu\text{m}$  in the lung (Amato-Lourenço et al., 2021), 3.3  $\mu\text{m}$  in liver (Horvatits et al., 2022), and 5–10  $\mu\text{m}$  in human placenta (Ragusa et al., 2021). Horvatits et al. (2022) stained the isolated particulate matter with Nile Red and measured only a few particles with Raman spectroscopy. The authors do not state the size of the identified MP; therefore, no conclusions can be drawn whether all small particles are of polymeric origin.

Next to the size and shape of NMPs, their concentration plays a decisive role. For instance, the concentration of NMP found in blood samples seems to be rather high since concentrations reported in surface waters or bottled waters were by a factor of 22 and 8.300 lower (1.6  $\mu\text{g}/\text{mL}$  in blood (Leslie et al., 2022), 0.073  $\mu\text{g}/\text{mL}$  in surface waters and 0.000193  $\mu\text{g}/\text{mL}$  in bottled drinking water (only PET detected) (Braun et al., 2021). One may assume that the constant exposure of humans to NMP may lead to their accumulation in tissues and blood, even exceeding environmental concentrations. However, whether an accumulation of NMP in human tissues and blood is realistic needs further investigation.

Here would like to emphasise that particle properties other than size or shape are rarely reported in these studies, although different properties can contribute to the particles' potential to cross biological barriers. To date, most studies used model NMP particles, like polystyrene spheres which do not resemble particles present within the exposure matrices. Environmentally relevant NMPs have various sizes and shapes with different surface modifications and are not uniform spherical particles of homogenous sizes. Furthermore, the use of model NMPs in effect studies has been considered insufficient since the choice of the commercial source of the model NMPs can significantly affect the experimental output, and the particles should be characterized in detail (Ramsperger et al., 2021). In contrast, weathered NMPs should be used

since it has been shown that an eco-corona (Ramsperger et al., 2020) or the artificial UV-aging of particles (Völkl et al., 2022) alters the surface of the particle leading to differences in the particle-cell interactions and cellular responses. This aspect is also highlighted by the fact that the MP found in human tissue samples is irregular, like fragments or fibres. To date, we have a discrepancy between the studies on the transport of spherical NMP across biological barriers and the properties of the particles described in the fate studies. Therefore, reliable statements of how non-spherical particles can potentially enter the tissues and whether the concentrations found in the tissues are meaningful cannot be made to date.

### 6.1. Risk assessments of NMP exposure to humans

The presence of NMP may cause oxidative stress and cytotoxicity, either due to the particles' physical or chemical properties or the exposed tissue's response (Prata et al., 2020). Altered metabolism, neurotoxicity, reproductive toxicity, and immune function disruption are also potential health risks (Prata et al., 2020; Rahman et al., 2021). However, these assumptions are predominantly based on observations in animal models or *in vitro* approaches. It remains unclear whether the toxicological effects observed in animal models are transferable to humans (SAPEA, 2019).

In general, it is doubted that without extensive standardization, representative reference materials, and inclusion of physicochemical properties and associated substances, a realistic assessment of human health risks is possible (Brachner et al., 2020; Vethaak and Legler, 2021). Toxic effects may also depend on specific properties such as shape, surface charge or residual monomers of the plastic particles. Kooi and Koelmans, therefore, propose to consider continuous scales for probabilistic risk assessment of microplastics (Kooi and Koelmans, 2019). Ultimately, however, the complex mixtures of different chemicals found in environmental samples of NMPs may present too high a hurdle to separate the different effects of combinations of chemicals and particles (Gouin et al., 2022). Recent studies pointed to the need for adopting tools and models to estimate the exposure and fate of NMPs to perform a risk assessment. For example, modelling human exposure to MP and the associated chemicals needs to consider MPs' characteristics and leaching rates of chemicals in a combined manner for a holistic risk assessment (e.g., Mohamed Nor et al., 2021). Screening and prioritization tools for hazard data are also needed to ensure the use of fit-for-purpose data for risk assessment (Gouin et al., 2022).

Overall, promising steps have been made toward identifying and prioritizing major research needs, limitations in microplastic risk assessment, and the development of the respective tools and models (Gouin et al., 2019; Mehinto et al., 2022). However, a fully operational human health risk assessment is not available to date. Even if only small fractions of NMP can overcome epithelial barriers, the long-term effects of persistent particles and associated chemicals should not be underestimated (Vethaak and Legler, 2021).

## 7. Conclusion

We describe in this review the various sources and exposure routes of how humans can come into contact with NMPs. We detected three main pathways of how NMPs enter food: First, the contamination of the environment with NMPs determines the contamination of food items (e.g., the contaminated waters determine the contamination of blue meat). Secondly, NMPs can enter food through industrial processing and thirdly, NMPs can enter food through packaging and atmospheric deposition. Concerning the sources, in almost all matrices, NMPs were detected, emphasizing various human exposure sources via drinking water, food, air and PCPs. It is widely accepted that as particle size decreases, interaction with tissue and individual cells increases. From the three exposure routes of NMPs to humans, size-dependent defence mechanisms occur for the skin and inhalation, whereas in principle

NMPs of any size can be ingested. The translocation through the skin is either restricted to particles in the lower nanometer size range or may occur via the transappendageal pathway, restricted to a very small percentage of the skin area (up to 1.3%). As described above, the respiratory system of humans is also equipped with size-dependent defense mechanisms, usually retaining larger NMPs before entering the deeper lung tissue. However, to date, the few studies on the fate of MPs in human tissues, also within the lung, detected particles in a size range of a few micrometers. The fact that it is often not stated in the presented studies which, or if, QA/QC measures were taken, makes it difficult to draw conclusions on the actual exposure level of biologically relevant particle sizes and whether the NMP found in human tissues and fluids are meaningful. Although first studies indicate the presence of small NMP in exposure matrices and human tissues and fluids, we highly recommend, to critically read and interpretate current literature, to not overinterpret the current understanding in NMP research regarding human health. Research into very small MPs and NPs is still in its infancy. Consistently further development of reliable methods for the isolation, purification and analysis of small MPs and NPs is urgently needed to make accurate statements regarding the exposure and fate of NMPs within the human body.

### Author statement

All authors contributed to conceptualization, resources and funding acquisition. AFRMR, HK, JB, MGJL, CL, BG, CRL, SP and HPG wrote the introduction. AFRMR, MGJL, CL, HPG and DK wrote the chapter of NMP in drinking water. AFRMR, HK, JB, MGJL, CL, RP, AU, EB, MP, IF, FBa, FBe, MZ, AT and VM wrote the chapter of NMP in food. AFRMR, MGJL, CL, JD and FP wrote the chapter of NMP in PCPs. AFRMR, HK, JB, MGJL, CL, FBe, MZ, MN, HW, AKA, SZN, SEH, TKE, PG, BCB, KCN, EB, MP, IF and FBA wrote the chapter of NMP in indoor air and workplaces. AFRMR, HK, JB, MGJL, CL, FP, HW, AKA, SZN, SEH, TKE, PG, BCB and KCN wrote the chapter of NMP translocation. AFRMR, HK, JB, MGJL, CL wrote the chapter of NMP fate in the human body, abstract and conclusion. AFRM, JB, MGJL, CL, DK, BG, CRL and SP wrote the Reasons why reported studies should be interpreted critically and risk assessment. AFRMR, HK, JB, MGJL, CL wrote the first draft of the manuscript and all authors reviewed and edited the manuscript. JB and AFRMR designed the graphical abstract.

### Declaration of Competing Interest

The authors declare no competing interests.

### Data availability

No data was used for the research described in the article.

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