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Recent Progress in Intestinal Toxicity of Microplastics and Nanoplastics: Systematic Review of Preclinical Evidence

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Abstract: The tremendous plastic production and poor post-use management are current and future sources of environmental and human contamination due to their degradation products: microplastics and nanoplastics (MNPLs). Methodological developments have allowed MNPLs to be detected in an increasing variety of human foods, as well as in stool and colonic mucosa. It was suggested early that the direct contact between MNPLs and intestinal tissues could represent a potential risk for human health. In order to assess this, over the last 3 years, numerous studies have evaluated the impact of MNPL ingestion on intestinal homeostasis in rodents. This comprehensive review reports the preclinical studies published between January 2021 and January 2024, and analyzes their contributions as well as their shortcomings. It shows that evidence is accumulating of the intestinal toxicity of spherical MNPLs, which lead to pro-inflammatory, pro-oxidative, barrier-disruptive and dysbiotic effects. However, the available literature has addressed only a minor part of the potential health issues of MNPLs. Many parameters contributing to MNPL toxicity need to be better taken into account in future studies. Particular attention should be paid to improve the representativeness of MNPLs, as well as to better consider the susceptibility factors of MNPL toxicity, generated especially by an underlying pathology or pathological imprinting.

Keywords: microplastic; nanoplastic; intestinal; colon; gut barrier; inflammation; oxidative stress; dysbiosis

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1. Introduction

Plastic is a long-carbon-chain polymer that is massively integrated in our daily life. Plastic products are used in packaging, building and construction, automotives, electricals and electronics, agriculture and houseware [1]. During the last 70 years, plastic production has extensively expanded, reaching 390.7 metric tons of plastic production worldwide in 2021 [1]. The accumulation of post-consumer plastic waste in the environment coupled with mismanaged waste programs have led to plastic contamination in all environmental niches [2]. Overall, nearly 60–75% of plastic products are discarded to the environment or landfilled, and this colossal plastic burden will remain in the earth for centuries [3]. Indeed, in the environment, large plastics undergo continuous physical, chemical and biological degradation processes, generating a broad amount of microplastics. Microplastics (MPLs) refer to small plastics ranging in size from 1 µm to 5 mm [4]. They can be further degraded into plastic particles with a size range between 1 and 1000 nm, known as nanoplastics (NPLs) [5]. Microplastics and nanoplastics (MNPLs) have many shapes such as granules, fragments, microbeads, fibers and foams [6]. MNPLs spread through the air, land and sea. The mass of MPLs which accumulates in the oceans has led to contamination by MPLs in fish, zooplankton, shrimp, crab, clam, mussel and many other aquatic organisms [7]. Microplastics can also be absorbed and accumulated by plants, such as rice, wheat, lettuce and other crops. Plants can absorb MPLs through their roots

and then transfer them to their aboveground parts [8,9]. Moreover, MPLs easily enter the human food chain as marine and terrestrial organisms ingest MPLs [10]. Overall, human food can be contaminated by plastic particles either through direct exposure to the environment or indirectly by the transfer of MPLs within the ecosystem [10]. Therefore, MPLs accumulate in the human food chain. They have been detected in water, tea, beer, white wine, energy drinks, soft drinks, fish, shellfish, salt, sugar, honey, milk, poultry meat, fruit and vegetables [11]. The most common detected MPLs in food are polyethylene terephthalate (PET), polyethylene (PE), polypropylene (PP), polystyrene (PS), polyvinyl chloride (PVC), polyamide (PA) and polycarbonate (PC) [11]. Still, there is a lack of data quantifying MNPLs in meat, cereals and many other food products, and the amount of MNPLs ingested by human through food is recognized to be underestimated [6]. Moreover, exposure to MPLs through dust also decisively contributes to MPL intake. The amount of MPLs ingested from exposure to indoor dust has been estimated to be 0.21, 0.23 and 0.6 MPL/kg bw/day for adults worldwide [12], in China [13] and in Iran [14], respectively. Infants and newborns are exposed to higher MPL concentrations, namely 3.04, 7.4 and 13.7 MPL/kg bw/day, respectively. Despite the knowledge gaps regarding human exposure to MNPLs, the total burden of human exposure to MNPLs has been recently estimated to be 2.93×10^{10} particle/year [6]. The contact between MPLs and the colonic epithelium has been confirmed by several studies describing the detection of MPLs in the stools of healthy adults [15–19]. MPLs have also been detected in the meconium and in infant stools [20,21]. MPLs are therefore present in the intestinal lumen, but could also penetrate the intestinal epithelium, as suggested by their detection in human colectomy specimens [22,23]. Indeed, MPL presence was reported in colons from healthy adults and from patients with colorectal carcinoma. Therefore, it is essential to determine the health impact generated by MPL exposure, particularly at the intestinal level. Numerous studies carried out mainly in aquatic organisms and to a lesser extent in rodents have since demonstrated the intestinal toxicity caused by the ingestion of MPLs. The available data were reviewed in 2020 [24,25]. Since then, knowledge of the effects of MNPLs has extended to mammals, thanks to numerous studies which have assessed the effect of ingestion of MPLs and NPLs in rodents. In comparison with previous studies, these new studies focus more closely on human physiology. They studied a wide variety of MPLs and NPLs; they addressed several types of polymers, presenting a wide variety of sizes, sometimes with different surface charges. They were carried out for varying durations, in healthy or pathological individuals. They strengthened the evidence of MNPL-induced gut toxicity, but also identified new intestinal adverse effects as well as novel pathophysiological mechanisms impaired by MNPL exposure. The aim of this work was to offer a comprehensive analysis of the recent literature in order to provide an up-to-date understanding of the research area of MNPL intestinal toxicity.

2. Methods

A systematic search for published articles and documents was conducted in databases such PubMed database (https://www-ncbi-nlm-nih-gov.proxy.insermbiblio.inist.fr, accessed on 29 February 2024), ScienceDirect (https://www-sciencedirect-com.proxy.insermbiblio.inist.fr, https://www-ncbi-nlm-nih-gov.proxy.insermbiblio.inist.fr, accessed on 29 February 2024), SpringerLink (https://link-springer-com.proxy.insermbiblio.inist.fr, https://www-ncbi-nlm-nih-gov.proxy.insermbiblio.inist.fr, accessed on 29 February 2024) and Google Scholar (https://scholar-google-com.proxy.insermbiblio.inist.fr, https://www-ncbi-nlm-nih-gov.proxy.insermbiblio.inist.fr, accessed on 29 February 2024), in the period from January 2021 to February 2024.

The search queries were “microplastic or nanoplastic” and “intestinal” and “mouse or rat or rodent” in titles/abstracts. All the relevant studies were retrieved by sorting the title and the abstract. Only studies aimed at studying the impact of MPLs and/or NPLs by ingestion in rodents were included. Publications including in vitro and in vivo studies were included but only in vivo data were reported. Studies reporting only data on the gut microbiota were included. Studies for which it was not possible to report a primary characterization of the MNPLs used, such as the type of polymer, were excluded.

3. Results and Discussion

The preclinical studies which assessed the intestinal toxicity of MNPLs in rodents are detailed in Table 1.

Table 1. Overview of rodent studies of the intestinal toxicity of MNPLs.

Sex Background Specie	Polymer Type, Shape, Mean Aerodynamic Diameter and Other Specificities of MPLs/NPLs	Exposure Conditions Concentration * Duration Administration Pathway	Main Alterations Observed	Reference
		Polystyrene (PS)		
Male C57BL/6 mice	Spherical 5 µm PS	500 µg/L so ≈0.11 mg/kg bw/day 4 weeks Drinking water	Increased intestinal permeability in mice with acute DSS [1]-induced colitis	[26]
Male C57BL/6 mice	Spherical 70 nm NPL and 5 µm MPL PS, pristine PS, negatively charged carboxylated PS (PS-COOH) and positively charged aminated PS (PS-NH2)	0.2 and 2 mg/kg bw/day 4 weeks Gavage	Gut toxicity PS-NH2 > PS-COOH > pristine PS Decreased expression of tight-junction proteins for PS-NH2 MPL and NPL Dysbiosis: MPL > NPL Chemically modified MNPL > pristine MNPL	[27]
Male C57BL/6 mice	Spherical 50, 500, 5000 nm individually and combined PS	2,5, 50, 250, 500 mg/kg bw/day 4 weeks Gavage	Numerous significant effects on duodenum, jejunum, ileum, colon: dose-dependent and size-dependent, including Decreased mucus Increased ROS [2] generation (DHE) Increased apoptosis (TUNEL) Increased caspase-3 Increased intestinal permeability (4 and 70 kDa dextran) and decreased Ecad levels Combined toxicity of 50 and 500 nm NPLs	[28]
Female C57BL/6 mice	Spherical 50 nm and 1 µm PS	0.2 mg/mouse so ≈9 mg/kg bw/day 12 and 23.7 weeks Drinking water	No effects under basal, acute colitis or chronic colitis conditions	[29]
Male C57BL/6 mice	Spherical 47 nm PS	0.2, 1 and 10 mg/kg bw/day 4.2 weeks Gavage	Slight dysbiosis (impact on 3 to 8 taxa/group) Slight intestinal damage (only Tff3 and Klf3 mRNA decrease at highest dose)	[30]
Male C57BL/6 mice	Spherical 5 µm PS	500 µg/L so ≈0.11 mg/kg bw/day 4 weeks Drinking water	In colon: Increased TNFα, IFNγ, IL1β, GPx Decreased Claudin1 and Occludin1 Worsened DSS [1]-induced colitis (colon length) Decreased glycine and taurine production only under DSS [1]-induced conditions	[31]

Table 1. *Cont.*

Sex Background Specie	Polymer Type, Shape, Mean Aerodynamic Diameter and Other Specificities of MPLs/NPLs	Exposure Conditions Concentration * Duration Administration Pathway	Main Alterations Observed	Reference
Male C57BL/6 mice	Spherical 5 µm PS	18 and 180 µg/kg bw/day 12.8 weeks Drinking water	Dysbiosis	[32]
Male ICR mice	Spherical 5, 50, 100 and 200 µm PS	80 mg/kg bw/day, including 20 mg/kg of 5, 50, 100 and 200 µm MPL 10 weeks Gavage	In normal-diet mice: induction of dysbiosis (including decreased Firmicutes/Bacteroides ratio) In high-fat-fed (HFD) mice: modification of HFD-induced dysbiosis (including worsening of Enterobacteriaceae abundance increase)	[33]
C57BL/6J mice (sex not provided)	Spherical 5 µm PS	0.5 and 5 µg/mouse so ≈0.023 and 0.23 mg/kg bw/day 2 and 9 weeks Gavage	DSS [1]-induced acute and chronic colitis exacerbation	[34]
Male C57BL/6 mice	Spherical 5 µm PS	0.1 mg/day so ≈4.5 mg/kg bw/day 6 weeks Gavage	Alterations in gut microbiota and metabolites	[35]
Male C57BL/6 mice	Crushed 51 and 88 µm PS	50 and 500 mg/kg bw/day 3 weeks Feed	Decreased SI [3] mucus layer thickness Increased SI [3] epithelial injury Fecal dysbiosis Host plasma lipid metabolism disturbance	[36]
Male C57BL/6 mice	Spherical 5 µm PS	100 µg/L so ≈0.02 mg/kg bw/day 6 weeks Drinking water	In colon: Decreased goblet cell number Increased crypt depth and density Decreased Tff3 and Muc2 mRNA Increased Il1β, Il6, Dll1, Dll4, Jag1, Notch1, Hes1, Lgr5, Bmi1, Olfm4 and c-Myc mRNA levels Increased c-MYC and PCNA protein levels Worsened DSS [1]-induced colitis (body weight, colon length, histological score, serum LPS, colon Il1β and Il6)	[37]
Male and female C57BL/6 mice	Spherical 71 nm PS	50, 250 or 1250 µg/mouse/day So ≈2.3, 11.5 or 57.5 mg/kg bw/day 7.52×10^{11}, 3.76×10^{12}, and 1.88×10^{13} particles/day 3 times per week during gestation Oropharyngeal aspiration	In adult male and female offspring: Duodenum, jejunum and ileum histomorphological alterations in female and male mice Small intestine oxidative stress Small intestine ferroptosis	[38]

Table 1. *Cont.*

Sex Background Specie	Polymer Type, Shape, Mean Aerodynamic Diameter and Other Specificities of MPLs/NPLs	Exposure Conditions Concentration * Duration Administration Pathway	Main Alterations Observed	Reference
Male C57BL/6 mice	Spherical 0.45–0.53µm PS COOH	1000 µg/L so ≈0.22 mg/kg bw/day 4 weeks Drinking water	On SI of high-fat-diet-fed mice: Decreased goblet cells Decreased mucus thickness Decreased villus height and higher crypt depth Increased innate lymphoid cells ILC1 and T bet^{+} ILC3 cells Increased M1/M2 macrophage ratio Decreased ILC3 cells Decreased palmitic acid, acetic acid, propionic acid and butanoic acid in feces Increased inflammatory cytokines and lipid metabolism gene expression	[39]
Male C57BL/6 mice	Spherical 0.05–0.1 µm and 9–10 µm PS	1 ppm, 1 mg/L so ≈0.22 mg/kg bw/day 12 weeks Drinking water	Size-dependent Gut dysbiosis (bacteria and fungi) Disturbed microbial metabolic pathways Altered microbial antibiotic resistance genes and virulence factors	[40]
Male C57BL/6 mice	Spherical 5 µm PS	0.1 mg/mouse so ≈4.5 mg/kg bw/day 6 weeks Gavage	Gut dysbiosis and variations in predicted functional pathways Modifications to metabolite profiles (bile acid metabolism enrichment) Increased bile acids, decreased purine and pyrimidine nucleosides Decreased fecal levels of acetic acid, propionic acid, butyric acid and isobutyric acid (SCFA)	[41]
Male BALB/c mice	Spherical 100 nm PS, PS-COOH and PS-NH2	1 mg/mouse/day so ≈45.5 mg/kg bw/day 4 weeks Gavage	Decreased villus length Increased crypt depth and lower ratio of villus length to crypt depth Increased the secretion of mucus in ileum Increased IL-17a-positive cells in the ileal lamina propria Increased ileal apoptosis (TUNEL) Increased necroptosis (RIPK3 and MLCK protein expression) Increased mitophagy (PINK1, PARKIN, SQSTM1/p62, LC3B, TOMM20 protein expression)	[42]

Table 1. *Cont.*

Sex Background Specie	Polymer Type, Shape, Mean Aerodynamic Diameter and Other Specificities of MPLs/NPLs	Exposure Conditions Concentration * Duration Administration Pathway	Main Alterations Observed	Reference
Male C57BL/6 mice	Spherical 100 nm NPL and 1 µm MPL PS	0.5 mg/mouse so ≈22.7 mg/kg bw/day 8.5 weeks Gavage	Decreased colon mucus secretion Increased gut permeability (FITC dextran) Size-dependent dysbiosis Altered serum metabolites	[43]
Male C57BL/6 mice	Spherical 5 µm PS	0.001, 0.1, 1 and 10 µg/mL so ≈0.002, 0.02, 0.2 and 2 mg/kg/day 10 weeks Drinking water	Dysbiosis from the 0.1 µg/mL concentration	[44]
Male C57BL/6 mice	Spherical 5 µm PS	10 mg/L so ≈2.3 mg/kg bw/day 6 weeks Drinking water	In distal colon of healthy mice: Increase in the number of endocrine cells Increase in the content of highly sulfated mucins in goblet cells Increase in the number of cells in the lamina propria Decrease in the volume fraction of macrophages Worsening of DSS [1]-induced colitis: greater prevalence of ulcers and inflammation; decrease in the content of neutral mucins in goblet cells	[45]
KN Mice (sex not provided)	Spherical 300 nm PS	12 and 500 mg/kg bw/day 4 weeks Gavage	Dose-dependent Increased gut permeability Increased ileum Muc2 expression Decreased jejunum and ileum villus number and length Decreased colon mucus thickness and goblet cells number Ileum and jejunum oxidative stress	[46]
Male Wistar rat	Spherical 50 nm and 5 µm PS	0.1 and 1 mg/kg bw/day 4 weeks Gavage	Higher for MPLs than NPLs: Decreased colon mucus secretion and MUC2 expression Decreased colon ZO-1 and occludin expression For both MPLs and NPLs: decreased colon exosomal miR-126a expression	[47]
Male C57/BL/6 mice	Spherical 5 µm PS	200 µg/L so ≈0.04 mg/kg bw/day 5 weeks Drinking water	With normal diet: Increased serum Diamine oxidase (DAO), D-Lactate, D-Lactate dehydrogenase (D-LDH) and intestinal fatty acid-binding protein (IFABP) Decreased ileum secretory IgA Fecal dysbiosis Worsened with dietary restriction: Decreased ileum mucus secretion Increased serum DAO, D-Lactate, IFABP and TNF-α levels	[48]

Table 1. *Cont.*

Sex Background Specie	Polymer Type, Shape, Mean Aerodynamic Diameter and Other Specificities of MPLs/NPLs	Exposure Conditions Concentration * Duration Administration Pathway	Main Alterations Observed	Reference
Female BALB/C mice	Spherical 20, 500, 5000 nm PS	6, 60, 600 µg/kg bw/day 2 or 4 weeks Gavage	Gut microbiota composition alterations Variation in short-chain fatty acid levels Modifications to intestinal permeability (decreased after 2 weeks, increased after 4 weeks) Increased leukocytes in SI (4 weeks) Decreased secretory IgA levels Decreased $CD4^+$ and $CD8^+$ T cells in MLN [4]	[49]
Female C57BL/6 mice	Spherical 50 nm PS	0.1, 1 or 10 mg/L so ≈0.02, 0.23 or 2.3 mg/kg bw/day 32 weeks Drinking water	Increased caveolin and clathrin levels (endocytosis proteins) Histological damage in jejunum, ileum, colon Decreased Claudin-1, Occludin, ZO-1 levels Increased ROS[2] and MDA levels Decreased SOD and GSH-Px levels Increased B lymphocytes in MLN[4] Decreased $\gamma\delta^+CD8^+$ and $CD3^+$ $CD8^+$ T cells in intestine Increased intestinal mucosal IL1β, IL-6 and TNF-α.	[50]
Male C57BL/6 mice	Spherical 0.5 and 5 µm PS	0.5 mg/mouse/day so ≈22.7 mg/kg bw/day 8 weeks Gavage	Decreased colon length (5 µm only) Increased colon IL6, TNFα, Il1β secretion (higher for 5 µm than 0.5 µm) Dysbiosis and variation in fecal metabolome (higher for 5 µm than 0.5 µm)	[51]
Male C57BL/6 mice	Spherical 0.2, 1 and 5 µm PS	1 mg/kg bw/day 4 weeks Gavage	In colon: 5 µm PS: Oxidative stress Increased inflammatory cytokines Impaired tight junctions and mucins Lower impairments for 1 µm Fewest impairments for 0.2 µm	[52]
Male ICR mice	Spherical 44 nm nonfunctionalized PS, 51 nm PS-NH2, 50 nm PS-COOH	80 µg/L 0.018 mg/kg bw/day 9 weeks Drinking water	Similar for the 3 NPLs: Increased colon histological score Decreased colon Ifnγ, Il6, Il10, Tff3 Increased Tlr3 expression NPL-specific variations in fecal microbiome and metabolome	[53]

Table 1. *Cont.*

Sex Background Specie	Polymer Type, Shape, Mean Aerodynamic Diameter and Other Specificities of MPLs/NPLs	Exposure Conditions Concentration * Duration Administration Pathway	Main Alterations Observed	Reference
Male BALB/C mice	Spherical 140 nm PS	5 mg/kg bw/day 4 weeks Gavage	Jejunum and colon mitophagy (increased secretion of LC3B2/LC3B-1, BNIP3, NIX and p62) Dysbiosis	[54]
Male ICR mice	Spherical 99 nm and 5 µm PS	200 or 500 µg/mouse so ≈9 or 22.5 mg/kg bw/day 5 weeks Gavage	Size- and concentration-dependent dysbiotic effects	[55]
Male C57BL/6 mice	Size and shape not provided PS NP	0.5 and 1.5 mg/mouse/day so ≈22.7 and 68 mg/kg bw/day 4 or 6 weeks Gavage	Activation of pro-inflammatory gene expression (RNA sequencing) Activation JAK-STAT and ERK1/2 signaling pathways Depletion of taurine in colon Increased gut permeability (FITC-dextran and reduced Tight-junction proteins) DSS [1]-induced colitis exacerbation	[56]
Male C57BL/6 mice	Spherical 200 and 800 nm Nile-red-labeled PS	10^9/mouse 3 times per week for 4 weeks Gavage	Disruptions to cecal microbiome and metabolome	[57]
		Polyethylene (PE)		
Female ICR mice	Spherical 1–10 µm PE	0.002 and 0.2 µg/g bw/day 4 weeks Gavage	At 0.2 µg dosage: Decreased colon mucin Decreased Il1β, ERK1, NF-κB, and increased Il10 and Il8 mRNA Dysbiosis	[58]
Male BALB/C mice	Spherical 61 µm PE	25 or 50 µg/mouse so ≈1.25 or 2.5 mg/kg bw/day 3 times in a week Gavage	Without *H. pylori* infection: Gastric pathological damage Increased gastric IL6 and TNF-α levels With *H. pylori* infection: Increased *H. pylori* gastric colonization Increased gastric injury Increased gastric inflammation (MPO, IL6, TNF-α)	[59]
Female C57BL/6 Mice	Spherical 36 and 116 µm PE	100 µg/g feed so ≈16 mg/kg bw/day 6 weeks Feed	Colon hyperproliferation Increased colon mucus and Muc2 expression Colon inflammation Whole-gut immune population and epithelial cell disturbances Dysbiosis	[60]
BALB/c mice (sex not provided)	Polydisperse, grinded 530 and 2300 nm PE	10 mg/kg bw/day in 0.5% CMC 1 week Gavage	Overt colitis Decreased colon length Increased colon Il1β, Th2, Treg, Th17 cells	[61]

Table 1. *Cont.*

Sex Background Specie	Polymer Type, Shape, Mean Aerodynamic Diameter and Other Specificities of MPLs/NPLs	Exposure Conditions Concentration * Duration Administration Pathway	Main Alterations Observed	Reference
Male C57BL/6 mice	Spherical 2.6 to 13 µm LDPE and oxidized LDPE	5 mg/mouse/day so ≈227 mg/kg bw/day 4 weeks Gavage	Higher for oxidized LDPE than LDPE Decreased duodenum length Increased duodenum and colon crypt depth Oxidative stress Increase in Tnfα, Il1β, Il6 expression in duodenum and colon Same extent for both LDPEs: dysbiosis	[62]
Male C57BL/6 mice	Spherical 5 µm PE	1 and 10 mg/L so ≈0.22 and 2.2 mg/kg bw/day 3 weeks Drinking water	Concentration-specific dysbiosis	[63]
Polyvinylchloride (PVC)				
Male C57BL/6 Mice	Spherical 2 µm PVC	100 mg/kg bw/day 8.5 weeks Gavage	Increased intestinal permeability Decreased mucus secretion Decreased colon Muc1, Muc2, Muc3, Klf4, Retnlb mRNA expression Gut dysbiosis Modification to fecal metabolic profile	[64]
Male C57BL/6 Mice	Spherical 2 µm PVC	0.5 mg/mouse So ≈22.7 mg/kg bw/day 8.5 weeks Gavage	Gut dysbiosis	[65]
Polypropylene (PP)				
Male C57BL/6 Mice	Irregular Grinded 8 and 70 µm PP	0.1, 1, 10 mg/mL So ≈22, 227 and 2272 mg/kg bw/day 4 weeks Gavage	Mild colon submucosa edema Colon oxidative stress and inflammation Disruption of intestinal barrier TLR4/NF-κB signaling pathway Colon apoptosis	[66]
Polyethylene terephthalate (PET)				
Male and female KM mice	Spherical 200 nm and 700 nm PET	200 mg/kg bw/day 4 weeks Gavage	LD50: 266 mg/kg bw for 200 nm-PET and 523 mg/kg bw for 700 nm-PET 200 nm PET only: Intestinal obstruction Perturbations to gut microbiome and metabolome	[67]

Table 1. *Cont.*

Sex Background Specie	Polymer Type, Shape, Mean Aerodynamic Diameter and Other Specificities of MPLs/NPLs	Exposure Conditions Concentration * Duration Administration Pathway	Main Alterations Observed	Reference
Female C57BL/6 mice	Pin made 1 µm PET	3×10^4/mouse Gavage 8 weeks	In colon: No evidence of impaired histomorphology and mucus barrier No low-grade inflammation 139 differentially expressed genes In gut immune cells: Oxidative phosphorylation and reactive oxygen species pathways enrichment Dysbiosis	[68]
		Several polymer types		
Kunming mice (sex not provided)	Spherical 150–130 µm PE, PET, PP, PS and PVC	4 mg/mouse/day So, ≈182 mg/kg/day 7 days	All: colon damage (PS > PVC > PET > PE > PP) Polymer-specific oxidative stress Polymer-specific dysbiosis	[69]
Male and female Wistar rats	Spherical 15–20 µm polyamide (PA) 40–48 µm PE	0.1%W/W (100 mg/kg) in feed So, ≈227 mg/kg/day 5 weeks Feed	Increased duodenum occludin and ZO1 expression	[70]
Male Sprague-Dawley rats	100 µm PP, PET, PS, Rayon, PE, polyoxymethylene (POM), polycarbonate (PC), PA, PVC, polyurethane (PU) mixture	12 mg/kg bw/day 6 weeks Gavage	Dysbiosis	[71]
BALB/C mice (sex not provided)	Spherical 500 nm PE 500 nm PS	10 mg/kg bw/day 1 week Gavage	Both PE and PS NPL: In colon: Decreased length Pathological damage Increased ROS [2] production Increased proportion of pro-inflammatory macrophages, Th2, Th17 and Treg cells PE NPL: promotes the development of CT26-luc cell tumor	[72]
Male C57BL/6J mice	Spherical 2 µm PVC 1 µm PS	0.5 mg/mouse day So ≈22.7 mg/kg bw/day 8.5 weeks Gavage	PS-PVC co-exposure: Decreased mucus secretion Increased gut permeability (FITC-dextran, serum LPS) Increased colon Il1β, Il6, Tnfα mRNA Decreased colon Muc2, Muc3, Klf4, Retnlb, Meprin-β, Claudin5, Claudin4, Tjp1 Dysbiosis	[73]

[1] DSS: dextran sodium sulfate. [2] ROS: reactive oxygen species. [3] SI: small intestine. [4] MLN: mesenteric lymph node. * A standardized method according to Zolotova et al. [45] (5 mL drinking water per day for a 22 g mouse) was used to convert concentrations in drinking water to mg/kg bw/day. A 22 g body weight was used to convert concentrations from mg/mouse to mg/kg bw/day.

Most of the preclinical studies focused on PS. There are a plethora of studies showing gut toxicity of 5 µm PS MPLs, which is characterized by impaired gut barrier and mucus production, increased oxidative stress and cytokine levels, and gut microbiota dysbiosis [26,31–35,37,41,44,45,48]. Most studies reported MPL toxicity in the colon, but when the small intestine was analyzed, impairments to the duodenum, jejunum and ileum were also reported [28,48]. Two studies found that gut toxicity occurred from a concentration of 0.1 mg/kg bw/day for 5 µm PS MPLs and worsened the intensity of DSS-induced colitis [26,31]. Similar effects were even found at the lowest dosage of 0.02 mg/kg bw/day [34,37]. The dysbiotic effects of 5 µm PS MPLs were detected from 0.02 mg/kg bw/day in male C57BL/6 mice [32,44] and from 0.006 mg/kg/bw/day in female BALB/C mice [49]. These findings related to 5 µm PS MPL are consistent with the ones observed for other sizes of MPLs [40,43], which all showed strong evidence of the gut toxicity of PS MPLs.

Numerous publications have also reported the gut toxicity of PS NPLs, which is, as for PS MPLs, characterized by impaired gut barrier function and mucus production, increased oxidative stress and cytokine levels, and gut microbiota dysbiosis [38,39,42,46,50,53,54,56,57]. Li et al. reported intestinal mechanical and immune barrier dysfunction in mice exposed to 0.02 mg/kg bw/day of PS NPLs [50]. Accordingly, colon inflammation was observed after exposure to PS NPLs at a similar concentration by Teng et al. [53]. The 0.02 mg/kg bw/day concentration can therefore be considered so far as the lowest observed adverse effect level for both PS MPL and PS NPL intestinal toxicity. Compared with PS MPLs, ingestion of PS nano-sized NPLs induced similar gut disturbances, except in the studies of Xiao et al. and Schwarzfisher et al., who showed, respectively, slight and null gut toxicity following exposure to PS NPLs [29,30]. PS NPL ingestion impaired both the colon and the small intestine epithelium. PS MNPL toxicity can be associated with disturbances to gut immune response, involving macrophages, innate lymphoid cells and B and T lymphocytes [39,49,50]. Overall, PS MNPL intestinal toxicity appeared in most studies after an exposure duration of about 4 weeks, but was also described after 2 and 32 weeks of exposure. Among the studies with exposure to both MPLs and NPLs in the same experimental conditions, four studies supported a greater intestinal toxicity of MPLs compared to NPLs [27,47,51,52]. The other five studies showed that the intestinal toxicity of NPLs was of a similar intensity to that of MPLs, but that the features of toxic effects were dependent on the size of the MNPLs [28,40,43,49,55]. The complete study performed by Zhang et al., which included different PS MNPL sizes and concentrations and 2-week and 4-week exposure durations, argued in favor of a greater influence of exposure duration and MNPL size compared to MNPL concentration on the gut toxicity of MNPLs [49]. Furthermore, the influence of the surface charge of PS NPLs on adverse gut effects was assessed: two studies consistently observed a gradually increasing gut toxicity from pristine PS NPLs, to negatively charged carboxylated PS NPLs and then positively charged aminated PS NPLs [27,42], whereas similar levels of colon impairments were observed for pristine PS, PS-COOH and PS-NH2 NPLs by Teng et al. [53].

PS was the only polymer that could be administered in the drinking water of rodents. Other polymers required administration by gavage or through feed. Oral administration of PE, PVC, PP and PET MPLs also promoted gut microbiota dysbiosis and permeability defects, but these effects were observed at the highest exposure concentrations (minimum 0.2 mg/kg for PE [58,63], 22 and 100 mg/kg for PVC [64,65], 22 to 2272 mg/kg for PP [66] and 200 mg/kg for PET [67]). However, the dosage of 0.02 mg/kg bw/day has never been assessed for these polymers. Therefore, to date, it remains difficult to assess the relative gut toxicity of the different polymers. The best way to achieve this goal is to compare the polymers under the same experimental conditions, as shown by Xie et al., who concluded that the pro-inflammatory properties on the colon followed this trend: PS > PVC > PET > PE > PP [69].

It must be emphasized that apart from the consistently described pro-inflammatory, pro-oxidative, barrier-disruptive and dysbiotic effects, other adverse gut effects have

been reported which deserve further investigation, such as the promotion of *H. pylori* infection [59], hyperproliferation and tumorigenesis [37,60,72], dyslipidemic effects [39] and alterations to microbial antibiotic resistance genes and virulence factors [40].

One important limitation is that most of the rodent studies have been performed with commercially available MNPLs. Therefore, they only reflect the toxicity of spherical MNPLs. They assessed only one of the many forms of MNPLs which are found in the environment and food [74]. Moreover, commercial MNPLs are devoid of additives and contaminants unlike MNPLs resulting from the degradation of industrial plastics. It is known that some plastic additives and contaminants have their own intestinal toxicity, such as bisphenols and phthalates [75,76]. Some plastic contaminants such as heavy metals and persistent organic pollutants could also present combined intestinal toxicity with MNPLs [77]. In addition to the known additives and contaminants of MNPLs, other unknown chemical products could additionally be released and alter gut homeostasis: this is the new avenue of research which was opened by Wang et al., who showed that human gut enzymes catalyzed the release of oligomer nanoparticles by polylactic acid. In mice, these oligomers induced small intestine and colon inflammation according to histological and molecular studies, associated with MMP12 inactivation [78]. An important limitation is therefore that the combined effect of MNPLs and their additives and contaminants is not taken into consideration in the studies using commercially available MNPL beads.

Furthermore, most of the studies did not consider either the mixture effects of various shapes and polymer types, or the weathering and aging of MNPLs. To date, only four studies have been performed on more realistic MNPLs [36,61,66,68]. They used ground or crushed MNPLs. Mouse exposure to pin-made PET MPLs did not induce colon barrier defects and inflammation. By contrast, it led to alterations in the gut immune transcriptome and metagenome [68]. Some adverse gut effects of spherical PET NPLs have also been shown at high concentrations in mice [67]. Ingestion of PET MPLs induced structural and functional alterations to duodenal myenteric neurons in pigs [79]. But the scarcity of studies precludes drawing conclusions on the toxicity of PET MPLs. Regarding the other polymers, studies on fragmented MPLs showed consistent evidence of pro-inflammatory effects induced in the small intestine for PS MPLs and in the colon for PE and PP MPLs. Feed contamination with crushed PS MPLs for 3 weeks induced small intestine epithelium damage and fecal dysbiosis [36]. Polydisperse, ground PE NPLs and MPLs led to overt colitis after only 1 week of exposure [61]. Colon oxidative stress, inflammation, barrier impairment and apoptosis were induced by oral administration of irregular ground PP MPLs [66]. These studies performed with more realistic MPLs tend to converge towards those performed with commercial microbeads. The types of damage observed appear similar, including pro-inflammatory, pro-oxidative, barrier-disruptive and dysbiotic effects. However, to date, the available data are too few and the protocols are too heterogeneous to determine whether real MPLs have increased or reduced toxicity compared to commercial microbeads.

Another important knowledge gap comes from the scarcity of research on the effects of mixtures of the various polymers. Except for the dysbiotic impact induced in rats by co-exposure to PP, PET, PS, rayon, PE, POM, PC, PA, PVC and PU [71], the cocktail effects induced by the ingestion of realistic mixtures of several polymers have been studied very little in mammals.

Another important issue is the individual susceptibility to MNPL toxicity. In addition to most of the studies carried out in healthy adult rodents, a few studies were performed in the presence of susceptibility factors. They suggested that the intestinal toxicity of MPLs could be worsened in undernourished patients as well as in patients with obesity [33,48]. Because MPLs are more likely to enter the intestinal epithelial cells in patients with leaky gut and PS MPLs exacerbated colitis in murine models [26,34], MPLs were proposed as emerging risk factors for inflammatory bowel disease [80]. Consistent with this hypothesis, Yan et al. showed that the fecal MPL concentration in IBD patients was significantly higher than that in healthy individuals. They also revealed a positive correlation between the fecal MPL concentration and the severity of IBD, suggesting that MPL exposure may be

related to the disease's development [18]. In IBD as in irritable bowel syndrome (IBS), the increased gut permeability may favor MNPLs crossing the gut barrier, inducing a vicious circle maintaining the barrier defects and subsequently the intestinal inflammation. MNPL exposure may also exacerbate IBD or IBS pathology by worsening dysbiosis, dysregulating the intestinal immune response or exerting direct inflammatory impacts and metabolic toxicity in intestinal epithelial cells, as supported by several in vitro studies on intestinal cell lines or organoids [81–83]. Of particular interest, a hyperproliferative effect induced by MPLs under basal conditions and a worsening of established colon cancer progress induced by NPL exposure have been reported, suggesting that MNPLs could favor the development of colorectal cancer [37,60,72]. These in vivo findings were reinforced by in vitro data showing that MNPLs may promote colorectal cancer by increasing the propensity for cell migration and the potential for pro-metastatic effects in human gastrointestinal cancer cells [84]. Lastly, it is worthy of note that gestational exposure to PS NPLs was reported to induce small intestine histological changes, oxidative damage and ferroptosis initiation in female and male offspring [38]. Extraintestinal health outcomes have been reported following in utero exposure to MNPLs in mice, further supporting the need to assess the transgenerational effect on MNPL ingestion on gut health [85–87].

4. Conclusions and Future Directions

During the last three years, it has been shown that in rodents, the ingestion of MNPLs impacts the main parameters of intestinal homeostasis, which are the barrier function, the immune response, the oxidative status and the balance of the intestinal microbiota. It is established that MNPL ingestion in healthy subjects disrupts intestinal functions, and critical studies showed that these disruptions could contribute to making individuals more susceptible to the development of inflammation, cancer or infections. However, despite these numerous advances, our knowledge of the intestinal impact of MNPLs remains limited. In order to address MNPLs in their whole physico-chemical complexity and to decipher their effects in various physiological and pathological states, more collaborative efforts must be developed involving experts from diverse fields (e.g., polymer chemistry, analytical chemistry, toxicology, pathophysiology). Future studies will need to better investigate the impact of realistic MNPLs by taking into consideration their diversity in terms of polymer type, shape and size. Above all, the presence in MNPLs of additives and contaminants that are likely to influence the overall toxicity of MNPLs must be better investigated. It is also essential to decipher the impact of MNPL ingestion in individuals weakened by an underlying pathology, particularly pathologies in which the intestinal barrier function is impaired, including inflammatory bowel diseases, irritable bowel syndrome and colorectal cancer [88], but also extraintestinal diseases such as metabolic and neurological diseases [89,90]. Finally, since pioneering studies have shown that gestational exposure to MNPLs could be hazardous for offspring, particular attention should be paid to the effects of MNPLs as determinants of health at early ages but also later in life.

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