Chapter 13
Micro- and Nano-plastics and Human Health

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Abstract Plastics are highly versatile materials that have brought huge societal benefits. They can be manufactured at low cost and their lightweight and adaptable nature has a myriad of applications in all aspects of everyday life, including food packaging, consumer products, medical devices and construction. By 2050, however, it is anticipated that an extra 33 billion tonnes of plastic will be added to the planet. Given that most currently used plastic polymers are highly resistant to degradation, this influx of persistent, complex materials is a risk to human and environmental health. Continuous daily interaction with plastic items allows oral, dermal and inhalation exposure to chemical components, leading to the widespread presence in the human body of chemicals associated with plastics. Indiscriminate disposal places a huge burden on waste management systems, allowing plastic wastes to infiltrate ecosystems, with the potential to contaminate the food chain. Of particular concern has been the reported presence of microscopic plastic debris, or microplastics (debris $\leq$1 mm in size), in aquatic, terrestrial and marine habitats. Yet, the potential for microplastics and nanoplastics of environmental origin to cause harm to human health remains understudied. In this article, some of the most widely encountered plastics in everyday use are identified and their potential hazards listed. Different routes of exposure to human populations, both of plastic additives, microplastics and nanoplastics from food items and from discarded debris are discussed. Risks associated with plastics and additives considered to be of most concern for human health are identified. Finally, some recent developments in delivering a new generation of safer, more sustainable polymers are considered.

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13.1 Introduction

If a visitor from 50 years ago were to turn up today, one of the first things he would notice (other than how much heavier we all were), would be how much plastic there is everywhere. We use plastics to wrap our food, we drink from plastic containers, cook with plastic utensils, deliver drugs to patients through plastic tubing. We increasingly use plastics and polymer composites in construction. Worldwide annual production of plastics is estimated to be in the region of 300 million tonnes. Plastic demand in the European Union alone for 2010 was estimated at 46.4 million tonnes, consisting of two main types: plastics used for packaging of food and consumer items, with the second group constituting plastics used in the construction industry (PlasticsEurope 2013). With overall recycling rates at around 57.9 %, this corresponds to around 24.7 million tonnes of plastic debris entering the waste stream each year. Waste disposal includes littering, land fill and the sewerage system and ultimately, a significant proportion of plastic waste ends up in the sea. Jambeck et al. (2015) estimated that 4.8 to 12.7 million tonnes of plastic waste entered the ocean in 2010.

Whilst these figures are alarming in terms of volume, it is not yet clear how this large scale and ubiquitous use affects human health. As an example, some 14.5 million tonnes per annum of plastic is used in the food packaging industry alone (European Plastics Converters). On the positive side, improvements in food packaging can prevent bacterial infections, such as Salmonella and other food borne disease (Hanning et al. 2009; European Commission 2014), and can prevent wastage and aid distribution. Conversely, migration of contaminants from food packaging into food is considered the main route of exposure of human populations to contaminants associated with plastics (Grob et al. 2006), with only a small fraction of the thousands of substances that may be present having been subject to extensive testing (Claudio 2012). Whilst rigorous standards are in place to regulate food-contact substances in terms of migration into food (EFSA 2011), it is less clear how these guidelines offer protection once the plastics themselves have been discarded to the environment. With only limited information available about rates of degradation and fragmentation, leaching of chemicals into environmental matrices, and entry into the food chain, it is almost impossible to estimate the cumulative risks of chronic exposure to plastics and their additives.

One way around this problem is to determine what chemicals are actually present in the human body. Human biomonitoring involves measuring the concentrations of environmental contaminants and/or their metabolites in human tissues or body fluids, such as blood, breast milk, saliva or urine. Biomonitoring is considered a gold standard in assessing the health risks of environmental exposures because it can provide an integrated measure of an individual's exposure to contaminants from multiple sources (Sexton et al. 2004). This approach has shown that chemicals used in the manufacture of plastics are certainly present in the human population. For some chemicals, their widespread presence in the general population at concentrations capable of causing harm in animal models has raised public health concerns (Talsness et al. 2009; Melzer and Galloway 2010). The National Health and Nutrition Examination Survey (NHANES) is a program of

studies designed to assess the health and nutritional status of adults and children in the United States and represents one of the most comprehensive human biomonitoring programs yet undertaken (http://www.cdc.gov/nchs/nhanes.htm). Of interest for this article, NHANES reports on several chemicals associated with the use or production of plastics, including bisphenol A, phthalates, styrene, acrylamide, triclosan and brominated flame retardants, and their concentrations in the general population.

This review considers the kinds of plastics in widespread, everyday use and the potential hazards they may cause. It reviews the routes of uptake of micro and nanoplastics into humans through the food chain and the potential consequences for human health. Health risks associated with microplastics and plastic-associated chemicals are discussed. Lastly, some new developments in alternative low toxicity polymers and novel nanocomposite materials are described and their potential benefits to human health discussed.

13.2 What Kinds of Plastics Are in Use?

The term plastic is used to describe plastic polymers, to which various additives are added to give desirable properties to the final product (OECD 2004). The demand for plastics in Europe alone is estimated to be 45.9 million tonnes in 2012 (PlasticsEurope 2013), with plastics demand by industry segment shown in Table 13.1. As can be seen, packaging, which includes food and beverage packaging, is the single largest category by a considerable margin. Plastics are generally divided into two types: thermoplastic, which soften on heating and can be remoulded, and thermosetting, in which case cross-linking in the polymers means they cannot be re-softened and remoulded. With reference to these properties, plastics can be further classified into seven different groupings based on their ease of recycling. Table 13.2 lists some examples of products made from these seven different plastics groups and the demand for different resin and polymer types based on this classification system (for Europe). As can be seen, the

Table 13.1 Plastics demand by industry segment in Europe, 2012

Industry segment	Volume (millions of tonnes)	Percentage of total
Packaging	18.1	39.4
Building and construction	9.32	20.3
Automative	3.76	8.2
Electronics and electrical	3.03	6.6
Agriculture	1.93	4.2
Other (furniture, health and safety, sport, consumer and household appliances, etc.)	10.3	22.4
Total (demand for 2012)	45.9	100.0

Figures are derived from PlasticsEurope (2013)

Table 13.2 European plastic demand by resin type

Code	Resin type	Example product	Volume of demand (millions of tonnes)	% of total European demand	% recycled[a]
1	PET polyethylene terephthalate	Soft drink bottle, polyester fibre	2.98	6.5	20
2	PE-HD polyethylene high density	Plastic bottle, plastic bag, bottle cap	5.51	12.0	11
3	PVC polyvinyl chloride	Water proof boot, window frame, plumbing pipe	4.91	10.7	0
4	PE-LD polyethylene low density	Wire cable, plastic bag, bucket, soap dispenser bottle, plastic tube	8.03	17.5	6
5	PP polypropylene	Stationary folder, plant pot, bags, industrial fibre	8.63	18.8	1
6	PS. PSE polystyrene	Food container, plastic cup, glasses frame, car bumper	3.40	7.4	1
7	O other (PC Polycarbonate, PLA polyamide, styrene, SAN acrylonitrile, acrylic plastics, PAN/ polyacrylonitrile, bioplastics)	Drink bottle, consumer item, clothing, medical equipment	9.82	19.8	0
Total			45.9	100.0	39

Figures are for 2012 and are derived from PlasticsEurope (2013). [a]Recycling figures derived from Engler (2012)

main classification group (code 7) makes up 19.8 % of total European demand, yet has a 0 % recycling rate. The second most commonly used plastic, polypropylene (18.8 % of demand), has a 1 % recycling rate.

13.3 Plastics and Human Health

Plastic polymers are generally considered to be inert and of low concern to human health, and health risks relating to their use are attributed to the presence of the wide range of plastic additives they may contain, together with residual monomers that may be retained within the polymer structure (Araujo et al. 2002). Plastics are synthesised from monomers, which are polymerised to form macromolecular chains. A range of additional chemicals may be added during the manufacturing process, including initiators, catalysts and solvents. Additives that can alter the nature of the

final plastic include stabilisers, plasticisers, flame retardants, pigments and fillers. Additives are not bound to the polymer matrix and because of their low molecular weight, these substances can leach out of the plastic polymer (Crompton 2007) into the surrounding environment, including into air, water, food or body tissues.

There are thousands of additives in routine use in the synthesis of plastic products. As comprehensively reviewed by Lithner et al. (2011), certain plastics types typically contain more additives than other types. Polyvinylchloride (PVC) is the polymer associated with the use of most additives, including heat stabilisers to keep the polymer stable during production, and plasticisers such as phthalates to allow flexibility (Lithner et al. 2011). Plasticisers may constitute a high percentage (up to 80 %) of the weight of the final product (Buchta et al. 2005). Polypropylene is highly sensitive to oxidation and typically contains significant amounts of antioxidants and UV stabilisers (Zweifel 2001). Other chemicals that may leach from plastics include nonylphenol from polyolefins, brominated flame retardants from acrylonitrile-butadienestyrene (ABS) or urethane foam and bisphenol A (BPA) from polycarbonate. The rate at which these substances are released from the product is governed by many factors, including the size and volatility of the additive, the permeability of the polymer itself (migration is greater for highly permeable polymers), and the temperature and pH of the surrounding medium (air, water, soil, body tissues) (Zweifel 2001).

Plastics may also pose a hazard due to the release of the constituent monomers themselves (Lithner et al. 2011). Most of the plastics in everyday use are highly resistant to microbial degradation. Instead, degradation and release of polymers is ultimately caused by exposure to abiotic factors such as ultraviolet (UV) light, heat, mechanical and/or chemical abrasion (Andrady 2015). Breaking of the chemical bonds in the polymer backbone leads to chain scission and depolymerisation; chain stripping occurs when side chains are broken and released. All of these processes proceed at different rates under different environmental conditions, e.g. variations in temperature and oxygen, and proceed at different rates for different polymer types, with polyesters, polycarbonate and polyurethane more prone to depolymerisation for example than polyethylene or polypropylene (Nicholson 1996; La Mantia 2002). It is therefore extremely difficult to predict the risks associated with exposure to plastics and their additives, given the vast complexity and variability of the available product combinations, their varied uses and eventual environmental distribution once discarded.

Lithner et al. (2011) addressed this complex problem by conducting a comprehensive hazard ranking of plastic polymers based on their chemical composition. They studied 55 of the most widely used polymer types with global production volumes of >10,000 tonnes per year. A model for ranking the hazard of each polymer was developed by ranking the constituent monomer chemicals according to internationally agreed criteria for identifying physical, environment and health risks. The polymer types that received the highest and the lowest hazard rankings according to this criteria are shown in Table 13.3. Table 13.4 shows the ranking for polymer types commonly reported in plastic and microplastic litter.

Table 13.3 Ranking of some plastic polymer types based on hazard classification of constituent monomers, adapted from Lithner et al. (2011)

Polymer	Monomer(s)/additives	Relative hazard score[a]	Recycling code	Constituents measured in NHANES?
Polymers with the highest relative hazard scores				
Polyurethane PUR as a flexible foam	Propylene oxide	13,844	6	
	Ethylene oxide			
	Toluene-diisocyanate			
Polyacrylamide PAN with co-monomers	Acrylonitrile	12,379	7	Acrylamide
	Acrylamide			
	Vinyl acetate			
Polyvinylchloride PVC, plasticised	With plasticiser	10,551	3	Benzyl butyl phthalate (BBP)
	Benzyl butyl phthalate (BBP) at 50 wt%			
Polyvinylchloride, PVC, unplasticised		10,001	3	
Polyurethane, PUR as a rigid foam	Propylene oxide	7384	6	
	4,4′-methylenediphenyl diisocyanate (MDI)			
	Cyclopentane			
Epoxy resins DGEBPA	**Bisphenol A**	7139	7	Bisphenol A
	Epichlorohydrin			
	4,4′-methylenedianaline			
Modacrylic	Acrylonitrile	6957		
	Vinylidene chloride			
Acrylonitrile-butadiene-styrene ABS	**Styrene**	6552	7	Styrene
	Acrylonitrile			
	1,3 butadiene			
Styrene- acrylonitrile SAN	**Styrene**	2788	7	Styrene
	Acrylonitrile			
High impact polystyrene HIPS	**Styrene**	1628		Styrene
Polymers with the lowest relative hazard scores				
Low density polyethylene LDPE	Ethylene	11	4	
High density polyethylene HDPE	Ethylene	11	2	
Polyethylene terephthalate PET	Terephthalic acid	4	1	
Polyvinyl acetate PVA	Vinyl acetate	1		
Polypropylene PP	Propylene	1	5	

[a]Relative hazard score derived from different constituent monomers. Higher ranking = greater hazard

Table 13.4 Plastics identified in microplastic debris and their relative hazard ranking

Polymer type	Density g/cm^3	Relative hazard score[a]
Polyethylene (low, high density)	0.917–0.965	11
Polypropylene	0.9–0.91	1
Polystyrene	1.04–1.1	1628–30
Polyamide		63–50
polyethylene teraphthalate	1.37–1.45	4
Polyvinylchloride	1.16–1.58	10,551–5001

[a]Relative hazard score derived from different constituent monomers. Higher ranking = greater hazard

Adapted from Hidalgo-Ruz et al. (2012) and Lithner et al. (2011)

As noted by the authors, the hazard ranking does not imply that the polymers themselves are hazardous, but rather that release of hazardous substances or degradation products may occur during the product lifecycle, i.e. from production through use of the product and its eventual discard to waste or into the environment. From this point of view, Table 13.3 also identifies polymers that may contain compounds that are currently the subject of biomonitoring activities under the NHANES program. Note that NHANES also monitors compounds that may be present in multiple, diverse items including many different types of plastics and plastics products, such as the microbial agent triclosan and the UV screen and printing ink additive benzophenone.

The polymers ranked as most hazardous were those produced from monomers classified as carcinogenic, mutagenic or both, leading to high hazard rankings for polyurethanes, polyvinylchloride, epoxy resins and styrenic polymers. One limitation of this approach noted by the authors was the lack of available chemical safety data for many of the substances they were considering. In particular, there was no hazard class available for chemicals suspected of being endocrine disruptors, including bisphenol A, phthalates, and epichlorohydrin. This toxicity endpoint was therefore not included in the hazard assessment. This represents a major limitation in our current ability to predict the risks associated with plastics associated chemicals, since so many of these are recognised to have endocrine disrupting abilities (Koch and Calafat 2009). Despite these limitations, this study represents an extremely useful attempt to identify those polymer types that could be a cause for concern due to the environmental and health effects of their constituent monomers.

13.4 Micro- and Nanoplastics

13.4.1 Occurrence of Micro- and Nanoplastics in the Environment

In addition to larger items of plastic litter, concern has been raised that microscopic plastic debris (microplastic) (<1 mm) may also be detrimental to the environment and to human health (Thompson et al. 2004; Cole et al. 2011).

Microplastics have been studied mostly in the context of the marine environment, and have been found to be a major constituent of anthropogenic marine debris. They consist of small plastic items, such as exfoliates in cosmetics, or fragments from larger plastic debris, including polyester fibres from fabrics, polyethylene fragments from plastic bags and polystyrene particles from buoys and floats (reviewed by Cole et al. 2011).

There is sparse information available on the presence of microplastics in environments other than the oceans, for example in terrestrial soils or freshwater environments. The presence of microplastic particles (Dubaish and Liebezeit 2013) and synthetic polymer fibres (Zubris and Richards 2005) has been reported in sewage sludge and in the soils to which they had been applied (Zubris and Richards 2005), where they were still detectable five years after application. A study of surface waters in the southern North Sea found microplastics and microfibres in all of the samples that were tested, with an increasing gradient towards land sources (Dubaish and Leibezeit 2013). Browne et al. (2011) showed that the polyester and acrylic fibres used in clothing closely resembled those found in coastal sediments that receive sewage discharges, suggesting that sewage effluents represent a significant source of microfibres from the washing of clothes, and that these are not wholly retained during wastewater treatment.

A study of beach sediments around Lake Garda, a subalpine lake in Italy, found microplastics at abundances of up to 1108 ± 983 microplastic particles/m^2 (Imhof et al. 2013), which is similar to the contamination levels reported for the Great Lakes in the USA (Zbyszewski and Corcoran 2011). These levels of contamination most likely originate from landfill, litter and wastewater sources, and are within the range of values reported for the abundance of plastic particles found in marine coastal sediments (0.21–77,000 particles/m^2), albeit at the lower end of exposures (Hidalgo-Ruz et al. 2012). This does, however, indicate that microplastics are present in both agricultural soils and freshwater sites. Knowledge on the occurrence of nanoplastics in aquatic environments and biota is extremely limited because no methods exist for the reliable detection of nanoplastics in samples (Koelmans et al. 2015).

13.4.2 Micro- and Nanoplastics and Human Health

In terms of human health risks, microplastics as contaminants in the wider environment represent a concern because it has been shown that they can be ingested by a wide range of aquatic organisms, both marine and freshwater, and thus have the potential to accumulate through the food chain. Aquatic organisms for which ingestion of microplastics has been documented in the field include those from across the marine food web, including turtles, seabirds, fish, crustaceans and worms (reviewed by Wright et al. 2013). Laboratory studies have confirmed that many other organisms have the capacity to ingest microplastics including zooplankton (Cole et al. 2013; Setälä et al. 2012). The majority of studies have documented microplastics in the guts of organisms, an organ that is not generally consumed directly by humans.

Exceptions to this include shellfish such as mussels, clams and some shrimps that are eaten whole or with their gut. The risk of ingesting microplastics contained within other tissues depends on the degree to which uptake of microplastics and translocation and redistribution and retention within other body tissues occurs. This concept is discussed further below, in relation to human ingestion.

In addition to the potential for ingestion to cause adverse biological effects due to gut blockages and/or damage, or the reduction in energy assimilation (Wright et al. 2013), the large surface area of microplastics means that environmental pollutants may sorb to the surface of the particles, with the potential to be transferred into body tissues once ingested. For a more comprehensive coverage of the uptake of microplastics by wildlife organisms, and the transfer to tissues of hydrophobic pollutants adsorbed from the surrounding environment, the reader is referred to excellent recent reviews (e.g. Engler 2012) and to other chapters in this issue (Koelmans 2015; Lusher 2015). Despite this concern, there is currently no available information to evidence the uptake or biological effects of microplastics originating from marine or terrestrial debris and subsequently ingested by humans through the food chain.

13.4.3 Ingestion of Micro- and Nanoplastics and Uptake Across the Gut

Whilst the potential clearly exists for microplastics to be present in food items, there is currently no evidence for the unintentional ingestion or subsequent translocation and uptake of microplastics into the human body through the diet. There is, however, a huge interest worldwide in the use of micro- and nanospheres as pharmaceutical drug delivery systems through oral, intravenous and transcutaneous routes (Kim et al. 2010), and in the migration of nanopolymers from packaging materials into food (EFSA 2011; Lagaron and Lopez-Rubio 2011). Based on these growing and fast moving fields, an enhanced understanding of the mechanistic pathways by which micro- and nanoparticles could enter the human body is starting to emerge, although many aspects of this field remain to be elucidated.

Following oral ingestion, the gut mucosa represents an important barrier, which has evolved to allow efficient uptake of nutritious items, whilst excluding potentially harmful substances or organisms. Significant uptake of microplastics into the body through this route is in theory then limited to particles that can enter the body through exploitation of existing routes. Following oral ingestion, uptake of inert particles across the gut has been widely studied (O'Hagan 1996). The 'persorption' of starch particles as large as 150 μm through the tips of the villi was described in detail by Volkheimer (1977). According to his observations, persorption of particles can occur as a passive process in areas of the gut where the intestinal mucosa is covered by a single layer of epithelium. Persorbed particles were detectable in the lumen of blood and lymph vessels within minutes, and were eventually eliminated in the urine, confirming that the translocation of relatively large, inert particles from the gut to other body fluids is possible (Volkheimer 1977).

Aside from this observation, digestive absorption of smaller particles proceeds through pinocytosis and vesicular phagocytic processes for materials in the nano and micron range. Particle size is one of the most important factors in determining the extent and pathway of uptake. Smaller particles are generally favoured over larger ones. For example, polystyrene microspheres of 50–100 nm were more readily absorbed across the Peyer's patches and the villi of the gut than larger particles of 300–3000 nm (Jani et al. 1992; Florence and Hussain 2001). On the other hand, the uptake of ultrafine polylysine dendrimers of 2.5 nm was lower than that of larger polystyrene particles of 100 nm–3 μm, suggesting that size is not the only deciding factor (Florence et al. 2000). Indeed, a combination of size, surface charge and hydrophilicity all contribute to uptake affinity (as discussed by Awaad et al. 2012). The predominant site of uptake for micron-scale particles in the gut is reported to be through gut-associated lymphatic tissue (GALT), specifically by the Microfold (M) cells of the Peyer's patches. M cells are specialised epithelial cells that lack the microvilli found on other gut epithelial cells and instead have broader (micro)folds and a thinner luminal surface that allows them to actively take up particulate matter from the intestine. The reported efficiency of this uptake varies depending on the study method, species and particle type. Uptake of polystyrene microspheres through the gut by this route was higher in species such as rabbits, which have a high abundance of M cells (Pappo et al. 1989), and was enhanced when food was also present, probably due to the delayed transit time through the gut (Ebel 1990). As an alternative route, uptake by enterocytes appears to be limited to a size range of around 100 nm (Jani et al. 1992). Awaad et al. (2012) used fluorescent organosilica particles, histological examination and quantitative analysis to confirm an optimal size range of around 100 nm for uptake of particles through the M cells of the Peyer's patches, with smaller and larger particles less likely to be taken up. They also identified two alternative uptake pathways by which nanoparticles passed between (paracellular-E uptake) or through (transcellular-E uptake) enterocytes in the Peyer's patches. These two pathways have previously been described as major mechanisms for larger particles of >1 μm outside of the Peyer's patches (Kreuter 1991), but had not previously been described in relation to nanoparticle uptake by the Peyer's patches.

Garrett et al. (2012) used a novel bio-imaging technique, multimodal nonlinear optical microscopy, to document uptake of polymeric nanoparticles by enterocytes in the mouse gut in vivo. They studied a novel amphipathic polymer specifically designed for drug delivery, ammonium palmitoyl glycol chitosan (GCPQ) of 30–50 nm in diameter and showed that after uptake by enterocytes, particles accumulated at the base of the villi. From there, they passed into the blood stream and were transported to the liver, where they were detectable in the hepatocytes and intracellular spaces, before recirculating through the bile to the small intestine (Garrett et al. 2012) to be excreted with faecal matter. This is similar to previous results for larger micron-scale polystyrene and latex particles, suggesting that both micron and nano-scale polymers are treated in a similar manner (Jani et al. 1996), with uptake across the gut, recirculation and eventual elimination through faecal matter and urine (Fig. 13.1).

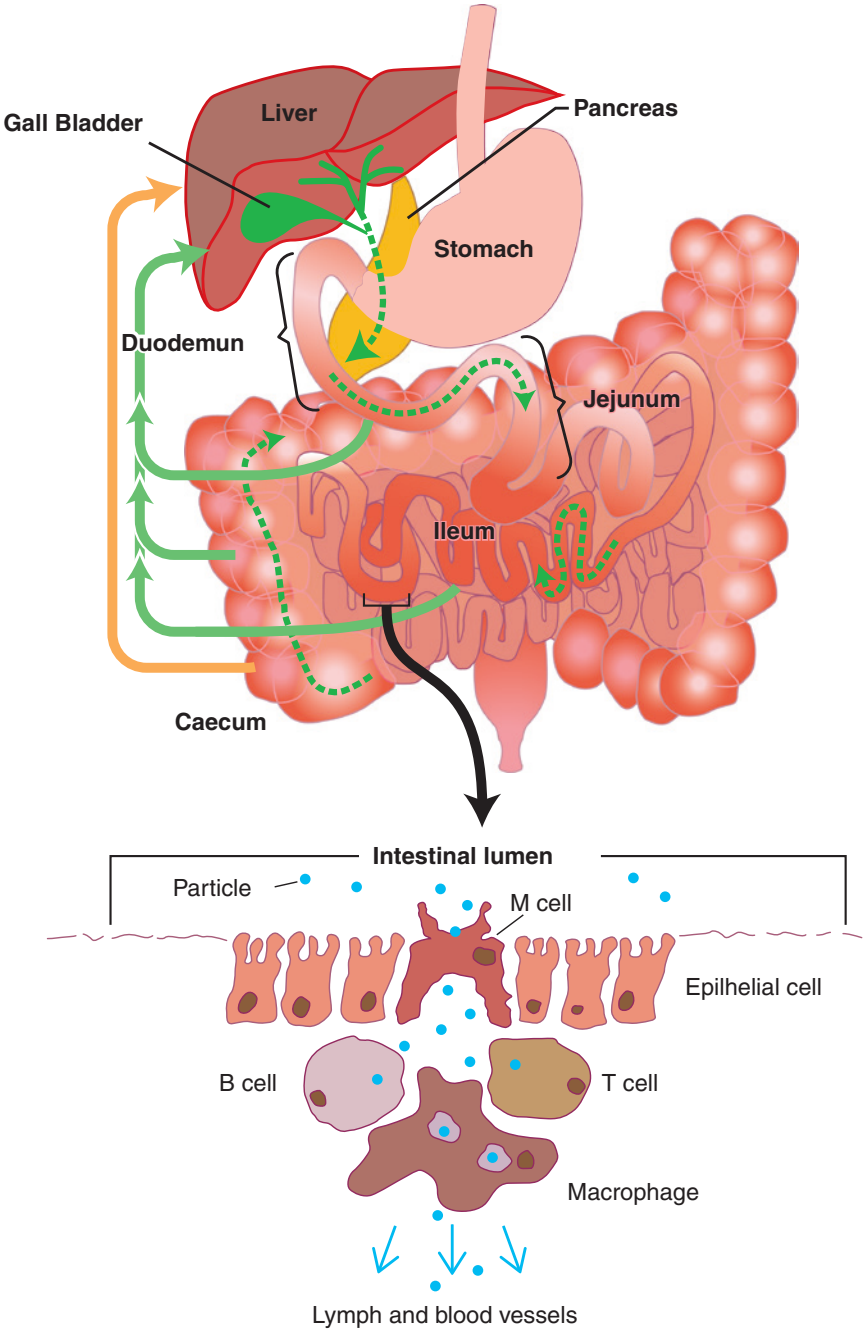


Fig. 13.1 A diagram illustrating a proposed recirculation pathway for polymer nanoparticles (ammonium palmitoyl glycol chitosan) after oral administration. The nanoparticles are taken up into the blood from the gut through M cells, and from there through the lymphatic system (shown in *yellow*) and into the liver and gall bladder. Particles are then re-released into the gut together with bile (shown in *green*) before excretion in faeces and urine. Adapted from Garrett et al. (2012)

This information is of high interest in terms of drug delivery, yet it also suggests that ample opportunity exists, following ingestion, for micro- and nanoplastics in food or water to enter, circulate and bioaccumulate within the body.

13.4.4 Interaction of Microspheres and Nanoparticles with Cells and Tissues

The behaviour of nano- and microplastics after they have entered the circulation from the gut is not fully understood, but has been the subject of study in relation to food packaging materials and nanomedicines. Certainly, in vivo behaviour will be dependent on numerous factors, such as the physico-chemical properties of the particles (size, surface charge, aspect ratio, porosity, surface corona) and the physiological state of the individual. Risk assessments of manufactured nanomaterials including titanium dioxide (Wang et al. 2007) and carbon (Poland et al. 2008) have shown comparable results to those shown above for nanopolymers, with uptake across the gut into the circulation and redistribution to the liver and spleen. Circulation time is highly dependent on the surface characteristics of the particle, with hydrophilic and positively charged particles showing enhanced circulation times (Silvestre et al. 2011).

13.4.5 Interactions with Biological Materials and Cells

Interaction of nanopolymers with cells and tissues has again been the subject of intensive study. Because of their surface properties, nanopolymers are predicted to adsorb macromolecules such as proteins and lipids from the surrounding body fluids onto their surface, in a process influenced by surface energy, charge and specific affinity for certain biomolecules. The resulting ‘corona’ will then influence the resulting behaviour and toxicity of the particle (Lundqvist et al. 2008; Tenzer et al. 2013). This process has been extensively studied for polymers intended for therapeutic use particularly using polystyrene as a model polymer, but little or nothing is known of how protein coronas may form on the types of polymers most commonly found in environmental debris.

The results from mechanistic studies of different types of particle show that the potential for cytotoxicity of circulating particles in vivo to cells and tissues is related to many factors, including size, shape, solubility, surface charge, surface reactivity and energy band structure (Nel et al. 2006; Burello and Worth 2011). For example, it would be reasonable to hypothesize that particles with a high abundance of reactive surface groups would be capable of denaturing surrounding lipids and proteins. As an illustration of this, the toxicity of silica nanoparticles in vivo was attributed to proton donating silanol groups on the surface of the

particles, leading to denaturation of membrane proteins and subsequent membrane damage. In this case, the reactivity of the surface hydrogen of silica bonds with membrane proteins led to their abstraction from the membrane, with subsequent membrane damage and distortion leading to haemolytic symptoms following exposure (Pandurangi et al. 1990).

Surface charge is also a strong attributing factor for toxicity (Geys et al. 2008). In inhalation studies in rats, the toxicity of acrylic ester nanopolymers in the size range 50–1500 nm was found to be low, and this was attributed to their anionic surface charge (Ma-Hock et al. 2012). Studies in which the surface charge of stearylamine-polylactic acid (PLA) polymers was modified from positive to negative showed that cationic particles showed higher pulmonary toxicity (Harush-Frenkel et al. 2010). This was attributed both to a higher localisation of cationic particles in the lung and to enhanced cellular uptake. Overall, the interaction of cationic polymers with the negatively charged cell surface has been proposed as a cause of their higher cytotoxicity (Fischer et al. 2003).

Translocation of nanopolymers into diverse tissues and cell types presents another point at which toxicity may occur. Translocation is dependent on interactions with the cell membrane and is most likely to proceed, as for uptake by enterocytes in the gut, through pinocytic, phagocytic and receptor-mediated endocytosis (Fruijter-Polloth 2012). A study, which measured the uptake rates of individual polystyrene microspheres into human astrocytes and lung carcinoma cells in culture found that the uptake rate differed for particles of different sizes, implying that there are differences in the mechanisms involved. Particles with a diameter of 40 nm showed higher uptake rates than either 20 or 100 nm particles. Since the van der Waals force between a sphere and a surface is proportional to the diameter of the sphere (Israelachvili 1992), it could be predicted that larger particles would be taken up faster. The conclusion was that the endocytic mechanism for internalisation of 40 nm particles exhibited faster kinetics, providing a privileged size gap for 40 nm particles (Varela et al. 2012).

Phagosomes containing particles may fuse with endosomes following internalisation, leading to accumulation of particles in lysosomes. Depending on the dose and type of particle, this has the potential to overwhelm lysosomal capacity and interfere with programmed cell death and pathways of cellular breakdown of pathogens (Fruijter-Polloth 2012). The numerous additional modes of toxicity that may result are again dependent on particle and cell type, and include the potential for oxidative damage, inflammation and accumulation in diverse tissue types (Silvestre et al. 2011; Nel et al. 2006, 2009). In theory, all organs may be at risk following chronic exposure to nanopolymers, including the brain, testis and reproductive organs, prior to their eventual excretion in urine and faeces (Jani et al. 1996; Garrett et al. 2012). Distribution to the foetus in utero is also a possibility that cannot be excluded. Given the long-term persistence of many polymer types, more research is required to adequately assess the risks that accumulation of micro- and nanoplastics in the body may pose.

13.5 Assessing the Risks that Micro- and Nanoplastics Pose to Human Health

13.5.1 Leaching of Toxic Chemicals from Plastics

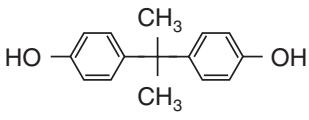
As discussed previously, plastics can contain complex mixtures of additives to enhance their physical properties, which can leach from the polymer into the surrounding milieu. Leaching will occur primarily at the surface of the plastic particle, with the possibility of constant diffusion of chemicals from the core of the particle to the surface. Thus, leaching from plastic particles could present a long-term source of chemicals into tissues and body fluids, despite the fact that many of these chemicals are not persistent and have short half lives in the body (Engler 2012). Plastics additives of concern to human health include phthalates, bisphenol A, brominated flame retardants, triclosan, bisphenone and organotins.

The potential migration of polymer constituents and additives into food and drinks is considered to be a major route of exposure of the human population and as might be expected is subject to extensive legislation. The measurement of migration levels is typically estimated from measurements using different solvents to simulate the receiving environment (e.g. foodstuffs), or can be estimated using partitioning models that consider aspects including the desportion rates from the polymers, dimensions of the polymer framework and dimensions of the diffusing molecules (Helmroth et al. 2002). The European Food Standards Agency has a total migration limit of 10 mg/dm^2 for additives within plastics intended for packaging use, with a more stringent migration limit of 0.01 mg/kg for certain chemicals of concern (Commission Directive 2007/19/CE that modifies Directive 2002/72/CE). This means that for an average 60 kg adult who consumes 3 kg of foods and liquids per day, exposures to individual substances from food packaging could be up to 250 μg/kg body weight per day (Muncke 2011).

13.5.2 Bisphenol a and Human Health

There is very little information on the leaching of additives into biological tissues directly, but one chemical monomer that has received considerable attention in relation to its human health effects is bisphenol A (Fig. 13.2). Bisphenol A (BPA) was first synthesised in the 1930s as a synthetic estrogen (Dodds and Lawson 1936) and is now a high-production volume chemical used as a monomer in the production of polycarbonate plastic and in the epoxy resins lining food and beverage cans. There are numerous studies showing that BPA can migrate out of polycarbonate (reviewed

Fig. 13.2 Bisphenol A



in Guart et al. 2013) and contaminate foodstuffs and drinks, and oral ingestion is considered the major route of exposure of the human population (Calafat et al 2008). Additional routes of exposure are predicted from the inhalation of household dusts and dermal uptake from printed materials (Ehrlich et al. 2014). BPA undoubtedly enters the human body, with studies showing exposure of >95 % of populations in USA, Europe and Asia (Galloway et al. 2010; Vandenberg et al. 2010).

Bisphenol A exerts its biological activity predominantly through interaction with steroid hormone receptors, showing both estrogenic and antiandrogenic activity and suppressing aromatase activity (Bonefeld-Jørgensen et al. 2007, Lee et al 2003). Additional receptor-mediated effects reported in various model systems include binding to the orphan estrogen-related receptor ERRα (Okada et al. 2008), thyroid hormone disruption (Moriyama et al. 2002), altered pancreatic beta cell function (Ropero et al. 2008) and obesity promoting effects (Newbold et al. 2008). There is growing evidence from epidemiological and laboratory studies that exposure to BPA at levels found in the general population, around 0.2–20 ng/ml (values given for urinary BPA), is associated with adverse human health effects, including the onset of obesity and cardiovascular disease (Lang et al. 2008; Melzer et al. 2010, 2012; Cipelli et al. 2013) and with numerous reproductive and developmental outcomes. These include increases in abnormal penile/urethra development in males, an increase in hormonally-mediated cancers including breast and prostate cancers, neurobehavioural disorders including autism and early sexual maturation in females (reviewed by vom Saal et al. 2007; Hengstler et al. 2011; Rochester 2013).

Whether the release of BPA from ingested micro- or nanoplastics directly into the body contributes to human exposure remains unknown. The current tolerable daily intake is 0.05 mg/kg/day (EFSA 2006) and compared with this, the median exposure of the general adult population globally has been estimated from human biomonitoring or urinary BPA to be 0.01–0.12 μg/kg/day (EFSA 2015). The concentrations of BPA in plasma are higher than would be predicted only from this level of exposure to BPA through food and drink (Mielke and Gundert-Remy 2009), and it is therefore plausible that other routes of exposure could occur, e.g. from ingestion of plastic particles containing BPA, which subsequently leaches into tissues. BPA can certainly be absorbed across body surfaces other than the gut. Gayrard et al. (2013) showed that BPA can be absorbed with relatively high efficiency sublingually, an effect likely enhanced by its low molecular weight and moderate water solubility, allowing it to penetrate the sublingual membrane.

There are no studies in humans of the transfer of BPA from plastic directly into tissues, but the potential for BPA to leach from ingested polycarbonate into aquatic species was explored by Koelmans et al. (2014) who used biodynamic modeling to calculate the relative contribution of plastic ingestion to total exposure to chemicals residing in the ingested plastic. They estimated plastic:lipid exchange coefficients for a range of plastic particle sizes for two species, fish and sediment-dwelling worms. They proposed that a continuous ingestion of plastic containing 100 mg/kg BPA would lead to a very low steady-state concentration of 0.044 ng/kg BPA in fish and 60 μg/kg (normalized to lipid) in worms. Whilst this represents a substantial exposure pathway, the risk of exposure through this route

was considered low in comparison with other pathways of exposure, based on the reported abundance of microplastics.

13.5.3 Safer Alternatives to BPA

Concern over exposure to BPA and its potential to cause harmful effects has led to worldwide efforts to formulate alternative polymer materials. This is a technically challenging area, largely because polycarbonate is such a useful material. It is an optically clear, strong and heat resistant plastic and hence has a wide range of uses. One promising formulation is a copolyester called Tritan^{TM}, which contains three different monomers, dimethyl terephthalate, cyclohexane dimethanol and tetramethyl cyclobutanediol (Eastman 2010). Studies have shown that it has a low migration potential, both for its constituent monomers and for the additives that are present in the polymer matrix. More importantly, the constituents and the leacheates from the polymer showed neither hormonal nor toxic activity. In a study by Guart et al. (2013), the leacheate from Tritan^{TM} and from polycarbonate bottles into water was collected and tested in a number of in vitro bioassays, including for estrogenic, (anti) androgenic activity and for retinoic acid and vitamin D type activities. The Tritan^{TM} leacheates showed no activity at any concentration, whereas the leacheate from polycarbonate showed estrogenic and antiandrogenic activity at higher concentrations (Guart et al. 2013). These findings are interesting, as they show the potential for newer, safer polymer alternatives to reduce unintended exposure of the human population.

13.5.4 Novel Polymer Formulations

In assessing the physical risks posed by ingestion of nano- or microplastics that unintentionally enter the food chain, much information and guidance can be gained from existing risk assessments performed for food packaging. For example, the European Food Safety Authority (EFSA) has produced detailed guidance for assessing the risks of exposure to nanomaterials, including nanocomposites, biopolymers and other complex materials, from their applications in the food chain (EFSA 2011). As detailed by EFSA, there are huge uncertainties that are associated with detecting, identifying and characterising different micro-, and nanoparticles and polymers in complex matrices such as food, even when the likely constituent substances are known, and these problems are multiplied where rates and sources of contamination remain unknown. In general, however, the considerations suggested by EFSA provide a useful framework applicable to the risks posed by microplastics and nanoplastics as contaminants in food.

Based on the guidance provided by EFSA, it can be predicted that the risks posed by micro- or nanopolymers to human health will be determined by the

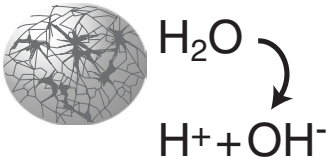
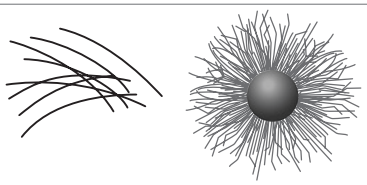
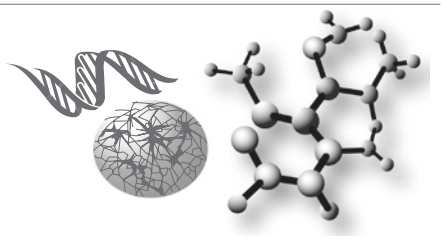
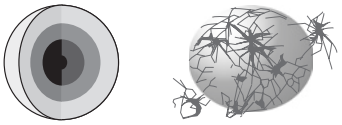
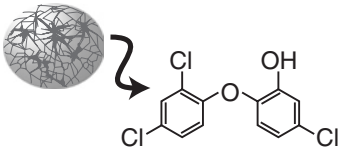
chemical composition and physico-chemical properties of the particles themselves, their potential for uptake and interactions with tissues, and the likely potential exposure levels. Actual information on migration rates of nanoparticles into food or food stimulants is sparse. Simon et al. (2008) derived a theoretical model to estimate migration rates of nanoparticles from a polymer matrix. The model predicted that migration from polymers of low dynamic viscosity would be limited to particles of <1 nm in diameter, even where the interaction between particle and polymer was negligible. These estimates are in accord with results from Schmidt et al. (2009) who used a combination of field flow fractionation and analytical chemistry techniques to study the migration of nanoparticles out of polylactic acid (PLA). Whilst migration out of the matrix did definitely occur, the resulting nanoparticle concentrations were well below the recommended migration limits. Migration may also be higher into acidic matrices (Mauricio-Inglesias et al. 2010). Table 13.5 compiles some of the indicators identified by EFSA to have the potential to lead to toxicity following uptake of nanoparticles in the diet. These include high levels of reactivity, complex morphologies, the ability to interact with biomolecules, stability and presence of toxic additives. Accordingly, one might expect the greatest hazard to human health to come from ingestion of complex, high aspect ratio nano-scale fibres, synthesised from mixed substances of variable persistence.

13.5.5 Nanopolymers and Nanofillers

There are many technological advances in the development of complex biocomposites and nanopolymers that are relevant for consideration here. Nanocomposites are complex macromolecular materials containing small quantities of nanoscale additives, or nanofillers. The most commonly employed nanofillers for food packaging (the most common type of plastic litter) are nanoclays. Other common nanofillers include nanocellulose fibres, carbon nanotubes, metals and oxides. Nanofillers are intended to enhance or improve the inherent properties of the polymer, including factors such as mechanical strength, thermal and ultraviolet stability, and gas and vapour barrier properties (Lagaron and Lopez-Rubio 2011). The high surface-to-volume ratio of nanofillers enhances their inherent chemical and mechanical properties compared with larger-scale versions of the same material, whilst allowing them to disperse within polymers without introducing structural defects. For example, addition of nanoclays can enhance the oxygen barrier properties of plastics, which makes them particularly attractive for keeping food from spoiling (Lagaron and Lopez-Rubio 2011).

The addition of nanomaterials into polymers can also cut down on the need for large amounts of additives, for example by acting as antioxidants or antimicrobial agents themselves (De Azedero 2013). In relation to plastic discarded to the environment, a major added benefit of nanofillers is that they may also be able to reduce the unintended migration of additives out of polymers (de Abreu et al. 2010).

Table 13.5 Indicators of potential toxicity for nanoparticles contained within food packaging

Characteristic of particle	Details	Example
High levels of reactivity	Catalytic, chemical or biological reactivity	
Complex morphology	Rigid, long tubes or fibres, high aspect ratios, hard fissures or edges, high porosity, mixed composites containing substances of diverse persistence and character	
Ability to interact with biomolecules	Binding or interaction with enzymes, DNA, steroid receptors, signal transduction pathways	
Stability: ability to undergo complex transformations	Polymer ageing, changes to surface properties, porosity, metabolites, changes or loss of coating (e.g. protein surface corona)	
Presence of antimicrobials	Release of biocides into surrounding tissues, unintended consequences for gut *flora*	

Adapted from EFSA (2011)

The migration of various polymer additives, including triclosan and diphenyl butadiene from polyamide into food stimulants was found to be up to six times lower when nanoclays were added to the polyamide. The nanoclay particles were thought to slow down the rate of migration of the additives due to their layering within the polymer matrix, creating a tortuosity effect (Fig. 13.3) (de Abreu et al. 2010). Thus, new advances in nanotechnology may bring unintended benefits in terms of the reduced leaching of their additives and hence the environmental safety of the polymers that contain them.

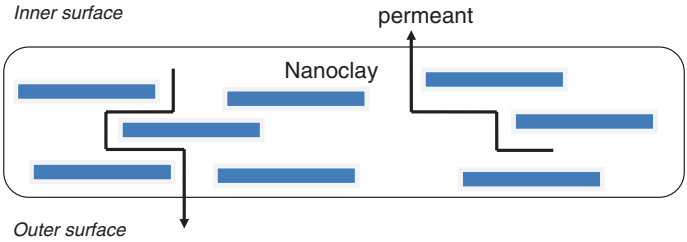


Fig. 13.3 Tortuosity effect of nanoclay in limiting the diffusion of permeants through polymers (adapted from Ray and Okamato 2003)

13.6 Conclusions and Future Work

This short account has identified some of the most widely encountered plastics in everyday use and illustrated some of the attempts that have been made to assess their potential hazards to human health. Different routes of exposure to human populations, both of plastic additives, micro- and nanoplastics from food items and from discarded debris are discussed in relation to the existing literature for nanomedicines and nanocomposite packaging materials, for which an increasing body of knowledge exists. It is clear that our understanding of the potential contamination of the human population by micro- or nanoplastics sourced from the environment is in its infancy, leaving many questions unanswered:

- Does significant bioaccumulation and trophic transfer for micro- and nanoplastics occur in the environment? If so, what species are most at risk?
- How does ageing of plastics affect their physico-chemical properties and subsequent toxicity?
- Following ingestion, does uptake of micro- and nanoplastics occur? Do proteins bind to the surface of the particles to form a protein corona? How does this vary for different plastic litter types and what cell types are most vulnerable to toxicity?
- What methods should we be using for locating, identifying and quantifying micro- and nanoplastics in complex matrices including biological tissues? Techniques mentioned in this chapter include field flow fractionation, multi-angled light scattering (MALS), inductively coupled plasma mass spectrometry (ICP-MS) and non-linear optical bioimaging. Further development of suitable methods for extracting micro- and nanoplastics from biological materials and for studying them in situ remains a compelling research gap for the future.

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