DEPARTMENT OF GENERAL SURGERY AND MEDICAL-SURGICAL SPECIALTIES
MASTER'S DEGREE PROGRAM IN MEDICINE AND SURGERY
UNIVERSITY OF CATANIA

Rossella Zanghì

MICROPLASTICS DETERMINATION IN HUMAN BLOOD AND RELATED DISEASES

Supervisor: Prof. Margherita Ferrante

Tutor: Eloise Pulvirenti

Academic Year 2022/2023

INDEX

INTRODUCTION

It was 1954 when Giulio Natta invented isotactic polypropylene, commonly known as “plastic”, a synthetic polymer that is usually made by adding various chemical additives to oil or gas-derived monomers during the polymerization process (Thompson et al., 2009). Until then, it was a feat that seemed impossible and thanks to its discovery he won the Nobel Prize in Chemistry in 1963. "Moplen", the first polypropylene brand, became a symbol of the economic boom, a real epochal revolution: from that moment, houses have been filled with plastic objects in the kitchen, household appliances, toys, personal hygiene accessories (Cipolloni et al., 2023).

Plastic has a lot of precious properties that make it commonly used in numerous commercial products: it is inexpensive, robust, lightweight, flexible, waterproof, easy to maintain and sterilize and has insulating qualities. Its use extend life of perishable food items and has a relevant role in packaging due to its versatility in terms of shape; helps to reduce fuel consumption in automotive and aerospace industries; the insulating properties is exploited in construction and electrical applications to improve the energy efficiency of housing; the lightweight property reduces the emission of greenhouse gases; the possibility of sterilization allow extensive production of medical devices like gloves, syringes, intravenous tubes, prosthetics, blood bags, dialysis machine (Fig. 1) (Parashar and Hait; 2021).

Biomedical waste	Plastic component
Masks, Face shield, Eye shield	Polypropylene (PP), Polycarbonate (PC), Polystyrene (PS)
Gowns	Low-density polyethylene (LDPE)
Hand sanitizer bottles, Aprons, Gloves, Goggles	Polyvinyl chloride (PVC)
Packaging materials	PP, PS, LDPE, High-density polyethylene (HDPE), polyethylene terephthalate (PET)
Plastic bottles	PET, PP

Fig. 1 Biomedical waste and their plastic component (Geyer et al., 2017; Parashar and Hait; 2021)

Although a lot of advantages, the same properties that make plastic so useful is also responsible of its potential harm: only 21% of global plastic products is recycled or incinerated (Lebreton and Andrady, 2019) and an amazing 31.9 million metric tons are released into the environment every year (Jambeck et al., 2015). The estimated total mass of plastic (8 billion tones) is more than twice as large as the combined mass of all land and marine species (Elhacham, 2020). In fact, plastic durability causes the persistence for thousands of years (Barnes et al., 2009) while its lightweight facilities the transport along distances via wind and air currents (Barnes, 2002). This phenomenon results in a virtually worldwide large distribution, extended in urban areas and in every earth habitat, for instance aquatic environment, coastlines, polar regions (González-Pleiter et al., 2020) and even also Mariana Trench, the deepest earth backdrop (Lebreton and Andrady, 2019).

As stated in a recent survey, Europe (the second-largest producer of plastic after China) releases 307-925 million pieces of debris into the ocean each year, 82% of which are made of plastic (González-Fernández et al., 2021). According to World Wildlife Fund (WWF), the primary cause of plastic garbage ending up in the ocean is human activity and ineffective waste management, which gets worse during the summer because of an increase in tourist traffic and leisure-related activities. Sea activities involving fishing, aquaculture, navigation of scatter pots, nets, and fish delivery boxes are next (with 22%). Scientists propose to formally declare that since the mid-1950s, the Holocene—a geological epoch that began 11,000 years ago at the end of the last ice age—has been replaced by the Anthropocene. This is based on overwhelming evidence that humans have altered atmospheric, geological, and hydrological processes. For millions of years, ice, rocks and sediments on Earth will bear evidence of human activity that has permanently affected the planet's geological processes and ecosystem. Soil erosion has increased due to road construction and deforestation; the increasing carbon dioxide emissions into the atmosphere are evident in polar ice caps; carbon particles are released into the atmosphere by fossil fuels; the soil has permanent traces of nitrogen and phosphorus from fertilizers used; radioactive particles have been dispersed worldwide by nuclear explosions. Plastic waste is now regarded as a geological marker (Cipolloni et al., 2023). In fact, some plastic particles journey ends in rocks where it could accumulate and stratify with a great conservation comparable to fossils (Corcoran, 2014). This phenomenon is so extensive that it is used as stratigraphic indicator of a new epoch known as "The plasticene" (Fig 2) (Stager, 2012; Reed, 2015).

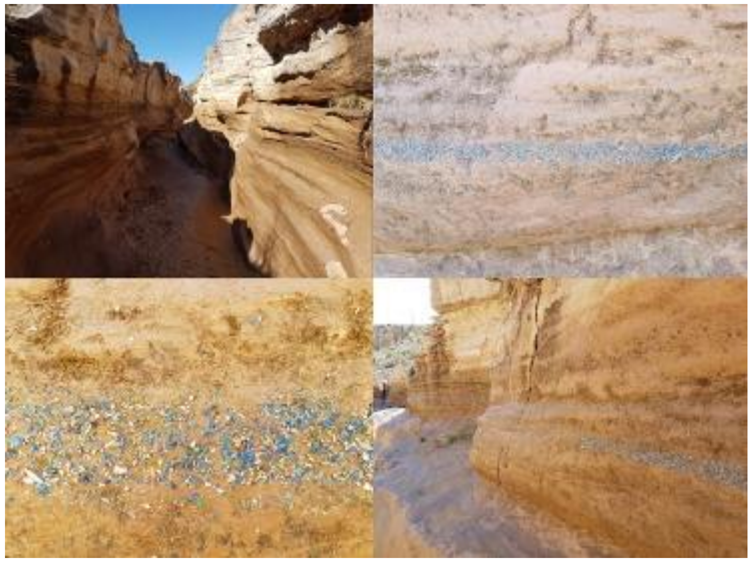

Fig. 2 Plastic layering in rocks in a Spanish Canyon, 2019 Stratigraphy, Sedimentology and Palaeontology | The Plastocene – Plastic in the sedimentary record (egu.eu)

Microplastics

What is it known today?

The impact of macroplastic waste (defined upper of 5 mm in diameter) has largely been documented in literature: through entanglement or ingestion, plastic debris can physically damage animals leading to lacerations, asphyxia, and malnutrition that may result in death (Wright,2013).In recent years it has been found that the most form of plastic waste are smaller pieces of plastic called "microplastics" (MPs) (Fig. 3) and “nanoplastics” (NPs). The term "microplastic" was originally used in 2004 by Richard Thompson, a marine researcher at the University of Plymouth in England. Upon collecting trash from beaches along the English Channel, he conducted an analysis and discovered materials like acrylic, polyester, polyethylene, polypropylene, polyamide, and different other types. Examining the plankton databases, were detected the same components, and it also appeared that the plastic quantities in plankton have been increasing since the 60s year after year, in conjunction with industrial production (Cipolloni et al., 2023). Currently, MPs lack a universally accepted definition. It is called a heterogeneous mixture of materials with a range of forms and sizes between 1 micrometer (μm) and 5 mm (millimeters) in diameter (http://www.issalute.it/).

MPs could be considered a emerging contaminant. According to the US Environmental Protection Agency (EPA), a "emerging contaminant" is any substance or chemical that presents a real, potential, or perceived threat to human health or the environment because it comes from a recent source or because a new pathway has developed, and no published health standards have been established for (https://www.epa.gov/dwucmr/occurrence-data-unregulated-contaminant-monitoring-rule#3). This discovery rises emerging public concerns due to the possible implications for ecosystem and human health: in 2019 World Health Organization (WHO) called for an assessment and research including standard methods for measuring their presence in the environment and their potential impact (World Health Organization, 2019). For instance, latest study affirm that MPs could act as condensation nuclei and contribute to clouding formation processes particles, generating local climate impact (Aeschlimann, 2002).

Fig. 3 Microplastics on fingers (https://www.medicalnewstoday.com/articles/could-microplastics-in-human-blood-pose-a-health-risk#An-innovative-detection-method)

Characterization, type and source

According to their origin, MPs are classified into primary and secondary types: primary types are intentionally manufactured in cosmetic products like scrub, toothpaste and sunscreen; secondary MPs accidentally originate from degradation of packaging, playgrounds synthetic turf and clothes, tires, illegal dumping, cigarette filters, wastewater sludge or medical devices (Wright and Kelly, 2017). This result from mechanical degradation (abrasion), chemical degradation (oxidation and chain scission through photodegradation on sunlight UV exposure, thermal degradation or from reactive chemicals like ozone) and biological degradation (biofilm formation on plastic surface, followed by oxidation or hydrolysis to break the polymer chains and resulting in small molecules that can pass through microorganisms cell walls and directly mineralized into CO_2 and H_2O). These different mechanisms are often synergistically or competitively linked with each other. For example, photodegradation can degrade plastic that is floating on the ocean's surface, increasing the likelihood that it will break and become pitted from mechanical abrasion. The resulting rough particles will then be more hospitable to microorganisms. The ensuing biofilm, however, could both increase the density of the particles and making them sink and inaccessible to other degradation sources, UV light included (Cholewinski et al., 2022).

All polymeric materials can be split into subclasses based on the synthesis process or material property and result in a large variety. Their classification is based on origin, structure, source, surface chemistry, molecular force and mode of polymerization. Heterogeneous mixture of materials of different shapes - fragments, spheres, granules, pellets, flakes or pearls have all been described as common MPs occurrence: the largest category detected in water and sediment is fibers (48.5%), followed by fragments, spherical beads, films, and foams (Burns et al., 2018).

High-density and low-density polyethylene (HDPE, LDPE), polypropylene (PP), polystyrene (PS), polyethylene terephthalate (PET), polyvinyl chloride (PVC), polycarbonate (PC), polymethyl methacrylate (PMMA), polymethyl methacrylate polyurethane (PU) and combinations of other plastics composed plastic waste (Kumar et al., 2011).

Analytical competence that might differ greatly amongst research organizations, limits the ability to report precise data on each of the MPs features and makes determining human exposure very difficult. In addition, only few polymers are used in the “pure” state: the most have ingredients like chemical additives and other materials added to improve their qualities, and this can change the density (Hahladakis, 2018). Fillers account for more than 50% of all additives used, followed by plasticizers, colorants, flame retardants (Stevens, 1993).

Medical devices during covid-19 pandemic

Even if early assessments on the COVID-19 pandemic's effects on the environment noted improvements in groundwater quality, beach cleanup, noise pollution, and air quality (lower levels of CO, NO2, NOx, PM2.5, PM10, and VOCs) as a result of numerous activities being halted (Rangel Alvarado et al., 2022; Mohamed et al., 2022), this was clearly temporal. It has been defined a catastrophic global health, environmental, and economic crisis that brought to significant changes in the production and use of plastic, medications (antibiotics, antivirals, glucocorticoids, etc.), disinfectants (bottled hand sanitizers, biocides, domestic disinfectants) and personal protective equipment (PPE) (gloves, gowns), single-use PPE like face masks (N95), surgical masks and hand gloves contain non-biodegradable plastic materials, resulted from the measures made to control the disease and treat those who have been afflicted (Fig. 4).

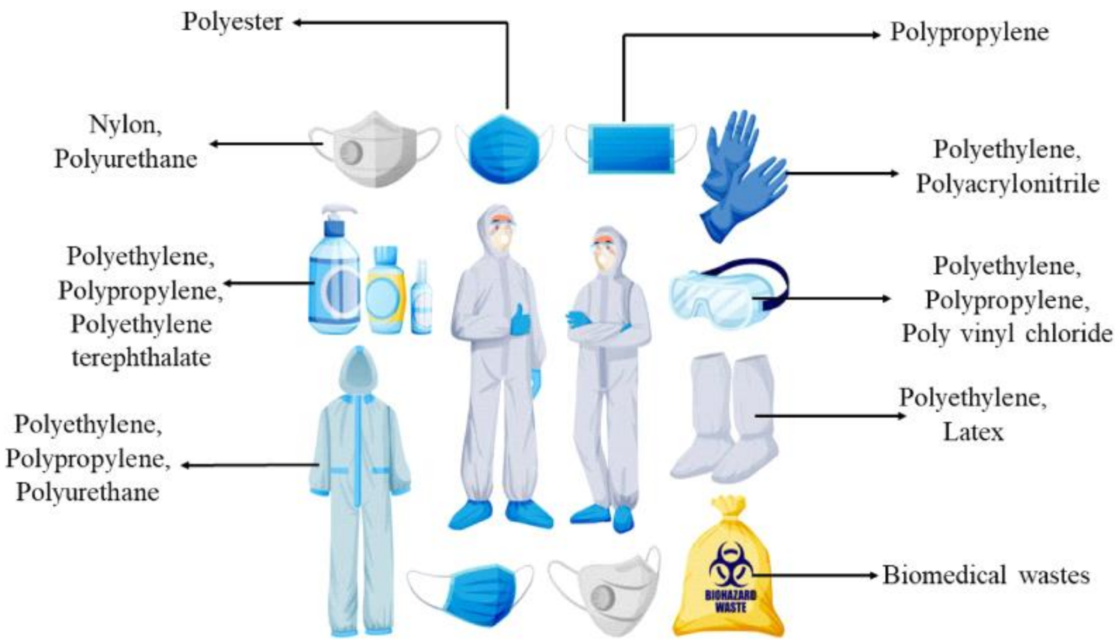

Fig. 4 PPE made from different type of plastic (Mohana et al., 2023)

The WHO calculated that in the early stages of efforts to contain the virus, 89 million medical masks, 76 million examination gloves, and 1.6 million pairs of goggles havebeen required per month globally (https://www.who.int/news/item/03-03-2020-shortage-of-personal-protective-equipment-endangering-health-workers-worldwide).It's possible that the pandemic's effects on the pattern of pollutants and the emergence of new ones will last far longer than first believed. In addition to the issue of the increased solid waste they represent, all these materials have the potential to produce MPs in the environment. To give an idea, Sun et al., calculated that, with all face masks discarded in 2020, the number of MPs that entered the coastal marine environment worldwide has been over 1370 trillion, with a daily release rate of 396 billion (Sun et al., 2021). Utilizing a face mask can release chemical compounds and microfibers; when abandoned in the aquatic environment, it would absorb different pollutants (Fig. 5) (Patrício Silva et al., 2021).

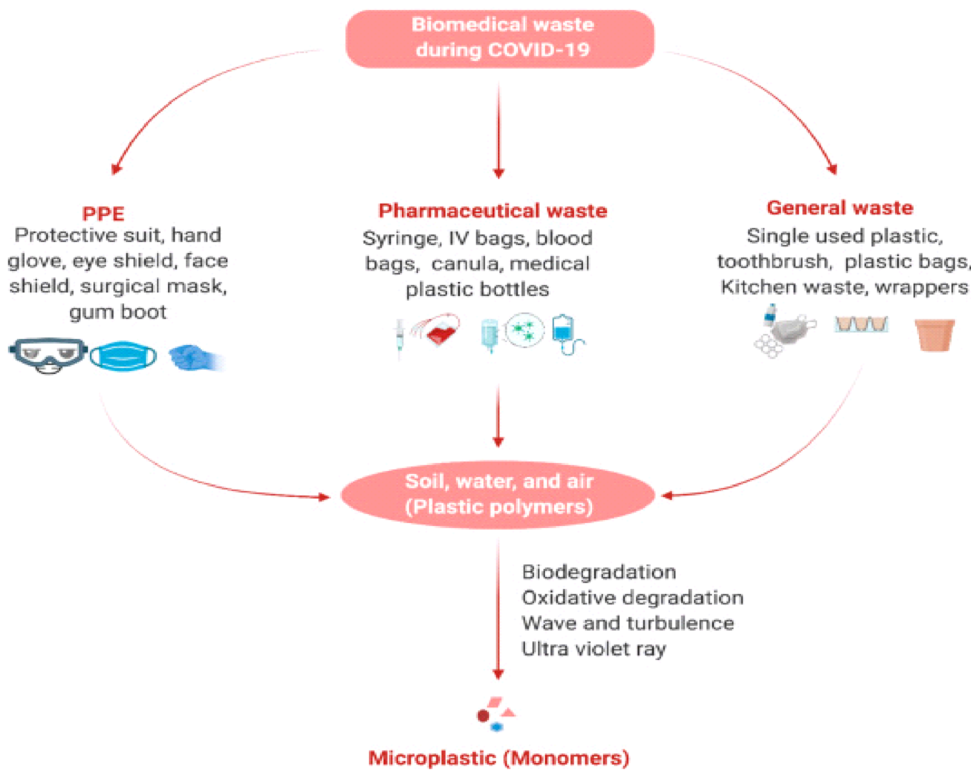

Fig. 5 From biomedical waste during COVID-19 pandemic to MPs (Masud et al., 2023)

Human exposure

Exposure routes

Even if MPs determination in human body remain a great field to explore, it is generally accepted that human intake of MPs occurs mostly through eating and inhalation. WWF's estimate states that the daily potential exposure is 700 mg/person (Senathirajah et al., 2021).

MPs can be found in drinking water, food (World Health Organization, 2019) and both indoor and outdoor air (Dris et al., 2017). In a study, human stool was found to include a variety of MPs, indicating accidental intake from various sources. Per 10 g of human stool, a median of 20 MPs (sized between 50 and 500 µm) were found in nine different forms, the most common were PP and PET (Schwabl et al., 2019).

Too small to be filtered by water purification systems, they pass through pipes and reach the sea or end up in farmland through irrigation systems. Plants could absorb MPs, making themselves carriers to animal tissue and human. In vegetables they could act similarly to the mode of uptake of the more studied carbon-nanomaterials (Dietz et al., 2011): from roots, in an appropriate size, they penetrate the seeds and could translocated to the shoot by endocytosis and in the aerial parts through capillary action (Husen et al., 2014). According to a study made in Catania, the Estimated Daily Intakes (EDIs) for adults and children for each type of vegetal and fruit is characterized by wide variability. The higher median level of MPs in fruit and vegetable samples is in apples editable part due to their high vascularization and long maturation timing, and in carrots for their fine roots. Conversely, the lower median level was observed in lettuce samples. There has been found

223000 particles per g in fruit and 100000 per g of vegetables from 1 to 3 μm. (Oliveri Conti et al., 2020).

MPs released into the environment has the potential to infiltrate the food chain also through shellfish and fish (Makhdoumi et al., 2022). Since fish's gastrointestinal systems are parts of the fish that can contain MPs, more pertinent human exposure may result from eating seafood such bivalves, crabs, and small fish that have not had their gastrointestinal tracts removed.

WWF found that Mediterranean Sea waters reaches the highest MPs concentration ever measured: a sad record of 1.9 million fragments per square meter. A study aims to quantify MPs < 3 μm presence in several edible seafood in this area: data revealed the concerning EDIs resulting from eating, even if the use of these foods may expose people to a minimal extent relative to the population that uses PET bottled mineral waters (Ferrante et al., 2022). In fact, it has been estimated that there are a hundred to a thousand MPs in bottled mineral water. Some of them come from bottling (to a lesser extent they are also found in glass). The cap is the weak point being high-density polyethylene (HDPE) which does not resist stress unlike PET (Oliveri Conti et al., 2020).

Other food samples in which MPs are reported are salt, with concentrations between 0.007 and 0.68 MPs per gram, beer in which fibers, fragments and granules of MPs amount to 0.025, 0.033 and 0.017 per millilitre, honey (0.166 fibers per gram), bottled water (94.37 MPs per litre), tap water (4.23 MPs per litre), and also milk, rice, sugar, nori seaweed (http://www.issalute.it/). Another possible source of MPs exposure has been proposed as airborne deposition on food. Catarino et al. calculated that exposure from deposition was more than from eating infected mussels when comparing direct contact to MPs from consumption of mussels with exposure in household dust (Catarino et al., 2018). Additionally, it appears that heating plastic containers increases dietary and inhalation exposure: large amounts of grains spill out of plastic containers in the microwave, as do tea bags and baby bottles made of nylon or PE that are used to prepare powdered infant formula by shaking in hot water.

Respiratory tract's epithelial surface, the primary point of contact between people and environment, is continuously exposed to a variety of particles floating in inspired air (Schraufnagel, 2020). According to the Global Burden of Disease project 4.2 million persons are thought to have died prematurely in 2015 because of exposure to airborne particulate matter (PM) (Forouzanfar et al., 2015): it is unclear which PM constituents provide the most threat to human health, even though MPs could be a factor (Wang et al., 2020). Liu et al. evaluated MPs exposure and calculated that in Shanghai, residents were exposed to 21 particles/day via inhalation (Liu et al., 2019). In lung tissue autopsies of 20 non-smoking adults aged 48–94 years MPs were detected in 65% and the most observed were fragments of synthetic polymer particles and fibers, especially PE, PP and cotton (Amato-Lourenço et al., 2021). As most people spend much of their time indoors, inhalation of indoor air is probably an important exposure pathway. In indoor environment, there could be counted 1500 MPs per cubic meter. Considering that an adult breaths 10 cubic meters of air per day, human could potentially inhale up to 15000 MPs in 24 hours (Cipolloni et al., 2023). According to many studies, most atmospheric MPs come from synthetic textiles, especially indoors where the concentration is bigger (Dris et al., 2017).

Another way of penetration of plastics could be dermal exposure when people wash themselves in MP-contaminated water or through surgical sutures using braided polyester

(PL) and monofilament PP. This exposure could result in lower inflammatory reaction than silk and fibrous encapsulation after 21 days (Salthouse and Matlaga, 1975); human epithelial cells could suffer oxidative stress (Schirinzi et al., 2017). To reach the systemic circulation, chemicals and other foreign agents such as particles, should penetrate the corneum stratum so it could be possible only for NPs: dermal exposure to MPs > 1 μm is limited by the barrier composed by several layers of corneocyte cells, proteins and intercellular lipids (Fig. 6) (Revel, 2018).

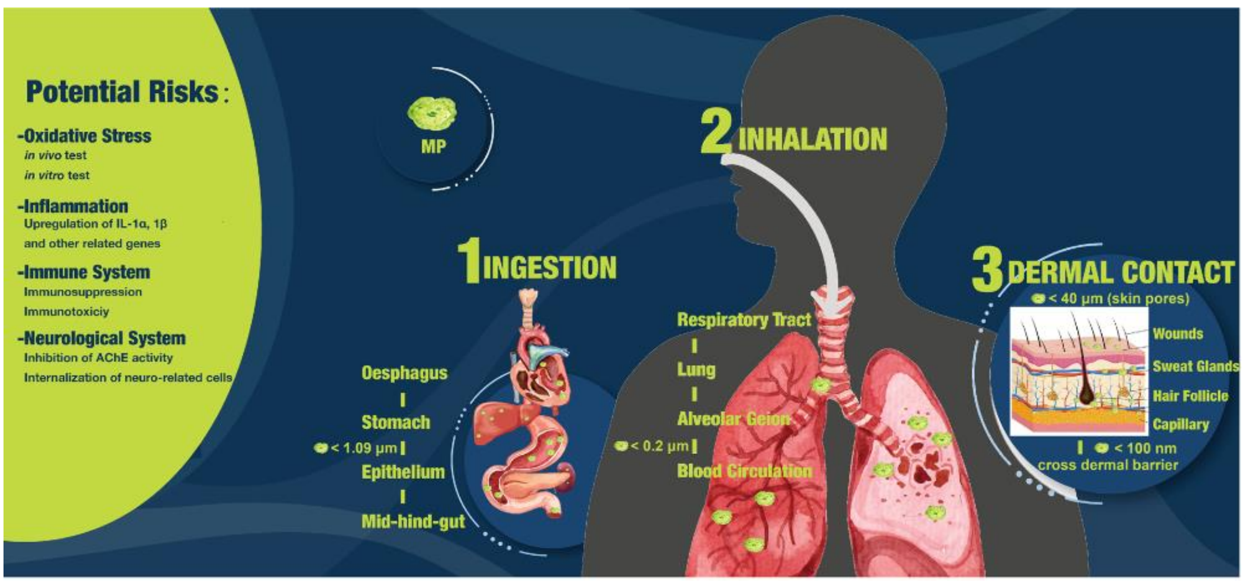

Fig. 6 Three main pathways for MPs entering into the human body. When ingested MPs are smaller than 1.09 μm, they could penetrate across the gut epithelium and enter the blood circulatory system. Airborne MPs could translocate into epithelial layers through the gas exchange. When > 0.2 μm are removed from the lymph into the intestine, while < 0.1 μm could accumulate in all organs. Dermal contact seems less prevalent and eventually occurs due to the skin pores (40-80 μm) (Wu et al., 2022)

Defence barriers and microplastics kinetic

Once enters the body a foreign substance may or not cross biological barriers: while some substances are eliminated, other could accumulate in lipid-rich tissues. Due of MPs widespread dispersion, there has been a growing interest in human absorption, distribution, metabolism (including possible toxicity), excretion processes (Vethaak and Legler, 2021) and potential tissues accumulation.

Airborne MPs could settle in the alveolar regions of human lungs and then move into epithelial layers because of gas exchange between the alveoli and capillaries (Barlow et al., 2017). When a particle accumulates in the respiratory system then is removed by several processes: sneeze, mucociliary clearance, alveolar macrophage phagocytosis, and lymphatic transfer (Lippmann et al., 1980). The mobility of mucus, a viscoelastic secretion that shields the mucosa from dehydration and serves as a medium for inhaled particles, is crucial for mucociliary clearance: it flows as a consequence of continuous ciliary action, and it is removed from the airway ingested into the digestive system. Clearance mechanism is influenced by the location of deposition and the physicochemical characteristics of the particles such as size, shape, and surface reactivity. This process happens in two stages: the first has a half-life of 3–12 hours in the tracheobronchial region and the second has an alveolar phase and may continue several months or more (MacNee et al.,1999). Particles inhaled can also travel to the lung's alveolar area and then enter the interstitium and potentially go to the lymph nodes.

The consumed MPs are immediately digested in the stomach between 2 and 6 hours after passing through the esophagus (Dawson et al., 2018) and carried to the midgut. Villous absorption is a passive phenomenon for microparticles of 5–150 μm from the intestinal lumen through gaps in the mucosa (Volkheimer, 1974). Only 0.3% of these particles, according to estimates, should be absorbed but as shown in a study of Schmidt et al., due to the upper permeability, inflamed tissue could transport more particles than a healthy one (Schmidt et al., 2013). Up to 130 μm, MPs can enter human tissues through paracellular transport (Cox et al., 2019) while smaller than 2,5 μm takes place across specialized "microfold cells" in Peyer's patches, rounded areas that make-up gastro-associated lymphoid tissue (O'Hagan, 1990) that transport particles to the underlying lamina propria by "transcytosis" (Dillon, 2019), and finally migrate to the blood via mesentery nodes and the thoracic lymph duct (Hussain et al., 2001). Insoluble MPs <1.09 μm could directly pass through the intestinal epithelium and enter the circulatory system.
Also in the gastrointestinal tract, mucus as a selectively permeable hydrogel, acts like a physical barrier to particles diffusion across the epithelial tissues. Mucin is the highly glycosylated protein with oligosaccharide sidechains that include terminal sialic acid and sulphate residues resulting in a net negative charge and primary structural element of the mucus layer (Lock et al., 2018). Through the digestive enzyme MPs are degraded and have the potential to become hydrophilic and pass through the urine or faeces. The polymers may wind up in the stool straight away if they are difficult to break down (Schwabl et al., 2019).

A study has been designed to clarify the uptake of MPs of 3 μm in blood and the excretion in urine of mammals after vein injection, gavage and pulmonary perfusion (Sun et al., 2022):

findings revealed that they could be detected in blood. From 100-nm to 3-μm PS MPs are excreted through the urine and penetrate through exocytosis and endocytosis near the tubular epithelial cells, or enter the peritubular capillaries (Pironti et al., 2023). If not removed by renal filtration or biliary excretion, MPs > 0.2 μm might be removed through splenic filtration (Rist et al., 2018) while NPs could flow and accumulate in liver and kidney (Vethaak and Legler, 2021) and maybe be retained in the brain (Gregory et al., 2020; McCright et al., 2022) or other organs passing through fenestrated capillaries (Fig. 7) (Heather, 2022). MPs contamination in kidney, spleen, and liver samples was evaluated by Horvatits et al.: the number of plastic particles of healthy tissue varied from 0 to 2.2 per gram; liver samples from patients with cirrhosis had an eight-fold higher level of plastic contamination (Horvatits et al., 2022).

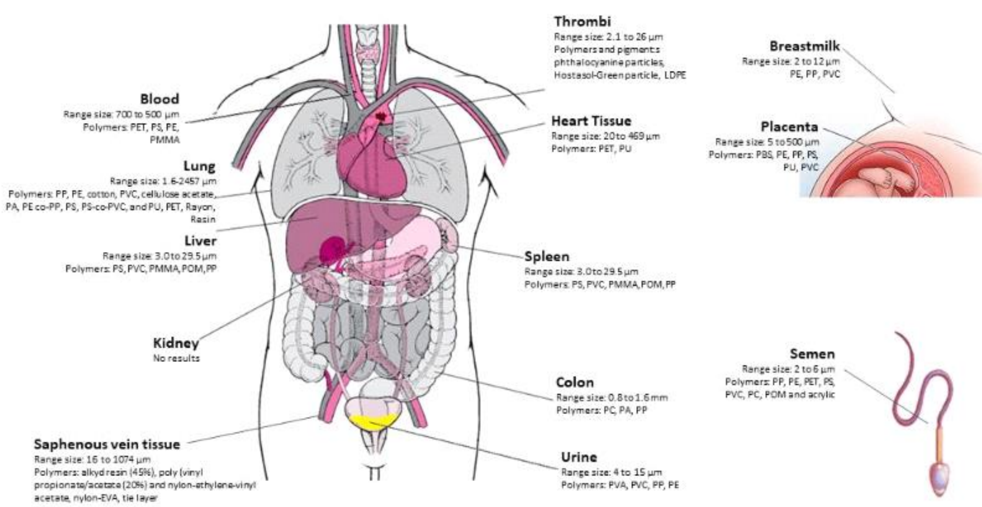

Fig. 7 MPs in human organ, tissues and fluids (La Porta et al., 2023)

Health impact

It seems almost obvious that humans cannot avoid MPs contamination. On the other hand, it is not clear whether this encounter is responsible for acute or chronic effects on human health or possibly involved in the illness event. Since polymers are often chemically inert, they are regarded as non-toxic. However, due to their tiny size and wide surface area, MPs and NPs, more so than their parent compounds, have greater reactivity which, depending on the exposure type and sensitivity, could be detrimental to organisms (https://www.issalute.it/). Growing research on their toxicity in vitro and in vivo suggests concerning effects on humans but evidence is still sparse, and this field of study is in its early stages. While studies on the interactions between MPs and human organs is ongoing, in vitro and in vivo studies and animal models are used to estimate potential impacts considering that is probably underrated, since particles that are not contaminated by microorganisms and chemicals are used in the laboratory. The consequences observed so far, depending on the mode of exposure, seem to be systemic (Fig. 8).

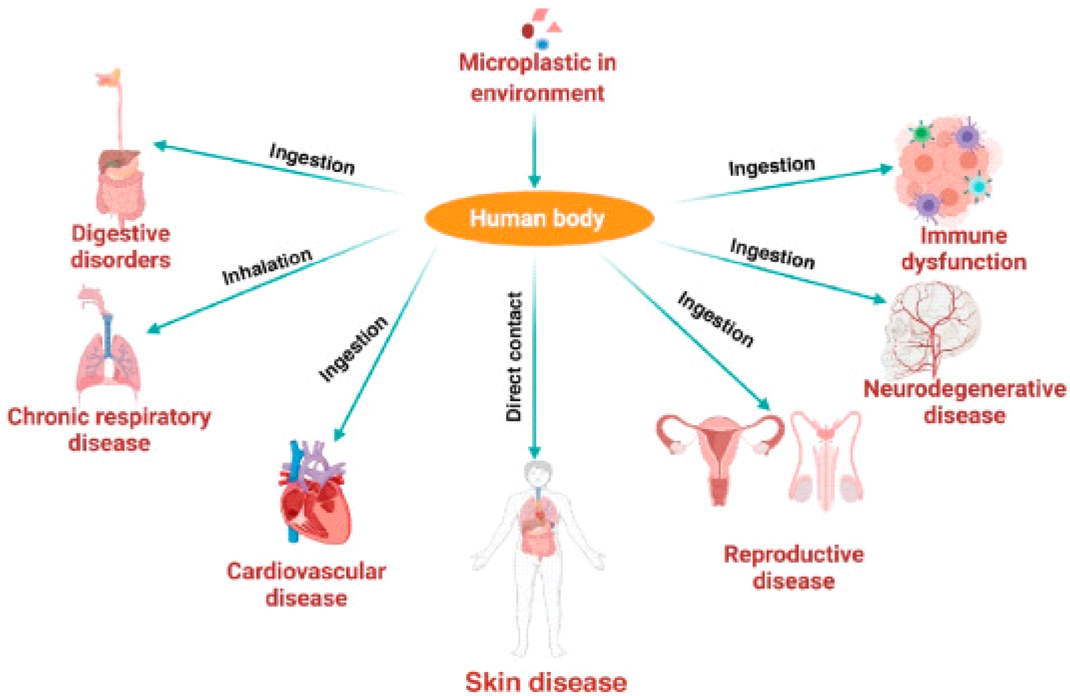

Fig. 8 An outline of the possible effects of microplastics on the various organs and systems in the human body (Masud et al., 2023)

Immune system

Plastic particles as foreign agents might trigger immunological response, which can lead to host toxicity (Zolnik et al., 2010). MPs physical presence could cause abrasive effects that result in inflammation, oxidative stress, and cytotoxicity (Schirinzi et al., 2017) (Fig. 9). Histamines and cytokines may be produced human cells exposed to PP (Hwang et al., 2019). Toll-like receptor 4 (TLR4), AP-1 transcription factor subunit and interferon regulatory factor 5 (IRF5) are expressed in the intestines of mice who consume PE (Li et al., 2019). PE particles were shown to induce cytokine activity like IL-6, IL-1β, and TNF-α(Green et al., 1998). Pulvirenti et al. reviewed, in vitro e in vivo, the MPs and NPs impact on inflammatory process: it appear to support a link between exposure to various MPs type and an increase in the proinflammatory interleukins IL6, IL8, IL1b, inflammation that could become chronic leading to more systemic inflammation and chronic obstructive pulmonary disease (COPD), asthma, inflammatory bowel disease (IBD); the interpretation of the data with regard to other interleukins studied (TNFα, MIP1β, INFΦ-1, INF-γ), growth factors such GCSF, FGF8, transcription factors like NFkB, Erk1, PPARγ , NRF2-H01, proteins ATT, GPR41-43, Myd88, CYP1A1, BMP, NKX2.5, MPO, COX1-2, D-LAC, BAD, LC3, p38, p62, cPLA2, MCP1 and oxidoreductases like SOD, CAT, GRD, GST, GPX needs greater caution because the literature currently has few heterogeneity studies. The increasing proinflammatory factors, verified for 3 μm MPs, results in a loss of epithelial integrity of the barrier cells and may be brought on by the production of the ZO-1 protein and a decrease in trans-epithelial electrical resistance (TEER). MPs may also play a role in ROS production, linked to inflammation, oxidative stress, permeability changes, histopathological damage (Pulvirenti et al., 2022).

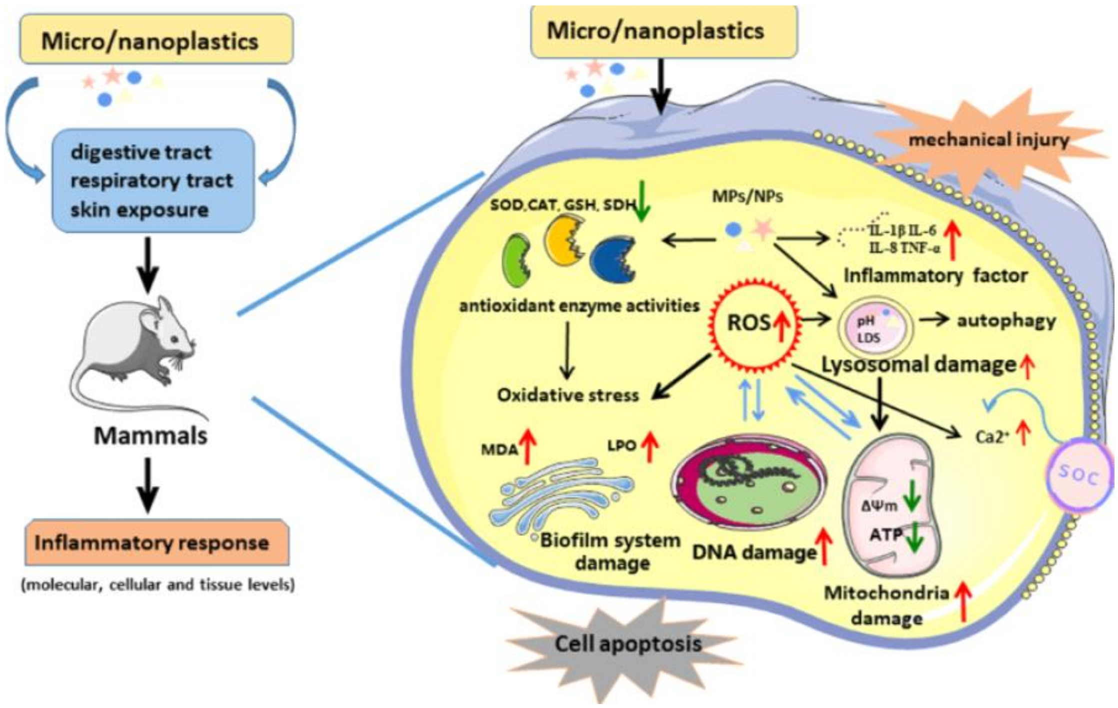

Fig. 9 Proinflammatory interleukins involved in MPs exposure (He T. et al., 2023)

A fish embryo toxicity test has been conducted on the zebrafish Danio rerio, subjected to 200 particles/mL of 10 μm PSMPs for 120 hours. Zebrafish showed elevated levels of oxidative stress (with higher amount of SOD1, SOD2, and CAT). Changes in the development of the larvae were noted, displaying severe malformations, mostly at the tail and column, along with a compromised integrity of the visual structure of the eyes. Conversely, no effect on the survival of developing zebrafish was found: the absence of lethal endpoints, indicates that the organism may be able to achieve adulthood using compensatory metabolic pathways, which include antioxidants (De Marco et al., 2022).

MPs may origin by the deterioration and corrosion of joint replacement prostheses. According to a study, PE particles were discovered in patients from post-mortem examinations, most of all had a size of less than 1 μm (Urban et al., 2000). According to

Zhang et al., mature osteoclasts rate of bone resorption increased when PMMA particles were added to each developmental stage of osteoclasts (Zhang et al., 2008) causing inflammation and prosthesis failure; granulomas in the liver, spleen, and abdominal lymph nodes were discovered because of a significant buildup of wear debris from a hip prosthesis.

Respiratory system

MPs produce respiratory discomfort in addition to cytotoxic and inflammatory effects (Di Dong et al., 2020). It has been known that daily exposure to pollution acts as an oxidant to the lungs, causing oxidative stress, inflammation, and carcinogenesis (Valavanidis et al., 2013). PS particles< 50 nm had genotoxic and cytotoxic effects on macrophages and lung epithelial cells (Calu-3 and THP1) (Paget et al., 2015). Furthermore, reactions to inhaled particles can manifest as acute asthma-like bronchial reactions, diffuse interstitial fibrosis and granulomas with fiber inclusions (extrinsic allergic alveolitis, chronic pneumonia), fibrotic and inflammatory changes in the bronchial and peribronchial tissue (chronic bronchitis), and lesions of the interalveolar septa (pneumothorax), depending on individual differences in metabolism and susceptibility (Prata et al., 2018). While most fibers can be cleared from the respiratory system, some will cause inflammatory responses and lesions (Prata, 2018), particularly in those whose clearance mechanisms are impaired (Gasperi et al., 2018). Clearing qualities are likewise determined by MPs size (Dawson et al., 2018) and accumulative effect is dependent on dose (Wright et al., 2017). "Flock workers lung" is an occupational interstitial lung disease that causes pulmonary fibrosis by inhalation of flock fibres of rotary-cut polyamide (nylon), or MPs such as PP and PE (Kern et al., 1998). Similarly, PVC industrial exposure could cause pneumoconiosis, a restrictive lung disease (Studnicka et al., 1995).

Digestive system

MPs could enter human gastric cells and after internalization, influence gene expression, inhibit cell viability and cause pro-inflammatory responses or morphological changes leading to adenocarcinoma (Forte et al., 2016) and colorectal cancer (Waring et al., 2018). By producing a wide range of compounds, including short-chain fatty acids, vitamins, and health-beneficial products like anti-inflammatory, analgesic, and antioxidant products, the active gut microbiota can improve digestion, control gene expression, and influence human immune and metabolic processes (Liu et al., 2021). Fungicides and pesticides in MPs can cause infections or alter the gut microbiota (Lu et al., 2019).

Reproductive system

Oxidative stress and inflammation brought on by plastic particles have the potential to harm sperm cells (Amereh et al., 2020; Xie et al., 2019; Hou et al., 2020). The embryo's life cycle is a delicate period where dangerous things could seriously interfere with the organism’s ability to develop and appears to be the primary target of plastic particles. Prenatal and postnatal exposure to PS MPs results in testis development disorder and male subfertility (Zhao et al., 2023). Chorion holes prevent plastic particles

>100 nm from migrating (Duan et al., 2020) but they could stick to its surface and lessen the embryo's ability to absorb oxygen, change heart rate and delay hatching (Chen et al., 2020). When oyster larvae are exposed to 1–5 μm MPs, their ability to swim is severely hindered, leading to significant developmental damage (Bringer et al., 2020).

Cardiovascular system

In plasma, proteins allow MPs their transport to distant organs including heart, causing pericardial edema, cardiotoxicity, thrombosis, damage to the vascular structure, and slowing in the heart rate. In a study, because of plastic fragment internalisation into cardiomyocytes, were observed oxidative stress, myocardial damage, fibrosis and impaired electrophysiological values (Persiani et al., 2023). In research conducted by Li et al. 6-week-old rats exposed to 0.5 μm PS particles for 90 days showed increased levels of cardiac injury markers (troponin I and creatine kinase-MB) (Li et al., 2019; Li et al., 2020). The investigated effects of carboxylate PS MPs on murine endothelial and immune cells involved in vascular inflammation, since they induce leukocytes adhesion. Also, in monocytic cells MPs enhanced pro-inflammatory cytokine expression and release (Vlacil et al., 2021).

Nervous system

In a study, various MPs with a diameter between 0.5 and 10 μm were exposed in mice brains. Mices exhibited blood–brain barrier disruption, lower level of dendritic spine density, hippocampus inflammatory response and cognitive (and memory) deficits compared with controls, in a concentration-dependent manner(Jin et al., 2022).MPs and NPs mostly cause oxidative stress and inhibits the AchE enzyme (Prust, 2020). Since smaller particles may more readily cross the blood-brain barrier, nanosized particles may be more neurotoxic (Mattsson et al., 2017). Zebrafish exposed to NPs had altered behaviour including reduced frequency of feeding and disturbances in their movement (Sarasamma, 2020). NPs could be also associated with an increased chance of developing Alzheimer's disease because of particles influence on protein fibrillation (Mahmoudi et al., 2013).

Urinary system

A first pioneering study demonstrated kidney MPs tissue accumulation in mice using fluorescent microspheres of 5 and 20 μm (They Deng et al., 2017).NPs exacerbate nephrotoxicity and apoptosis in mice kidney cells by activating the oxidative stress–endoplasmic reticulum pathway (Li et al., 2023). Six weeks of NPs exposure in murine, showed reduction of the kidney function due to tubular atrophy, glomerular collapse (Tang et al., 2023). In another study, mices treated to NPs and MPs showed large increases inMCP-1, TNF-α, IL-6, and IL-10, as well as inhibition of CAT: kidney injury was histologically confirmed and result in higher mortality (Meng et al., 2022).MPs has been shown to adsorb cadmium inducing in mices nephrotoxicity and a severe biological response: a decrease in antioxidant enzyme activities like SOD and CAT, an increase of autophagy markers LC3-II, ATG5, ATG7,Beclin-1 and kidney fibrosis markers such as α-SMA, TGF-β1 and COL4A (Zou et al., 2022).Through histology analysis, mice treated with various diameters of MPs from 0.5 to5 μm, demonstrated after 8-week of exposition, mesangial matrix expansion, endocapillary proliferation and tubulointerstitial fibrosis with high-collagen deposition; molecular analysis showed oxidative stress induction and increased levels of inflammation markers IL-1β and MCP-1 and higher αSMA expression; serum creatinine levels resulted higher (Xiong et al., 2023).

In a study conducted in 1985 it has been demonstrated that there is substantial exposure in the systemic circulation to diethylhexyl phthalate (DEHP), a plasticizer in plastic production, during hemodialysis. The length of time that patients had been receiving dialysis treatment was not a determinant of circulating concentrations of DEHP. In contrast, it correlated strongly with the duration (in years) of dialysis treatment (Pollack et al., 1985). MPs and DEHP have a synergistic toxic effect on kidney cells (Sun et al., 2023).

Miscellany and additives

Other effects related to MPs in the bloodstream could be pulmonary hypertension, artery occlusions, elevated coagulability, systemic lupus erythematosus, autoimmune rheumatic disease (Prata, 2018; Churg and Brauer, 2000; Canesi et al., 2015; Fernandes et al., 2015; Bernatsky et al., 2016). In a study MPs have been identified in ten human placentas using transmission electron microscope (TEM) and scanning electron microscope (SEM): it has been conjectured that there may be a relationship between MPs presence and significant ultrastructural changes in certain intracytoplasmic organelles such as the mitochondria and endoplasmic reticulum. The unbreakable particles found may play a role in the activation of pathological traits like inflammation, apoptosis, and oxidative stress that are typical of metabolic disorders that underlie obesity, diabetes, and metabolic syndrome (Ragusa et al., 2022).

Mesenchymal stromal cells (MSCs) are a subpopulation of stem cells that can differentiate into chondrocytes, osteocytes, adipocytes, and smooth muscle cells and are found in the stromal component of several tissues as well as bone marrow or the adipose tissue. In a study, human bone marrow mesenchymal stromal cells and adipose mesenchymal stromal cells were subjected to different diameters of MPs-PET (1 and 2.6 μm) to examine their effects: MPs exposure alter the potential differentiation and decrease the proliferation from both tissues. Reduction of cycling cells could either indicate that cells entered quiescence or, alternatively, MPs may produce genotoxic damages, which trigger senescence or apoptosis (Najahi et al., 2022).

In an investigation, it has been found that MPs < 1 μm may accumulate in the liver cells causing, even at modest concentrations, liver dysfunction and damage. The cGAS/STING signalling pathway is activated because of nuclear DNA damage which is the mechanism behind liver fibrosis (Shen et al., 2022) and hepatocellular carcinoma (Erkekoglu et al., 2017).

MPs could absorb pesticides such as Carbendazim, Dipterex, and Malathion in the soil (Wang et al., 2020). The antibiotic-resistant bacteria that have been discovered on certain MPs are an additional topic of research (Yang et al. 2019), particularly to Erythromycin, Penicillin, Sulfafurazole, and Tetracycline: in a recent study it is been found that MPs can give bacteria a useful surface on which to grow a biofilm and promote horizontal gene transfer which may result in the enrichment of superbugs (Zhang et al., 2020). It has been demonstrated that in the marine environment, bacteria may quickly colonize MPs surfaces

(Harrison et al., 2014; Wagner et al., 2014) and form microbial biofilms (Lobelle and Cunliffe, 2011). Using a SEM, Zettler et al. examined plastic marine trash and discovered that Vibrio was the most prevalent genus (Zettler et al., 2013). In another study MPs and associated biofilms have been analyzed in raw sewage, effluent water, and sludge from two wastewater treatment plants (WWTPs): MPs in WWTPs effluent included several taxa linked to plastic breakdown like Klebsiella, Pseudomonas, and Sphingomonas indicating that diverse bacterial assemblages colonize MPs and that WWTPs can play a significant role in modifying the fate of MPs in the environment (Kelly et al., 2021). A study in Scotland found that nurdles or "mermarid tears", plastic pellets derived from the hydrocarbons refining, contain Escherichia Coli (Cipolloni et al., 2023). Bacillus cereus and Stenotrophomonas Maltophilia have been detected in MPs collected off the coast of Belgium (http://www.issalute.it/). The possibility of germs spreading through the airborne MPs should not be disregarded. Microorganisms may enter the lungs through MPs surfaces where they adhere to shield against UV rays, posing a further risk of infection to human health (Prata et al., 2018).

The suspected harm of MPs is not only confined to these particles but also to plastic additives, used to improve plastic quality and to environmental contaminants, whose detrimental effects are well-known: this is known as the "trojan horse effect" (Fig. 10) (Hu et al., 2022). Evidence suggest additives may be poisonous, carcinogenic, mutagen (Gasperi et al., 2018) or could act as endocrine disruptors. Often referred as hormonally active agents or endocrine disruptive chemicals (EDCs), endocrine disruptors are present in a large variety of industrial products and are substances that could modify and interfere with the functioning of the endocrine system. Causing disruptions to the body's natural hormone synthesis, secretion, transport, binding, action, or elimination, these alterations may lead to malignant tumors, congenital anomalies, and developmental disorders (www.niehs.nih.gov/health/topics/agents/endocrine/). Fucic et al. highlighted related malignancies, such as colorectal, pleural, and bladder cancer, that have estrogen/testosterone coupling receptors (Fucic et al., 2018). Wang Q. et al., found that PS particles with decreasing particle sizes were absorbed at increasing rates from colon cancer Caco-2 cells (Wang et al, 2020). PVC is possibly the most harmful material due to its carcinogenic monomer and several hazardous additives (Lithner et al., 2011). Commonly used to provide flexibility, over 80% of plasticizers used worldwide are phthalates, present in household dust (Ait Bamai et al., 2014a), human urine (Jornet-Martınez et al., 2015) and breastmilk (Main et al., 2006; H¨ogberg et al., 2008). Phthalates and bisphenols are lipophilic so are could easily absorbed by the skin. Changes in pH or temperature favor their release from the plastic matrix to which they are linked, causing their ingestion. Once enter the body, they could bind steroid receptors and modulate the signalling pathways that are generally activated by endogenous ligands (Acconcia et al.,2015; Balaguer et al., 2017). Pharmaceutical formulations contain a variety of phthalates as excipients, including diethyl phthalate (DEP), dibutyl phthalate (DBP), dimethyl phthalate (DMP), dioctylphthalate (DOP), hypromellose phthalate (HMP), cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), and PET (http://www.fda.gov/Drugs/InformationOnDrugs/ucm080123.htm). Study suggests there may be a link between phthalates level and occurrence of asthma and allergies, especially in children (due to their immature defence mechanisms that make them particularly vulnerable) (Ait Bamai et al., 2014b) and that they are potentially linked to cancer (Hauser et al., 2005), cardiovascular and all-cause mortality (Trasande et al., 2022). Phthalates could also be a reproductive toxicant, giving adverse birth outcomes (Peretz et al., 2014) and a shorter pregnancy (Latini et al., 2003).

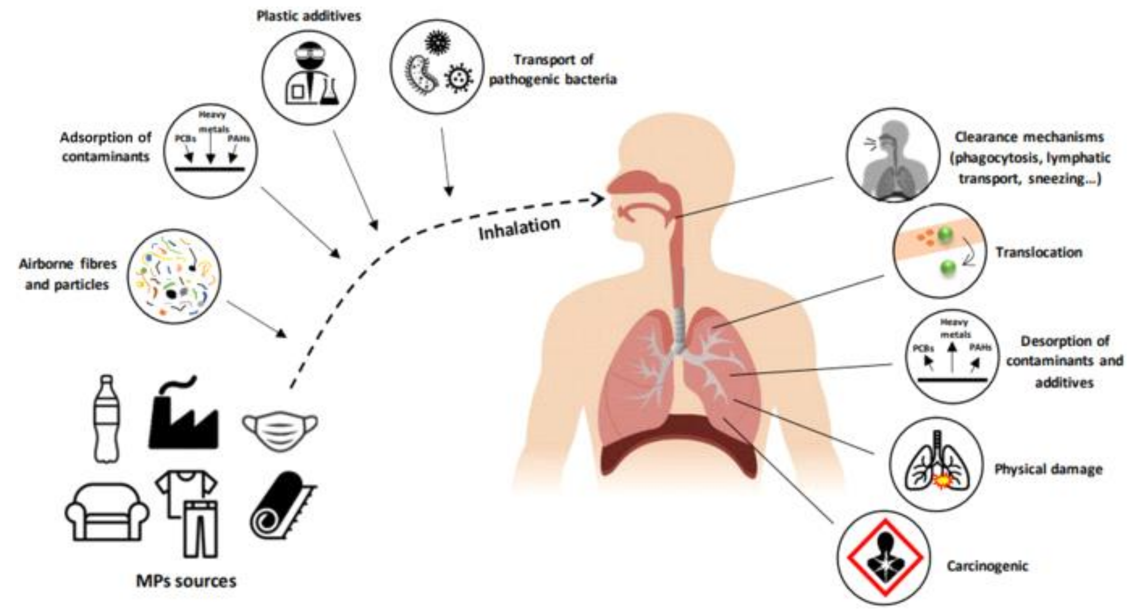

Fig. 10 How could MPs sources encounter human body and cause adverse effects (Torres-Agullo et al., 2021).

In six European nations, Ahrens et al. conducted a comprehensive multi-centre investigation that show a correlation between the risk of extrahepatic biliary tract cancer in men and exposure to EDCs at work: the gathered information indicates that the endocrine disruption has increased because of several MPs derivatives and that exposure to estrogenic endocrine-disrupting substances such as polychlorinated biphenyls (PCBs), bisphenol A (BPA), and alkylphenols increased the incidence of extrahepatic biliary tract cancer, with PCB exposure being statistically significant (Ahrens et al., 2007). The effect of PCBs could be inflammatory stress and change in KRAS for exocrine pancreatic cancer (Lin et al., 2014) and have also been shown in multiple investigations to cause hepatic lesions (Ludewig et al., 2012). Donato et al. in 2021 performed an analysis on patients with hepatocarcinoma who had large levels of PCB in their serum before receiving the diagnosis. The study's findings supported prior liver involvement from HBV, HCV, and alcohol intake, but PCB involvement may have had a role in the possible development of hepatocarcinoma in heavily industrialized areas (Donato et al., 2021).Since it has been linked in multiple studies to obesity, heart disease, reproductive disorders, and breast cancer (Cingotti et al., 2019), BPA has received more attention regarding human safety. BPA can migrate and store in different tissues, bringing the concept of bioaccumulation (Segovia-Mendoza et al., 2022). Also the EU General Court affirmed that BPA is a "substance of serious concern" due to its ability to disrupt human hormones. Women with polycystic ovary syndrome (PCOS) have greater levels of BPA in their bodily fluids, and this substance may have a role in the etiology of hyperandrogenism and hyperinsulinemia. It appears that a mother's prenatal exposure to BPA may also contribute to the development of PCOS in her female offspring (Rutkowska et al., 2014). High levels of heavy metals harm cells and tissues, which can result in a few negative consequences and illnesses. The toxicity is contingent upon a multitude of circumstances, including chemical species, dosage, the way the subject is exposed, age, sex, genetics features and nutritional status (Cima et al., 2011). As, Cd, Cr, Pb and Cu in additives are categorized as "known" or "probable" human carcinogens by the US Environmental Protection Agency and the International Agency for Research on Cancer based on evidence from epidemiological and experimental studies that have shown a correlation between exposure to those elements and cancer incidence on humans and animals (Tchounwou et al., 2012). Additionally, because they can imitate estrogen activation, also Al, Sb, Ba, Cr, Co, Hg, Ni, Se, Sn are classified as metal–estrogens and regarded as hazardous maybe connected to breast cancer (Byrne et al., 2013).

The complete health hazards associated with MPs for humans are yet unknown, and further research is needed to understand the underlying mechanisms, for example there is an urgent need to develop more sophisticated methods for precisely measuring the rates of MPs uptake, distribution and eventually removal in people (Wu et al., 2022). The reduction of MPs encountering human body also requires virtuous global policies to manage the plastic waste according to the circular economy.

Linear or circular economy?

Transition global calls

The worldwide quest to achieve all 17 Sustainable Development Goals (SDGs) between 2015 and 2030 is bringing about several changes in all facets of the economy and society. Achieving several SDGs, including SDG 12 on responsible consumption and production, will be made easier by the shift from a linear to a circular economy (Fig. 11) (WHO EURO, 2019).

Fig. 11 Sustainable Development Goals (https://ubqmaterials.com/blog-post/what-are-the-17-sustainable-development-goals-sdgs/)

Even though it is nearly impossible to think of another substance that can supply plastic benefit, since numerous researchers have reported this kind of pollution and maybe consequences on human health, numerous strategies have been presented for recovering and recycling plastic garbage (Cruz et al., 2023). In fact, complete degradation of plastic requires engineering solutions because natural degradation can take between 500 and

1000 years to deteriorate if disposed improperly (Alhazmi et al., 2021)and is an incredibly sluggish process that can release tiny bits of MPs and NPs. According to European Commission, making the shift to a more circular plastic economy is thought to be essential to slowing this phenomenon (European Commission, 2018).

The foundation of the circular economy is the idea that materials should not flow continuously linearly from production, through consumption, to end-of-life, but rather should loop back into the value chain. Nevertheless, according to the Organization for Economic Co-operation and Development (OCSE) data the conventional lifespan of most plastic materials is linear, with 79% of all plastic manufactured ending up in landfills or environment, while the remaining portion is recycled (9%) or burned (12%). Recycling has grown since the 1980s; in 1988 it has been established the Council for solid waste solutionsSociety to face and solve materials disposal. Plastic was therefore catalogued into seven categories, based on the material of which they are made.

Although the most common type of recycling is mechanical, not all garbage can be recycled mechanically because it may has been polluted during disposal or it may has been mixed with other substances (Rosenboom et al., 2022). This is where methods like chemical recycling could come into play (Klemencová et al., 2020) including hydrocracking, gasification, pyrolysis, and depolymerization (Grigore, 2017). Another end-of-life (EOL) option is biodegradation: bacteria and fungi utilize plastic elements as the sole carbon and energy source. Ideonella Sakaiensis PETase, for example, is used for easily hydrolysable polymers like PET into its monomeric building blocks (Sevilla et al., 2023). However, biodegradation should only be carried out in controlled industrial settings to guarantee complete digestion without uncontrollably occurring side effects like MPs formation or contaminant leakage (Rosenboom et al., 2022).

Bioplastic

Plastic matter could be defined bioplastic when biobased, derived entirely or partially from plant sources (corn, tapioca, potatoes, sugar cane, cut grass clippings, vegetable oils, algae, cellulose, and organic waste):contrary to popular belief, is not always biodegradable. Polylactic acid (PLA) is a non-biodegradable bioplastic, well-known material derived from corn cobs: sugar is taken from starch which, through fermentation, produces lactic acid and then, through a polymerization process, is changed into polyester. In contrast, fossil but biodegradable plastics are medical suture resorbable stitches: formed of polycaprolactone (PCL) or polyglycolic acid (PGA), highly biodegradable plastic polymers that microbe's breakdown in a couple of weeks without leaving any residue.

To achieve the climate neutrality action goal by 2050, the European Green Deal aims to make the EU a competitive, resource-efficient, modern economy by the middle of the century, with no net emissions of greenhouse gases: the primary objective is to use the substantial potential in global markets for sustainable products and services, as well as low-emission technologies (https://assets.kpmg.com/content/dam/kpmg/be/pdf/2023/From-Linear-to-Circular-Sustainability-in-the-Medical-Device-Industry.pdf). The manufacture of plant-based bioplastics arouses a lot of interest since generates fewer greenhouse gases than petrochemical plastics. Italy produces two-thirds of all biodegradable bioplastics in Europe. Non-biodegradable bioplastics account for over half of the total and bioplastics for only

0.5% of the 400 million tons of plastic produced each year. Traditional plastic, on the other hand, has advantageous properties such as resistance, gas barrier effect for food preservation, and pricing.

Another critical consideration in a model circular economy with little environmental impact, is whether it is compostable. When compostable, a plastic object develops into natural fertilizer after three months if supplied to industrial composting sites, under optimal conditions including the presence of oxygen and bacteria, a temperature of 60 degrees Celsius, and a 40% humidity. On the other hand, a test conducted by the University of Padua's laboratory revealed that the bioplastic granules abandoned in the environment degrade slowly and partially. For example, PLA is a heavy polymer and tends to sink away from UV light, which would contribute to photodegradation. Bioplastics, if not properly separated, can pollute just as much as conventional plastics (Cipolloni et al., 2023).

"3R" hierarchy

In order to reduce plastic waste and its negative effects on the environment, circular economy technologies and concepts must be implemented at every stage of the plastic supply chain, including design, production, use, and EOL (Syberg et al., 2022): this concept can be reassumed in "3 R" hierarchy: reduce, reuse, recycle (Fig. 12).

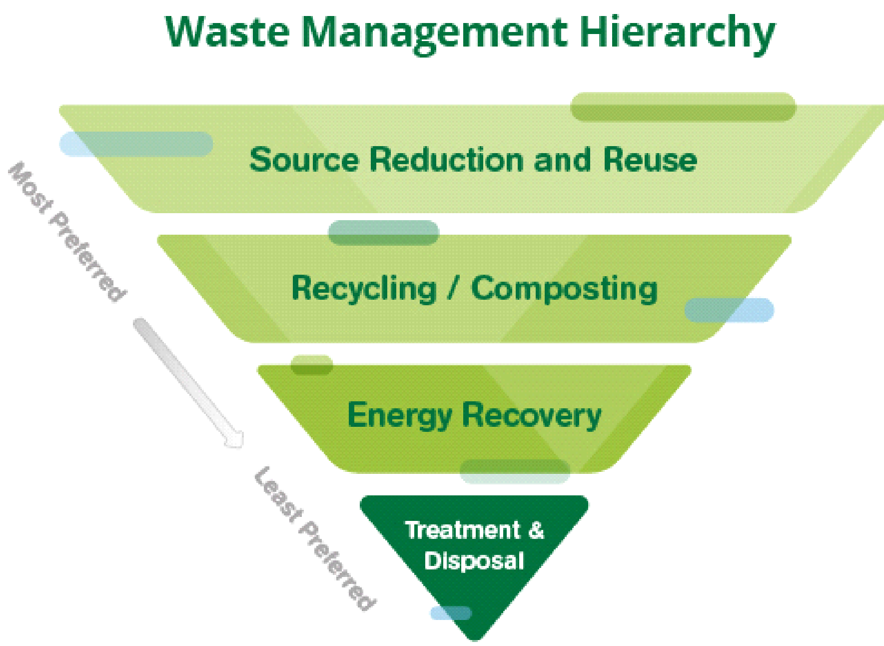

Fig. 12 Circular economy (https://fresh-lock.com/blog/flexible-packaging-circular-economy).

Due to overpackaging, 40% of global plastic production is disposable. That is why reduction is at the base of the pyramid in a circular waste management strategy.

Reducing MPs can therefore be achieved by decreasing the wear and fragmentation of these items during their life cycle, since these processes are usually the cause of MPs release. Thus, it's crucial to take some factors into account to prevent conflicts between the goal of promoting the circular transition and the initiatives to lessen the contamination. In 2017 the European Commission asked to the European Chemicals Agency (ECHA) to evaluate the scientific evidence for acting on MPs intentionally added to products to prevent the release of 500000 tones of MPs over 20 years. Many options for reducing the releases of unintentionally formed MPs are being considered as part of Plastics Strategy and the new circular economy action plan. For example, there is a new proposal in packaging regulation that askes to reduce the amount of this kind of waste in a percentage of 15% before 2040 or the last adopted restriction started on September 2023, the ban on loose glitter and microbeads (https://echa.europa.eu). Prioritizing durability over single-use items and designing with the possibility of recycling in mind should be the first goal of future research and development in product design and the use of new polymers, delaying their disposal. Additionally, the future generation of polymers must have far lower environmental turn-over durations than current polymers. Thirdly and finally, recycling is important since it is not possible to dispose of waste in a sustainable manner. Measures have been taken to guarantee that recycling items made of plastic does not lead to a rise in the MPs amount that are released into the environment. Such recycling operations ought to fall within the broader producer responsibility umbrella (Syberg et al., 2022). The cost-competitiveness of long-standing plastic industry processes and linear business models means that putting these measures into action would require not just technology advancement, but also financial incentives provided by lawmakers and economic investment. The estimated $55 billion in annual global earnings from chemical recycling makes the financial outlay well worth it (Rosenboom et al., 2022).

Sustainability in medical device industry: the goal of the green dialysis

The EU's Medical Device Regulation and the need to trace a device through its whole lifecycle, including disposal, have changed over time. Single-use disposable (SUD) devices are sterile, which lowers costs and guarantees that operations always have access to ready-to-use supplies at a minimal risk of infection. After use, these devices are frequently incinerated and released harmful greenhouse gases.

Each medical device is different and there is not a "one-size-fits-all" approach to enhance sustainability, but producers may consider some universal factors according to KPMG.

- use a bio-based plastic, stainless steel or glass and utilize fewer distinct materials to make it simpler to recycle;
- make the product lighter or smaller to reduce the carbon emissions associated with distribution;
- use less water and energy;
- reduce waste and making packaging materials compostable or recyclable;
- select production and warehouse sites to reduce the need for long-distance transportation;
- convert a one-time use gadget to a reusable one and question if it is possible to send it back to the manufacturer for repair.

The SUD device industry gave rise to strategies like reprocessing of discarded devices, which give hospitals an option instead of burning valuable materials. Reprocessing is the act of preparing a used device for safe reuse, as defined by the Medical Device Regulation (EU) 2017/745. It includes testing and restoring the device's technical and functional safety, as well as cleaning, disinfecting and sterilizing. A reprocessing example in medical devices is the PenCycle initiative, which Novo Nordisk introduced in the UK in 2021 and deals with insulin for diabetics. Patients who use pre-filled insulin administration devices can return them for recycling to local community pharmacies or prepaid royal mailboxes. The pen is shipped to the Novo Nordisk headquarters in Denmark, where plastic is recycled and used to make a variety of products, including lightbulbs and chairs(https://assets.kpmg.com/content/dam/kpmg/be/pdf/2023/From-Linear-to-Circular-Sustainability-in-the-Medical-Device-Industry.pdf). Unfortunately, this kind of virtous disposal cannot be applied in Italy since the continued use of single-use devices is only allowed on Member State territory if approved by national law. Legislative Decree 137/2022published in the Official Gazette aim to ensure compliance with the provisions of Regulations (EU) 2017/745 and 2017/746, does not permit the reprocessing of single-use devices and the subsequent usage (https://www.salute.gov.it/).

The dialysis industry is one of the resource-intensive industries with a higher average carbon footprint than the other healthcare sectors. It generates between 1.5 and 8 kg of waste per treatment. Dialysis-related disposable waste is divided into contaminated (which were in contact with biological fluids) and non-contaminated, the larger part made of plastic and include tubing and filters. Numerous other elements of the hemodyalisis (HD) treatment contribute to this resource use: the supplies needed for each therapy, such as bloodlines, concentrates, syringes, needles, and dialyzers and also non-treatment factors like patient travel, goods transportation, water for purification systems to produce dialysis fluid, and energy to heat the dialysis fluid and run the dialysis machine (Gauly et al., 2022). In addition to ecological considerations, due to the dispose of potentially dangerous or contaminated garbage, waste management has a significant financial impact (Vaccari et al, 2018). Hazardous or contaminated trash needs to be sterilized or burned before being disposed in a landfill. In Italy, waste management is regulated by D.P.R. 254/03 and D. Lgs 152/2006, applying the legislation of the Waste Management Act which defines the different types of hospital and medical waste and rules the transportation and final disposal. Although "the 3R" are becoming more widely known, there are still few good examples, especially in the field of nephrology (Bistulfi 2013). Recently, the fourth R—repair—was added, demonstrating the rising recognition of the significance of eschewing a disposable mindset (fig. 13).

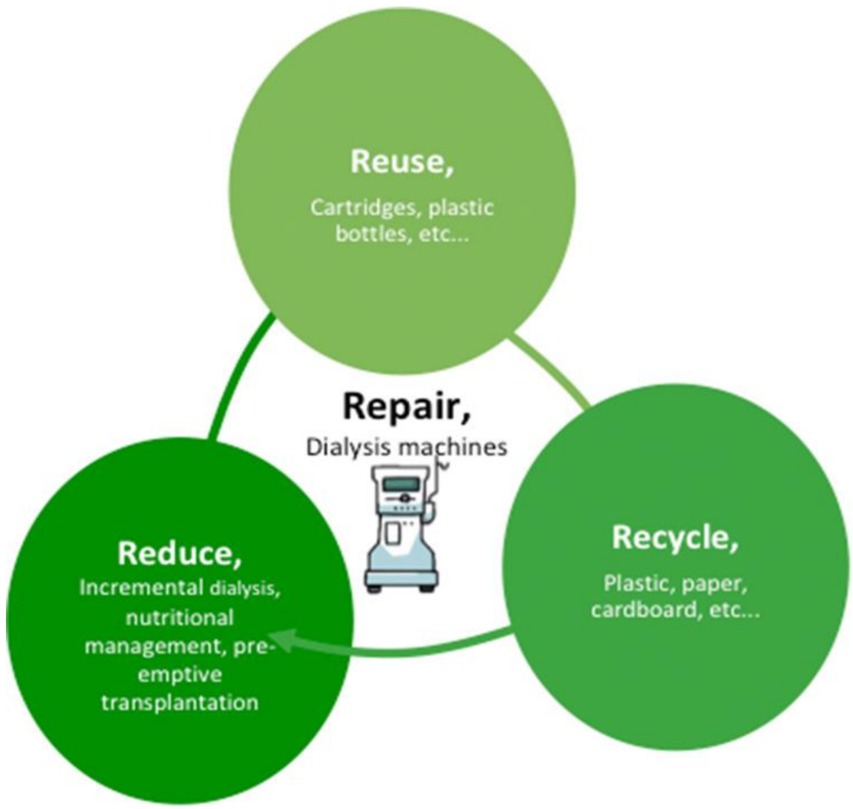

Fig. 13 Repair, the fourth R—repair— of circular economy strategy in Dialysis machines disposal.

The first concern "reducing" can be addressed on many fronts: fewer patients initiating dialysis through prudent use of conservative and nutritional treatment; fewer water wastes through dialysate flow tailored to individual needs; fewer contaminated wastes through meticulous triage of dialysis waste products. With collaboration between doctors and manufacturers, other factors like lessening the impact of packaging or optimizing some dialysis components might become viable.

"Reuse" is frequently associated with negative connotations in medicine. Bicarbonate cartridges are one example of a dialysis disposable that has a lot of potential for reuse as long as it is not in touch with blood. The practice has been outlawed in Italy likely due in part to the increased risk of infection that is frequently reported. Also, most indicators of "biocompatibility" are indirect, such as pre-dialysis beta2-microglobulin level, and because dialysis is a common field, it is challenging to separate the impact on mortality from that of the overall patient care, of which reuse may be a reflection (Argyropoulos et al, 2015). "Recycling" is another topic frequently disregarded. While certain non-contaminated plastic products may be recycled, this seldom happens and even if it occurs, it is outside of the control of dialysis facilities without specific initiatives.

Waste that is "not recyclable" or maybe polluted might change at a high temperature—this frequently involves the extracorporeal system in HD. It would be ideal to replace PVC with polymers devoid of chlorine to reduce the production of dioxins and furans during combustion, which are produced at inadequately high temperatures (James, 2010). Furthermore, because plasticizers integrated into PVC polymers may pose health hazards and migrate depending on the type of plasticizer, patients receiving dialysis should not use medical devices containing PVC for an extended period (Hoenich et al., 2005). PVC can be substituted with polyolefins, which are chlorine-free polymers. This polymer may lessen the environmental impact of medical waste as well as patient exposure to PVC and plasticizers (Mettang et al., 2000).

Another issue that stands in stark contrast to the current mindset is "repair" which greatly adds to the amount of electronic waste (e-waste) generated: a dialysis machine should be able to be broken down into its constituent parts such as plastic or metal and each of those parts should be able to be reused without losing its original "value" (Piccoli, 2015).

The chemist Antoine Lavoisier is credited with the law of conservation of mass, which states that "nothing is lost, nothing is created, everything is transformed." This law is related to the theory that "in everything there is a share of everything" put forth by the philosopher Anaxagoras. This theory is frequently cited as the foundation for the circular economy concept, which maintains that a different approach is feasible and can benefit both the planet and the end-users (Fig. 14) (Stahel, 2016).

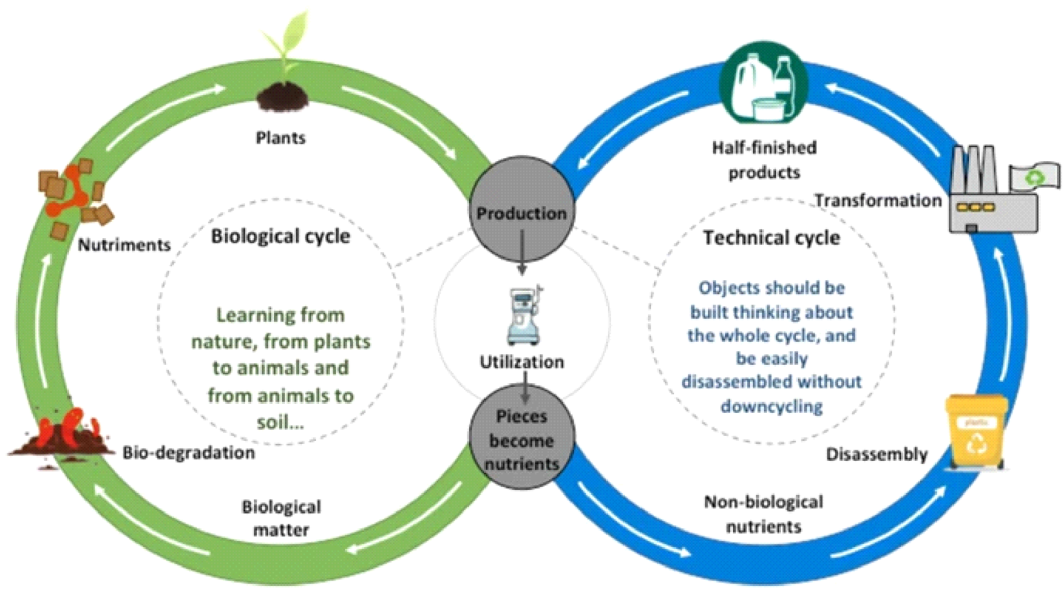

Fig. 14 The circular model: organic waste nourishing plants continuously recycled in the biosphere. This should happen also to technical waste that could nourish the technical cycle (Piccoli et al., 2020).

Green dialysis is a comprehensive strategy that supports the community and enhances patient care (Gauly et al., 2022). The position statement that addresses waste management and reducing the dialysis carbon footprint, regards technology (water and energy efficiency, waste control, and industrial design) and clinical practice(dietary management, physical activity and selecting renal replacement medication). Also, a workable way to increase awareness and emphasize the need for cooperation would be to systematically adopt a checklist for comparing information on the various steps involved in the machines production and disposables. The list can consist of: information about the origins of the parts in dialysis machines, the recyclability and reusability of all or part of the materials, data on packaging (paper, plastic, printed matter, labels, production sites), detailed information on the components of non-contaminated materials (recyclable, non-recyclable, partially recyclable), inquiries about hidden substances in disposables (not disclosed in tiny amounts); assistance from the sector in locating machines and disposables recycling facilities (Piccoli et al., 2020).

Microplastics in blood

Human body weight is composed of 6–7% blood compartments and serves as a channel for the movement of nutrients but it is also a harmful particles carriers to various tissues and organs. In 2022, 22 volunteers participated at the Dutch experiment that looked for the presence of MPs in the blood: 17 tested resulted positive. The polymer that has been most frequently found is PET, followed by PS, PE and PMMA, in amounts of about 1.6 micrograms per ml of blood (Leslie et al., 2022). As said before, the uptake of plastic particles in human bloodstream occurs via mucosal contact (either ingestion or inhalation). The MPs detection in human samples in healthy volunteers has stimulated research in correlating the presence of MPs with diseases or in specific clinical settings. Even if more research is needed, blood could be an appropriate matrix for human biomonitoring of MPs and to address concerns about potential accumulation among occupationally exposed workers, environmental factors that contribute to internal exposure, and potential toxicological and health effects on humans that may arise from various exposure scenarios (Vethaak, 2021).

Chronic kidney disease and dialysis

Chronic kidney disease (CKD) can be described as kidney damage (referred to pathologic abnormalities suggested by imaging studies or renal biopsy, abnormalities in urinary sediment, or increased urinary albumin excretion rates). Another definition is the glomerular filtration rate (eGFR) reduction less than 60 ml/min/1.73 mt2, for 3 o more months (Kidney Int Suppl., 2011). This results in renal replacement therapy to remove excess water, solutes and toxins and ensuring homeostasis maintenance. The general population CKD prevalence is around 10% to 14% (Coresh et al., 2003). Worldwide, CKD accounted for 1% of disability-adjusted life-years. The 2012 KDIGO (Kidney Disease: Improving Global Outcomes) CKD classification suggests specifics about the causes and classifies into groups based on glomerular filtration rate including the staging on urinary albumin-creatinine ratio in an early morning "spot" urine sample (Inker et al., 2014).The most common primary diseases causing CKD and ultimately end-stage renal disease (ESRD) are diabetes mellitus (30%-50%), hypertension (27.2%), glomerulonephritis (8.2%), chronic tubulointerstitial nephritis (3.6%), cystic diseases (3.1%), vasculitis (2.1%), plasma cell dyscrasias or neoplasm (2.1%) (Webster A.C et al., 2017).

The processes that cause CKD might be prerenal (lower renal perfusion pressure), intrinsic renal (vessel, glomerular, or tubule-interstitium pathology), or postrenal (obstructive). Patients with chronic prerenal illness may have heart failure or cirrhosis with a consistently reduction of renal perfusion and are at a higher risk of experiencing numerous episodes of intrinsic kidney injury, such as acute tubular necrosis (ATN).

Nephrosclerosis is the most prevalent chronic renal vascular disease which causes blood damage to arteries, glomeruli, and tubulo-interstitium. Also, renal artery stenosis from atherosclerosis or fibromuscular dysplasia can cause ischemic nephropathy, glomerulosclerosis and tubulointerstitial fibrosis (Textor, 2004). Nephritic pattern is characterized by abnormal urine microscopy with red blood cell casts, dysmorphic red cells and variable proteinuria (Kitamoto et al., 1993). Post-streptococcal GN, infective endocarditis, shunt nephritis, IgA nephropathy, lupus nephritis, Goodpasture syndrome, and vasculitisare the most common causes (Khanna et al., 2011). Nephrotic pattern is associated with proteinuria, commonly caused by focal segmental glomerulosclerosis, membranous GN, membranoproliferative GN, diabetic nephropathy, amyloidosis. The most common chronic tubulointerstitial disease is polycystic kidney disease; nephrocalcinosis (due to hypercalcemia and hypercalciuria), sarcoidosis, Sjogren syndrome and reflux nephropathy are next (Aeddula and Baradhi, 2023). Chronic obstruction causes postrenal nephropathy that may be due to prostatic disease, nephrolithiasis, retroperitoneal fibrosis or abdominal/pelvic tumor with mass ureter effect.

Treatment includes adjusting drug doses for the eGFR level, placing an arteriovenous fistula or graft to preparation of renal replacement therapy, correct potential causes of acute kidney injury like infections, drugs that reduce the GFR, hypovolemia. Also establishing blood pressure and proteinuria goal, smoking cessation (Hallan et al., 2011) bicarbonate supplementation (De Brito-Ashurst et al., 2009) and protein restriction should be met to slow CKD progression. Options for renal replacement therapy are HD (home or in-centre) performed after stable vascular access, peritoneal dialysis (PD) (continuous or intermittent) performed after placing a peritoneal catheter and kidney transplantation.

Indications for renal replacement therapy is urgent for pericarditis or pleuritis, progressive uremic encephalopathy or neuropathy, bleeding diathesis attributable to uremia. Other renal replacement indications are hypertension, fluid overload and metabolic disorders poorly responsive to medications, persistent nausea and vomiting, malnutrition. The patients affected by CKD that become eligible to be listed for donor renal transplant program have eGFR < 20 ml/min/1.73m2. Conservative ESRD therapy is also an option for all patients who decide not to pursue renal replacement therapy and includes the management of symptoms.

HD is the most common used dialysis type. Its apparatus includes a blood circuit, a dialysate solution circuit and a dialyzer composed by a semipermeable membrane that bridges them (fig. 15) (Murdeshwar et al., 2023). Dialysate consists of highly purified water with sodium, potassium, magnesium, calcium, bicarbonate, chloride, and dextrose: it flows to the dialyzer and then to the blood while toxins, urea and other small particles (larger one, such as proteins and blood cells, cannot pass through the small pores of the membrane) move away from the blood. Solutes moves to the lowest concentration (diffusive clearance) and though water osmotic force that pushes through the membrane (convective clearance). “Countercurrent” flow maximizes the concentration difference of waste products between blood and dialysate. The gradient is maintained by continuously refilling fresh dialysis solution in the dialyzer and replacing dialysed with undialysed blood.

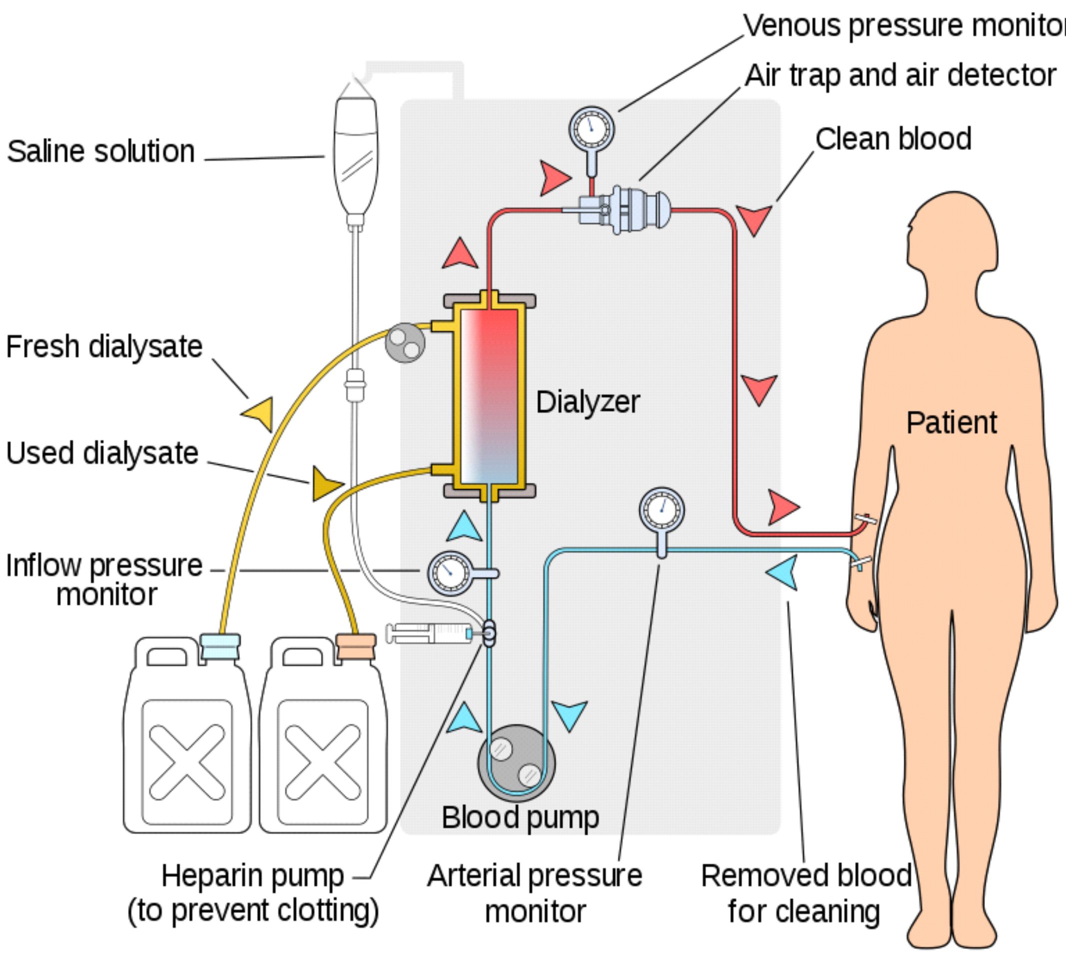

Fig. 15 Hemodialysis (https://it.wikipedia.org/wiki/Emodialisi)

The dialyzer is composed by an artificial filter containing capillary hollow fibers with microscopic pores in the wall and compose the semipermeable membrane. Regenerated cellulose, with its strongly hydrophilic nature, enables miniaturization of the dialyzer with lower membrane thickness. Biocompatible synthetic membranes made of polysulfone provide a semi-permeable interface with lower complement cascade activation compared to the older bio-incompatible ones. Other materials commonly used are PP, PE, PC, PL, polyethersulfone (PES), polysulfone (PSU) (https://www.medicalexpo.it/fabbricantemedico/filtro-dialisi).

Major Depressive Disorder

Major Depressive Disorder (MDD) could be diagnosed in presence of "persistently low or depressed mood, anhedonia or decreased interest in pleasurable activities, feelings of guilt or worthlessness, lack of energy, poor concentration, appetite changes, psychomotor retardation or agitation, sleep disturbances or suicidal thoughts". According to the Diagnostic and Statistical Manual of Mental Disorders, to define the diagnosis must occur five of the mentioned symptoms causing social or occupational impairment. Biological, genetic, environmental and psychosocial factors are included in the etiology as a multifactorial scenario. Depressive patients have been found to have lower anterior brain metabolism on the left side and elevated hyperintensities in the subcortical areas on brain imaging, abnormalities in neurotransmitters such serotonin, norepinephrine and dopamine, lower plasma, cerebrospinal fluid and GABA levels. Also, thyroid and growth hormonal abnormalities could be implicated. Multiple emotional traumas can cause structural changes in the cerebral cortex, leading to severe depression later in life (Vogelzangs et al., 2012; Pochigaeva et al., 2017). According to the cognitive theory, MDD occurs because of cognitive distortions in persons who are susceptible to.MDD is also associated with shorter telomere length (TL), a biomarker of cellular aging (Malouffand Schutte, 2017): due to adverse life experiences,shorter TL triggercellular senescence, differentiation, and/or apoptosis(Cesare and Redder,2010).
MDD is a highly prevalent psychiatric disorder, and the incidence has recently been

increased at a worldwide level. It has a prevalence of 12%, double in women (De Villiers et al., 1989). WHO rated MDD as the third cause of the global disease burden in 2008 and predicts that it will rise to the top by 2030 (National Institutes of Health, 2007). Recent surveys show increasing incidence in younger population due to alcohol or drugs abuse. It is found to be more prevalent in rural than in urban areas. No difference instead has been found among races or socioeconomic status. Environmental pollutants - industrial compounds, fungicides, pesticides, plastics and plasticizers - are considered as a crucial etiologic factor (England et al., 2009). Public concern has emerged about the EDCs effect on neural and neuropsychiatric disorders through the dysregulation of hypothalamic-pituitary-gonadal adrenal axis (Liu et al. 2016) includingattentiondeficit/hyperactivitydisorder,autismspectrumdisorder and MDD (Shoaff et al., 2020; De Cock et al., 2012). Exposure to plasticizers like bisphenols and phthalates, during neonatal period, may be linked to an increased risk of developing MDD (Segovia-Mendoza et al., 2020) due to the impairment of methylation profile in the brain (Kajta and Wojtowicz, 2013). BPA and phthalates have also been associated with a polarization oftheTh2response (Nava-Castro, 2020; Hansen, 2015) and theprevalenceoftheTh2responseis associated with the presence of MDD (Pavon et al., 2006). In a study in Mexico, it has been quantified through a gas chromatograph-mass spectrometer the serum levels of two bisphenols (BPA and BPS) and four phthalates like DEHP, DBP, butylbenzylphthalate (BBP), and di-ethyl-phthalate (DEP): results showed increasing BBP levels in MDD patients much higher in women (~500 ng/mL) than in men (≤10 ng/mL) possibly due to cosmetics and medication use, considering that phthalates are utilized in the capsules manufacture or drug packaging (Segovia-Mendoza M. et al., 2022). BBP lipophilic characteristics could favor the migration and storage to the central nervous system level, and this could be an explanation of MDD (Dominguez-Romero et al., 2019).

MATERIALS AND METHODS

Samples collection

Funded through the University Inventive Plan for Research 2020/2022, the protocol of MPs extraction has been drawn up in accordance with the standard of EU Good Clinical Practice and according to the Declaration of Helsinki, it has been approved by the Independent Ethics Committee of the Hospital University "Policlinico-San Marco" (ex Policlinico – Vittorio Emanuele) in Catania.

Ten patients suffering from CKD, undergoing HD treatment within 6 months, belonging to the nephrology department of the University Hospital Policlinico-San Marco and ten patients suffering from MDD, referred to the psychiatric department at the same hospital, were recruited at the hygiene operating unit. The inclusion criteria were represented by these diseases, therefore all patients not affected were excluded. In addition, 10 health volunteers controls(CTRLs) were considered.

After giving a information questionnaire and explain the research aim, all subjects involved gave their informed consent in accordance with the rules for the protection of individuals and respect to the processing of personal data – Regulation (EU) No 679/2016. Blood samples were taken by peripheral venous catheterization and collected in three sterile of 3 ml glass tubes for each patient, transported in ice containers to the environmental and food hygiene laboratory and then stored in freezer at -80 degrees until extraction occurred.

Microplastics extraction

Samples preparation for microscopic analysis involves the MPs extraction from the blood. The protocol used for extraction is called "Method for extraction and determination of microplastics in samples with organic and inorganic matrices": developed in 2019 by Ferrante et al. at the Environmental and Food Hygiene Laboratories of the Department of Medical, Surgical Sciences and Advanced Technologies “G.F. Ingrassia” (Hygiene and Public Health, University of Catania) it is protected on a national and international level. The approach of this investigation is based on the sedimentation of particles with densities greater than 1 g/cm3 and can be applied to both biological (tissues, blood, urine, etc.) and inorganic samples (food, water, soil, waste, and air).
After the acid digestion of the sample matrix, MPs are separated by sedimentation in dichloromethane (CH_2Cl_2) and then dispersed among metallic stubs in preparation for microscopic analysis.
Nitrile gloves and a horizontal laminar flow cabinet are required to lessen the chance of ambient dust contaminating samples. Additionally, no inorganic carbon-based plastic goods or components are used: all the operations materials are limited to glass containers cleaned twice with ultrapure water. Each reagent used during the analysis is filtered with glass filters of the size of 0.22 μm by a ultra-vacuum pump (Ferrante et al., 2020).

To our MPs extraction from blood samples aliquots of 0.5 grams are placed in a 40 mL vials. Degradation of organic matter are performed by acid digestion: after adding 65% nitric acid and hydrogen peroxide 30%, the samples undergo an incubation process at 60 Celsius degrees for 24 hours in a digestion system (Fig. 16).

Fig. 16. Vials in the digestion system

After digestion, CH2Cl2 and ultrapure water are added to each sample. CH2Cl2 is a non-polar solvent with a symmetrical molecular structure that retains organic substances like plastic (Fig 17).

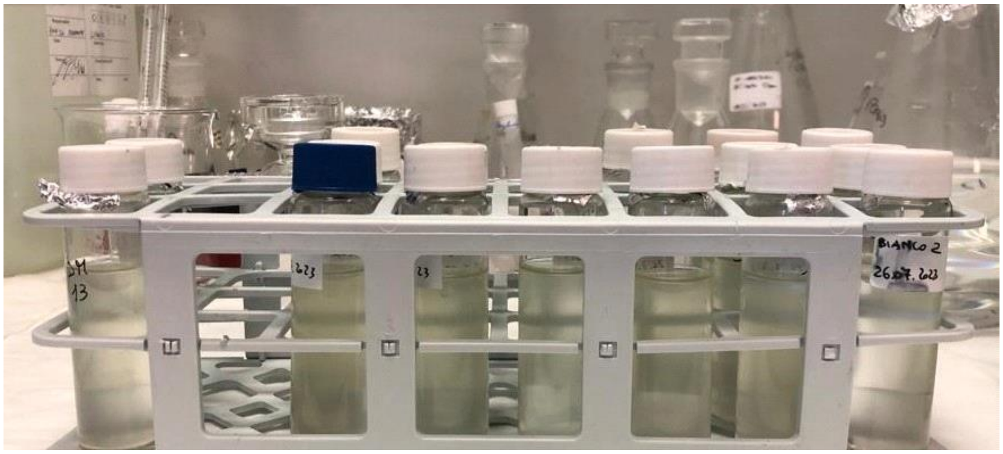

Fig 17. Vials containing digested human blood, ultrapure water and CH2Cl2.

The samples are vortexed and centrifuged for 4 minutes at 3500 rpm. After centrifugation, CH2Cl2 is placed in a glass tube and evaporates to a volume of 3 ml. The residual solvent containing the MPs extracted is distributed on a copper aluminium stub that has a 25 mm diameter. Subsequently, each stub is coated with gold using the metallizer becoming ready to SEM analysis (Fig. 18, Fig. 19).

Fig. 18 Stubs Metallizer

Fig. 19 Metallized stubs containing blood samples at the end of the extraction.

SEM Analysis

The samples are analysed by scanning electron microscope(Fig. 20) coupled with an energy dispersion detector (SEM-EDX), which allows to obtain compositional information related to the sample under examination.

Fig. 20 Scanning electron microscope (SEM)

A Tungsten filament emits a concentrated stream of primary electrons directed from a series of electromagnetic lenses. An objective lens, in addition to further refocusing the beam, imposes a controlled deflection to allow the scanning of sample areas. The interaction between the electron and matter is revealed and transformed into an electrical signal which, when treated and amplified, is transformed into a visual signal: 1 pixel of a monochrome monitor is associated with 1 point of the sample, that is as brighter as the more intense is the signal. The final magnification of the image is given by the ratio between the size of the screen on which the image is observed and the actual size of the sample portion on which the beam is scanned: the higher is the magnification, the smaller is the scanned area.

Our SEM-EDX, using a microanalysis software (Aztec), allows to identify number and size of particles. Using a magnification of 1500x, the counting method was used to a 1.0 mm^2 overall reading area within the stub, or 25 fields.

Particle identification is based on the inclusion criteria revealed at the spectrum analysis: presence of elements such as C, Au, Al, Cu, Cl, O, with percentages of carbon greater than 50% (Fig. 21), defined margins and particle sizes <10 μm.

	Wt%	σ
C	80.8	0.2
O	13.7	0.2
Al	5.2	0.0
Cl	0.2	0.0
Cu	0.2	0.0

Fig. 21 Spectrum Aztec analysis of a MP showing elements contained and their percentage

RESULTS

MPs detection in analyses samples

The aim of the study is to estimate environmental MPs exposure in patients blood of two different diseases in order to relate MPs with the pathologies examined. The analysis is performed on blood samples of emodialized patients suffering from CKD, patients affected by MDD and healthy volunteers controls (CTRLs). After extraction and stubs metallization, the samples are detected at the SEM to estimate the concentration of particles <10 μm(Fig. 22, Fig. 23, Fig. 24), the most harmful that could accumulate in human body.

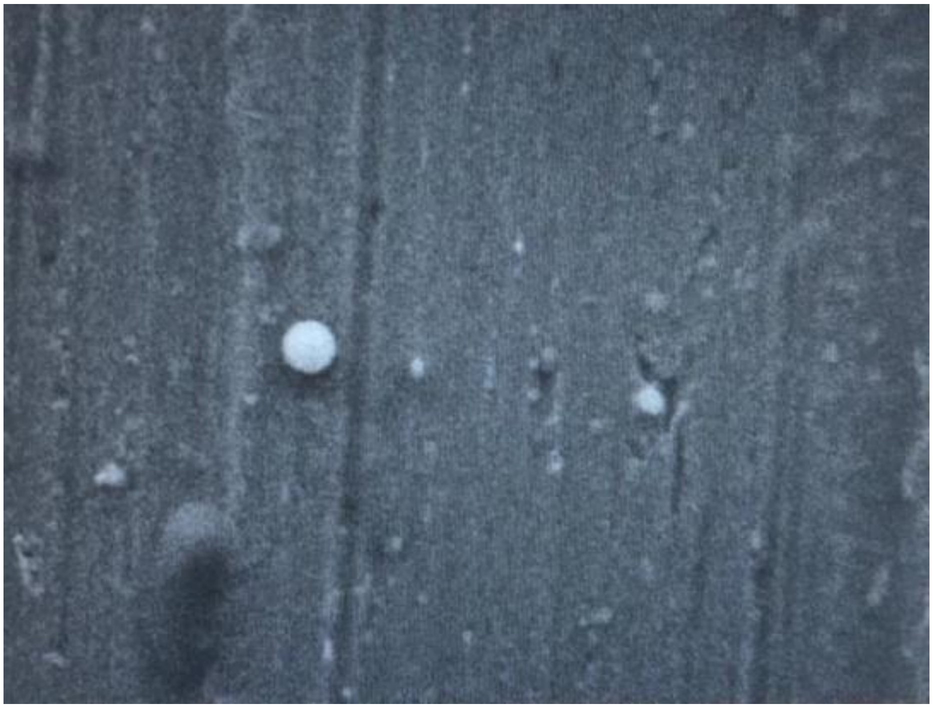

Fig. 22 A spheric MP detected with SEM.

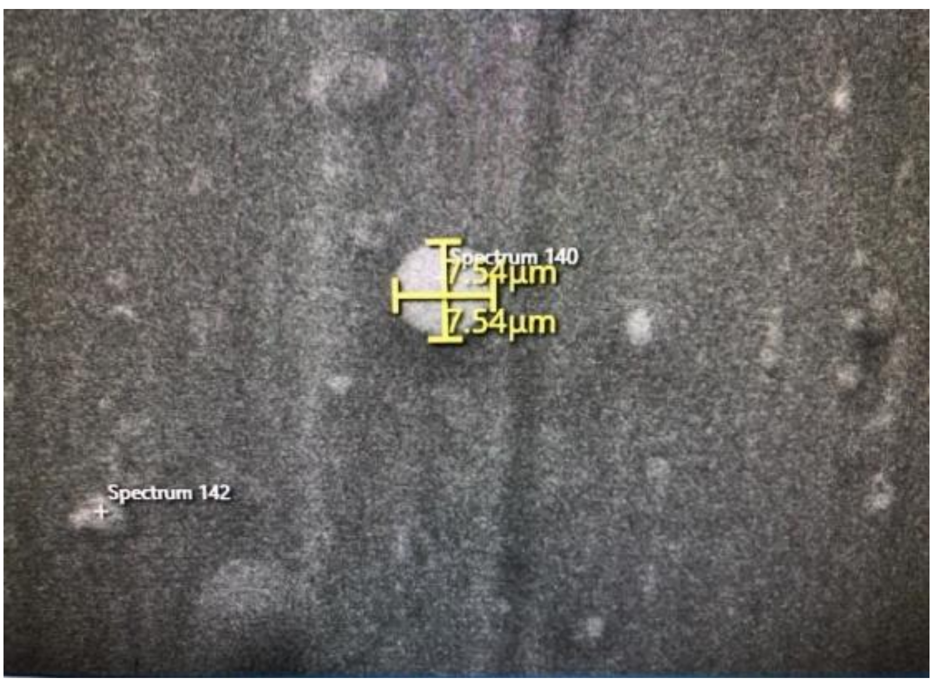

Fig. 23 MP dimensions.

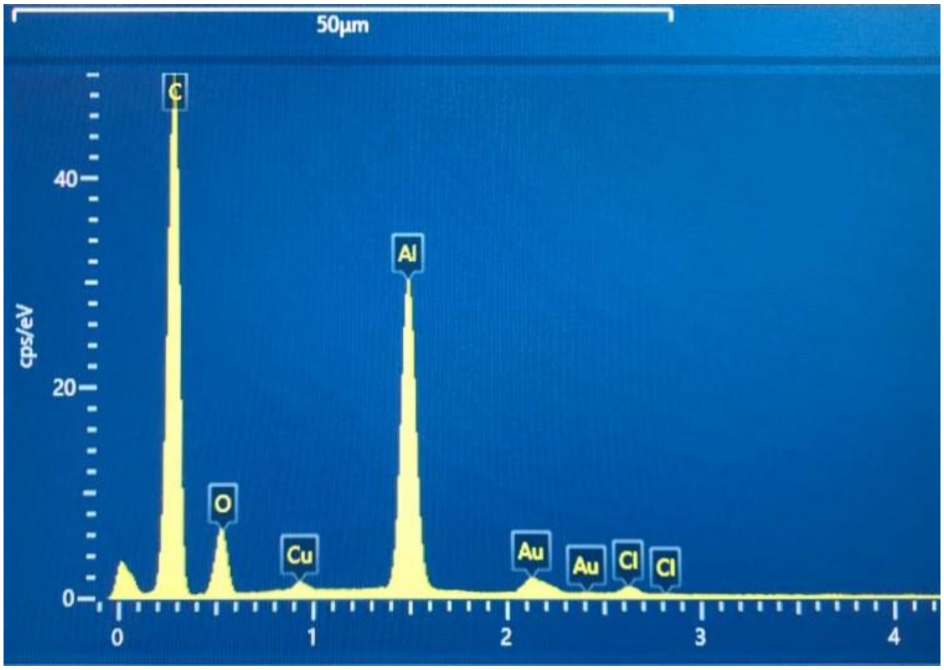

Fig. 24 Particle spectrum analysis. According to carbon percentage detected, the particle is identified as a MP.

MPs concentration

Data on samples are collected and processed. Table 1, 2 and 3 show the MPs concentration values detected by quantitative SEM/EDX analysis with a magnification of 1500x that allows to visualize MPs<10 µm.

CTRLs	CONC.FINALE MPS (p/g)	DIAMETRO MEDIO (µm)
CTRL_P2	0,00	5,60
CTRL_P3	0,00	6,82
CTRL_P5	1665,40	3,94
CTRL_P6	5789,13	3,70
CTRL_P7	2491,55	2,72
CTRL_P9	3309,40	2,50
CTRL_P16	4137,58	3,64
CTRL_P20	2478,57	4,30
CTRL_P23	2502,64	4,44
CTRL_P42	1661,70	5,58

Table 1. Final MPs concentration (p/g) and average diameter of particles detected in blood samples from CTRLs.

CKD	CONC.FINALE MPS (p/g)	DIAMETRO MEDIO (μm)
D6	8196,20	4,52
D8	14636,77	4,88
D9	13396,23	4,38
D10	7479,18	4,14
D11	21246,76	4,14
D12	19257,08	3,76
D13	15846,87	4,28
D14	13119,14	4,28
D15	19777,04	4,66
D16	9132,01	3,34

Table 2. Final MPs concentration (p/g) and average diameter of particles detected in blood samples from CKD patients.

MDD	CONC.FINALE MPS (p/g)	DIAMETRO MEDIO (μm)
DM10	12566,70	4,32
DM11	11062,67	4,84
DM12	12076,56	2,92
DM14	19230,49	3,52
DM15	10921,57	2,82
DM16	10277,94	2,30
DM17	21758,86	3,62
DM21	21968,88	5,06
DM26	14204,97	2,24
DM30	21741,54	4,02

Table 3. Final MPs concentration (p/g) and average diameter of particles detected in blood samples from MDD patients.

The smallest particle discover in healthy volunteers is 2,72μm in diameter and the biggest one has a value ugual to 6,82μm. In dialyzed CDK patients blood samples the smallest MP has a diameter of 3,34 μm and the greatest has number ugual to 4,88 μm. The smallest MP identified in MDD patients blood samples has a diameter of 2,24 μm and the biggest a number of 5,06 μm.

As shown in histograms below the lowest MPs concentration detected in blood samples from healthy volunteers, deprived of "white" analisys control, is 0p/g while the highest concentration is 5789,13 p/g (Fig. 24).

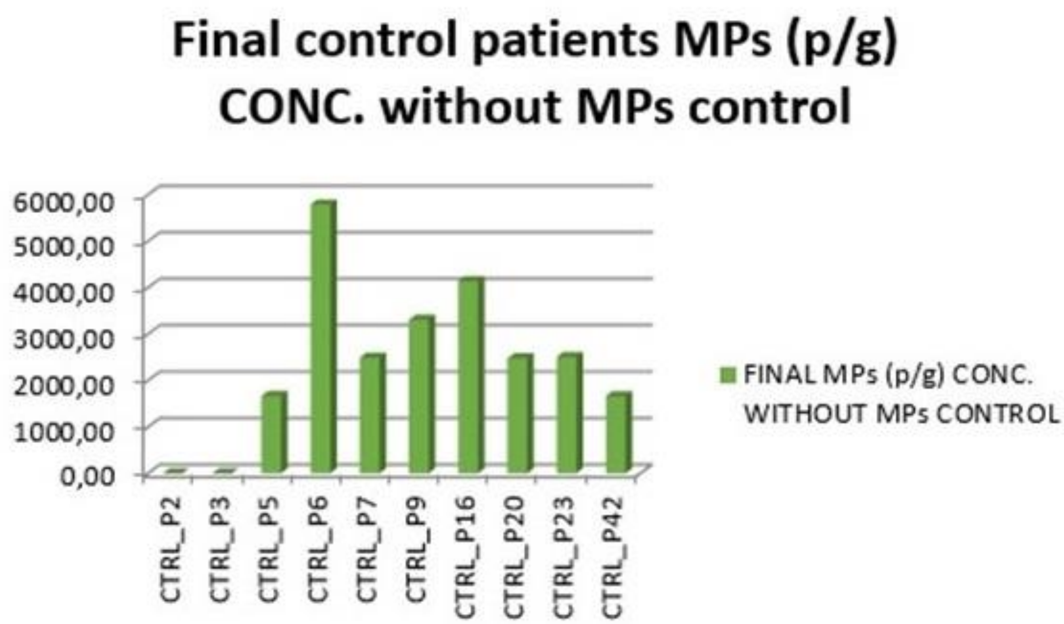

Fig. 24 Histogram showing MPs concentrations detected in individual samples of healthy volunteers.

The lowest MPs concentration, deprived of “white” analisys control, detected in dialyzed CKD patients blood samples is 7479,18 p/g while the highest concentration is 21246,76 p/g (Fig. 25).

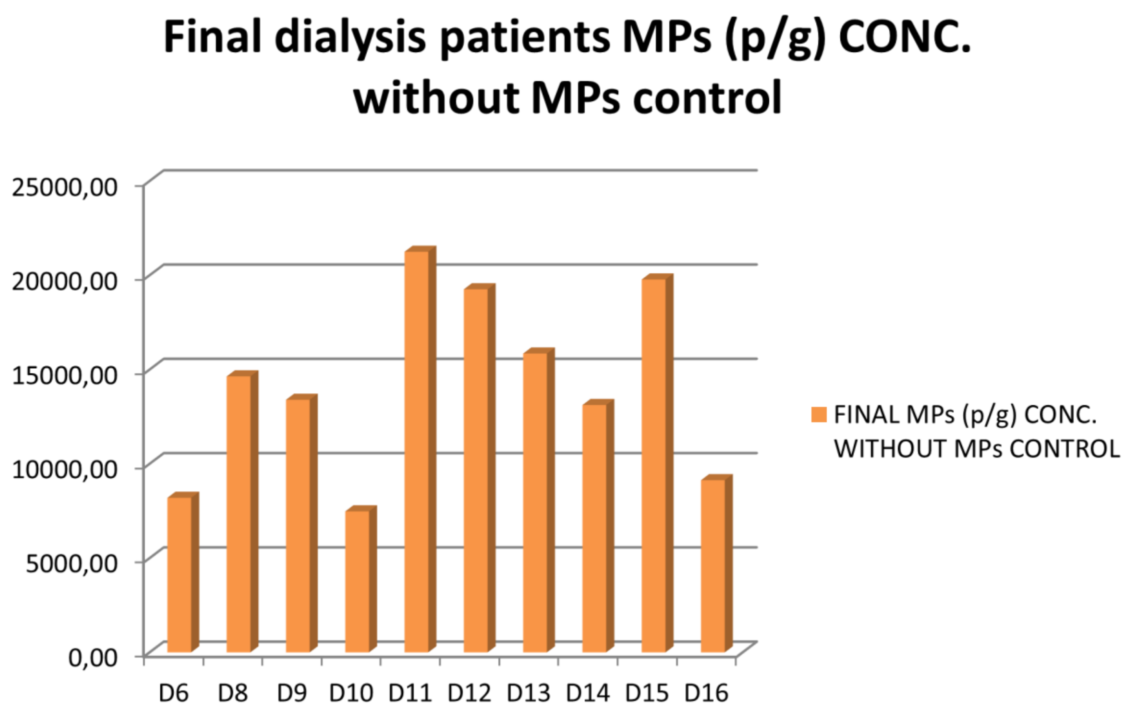

Fig. 25Histogram showing MPs concentrations detected in individual samples of dialysis CKD patients.

The lowest concentration of MPs detected in ten blood samples from patients with MDD, deprived of “white” analisys control, is 10277,94 p/g while the highest concentration has a number of 21758,86 p/g(Fig. 26).

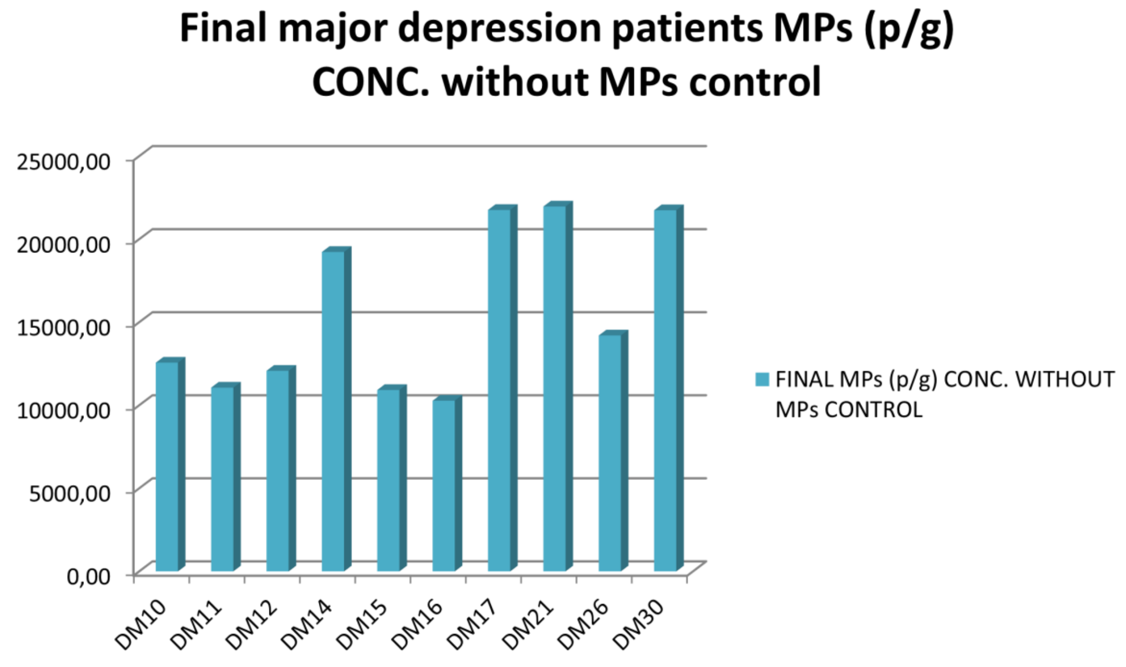

Fig. 26 Histogram showing MPs concentrations detected in individual samples of MDD patients.

Our analysis suggests the mean MPs values in healthy volunteers is 2403,6 p/g (Fig. 27), in dialyzed CKD patients there is a MPs concentration of 14208,73 p/g (Fig. 28) while the mean MPs concentration of MDD patients is 15581,02 p/g (Fig. 29).

Mean MPs concentration value of healthy volunteers	**2403,6 p/g**

Fig. 27Mean MPs concentration value of healthy volunteers

Mean MPs concentration value of dialysates CKD patients	**14208,73 p/g**

Fig. 28Mean MPs concentration value of dialysates CKD patients

Mean MPs concentration value of MDD patients	**15581,02 p/g**

Fig. 29Mean MPs concentration value of MDD patients

Dialysed patients affected by CKD shows a MPs concentration upper than healthy volunteer controls, but the highest MPs concentration value detected is in MDD patients (Fig. 30).

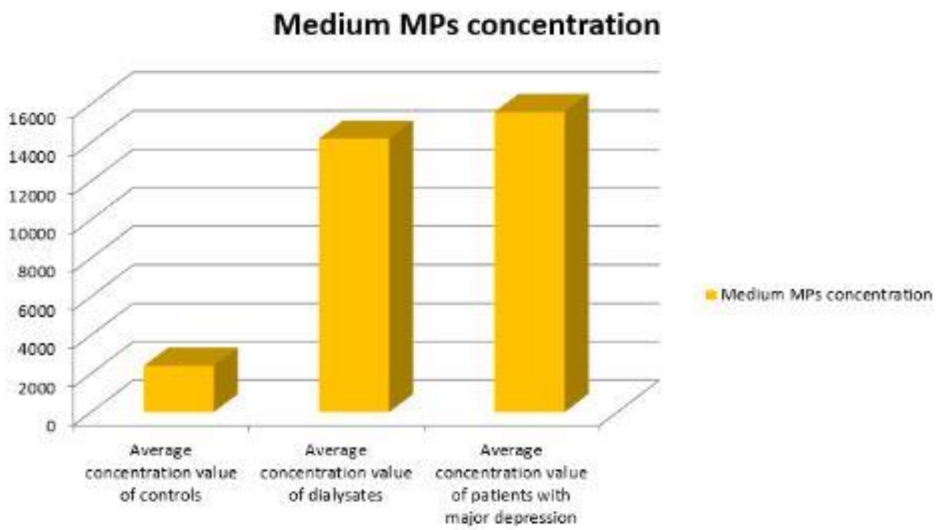

Fig. 30Histogram showing MPs concentrations detected in all study subjects.

DISCUSSION

Our study reveals a higher MPs concentration in subjects suffering from different pathology compared to healthy control volunteers.

In particular, the concentration found in dialysis subjects is almost 6 times higher than in controls witch respectively account of 14208,73 p/g against 2403,6 p/g. According to Italian National Institute of Health, only MPs with a diameter < 150 μm could pass through intestinal barrier even if the estimated 0,3% could increase due to inflammation (Schmidt et al., 2013). When < 1,5 μm in diameter, MPs could travel from the bloodstream and accumulate in various organs, including kidneys (Zou et al., 2022). It is suspected that the greater MPs concentration founded in emodialised CKD patients could be linked to the particles released by dialysis plastic devices through mechanical degradation, particularly referring to the filters. MPs could be related to the chronic failure pathogenesis: this assumption is based on previous study that show mice exposed to MPs had kidney injury histologically confirmed, and a higher mortality resulted by the MPs presence (Meng et al., 2022). MPs exposure has an impact on inflammatory processes with an increase in IL-6, IL-8, IL1b and mostly causes oxidative stress that ultimately could lead to kidneys injury (Pulvirenti et al., 2022). Other potential MPs harmful impact could be extended to additives used to improve plastic quality that may be poisonous, mutagen and carcinogenic or act as ECDs (Gasperi et al. 2018). For example, DEHP used as plasticizer in plastic production, has a synergistic toxic effect on kidney cells (Sun et al., 2023), the same that has been observed in Cd exposure (Zou et al., 2022). In addition, DEHP quantity strongly correlated with the dialysis treatment duration in years (Pollack et al., 1985): this supports our idea that MPs could be released by the dyalizer.

Also MDD patients show to have a higher MPs concentration in blood samples compared to controls, and a greater presence compared to dialysed CKD patients, with an amount of 15581,02 p/g (almost 7 times higher than the control value). As known, MDD is a multifactorial disease and environmental pollutants are considered crucial etiologic factor (England et al., 2009) so MPs cannot be excluded as a contributing cause even if, studies conducted to date, have shown only NPs and their fat-soluble particles eventually attached could penetrate the blood brain barrier (Mattsson et al., 2017). NPs could cause oxidative stress and inhibit the AchE enzyme, resulting in neurological impairment (Prust, 2020). However, mice brains exposed to MPs, exhibited blood–brain barrier disruption, lower level of dendritic spine density, hippocampus inflammatory response and also cognitive and memory deficits compared with controls, in a concentration-dependent manner (Jin H. et al., 2022). The same additives with the "trojan horse effect" could be described in MDD since many drugs still use phthalates as excipient even though AIFA carried out a dose restriction in 2018 when adverse reproductive and/or developmental effects have been observed for DBP and DEP, with a permitted daily exposure of 0,01 and 4 mg/kg/day respectively (www.aifa.gov.it/documents/20142/0/guideline-phthalates_04.10.2018.pdf). BPA and phthalates have also been associated with a polarization of the Th2 response (Nava-Castro, 2020; Hansen, 2015) and theprevalenceoftheTh2responsehasbeenassociatedwiththepresenceofMDD (Pavon et al., 2006). The risk is particularly high if the exposure occurs during neonatal period, when plasticizers may be linked to an increased risk of developing MDD in the future (Segovia-

Medonza et al., 2020) due to the methylation impairment profile in the brain (Kajta and Wojtowicz, 2013). MPs-PET exposure in MSCs alters their potential differentiation and decreases the proliferation: it could either indicate quiescence or genotoxic damages which trigger senescence or apoptosis (Najahi et al., 2022).Even if these results come from study conducted in bone marrow and adipose cells, neuronal cells exposed to MPs could undergo senescence with a mechanism similar to mesenchymal cells and cause MDD. In fact, it is known that cellular senescence associated with a reduction in TL is a cause of MDD (Cesare and Redder, 2010; Malouff and Schutte, 2017).

Our study limitations occur due the fact that patients medical history is not considered, such as their employment status or any other comorbidities that could relate with the concentration of MPs detected. MPs with irregular shape or> 10 μm have been excluded, so the concentration founded could be underestimated. On the other hand, blood sample taken by a single-used-intravenous-butterfly-needle-set is composed of plastic components that could cause MPs contamination during sampling even if, due to the brief exposure, it is supposed to be irrelevant. Through our analysis it is not possible to trace the plastic material types that could contaminate human body and therefore the environmental exposure main sources cannot be suspected. Furthermore, it is not possible, except for metals, to detect the toxic compounds that could be linked to MPs and to estimate their potential dangerous effects. However, metals are not taken into consideration during SEM/EDX analysis, to be sure that the particles accounted are exclusively attributable to plastic material. Despite limitations, our analysis may still be useful for future study providing information on potential outcomes that could help to confirm the hypothesis of an association between exposure to various types of MPs and related suspected diseases.

CONCLUSIONS

Plastic has become essential in our lives. Since many products respect a linear economy, for example medical SUD devices, plastic production unavoidably lead to a large amount of waste.

Waste management has enormous ecosystem impact, can be considered a global economy issue and a public health matter since inappropriate disposal could release MPs: even if are not exactly known the completely MPs human effects, the in vitro and in vivo studies strengthen the hypothesis that they could be unsafe. Human exposure is certain and occurs through the mucosa, via ingestion or inhalation as demonstrated by the discovery that MPs could penetrate the systemic circulation and even accumulate in various organs. Our analysis strengthened the MPs presence in human blood with a higher concentration in subjects with disease compared to healthy volunteers. There are not enough supporting studies that can relate MPs in blood to etiophatogenesis nor disease progression or prognosis even if the association could be suspected. In our project, other matrices will be analysed in the near future, such as urine samples from MDD affected patients and CKD affected individuals not undergoing dialysis treatment and other link between MPs and disease, like IBD or colorectal cancer, will be investigated from blood, urine samples and intestinal biopsies.

Because of its versatility and low cost, it is impossible and unnecessary to replace all plastic manufacture but defence strategies like circular economic policies and research investments aim to study human effects should be implemented and finally, to hinder oxidative stress (a phenomenon that can lead to several damages), healthy lifestyle should be encouraged.

ABBREVIATIONS

ATN=Acute tubular necrosis

BPA=Bisphenol A

CAP=Cellulose acetate phthalate

CH2Cl2=Dichloromethane

CKD=Chronic kidney disease

COPD=Chronic obstructive pulmonary disease

CTRLs=Healthy volunteers controls

DBP= Dibutylphthalate

DEHP= Diethylhexylphthalate

DEP=Diethylphthalate

DMP=Dimethylphthalate

DOP=Dioctylphthalate

EDCs=Endocrine disruptive chemicals

EDIs=Estimated Daily Intakes

EDX=Energy dispersion detector EDX

ECHA=European Commission asked to the European Chemicals Agency

eGFR=Estimated glomerular filtration rate

EOL=End-of-life

ESRD=End-stage renal disease

HD=Hemodialysis

HMP=Hypromellosephthalate

IBD=Inflammatory bowel disease

IRF5= Interferon regulatory factor 5

KDIGO=Kidney Disease: Improving Global Outcomes

MDD=Major depressive disorder

MPs=Microplastics

MSCs=Mesenchymal stromal cells

NPs = Nanoplastics

OCSE=Organization for Economic Co-operation and Development

PC=Polycarbonate

PCB=Polychlorinated biphenyls

PCL=Polycaprolactone

PCOS=Polycystic ovary syndrome

PD=Peritoneal dialysis

PES=Polyethersulfone

PE=Polyethylene

PET=Polyethylene terephthalate

PGA=Polyglycolic acid

PL=Polyester

PLA=Polylactic acid

PM=Particulate matter

PMMA=Polymethyl methacrylate

PP=Polypropylene

PPE=Protective equipment

PS=Polystyrene

PSU=Polysulfone

PVAP=Polyvinyl acetate phthalate

PVC=Polyvinyl chloride

PU=Polyurethane

SDGs=Sustainable Development Goals

SEM=Scanning electron microscope

SUD=Single-use disposable

TL=Telomere length

TLR4=Toll-like receptor 4

TEER=Trans-ephitelial electrical resistance

TEM=Transmission electron microscopy

WHO=World Health Organization

WWTPs=Wastewater treatment plants

REFERENCES

Acconcia F., Pallottini V., Marino M.; Molecular Mechanisms of Action of BPA; Dose Response, 2015; 13:1–9

Aeddula N.R., Baradhi K.M.; Reflux Nephropathy; StatPearls Publishing, Treasure Island (FL), 2023.

Aeschlimann M., Li G., Kanji Z.A., Mitrano D.M.; Microplastics and nanoplastics in the atmosphere: the potential impacts on cloud formation processes; Nat Geosci. 2022 Dec; 15:967-975.

Argyropoulos C., Roumelioti M.E., Sattar A., Kellum J.A., Weissfeld L., Unruh M.L.; Dialyzer reuse and outcomes of high flux dialysis; PLoS ONE, 2015; 10(6): e0129575.

Ahrens W., Mambetova C., Bourdon-Raverdy N., Llopis-González A., Guénel P., Hardell L., Merletti F., Morales-Suárez-Varela M., Olsen J., Olsson H.; Occupational exposure to endocrine-disrupting compounds and biliary tract cancer among men; Scand. J. Work Environ. Health 2007; 33, 387–396.

Ait Bamai Y., Araki A., Kawai T., Tsuboi T., Saito I., Yoshioka E., Kanazawa A., Tajima S.; Associations of phthalate concentrations in floor dust and multi-surface dust with the interior materials in Japanese Dwellings; Science of the Total Environment, 2014a; 468–469: 147–157.

Ait Bamai Y., Shibata E., Saito I., Araki A., Kanazawa A., Morimoto K., Nakayama K., Tanaka M.; Exposure to house dust phthalates in relation to asthma and allergies in both children and adults; Science of the Total Environment 2014b; 485–486: 153–163.

Alhazmi H., Almansour F. H., Aldhafeeri, Z.; Plastic waste management: A review of existing life cycle assessment studies; Sustainability (Switzerland), 2021; 13(10), 1–21.

Amato-Lourenço LF., Carvalho-Oliveira R., Junior GR., Dos Santos Galvao L., Ando RA., Mauad T.; Presence of airborne microplastics in human lung tissue; J Hazard Mater, 2021; 416:126124.

Amereh F.; Babaei M.; Eslami A.; Fazelipour S.; Rafiee M.; The emerging risk of exposure to nano(micro)plastics on endocrine disturbance and reproductive toxicity: from a hypothetical scenario to a global public health challenge; Environ. Pollut. 2020; 261, 114158.

Balaguer P., Delfosse V., Grimaldi M., Bourguet W.; Structural and functional evidences for the interactions between nuclear hormone receptors and endocrine disruptors at low doses; Comptes Rendus Biol., 2017; 340:414–420.

Barlow C.A., Grespin M., Best E.A.; Asbestos fiber length and its relation to disease risk; Inhal. Toxicol.,2017; 29, 541–554.

Barnes, D. K. A.; Invasions by marine life on plastic debris; Nature, 2002; 416: 808–809.

Barnes D. K. A., Galgani F., Thompson R.C., Barlaz. M.; Accumulation and fragmentation of plastic debris in global environments. Philosophical Transactions of the Royal Society, 2009; B 364: 1985–1998.

Bernatsky S., Smargiassi A., Barnabe C.; Fine particulate air pollution and systemic autoimmune rheumatic disease in two Canadian provinces; Environ. Res., 2016; 146pp. 85-91

Bistulfi G.; Sustainability: reduce, reuse and recycle lab waste; Nature, 2013; 502(7470):170.

Bringer A., Cachot J., Prunier G., Dubillot E., Clérandeau C., Thomas H.; Experimental ingestion of fluorescent microplastics by pacific oysters, Crassostrea gigas, and their effects on the behaviour and development at early stages; Chemosphere 2020; 254, 126793.

Brown, A.; Planetary health digest; Lancet Planet. Health 2019; 3, 378.

Burns E.E., Boxall ABA; Microplastics in the aquatic environment: evidence for or against adverse impacts and major knowledge gaps; Environ Toxicol Chem., 2018; 37(11):2776–96.

Byrne C.; Divekar S.D.; Storchan G.B.; Parodi D.A.; Martin M.B.; Metals and breast cancer; J. Mammary Gland Biol. Neoplasia 2013; 18, 63–73.

Canesi L., Ciacci C., Bergami E.; Evidence for immunomodulation and apoptotic processes induced by cationic polystyrene nanoparticles in the hemocytes of the marine bivalve Mytilus; Mar. Environ. Res., 2015, 111 pp. 34-40.

Catarino A.I., Macchia V., Sanderson W.G., Thompson R.C., Henry T.B.; Low levels of microplastics (MP) in wild mussels indicate that MP ingestion by humans is minimal compared to exposure via household fibres fallout during a meal; Environ Pollut. 2018; 237:675–84.

Cesare A.J. and Reddel R.R.; Alternative lengthening of telomeres: models, mechanisms and implications; Nat. Rev. Genet, 2010; 11 pp. 319-330. Abb M., Heinrich T., Sorkau E., Lorenz W.; Phthalates in house dust; Environment International, 2009; 35: 965–970.

Chen J.C., Chen M.Y., Fang C., Zheng R.H., Jiang Y.L., Zhang Y.S., Wang K.-J., Bailey C., Segner H., Bo J.; Microplastics negatively impact embryogenesis and modulate the immune response of the marine medaka Oryzias melastigma; Mar. Pollut. Bull., 2020; 158, 111349.

Cholewinski A., Dadzie E., Sherlock C., Anderson W.A., Charles T.C., Habib K., Young S., Zhao B; A critical review of microplastic degradation and material flow analysis towards a circular economy; Environmental Pollution, 2022; Volume 315, 15, 120334.

Churg A., Brauer M.; Ambient atmospheric particles in the airways of human lungs; Ultrastruct. Pathol., 2000; 24 pp. 353-361.

Cima F. Tin; Environmental Pollution and Health Effects; Encycl. Environ. Health 2011; 351–359.

Cingotti N., Jensen G.K.; Health and Environment Alliance (HEAL). Food Contact Materials and Chemical Contamination; Health and Environment Alliance: Brussels, Belgium, 2019.

Cipolloni D., Paoli T., Vecchia P.; Plastic sickness, truth and lies about the material that has submerged the world and entered our blood; Under Investigation, 2023.

Corcoran P.L., Moore C.J., Jazvac K.; An anthropogenic marker horizon in the future rock record; GSA Today 2014; 24, 4–8.

Coresh J., Astor B.C., Greene T., Eknoyan G., Levey A.S.; Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey; Am J Kidney Dis., 2003; 41(1):1-12.

Cox K.D., Covernton G.A., Davies H.L., Dower J.F., Juanes F., Dudas S.E.; Human consumption of microplastics; Environ. Sci. Technol. 2019; 53, 7068–7074.

Cruz J.N., Martínez K.D., Ávila J.J.L., Hernández I.P., De Lourdes Castellanos Villalobos M.; Recovery of plastic waste through its thermochemical degradation: a review; Environ Monit Assess 2023; 195:1166.

Dawson A.L., Kawaguchi S., King C.K., Townsend K.A., King R., Huston W.M., Bengtson Nash S.M.; Turning microplastics into nanoplastics through digestive fragmentation by Antarctic krill; Nat. Commun. 2018; 9, 1–8.

De Brito-Ashurst I., Varagunam M., Raftery M.J., Yaqoob M.M.; Bicarbonate supplementation slows progression of CKD and improves nutritional status; J Am Soc Nephrol., 2009; 20(9):2075-84.

De Cock M., Maas Y.G., van de Bor M.; Does perinatal exposure to endocrine disruptors induce autism spectrum and attention deficit hyperactivity disorders? Review. Acta Paediatr., 2012; 101:811–818.

De Marco G., Oliveri Conti G., Giannetto A., Cappello T., Galati M., Iaria C., Pulvirenti E., Capparucci F., Mauceri A., Ferrante M., Maisano M.; Embryotoxicity of polystyrene microplastics in zebrafish Danio rerio; Environmental Research, 2022; Volume 208, 112552.

De Villiers A.S., Russell V.A., Carstens M.E., Searson J.A., van Zyl A.M., Lombard C.J., Taljaard J.J.; Noradrenergic function and hypothalamic-pituitary-adrenal axis activity in adolescents with major depressive disorder; Psychiatry Res., 1989; 27:101–109.

Di Dong C., Chen C.W., Chen Y.C.; Polystyrene microplastic particles: in vitro pulmonary toxicity assessment; J. Hazard Mater., 385, 2020; Article 121575.

Dietz M.M., Herth S.; Plant nanotoxicology; Trends in Plant Science, 2011; volume 16, issue 11, P582-589.

Dillon A., Lo DD.; M cells: Intelligent engineering of mucosal immune surveillance; Front immunol. 2019; 10:1499.

Dominguez-Romero E., Scheringer M.; A review of phthalate pharmacokinetics in human and rat: What factors drive phthalate distribution and partitioning? Drug Metab. Rev., 2019; 51:314–329.

Donato F.; Moneda M.; Portolani N.; Rossini A.; Molfino S.; Ministrini S.; Contessi G.B.; Pesenti S.; De Palma G.; Gaia A.; Polychlorinated biphenyls and risk of hepatocellular carcinoma in the population living in a highly polluted area in Italy; Sci. Rep. 2021; 11, 3064.

Dris R., Gasperi J., Mirande C., Mandin C., Guerrouache M., Langlois V.; A first overview of textile fibers, including microplastics, in indoor and outdoor environments; Environ Pollut. 2017; 221:453–8.

Duan Z., Duan X., Zhao S., Wang X., Wang J., Liu Y., Peng Y., Gong Z., Wang L.; Barrier function of zebrafish embryonic chorions against microplastics and nanoplastics and its impact on embryo development; J. Hazard. Mater. 2020; 395, 122621.

Elhacham E.; Global human-made mass exceeds all living biomass; Nature, 2020; 588(7838):442–444.

England M.J., Sim L.J.; Depression in Parents, Parenting, and Children: Opportunities to Improve Identification, Treatment, and Prevention.; National Research Council, 2009.

Erkekoglu P., Oral D., Chao M.-W., Kocer-Gumusel B.; Hepatocellular Carcinoma and Possible Chemical and Biological Causes: A Review; J. Environ. Pathol. Toxicol. Oncol. 2017; 36, 171–190.

European Commission; Communication from the commission to the european parliament, the council, the European economic and social committee and the committee of the regions: a European strategy for plastics in a circular economy. COM (2018) 28 final, SWD (2018) (1), 1–18.

Fernandes E.C., Silva C.A., Braga A.L.F.; Exposure to air pollutants and disease activity in juvenile-onset systemic lupus erythematosus patients; Arthritis Care Res., 2015; 67 pp. 1609-1614.

Ferrante M., Zuccarello P., Chaima A., Fiore M., Cristaldi A., Pulvirenti E., Favara C., Copat C., Grasso A., Missawi O., Oliveri Conti G., Mohamed B.; Microplastics in fillets of Mediterranean seafood. A risk assessment study; Environmental Research, 2022; Volume 204, Part C, 112247.

Ferrante M., Oliveri Conti G., Zuccarello P.; Patent method for the extraction and determination of micro- and nano- plastics in organic and inorganic matrix samples: An application on vegetals; MethodsX 7, 2020; 10 0989

Forouzanfar M.H., Afshin A., Alexander L.T., Anderson H.R., Bhutta Z.A., Biryukov S.; Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: A systematic analysis for the Global Burden of Disease Study 2015; Lancet. 2016; 388(10053):1659–724.

Forte M., Iachetta G., Tussellino M., Carotenuto R., Prisco M., De Falco M., Laforgia, V., Valiante S.; Polystyrene nanoparticles internalization in human gastric adenocarcinoma cells; Toxicol. Vitr., 2016; 31, 126–136.

Fucic A., Galea K.S., Duca R.C., El Yamani M., Frery N., Godderis L., Halldorsson T.I., Iavicoli I., Ndaw S., Ribeiro E.; Potential Health Risk of Endocrine Disruptors in Construction Sector and Plastics Industry: A New Paradigm in Occupational Health; Int. J. Environ. Res. Public Health 2018; 15, 1229.

Gasperi J., Wright S.L., Dris R., Collard F., Mandin C., Guerrouache M., Langlois V., Kelly F.J., Tassin B.; Microplastics in air: Are we breathing it in? Current Opinion in Environmental Science & Health 2018; 1: 1–5.

Gauly A., Fleck N., Kircelli F.; Advanced hemodialysis equipment for more eco-friendly dialysis; Int Urol Nephrol 54; 2022; 1059–1065.

Geyer R., Jambeck J.R., Law K.L.; Production, use, and fate of all plastics ever made; Sci. Adv., 3 (7), 2017; pp. 25-29, 10.1126/sciadv.1700782.

González-Fernández D.; Floating macrolitter leaked from Europe into the ocean; Nat Sustain, 2021; 4(6):474–483.

González-Pleiter M., Velázquez D., Edo C., Carretero O., Gago J., Barón-Sola A., Hernández L.E., Yousef I., Quesada A., Leganés F., Rosal R., Fernández-Piñas F.; Fibers spreading worldwide: microplastics and other anthropogenic litter in an Arctic freshwater lake; Sci. Total Environ., 722, 2020; Article 137904.

Green T.R., Fisher, Stone J., M.; Polyethylene particles of a "critical size" are necessary for the induction of cytokines by macrophages in vitro; Biomaterials, 19, 1998; pp. 2297-2302.

Gregory J.V., Kadiyala P., Doherty R., Cadena M., Habeel S., Ruoslahti E., Lowenstein P.R., Castro M.G., Lahann J.; Systemic brain tumor delivery of synthetic protein nanoparticles for glioblastoma therapy.; Nat. Commun. 2020; 11, 1–15.

Grigore M.E.; Methods of recycling, properties and applications of recycled thermoplastic polymers; Recycling, 2(24) 2017; 2040024.

Jambeck J. R., Geyer R., Wilcox C., Siegler T., Perryman M., Andrady A., Narayan R., Law. K.; Plastic waste inputs from land into the ocean; Science, 2015; 347: 768–771.

James R.; Incineration: why this may be the most environmentally sound method of renal healthcare waste disposal; J Ren Care, 2010; 36:161–169

Jin H., Jiang C., Yang C., Li L., Pan M., Li D., Han X., Ding J.; Evaluation of Neurotoxicity in BALB/c Mice following Chronic Exposure to Polystyrene Microplastics Environmental Health Perspectives, Volume 130, Issue 10; 2022.

Jornet-Martınez, N., Anto´n-Soriano C., Campı ´ns-Falco´ P.; Estimation of the presence of unmetabolized dialkyl phthalates in untreated human urine by an on-Line miniaturized reliable method; Science of the Total Environment, 2015; 532: 239–244.

Kidney Int Suppl; Chapter 1: Definition and classification of CKD; 2011, 2013; 3(1):19-62.

Hauser R.; Calafat A.M.; Phthalates and human health; Occup. Environ. Med. 2005; 62, 806–818.

Hahladakis J.N., Velis C.A., Weber R., Iacovidou E., Purnell P.; An overview of chemical additives present in plastics: Migration, release, fate and environmental impact during their use, disposal and recycling; J Hazard Mater, 2018; 344:179–99.

Hallan S.I., Orth S.R.; Smoking is a risk factor in the progression to kidney failure; Kidney Int., 2011; Sep;80(5):516-23.

Najahi H., Alessio N., Squillaro T, Oliveri Conti G., Ferrante M., Di Bernardo G., Galderisi U., Messaoudi I., Minucci S., Banni M.; Environmental microplastics (EMPs) exposure alter the differentiation potential of mesenchymal stromal cells; Environmental Research, 2022; Volume 214, Part 4, 114088.

Hansen J.F., Nielsen C.H., Brorson M.M., Frederiksen H., Hartoft-Nielsen M.-L., Rasmussen Å.K., Bendtzen K., Feldt-Rasmussen U.; Influence of phthalates on in vitro innate and adaptive immune responses; PLoS ONE, 2015; 10: e0131168.

Harrison J.P., Schratzberger M., Sapp M., Osborn A.M.; Rapid bacterial colonization of low-density polyethylene microplastics in coastal sediment microcosms; BMC Microbiology 2014; 14: 232.

He T., Qu Y., Yang X., Liu L., Xiong F., Wang D., Liu M., Sun R.; Research progress on the cellular toxicity caused by microplastics and nanoplastics; Journal of Applied Toxicology, 2023; 43(11), 1576–1593.

Heather A., Leslie A., Martin J.M.; Van Velzen A., Sicco H., Brandsma A, Dick A., Vethaak A.B., Juan J., Garcia-Vallejo C., Lamoree M. H.; Discovery and quantification of plastic particle pollution in human blood; Environment International, 2022; 163 (107199).

Hou B.; Wang F.; Liu T.; Wang Z.; Reproductive toxicity of polystyrene microplastics: In vivo experimental study on testicular toxicity in mice; J. Hazard. Mater., 2020; 405, 124028. HorvatitsT.,Tamminga M., Liu B.;Microplastics detected in cirrhotic liver tissue;eBioMedicine, 2022.

Hoenich N.A., Levin R., Pearce C.; Clinical waste generation from renal units: implications and solutions; Semin Dial, 2005; 18:396–400

Ho¨gberg J., Hanberg A., Berglund M., Skerfving S., Remberger M., Calafat A.M., Filipsson A.F., Jansson B.; Phthalate diesters and their metabolites in human breast milk, blood or serum, and urine as biomarkers of exposure in vulnerable populations; Environmental Health Perspectives, 2008; 116: 334–339.

Hu L.; Zhao Y.; Xu H.; Trojan horse in the intestine: A review on the biotoxicity of microplastics combined environmental contaminants; J. Haz. Mat. 2022; 439, 129652.

Huang J., Wen B., Zhu J., Zhang Y., Gao J., Chen Z.; Exposure to microplastics impairs digestive performance, stimulates immune response and induces microbiota dysbiosis in the gut of juvenile guppy (Poecilia reticulata); Sci. Total Environ. 2020; 733, 138929.

Husen A., Siddiqi K.S.; Carbon and fullerene nanomaterials in plant system; J. Nanobiotechnol. 12, 2014; p. 16.

Hussain N., Jaitley V., Florence A.T.; Recent advances in the understanding of uptake of microparticulates across the gastrointestinal lymphatics; Adv Drug Deliv Rev., 2001; 50(1–2):107–42.

Hwang, J., Choi D., Han S., Choi J., Hong. J.; An assessment of the toxicity of polypropylene microplastics in human derived cells; Science of the Total Environment, 2019; 684: 657–669.

Inker L.A., Astor B.C., Fox C.H., Isakova T., Lash J.P., Peralta C.A., Kurella Tamura M., Feldman H.I. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis. 2014 May;63(5):713-35.

Kajta M., Wojtowicz A.K.; Impact of endocrine-disrupting chemicals on neural development and the onset of neurological disorders; Pharmacol. Rep., 2013; 65:1632–1639.

Kelly J.J., London M.G., McCormick A.R., Rojas M., Scott J.W., Hoellein T.J.; Wastewater treatment alters microbial colonization of microplastics; PLoS ONE, 2021; 16(1): e0244443.

Kern D.G., Crausman R.S., Durand K.T.H., Nayer A., Kuhn III C.; Flock worker's lung: chronic interstitial lung disease in the nylon flocking industry; Ann. Intern. Med., 129, 1998; pp. 261-272.

Khanna R.; Clinical presentation & management of glomerular diseases: hematuria, nephritic & nephrotic syndrome; Mo Med., 2011; 108(1):33-6.

Kitamoto Y., Tomita M., Akamine M., Inoue T., Itoh J., Takamori H., Sato T.; Differentiation of hematuria using a uniquely shaped red cell. Nephron, 1993; 64(1):32-6.

Klemencová K., Grycová B., Inayat A., Lestinský, P.; Thermo-catalytic degradation of polystyrene over α-Fe2O3; Nanocon, 2020.

Kumar S., Panda A. K., Singh R. K.; A review on tertiary recycling of high-density polyethylene to fuel; Resources, Conservation and Recycling, 2011; 55(11), 893910.

La Porta E., Exacoustos O., Lugani F., Angeletti A., Chiarenza D.S., Bigatti C., Spinelli S., Kajana X., Garbarino A., Bruschi M.; Microplastics and Kidneys: An Update on the Evidence for Deposition of Plastic Microparticles in Human Organs, Tissues and Fluids and Renal Toxicity Concern; Int. J. Mol. Sci., 2023; 24, 14391.
Latini G., De Felice C., Presta G., Del Vecchio A., Paris I., Ruggieri F., Mazzeo P.; In utero exposure to Di-(2Ethylhexyl) phthalate and duration of human pregnancy; Environmental Health Perspectives, 2003; 111: 1783–1785.

Lebreton L. and Andrady A.; Future scenarios of global plastic waste generation and disposal; Palgrave Commun. 2019; 5, 1–11.

Leslie H.A., Van Velzen M.J., Brandsma S.H., Vethaak A.D., Garcia-Vallejo J.J., Lamoree M.H.; Discovery and quantification of plastic particle pollution in human blood; Environ. Int. 2022; 163, 107199.

Li B., Ding Y., Cheng, X., Sheng, D., Xu, Z., Rong, Q., Wu, Y., Zhao, H., Ji, X., Zhang, Y.; Polyethylene microplastics affect the distribution of gut microbiota and inflammation development in mice; Chemosphere 2019; 244, 125492.

Li H., Kilgallen A.B., Münzel T., Wolf E., Lecour, S., Schulz, R., Daiber, A., Van Laake, L.W.; Influence of mental stress and environmental toxins on circadian clocks: Implications for redox regulation of the heart and cardioprotection; J. Cereb. Blood Flow Metab, 2019; 177, 5393–5412.

Li Z.; Xu, T.; Peng L.; Tang X.; Chi Q.; Li M.; Li S. Polystyrene nanoplastics aggravates lipopolysaccharide-induced apoptosis in mouse kidney cells by regulating IRE1/XBP1 endoplasmic reticulum stress pathway via oxidative stress; J. Cell. Physiol., 2023; 238, 151–164.

Li Z., Zhu S., Liu Q., Wei J., Jin, Y., Wang, X., Zhang L.; Polystyrene microplastics cause cardiac fibrosis by activating Wnt/βcatenin signaling pathway and promoting cardiomyocyte apoptosis in rats; Environ. Pollut., 2020; 265, 115025.

Lin M., Wu T., Sun L., Lin J.J., Zuo Z., Wang C.; Aroclor 1254 causes atrophy of exocrine pancreas in mice and the mechanism involved; Environ. Toxicol., 2014; 31, 671–678.

Lippmann M., Yeates D.B., Albert R.E.; Deposition, retention, and clearance of inhaled particles; Br J Industr Med., 1980; 37(4):337–62.

Lithner D., Larsson A., Dave G.; Environmental and health hazard ranking and assessment of plastic polymers based on chemical composition; Science of the Total Environment, 2011; 409: 3309–3324.

Liu B.N.; Liu X.T.; Liang, Z.H.; Wang, J.H.; Gut microbiota in obesity; World J. Gastroenterol, 2021; 27, 3837–3850.

Liu T., Jia Y., Zhou L., Wang Q., Sun D., Xu J., Wu J., Chen H., Xu F., Ye L.; Effects of Di-(2-ethylhexyl) Phthalate on the Hypothalamus-Uterus in Pubertal Female Rats; Int. J. Environ. Res. Public Health, 2016; 13:1130.

Liu K., Wang X., Fang T., Xu P., Zhu L., Li D.; Source and potential risk assessment of suspended atmospheric microplastics in Shanghai.; Sci Total Environ., 2019; 675:462–71.

Lobelle D., Cunliffe M.; Early microbial biofilm formation on marine plastic debris; Marine Pollution Bulletin, 2011; 62: 197–200.

Lock J.Y., Carlson T.L., Carrier R.L.; Mucus models to evaluate the diffusion of drugs and particles; Adv Drug Deliv Rev. 2018; 124:34–49.

Lu L., Luo T., Zhao Y., Cai C., Fu Z., Jin Y.; Interaction between microplastics and microorganism as well as gut microbiota: A consideration on environmental animal and human health; Science of the Total Environment, 2019; 667: 94–100.

Ludewig G.; Robertson L.W.; Polychlorinated biphenyls (PCBs) as initiating agents in hepatocellular carcinoma; Cancer Lett., 2012; 334, 46–55,

MacNee W., Donaldson K.; Particulate air pollution and health; Amsterdam: Elsevier, 1999; 1999:653–72.

Mahmoudi, M., Kalhor, H.R., Laurent, S., Lynch, I.; Protein Fibrillation and Nanoparticle Interactions: Opportunities and Challenges; Nanoscale 2013, 5, 2570–2588.

Main K., Mortensen G., Kaleva M., Boisen K., Damgaard I., Chellakooty M., Schmidt I., Suomi A.M.; Human breast milk contamination with phthalates and alterations of endogenous reproductive hormones in infants three months of age; Environmental Health Perspectives, 2006; 114: 270–276.

Makhdoumi P., Hossini H., Pirsaheb M.; A review of microplastic pollution in commercial fish for human consumption; Rev Environ Health, 2022; 10.1515/reveh-2021-0103.

Malouff J.M., Schutte N.S.; A meta-analysis of the relationship between anxiety and telomere length Anxiety, Stress, Coping, 30, 2017; pp. 264-272.

Masud R.I., Suman K.H., Tasnim S., Begum M.S., Sikder M.H., Uddin M.J., Haque M.N.; A review on enhanced microplastics derived from biomedical waste during the COVID-19 pandemic with its toxicity, health risks, and biomarkers; Environ Res., 2023; Jan 1;216(Pt 1):114434.

Mattsson K.; Johnson E.V.; Malmendal A.; Linse S.; Hansson L.A.; Cedervall T.; Brain damage and behavioural disorders in fish induced by plastic nanoparticles de-livered through the food chain; Sci. Rep., 2017; 7, 11452.

McCright J., Skeen C., Yarmovsky J., Maisel K., Nanoparticles with dense poly (ethylene glycol) coatings with near neutral charge are maximally transported across lymphatics and to the lymph nodes; Acta Biomater, 2022; 145, 146–158.

Meng X.; Zhang J.; Wang W.; Gonzalez-Gil G.; Vrouwenvelder J.S.; Li Z.; Effects of nano- and microplastics on kidney: Physicochemical properties, bioaccumulation, oxidative stress and immunoreaction; Chemosphere 2022; 288 Pt 3, 132631.

Mettang T., Pauli-Magnus C., Alscher D.M., Kirchgessner J., Wodarz R., Rettenmeier A.W., Kuhlmann U.; Influence of plasticizer-free CAPD bags and tubings on serum, urine, and dialysate levels of phthalic acid esters in CAPD patients; Perit Dial Int, 2000; 20:80–84

Mohamed B.A., Fattah I.M.R., Yousaf B., Periyasamy S.; Effects of the covid-19 pandemic on the environment, waste management, and energy sectors: a deeper look into the long-term impacts; Environ Sci Pollut Control Ser., 2022; 29:46438–46457.

Mohana A.A., Islam M.M., Rahman M., Pramanik S.K., Haque N., Gao L., Pramanik B.K; Generation and consequence of nano/microplastics from medical waste and household plastic during the COVID-19 pandemic; Chemosphere, 2023; Jan;311(Pt 2):137014.

Murdeshwar H.N., Anjum F.; Hemodialysis,; StatPearls Publishing, 2023; PMID: 33085443.

Najahi H., Alessio N., Squillaro T., Conti G.O., Ferrante M., Di Bernardo G., Galderisi U., Messaoudi I., Minucci S., Banni M.; Environmental microplastics (EMPs) exposure alter the differentiation potential of mesenchymal stromal cells.; Environ Res., 2022;214(Pt 4):114088.

National Institutes of Health; Information about Mental Illness and the Brain; NIH Curriculum Supplement Series, 2007.

Nava-Castro K.E., Togno-Peirce C., Palacios-Arreola M.I., Del Rio-Araiza V.H., Hernandez-Bello R., Morales Montor J.; Bisphenol A induces protection through modulation of the immune response against the helminth parasite Taenia crassiceps; Parasite Immunol., 2020; 42: e12733.

O'Hagan DT; Intestinal translocation of particulates — Implications for drug and antigen delivery; Adv Drug Delivery Rev., 1990; 5(3):265–85.

Oliveri Conti G., Ferrante M., Banni M., Favara C., Nicolosi I., Cristaldi A., Fiore M., Zuccarello P.; Micro- and nano-plastics in edible fruit and vegetables. The first diet risks assessment for the general population; Environmental Research 2020; volume 187, 109677.

Paget V.; Dekali S.; Kortulewski T.; Grall R.; Gamez C.; Blazy K.; Aguerre-Chariol, O.; Chevillard S.; Braun A.; Rat P.; Specific Uptake and Genotoxicity Induced by Polystyrene Nanobeads with Distinct Surface Chemistry on Human Lung Epithelial Cells and Macrophages; PLoS ONE, 2015; 10, e0123297.

Parashar N. and Hait S.; Plastics in the time of COVID-19 pandemic: protector or polluter? Sci. Total Environ., 759, 2021

Patrício Silva A.L., Prata J.C., Mouneyrac C., Barcelò D., Duarte A.C., Rocha-Santos T. Risks of covid-19 face masks to wildlife: present and future research needs; Sci Total Environ., 2021.

Pavon L., Sandoval-Lopez G., Eugenia Hernandez M., Loria F., Estrada I., Perez M., Moreno J., Avila U., Leff P., Anton B.; Th2 cytokine response in Major Depressive Disorder patients before treatment; J. Neuroimmunol., 2006; 172:156–165.

Peretz J., Vrooman L., Ricke W.A., Hunt P.A., Ehrlich S., Hauser R., Padmanabhan V., Taylor H.S.; Bisphenol a and reproductive health: Update of experimental and human evidence, 2007–2013. Environmental Health Perspectives, 2014; 122: 775–786.

Persiani E., Cecchettini A., Ceccherini E., Gisone I., Morales, M.A., Vozzi, F.; Microplastics: A Matter of the Heart (and Vascular System); Biomedicines 2023; 11, 264.

Piccoli G.B., Nazha M., Ferraresi M., Vigotti F.N., Pereno A., Barbero S.; Eco-dialysis: the financial and ecological costs of dialysis waste products: Is a 'cradle-to-cradle' model feasible for planet-friendly haemodialysis waste management? Nephrol Dial Transplant, 2015; 30(6):1018–1027.

Piccoli G.B., Cupisti A., Aucella F., Regolisti G., Lomonte C., Ferraresi M., Claudia D., Ferraresi C., Russo R., La Milia V., Covella B., Rossi L., Chatrenet A., Cabiddu G., Brunori G.; On the Behalf of Conservative treatment, Physical activity and Peritoneal dialysis project groups of the Italian Society of Nephrology; Green nephrology and eco-dialysis: a position statement by the Italian Society of Nephrology; J Nephrol., 2020 Aug; 33(4):681-698.

Pironti C., Notarstefano V., Ricciardi M., Motta O., Giorgini E., Montano L.; First Evidence of Microplastics in Human Urine, a Preliminary Study of Intake in the Human Body; Toxics 2023; 11, 40.

Pochigaeva K., Druzhkova T., Yakovlev A., Onufriev M., Grishkina M., Chepelev A., Guekht A., Gulyaeva N.; Hair cortisol as a marker of hypothalamic-pituitary-adrenal Axis activity in female patients with major depressive disorder.; Metab. Brain Dis., 2017; 32:577–583.

Pollack G.M., Buchanan J. F., Slaughter R. L., Kohli R. K., Shen D. D.; Circulating concentrations of di(2-ethylhexyl) phthalate and its de-esterified phthalic acid products following plasticizer exposure in patients receiving hemodialysis; Toxicology and Applied Pharmacology, 1985, Volume 79, Issue 2, Pages 257-267.

Prata J.C.; Airborne microplastics: Consequences to human health? Environ. Pollut, 2018; 234, 115–126.

Prust M., Meijer J., Westerink R.H.S.; The plastic brain: neurotoxicity of micro- and nanoplastics. Part Fibre Toxicol 17, 24, 2020.

Pulvirenti E., Ferrante M., Barbera N., Favara C., Aquilia E., Palella M., Cristaldi A., Oliveri Conti G., Fiore M.; Effects of Nano and Microplastics on the Inflammatory Process: In Vitro and In Vivo Studies Systematic Review; Front. Biosci. (Landmark Ed) 2022; 27(10), 287.

Ragusa A., Matta, M., Cristiano L., Matassa R., Battaglione E., Svelato A., De Luca C., D'Avino S., Gulotta A., Rongioletti M.C.A.; Deeply in Plasticenta: Presence of Microplastics in the Intracellular Compartment of Human Placentas; Int. J. Environ. Res. Public Health 2022; 19, 11593.

Rangel Alvarado R., Pal D., Ariya P.; Pm2.5 decadal data in cold vs. mild climate airports: covid-19 era and a call for sustainable air quality policy. Environ Sci Pollut Control Ser. 2022; 29:58133–58148.

Reed C.; Dawn of the Plasticene age; New Scientist., 2015; 225, 28–32.

Revel M, Châtel A, Mouneyrac C.; Micro(nano)plastics: A threat to human health? Curre Opin Environ Sci Health, 2018; 1:17–23.

Rist S., Almroth B.C., Hartmann N.B., Karlsson T.M.; A critical perspective on early communications concerning human health aspects of microplastics; Sci. Tot. Environ., 2018; 626, 720–726.

Rosenboom JG., Langer R., Traverso G.; Bioplastics for a circular economy; NatRev Mater 7, 2022; 117–137.

Rutkowska A., Rachoń D.; Bisphenol A (BPA) and its potential role in the pathogenesis of the polycystic ovary syndrome (PCOS); Gynecol Endocrinol., 2014; 30(4):260-5.

Sarasamma S., Audira G., Siregar P., Malhotra N., Lai Y.-H., Liang, S.-T., Chen J.-R., Chen K.H.-C., Hsiao C.D.; Nanoplastics Cause Neurobehavioral Impairments, Reproductive and Oxidative Damages, and Biomarker Responses in Zebrafish: Throwing up Alarms of Widespread Health Risk of Exposure; Int. J. Mol. Sci. 2020; 21, 1410.

Salthouse T.N., Matlaga B.F.; Significance of cellular enzyme activity at nonabsorbable suture implant sites: silk, polyester, and polypropylene; J. Surg. Res., 19 (2), 1975; pp. 127-128.

Schirinzi G.F., Pérez-Pomeda I., Sanchís, J., Rossini, C., Farré M., Barceló D.; Cytotoxic effects of commonly used nanomaterials and microplastics on cerebral and epithelial human cells; Environ. Res. 2017; 159, 579–587.

Schmidt C., Lautenschlaeger C., Collnot E.M., Schumann M., Bojarski C., Schulzke J.D.; Nano- and microscaled particles for drug targeting to inflamed intestinal mucosa: A first in vivo study in human patients; J Controlled Release, 2013; 165(2):139–45.

Schraufnagel D.E.; The health effects of ultrafine particles; Exp Mol Med. 2020; 52(3):311–17.

Schwabl P., Köppel S., Königshofer P., Bucsics T., Trauner M., Reiberger T., Liebmann B.; Detection of Various Microplastics in Human Stool: A Prospective Case Series; Ann Intern Med., 2019; Oct 1;171(7):453-457.

Segovia-Mendoza M., Nava-Castro K. E., Palacios-Arreola M. I., Canales C. G., Morales-Montor J.; How microplastic components influence the immune system and impact on children health: Focus on cancer; 2020.

Segovia-Mendoza M., Palacios-Arreola M.I., Pavón L., Becerril L.E., Nava-Castro K.E., Amador-Muñoz O., Morales-Montor J.; Environmental Pollution to Blame for Depressive Disorder? Int J Environ Res Public Health, 2022; 19(3):1737.

Senathirajah K., Attwood S., Bhagwat G., Carbery M., Wilson S., Palanisami T.; Estimation of the mass of microplastics ingested – A pivotal first step towards human health risk assessment; J Hazard Mater, 2021; 404(B):124004.

Sevilla M.E., Garcia M.D, Castillo Y.P., Jaramillo V.A., Casado S., Karla Vizuete, Debut A., Mejia L.C.; Degradation of PET Bottles by and Engineered Ideonella sakaiensis PETase; Polymers (Basel), 2023; 3;15(7):1779.

Shen R., Yang K., Cheng X., Guo C., Xing X., Sun H., Liu D., Liu X., Wang D.; Accumulation of polystyrene microplastics induces liver fibrosis by activating cGAS/STING pathway; Environmental Pollution, 2022; Volume 300, 118986.

Shoaff J.R., Coull B., Weuve J., Bellinger D.C., Calafat A.M., Schantz S.L., Korrick S.A.; Association of Exposure to Endocrine-Disrupting Chemicals During Adolescence with Attention-Deficit/Hyperactivity Disorder–Related Behaviors; JAMA Netw. Open., 2020; 3:e2015041.

Stager C.; Deep Future: The Next 100,000 Years of Life on Earth; Thomas Dunne Books: New York, NY, USA, 2012.

Stahel W.R.; The circular economy; Nature 2016; 531(7595):435–438.

Stevens M.P.; Polymer additives: Part I. Mechanical property modifiers; J Chem Educ. 1993; 70(6):444–8.

Studnicka M.J., Menzinger G., Drlicek M., Maruna H., Neumann M.G.; Pneumoconiosis and systemic sclerosis following 10 years of exposure to polyvinyl chloride dust Thorax, 50 (1995), pp. 583-585.

Syberg K., Nielsen M.B., Oturai N.B., Westergaard Clausen L.P., Ramos T.M., Foss Hansen S.; Circular economy and reduction of micro(nano)plastics contamination; Journal of Hazardous Materials Advances; Volume 5, February 2022, 100044.

Sun J., Yang S., Zhou G.-J., Zhang K., Lu Y., Jin Q.; Release of microplastics from discarded surgical masks and their adverse impacts on the marine copepod tigriopus japonicus; Environ Sci Technol Lett. 2021; 8:1065–1070.

Sun W., Jin C., Bai Y., Ma R., Deng Y., Gao Y., Pan G., Yang Z., Yan L.; Blood uptake and urine excretion of nano- and micro-plastics after a single exposure; Science of the total environment 848, 2022; 157639.

Sun X.; Zhang W.; Wang Y.; Zhang Y.; Liu X.; Shi X.; Xu S.; Combined exposure to di(2-ethylhexyl) phthalate and polystyrene microplastics induced renal autophagy through the ROS/AMPK/ULK1 pathway; Food Chem. Toxicol., 2023; 171, 113521.

Tang Y.; Zhao R.; Pu Q.; Jiang S.; Yu F.; Yang Z.; Han T.; Investigation of nephrotoxicity on mice exposed to polystyrene nanoplastics and the potential amelioration effects of DHA-enriched phosphatidylserine; Sci. Total Environ. 2023; 892, 164808.

Tchounwou P.B.; Yedjou C.G.; Patlolla A.K.; Sutton D.J.; Heavy Metals Toxicity and the Environment; Exp. Suppl. 2012; 101, 133–164.

Textor S.C.; Ischemic nephropathy: where are we now? J Am Soc Nephrol., 2004; (8):1974-82.

They Deng Y.; Zhang Y.; Lemos B.; Ren H.; Tissue accumulation of microplastics in mice and biomarker responses suggest widespread health risks of exposure; Sci. Rep. 2017; 7, 46687.

Thompson R.C., Swan S.H., Moore C.J., Vom Saal F.S.; Our plastic age; Philos Trans R Soc Lond B Biol Sci., 2009; 364(1526):1973-6.

Torres-Agullo A, Karanasiou A, Moreno T, Lacorte S. Overview on the occurrence of microplastics in air and implications from the use of face masks during the COVID-19 pandemic. Sci Total Environ. 2021 Dec 15; 800:149555.

Trasande L., Liu B., Bao W.; Phthalates and attributable mortality: A population-based longitudinal cohort study and cost analysis; Environmental Pollution, 2022; Volume 292, Part A, 118021.

Urban R.M., Jacobs J.J., Tomlinson M.J., Gavrilovic J., Black J., Peoc'h M.; Dissemination of wear particles to the liver, spleen, and abdominal lymph nodes of patients with hip or knee replacement; The Journal of Bone and Joint Surgery, 2000; 82: 457.

Vaccari M., Tudor T., Perteghella A; Costs associated with the management of waste from healthcare facilities: an analysis at national and site level; Waste Manag Res, 2018; 36(1):39–47.

Valavanidis A., Vlachogianni T., Fiotakis K., Loridas S.; Pulmonary oxidative stress, inflammation and cancer: Respirable particulate matter, fibrous dusts and ozone as major causes of lung carcinogenesis through reactive oxygen species mechanisms; Int. J. Environ. Res. Public Health, 2013; 10, 3886–3907.

Vethaak A.D., Legler J.; Microplastics and human health; Science, 2021; 371, 672–674.

Vlacil A.K., Ba¨nfer S., Jacob R., Trippel N., Kuzu I., Schieffer B.; Polystyrene microplasticparticles induce endothelial activation; PLoS ONE, 2021; 16(11): e0260181.

Vogelzangs N., Duivis H.E., Beekman A.T., Kluft C., Neuteboom J., Hoogendijk W., Smit J.H., De Jonge P., Penninx B.W.; Association of depressive disorders, depression characteristics and antidepressant medication with inflammation; Transl. Psychiatry, 2012; 2:e79.

Volkheimer G.; Passage of particles through the wall of the gastrointestinal tract; Environ Health Perspect, 1974; 9:215–25.

Wagner M., Scherer C., Alvarez-Mun˜oz D., Brennholt N., Bourrain X., Buchinger S., Fries E., Grosbois C.; Microplastics in freshwater ecosystems: What we know and what we need to know; Environmental Sciences Europe, 2014 26:(1):12.

Wang Q., Bai J., Ning B., Fan L., Sun T., Fang Y., Wu J., Li S., Duan C., Zhang Y., Liang J., Gao Z.; Effects of bisphenol a and nanoscale and microscale polystyrene plastic exposure on particle uptake and toxicity in human Caco-2 cells; Chemosphere, 254, 2020; Article 126788.

Wang Z., Lin T., Chen W.; Occurrence and removal of microplastics in an advanced drinking water treatment plant (ADWTP); Sci Total Environ. 2020; 700:134520.

Waring R.H., Harris R.M., Mitchell S.C.; Plastic contamination of the food chain: a threat to human health? Maturitas, 115, 2018; pp. 64-68.

Webster A.C., Nagler E.V., Morton R.L., Masson P.; Chronic Kidney Disease; Lancet., 2017; 389(10075):1238-1252.

WHO EURO; From Linear to Circular Economy: Health Implications of Sustainable Consumption and Production, 2018.

World Health Organization; Microplastics in drinking-water; Geneva,2019.

Wright S. L., Thompson R. C., Galloway T. S.; The physical impacts of microplastics on marine organisms: a review; Environmental Pollution, 2013; 178: 483–492.

Wright S.L. and Kelly F.J.; Plastic and Human Health: A Micro Issue? Environ. Sci. Technol., 2017; 51, 6634–6647.

Wu P., Lin S., Cao G., Wu J., Jin H., Wang C., Wong M.H., Yang Z., Cai Z.; Absorption, distribution, metabolism, excretion and toxicity of microplastics in the human body and health implications; Journal of Hazardous Materials, 2022; 437, 129361.

Xie X., Deng T., Duan J., Xie J., Yuan J., Chen M.; Exposure to polystyrene microplastics causes reproductive toxicity through oxidative stress and activation of the p38 MAPK signaling pathway; Ecotoxicol. Environ. Saf., 2019; 190, 110133.

Xiong X., Gao L., Chen C., Zhu K., Luo P., Li L.; The microplastics exposure induce the kidney injury in mice revealed by RNA-seq.; Ecotoxicol. Environ. Saf., 2023; 256, 114821.

Yang Y.F., Chen C.Y., Lu T.H., Liao C.M.; Toxicity-based toxicokinetic/ toxicodynamic assessment for bioaccumulation of polystyrene microplastics in mice; J. Hazard. Mater., 2019; 366, 703–713.

Zhao T., Shen L., Ye X., Bai G., Liao C., Chen Z., Peng T., Li X., Kang X., An G.; Prenatal and postnatal exposure to polystyrene microplastics induces testis developmental disorder and affects male fertility in mice; Journal of Hazardous Materials, 2023; Volume 445, 130544.

Zettler E.R., Mincer T.J., Amaral-Zettler. L.A.; Life in the 'plastisphere': Microbial communities on plastic marine debris; Environmental Science and Technology, 2013; 47: 7137–7146.

Zhang H., Ricciardi B.F., Yang X., Shi Y., Camacho N.P., Bostrom M.P.G.; Polymethylmethacrylate particles stimulate bone resorption of mature osteoclasts in vitro; Acta Orthopaedica, 2008; 79: 281–288.

Zhang Y., Lu J., Wu J., Wang J., Luo Y.; Potential risks of microplastics combined with superbugs: Enrichment of antibiotic resistant bacteria on the surface of microplastics in mariculture system; Ecotoxicol Environ Saf. 2020; 15; 187:109852.

Zolnik B.S., González-Fernaández A., Sadrieh N., Dobrovolskaia M.A.; Nanoparticles and the Immune System; Endocrinology, 2010; 151, 458–465.

Zou H., Chen Y., Qu H., Sun J., Wang T., Ma Y., Yuan Y., Bian J., Liu Z.; Microplastics Exacerbate Cadmium-Induced Kidney Injury by Enhancing Oxidative Stress, Autophagy, Apoptosis, and Fibrosis; Int. J. Mol. Sci., 2022; 23, 14411.

WEBSITES

http://www.issalute.it/

www.niehs.nih.gov/health/topics/agents/endocrine/

https://op.europa.eu/en/publication-detail/-/publication/8e12a450-cb71-4356-bd3b-8a9f980208a0

https://www.who.int/publications/i/item/9789240054608

https://www.who.int/news/item/22-08-2019-who-calls-for-more-research-into-microplastics-and-a-crackdown-on-plastic-pollution

https://www.medicalnewstoday.com/articles/could-microplastics-in-human-blood-pose-a-health-risk#An-innovative-detection-method

https://www.epa.gov/dwucmr/occurrence-data-unregulated-contaminant-monitoring-rule#3

https://environment.ec.europa.eu/strategy/plastics-strategy_en

https://www.who.int/news/item/03-03-2020-shortage-of-personal-protective-equipment-endangering-health-workers-worldwide

https://fresh-lock.com/blog/flexible-packaging-circular-economy

https://ubqmaterials.com/blog-post/what-are-the-17-sustainable-development-goals-sdgs/

https://assets.kpmg.com/content/dam/kpmg/be/pdf/2023/From-Linear-to-Circular-Sustainability-in-the-Medical-Device-Industry.pdf

https://it.wikipedia.org/wiki/Emodialisi aifa.gov.it/documents/20142/0/guideline-phthalates_04.10.2018.pdf

Stratigraphy, Sedimentology and Palaeontology | The Plastocene – Plastic in the sedimentary record (egu.eu)