



Microplastics and nanoplastics in haemodialysis waters: Emerging threats to be in our radar

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ABSTRACT

Microplastics are present in the environment, in drinking water, in human blood and there is evidence of nanoplastics in tap water. The objective of this work was to analyze the possibility of hemodialysis patients being contaminated by micro and nanoplastics (MNPs) during dialysis treatment. The motivation for this investigation is the fact that hemodialysis patients use about 300–600 L of drinking water per week, which may be contaminated by MNPs. A literature review, a field investigation in a London hospital and an estimation of MNPs intake in patients were carried out. The results showed potential points of risk of contamination of patients by MNPs in hemodialysis. It was also estimated that for a filtration efficiency of 99 % for MNPs, the amount of microplastics that can penetrate the kidneys of patients is 0.0021–3768 particles/week. The assessment concludes that hemodialysis patients are at high risk of MNP contamination.

1. Introduction

Chronic kidney disease (CKD) is now emerging as one of the most severe non-communicable global public health priorities, associated with increased morbidity, mortality and high healthcare costs. Worldwide, kidney replacement therapy (KRT) is used by about 3 million people. Haemodialysis (HD) accounts for about 69 % of all KRT and 89 % of all dialysis therapies (Bello et al., 2022). In the UK, HD continues to expand, with more than 25,000 patients receiving treatment (Ashby et al., 2019). HD is an established treatment for patients with end-stage CKD, removing waste products of metabolism and restoring acid-base and volume homeostasis by the passage of blood through a capillary dialyser, where blood is separated from a counter-current flow of

dialysate by a thin membrane, which acts as a semi-permeable membrane. Dialysis was first described by the British chemist Thomas Graham in 1854. Graham is considered the father of modern dialysis. He was a professor at Anderson University in Glasgow and University College London (Gottschalk and Fellner, 1997). Around the same time, the physician Richard Bright described the clinical features and diagnosis of renal failure. Bright, a physician at Guy's Hospital in London, was the first to describe the clinical manifestations of the renal disorder known as Bright's disease or nephritis (Bright, 1955). Interestingly, both proposed the basis of a treatment for kidney failure and predicted that it would take about 60 years to develop the system to be used for patients. Dialysis equipment underwent continuous improvement during the 1940s and 1950s, when the first disposable haemodialyser appeared,

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with further significant advances in the 1960s (Carvalho et al., 2022).

As the blood of dialysis patients potentially requires between 300 and 600 L of dialysate (solution composed of water and solutes such as sodium, potassium, bicarbonate, calcium, magnesium, acetate, and glucose) per week, the quality of the water used for HD treatment is important (Bookshelf et al., 2015; Chaoui et al., 2022).

During HD or haemodiafiltration (HDF) treatment, blood is pumped from the patient, either using an arterio-venous fistula, graft or a central venous catheter, at a flow rate of 250–450 mL/min through a hollow fibre capillary dialyser containing up to 15,000 fibres. The material composition of dialysis membranes typically includes a basic cellulose or synthetic polymer, with synthetic membranes now dominating the market. The synthetic polymers used include polysulfone (PSU), polyethersulfone (PES), polymethylmethacrylate, polyester polymer alloy, polyacrylonitrile, polycarbonate, polyamide (PAM) and polyethylene-co-vinyl alcohol. The basic polymer is then modified, typically by adding acetate groups, and polyvinyl pyrrolidone to PS and PES membranes, along with plasticisers. Manufacturers differ in the amounts and combinations of plasticisers used and also the methods of sterilization. Synthetic polymers have physicochemical advantages over cellulosic membranes, including higher solute removal capacity, larger pore sizes, greater hydraulic permeability and higher filtration capabilities (Yi Chun Chen et al., 2022; Yee An Chen et al., 2022). These fibres are enclosed in a sturdy plastic casing. It is worth mentioning that the header and casing are designed to exclude potentially toxic plasticizers, particularly bisphenol and high molecular weight phthalates.

Fig. 1 shows a dialyser and the basic construct of a dialyser with blood and dialysate flows. As blood flows through the dialyser, it is exposed to the dialysis solution (dialysate) through a semi-permeable membrane. Most transfer of solutes between blood and dialysate occurs by diffusion. Although excess fluid and toxins are removed from the blood to the dialysate, as diffusion is a random process, equally substances in the dialysate can diffuse from the dialysate into the blood down a concentration gradient. Thanks to advancements in membrane technology and innovative designs aimed at enhancing solute clearance, the pores within the dialyzer membrane have significantly increased in size. Consequently, this allows for the transfer of middle-sized molecules (10–40 kDa).

Additionally, owing to the varying hydrostatic pressure between the blood and dialysate flows entering and exiting the dialyzer, the dialysate now directly enters the patient's bloodstream during a standard high-flux and middle cut-off dialyzer treatment in HD. Depending upon the choice of dialyser, and duration of the treatment session, between 6 and 15 L of dialysate may pass directly into the blood. Haemodiafiltration (HDF) is a modification of standard HD, during which a hydrostatic pressure is exerted as blood flows through the dialyser, removing litres of plasma water each session. Dialysate water is pumped directly into the patient's blood stream to prevent dehydration. Depending on whether HDF is in post- or pre-dilution mode, between 20 and 45 L of

dialysate will directly enter the blood during a single treatment. In the UK, the National Institute for Health and Care Excellence now recommends HDF as the preferred treatment for all HD patients. A detailed description of the entire water filtration process for HD as well as the storage system can be found in the [Supplementary Material](#) (Text S.1, Figures S.1 to S.3). These figures suggest that there is an eminent risk of micro and nanoplastics (MNPs) (1 nm to <5 mm) (Frias and Nash, 2019) contamination by the patient. This is because the treatment system has filtration devices that may potentially not remove certain sizes of microplastics, and it has components made of plastics which can potentially release microplastics and their additives. Therefore, we hypothesise that HD patients are at high risk of microplastic and their additive contamination during HD treatment. Therefore, the aim of this work was to analyze the possibility of hemodialysis patients being contaminated by micro and nanoplastics (MNPs) during dialysis treatment.

This opinion article seeks to draw attention to the need to carry out quantitative analyzes of MNPs in HD, since, from a theoretical point of view, the estimates made based on secondary data from MNPs found in water treatment plants (Pivokonský et al., 2018, 2020; Mintenig et al., 2019; Pivokonský et al., 2020; Barbier et al., 2022; Li et al., 2022) indicate contamination of patients by these emerging risks.

In our review, we found no articles raising the risk of exposure to MNPs in HD treatment. Our review also points out possible filtration failures and hardware points of possible release of MNPs, even after filtration process. Therefore, as research gaps, we cite the need to quantitatively assess the presence of MNPs and their additives in HD water after filtration, to investigate whether reverse osmosis membranes are sufficient to filter MNPs and additives. Due to the deterioration of RO membranes made from synthetic polymers, it is important to investigate whether they can be a source of MNPs for the patient. It is also important to investigate whether post-filtration distribution and storage systems can contribute to the formation of MNPs, carry out research aimed at developing more efficient filtration systems for hemodialysis water and investigate the correlation between contamination of patients undergoing hemodialysis by MNPs and possible reduction in life expectancy.

2. Drinking water contamination by MNPs

According to the Organisation for Economic Co-operation and Development (OECD, 2022), global plastic use is projected to nearly triple between 2019 and 2060, increasing from 460 million tonnes (Mt) to 1231 Mt annually. The leakage of plastics environmentally and terrestrially is projected to expand from 22 Mt, from 2019 to 44 Mt by 2060. This is a highly uncertain projection, with estimates ranging from 34 to 55 Mt (OECD, 2022). Around 90 % of the world's total plastic production consists of polyethylene terephthalate (PET), high-density polyethylene (HDPE), PVC, low-density polyethylene (LDPE), polypropylene (PP), polystyrene (PS) and polyurethane (PUR) (Boyle and

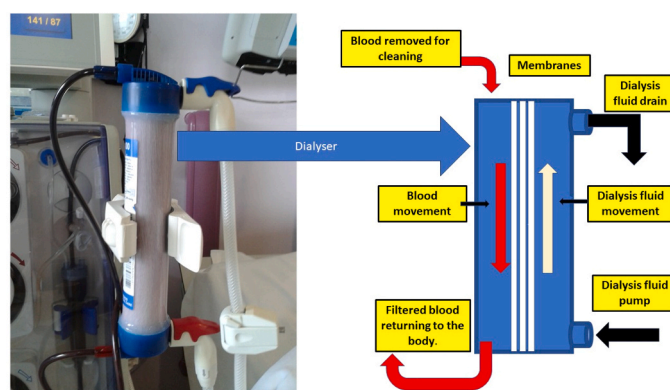


Fig. 1. Dialysers and scheme to the blood purification system. Photo: R.S. Passos.

Örmeçi, 2020). Most of these plastics are persistent in the environment and can only degrade into microplastics and subsequently into nanoparticles (Urbanek et al., 2018).

Evidence of microplastics in drinking water as well as in lakes and rivers is well established (Peng et al., 2018; Estuary et al., 2018; WHO, 2019; Danopoulos et al., 2020; Li et al., 2020). Despite the detection difficulties, nanoplastics in drinking water in plastic bottles and taps have also been reported (Huang et al., 2022; Li et al., 2022). The detection of MNPs in drinking water has sparked concerns regarding the effectiveness of drinking water treatment plants (DWTPs) in capturing and preventing the entry of MNPs into the drinking water system (J. Lee et al., 2023; Kundu et al., 2021; M. Lee Pulido-Reyes et al., 2023, 2022; Sun et al., 2022; Yongli Zhang et al., 2020; Yue Li et al., 2020). MNPs are removed to certain extent from drinking water by conventional methods such as sand filtration, coagulation-flocculation, and membrane filtration, where the removal efficiency varies according to the method and particle size. For example, it was found that sand filtration of nanoplastics had a removal efficiency that ranged from 32 % to 92 % (Keerthana Devi et al., 2022). Development of advanced filtration processes, with nanofiltration membrane (efficiency of 99 %) and centrifugation (efficiency of 98.4 %), open a way for the removal of nanoplastics (Keerthana Devi et al., 2022). The most widely used water treatment process by DWTPs is membrane filtration, using a variety of materials, including PES, PVC, PP, and polyvinylidene fluoride (PVDF) (Ding et al., 2021). The effects of physical cleaning, chemical agents, mechanical stress, ageing, and wear, increase the possibility of membrane rupture during long-term use, which has raised concerns as to whether these membranes have not been a source of microplastics themselves (Ding et al., 2021).

In their formulation, plastics are composed of polymers or polymer blends and plastic additives. Additives are substances that give plastic the desired properties. Additive formulations include functional agents such as plasticisers, impact modifiers, flame retardants, and inert or reinforcing fillers. Stabilisers such as antioxidants, ultraviolet (UV) filters and thermal stabilisers, as well as lubricants and colourants are also included. Inert fillers provide strength, improve flow and shrinkage of plastics, and include asbestos, glass, rutile, silica, talc, clays, chalk, aluminium oxide, soot and carbon nanotubes. During polymer manufacture, additives are incorporated into polymers which are not chemically bound. In this sense, and due to their low molecular weight, plastic additives can leach and pass into the external medium along a concentration gradient (Baj et al., 2022; Gopinath et al., 2022).

Chemical leaching is facilitated by the increase of the active surface area in contact with the external medium due to the decrease in particle size. If MNPs accumulate in living organisms, they can become a source of plastic chemical additives and polymer monomers for tissues and fluids (Llorca and Farré, 2021; Gopinath et al., 2022).

Drinking water used for HD can originate from surface water (i.e. rivers and lakes) or groundwater. In general, potable water used for HD, depending on the local geography, may go directly from a DWTPs to the hospital, or it may come from an existing artesian well in the hospital or clinic, or from an artesian well of a water distributor, which will transport this potable water by water trucks. These waters can be contaminated by various MNP sources. In the case of surface water, atmospheric pollution from synthetic fibres, resuspended tyre dust from urban transport systems and vehicles, plastic particles emitted from incineration, industries (including wastewater treatment works) and agriculture are the main sources of contamination (Amato-Lourenço et al., 2020; Yulan Zhang et al., 2020). Plastics present in water, due to sunlight, UV, weather, and microorganisms, undergo a process of degradation and fragmentation, forming microplastics. After which, colonisation with microorganisms leads to the formation of biofilms and causes further biodegradation of micro to nanoplastics, which also may have additional additives. In addition, domestic or industrial effluents are also sources of contamination of rivers and lakes with microplastics (Urbanek et al., 2018). Extensive research has been conducted on the

compounds that adhere to the surface of microplastics, raising concerns about potential chemical impacts, particularly related to heavy metals and highly hydrophobic contaminants (Costigan et al., 2022). Among the highly hydrophobic contaminants, persistent organic pollutants (POPs), including polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), dichlorobiphenyl trichloroethane (DDTs), hexachlorocyclohexanes (HCHs) and polycyclic aromatic hydrocarbons (PAHs), were investigated, as well as the potential for microplastics to interact with other emerging pollutants, such as active pharmaceutical compounds (PhACs), antibiotics, or UV filters (Menéndez-Pedriz and Jaumot, 2020).

Microplastics in groundwater can have several sources, including the atmosphere, interaction with surface water bodies, urban infrastructure or agricultural soils. Evidence of potential groundwater contamination by microplastics has been found (Alvarado-Zambrano and Rivera-Hernández, 2022; Ding et al., 2021; Goepfert and Goldscheider, 2021; Severini et al., 2022). Atmospheric inputs, tyre wear and common agricultural practices, such as the application of compost, biosolids from wastewater treatment plants (WWTPs) or mulch, introduce MNPs and organic contaminants into the soil. Bioturbation, cultivation or preferential flow paths increase the vertical transport of MNPs formed by the degradation of plastics (Moeck et al., 2022). MNPs containing organic contaminants are suspected to relocate vertically towards the groundwater. Heavy metals are transported by microplastics increasing the contamination load of freshwater systems, which supply water treatment plants for HD (Baj et al., 2022; Liu et al., 2022).

Therefore, it becomes evident that the drinking water which potentially serves hospitals and dialysis centres may be at risk of contamination by MNPs and their additives.

3. Toxicological risks to human health from MNPs contamination

There is concern about the toxicity and health effects associated with microplastics (Kumar et al., 2023). However, in the case of dialysis patients, the main potential route of penetration would be during the dialysis treatment, where water passes through a dialyser and comes into contact with the patient's blood or passes directly into the blood. As dialysis patients pass little or minimal urine, they are less able to excrete MNPs, so they are potentially at greater risk of accumulating these potentially harmful compounds. Therefore, if the dialysate is contaminated by MNPs and their additives, these contaminants will be transported into the blood and directly enter the human body of dialysis patients. Blood is a liquid tissue and plays a key role in the circulatory system. It is through the bloodstream that oxygen and nutrients reach the cells. Thus, if the blood becomes contaminated by MNPs during HD treatment, then the entire human system will be potentially contaminated at the cellular level. After entering the human body, MNPs can be taken up into cells by phagocytosis, micropinocytosis, clathrin-mediated endocytosis and cavity-mediated endocytosis. The size, surface area, charge, and chemistry of the cells define the number of MNPs that are absorbed (Yee et al., 2021).

Recent research has analyzed the responses of human embryonic kidney 293 T cells to PS nanoplastics, focusing mainly on the effects of particle size and Pb^{2+} enrichment. It was observed that, for particles larger than 100 nm, there is no obvious cell death. However, as the particle size decreases from 100 nm, cell mortality increases. The study also showed that, compared to human liver LO2 cells, although the internalization of the polystyrene nanoplastics in LO2(liver) cells is at least 5 times higher than in 293 T(kidney) cells, the mortality of LO2 cells is lower than that of 293 T cells. That is, 293 T cells from human kidney are less resistant than LO2 cells from human liver to PS nanoplastics (Yu Li et al., 2023).

In vitro studies of exposure to PS-microplastics ($3.54 \pm 0.39 \mu\text{m}$) in human embryonic kidney 293 (HEK293) showed that antioxidant enzymes were inhibited, which led to induced ROS cytotoxicity and

apoptosis induced by PS- microplastics and autophagy. It was also verified that PS- microplastics caused inhibition of NLRP-3, therefore decreasing inflammatory response. Thus, exposure to realistic concentrations of PS-MNPs has been shown to have the potential to influence kidney health in humans (Y. C. Chen et al., 2022). PS nanoplastics enter Human Renal Epithelial Cell (HRCE) by multiple mechanisms that are both energy-dependent(endocytosis) and energy-independent (Lai et al., 2022). MNPs have been shown to stimulate the production of cytokines, producing local and systemic inflammation in rat kidneys (Khan and Jia, 2023).

Plastic additives present in the plastic formulation may release toxic substances. It should be noted that the potential effects of MNPs span a wide range of polymers and chemical additives, showing various physicochemical and toxicological properties, size, shape and surface properties, all of which can influence the toxicological effects of MNPs in humans (Sangkham et al., 2022; Lai et al., 2022; Baj et al., 2022; Kannan and Vimalkumar, 2021; Llorca and Farré, 2021).

Microplastic additives, including organotins, phthalates, and bisphenols, cause adverse effects to human cell lines in culture through activation of nuclear receptors, peroxisome proliferator-activated receptors (PPARs) α , β and γ and retinoid X receptors (RXR). These effects affect cellular energy production, increase cytotoxicity, oxidative stress, immunotoxicity, altered adipogenesis and thyroid hormone disruption (Llorca and Farré, 2021). PVC, commonly used in the tubing in HD extracorporeal circuits, leaches endocrine disrupting agents such as phthalates and bisphenol A (BPA), which are currently considered "substances of very high concern" when in contact with water (Boyle and Örmeci, 2020).

Table 1 shows plastics used in the manufacture of water storage tanks and distribution systems for HD and the types of additives used in the manufacture of these plastics. Column 1 of this table presents the plastics used in the manufacturing of water storage tanks and distribution systems. In column 2, plastic additives used in manufacturing of water storage tanks and distribution systems are listed. Therefore, there is an eminent risk that these plastic materials may be releasing MNPs and additives to the HD water. It can be seen that PVC alone or a combination is the most used among plastic materials. This raises concern about possible patient contamination due to its additives (phthalates and bisphenols).

4. Potential contamination of patients by MNPs during haemodialysis treatment

The rigour of the quality assurance of HD water is essential to ensure patient safety, and if control standards are not properly respected, then patients may die. Established risk management techniques such as the Hemo Pause checklist and Failure Mode and Effect Analysis (FMEA) (Arenas Jiménez et al., 2017) have been used as strategies to identify possible failures during patient treatment, their causes, consequences and to establish preventive measures.

As MNPs are an emerging risk, there are many doubts as to absolute

Table 1

Plastics and additives that may be found in haemodialysis.

Plastics used in the manufacturing of water storage tanks and distribution systems	Plastic additives used in manufacturing of water storage tanks and distribution systems
<ul style="list-style-type: none"> • Polyvinyl chloride (PVC) (Tereshchenko and Posnack, 2019) (Total Water Treatment Systems (n.d.)) • Chlorinated polyvinyl chloride (CPVC) (Finotti Jr, 2017) • Cross-linked polyethylene (PEX). (Finotti Jr, 2017) • Natural polypropylene (unpigmented) (Total Water Treat. Syst., 2023.) 	<ul style="list-style-type: none"> • Di(2-ethylhexyl) phthalate (DEHP) (Tereshchenko and Posnack, 2019) • Bisphenol-A (BPA) (Tereshchenko and Posnack, 2019) • Organotins (Blunden and Evans, 1990)

toxicity, and further research is required to determine risk assessment and the effects of exposure to MNPs on human health. It is not yet possible to know whether HD patients may be contaminated or whether this results directly in patient morbidity and mortality.

Information from the manufacturers of RO membranes indicates that RO membranes are very efficient and capable of filtering smaller particles than nanoplastics. For example, nanofiltration can remove particles $> 0.001 \mu\text{m}$, while ultrafiltration can remove particles $> 0.01 \mu\text{m}$ (WHO, 2019). Currently, while it is not feasible to definitively confirm whether HD patients are being exposed to contamination from MNPs and their additives, it is equally impossible to dismiss the potential risks they may face. Therefore, it is crucial to acknowledge that the potential for contamination cannot be ruled out, and there is a possibility of it occurring through various means. Some of the HD RO failures may include (Dheda et al., 2015):

- Failures in the filtration process, damaging the RO membrane, allowing the passage of MNPs that can then reach the patient,
- Use of RO membranes made of synthetic material and their deterioration could become another source of MNPs,
- Use of plastic pipes to transport water during the process of making dialysate
- Use of plastic manufactured water storage tanks,
- Use of plastic piping for water distribution after storage in Tanks,
- MNPs could leach from the acid concentrate containers and bicarbonate bag located after the RO,
- The presence of visible light may be a factor contributing to the degradation of plastic materials after water filtration (but likely to have limited role),
- Presence of biofilms and interaction with microplastics may contribute to the formation of nanoplastics,
- The dialyser could be a source of MNPs, as the majority of dialysers used worldwide are made of plastic polymer materials, and sterilisation techniques, particularly those using irradiation, can cause changes to the plastic polymer and plasticisers.

In addition, the filtration failures related to RO membranes may be due to Dheda et al. (2015):

- Failed softener system upstream leading to damage of the RO membranes
- Failure with the carbon filter allowing the passage of strong oxidising agents, including chlorine, chloramine and nitrogen dioxide.
- Failure to control the pH of the water, which must be between 5 and 8.5. Values greater than 8.5 interfere with the absorption of chloramine from activated carbon filters, decreasing their effectiveness and also reducing the efficiency of the reverse osmosis membrane.
- Decreased RO membrane filtration efficiency over time due to: fouling - the entrapment of particles in the membrane; desquamation - deposition of, for example, calcium salts; and increased membrane degradation.

A study of over 600 autopsies of reverse osmosis membranes from various locations around the world was undertaken by the Genesys Membrane Products (GMP) laboratory and provided very valuable information on membrane failure. It was shown that in almost 75 % of cases, fouling is the main cause of membrane failure.

With this in mind, we have estimated the potential number of MNPs in the kidneys of patients undergoing HD treatment (Table 2), considering water consumption values of 300 L per week or 600 L per week for patients having 1 or 2 HD treatments per week, respectively. Due to the lack of data on MNPs after the HD water treatment system, we considered two assumptions. First, the RO system removes 99 % of drinking water MNPs, and secondly, the RO system does not effectively remove the MNPs, allowing all MNPs present in the mains drinking water entering the HD machine. Estimated MNPs intake values were calculated by multiplying the MNP concentration by the estimated range of weekly water consumption values for each patient (300 L/week and

Table 2

Estimates of microplastics in the kidneys of patients undergoing haemodialysis procedures, considering the presence of microplastics in drinking water.

Microplastics Country & Reference	DWTP configuration	Concentration of microplastics in treated water (particles/L)	Particle size	Type of plastics	Number of microplastics potentially entering kidney patients, considering RO efficiency of 99 % (particles/week)			
					300 L/week		600 L/week	
Czech Republic (Pivokonský et al., 2020)	Coagulation + Filtration Deep bed filtration Ozonation + granular activated carbon (GAC)	14	Prevalent type of MPs was fragments < 10 µm	PET, PVC, PE, and PP	42	84	4200	8,400
Czech Republic (Pivokonský et al., 2020)	Coagulation + Filtration Deep bed filtration Ozonation + granular activated carbon (GAC)	151	Prevalent type of MPs was fragments < 10 µm	PET, PVC, PE, and PP	453	906	45,300	90,600
Czech Republic (Pivokonský et al., 2018)	Coagulation/flocculation and sand filtration	628	1–10 µm	PET, PE and PP	1884	3768	188400	376,800
Czech Republic (Pivokonský et al., 2018)	Coagulation/flocculation and sand filtration	338	1–10 µm	PET, PE and PP	1014	2028	101,400	202,800
Czech Republic (Pivokonský et al., 2018)	Coagulation/flocculation and sand filtration	369 n	1–10 µm	PET, PE and PP	1107	2214	110,700	221,400
France (Barbier et al., 2022)	Pre-ozonation, Coagulation-flocculation (C-F), sedimentation, sand filtration (SF), ozonation, granular activated carbon filtration (CAGF), Ultraviolet (UV), chlorination	0.022 (Higher value)	25–5000 µm	PE and PS	0.066	0.132	6.60	13.20
France (Barbier et al., 2022)	C-F, sedimentation, SF, ozonation, CAGF, UV, chlorination	0.260 (Higher value)	25–5000 µm	PE, PP, and PET	0.78	1.56	78	156
France (Barbier et al., 2022)	Conventional file: C-F, sedimentation, SF, ozonation, GACF, UV, chlorination Nanofiltration file: C-F, lamellar settling, ozonation, sand + anthracite filtration, microfiltration, nanofiltration, degassing, UV, mix with water produced from the conventional file	0.090 (Higher value)	25–5000 µm	PE, PVC, and PET	0.27	0.54	27	54
Germany * (Mintenig et al., 2019)	Aeration and filtration	0.0007 (Higher value)	50–150 µm	Polyester (PEST), PVC, PA, PE and epoxy resin (Additive)	0.0021	0.0042	0.21	0.42
Nanoplastics Country & Reference	DWTP configuration	Concentration of nanoplastics in treated water (µg /L)	Particle size	Type of plastics	Mass of nanoparticles potentially entering kidney patients, considering RO efficiency of 99 % (mg/week)		Mass of nanoparticles potentially entering kidney patients, considering RO does not remove the microplastics (mg/week)	
					300 L/week		600 L/week	
China* * (Yu Li, Wang, and Guan 2022)	Not specified	2.08 µg/L (Higher value)	58–255 nm	PO, PS, PVC, PA ***	6.24 µg	12.48 µg	624 µg	1248 µg

(*) DWTP treating groundwater, while the others use surface water.

(**) Tap water.

(***) And plastic additives, such as ethylene-methyl methacrylate copolymer (E-MMA), methyl methacrylate-butadiene-styrene copolymer (MBS), and poly(n-butyl methacrylate).

600 L/week). For the lower estimates, a MNP removal of 99 % was applied, assuming the highest RO filtration efficiency. The highest MNP values entering the kidney was calculated by multiplying the concentration of MNPs by the estimated weekly water consumption per patient, assuming 100 % failure of the RO filtration system (i.e. 0 % MNP removal). Eight studies on DWTP-treated water were selected, five from the Czech Republic and three from France, treating surface water, and one study from Germany, treating groundwater. In the case of nanoplastics, the study was carried out in China. They analyzed tap water and did not specify the type of municipal water treatment system used. However, there is no reason to believe that the water that arrives at home is different from that which arrives at clinics or hospitals for the treatment of patients undergoing HD. In this case, it is important to note that the measurement units of concentration of nanoplastics are different from microplastics. Table 2 shows an important difference between the data from Czech Republic and France. This may be attributed to the influent water quality, size of microplastic particles, and treatment system efficiency. It is apparent that the DWTPs in France are using advanced treatments such as pre-oxidation, oxidation and membrane filtration. However, it is important to highlight that a recent review reported the fragmentation and formation of smaller sizes of microplastics after AOPs (Santos et al., 2023). In addition, it is noted that the DWTPs in France (Barbier et al., 2022) were using sedimentation after coagulation-flocculation, which has been reported to be more effective in removing microplastics (C. Li et al., 2021). On the other hand, the estimates of microplastics from Germany DWTP (Minténig et al., 2019), treating groundwater, were found to be low (0.0021–0.42 particles per week) compared to those treating surface water. In general, groundwaters are well protected from particulate contamination (WHO, 2019).

Furthermore, in most parts of the world, the drinking water that is supplied to households, hospitals, industries etc., is disinfected with chlorine or chlorine compounds (e.g. chloramines) to inactivate harmful pathogens. Water chlorination is country-dependent, and the dosage of chlorine substances added in the water depends on chlorine demand which is dependent on the untreated water quality (e.g. natural organic matter (NOM) content) which is also variable across regions. So, depending on content and type of NOM present, the quantity of chlorine used, pH temperature, and reaction time (Chowdhury et al., 2010), disinfection by-products (DBPs) may be produced from reactions between chlorine and halides with NOM (Ou et al., 2020). Water quality regulations for DBPs such as trihalomethanes (THMs) have become more stringent due to DBP health concerns (e.g. cancer of kidney, bladder, liver, and colorectal) (Yan Zhang et al., 2022). The level of DBPs in the finished water are kept under legal limits via filtration with carbon columns at the water treatment plants. Therefore, as HD water treatment also makes use of a carbon filter (Fig. S1), a failure of this filter may allow the passage of DPBs as well as MNPs and plastic additives to the next treatment stage.

5. Future perspectives on haemodialysis treatment

Given the various pathways that can potentially lead to contamination of patients with MNPs during HD treatment, it is necessary for dialysis centres to establish a water quality monitoring programme to assess this emerging risk. Although it is not standardised and there are no acceptable exposure limits, we should not ignore the WHO report published in 2021 on a Global patient safety action plan 2021–2030 towards eliminating avoidable harm in health care (“Global Patient Safety Action Plan 2021–2030 towards Eliminating Avoidable Harm in Health Care”, 2021), establishing several strategies for patient safety. In summary, this report recommends (“Global Patient Safety Action Plan 2021–2030 Towards Eliminating Avoidable Harm in Health Care”, 2021):

- to develop a system for rapidly implementing recommendations from analyses of adverse events and through proactive risk management,
- to designate an officer or a team responsible for patient safety and clinical risk management in each healthcare facility to minimise patient harm, manage risks and improve patient safety, and
- to implement clinical risk management activities to improve patient care.

Risk management can be adopted by all organisations, regardless of their size, field of activity, number of employees and level of risk. One model that can be used is the International Organization for Standardization -ISO 31000:2018 Risk Management — Guidelines (International Organization for Standardization(2018)ISO 31000, Risk Management – Guidelines (ISO Standard No. 31000:2018), 2018). This international standard recommends basically three steps for risk management in this order: ‘Risk Identification’, ‘Risk Analysis’, and ‘Risk Evaluation’, which should be followed by the ‘Treatment of Risk’. The objective of ‘Risk Identification’ is to identify the sources of risk, carry out their characterization, including from a toxicological point of view and, if possible, determine the dose/response relationship. This study focuses on risk identification, which is located in Sections 2 and 3. Also, in our ‘Risk Identification’ process, the risk of reduced filtration efficiency of the RO membrane and its potential causes and consequences (which can lead to patient contamination) was chosen (see Table 2).

‘Risk Analysis’ can be conducted with varying degrees of detail and complexity, depending on the purpose of the analysis, the availability and reliability of the information, and the resources available. Analysis techniques may be qualitative, quantitative, or a combination, depending on the circumstances and intended use. ‘Risk Evaluation’ aims to support decision-making.

With regard to ‘Risk Treatment’ and considering the different possibilities of contamination paths for MNPs presented in our paper, it is still possible, depending on the technical feasibility and cost-benefit analysis, to propose the use of RO membrane systems constituted of non-plastic materials, replace plastic water storage tanks by stainless steel tanks, replace plastic manifolds by glass or stainless steel tubes, and replace polymer dialyzers by modified cellulosic ones. For greater redundancy, it is suggested the installation of a nanofilter proximal to the return blood access (fistula/venous catheter or blood leaving the dialysis circuit to the patient) as this would potentially prevent micro-particles generated in the plastic tubing and dialyser of the dialysis circuit being returned to the patient.

It is important to remember that the idea of defining risk from a strategic point of view, the ISO 3100:2018 states that risk may be seen as a threat or an opportunity. For example, healthcare institutions can look for opportunities to improve their clinical care of patients through improvements designed to increase patient safety. Research support will always be an opportunity to improve the institution’s image in society to fulfil its social responsibility in promoting patient health and safety and to reduce the costs of future patient treatment needs due to the accumulation of potentially toxic MNPs. In the case of HD patients, this becomes even more relevant, as they already have vulnerable health and potentially other comorbidities, such as diabetes and hypertension. Therefore, a strategic view of risk management and thinking about opportunities can potentially increase patient survival.

Finally, we recommend implementing a comprehensive water quality monitoring program designed specifically for HD to proactively prevent any adverse effects in HD patients. This proposed recognition program aims to ensure the highest standards of water quality during HD treatment, thus safeguarding the wellbeing of patients and minimizing any potential side impacts.

6. Limitations

The main aim of this article was to draw attention of the scientific

community, governments, health care institutes and suppliers of HD treatment systems to the potential exposure and contamination of HD patients to MNPs and their additives, and to highlight the urgent need for research on this topic. One of the limitations of this research is that this work has used secondary data not collected by the authors. Thus, the estimated values of MNPs that enter the kidney of patients may not represent the reality. Another limitation is the water consumption in HD which was adopted based on published literature assumed to estimate the MNPs concentration entering patients.

Therefore, there is an urgent need of in situ research to determine the concentrations of MNPs in HD water treatment systems, considering that water quality and water storage and distribution systems may vary from HD centre to centre. It is possible, for example, that storage and distribution systems for HD water in stainless steel present a lower risk of exposure to the patient. Also to better estimate the amount of MNPs that penetrate the patient's kidney, it is necessary to have accurate water consumption volumes, which may vary according to the location and type of treatment.

7. Conclusion

Microplastics and nanoplastics are now part of our daily life due to the degradation of thousands of tonnes of plastics dumped into the environment by humans and by the ubiquity of plastics in many aspects of our daily life, including HD treatment. The response to the contamination of oceans, rivers, lakes, soil and air, is inexorably linked to the contamination of food and human beings, with adverse health consequences that are being unveiled, although further research is required to better understand the spectrum of effects of MNPs on human health and wellbeing.

In this context, HD patients may be at greater risk due to potential increased exposure during dialysis treatment and their inability to excrete these potential toxins in their urine.

Failures or inefficiency in the filtration systems of drinking water treatment plants (DWTPs) can be a source of MNPs for clinics and hospitals treating patients for HD. In addition, water filtration systems used for HD can also fail potentially contaminating patients. Even if HD water filtration systems do not fail, membranes, storage tanks and distribution systems made from plastic materials, in theory, are likely to be sources of MNPs for HD patients. Thus, we propose a reconnaissance program to monitor the quality of water used for HD, considering the potential presence of MNPs and their additives, to avoid side effects for HD patients.

In addition, a risk management strategy should be implemented by health institutions, and further research is required to establish the toxicity of MNPs in dialysis patients, and determine a critical exposure threshold.

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CRediT authorship contribution statement

Robson S. Passos: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Visualization, Writing – original draft. **Andrew Davenport:** Formal analysis, Resources, Writing – review & editing. **Rosa Busquets:** Formal analysis, Writing – review & editing. **Clare Selden:** Formal analysis, Writing – review & editing. **Luiz B. Silva:** Formal analysis, Writing – review & editing. **J. Santos Baptista:** Formal analysis, Writing – review & editing. **Damià Barceló:** Conceptualization, Formal analysis, Writing – review & editing. **Luiza C. Campos:** Conceptualization, Methodology, Formal analysis, Resources, Project administration, Supervision, Writing – review & editing.

Declaration of Competing Interest

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

Data Availability

Data will be made available on request.

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Appendix A. Supporting information

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