Supplementary Box 1.

Knowledge gap: tubular handling of micro- and nanoplastics

At present, no experimental or clinical data define a maximal tubular uptake capacity or saturation threshold for micro- and nanoplastics (MNPs). Unlike physiological solutes, MNPs are internalized by renal tubular cells through non-specific endocytic mechanisms rather than carrier-mediated transport, precluding the definition of a classical tubular reabsorption limit. Quantitative dose–response relationships, intracellular accumulation thresholds and potential saturation phenomena remain unknown and represent a critical area for future investigation. This differentiates MNP handling from classical nephrotoxins and solutes traditionally modeled in renal physiology.

Supplementary Box 2.

Micro- and nanoplastics (MNPs) and the kidney: what is known and what remains to be clarified

What is currently supported by evidence (a nephrologist-oriented overview)

- Systemic translocation of MNPs from primary exposure sites (mainly gastrointestinal and respiratory) to the internal milieu has been demonstrated in experimental models (cellular and animal studies). In humans, evidence is currently indirect.
- Presence of microplastics in human urine and renal tissue has been documented, indicating that at least a fraction of absorbed particles can reach the renal compartment and/or be eliminated through the urinary system.
- Tubular uptake of MNPs has been demonstrated in vitro and in vivo, particularly in proximal tubular epithelial cells, through endocytic mechanisms involving clathrin- and caveolin-mediated pathways.
- The proximal tubule is biologically vulnerable to toxic insults due to its high metabolic demand, intense endocytic activity, and mitochondrial richness.

What is hypothesized but not directly demonstrated

- Glomerular filtration of MNPs has been hypothesized only for ultrasmall nanometric fractions, based on studies with engineered nanoparticles. This mechanism has not been demonstrated for environmentally relevant MNPs, nor directly confirmed in humans.
- The biological pathways by which MNPs detected in human urine and renal tissue reach the kidney (filtration, cellular uptake, release into the tubular lumen) remain incompletely characterized.

What is currently not demonstrated

- Active tubular secretion of MNPs via specific renal transporters has not been demonstrated, either in humans or in experimental models.
- Direct causal evidence linking MNP accumulation to defined renal injury patterns in humans is still lacking.

Key message for nephrologists

Current evidence supports the biological plausibility of renal exposure to MNPs, but mechanistic pathways and clinical relevance in humans remain largely unresolved, underscoring the need for targeted translational and clinical research.

Supplementary Box 3. Ferroptosis as an emerging mechanism in micro- and nanoplastics–associated renal toxicity

What is ferroptosis

Ferroptosis is a regulated, non-apoptotic form of cell death driven by iron-dependent lipid peroxidation and oxidative stress, characterized by mitochondrial dysfunction, accumulation of reactive oxygen species, and failure of antioxidant defense systems, particularly the glutathione–GPX4 axis. Unlike apoptosis or necrosis, ferroptosis is tightly linked to cellular redox balance, lipid metabolism, and iron homeostasis.

Ferroptosis as a convergent pathway in kidney diseases

Beyond experimental toxicology, ferroptosis has recently been proposed as a convergent metabolic executioner across a broad spectrum of kidney diseases, encompassing acute kidney injury, diabetic nephropathy, tubulo-interstitial fibrosis, lupus nephritis, autosomal dominant polycystic kidney disease, renal cell carcinoma, and contrast-induced nephropathy. Importantly, susceptibility to ferroptotic injury appears to be cell type–specific: tubular epithelial cells are particularly vulnerable due to mitochondrial dysfunction and high metabolic demand; podocytes may undergo ferroptosis in the context of iron overload and altered lipid handling; and immune cells (e.g. macrophages and neutrophils) display context-dependent ferroptosis regulation, governed by distinct molecular modulators such as Nrf2, heme oxygenase-1, and sirtuin pathways.

Experimental links between MNPs and ferroptosis

Experimental studies suggest that exposure to micro- and nanoplastics can activate molecular pathways implicated in ferroptosis, including increased oxidative stress, mitochondrial injury, disruption of iron homeostasis, and enhanced lipid peroxidation. These observations derive predominantly from in vitro renal cell models and animal studies and support a biologically plausible link between MNPs exposure and ferroptosis-related cellular stress.

Current limitations and knowledge gaps

To date, direct evidence of ferroptosis induced by MNPs in the human kidney is lacking. Available data are largely experimental, and the relative contribution of ferroptosis compared with other forms of regulated cell death remains undefined. Whether ferroptosis represents a primary driver of injury or a secondary amplification mechanism in chronic low-grade exposure scenarios remains to be clarified.

Key message for nephrologists

Ferroptosis provides a unifying mechanistic framework linking oxidative stress, mitochondrial dysfunction, and iron dysregulation in kidney disease. Its involvement in micro- and nanoplastics–associated renal toxicity is biologically plausible but, at present, remains hypothetical and unproven in humans.

Key References [12–14]

Supplementary Table S1: Potential immune pathways implicated in MNP-associated renal toxicity.

Immune component	Level of evidence	Main immune alterations	Experimental setting	Key references
Innate immune activation	Strong	Activation of pro-inflammatory signaling pathways (NF-κB, NLRP3 inflammasome); increased production of IL-6, TNF-α and IL-1β	In vitro renal cell models; animal models	[12,13]
Macrophage response	Moderate	Predominant M1-like polarization; sustained macrophage activation; impaired resolution of inflammation	In vitro and in vivo experimental models	[7,8,13]
Tubulo-interstitial inflammation	Moderate	Recruitment of immune cells into the tubulo-interstitial compartment; persistence of low-grade chronic inflammation	Animal models of prolonged exposure	[3,9]
Innate–adaptive immune crosstalk	Limited / indirect	Altered antigen-presenting cell signaling and immune modulation without evidence of renal-specific adaptive immune responses	Experimental and toxicological models	[7,8]
Human evidence	Preliminary	Indirect evidence of immune activation; no direct demonstration of causal immune-mediated renal injury in humans	Observational data	—

Footnote / Legend: Supplementary Table S1 summarizes the current experimental evidence supporting the involvement of immune pathways in micro- and nanoplastic (MNP)–associated renal toxicity. Available data predominantly implicate innate immune activation and sustained inflammatory responses, while evidence for adaptive immune involvement remains limited and indirect. To date, direct causal links between MNP exposure, immune dysregulation and renal injury in humans have not been demonstrated.

Abbreviations: MNPs, micro- and nanoplastics; **NF-κB**, nuclear factor kappa-B; **NLRP3**, NOD-like receptor family pyrin domain-containing 3; **IL**, interleukin; **TNF-α**, tumor necrosis factor-alpha.

Supplementary Box 4.

Knowledge gap: MNP removal during dialysis techniques

Despite the widespread use of convective dialysis techniques, including hemodiafiltration, direct measurements assessing the clearance of micro- and nanoplastics during extracorporeal treatments are currently lacking. While convective ultrafiltration could theoretically enhance the removal of selected low–molecular weight plastic-associated additives, the impact of dialysis modality on circulating MNP burden remains unknown. Moreover, prolonged blood contact with plastic-based components along the extracorporeal circuit persists irrespective of dialysis technique, potentially maintaining continuous exposure. Dedicated analytical studies are required to quantify MNPs in blood, dialysate and ultrafiltrate across different dialysis modalities.