European Journal of Histochemistry 2025; volume 69:4226

Forever particles: histochemistry in the plasticene age

Beatrice Camia,[1] Andrea Casasco,[1,2] Manuela Monti[1,3]

[1]Section of Histology and Embryology, Department of Public Health, Experimental and Forensic Medicine, University of Pavia
[2]Italian Diagnostic Center (CDI), Milan
[3]Regenerative Medicine Research Center, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

ABSTRACT

The statement "Plastics define the way we live today" summarizes the findings of the Plastic Europe 2020 final document (https://plasticseurope.org/knowledge-hub/plastics-the-facts-2020/). Sadly, this also means that the plastic waste generated over the next decade is likely to become unmanageable. By 2050, plastic usage is expected to triple, resulting in a similar increase in plastic waste, with approximately half of it ending up in landfills. Emerging research indicates that micro and nanoplastics have been found in various human organs, including the gonads, placenta, blood, arteries, lungs, liver, kidney, and even the brain. This raises significant questions about their pervasive presence within our bodies and their potential threat to health. In addition to their harmful effects, these "forever particles" (micro/nanoplastics) can serve as Trojan horses, transporting additional pollutants such as bacteria and heavy metals into our bodies. In this review, we explore key aspects of the plastics crisis and urge the scientific community -especially those in the fields of cytochemistry and histochemistry, which adeptly connect morphology with function- to investigate the harmful effects of micro and nanoplastics that we encounter daily through ingestion or inhalation. This research should focus on various physiological levels, including DNA, cells, and tissues.

Key words: Microplastic; nanoplastic; plasticene; cyto-histochemistry; health; reproductive systems.

Correspondence: Manuela Monti, Section of Histology and Embryology, Department of Public Health, Experimental and Forensic Medicine, University of Pavia, Campus della Salute, viale Golgi 19, 27100 Pavia, Italy.
E-mail: manuela.monti@unipv.it

Contributions: all the authors made a substantive intellectual contribution, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare no competing interests, and all authors confirm accuracy.

Introduction

Impact of micro- and nanoplastics on environment and health

The debate over the term *Anthropocene* to describe the new era of human impact on Earth seems outdated. A more fitting term might be *Plasticene* since plastics are now ubiquitous in our environment: in water, air, landfills, and even in our food.[1] More notably, these plastics have infiltrated our bodies. This undeniable reality is essential when considering any new terminology to define this new human era.

The annual production of plastic has surged dramatically over the years, from 2 million tons in 1950 to 460 million tons in 2019. Projections suggest that this number could triple by 2060.[2,3] Plastic materials, which are synthetic or semi-synthetic organic polymers, are distinguished by their malleability and resilience. However, they can decompose over time, generating small particles that pollute the environment.

Plastic degradation refers to any chemical change that compromises the properties of plastics and can occur through various mechanisms. The primary process is photo-oxidation induced by ultraviolet radiation, which weakens plastic materials, making them fragile and more susceptible to fragmentation. This, in particular, is exacerbated by rising temperatures due to climate change. Additionally, biodegradation occurs alongside photo-oxidation but takes place over much longer timeframes and has limited effectiveness. As plastic materials weaken, they are subjected to mechanical stresses, such as wave action, contact with sand or rocks, or interaction with marine organisms, leading to fragmentation into increasingly smaller particles, ultimately resulting in micro- and nanoplastics.[4]

Plastic particles are generally classified into two main types: primary particles, which are intentionally manufactured and added to products like cosmetics, and secondary particles, which are formed during the usage and disposal of plastic items. A common classification method by size includes macroplastics (1 cm - 100 cm), mesoplastics (1 mm - 1 cm), microplastics (1 μm - 1 mm), and nanoplastics (1 nm - 1 μm).[3]

Among plastic debris, micro- and nanoplastics are particularly concerning due to their widespread presence in the environment and ability to accumulate in various tissues and organs within both humans and animals. Despite a growing number of studies, many unknowns remain regarding the mechanisms of nanoplastic bioaccumulation, their interactions with biological systems, and their impacts across generations. Currently, accurately measuring human exposure and assessing the potential risks to reproductive health remains extremely challenging. These particles are now ubiquitous on our planet, with notably high concentrations found in ocean environments. Our daily lives are filled with plastic, often without our awareness. Many everyday objects release plastic particles into outdoor and indoor environments, leading to air, water, and food contamination, thereby exposing humans and animals to micro- and nanoplastic pollutants.

Human and animal exposure to these pollutant particles primarily occurs through food ingestion, inhalation of airborne particles, direct skin contact, and, in some cases, the use of plastic medical devices.[5] Once internalized, plastic particles can accumulate in various tissues and act as endocrine disruptors, altering normal hormonal function and leading to severe adverse health effects. Of particular concern is the accumulation of micro- and nanoplastics in reproductive organs, which may affect fertility.

Significant sources of exposure include food containers, packaging, and plastic bottles that can release particles, especially when subjected to high temperatures or prolonged use.[6] Another substantial contributor is synthetic fabrics such as polyester, nylon, and acrylic, which release plastic fibers during machine washing. These particles are not always filtered out by wastewater treatment plants, ultimately reaching seas and rivers and contributing to aquatic pollution.[7] Additionally, cigarettes and their filters represent a significant source of plastic pollution,[8] as do many cosmetic and personal care products, which often contain microplastics in the form of microbeads used as exfoliating agents in scrubs and toothpaste.

A critical factor in the contamination from micro- and nanoplastic is tire wear. As vehicles drive on asphalt, friction generates plastic dust that disperses into the environment, contaminating both air and soil. Each year, significant amounts of microplastics from tires enter surface waters, exacerbating the issue of marine pollution.[9]

As previously mentioned, the body can internalize these plastic particles through various mechanisms, depending on their size. In 2021, Liu *et al.*[10] demonstrated that the smallest particles are primarily internalized through clathrin- and caveolin-mediated endocytosis, while larger particles (ranging from 0.5 - 1 μm) mainly enter the body *via* micropinocytosis.[11]

We encounter various types of plastic in our daily lives. Some of the most common and significant in terms of health impact include bisphenols (BPA), phthalates, polypropylene (PP), polystyrene (PS), polyethylene terephthalate (PET), low- and high-density polyethylene (LDPE and HDPE), polyvinyl phloride (PVC), polycarbonate (PC), and epoxy resins.[12]

Main deposition sites for these plastics include the lungs,[13] intestines, brain,[14] placenta,[15] and blood.[16] However, nanoplastics can undergo further internalization processes, allowing them to cross multiple biological barriers and accumulate in both male and female reproductive systems, which are particularly sensitive to these pollutant substances.[17,18].

Recent evidence indicates that the accumulation of micro- and nanoplastics in the reproductive system can compromises the fertility of affected individuals and may lead to transgenerational consequences. Exposure to these particles may induce epigenetic alterations in gametes and reproductive tissues, potentially affecting embryonic development and the health of future generations[19] (Figure 1).

Toxic effect of micro- and nanoplastics on reproductive systems

Micro- and nanoplastics can accumulate in various organs through processes like passive and active transport as well as endocytosis. Once in the body, these particles can enter the bloodstream and surpass physiological barriers, including the blood–testis barrier (BTB) and the placental barrier, leading to their accumulation in the testes, ovaries, and placenta.[5]

The male and female reproductive systems are incredibly complex and are among the most delicate systems in the human body. Their proper functioning relies on a precise balance of cellular and hormonal processes that facilitate the production of germ cells, fertilization, and embryonic development. However, this delicacy makes these systems particularly susceptible to the accumulation of external substances, such as environmental pollutants, toxins, and micro- and nanoplastics. These substances can act as endocrine disruptors, interfering with the normal hormonal activity essential for gamete formation (including oocytes and spermatozoa).[20] The accumulation of these pollutants can compromise the quality of germ cells, negatively affect normal embryonic development, and induce oxidative stress and inflammation in reproductive organs.[21,22]

The intrinsic vulnerability of reproductive systems, combined with increasing exposure to pollutants, raises significant concerns for the reproductive health of both humans and animals.

This issue is part of a larger trend, as infertility is becoming more common worldwide. Contributing factors to this trend include environmental pollution, rising stress levels, modern dietary habits, and daily exposure to endocrine disruptors. Understanding the impact of micro- and nano-plastics in this scenario is essential for developing effective prevention strategies and safeguarding reproductive health.

Male reproductive system

There is substantial evidence in the literature indicating that the accumulation of micro- and nanoplastics significantly affect the male reproductive system. In particular, sperm cells are especially vulnerable to these harmful effects. Due to their small size, micro- and nanoplastics can penetrate and accumulate at various levels within the male reproductive system, resulting in damage on multiple fronts.

Research has shown that PS has toxic effects, particularly in rodents, like mice and rats. Its presence leads to the overproduction of reactive oxygen species (ROS), which causes oxidative stress and severe inflammatory conditions. This inflammatory state is characterized by elevated levels of inflammatory interleukins and chemokines, including Interleukin-6 (IL-6), Monocyte chemoattractant protein-1 (MCP-1), and C-X-C motif chemokine ligand-10 (CXCL-10), as well as elevated levels of Tumor necrosis factor-α (TNF-α). These conditions contribute to decreased sperm quality and quantity, atrophy and apoptosis during spermatogenesis, and a higher incidence of sperm deformities.[23-25] The influence of micro- and nanoplastics can lead to significant alterations in hormonal profiles, particularly a decrease in testosterone levels suggesting potential dysfunction of the hypothalamus-pituitary-testis axis.

Additionally, germ cells may experience severe damage, resulting in a reduction in the number of spermatids and various morphological and functional abnormalities in spermatozoa. These defects can manifest as double tails, swollen necks, small heads, or the absence of either a head or tail. Other abnormalities may include double heads or bent tails, all of which contribute to a significant reduction in sperm motility.[26]

Histological analyses have shown significant changes in testicular structure, including degeneration of seminiferous tubules and Sertoli cells. The reduction in the size of Sertoli cells leads to a loss of crucial intercellular junctions, such as tight junctions, which weakens the BTB.[27] This highly specialized structure is essential for protecting and supporting the delicate process of spermatogenesis.

Furthermore, the accumulation of plastic particles in the male reproductive system can notably decrease the expression of genes involved in gamete maturation, such as *Plzf* and *Dazl*.[27]

Studies using murine models have demonstrated that PET nanoparticles (NPs) can cause significant alterations in the male reproductive system. These changes include a decrease in sperm concentration, an increase in morphological and functional abnormalities of gametes, and alterations in the germinal epithelium, characterized by numerous vacuoles, reduced sperm density, and increased interstitial space.[28]

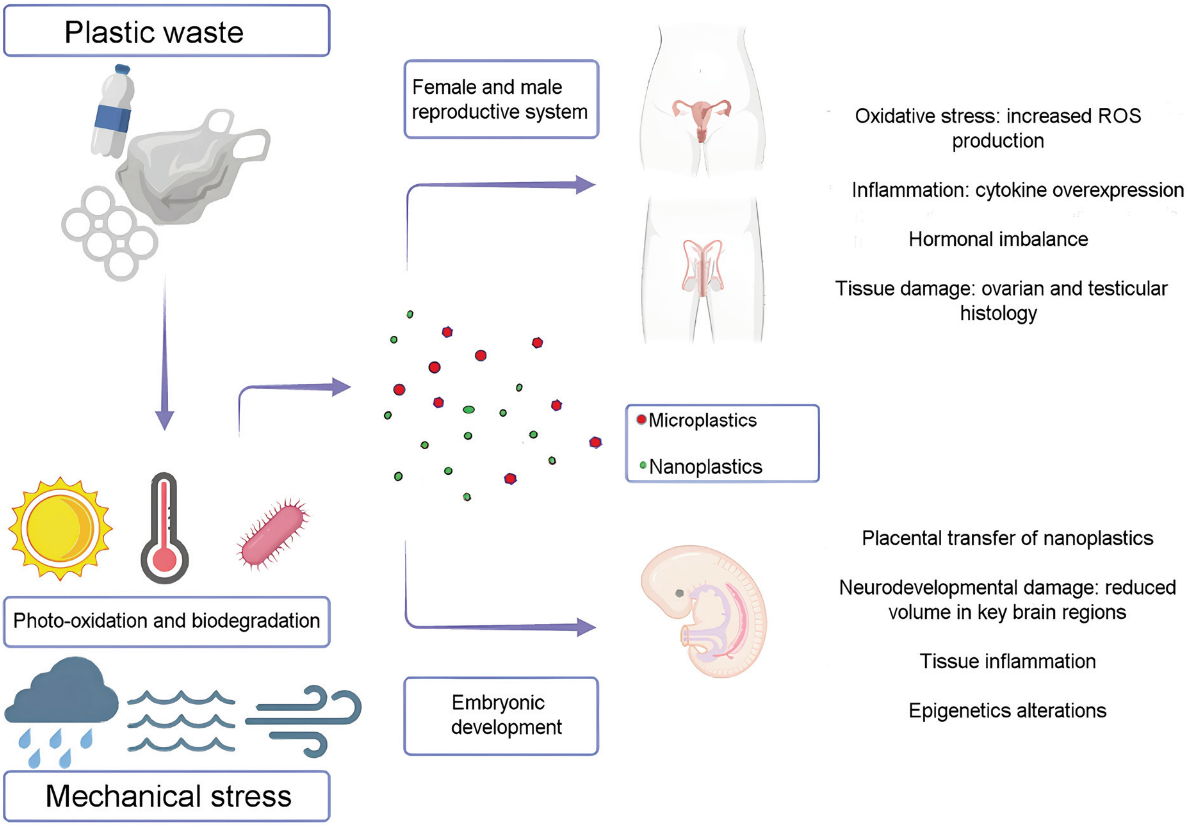

Figure 1. The illustration emphasizes the transition from environmental plastic waste to potential human health risks through micro- and nanoplastic exposure. Created in BioRender.com.

Female reproductive system

Micro- and nanoplastics have a significant impact on the female reproductive system. Research indicates that these plastic particles can disrupt normal functioning in various ways, primarily affecting the uterus and ovaries. These disruptions may also have transgenerational effects that influence embryonic development.

Studies using animal models have demonstrated that the accumulation of plastic NPs in the female ovaries creates a hostile microenvironment for processes such as oogenesis, fertilization, implantation, and subsequent embryonic development.[29]

The presence of plastic particles can trigger a severe inflammatory response in the ovaries and uterus, caused by increased levels of inflammatory interleukins like IL-6 and IL-10, as well as TNF-α. These factors can lead to inappropriate activation of the immune system.[30] Additionally, plastic debris elevates the production of ROS, resulted in increased oxidative stress. Both inflammatory responses and oxidative stress can cause fibrosis in uterine and ovarian tissues, which may lead to premature decline in female reproductive age.[31]

Specifically, the presence of PS-NPs in the ovaries can cause significant damage to ovarian follicles and germ cells by altering specific pathways. Studies have shown that these NPs can drastically reduce oocytes quality, size, and quantity within ovarian follicles.[32] In murine models, oocytes have been found to be reduced in size, and defects in maturation processes, spindle formation, and ovulation have been displayed. Furthermore, these oocytes appear more susceptible to cell death due to increased apoptotic processes affecting germ cells.[33]

The presence of nanoplastics in the female reproductive system can lead to significant hormonal imbalances, which may profoundly affect female fertility. Once these plastic fragments are internalized, they can act as endocrine disruptors. This results in increased levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), while causing a drastic decrease in estradiol, a hormone essential for regulating the menstrual cycle and maintaining reproductive health.[34]

At the histological level, the number of ovarian follicles is generally reduced. Specifically, there is a significant decrease in antral follicles and an alarming increase in atretic follicles, which leads to an overall reduction in ovarian reserve.[30,35] This situation is likely a result of the significant alterations, imbalances, and anomalies previously mentioned.

Additionally, considerable morphological changes have been observed, including abnormal dilation of the Fallopian tubes, increased interstitial density, and irregularities in the corona radiata and granulosa cells. Furthermore, the development of reproductive organs, such as the uterus and ovaries, appears to be reduced in size compared to what is considered a "healthy" condition.[29]

Evidence suggests that micro- and nanoplastics may play a crucial role in women with tumors affecting reproductive organs. Traces of plastic debris have been found in areas impacted by tumors following biopsies. Some studies indicate that plastic NPs might interact with the tumor microenvironment to promote tumor growth, and in some cases, they could hinder the effectiveness of oncological therapies.[36]

Embryonic development

In recent years, the intergenerational transmission of physiological damage caused by micro- and nanoplastic pollution has gained significant attention, emerging as a critical issue in biomedicine amid climate change.

Exposure to these particles poses health risks and negatively impacts reproductive functions in both males and females, potentially affecting the development of future generations. This raises concerns about the persistence of plastic toxicity within the body and its potential transmission through germ lines.

Studies on the effects of nanoplastics on embryonic development have shown that exposure during gestation in rodents is linked to various adverse outcomes. Notably, nanoplastics can cross the placental barrier and infiltrate fetal tissues, interfering with the formation of essential organs such as the central nervous system and liver.[19] Such exposure can lead to structural alterations in fetal brains, including changes in the volume of specific regions and disruptions in neurological development stages.[19] These effects may vary depending on the sex of the fetus. For example, male fetuses exposed to nanoplastics have shown a reduction in the volume of the visual cortex, while differences in the medulla and other areas of the central nervous system have been observed in female fetuses.

Transgenerational effects extend beyond the brain. The accumulation of nanoplastics in the livers and intestines of fetuses can lead to metabolic disorders and inflammation, potentially affecting reproductive health and muscle growth in offspring. These effects depend on the dose and duration of exposure, highlighting the adverse impact of nanoplastics on normal physiological and anatomical development in fetuses.[19,37]

The role of cyto- and histochemistry in evaluating the effects of micro- and nanoplastic on human and animal models

Cyto- and histochemistry (CHC) offer critical insights into the cellular and subcellular impact of micro- and nanoplastic exposure by enabling the localization, visualization, and quantification of tissue structural and biochemical changes.

Before delving into how these techniques enhance our understanding of cellular and tissue damage caused by specific plastic particles, particularly in the reproductive systems -which is the primary focus of this review- we will highlight the most recent studies conducted on various other tissues (Table 1). This will emphasize the significance of these investigations in assessing how different types and sizes plastic of particles of are transported within animal bodies and their potential harmful effects on the normal physiology of organs and tissues.

Gastrointestinal system

As specified above, this system is one of the primary routes of exposure to microplastics and nanoplastics, as these particles are often ingested through contaminated food and water. Immunohistochemistry (IHC) studies on animal models have demonstrated that micro- and nanoplastics can damage the intestinal lining, leading to inflammation, alterations in gut microbiota, and disruptions in intestinal permeability.[6] Markers of epithelial cell integrity, such as zonula occludens-1 and claudins, are downregulated in the intestines of exposed animals, suggesting that microplastics compromise the intestinal barrier.[84,85] CHC analysis has also shown increased expression of pro-inflammatory cytokines, such as TNF-α and IL-8, in the intestinal tissues, indicating that microplastics may provoke an immune response in the gut.

In 2024, Saleh and co-authors[86] employed hematoxylin and eosin (H&E) staining and PAS-Alcian Blue reaction to reveal villus shortening and deformation, goblet cell hyperplasia, nuclear pyknosis, and lamina propria degeneration in mice exposed to different concentrations of PS microplastics for 15 days. Furthermore, Kamel *et al.*[87] reported that exposure to PET nanoplastics resulted in hepatocellular degeneration, sinusoidal congestion, and bile duct hyperplasia in mice exposed to various doses over 30 days. Histochemical staining indicated increased lipid peroxidation and oxidative stress, validated by elevated levels of malondialdehyde and reduced glutathione.

Table 1. Papers published between 2017 and 2025 that primarily utilized cyto- histochemical techniques to assess the effects of plastics of various types and sizes on human and animal organs, tissues, and cultured cells.

Tissue/system	Species	Plastic type	Key findings	Techniques	References
Multi-organ	Fish	PS MPs	Altered behavior, energy reserve, and nutritional composition	Histology, biochemical assays	Yin *et al.*, 2018[38]
Multiple tissues	Fish (*Cyprinus carpio*)	PE MPs	Combined exposure with 4-nonylphenol increased tissue damage	Histopathological and histochemical biomarkers	Ammar *et al.*, 2023[39]
Bone, cartilage, intervertebral discs	Human	PP, PS, EVA	Microplastics accumulate in skeletal tissues; affect inflammatory and bone morphogenetic cytokines	Histological analysis, spectroscopy techniques	Yang *et al.*, 2025[40]
Blood	Human	PET, PE	Microplastics detected in human blood; potential systemic exposure	Pyrolysis gas chromatography/mass spectrometry	Leslie *et al.*, 2022[16]
Brain (olfactory bulb)	Human	MPs	The olfactory pathway can be a potential entry route for microplastics into the brain	Histological analysis, spectroscopy techniques	Amato-Lourenço *et al.*, 2024[41]
Brain, liver, kidney	Human	MPs	Microplastics detected in human brain tissues; higher levels in individuals with dementia	Histological analysis, spectroscopy techniques	Nihart *et al.*, 2025[42]
Cardiac connective tissue	Mouse	PS NPs	Exposure to PS nanoplastics exacerbated myocardial fibrosis and autophagy *via* the ROS/TGF-β1/Smad signaling pathway, indicating potential cardiac connective tissue damage	Histopathological examination; immunohistochemistry for fibrosis markers	Lin *et al.*, 2022[43]
Cardiomyocytes	ICR Mice and H9C2 cells	PP	PP microplastics induced cardiomyocyte apoptosis through oxidative stress and activation of the MAPK-Nrf2 signaling pathway	Flow cytometry; western blotting; mitochondrial membrane potential assay	Lu *et al.*, 2024[44]
Digestive system (duodenum)	Pig	PET	Exposure to PET microplastics led to histological changes in the duodenum,	Hematoxylin and Eosin staining; electron microscopy	Gałęcka *et al.*, 2024[45]

Table 1. Continued from previous page.

			including injury to villi, accumulation of cellular debris, and eosinophil infiltration; alterations observed in intramural neurons, indicating potential neurotoxic effects		
Digestive system (jejunum)	Pig	PET	Oral exposure to PET MPs affected neurochemical plasticity of reactive neurons in the jejunum; observed changes in the population of neurons positive for selected neurotransmitters; histological alterations included injury to villi and eosinophil infiltration.	Hematoxylin and Eosin staining; immunofluorescence	Gałęcka *et al.*, 2024[46]
Eye development and visual behavior	Zebrafish larvae	Biodegradable plastics (PGA, PLA, PBS, PHA, PBAT)	Exposure to biodegradable MPs leads to decreased survival rates, reduced body length, smaller eyes and heads, and impaired retinal development, affecting visual function.	Histological analysis of retinal layers; gene expression studies	Wen *et al.*, 2024[47]
Gastrointestinal connective tissue	Flesh-footed shearwater (*Ardenna carneipes*)	MPs, NPs	Chronic ingestion of plastics led to a novel fibrotic disease termed "plasticosis," characterized by inflammation, scarring, and loss of glandular tissue in the proventriculus	Masson's trichrome staining	Charlton-Howard *et al.*, 2023[48]
Liver	Mouse	PS MPs	Activation of pyroptosis and ferroptosis involved in hepatotoxicity	Histological analysis, IHC	Mu *et al.*, 2022[49]
Liver, gill, intestines	Zebrafish	PS (PS)	Exposure to PS microplastics led to accumulation in liver, gills, and intestines; associated with inflammation, lipid	Histological examination; biochemical assays	Dzierżyński *et al.*, 2024[50]

Table 1. Continued from previous page.

			accumulation, and oxidative stress; highlights potential toxicological effects of microplastics in aquatic organisms		
Liver and testis	Mouse	PS NPs	Maternal exposure led to hepatic and testicular toxicity in offspring	H&E staining, immunohistochemistry for oxidative stress markers	Huang *et al.*, 2022[51]
Lung cells (A549)	Human	Waste-derived MPs	MPs internalized in lung cells; potential cytotoxic effects	µRaman imaging, TEM	Bengalli *et al.*, 2022[52]
Lung cells	Human (*in vitro*)	PE MPs, PE NPs	Induced epithelial–mesenchymal transition in bronchial and alveolar epithelial cells	Histology, molecular assays	Traversa *et al.*, 2024[53]
Lung epithelium	Human (*in vitro*), mouse (*in vivo*)	PVC	PVC MPs induced cellular senescence in human lung epithelial cells and mouse lungs *via* reactive oxygen species signaling; effects mitigated by antioxidants	Senescence-associated β-galactosidase staining, ROS assays	Jin *et al.*, 2024[54]
Lung	Human	Various MPs	Detected microplastics in human lung tissue	µFTIR spectroscopy, histological analysis	Jenner *et al.*, 2022[55]
Lung	Mouse	PS MPs	Induced pulmonary fibrosis *via* oxidative stress and Wnt/β-catenin pathway	Masson's trichrome staining, immunohistochemistry for fibrosis markers	Li *et al.*, 2022[56]
Lung	Mouse	PS MPs	Triggered inflammation through TLR2 and NF-κB pathway	Immunohistochemistry for TLR2, NF-κB, and pro-inflammatory cytokines	Cao *et al.*, 2023[57]
Lung	Mouse	PP NPs	Caused mitochondrial damage and lung inflammation *via* p38-mediated NF-κB pathway	H&E staining, IHC for mitochondrial and inflammatory markers	Woo *et al.*, 2023[58]
Lung	Rat	PP	Inhaled PP MPs, induces persistent lung inflammation and has the potential for lung disorder	Histology, qRT-PCR	Tomonaga *et al.*, 2024[59]
Lung	Mouse	PS NPs	Activated ferroptosis leading to lung injury	H&E staining, immunohistochemistry for ferroptosis markers	Wu *et al.*, 2024[60]

Table 1. Continued from previous page.

Macrophages	Mouse	MPs	Induced apoptosis by promoting ROS generation and altering metabolic profiles	Histology, IHC	Wang *et al*., 2024[61]
Myocardial tissue	Carp *(Cyprinus carpio)*	PS	PS MPs induced myocardial inflammation, apoptosis, and necrosis *via* the TLR4/NF-κB pathway	Hematoxylin and Eosin staining; TUNEL assay; Acridine Orange/Ethidium Bromide staining	Zang *et al*., 2023[62]
Myocardial tissue	Wistar rats	PS	Long-term exposure to PS MPs caused lipid metabolism disorders, increased oxidative stress, and inflammation in myocardial tissue	Hematoxylin and Eosin staining; biochemical assays; untargeted metabolomics analysis	Song *et al*., 2024[63]
Preimplantation embryo development	Mouse	BPA, BPF	Brief exposure to BPA or BPF during blastocyst formation disrupts cytoskeletal organization, cell division, and lineage specification, leading to impaired embryo hatching	Immunofluorescence staining for F-actin, NANOG, and CDX2; DAPI staining	Yang *et al*., 2022[64]
Preimplantation embryo development	Mouse	PS NPs	PS NPs impair sperm metabolism, leading to reduced fertilization rates and compromised pre-implantation embryo development	Sperm motility assays; metabolic profiling	Liu *et al*., 2025[65]
Nasal lavage fluid	Human	Various MPs	Microplastics found in nasal lavage fluid; potential respiratory exposure	FTIR spectroscopy	Amato-Lourenco *et al*., 2021[13]
Neural crest cell migration and organogenesis	Chicken embryo	PS NPs	PS nanoplastics bind to neural crest cells, leading to their death and impaired migration, resulting in severe congenital malformations, including heart defects	*In vivo* imaging; morphological assessments	Wang *et al*., 2023[66]
Skeletal muscle (tibialis anterior)	Mouse	PS	PS MPs exposure led to overproduction of reactive oxygen	Hematoxylin and Eosin staining; Oil Red O staining	Shenchen *et al*., 2021[67]

Table 1. Continued from previous page.

			species, impaired muscle regeneration, reduced muscle fiber size, and increased lipid deposition.		
Skeletal muscle	Piglets	PS	PS MPs exposure reduced meat quality, decreased muscle fiber density, and impaired angiogenesis *via* upregulation of thrombospondin 1.	Histological analysis; metabolomic analysis	Yang *et al*., 2024[68]
Ovary	Rat	PS MPs	Induced granulosa cell apoptosis and fibrosis *via* oxidative stress	Hematoxylin and Eosin staining, TUNEL assay, IHC for oxidative stress markers	An *et al*., 2021[69]
Ovary	Rat	PS MPs	Triggered pyroptosis and apoptosis in granulosa cells through NLRP3/Caspase-1 pathway	IHC for NLRP3, Caspase-1, and IL-1β	Hou *et al*., 2021[70]
Ovary	Mouse	PS MPs	Caused female reproductive toxicity and hormonal imbalance	Hematoxylin and Eosin staining, IHC for hormone receptors	Liu *et al*., 2022[30]
Ovary	Rat	PS MPs	Caused ovarian toxicity associated with oxidative stress and activation of PERK-eIF2α-ATF4-CHOP pathway	Hematoxylin and Eosin staining, IHC for endoplasmic reticulum stress markers	Wang *et al*., 2023[71]
Ovary	Mouse	PS NPs	Affected ovarian granulosa cells leading to reproductive toxicity	IHC for apoptosis and oxidative stress markers	Zeng *et al*., 2023[72]
Ovary	Rat	PS	Chronic exposure caused granulosa cell apoptosis *via* NLRP3/Caspase-1 pathway; decreased antioxidant enzyme levels; increased inflammatory markers	TEM, Hematoxylin and Eosin staining, IHC, ELISA, TUNEL assay, Western blotting	Balali *et al*., 2024[29]
Ovary and endometrium	Rat	PS	Short-term exposure led to decreased endometrial gland	Hematoxylin and Eosin staining, hormone assays	Wang *et al*., 2025[73]

Table 1. Continued from previous page.

			thickness, altered hormone levels, and potential oocyte overactivation		
Placenta	Human	MPs	First evidence of microplastics in human placenta	Histological analysis, spectroscopy techniques	Ragusa *et al.*, 2021[15]
Placenta	Human	PE, PP	Microplastics found in all 62 human placentas examined; potential impact on fetal development	Histological analysis, spectroscopy techniques	Garcia *et al.*, 2024[74]
Reproductive system	Mouse	PS MPs	Compared reproductive effects in male and female mice	Histological analysis, IHC for reproductive markers	Wei *et al.*, 2022[34]
Skeletal tissue	Human	PP, PS, EVA	Microplastics present in bone, cartilage, and intervertebral discs; higher accumulation in intervertebral discs; affected inflammatory and bone morphogenetic cytokines	Histological staining; serum biomarker analysis (TNF-α, PINP, TRACP-5b)	Yang *et al.*, 2025[75]
Spleen	Mouse	PS NPs	Exacerbated lipopolysaccharide-induced necroptosis and inflammation *via* ROS/MAPK pathway	Histology, IHC	Tang *et al.*, 2022[76]
Testis	Rat	PS MPs	Disrupted blood-testis barrier *via* MAPK-Nrf2 signaling pathway	IHC for tight junction proteins and oxidative stress markers	Li *et al.*, 2021[77]
Testis	Swine	PS MPs	Induced apoptosis and necroptosis *via* ROS/MAPK/HIF1α pathway	Histology, IHC	Wang *et al.*, 2022[78]
Testis	Mouse	PS MPs	Led to premature testicular aging and disrupted spermatogenesis	Hematoxylin and Eosin staining, IHC for aging markers	Wu *et al.*, 2023[79]
Testis	Mouse	PS NPs	Induced mitochondrial impairment and cytomembrane destruction in Leydig cells	IHC for mitochondrial markers, oxidative stress assays	Sun *et al.*, 2023[80]
Testis	Rat	PS MPs	Induced adverse effects on blood-testis barrier integrity	Hematoxylin and Eosin staining, IHC for junctional proteins	Jiang *et al.*, 2024[81]

Table 1. Continued from previous page.

Testis	Mouse	PET-MPs	Long-term ingestion led to reduced testes weight, inhibited GnRH secretion, and decreased testosterone levels, affecting spermatogenesis	Histology, hormonal assays	Jeong *et al*., 2025[82]
Testis and semen	Human	Various MPs	Detected microplastics in human testis and semen samples	Histological analysis, spectroscopy techniques	Zhao *et al*., 2023[83]

PS, polystyrene; MP, microplastics; PP, polypropylene; EVA, ethylene-vinyl acetate; PET, PE terephthalate; polyethylene, PE; NPs, nanoplastics; PGA, polyglycolide; PLA, polylactic acid; PBS, polybutylene succinate; PHA, polyhydroxyalkanoates; PBAT, polybutylene adipate terephthalate; IHC, immunohistochemistry; TEM, transmission electron microscopy; PVC, polyvinyl chloride; BPA, bisphenol A; BPF, bisphenol F.

More recently, Li and co-authors showed that immunohistochemical analysis of mouse liver tissue exposed to various concentrations of PS particles for 12 weeks revealed increased expression of inflammatory markers such as TNF-α and IL-6, along with changes in the activity of liver enzymes involved in detoxification.[88] These analyses also identified high levels of liver fibrosis and alterations in liver structure, suggesting that microplastics trigger an immune response.[88]

Respiratory system

Research on the effects of micro- and nanoplastics on the lungs has demonstrated that the accumulation of substances leads to chronic inflammation, fibrosis, and impaired lung function. For instance, a histopathological analysis of lung tissue from mice stimulated with PP for 29 days revealed lung injuries, including the infiltration of inflammatory cells into the perivascular and parenchymal spaces, as well as alveolar epithelial hyperplasia.[58] Additionally, fluorescence staining of mitochondria showed damage and dysfunction in human lung epithelial cells exposed to PP for 16 hours.[58] Another recent study investigated the effect of tracheal instillation of plastic NPs over seven consecutive days in a mouse model.[89] H&E staining indicated lymphocytic inflammation in a bronchiolocentric pattern, while Masson trichrome staining revealed an increased presence of collagen deposits in the treated group compared to the control group. Further cellular and molecular analysis of a human bronchial epithelial cell line exposed to various concentrations of NPs showed increased levels of Fe^{2+}, ROS, and ferroptotic proteins. This suggests that exposure to NPs may induce ferroptosis in bronchial epithelial cells by activating the HIF-1a/HO-1 signaling pathway.[89] Interestingly, ferroptosis is also the mechanism that induces ovarian tissue fibrosis after microplastic exposure in avian species, such as Muscovy female ducks, as demonstrated by IHC experiments.[90] Other studies have indicated that prolonged exposure to micro- and nanoplastics can lead to respiratory diseases, such as asthma and pneumoconiosis.[91-93] However, the precise mechanisms by which these substances contribute to the development of respiratory diseases are still not fully understood.

Brain and neural tissue

Neurotoxicity is a significant concern linked to exposure to micro- and nanoplastics, primarily due to their ability to cross the blood-brain barrier.[94] IHC studies conducted on rat brains exposed to these particles have shown alterations in the expression of glial fibrillary acidic protein, a marker of astrocyte activation, and ionized calcium-binding adapter molecule 1, which indicates microglial activation.[95] These findings suggests that microplastics and nanoplastics may induce neuroinflammation in the brain. Additionally, a study involving mice exposed to PS microplastics for eight weeks utilized immunoblotting and immunofluorescence techniques to demonstrate that plastic particles accumulated in the hippocampus. This localization correlated with increased neuroinflammation and impairments in learning and memory behaviors.[96] Interestingly, a recent study established a connection between acute exposure to microplastics and changes in behavior and inflammation in both young and old mice. The authors designed a behavioral assay to measure various parameters, such as distance traveled, rearing activity, and time spent in different areas between control and plastic-exposed groups. To explore the biological mechanisms behind these behavior changes, the authors examined various organs - including the gastro-intestinal tract, heart, spleen lungs, brain, liver, and kidneys - and found plastic particles present in all of them, along with altered factors as demonstrated by immunofluorescence experiments.[97]

Reproductive systems

Ovary

The ovary is a highly sensitive organ that plays a crucial role in reproductive health by producing oocytes and secreting hormones such as estrogen and progesterone. Research on animals exposed to micro- and nanoplastics has raised concerns about the potential disruption of ovarian function caused by these particles.

In 2021, Hou and collaborators[70] demonstrated that exposure to PS microplastic led to pyroptosis and apoptosis in rat ovarian granulosa cells via the NLRP3/ Caspase-1 signalling pathway, as shown in their histological analyses. These findings were supported by more recent studies that examined the effects of high doses of PS-microplastics over a 35-day period in a mouse model. Histological analysis using H&E staining and IHC revealed an increased number of atretic follicles and a high rate of apoptosis in granulosa cells, indicated by a positive signal for cleaved caspase 3 and a decreased signal for Bcl-2. Additionally, there was excessive production of ROS.[98,99] Another key observation from the CHC studies is the disruption of folliculogenesis, the process by which ovarian follicles mature. Exposure to microplastics has been shown to alter the expression of FSH receptors and disrupt the balance of sex hormones, including estrogen.[98,100] Other recent studies involving rats,[69] confirmed that PS microplastics induce apoptosis in granulosa cells and cause fibrosis in the ovaries due to oxidative stress, thereby decreasing the ovarian reserve capacity.

CHC studies have revealed some morphological and functional effects of exposure to plastics and their derivatives in humans, although these effects are generally less pronounced than those observed in laboratory animals.

Elevated urinary concentrations of BPA and Phthalates have been linked to several reproductive issues in women undergoing assisted reproductive technologies. Specifically, these chemicals have been associated with a decreased count of antral follicle, disrupted menstrual cycles, and reduced oocyte quality. A study by Mínguez-Alarcón and collaborators[101] showed that higher urinary BPA levels were inversely associated to both the number of retrieved oocytes and peak estradiol levels during *in vitro* fertilization.

Additionally, long-term exposure to these chemicals has also been associated with an earlier onset of menopause, potentially shortening the reproductive window significantly.[102,103] Evidence indicates a dose-response relationship, where higher concentrations of endocrine-disrupting chemicals correlate with more severe reproductive impairments. Emerging research suggests that these endocrine disruptors may have transgenerational effects. Prenatal exposure to BPA and Phthalates can affect fetal ovarian development, leading to altered reproductive functions later in life. Some animal studies suggest that these impacts may persist across several generations.[104] While the available research is substantial, most human studies rely on observational data, making it difficult to establish a causal relationship. Moreover, individual susceptibility, genetic predispositions, and sources of exposure vary considerably. More longitudinal and mechanistic studies are needed to better understand the dose thresholds and long-term reproductive consequences.

Testis

CHC is a valuable tool for identifying specific protein markers in testicular tissues, providing insights into cellular changes, apoptosis, oxidative stress, hormone receptor expression, and the integrity of the BTB. Studies involving human and animal testicular tissues exposed to plastic and plastic-derived chemicals have revealed several critical effects: reduced expression of androgen receptors in Leydig and Sertoli cells,[105] which is linked to damage in the mitochondria-endoplasmic reticulum;[106] increased apoptotic markers such as caspase-3 and *Bax*, alongside decreased levels of *Bcl-2*;[107] altered expression of Sertoli cell markers (*e.g.*, vimentin, transferrin),[108] and changes in tight junction proteins like occludin, claudin, and ZO-2, indicating compromised BTB integrity.[109]

These molecular changes correlate histopathological findings, including seminiferous tubule atrophy, germ cell sloughing, and interstitial fibrosis.

While much of the CHC data comes from animal studies, there is limited yet significant evidence from human research. For instance, several years ago, Zhang and collaborators found that testicular biopsies from infertile men exhibited reduced androgen receptor expression and altered localization of estrogen receptor (ERα, ERβ), particularly among those with higher environmental exposure to BPA and phthalates.[110] Additionally, studies analyzing oxidative stress biomarkers, such as 8-OHdG (8-hydroxy-2′-deoxyguanosine) have shown DNA damage in human testicular tissues after exposure to BPA and nonylphenol. However, the health risks associated with chronic, low-dose BPA exposure in the population remain controversial.[111] Recent ultrastructural and spectroscopy studies have indicated that exposure to microplastics is associated with reduced sperm quality and quantity.[112,113]

The findings from CHC help bridge the gap between environmental exposure and clinical outcomes such as oligospermia, azoospermia, testicular dysgenesis, hormonal imbalances, and infertility-related cancers (*e.g.*, testicular germ cell tumors). These studies support the development of biomarkers for early detection of testicular damage related to endocrine-disrupting chemicals and offer pathways for potential therapeutic interventions or strategies to minimize exposure.

Immuno cyto-histochemical studies provide strong visual and molecular evidence that chemicals derived from plastics negatively affect both animal and human tissues and organs. These findings highlight the need to regulate plastic exposure, especially for vulnerable groups such as neonates, adolescents, and individuals of reproductive age. Future research should prioritize longitudinal studies, improve the quantification of exposure levels, and integrate IHC with genomics and proteomics to gain a deeper understanding of the damage caused and to identify potential strategies for prevention or reversal.

Acknowledgements

The authors express gratitude to Prof. CarloAlberto Redi for his critical reading and valuable suggestions. This work was supported by the "Fondazione Umberto Veronesi per il progresso delle scienze" to MM.

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Received: 24 April 2024. Accepted: 9 June 2025.

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European Journal of Histochemistry 2025; 69:4226
doi:10.4081/ejh.2025.4226