

Impact of Microplastics and Nanoplastics on Female Reproductive Health: Ovarian Function, Pregnancy Outcomes, and Placental Transfer

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ABSTRACT

The plastic waste problem is one of the top environmental and public health issues of the 21st century, and the world produces about 460 million tonnes of plastic annually. Micro and nanoplastics are therefore a constant presence for humans in daily life via food, water, air, and consumer products, and have been found in human blood and placental tissue. Microplastic exposure causes disruption of folliculogenesis (maturation of ovarian follicles and the oocytes these follicles contain), ovarian fibrosis, hormone imbalance and impaired oocyte quality in females. More critically, microplastics cross the placental barrier and raise questions about fetal development, of which microplastics are a pressing issue. Maternal exposure is directly associated with poor pregnancy outcomes such as growth restriction of the fetus and developmental abnormalities. While some of the evidence is from animal models, there is a growing number of human studies with accumulating evidence that suggest tissue bioaccumulation and association with adverse reproductive outcomes. Critical knowledge gaps include lack of longitudinal human cohort studies, lack of standardized exposure assessment protocols and lack of knowledge of chronic low-dose effects and transgenerational effects. This review stresses the urgent need for comprehensive research, exposure mitigation strategies and policy interventions for protecting female reproductive health and maternal-fetal wellbeing from this emerging environmental threat.

Keywords: microplastics; nanoplastics; reproductive toxicity; fertility; endocrine disruption

INTRODUCTION

The growth of plastic pollution has become one of the biggest challenges for the environment and public health in the 21st century. The global plastic production has reached to about 460 million tons of plastic each year, and this number is forecasted to triple by 2060.^[1] Microplastics (MPs, <5mm) and nanoplastics (NPs, <1mm) have become ubiquitous across all ecosystems on Earth, from the deepest ocean trenches to the highest mountain peaks, and human exposure occurs through contaminated food, water and air.^[2] The ubiquity of these synthetic particles, in combination with their persistence in the environment and ability to bioaccumulate in human tissues, has been met with a dramatic uptick in research funding and scientific interest as more than 2500 peer-reviewed publications have been published in the last five years alone on the health effects of microplastics, indicating the growing recognition of this threat to human health in both developed and developing nations.

Increasing awareness of microplastic contamination has stimulated the research institutions and public health agencies internationally to investigate the biological consequences of human exposure. Several recent studies have documented the presence of MPs in the blood,^[3] placental tissue,^[4] and lung tissue,^[5] showing the presence of the bioaccumulation of MPs throughout multiple organ systems. The presence of these particles in reproductive organs has been of particular concern because the growing body of evidence from toxicological, epidemiological and clinical research demonstrates associations between MP exposure and adverse reproductive outcomes ranging from altered hormone levels, impaired oocyte quality and impaired fertility across a range of biological systems and exposure scenarios.^[6,7]

Microplastics and nanoplastics are a heterogeneous group of synthetic polymer particles of different sizes, shapes, chemical composition and surface properties, which can either originate from deliberate production (primary MPs) or from the fragmentation process of larger plastic objects in the environment (secondary MPs). Since the first formal definition of microplastics in the early 2000s, understanding of these particles has shifted from simple characterization of their physical properties to an appreciation of the complex biological interaction involving mechanisms in the uptake and transport of particles into cells, capacity to carry co-contaminants, and potential to activate multiple toxicological pathways ranging from oxidative stress, inflammation and endocrine disruption.^[8,9]

While much research has been done to examine the impacts of single polymer types (especially polystyrene) on specific reproductive endpoints in isolated model systems, little research has been done that synthesizes the breadth of reproductive health impacts across female reproductive biology and diverse exposure pathways, multiple mechanistic pathways and the continuum from cellular effects to clinical outcomes. Most studies focus on individual reproductive parameters in individual species generating a fragmented evidence base that obfuscates the integrated picture of how MP and NP exposure is affecting human reproductive capacity across the life span.

Technological advances in analytical chemistry such as Raman spectroscopy, pyrolysis gas chromatography-mass spectrometry and advanced imaging techniques have facilitated the development of more sophisticated detection and characterization of MP and NPs in samples of environmental and

biological origin. Concurrently, advances in toxicological assessment approaches, such as high-throughput screening platforms, omics technologies, and computational modeling approaches, have accelerated studies of biological mechanisms of MP toxicity and allowed for more nuanced understanding of dose-response relationships and species-specific vulnerabilities in more recent years.

Understanding reproductive health effects of MP and NP exposure has important implications for future research in both developed countries with developed healthcare systems and reproductive medicine and resource-constrained countries where environmental exposures may be higher and access to healthcare may be more limited. Comprehensive knowledge about exposure pathways and mechanistic toxicity, and reproductive outcomes can help to inform exposure mitigation strategies, clinical screening protocols for at-risk populations, and evidence-based interventions to promote reproductive health and contribute to global health equity and the maintenance of human fertility of diverse populations.

It is important to understand the effects of MP and NP exposure on various aspects of reproductive biology from molecular and cellular mechanisms to tissue pathology, hormonal control, gamete function, and clinical fertility outcomes in order to help researchers, clinicians, public health practitioners, and policymakers create comprehensive strategies to assess risk and protect vulnerable populations and implement effective prevention measures. A systematic synthesis of evidence from all of these levels of biological organization is necessary for the translation of findings from the laboratory to actionable public health interventions.

It is equally important to examine the methodological challenges and knowledge gaps that currently limit the understanding of MP and NP reproductive toxicity, such as the preponderance of animal model data with questionable human translational relevance, the lack of standardised exposure assessment protocols, limited longitudinal human cohort studies, and incomplete characterization of mixture effects when more than one polymer type is present and co-contaminants are present. To the best of the knowledge of these authors, there have been limited comprehensive reviews to synthesize the evidence across the entire spectrum of reproductive health effects, including those affecting the reproductive systems of both males and females, the mechanistic pathways and exposure routes, as well as from experimental models to human populations.

Therefore, this review is aimed at synthesizing the evidence on the role of microplastics and nanoplastics in affecting human reproductive health by examining evidence of exposure pathways, bioaccumulation patterns, toxicological mechanisms and reproductive outcomes in female reproductive systems, as well as identifying critical knowledge gaps and research priorities that will help move research forward in order to better understand this novel threat to human fertility.

More specifically, this review focuses on the following research questions:

RQ1: What are the exposure pathways, bioaccumulation patterns and toxicological mechanisms of microplastics and nanoplastics on human reproductive health?

RQ2: What are the documented impacts of microplastic and nanoplastic exposure on the reproductive systems of males and females, and what are the knowledge gaps that are important to learn and require future research?

This review is presented in the following manner. The research methodology used for literature search, study selection and evidence synthesis is described in the next section. This is followed by a detailed characterization of microplastics and nanoplastics, including their sources, composition and physicochemical properties. The study then discusses pathways of exposure to humans and accumulation patterns in reproductive tissues. Next, the study looks at the mechanisms for reproductive toxicity such as oxidative stress, inflammation, endocrine disruption and DNA damage. Subsequently, the study provides a detailed assessment of impacts on female reproductive health, in which the evidence from cell, animal and human studies are synthesized. Finally, the conclusion section discusses the main findings, public health implications, limitations of the study and priorities for future research to reduce this emerging threat to human fertility.

METHODOLOGY

Research Design

This study uses the systematic review of literature to discuss the effects of microplastics and nanoplastics on the reproductive health of females, focusing on exposure, bioaccumulation, toxicological mechanisms and reproductive outcomes based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The study-selection workflow used in this review is shown in Figure 1, and PRISMA is an evidence-based reporting framework that ensures a standardized checklist and a four-phase flow diagram for transparently reporting the identification, screening and selection of studies for a systematic review. The reporting of the screening and selection process is covered by the PRISMA framework, which is separate from the study specific eligibility criteria applied here, and presented separately in Table 1.

Literature Search Survey

A comprehensive literature search was performed via multiple databases with the aim of ensuring wide coverage of research relating to microplastics and nanoplastics and female reproductive health. The main databases were PubMed, Web of Science, Scopus, Google Scholar and ScienceDirect (Elsevier). The search strategy used free-text keywords with boolean (Boolean= conjunction that can effectively link search terms). The literature search was made using primary terms such as "microplastics," "nanoplastics," "plastic particles," "MPs," and "NPs." Secondary terms were "female reproductive health," "reproductive toxicity," "ovarian function," "fertility," "pregnancy outcomes," "placental transfer," "endocrine disruption," "oocyte quality" and "folliculogenesis." This strategy ensured capturing of the core concepts relevant to microplastic/nanoplastic exposure and female reproductive health, variations in terms and related biological mechanisms to ensure a comprehensive coverage of relevant research domains. Inclusion criteria and exclusion criteria

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The inclusion and exclusion criteria applied to the search are presented below.

Table 1. *Inclusion and exclusion criteria for study selection*

Criterion	Inclusion Criteria	Exclusion Criteria
Temporal scope	Published between 2015 and 2024	Published before 2015
Language	Published in English	Other languages
Content relevance	Addressed microplastics/nanoplastics effects on female reproductive health, toxicological mechanisms, bioaccumulation patterns, or biological effects directly applicable to humans	Addressed and solely focused on male reproductive health, environmental distribution without health impacts, or general plastic pollution without specific reproductive outcomes
Publication type	Peer-reviewed journal articles, systematic reviews, meta-analyses, technical reports from recognized institutions, and research documents from authoritative sources	Lacked peer review or institutional authorization, opinion pieces without empirical data
Disciplinary scope	Toxicology, reproductive biology, environmental health, endocrinology, materials science, public health	Addressed only theoretical possibilities without empirical grounding or lacked biological specificity
Study type	In vitro studies, in vivo animal studies, human cohort studies, epidemiological studies, case-control studies, mechanistic studies	Pure modeling studies without experimental validation, studies on non-reproductive organs only
Geographic scope	International coverage with no geographic restrictions	
Access limitation	Full text available through institutional subscriptions or open access repositories	Full text unavailable through institutional subscriptions or open access repositories

Study Selection Process

Study selection was based on a systematic 4-step procedure. Database searches produced some 958 potentially relevant records that were narrowed down to 893 after duplicate elimination. The screening of titles and abstracts reduced the pool to 424 records for full-text study review that led to 83 studies included in the final analysis. The research papers were then categorized by main focus area, such as exposure pathways, toxicological mechanisms, ovarian function impacts, pregnancy outcomes and placental transfer to ensure balanced representation of microplastics/nanoplastics reproductive health research areas.

Data Extraction and Analysis Framework

A systematic data extraction framework was used to collect important information from the included studies. The framework contained study information such as author(s), year of publication, study type (in vitro and in vivo animal study, human study), research methodology, sample size, particle type and size, exposure concentration and duration and geographic location. Technical specifications included microplastic/nanoplastic characteristics that were described (polymer choice, size, shape, surface modifications), biological endpoints measured, exposure methods, performance measures, test systems (cell lines, animal models, human subjects), and validation procedures.

Challenges and limitations included methodological limitations, exposure assessment methods, translation relevance and knowledge gaps. The analysis used a narrative synthesis approach, which is appropriate in the case of the heterogeneous methodologies and research questions of the included studies and is consistent with recommendations for performing a systematic review in toxicology and environmental health literature.

Stage 1: Initial Screening

Initial database searches produced 958 or so potentially relevant records. Duplicate records were identified and removed using both automated (for example, EndNote, Mendeley) and manual verification, and 893 unique records were identified for screening.

Stage 2: Title and Abstract Screening

A title and abstract screening was carried out based on the predetermined inclusion and exclusion criteria. This stage led to the advancement of 424 records to full text review.

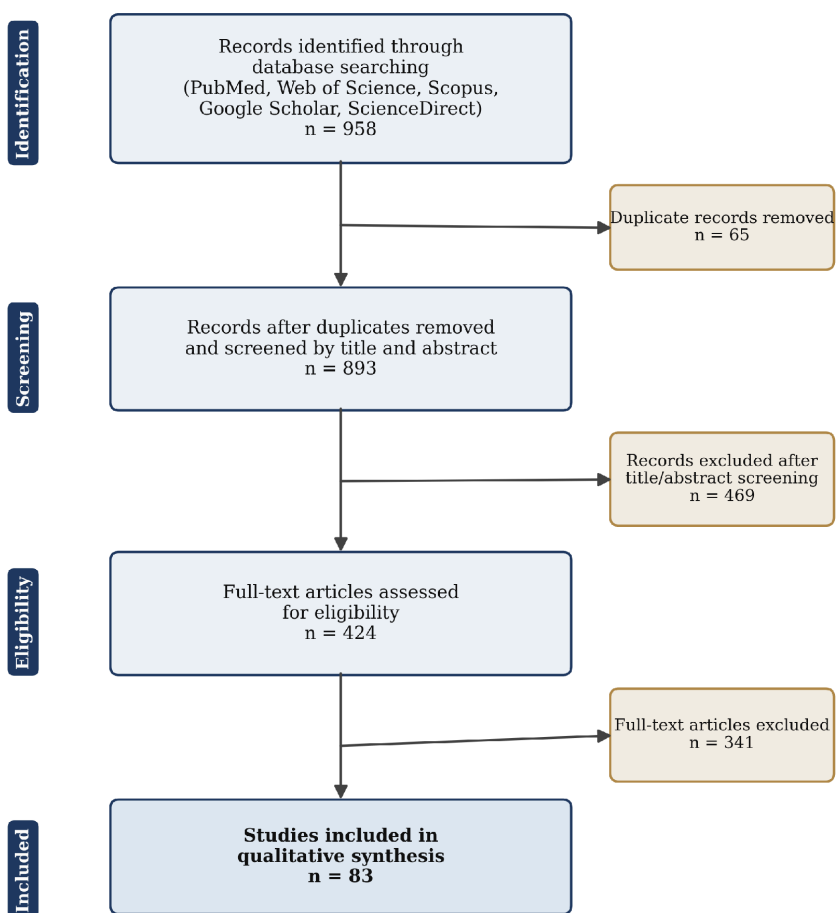
Stage 3: Full-Text Assessment

Full text articles were retrieved and evaluated for final inclusion. Studies were classified according to the main area of focus (exposure pathways and bioaccumulation, ovarian toxicity and folliculogenesis, hormonal disruption and endocrine effects, pregnancy outcomes, placental transfer and fetal effects, molecular mechanisms) in order to achieve a balance in the coverage of microplastics/nanoplastics reproductive health studies. This process resulted in 83 studies for final inclusion in the systematic review.

Stage 4: Data Synthesis

Data synthesis of included studies was performed following a narrative approach because of the heterogeneity of study designs, scenarios of exposure, and outcome measures. Key findings were organized thematically by the research questions, and attention was paid to the particle characteristics (size, type, concentration, exposure models (in vitro, in vivo, human), and biological endpoints (measured). Figure 1 shows the entire process in diagram form.

Figure 1. PRISMA Flow Diagram for Study Selection Process



PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram illustrating the systematic study selection process for the literature review on microplastics and nanoplastics impacts on female reproductive health.

RESULTS AND DISCUSSION

Microplastics (MPs) and nanoplastics (NPs) are particles of synthetic polymers that have become universal environmental contaminants with potential major implications for human health. Although there is no universally established definition, MPs are usually defined as plastic particles when their size is up to 5 mm, without a clear lower size limit. NPs are generally considered particles in the submicron size range, i.e. less than 1 mm or 0.001 mm.^[8] Together, MPs and NPs represent a diverse selection of different types of synthetic particles with varying size, shape, polymer composition and origin.

Classification and Paths of Formation

MPs and NPs are divided into two main categories according to the ways of formation: primary and secondary microplastics.^[10,11] Primary MPs are produced as small plastic particles for specific industrial use and consumer goods. These particles enter water bodies via wastewater discharged by rivers and sewage treatment plants. Common sources of primary MPs include personal care products such as toothpaste, facial cleansers and cosmetics which contain intentionally added microbeads.^[10, 11]

In contrast, secondary MPs are produced by the environmental breakdown of larger pieces of plastic. These irregularly-shaped particles are a product of different physical and chemical processes, such as fragmentation, photodegradation, mechanical abrasion, and biological transformation of bulk plastics in the environment. According to survey data, secondary MPs are the main fraction of microplastic pollution in environmental systems.^[2]

Polymer Composition and Material Choice

The most common types of polymers in environmental MPs and NPs are polystyrene (PS), polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC), and polycarbonate (PC).^[11] However, a systematic review of the research methodologies shows that there is a large gap between the types of materials used in experimental research and those most abundant in environmental settings.

In a thorough review of 83 studies that have examined the health effects of MP and NP, the use of PS as experimental material was the most frequently employed polymer by 41 studies, with a total of 11 studies that used PS as experimental material in their investigation, the most common polymer used in toxicological studies. This preference is practical, given that PS particles are easily obtained from several commercial sources in standardized sizes, making it easier to fluorescence-label and modify the particle surface to improve its usefulness for experimentation.

In spite of being convenient for research, PS has a lower environmental abundance with respect to other polymers, such as PE and PP, considering both the amount produced and its prevalence as an environmental pollutant.^[12] This disparity calls into question the ecological relevance of PS-focused studies to the assessment of real-world human health risks. Furthermore, commercially available PS particles are mainly spherical micro- or nanospheres that cannot represent the wide range of morphologies of MP and NP fragments formed during environmental degradation processes.

Beyond PS, PE was the second most studied material with a total of 14 studies, followed by PP 10 studies, polyethylene terephthalate (PET) nine studies and PVC eight studies.^[9] Two studies have used in vitro cell culture models to investigate the biological effects of tire wear particles (TWP), which are a major contributor to microplastic pollution in the environment.^[13,14] Other types of polymers, such as poly(methyl methacrylate) (PMMA), poly(lactic-co-glycolic acid) (PLGA), polyamide 6 (PA6), polyurethane (PU), polylactic acid (PLA), phenol-formaldehyde resin microplastics (PF-MP) and synthetic polymer microspheres (SPM) received few attention because they were mentioned in only one publication among the reviewed publications.

Morphological Characteristics and Size Distributions

Particle morphology is one of the most important characteristics that affects MP and NP behavior and biological interactions. Analysis of published research shows that 73 percent of studies (n = 61) used spherical particles, mainly because they are commercially available and available from manufacturers with ease.^[9] However, this methodological convenience entails a possible bias because spherical particles might not be a good representation of the irregular morphologies typical for MPs and NPs in the environment.

To overcome this limitation, it has been the practice of some researchers to adopt methods to generate more environmentally relevant particle shapes. About 10 percent of the studies (n = 8) made irregular MP particles through mechanical fragmentation methods such as ball milling, homogenizer grinding, or cryogenic milling and sieving for size fractionation.^[15,13] These methods give particles with random morphologies that simulate the properties of MP produced by the natural degradation of bulk plastics. Notably, 17 percent of studies (n = 14) did not report particle shape, which can be considered a major methodological gap in the literature.^[9]

In one example of the synthesis of particles with important biological properties,^[16] examined the pulmonary toxicity of PS particles of sizes from 1.67 to 2.17 μm with poly (N-vinylpyrrolidone) as the stabilizer and 2,2-azobis (2-methylpropionitrile) as the radical initiator.

Particle size is another essential parameter affecting the toxicity of MP and NPs in a big way. Several studies have shown that particle size plays an important role in the determination of cellular uptake and biological effects.^[17] Analysis of size distributions in published research shows the most common investigated size distributions for MPs are 1-50 μm and 50-150 μm .^[9] For NP research, investigators mostly use commercially available particles with standardised dimensions of 50, 100, 200, 500 and 1000 nm .

nm. However, the use of spherical particles with defined size leaves a knowledge gap on the health consequence of irregularly shaped and randomly-sized NPs and contributes to uncertainty in human health risk assessment for nanosized plastic exposures.

Physicochemical Properties and Behavior in the Environment

MPs and NPs have a number of unique physicochemical characteristics affecting their environmental persistence, transport, and their biological interactions.^[18] First, these particles show incredible resistance to degradation by chemical inertness and corrosion resistance that results in long-term persistence in the environment. Second, their great specific surface area compared to their mass offers a lot of adsorption sites, making it easy to bind heavy metals, pathogens, persistent organic pollutants and other environmental contaminants. This sorption capacity allows MP and NPs to act as vector substances for co-contaminants and therefore may increase their toxicological importance.

Third, the low density of most plastic polymers makes MPs and NPs buoyant and therefore allows for their dispersion and long-range transport through aquatic and atmospheric environments. Finally, their small sizes on the scale of micrometres and nanometers allow the latter to cross various biological barriers and enter organisms at several levels of organization, from tissues to cells and potentially subcellular compartments, exerting direct and indirect biological effects.^[18]

These combined characteristics, involving environmental persistence, contaminant sorption capacity, mobility and biological penetration potential, are indicative of the complex nature of MP and NP pollution, as well as the need for detailed characterization in studies examining their impacts on biological systems, specifically reproductive health.

Exposure Routes and Bioaccumulation

Human exposure to MP and NP occurs in a variety of ways and leads to bioaccumulation in a variety of organ systems. Understanding these exposure routes and patterns of distribution is key to understanding possible health outcomes, especially on reproductive function. This section discusses the major ways people can be exposed, namely ingestion, inhalation, and skin absorption, and considers the available evidence for the occurrence of bioaccumulation in human tissues with special emphasis placed on the reproductive organs and related biological fluids.

Routes of Human Exposure

Ingestion by Contaminated Food and Water. Oral ingestion is the main route of human exposure to MPs and NPs, and contamination has been reported in a wide variety of food sources and drinking water supplies. Marine organisms should not be overlooked as an important pathway of exposure since over 690 species, such as commercially important fish and shellfish, have been reported to contain MPs that bioaccumulate and biomagnify up the trophic levels to reach human consumers.^[2] Beyond seafood, MPs have been found in many terrestrial food products, such as honey, beer, table salt and milk, suggesting that the MP contamination of the food supply is widespread.^[19]

Following their ingestion, submicron MPs and NPs, especially those smaller than 100 nm, may be able to traverse the cell membrane and pass through the intestinal epithelial barrier, potentially reaching the bloodstream.^[9] This translocation allows for systemic distribution in the secondary organs. Given the fact that the intestinal blood flow is channelled through the hepatic portal system, the liver is a prime target for particle accumulation after intestinal absorption. Furthermore, the MPs and NPs can cross the blood-brain barrier and accumulate in neural tissue and display neurotoxic effects.

Inhalation of Airborne Particles. Atmospheric deposition of MPs and NPs has become a major part of air pollution with documented exposure to air-pollution-associated exposure by inhalation of airborne particles.^[20,21] Indoor air concentrations are usually higher than outdoor levels because of abrasion of synthetic textiles, degradation of plastic building materials and concentration in enclosed environments. The abundance and the deposition rate of MPs in indoor air differ considerably in different spaces, depending on the room function, the occupancy patterns, and the amount of air infiltration from the outside.^[20]

Indoor dust samples have shown significant MP contamination with concentrations of polyethylene terephthalate (PET) and polycarbonate (PC) from 38-120,000 and <0.11-1,700 mg/g, respectively, across 12 countries.^[19] In educational environments, MP abundance in school dust was as high as 195 particles/g^[19], which might be especially vulnerable for children who spend long periods of time in these environments.

Respirable MPs (i.e., particles that can reach the alveolar region where the gas exchange is taking place) are of special concern because of their potential to cross the alveolar epithelial barriers and extrapulmonary translocation to secondary organs.^[9] Due to the size-dependent depositional patterns in the respiratory tract, the fate of the particles within the respiratory system is determined by particle size, with smaller particles showing greater potential for deep lung penetration and subsequent systemic distribution.

Absorption and Penetration through the Skin. While dermal exposure is thought to be the least important route of MP and NP entry, experimental evidence shows that NPs can cross the dermal barrier using several mechanisms. Three major routes of penetration are cellular bypass for the tiniest particles (less than 1-4 nm), the follicular and glandular pathways through sweat glands and hair follicles for particles between 4-20 nm in diameter, and penetration through compromised skin for larger particles (21-45 nm) have been described.^[22, 23] With severely compromised skin integrity, larger NPs may find dermal penetration.

However, the fact that the regulatory phase-out of microbeads in personal care products and detergents in many jurisdictions has greatly lowered levels of exposure from this source by the skin.^[9,24] Consequently, dermal absorption is a relatively unimportant route of exposure relative to ingestion and inhalation routes under normal circumstances, although it may be of importance in people with impaired skin barriers or with specific occupational exposures.

Detection of MP's and NP's in Human Tissues. Direct evidence for exposure of humans to and bioaccumulation of MPs and NPs has been observed from detection studies in several different tissue types and biological fluids. MPs have been found in human faeces,^[25] confirming exposure through diet and also proving that particles are excreted through the gastrointestinal tract. However, fecal excretion is not complete elimination since MP have also been identified in colectomy specimens,^[26] which confirms particle translocation into colonic tissue.

More worrying evidence is the prevalence of MPs being detected in human blood,^[3] confirming that they have the ability to circulate throughout the body and spread to widespread organs throughout the body. Tissue-specific detection has found MPs in cardiac thrombi with particle sizes around 5 mm^[27], hepatic tissue with particles 4-30 mm^[28] and cardiac tissue samples from patients undergoing cardiac surgery, where MPs (20-500 um) were found in myocardial tissue and also in pericardial effusion.^[4] These results show particle translocation, organ accumulation and lodging in cardiovascular tissues.

Respiratory tract contamination has been documented in both the upper and lower respiratory tract. MPs have been found in sputum, samples from the nasal cavity,^[29] and deep parts of the respiratory tract such as alveolar tissue and lung parenchyma.^[5,30] While direct causal links between MP exposure and certain respiratory diseases are yet to be determined, there is emerging evidence that exposure to MPs can affect the composition and function of pulmonary surfactant, which could affect lung cell integrity and predispose to respiratory disorders, such as fibrosis, frosted glass nodules, and asthma.^[16,31,32,33,34]

Bioaccumulation in Reproductive Tissues and Placental Transfer. In case of particular concern for reproductive health, MPs and NPs are found in placental tissue from pregnant women,^[4] leading to major questions about maternal-fetal transfer and potential effects on fetal development. The detection of MPs in neonatal meconium is a new piece of evidence for transplacental particle transfer.^[35,36] This transfer happens through transcellular and paracellular pathways through the placental barrier.^[37]

The mechanisms resulting from the effects of MP on placental barrier function include the production of reactive oxygen species (ROS), the occurrence of placental metabolic dysregulation and the generation of inflammatory responses.^[14]

These effects could affect the growth and development of the fetus, which can contribute to adverse pregnancy outcomes such as fetal growth restriction, low birth weight, and pregnancy loss.^[37,38,39,40]

Mechanisms of Tissue Distribution & Organ-Specific Accumulation

Gastrointestinal Tract and Liver System. At the cellular level, MP exposure in the intestinal epithelial cells results in oxidative stress. Minuscule polystyrene (PS) microspheres (5 mm) induced higher mitochondrial depolarization in both colonic (CCD841CoN) and small intestinal (HIEC-6) epithelial cell lines.^[2] Consequences of intestinal MP exposure are intestinal barrier dysfunction, metabolic disorders, dysregulated immune responses, chronic inflammation and even the development of intestinal pathologies.^[23,32,37,41,42,43] Besides, the MPs may impair nutrient absorption and interfere with intestinal homeostasis, contributing to the development of gastrointestinal diseases.

Respiratory System. In the respiratory system, the MPs interact with pulmonary surfactants - complex mixtures of lipids and proteins that decrease the surface tension and preserve the stability of the alveoli. MPs modify several parameters of the lung simulated surfactant, such as phase behavior, surface tension, and membrane structure, in addition to an elevated reactive oxygen species concentration in vitro.^[33] Through alteration of the composition of the pulmonary surfactant, the MPs mediate contact with lung cells and cause ROS-mediated DNA injury, which plays a key role in pulmonary damage.

Cardiovascular System, Hematological Systems. After being released into systemic circulation, both the MPs and NPs interact with several components of the blood such as plasma proteins, erythrocytes, platelets, and peripheral blood lymphocytes. In addition to this, MPs quickly adsorb plasma proteins, creating a multilayered protein corona on their surface.^[15] This corona affects particle physicochemical properties, dispersion behavior and interactions with the surrounding biological matrix, which eventually influences particle uptake and toxicity profiles. Direct reactions with blood cells can result in erythrocyte cytoskeleton damage and platelet aggregation,^[44] which can lead to the development of thrombotic danger.

Central Nervous System. PS-NPs show the ability to cross the blood-brain barrier (BBB) and have neurotoxic effects.^[45] Exposure of human neuroblastoma cells to PS-NPs (0.03-1 μ m) for 48 hours causes several adverse effects, such as decreased cell viability, oxidative stress, mitochondrial dysfunction, and apoptosis.^[46,47,48] Beyond direct neurotoxicity, MPs can have indirect effects through the gut-brain axis, since the intestinal microflora is implicated in the functioning of the central nervous system, including mood and cognitive function. MP-induced dysbiosis of the gut microbiota may lead to neuroinflammation and behavioral changes via gut-brain signal pathways.^[49]

Particle Elimination and Clearance Mechanisms

While the exact amount of MPs and NPs that reach the human body is unclear, it is known that most of them are eliminated by faecal excretion, intestinal mucus layer sequestration, and mucociliary clearance in the respiratory tract. Fecal MP concentrations show a large inter-individual variation depending on dietary intake patterns as well as individual physiological characteristics,^[25] which reflects variable exposure levels and efficiency of clearance across populations.

MPs and NPs as Vectors for Co-Contaminants. Beyond their direct physical and chemical effects, MPs and NPs act as vectors for other environmental contaminants such as heavy metals, polycyclic aromatic hydrocarbons (PAHs) and persistent organic pollutants (POPs). Following ingestion or inhalation, these sorbed contaminants can desorb inside the body, leading to combined toxic effects, increased oxidative stress and increased inflammatory responses.^[50] MPs and NPs are also substrates for microbial colonization, which creates a "plastisphere" microbiome, that has the potential to transport pathogenic microorganisms into host tissues.^[51] Furthermore, particle interactions with biological macromolecules such as proteins and lipids can alter cell signaling pathways, immune responses and metabolic homeostasis.^[17]

Mechanisms Responsible for Reproductive Toxicity. The reproductive toxicity of microplastics (MPs) and nanoplastics (NPs) is the result of multiple connected molecular and cellular mechanisms. These

mechanisms include cell uptake and intracellular distribution, oxidative stress induction, inflammatory cascade activation, endocrine disruption, DNA damage, epigenetic changes and interference with important cellular signaling pathways. Understanding these mechanisms is critical for describing how MP and NP exposure impairs reproductive function in different species of mammals, including humans.

Mechanisms of Cellular Uptake and Distribution. Particle size is a key factor in determining the efficiency of cellular uptake and tissue distribution patterns. MPs in the range of 0.1-10 μm exhibit the ability to cross biological membranes, to pass through the blood-brain barrier and to cross the placental barrier, increasing the bioaccumulation potential in secondary biological tissues such as liver, brain and the reproductive organs.^[7] Size dependent translocation has some specific patterns since smaller particles (less than 150 μm) are able to cross gastrointestinal epithelium while smaller particles (less than 5 μm) are phagocytized by macrophages and are transported to systemic circulation and lymphoid organs (spleen).

The large surface area and hydrophobic nature of MPs mean that they are an efficient vector for co-contaminants, such as endocrine-disrupting chemicals (EDCs), heavy metals and other toxic organic compounds. This phenomenon is referred to as the "Trojan Horse Effect" that enables bioaccumulation and biomagnification of several toxicants through food chains, which leads to synergistic effects and manifests as behavioral, histological and biomolecular deviations in exposed organisms.^[7]

Oxidative Stress and Formation of Reactive Oxygen Species

Oxidative stress is a key mechanism of MP and NP induced reproductive toxicity. Following internalization into cells, these particles lead to interference with mitochondrial activity and induction of excess reactive oxygen species (ROS) production to the point of overloading endogenous antioxidant defense systems. This imbalance between the generation of ROS and antioxidant capacity leads to oxidative damage to the cellular macromolecules including lipids, proteins and nucleic acids.

Key antioxidant defense molecule and enzymes modulated during oxidative stress responses include nuclear factor erythroid 2-related factor 2 (Nrf2), heme oxygenase-1 (HO-1), superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), reduced glutathione (GSH) and NADPH oxidase 4 (NOX4).^[52,53] The expression and activity of these defensive molecules are responsible for cellular capacity to minimize oxidative damage.

Multiple molecular pathways have been involved in orchestrating the cellular responses to oxidative stress. Nuclear factor kappa B (NF- κ B) is a master transcriptional regulator of inflammatory responses by modulating pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1 β (IL-1 β) and tumor necrosis factor- α (TNF- α).^[54,55] On the other hand, Nrf2 is a key transcription factor that mediates antioxidant defense by inducing cytoprotective gene expression programs.^[56,57,58]

These pathways are subject to complex cross regulation: Nrf2 activation boosts HO-1 expression that suppresses inflammation through inhibition of the NF- κ B signaling.^[59] Reciprocally, NF- κ B can block Nrf2 signaling, leading to a dynamic regulatory network. Polystyrene MP and NP (PS-MNP) exposure

interferes with this balance by activating NF- κ B, increasing pro-inflammatory cytokines concentrations, and at the same time inhibiting the expression of Nrf2 and HO-1, which increases inflammatory responses.^[60]

The severity of oxidative stress and antioxidant enzymes expression patterns are critically dependent upon the exposure duration and particle size. Chronic exposure (around 8 weeks) leads to an increase in expression of antioxidant enzymes as an adaptive response of the cell but acute exposure (72 h) leads to a reduction in antioxidant capacity.^[61,62] Extended MP exposure (12 days) induces higher levels of oxidative stress than short term exposure (48 hours), suggesting time dependent accumulation of oxidative damage.

Particle size is another factor that will affect the intensity of oxidative stress. Research on human lung epithelial A549 cells treated with PS-NPs and phthalate esters showed a concentration-dependent effect with low concentrations resulting in negligible oxidative stress and high concentrations causing significant oxidative damage.^[63] This dose-response relation suggests the occurrence of threshold effects in the manifestation of toxicity.

Inflammatory Responses and the Activation of Inflammasomes

Oxidative stress activates the NLRP3 inflammasome, a multiprotein complex that acts as an important mediator of inflammatory responses. NLRP3 activation leads to the activation of caspase-1, which processes pro-inflammatory cytokine precursors to mature, biologically active forms of cytokines^[65, 66] and triggers pyroptosis -- a form of inflammatory programmed cell death.^[67]

Pyroptotic cell death leads to excessive release of pro-inflammatory cytokines, which damage tissues and organs. PS-NPs^[14,60] and PS-MPs^[37,68] stimulate these inflammatory pathways, which result in significant increases of cytokines (IL-1b, IL-6, IL-18) and other inflammatory mediators (TNF-a, MCP-1, CXCL10). This inflammatory cascade is reflected in the reproductive organs, causing inflammation in ovaries^[14,60] and testes.^[37,68]

Tissue-specific inflammatory processes have been reported in several different organ systems. Kidneys,^[11] intestinal epithelia,^[69] and gastric cell lines^[49,70] exposed to MNPs show similar oxidative stress and inflammatory responses, proving the systemic nature of the MNP-induced inflammation.

Ovarian Fibrosis and Activation of Wnt/b-Catenin Pathway

Oxidative stress is involved in the development of ovarian fibrosis by the activation of the Wnt/b-catenin signaling pathway in ovarian tissue and granulosa cells. This pathway activation leads to an increase in the expression of fibrosis-related genes,^[71] enhances the proliferation of fibroblasts and leads to the differentiation of fibroblasts into myofibroblasts. These activated myofibroblasts produce excessive amounts of collagen types I and III, leading to progressive ovarian fibrosis.^[71]

Experimental evidence in rats treated for 90 days by 0.5 mm PS-MPs at doses 0, 0.015, 0.15 and 1.5 mg/day showed that oxidative damage by ROS is responsible for ovarian injury via several mechanisms.

These include apoptotic cell death, tissue fibrosis and upregulation of the Wnt/b-catenin signaling pathway. Additionally, some important markers of fibrosis, such as transforming growth factor- β (TGF- β), fibronectin, and α -smooth muscle actin (α -SMA), had higher expression in the ovarian tissue.^[71]

PS-MPs cause ovarian fibrosis by the concerted activation of the Wnt/b-catenin signaling pathway and the induction of granulosa cell apoptosis by oxidative stress, ultimately leading to the decreased ovarian reserve capacity.^[71] The combined exposure to PS-MPs and di(2-ethylhexyl) phthalate (DEHP) shows synergistic toxicity: the two compounds increase ROS production and cause oxidative stress and cell cycle arrest and necroptosis in ovarian granulosa cells through activation of the CNR1/CRBN/YY1/CYP2E1 signaling axis in mice.^[48]

Endocrine Interference and Hormonal Interference

Endocrine Disruption Thyroid. Chronic exposure to plastic particles and associated chemicals affects thyroid endocrine functions by interfering with its ability to regulate growth, development, metabolism and reproduction.^[7] MP additives and co-contaminants, such as polybrominated diphenyl ethers (PBDEs), bisphenol A (BPA), phthalates and organotins, are TDCs, or thyroid-disrupting chemicals, which interfere with the synthesis, secretion and action of thyroid hormones.

Following gastrointestinal absorption, TDCs disrupt thyroxine (T4) and triiodothyronine (T3) biochemical pathways. Their systemic circulation has negative effects on thyroid hormone production and metabolism, and in particular, it has consequences for brain development during the critical developmental windows.^[7] Multiple TDCs form complexes with thyroid hormone transport proteins in the blood to be transported to the brain to bind thyroid hormone receptors, causing disruption to thyroid-dependent neurodevelopment.

TDCs are part of the prevalence of a subclinical thyroid disease (SCTD) that is manifested by anomalous levels of TSH in the absence of clinical overt symptoms.^[7] BPA in particular affects the action of thyroid hormones by preventing T3 from binding its receptor and inhibiting thyroid hormone receptor-mediated transcriptional activity.^[7] Similarly, phthalates affect thyroid function by several mechanisms, such as interference with gene expression in the hypothalamic-pituitary-thyroid (HPT) axis, T3-protein binding inhibition, antagonistic receptor interaction, and disruption of thyroid receptor transcriptional activity.^[7]

PBDEs and polybrominated biphenyls (PBBs) used as flame retardants in plastics decrease the circulating thyroid hormone concentrations and are associated with impaired thyroid function.^[7] Experimental studies in rats showed that five weeks of exposure to PS-NP (1, 3, 6 and 10 mg/kg/day) inhibited serum levels of T3, free T3 (FT3) and free T4 (FT4), which confirmed dose-dependent thyroid hormone suppression.^[7] The lipophilic nature of PBDEs and PBBs promotes their concentration in wildlife and marine organisms after they are exposed to the environment.

At the molecular level, PBDEs work by interfering with the HPT axis by altering the transcription of several genes that are related to thyroid function, such as thyroid-stimulating hormone beta subunit (tshb), type 2 deiodinase (dio2), and NK2 homeobox 1 (nkx2.1).^[7] These genes are involved in the control of

thyroid development and TSH production and are extremely sensitive to PBDE exposure and consequently are potential targets for endocrine disruption.

Endocrine Disruption in the Reproductive System. MPs are transport vectors of composite EDCs that cause various reproductive endocrine disorders such as infertility, precocious puberty, hormone-dependent tumors, metabolic dysfunction, disruption of granulosa cell steroidogenesis, and polycystic ovary syndrome (PCOS).^[7] Endocrine disrupting (plastic additives) - PBDE's, BPA, Phthalates, Organotins, Nonylphenols, Octylphenols, Biocides (Tributyl Tin (TBT), Mercury, Arsenic, Copper, Cadmium, Lead) have the ability to cross the placental barrier from maternal to fetal circulation and cause neurodevelopmental abnormalities in offspring.^[7]

BPA affects oocyte development in mice and non-human primates^[7] and the steroidogenesis in granulosa cells from multiple species in humans, sheep, and swine, as well as those in mice.^[7] These effects disrupt the female reproductive function by impairing folliculogenesis and steroid hormone production necessary for normal ovarian cyclic function and fertility.

Pathways of DNA Damage and Cell Death

In the placental cells, high concentrations of ROS cause DNA damage, inflammation, and apoptosis and therefore may impact the course of pregnancy.^[72] Liver and lung cells exposed to MPs show significant changes in metabolic and proliferative activities,^[61] which proves that MP-induced cellular dysfunction is not confined to reproductive tissues only but also affects many organ systems that are vital for overall health.

Heavy Metal Co-Contaminants and Neuroendocrine Disturbance

Heavy metals carried by MPs may cause neurotoxic effects, which indirectly affect the reproductive function by disrupting the function of the hypothalamic-pituitary axis. Mercury exposure changes circulating levels of hormone follicle-stimulating hormone (FSH), luteinizing hormone (LH), inhibin, and androgens resulting in reproductive disruption due to pathogenic changes in both the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal (HPG) axes.^[73,74,75] Increased HPA axis hormones concentrations occur after heavy metal exposure,^[32] with some metals found in electronic waste increasing secretion of corticotropin-releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH).^[32]

Lead interferes with neurotransmission in the brain^[15] which affects the regulation of neurotransmitters in the hypothalamus and has a negative effect on gonadotropic hormone function due to the changing HPG axis control.^[73,76] Chromium enhances the function of glutathione reductase and the amount of metallothionein isoform 3 (MT3) in the hypothalamus.^[77] Combined chromium and exposure to benzene alters neuroendocrine and lymphoid systems by interfering with the HPA axis.^[78]

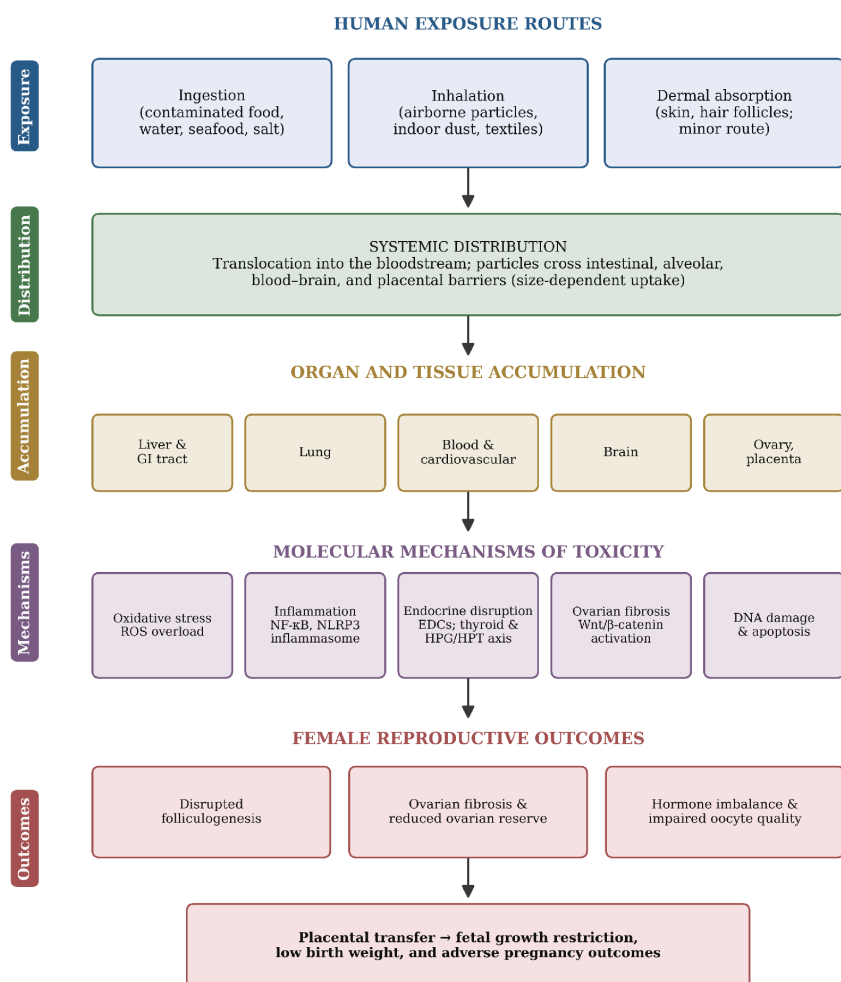
Mercury suppresses the secretion of the pituitary hormones LH and FSH that affect ovarian function and menstrual cycles in females.^[75] Cadmium and arsenic produce a xenoestrogenic effect in the pituitary

gland and reduce LH secretion.^[79] Mercury bioaccumulation in the pituitary and thyroid glands causes endocrine toxicity through alteration of hypothalamic-pituitary-thyroid/gonadal axes.^[80] As powerful EDCs, cadmium and arsenic adversely affect endocrine function by changing the secretion pattern of hormones.^[81]

Arsenic causes neurological abnormalities, elevates mRNA gene expression of oxidative response, oxidative stress, and apoptosis.^[79] Combined lead and cadmium exposure have a greater impact on LH and FSH levels in proestrus rats than does lead alone, with lead exposure having a specific effect on reducing the fluidity of the pituitary membrane.^[82] Chromium-induced endocrine disruption increases superoxide dismutase activity in the anterior pituitary and produces oxidative stress in pituitary tissue.^[83]

Figure 2 brings together the findings discussed above to summarise the pathways of exposure to microplastics and nanoplastics in the human host, systemic distribution, accumulation in organs, the molecular mechanisms, and female reproductive outcomes.

Figure 2. Simplified overview of the impact of micro and nanoplastics on body systems and molecular processes and the resulting negative effects on female reproduction.



CONCLUSION

This comprehensive review identifies microplastics (MPs) and nanoplastics (NPs) as emerging threats to female reproductive health with converging evidence from cellular, animal and human studies documenting substantial and adverse effects across multiple biological systems. The ubiquity of human exposure by ingestion, inhalation, and dermal contact, together with the detection of MPs in the blood and placenta tissue, establishes the systemic bioaccumulation of MPs in reproductive organs. Multiple interrelated mechanisms are involved in reproductive toxicity, including the creation of oxidative stress, activation of the inflammatory cascade, endocrine perturbation that includes thyroid and gonadal hormone disruption, DNA injury and disruption of important cell signaling pathways.

In females, evidence suggests disruption of folliculogenesis, ovarian fibrosis, hormone imbalance and egg quality compromise. Placental transfer of MPs raises important issues of fetal development since associations between maternal exposure and adverse pregnancy outcomes such as fetal growth restriction and developmental abnormalities have been documented. These findings underscore the need for research specifically focused on female reproductive toxicology as evidence in this area is currently limited when compared to other areas of MP research.

There are several limitations that should be acknowledged. First of all, the narrative review design does not allow for quantitative meta-analysis or accurate effect size estimation across heterogeneous studies. Second, most mechanistic data is from animal models, and the translation to humans remains to be validated by prospective human research. Third, the field is not standardised in terms of exposure assessment methodologies, particle characterization protocols, and outcome measurement approaches, which reduces the comparability of studies. Fourth, most studies in place focus on polystyrene particles, which may not represent the toxicity profile of other polymers that are present in the environment. Fifth, synergistic effects of MP mixtures with co-contaminants including endocrine-disrupting chemicals and heavy metals are incompletely characterized. Finally, long-term effects of chronic low-dose exposure and the transgenerational effects need further study.

The public health implications are huge. Increasing rates of infertility and poor pregnancy outcomes among human populations are not fully explained, and MP exposure is one possible factor that needs urgent investigation. The finding of MPs in human placental and reproductive tissues at levels associated with adverse effects in animal models implies that current exposure from the environment may already be affecting reproductive health in the population on a large scale. These findings call for immediate policy responses such as reduction of the production and release of plastics, developing exposure mitigation strategies, and setting the regulatory guidelines for acceptable MP concentrations in food, water and consumer products.

Future research priorities include: prospective human cohort studies with validated exposure biomarkers relating MP burden to female reproductive outcome; mechanistic studies to elucidate size-dependent, polymer-specific and mixture toxicity in ovarian and placenta tissues; evaluation of vulnerable populations such as pregnant women or occupationally exposed individuals; evaluation of intervention strategies to reduce maternal exposure; and development of standardised methodologies for detection and quantification of MPs in reproductive and placenta tissues. Particular emphasis should be given to understanding the effects of transgenerational effects, maternal-fetal transference mechanisms, and low dose chronic exposure scenarios relevant to the real world situation.

As plastic production keeps on escalating globally (up to an estimated 460 million tons annually), the reproductive health consequences of MP and NP exposure are not simply an environmental issue, but a fundamental threat to the fertility of humans and future generations - a silent crisis that demands scientific attention and strong public health action today.

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