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A Comparative Review of Microplastic-Induced Male Reproductive Toxicity: Polymer Types and Size Effects

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Other. This protocol is registered retrospectively. REASON FOR RETROSPECTIVE REGISTRATION: This systematic review was initially conducted without prospective protocol registration. The review followed PRISMA 2020 guidelines throughout, including comprehensive literature searches in PubMed/MEDLINE and Web of Science (database inception to May 9, 2026), dual independent screening (F.W. and Y.L.), and systematic data extraction. At the request of the journal editor, we are now registering the protocol retrospectively with INPLASY to enhance transparency and align with best practices in evidence synthesis reporting. The review has been completed, including literature screening, data extraction, evidence synthesis, and risk of bias assessment using NOS (for human studies) and SYRCLE (for animal studies). The manuscript has been submitted for peer review. No changes were made to the methodology between protocol development and study completion.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202680040

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 August 2026 and was last updated on 10 August 2026.

INTRODUCTION

Review question / Objective The aim of this systematic review is to systematically compare the differential characteristics and mechanisms of male reproductive toxicity induced by microplastics (MPs) and nanoplastics (NPs) of different polymer types and particle sizes, integrating both human epidemiological evidence and animal experimental data.

The review addresses the following questions:
(1) What are the detection characteristics (polymer composition, abundance, size distribution) of microplastics in the human male reproductive system, and what are their associations with semen quality parameters?
(2) What are the differential effects of various polymer types (non-polystyrene vs. polystyrene) on male reproductive endpoints in rodent models?
(3) What is the relationship between particle size and male reproductive toxicity, and does the

toxicity follow a monotonic or non-monotonic pattern?

Rationale Microplastics and nanoplastics (MNPs) have been detected in human semen and testis, with epidemiological evidence suggesting associations with declining semen quality. However, existing reviews have largely focused on single mechanisms (e.g., oxidative stress) or pooled average effects, lacking systematic comparison across polymer types and particle sizes. Animal experiments are heavily concentrated on polystyrene (PS), whereas data on high-abundance environmental plastics such as polyethylene (PE), polyvinyl chloride (PVC), and polyamide (PA) remain fragmentary. This knowledge gap creates a disconnect between real-world human exposure signals and experimental evidence. A systematic comparison of polymer-type and size-dependent reproductive toxicity is urgently needed to inform risk assessment and regulatory decisions.

Condition being studied Male reproductive toxicity induced by microplastics and nanoplastics, including impaired spermatogenesis, reduced sperm quality (count, motility, morphology), hormonal disruption (testosterone suppression), and testicular histopathological damage.

METHODS

Search strategy Databases: PubMed/MEDLINE and Web of Science Core Collection
Search period: Database inception to May 9, 2026

PubMed search strategy:
Search terms combined two categories using Boolean operators:
(1) Male reproductive terms: (epididymis OR epididymides OR testis OR testes OR testicle OR spermatogenesis OR sperm OR "male fertility" OR "male infertility" OR "male reproductive system" OR "male reproduction" OR spermatogonia OR spermatocyte OR spermatid OR "Sertoli cell" OR "Leydig cell" OR testosterone)
(2) Microplastic terms: (microplastic* OR nanoplastic*)
Exclusion filters: NOT (Review[Publication Type]) NOT (mollusc* OR bivalve* OR oyster* OR mussel* OR clam* OR scallop* OR snail* OR gastropod* OR cephalopod* OR crustacean* OR shrimp* OR crab* OR lobster* OR barnacle* OR copepod* OR fish OR fishes OR teleost* OR zebrafish OR marine OR seafood OR shellfish OR aquatic OR freshwater OR plankton OR algae OR seaweed OR coral* OR sponge*)

Web of Science search strategy:
TS=(epididymis OR epididymides OR testis OR testes OR testicle OR spermatogenesis OR sperm OR "male fertility" OR "male infertility" OR "male reproductive system" OR "male reproduction" OR spermatogonia OR spermatocyte OR spermatid OR "Sertoli cell" OR "Leydig cell" OR testosterone) AND TS=(microplastic* OR nanoplastic*) NOT DT=(Review) NOT TS=(mollusc* OR bivalve* OR oyster* OR mussel* OR clam* OR scallop* OR snail* OR gastropod* OR cephalopod* OR crustacean* OR shrimp* OR crab* OR lobster* OR barnacle* OR copepod* OR fish OR fishes OR teleost* OR zebrafish OR marine OR seafood OR shellfish OR aquatic OR freshwater OR plankton OR algae OR seaweed OR coral* OR sponge*)

For epidemiological studies, additional population-specific search restrictions were applied. Manual supplementary searches through reference lists identified no additional records.

Participant or population Human studies: Male participants of any age from whom semen and/or testicular tissue samples were collected for microplastic detection. Both healthy individuals and those with fertility disorders were included. No exclusions based on ethnicity or geographic region.

Animal studies: Male rats (Rattus norvegicus) and mice (Mus musculus) of any strain exposed to microplastics or nanoplastics via any route (oral, inhalation, injection) with reported reproductive toxicity endpoints.

Intervention Exposure to microplastics (<5 mm) and nanoplastics (<1 um) of any polymer type, particle size, shape, and surface chemistry. For human studies, this refers to the detection of microplastics in biological samples (semen, testicular tissue). For animal studies, this refers to controlled administration of MP/NP particles via oral gavage, drinking water, or other routes.

Comparator For human studies: Comparison between different microplastic exposure levels, polymer types, or between exposed and non-exposed groups (where detectable).
For animal studies: Control groups receiving vehicle solution (ultrapure water, saline, PBS, or corn oil) without microplastic/nanoplastic particles.

Study designs to be included Human studies: Cross-sectional studies, case-control studies, and cohort studies reporting microplastic detection in male reproductive samples.Animal studies: In vivo experimental studies using rat or mouse models

with controlled MP/NP exposure and reproductive endpoint assessment. Excluded: pure in vitro experiments, studies on non-mammalian species, reviews, conference abstracts, and editorials.

Eligibility criteria Inclusion criteria:
- Original research articles published in English
- Human studies: detection of MPs/NPs in semen, seminal plasma, or testicular tissue with reported detection methods
- Animal studies: in vivo rodent experiments with clearly reported MP/NP particle size, dose, exposure route, and reproductive toxicity endpoints (sperm quality, hormone levels, and/or testicular histopathology)
- For polymer type comparison (Table 2): non-PS polymer studies
- For size comparison (Table 3): studies including at least two different particle sizes within the same experimental design

Exclusion criteria:
- Non-original articles (reviews, commentaries, conference abstracts)
- Pure in vitro or ex vivo experiments
- Non-mammalian species (aquatic organisms, invertebrates)
- Studies not reporting male reproductive endpoints
- Animal studies with unclear particle size reporting.

Information sources Electronic databases:
- PubMed/MEDLINE (via PubMed interface)
- Web of Science Core Collection

Other sources:
- Reference list screening of included studies and relevant reviews
- No grey literature databases, trial registries, or conference proceedings were searched.

Main outcome(s) Primary outcomes:
1. Human studies: Microplastic detection characteristics (polymer composition, abundance, size distribution) in semen and testicular tissue; associations with semen quality parameters (sperm concentration, total count, progressive motility, normal morphology)
2. Animal studies — Polymer type comparison: Sperm quality parameters (count, motility, abnormality rate), serum/intratesticular testosterone levels
3. Animal studies — Size comparison: Size-dependent differences in sperm quality, hormone levels, and testicular histopathology.

Additional outcome(s) Secondary outcomes:
- Testicular histopathological changes (seminiferous tubule damage, cell loss)
- Blood-testis barrier integrity markers
- Oxidative stress biomarkers (MDA, SOD, GSH, CAT)
- Inflammatory markers (TNF-alpha, IL-1beta, IL-6)
- Molecular pathway alterations (transcriptomic, proteomic analysis)
- Body weight and organ coefficients (testis, epididymis weight/body weight ratio).

Data management Study selection and data extraction were performed independently by two reviewers (F.W. and Y.L.). Disagreements were resolved through discussion or by a third adjudicator (W.X.).

Software used:
- EndNote X9: reference management and deduplication
- Microsoft Excel: data extraction and management

Data extraction form included: first author, publication year, polymer type, particle size, dose, exposure route and duration, animal strain (age/weight), sample size, reproductive toxicity endpoints (with specific values), molecular mechanisms, and whether additives or aging treatment were present.

Quality assessment / Risk of bias analysis For human epidemiological studies (n=12): The Newcastle-Ottawa Scale (NOS) adapted for cross-sectional studies was applied retrospectively. The adapted NOS assesses three domains — Selection (5 items: representativeness, sample size justification, non-respondents, exposure tool description, exposure validation), Comparability (2 items: age control, additional factor control), and Outcome (2 items: outcome assessment quality, statistical test) — with a maximum score of 10 stars. Quality was classified as Low (0-3 stars), Medium (4-7 stars), or High (8-10 stars).

NOS Results: Mean score 5.8/10 (range 3-8). Three studies rated High quality (Zhao 2023, Zhang 2024, Kong 2025; all 8/10), 7 studies Medium quality (5-7/10), 2 studies Low quality (3/10). Common limitations: absence of sample size justification (0/12), non-respondent analysis (0/12), and confounder adjustment (7/12 with no multivariate adjustment).

For animal experimental studies (n=19): The SYRCLE Risk of Bias tool for animal studies was applied retrospectively. This tool assesses 10 items across selection (Q1-Q3), performance (Q4-Q5),

detection (Q6-Q7), attrition (Q8), reporting (Q9), and other bias (Q10) domains. Two reviewers independently assessed all studies using different interpretation thresholds (conservative vs. pragmatic).

SYRCLE Results: Under conservative interpretation, 0 studies Low risk, 13 Moderate, 5 Unclear, 1 High risk. Under pragmatic interpretation, 10 studies Low risk, 8 Moderate, 1 High risk (Kanzova et al. 2026 — Rhodamine B fluorescent labeling). Universal limitations: no detailed randomization methods (100%), no blinding reported (100%), allocation concealment not addressed (100%). Strengths: standardized housing (100%), complete outcome data (100%), consistent reporting (100%).

GRADE assessment was not performed due to the narrative synthesis design (no meta-analysis was conducted).

Strategy of data synthesis Due to high methodological heterogeneity among included studies in polymer type, particle size range, exposure protocols, and outcome measures, a narrative synthesis was performed instead of a meta-analysis.

The narrative synthesis was organized into three parts:
1. Epidemiological evidence synthesis: Summary of study characteristics, MP detection profiles, polymer composition patterns, and associations with semen parameters.
2. Polymer type comparison (Table 2, animal experiments): Toxicity characteristics for each non-PS polymer (PA, PMMA, PTFE, PET, PLA, PE), cross-polymer comparisons, and matched PS reference analysis.
3. Particle size effect comparison (Table 3, animal experiments): Intra-micron, intra-nano, and cross-level (nano vs. micro) comparisons focusing on size-dependent toxicity patterns.

For studies comparing different particle sizes, if direct statistical comparisons between size groups were available, they were extracted directly; if only comparisons with control groups were reported, two independent reviewers ranked relative toxicity based on the magnitude and significance of changes in key endpoints.

Subgroup analysis Planned subgroup analyses:
- By polymer type: PS vs. non-PS (PA, PMMA, PTFE, PET, PLA, PE)
- By particle size range: nanoparticles (10 um).

Sensitivity analysis Not applicable — no meta-analysis was conducted. Sensitivity considerations were addressed qualitatively by:
- Acknowledging limitations of cross-study comparisons due to methodological heterogeneity (strain differences, age at exposure, exposure protocols)
- Reporting methodological limitations (age discrepancy PN28 vs. PN35, strain differences ICR vs. C57BL/6 vs. BALB/c) as potential confounders.

Language restriction Only studies published in English were included. No language restrictions were applied during the initial search, but the search terms were in English and the databases index primarily English-language literature.

Country(ies) involved China (all authors are affiliated with Chinese institutions: Academy of Forensic Science, Shanghai; Nantong University, Nantong, Jiangsu).

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2. Hooijmans CR, Rovers MM, de Vries RB, et al. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol. 2014;14:43.
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Other relevant information Author contributions:
F.W., D.M., and W.X. designed the research study. F.W. and Y.L. performed the research (literature screening, data extraction). F.W., Y.L. and S.G. wrote the original draft. D.M. and W.X. reviewed and edited the manuscript. F.W., D.M., and W.X. acquired funding. All authors contributed to editorial changes and approved the final manuscript.

Registration note: This protocol is being registered retrospectively following review completion, at the request of the journal editor. The review was conducted following PRISMA 2020 guidelines. No methodological changes were made between protocol development and review completion.

Keywords microplastics; nanoplastics; male reproductive toxicity; polymer type; size effect.

Dissemination plans The completed systematic review manuscript has been submitted to a peer-reviewed journal for publication. The INPLASY registration number will be provided to the journal

editor upon registration. Results will be disseminated through the published article, conference presentations, and academic social networks.

Contributions of each author

Author 1 - Feixiang Wang - Conceived the review; designed the review; coordinated the review; data collection; data management; data analysis; data interpretation; wrote the protocol/review; obtained funding.
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