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Original Research Article

# Micro-nanoplastics pollution and mammalian fertility: A systematic review and meta-analysis

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ABSTRACT

*Micro:* and nanoplastics (MNPs) are fragments derived from physical, chemical, or biological degradation of plastic items. MNPs are one of the main sources of both marine and terrestrial plastic pollution. This study systematically and meta-analytically assesses the reproductive toxicity in mammals of key plastic components found in MNPs, focusing on polystyrene (PS), polyethylene (PE), polypropylene (PP), polyethylene terephthalate (PET), and polyvinyl chloride (PVC). PubMed, Medline, and CAB Abstracts databases were used to identify the relevant scientific papers, and 79 articles were selected for the systematic review. Six articles included two different species, and 19 papers contained both in vivo and in vitro studies, resulting in a total of 102 experiments being considered and analysed in the meta-analysis. Interest in the reproductive toxicity of MNPs in mammals has increased, peaking in the last two years. Five species (rat, mouse, bovine, pig, and human) have been studied, with most experiments carried out in vivo in mice, focusing on male fertility. The most studied plastic polymer is PS, and both micro- and nanoparticles were tested at single or multiple concentrations. Toxic effects are documented across various species, particle size, and polymer type. A pronounced concentration-dependent toxicity has been observed, particularly at high concentrations/doses of MNPs. There is a gap in research on food-producing animals, which are both relevant models for human health and potential vectors for MNPs into the human food supply chain. Overall, these findings emphasizpe the importance of continued research to elucidate the pathways and mechanisms through which MNPs impact mammalian reproductive health, ultimately advancing our understanding of how these pervasive pollutants interact with biological systems across diverse species.

## 1. Introduction

Synthetic polymers appeared in the late 19th century, around the 1860s; however, it was after the Second World War that plastics were massively used. Currently, plastic poses a significant threat as it has become the main source of marine and terrestrial pollution [1–3]. This threat is exacerbated by the secondary by-products resulting from the fragmentation and leaching of plastic items. Plastic materials, along with their fragmentation products — particles or particulates — have been detected in numerous ecosystems for over 50 years, leading researchers to call the current era as 'The Plasticine Era' [4] or 'The Plastic Age' [5].

Depending on their size, but not the composition, plastic fragments can be divided into various categories: mega- (>50 cm), macro- (5–50 cm), meso- (0.5–5 cm), micro- (<0.5 mm), and nanoplastics (<100 nm) [6]. Indeed, plastic pollution is predominantly made of polymers like polystyrene (PS), polyethylene (PE), polypropylene (PP), polyethylene terephthalate (PET) and polyvinyl chloride (PVC). Of particular concern are microplastics (MPs) and nanoplastics (NPs), due to their dimensions, representing biological hazards for humans and other living organisms. Indeed, the minute size of MNPs enables them to cross biological barriers, infiltrating organs and causing disruptions in various physiological functions [7]. Humans and other animals are exposed to plastic particles by ingestion of contaminated food, inhalation or filtration, and transdermal absorption [8–10]. MNPs have been detected in blood [11], lungs [12], faeces [13,14], kidneys, gastrointestinal tract, ovaries [15–18], placenta [19], semen and testes [20,21] of both terrestrial and aquatic organisms. Moreover, MNPs may facilitate the binding and

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transport of chemical contaminants and microbial agents due to their chemical-physical properties [22–25]. In addition, toxic chemicals associated with MPs like heavy metals, persistent organic pollutants, polychlorinated biphenyls polycyclic aromatic hydrocarbons, and organic pesticides [26] have been reported.

MNPs represents a biological hazard for riverine macroinvertebrates and amphibians, by inhibiting their growth and feeding, threatening their survival [27,28]. MNPs negatively affect both male and female reproductive systems of aquatic animals, impairing gonads, gametes, oocyte numbers, and embryo development [29]. For example, PS-MPs reduced oocyte number and diameter, as well as sperm velocity in oysters (*Crassostrea gigas*), leading to lower larval yield and impaired development [30]. In female guppies (*Poecilia reticulata*), exposure to PS-NPs decreased pregnancy rates and embryo production [31]. Similarly, MNPs exposure impaired fertilization rates and egg production in the freshwater species zebrafish (*Danio rerio*) and in the marine species medaka (*Oryzias melastigma*) [32–36], while PE-MPs led to increased sex steroid levels over time in maturing broodstock Atlantic cod (*Gadus morhua*) [37]. On the other hand, exposure of embryos to amino-nanopolystyrene induced no apparent intergenerational effects in the oyster (*Crassostrea gigas*) [38].

There is growing interest in understanding how MNPs interact with mammalian cells, particularly regarding their potential implications for reproductive health [7,39]. Today, half of the countries worldwide exhibit fertility rates below the replacement level, with many predicted to experience population declines of over 50 % between 2017 and 2100, leading to significant demographic shifts [39]. While the decline in the number of children born per woman over the past 60 years was primarily a matter of choice, there are now serious difficulties with conception [8]. Widespread infertility in both sexes has become a major health issue, increasing the demand for assisted reproduction [40]. The decline in child births, particularly in industrialized regions, raises the question of whether behavioural and economic factors alone can explain this trend or if biological factors also play a role [40]. Although declining male fertility is a contentious issue, substantial evidence suggests that semen parameters are deteriorating, with potential causes including obesity, diet, chronic diseases, and exposure to environmental toxins [9].

Therefore, the present study aims to systematically review and meta-analyse the impact of the most common polymers used to produce plastics (PS, PE, PP, PET, and PVC) on mammalian fertility.

## 2. Methodology

### 2.1. Literature search

A systematic review was performed using three internet databases (PubMed, Medline – Ovid, and CAB Abstracts - Ovid), in order to identify research works investigating the effects of plastic materials and their fragments on mammalian fertility. Each database was searched using specific Boolean operators and terms as keywords: (fertility OR reproduct*) AND (plastic OR particulate) AND (polystyrene OR polyethylene OR polypropylene OR polyethylene terephthalate OR polyvinyl chloride). The search keywords were tailored to the individual settings of each database. The search included all publications from 2013, when the first paper related to the topic of the present study was published [41], until August 20th, 2024, encompassing a decade of publications. No additional filters were applied to the literature search.

### 2.2. Selection and exclusion criteria

The screening process was conducted by two reviewers (BM and AMV), who initially focused on the title and abstract of each study to identify papers specifically addressing the effects of micro- and nanoplastics on mammalian fertility. Duplicate papers were removed, and articles were classified as “eligible”, “non-eligible”, or “possibly eligible”. The exclusion criteria were established prior to search and strictly applied during the screening. These criteria were: (1) studies unrelated to the topic; (2) review articles; (3) studies involving non-mammalian species; (4) studies utilizing MNPs in combination with other toxic compounds but not alone; and (5) studies with inconsistent results regarding the effects of MNPs on fertility. The inclusion of “possibly eligible” articles and any disagreements between reviewers were discussed with a third author (EI). Subsequently, the pre-selected studies were thoroughly reviewed (AMV) to collect the relevant data.

### 2.3. Quality assessment

Manuscripts were evaluated separately for technical quality and alignment with the review’s objectives, based on experimental design soundness, clarity of methodology description, the relevance of the study’s aims, and its focus on MNPs’ effects on fertility. Ratings were assigned for each criterion (0 for absent, 1 for present). The technical quality assessment considered whether the methodology was adequately described and aligned with the study’s aim. For suitability, the focus was on relevant objectives, specifically whether MNPs were tested for their impact on gamete competence, physiological parameters of reproduction-related cells, and/or embryo development. The maximum possible score was 4. The studies were then classified using the Klimisch categories [42]: reliable without restrictions (score 4), reliable with restrictions (score 3), not reliable (score 2), or not assignable (score 1). No studies were excluded based on this evaluation, but the quality assessment was considered during the discussion to enhance the credibility of each article.

### 2.4. Data extraction

The selected papers were comprehensively analysed according to the scope of this systematic review and the inclusion criteria. All manuscripts were read thoroughly to ensure accurate data extraction. Data were extracted based on various parameters, including the research group, year of publication, species, type of study, polymer, particle size, concentration, target cell/organ gender, and categorization of effects (positive, negative, or no effects). A structured data table was created in Excel format (Data extraction supplementary file). A higher occurrence of negative effects compared to the total events in the control group within each experiment was considered a benchmark for toxicity. Accordingly, studies were classified as either “toxic” (≥50 % negative effects), “toxic conc” (≥50 % negative effects for certain concentrations), “toxic size” (≥50 % negative effects for certain sizes), “slightly toxic” (<50 % negative effects), or “non-toxic” (no negative effects).

### 2.5. Meta-analysis

The meta-analysis was conducted on the manuscripts selected for the systematic review. Six articles included experiments on two species, and 19 papers contained both in vivo and in vitro studies, yielding a total of 102 experiments from 79 articles for the meta-analysis. The variable ‘toxicity’ was evaluated, and a subgroup meta-analysis was performed to assess the effects of factor such as species, type of study, polymer, size, concentration, and gender. The results were presented as the risk ratios with 95 % confidence intervals (CI). Heterogeneity in the estimates was assessed using the $I^2$statistic. A fixed-effect model was used when $I^2 < 30$ %, a DerSimonian-Laird random-effects model for $I^2 = 30$–50 %, and a Restricted Maximum Likelihood random-effects model when $I^2$was >50 %. The coefficients of the model were estimated using the Wald test, which assesses the significance of each predictor variable in the context of the overall model. All analyses were performed using JASP software (version 0.19.1, University of Amsterdam, The Netherlands).

## 3. Results

The literature search initially identified 1163 manuscripts. After prescreening, 77 duplicate records were removed. Of the remaining papers, 1009 were excluded for not meeting the inclusion criteria. Two additional articles were retrieved from the references of other papers and included in the systematic review, bringing the total number of manuscripts to 79. All articles were included in the meta-analysis (Fig. 1).

### 3.1. Quality assessment

The quality assessment is provided in Supplementary Table 1. According to the Klimisch criteria, all evaluated articles were classified as reliable without restrictions, except for one article [44], which was deemed reliable with restrictions. The 'MNPs effect on fertility' was scored 0 for this article, as the cells used were only indirectly related to reproductive cells.

### 3.2. Characterization of the eligible studies

The number of publications on this topic has progressively increased from 2018 to 2024, peaking in the last two years, with 28 articles published in 2023 and 19 articles in the first eight months of 2024 (Fig. 2A). Overall, the reproductive toxicity of MNPs was investigated in five mammalian species: rat (n = 15 experiments) [13–25], mouse (n = 67) [7,18,26–28,45,46–92], bovine (n = 3) [93,94], pig (n = 3) [44,95,96], and human (n = 14) [49,59,75,86,89,90,97–101]. Five studies involved both human and mouse species [50,75,86,89,90], and one study included both human and bovine [94]. The mouse was the most intensively investigated species (Fig. 2B).

Both in vivo and in vitro experiments were conducted in 19 manuscripts [7,16,18,50,57,60,64,66,67,70,72,75,82,86,87,89,90,92,94], although the majority of experiments overall were in vivo (70 %).

In four experiments a mixture of MPNs was detected in human testes and semen (PS, PE, PP, and PVC) [59], seminal fluid (PS, PE, PVC, acrylonitrile-butadiene-styrene, polycarbonate, polyethylene terephthalate, PP, and polytetrafluoroethylene) [100], or in human and cow follicular fluid (47 different MP polymers) [94]. Polystyrene was the primary synthetic polymer tested in the other experiments (n = 93), with only five experiments testing other MNPs polymers (PE n = 2, PP n = 2, PVC n = 1).

MPs were used in 39 experiments (38.2 %), while NPs in 44 (43.1 %).

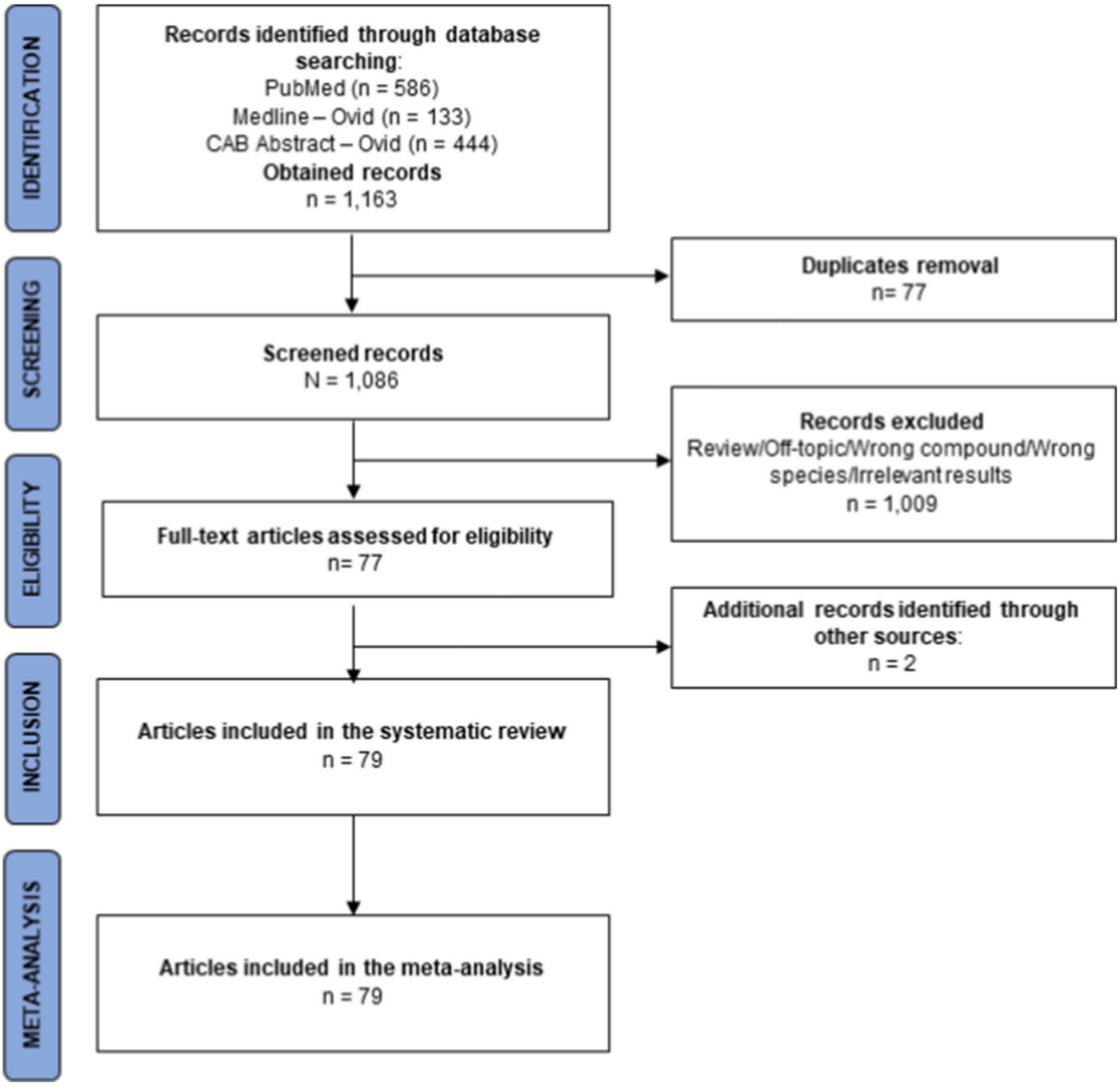

**Fig. 1.** PRISMA flow diagram of the systematic review 'Micro-nanoplastics pollution and mammalian fertility: a systematic review and meta-analysis' according to Moher et al. (2009) [43].

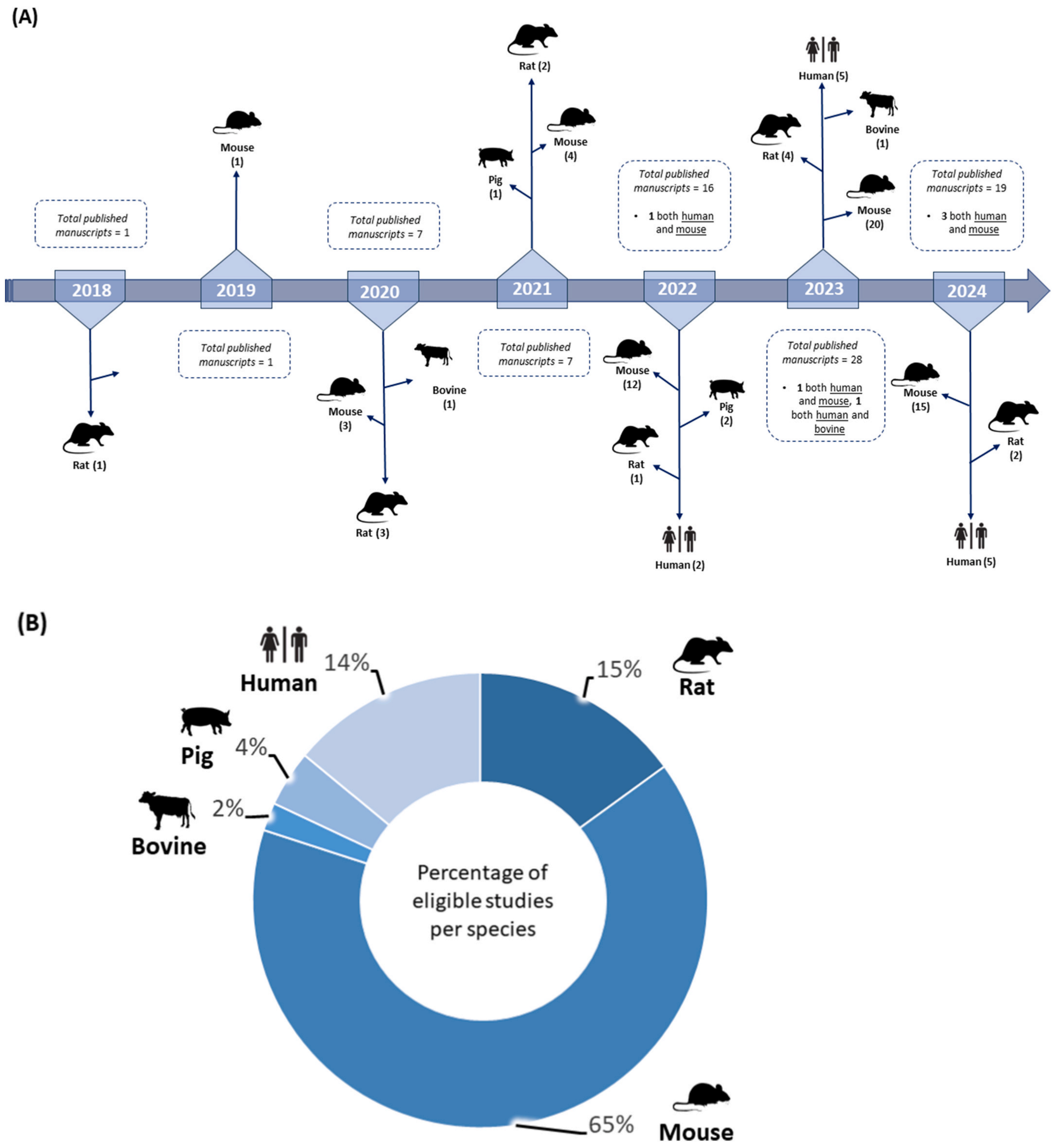

**Fig. 2.** The investigation on reproductive toxicity of MNPs in mammals through time. (A) The timeline displays all studies on the reproductive toxicity of MNPs in mammals, organized by species. (B) A pie chart illustrating the percentage of studies evaluating the reproductive toxicity of MNPs in various mammalian species.

In nine experiments (8.8 %), both micro- and nanoplastics were tested concurrently, while in 10 others (9.8 %), it was impossible to classify MNPs by size due to missing information [14], or because the MNPs were tested for their presence in surgical mesh [17], reproductive tissues or fluids [59,86,90,94,100], contaminated food [23], or the environment [99]. In these experiments, determining the concentration of MNPs was also not applicable.

In most experiments, the effects of MNPs on male fertility were investigated (n = 64). Two studies examined both male and female fertility [28,47]. It was not possible to classify gender in two in vitro experiments, as the target cells were not directly related to male or female fertility: adipose stromal cells [44] and mouse embryos [90].

Overall, 74 % (n = 75) of the evaluated experiments were classifies as “toxic”, 23 % (n = 23) showed toxic effects only at some MNPs concentrations, 1 % (n = 1) showed toxicity only for certain sizes, 1 % (n = 1) showed toxicity for both certain sizes and concentrations, and only

2 % (n = 2) of the experiments showed low toxicity levels.

### 3.3. Laboratory rodents

Eighty-two experiments on laboratory animals (mice and rats) were extracted (Table 1). The earliest study among those selected was conducted on rats in 2018 [14], and since then, articles on the reproductive toxicity of MNPs in rodents have been continuously published throughout the analysed period. Most of the experiments were in vivo (78 %), with the first in vitro study appearing in 2020, representing 13 % of total experiments that year (1/8), followed by 14 % in 2021 (1/7), 14 % in 2022 (2/14), 26 % in 2023 (8/31), and 29 % in 2024 (6/21). The cell types investigated in vitro included granulosa cells [16,73,92,102], spermatogonia/spermatocyte-derived cell lines [7,52,64,82], endometrial epithelial cells [57], Sertoli cells [67,72,84], Leydig cells [60,70,71,84,87], oocytes [92], and embryos [90]. Polystyrene was the most frequently tested polymer (n = 78), with experiments equally distributed for both micro- and nanoparticles (36/82 MPs, 35/82 NPs, and 8/82 both), and single and multiple concentrations. Most of the studies focused on male fertility (72 %), while 24 % focused on female fertility and 3 % on both. Toxic effects were observed in all experiments, with 78 % classified as “toxic”, including those using both single (n = 36) and multiple (n = 26) concentrations.

### 3.4. Farm animals

Six experiments on farm animals (bovine and pig) were extracted (Table 2). The first experiment was conducted on cattle in 2020 [93], followed by 5 additional studies on the reproductive toxicity of MNPs in livestock, with no manuscript published in 2024. Most of the experiments were in vitro (5/6, 83 %), with only one in vivo study detecting MNPs in cow follicular fluid [94]. The cell types investigated in vitro included oviductal epithelial cells and embryos [93], granulosa cells [96], adipose stromal cells [44], testis cells [95], and oocytes [94]. Polystyrene was the only polymer tested (n = 5), while PVC was the most abundant MP polymer detected in bovine follicular fluid [94]. Experiments were evenly divided between micro (n = 3) and nano (n = 3) particles, while in only one study testing a single concentration of PS [94]. Most studies focused on female fertility (4/6, 67 %). Toxic effects were observed in all experiments, with 67 % classified as “toxic conc”, including those using only multiple concentrations (n = 4).

### 3.5. Human

Fourteen experiments on humans were extracted (Table 3). The first studies were conducted in 2022 [50,97], making humans the last mammalian species to be investigated. The number of experiments on reproductive toxicity of MNPs in humans increased in 2023 (n = 5) and 2024 (n = 8). Just over half of the experiments were in vitro (8/14, 57 %), while the in vivo studies mainly focused on detecting MNPs in reproductive system cells or organs [59,86,89,94,100], with one study evaluating reproductive hormones after environmental exposure [99]. The cell types investigated in vitro included granulosa cells or granulosa-like tumor cells [49,75,101], placenta-related cells [89,90,97], spermatozoa [98], and endometrial organoids [86]. Polystyrene was the only polymer tested in vitro (n = 8), with most of experiments focusing on nanoparticles (6/8, 75 % vs 1/8 MPs and 1/8 both) and using multiple concentrations (7/8, 88 %). Most studies (71 %) assessed the reproductive toxicity of MNPs in females. Toxic effects were observed in all experiments, with 64 % classified as “toxic”.

### 3.6. Meta-analysis - toxicity

The overall risk ratio indicated that MNPs negatively impact fertility in mammals, demonstrating a strong toxicity effect ($P < 0.001$) across the experiments included in the meta-analysis (Table 4). The results are graphically summarised in a forest plot (Fig. 3). Furthermore, in evaluating the subgroup analyses for all 102 experiments, it was found that species, type of study, polymer, size, and gender did not significantly influence the overall results. In contrast, different concentrations of MNPs had a significant impact ($P < 0.05$) on the observed effects (Table 4). This highlights the importance of considering concentration levels when assessing the effects of MNPs, as this could be crucial for understanding their potential reproductive toxicity.

## 4. Discussion

This systematic review and meta-analysis evaluated whether exposure to micro- and nanoplastic particles affects mammalian fertility. Data from this study highlight an increasing scientific interest in the reproductive toxicity of MNPs, with a significant rise in publications on the topic since 2018, peaking in the last two years. The toxic effects of MNPs on fertility have been documented across various mammalian species, with laboratory rodents, particularly mice, being the most extensively studied [105,106]. Experimental approaches predominantly included in vivo studies, reflecting the interest in detecting the direct and systemic effects of MNPs on reproductive function.

The preference for in vivo animal models, especially laboratory rodents, underscores their value in biomedical research, as they enable investigation into physiological, biochemical, and genetic responses in conditions that closely mirror real-life biological environments [107]. Research on the effects of MNPs reveals concerning evidence of their impact on cellular and systemic health. Chronic exposure leads to particle accumulation in various organs, where they trigger the production of reactive oxygen species and initiate inflammatory signalling cascades. This inflammation can have severe consequences, including cellular autophagy, and different forms of cell death such as apoptosis, necroptosis, and pyroptosis [108]. Furthermore, mitochondrial damage is a significant consequence of oxidative stress induced by MNPs. This damage disrupts mitochondrial function, particularly the electron transport chain, resulting in impaired ATP production and a decrease in mitochondrial membrane potential, which is crucial for cellular energy balance [109]. Moreover, mitochondrial damage leads to the formation of superoxide radical ($O_2^{\bullet -}$), which is a highly reactive free radical and can undergo further reduction to form hydrogen peroxide ($H_2O_2$) [109,109]. This persistent condition can lead to cell cycle arrest, promote cellular senescence, a condition associated with aging and tissue dysfunction [110].

In addition, chemicals commonly found in plastics exhibit endocrine-disrupting properties, interfering with hormonal functions by mimicking or interfering with natural hormones, which may compromise fertility by affecting key processes in the reproductive system. MNPs present in the male and female reproductive tracts may act as carriers of endocrine-disrupting chemicals, including steroid hormones and other hydrophobic contaminants. Due to their large surface area and hydrophobicity, MNPs readily adsorb environmental pollutants such as bisphenol A, phthalates, and persistent organic pollutants, which are known to interfere with endocrine signaling and reproductive function [4,111,112]. Chemicals associated with plastics are known to disrupt critical endocrine processes, including the hypothalamic-pituitary-gonadal axis, and testosterone biosynthesis [113]. Moreover, the adsorption of steroid molecules onto various materials, particularly plastics, is well documented [114]. For instance, polyethylene terephthalate has been used as an adsorbent for extracting and preconcentrating steroid hormones from river water [115]. Beyond their role as carriers, MNPs themselves (e.g. PVC, PS) have been directly implicated in endocrine disruption in both male and female mammalian reproductive systems. In males, exposure of reproductive cells to MNPs leads to alterations in hormonal levels, including testosterone [14,15,20,22,24,47,51,54–56,59,60,62,63,65,70,82,85], luteinizing hormone [15,20,22,24,47,51,55], follicle-stimulating hormone [15,20,22,47,51,55,59,60], estradiol [47], and inhibin B [59]. Similarly, female reproductive biology is affected by exposure to MNPs,

**Table 1**
Compilation of the experiments in mouse and rat evaluating the effects of MNPs on reproductive system. Data are presented according to year, species, type of study, polymer, size, concentration, gender, and reproductive toxicity.

| Reference | Year | Species | Type of Study | Polymer | Size | Concentration | Gender | Reproductive toxicity |
|---|---|---|---|---|---|---|---|---|
| Archana et al., 2018 [14] | 2018 | rat | in vivo | PVC | NR | single | male | toxic |
| Xie et al., 2019 [26] | 2019 | mouse | in vivo | PS | micro | multiple | male | toxic conc |
| Amereh et al., 2020 [15] | 2020 | rat | in vivo | PS | nano | multiple | male | toxic |
| An et al., 2020 1 [16] | 2020 | rat | in vivo | PS | micro | multiple | female | toxic conc |
| An et al., 2020 2 [16] | 2020 | rat | in vitro | PS | micro | multiple | female | toxic conc |
| Damous et al., 2020 [17] | 2020 | rat | in vivo | PP | NA | NA | male | toxic |
| Hou et al., 2020 [18] | 2020 | mouse | in vivo | PS | micro | multiple | male | toxic |
| Jin et al., 2020 [27] | 2020 | mouse | in vivo | PS | micro | single | male | toxic |
| Park et al., 2020 [28] | 2020 | mouse | in vivo | PE | micro | multiple | both | toxic |
| Hou et al., 2021 1 [102] | 2021 | rat | in vivo | PS | micro | multiple | female | toxic conc |
| Hou et al., 2021 2 [102] | 2021 | rat | in vitro | PS | micro | multiple | female | toxic |
| Hu et al., 2021 [45] | 2021 | mouse | in vivo | PS | micro | single | female | toxic |
| Li et al., 2021 [19] | 2021 | rat | in vivo | PS | micro | multiple | male | toxic conc |
| Liu et al., 2021 [46] | 2021 | mouse | in vivo | PS | micro | single | female | slightly toxic |
| Wei et al., 2021 [47] | 2021 | mouse | in vivo | PS | micro | single | both | toxic |
| Xu et al., 2021 [48] | 2021 | mouse | in vivo | PS | nano | single | male | toxic |
| Haddadi et al., 2022 [13] | 2022 | rat | in vivo | PS | micro | single | female | toxic |
| Huang et al., 2022a [49] | 2022 | mouse | in vivo | PS | nano | multiple | female | toxic conc |
| Huang et al., 2022b 1 [50] | 2022 | mouse | in vivo | PS | nano | multiple | female | toxic conc |
| Jin et al., 2022 [51] | 2022 | mouse | in vivo | PS | micro | multiple | male | toxic |
| Li et al., 2022a [52] | 2022 | mouse | in vitro | PS | nano | single | male | toxic |
| Li et al., 2022b [53] | 2022 | mouse | in vivo | PS | nano | single | male | slightly toxic |
| Liu et al., 2022 [103] | 2022 | mouse | in vivo | PS | micro | single | male | toxic |
| Nikolic et al., 2022 [54] | 2022 | mouse | in vivo | PS | both | multiple | male | toxic conc |
| Wen et al., 2022a [55] | 2022 | mouse | in vivo | PS | micro | multiple | male | toxic conc |
| Wen et al., 2022b [56] | 2022 | mouse | in vivo | PS | micro | multiple | male | toxic |
| Wu et al., 2022 1 [57] | 2022 | mouse | in vivo | PS | micro | single | female | toxic |
| Wu et al., 2022 2 [57] | 2022 | mouse | in vitro | PS | micro | single | female | toxic |
| Yang et al., 2022 [58] | 2022 | mouse | in vivo | PS | both | single | male | toxic |
| Zhao et al., 2022 [59] | 2022 | mouse | in vivo | PS | micro | multiple | male | toxic |
| Cai et al., 2023 1 [60] | 2023 | mouse | in vivo | PS | nano | single | male | toxic |
| Cai et al., 2023 2 [60] | 2023 | mouse | in vitro | PS | nano | multiple | male | toxic |
| Cui et al., 2023 [61] | 2023 | mouse | in vivo | PS | micro | multiple | male | toxic |
| Fu et al., 2023 [62] | 2023 | mouse | in vivo | PS | nano | multiple | male | toxic conc |
| Hamza et al., 2023 [20] | 2023 | rat | in vivo | PS | both | single | male | toxic |
| Hwang et al., 2023 [21] | 2023 | rat | in vivo | PS | micro | single | male | toxic |
| Ijaz et al., 2023 [22] | 2023 | rat | in vivo | PS | nano | single | male | toxic |
| Lan et al., 2023 [63] | 2023 | mouse | in vivo | PS | micro | single | male | toxic |
| Li et al., 2023 1 [64] | 2023 | mouse | in vivo | PS | nano | multiple | male | toxic |
| Li et al., 2023 2 [64] | 2023 | mouse | in vitro | PS | nano | multiple | male | toxic |
| Liu et al., 2023 [65] | 2023 | mouse | in vivo | PS | micro | single | male | toxic |
| Lu et al., 2023 1 [66] | 2023 | mouse | in vivo | PS | both | multiple | male | toxic size/conc |
| Lu et al., 2023 2 [66] | 2023 | mouse | in vitro | PS | both | multiple | male | toxic |
| Ma et al., 2023a 1 [67] | 2023 | mouse | in vivo | PS | nano | multiple | male | toxic |
| Ma et al., 2023a 2 [67] | 2023 | mouse | in vitro | PS | nano | multiple | male | toxic conc |
| Ma et al., 2023b [68] | 2023 | mouse | in vivo | PS | nano | single | male | toxic size |
| Rao et al., 2023 [69] | 2023 | mouse | in vivo | PS | micro | single | male | toxic |
| Sui et al., 2023 1 [70] | 2023 | mouse | in vivo | PS | nano | single | male | toxic |
| Sui et al., 2023 2 [70] | 2023 | mouse | in vitro | PS | nano | multiple | male | toxic |
| Sun et al., 2023 [71] | 2023 | mouse | in vitro | PS | nano | multiple | male | toxic conc |
| Uhuo et al., 2023 [23] | 2023 | rat | in vivo | PE | NA | NA | male | toxic |
| Wu et al., 2023a 1 [73] | 2023 | mouse | in vivo | PS | micro | single | female | toxic |
| Wu et al., 2023a 2 [73] | 2023 | mouse | in vitro | PS | micro | multiple | female | toxic |
| Wu et al., 2023b 1 [72] | 2023 | mouse | in vivo | PS | micro | multiple | male | toxic |
| Wu et al., 2023b 2 [72] | 2023 | mouse | in vitro | PS | micro | multiple | male | toxic |
| Xu et al., 2023 [74] | 2023 | mouse | in vivo | PS | nano | single | male | toxic |
| Zeng et al., 2023 2 [75] | 2023 | mouse | in vivo | PS | nano | single | female | toxic |
| Zhang et al., 2023a [76] | 2023 | mouse | in vivo | PS | nano | single | male | toxic |
| Zhang et al., 2023b [77] | 2023 | mouse | in vivo | PS | micro | single | male | toxic |
| Zhang et al., 2023c [78] | 2023 | mouse | in vivo | PS | both | single | male | toxic |
| Zhou et al., 2023 [79] | 2023 | mouse | in vivo | PS | nano | single | male | toxic |
| Dou et al., 2024 [80] | 2024 | mouse | in vivo | PS | micro | single | female | toxic |
| Ebrahim et al., 2024 [24] | 2024 | rat | in vivo | PS | nano | multiple | male | toxic |
| Fang et al., 2024 [81] | 2024 | mouse | in vivo | PS | micro | multiple | male | toxic |
| Fu et al., 2024 1 [82] | 2024 | mouse | in vivo | PS | nano | single | male | toxic |
| Fu et al., 2024 2 [82] | 2024 | mouse | in vitro | PS | nano | multiple | male | toxic |
| Gao et al., 2024a [83] | 2024 | mouse | in vivo | PS | nano | single | male | toxic |
| Gao et al., 2024b [104] | 2024 | mouse | in vivo | PS | micro | single | male | toxic |
| Grillo et al. 2024 [84] | 2024 | mouse | in vitro | PS | micro | multiple | male | toxic |
| Hu et al. 2024 [25] | 2024 | rat | in vivo | PS | nano | multiple | male | toxic |
| Jin et al. 2024 [85] | 2024 | mouse | in vivo | PS | micro | single | male | toxic |
| Liang et al. 2024 1 [7] | 2024 | mouse | in vivo | PS | nano | multiple | male | toxic |
| Liang et al. 2024 2 [7] | 2024 | mouse | in vitro | PS | nano | multiple | male | toxic |

(continued on next page)

**Table 1** (*continued*)

| Reference | Year | Species | Type of Study | Polymer | Size | Concentration | Gender | Reproductive toxicity |
|---|---|---|---|---|---|---|---|---|
| Qu et al. 2024 1 [87] | 2024 | mouse | in vivo | PS | both | single | male | toxic |
| Qu et al. 2024 2 [87] | 2024 | mouse | in vitro | PS | both | multiple | male | toxic |
| Qu et al. 2024 3 [87] | 2024 | mouse | in vivo | PS | micro | multiple | female | toxic |
| Sharma et al. 2024 [88] | 2024 | mouse | in vivo | PS | nano | single | male | toxic |
| Wan et al. 2024a 2 [90] | 2024 | mouse | in vivo | PS | nano | single | female | toxic |
| Wan et al. 2024b 3 [89] | 2024 | mouse | in vitro | PS | nano | multiple | NA | toxic conc |
| Xiong et al. 2024 [91] | 2024 | mouse | in vivo | PS | nano | single | female | toxic |
| Xue et al. 2024 1 [92] | 2024 | mouse | in vivo | PS | nano | single | female | toxic |
| Xue et al. 2024 2 [92] | 2024 | mouse | in vitro | PS | nano | multiple | female | toxic conc |

Abbreviations: PE = polyethylene, PP = polypropylene, PS = polystyrene, PVC = polyvinyl chloride, NA = not applicable, NR = not reported, toxic conc = toxic in relation to concentration, toxic size = toxic in relation to size.

**Table 2**
Compilation of the experiments in bovine and pig evaluating the effects of MNPs on reproductive system. Data are presented according to year, species, type of study, polymer, size, concentration, gender, and reproductive toxicity.

| Reference | Year | Species | Type of Study | Polymer | Size | Concentration | Gender | Reproductive toxicity |
|---|---|---|---|---|---|---|---|---|
| Barbato et al., 2020 [93] | 2020 | bovine | in vitro | PS | nano | multiple | female | toxic conc |
| Basini et al., 2021 [96] | 2021 | pig | in vitro | PS | nano | multiple | female | toxic conc |
| Basini et al., 2022 [44] | 2022 | pig | in vitro | PS | nano | multiple | NA | toxic conc |
| Wang et al., 2022 [95] | 2022 | pig | in vitro | PS | micro | multiple | male | toxic conc |
| Grechi et al., 2023 2 [94] | 2023 | bovine | in vivo | Mix | NA | NA | female | toxic |
| Grechi et al., 2023 3 [94] | 2023 | bovine | in vitro | PS | micro | single | female | toxic |

Abbreviations: PS = polystyrene, Mix = mixture, NA = not applicable, toxic conc = toxic in relation to concentration.

**Table 3**
Compilation of the experiments in human evaluating the effects of MNPs on reproductive system. Data are presented according to year, species, type of study, polymer, size, concentration, gender, and reproductive toxicity.

| Reference | Year | Species | Type of Study | Polymer | Size | Concentration | Gender | Reproductive toxicity |
|---|---|---|---|---|---|---|---|---|
| Huang et al., 2022b 2 [50] | 2022 | human | in vitro | PS | nano | multiple | female | toxic conc |
| Shen et al., 2022 [97] | 2022 | human | in vitro | PS | both | multiple | female | toxic conc |
| Contino et al., 2023 [98] | 2023 | human | in vitro | PS | nano | multiple | male | toxic conc |
| Grechi et al., 2023 1 [94] | 2023 | human | in vivo | Mix | NA | NA | female | toxic |
| Razak et al., 2023 [99] | 2023 | human | in vivo | PP | NA | NA | male | toxic |
| Zeng et al., 2023 1 [75] | 2023 | human | in vitro | PS | nano | multiple | female | toxic conc |
| Zhao et al., 2023 [59] | 2023 | human | in vivo | Mix | NA | NA | male | slightly toxic |
| Li et al., 2024 [100] | 2024 | human | in vivo | Mix | micro | NA | male | toxic |
| Qin et al., 2024 1 [86] | 2024 | human | in vivo | PS | NA | NA | female | toxic |
| Qin et al., 2024 2 [86] | 2024 | human | in vitro | PS | micro | single | female | toxic |
| Wan et al., 2024a 1 [90] | 2024 | human | in vitro | PS | nano | multiple | female | toxic |
| Wan et al., 2024b 1 [89] | 2024 | human | in vivo | PS | NA | NA | female | toxic |
| Wan et al., 2024b 2 [89] | 2024 | human | in vitro | PS | nano | multiple | female | toxic |
| Wang et al., 2024 [101] | 2024 | human | in vitro | PS | nano | multiple | female | toxic |

Abbreviations: PP = polypropylene, PS = polystyrene, Mix = mixture, NA = not applicable, NR = not reported, toxic conc = toxic in relation to concentration.

**Table 4**
Effects of MNPs on mammalian fertility. Subgroup analysis was performed on species, type of study, polymer, size, concentration, and gender.

| Meta-analysis | $I^2$(%) | Test omnibus P-value |
|---|---|---|
| Overall | 50.317 | <0.001 |
| Species | 50.005 | 0.383 |
| Type of study | 50.387 | 0.376 |
| Polymer | 49.733 | 0.474 |
| Size | 43.682 | 0.744 |
| Concentration | 40.572 | 0.036 |
| Gender | 50.391 | 0.456 |

with changes observed in sex steroid levels, including testosterone [47,80], luteinizing hormone [47,91], follicle-stimulating hormone [47,91], estradiol [13,47,50,91,92], anti-Müllerian hormone [16,50,75], and progesterone [80]. Furthermore, MNPs contribute to endocrine disruption by inactivating key cellular messenger enzymes involved in molecular hormone response pathways, such as protein kinase A [51,97]. These disruptions underline the potential of MNPs to impair fertility and adversely affect reproductive outcomes, raising important questions about their long-term effects on human and animal health.

In the context of animal models, laboratory rodents, such as mice and rats, were the primary focus, with a significant proportion of experiments showing toxic effects. Farm animals, such as bovine and pigs, were also used to assess MNP effects on mammalian reproductive biology. Including farm animals in toxicological studies is valuable as, alongside relevant in vitro studies, research on these species provides a reliable approach to identifying toxic properties of chemicals and assessing potential risks to human and environmental health in the absence of human data [116]. Swine, in particular, are frequently used in translational research as an alternative to non-human primates due to their anatomical, physiological, and genetic similarities to humans, making them ideal models in toxicology and other preclinical studies [117,118]. However, the limited number of studies on farm animals represents a research gap that warrants greater attention to draw conclusions applicable to a broader range of species, including humans. It should be emphasized that there are at least three main reasons why it is crucial to consider farm animals in studies on plastic pollution. First, environmental MNPs pollution is increasing, leading to greater exposure of farm animals through food, water, and air. The infiltration of these

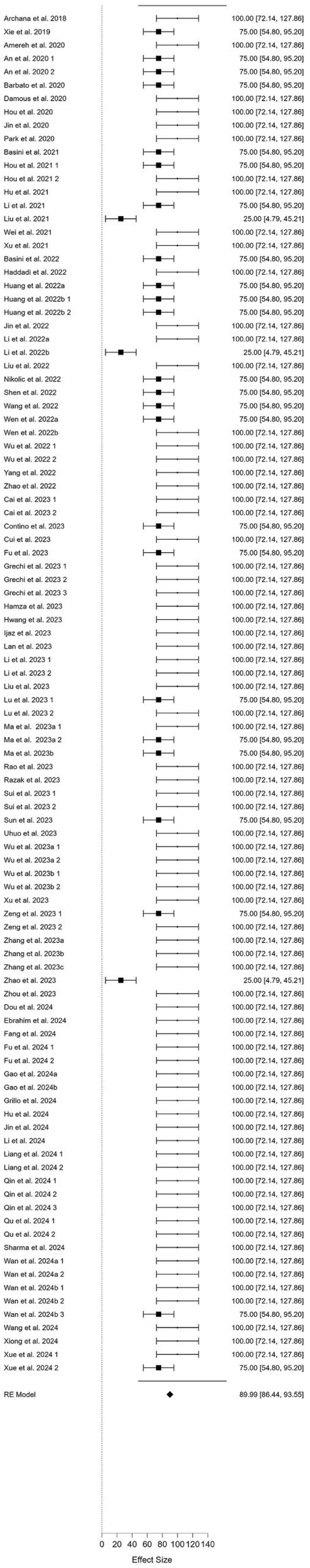

**Fig. 3.** Forest plot of effect estimates for the toxicity of MNPs on mammalian fertility. The horizontal bars represent the 95 % Cis for the risk ratio (RR) of each experiment included in the meta-analysis. The centre point of each bar indicates the estimated RR value. The vertical dotted line represents an RR of 0, indicating no effect.

particles into the natural environment makes it essential to understand their effects on the ecosystem and the animals living within it. Second, exposure to MNPs can have serious health implications for livestock, particularly on the reproductive health. Farm animals must maintain high fertility rates to avoid economic losses for farmers. However, in recent decades, fertility rates have experienced a sharp decline, largely due to intensive farming practices and climate change. On top of these factors, the accumulation of MNPs has added another layer of concern, for the potential negative effects on both male and female fertility. This growing issue underscores the complex interplay between environmental, industrial, and biological factors that influence reproductive health in farm animals and highlights the need for further research into how MNPs contribute to these ongoing challenges. Third, farm animals are an important part of the human food chain, and MNPs can enter the food supply through products like milk, eggs, and meat. As a result, the contamination of farm animals with MNPs presents a health risk for humans, making it crucial to assess and mitigate these risks to protect public health. These three reasons highlight the importance of including farm animals in studies on MNPs pollution, as they can help bridge the gap between environmental, animal, and human health.

Toxicological studies on humans regarding the effects of micro MNPs have only emerged relatively recently, and much of the research conducted so far has been limited in scope and methodology. Most of these studies have primarily focused on female reproductive health, with most of the research being carried out in vitro, meaning outside of a living organism. This in vitro approach, while valuable for initial insights, cannot fully replicate the complex biological processes and interactions that occur within a living organism, thus leaving significant gaps in our understanding of the actual in vivo effects of MNPs on human reproductive systems [119]. To date, only a single study has assessed the in vivo effects of environmental exposure to MNPs in humans, highlighting the limited data available on this critical issue [120]. This lack of comprehensive research makes it difficult to draw definitive conclusions about the long-term risks posed by MNPs to human health, particularly reproductive health. Despite these gaps, preliminary findings from existing studies suggest a significant potential risk, especially concerning female reproductive health. This is reflected in the high prevalence of studies that have demonstrated the potential for MNPs to affect various aspects of female fertility, including oocyte quality, hormonal balance, and reproductive organ function [121]. The current body of research underscores the need for more extensive studies, particularly those focusing on the long-term in vivo effects of MNPs exposure, on both male and female reproductive systems. Given the growing presence of MNPs in the environment and their potential to enter the human body through food, water, and air, it is critical to continue investigating how these particles interact with human biology and contribute to reproductive health issues. Without a more thorough understanding of these potential risks, public health strategies aimed at mitigating the effects of plastic pollution will remain incomplete, and the full scope of its impact on human health may not be fully realized [122].

Among the synthetic polymers examined, polystyrene, a low-cost chemically stable and persistent polymer widely used in industrial applications, was the most frequently tested. Only a small percentage of studies considered other polymer types, such as polyethylene, polypropylene, and polyvinyl chloride. The monomer of PS, which can be released during melting or polymerization processes, is classified as a potentially carcinogenic substance by the International Agency for Research on Cancer (IARC) [123]. This categorization highlights the need for increased vigilance in monitoring polystyrene contamination and further research into its effects on reproductive health. Moving forward, testing a broader range of plastic polymers in toxicological studies will be essential to fully elucidate the impact of diverse plastic pollutants on mammalian reproductive biology. Additionally, four studies detected mixtures of MNPs in human and bovine reproductive fluids, suggesting potential exposure and bioaccumulation of these substances in higher organisms [59,94,100]. However, regarding the limitations of the studies, it should be noted that in some experiments, it was not possible to classify MNPs by size due to missing information, limiting the interpretability of results concerning particle size. Additionally, despite the large number of studies on mice and rats, the heterogeneity of methodologies used (e.g., types of polymers tested, exposure conditions, and toxicity evaluation techniques) poses a challenge in directly comparing results, suggesting a need for standardized research protocols. The extensive use of PS contributes to its prevalence as an environmental pollutant [123,124].

Our meta-analysis confirmed that MNPs exert various toxic effects that are independent of particle size, study type, polymer composition, or gender. However, the findings indicate that the toxicity of MNPs is dose-dependent, with toxic effects observed primarily at high concentrations. This is particularly evident in the meta-analysis, which revealed a significant correlation between MNP concentration levels and observed toxic effects on fertility. Hence, it is important to consider MNPs concentration as a critical factor in toxicity assessment, as lower concentrations may not show significant effects in the short term, although they could be relevant in cases of chronic exposure. Moreover, this finding highlights the importance of identifying specific doses and exposure conditions under which the biological toxicity of MNPs might be reduced. Such knowledge could contribute to establishing regulatory guidelines for MNPs concentrations in the environment [125]. Furthermore, future toxicological tests on mammalian reproductive systems should incorporate MNPs concentrations that reflect environmentally relevant concentrations, which are observed across ecosystems and to which humans are routinely exposed [105,106,116]. In addition to the concentration, other physical characteristics of MNPs—such as shape, surface charge, weathering effects, and the presence of attached pollutants—are likely involved in the mechanisms underlying their interactions with reproductive cells. Integrating these factors into future studies could further enhance the understanding and mitigation of MNP toxicity [117].

Another notable observation is that the toxic effects of MNPs on male fertility have been more extensively studied than those on female fertility, with 72 % of the experiments focused on male models. Although this may reflect the relative ease of analysing male reproductive parameters in experimental settings, it also suggests an opportunity to further investigate the effects of MNPs on female reproductive physiology, which may respond differently to toxic stimuli. Moreover, expanding research to include both male and female reproductive outcomes will provide a more comprehensive assessment of MNP toxicity and its potential risks across sexes. Particularly, studying the effects of MNPs in female subjects means not only verifying their impacts on adult ovarian function but also to studying their transgenerational effects. Indeed, the disturbance in fetal development is caused not only by indirect factors, such as oocytes damages induced by plastic particles, but also by direct factors, such as the passage of MNPs through the placental barrier [126]. Indeed, using mouse as mammal models, it has been revealed that the exposure of pregnant mice to MNPs during the peri-implantation stage significantly increases their absorption rate in the embryo, exerting adverse effects on embryo development by disturbing the maternal-foetal immune balance. Moreover, the maternal exposure of pregnant mice to MNPs results in a birth rate decline and a decrease in the offspring birth weight [127]. MNPs have been detected in the placenta, fetal heart, liver, kidney, lungs, and brain [128]. Furthermore, MNPs exposure of the mother seems to cause neurophysiological and cognitive deficits, especially in female offspring [129], but the underlying reason and mechanism need to be explored.

## 5. Conclusions

This systematic review and meta-analysis support the hypothesis that MNPs can have significant toxic effects on mammalian fertility, with particular relevance for reproductive health. Toxic effects are documented across various species, particle size, and polymer type. A pronounced concentration-dependent toxicity has been observed, particularly at high concentrations/doses of MNPs, suggesting that dose levels are critical in determining the severity of reproductive impacts. The adoption of standardized protocols and more detailed analytical methodologies that consider both particle size and concentration will be essential to fully understand the implications of MNPs for reproductive health across species and environmental contexts. The analysis also indicates that while both male and female reproductive systems are vulnerable to MNP toxicity, research has disproportionately focused on male fertility, highlighting a need for more balanced investigations. Polystyrene was identified as the most extensively studied polymer, with limited data on other common plastics, such as polyethylene and polypropylene. Given the variations in chemical properties across polymers, this suggests that future studies should expand to include a wider array of plastic types to fully assess the diversity of potential reproductive impacts. To address the full scope of their biological impacts, environmentally realistic exposure levels and particles that reflect the diversity of MNPs encountered in natural settings should be prioritized. By incorporating these real-world elements, toxicological studies can provide a clearer picture of MNP risks. Additionally, the observed toxic effects across in vivo and in vitro models underscore the physiological relevance of MNP exposure and the importance of considering both environmental and laboratory conditions. The findings further underline a crucial gap in research on food-producing animals, which are both relevant models for human health and potential vectors for MNPs into the human food supply chain. Overall, these findings emphasize the importance of continued research to elucidate the pathways and mechanisms through which MNPs impact mammalian reproductive health, ultimately advancing our understanding of how these pervasive pollutants interact with biological systems across diverse species.

## CRediT authorship contribution statement

**Alessandro Marino Volsa:**Writing – original draft, Visualization, Methodology, Data curation. **Eleonora Iacono:**Writing – original draft, Validation. **Barbara Merlo:**Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization.

## Declaration of competing interest

I have nothing to declare.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.theriogenology.2025.117369.

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