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# Microplastics May Be a Significant Cause of Male Infertility

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**Abstract**

Due to the problematic degradation properties of plastics, the decomposition of plastic results in the formation of numerous microplastics (MPs), less than 5 mm in diameter. These MPs enter the soil and the ocean, eventually passing through the air, water, or food chain back to the human body and harming human health. In the last 80 years, male semen analysis parameters have shown a significant decline for unknown reasons, speculated to be caused by pollutants. No studies examined the relationship between human MP exposure and male infertility. In this article, we reviewed the relevant animal experimental research literature in recent years and calculated that the minimum human equivalent dose of MPs leading to abnormal male semen quality is 0.016 mg/kg/d. The literature comparison found that MP exposure in Japan and South Korea was close to this value. These results suggest that MPs can affect male semen quality and that MPs may significantly impact male fertility.

**Keywords**

microplastics, male infertility, sperm quality

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## The Problem of Plastic Pollution Cannot Be Ignored

Since the 1950s, plastic products have been used in our daily lives. Because plastic takes hundreds of years to degrade, it has become one of the modern-day issues that threaten human health and survival (Guzzetti et al., 2018). Plastic pollution has now reached a level that urgently needs to be addressed. Out in the Pacific Ocean, between California and Hawaii, an island of plastic waste six times the size of the United Kingdom has formed, known as the "eighth continent." This massive island of garbage is also known as the "Great Pacific Garbage Patch" (Lebreton et al., 2018). This garbage patch has grown over the past 60 years. At the same time, a 7- to 11-km long plastic deposit has been found in the deepest part of the world, the Marianas Trench (Peng et al., 2018). The United Nations Environment Programme (UNEP) estimates that by 2050, the amount of plastic in the oceans (by weight) will be higher than that of fish (World Economic Forum, 2016).

The primary method of disposal of plastics worldwide is in landfills, which does not effectively degrade plastics. Due to their physical and chemical properties, plastics in landfills will breakdown into microplastics (MPs) smaller than 5 mm and enter the soil and the ocean (Rochman, 2018). In addition, we often contact MPs in our daily lives, such as those in cosmetics, toothpaste, and detergents (Lassen et al., 2015). MPs are a growing global problem due to their considerable presence in the near future and their persistent toxicity to future generations (Shahul Hamid et al., 2018).

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## Main Routes of Ingestion and Exposure to MPs in Humans

### *Air Intake*

People routinely inhale MPs. For example, human inhalation levels of 360 to 150,000 and 0.88 to 270 ng/kg/d polyethylene terephthalate microplastics (PET-MPs) and polycarbonate microplastics (PC-MPs), respectively, have been reported in 12 countries (Zhang et al., 2020). Studies have estimated the inhalation of MPs in China and reported that the median human inhalation of PET-MPs and PC-MPs was 6,500 to 89,700 and 0.5 to 7.37 ng/kg/d, respectively (Liu et al., 2019). Studies have discovered significantly higher inhalation levels of MPs in infants or children than in adults. MP inhalation in children is at least five times higher than that in adults, implying a higher potential risk of MP inhalation in infants or children than in adults (Abbasi et al., 2019). A recent study using a breathing thermal manikin to simulate exposure to MPs in indoor air showed that the manikin inhaled a total of 272 MPs over 24 hr, with an average of $9.3 \pm 5.8$ particles per cubic meter (Vianello et al., 2019).

### *Food and Water Intake*

Many studies have examined the occurrence of MPs in food and water. One study has suggested that the annual intake of MPs accounts for approximately 15% of Americans' caloric intake, at 39,000 to 52,000 particles. When inhalation is considered, the estimates of MP intake increase to 74,000 to 121,000 particles. In addition, people who drink only plastic bottled water may consume an additional 90,000 MPs per year compared with those who drink only tap water, consuming an additional 4,000 MPs per year (Cox et al., 2019). The median intake of MPs (1–5,000 μm) is 553 particles/person/day (184 ng/person/day) for children and 883 particles/person/day (583 ng/person/day) for adults. MP intake can irreversibly accumulate to $8.32 \times 10^3$ particles/person (6.4 μg/person) by the age of 18 years and $5.01 \times 10^4$ particles/person (40.7 μg/person) by the age of 70 years (Mohamed Nor et al., 2021).

## MPs Can Enter the Human Body Through the Food Chain and Affect the Male Reproductive System

Because of their small size, MPs can quickly enter an organism, adversely affect normal physiological functions, and be passed along the food chain, through which they are biologically enriched and amplified (van Raamsdonk et al., 2020). Humans are at the top of the food chain and thus are presumably the most affected. It is estimated that between 5 and 13 million tons of plastic waste enters the oceans each year, is subsequently ingested by aquatic organisms such as fish and crustaceans, and finally enters the human diet through the food chain (Jambeck et al., 2015). MPs have been found in human feces (W. Huang, Yin, et al., 2021). It is widely believed that MP particles are not harmful to human health or at worst pose little risk to human health. However, direct contact with MP particles can have adverse effects at the cellular level (Hwang et al., 2020). The ingestion of MPs can cause intestinal damage due to their small size and ability to absorb various toxic substances, heavy metals (C. Huang, Ge, et al., 2021), additives, and chemicals such as phthalate esters (PAEs; Deng et al., 2021). In summary, ingestion of MPs can cause mechanical damage to the intestines, reduce fertility, affect the growth rate of organisms, and have long-term adverse effects on the ecosystem (Horton et al., 2020; Prata et al., 2020).

It is estimated that approximately 15% of childbearing couples worldwide suffer from infertility; the incidence is increasing every year, nearly half of which is caused by male factors (Inhorn & Patrizio, 2015). The quality of human semen has gradually decreased with modernization. For example, from 1940 to 1990, the concentration of male sperm dropped from $113 \times 10^6$/ml to $66 \times 10^6$/ml (Carlsen et al., 1992). In addition, the World Health Organization (WHO) has published six editions of the *Laboratory Manual for the Examination and Processing of Human Semen* (referred to as the Manual). In the first edition, published in 1980, the normal value for semen concentration was $60 \times 10^6$/ml (WHO, 1980), but by the publication of the fifth edition in 2010, this value was reduced to $15 \times 10^6$/ml (WHO, 2010), although the value in the sixth edition is still at a similar level ($16 \times 10^6$/ml; WHO, 2021).

In summary, semen quality in men has declined significantly over the last 80 years, with sperm concentration dropping to approximately one seventh of its original value. This timing coincides with the development of plastics. Of course, other factors may have also contributed to the decline in male fertility. Nevertheless, the most persistent threat to humanity by far is plastic pollution. Some retrospective and basic scientific studies have suggested that this decline in sperm parameters may be related to obesity, diet, and environmental toxins (Mann et al., 2020).

### *Ingestion of MPs Can Lead to Reduced Sperm Quality*

The effects of MPs on marine organisms and terrestrial mammals have been well documented (Sharma & Chatterjee, 2017; Xu et al., 2020; Yong et al., 2020) and

mainly include impacts to the reproductive system (Sharifinia et al., 2020), immune system, and digestive system (Y. Jin et al., 2019; B. Li et al., 2020). In recent years, the effects of MPs on the reproductive system have attracted increasing attention. Polystyrene microplastics (PS-MPs) exert significant toxic effects on the reproductive system of male mice. After 28 days of exposure to PS-MPs, sperm quality and testosterone levels in mice decreased. A hematoxylin and eosin (H&E) stain showed disorganized spermatogonia, multinucleated gonadotrophic cells in the germinal tubules, inflammation in the testes, and disruption of the blood–testis barrier. PS-MPs at sizes of 0.5, 4, and 10 μm were able to enter the three testicular cell types in vitro (H. Jin et al., 2021). Prenatal polystyrene nanoplastics (PS-NPs) exposure in pregnant mice reduced testicular weight in offspring, destroyed reproductive epithelium, and reduced sperm count (T. Huang et al., 2022).

PS-MP exposure can lead to vas deferens damage, decreased sperm viability and concentration, increased sperm malformation, disruption of blood–testis barrier integrity, and spermatogenic cell apoptosis by activating the p38 MAPK-nuclear factor erythroid-2 related factor 2 (Nrf2) pathway (S. Li et al., 2021). A similar study reported that PS-MPs induced reproductive toxicity in mice through oxidative stress and activation of the p38 MAPK signaling pathway, resulting in a significant decrease in sperm count and motility, a significant increase in sperm malformation in mice, and a substantial reduction in serum testosterone levels (Xie et al., 2020). The number of viable spermatozoa in the epididymis was significantly reduced, and the sperm malformation rate increased after exposure to 5 μm PS-MPs. In contrast, sperm cells at all testis levels showed atrophy, abscission, and apoptosis, which were closely associated with the Nrf2/HO-1/ nuclear factor–κB (NF-κB) pathway (Hou et al., 2021).

The toxicity of MPs is enhanced when mixed with other environmental pollutants. Coexposure to MPs and the heavy metal cadmium (Cd) for 28 days in earthworms resulted in a significant increase in the avoidance response, a decrease in weight, reduced reproduction, more considerable inhibition of superoxide dismutase (SOD) and peroxidase (POD) activity, and an increase in glutathione (GSH) and malondialdehyde (MDA) activity. Histopathological alterations and DNA damage in earthworm spermatozoa were significantly correlated with the dose of MPs. MPs significantly increased the soil diethylenetriaminepentaacetic acid (DTPA)-Cd concentration in low- and high-contaminated soils by 1.20-fold and 1.43-fold, which subsequently increased Cd accumulation in earthworms by 2.65-fold and 1.42-fold, respectively, indicating that MPs can exacerbate the combined toxicity of Cd to earthworms (C. Huang, Ge, et al., 2021). Mice exposed to PAE-contaminated MPs for 30 days showed a significant increase in the accumulation of PAEs in their livers and intestines. Compared with exposure to MPs alone, MPs contaminated with PAEs induced more substantial reproductive toxicity, as evidenced by more significant alterations to sperm and spermatozoa physiology (Deng et al., 2021).

### *Ingestion of MPs Can Lead to Increased Sperm DNA Fragmentation*

The current primary clinical laboratory test for male sperm quality is semen analysis. Studies have confirmed that semen analysis provides normal results in at least 50% of infertile patients (Le et al., 2019). While semen analysis can provide a general picture of the morphological aspects of sperm, it cannot evaluate the most critical material in sperm that determines the embryo's fate: sperm DNA. Half of the chromosomes of a fertilized egg originate from sperm, so genetic information is crucial for the offspring. The genetic material carried by sperm encodes specific essential genes for human growth, development, and reproduction, particularly the development of the reproductive system in male offspring (Casanovas et al., 2019).

The DNA fragmentation index (DFI) is an indicator of the integrity of sperm DNA. The DFI is significantly higher in infertile patients than in the normal population (Esteves et al., 2017). Men with a history of recurrent spousal miscarriages had a considerably higher DFI than men without a marital history of related issues. However, both groups had normal semen analysis results (McQueen et al., 2019). Studies in the literature have reported that conception rates are significantly reduced, and that infertility or miscarriage can occur, when the DFI is greater than 27% (Corona et al., 2019). Therefore, sperm DFI plays a crucial role in the process of normal pregnancy. The DFI is also a widely used indicator in clinical practice to assess male fertility. The causes of sperm DFI are complex; the main factors are exposure to toxic substances or age (Zeqiraj et al., 2018). Furthermore, exposure to nanoplastics (NPs) with a mean diameter of 38.92 nm for 5 weeks at 1, 3, 6, and 10 mg/kg/day in rats resulted in different degrees of increased sperm DFI (Amereh et al., 2020). Sperm prokaryotic DNA damage to globular star sea urchins caused by MPs can be transmitted to offspring (Trifuoggi et al., 2019).

## Possible Mechanisms of Reproductive Toxicity of MPs

### *Oxidative Stress*

It has been found that oxidative stress is the primary mechanism of MP-induced reproductive toxicity. The main means of oxidative stress induced by MPs maybe

those nanoparticles interfere with electron transfer of intracellular mediators, thus causing reactive oxygen species (ROS) production and redox function destruction (Fu et al., 2014). The carboxylated PS-MPs induced oxidative stress in oyster sperm cells, resulting in loss of fertilization ability of oocytes (Gonzalez-Fernandez et al., 2018). PS-MPs lead to ovarian granulosa cell apoptosis through oxidative stress, resulting in ovarian fibrosis in rats and ultimately reduced ovarian ovulation function (An et al., 2021). However, excessive production of ROS can lead to embryonic toxicity through oxidative stress damage such as lipid peroxidation or DNA breakage (Kang et al., 2018).

### *Disruption of the Hypothalamic–Pituitary–Gonadal (HPG) Axis*

MPs have been found to disrupt the reproductive endocrine system by disrupting the HPG axis (Wang et al., 2019). After exposure to PS-MPs, the serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone (T) in male mice decreased, and the estradiol level increased, while the changes in serum FSH and T levels in female mice were reversed (Wei et al., 2022). Similar results were found in male rats (Ijaz et al., 2021). Therefore, the reproductive endocrine disorder induced by MPs may be caused by disrupting the HPG axis and steroid production pathway, disrupting the balance of sex hormones and delaying gonad maturation, which may be the potential mechanism of MPs hindering the development of embryos and progeny (Wang et al., 2019).

### *Energy Consumption*

Reproduction is an energy-consuming process, and inadequate nutrient intake can adversely affect the reproduction of an organism. MPs can affect reproduction by altering an organism's food consumption and energy allocation (Sussarellu et al., 2016). MPs can also reduce the activities of succinate dehydrogenase and lactate dehydrogenase in oysters during spermatogenesis, indicating that MPs can hinder the energy supply during spermatogenesis and affect the quality of sperm (Xie et al., 2020).

### *Microcirculation Dysfunction*

Microcirculation disturbance caused by MPs is a pathogenic mechanism that has just been discovered in recent years. MPs or NPs can cause developmental disorders and increased embryo mortality in zebrafish, especially NPs. Both MPs and NPs can cause significant deterioration of peripheral microcirculation in the tail region (S. H. Park & Kim, 2022). Although few studies on the mechanism, more reports are expected to reveal the exact mechanism in the future.

## Are Current Levels of MP Exposure in Humans Capable of Causing Damage to the Male Reproductive System?

A literature search revealed that research on biological exposure to MPs is in its infancy. No studies on how MPs might affect the human reproductive system have been reported. Their effects on the reproductive system have been observed only in some marine organisms and other mammals. More direct evidence is needed on how MPs enter the human body, the dose in human tissues (blood, testes, etc.), whether this dose correlates with semen quality, the quantity that causes damage to the male reproductive system, and the specific pathways by which the reproductive system is damaged.

Although there is a lack of evidence related to human MPs as described above, we can screen for and collate those studies in which MPs in rodents caused damage to the male reproductive system and calculate the corresponding human equivalent dose (HED) of contamination by the body surface area method (Nair & Jacob, 2016), as detailed in Table 1.

Based on the available rodent doses described above, it was found that the minimum dose to cause a decrease in sperm quality in rats was 0.015 mg/d (0.1 mg/kg, 0.15 kg of rats' body weight); the minimum HED of MPs was 0.016 mg/kg (0.1 mg/kg ÷ 6.2) based on the body surface area method. It can be calculated at 0.016 mg/kg/d = 16 μg/kg/d = 960 μg/person after conversion. A comparison with the data discussed in the "Food and Water Intake" section reveals that this value is 24 times the cumulative dose at age 70 (40 μg/person) and 150 times the cumulative dose at age 18 (6.4 μg/person). However, these values are based on the average intake. According to the "Air Intake" section, MPs' inhalation doses vary considerably between countries, such as Japan and Korea (Zhang et al., 2020). The inhalation doses of PET-MPs for adults in Japan and Korea are the highest among the 12 studied countries, at 11,000 and 12,000 ng/kg/d, equivalent to 11 and 12 μg/kg/d, respectively. This is very close to the minimum HED we calculated in the present study (16 μg/kg/d). Current exposure to MPs in some countries may already be at the minimum HED, which may cause reproductive damage.

## Conclusion and Outlook

While the detection and quantification of MPs in the environment remain a challenge, we expect that the increasing number of polymer applications indicates that the number of MPs released into the environment will only increase (Gonzalez-Fernandez et al., 2018). MP exposure is currently very close to our calculated

**Table 1.** Dosage of MPs Exposure in Male Rodents and HED.

| Literature | Animal | MPs type | MPs diameter | MPs dosage | Exposure days | Impact | HED |
|---|---|---|---|---|---|---|---|
| S. Li et al. (2021) | Rats | PS-MPs | 38.92 nm | 0.015 mg/d | 90 d | ABCEF | 0.016 mg/kg/d |
| Xie et al. (2020) | Mice | PS-MPs | 5 μm | 0.01 mg/d | 42 d | ABC | 0.041 mg/kg/d |
| Amereh et al. (2020) | Rats | PS-MPs | 25, 50 nm | 1 mg/kg | 35 d | ACDG | 0.161 mg/kg/d |
| Hou et al. (2021) | Mice | PS-MPs | 5 μm | 60–70 μg/d | 35 d | AC | 0.244 mg/kg/d |
| E. J. Park et al. (2020) | Mice | PE-MPs | 40–48 μm | 3.75 mg/kg | 90 d | H | 0.305 mg/kg/d |
| Wei et al. (2022) | Mice | PS-MPs | 5 μm | 0.1 mg/d | 30 d | ABCG | 0.406 mg/kg/d |
| Ijaz et al. (2021) | Rats | PS-MPs | 10 μm | 20 μg/l | 60 d | ABG | 1.075 mg/kg/d |
| H. Jin et al. (2021) | Mice | PS-MPs | 0.5,4,10 μm | 1 mg/d | 28 d | AC | 4.065 mg/kg/d |
| Deng et al. (2021) | Mice | PE-MPs | 0.4–5 μm | 100 mg/kg | 30 d | B | 8.13 mg/kg/d |

*Note.* Impact: A = decreased sperm motility; B = decreased sperm density; C = increased sperm malformation rate; D = sperm DNA damage; E = destruction of the blood-testosterone barrier; F = spermatogenic cell apoptosis; G = changes in sex hormone levels; H = affect offspring. MPs = microplastics; HED = human equivalent dose; PS = polystyrene; PE = polyethylene.
Calculation formula (Nair & Jacob, 2016):
Rats: X mg/d = (X ÷ 0.15)/kg = Human: Y mg/kg × 6.2.
Mice: X mg/d = (X ÷ 0.02)/kg = Human: Y mg/kg × 12.3.

minimum equivalent human dose in some countries. We propose the following recommendations for future research: (1) Experimental animal studies should be conducted to observe the effects of chronic low-dose MP exposure on the male reproductive system based on current human MP exposure; (2) studies should be conducted on MP exposure in the human body, especially in young children, to clarify the MP exposure of males in different regions, including observation of the effects on semen, blood, feces, and urine, and to clarify the relationship between MP exposure and semen parameters; (3) further research is needed on the mechanisms underlying the deposition and clearance of MPs in the human body; and (4) possible routes of MP intake, including air, water, and food, should be monitored.

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