Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 10 [4] March 2021 : 88-101

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

REVIEW ARTICLE **OPEN ACCESS**

Nanoscale Materials and their Effects on Male Reproductive System: A Comprehensive Review

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ABSTRACT
There are numerous chemical substances that man has produced, many of them, apart from other factors, are toxic to the male reproductive function in animals, including man. A new addition in this list is the nanoscale materials. Worldwide production of nanomaterials is increasing at high rates. Response of the male reproductive system towards exposure to nanomaterials is being studied across the world. Studies have demonstrated adverse effects on male reproductive function in various animals and human resulting from exposure to nanomaterials. The review focuses on properties, types, applications of engineered nanomaterials and human exposure scenarios followed by a detailed review of recent reports on male reproductive toxicity. It also highlights the challenges associated with nanotoxicity studies.
Keywords: *Nanomaterials, Reproduction, Nanoparticles, Nanotoxicity*

Received 29.09.2020 Revised 05.11.2021 Accepted 21.02.2021

INTRODUCTION

According to a widely accepted definition, 'nanoparticles' (NPs) can be described as solid colloidal particles having at least one dimension in the range of 1-100 nm. Various natural processes including forest fires, photochemical reaction, volcanism etc. produce nanoparticles of various kinds. Nanoparticles are also generated from power plants due to combustion of coal, natural gas and oil (Table 1). However, the concern of this review is not these naturally or accidentally produced nanoparticles. It is the man-made or engineered nanoparticles or nanomaterials (NMs) which are getting utmost attention around the globe for various reasons. Despite of subtle difference, the terms nanoparticle and nanomaterial will be used interchangeably in this review. In general, there can be two approaches for the production of engineered nanomaterials. One approach is to break down solids into smaller particles (top-down approach). The second, on the other hand, involves combining atoms and molecules to produce nanomaterials (bottom-up approach) (Fig. 1). Graphene oxide (GO) exfoliation from graphite, wet grinding of metallic ores to form metallic NPs are examples of top-down synthesis. Colloidal synthesis of gold nanoparticles, iron oxide nanoparticles, silver nanoparticles, semiconductor quantum dots (QDs) etc. using various chemical methods are the examples of bottom up approach.

Table 1. Types of nanomaterials. List of NMs in not exhaustive.

Basis of classification	Types	Examples
Origin	Natural	Volcanic ash, viruses
	Incidental	Cooking fumes, diesel exhaust
	Engineered	Carbon nanotubes, graphene oxide, quantum dots
Morphology	Rod	Gold nanorods, Zn nanorods, other rod-shaped metallic nanoparticles
	Flower shaped	Gold nanoflower, SnO_2 nanoflowers
	Fiber	Carbon nanotubes, polymer composite nanofibers
	Sphere	Titanium oxide (TiO_2), Zinc oxide (ZnO), other metallic NPs with spherical shape
	Sheet	Graphene
Dimensionality (D)	0D	Smoke, diesel fumes, TiO_2 Cont.....
	1D	Nanotubes, fibers and rods

	2D	Graphene sheets
	3D	Polycrystals
Crystallinity	Amorphous	Carbon black, silica nanoparticles
	Crystalline	Nanodiamonds, graphene, liquid-crystalline nanoparticles
Chemical nature	Metal	Pure metallic nanocolloids (Ag, Au, Cu, Fe) Bimetallic nanocolloids (Pt-Ru, Pt-Ni) Metal oxides (TiO_2, ZnO, Fe_2O_3)
	Semi-metal	Er-As nanoparticles, carbon nanotubes
	Non-metal	Silica NPs, liposomes, dendrimers, micelles

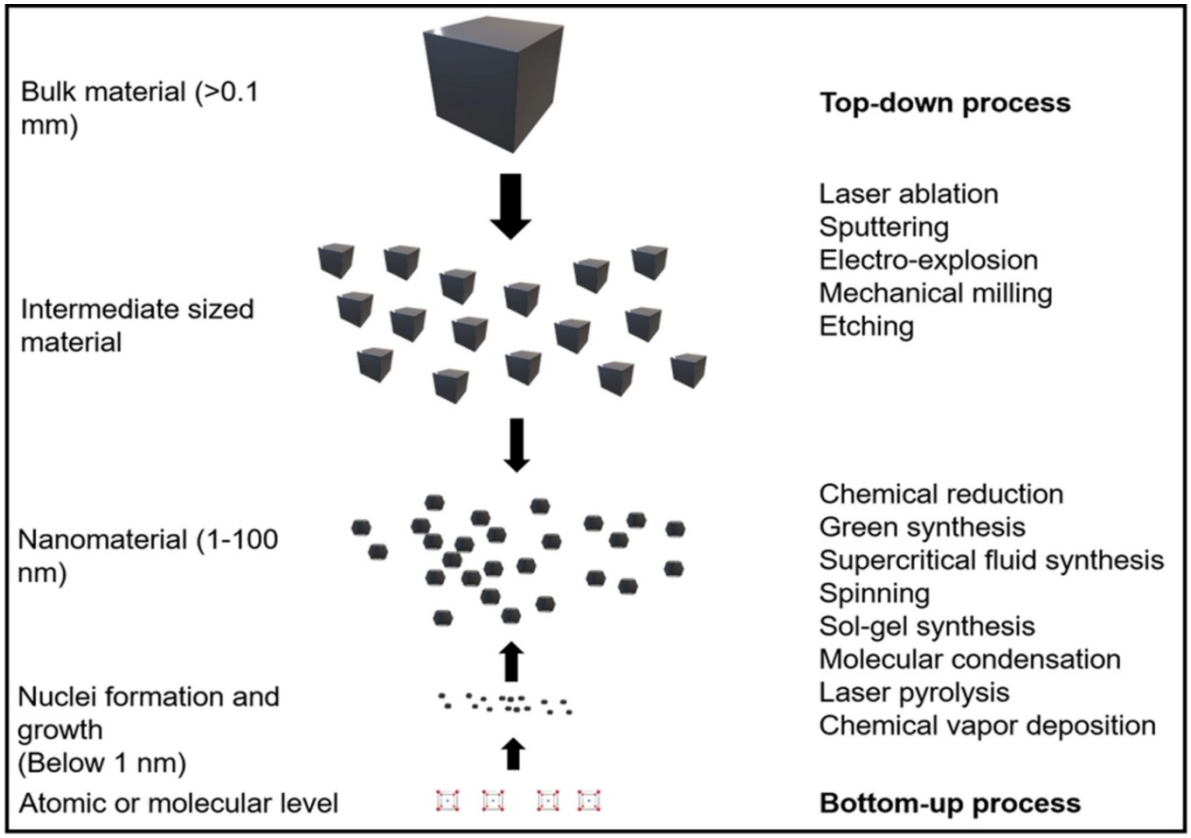

Fig. 1: Two approaches for the production of nanomaterials.

TYPES AND PROPERTIES OF NANOMATERIALS

Nanomaterials can be of several types. For convenience, they are classified on the basis of various attributes like origin, shape, crystallinity, chemical nature as shown in table 1. As the size of materials reaches nanoscale their physico-chemical properties change drastically because of two interesting phenomena: first, the quantum effect; and second, the surface effect. The mass of NMs is extremely small, so gravitational forces become negligible. Instead, electrostatic forces become dominant and at this size wave like property of matter has a more pronounced effect. Due to these reasons, several quantum phenomena such as quantum tunneling, quantum confinement, quantization of energy take place. These are collectively termed as quantum effects. Quantum confinement increases the energy of the band gap of materials which influences their electrical and optical properties, for instance, materials at nanoscale may show quantum fluorescence as shown by QDs [1, 2]. Remarkable new magnetic properties (like the giant magnetoresistance effect) may also come into effect at nanoscale [3]. NMs have far greater surface area when compared to bulk-scale materials of similar mass. Increase in the surface area directly influences the surface energy of the material and chemical reactivity [4]. Optical properties also change due to scattering and absorption of light. With decreasing size of material, binding energy per atom is decreased which results in reduction of melting point [5]. These effects are referred to as surface effects. Another

interesting feature of NMs is that their properties can be controlled by modifying their size and shape. Moreover, chemical reactivity and other physical attributes can also be customized by adding various functional groups to their structure. This tunability of properties make NMs very useful in improving the current materials or development of novel materials that have exceptional properties.

APPLICATIONS OF NANOPARTICLES

Nanoparticles are silently and swiftly entering into our lives. Nanochips are being integrated into communication devices. Nano-coatings are being applied on personal vehicles to make them more lustrous. Nanoparticles are being mixed in cosmetics that make skin glow more. Nanoparticles are being mixed in food products as effective preservatives. Industries are now producing various nanomaterials at bulk level. There are around 1800 commercial products having nanoparticles in some form, including medicines, food products, clothing, sports appliances, cosmetics and electronic materials [6, 7].Major biologically relevant areas where nanoparticles are being used for various purposes are described below (Fig. 2).

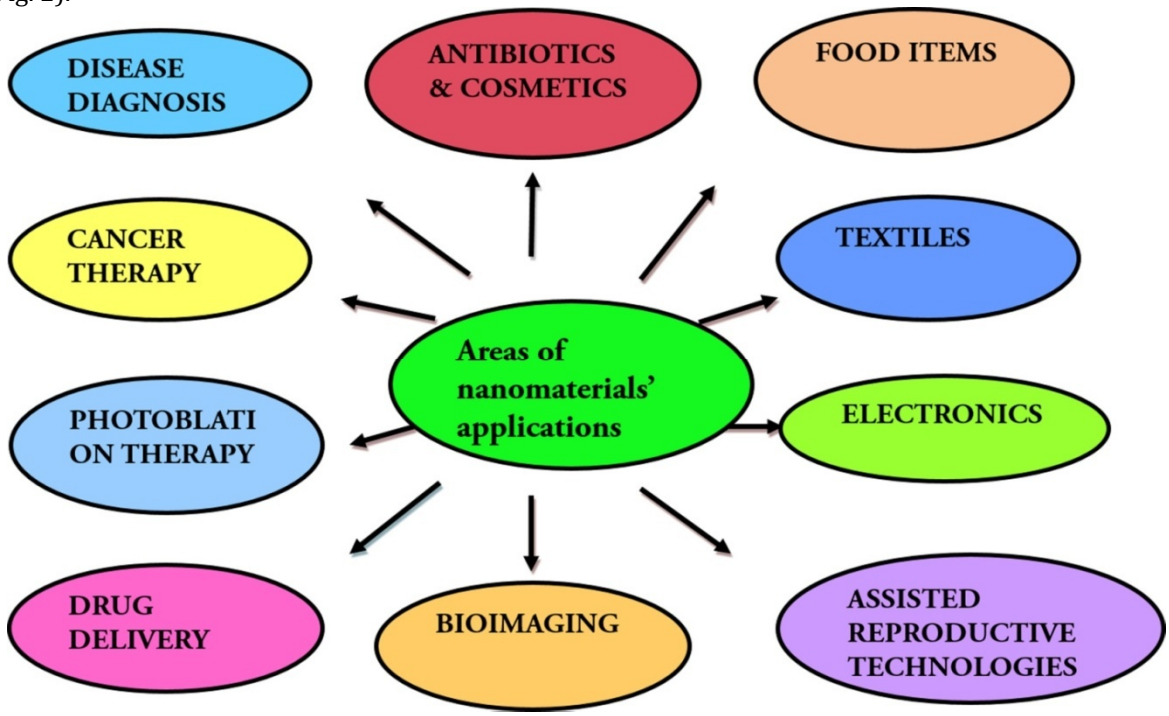

Fig. 2: Various areas in which nanomaterials are being used for different purposes.

Biomedicine

In biomedical science, nanoparticles are used for disease diagnosis, drug delivery, cancer therapy, photoablation therapy etc. Gold nanoparticles (GNPs) are commonly used in drug delivery in cancer patients [8]. Platinum nanoparticles (PtNPs) have anti-inflammatory activity. They are used in nanomedicine due to their catalytic activity and ability to diminish the intracellular reactive oxygen species level [9].Silver nanoparticles (AgNPs) show antibacterial, antifungal, antiviral and antiparasitic activities. They can also be used in drug delivery as important vehicle in cancer therapy [10].Iron oxide (IONPs)nanoparticles have potential to be used as vehicle for targeted drug delivery in cancer therapy [11].

Bio-imaging:

Non-invasive techniques for bio-imaging are highly beneficial for biomedical applications. For instance, super-paramagnetic magnetite nanoparticles coated with dextran can function as image-enhancement agents in magnetic resonance imaging [12]. Similarly, dextran-coated super paramagnetic iron oxide nanoparticles were used for bioimaging [13]. Due to extremely small diameter combining with high tensile strength, carbon nanotubes (CNTs) are highly useful as probe tips for atomic-force microscopy. Single-walled CNTs (SWCNTs) functionalized with bio-molecules can be attached to AFM tips which can be used for "molecular-recognition" to study intermolecular chemical forces especially in macromolecules [14]. Intracellular imaging is becoming increasingly convenient with the development of intrinsically fluorescent nanoparticles, for instance, carbon-nanodots and quantum dots.

Drug delivery

Targeted drug delivery, in spite of huge progress, remains a distant goal in therapeutics. NMs offer a lucrative choice for the purpose. Nanospheres composed of biodegradable polymer incorporated drugs allowed their timely release at targeted site [15].Cai *et al*. (2005) designed vehicle for delivery of DNA plasmids using nickel-embedded carbon nanotubes into Bal17 B-lymphoma, *ex vivo* B cells and primary neurons. Results demonstrated significant improvement in transduction efficiency in all cells tested without affecting viability [16]. Attachment of anticancer drugs, such as docetaxel with nanoparticles tagged with cell specific ligands is a highly successful approach in cancer treatment [17].

Assisted Reproductive Technologies

Nanoparticle based intracellular tags for sex sorting, genetic labeling and selective isolation of good-quality livestock sperms from defective sperms are some reported applications of nanoscale materials [18].

Other applications of NMs include cosmetics, textiles, electronics, nano scaffolds, coatings, scratch resistant materials, nano sensors, nanocomposites, water remediation, pollutant removal, etc [19, 20, 21, 22, 23].Detailed review of these applications is beyond the scope of the current article.

POTENTIAL ROUTES OF EXPOSURE TO HUMAN

Human is exposed to naturally generated nanomaterials on daily basis. This type of exposure is called incidental exposure. Accidental exposure to natural or man-made NMs is also very common [24].However,human exposure to engineered nanoparticles may take place at manufacturing sites or use sites, and/or disposal sites. Occupational exposure occurs primarily at manufacturing sites or disposal site. Accidents may also result in mass exposure to human as well as other living forms in the environment. There are number of routes associated with nanoparticle entry into human bodies more likely through inhalation, ingestion and dermal route. Once inside body, they can travel to other organs of the body through connective tissues and can induce localized and/or systemic toxic effects (Fig. 3)

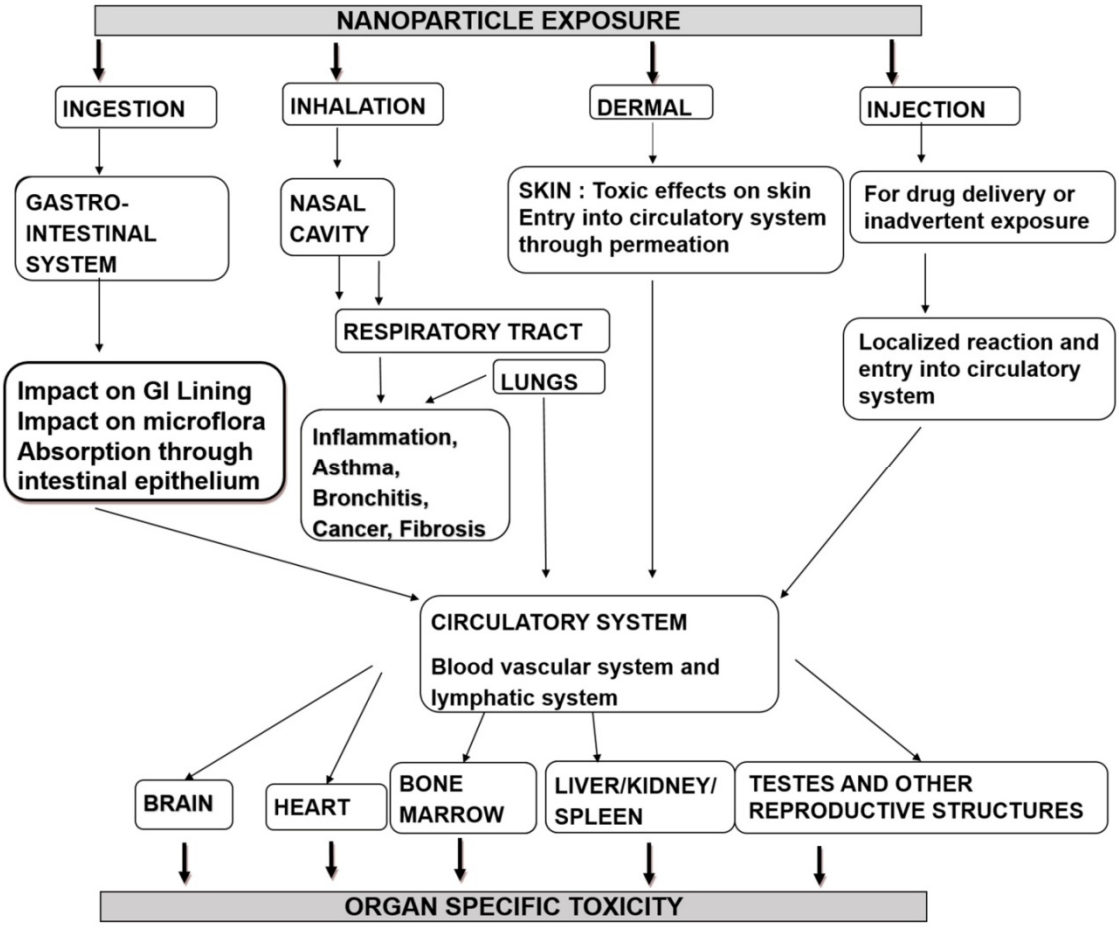

Fig. 3: The predominant routes of NPs exposure, uptake, translocation and potential risks.

Male Reproductive system: Function, Issues and Status

The male reproductive system includes various reproductive organs and glands. Penis, scrotum, and testicles are the external genitalia. Epididymis, vas deferens, ejaculatory ducts, urethra, seminal vesicles, prostate gland and bulbourethral glands are located inside the body and are called internal genitalia. The function of the male reproductive system can be summarized as production of mature and functional sperms, synthesis of androgens, discharging sperms in the female reproductive tract with a protective fluid during copulation. Inability to perform any of the functions mentioned above leads to infertility. Infertility due to male factor has increased to alarming levels in 21st century.

Exact cause of male infertility is hard to ascertain, however, there are several risk factors related with environmental, nutritional, socioeconomic conditions which have been linked with male infertility. Studies have demonstrated that a variety of factors, such as exposure to industrial chemicals, heavy metals, pesticides, alcoholism, obesity, inactive lifestyles, tobacco, oxidative stress, inadequate nutrient intake, various physiological factors and genetic factors can affect male fertility [25, 26]. Considering the above points, it is essential that interactions this new class of industrial chemicals with reproductive system is thoroughly examined. This is why reproductive toxicity of nanoparticles is becoming an important part of nano-science research [27].

Effects of nanomaterials on male reproductive system

Biodistribution of nanoparticles

Toxicity due to nanoparticle exposure is affected by plenty of factors such as nanoparticle stability *in vivo*, their toxicokinetic profile, absorption, distribution, conversion to more toxic metabolites, interaction with macromolecules [28]. Liver and spleen are major target organs to various types of nanoparticles. In a bio-distribution study conducted by Ashraf et. al. (2015), it was found that AgNPs and dextran-coated AgNPs accumulate in spleen and liver after intravenous administration [29]. Similarly, ^{125}I-Radiolabeled Fe_3O_4-Ag heterodimer nanoparticles mainly accumulated in the liver and spleen [30]. Laser-ablated dextran-coated AuNP (AuNPd) of a hydrodynamic size of about 46 nm under intravenous administration in mice, showed that AuNPd were rapidly cleared from the systemic circulation and accumulation took place mainly in liver and spleen [31]. Gold nanoparticles with a lesser size (20 nm) accumulated mostly in lungs and brain whereas relatively low in heart, stomach and pancreas [32]**.** After intratracheal instillation, bismuth selenide NPs were observed to accumulate in lungs and liver in significant quantity [33]. Intraperitoneal exposure also results into systemic transportation to various organs in tested *in vivo* models. For instance, Pham et al. (2018) reported that maghemite iron oxide nanoparticles of 10 and 25 nm size transported to body fluids and all organs of body except brain. The NPs were cleared from body after 7 days post injection. Clearance from body is greatly affected by the nature of the NPs [34]. Functionalized SWCNT which is a long cylindrical shaped NM (with a diameter of 1.4 nm and length of 0.1–1 μm) in athymic mice distributed in liver, kidney, spleen and bone. CNTs remained in intraperitoneal cavity for longer time and did not translocate much through body fluids [35].

Studies have revealed that nanoparticles cross blood-testis-barrier (BTB) and make entry into testicular tissue. Spherical nanoparticles like gold, silica nanoparticles easily enter testis [36]. In a study by Bai et al. (2010) ^{64}Cu-labeled carboxylated CNTs were shown to enter into testis after an intravenous injection. Accumulation of nanotubes increased with time and amount of dose administered [37].Permeation leads to entry of titanium oxidenanoparticles into the skin. Study conducted byWu et al. (2009)onhairless mouse exposed with titanium oxidefor 60 days found accumulation of titanium oxide in spleen, kidney, lungs and brain [38].Translocation of nanoparticles from the circulatory system into the kidney takes place after ingestion. Renal toxicity of cadmium sulphide nanoparticles was reported showing loss of alkaline phosphatase from the brush border of proximal convoluted tubules [39].Above reports clearly indicate that most NMs can transport to various body organs and may accumulate. Many of NMs have the ability to cross BTB.

Testicular toxicity

Exposure to nanoparticles adversely affects male reproductive system including both structural and functional aspects. Metallic nanoparticles owing to their spherical nature and diameter generally below 30 nm easily cross BTB and lead to considerable toxic changes in testicular tissue. Lan and Yang (2012) and Hong et al. (2015) reported decreased sperm production in testis due to exposure of metallic nanoparticles which also accompanied with changes in expression of spermatogenesis regulating genes [40, 41]. A sub-chronic oral exposure of PVP-coated AgNPs to rats, resulted in altered testicular histology and sperm morphological abnormalities**.** Normal sperm morphology and viability was disrupted. At a high concentration (300 mg/kg) they can also reduce the number of seminiferous tubules, spermatogonia, Sertoli cells and Leydig cells [42]. In a recent study, testicular toxicity due to silver nanoparticles was examined in Sprague Dawley rat. Rats were exposed orally to AgNPs at two dose levels, 5.36 mg/kg and 13.4 mg/kg of AgNPs for six months. The results indicated clear fall in testosterone level

and a significant hike in LH levels. The testicular tissue had significantly reduced SOD activity and elevated MDA level in both treated groups. Ultrastructural examination revealed vacuolations in Sertoli cells and abnormalities in spermatogenic cells. Sperm viability and chromatin integrity was also affected adversely [43].

Similarly, exposure to zinc oxide nanoparticles (ZnO) resulted in apoptosis in testicular cells and structural changes in seminiferous epithelium and sperm anomalies [44]. Accumulation of Copper oxide (CuO) nanoparticles in testis of mouse may affect sperm morphology [45]. Spherical shaped nickel nanoparticles of 90 nm size can change motility and decrease the levels of FSH and testosterone in rats. At higher doses nickel nanoparticles induce significant structural damage to the testis [46]. Iron oxide nanoparticles of 20-80 nm size have adverse effects on sperms and Leydig cells in mouse [47]. Repeated exposure iron oxide nanoparticles in mouse led to accumulation of the particles in testis where they induced oxidative stress and apoptosis [48].

With respect to the effects due to non-metallic or semi-metallic particles having different shapes, different outcomes have been reported. A study conducted by Nirmal et al. (2017a)on Wistar rats, exposure to 2.0 and 10.0 mg/kg bwt doses of OH-f MWCNTs resulted in sperm dysfunction and degeneration in seminiferous tubules [49]. In another study by the same group, Wistar rats were exposed with high doses of nanoscale GO (NGO) intraperitoneally which reduced sperm motility and total sperm count and increased sperm abnormalities [50]. Bai et al. (2010), demonstrated the reversible effect of multiwalled carbon nanotubes on adult male mice. Their study reported structural damage to seminiferous tubules and increased serum testosterone levels which were repaired after a recovery period of 30 days [37].

It is, thus, apparent that nanoparticles have a considerable negative impact on testicular tissue including damage to Leydig cells, Sertoli cells, spermatogenesis and sperm quality. Various studies have proved that toxicity in testis is caused due to combination of factors. Oxidative stress is a key factor responsible for nanoparticle mediated tissue damage. Oxidative stress becomes more harmful especially in testes because of two reasons: high metabolism due to continuous sperm production and presence of high amount of unsaturated fatty acids [51]. Oxidative stress leads to damage in biomolecules like protein, lipid and DNA. Increased oxidative stress is linked with testicular toxicity such as effects on steroidogenesis, loss of germ cell, apoptosis and disruption of germinal epithelium [52, 53, 54]. Apoptosis of Leydig and Sertoli cells through DNA injury was reported in *in vitro* study after incubation with ZnO nanoparticles [44].*In vivo* studies have also shown damage to through oxidative stress and DNA after exposure to nanoparticles [48, 55]. The impact of nanoparticles on Leydig cells induces a decrease in testosterone levels with impairment of Sertoli cells; due to their multifunctional role in supporting spermatogenesis, the fertility potential may be hampered. Impairment of sperm quality in a dose-dependent manner was reported in most of the studies as a result of nanoparticles exposure.

Epididymal toxicity

Xu *et al.* (2014) studied effects of silica NPs (SiNPs) on epididymal physiology in mice. Notably, control and treated groups had 24 animals in each group. A total of 5 doses were administered over a span of 13 days at a dose level of 20 mg/kg. Results demonstrated a dose-dependent decrease in quality and quantity of epididymal sperms. However, these effects were reversible in 60 days after the first dose [56]. Gold and silver NPs of spherical shape (having diameter of 10-15 nm) were injected intraperitoneally to 1 month and 6-months old rats at 1 mg/kg dose level for 10 days. The exposure decreased diameter and height of epididymal tubules in both young and adult animals. A decrease in the cross-sectional area of nuclei in epididymal epitheliocytes was also observed. GNPs showed lesser toxicity as compared to AgNPs [57]. Bai *et al.* (2010) tested toxicity of carboxyl- and amine-functionalized MWCNTs after a repeated intravenous exposure at a dose level of 5 mg/kg. The exposure did not affect epididymal histology [37]. Examination of histology demonstrated normal lumen and epithelial lining of epididymis in treated (10.0 mg/kg) as well as control group with both OH-functionalized MWCNTs and GO in our previous reports [49, 50]. These results are in contrast with the findings of Farombi et al. (2014). They reported hyperplasia of epithelial cells and loss of sperms from the lumen in epididymis at a dosage of 1.0 mg/kg of functionalized MWCNTs [58].

Effects on sperms

Spherical metallic nanoparticles have been reported to internalize into spermatozoa and affect their quality. AgNPs of 20 nm were found to induce DNA damage in germ cells after oral exposure in rats [59]. In another study, Yoisungnern et al. (2015) have clearly shown that following direct exposure, AgNPs were internalized into human spermatozoa. Once internalized, they reduce sperm viability and motility. ROS generation was found to be elevated and morphological abnormalities increased significantly. Further, sperms had poor fertilization potential [60]. Polyvinil pyrrolidone (PVP)-coated AgNPs induce significant amounts of abnormalities in sperms [61]. *In vivo* study done using spherical shaped nickel nanoparticles (90 nm) reported adverse effects on sperm motility and decrease in the levels of FSH and

testosterone in rats [46]. AuNPs demonstrated dose and time-dependent toxic effects on sperms in mice. Treated groups were intraperitoneally injected 40 and 200 µg/kg/day water dispersible AuNPs for 7 and 35 days. There were clear cut evidences of reduction in motility, viability and increase in structural abnormalities in sperms. Chromatin quality was also affected by the exposure especially at higher dose for longer duration [62]. Wistar rats exposed with high doses of NGO intraperitoneally. Exposure to NGO reduced sperm motility and total sperm count and increased sperm abnormalities observed [50]. Cerium oxide nanoparticles, in recent study were found to induce changes in sperm motility and viability in mice. Exposure considerably enhanced total number of abnormal sperms [63]. Study by Miura et al. (2017) and Miura et al. (2019)demonstrated that Titanium NPs (TiNPs) elicit "biphasic effects" in male C57BL/6J mice. Sperm motility was found to be drastically affected. However, sperm count was not affected. Direct incubation of sperms with TiNPs affected sperm motility and decreased ATP level [64, 65]. Toxicity of nanomaterials on male reproductive structures is summarized in Table 2.

Table 2. Major studies summarizing toxicity of engineered nanomaterials on male reproductive system.

Nano-particles	Size (nm)	Study model	Dosage level and exposure route	Key findings	Reference
TiO_2	25	Mouse	9.38, 18.75, 37.50, 75.00 & 150.00 mg/kg bwt for 5 days; 0.5 ml/mouse for 10 weeks. Intraperitoneal	Increase in abnormal sperm cells; disrupted the normal cellular structure of testis	[75]
TiO_2 &Ag	50 and 20	Mouse	10, 100, 1000 mg/kg bwt single dose. Oral,	Decreased developmental process, increased fetal defects and mortality	[76]
Anatase TiO_2	5-10	Male Mice	0, 10, 50, and 100 mg/kg bwt. Intragastric	Increased sperm malformation, reduced germ cell number, increased spherospermia, interstitial glands vacuole, malalignment, and vacuolization of spermatogenic cells	[77]
TiO_2	150 d.m. (Z-average in suspension)	Male C57BL/6J mic	0.1, 1, 2, and 10 mg/kg bwt/week for 4 weeks. Intravenous,	Reduced motile sperm percent and progressive sperm percent. Reduced sperm numbers in cauda epididymis	[64]
TiO_2	150 d.m. (Z-average in suspension)	Male C57BL/6J Mice	10, 50 mg/kg bwt single dose. Intravenous and Direct incubation of sperms with TiO_2	Reduced sperm motility and Reduced sperm motility, [3H]-thymidine incorporation, and ATP level	[65]
COOH and NH_2-MWCNT	Diameter 20-30 nm Length 0.5∼2.0 µm	BALB/c mice.	Single dose of 5 mg/kg Or 5 doses over 13 days at 5 mg/kg per dose. Intravenous	Repairable changes in seminiferous tubules. Hormonal level unaffected.	[37]
MWCNT	Diameter 4.5 nm ± 0.5 nm Length 3∼6µm	Mice GC-2spd	0, 0.05, 0.25, 0.5, 1, 5 µg/mL for 24 h	Mitochondrial DNA damage in spermatocyte	[78]
OH-f MWCNT	10-20	Wistar rat	2.0 mg/kg & 10.0 mg/kg bwt single dose. Intraperitoneal	Degenerative changes in seminiferous tubules and altered sperm health	[49]
Nano-graphene oxide	Thickness: 0.8-2 nm Lateral size: 5.0-10µm	Wistar rat	10.0 mg/kg bwt. repeated doses for 15 days and 30 days. Intraperitoneal	Decreased sperm motility, total sperm count; increased sperm abnormalities	[50]

Ag and TiO_2	20 and 21	Ntera2 (NT2, and primary testicular cells from C57BL6 mice of wild type (WT) and 8-oxoguanine DNA glycosylase knock-out	10/50/100 µg/ml for 24/48/72 hrs	Ag NP more cytotoxic cytostatic causing apoptosis & necrosis	[55]
Ag	70	Rat	25, 50, 100 & 200 mg/kg/day for 45 days. Oral	Decrease in the number of Leydig cells & changes in sperm morphology	[79]
Ag	45	Rabbit	0.6 mg/kg of bwt. Intravenous	No significant changes of semen volume, concentration, libido, testosterone. some morphological changes in Sertoli and Leydig cells	[80]
Ag	20	Rat	0.07, 0.14 & 0.28 mg for 5 weeks by gavage	Reduced sperm quality in a dose dependent manner	[81]
Ag	60-80	Rat	30, 125 & 300 mg/kg of Ag NPs. Intraperitoneal	Significant decrease in sperm count, Leydig cells & Sertoli cells	[42]
Au	9	Human	Concentration 44 ppm, a mixture of 500 µL of NPs solution and semen	25% of sperms were immotile	[82]
Au	50	Human	7000 mg/ml concentration, a mixture of 700 µL of Au NPs	Motility of sperm was affected	[83]
Au	10-30	Mouse	40 and 200 µg/kg/ day soluble Au NPs for 7 and 35 days. Intraperitoneal	Decrease in motility and increase in abnormal spermatozoa	[62]
ZnO	50	Human	Semen incubated with (10, 100, 500, and 1000 µg/ mL NPs) for 45, 90, and 180 minutes	Cytotoxicity is dose and time dependent; cell death percentage (20.8%, 21.2%, and 33.2%) after 45, 90, and 180 minutes, respectively	[84]
ZnO	70	Leydig cells and Sertoli cell lines Mouse	Leydig cell and Sertoli cell incubated with 5 µg/mL for 12 and 24 hours 1.0mg/kg and 5.0 mg/kg NPs. Intravenous	Increased mitochondrial-mediated apoptosis. A significant loss of male germ cells Apoptosis in testicular cells	[44]
ZnO	<50	Mouse	300 and 2000 mg/ kg bwt for 2 days. oral	Mildly genotoxicity dose-dependent; affected sperm quality; ROS and chromosome aberration	[85]
CuO	<50	Swiss Albino mice	5, 10, 20 and 40 mg / kg. B. wt. for 7 days. oral	Sperm count and morphology adversely affected	[45]
Ni	90	Rat	(45, 15 and 5 mg/ kg/day) and group (45 mg/kg/ day) for 10 weeks by gavage	Changes on motility; levels of FSH and testosterone decreased; testis damage in highest dose	[46]

Fe_2O_3	20-30	Mouse	5, 10, 20, 40 mg/kg for 2 weeks. Intraperitoneal	Adverse effects on sperm and Leydig cells.	[47]
Fe_2O_3	<50	Mouse	25 and 50 mg/kg once a week for 4 weeks. Intraperitoneal	Ability to cross BTB; testicular toxicity (oxidative stress and apoptosis)	[48]
Fe_3O_4		Human semen	10 µg/ml for 4h incubation	Cell disintegration, permeability and distribution on middle piece; significant percentage of DNA damage	[86]
Fe_3O_4	30	Spermatozoa of Rainbow trout	50, 100, 200, 400, 800 mg/L at 4 ^{0}C for 24 h	Decreased velocities after treatment with 400 mg/L. Decreased SOD and CAT activities after 100 mg/L	[87]
PbSe	8 ± 3.4, 30 ± 11.2, and 70 ± 29.6	Rat	10 mg/kg/week for 60 days. Intraperitoneal.	Reduction in the quantity and quality of sperm	[88]
CdSeQDs	2.4	BALB/c mice	10, 20 and 40 mg/kg b. wt. Single dose, Intraperitoneal	Decrease in lamina propria, destruction in interstitial tissue, deformation of seminiferous tubes, and reduction in number of spermatogonia, spermatocytes, spermatids, and matured sperms	[89]
CdSe:ZnS QDs	3.0	BALB/c mice	10, 20 and 40 mg/kg b. wt. Intraperitoneal	Decrease in lamina propria; destruction in interstitial tissue; deformation of seminiferous tubules; and a reduction in number of spermatogonia, spermatocytes, and spermatids. No adverse effects on epididymis	[90]
CeO_2		Balb/c Mice	100, 200 and 300 µg/kg bwt thrice in a week for five consecutive weeks. Intraperitoneal	Reduced antioxidant enzymes activity, levels of glutathione and total nitric oxide. Decreased sperm motility and count, increased total sperm binormality in mice, congestion and egeneration of seminiferous tubules decrease in FSH, LH, testosterone	[63]
CeO_2	27.62 ± 3.01	Male Mice	20-40 mg/kg bwt /day for 32 days. oral	Sperm DNA damage, decreased the testis weight, DSP and sperm motility. reduction in testosterone levels and marker enzymes activities	[91]
SiO_2	10-15	Mice	Single dose, 333.33 mg/kg b. wt. /day. Orally,	Congestion in testis, disruption and reduction of the spermatogenesis, necrosis and edema in testis	[92]
SiO_2	64.43±10.50	Mice	20 mg/kg bwt every 3 days, five times over a 13-day period. Intravenous through tail vein	Adverse effects on maturation process of sperm in the epididymis by causing oxidative stress and damage to the mitochondrial structure. Toxicity is reversible.	[56]
Si	57.66	C57Male Mice	2 mg/kg bwt every 3 days for 45 days. Tracheal perfusion	Apoptosis and necrosis in the spermatogenic cells by activating the RIPK1 pathway due to oxidative stress. Toxicity is reversible.	[93]
SiO_2	10-30	Male Rat	1, 10 ,100 mg/kg/day bwt for 22 days Oral gavage	Significant ($p<0.05$) decrease in expression level of Cyp19a1 and Cyp17a1 genes in test is tissue	[94]
Mn_3O_4	<50	Male rats	10 mg/kg bwt/week for 0, 60 and 120 days. Intravenous through tail vein	Increased oxidative stress reduced the quantity and the quality of sperms	[95]

Alleviation of toxicity

The biggest concern with the widespread use of NMs is their toxicity to living cells. Therefore, alleviating or reducing toxicity of NMs remains a much-coveted goal for researchers around the globe. Zhao et al. (2013) studied variation in toxicity of nanosized hydroxyapatite (nHA) due to shape modifications. Examining various in vitro cytotoxicity endpoints, the group conclusively showed that needle and plate shaped nHA exhibited high toxicity while spherical and rod-shaped nHA, despite of greater cellular interaction, showed fewer toxic effects [66]. Cai et al. (2017) demonstrated that coating of metal oxide nanoparticles with EDTMP which forms a stable hexadentate coordination can significantly reduce their toxicity [67].

Poly ethylene glycol (PEG) coating can ameliorate the toxic effects of Ag NPs. Ag NPs functionalized with bovine serum albumin (BSA) and PEG, were found to be non-toxic [68]. Surprisingly, toxicity can also be reduced by combining different nanoparticles in a particular manner. For instance, if a silica coating is applied over the ZnO NPs, it reduces its toxicity to cells without affecting the desired property. The coating prevents the dissolution of zinc ions from the nanoparticles in solution [69].Covalent surface modification of SNPs withvinyl- and aminopropyl/vinyl modified clearly showed highly reduced cytotoxic and genotoxic effects in peripheral blood lymphocytes [70].

Orazizadeh et. al. (2014) used beta-carotene (BC) as ameliorative agent against reproductive toxicity induced by titanium oxide nanoparticles in male mice. The findings demonstrated that the beta-carotene overcome the toxic effect caused by titanium oxide nanoparticles [71]. In another study conducted by Elnagar et. al.(2018),N-acetylcysteine (NAC) was tested for its protective role against testicular toxicity caused by titanium oxide [72]. Curcumin (Cur) is one of the most commonly used spice in cooking. It has ameliorative effect on testicular toxicity caused by exposure of titanium oxide nanoparticles [73]. ZnO nanoparticles are frequently used in cosmetic and food industry but its accumulation in the tissues also causes toxicity. Naringenin (Nar) having anti-oxidant property, was found effective against toxic effects of zinc oxide nanoparticles. Use of naringenin with ZnO nanoparticles was suggested to overcome hazardous effects [74].It is clear from the above discussion thattoxic effects of nanoparticles can be partially or fully mitigated. Suitable shape modification, size modification, surface coatings, functionalization, making a combination with natural products or other substances are some approaches to attenuate toxic effects of biomedically important nanoparticles.

CONCLUSION

With the expansion and production of nanomaterials for industrial purposes and nanomedical applications, exposure chances are also increasing. Many research reports have documented their adverse effects on animals and environment. Male reproductive toxicity is a special concern because of its current relevance. Issues related with male reproduction are complex, involving extremely sensitive and delicate gamete producing tissues which have an essential function of the transmission of genetic information from the parent to the progeny. Due to their nature, these biological systems are highly sensitive to the action of numerous environmental factors, including engineered nanoparticles. In this review, nanomaterials of different types and their applications have been described. Further, review equally stressed the studies dealing with the effects of nanoparticles on male reproductive structures. Evidently, there appears lack of unified guidelines for determination of dose levels and parameters of study for nanotoxicity. Contrasting results have been published by researchers. Separate guidelines become more important considering the fact that nanotoxicity is greatly affected by properties of nanoparticle like shape, size, functionalization status, dosage level, route of administration and choice of animal model. That is why, despite of much research, conclusive statements cannot be made. Altogether a combined and holistic approach of *in vitro, in vivo*, and *in silico* information will allow a better understanding of the interaction of nanoparticles with living systems. There is a need to develop sensitive methods to analyze subtle changes taking place in germ cells due to the exposure especially at lower doses. The number of new nanoparticles, especially biomedically relevant, is increasing day by day for instance, fluorescent carbon dots, polymeric nanoparticles, novel quantum dots etc. Continued assessment of reproductive toxicity of these tiny materials is to be done. Nanomaterials and nanotechnology are useful and unavoidable reality of the world today, it is quite essential to establish ways to alleviate the toxicity inflicted by these wondrous materials. It is the preparedness and scientific awareness which can prevent these materials from becoming bane instead of boon for humanity.

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CITATION OF THIS ARTICLE

G S Verma, N K Nirmal, P J John. Nanoscale Materials and their Effects on Male Reproductive System: A Comprehensive Review . Bull. Env.Pharmacol. Life Sci., Vol10[4] March 2021 : 88-101