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Review Article

A review: Effect of silver nanoparticles on human health following various routes of administration

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ABSTRACT

Individuals are employing silver nanoparticles in a wide range of medications, scientific studies and medical devices, which necessitates more study in order to understand the long-term implications of exposure. It is not always possible to avoid exposure to silver nanoparticles if they are spread across a large area, such as an industrial site. Silver nanoparticles can be inhaled, ingested, or interact with the skin. People's health is impacted by several aspects, including how much exposure (how much), how long they have had it (how long it is been), what form of exposure they have used, what other chemicals present in the environment (such pesticides), and how healthy they are at the time of exposure. Toxicology following exposure to silver in a variety of ways necessitates additional investigation, even though several studies have already been published (AgNPs).

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1. Introduction

1.1. What is silver nanoparticles?

It has become more common to use silver nanoparticles (AgNPs) as antibacterial agents in many textiles and medical devices, including freezers and washing machines. While the word "nanomaterials" has generally been used to describe particles smaller than 100 nm, the phrase "Nano silver" is increasingly becoming popular, particularly in the context of commercial goods that incorporate nanomaterials with a high silver content. However, while nano-silver has been widely employed in everyday things such as clothing or electronic appliances, it has not been widely used in the medical or pharmaceutical industries.[1] There are 1628 goods on the market that self-identify as containing nanomaterials, including 383 that include silver nanoparticles, such as baby blankets and kids' plush toys, according to the Inventory of Nanotechnology in Consumer Goods.[2]

1.2. How might i be exposed to silver nanoparticles?

Public exposure to silver nanoparticles arises owing to their widespread usage in many biomedical applications such as medical diagnostics and treatment and cosmetics. They are also used in the delivery of drugs and the coating of medical devices. Silver nanoparticles are also used in a wide range of consumer items, including food packaging, which is used to pack meat, fruit, and dairy products. Increased application of silver nanoparticles in several contexts improves chances of biological interactions and their potential toxicity to general population.[3] Silver nanoparticles are found in cosmetics at concentrations of 0.002-0.02 ppm. Many common household items, including face masks, cloths, toothpaste, shampoo and detergent, contain silver nanoparticles at concentrations of 1.4 to 270,000 micrograms of silver per kilogramme of product. Medical equipment (catheters) and wound dressings can be coated with nanosilver in a concentration range of 50–60 g

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Table 1: Possible routes of human exposure to silver nanoparticles [4]

S.No	Route of exposure	Sources of exposure
1.	Respiratory system	Handling AgNPs in manufacturing or research facilities, Aerosols directly applied in the nasal or oral cavities, Sprays (e.g., deodorants, shoe sprays, cleaning products), Air filters, breathing masks, Ambient airborne AgNPs
2.	Skin	Wound dressings, Antibacterial textiles (e.g., sheet, towels, socks, underwear, fitness wear), Antibacterial surfaces, paints, Cosmetic products (e.g., lotions, roll-on deodorants, hair products), Computer hardware and mobile devices
3.	Gastrointestinal Tract	Food packaging, cooking utensils and coatings Water filters Health supplements Oral hygiene products (e.g., toothpastes, toothbrushes)
4.	Reproductive System	Contraceptive devices Feminine hygiene products
5.	Circulatory System	Intravenous injection of AgNP-enabled drugs or drug delivery/diagnostic systems, Implants, medical catheters"

cm3.

1.3. How can silver nanoparticles enter and leave my body?

If you eat food packaged in silver nanoparticles packaging, or if you use nanosilver-coated toothbrushes, food storage containers, and even infant bottles and pacifiers, silver nanoparticles may enter the body through the oral route.or through dermal route after using cosmetics, sunscreens, textiles and clothing imbedded with silver nanoparticles.[5] Silver nanoparticles may also enter into body through inhalational route from occupation site.[6] In a few investigations, workers were exposed to low levels of silver nanoparticles below the threshold limit values for a short period of time, despite a dearth of occupational studies.[7] Ureter and faeces are the primary routes via which silver nanoparticles that are ingested or inhaled exit the human body.[8] It is unclear how much of the silver that is absorbed via the skin is excreted in the urine or other bodily waste. Silver nanoparticles have also been shown to build up in the tissues and organs of the body, according to research.[9]

1.4. How can silver nanoparticles affect my health?

To achieve the minimal skin tissue dosage linked with argyria in humans, exposure to silver nanoparticles of 15 nm diameter for 45 years or 253 nm diameter silver nanoparticles (8-hour time weighted average) for 100 nm diameter was estimated.[10] Silver nanoparticles also shows some unacceptable toxic effects on human health along with their antimicrobial and antifungal activity. Many physical and chemical features of silver nanoparticles have been connected to their toxic qualities, such as their size, composition, reactivity and the ease with which they may be aggregated. Silver nanoparticles that are smaller are assumed to be more poisonous than those that are larger, however this is not always the case. The toxicity of silver nanoparticles has been examined both in vitro and in vivo. In both scenarios (in vitro and in vivo), smaller silver nanoparticles were more toxic than bigger ones. Because of the coating on the silver nanoparticles, their toxicity may also be influenced. There are a number of physical and chemical properties that may be affected by surface coatings on silver nanoparticles. According to a new study, certain silver nanoparticles that are not coated appear to be less dangerous than those that are. It has been shown that the distribution and kinetic profile of silver nanoparticles change according to gender, and this may be used to predict the toxicity of silver nanoparticles.[11]

1.5. What level of exposure has resulted in harmful health effects?

It has been found that silver nanoparticles with a concentration of 12.5-20.0 ppm are toxic to human mesenchymal stem cells and peripheral blood mononuclear cells, as well as Escherichia coli and Staphylococcus aureus. Human cells and bacteria are both killed by silver nanoparticles if they are present at the same quantity. Nanoparticle size is an important factor in the silver nanoparticle toxicity.[12] More long-term, wide-range dosages of silver nanoparticles, ideally employing several particle sizes, are needed to properly evaluate the potential toxicities of silver nanoparticles on human health.[13] However, despite the fact that silver nanoparticles have shown positive effects, there have also been reports of negative side effects. An investigation of the effects of nano-silver on the production of cytokines by peripheral blood mononuclear cells and their proliferation was the primary goal of this study (PBMCs). Nano-cytotoxicity silver's against human PBMCs was investigated in further investigations. Different nanosilver concentrations were shown to have different effects on healthy human blood cells (PBMC) that were stimulated by phytohaemagglutinin (PHA) (PHA). The PBMC proliferative supernatant was analysed using an ELISA, and it was determined to be much higher than usual. The activation status of PBMCs was determined using interleukin-5, interferon-gamma, and tumour necrosis factor-alpha protein levels in PBMCs. PHA-induced cytokines, which were previously found to be lethal to PBMC cells at this dose, were suppressed by

nano-silver (IL-5: at 10 ppm, INF-gamma and TNF-alpha at 3 ppm). A concentration-dependent effect on cytokine production was seen when AgNPs were used at high dosages. Inflammatory and immunologic illnesses may be treated with nano-silver, according to these studies.[14]

1.6. Is there a medical test to determine whether i have been exposed to silver nanoparticles?

Exposed persons' urine, faeces and bodily tissues contain silver nanoparticles. Research on the release of silver from silver nanoparticles in the body required ICP-MS analysis of all tissues, faeces, and urine samples to determine their silver concentration. Analysis of the research participants' tissues using an inductively coupled plasma mass spectrometer revealed silver.[15]

2. Health Effects

2.1. Introduction

An overview of recent research and their findings on the health consequences resulting from exposure to silver nanoparticles is provided in this chapter. With the use of toxicological research, epidemiological studies, and statistics on environmental exposure, this report aims to show what the safest amounts of silver nanoparticle exposure are for humans. An overview of silver nanoparticles' toxicity is provided here to help public health authorities, physicians, and toxicologists as well as other interested individuals and organisations better understand how exposure to silver nanoparticles affects various health outcomes. Workers that make or use silver nanoparticles may breathe in dusts containing silver nanoparticles or have direct skin contact. Medical professionals and patients may also breathe in dusts or have direct skin contact during medical procedures using silver nanoparticles. The general population may breathe in dusts or have direct skin contact while using consumer products that contain silver nanoparticles, such as personal sanitizing sprays or laundry additives. Exposure may also occur through the ingestion of drinking water due to its use in water treatment.[16] In addition to releasing silver, the silver nanoparticles also release silver in various oxidation states, which are seen in nature. Most often encountered in nature are elements with zero oxidation and the silver ion, which is monovalent. These chemical forms of silver have been the focus of the majority of toxicological investigations. It was found that no toxicological studies had been done on the health consequences of silver compounds having oxidation states of +2 or +3. Silver nanoparticles can be found in medical, food packaging, and consumer items. As a result of the widespread usage of silver nanoparticles-containing medicinal and cosmetic products, silver nanoparticles may be absorbed into the human dermis.

2.2. Discussion of health effects by route of exposure

Resident and workers near hazardous waste sites should be aware that the data in this area is broken down into exposure routes (inhalation, oral, and/or cutaneous) and health consequences (death, systemic; immune; neurological; developmental; reproductive). Acute, intermediate, and long-term exposures are all included in the data. Reports of NOAELS or LOAELs, the lowest recorded adverse effects, were made in studies (LOAELS).

2.2.1. Information about minimal risk associated with silver nanoparticles.Table 2

2.2.1.1. Death. Inhalation of silver nanoparticles has not been proved to cause death in humans or animals.

2.2.1.2. Systemic effects. When silver nanoparticles were inhaled, there were no significant alterations to haematological a[18]d blood biochemical indicators over 28 days. "In a 90-day inhalation study, tidal volume and inflammatory responses in the lungs were decreased.[19] Studies on the long-term deposition of silver nanoparticles in the lungs and liver after inhalation exposure to silver nanoparticles have found these organs to be the principal targets.[20] Activation of mitogen activated protein kinase (MAPK) signalling in the lungs when silver nanoparticles are breathed has been shown to produce acute toxicity in the lun"g.[21]

2.2.1.3. In vivo toxicity of silver nanoparticles to mammalian animal models after inhalational exposureTable 3[22].

2.2.1.4. Immunological effects. Pathogen-associated chemical patterns may be recognised by these cells, which activate the innate immune system through pattern recognition (PRRs). Plants, invertebrates, and vertebrates all have Toll-like receptors (TLRs), which are a basic defensive system against bacteria, fungus, and viruses, as well as a signalling mechanism. innate immunity relies heavily on Toll-like receptors (TLRs). When a pathogen's microbial components are recognised by a TLR, the inflammatory response is triggered, which in turn activates adaptive immunity. It is concluded that TLRs are PRRs that identify molecules shared by pathogens but distinct from those of the host. Toll-like receptor (TLR)-1, 2, 4, 5, and 6 are present on the cell surface, whereas TLR-3, 7, and 9 are found in the endocytic compartments and identify viral products.

2.2.1.5. Neurological effects. Nanoparticle-induced brain injury in newborns, children, and humans cannot be quantified in terms of dosage and time course because of the lack of practical methods. Silver nanoparticles' impact on the development of human and rat embryonic neural stem cells are researched in a similar fashion (NSCs).

Table 2: Levels of significant exposure of silver nanoparticles [17]

	Species	Route	Exposure frequency/ Duration	Effect NOAEL (mg Ag/kg/day)	LOAEL (Effect)"
Acute exposure	Albino rat	Intrap-eritoneal	5 days/once in 48 hours	NA	2000
Intermediate exposure	Wistar rat	Oral	90 days	30	125

Table 3: Toxicity assessment of Ag NPs

S.NO	Size of AgNPs TEM size	Toxicity assessment of Ag NPs Organisms	Doses	Exposure method and time	Major outcomes
1.	18nm	Sprague-Dawley rat	1.73×104/cm3, 1.27×105/cm3, 1.32×106 particles/cm3	Inhalation exposure: 6h/day, 5 days/week, for 28 days	No significant changes in the hematology and blood biochemical values in either the male or female rats.
2.	18nm	Sprague-Dawley rat	1.73×104/cm3, 1.27×105/cm3, 1.32×106 particles/cm3	Inhalation exposure: 6 h/day, 5 days/week, for 90 days	Decreased tidal volume and alveolar inflammation. Increased bile duct hyperplasia and liver inflammation.
3.	13–15 nm	Sprague-Dawley rat	1.73×104/cm, 0.5 μg/m3, 1.27×105/cm3, 3.5 μg/m3 and 1.32×106 particles/cm3, 61 μg/m3	Inhalation exposure: 6h/day, 5 times/week, 28 days	Size and number of goblet cells containing neutral mucins increased in lungs.
4.	22nm	C57BL/6 mice	1.91×107 particles/cm3	Inhalation exposure 6 h/day, 5 days/week, 14 days	Expression of several genes in brain associated with motor neuron disorders, neurodegenerative disease and immune cell function

Note: Ag NPs, silver nanoparticles; TEM, transmission electron microscopy.

It was shown that after 24 hours of exposure to silver nanoparticles, the viability and proliferation of NSC were significantly decreased. Silver nanoparticles dramatically reduce the viability of NSCs. For both rat and human NSC models, silver nanoparticle-induced apoptosis and necrosis appear to be dose-dependent as well as time-consuming (add supporting data). Rat NSCs were analysed using the TUNEL test to determine the extent of Ag-NP-induced cell death. Since DNA strands are broken, the TUNEL test is widely accepted to be able to diagnose apoptotic cell death. In the absence of any TUNEL-positive cells, the study was declared a success. There were a lot of TUNEL-positive cells that showed typical DNA fragmentation associated with apoptosis following Ag-NP treatment. There were more than seven times as many TUNEL-positive cells after 24 hours of 5-g/ml Ag-NP treatment, compared to the control group, and the difference between the two groups was only 0.0001.[23]

2.2.1.6. Developmental effects. When it comes to AgNPs' developmental toxicity, there are conflicting findings in the scientific literature. There is a lot of evidence that AgNPs have the potential to harm embryos and foetuses in a variety of ways. Even at large dosages (up to 1000 mg/kg/day), several investigations revealed no negative impact on the growth of AgNPs, despite their presence.

Developmental toxicities associated with AgNPs may include embryo and foetal size reductions, poor survival rates as well as outward deformities. There were reports of abortion in rats fed AgNP intraperitoneally every other day between the 7th and 18th days of pregnancy. A rise in the number of resorbed and emaciated newborns was found in pregnant mice exposed to AgNPs, as was a decrease in body weight and placental size. Morphological abnormalities and foetal survival are two of the toxic consequences of AgNP on embryogenesis. As a result of AgNP injection into pregnant mice, the resulting embryos were significantly smaller, however compared to the AgNP levels in the developing foetus and mother's liver, spleen, and visceral

yolk sac, this silver content was negligible. Following AgNP exposure, there are also apparent anomalies, such as a small head, scoliosis, lordosis, a short thorax and trunk, and fused fingers.

2.2.1.7. Reproductive effects. Silver nanoparticles may pose a risk to reproductive health since they can reach the testicles after inhalation and have been shown to induce toxicity to Leydig cells. Stem cell spermatogenesis is disrupted by silver nanoparticles. An inhalation exposure of silver nanoparticles (0.6–3.0 106 particles/cm3) was studied in rats over the course of 90 days to see what effects there might be. Testes were discovered to contain silver nanoparticles, showing that the circulating blood is responsible for dispersing the particles throughout the body. But there was no in-depth examination of the histology of the testis. It is challenging to extrapolate these values to human exposures, despite the fact that this work provides one of the most relevant models to date for long-term exposure to silver nanoparticle contaminants. Inhalation of silver nanoparticles in the workplace has not been well studied due to the lack of available data. Silver nanoparticle accumulation in the human testis seminiferous epithelium after chronic exposure has yet to be identified, hence further research is needed on this subject. However, the possibility of human exposure necessitates a mechanistic knowledge of their toxicity in order to determine risk.[24]

2.2.1.8. Genotoxic effects. An in-vivo micronuclei assay, developed by the OECD 474, was used to assess the cytogenetic damage produced by silver nanoparticles. Male and female rats were treated to silver nanoparticles at varying dosages for 90 days, according to test guideline 413 of the OECD. The results of the micronucleus assay were obtained. To our knowledge, this is the first study to show an increase in MN PCEs among male rats, but not among male and female rats compared to the negative controls (Tables 1 and 2). PCE/(PCE + NCE) ratios in male and female rats treated with silver nanoparticles did not differ significantly.indicating that bone marrow cytotoxicity was not present (Tables 1 and 2).[25]

2.2.2. Oral exposure

Tests for silver nanoparticles (56nm) in F344 rats during 13 weeks (90 days) were conducted according to OECD guideline 408 and GLPs (GLP). There were four treatment groups: vehicle control, low-dose (30 mg/kg), middle-dose (125) and high dose (500 mg/kg). Ten rats were randomly assigned to each of the four groups. On average, male and female rats at five weeks of age were around the same size and weight (99g each). It was determined that the distribution of silver in the body was studied 90 days following exposure to the chemical. Even though they consumed the same amount of food and water throughout the treatment period, male rats lost weight considerably (P 0.05) in the fourth week. As silver nanoparticles were administered to male and female rats at doses more than 125 mg/kg, substantial modifications in alkaline phosphatase and cholesterol levels were observed. When histopathological examinations were carried out on the animals that had been treated, bile-duct hyperplasia was shown to be more common. The accumulation of silver in all tissues studied was likewise dose-dependent. When it comes to the buildup of silver in the kidney, female kidneys were shown to be twice as likely to have the metal in their tissues as male kidneys. Male and female rats exposed to silver nanoparticles had the most severe liver damage. 30 mg/kg is the NOAEL, whereas 125 mg/kg is the LOAEL (lowest observed adverse effect limit).[26]

2.2.2.1. Death. When taken orally, silver nanoparticles have not been proven to cause mortality in people, according to current research. There has been an increase in animal fatalities due to dose-dependent toxicity.[27]

2.2.2.2. Systemic effects. When Wistar rats were exposed to silver nanoparticles orally, lipid peroxidation was seen, as well as alterations in GSH, SOD, and catalase concentrations.[28] It was shown that repeated dosing toxicity may be studied by administering silver nanoparticles (42 nm) to mice for 28 days. High-dose silver nanoparticles (0.25 mg/kg, 0.50 mg/kg, and 1.00 mg/kg) were shown to cause liver and kidney damage in the high-dose-treated group (1.00 mg/kg). Repeated oral treatment of these chemicals increased the levels of toxicology indicators including IFN-gamma and TGF-beta in a dose-dependent way as well. In addition to IFN-gamma and TGF-beta, this molecule contains Additionally, IgE production increased and B cells in lymphocytes were dispersed following the treatment. Nano-sized AgNPs have been shown to cause organ damage and inflammation in mice after repeated oral treatment.[29] In a research published in the Journal of Nanoparticle Research, 80% of silver nitrate nanoparticles were found to have diffused throughout the body of mice that received AgNPs 1 mg/kg via oral administration for 14 days.Small-sized silver nanoparticles boosted blood levels of TGF- substantially, whereas large-sized silver nanoparticles did not, according to this study. The phenotypic study also showed that silver nanoparticles of smaller size boosted B cell distribution, whereas silver nanoparticles of larger size did not.[30]

Note. RBC (M/L) stands for red blood cells, whereas WBC (K/L) refers to white blood cells. Hemoglobin; Hematocrits, or HCT (percent); MCHC (g/dL), RDW (percent), Red cell distribution width; "PLT" stands for Platelets (K/L). Amount of typical platelets (MPV) Each kind of white blood cell is represented by a percentage. Eosinophils account for a large portion of the EOS population. Percentage of basophils. * To be deemed significant, the experimental and control groups must vary

Table 4: Frequency of MN PCEs and PCE / (PCE + NCE) ratio in bone marrow of male rats

Dose	No. of rats	Frequency of MN PCEs in every 2000 PCEs (Mean ± SE, %)	PCE/(PCE + NCE) (Mean ± SE, %)
0	10	0.14 ± 0.10	0.36 ± 0.10
Low	10	0.13 ± 0.09	0.39 ± 0.07
Middle	10	0.21 ± 0.09	0.31 ± 0.05
High	10	0.18 ± 0.13	0.30 ± 0.08

Table 5: Frequency of MN PCEs and PCE / (PCE + NCE) ratio in bone marrow of male rats**"**

Dose (mg/kg/day)	No. of rats	Gender	Frequency of MN PCEs in every 2000 PCEs (Mean ± SE, %)	PCE/(PCE + NCE) (Mean ± SE, %)
0	10	Female	0.14 ± 0.08	0.29 ± 0.08
Low	10	Female	0.09 ± 0.06	0.30 ± 0.09
Middle	10	Female	0.08 ± 0.06	0.35 ± 0.08
High	10	Female	0.13 ± 0.10	0.31 ± 0.08

by 0.05.[31]

2.2.2.3. Immunological effects. Silver nanoparticles, on the other hand, were tested on mice to determine if they influenced their immune systems. These indications include CD3 T cells, B cells, NK cells, NKT cells, CD3-CD49b- NK cells, and CD3+-CD49b+ NKT cells, which are used to assess the immune system's effect on the body. Silver nanoparticles (10-20 nm, depending on the manufacturer) and de-mineralized water are combined together to generate a stock solution of 50 ppm of silver nanoparticles in water. For 28 days, mice were fed water with three different concentrations of the stock solution to see how it affected their health.Control animals were given distilled water, as well as their own.

Red blood cell characteristics, total white blood cell count, lymphocytes and granulocytes and percentage of each, were unaffected by the silver nanocolloid dosage examined. As a result, all groups receiving AgNPs had a considerable drop in the proportion of monocytes (0.25ppm, while the other groups saw an even more significant decline). Overall monocyte counts in animals treated with nanosilver were lower than those in the control group, despite the fact that the changes were only statistically significant for groups given 2.5 ppm (p 0.01) and 25 ppm (p 0.05). For the highest dose of colloid, there was a statistically significant drop in platelet counts compared to the control group.[32]

2.2.2.4. Neurological effects. There was an increase in dopamine and 5-HT concentrations in the brain following 28 days of oral treatment with silver nanoparticles at 9 mg Ag/kg bw/day each.[33]

2.2.2.5. Developmental effects. Scientists looked studied the effects on zebrafish embryonic development of nanoparticles of stable, non-aggregated silver (11,6 3.5 nm diameter).[1] Passive infiltration of embryos by silver nanoparticles through the chorion pore canal system has been demonstrated. Silver nanoparticle concentration affects toxicity as well as the sorts of defects seen in zebrafish embryos, according to the study's findings. Using embryos exposed to the same dose of silver nanoparticles, the researchers grew both normal and malformed zebrafish, and discovered that certain embryos are more resistant to the toxins than others. According to a comparison of other compounds, silver nanoparticles had similar effects to cadmium, dichloroacetic acid, and 2,3,7,8-tetrachlorophenoxyacetic acid when compared.

2.2.2.6. Reproductive effects. Wistar rats were divided into five groups: a control, three experimental (n=15 each), and a control group. Oral administration of silver nanoparticles was used to test the various hypotheses. The experimental groups were given silver nanoparticles (60 nm in diameter) at dosages ranging from 25 to 200 mg/kg/day.During the 45-day spermatogeneic period, blood samples from the rats were taken for the measurement of testosterone, LH, and FSH. To determine sperm parameters and Leydig cells, each rat's epididymis and testis were dissected.High concentrations of the experimental groups showed statistically significant reductions in Leydig cells compared to the control group. There was no statistically significant drop in FSH levels whereas testosterone declined and LH rose at higher doses (p 0.05). There was a significant decrease in motility and normal sperm morphology in the experimental groups as compared to the control group. At high dosages, spermatogenesis, sex hormone levels, and the reproductive potential of spermatozoa in rats are impacted.[34]

2.2.2.7. Genotoxic effects. A Reliene study found that in utero exposure to AgNPs resulted in a high frequency of 70 kb DNA deletions in the RPE of infected mice. A daily dose of AgNPs was given to the ladies during their pregnancies between 9.5 and 13.5 days. There are

Table 6: Hematological values for male and female rats after 90-day oral administration of silver nanoparticles (mean ± SD).

	Dose (mg/Kg)			
	0 (n=8)	30 (n=10)	125 (n=10)	500 (n=9)
WBC				
Male rat	8.33 ± 1.25	8.22 ± 1.44	8.17 ± 1.28	8.21 ± 1.07
Female rat	5.46 ± 1.36	5.46 ± 1.36	5.11 ± 0.67	5.90 ± 0.97
RBC				
Male rat	8.98 ± 0.32	9.13 ± 0.66	8.88 ± 0.24	9.07 ± 0.35
Female rat	8.46 ± 0.22	8.41 ± 0.34	8.19 ± 0.32	8.28 ± 0.24
Hb				
Male rat	16.67 ± 0.40	16.76 ± 1.10	16.47 ± 0.53	16.93 ± 0.68
Female rat	16.24 ± 0.81	16.16 ± 0.75	15.82 ± 1.02	16.14 ± 0.85
HCT				
Male rat	36.96 ± 1.41	37.80 ± 2.90	36.97 ± 1.46	37.84 ± 2.12
Female rat	34.45 ± 2.50	34.40 ± 1.80	34.33 ± 1.82	34.51 ± 2.13
MCV				
Male rat	41.17 ± 0.58	41.38 ± 0.72	41.62 ± 0.77	41.72 ± 0.92
Female rat	40.70 ± 1.96	40.91 ± 1.62	41.95 ± 1.81	41.71 ± 2.45
MCH				
Male rat	18.58 ± 0.34	18.34 ± 0.40	18.55 ± 0.58	18.67 ± 0.37
Female rat	19.20 ± 0.56	19.24 ± 0.81	19.34 ± 1.36	19.50 ± 0.96
MCHC				
Male rat	45.13 ± 1.08	44.38 ± 1.31	44.59 ± 1.69	44.79 ± 1.25
Female rat	47.21 ± 1.80	47.02 ± 1.63	46.09 ± 1.96	46.84 ± 2.41
RDW				
Male rat	17.98 ± 0.78	17.83 ± 0.68	17.83 ± 1.04	18.10 ± 0.86
Female rat	19.33 ± 2.44	19.18 ± 2.62	18.85 ± 2.55	19.04 ± 2.46
PLT				
Male rat	738.22 ± 53.33	731.56 ± 105.79	725.40 ± 45.43	718.50 ± 72.05
Female rat	765.75 ± 110.30	718.30 ± 68.56	712.70 ± 55.93	688.89 ± 34.71
MPV				
Male rat	6.86 ± 0.29	6.84 ± 0.19	6.83 ± 0.27	6.64 ± 0.28
Female rat	6.56 ± 0.71	6.74 ± 0.21	6.95 ± 0.28	6.70 ± 0.22
NEU				
Male rat	26.13 ± 3.30	26.72 ± 3.14	26.76 ± 4.14	27.12 ± 2.62
Female rat	24.93 ± 2.88	27.37 ± 3.70	26.32 ± 6.70	24.06 ± 3.49
LYO				
Male rat	69.77 ± 3.39	68.21 ± 3.45	68.93 ± 5.30	69.34 ± 3.13
Female rat	71.48 ± 3.83	68.32 ± 4.60	69.59 ± 7.53	71.22 ± 3.83
MONO				
Male rat	3.78 ± 0.80	4.57 ± 1.12	3.98 ± 1.19	3.35 ± 0.80
Female rat	3.00 ± 1.17	3.85 ± 1.13	3.65 ± 0.79	4.54 ± 0.60*
EOS				
Male rat	0.25 ± 0.40	0.39 ± 0.50	0.25 ± 0.21	0.15 ± 0.08
Female rat	0.42 ± 0.52	0.36 ± 0.17	0.39 ± 0.37	0.18 ± 0.15
BASO				
Male rat	0.08 ± 0.14	0.12 ± 0.22	0.09 ± 0.08	0.04 ± 0.03
Female rat	0.17 ± 0.25	0.11 ± 0.09	0.15 ± 0.19	0.01 ± 0.02

Table 7: Effect of 28-day oral administration of silvernanocolloid

AgNPs dose (ppm)/group	CD3 T cells	CD19 B cells	CD4+ Th cells	CD8+ Tc cells	CD4+CD8+ DP T cells	CD3- CD49b+ NK Cells	CD3+ CD49b+ NKT cells	CD4:CD8 ratio
0 (control)	58.125 ±9.046	43.275 ±4.852	40.15 ±6.469	8.41 ±1.07	1.597 ±0.258	2.557 ±1.057	1.241 ±0.372"	4.786 ±0.646
0.25	66.52 ±3.059	38.78 ±3.657	48.44 ±2.987	9.824 ±0.508	2.812** ±0.452	0.712** ±0.305	0.366*** ±0.141	4.462 ±0.594
2.5	45.65 ±12.848	52.825 ±7.91	35.225 ±8.843	7.922 ±1.723	2.535* ±0.632	1.351 ±0.706	0.584** ±0.252	4.936 ±0.301
25	59.7 ±1.509	42.64 ±1.467	44.8 ±3.717	7.6 ±0.28	1.74 ±0.12	2.42 ±0.382	1.47± 0.253	5.897* ±0.477

How the data is presented: Means SD (standard deviation) For the control and experimental groups, the *p-values (**p-values 0.01 and ***-p-values 0.01 respectively) show that there is significant difference.

Table 8: Comparing the number of Leydig cells in experimental and control groups

Groups	**Number of Leydig cells in each field (mean±SD)s**
Control (A)	22 ± 3.39
Experimental (B) 25 mg/kg	21.4 ± 2.30*
Experimental (C) 50 mg/kg	20.4 ± 2.30*
Experimental (D) 100 mg/kg	19.8 ± 0.83*
Experimental (E) 200 mg/kg	18.4 ± 0.54*

* Statistically significant difference ($p<0.05$) between experimental and control groups.

Table 9: Concentration of FSH, LH and testosterone in different groups

Groups	**FSH concentration (MIU/ml) (mean ± SD)**	**LH concentration (MIU/ml) (mean ± SD)**	**Testosterone concentration (mg/ml) (mean ± SD)**
Control (A)	0.23 ± 0.13	0.19 ± 0.08	4.70 ± 1.39
Experimental (B) 25 mg/kg	0.22 ± 0.10	0.19 ± 0.07	4.70 ± 1.30
Experimental (C) 50 mg/kg	0.19 ± 0.07	0.22 ± 0.12*	3.80 ± 1.64*
Experimental (D) 100 mg/kg	0.21 ± 0.13	0.24 ± 0.05*	3.10 ± 0.74*
Experimental (E) 200 mg/kg"	0.20 ± 0.10	0.37 ± 0.05*	2.30 ± 0.83*

no deletions in the RPE after birth, thus the children were held for 20 days to repair the mutation, and the number of eye spots was counted. Embryonic development is aided by this test because it causes gene expression to be disrupted when an experimental drug is introduced.Wild-type and Myh/mice treated with AgNP had considerably larger rates of DNA deletions than their respective controls. Embryos whose mothers ingested AgNPs during pregnancy underwent large-scale genomic rearrangements, according to these findings.

2.2.2.8. Cancer. Animal studies have demonstrated the ability of AgNPs to cause oxidative stress in rats as well as cell death and necrosis. There are several ways in which AgNPs can induce cell death and damage to the DNA of cells, including oxidative DNA damage, DNA strand breakage, phosphorylated histone H2AX (g-H2AX) foci and the creation of micronuclei. Acidic stomach conditions may alter AgNPs' chemical properties, causing them to have distinct effects on cultivated cells as well as animals who ingested them. Examples include citrate-coated AgNPs that aggregation and partial reactivity to AgCl in synthetic human stomach fluid Citrate-coated AgNPs were shown to have just a 1% to 4% systemic bioavailability when fed orally in rats, according to another study. As a result, it is still unknown if AgNPs cause oxidative damage or if they are genotoxic when consumed orally.

2.2.3. Dermal exposure

2.2.3.1. Death. No mortality rate was recorded up to 10000 μg/mL of silver nanoparticles in guinea pigs.

2.2.3.2. Systemic effects. In Guinea Pigs, it has been found that silver nanoparticles absorbed via the skin can cause heart, bone, and kidney damage. They can be harmful depending on their size and form as well as the chemical composition and surface area of the nitrates they are made up of. Additionally, this study looked at the route of administration and how often the drug was taken. The interaction patterns of silver particles with subcellular

components may alter with each major change in their size. Indeed, silver nanoparticles were shown to have a bigger surface area, more silver ions released, and direct contact with RBCs, which led to higher levels of in vitro hemolysis than micronized particles. An increase in Kupffer cells, hyperemia, swelling of the liver cells, and an alteration in lipid composition were all shown to be time-dependent in studies on mice that examined the liver's pathology.[35]

2.2.4. Reproductive effects

A wide variety of commercial goods, including contraceptives and feminine hygiene products, presently include silver nanoparticles. Through mitochondrial dysfunction and membrane leaking, silver nanoparticles damaged germline stem cells and induced apoptosis to occur.[36]

3. Toxicokinetic

Despite the fact that most toxicological research on silver nanoparticles has focused on inhalation and oral delivery, skin contact is the most common route via which humans are exposed to these nanoparticles.

4. Conclusion and Future Prospective

Currently available information on Ag-NPs focuses on the health consequences of inhalation, oral, and cutaneous exposure to silver on people and animals. In order to demonstrate the current state of knowledge on the health impacts of silver nanoparticles, the data presented here will be used. Case reports and animal research are the only sources of information that have been discovered so far. There are not enough facts to pinpoint a certain organ as a target. Acute-duration exposure pharmacokinetic data, which would have been useful in identifying target organs across routes, was also missing. In order to better understand how site-specific factors affect toxicity, silver nanoparticle toxicity data would be helpful. For the better understanding of effect of silver nanoparticles on humans further studies are needed.

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6. Compliance With Ethics Requirements

In this article, there are no research involving human or animal participants.

7. Source of Funding

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8. Conflict of Interest

None.

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