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REVIEW

Biological Safety Analysis of Nanoparticles: Exploring Toxicity, Mechanisms, and Safety Factors for Pharmaceuticals

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Background: With the rapid advancement of nanotechnology, nanoparticles (NPs) have been widely applied in fields such as drug delivery, medical imaging, and disease therapy, owing to their unique physicochemical and biological properties. However, as NPs become increasingly prevalent in industrial production and daily life, the frequency and routes of human exposure have significantly increased, making the safety issues arising from their interactions with biological systems a major focus of public health concern.

Methods: This review systematically retrieved relevant literature from databases including PubMed and Web of Science over the past 15 years, focusing on toxicological studies of NPs at the organ and system levels.

Results: It summarizes the key mechanisms of nanotoxicity and the critical factors influencing safety evaluation. The findings indicate that NPs toxicity primarily targets the liver, kidneys, nervous system, and immune system. Oxidative stress, inflammatory responses, and DNA damage represent the major common mechanisms of nanotoxicity, while physicochemical properties such as particle size, surface charge, and protein corona formation are the core factors affecting safety.

Conclusion: Based on these findings, this review analyzes the limitations of existing research in the context of the current research landscape, aiming to provide theoretical support for the safe application of NPs and to offer a reference for the establishment of a systematic nanotoxicity safety evaluation framework.

Keywords: nanoparticles, biological safety, toxicity mechanism, safety factors

Introduction

Nanoparticles (NPs) refer to a class of tiny particles where at least one dimension in their three-dimensional spatial scale ranges from 1 to 100 nanometers (nm), with sizes falling between individual atoms/molecules and macroscopic materials. This unique scale endows NPs with distinctive physical, chemical, and biological properties: the small-size effect enables them to easily penetrate biological barriers, the high specific surface area enhances their interactions with biomolecules, and the surface activity allows flexible regulation of their biological targeting ability.[1] Leveraging these advantages, NPs have been widely applied in fields such as drug delivery, medical imaging, and food additives, and have become one of the core materials driving technological innovations across multiple disciplines.[2–4]

However, with the extensive penetration of NPs into manufacturing fields and daily life scenarios, they have transformed from a type of specialized technical material into non-negligible environmental and biological exposure factors. Throughout their entire life cycle (production, use, and disposal), NPs may enter organisms through multiple pathways, including inhalation, dermal contact, oral ingestion, and intravenous injection. Early studies, limited by detection technologies and experimental models, once assumed that some NPs possessed good biocompatibility and were even used as "safe carriers" in

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the food and pharmaceutical fields. In recent years, however, with the in-depth development of nanotoxicology research, a growing body of evidence has demonstrated that due to their nanoscale size and unique surface properties, NPs are difficult to be efficiently degraded or cleared by the metabolic systems of organisms, leading to gradual accumulation in organs or tissues such as the liver, kidneys, and spleen. This accumulation effect further amplifies the interactions between NPs and cells, tissues, and organs, disrupts the physiological balance of the organism, and triggers potential toxic risks.

Existing studies have shown that NPs exposure can induce adverse effects such as hepatotoxicity, nephrotoxicity, neuroinflammation, and immunotoxicity. However, several critical knowledge gaps remain. First, the causal links between specific physicochemical properties and toxicological outcomes are poorly understood due to the lack of systematic structure–activity relationship studies. Second, the long-term health effects of chronic low-dose NPs exposure—a scenario more relevant to real-world conditions—remain largely unexplored. Third, most nanotoxicity assessments focus on single NPs types under idealized conditions, while real-world exposure involves complex NPs mixtures, whose potential synergistic or antagonistic effects are virtually unknown. Meanwhile, regulatory frameworks face major challenges, including the absence of standardized testing protocols, validated in vitro–in vivo extrapolation models, and appropriate dose metrics. These issues collectively impede the development of systematic nanotoxicity safety evaluation frameworks and the safe translation of nanotechnology.

Therefore, greater emphasis must be placed on the toxicological assessment of NPs to ensure their safety in applications across various fields. This issue has been identified by institutions such as the United States Environmental Protection Agency (EPA), the World Health Organization (WHO), and the Organization for Economic Co-operation and Development (OECD), and has attracted widespread attention in the scientific community. According to surveys, the number of scientific articles published on "nanotoxicity" or "nanotoxicology" in the past decade has gradually increased (based on the Web of Science database, there are approximately 6148 such articles to date, while the number was almost negligible before 2005).

Applications

Owing to their unique physicochemical properties, NPs have been widely applied in multiple critical fields of production and daily life, covering the pharmaceutical, food, and industrial sectors. Their specific application scenarios are shown in Figure 1 and Table 1. Among these fields, the pharmaceutical sector is where the application of NPs is most concentrated and the research is most in-depth, mainly manifested in the construction of drug delivery systems, disease treatment and adjuvant therapy, diagnostic imaging, and other aspects. The details of these applications are illustrated in Figure 2, and the representative marketed nanomedicines are also presented in Table 2.

In terms of disease treatment, NPs can exert therapeutic effects on a variety of diseases, including diabetes and its complications, allergic inflammatory responses, amyotrophic lateral sclerosis (ALS), and diseases induced by oxidative stress (eg, Alzheimer's disease, ischemic stroke, retinal damage, chronic inflammation, and cancer).[15,17,30,42] Meanwhile, NPs also exhibit significant advantages in adjuvant therapy: they can assist in tumor phototherapy, synergize with chemotherapy and photothermal therapy, and enhance the efficacy of chemodynamic therapy and photodynamic therapy.[11,14,27,39] As drug and gene delivery carriers, certain NPs can function as oxygen generators to alleviate hypoxic tumor microenvironments, while also loading drugs to facilitate their attachment to cancer cells.[40,59] Alternatively, NPs can be used in the field of bone tissue engineering to promote cell growth and tissue regeneration.[19,47] Furthermore, within tissues, they can act as nanozyme, exerting anti-inflammatory, anticancer, and angiogenesis-promoting effects.[41] In the fields of diagnostic imaging and therapy, the application of metal NPs is widespread. They can serve as contrast agents and diagnostic tools for optical imaging, Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), Computed Tomography (CT), ultrasound imaging, and multimodal imaging for early diagnosis.[9,25,26,37,45]

In addition to their role in medicine, NPs can be applied to food as anti-caking agents, adsorbents, thickening agents, and other additives in food products.[3,4] In industrial applications, metal NPs, as pigments, can fully leverage their unique optical properties, excellent stability, and advantages of the small size effect.[8]

Systemic Toxicity

NPs can enter the body by inhalation, skin, oral and intravenous injection. On the one hand, it will have toxic side effects on target organs or metabolic organs such as lungs, liver and kidneys. On the other hand, it can also reach other tissues

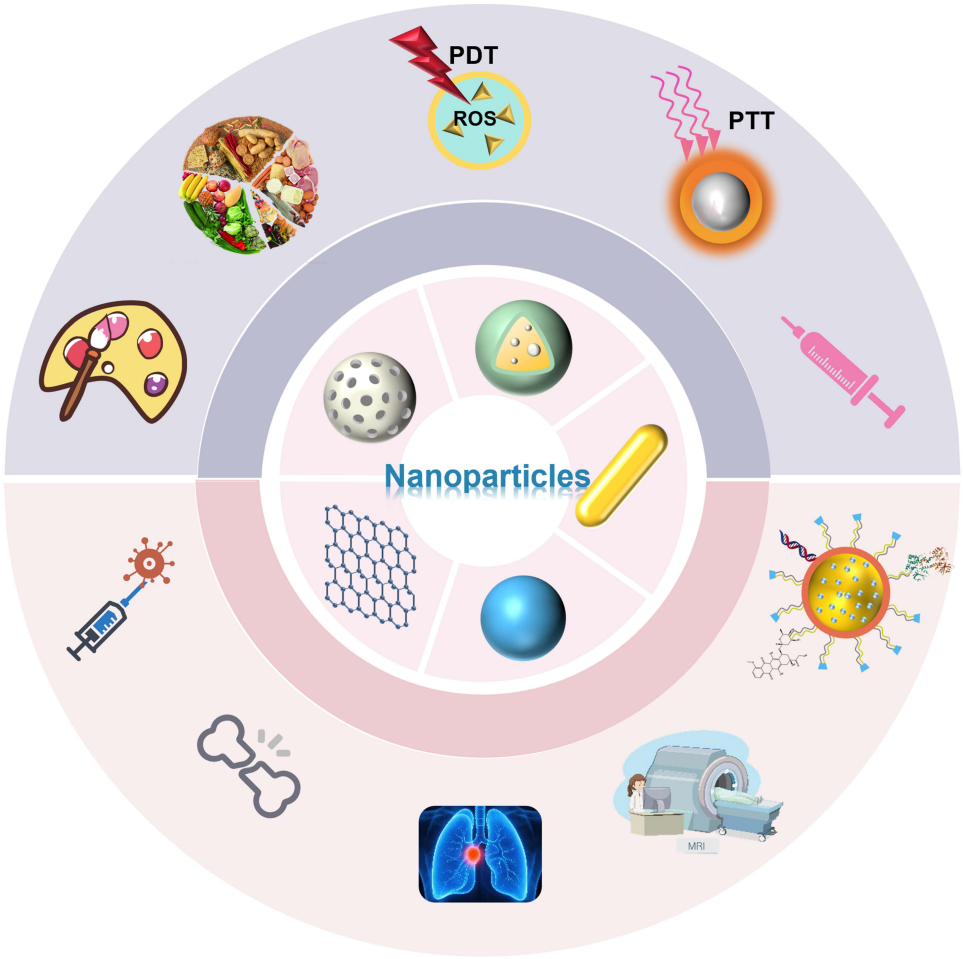

Figure 1 The Applications of Nanoparticles. Nanoparticles come in various shapes such as spherical, rod-like, and mesh-like etc, they are widely used, not only used as pigments and food additives, but also extensively applied in fields such as photothermal therapy, therapeutic agents, drug delivery systems, molecular imaging, biosensors, tissue engineering, and vaccine adjuvants.

through the blood circulation and cause tissue damage and systemic damage. Certain NPs with special properties can also cross the Blood-Brain Barrier (BBB) and cause nerve damage. In this section, the damage of NPs to various tissues or systems is summarized by classifying toxicity in general tissues from a macroscopic perspective. The organ and systemic toxicity of NPs is detailed in Figure 3 and Table 3.

Table 1 Application of Representative Nanoparticles

Type	Name	Application	Reference
Metal	TiO_2 NPs	Food whitening agent	[5–7]
		Pigment	[8]
		Contrast agents, diagnostic agents and therapeutic agents	[9]
		Drug delivery	[10]
		Tumor phototherapy, Photothermal therapy (PTT)	[11]
		Tissue regeneration	[12]

(*Continued*)

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Table 1 (Continued).

Type	Name	Application	Reference
	ZnO NPs	Drug delivery	[13]
		Synergistic chemotherapy and photothermal therapy for tumor treatment	[14]
		Treatment of diabetes and diabetic complications	[15,16]
		Allergic inflammatory response	[17]
	Al_2O_3 NPs	Antacid ingredients	[18]
		Bone repair and porcelain dental materials	[19]
		Drug loading, controlled drug targeting release	[20,21]
		Vaccine adjuvant	[22]
	AuNPs	Antibacterial agent	[23,24]
		Bioimaging	[25,26]
		Photothermal therapy	[27]
		Biosensor	[28,29]
		Treatment of amyotrophic lateral sclerosis	[30]
	IONPs	Neuroimaging	[31–34]
		Drug and gene delivery	[35,36]
		Iron deficiency in chronic kidney disease (CKD), Liver lesion imaging, lymph node metastasis imaging	[37,38]
	CuO NPs	Load drugs to facilitate their attachment to cancer cells	[39,40]
		Chemodynamic and photothermal synergistic therapy, Copper death therapy	[39]
	CeO_2 NPs	Anti-inflammatory, anti-cancer, and pro-angiogenic	[41]
		Treatment of oxidative stress-induced diseases, such as Alzheimer's disease, ischemic stroke, retinal damage, chronic inflammation, and cancer.	[42]
Non-metal	SiO_2 NPs	Food additive, SiO2 (E551), as an anti-caking agent; adsorbent; thickening agent; clarifying agent; filter aid; carrier, etc, in food additives	[3,4]
		Drug delivery and cancer therapy	[43,44]
		Optical imaging, magnetic resonance imaging (MRI), positron emission tomography, computed tomography, ultrasound imaging, and multimodal imaging for early diagnosis	[45]
	GO-NPs	Cell growth scaffold	[46]
		Promote the adhesion, proliferation, and differentiation of stem cells; for use in bone tissue	[47]
		Determination of glucose content, bacterial analysis, and detection of DNA and proteins	[48]
		Drug carrier	[49]
		Photothermal therapy (PTT)	[50]
	PEG NPs	Enhance drug targeting	[51]
		Promote cell growth and tissue repair	[52]
		Biosensor	[53]
		Controlled drug release	[54]

(*Continued*)

Table 1 (Continued).

Type	Name	Application	Reference
	Liposome	Drug delivery	[55,56]
		Radioactive tracer	[57]
		Probe carrier	[58]
	HB	Oxygen generator	[59,60]
		Drug carrier	[61]

Hepatotoxicity

Upon ingestion and subsequent entry into the systemic circulation as drug carriers, NPs may accumulate in potential target organs. Notably, NPs tend to accumulate in the liver to a greater extent than in other organs, where they may interact with hepatocytes. This interaction plays a critical role in determining the in vivo fate of NPs and the manifestation of hepatotoxicity. Presently, research on the hepatotoxicity of NPs primarily focuses on organ- and cellular-level investigations.

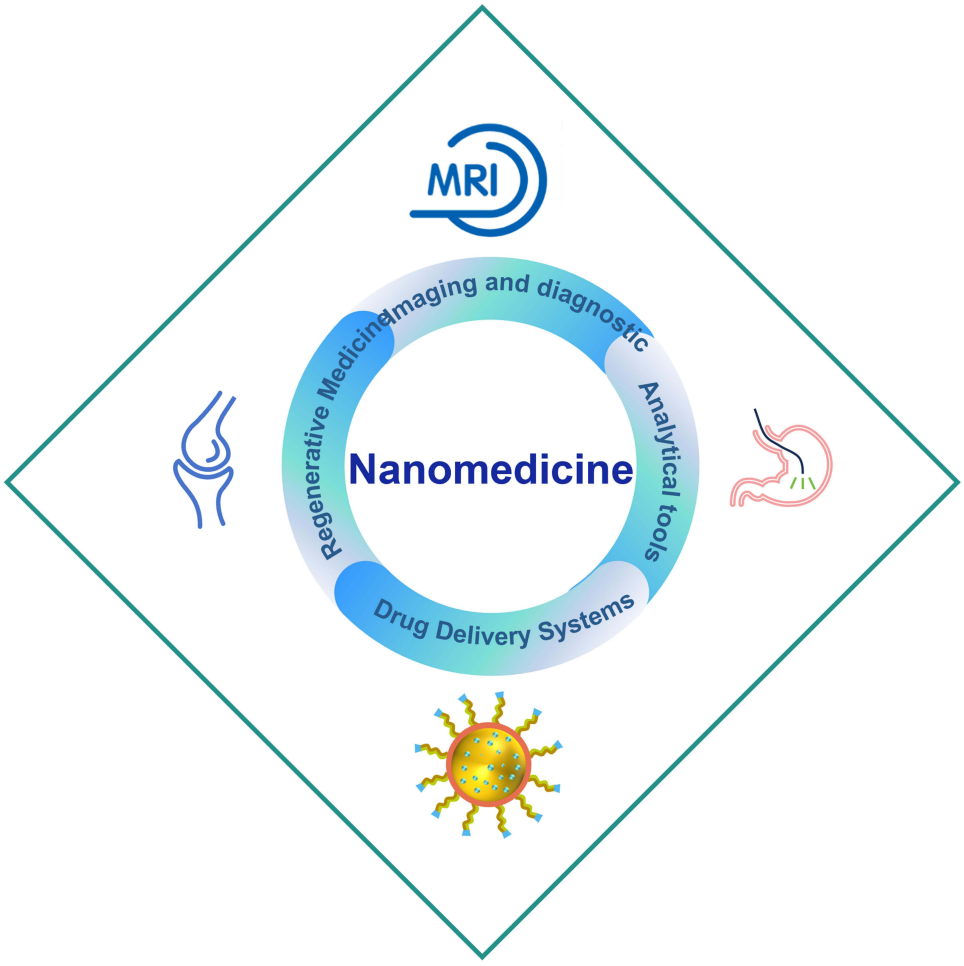

Figure 2 Application of Nanotechnology in Human Medicine. Nanotechnology is now widely used in medicine in regenerative medicine, imaging and diagnostics, analytical tools and drug delivery systems.

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Table 2 Representative Marketed Nanomedicine

Type	Active Ingredient	Carrier	Indication	Approval	Reference
Nanocrystalline drugs	Aristan	–	Prevention of acute and delayed nausea and vomiting caused by highly emetogenic antitumor chemotherapy drugs	2003	[62]
	Rapamycin	–	Macrolide immunosuppressants	2010	[63]
	Dantrolene sodium	–	Malignant hyperthermia	2014	[64]
Liposomes nanomedicine	Doxorubicin	Zwitterionic phosphatidylcholine, negatively charged phosphatidylglycerol, and cholesterol	Metastatic ovarian cancer and HIV-associated Kaposi's sarcoma	1995	[65]
	Amphotericin	DMPC and DMPG	Antifungal drugs	1995	[66]
	Vitiloxifene	DMPC and EPG	Subretinal choroidal neovascularization caused by wet age-related macular degeneration	2000	[67]
	Paclitaxel	Phosphatidylcholine, cholesterol	Ovarian cancer, non-small cell lung cancer, breast cancer	2003	[68]
	Bupivacaine	Cholesterol, 1,2-Dipalmitoyl-sn-glycero -3-phospho-(1'-rac-glycerol) (sodium salt), Tricaprylin, 1,2-Dierucoyl-sn-glycero -3-phosphocholine	Postoperative local analgesia	2011	[69]
	Vincristine sulfate	Phospholipids, cholesterol	Philadelphia chromosome-negative acute lymphoblastic leukemia in adults	2012	[70]
	Irinotecan	DSPC, Chol, DSPE-MPEG2000	Metastatic pancreatic cancer	2015	[71]
	Daunorubicin	Phospholipids, sphingomyelin, and cholesterol	Treat acute myeloid leukemia	2017	[72]
	Amikacin hydrochloride	Cholesterol, dipalmitoylphosphatidylcholine	Antibiotics	2018	[73]
	mRNA Vaccines	DSPC, cholesterol, cationic lipids, PEG-modified lipids	Prevent COVID-19 infection	2020	[74]
	Mitoxantrone Hydrochloride	Hydrogenated soy phosphatidylcholine, egg phosphatidylethanolamine, cholesterol	Relapsed/Refractory acute myeloid leukemia	2022	[75]
Polymer nanomedicine	Recombinant human erythropoietin	Methoxy Polyethylene Glycol	Anemia	2018	[76]
	Triamcinolone acetonide	Poly(lactic-co-glycolic acid)	Knee arthritis	2017	[77]
	Leuprolide	DSPC, cholesterol, DSPE-MPEG2000	Prostate cancer	2002	[78]
	Paclitaxel	Polyethylene glycol-poly(lactic acid)	Ovarian cancer, non-small cell lung cancer, breast cancer, pancreatic cancer, etc	2006	[79]
Protein nanomedicine	Paclitaxel	Albumin	Metastatic breast cancer, lung cancer, pancreatic cancer, etc	2005	[80]
	Diphtheria toxin	Genetically engineered recombinant fusion protein (containing IL-2)	Leukemia, T-cell lymphoma	1999	[81]

(*Continued*)

Table 2 (Continued).

Type	Active Ingredient	Carrier	Indication	Approval	Reference
Inorganic nanomedicine	IONPs	Multichain carboxymethyl polysaccharide encapsulation	Anemia, contrast agent	2009	[82]
	Hafnium Oxide NPs	-	Locally advanced squamous cell carcinoma	2019	[83]
	Carboxymaltose iron colloid	Ferumoxytol	Iron-deficiency anemia	2013	[84]
Viral vector nanomedicine	Murine leukemia virus	Carrying an N-terminally truncated human ccng1 construct	Lung cancer, breast cancer, colorectal cancer, etc	2007	[85]
	P53	Recombinant adenovirus	Head and neck squamous cell carcinoma, lung cancer, etc	2004	[86]

Titanium dioxide (TiO_2) NPs were initially considered harmless substances; however, with the advancement of research, their low toxicity has been called into question. Studies have found that TiO_2 NPs are a major component of environmental pollutants, with as much as 760 tons of these particles entering soils each year through wastewater and sludge.[87,88] TiO_2 NPs have been classified by the International Agency for Research on Cancer (IARC) as a Group 2B carcinogen, meaning they are possibly carcinogenic to humans.[89] The European Union (EU) announced a ban on its use in food starting in August 2022. Oral administration of TiO_2 NPs induces hepatotoxicity, manifested as disruption of biomarkers and imbalance in the oxidative and antioxidant systems,[90] while intraperitoneal injection of TiO_2 NPs has been observed to result in mitochondrial damage in the liver and hepatocyte apoptosis.[91] A single administration of

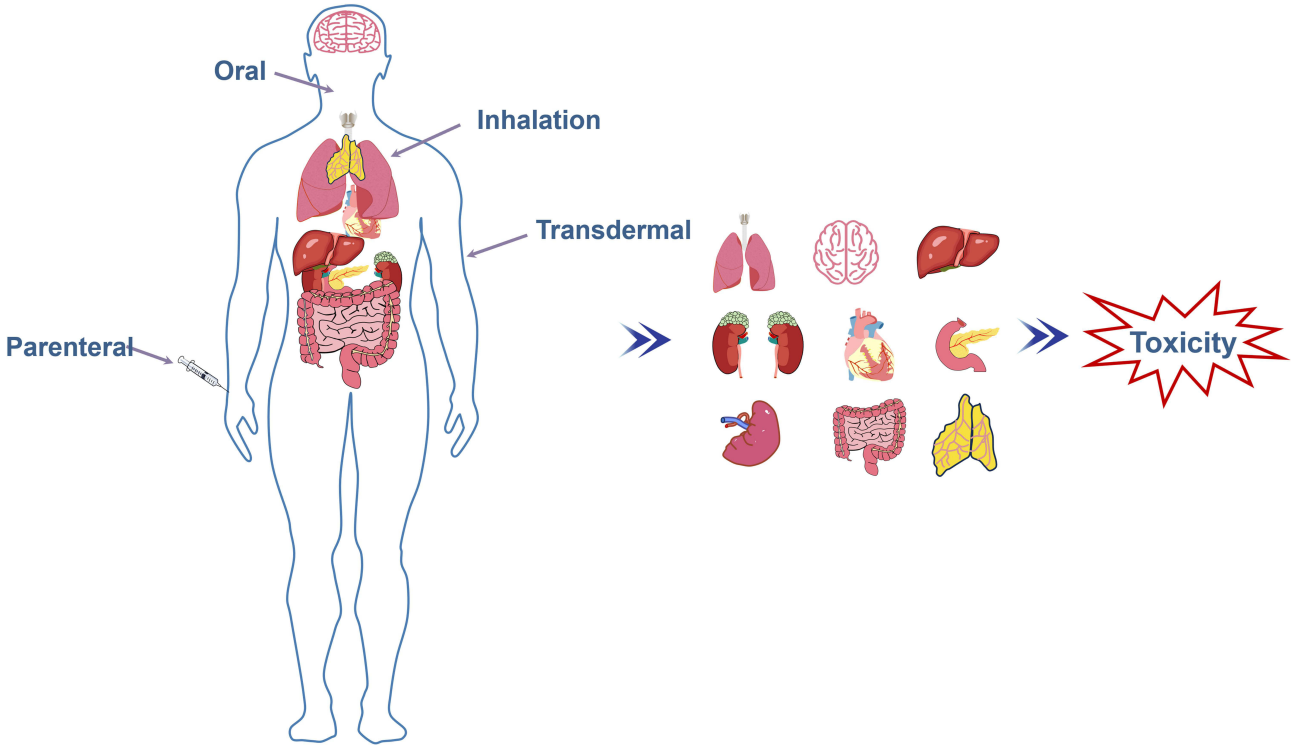

Figure 3 Systemic Toxicity of Nanoparticles. Nanoparticles can enter the human body through various means such as oral ingestion, inhalation, injection, and transdermal absorption, thereby causing toxic effects on numerous tissues and organs including the lungs, brain and nervous system, liver, kidneys, heart, intestines, reproductive system, as well as embryos and the immune system.

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Table 3 OrganSystem Toxicity of Nanoparticles

		Hepatotoxicity	Nephrotoxicity	Neurotoxicity	Pulmonary Toxicity	Reproductive and Embryotoxicity	Enterotoxicity	Immunotoxicity	Cardiotoxicity
Metal oxides	**TiO2 NPs**	√	√	√	√	√	√	√	√
	ZnO NPs	√	√	√	√				
	Al_2O_3 NPs	√	√	√					
	IONPs	√	√	√	√			√	√
	CuO NPs						√		
	CeO_2 NPs						√		
Metal	**AuNPs**	√	√	√			√	√	
	AgNPs								√
	CuNPs						√		
Non-metal	**SiO_2 NPs**	√			√			√	
	GO-NPs					√		√	
	Fullerenol NPs					√			
	PEG NPs							√	

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5 g/kg of TiO_2 NPs according to the OECD procedure revealed eosinophilic degeneration and patchy necrosis of hepatocytes around the central vein of the liver in mice.[92] Furthermore, studies have detected residual TiO_2 in the liver of humans who have received titanium implants.[93]

The hepatotoxicity of ZnO NPs has been reported across a range of toxicological studies, from cellular models to animal studies.[94] The inclusion of ZnO NPs in the diet has been linked to liver damage, while both intraperitoneal (i.p.) and intravenous (i.v.) administration of ZnO NPs have been shown to induce hepatotoxicity.[95,96] Inflammatory cell infiltration, dilated hepatic sinusoids, Kupffer cell proliferation, necrosis and other changes in liver tissues were observed in rats after 21 days of exposure to ZnO NPs.[97] Additionally, studies have found that ZnO NPs can induce various symptoms of liver damage, such as decreased GSH levels and increased Lactate Dehydrogenase (LDH) and Malondialdehyde (MDA) levels.[98] In addition to single-agent administration, co-administration of ZnO NPs (80 μg/kg) and CeO_2 NPs (50 μg/kg) at extremely low doses has also been shown to induce oxidative stress-mediated inflammation and result in liver necrosis.[99] However, modification of ZnO NPs can reduce their hepatotoxicity. For instance, MgO/ZnO core/shell NPs (MgO/ZnO CS NPs), synthesized from MgO and ZnO, exhibited no severe degeneration or necrosis at a dose of 10 mg/mL, with toxicity significantly lower than that of ZnO NPs administered alone.[100]

The liver has been identified as the primary organ where Al_2O_3 NPs accumulate during biodistribution within the body.[101] Some studies have demonstrated its ability to increase p53 and Nrf2 levels, to reduce Hsp70 levels, and to promote apoptosis in liver tissue.[102] Al_2O_3 NPs also induced a significant decrease in all antioxidant parameters (eg, Superoxide Dismutase (SOD), and Glutathione (GSH), and Catalase Activity (CA) in rat liver, and an even lower decrease in antioxidant parameters was observed after combining ZnO NPs.[103]

Hepatotoxicity of Iron Oxide Nanoparticles (IONPs) may be correlated with COX-2 mediated ER-mitochondrial Ca^{2+}.[104] Focal areas of perivascular round cell aggregates as well as necrosis in the liver of mice exposed orally to IONPs for 28 days.[105] Moreover, IONPs can disrupt lipid metabolism through the gut-liver axis, indirectly contributing to liver injury.[106]

In addition to metal oxide NPs, the hepatotoxicity of AuNPs has also been reported. Following injection, AuNPs can persist in the liver and spleen for up to 7 days, inducing acute inflammatory responses and hepatocyte apoptosis.[107] AuNPs exacerbate other disease-induced liver injury, such as aggravating the hepatotoxic effects of LPS by amplifying Reactive Oxygen Species (ROS)-dependent crosstalk in hepatic macrophages and hepatocytes.[108] Alternatively, it worsens adriamycin-induced liver injury by inhibiting metabolic enzyme activities and the Nrf2/antioxidant axis in the liver.[109–111] SiO_2 NPs are also capable of promoting hepatic steatosis and liver injury, which exacerbate the progression of metabolic fatty liver disease.[112]

Nowadays, a multitude of new techniques have been used to evaluate the hepatotoxicity of NPs, including inductively coupled plasma-atomic emission spectroscopy,[96] liver organoids,[113] signaling pathways analyzed by Gene Expression Omnibus Dataset,[114] Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) Metabolomics-based analysis,[115] various hepatocyte models,[116] etc. It is believed that with the development of the technology, the mechanism of liver injury by NPs will become better understood, which will be of greater help for future research.

Nephrotoxicity

The kidney, as an important eliminatory organ of nanomedicines, depends on size in terms of both the clearance pathway and intra-organ transport.[117–119] In general, NPs smaller than 6 nm are more readily filtered and cleared by the kidneys, while larger NPs are unable to pass through the glomerular filtration barrier (GFB), leading to their accumulation in glomerular and tubular cells, which disrupts normal kidney function by causing oxidative stress, DNA damage, inflammation, and autophagy.[119] Exploring the damage caused by NPs to the kidneys is essential for a more comprehensive understanding of the clearance process of NPs in vivo.

TiO_2 NPs exhibit only slight toxicity at lower concentrations when co-cultured with IP15 cells.[120] However, prolonged administration or high doses may lead to oxidative stress and cause damage to the kidneys. Small-sized TiO_2 NPs (5 nm, 6.9 nm) accumulate in the kidneys and induce significant histopathological changes.[121,122] The renal toxicity of TiO_2 NPs is manifested in several ways, including the upregulation of IL-2, IL-4, IL-6, and NF-κB, as well as the attenuation of antioxidant stress responses in renal tissue cells.[123,124] It causes injury to proximal renal tubular cells, as well as tubular dilation and cellular desquamation;[125] and activation of the TGF-β/SMAD/p38MAPK and Wnt

signaling pathways, which contribute to renal fibrosis in rats.[126–128] Additionally, studies have reported on the safety of TiO_2 NPs in relation to kidney function.[129] Therefore, the nephrotoxicity of TiO_2 NPs should not be generalized. Their potential effects and mechanisms of action on the kidneys must be thoroughly investigated, using the human maximum exposure criterion, to gain a deeper understanding of their safety and potential risks.

ZnO NPs are among the most nephrotoxic metal NPs when compared to other types of NPs.[120,130–132] Lipidomic analysis revealed that 3 nm ZnO NPs exhibited the highest toxicity in renal cells, primarily by disrupting sphingolipid metabolism and autophagy processes through the elevation of ceramide levels.[133] It was demonstrated that the toxicity of ZnO NPs is associated with TRPML1 channel activation, which mediates the release of Zn^{2+} and induces autophagy and cell death in human kidney cells.[134,135] HIF is one of the targets through which ZnO NPs induce kidney injury. Treatment with ZnO NPs in HEK-293 cells and BALB/c mice resulted in a significant increase in the expression of HIF-1α, along with changes in renal pathology, serum creatinine, and blood urea nitrogen levels.[136,137] CuO/ZnO core/shell NPs (CuO/ZnO CS NPs), synthesized from CuO and ZnO, induced significant kidney injury in mice when administered via gavage at a dose of 20 mg/L. However, at a dose of 40 mg/L, the extent of kidney injury was alleviated, exhibiting a unique pattern of "more significant injury at lower doses." This phenomenon may be attributed to the adaptive response of mice to nanoparticle exposure at higher doses, specifically through "reduced absorption or accelerated excretion".[138]

Polyethylene Glycol-AuNPs (PEG-AuNPs) (45 nm) significantly induced fuzzy swelling, edema, and vacuolar degeneration in multiple regions of the epithelial lining of the mouse renal tubules.[139] LA-ICP-MS imaging clearly delineated the pathways of PEG-AuNPs in the kidney. One hour after injection, PEG-AuNPs rapidly entered the kidney via the bloodstream, accumulating primarily in the renal cones and renal pelvis. Four hours later, the signal in the renal pelvis weakened, while the signal in the renal cone region increased. After 24 hours, the signal was concentrated in the renal medulla and renal cortex.[140] It was found that AuNPs also exacerbate renal damage caused by certain nephrotoxic substances (CDPP, PQ, 5-ASA) by increasing levels of renal blood urea nitrogen (BUN), creatinine (Cr), and IL-6.[141] Therefore, treatments or diagnostic imaging involving preparations containing AuNPs should be avoided in patients with renal injury induced by related substances.

IONPs, commonly used as MRI contrast agents, can also exacerbate kidney damage to some extent. Szalay et al found that IONPs induced a viable, concentration-dependent decrease in Vero cells (African green monkey kidney cell line) after 24 hours of exposure.[142] Kumari et al showed that 28 days of repeated oral administration of IONPs led to focal tubular injury and red medullary congestion in the kidneys.[105] Another study found that a ten-day gavage of IONPs increased MDA levels, a marker of oxidative stress, altered blood chemistry biomarkers (such as total bilirubin [TBil], blood urea nitrogen [BUN], and creatinine [CREA]), and induced damage and desquamation of renal tubular epithelial cells in mice. Additionally, the study suggested that pomegranate extracts could help alleviate the kidney damage caused by IONPs.[143]

Aluminum is added to various daily products and is now reported to enter the human body through contaminated food and water. Its effects on cellular structures and macromolecules have been observed in both in vitro and in vivo studies, contributing to nephrotoxicity, oxidative stress, apoptosis, and other potential hazards.[144–148] Environmental Al_2O_3 NPs lead to elevated levels of catalase, superoxide dismutase, and thiobarbituric acid-reactive substances, as well as reduced glutathione concentrations in the kidneys of aquatic animals.[149] In addition, Al_2O_3 NPs caused significant increases in mammalian serum urea, creatinine, chloride, calcium, MDA, DNA damage, LDH, Tumor Necrosis Factor (TNF), and Proliferating Cell Nuclear Antigen (PCNA) expression, along with significant decreases in serum potassium, renal SOD, and GSH.[101,150,151] Co-exposure to Al_2O_3 NPs and ZnO NPs results in more pronounced hepatorenal toxicity and systemic inflammation.[103] Similar to many NPs, the relatively high surface area and reactivity of Al_2O_3 NPs contribute to their toxic effects. Therefore, co-exposures of this kind should be minimized to protect biological health and safety.

Neurotoxicity

Neurotoxicity is a potential adverse effect that may be either reversible or irreversible, and it can impact the structure, function, or biochemistry of neurons within the nervous system.[152] Numerous studies have demonstrated that the neurotoxicity of NPs is primarily driven by oxidative stress induced by free radicals.[89] TiO_2 NPs not only reduce PC12 cell viability, induce apoptosis, inhibit synaptic growth, and disrupt the ubiquitin-proteasome system,[153] but they also increase HT22 cell apoptosis through calcium imbalance-mediated endoplasmic reticulum stress.[154] Additionally, TiO_2 NPs enhance BBB permeability and

induce mitochondrial damage, autophagy, neuroinflammation, and apoptosis in primary rat cortical astrocyte cells.[155–157] Compared to other metals, TiO_2 NPs are more likely to induce neuronal apoptosis, cognitive impairment, and synaptic plasticity dysfunction in the offspring of rodents.[158,159] Exposure to TiO_2 NPs during gestation results in neurobehavioral deficits in both the dams and their offspring, which are linked to damage to the gut-brain axis.[160,161] TiO_2 NPs cause anxiety-like behavior, cognitive impairments, and oxidative damage in the hippocampus, particularly during the adolescent stages of neurodevelopment.[162] Neurotoxicity, including mitochondrial dysfunction, apoptosis, and alterations in neuronal structure and function, is observed with adult exposure.[163–165]

As early as 1980, Kozik et al observed morphological changes in the hippocampal cortex and basal ganglia of rats following the ingestion of high doses of ZnO.[166] In 2009, the toxicity of ZnO NPs to neural stem cells was revealed to be related to Zn^{2+}.[167] The neurotoxic effects of ZnO NPs are associated with multiple signaling pathways, primarily including JNK, cAMP/CREB, PINK1/parkin-mediated mitochondrial autophagy, Ca^{2+}-dependent NF-κB, ERK, p38, AK2-STAT3, and CAMK2A/CAMK2B signaling pathways.[168–173] The neurotoxicity of ZnO NPs has also been confirmed in 3D brain organoids.[174]

Research indicates that, in contrast to other crystal forms, η-Al2O3 NPs manifest more pronounced cytotoxic effects on N_2A neuroblastoma cells.[175] γ-Al_2O_3 NPs affect neural stem cell viability and structure at high concentrations.[176] Al_2O_3 NPs impair neurobehavioral function in ICR mice and are more toxic to the brain compared to nanocarbon and micron-sized Al_2O_3 of the same size.[177] Its neurotoxicity is also manifested by altering neurotransmitter levels in rodents, affecting the expression of antioxidant mRNA, causing morphological changes in neuronal cell nuclei and acetylcholinesterase activity, and increasing the expression of β-amyloid protein.[178–180]

AuNPs have relatively low neurological damage than other metals, and can treat neurodegenerative diseases at low doses, yet some neurotoxicity has been reported.[181,182] Dose-dependent toxicity of AuNPs on glial cells and neural progenitor cells.[183] Glucose-coated AuNPs enter the rat brain through the BBB within 10 min of carotid artery injection, resulting in damage to the rat brain antioxidant enzyme glutathione peroxidase, and may further lead to oxidative stress and DNA damage.[184,185]

It has been confirmed that IONPs can cross the BBB and reach the brain directly via the olfactory nerves after nebulized administration. They can also cause pathological changes in the olfactory bulb, hippocampus, and striatum. The mechanism behind their ability to traverse the BBB may be related to the damage they cause to endothelial cells.[186,187] Several studies have reported that exposure to IONPs in rats induces neuroinflammation, activates antioxidant responses and increases α-synuclein expression, decreases dopamine levels, causes degeneration in the hippocampus and striatum.[105,188–191]

Pulmonary Toxicity

As the main organs of the respiratory system, the lungs undertake the key function of gas exchange and are also an important gateway for various substances in the environment to enter the body. Compared with other particle sizes, NPs are more likely to enter and be deposited in the lungs and cause higher toxicity due to their smaller size and higher specific surface area.[192,193]

The pulmonary toxicity of many NPs has been demonstrated. Inhalation of TiO_2 NPs resulted in the formation of two distinct histopathological features of pneumoconiosis in rats, namely Fibrotic Pulmonary Dust Foci and Dust Macules.[194] Inhalation of various doses of TiO_2 NPs resulted in distinct toxic effects. Low doses (0.5 mg/kg) primarily induced lymphocyte and macrophage aggregation, leading to emphysema and rupture of the alveolar septa. In contrast, high doses (4 mg/kg) caused thickening of the alveolar walls and interstitial tissue, along with collapse of the terminal bronchioles.[195] Inhalation of IONPs and ZnO NPs induces considerable lung tissue damage in rats.[196] It was observed that intratracheal instillation of ZnO NPs caused inflammatory cell infiltration in the alveoli of rats.[197] Research has shown that IONPs (22 nm) cause greater destruction of lung epithelial cells compared to submicron (280 nm) IONPs.[198] However, inhalation of micrometer-sized ZnO particles triggered a more pronounced systemic inflammatory response compared to ZnO NPs.[199] This difference in toxicity may be related to the intrinsic properties of the metal particles themselves. The short-term pulmonary toxicity of CuO NPs was primarily characterized by acute lung inflammation and injury, whereas long-term exposure led to chronic inflammation and fibrosis. This toxic effect was associated with increased overexpression and secretion of MMP-3 in the lungs of mice.[200]

In addition to metal oxide NPs, the lungs are also highly sensitive to the toxicity of inhaled SiO_2 NPs. This toxicity primarily occurs through the activation of the VEGFC/D-VEGFR3 signaling pathway in lung and lymphatic tissues, leading to pulmonary inflammation, lymphatic endothelial cell damage, and the formation and remodeling of pulmonary lymphatic vessels.[201] Cationic liposomes can also induce pulmonary toxicity, with polyvalent cationic liposomes being more likely to cause dose-dependent toxicity and lung inflammation compared to monovalent cationic liposomes.[202]

Reproductive and Embryotoxicity

The reproductive system consists of various organs, each with varying sensitivities to potential harmful factors and substances. Currently, research on the reproductive toxicity of nanomaterials primarily focuses on their effects on reproductive organs, germ cells, and fetal development.[203–206]

Reproductive toxicity of TiO_2 NPs has been observed in both male and female animals. In female mice, exposure to TiO_2 NPs for 60 days results in decreased ovarian weight and disrupts the development of ovarian follicles via the TGF-β signaling pathway.[207] In addition, TiO_2 NPs caused a significant increase in MDA and estrogen levels in female mice, and significantly reduced fertilization rate, pregnancy rate, and number of deliveries.[208] TiO_2 NPs primarily impacted testicular morphology, sperm characteristics, and reproductive hormones in male mice. This was demonstrated by significant pathological changes and histomorphometric alterations in the testes, a reduction in sperm count, abnormalities in sperm quality, and a decrease in luteinizing hormone levels.[209–212] Furthermore, studies have suggested that the reproductive toxicity of TiO_2 NPs may be linked to mechanisms involving oxidative stress, apoptosis, inflammation, and interference with steroidogenesis.[213–215]

Carbon-based nanomaterials, such as graphene oxide and fullerenes, have also been a recent focus of research regarding their potential toxicity to the reproductive system. They have been shown to affect reproductive cells in mice, the pregnancy process, and fetal development to some extent.[216,217] Exposure to Graphene Quantum Dots results in a significant decrease in the rate of first polar body extrusion in mouse oocytes and notably affects the mean fetal length. However, this effect does not carry over to the second generation of offspring.[218] On the other hand, exposure to graphene oxide NPs (GO-NPs) caused dose-dependent pregnancy complications in pregnant mice, impacting placental barrier function. This was evidenced by a 30–80% reduction in the expression of tight junction proteins and vascular endothelial growth factor in placental tissue.[219] In male mice, GO-NPs can cause significant histological damage to the testes, along with a notable loss of mitochondrial membrane potential in cells. This is accompanied by a decrease in sperm count and an increase in sperm deformity rates. However, the effects on sperm can be reversed after exposure is discontinued.[220,221] Fullerenol NPs have been found to interfere with the strict process of oocyte meiotic resumption, possibly through the modulation of the EGFR-ERK1/2 signaling pathway and the expression and distribution of CX43.[222]

Enterotoxicity

The intestine, as a core component of the digestive system, plays a vital role in food digestion, nutrient absorption, and waste excretion. The potential intestinal toxicity of NPs has become one of the current research hotspots. The mechanisms through which they impact intestinal health are diverse, including direct damage to intestinal tissue, disruption of the gut barrier function, induction of intestinal inflammation, and alterations to the composition of the gut microbiota.[223,224]

In the food industry and drug delivery field, metal NPs, which are widely used, can cause intestinal toxicity when they reach a certain concentration.[225–228] Among them, TiO_2 NPs exhibit the most noticeable toxicity. Their intestinal toxic effects include increased mucosal permeability, impaired intestinal barrier function, induced gut microbiota imbalance, and elevated levels of lipopolysaccharides. These effects further lead to intestinal oxidative stress, inflammation, and intestinal-related metabolic disturbances. Further studies have found that the toxic mechanism of TiO_2 NPs may be associated with the activation of the intestinal PKC/TLR4/NF-κB signaling pathway.[227,229,230] TiO_2 NPs have a significant impact on the gut microbiota of juvenile grouper, particularly on the genera *Lactobacillus* and *Nautella*. Changes in these bacterial populations can further trigger immune responses and alterations in metabolic products.[231] CuO NPs can induce intestinal toxicity in zebrafish by altering the microbial abundance of Short-Chain Fatty Acids and Lipopolysaccharide (LPS) metabolism, which inhibits the key immune-regulatory pathway TLR4/MyD88/NF-κB.[232] CeO_2 NPs cause shedding of the intestinal epithelial

tissue in rats, damage or disappearance of the glandular structure in the lamina propria, and induce changes in the structure and abundance of the intestinal microbiota.[233]

In addition to common metal oxide nanomaterials, the intestinal toxicity of metal NPs has been demonstrated. Cu NPs for smart drug delivery systems were found to cause dose-dependent damage to piglet intestinal epithelial cells accompanied by an increase in the oxidative stress markers MDA content and Metallothionein values.[234,235] The toxic effects of Au-NPs on intestinal cells were less severe, with a decrease in colony-forming ability observed only after prolonged exposure to high concentrations.[236]

Immunotoxicity

The immunotoxicity of NPs is a complex and multifaceted phenomenon. Different nanoparticle drug carriers have varying effects on immune cells; some can activate immune responses, while others may suppress immune activity.[237–239]

The immunotoxicity of TiO_2 NPs manifests as the inhibition of lymphocyte proliferation and macrophage Nitric Oxide (NO) production in vitro, with this suppressive effect being dose-dependent. In mice exposed to TiO_2 NPs, significant impairments in the development and proliferation of B cells and T cells are observed, along with a reduction in macrophage activity and a decrease in Natural Killer cell numbers. This disruption leads to a diminished immune response against tumor cells, ultimately resulting in enhanced tumor growth in the mice.[240] The immune toxicity induced by TiO_2 NPs is reduced when they are embedded in mesoporous silica NPs (MSN) to form new TiO_2@MSN particles, showing lower toxicity compared to TiO_2 NPs alone.[241]

In studies on the immunotoxicity of SiO_2 NPs, SNP50, SNP100 (non-porous SiO_2 NPs), and Meso100, HMSNP100 (mesoporous SiO_2 NPs) exhibited no signs of immunotoxicity.[242] However, MSN with an average diameter of 160 nm can induce severe skin inflammatory responses, leading to a significant increase in immunoglobulins, serum histamine, and Th1/Th2/Th17 cytokines. This toxic response is associated with the protein corona on the MSN surface.[243]

Gold nanorods (Au NRs) can cause significant changes in nearly all immune cell subpopulations in the peripheral blood of mice, further disrupting both innate and adaptive immune responses.[244] A study by Massich et al found that compared to lipid complexes carrying the same DNA sequence, densely functionalized, oligonucleotide-modified AuNPs triggered a significant 25% reduction in innate immune responses.[245] There have also been reports on the immunotoxicity of non-metallic NPs, such as GO, carbon black NPs, and carbon nanotubes.[246–248]

Exosomes induced by IONPs can trigger immune activation and inflammatory responses associated with nanoparticle exposure.[249] Park et al found that IONPs trigger the autophagic process before apoptosis by causing mitochondrial dysfunction and endoplasmic reticulum stress in RAW264.7 cells, leading to an increase in leukocyte and neutrophil levels, IL-8 secretion, and lactate dehydrogenase release.[250] Follow-up studies have confirmed the immune-stimulating effects of IONPs on the spleen and lungs. These effects are mainly characterized by mitogen-induced proliferation of splenic lymphocytes, increased IL-1β secretion, the induction of a Th1-polarized inflammatory response in the lungs, enhanced chemokine secretion, and the upregulation of antigen-presenting proteins, leading to elevated levels of neutrophils, lymphocytes, and eosinophils.[251–254]

Most NPs carriers are considered non-toxic and biocompatible; however, there have still been reports of immune toxicity associated with certain NPs carriers. For example, Ambisome (amphotericin B liposome) has been reported to cause allergic reactions not previously associated with amphotericin B. This is likely due to the lipid components of the drug, which may trigger a direct and potentially fatal reaction.[255] Lipid-based NPs (LNPs), which are commonly used for their low immunogenicity, are more prone to triggering the body's immune response following surface modification.[239,256] Cationic liposomes can trigger macrophage cytotoxicity by reducing the synthesis of NO and TNF-α in macrophages activated by LPS/IFN-γ.[257] The immunotoxicity of PEG-modified NPs is also one of the current research focuses. Currently, allergic or hypersensitivity reactions have been reported for PEG 6000, PEG 3350, and PEG-containing barium contrast agents. The primary allergic symptoms include urticaria, dizziness, hypotension, angioedema, and transient episodes of tachycardia.[258–260] The formation of anti-PEG antibodies after human exposure to PEG additives is one of the causes of allergic reactions associated with relevant drugs. Reports have shown that anti-PEG antibodies are present in the plasma of 25% of healthy blood donors, and these pre-existing anti-PEG antibodies may exacerbate the immune response of subjects to PEG-containing drugs.[261–265]

The mechanism behind PEG drug allergic reactions and hypersensitivity caused by anti-PEG antibodies is closely related to complement activation. Kozma et al revealed its role in complement activation-related pseudo-allergy (CARPA) induced by PEGylated liposomes and PEG-G-CSF (polyethylene glycol-conjugated granulocyte colony-stimulating factor).[266]

Cardiotoxicity

At present larger number of studies have reported the cardiotoxicity of TiO_2 NPs, IONPs and AgNPs.[267,268] Acute exposure to TiO_2 NPs can induce dose-dependent cardiac toxicity, manifested as damage and alterations to myocardial fibers and cardiomyocytes.[269] Long-term exposure to TiO_2 NPs leads to the accumulation of titanium in the heart, triggering inflammatory responses, myocardial cell necrosis, and biochemical dysfunction of the heart.[270] Nichols et al observed that the diastolic dysfunction induced by TiO_2 NPs in the heart could be alleviated through the overexpression of a novel mitochondrial-targeted antioxidant enzyme, phospholipid hydroperoxide glutathione peroxidase (mPHGPx).[271] IONPs can induce a reduction in heart rate, cardiac blood accumulation, and pericardial edema in zebrafish embryos. Intraperitoneal injection of IONPs in mice leads to dose-dependent oxidative damage to myocardial cells.[157,272] The research conducted by Mohamed et al found that after administering IONPs to rats, cardiac toxicity was observed, characterized by a significant increase in Creatine Kinase Isoenzyme MB and LDH levels, along with an upregulation of TNF-α expression and a downregulation of HSP70 in heart tissue. Coating the NPs with rutin (Ru) significantly mitigated these toxic effects.[273] The primary cardiac toxicity of Ag NPs is the induction of significant DNA base oxidation in the heart, primarily manifested by an increase in 8-Hydroxy-2'-deoxyguanosine levels. This toxic effect is more pronounced when Ag NPs are used in combination with IONPs.[274]

Factors Influencing the Safety of NPs

The interaction between NPs and the body is closely related to the physico-chemical properties of NPs. Different physicochemical properties lead to different mechanisms and outcomes of toxicity induced by NPs in the organism. This section summarizes the key factors affecting the safety of NPs, in order to provide references for ensuring the safety and effectiveness of NPs and establishing a strict and comprehensive quality control system. Factors influencing the safety of NPs is illustrated in Figure 4.

Size and Surface Area

The size and surface characteristics of NPs influence their interaction with biological systems. Their size impacts both distribution and toxicity. NPs with varying sizes accumulate differently in organs such as the lungs, liver, and kidneys, which is partly due to the filtration structures in these organs.[275] The transmembrane transport of NPs varies with particle size. Smaller particles primarily pass through the membrane via passive diffusion, while larger particles enter the cell through endocytosis.[276] Typically, the toxicity of NPs is positively correlated with their size. For instance, the larger the particle size of TiO_2 NPs, the greater the toxicity to the liver.[92,277,278] Larger-sized IONPs are more easily absorbed by the spleen.[279,280] The larger the size of Al_2O_3 NPs, the more pronounced their effect in inducing inflammation in the kidneys.[281]

However, the impact of size on the toxicity of NPs is also a subject of debate. For human dermal fibroblasts, 45 nm AuNPs are more toxic than 13 nm AuNPs.[282] Nevertheless, smaller-sized AuNPs exhibit greater toxicity to macrophages, fibroblasts, melanoma cells, and epithelial cells. This may be due to the fact that smaller AuNPs are more likely to enter the cell nucleus and disrupt DNA structure.[278,283] Smaller-sized AuNPs are also more likely to accumulate in the kidneys and liver. One of the reasons for this phenomenon is the different bridging reactions mediated by the Wnt/β-catenin signaling pathway.[284,285] In addition, the size of AuNPs also affects the body's response in terms of activating innate immune signaling pathways. 4.5 nm AuNPs preferentially activate the NLRP3 inflammasome to promote Caspase-1 maturation and IL-1β production, while AuNPs larger than 10 nm are more likely to trigger the NF-κB signaling pathway.[286] The effect of SiO_2 NPs particle size on their toxicity follows a similar pattern to that of AuNPs. Hepatotoxicity and nephrotoxicity of SiO_2 NPs are more severe for small particle size, and the smaller the particle size of SiO_2 NPs in amorphous structure, the more toxic it is.[287,288] But some studies have also shown that large-sized

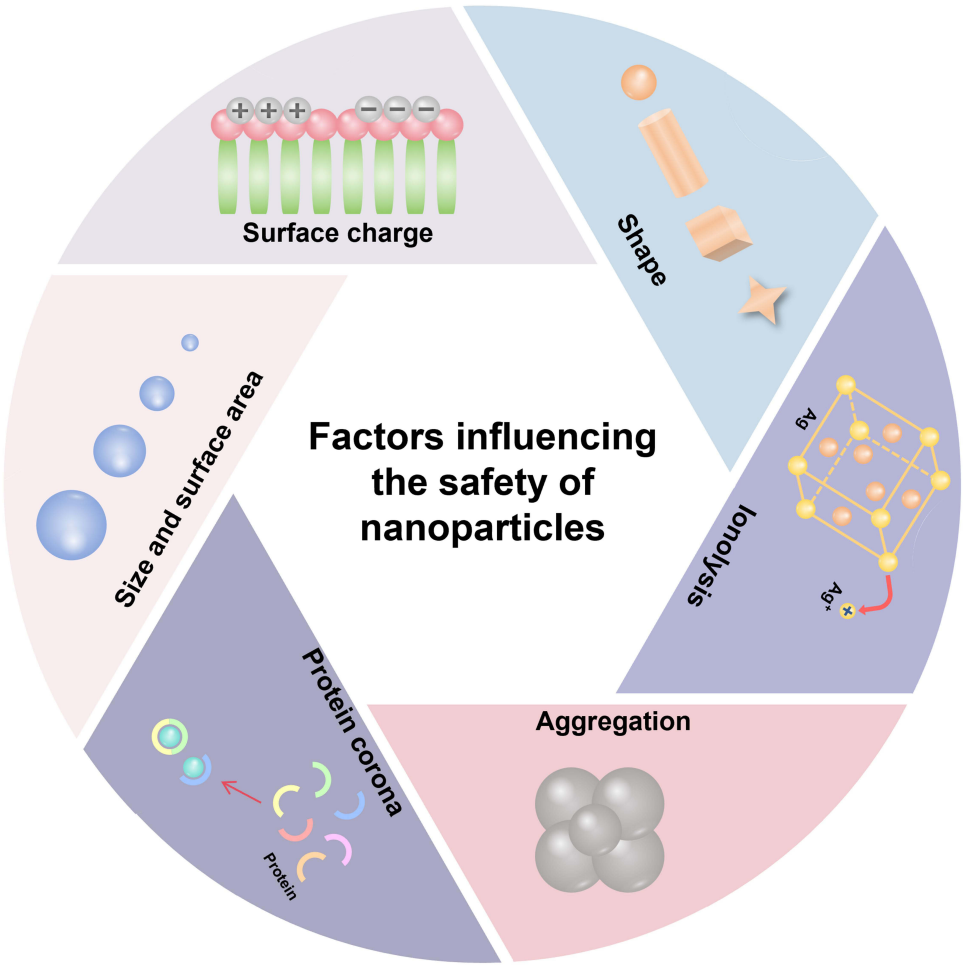

Figure 4 Factors Influencing the Safety of Nanoparticles. The different physicochemical properties of nanoparticles, such as size and surface area, surface charge, shapes, Ion dissolution, aggregation, and protein Corona, determine the differences in their distribution and behavior patterns in various tissues and organs of the body, thereby leading to the differences in toxicity of different nanoparticles in the body.

SiO_2 NPs exhibit greater toxicity due to increased surface contact area, easier cellular uptake, and susceptibility to membrane disruption.[289–291]

In summary, the impact of size on the toxicity of NPs is not absolute; it is also influenced by multiple factors such as cell and tissue type and the properties of the NPs. Therefore, a comprehensive, multifaceted approach is required to gain a deeper understanding of the mechanisms behind the various toxic effects of NPs and further promote the development of nanomedicine.

Surface Charge

The interaction of NPs with biological systems depends strongly on their surface charge, which in turn is influenced by the molecular structure of the coating material. The surface charge influences colloidal behavior, selective absorption, plasma protein binding, transmembrane permeability, and the integrity of the BBB.[292] Based on charge properties, surface charge can be classified into three categories: positive, negative, and neutral charge.[293,294] Positively charged NPs are more likely to interact with negatively charged glycoproteins on cell membranes, making them more readily absorbed by cells. As a result, they exhibit stronger cytotoxicity compared to negatively charged or neutral NPs, and are also more likely to participate in the regulation and replenishment processes in blood and biological fluids.[295–297] Cationic functional groups in the structure of AuNPs are more likely to cause cell membrane rupture. The membrane-disrupting activity is influenced by the nature of the positive charge and the characteristics of the underlying chains. The higher the charge density, the more severe the damage to

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the cell membrane.[298–300] For example, carboxyl-PEG-modified AuNPs display greater cytotoxicity than citrate-coated AuNPs, while cationic BPEI (branched polyethyleneimine)-modified AuNPs show the highest cellular uptake and toxicity response.[301,302] Except for AuNPs, positively charged AgNPs, IONPs and CeO_2 NPs are more toxic than their negatively charged counterparts.[303–305]

It has been demonstrated that the toxicity of NPs' surface charge is influenced by their chemical composition, with cationic AuNPs being toxic and anionic ones non-toxic when the surface groups contain only the external chemical composition of carbon, hydrogen and oxygen.[306] Whereas, when the surface groups consisted of carbon, hydrogen, oxygen and sulfur, both positively and negatively charged AuNPs were cytotoxic, and the negative charge was more toxic.[307] In addition to this, the surface properties of the NPs interact with the protein crowns adsorbed on their surfaces, leading to altered cellular uptake mechanisms, loss of enzyme activity, and ultimately disruption of biological processes.[308–310]

Shapes

NPs have characteristic shapes such as spherical, cylindrical, ellipsoidal, cubic, rod-shaped and flaky, and different shapes have different effects on their toxicity magnitude.[311] It has been shown that the nephrotoxicity produced by mesoporous SiO_2 NPs in ICR mice depends strongly on their shape.[312] In general, spherical NPs are more amenable to cytophagy, but are less toxic than other shapes, especially NPs with higher aspect ratios (including tubes, ribbons, rods, and wires and polyhedra, etc).[313] Spherical TiO_2 NPs are much less toxic to macrophages than dendritic and spindle-shaped.[314] Different shapes of NPs displayed different toxicity in different types of cells. Rod-shaped CeO_2 NPs exhibited more significant toxicity to macrophages than cubic and octahedral CeO_2 NPs particles, whereas wire bundles and cubic CeO_2 NPs with sharp edges were more toxic to human bone marrow cell lines.[315,316] Flower-shaped AuNPs were more toxic to human endothelial cells, whereas spherical and rod-shaped AuNPs were much more toxic than stellate prismatic and mirror-shaped AuNPs in HEK293T cells.[317,318]

Therefore, in the safety evaluation of nanopharmaceuticals, the influence brought by their shapes needs to be paid close attention to, and advanced mathematical models can be developed with the help of various imaging techniques to predict their behaviors in organisms, which can provide the basis for the establishment of an accurate and efficient method for the characterization of the shapes and homogeneity of NPs.

Ion Dissolution

The dissolution and ionization properties of nanomaterials are determined by their chemical composition, which can be influenced by environmental factors such as pH and ionic strength. These properties are crucial in assessing the potential toxicity of NPs. Cho et al investigated the toxicity of 15 different metal/metal oxide NPs, exploring the relationship between various physicochemical parameters, including zeta potential and solubility, and their potential to induce pulmonary inflammation The results revealed that under acidic conditions (pH 5.5), a higher positive zeta potential increased the likelihood of lysosomal dissolution and the release of toxic metal ions, which, in turn, triggered a more pronounced inflammatory response.[319] The dissociated Ag^+ ions have been identified as the principal cause behind the mitochondrial damage, reactive oxygen species production, and apoptosis induced by AgNPs.[320]

Similarly, the dissolved Zn^{2+} ions are the predominant cause of neurotoxicity in mouse neural stem cells triggered by ZnO NPs. Surface coating with iron effectively alleviates this detrimental effect.[167,321] However, for Cu NPs, their predominant form of toxicity is not the dissociated ions, but rather the particles themselves.[322] In addition to ions, the release of surface modifications on NPs can also contribute to significant cytotoxicity. For instance, spherical CTAB (cetyltrimethylammonium bromide)-functionalized AuNPs demonstrate enhanced toxicity compared to their rod-shaped equivalents. This can be attributed to the more facile release of CTAB from the surface of the spherical particles.[323] When polystyrene sulfonate and polyallylamine hydrochloride coatings are applied to the surface of these AuNPs, their toxicity is markedly diminished.[324] In addition to coating modification, the toxicity of NPs can also be mitigated by designing a shell structure to encapsulate the NPs. For instance, designing a MgO shell around AgO NPs can slow down the release rate of Ag^+, ensuring that Ag^+ is released in a "slow and sustained" manner and thereby avoiding the toxicity caused by excessively high local Ag^+ concentrations.[325]

Toxicity Related to the Biotransformation of Nanomaterials

Aggregation

The influence of aggregation on the toxicity of NPs remains a contentious issue. The interactions of aggregates with receptors and membrane proteins may differ from the internalization pathways observed with individual NPs.[326] AuNPs, transported through the endolysosomal pathway, are susceptible to disintegration in the acidic microenvironment (pH 4.5–6). This degradation induces the formation of aggregates that remain sequestered within the cell, owing to the disruption of intracellular structures.[327,328] The aggregates that form may lead to vascular thrombosis, subsequently impairing the uptake and targeted delivery of the NPs.[329] In general, aggregates can attenuate adverse effects by decreasing the specific surface area and restricting interactions with cellular structures.[330] For instance, larger aggregates of AgNPs can markedly reduce hemolytic toxicity compared to their smaller counterparts.[331,332] However, in macrophages, larger aggregates can enhance the delivery of the smaller initial NPs, leading to a more pronounced toxic effect.[333]

Protein Corona

NPs with elevated surface energy, upon introduction into intricate physiological fluids, are capable of progressively and selectively adsorbing biomolecules from the surrounding milieu, thereby forming a biomolecular corona composed of proteins, lipids, carbohydrates, nucleic acids, and other components. The protein fraction of this corona is specifically designated as the protein corona.[334,335] The protein corona can influence the toxicity of NPs through mechanisms such as modulating cellular recognition, triggering immune responses, altering the biocompatibility of the particles, and affecting hepatic metabolism.[109,336–339] The protein corona formed by the binding of ZnO NPs with proteins in brain homogenates can also impact physiological functions by altering protein conformation and either inhibiting or enhancing enzymatic activity.[340]

The influence of the protein corona on NPs toxicity is dual-faceted. On one hand, it can mitigate toxicity by preventing the dissolution and release of ions from the NPs, thereby reducing the likelihood of their uptake by cells.[109] On the other hand, the protein corona has been demonstrated to activate the endoplasmic reticulum stress pathway and the TGF-β/Smad 2 pathway in rats, subsequently inducing pulmonary fibrosis.[341] For mesoporous SiO_2 NPs, the protein corona formed on their surface can significantly elevate the expression of cytokines specific to atopic dermatitis in mice, as well as increase the infiltration of immune cells.[243] Studies have further indicated that the protein corona can modulate hemolysis, platelet activation, and tumor metastasis, thereby intensifying the toxicity to cells or the organism.[342–344]

Distinct forms of protein coronas can provoke varied toxicological outcomes. In contrast to the Human Serum Albumin corona, the Haptoglobin corona is correlated with increased cellular internalization and a diminished hepatocyte survival rate.[109] The CdS NPs coated with PC proteins primarily induce apoptosis by enhancing the expression of the FcγRIIB receptor on macrophage surfaces, thereby activating the AKT/Caspase-3 signaling pathway.[345]

Mechanisms of Nanoparticle Toxicity

NPs can cause damage to different tissues or systems through a variety of mechanisms. At present, research on these mechanisms mainly focuses on oxidative stress, DNA damage, and inflammatory responses. This section summarizes the toxicity mechanisms of NPs, providing certain references for researchers to better understand the interactions between NPs and the body. The toxicity mechanism of NPs is illustrated in Figure 5.

Oxidative Stress

ROS in the body are a group of highly reactive oxygen-containing molecules that mainly function in signal regulation. Under normal physiological conditions, the production and clearance of ROS maintain a dynamic balance, thereby preserving homeostasis. However, when ROS production exceeds the body's capacity for clearance, it can lead to an imbalance in homeostasis, triggering oxidative stress and subsequently damaging cellular structures.[346] Studies have demonstrated that NPs can induce intracellular oxidative stress by activating oxidative stress signaling pathways or suppressing the activity of antioxidant systems. This results in the excessive accumulation of intracellular ROS or an imbalance in the NO/NOS system, ultimately leading to tissue or organ toxicity.[347] For example, compared to conventional ZnO, ZnO NPs exhibit more severe oxidative stress at the cellular level, which in turn induces more pronounced liver damage in rats.[348] The transcriptional level of the SOD1 gene in mice induced by Ag NPs was significantly higher than that in the control group, accompanied by more

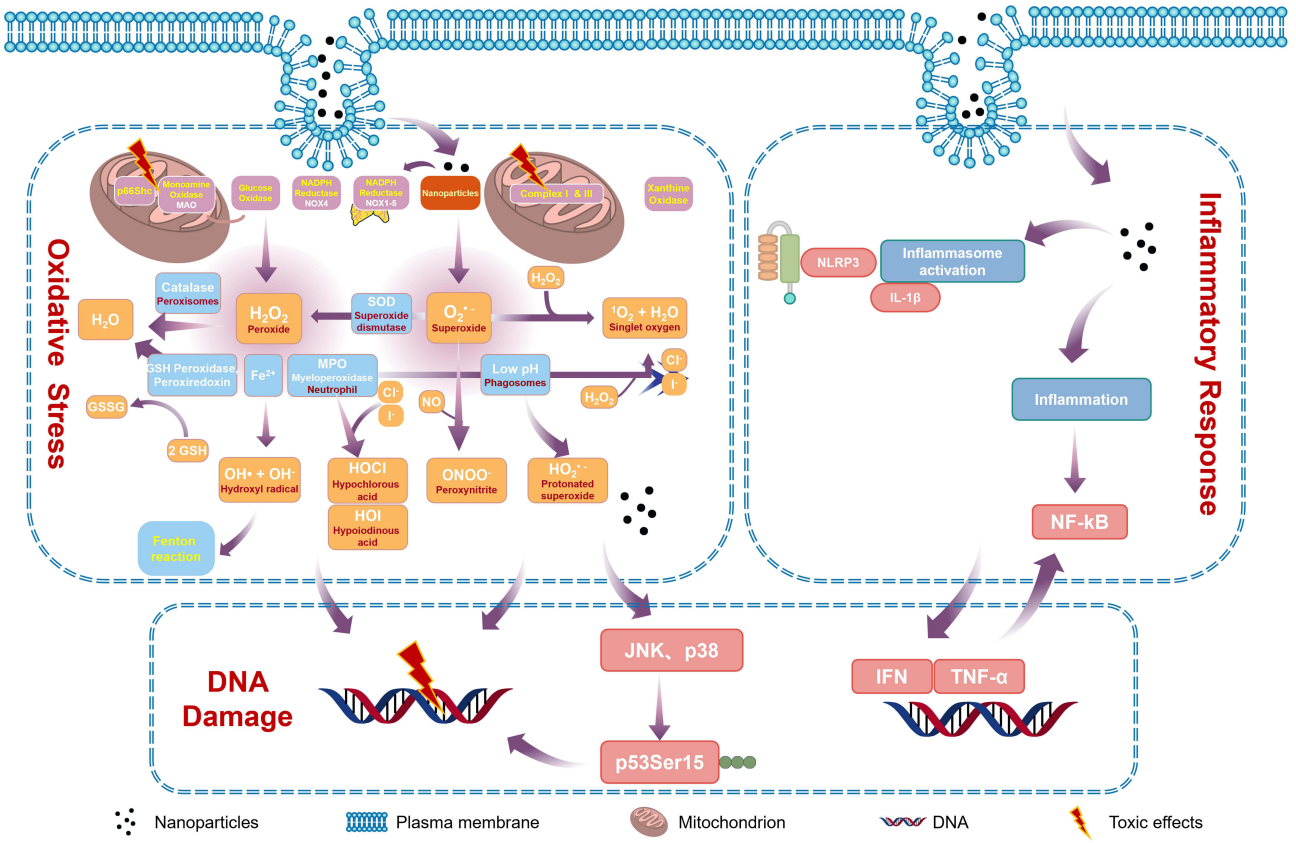

Figure 5 Toxicity Mechanism of Nanoparticles. Nanoparticles mainly exert toxic effects through oxidative stress, DNA damage, and inflammatory responses, leading to the destruction of cell structure and function, and subsequently inducing tissue and organ toxicity.

severe lung damage.[349] Exposure to TiO_2 NPs induces oxidative stress, which causes hippocampal cell apoptosis in rats and mice, ultimately leading to impairments in motor function and spatial recognition memory.[349] TiO_2 NPs can downregulate the levels and activities of antioxidant enzymes such as Catalase, Glutathione Peroxidase 1, and SOD in human thyroid follicular epithelial cells, while upregulating the levels of ROS and MDA induced by oxidative stress. This, in turn, leads to damage to the cell's structure and function.[350] Moreover, certain metal NPs can release metal ions, participate in Fenton or Fenton-like reactions, and promote the accumulation of ROS within cells, thereby further inducing oxidative stress.[351,352]

DNA Damage

Humans are typically exposed to NPs through inhalation (respiratory tract), ingestion (gastrointestinal tract), dermal contact, and injection (circulatory system).[353–356] When NPs enter the human body, they may traverse various cellular barriers and reach sensitive organs such as the lungs, liver, and kidneys. This can result in mitochondrial damage, DNA mutations, and ultimately lead to cell apoptosis or death.[357–359]

NPs-induced DNA damage can be categorized into direct and indirect damage. Direct damage refers to covalent interactions between NPs and DNA molecules, resulting in alterations to the structure and properties of the DNA. The hepatotoxicity mechanism of TiO_2 NPs in mice involves direct DNA damage. Specifically, TiO_2 NPs insert base pairs into DNA or bind to DNA nucleotides, accumulating in liver DNA through Ti-O(N) and Ti-P bonds. This leads to DNA strand breaks in the liver and alters the conformation of the DNA.[360] ZnO NPs have been found to significantly increase the mutation frequency of the HGPRT gene and, to some extent, interfere with DNA damage and repair processes.[361,362] Positively charged AuNPs have the ability to strongly interact with the negatively charged DNA in cells, resulting in DNA damage and disrupting the normal progression of the cell cycle, which causes an extension of certain cell cycle phases. This process could also play a role in promoting carcinogenesis.[295,363]

Indirect damage refers to DNA damage that occurs as a consequence of other toxic effects caused by NPs. The principal mechanism through which NPs induce toxicity is the damage to DNA caused by oxidative stress and inflammation triggered by ROS.[364–366] For instance, ZnO NPs can trigger oxidative stress, activate JNK and p38 pathways, and facilitate the phosphorylation of p53Ser15, ultimately resulting in DNA damage and apoptosis in human liver cells.[367] Al_2O_3 NPs induce DNA damage in mouse neuronal cells via ROS-mediated indirect injury, while Co and Cr NPs trigger the release of IL-6, which indirectly causes DNA damage in neurons and astrocytes derived from neural progenitor cells.[368]

Inflammatory Response

Inflammation is a defense mechanism against the invasion of harmful substances into the body. It helps eliminate harmful factors and damaged tissues, restoring cells and tissues to their normal function. The vast majority of nanomedicines are exogenous substances that have the potential to trigger a series of excessive inflammatory responses upon entering the body.[369] It has been found that NPs predominantly trigger inflammatory responses by promoting the release of inflammatory factors and inducing the activation of inflammatory vesicles.[200,370,371] For example, TiO_2 NPs upregulate the expression of inflammatory factors such as TNF-α, IL-1β, NF-κB, IFN-α, and IFN-β. Moreover, the entry of MnO_2 NPs into the organism results in a significant increase in IL-1β and TNF-α levels.[372,373] SiO_2 NPs can regulate the transcription and release of pro-inflammatory cytokines by participating in the activation of inflammasomes, as well as activate key pathways related to inflammation and cell death.[371] CuO NPs induce pulmonary inflammation via triggering cellular cuproptosis.[374]

Apart from the previously discussed mechanisms, NPs can also impair cellular structure and function through multiple routes, including gene mutations, mitochondrial damage, and fibrosis, which in turn can cause toxicity across various organs. As nanotechnology continues to evolve and its applications broaden, there is an increasing necessity to thoroughly elucidate the toxicity mechanisms of NPs, investigate their potential toxic pathways, and establish accurate methods to quantify the degree of influence from each mechanism, thereby gaining a more profound understanding of the inherent toxicity of NPs.

Conclusion and Discussion

The toxicity and safety of NPs represent a critical issue that limits their widespread application. This review systematically synthesizes the toxicological characteristics, regulatory factors, and underlying mechanisms of NPs. The main findings are as follows: in terms of toxic manifestations, NPs exhibit significant organ- and system-specific toxicity, with the liver, kidneys, and nervous system being the primary target organs. Regarding regulatory factors, physicochemical properties such as particle size, surface charge, shape, and ion release are key variables determining toxic outcomes. In terms of mechanisms, oxidative stress, DNA damage, and inflammatory responses constitute the core pathways of NPs-induced toxicity.

These findings provide important insights for further research. First, the specificity of target organs suggests that safety evaluation of NPs should prioritize the toxic risks to specific organs based on the application scenario. Second, the correlation between physicochemical properties and toxic effects indicates that toxicity reduction can be achieved through optimization of parameters such as particle size and surface modification while preserving functionality. Third, elucidation of the core toxicity mechanisms provides a theoretical basis for the development of in vitro alternative testing methods and the identification of early biomarkers.

To address the toxicity challenges associated with NPs, future efforts can focus on the following strategies. The first is design optimization: modulating the biodistribution and metabolic behavior of NPs through surface modification or smart responsive designs to reduce accumulation in non-target organs. The second is the establishment of a full life-cycle assessment framework: integrating emerging technologies such as organ-on-a-chip and multi-omics analysis to construct a toxicity evaluation system covering the entire process from synthesis to application, metabolism, and excretion. Finally, the development of "smart detoxification" strategies leveraging emerging technologies offers a promising approach for toxicity intervention.

In summary, based on a systematic summary of research progress in NPs toxicity, this review identifies key scientific issues and existing limitations, and proposes feasible pathways for toxicity reduction and evaluation optimization, thereby providing theoretical support for improving the safety assessment of nanoparticles.

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