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Silica nanoparticle toxicity: cellular mechanisms, neurotoxicological concerns, and environmental perspectives

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Engineered silica nanoparticles (SiNPs) are increasingly employed in various domains, including biomedicine and industry, owing to their tunable physicochemical properties. However, their extensive application has raised concerns about their potentially detrimental effects on human health and ecosystems. This mini-review summarizes current knowledge of the cellular mechanisms underlying SiNP cytotoxicity, with a focus on oxidative stress, NOD-like receptor protein 3 (NLRP3) inflammasome-mediated inflammation, lysosomal destabilization, mitochondrial dysfunction, genotoxicity, and autophagy modulation. We emphasize the critical influence of SiNP properties such as size, surface chemistry, shape, and synthesis method on these biological responses. Particular attention has been given to neurotoxicity, which is a growing concern owing to the potential of SiNPs to cross the blood-brain barrier. Additionally, we briefly address environmental considerations, recognizing the need to understand the fate and impact of SiNPs within ecosystems. Finally, we discuss mitigation strategies, including surface engineering and safer-by-design approaches, and delineate the key knowledge gaps and future research directions essential for the sustainable development and safe application of SiNP-based technologies in the context of both human health and environmental safety.

KEYWORDS

silica nanoparticles (SiNPs), cytotoxicity, neurotoxicity, environmental impact, nanotoxicology, neurodegeneration

1 Introduction

Nanotechnology, with nanoparticles (NPs) at its core, is a crucial driving force behind innovation in the 21st century. Among NPs, silica nanoparticles (SiNPs), especially amorphous forms such as mesoporous silica nanoparticles (MSNs), have gained considerable attention owing to their simple synthesis, customizable pore sizes, large surface areas, ease of surface functionalization, and initial perception of biocompatibility (Liu and Sayes, 2022). These versatile properties render them strong candidates for drug delivery, bioimaging, diagnostics, and therapy applications (MacCuaig et al., 2022). For example, MSNs can be loaded with therapeutic agents and equipped with multifunctional caps that respond to specific stimuli, enabling controlled drug release and enhanced therapeutic efficacy (Geng et al., 2017). Furthermore, SiNPs and their composites, such as Se@SiO2, are being explored for their inherent therapeutic effects, which include

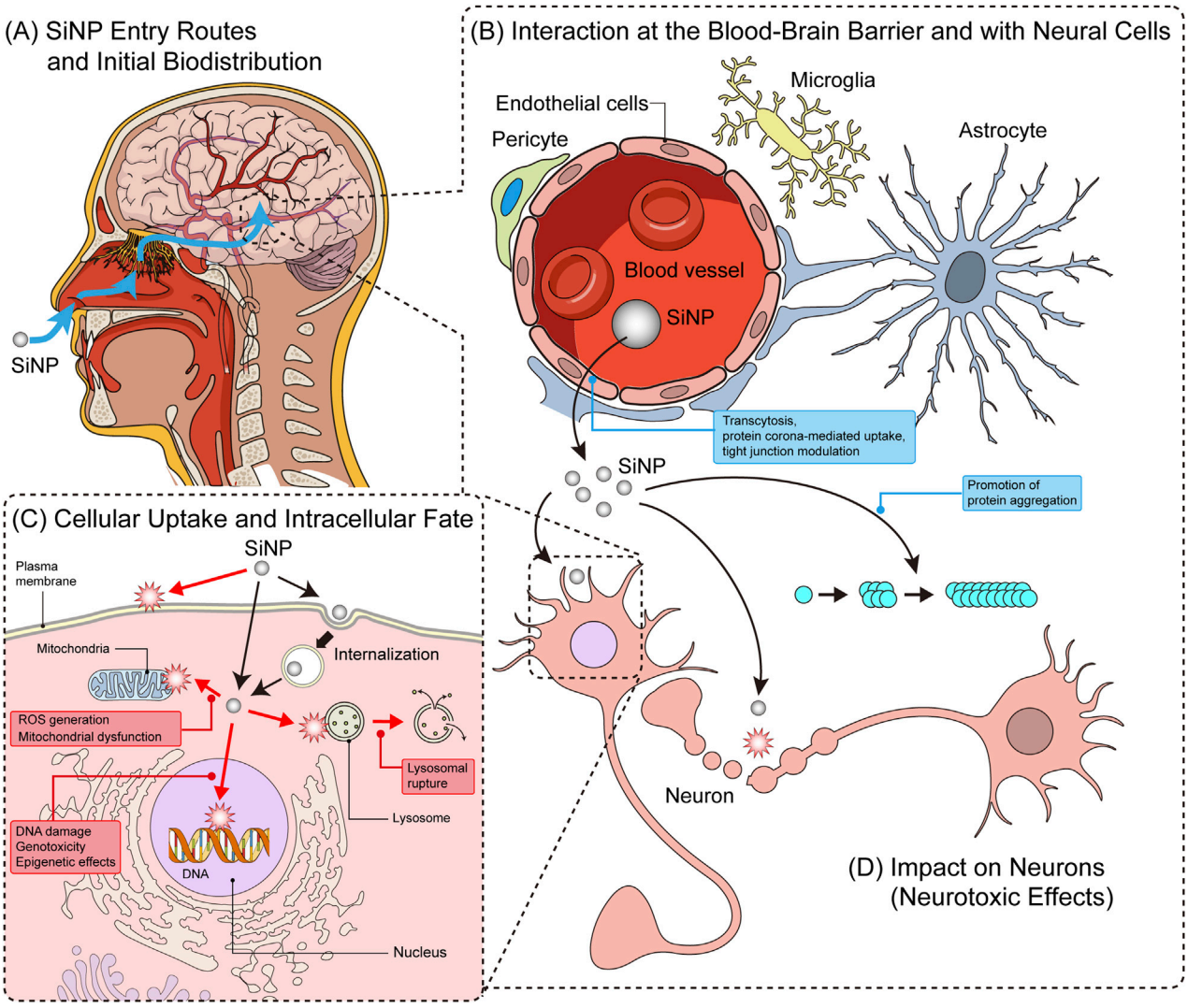

FIGURE 1
Overview of silica nanoparticle exposure, biodistribution, and toxicity pathways. This figure illustrates the routes of silica nanoparticle (SiNP) exposure; its distribution within the body, including the crossing of biological barriers; and the primary cellular and neuronal mechanisms of SiNP toxicity. **(A)** SiNP entry routes and initial biodistribution. SiNPs can enter the body through nasal cavity inhalation, enabling direct transport to the brain via the olfactory route or through the respiratory and digestive tracts into the systemic circulation. **(B)** Interaction at the blood-brain barrier and with neural cells. Circulating SiNPs may cross the blood-brain barrier (BBB), which is the interface between endothelial cells, pericytes, astrocytic endfeet, and microglia. BBB crossing occurs through transcytosis, protein corona-mediated uptake, or tight junction modulation. In the brain, SiNPs interact with the neurons, astrocytes, and microglia. **(C)** Cellular uptake and intracellular fate. SiNPs are internalized via endocytosis and accumulate in lysosomes. SiNPs disrupt lysosomal integrity and cause lysosomal rupture/permeabilization (LMP). Intracellular SiNPs or lysosomal leakage can damage the mitochondria, leading to the generation of reactive oxygen species (ROS) and mitochondrial dysfunction. SiNPs may also interact with the nucleus, thereby contributing to DNA damage and epigenetic effects. Red arrows indicate proposed pathways leading to cellular stress and damage. **(D)** Impact on neurons (neurotoxic effects). The interaction between SiNPs and neurons results in various neurotoxic effects. SiNP accumulation or cellular stress (as shown in **C**) within the brain can promote protein aggregation in neurodegenerative diseases (e.g., α-synuclein, as shown conceptually in **B**). The physicochemical properties of the SiNPs influence these processes. This figure was created by modifying a figure from Mind the GRAPH.

promoting wound healing through their antioxidant properties (Yang et al., 2022) and preventing cancer metastasis without additional drug loading (Lee et al., 2024).

Despite their widespread promise, the increasing production and use of SiNPs has raised concerns regarding their potential adverse health effects following environmental or occupational exposure or biomedical administration (Liang et al., 2023). This growth is driven by recent advancements in precision synthesis and the development of advanced "smart" nanomaterials for specific applications. Numerous studies have examined the cytotoxicity of SiNPs in various biological systems, revealing that complex interactions are heavily dependent on the physicochemical characteristics of the NPs and their biological context (Liu and Sayes, 2022; Yang et al., 2022; Napierska et al., 2010). This underscores the need for a comprehensive understanding of their potential biological and ecological impacts, aligning with the scope of the research topic "Engineered Nanomaterials: Understanding their Toxicity and Environmental Impacts."

This mini-review provides a comprehensive overview of SiNP cytotoxicity by connecting cellular mechanisms, neurotoxicological concerns, and environmental impacts, enabling to enable a more holistic risk assessment. By examining how NP properties influence these interconnected pathways, this review aims to offer valuable insights into the development of safer and more sustainable SiNP-based technologies (Figure 1).

2 Environmental fate and ecotoxicity of SiNPs

Widespread use of SiNPs requires an understanding of their environmental dynamics (transport, transformation, and persistence), which will enables the assessment of ecosystem exposure risks (Handy et al., 2008; Kahru and Dubourguier, 2010). The behavior of SiNPs is complex in both aquatic and terrestrial environments and is governed by their interactions with natural components such as organic matter, ions, and mineral surfaces. These interactions determine their aggregation state, sedimentation, dissolution rate, and ultimately, their availability to organisms (Hotze et al., 2010; Lowry et al., 2012). The surface properties (including charge and coating) of the engineered SiNPs play a pivotal role in these environmental interactions, often through the formation of an "eco-corona" that dictates their subsequent biological identity and impact (Mahmoudi et al., 2023).

Consequently, the ecotoxicity of SiNPs has been a major focus of research, with laboratory studies demonstrating the potential adverse effects across various trophic levels. For example, certain SiNPs have shown toxicity toward the following:

- Aquatic organisms: including algae (e.g., reduced photosynthesis and growth inhibition (Van Hoecke et al., 2008)), invertebrates such as *Daphnia magna* (e.g., reduced mobility and impaired reproduction (Kim et al., 2021)), and fish (e.g., oxidative stress, gill damage, and developmental effects (Duan et al., 2013)).
- Terrestrial organisms: Including soil invertebrates such as the nematode *Caenorhabditis elegans* (e.g., effects on lifespan and behavior (Zhang et al., 2020)) and plants (e.g., altered root growth and impact on germination (Rico et al., 2011)).

Mechanistically, SiNP ecotoxicity is often similar to that observed in mammalian systems, including reactive oxygen species (ROS) generation, membrane disruption, and inflammatory-like responses, although organism-specific sensitivities also exist (Nel et al., 2006). However, a critical challenge remains in extrapolating laboratory findings to real-world ecosystem risks. The complex interplay of environmental factors and the discrepancy between high laboratory test concentrations and lower, environmentally relevant levels underscore the need for more sensitive, long-term studies and realistic exposure designs.

3 Health concerns and key mechanisms of SiNP cytotoxicity

SiNP interactions with cells can trigger a cascade of events leading to cellular dysfunction and death. Several interconnected mechanisms have been identified (Figure 2).

3.1 Oxidative stress

Oxidative stress is one of the most extensively studied mechanisms underlying SiNP toxicity (Aouey et al., 2024; Eom and Choi, 2011; Kamikubo et al., 2019). SiNPs can generate ROS directly from their surface reactivity or indirectly by impairing cellular antioxidant systems and damaging the mitochondria (Liang et al., 2023). This flood of ROS damages critical molecules like DNA (Zheng et al., 2024), proteins, and lipids, leading to widespread cellular injury, inflammation, and apoptosis (Cheng et al., 2023). While cells attempt to counteract this stress by activating antioxidant defense pathways such as the nuclear factor erythroid 2-related factor 2/antioxidant response element pathway, this oxidative damage is a key contributor to the organ-level pathologies described in Section 3.7.

3.2 Inflammatory responses and inflammasome activation

SiNPs are also well-known for inducing strong innate immune and inflammatory responses (Chen et al., 2018). A key pathway involved is the activation of the NLRP3 inflammasome, typically initiated when immune cells, such as macrophages, engulf SiNPs. The particles can then destabilize the lysosome from within, releasing contents such as Cathepsin B, which triggers inflammasome assembly and the release of interleukin-1β (IL-1β) and interleukin-18 (IL-18). In parallel, SiNP exposure has been shown to elevate circulating levels of additional pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-8 (IL-8), suggesting activation of broader inflammatory networks beyond NLRP3 inflammasome signaling. The intensity and pattern of this cytokine release are strongly influenced by SiNP characteristics, particularly their size, shape, and surface chemistry (Sun et al., 2015) and is a key factor in inflammatory diseases such as silicosis and pulmonary fibrosis (Liu et al., 2024).

3.3 Lysosomal dysfunction

Lysosomes play a central role in the SiNP toxicity pathways. Following endocytosis or phagocytosis, SiNPs often accumulate within lysosomes (Morishige et al., 2010). This accumulation can lead to lysosomal membrane permeabilization or rupture (lysosomal destabilization), releasing lysosomal enzymes into the cytoplasm and triggering cell death pathways and inflammasome activation (Morishige et al., 2010; Wei et al., 2024; Hornung et al., 2008). Furthermore, SiNP accumulation can impair lysosomal function, leading to lysosomal swelling and disruption of processes like autophagy (Gupta et al., 2023).

3.4 Mitochondrial dysfunction

Mitochondria have been identified as vulnerable organelles in SiNP-induced toxicity. SiNPs can induce mitochondrial damage through direct interactions following cellular uptake or indirectly via oxidative stress (Chen et al., 2018; Kumarathasan et al., 2022).

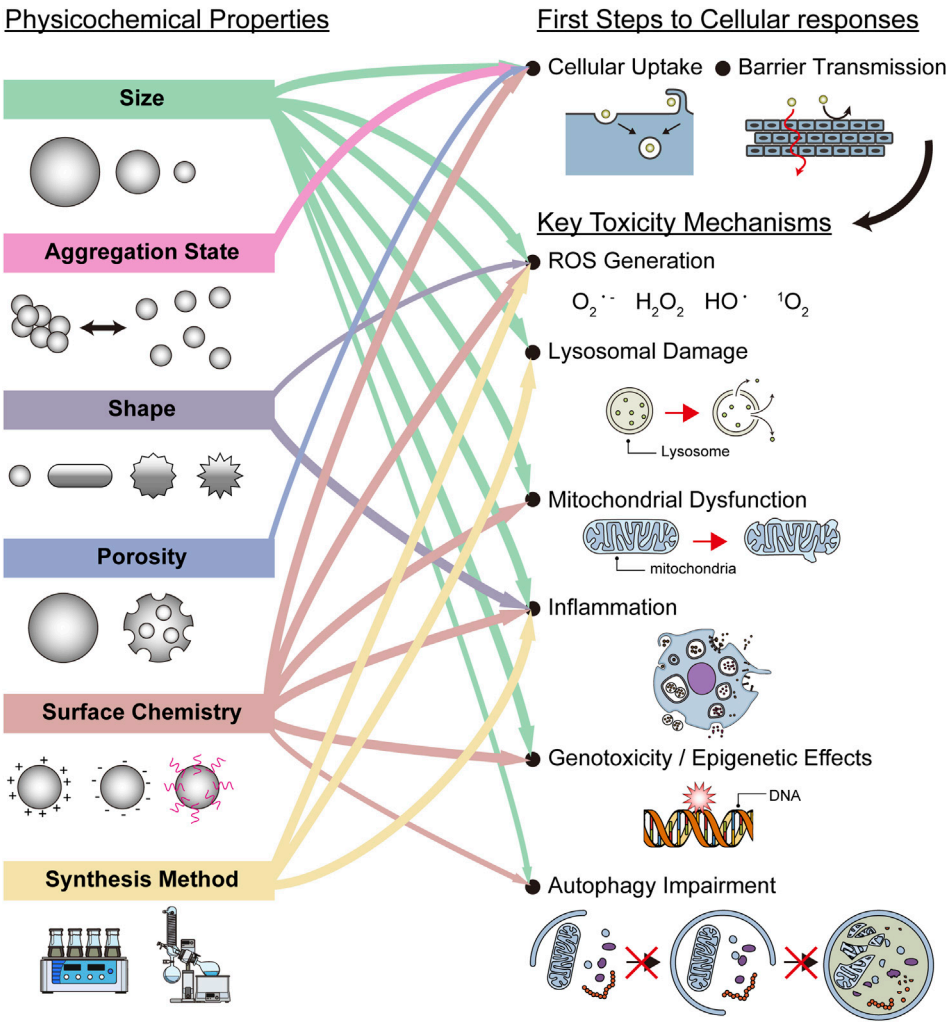

FIGURE 2
Influence of physicochemical properties on SiNP toxicity pathways and outcomes. This schematic illustrates how the diverse physicochemical properties of silica nanoparticles (SiNPs) affect their biological interactions and cellular toxicity. Physicochemical Properties (left), Initial Cellular Responses (middle-right, upper), and Key Toxicity Mechanisms (right, lower) are displayed, with the thickness indicating the strength of the influence. Please refer to the main text for a detailed explanation. This figure was created by modifying a figure from Mind the GRAPH.

Reported effects include alterations in mitochondrial morphology (e.g., swelling) (Solarska-Sciuk et al., 2022), decreased mitochondrial membrane potential (Ahamed et al., 2019), reduced ATP production (Kumarathasan et al., 2022), and changes in the expression of mitochondrial proteins involved in the respiratory chain and stress responses (Kumarathasan et al., 2022). Mitochondrial dysfunction contributes significantly to ROS production, energy depletion, and initiation of mitochondria-dependent apoptosis (Liang et al., 2023). Protecting mitochondrial function, for example, by using antioxidant Se@SiO2 NPs, can mitigate SiNP-induced cellular injury (Yang et al., 2022).

3.5 Genotoxicity and epigenetic effects

In addition to their immediate cytotoxic effects, SiNPs have raised concerns regarding long-term genetic and epigenetic damage (Zheng et al., 2024). They can cause genotoxicity both directly and indirectly, resulting in DNA strand breaks and chromosomal abnormalities and can alter the epigenetic landscape by changing DNA methylation patterns or microRNA expression profiles. Such alterations can have lasting consequences, including risks of carcinogenicity or reproductive toxicity, especially as smaller nanoparticles are known to cross protective biological barriers, such as the placental and blood-testis barriers.

3.6 Autophagy modulation

Autophagy is a cellular self-degradation process that is crucial for the removal of damaged organelles and protein aggregates. SiNPs have complex effects on autophagy. Recent findings suggest that SiNPs may induce autophagy along with other forms of regulated cell death, including apoptosis and necroptosis, depending on the cell type and

TABLE 1 Summary of key studies on health concerns induced by silica nanoparticle (SiNP) exposure.

Organ	Health concern/ Endpoint	SiNP characteristics (size, type, surface)	Exposure model (species, route)	Key mechanistic finding	Key reference
Central nervous system	Neurobehavioral abnormalities	Amorphous SiNP (10 nm)	Mouse (ip)	Enhancement of anxiety and depression	(Jarrar et al., 2021)
	Neuroinflammation	Silica particles (500–1,000 nm)	Mouse (it)	Pro-inflammatory cytokines release	(Suman et al., 2022)
Lung	Silicosis	Crystalline silica, respirable dust (10–100 nm	Human (Occupational inhalation), mouse (orotracheal)	Chronic inflammation; inflammatory cytokines release	(Peng et al., 2022)
	Pulmonary fibrosis	Amorphous Silica particles (59.71 ± 8.11 nm)	Mouse (it)	Inflammation	(Li et al., 2022)
Liver	Fatty liver disease	SiNP (53.27 ± 5.30 nm)	Mouse (iv)	Disruption of lipid metabolism; Oxidative stress	(Sun et al., 2024)
	Amyloidosis lesions	Amorphous SiNP (20 nm)	Mouse (drinking water)	Amyloidosis lesions, inflammation	(Boudard et al., 2019)
Kidney	Inflammation, fibrosis	Amorphous SiNP (200, 300 nm)	Rat (oropharyngeal)	Inflammation	(Sasai et al., 2022)
	Fibrosis	Amorphous SiNP (11 ± 3 nm)	Rat (ip)	Oxidative Stress	(Aouey et al., 2024)
Immune system	Systemic sclerosis	Crystalline silica dust	Human (Occupational inhalation)	SiNP in serum	(Ferri et al., 2018)

Abbreviations: ip, intraperitoneal; it, intratracheal; iv, intravenous.

exposure conditions (Solarska-Sciuk et al., 2022). However, SiNPs can also impair autophagic flux, often by disrupting lysosomal function, leading to the accumulation of autophagosomes and potentially contributing to cell death (Wei et al., 2024; Solarska-Sciuk et al., 2022). The net effect of autophagy modulation (protective vs. detrimental) depends on the specific SiNP properties, cell type, and exposure conditions (Chen et al., 2018).

3.7 Key health concerns and systemic effects

As summarized in Table 1, studies involving animal models and humans have indicated that SiNP exposure can affect a broad range of organs and biological systems. The documented health concerns are diverse, ranging from organ-specific pathologies—such as silicosis and fibrosis in the lung (Peng et al., 2022; Li et al., 2022), hepatic lipid dysregulation associated with ferroptosisfatty liver disease and amyloidosis lesions (Sun et al., 2024; Boudard et al., 2019), and kidney inflammation and fibrosis (Aouey et al., 2024; Sasai et al., 2022)—to neurobehavioral abnormalities and neuroinflammation in the central nervous system (Jarrar et al., 2021; Suman et al., 2022).

In addition to direct organ toxicity, SiNP exposure has been linked to systemic effects. Although rare, chronic silica exposure has been linked to systemic sclerosis (also known as Erasmus syndrome), a serious autoimmune condition (Ferri et al., 2018). Evidence of particle translocation from the lungs comes from investigations on occupational exposure to silica dust. These studies identified nano- to micro-sized silica particles in the blood of exposed individuals and found that their levels were positively correlated with pulmonary fibrosis and serum Si levels (Ferri et al., 2018).

4 Influence of physicochemical properties

The biological effects of SiNPs are not uniform but are strongly modulated by their physicochemical properties.

4.1 Size

Generally, smaller SiNPs exhibit greater cytotoxicity than their larger counterparts, which can be attributed to their higher surface-area-to-volume ratios, potentially increased reactivity, and more efficient cellular uptake. However, this trend is not always consistent because factors such as aggregation in biological media can complicate size-dependent effects (Kamikubo et al., 2019). Size also dictates biodistribution and brain accumulation patterns (Wei et al., 2024).

4.2 Surface properties

Surface chemistry, particularly the density and type of surface groups (e.g., silanols and strained rings), charge, and hydrophilicity, critically determines interactions with biological membranes and biomolecules, influencing uptake, ROS generation, inflammatory potential, and overall toxicity (Yang et al., 2022; Zheng et al., 2024; Morishige et al., 2010; Wei et al., 2024). The protein corona formed *in vivo* further modifies these interactions. Surface functionalization is a key strategy for modulating these interactions, reducing toxicity (Liu and Sayes, 2022; Zheng et al., 2024; Morishige et al., 2010), and influencing environmental behavior (Hotze et al., 2010; Lowry et al., 2012).

4.3 Shape

The shape of NPs influences their cellular interactions, uptake efficiency, and toxicity mechanisms. For instance, rod-shaped MSNs exhibit uptake and toxicity profiles that differ from those of spherical MSNs, particularly under shear stress conditions relevant to intravenous administration, where mechanical damage becomes a more prominent factor for rods (Geng et al., 2017).

4.4 Synthesis method

Different synthesis methods (e.g., Stöber vs. pyrolytic) yield SiNPs with distinct surface characteristics (e.g., silanol density and presence of strained rings) and aggregation states, resulting in significantly different toxicological profiles; pyrolytic silica is often more reactive and cytotoxic (Zhang et al., 2012).

4.5 Aggregation state

SiNPs tend to aggregate in biological media, affecting their effective hydrodynamic size and surface area available for interaction, thereby influencing toxicity outcomes and transport (Zhang et al., 2012).

4.6 Porosity and degradation

Although porosity is exploited for cargo loading in MSNs, it may also influence the surface area available for interaction and degradation kinetics (Cheng et al., 2023). Its biodegradability (dissolution into nontoxic silicic acid under physiological conditions) varies depending on its structure and synthesis, impacting long-term accumulation and environmental persistence.

5 Neurotoxicity: a growing concern

The nervous system is increasingly recognized as a potential target for SiNP toxicity, owing to the ability of certain SiNPs to traverse biological barriers, most notably the blood-brain barrier (BBB), and interact with sensitive neuronal and glial cells (Wei et al., 2024). Indeed, SiNPs, including mesoporous variants, have been actively investigated for their capability of central nervous system drug delivery. Successful BBB penetration by SiNPs has been demonstrated *in vivo*, although it is critically dependent on optimizing physicochemical properties such as size (typically <100 nm), surface charge, and surface modifications (Chen et al., 2022; Chen et al., 2024; Feng et al., 2023). The proposed transport mechanisms include receptor-mediated or adsorptive transcytosis, which is often facilitated by the *in vivo* protein corona and potentially transient modulation of tight junctions. Recent advances have focused on rational design, leveraging specific surface characteristics and protein-corona interactions to enhance targeted brain delivery, while maintaining BBB integrity (Chen et al., 2022; Chen et al., 2024; Feng et al., 2023) (Figure 1).

Once SiNPs gain access to the central nervous system, several neurotoxic effects are observed.

5.1 Direct effects on neurons

In vitro studies using primary cultured neurons have demonstrated that SiNPs induce oxidative stress and cell death (Kamikubo et al., 2019). This toxicity is often size-dependent, with smaller particles typically being more potent (Kamikubo et al., 2022). SiNPs can also impair neuronal development by inhibiting neurite outgrowth and branching (Kamikubo et al., 2022), suggesting potential developmental neurotoxicity. These mechanisms often involve oxidative stress, and antioxidant pretreatment offers protection (Liu and Sayes, 2022).

5.2 Brain accumulation and route-dependent toxicity

SiNPs can reach the brain following systemic or direct (e.g., intranasal) exposure (Jarrar et al., 2021; Suman et al., 2022). Studies in mice have shown that the exposure routes have a significant impact on neurotoxicity. Intranasal exposure leads to more pronounced brain damage, inducing both apoptosis and autophagy, than intravenous injection, which primarily induces autophagy, even at similar brain accumulation levels (Wei et al., 2024). This highlights the importance of considering the exposure pathways in neurotoxicity risk assessments.

5.3 Role in neurodegeneration

Emerging evidence suggests that SiNPs contribute to neurodegenerative processes. One study demonstrated that SiNPs promote the aggregation of α-synuclein, a hallmark protein in Parkinson's disease (PD) pathology, both *in vitro* and *in vivo* (Yuan et al., 2021). Specifically, in a murine model of PD, repeated intranasal exposure to SiNPs led to dopaminergic neuronal loss in the substantia nigra pars compacta and motor dysfunction, paralleling clinical symptoms. This was accompanied by α-synuclein aggregation in the striatum and midbrain, as well as upregulation of markers of mitochondrial stress, oxidative damage, and apoptosis in nigral neurons. These effects suggest that SiNPs may serve as environmental risk factors contributing to the development or progression of PD-like neurodegeneration.

6 Mitigating cytotoxicity and sustainable nanotechnology

Given the potential toxicity of SiNPs, the development of strategies to enhance their safety is imperative for their successful application.

6.1 Surface engineering

The modification of the SiNP surface is the most common approach. Coating with biocompatible polymers, such as polyethylene glycol or chitosan, can shield reactive surface groups, reduce protein adsorption (opsonization), alter

biodistribution, and decrease cytotoxicity and immunogenicity (Kamikubo et al., 2019; Kumarathasan et al., 2022). Functionalization with specific chemical groups (e.g., amino and carboxyl) or silanization can mitigate the interactions that cause membrane disruption and inflammasome activation (Eom and Choi, 2011; Morishige et al., 2010). However, coating selection requires careful consideration, because certain modifications may have unintended consequences, such as specific polyethylene glycol lengths that potentially exacerbate vascular lesions (Chen et al., 2022).

6.2 Safer-by-design

A more fundamental strategy is safer-by-design, which aims to minimize the inherent toxicity by controlling the properties of the NPs during synthesis. Adjusting the surface silanol density, eliminating reactive sites through calcination or metal doping (e.g., Ti and Al), or selecting synthetic routes that yield less-reactive particles (e.g., colloidal methods over pyrolytic methods) are key examples (Sun et al., 2015; Zhang et al., 2012). A crucial element of this design philosophy is engineering biodegradability. By utilizing the ability of SiNPs to decompose into nontoxic silica under physiological conditions, long-term accumulation and associated chronic toxicity can be prevented. (MacCuaig et al., 2022). This concept aligns directly with the principles of the circular economy; it involves designing particles that, after their intended use, can be assimilated back into natural silicon cycles. This "benign-by-design" strategy is a meaningful way to close the material loop and ensure the long-term sustainability of SiNP applications. Therefore, controlling the degradation rate to match the therapeutic window is a key challenge in this approach.

6.3 Composite materials

Designing composite NPs, in which the silica matrix provides a structure and another component offers therapeutic benefits (e.g., the antioxidant Se in Se@SiO2), can leverage the properties of silica while mitigating its toxicity (Yang et al., 2022).

Combining these approaches will enable the production of safer SiNPs, which will promote their use in sensitive applications such as drug delivery and regenerative medicine (Janjua et al., 2023).

7 Conclusion and future perspectives

The multifunctionality of SiNPs enables a wide range of promising applications, particularly in the field of biomedicine; however, these properties may also cause cytotoxicity and ecotoxicity. This review integrates the current understanding of key mechanisms underlying the adverse effects of SiNPs. These include oxidative stress, inflammation, lysosomal and mitochondrial dysfunction, and genotoxicity. Neurotoxicity has become a significant issue, with evidence indicating that SiNPs can harm nerve cells, impair development, and worsen neurodegenerative diseases, such as Parkinson's disease. The intricate relationship between the physicochemical properties of SiNPs and their toxic effects on different organisms, including human and environmental cells, underscores the necessity for a thorough and integrated risk assessment approach.

Strategies focusing on surface modification and safer-by-design principles show great potential for reducing toxicity; however, the development of biodegradable SiNPs and composite materials opens up new possibilities for improving safety. Nevertheless, significant gaps remain in our knowledge. Future research should focus on several key areas to fill these gaps and ensure safe and sustainable use of SiNPs.

1. Investigating long-term and low-dose effects: Beyond acute toxicity testing, chronic effects under actual environmental and occupational exposure scenarios (including co-exposure to other substances) should be investigated (Ahamed et al., 2019).
2. Assessing vulnerable populations: Focusing on the effects on sensitive life stages or individuals with pre-existing conditions.
3. Improving predictive models: Utilizing validated advanced *in vitro* models (e.g., primary neurons (Kamikubo et al., 2019; Kamikubo et al., 2022), organoids, or dechorionated zebrafish embryos (Kim et al., 2024)) and proteomics (Kumarathasan et al., 2022) and lipidomics (Gupta et al., 2023) to better predict *in vivo* human and ecological responses.

A deeper mechanistic understanding derived from such focused efforts is essential to guide the rational design of safer and more effective SiNPs for biomedical and other applications, considering both human health and environmental sustainability.

Author contributions

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The author(s) declare that Generative AI was used in the creation of this manuscript. Language Enhancement and Editing: Assistance with improving grammar, spelling, punctuation, clarity, and conciseness of the English text. This included

rephrasing sentences for better flow and readability. Literature and Citation Assistance: Assistance with citation formatting. It is affirmed that all scientific interpretations, conclusions, and the final intellectual content of the manuscript are solely the work and responsibility of the human author. All AI-generated suggestions or text were critically reviewed, edited, and verified by the author for accuracy and appropriateness before incorporation into the manuscript.

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