

Systemic Toxicological Effects of Silicates and Their Molecular Mechanisms, Organ Injury, and Public Health Implications: A Review

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ABSTRACT

Review

Silicates comprise a chemically diverse class of inorganic compounds widely used in industrial manufacturing, construction, consumer products, food processing, and biomedical applications. Inhalation of crystalline silica is well established as a cause of silicosis and lung cancer and crystalline silica has been classified as a Group 1 human carcinogen. However, emerging evidence suggests that other forms including soluble silicates and engineered silica nanoparticles may exert systemic toxicological effects beyond the respiratory tract. Toxic potential appears to depend strongly on crystallinity, solubility, particle size, and surface reactivity. Proposed mechanisms include oxidative stress, mitochondrial dysfunction, inflammasome activation, cytokine dysregulation, and fibrotic signaling pathways. Experimental and epidemiological studies indicate that renal, hepatic, metabolic, and immunological disturbances may occur following chronic exposure, particularly in occupational and nanoparticle contexts. The increasing use of amorphous silica in food and consumer products has also prompted renewed evaluation of ingestion-related safety. This review synthesizes mechanistic, experimental, and epidemiological evidence to clarify current understanding and identify areas requiring further investigation.

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INTRODUCTION

Silicates are one of the most common mineral groups in the Earth’s crust. Their basic unit, the silicon-oxygen tetrahedron (SiO₄⁴⁻), can form both crystalline and amorphous structures. These structures are useful in many industrial and biomedical fields (1). Silicon dioxide (SiO₂), or silica, occurs as crystalline forms like quartz, cristobalite, and tridymite, along with amorphous forms used in medicines, cosmetics, and food additives. For many years, concerns about toxicity mainly focused on inhalation of crystalline silica. This view was valid. Exposure to crystalline silica is closely linked to silicosis, pulmonary fibrosis, and lung cancer (2,3). The International Agency for Research on Cancer (IARC, 2012) classifies crystalline silica as a cancer risk to humans (4). Recently, however, the study of silicate toxicity has broadened. Researchers are currently investigating the potential effects of soluble silicates, long-term low-dose ingestion, and exposure to engineered silica nanoparticles (SiNPs), which may act differently in the body compared to larger materials (1,5). Sodium silicate (Na₂SiO₃), commonly used in detergents, for stabilizing cement, for preventing corrosion, and for treating water, can lead to possible systemic exposure through ingestion or skin contact (6). Silica nanoparticles (SiNPs) rank among the three most widely used nanomaterials globally (7). Simultaneously, the rise of nanotechnology

has boosted the production of silica nanoparticles. These materials might show different patterns of cellular absorption and movement within cells (8). This review examines silicate toxicity by combining information on physical and chemical properties, molecular mechanisms, specific organ effects, nanotoxicology, and regulatory issues.

Physicochemical Determinants of Silicate Toxicity
Crystallinity

Crystallinity is seen as a critical factor in determining pathogenicity. Crystalline silica has an organized lattice structure that can create surface radicals and reactive oxygen species (ROS) when it interacts with biological fluids (9, 10). Surface silanol groups can enhance interactions with membranes and increase cytotoxicity (10). In contrast, amorphous silica does not have long-range structural order and has typically been viewed as less fibrogenic. However, nanoscale amorphous silica can trigger oxidative and inflammatory responses under certain conditions, especially when its particle size and surface chemistry promote cellular uptake (1).

Particle Size, Surface Area, and Solubility
Particle size significantly affects biodistribution and biological reactivity. Silica nanoparticles that are less than 100 nm in size have high surface area to volume ratios, which can

Table 1. Comparative toxicological profile of silicate forms

Silicate form	Feature	Exposure route	Toxicological concern	Interpretation
Crystalline silica	Ordered crystal structure; highly reactive surface	Occupational inhalation	Pulmonary fibrosis, inflammation, autoimmune and renal associations	Toxicity strongly linked to respirable particle size and chronic inhalation
Amorphous silica	Non-crystalline structure	Food additives, industrial and environmental exposure	Generally lower toxicity than crystalline silica, but dose-dependent organ effects reported	Effects depend on purity, dose, particle size and solubility
Silica nanoparticles	Nanoscale size; high surface area	Biomedical, occupational and environmental exposure	Oxidative stress, inflammation, liver/kidney effects in animal models	Primary size alone is insufficient for determination of toxicity; agglomeration and protein corona matter
Soluble silicates	Dissociable alkaline salts	Industrial, detergent and chemical exposure	Irritation and possible systemic effects at high dose/repeated exposure	Toxicity depends on alkalinity, dose, route and exposure duration

lead to more ROS generation and easier cellular internalization (8). Smaller particles are more likely to be taken up by endocytic pathways, and they may gather in lysosomes and mitochondria, where additional oxidative stress can occur (11). Soluble silicates, such as sodium silicate and sodium metasilicate, dissociate in water to produce alkaline solutions that can damage epithelial barriers (12). While soluble forms tend to be less persistent than crystalline silica, repeated exposure can still cause chemical irritation and oxidative injury.

Particle size should be considered as a dynamic property of silica nanoparticles as it can be different after manufacture depending on the nature of the material, the route of delivery to the body, and the circulation and disposition of the nanomaterial with the human body. For instance, in water or protein-rich biological environments, silica nanoparticles can aggregate, clump together, partially dissolve, or form protein layers around themselves. These changes can alter the hydrodynamic size of the nanoparticles, their surface charge, sedimentation, cellular uptake, and amount delivered to various tissues in the body. Therefore, focusing on primary particle size alone may not give a complete picture of toxicity; it is essential to consider hydrodynamic size, zeta potential, agglomeration state, dissolution behavior, surface chemistry, and the biological medium used for exposure assessment (13,14). Since silicate toxicity changes based on crystallinity, solubility, particle size, surface reactivity, and exposure route, different types of silicates have varying toxicological profiles. A comparative summary of these types appears in Table 1.

Molecular Mechanisms of Silicate-Induced Toxicity ***Oxidative Stress and Redox Imbalance***

Oxidative stress is often seen as a key factor in silicate toxicity. However, it should not be viewed as a single starting point for all types of silicates. For crystalline silica, reactive surface silanol groups and interactions between the particles and cell membranes may trigger early production of reactive oxygen species (ROS). Later processes, like phagocytosis, lysosomal damage, mitochondrial dysfunction, and activation of inflammasomes, might further increase ROS production and inflammation. Depending on factors like crystallinity, solubility, particle size, surface chemistry, and how exposure occurs, ROS generation can act as both an initial trigger and to maintain inflammation, fibrosis, and overall toxicity (8, 10,15,16). When crystalline silica is engulfed by macrophages, it can stimulate the production of superoxide anions and hydroxyl radicals (1,8). These reactive species can lead to

lipid peroxidation, DNA strand breaks, and protein oxidation (9). Studies show that both *in vitro* and *in vivo* models show increased levels of malondialdehyde (MDA) and decreased antioxidant enzyme activity after silica exposure. Ongoing oxidative imbalance can activate inflammation pathways and contribute to cell death (15,16).

NOD-like receptor family pyrin domain containing 3 (NLRP3) Inflammasome Activation

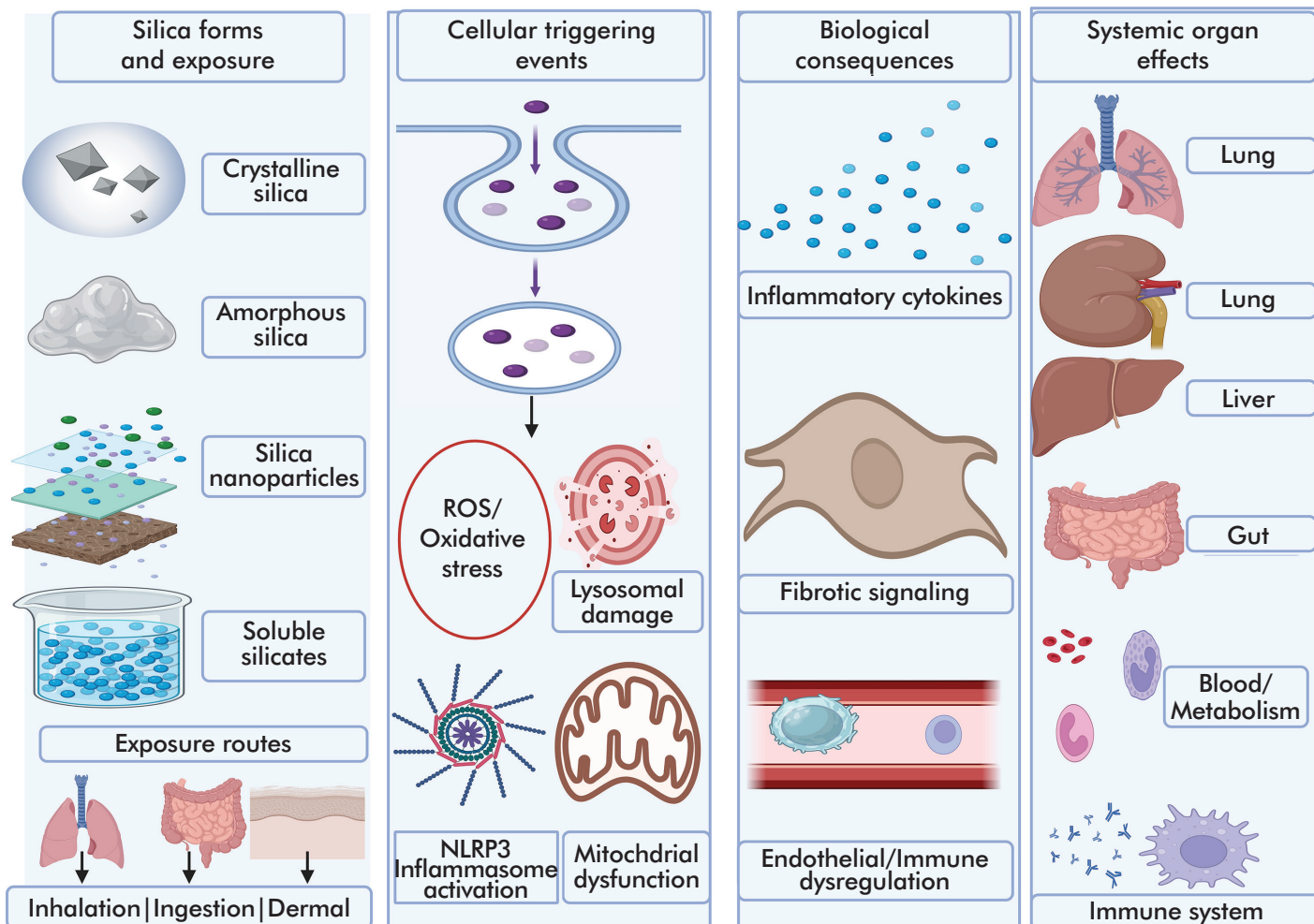
Silica particles can activate the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome after lysosomes in macrophages break down (16). This leads to the activation of caspase-1 and the release of interleukin-1 β , which boosts inflammatory processes (15). NLRP3 signaling has been identified as a major factor in silicosis and fibrotic development (3). The main molecular and organ-level processes by which various silicate forms may lead to systemic toxicity are outlined in Figure 1.

Mitochondrial Dysfunction and Apoptosis

Exposure to silica nanoparticles has been linked to disruption of mitochondrial membrane potential and the activation of intrinsic pathways that lead to cell death. Mitochondrial production of ROS can further worsen cellular damage. Transforming growth factor- β (TGF- β) signaling is crucial in fibrosis caused by silica. Long-term exposure might lead to increased fibroblast growth and collagen buildup through TGF- β /SMAD pathways (10). The main molecular and organ-level processes by which various silicate forms may lead to systemic toxicity are outlined in Figure 1. Inhalation of respirable crystalline silica is the most well-established silicate-mediated medical condition. Following alveolar deposition, inhaled particles are taken up by macrophages, leading to ongoing inflammatory signaling and fibroblast recruitment. Recurrent cycles of macrophage activation and cell death are believed to perpetuate injury and fibrosis. Epidemiological evidence continues to highlight that occupational silica exposure as a significant health burden globally, in particular in low- and middle-income countries that lack sufficient dust control. Besides silicosis, exposures to silica can lead to an increased risk of tuberculosis and lung cancer. The spectrum of diseases linked to silica exposure, besides classical fibrosis, extends to autoimmune diseases such as systemic sclerosis and rheumatoid arthritis (17); causality is difficult to determine, but immune dysfunction is biologically plausible following chronic exposure to silica.

Figure 1: Integrated mechanistic pathway of silicate-induced systemic toxicity.

Different silicate forms, including crystalline silica, amorphous silica, silica nanoparticles, and soluble silicates, may enter the body through inhalation, ingestion, or dermal exposure. Toxicological outcomes are influenced by crystallinity, particle size, surface reactivity, solubility, agglomeration, and protein corona formation. These determinants modulate cellular uptake, lysosomal destabilization, ROS generation, mitochondrial dysfunction, NLRP3 inflammasome activation, cytokine release, and fibrotic signaling, resulting in pulmonary, renal, hepatic, immune, cardiovascular, metabolic, and reproductive effects. Created in BioRender. CAMRET, C. (2026) <https://BioRender.com/l85kpu5>.



Renal and Hepatic Toxicity

Although lung disease dominates clinical discussions of silicate-mediated disease, the matter of systemic organ toxicity deserves additional attention. Different silicate forms can cause different incidence of nephrotoxicity (1,11) due to several variables including: dose, duration of exposure and nature of the silicate itself. Exposure of mice to sodium metasilicate caused a disruption in mitochondrial function in renal proximal tubules, indicating potential tubular toxicity following recurrent exposure (18). Repeated oral exposure to synthetic amorphous silica led to renal histopathological changes, including epithelial tubule vacuolation, inflammation and glomerular changes (19). Inhaled silica nanoparticles

were shown to induce renal tubular injury, including initial tubule damage and subsequent chronic kidney disease, in rat models (20), indicating that physicochemical characteristics and route of exposure play a significant role in the development of nephrotoxicity. In general, these effects must be considered within the context of a particular silicate form and do not extend to all silicates. In the occupational setting, there are links between silica exposure and increased risk of Chronic Kidney Disease CKD (21,22), however dose is difficult to measure, the dose-response is difficult to evaluate, and inflammatory mediators may account for nephron injury. Animal models indicate that exposure to silica nanoparticles leads to the modulation of enzyme activities in the liver,

increased lipid peroxidation, and enhanced levels of inflammatory cytokines (23,24). Biodistribution studies indicate the deposition of nanosilica into hepatic Kupffer cells, and the liver is a site of nanoparticle processing (25,26,27). Although animal models may suggest some forms of liver damage resulting from silica exposure, there are limited data available to confirm any relevance to humans (28,29).

Hematological and Metabolic Alterations

The exposure to nanosilica nanoparticles has been associated with increases in white blood cell count, modulation of platelet count and an elevation in systemic inflammatory markers (30). It is plausible that chronic inflammation would lead to a dysmetabolic state and dyslipidemia, especially considering that in mice exposures to nanosilica particles caused a promotion of TLR5 signaling and increase in pro-inflammatory cytokines, while *in vitro* they demonstrated the capacity to enhance inflammatory cytokine expression and increase inflammation (31). Nevertheless, there are limited human data and metabolic abnormalities may be linked to dose, duration, and route of exposure as well as characteristics of the nanoparticle itself.

Ingestion Exposure and Food-Grade Silica

E551 amorphous silica is widely consumed in foodstuffs based on its use as an anti-caking agent. The European Food Safety Authority (EFSA) concluded (in 2018) that exposures from foodstuffs are unlikely to represent a health risk for the general population (32). Nevertheless, it has been shown that food-grade silica may also contain nano fractions (33). As nanoparticles may possess different absorption kinetics as compared to bulk matter, there are some uncertainties regarding chronic low-dose ingestion. At present the level of long-term systemic bioaccumulation has not been definitively proven, and human follow-up data are very limited. Widespread usage of nanotechnology has brought the issue of silica nanoparticle safety under closer examination. Functionalization of nanoparticle surfaces can alter their biological performance dramatically either by reducing or enhancing cellular responses. It is important to note that current toxicological assessments are conducted under short-term, high dose studies and these models might not be relevant to ongoing occupational or environmental exposure.

Immunological and Autoimmune Effects

Whilst pneumoconiosis has long been recognized as the “classic” manifestation of crystalline silica exposure to lungs,

it appears that the immunologic effects may not be restricted to localized tissue remodeling. The epidemiological link between silica exposure and autoimmune disease, such as SLE, SSc and RA has been described (17,34,35). Mechanisms involved may cause chronic release of IL-1 induced by sustained activation of NLRP3 inflammasome via lysosomal disruption, leading to autoreactive lymphocytes. Nanosilica has also shown immune stimulating potential *in vitro*. Exposure of human immune cells to nanosuspensions *in vitro* has been linked to increased production of IL-6 and TNF-alpha. The relevance of these findings to clinical practice remains questionable at this point.

Cardiovascular and systemic inflammatory consequences

Chronic stimulation of the inflammatory pathway following silica exposure could extend into the cardiovascular system. Some epidemiological studies claim an association between occupational silica exposure and increased mortality due to cardiovascular diseases (CVD) (36). It is difficult to attribute such conditions solely to silica due to the presence of confounding factors such as smoking or other co-exposures. Mechanistically, the occurrence of oxidative stress might cause reduced bioavailability of nitric oxide and impaired vascular smooth muscle function (8). Animal data show that chronic exposure to nanoparticles can cause endothelial and coagulation abnormalities (1); however large human studies do not support a direct causal relationship to CVD.

Reproductive and developmental toxicity

Evidence for the reproductive toxicity of silicates is relatively scarce. *In vivo*, nanoscale silica has shown a capacity to cross the placental barrier (37) and to cause damage to the placenta and affect embryonic development during pregnancy. The risk associated with soluble silicates appears low in oral animal studies; but maternal toxicity can be observed at doses where GI irritation occurs, due to the high alkalinity of the substances. As for amorphous silica E551, a conclusion of low risk regarding reproduction has been stated by EFSA (32). However, the widespread increased utilization of nanotechnology highlights the importance of continued assessment of potential reproductive toxicity using new studies, and new techniques, to identify other possible risks in the future.

Epidemiological studies beyond the lung

In a reported study, there was an apparent increased risk for

autoimmune disease in workers exposed to silica (38). There is also some evidence linking occupational exposure to silicates to elevated risk of death from kidney disease. In these studies, the lack of proper controlling variables and the issue of co-exposures to toxins (such as heavy metals), confounds interpretation of results regarding the possible link between silica exposure and cardiovascular diseases and kidney mortality. Dose-response curves for systemic outcomes are poorly defined, thus dose-assessment in longitudinal studies incorporating a biomarker exposure assessment would be a valuable way to improve interpretation of data in the future.

Candidate Biomarkers for Early Detection of Systemic Silicate Toxicity

While no single marker has been validated for early systemic silicate toxicity other than lung damage, evidence suggests that multi-marker approaches may provide a useful approach for future surveillance and mechanisms research. Inflammatory markers including IL-6, IL-8, TNF, IL-1, CRP, ferritin, LDH, and alpha-1 antitrypsin have been implicated in systemic inflammation related to silica exposure (39). CC16 and KL-6 as indicators of epithelial lung injury and fibrotic activity have also been considered as lung markers, along with neopterin, which can reflect macrophage activation and oxidative immune response (40). For kidney injury, KIM-1 and L-FABP have been suggested as early indicators of silica-related kidney damage, with other indicators including 2-microglobulin, albuminuria, and N-acetyl-D-glucosaminidase have been proposed as general markers of tubular or glomerular kidney injury (41). Multi-marker approaches considering a combination of exposure, inflammatory, oxidative and organ specific markers alongside clinical outcomes should be a key future focus to improve understanding of critical toxicological effects of silicates (40,42).

Public health issues

Silica exposure is a worldwide occupational hazard. A Global Burden of Disease Study reported that occupational silica exposure contributes to global disability-adjusted life years (43). Public health emphasis is on control of dust, screening for silicosis, improving worker education regarding risks, investigating food grade silica safety, and extended monitoring to determine the long-term effects of exposure to nanomaterial silica. A generalized model for silicate toxicity combines particle deposition or ingestion, ROS generation, lysosome destabilization, NLRP3 activation, sustained cytokine signaling, and fibrosis or systemic damage to other organs. Lung fibrosis is mainly related to crystalline silica, but soluble silica might produce direct irritative and oxidative injury. The systemic biodistribution of nanosilica and the possibility of epigenetic alteration leads to organ-specific responses that will be modulated by the route of exposure, dose, particle features and individual susceptibility.

CONCLUSION

Silicates represent a diverse group of materials whose toxicological effects vary with crystallinity, solubility, particle size, and exposure route. Crystalline silica remains a well-established pulmonary hazard. Systemic consequences including renal, hepatic, immune, cardiovascular, and metabolic effects are increasingly documented in experimental models and supported, in some cases, by epidemiological associations. Nanotechnology has expanded both applications and uncertainties for silicates. While current regulatory frameworks emphasize inhalation risk, broader systemic exposure considerations may require more integrated assessment strategies. This, combined with continued multidisciplinary research on the links between exposure to toxicity, will be necessary to clarify future long-term health implications for advanced applications of silicates for a multitude of uses.

CONFLICT OF INTEREST

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