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Biodistribution and Systemic Toxicity of Nickel Particulates: Immune and Organ-Level Effects

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Abstract

Nickel-based particulates, including nickel nanoparticles and nickel oxide nanoparticles, are increasingly utilized in industrial and medical applications. However, there are significant concerns regarding their systemic toxicity. Due to their small size and high reactivity, these particles can deposit in the respiratory tract particularly the lungs and subsequently translocate into the bloodstream following inhalation, and ingestion. Evidence indicates that smaller particles exhibit broader biodistribution, with nanoparticles accumulating in organs such as the liver, kidneys, spleen, brain, and heart. Nickel particulates elicit robust immune responses, resulting in the release of inflammatory mediators, induction of oxidative stress, and genotoxic effects. Documented toxicities in the liver, kidneys, spleen, heart, blood, and brain are primarily attributed to particle dissolution, nickel ion release, and reactive oxygen species generation. In summary, nickel-based particulates induce complex, multi-organ toxicity influenced by particle size, solubility, and exposure route. This review outlines the principal mechanisms of nickel toxicity and underscores the necessity for improved risk assessment and longitudinal studies to inform occupational and environmental health policies.

Keywords: Nickel nanoparticles; Nickel oxide nanoparticles; Biodistribution; Systemic toxicity; Oxidative stress

1. Introduction

Nickel-based particulates, including nickel nanoparticles (NiNPs) and nickel oxide nanoparticles (NiO NPs), have attracted considerable scientific and regulatory interest due to their expanding industrial, medical, and technological applications, as well as their demonstrated capacity to enter systemic circulation following inhalation, oral exposure, or parenteral administration[1]. Due to their nanoscale dimensions, these materials display increased pulmonary deposition, efficient cellular uptake, and greater translocation across biological barriers into the bloodstream, which facilitates distribution to multiple secondary organs[2,3]. Experimental evidence increasingly demonstrates that such systemic dissemination is linked to immune activation, oxidative stress, and organ-specific toxicity affecting the liver, kidneys, cardiovascular system, and central nervous system. Therefore, comprehensive knowledge of the biodistribution, immune interactions, and toxicological profiles of nickel-based particulates is critical for advancing mechanistic toxicology, refining occupational exposure limits, and guiding risk assessment and public health policy.

2. Physicochemical Properties of Nickel-Based Nanoparticles

The biological behavior and systemic toxicity of nickel-based nanoparticles (NBNs), including Ni and NiO at the nanoscale, are fundamentally determined by their physicochemical properties. These characteristics influence particle stability, interaction with biological membranes, cellular uptake, biodistribution, and mechanisms of toxicity. Key

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properties with established toxicological relevance include particle size and surface area, morphology, surface charge, solubility and dissolution kinetics, and surface functionalization or coating[4].

2.1. Particle Size and Surface Area

Particle size is one of the most critical determinants of nanoparticle behavior in biological systems. Nanoparticles with diameters less than 100 nm have a high surface area to volume ratio, which enhances their surface energy and reactivity with biological molecules[5]. Smaller particles also exhibit increased cellular uptake via endocytosis and are more likely to translocate across epithelial barriers following inhalation or parenteral administration[6]. Increased surface area also contributes to higher rates of reactive oxygen species (ROS) generation, a key driver of oxidative stress in target organs[4].

2.2. Morphology and Shape

Nanoparticle shape influences cellular internalization and tissue distribution. Spherical particles are internalized more readily via clathrin-mediated pathways, whereas rod- or fiber-like particles may interact differently with membrane lipids and cytoskeletal structures[7]. Morphological differences have been shown to affect biodistribution and clearance rates, with non-spherical particles exhibiting prolonged circulation times and altered organ accumulation profiles compared to spherical counterparts[8].

2.3. Surface Charge (Zeta Potential)

Surface charge, typically quantified as zeta potential, modulates nanoparticle interactions with proteins and cell membranes. Positively charged nanoparticles tend to form strong electrostatic interactions with negatively charged cellular membranes and serum proteins, enhancing uptake and potentially triggering immune responses[9]. Neutral or slightly negative particles may evade rapid clearance, resulting in prolonged systemic circulation and extended organ exposure and thus greater toxicity[10].

2.4. Solubility and Dissolution Kinetics

Solubility and the dissolution rate of nickel nanoparticles in biological fluids determine the extent of ionic release, particularly Ni^{2+} ions, which contribute significantly to toxicity[11]. Particles that dissolve readily in lysosomal or cytosolic conditions can release ions that disrupt cellular redox balance, protein function, and DNA integrity[12]. The dissolution process is highly dependent on particle size, surface coating, and crystallinity, with smaller, less crystalline nanoparticles typically exhibiting higher dissolution rates[12].

2.5. Surface Functionalization and Protein Corona Formation

Surface coatings and the formation of a protein corona upon exposure to biological fluids alter nanoparticle identity and biological responses[13]. Adsorption of serum proteins onto NBNs can mask the original surface, affecting recognition by immune cells and uptake pathways. Functionalization with polymers or targeting ligands can improve dispersion stability, reduce aggregation, or promote selective tissue targeting, but may also modify toxicity profiles[12]. The composition of the protein corona changes dynamically with time and biological milieu, influencing biodistribution and cellular fate.

2.6. Aggregation and Agglomeration

Nanoparticles seldom remain as isolated primary particles in biological environments; they tend to aggregate or agglomerate due to van der Waals forces and ionic interactions[14]. Aggregation increases effective particle size, which can reduce cellular uptake but enhance deposition in organs with high phagocytic activity (e.g., liver, spleen) due to recognition by the mononuclear phagocyte system. Agglomerate size and stability also affect clearance by the reticuloendothelial system and influence circulatory half-life.

2.7. Biodistribution and Translocation

Nickel-based particulate biodistribution is strongly influenced by particle size, surface properties, and route of exposure. Despite limited direct human data, multiple experimental studies in rodents have demonstrated that NiNPs and NiO NPs can reach and affect extrapulmonary organs beyond the site of initial exposure. Intravenous administration of NiNPs in Sprague Dawley rats demonstrated widespread organ involvement, including pathological changes in the liver, spleen, and lungs, with evidence of inflammatory infiltration and histological disruption after 14 days[15].

Chronic inhalation exposures to NiO NPs in rats have also demonstrated systemic translocation following respiratory uptake. Prolonged inhalation of NiO NPs (up to 10 months) resulted in systemic toxicity, including hepatic and renal

damage, transient erythropoiesis stimulation, and evidence of brain penetration via the olfactory pathway[16]. Controlled intraperitoneal injection studies further demonstrated that NiO NP exposure induces hepatorenal oxidative stress and histological alterations in rats[17].

Mechanistic reviews indicate that smaller NiO nanoparticles are more readily absorbed and distributed into systemic circulation following pulmonary exposure compared to larger particles[18]. Collectively, these findings support a model in which NiNPs and NiO NPs deposit at the initial site of exposure, enter systemic circulation, and distribute to secondary organs, where they exert toxic effects via inflammation, oxidative stress, and disruption of cellular and biochemical processes[19].

2.8. Immune Modulation and Inflammation

Nickel particulates induce strong innate immune activation. Nickel nanoparticles trigger neutrophilic inflammation and secondary genotoxicity[20]. IL-6 and TNF-α upregulation has been observed in bronchial epithelial cells[21]. Cytokine responses also occur systemically; increased ROS and DNA damage markers were detected in rat lymphocytes following oral exposure[22]. Long-term inhalation enhances vascular inflammation relevant to atherosclerosis, with chronic exposure exacerbating plaque formation in hyperlipidemic mice and elevating systemic IL-1β and oxidative stress[23]. These findings indicate that nickel particulates behave as chronic inflammatory stimuli.

2.9. Hepatic Effects

The liver is a major deposition site and consistent target organ. NiO NPs activate endoplasmic reticulum stress pathways, resulting in hepatocyte apoptosis[24]. Dose-related increases in liver weight and histopathological changes, including cellular edema and loss of sinusoidal spaces, have also been reported[25]. Additionally, elevated serum markers of hepatic injury and lipid peroxidation were observed[26], consistent with toxicity mediated by dissolution, oxidative stress, and inflammation.

2.10. Renal and Splenic Toxicity

Kidneys are affected in multiple systemic exposure models. Altered biochemical indicators of renal function were documented following repeated intraperitoneal NiO NP injections[26]. Oral exposure produced elevated creatinine levels and oxidative damage in renal tissues[22]. Spleen toxicity, characterized by alterations in immune cell distribution and oxidative stress biomarkers, was also documented in repeated-dose inhalation experiments[16].

2.11. Neurotoxicity

Although brain burdens are lower than liver or kidney, NiNPs can cross biological barriers. DNA damage has been observed in brain tissues after oral dosing[22], linked to systemic inflammation and circulating nickel ions.

2.12. Cardiovascular and Hematological Effects

Cardiovascular toxicity is clinically relevant. Chronic exposure exacerbates atherosclerotic lesions[23]. Systemic oxidative stress, endothelial dysfunction, and lipid perturbations are implicated. Hematotoxicity is characterized by changes in red blood cell indices and leukocyte distribution; persistent alterations in circulating blood cells were reported following chronic inhalational exposure[16].

2.13. Genotoxicity and Oxidative Stress

NiNPs consistently induce oxidative stress across multiple organ systems. Acute ROS generation was demonstrated in lung tissue and cultured cells[27]. Genotoxicity, including micronucleus formation, has been reported[28]. Several studies confirm increased malondialdehyde, reduced antioxidant enzyme activity, and ROS-driven DNA injury[29].

3. Conclusion

Nickel particulates exhibit complex systemic toxicity influenced by particle size, solubility, and exposure route. Biodistribution studies demonstrate multi-organ accumulation. Immune modulation and oxidative stress are primary drivers of toxicity in the liver, kidney, spleen, cardiovascular system, and brain. Further research is necessary to define dose thresholds, dissolution kinetics, and long-term exposure implications

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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