

Iron Oxide Nanoparticles as Emerging Toxicological Entities: Exposure Pathways, Toxicokinetics, and Organ-Specific Risk Assessment

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ABSTRACT

Background: Iron oxide nanoparticles (IONPs) have become integral to a wide range of biomedical, industrial, food, agricultural, and environmental applications due to their magnetic properties, tunable surface chemistry, and perceived biocompatibility. However, the rapid expansion of their production and use has positioned IONPs as emerging toxicological entities of increasing relevance to human and environmental health. Growing evidence indicates that nanoscale iron exhibits biological behaviors and toxicological profiles distinct from bulk or ionic iron, necessitating a dedicated toxicological framework for risk assessment.

This review aims to critically evaluate iron oxide nanoparticles from a toxicology-centered perspective, with emphasis on exposure pathways, toxicokinetics, and organ-specific risk assessment. Human exposure to IONPs occurs through multiple routes, including inhalation in occupational settings, oral ingestion via food additives and contaminated water, dermal contact through cosmetics and consumer products, and intentional intravenous administration in medical applications. Once internalized, IONPs undergo complex absorption, distribution, metabolism, and excretion processes that are strongly influenced by particle size, surface charge, coating composition, aggregation state, and protein corona formation. These toxicokinetic determinants govern systemic biodistribution, persistence, and clearance, thereby shaping downstream toxicological outcomes.

At the molecular and cellular levels, IONPs induce toxicity primarily through iron-mediated oxidative stress, mitochondrial dysfunction, inflammatory signaling, disruption of iron homeostasis, and interference with cellular structures and signaling pathways. Organ-specific accumulation patterns give rise to differential risk profiles, with the liver, cardiovascular system, lungs, kidneys, immune system, and central nervous system displaying variable susceptibility depending on exposure route and nanoparticle characteristics. Importantly, chronic low-dose exposure and repeated administration raise concerns regarding bioaccumulation, delayed toxicity, and long-term health consequences that remain insufficiently characterized.

In conclusion, iron oxide nanoparticles should no longer be regarded solely as functional nanomaterials but as biologically active agents requiring rigorous toxicological evaluation. Integrating exposure science, toxicokinetics, mechanistic insights, and organ-specific risk assessment is essential for the development of safer-by-design IONPs, improved regulatory frameworks, and responsible translation of nanotechnology into clinical, industrial, and consumer domains.

Keywords: Iron Oxide Nanoparticles, Toxicological Entities, Toxicokinetics

INTRODUCTION

Iron oxide nanoparticles (IONPs) have gained unprecedented attention over the past two decades due to their extensive integration into biomedical technologies, industrial processes, food systems, agriculture, and environmental remediation. Their unique magnetic behavior, nanoscale size, and adaptable surface chemistry have enabled applications ranging from magnetic resonance imaging and drug delivery to food pigmentation, wastewater treatment, and soil enrichment. As production volumes and exposure scenarios expand, IONPs are increasingly encountered not only as engineered medical tools but also as unintentional environmental and occupational contaminants, positioning them as emerging entities of toxicological concern [1].

From a toxicology standpoint, iron oxide nanoparticles represent a distinct category of metal-based nanomaterials whose biological behavior cannot be extrapolated directly from bulk iron oxides or conventional iron salts. At the nanoscale, increased surface area, altered redox activity, and enhanced cellular uptake confer properties that profoundly influence their interaction with biological systems. These characteristics enable IONPs to cross biological barriers, interact with intracellular organelles, and participate in redox reactions that may disrupt cellular homeostasis [2]. Consequently, nanoscale iron challenges traditional paradigms of iron safety and necessitates reevaluation through a nanotoxicological lens.

Human exposure to IONPs is multifaceted and continues to diversify. Occupational inhalation occurs during nanoparticle synthesis, pigment manufacturing, welding, and handling of magnetic materials, while oral exposure arises from the intentional use of iron oxide pigments and fortificants in food products. Dermal contact is relevant through cosmetics and consumer goods, and intravenous exposure is inherent to diagnostic and therapeutic nanomedicine applications. Environmental dissemination through air, soil, and water further broadens exposure potential across populations, including vulnerable groups such as workers, children, and patients with pre-existing disease [3].

Toxicological risk associated with IONPs is governed not only by exposure but also by their toxicokinetics, encompassing absorption, distribution, metabolism, and excretion. These processes are highly dependent on physicochemical attributes such as particle size, surface charge, crystallinity, coating materials, and aggregation behavior. Upon entering the body, IONPs interact with proteins to form a dynamic protein corona, which modifies their biological identity and influences biodistribution, cellular uptake, and clearance pathways [4]. Understanding these kinetic processes is essential for predicting systemic exposure and organ-specific toxicity.

Accumulating experimental and translational evidence indicates that iron oxide nanoparticles can induce adverse effects through mechanisms including oxidative stress, mitochondrial dysfunction, inflammatory signaling, disruption of iron homeostasis, and interference with cellular structures and signaling pathways. Organ-specific accumulation patterns further modulate toxicity, with certain tissues exhibiting heightened vulnerability depending on exposure route and nanoparticle characteristics [5]. Despite growing recognition of these risks, standardized toxicological assessment strategies and long-term exposure data remain limited.

The aim of this review is to critically analyze iron oxide nanoparticles as emerging toxicological entities by integrating current knowledge on exposure pathways, toxicokinetics, and organ-specific risk assessment. By adopting a toxicology-driven framework, this article seeks to bridge existing gaps between nanomaterial design, biological behavior, and safety evaluation, thereby supporting informed risk management and the development of safer iron oxide nanoparticle applications [6].

Exposure Pathways

Human and environmental exposure to iron oxide nanoparticles (IONPs) occurs through multiple, often overlapping pathways, reflecting their widespread use across medical, industrial, food, agricultural, and environmental sectors. From a toxicological perspective, understanding exposure routes is fundamental, as they determine the initial biological barriers encountered, absorption efficiency, biodistribution patterns, and ultimately organ-specific risk. Unlike conventional iron compounds, IONPs exhibit nanoscale-dependent behaviors that enhance their mobility, persistence, and biological reactivity, thereby expanding both intentional and unintended exposure scenarios [7].

Inhalation represents one of the most significant exposure routes, particularly in occupational and environmental settings. Workers involved in nanoparticle synthesis, pigment production, welding, mining, and materials processing may inhale airborne IONPs generated during high-temperature or mechanical operations. Due to their small aerodynamic diameter, these particles can penetrate deeply into the respiratory tract and deposit in the alveolar region. Once deposited, IONPs may be internalized by alveolar macrophages or translocate across the air–blood barrier into systemic circulation, initiating both local pulmonary effects

and secondary systemic toxicity [8]. Environmental dispersion of iron oxide nanoparticles through industrial emissions further raises concerns regarding chronic low-level inhalation in surrounding communities.

Oral exposure constitutes another major pathway, particularly through the intentional use of iron oxide pigments and additives in food products. Iron oxides are authorized as food colorants under additive codes such as E172, and nanoscale fractions have been identified within commercially available products. Ingestion may also occur through contaminated drinking water, soil-to-crop transfer, or accidental ingestion of particulate matter. Within the gastrointestinal tract, IONPs interact with digestive fluids, mucus layers, and intestinal epithelial cells, where partial dissolution and aggregation may occur. Although systemic absorption is generally limited, repeated or high-dose exposure raises concerns about localized gastrointestinal effects, gut microbiota disruption, and downstream liver exposure via the portal circulation [9].

Dermal exposure arises primarily from the use of cosmetics, sunscreens, topical formulations, and occupational contact with nanoparticle-containing materials. The intact stratum corneum provides an effective barrier against most particulate matter; however, nanoparticle size, surface charge, formulation type, and skin condition significantly influence penetration potential. Smaller IONPs or those incorporated into lipid-rich or semi-solid formulations may penetrate superficial skin layers, particularly when the barrier is compromised by abrasion, inflammation, or ultraviolet radiation. While systemic absorption through skin is typically low, repeated dermal exposure may elicit localized oxidative stress and inflammatory responses [10].

Intravenous exposure represents a unique and highly relevant route in biomedical applications, where iron oxide nanoparticles are intentionally introduced into systemic circulation as diagnostic or therapeutic agents. This exposure bypasses external biological barriers and leads to immediate interaction with blood components, plasma proteins, and vascular endothelium. Formation of a protein corona occurs rapidly, influencing nanoparticle recognition by immune cells and dictating biodistribution and clearance. Although this route is controlled and dose-defined, it carries inherent toxicological risks related to organ accumulation, oxidative stress, and immune activation, particularly with repeated administration or inadequate surface modification [11].

Environmental exposure pathways further broaden the toxicological relevance of iron oxide nanoparticles. Release into soil and water systems through industrial waste, agricultural applications, and remediation technologies can lead to uptake by plants, microorganisms, and aquatic organisms. These interactions facilitate entry into the food chain, creating indirect exposure routes for humans and wildlife. Environmental transformation processes, such as aggregation, dissolution, and surface modification, may alter nanoparticle behavior and toxicity, complicating risk assessment across ecosystems [12].

Collectively, the diversity of exposure pathways underscores the need for route-specific toxicological evaluation of iron oxide nanoparticles. Inhalation, ingestion, dermal contact, intravenous administration, and environmental dissemination each impose distinct biological challenges and risk profiles. Integrating exposure science with toxicokinetics is therefore essential for accurately predicting organ-specific toxicity and for developing regulatory strategies that reflect real-world exposure scenarios [13].

Toxicokinetics of Iron Oxide Nanoparticles (Absorption, Distribution, Metabolism, and Excretion)

The toxicokinetic behavior of iron oxide nanoparticles (IONPs) plays a central role in determining their biological fate and toxicological risk. Unlike soluble iron salts, IONPs exhibit particle-specific absorption, distribution, metabolism, and excretion (ADME) profiles that are strongly influenced by nanoscale physicochemical properties such as size, surface charge, coating composition, crystallinity, and aggregation state. These parameters govern systemic exposure, organ accumulation, persistence, and clearance, thereby shaping both acute and chronic toxicological outcomes [14].

Absorption of IONPs varies markedly depending on the route of exposure. Following inhalation, deposited nanoparticles in the alveolar region may be phagocytosed by alveolar macrophages or internalized by epithelial cells. A fraction of these particles can translocate across the air–blood barrier and enter systemic circulation, particularly when particles are ultrafine or surface-modified to enhance dispersibility [15]. Oral absorption through the gastrointestinal tract is generally limited; however, nanoscale dimensions facilitate interaction with intestinal epithelium via transcellular endocytosis, M-cell uptake in Peyer’s patches, or paracellular transport under inflammatory conditions. Smaller particles exhibit higher absorption efficiency, whereas aggregation and dissolution within gastric fluids may reduce systemic uptake [16]. Dermal absorption remains minimal under intact skin conditions but may increase when barrier integrity is compromised, allowing penetration into superficial epidermal layers [17]. Intravenous administration, in contrast, results in immediate and complete systemic bioavailability, bypassing absorptive barriers

entirely [18].

Once absorbed, distribution of IONPs is primarily governed by the mononuclear phagocyte system. Circulating nanoparticles rapidly interact with plasma proteins, forming a dynamic protein corona that alters their biological identity and influences recognition by immune cells. As a result, IONPs preferentially accumulate in organs rich in phagocytic activity, particularly the liver, spleen, and to a lesser extent the lungs and bone marrow [19]. Particle size and surface coating strongly modulate distribution patterns; smaller or stealth-coated nanoparticles may evade rapid sequestration and reach secondary organs such as the heart, kidneys, and central nervous system. In certain cases, ultrasmall IONPs have demonstrated the ability to cross the blood–brain barrier, raising concerns regarding neurotoxicity [20].

Metabolism of iron oxide nanoparticles involves partial intracellular degradation rather than classical enzymatic biotransformation. Following cellular uptake, IONPs are trafficked to lysosomes, where acidic conditions promote dissolution of the iron oxide core and release of Fe^{2+} and Fe^{3+} ions. These ions may subsequently enter endogenous iron metabolic pathways, becoming incorporated into ferritin or hemosiderin pools [21]. While this process facilitates physiological iron recycling, excessive or chronic exposure can overwhelm regulatory mechanisms, leading to iron overload, oxidative stress, and disruption of iron homeostasis. The rate and extent of degradation are influenced by surface coatings, with biodegradable or citrate-coated nanoparticles degrading more rapidly than silica- or polymer-coated formulations [22].

Excretion of IONPs and their degradation products occurs predominantly through hepatobiliary and renal pathways. Larger particles and those retained within macrophages are typically cleared via biliary secretion into feces, whereas smaller nanoparticles or released iron ions may be filtered by the kidneys and excreted in urine [23]. Surface modification significantly affects clearance kinetics; polyethylene glycol-coated nanoparticles often exhibit prolonged circulation times and delayed elimination, increasing the potential for tissue accumulation. Several studies report incomplete excretion and long-term retention of iron oxide nanoparticles in organs following repeated exposure, highlighting concerns regarding cumulative toxicity [24].

In summary, the toxicokinetics of iron oxide nanoparticles are complex and highly dependent on exposure route and nanoparticle design. Variability in absorption efficiency, preferential organ distribution, lysosomal metabolism, and slow or incomplete excretion collectively contribute to organ-specific risk profiles. Understanding these ADME processes is essential for predicting long-term toxicity, informing safer nanoparticle design, and supporting evidence-based regulatory decision-making for iron oxide nanoparticle applications [25].

Organ-Specific Risk Assessment

Organ-specific risk assessment of iron oxide nanoparticles (IONPs) integrates exposure pathways, toxicokinetic behavior, and mechanistic toxicity to identify tissues most vulnerable to adverse effects. Due to their preferential biodistribution, persistence, and iron-mediated reactivity, IONPs pose differential risks across organ systems, with susceptibility strongly influenced by particle size, surface chemistry, dose, exposure duration, and route of entry. A toxicology-based assessment therefore requires evaluating both target-organ accumulation and downstream functional consequences [26].

The liver represents the highest-risk organ following systemic exposure to iron oxide nanoparticles. As the primary site of nanoparticle sequestration and iron metabolism, the liver accumulates substantial quantities of IONPs through Kupffer cell uptake and hepatocellular internalization. This accumulation predisposes hepatic tissue to oxidative stress, lysosomal destabilization, mitochondrial dysfunction, and inflammatory signaling driven by iron ion release. Biochemical alterations, including elevated serum transaminases and disrupted lipid metabolism, alongside histopathological changes such as hepatocellular degeneration and inflammatory infiltration, underscore the liver's central role in IONPs-associated toxicity. Chronic exposure further increases the risk of iron overload and progressive liver injury [27].

The cardiovascular system constitutes a critical secondary risk domain, despite lower overall nanoparticle accumulation compared with the liver. Endothelial cells and cardiomyocytes are highly sensitive to iron-mediated oxidative stress, and exposure to circulating IONPs can impair endothelial nitric oxide signaling, promote vascular inflammation, and induce thromboinflammatory responses. In the myocardium, mitochondrial damage and oxidative injury compromise energy production and contractile function, increasing the risk of arrhythmias and myocardial dysfunction. These effects are particularly relevant under conditions of repeated exposure, high-dose administration, or in individuals with pre-existing cardiovascular disease [28].

Pulmonary risk is especially pronounced following inhalation exposure. Deposition of IONPs in the alveolar region triggers local

oxidative stress, macrophage activation, and inflammatory cytokine release. While some particles are cleared via mucociliary transport or phagocytosis, others translocate into systemic circulation, contributing to extrapulmonary toxicity. Repeated inhalation exposure has been associated with alveolar thickening, interstitial inflammation, and compromised lung function in experimental models, indicating potential long-term respiratory risk [29].

Renal toxicity represents a moderate but clinically relevant concern, particularly for ultrasmall nanoparticles or degradation products capable of glomerular filtration. Accumulation in renal tubular cells may induce oxidative stress, mitochondrial injury, and apoptotic signaling, leading to impaired reabsorption capacity and functional stress. Although kidney exposure is generally lower than hepatic or pulmonary exposure, chronic or high-dose conditions may exacerbate nephrotoxic outcomes, especially in susceptible populations [30].

The immune system plays a dual role as both a mediator and target of IONPs toxicity. Macrophages in the liver, spleen, and lungs actively internalize nanoparticles, leading to immune activation, cytokine release, and oxidative stress. While acute immune responses may facilitate clearance, chronic exposure can result in immune dysregulation, altered cytokine profiles, impaired phagocytic function, and potential immunosuppression. These effects raise concerns regarding increased susceptibility to infection and altered inflammatory homeostasis [31].

Neurotoxicity constitutes an emerging area of concern, particularly for ultrasmall iron oxide nanoparticles capable of crossing the blood–brain barrier or entering the central nervous system via olfactory pathways. Accumulation in neural tissue has been linked to oxidative stress, mitochondrial dysfunction, altered neurotransmitter balance, and behavioral deficits in experimental models. Although brain exposure is generally limited, the central nervous system’s sensitivity to iron dysregulation necessitates cautious evaluation, especially for medical applications involving repeated systemic administration [32].

The gastrointestinal tract represents a localized risk following oral exposure. While systemic absorption of IONPs is relatively low, prolonged contact with intestinal epithelium may disrupt barrier integrity, alter gut microbiota composition, and induce local inflammatory responses. Secondary hepatic exposure via the portal circulation further contributes to systemic risk. These effects are particularly relevant in the context of food additives and chronic dietary intake [33].

Overall, organ-specific risk assessment reveals that iron oxide nanoparticles pose the greatest toxicological threat to organs involved in clearance, iron metabolism, and high oxidative demand. The liver and cardiovascular system emerge as priority targets, followed by lungs, kidneys, immune organs, and the central nervous system. Integrating organ-specific vulnerability with toxicokinetic data is essential for accurate risk characterization, identification of susceptible populations, and development of safer nanoparticle formulations and exposure guidelines [34].

Regulatory and Risk Management Perspectives

The accelerating incorporation of iron oxide nanoparticles (IONPs) into healthcare, food systems, consumer products, and environmental technologies has created a pressing need for regulatory frameworks that can reliably evaluate nanoparticle-specific hazards and guide risk management. Traditional regulatory approaches based on bulk chemical identity are insufficient for IONPs because nanoscale materials exhibit distinct physicochemical behaviors, exposure profiles, and toxicokinetic patterns. As a result, regulatory agencies increasingly emphasize the requirement for comprehensive characterization, toxicokinetic evaluation, and organ-specific toxicity testing to ensure safe use across intended applications [35].

In biomedical contexts, regulatory oversight focuses on manufacturing quality, reproducibility, and biocompatibility, given that intravenous administration results in direct systemic exposure. Guidance commonly emphasizes Good Manufacturing Practice compliance, control of particle size distribution and surface chemistry, and detailed evaluation of biodistribution, clearance, and long-term tissue retention. These requirements reflect recognition that nanoparticle persistence in clearance organs may produce delayed toxicity that is not captured in short-term safety testing. Such concerns are particularly relevant for repeated imaging or therapeutic use, where cumulative exposure may increase hepatic, cardiovascular, and immunological risk [36].

For food-related exposure, regulatory considerations extend beyond classical nutritional iron assessment because iron oxide pigments and additives may contain nanoscale fractions with altered biological reactivity. Evidence demonstrating the presence of iron oxide nanoparticles in food-grade pigment E172 has intensified calls for clearer distinction between micro- and nano-sized forms in commercial products. Risk management in this area requires validated analytical methods to identify and quantify nanoparticle fractions, standardized testing for gastrointestinal and systemic effects, and evaluation of chronic low-dose exposure

scenarios. Regulatory attention has therefore increasingly focused on harmonizing approaches for assessing nanomaterials in the food and feed chain, recognizing that traditional toxicological assumptions may not be appropriate for nanoparticle-containing additives [37].

Occupational and environmental risk management presents additional regulatory challenges because inhalation exposure and environmental dispersion may involve complex mixtures of particles with variable size, aggregation, and surface modification. Risk control strategies typically include engineering controls, personal protective equipment, exposure monitoring, and workplace standards designed to limit airborne nanoparticle concentrations. However, the lack of universally validated exposure thresholds specific to iron oxide nanoparticles complicates enforcement and hazard communication. Environmental release pathways, including wastewater discharge and soil contamination, further require consideration of nanoparticle persistence, transformation, and potential entry into the food chain [37].

A major regulatory challenge for IONPs is the absence of globally harmonized testing protocols for nanoparticle toxicity and toxicokinetics. Variability in experimental design, dose metrics, dispersion conditions, and biological models limits cross-study comparability and complicates evidence synthesis for regulatory decision-making. Several reviews emphasize that nanoparticle-specific factors, such as protein corona formation, dissolution kinetics, and aggregation behavior in biological media, can drastically alter toxicity outcomes and must be integrated into standardized test methods. Without such harmonization, risk assessments may underestimate hazards for certain formulations or exposure scenarios [37].

Risk management approaches increasingly prioritize safer-by-design strategies that incorporate toxicological principles into nanoparticle engineering. Surface functionalization to reduce aggregation, minimize iron ion release, and limit nonspecific cellular uptake is viewed as a key pathway for mitigating toxicity while preserving functional performance. Designing nanoparticles with predictable degradation and clearance profiles is also critical for reducing long-term tissue retention and cumulative organ toxicity. These strategies align with the emerging concept that regulatory evaluation should not only identify hazards but also encourage engineering solutions that reduce toxic potential at the material design stage [37].

Overall, regulatory and risk management perspectives highlight that iron oxide nanoparticles require a tailored framework integrating physicochemical characterization, exposure assessment, toxicokinetics, and organ-specific toxicity profiling. Progress in this area will depend on improved analytical methods for nanoparticle detection in complex matrices, standardized international testing guidelines, and stronger alignment between toxicological evidence and policy development. Such advances are necessary to support responsible innovation while ensuring that the expanding use of iron oxide nanoparticles does not outpace safeguards for human and environmental health [37].

Conclusion

Iron oxide nanoparticles have transitioned from specialized functional materials to widely distributed agents across medical, industrial, food, and environmental domains, bringing with them complex toxicological challenges. As their production and application continue to expand, it is increasingly clear that iron oxide nanoparticles cannot be evaluated solely through the lens of conventional iron chemistry. At the nanoscale, altered physicochemical properties fundamentally change their biological interactions, toxicokinetic behavior, and risk profile.

This review highlights that exposure to iron oxide nanoparticles occurs through diverse and often overlapping pathways, including inhalation, oral ingestion, dermal contact, intravenous administration, and environmental dissemination. Once internalized, these nanoparticles exhibit complex absorption, distribution, metabolism, and excretion patterns that are strongly influenced by particle size, surface chemistry, coating stability, and aggregation behavior. Preferential accumulation in clearance organs and prolonged tissue retention underscore the importance of toxicokinetics in shaping long-term risk.

Organ-specific risk assessment reveals that toxicity is not uniformly distributed across biological systems. Organs involved in filtration, iron handling, and high metabolic demand—particularly the liver, cardiovascular system, lungs, kidneys, immune organs, and, under certain conditions, the central nervous system—display heightened vulnerability. The underlying mechanisms of toxicity are largely driven by iron-mediated oxidative stress, mitochondrial dysfunction, inflammatory signaling, and disruption of iron homeostasis, with severity modulated by exposure route and nanoparticle design.

Collectively, these findings reinforce the need to recognize iron oxide nanoparticles as emerging toxicological entities rather than inherently benign materials. Future progress depends on integrating exposure science, toxicokinetics, mechanistic

toxicology, and organ-specific risk assessment into a unified framework that informs both material design and regulatory decision-making. Emphasizing safer-by-design strategies, standardized testing protocols, and long-term exposure studies will be essential to ensure that the benefits of iron oxide nanoparticle technologies are realized without compromising human or environmental health.

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