Iron Oxide Nanoparticles: Physicochemical Determinants, Multifunctional Applications, and Toxicological Implications Across Biological Systems

Mie Mohammed Samir Gomaa[1], Nashwa Mohamad Mohamad Shalaby[1], Mohamed Abdelrahman Ghoneim Shaheen[2], Hoda Gamal Ghonemy Ibrahim [1]

1 Forensic Medicine and Toxicology Department, Faculty of Medicine, Zagazig University,
2 Medical Histology and Cell Biology Department, Faculty of Medicine, Zagazig University
Corresponding Author: Hoda Gamal Ghonemy Ibrahim

Received: 28 October 2024, **Accepted:** 17 November 2024, **Published:** 20 November 2024

Abstract

Background: Iron oxide nanoparticles (IONPs) have emerged as one of the most extensively investigated nanomaterials owing to their unique magnetic properties, versatile surface chemistry, and broad applicability across biomedical, industrial, food, environmental, and agricultural sectors. Their increasing integration into clinical imaging, drug delivery, food additives, cosmetics, and environmental remediation has markedly expanded the potential for human exposure, raising critical toxicological and regulatory concerns. At the nanoscale, iron oxide exhibits physicochemical behaviors distinct from its bulk counterpart, including enhanced surface reactivity, redox activity, and altered biodistribution, which collectively govern its biological interactions and safety profile.

This review aims to provide a comprehensive toxicology-oriented synthesis of iron oxide nanoparticles, emphasizing how physicochemical determinants—such as particle size, surface charge, coating, crystallinity, and oxidation state—dictate biological fate, toxicokinetics, and mechanistic toxicity across biological systems. Particular focus is placed on the liver and cardiovascular system, which represent primary and highly vulnerable target organs due to their central roles in nanoparticle clearance, iron metabolism, and systemic homeostasis.

Available evidence demonstrates that IONPs undergo complex absorption, distribution, metabolism, and excretion processes that favor accumulation in the liver and, to a lesser extent, the heart. Hepatic uptake by Kupffer cells and hepatocytes leads to lysosomal degradation, iron ion release, oxidative stress, inflammatory signaling, and disruption of iron homeostasis, manifesting as biochemical, histopathological, and functional liver injury. In the cardiovascular system, IONPs induce endothelial dysfunction, mitochondrial impairment, thromboinflammatory responses, and myocardial oxidative damage, particularly following exposure to ultrasmall or uncoated nanoparticles. At the molecular level, toxicity is mediated by reactive oxygen species generation, mitochondrial dysfunction, genotoxicity, ferroptosis, and apoptosis, with severity strongly influenced by dose, exposure duration, and surface modification. While other organs—including kidneys, lungs, brain, immune, reproductive, and gastrointestinal systems—also exhibit susceptibility, hepatic and cardiac toxicities consistently emerge as dominant and dose-limiting outcomes.

Conclusion: Although iron oxide nanoparticles offer substantial technological and therapeutic benefits, their safety cannot be assumed based solely on bulk iron biocompatibility. A toxicology-driven understanding that integrates physicochemical design with organ-specific risk is essential for safer development and regulatory evaluation. Future research should prioritize long-term, low-dose exposure studies, standardized toxicity testing, and safer-by-design strategies to minimize hepatotoxic and cardiotoxic risks while preserving functional performance.

.

Keywords: *Iron Oxide Nanoparticles, Toxicological Implications, Biological Systems*

Introduction

Iron oxide nanoparticles (IONPs) have emerged as a cornerstone of modern nanotechnology due to their unique magnetic behavior, tunable surface chemistry, and relative biocompatibility compared with other metal-based nanomaterials. These properties have driven their extensive use across biomedical, industrial, food, environmental, and agricultural sectors. In contrast to bulk iron oxides, nanoscale iron oxide exhibits enhanced surface area, increased surface energy, altered electronic structure, and size-dependent magnetic responses, enabling advanced applications such as magnetic resonance imaging (MRI), targeted drug delivery, magnetic hyperthermia, biosensing, and environmental remediation [1]. However, these same physicochemical attributes that confer functional advantages also significantly influence biological interactions and raise critical toxicological concerns [2].

The rapid expansion of IONPs into clinical and consumer-facing applications has markedly increased the probability of human exposure through multiple routes, including intravenous injection in medical imaging and therapy, inhalation in occupational and industrial settings, ingestion through food additives such as E172, and dermal contact via cosmetics and environmental sources [3]. Unlike conventional iron compounds, nanoparticles possess the ability to cross biological barriers, undergo cellular internalization, and interact directly with intracellular organelles. Once internalized, IONPs may partially degrade, releasing bioactive iron ions that can participate in redox cycling and Fenton-like reactions, thereby promoting oxidative stress and cellular injury [4].

From a toxicological perspective, the liver represents the primary target organ for iron oxide nanoparticles following systemic exposure. This is largely attributable to the liver's central role in nanoparticle clearance, iron storage, and metabolic regulation. Kupffer cells and hepatocytes efficiently sequester circulating IONPs, leading to preferential hepatic accumulation [5]. Experimental studies consistently demonstrate that this accumulation can trigger lysosomal iron release, oxidative stress, mitochondrial dysfunction, inflammatory signaling, and disruption of iron homeostasis, ultimately manifesting as hepatocellular injury, altered liver enzyme profiles, and histopathological damage [6]. Importantly, the severity of hepatotoxicity is strongly modulated by nanoparticle size, surface charge, coating composition, dose, and exposure duration [7].

In parallel, increasing evidence highlights the cardiovascular system as a critical yet underappreciated target of IONPs toxicity. Endothelial cells and cardiomyocytes are particularly vulnerable to iron-mediated oxidative stress due to their high metabolic demand and sensitivity to redox imbalance. Studies have shown that IONPs can induce endothelial dysfunction, impair nitric oxide signaling, and activate thromboinflammatory pathways, potentially increasing the risk of vascular injury and coagulation disturbances [8]. Moreover, ultrasmall or poorly surface-modified IONPs have been reported to accumulate in cardiac tissue, where they disrupt mitochondrial function, reduce ATP production, and promote myocardial oxidative damage, leading to functional cardiac impairment in experimental models [9].

Despite the growing body of literature on iron oxide nanoparticles, many existing reviews primarily emphasize synthesis strategies and applications, while toxicological aspects are often treated superficially or generalized across organ systems. Furthermore, available studies frequently examine toxicity in isolated organs without integrating physicochemical determinants, toxicokinetics, and mechanistic pathways into a unified framework that explains organ-specific vulnerability. Long-term and low-dose exposure scenarios—highly relevant for food-grade nanoparticles, occupational exposure, and repeated clinical administration—remain insufficiently characterized, particularly with respect to cumulative hepatic and cardiovascular burden [10].

Aim and research gap:

The aim of this review is to provide a comprehensive, toxicology-oriented synthesis of iron oxide nanoparticles that explicitly links physicochemical characteristics to biological fate, molecular mechanisms of toxicity, and systemic outcomes across biological systems. By placing particular emphasis on the liver and cardiovascular system, this review addresses a critical gap in current

knowledge: the lack of integrated analyses explaining why these organs represent dominant targets of IONPs-induced toxicity. Such an approach is essential for advancing safer-by-design nanomaterials, improving translational risk assessment, and guiding regulatory frameworks to ensure the responsible and safe use of iron oxide nanoparticles.

Physicochemical Determinants Governing the Biological Behavior of Iron Oxide Nanoparticles

The physicochemical characteristics of iron oxide nanoparticles (IONPs) constitute the primary determinants of their biological interactions, toxicokinetic behavior, and toxicological outcomes. Parameters such as particle size, morphology, crystal structure, surface charge, coating composition, and oxidation state collectively influence cellular uptake, biodistribution, degradation, and organ-specific toxicity. From a toxicology standpoint, understanding these determinants is essential for explaining why the liver and cardiovascular system consistently emerge as dominant targets following exposure to IONPs [11].

Particle size is among the most critical factors dictating the biological fate of IONPs. Nanoparticles typically ranging from 1 to 100 nm exhibit size-dependent magnetic behavior and biological reactivity, with particles below approximately 20 nm often displaying superparamagnetism and enhanced cellular internalization [12]. Smaller IONPs possess a higher surface-area-to-volume ratio, which increases surface reactivity and accelerates iron ion release under physiological or lysosomal conditions. Toxicological studies demonstrate that ultrasmall nanoparticles exhibit higher permeability across biological barriers, increased accumulation in metabolically active organs such as the liver and heart, and greater potential to induce oxidative stress and mitochondrial dysfunction compared with larger aggregates [13].

Morphology and crystallinity further modulate IONPs toxicity by influencing surface reactivity and magnetic behavior. Spherical particles are generally more thermodynamically stable and exhibit predictable biological interactions, whereas non-spherical forms such as rods, cubes, or plates may induce greater membrane perturbation and cytoskeletal stress upon cellular contact [14]. Crystalline phase also plays a decisive role; magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3), which possess inverse spinel structures, show different redox activities and dissolution profiles compared with hematite (α-Fe_2O_3). These differences directly affect iron ion release, reactive oxygen species generation, and downstream cellular damage, particularly in hepatocytes and cardiomyocytes [15].

Surface charge and zeta potential are key predictors of colloidal stability and nanoparticle–cell membrane interactions. Positively charged or weakly stabilized IONPs tend to interact strongly with negatively charged cellular membranes, leading to enhanced uptake, lysosomal accumulation, and cytotoxicity [16]. In contrast, negatively charged or neutral nanoparticles generally exhibit reduced nonspecific interactions and improved circulation profiles. Toxicological evidence indicates that surface charge strongly influences hepatic uptake by Kupffer cells and endothelial interactions within the cardiovascular system, thereby shaping organ-specific toxicity patterns [17].

Surface functionalization and coating materials are widely employed to improve colloidal stability, biocompatibility, and targeting efficiency of IONPs. Common coatings such as dextran, polyethylene glycol, silica, citrate, and polymers reduce aggregation, modulate protein corona formation, and attenuate rapid clearance by the mononuclear phagocyte system [18]. Importantly, surface coatings significantly mitigate hepatotoxic and cardiotoxic effects by limiting iron ion dissolution and reducing reactive oxygen species generation. However, coating composition and thickness also affect degradation kinetics; poorly designed or unstable coatings may degrade in lysosomal environments, leading to delayed iron release and chronic oxidative stress in the liver and heart [19].

Oxidation state and redox activity represent central toxicological features of iron oxide nanoparticles. Magnetite contains both Fe^{2+} and Fe^{3+} ions, enabling participation in redox cycling and Fenton-like reactions that generate highly reactive hydroxyl radicals. Under acidic intracellular conditions, partial oxidation of Fe_3O_4 to γ-Fe_2O_3 can occur, altering magnetic properties while maintaining redox activity [20]. Excessive or uncontrolled iron ion release disrupts cellular iron homeostasis, overwhelms ferritin storage capacity, and amplifies oxidative damage, particularly in organs with high metabolic demand

such as the liver and myocardium [21].

Protein corona formation is another critical determinant influencing the biological identity of IONPs once they enter biological fluids. Adsorption of plasma proteins onto the nanoparticle surface modifies cellular recognition, uptake pathways, and biodistribution. The composition of the protein corona is dictated by nanoparticle size, surface charge, and coating chemistry, and it can either attenuate or exacerbate toxicity. In hepatic and cardiovascular contexts, protein corona composition affects macrophage uptake, endothelial interactions, and inflammatory signaling, thereby modulating organ-specific responses [22].

Collectively, these physicochemical determinants do not act in isolation but interact dynamically to define the biological fate and toxicological profile of iron oxide nanoparticles. Subtle variations in size, surface chemistry, or redox behavior can dramatically shift the balance between biocompatibility and toxicity. Understanding these relationships provides the foundation for interpreting toxicokinetic behavior and mechanistic toxicity in the liver and cardiovascular system, and it underpins safer-by-design strategies aimed at minimizing adverse health effects while preserving functional performance [23].

Multifunctional Applications Driving Human Exposure to Iron Oxide Nanoparticles

The rapid expansion of iron oxide nanoparticles (IONPs) across diverse technological sectors has significantly increased the likelihood of human exposure, both intentional and unintentional. Their multifunctionality—stemming from tunable magnetic, surface, and redox properties—has positioned IONPs as indispensable tools in medicine, food systems, industry, agriculture, and environmental remediation. From a toxicological standpoint, the nature, frequency, and route of exposure associated with these applications critically influence internal dose, biodistribution, and the burden placed on sensitive organs, particularly the liver and cardiovascular system [24].

Biomedical applications represent one of the most direct and biologically relevant exposure scenarios for IONPs. Superparamagnetic iron oxide nanoparticles are widely used as contrast agents in magnetic resonance imaging, carriers for targeted drug delivery, mediators of magnetic hyperthermia, and platforms for theranostic applications [25]. In these settings, IONPs are often administered intravenously, bypassing protective biological barriers and entering systemic circulation immediately. Following injection, nanoparticles interact with plasma proteins, form a protein corona, and are rapidly sequestered by the mononuclear phagocyte system, leading to preferential accumulation in the liver and spleen [26]. Repeated clinical administration or high cumulative doses may therefore impose sustained oxidative and inflammatory stress on hepatocytes and hepatic macrophages, with secondary cardiovascular effects arising from systemic iron dysregulation [27].

Beyond clinical use, iron oxide nanoparticles are increasingly incorporated into food products under the European food additive code E172, where they function as colorants and iron fortification agents. At the nanoscale, these particles exhibit improved dispersion and stability within food matrices, enhancing visual quality and iron bioavailability [28]. However, oral exposure raises toxicological concerns, as ingested IONPs may interact with the gastrointestinal epithelium, gut microbiota, and intestinal immune system. Although systemic absorption is generally limited, chronic intake can lead to low-level translocation of nanoparticles or released iron ions into circulation, ultimately contributing to hepatic iron accumulation and altered liver–heart axis signaling [29].

Industrial and occupational applications constitute another major exposure domain. IONPs are used extensively as pigments in paints, plastics, cosmetics, and construction materials, as well as in magnetic fluids, mechanical seals, sensors, and energy storage devices [30]. Workers involved in nanoparticle synthesis, pigment production, welding, and manufacturing processes may be exposed to airborne iron oxide nanoparticles through inhalation. Inhaled nanoparticles can deposit in the alveolar region, translocate into systemic circulation, and subsequently accumulate in the liver and cardiovascular tissues, where they may induce oxidative stress, endothelial dysfunction, and inflammatory responses [31].

Environmental applications of IONPs, including wastewater treatment, heavy metal adsorption, catalytic

degradation of organic pollutants, and air pollution control, further expand the exposure landscape [32]. While these technologies offer substantial environmental benefits, they also raise concerns regarding nanoparticle release into soil, water, and air. Environmental dispersion may result in indirect human exposure through contaminated drinking water, food chains, or ambient air, leading to chronic low-dose exposure scenarios. Such exposures are particularly relevant for long-term hepatic and cardiovascular toxicity, where cumulative iron burden and persistent oxidative stress may not manifest as acute toxicity but contribute to subclinical organ dysfunction [33].

Agricultural applications, including nanofertilizers, soil remediation agents, and post-harvest antimicrobial coatings, represent an emerging source of exposure [34]. Iron oxide nanoparticles are used to improve iron availability in crops and enhance plant growth; however, their persistence in soil and uptake by plants may introduce nanoparticles into the human food chain. Continuous dietary exposure, even at low concentrations, may gradually influence systemic iron homeostasis, placing additional stress on the liver and cardiovascular system, especially in vulnerable populations [35].

Collectively, the multifunctional applications of iron oxide nanoparticles generate complex and overlapping exposure pathways that challenge traditional toxicological risk assessment. The diversity of exposure routes—intravenous, oral, inhalational, dermal, and environmental—underscores the necessity of evaluating cumulative and organ-specific toxicity rather than isolated exposure events. Given the liver's central role in nanoparticle clearance and iron metabolism, and the heart's susceptibility to iron-mediated oxidative injury, these applications collectively reinforce the need for toxicology-driven design, exposure control, and regulatory oversight of iron oxide nanoparticles [36].

Human Exposure Routes and Internalization of Iron Oxide Nanoparticles

Human exposure to iron oxide nanoparticles (IONPs) occurs through multiple routes that differ markedly in their efficiency of absorption, internal dose, and subsequent organ distribution. The route of exposure is a critical determinant of toxicokinetic behavior and strongly influences the extent to which the liver and cardiovascular system are burdened by nanoparticle accumulation. Understanding these exposure pathways is therefore essential for interpreting organ-specific toxicity and for designing appropriate risk assessment strategies [37].

Inhalation represents a major unintentional exposure route, particularly in occupational and industrial settings such as nanoparticle synthesis, pigment production, welding, and manufacturing processes. Due to their ultrafine size, inhaled IONPs can penetrate deeply into the respiratory tract and deposit in the alveolar region [38]. Once deposited, nanoparticles may be phagocytosed by alveolar macrophages or directly translocate across the air–blood barrier into systemic circulation. This translocation enables redistribution to secondary organs, most notably the liver, where nanoparticles are rapidly sequestered by Kupffer cells, and the cardiovascular system, where they interact with endothelial cells and circulating blood components [39]. Repeated or chronic inhalation exposure has been associated with pulmonary inflammation that may amplify systemic oxidative stress, thereby indirectly exacerbating hepatic and cardiac injury [40].

Oral exposure occurs intentionally through food additives such as E172 and iron-fortified products, as well as unintentionally through contaminated food and drinking water. Following ingestion, IONPs encounter the acidic gastric environment and digestive enzymes, which may induce partial aggregation or dissolution of surface iron ions [41]. Absorption across the gastrointestinal tract is generally limited; however, small or surface-modified nanoparticles may cross the intestinal epithelium via M cells in Peyer's patches, transcellular endocytosis, or paracellular diffusion [42]. Even low levels of systemic uptake can be toxicologically relevant under chronic exposure conditions, as repeated ingestion may lead to cumulative hepatic iron loading and subtle alterations in liver–heart metabolic signaling [43].

Dermal exposure to iron oxide nanoparticles arises primarily from cosmetics, topical formulations, occupational contact, and environmental contamination. The intact stratum corneum provides an effective barrier against nanoparticle penetration; nevertheless, particle size, surface charge, formulation type, and skin integrity significantly influence permeability [44]. Experimental studies indicate that very small IONPs or those incorporated into specific semi-solid formulations may penetrate into the viable

epidermis, particularly when the skin barrier is compromised by inflammation, abrasion, or ultraviolet radiation [45]. While systemic absorption through the skin is generally minimal, localized oxidative stress and inflammatory responses may contribute indirectly to systemic effects, especially under conditions of repeated exposure [46].

Intravenous administration constitutes the most direct and efficient exposure route and is primarily associated with biomedical applications such as MRI contrast enhancement, magnetic hyperthermia, and targeted drug delivery. This route bypasses all external biological barriers and introduces IONPs directly into systemic circulation [47]. Immediately after injection, nanoparticles interact with plasma proteins and form a protein corona that influences circulation time, cellular uptake, and clearance [48]. The liver rapidly removes a substantial fraction of circulating IONPs via the mononuclear phagocyte system, resulting in high hepatic accumulation. Simultaneously, circulating nanoparticles and released iron ions can interact with vascular endothelium and cardiac tissue, contributing to oxidative stress, endothelial dysfunction, and myocardial injury [49].

Across all exposure routes, internalization of iron oxide nanoparticles typically occurs through endocytic pathways, including clathrin-mediated endocytosis, caveolae-dependent uptake, and macropinocytosis, depending on particle size and surface characteristics [50]. Once internalized, IONPs are trafficked to endosomes and lysosomes, where acidic conditions promote partial degradation and iron ion release. This intracellular processing represents a critical step linking exposure to toxicity, as liberated iron ions participate in redox reactions that drive oxidative stress, mitochondrial dysfunction, and inflammatory signaling in hepatocytes, endothelial cells, and cardiomyocytes [51].

Overall, the diversity of exposure routes and internalization mechanisms underscores the complexity of IONPs toxicology. While intravenous exposure leads to high and immediate hepatic and cardiovascular burden, inhalation and oral routes contribute to chronic, low-dose exposure scenarios with cumulative effects. These pathways collectively highlight the need to consider exposure route–specific toxicokinetics when evaluating liver and heart toxicity associated with iron oxide nanoparticles [52].

Toxicokinetics of Iron Oxide Nanoparticles (ADME)

The toxicokinetic behavior of iron oxide nanoparticles (IONPs), encompassing absorption, distribution, metabolism, and excretion (ADME), plays a decisive role in determining their systemic toxicity and organ-specific effects. Unlike conventional chemicals, the ADME profile of nanoparticles is highly dependent on physicochemical properties such as size, surface charge, coating, aggregation state, and redox activity. These parameters collectively shape the internal dose, persistence, and biological reactivity of IONPs, with the liver and cardiovascular system consistently emerging as principal sites of accumulation and toxicity [53].

Absorption of IONPs varies substantially according to the route of exposure. Intravenous administration results in immediate and complete systemic availability, whereas inhalational and oral routes lead to partial and often heterogeneous absorption profiles. Inhaled nanoparticles deposited in the alveoli may translocate across the pulmonary epithelium into the bloodstream, while orally ingested IONPs exhibit limited but measurable uptake through specialized intestinal pathways, particularly when particles are ultrasmall or surface-modified [54]. Dermal absorption remains comparatively low; however, compromised skin integrity or prolonged exposure may enhance penetration. From a toxicological perspective, even low absorption efficiency can be relevant when exposure is chronic, as repeated uptake may result in cumulative internal burden over time [55].

Following absorption, distribution of IONPs is dominated by the activity of the mononuclear phagocyte system, which rapidly clears nanoparticles from circulation. The liver is the primary deposition site, owing to its fenestrated sinusoidal endothelium and high density of Kupffer cells capable of nanoparticle sequestration [56]. Biodistribution studies consistently demonstrate that a substantial fraction of administered IONPs accumulates in hepatic tissue within hours of exposure. Secondary accumulation occurs in the spleen, lungs, and, to a lesser extent, the heart. Importantly, ultrasmall nanoparticles and those with stealth coatings may evade immediate clearance, prolong circulation time, and increase the probability of cardiac exposure through endothelial interaction and myocardial uptake [57].

Cardiovascular distribution of IONPs, although quantitatively lower than hepatic accumulation, is toxicologically significant due to the heart's sensitivity to oxidative stress and mitochondrial dysfunction. Circulating nanoparticles can interact directly with vascular endothelium, leading to endothelial activation, altered nitric oxide signaling, and promotion of thromboinflammatory responses [58]. In experimental models, iron oxide nanoparticles have been detected within cardiac tissue following systemic exposure, particularly when particle size is below 20 nm or when surface coatings delay hepatic clearance. Such distribution patterns suggest that the heart may be exposed both directly to nanoparticles and indirectly to iron ions released from hepatic degradation processes [59].

Metabolism of iron oxide nanoparticles primarily occurs at the intracellular level following endocytic uptake. Within lysosomes, acidic pH conditions promote partial dissolution of the iron oxide core, releasing Fe^{2+} and Fe^{3+} ions into the cytosol [60]. These ions may enter endogenous iron metabolic pathways, becoming incorporated into ferritin or hemosiderin pools. While controlled metabolism facilitates eventual clearance, excessive or repeated exposure can overwhelm iron storage mechanisms, disrupt systemic iron homeostasis, and amplify oxidative stress through Fenton chemistry. In the liver, this process manifests as hepatocellular oxidative injury and inflammatory signaling, whereas in the heart it may impair mitochondrial function and energy metabolism [61].

Excretion of IONPs and their degradation products occurs primarily through hepatobiliary and renal pathways. Larger particles and aggregated forms are preferentially eliminated via bile and feces following hepatic processing, whereas ultrasmall nanoparticles or dissolved iron ions may be filtered by the kidneys and excreted in urine [62]. Surface functionalization significantly influences clearance efficiency; for example, polyethylene glycol–coated nanoparticles often exhibit prolonged circulation times and delayed excretion, increasing the risk of long-term tissue retention. Several studies report minimal excretion and persistent tissue presence months after exposure, raising concerns about cumulative toxicity and chronic hepatic and cardiovascular effects [63].

Overall, the toxicokinetic profile of iron oxide nanoparticles is characterized by rapid hepatic uptake, variable cardiac exposure, partial intracellular metabolism, and often slow or incomplete elimination. These features underscore the importance of considering ADME behavior when interpreting toxicity data and designing safer nanomaterials. In particular, the strong affinity of IONPs for the liver and their capacity to influence cardiovascular physiology highlight the need for long-term toxicokinetic studies that integrate physicochemical design with organ-specific risk assessment [64].

Molecular Mechanisms of Iron Oxide Nanoparticles–Induced Toxicity

The toxicity of iron oxide nanoparticles (IONPs) is mediated by a complex network of interconnected molecular and cellular mechanisms that are strongly influenced by nanoparticle physicochemical properties and toxicokinetic behavior. These mechanisms collectively explain how IONPs translate from inert-looking materials into biologically active agents capable of inducing organ-specific injury. Among exposed organs, the liver and cardiovascular system are particularly vulnerable due to their central roles in iron handling, metabolic regulation, and redox balance [65].

Oxidative stress represents the central and initiating mechanism of IONPs-induced toxicity. Following cellular internalization, iron oxide nanoparticles undergo partial degradation within lysosomes, releasing Fe^{2+} and Fe^{3+} ions that actively participate in Fenton and Haber–Weiss reactions. These reactions generate highly reactive hydroxyl radicals and superoxide anions, leading to excessive reactive oxygen species (ROS) accumulation [66]. Elevated ROS levels overwhelm endogenous antioxidant defenses, including superoxide dismutase, catalase, and glutathione peroxidase, resulting in lipid peroxidation, protein oxidation, and oxidative DNA damage. In hepatocytes, this oxidative burden disrupts metabolic pathways and membrane integrity, while in cardiomyocytes it compromises contractile function and electrical stability [67].

Mitochondrial dysfunction is a downstream but critical consequence of iron-mediated oxidative stress. Mitochondria are particularly susceptible to iron overload due to their role in electron transport and energy production. IONPs-induced ROS damage mitochondrial membranes, impair electron transport chain complexes, and reduce mitochondrial membrane potential, ultimately leading to decreased ATP

synthesis [68]. In the liver, mitochondrial dysfunction manifests as impaired β-oxidation, altered glucose metabolism, and activation of cell death pathways. In cardiac tissue, where energy demand is exceptionally high, mitochondrial impairment leads to contractile dysfunction, arrhythmogenic susceptibility, and increased risk of cardiomyocyte apoptosis [69].

Inflammatory signaling is closely linked to oxidative stress and plays a pivotal role in amplifying IONPs toxicity. ROS activate redox-sensitive transcription factors, particularly nuclear factor kappa B (NF-κB), resulting in the upregulation of pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin-6, and interleukin-1β [70]. In the liver, activation of Kupffer cells further propagates inflammatory cascades, promoting hepatocellular injury and fibrosis under chronic exposure conditions. Within the cardiovascular system, inflammatory mediators contribute to endothelial activation, increased vascular permeability, and promotion of thromboinflammatory processes that may predispose to vascular dysfunction [71].

Disruption of iron homeostasis is another defining mechanism underlying IONPs-induced toxicity. Under physiological conditions, intracellular iron is tightly regulated by ferritin storage and ferroportin-mediated export. Excessive iron release from degraded nanoparticles can overwhelm these regulatory systems, leading to labile iron pool expansion and sustained oxidative stress [72]. In the liver, iron overload interferes with hepcidin signaling and systemic iron balance, potentially affecting distant organs including the heart. Cardiac iron accumulation, even at low levels, sensitizes cardiomyocytes to oxidative injury and mitochondrial damage, contributing to functional impairment [73].

Genotoxicity and DNA damage have been reported as both direct and indirect consequences of IONPs exposure. Direct interactions between nanoparticles and nuclear DNA can disrupt chromatin structure and interfere with replication and transcription processes. Indirectly, ROS generated during iron redox cycling induce oxidative DNA lesions, strand breaks, and base modifications [74]. Inhibition of DNA repair enzymes by surface-modified IONPs has also been documented, increasing the likelihood of mutation accumulation. In hepatocytes, such genotoxic stress may predispose to long-term genomic instability, while in vascular cells it may impair regenerative capacity and endothelial integrity [75].

Programmed cell death pathways, including apoptosis and ferroptosis, represent terminal outcomes of sustained IONPs-induced cellular stress. Mitochondrial damage and oxidative imbalance trigger intrinsic apoptotic pathways through cytochrome c release and caspase activation. Concurrently, iron-driven lipid peroxidation promotes ferroptosis, a regulated form of cell death characterized by iron dependency and membrane lipid damage [76]. These pathways are particularly relevant in the liver, where ferroptosis contributes to hepatocellular injury, and in the heart, where loss of cardiomyocytes has limited regenerative potential and profound functional consequences [77].

In summary, iron oxide nanoparticles induce toxicity through a multifactorial mechanism involving oxidative stress, mitochondrial dysfunction, inflammation, iron homeostasis disruption, genotoxicity, and regulated cell death. These mechanisms converge most prominently in the liver and cardiovascular system, explaining their heightened susceptibility to injury. Understanding these pathways provides a mechanistic foundation for interpreting organ-specific toxicity and for developing safer-by-design strategies aimed at minimizing hepatic and cardiac risks associated with iron oxide nanoparticle exposure [78].

Hepatic Toxicity of Iron Oxide Nanoparticles

The liver represents the primary target organ for iron oxide nanoparticles (IONPs)–induced toxicity due to its central role in blood filtration, nanoparticle clearance, and systemic iron homeostasis. Following systemic exposure, whether through intravenous administration, inhalation, or oral uptake, IONPs are rapidly sequestered by the liver via the mononuclear phagocyte system. Kupffer cells and, to a lesser extent, hepatocytes efficiently internalize circulating nanoparticles, leading to preferential hepatic accumulation that far exceeds deposition in most other organs [79]. This dominant hepatic burden explains why liver toxicity consistently emerges as the most frequently reported adverse outcome in both experimental and translational studies.

At the cellular level, hepatic uptake of IONPs is primarily mediated by Kupffer cells through

phagocytosis and receptor-mediated endocytosis. Once internalized, nanoparticles are trafficked to lysosomes, where acidic conditions promote partial degradation of the iron oxide core and subsequent release of Fe^{2+} and Fe^{3+} ions [80]. While this process is intended to facilitate iron recycling, excessive or repeated nanoparticle exposure overwhelms lysosomal handling capacity, resulting in lysosomal membrane permeabilization and leakage of redox-active iron into the cytosol. This event represents a critical trigger for oxidative stress and inflammatory signaling in hepatic tissue [81].

Oxidative stress is a hallmark mechanism of IONPs-induced hepatotoxicity. The liberated iron ions actively participate in Fenton-like reactions, generating hydroxyl radicals that initiate lipid peroxidation of hepatocyte membranes and oxidative modification of proteins and nucleic acids. Experimental studies consistently report elevated hepatic malondialdehyde levels, depletion of antioxidant enzymes such as superoxide dismutase and catalase, and increased glutathione consumption following IONPs exposure [82]. This oxidative imbalance disrupts normal metabolic processes, including lipid metabolism and glucose regulation, thereby compromising overall liver function.

Mitochondrial dysfunction further amplifies hepatic injury induced by iron oxide nanoparticles. Mitochondria in hepatocytes are highly susceptible to iron-mediated oxidative damage due to their role in energy metabolism and β-oxidation. Accumulation of IONPs or released iron within mitochondria impairs electron transport chain activity, reduces mitochondrial membrane potential, and diminishes ATP production [83]. These alterations not only compromise hepatocellular energy supply but also promote mitochondrial permeability transition and cytochrome c release, thereby activating intrinsic apoptotic pathways. Sustained mitochondrial injury has been linked to progressive hepatocellular degeneration under chronic exposure conditions [84].

Inflammatory responses play a central role in the progression of IONPs-induced liver toxicity. Activation of Kupffer cells by internalized nanoparticles and oxidative stress leads to the release of pro-inflammatory cytokines, including tumor necrosis factor-α, interleukin-6, and interleukin-1β. These mediators propagate inflammatory signaling within hepatic tissue, promote leukocyte infiltration, and exacerbate hepatocyte injury [85]. Chronic inflammation may further stimulate stellate cell activation and extracellular matrix deposition, raising concerns about fibrosis development following long-term or repeated exposure to iron oxide nanoparticles [86].

Biochemical and histopathological alterations provide clear evidence of hepatotoxicity associated with IONPs. Numerous in vivo studies report dose-dependent elevations in serum liver enzymes such as alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase, indicating compromised hepatocellular membrane integrity [87]. Histological examinations frequently reveal centrilobular degeneration, hepatocyte vacuolization, sinusoidal congestion, inflammatory cell infiltration, and Kupffer cell hyperplasia. In some models, prolonged exposure leads to visible iron deposition within hepatic tissue, further intensifying oxidative stress and inflammatory damage [88].

The severity of hepatic toxicity is strongly modulated by nanoparticle physicochemical properties. Smaller particles, uncoated or positively charged surfaces, and magnetite-based formulations with higher redox activity are consistently associated with greater hepatotoxic potential. In contrast, surface functionalization with biocompatible coatings such as polyethylene glycol or dextran reduces aggregation, limits iron ion release, and attenuates oxidative and inflammatory responses in the liver [89]. These findings underscore the importance of nanoparticle design in mitigating hepatic risk while maintaining functional performance.

In summary, hepatic toxicity of iron oxide nanoparticles arises from a convergence of high organ accumulation, lysosomal degradation, oxidative stress, mitochondrial dysfunction, and inflammatory signaling. The liver's physiological role in nanoparticle clearance and iron metabolism renders it uniquely susceptible to injury, particularly under conditions of high dose, repeated exposure, or inadequate surface modification. Given the liver's influence on systemic iron balance and downstream cardiovascular effects, hepatotoxicity represents a pivotal determinant of whole-body toxicity associated with iron oxide nanoparticles and warrants focused consideration in both risk assessment and safer-by-design strategies [90].

Cardiovascular Toxicity of Iron Oxide Nanoparticles

The cardiovascular system represents a critical secondary target of iron oxide nanoparticles (IONPs)–induced toxicity, particularly in the context of systemic exposure and repeated administration. Although cardiac accumulation of IONPs is generally lower than hepatic deposition, the heart and vascular system are highly sensitive to iron-mediated oxidative stress, mitochondrial dysfunction, and inflammatory perturbations. Consequently, even modest nanoparticle exposure may translate into significant functional and structural cardiovascular effects, especially under chronic or high-dose conditions [91].

Endothelial dysfunction is one of the earliest and most consistently reported cardiovascular effects of IONPs exposure. Circulating nanoparticles and released iron ions interact directly with vascular endothelial cells, leading to excessive reactive oxygen species generation and impairment of endothelial nitric oxide synthase activity. This results in reduced nitric oxide bioavailability, increased vascular tone, and compromised endothelial barrier integrity [92]. Experimental studies demonstrate that IONPs promote endothelial activation characterized by increased expression of adhesion molecules and pro-inflammatory mediators, thereby facilitating leukocyte adhesion and vascular inflammation [93].

Oxidative stress plays a central role in mediating cardiac toxicity associated with iron oxide nanoparticles. Iron released from degraded nanoparticles participates in Fenton-like reactions within cardiac tissue, generating highly reactive oxygen species that damage cardiomyocyte membranes, proteins, and mitochondrial DNA. The myocardium is particularly vulnerable to oxidative injury due to its high oxygen consumption and limited antioxidant reserve. Several in vivo studies report increased cardiac lipid peroxidation, depletion of antioxidant enzymes, and elevated oxidative biomarkers following systemic exposure to IONPs [94].

Mitochondrial dysfunction is a key downstream consequence of oxidative stress in cardiomyocytes. Accumulation of iron ions within mitochondria disrupts electron transport chain function, reduces mitochondrial membrane potential, and impairs ATP production. These alterations compromise myocardial contractility and electrical stability, predisposing the heart to arrhythmias and functional decline [95]. Ultrasmall iron oxide nanoparticles have been shown to induce pronounced mitochondrial damage in cardiac tissue, leading to cardiomyocyte apoptosis and, in severe cases, acute cardiac failure in experimental models [96].

Thromboinflammatory responses represent another important mechanism of IONPs-induced cardiovascular toxicity. Interaction of nanoparticles with blood components, including platelets and coagulation factors, can promote platelet activation and aggregation. Concurrent endothelial injury and inflammatory cytokine release further amplify pro-thrombotic signaling pathways. In vitro and ex vivo studies using whole-blood models demonstrate that IONPs can activate complement pathways and induce a thromboinflammatory phenotype, raising concerns about microvascular obstruction and impaired tissue perfusion [97].

Cardiac accumulation of iron oxide nanoparticles, although limited compared with hepatic uptake, has been documented in several biodistribution studies. Nanoparticles with small size, delayed clearance, or insufficient surface stabilization are more likely to evade rapid hepatic sequestration and reach cardiac tissue via systemic circulation. Once deposited in the myocardium, IONPs may persist for extended periods, leading to localized iron overload and sustained oxidative stress [98]. This phenomenon is particularly relevant in the context of repeated clinical administration or prolonged environmental exposure.

Functional and structural alterations of the heart have been observed following exposure to iron oxide nanoparticles. Animal studies report dose-dependent changes in heart rate, myocardial contractility, and electrocardiographic parameters, alongside histopathological findings such as cardiomyocyte degeneration, interstitial edema, and inflammatory infiltration [99]. Although some effects appear reversible following cessation of exposure, others persist and may predispose to long-term cardiovascular dysfunction, especially in susceptible individuals or those with pre-existing cardiac conditions.

The extent of cardiovascular toxicity is strongly influenced by nanoparticle physicochemical properties.

Smaller particles, uncoated or positively charged surfaces, and formulations with high redox activity are associated with increased cardiotoxic potential. In contrast, surface modification with biocompatible coatings reduces oxidative stress, limits endothelial interaction, and improves cardiovascular safety profiles [100,101]. These observations highlight the importance of rational nanoparticle design in minimizing unintended cardiac effects.

Conclusion

Iron oxide nanoparticles have emerged as highly versatile nanomaterials with wide-ranging applications spanning nanomedicine, food technology, industry, agriculture, and environmental remediation. Their unique magnetic properties, tunable surface chemistry, and relative biocompatibility have driven rapid adoption across multiple sectors. However, as this review has demonstrated, the same physicochemical features that confer functional advantages also govern biological interactions and underpin toxicological risk.

From a toxicology-centered perspective, the liver and cardiovascular system clearly represent the most vulnerable target organs following exposure to iron oxide nanoparticles. The liver acts as the primary sink for circulating nanoparticles due to its anatomical structure, high phagocytic capacity, and central role in iron metabolism. Preferential hepatic accumulation leads to lysosomal degradation, iron ion release, oxidative stress, mitochondrial dysfunction, and inflammatory signaling, which together drive hepatocellular injury and may disrupt systemic iron homeostasis. In parallel, the cardiovascular system is highly sensitive to iron-mediated oxidative imbalance, even at lower levels of nanoparticle accumulation. Endothelial dysfunction, mitochondrial impairment in cardiomyocytes, thromboinflammatory activation, and myocardial oxidative injury collectively contribute to cardiotoxic outcomes that may have significant functional and clinical implications.

Importantly, the severity and nature of these toxic effects are not intrinsic properties of iron oxide nanoparticles alone but are strongly dictated by their physicochemical determinants, including particle size, surface charge, coating composition, crystallinity, and redox activity. Subtle modifications in nanoparticle design can shift the balance from relative biocompatibility to pronounced organ toxicity, underscoring the necessity of integrating toxicological considerations early in the development process. Repeated or chronic exposure scenarios—particularly relevant for food additives, occupational environments, and clinical re-administration—pose additional risks that may not be captured by short-term toxicity studies.

Overall, the findings synthesized in this review highlight the need to move beyond generalized safety assumptions and toward a mechanistic, organ-specific evaluation of iron oxide nanoparticles. Emphasis on hepatic and cardiovascular toxicity provides critical insight into systemic risk and offers a framework for safer-by-design strategies aimed at minimizing adverse outcomes while preserving functional performance. Future research should prioritize long-term exposure studies, standardized toxicological testing protocols, and closer alignment between nanoparticle engineering, toxicokinetics, and regulatory science. Such efforts are essential to ensure that the continued advancement of iron oxide nanopaterials is matched by robust protection of human health.

References

1. Samrot AV, Sahithya CS, Selvarani J, Purayil SK, Ponnaiah P. A review on synthesis, characterization and potential biological applications of superparamagnetic iron oxide nanoparticles. *Curr Res Green Sustain Chem.* 2021;4:100042.
2. Valdiglesias V, Fernández-Bertólez N, Kiliç G, et al. Are iron oxide nanoparticles safe? Current knowledge and future perspectives. *J Trace Elem Med Biol.* 2016;38:53-63.
3. Tripathy DB, Pradhan S. Nanoparticles induced health hazards through environmental exposure and direct contact. *Proc Inst Mech Eng Part N.* 2024;23977914241312438.
4. De Matteis V. Exposure to inorganic nanoparticles: routes of entry, immune response, biodistribution and toxicity. *Toxics.* 2017;5(4):29.

5. Arami H, Khandhar A, Liggitt D, Krishnan KM. In vivo delivery, pharmacokinetics, biodistribution and toxicity of iron oxide nanoparticles. *Chem Soc Rev.* 2015;44(23):8576-8607.
6. Vakili-Ghartavol R, Momtazi-Borojeni AA, Vakili-Ghartavol Z, et al. Toxicity assessment of superparamagnetic iron oxide nanoparticles in different tissues. *Artif Cells Nanomed Biotechnol.* 2020;48(1):443-451.
7. Malhotra N, Lee JS, Liman RAD, et al. Potential toxicity of iron oxide magnetic nanoparticles: a review. *Molecules.* 2020;25(14):3159.
8. Gerogianni A, Bal M, Mohlin C, et al. Iron oxide nanoparticle-induced thromboinflammatory response. *Front Immunol.* 2023;14:1101387.
9. Wu L, Wen W, Wang X, et al. Ultrasmall iron oxide nanoparticles cause significant toxicity by inducing acute oxidative stress. *Part Fibre Toxicol.* 2022;19(1):24.
10. Nowak-Jary J, Machnicka B. Comprehensive analysis of the potential toxicity of magnetic iron oxide nanoparticles. *Int J Mol Sci.* 2024;25(22):12013.
11. Khan AU, Chen L, Ge G. Recent development for biomedical applications of magnetic nanoparticles. *Inorg Chem Commun.* 2021;134:108995.
12. Baabu PRS, Kumar HK, Gumpu MB, et al. Iron oxide nanoparticles: properties and biological applications. *Materials.* 2022;16(1):59.
13. Geppert M, Himly M. Iron oxide nanoparticles in bioimaging–an immune perspective. *Front Immunol.* 2021;12:688927.
14. Ioncica MC, Bandyopadhyay S, Bali N, et al. Rheological characteristics and aggregation of IONPs. *Magnetochemistry.* 2023;9(4):99.
15. Girardet T, Venturini P, Martinez H, et al. Spinel magnetic iron oxide nanoparticles. *Appl Sci.* 2022;12(16):8127.
16. Serrano-Lotina A, Portela R, Baeza P, et al. Zeta potential as a tool for functional materials development. *Catal Today.* 2023;423:113862.
17. Safi M, Courtois J, Seigneuret M, et al. Effects of aggregation and protein corona on cellular internalization. *Biomaterials.* 2011;32(35):9353-9363.
18. Zhu N, Ji H, Yu P, et al. Surface modification of magnetic iron oxide nanoparticles. *Nanomaterials.* 2018;8(10):810.
19. Portilla Y, Fernández-Afonso Y, Pérez-Yagüe S, et al. Nanoparticle degradation kinetics in vivo. *J Nanobiotechnology.* 2022;20(1):543.
20. Meftah S, Ngo AT, Bouteiller L, et al. Synthesis and magnetic properties of maghemite nanoparticles. *Langmuir.* 2024;40(43):22673-22683.
21. Luo C, Li Y, Yang L, et al. Superparamagnetic iron oxide nanoparticles exacerbate oxidative stress. *Arch Toxicol.* 2015;89(3):357-369.
22. Cameron SJ, Sheng J, Hosseinian F, Willmore WG. Nanoparticle stress response pathways. *Int J Mol Sci.* 2022;23(14):7962.
23. Heuer-Jungemann A, Feliu N, Bakaimi I, et al. Role of ligands in nanoparticle synthesis and applications. *Chem Rev.* 2019;119(8):4819-4880.
24. Chand K, Vasquez-Guardado ES. Magnetic nanoparticles in life sciences. *ChemistryOpen.* 2025;2500214.
25. Wáng YXJ, Idée JM. Clinical research on SPIONs for MRI. *Quant Imaging Med Surg.* 2017;7(1):88.
26. Feng Q, Liu Y, Huang J, et al. Uptake and clearance of iron oxide nanoparticles. *Sci Rep.* 2018;8(1):2082.
27. Montiel Schneider MG, Martín MJ, Otarola J, et al. Biomedical applications and perspectives. *Pharmaceutics.* 2022;14(1):204.
28. Voss L, Hsiao IL, Ebisch M, et al. Iron oxide nanoparticles in food pigment E172. *Food Chem.* 2020;327:127000.
29. Voss L, Hoché E, Stock V, et al. Intestinal and hepatic effects of iron oxide nanoparticles. *Arch Toxicol.* 2021;95(3):895-905.
30. Pfaff G. Iron oxide pigments. *Phys Sci Rev.* 2021;6(10):535-548.
31. Kornberg TG, Stueckle TA, Antonini JM, et al. Pulmonary exposure to iron oxide nanoparticles. *Nanomaterials.* 2017;7(10):307.
32. Keshta BE, Gemeay AH, Sinha DK, et al. Magnetic iron oxide nanoparticles in wastewater treatment. *Results Chem.* 2024;7:101388.
33. Yang H, Liu L, Shu Z, et al. Environmental and human health threat of IONPs. *J Environ Sci.* 2025;152:188-202.
34. Shirsat S, K S. Iron oxide nanoparticles as micronutrient fertilizer. *J Plant Nutr Soil Sci.* 2024;187(5):565-588.
35. Maharramov AM, Hasanova UA, Suleymanova IA, et al. Nanoparticles in food chain toxicity. *SN Appl Sci.* 2019;1(11):1362.
36. Murali S, Thomas J, Abraham J, et al. Nanotoxicology in metabolic organs. *OpenNano.* 2025;100266.
37. Forest V. Nanoparticles and combined environmental exposure. *NanoImpact.* 2021;23:100344.
38. Guo C, Weber RJ, Buckley A, et al. Pulmonary effects of iron oxide nanoparticles. *Int J Mol Sci.* 2021;22(2):556.
39. Jacinto C, Javed Y, Lavorato G, et al. Biological fate of magnetic nanoparticles. *Nanoscale Adv.* 2025;7:2818-2886.
40. Ying H, Ruan Y, Zeng Z, et al. Size-dependent macrophage activation. *Int Immunopharmacol.* 2022;105:108533.
41. Ajinkya N, Yu X, Kaithal P, et al. IONPs synthesis to applications. *Materials.* 2020;13(20):4644.
42. Strugari AF, Stan MS, Gharbia S, et al. Nanoparticle intestinal transport. *Nanomaterials.* 2018;9(1):5.
43. Li J, Wang L, Li S, et al. Sustained oral intake of nano-iron oxide. *NanoImpact.* 2023;30:100464.

44. Gimeno-Benito I, Giusti A, Dekkers S, et al. Dermal penetration of nanoparticles. *Regul Toxicol Pharmacol.* 2021;119:104836.
45. Jung E, Hui X, Zhu H, et al. Skin penetration of iron nanoparticles. *Toxicol Res Appl.* 2019;3:2397847319893054.
46. Murray AR, Kisin E, Inman A, et al. Dermal toxicity of iron oxide nanoparticles. *Cell Biochem Biophys.* 2013;67(2):461-476.
47. Albarqi HA, Demessie AA, Sabei FY, et al. Systemic magnetic hyperthermia. *Pharmaceutics.* 2020;12(11):1020.
48. Figueiredo Borgognoni C, Kim JH, Zucolotto V, et al. Macrophage responses to metal oxide nanoparticles. *Artif Cells Nanomed Biotechnol.* 2018;46(sup2):694-703.
49. Wu JR, Hernandez Y, Miyasaki KF, et al. Nanomaterials and BBB dysfunction. *Adv Drug Deliv Rev.* 2023;197:114820.
50. Mulens-Arias V, Rojas JM, Sanz-Ortega L, et al. Nanoparticles impair angiogenesis. *Nanomedicine.* 2019;21:102063.
51. Ghosh S, Ghosh I, Chakrabarti M, Mukherjee A. Genotoxicity of SPIONs. *Food Chem Toxicol.* 2020;136:110989.
52. Nowak-Jary J, Machnicka B. Pharmacokinetics of magnetic nanoparticles. *J Nanobiotechnology.* 2022;20(1):305.
53. De Matteis V. Routes of nanoparticle entry and toxicity. *Toxics.* 2017;5(4):29.
54. Attia NF, Abd El-Monaem EM, El-Aqapa HG, et al. Pharmaceutical applications of IONPs. *Appl Surf Sci Adv.* 2022;11:100284.
55. Lewinski NA, Berthet A, Maurizi L, et al. Removal of iron oxide nanoparticles from skin. *J Occup Environ Hyg.* 2017;14(8):D115-D119.
56. Feng Q, Liu Y, Huang J, et al. Distribution and clearance of IONPs. *Sci Rep.* 2018;8(1):2082.
57. McKiernan EP, Moloney C, Chaudhuri TR, et al. PEG layers and in vivo efficacy. *Acta Biomater.* 2022;152:393-405.
58. Gerogianni A, Bal M, Mohlin C, et al. Thromboinflammatory response. *Front Immunol.* 2023;14:1101387.
59. Baratli Y, Charles AL, Wolff V, et al. Mitochondrial effects of IONPs. *Toxicol In Vitro.* 2013;27(8):2142-2148.
60. Levada K, Pshenichnikov S, Omelyanchik A, et al. Lysosomal permeabilization in liver cells. *Nano Converg.* 2020;7(1):17.
61. Fibach E, Rachmilewitz EA. Iron overload in disease. *La Presse Médicale.* 2017;46(12):e296-e305.
62. Zhu GH, Gray AB, Patra HK. Nanoparticle clearance. *Trends Pharmacol Sci.* 2022;43(9):709-711.
63. Zhou H, Ge J, Miao Q, et al. Biodegradable inorganic nanoparticles. *Bioconjug Chem.* 2019;31(2):315-331.
64. Chen Y, Hou S. Effects of IONPs on cells. *Cell Death Discov.* 2023;9(1):195.
65. Siddiqui MA, Wahab R, Saquib Q, et al. Cytotoxicity and oxidative stress. *J Trace Elem Med Biol.* 2023;80:127302.
66. Mesárošová M, Kozics K, Bábelová A, et al. ROS-mediated genotoxicity. *Toxicol Lett.* 2014;226(3):303-313.
67. Ezealigo US, Ezealigo BN, Aisida SO, Ezema FI. IONPs in biological systems. *JCIS Open.* 2021;4:100027.
68. Yao Y, Zhang T, Tang M. Mitochondrial toxicity of nanomaterials. *Environ Pollut.* 2024;343:123231.
69. Li RL, Wang LY, Duan HX, et al. Mitochondrial dysfunction and apoptosis. *Front Pharmacol.* 2022;13:937289.
70. Cameron SJ, Sheng J, Hosseinian F, Willmore WG. Stress response pathways. *Int J Mol Sci.* 2022;23(14):7962.
71. Kay J, Thadhani E, Samson L, Engelward B. Inflammation-induced DNA damage. *DNA Repair.* 2019;83:102673.
72. Luo C, Li Y, Yang L, et al. ROS-mediated stress. *Arch Toxicol.* 2015;89(3):357-369.
73. Wang H, Jia L, Yin R, et al. Ferroptosis and disease. *J Mol Neurosci.* 2025;75(2):76.
74. Zou J, Wang X, Zhang L, Wang J. Iron nanoparticles and gene expression. *Chem Res Toxicol.* 2015;28(3):373-383.
75. Coskun E, Singh N, Scanlan LD, et al. DNA repair inhibition by IONPs. *Nanomedicine.* 2022;17(26):2011-2021.
76. Tummers B, Green DR. Caspase-8 regulation. *Immunol Rev.* 2017;277(1):76-89.
77. Bi J, Mo C, Li S, et al. Immunotoxicity of metal nanoparticles. *Biomater Sci.* 2023;11(12):4151-4183.
78. Fernández-Bertólez N, Costa C, Brandão F, et al. Toxicological aspects of IONPs. In: *Nanotoxicology in Safety Assessment of Nanomaterials.* Springer; 2022:303-350.
79. Chrishtop VV, Mironov VA, Prilepskii AY, et al. Organ-specific toxicity. *Nanotoxicology.* 2021;15(2):167-204.
80. Levada K, Pshenichnikov S, Omelyanchik A, et al. Hepatic autophagy and apoptosis. *Nano Converg.* 2020;7(1):17.
81. Han J, Tian Y, Wang M, et al. Proteomics-based toxicity evaluation. *Front Pharmacol.* 2022;13:1011065.
82. Naqvi S, Samim M, Abdin M. Concentration-dependent toxicity. *Int J Nanomedicine.* 2022;17:1459-1474.
83. Baratli Y, Charles AL, Wolff V, et al. Mitochondrial chain impairment. *Toxicol In Vitro.* 2013;27(8):2142-2148.
84. Zhang X, Zhang H, Liang X, et al. Autophagosome accumulation. *Mol Pharm.* 2016;13(7):2578-2587.
85. Cameron SJ, Sheng J, Hosseinian F, Willmore WG. Nanoparticle inflammation. *Int J Mol Sci.* 2022;23(14):7962.
86. Gao C, Wang M, Zheng Y, et al. Hepatotoxicity of nanomaterials. *Nanotechnol Rev.* 2024;13(1):20240074.
87. Thakur S, Kumar V, Das R, et al. Biomarkers of hepatic toxicity. *Curr Ther Res.* 2024;100:100737.
88. Yue L, Qidian L, Jiawei W, et al. Airway inflammation via TLR signaling. *Environ Toxicol.* 2022;37(4):925-935.
89. Shakra MESAE, Salah El-Din RM, Hamouda SYM, et al. Hepatotoxicity of coated vs bare IONPs. *Egypt J Hosp Med.* 2019;76(2):3607-3617.
90. Vakili-Ghartavol R, Momtazi-Borojeni AA, Vakili-Ghartavol Z, et al. Tissue toxicity of SPIONs. *Artif Cells Nanomed Biotechnol.* 2020;48(1):443-451.
91. Wu L, Wen W, Wang X, et al. Acute multi-organ toxicity. *Part Fibre Toxicol.* 2022;19(1):24.
92. Gerogianni A, Bal M, Mohlin C, et al. Endothelial response. *Front Immunol.* 2023;14:1101387.
93. Mulens-Arias V, Rojas JM, Sanz-Ortega L, et al. Angiogenesis impairment. *Nanomedicine.* 2019;21:102063.
94. Baratli Y, Charles AL, Wolff V, et al. Cardiac oxidative stress. *Toxicol In Vitro.* 2013;27(8):2142-2148.

95. Yao Y, Zhang T, Tang M. Mitochondrial toxicity mechanisms. *Environ Pollut.* 2024;343:123231.
96. Wu L, Wen W, Wang X, et al. Cardiac toxicity of ultrasmall IONPs. *Part Fibre Toxicol.* 2022;19(1):24.
97. Gerogianni A, Bal M, Mohlin C, et al. Thromboinflammatory activation. *Front Immunol.* 2023;14:1101387.
98. Feng Q, Liu Y, Huang J, et al. Cardiac biodistribution of IONPs. *Sci Rep.* 2018;8(1):2082.
99. Baratli Y, Charles AL, Wolff V, et al. Myocardial functional changes. *Toxicol In Vitro.* 2013;27(8):2142-2148.
100. McKiernan EP, Moloney C, Chaudhuri TR, et al. Cardiovascular safety of PEGylated IONPs. *Acta Biomater.* 2022;152:393-405.
101. Nowak-Jary J, Machnicka B. Systemic effects of magnetic nanoparticles. *Int J Mol Sci.* 2024;25(22):12013.