Challenges of Nanocarrier Degradation in Animal Tissues: Biocompatibility and Toxicodynamic Effects on Performance, Health, and Welfare

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Abstract

Nanocarrier-based drug delivery systems have gained substantial attention in animal health applications due to their potential for controlled release, improved bioavailability, and targeted delivery. However, the degradation of these nanocarriers within biological systems introduces significant biocompatibility challenges that can compromise animal health, performance, and welfare. This study explores the toxicodynamic implications of nanocarrier decomposition in animal tissues, focusing on physicochemical instability, immune activation, oxidative stress, and systemic toxicity. Degraded nanocarriers may alter surface charge, hydrophobicity, and solubility, which not only disrupt tissue integrity but also provoke inflammatory responses and oxidative damage through the generation of reactive oxygen and nitrogen species. Additionally, cellular dysfunction is often observed due to mitochondrial impairment, lysosomal destabilization, and DNA damage. Hepatorenal complications arise from the accumulation of degradation residues, while interference with endocrine and reproductive systems may further impact fertility and hormonal regulation. Neurological and behavioral disturbances linked to blood-brain barrier disruption and neurotransmitter imbalance reflect broader welfare concerns. Cumulatively, these effects can impair feed intake, reduce productivity, and heighten susceptibility to disease, ultimately challenging sustainable animal production. The findings emphasize the need for designing nanocarriers with controlled degradation profiles and enhanced biocompatibility, supported by robust in vivo assessments. Addressing these challenges is critical to ensure safe and effective integration of nanotechnologies in veterinary and livestock systems.

Keywords: Biocompatibility, degradation, health, nanocarriers, performance, toxicodynamics, welfare

Introduction

Nanocarriers have emerged as advanced platforms for drug delivery, offering site-specific targeting, controlled release, and enhanced bioavailability of therapeutic agents. Their application in veterinary medicine and animal production systems is expanding, driven by the need for more efficient, residue-free, and responsive interventions. These nano-scale vehicles, including liposomes, dendrimers, micelles, and polymeric nanoparticles, interact closely with biological systems, thereby demanding high levels of biocompatibility. However, while the initial focus has often been on their synthesis and functionality, the long-term implications of their degradation products within animal tissues remain underexplored. As these carriers undergo breakdown through enzymatic, hydrolytic, or oxidative pathways, the resulting by-products may interact unpredictably with host physiology, posing potential threats to animal health and performance.

The toxicodynamic responses elicited by degraded nanocarriers span multiple biological domains. Fragmented nanoparticles may disrupt cellular membranes, impair organelle function, and activate immune and inflammatory cascades [1]. Accumulated residues in organs such as the liver, kidney, and brain may compromise metabolic functions, induce oxidative and nitrosative stress, and even alter gene expression profiles through epigenetic modifications. Furthermore, chronic exposure may affect neurobehavioral functions, endocrine signaling, and reproductive capacity, raising significant concerns regarding animal welfare and sustainable production [2]. The lack of detailed mechanistic insight into how nanocarrier degradation influences systemic biocompatibility hinders the development of safer nanotechnologies for livestock and companion animals alike.

This study introduces a comprehensive framework for assessing biocompatibility challenges associated with nanocarrier degradation in animal systems. Unlike previous approaches that predominantly focus on initial nanoparticle properties, this investigation emphasizes the downstream effects of nanocarrier decomposition, integrating toxicodynamic parameters with indicators of health, productivity, and welfare. By categorizing effects across key physiological domains, the study offers a novel perspective that bridges material science and veterinary toxicology. This integrative approach not only elucidates potential biological hazards but also guides the design of safer nanocarrier systems tailored for animal applications, thereby addressing a critical gap in current veterinary nanotechnology research.

Physicochemical Alterations

Instability of surface charge promotes unintended cellular interaction

The surface charge of nanocarriers plays a crucial role in determining their interaction with cell membranes. Instability in the charge can result in increased non-specific adsorption, leading to unintended cellular uptake. This can cause the nanocarriers to interact with non-target tissues, thereby affecting cellular functions [3]. The unintended binding to negatively charged cellular components, such as glycoproteins, could trigger immune responses or disrupt normal cell signaling, contributing to inflammation and toxicity. Altered surface charge during degradation may also enhance nanoparticle aggregation, leading to larger structures that compromise targeted drug delivery, thus reducing therapeutic efficacy.

Altered hydrophobicity interferes with membrane integrity

Nanocarriers with altered hydrophobicity following degradation may disrupt the lipid bilayers of cell membranes. When the hydrophobicity of the nanocarrier surface changes, it can result in improper integration into the cellular membrane, causing destabilization [4]. This destabilization leads to the formation of pores or gaps within the membrane, allowing for the leakage of intracellular contents. Membrane integrity is essential for maintaining cellular homeostasis, and its disruption could lead to cell death, compromised nutrient transport, and the release of pro-inflammatory cytokines. In turn, this could exacerbate immune activation and initiate toxicological responses within tissues.

Morphological changes in degraded fragments hinder targeted delivery

Degradation of nanocarriers often leads to the formation of smaller, irregularly shaped fragments. These fragments, unlike their intact counterparts, may have different surface properties and morphologies, which hinder their ability to precisely target specific cells or tissues [5]. The loss of a defined structure compromises the carrier's ability to recognize and bind to target receptors, thereby reducing the effectiveness of drug delivery. This morphological change can also alter the pharmacokinetics, leading to premature release of the therapeutic agents or misdirected accumulation in non-target areas. Such alterations significantly impair the therapeutic outcomes intended by nanocarrier systems.

Decreased solubility leads to tissue accumulation and cytotoxicity

Degraded nanocarriers may exhibit decreased solubility, leading to their accumulation in tissues. Poor solubility can prevent the nanocarriers from being effectively cleared from the system, resulting in prolonged retention in organs such as the liver, kidney, and spleen. This accumulation can cause cytotoxicity through chronic exposure to degradation products. The accumulation of insoluble particles can lead to cellular stress, inflammatory responses, and organ dysfunction. The persistent presence of these particles can exacerbate oxidative damage, impair cellular repair mechanisms, and contribute to the onset of chronic diseases or functional impairments in target tissues, ultimately hindering overall animal health.

Immune System Activation

Stimulation of innate immune responses triggers inflammation

The degradation of nanocarriers can activate the innate immune system, leading to the release of pro-inflammatory cytokines and chemokines [6]. These immune responses are part of the body’s natural defense mechanism, but excessive activation can result in prolonged inflammation. Inflammation can cause tissue damage, compromise organ function, and increase susceptibility to secondary infections. Furthermore, inflammatory mediators may recruit immune cells to the site of nanocarrier degradation, amplifying the immune response and leading to an environment that is hostile to normal cellular function. This activation can have systemic implications, disrupting homeostasis and overall animal health.

Activation of toll-like receptors leads to immunopathology

Toll-like receptors (TLRs) are key components of the innate immune system, responsible for detecting foreign particles, including degraded nanocarriers. When these receptors are activated by nanocarrier fragments, they trigger a cascade of immune responses that may result in immunopathology. This includes the activation of macrophages and dendritic cells, leading to the release of inflammatory mediators such as cytokines and interleukins [7]. While this

response is protective, excessive or prolonged activation of TLRs can result in pathological immune responses, including autoimmunity or tissue damage. Such immune dysregulation further complicates the biocompatibility of nanocarriers and impairs the health of the animal.

Chronic immune activation disrupts tissue homeostasis

Chronic activation of the immune system due to the persistent presence of nanocarrier degradation products can disrupt tissue homeostasis, leading to long-term organ dysfunction [8]. Continuous inflammation and immune cell infiltration can impair the function of vital organs, including the liver, kidneys, and lungs. Additionally, the prolonged immune response may cause fibrosis and scarring of tissues, further hindering organ function. This disruption of homeostasis can also alter metabolic pathways, reduce nutrient absorption, and impair cellular repair mechanisms. Over time, chronic immune activation may result in systemic inflammatory diseases, which significantly impact animal welfare and productivity.

Hypersensitivity reactions impair systemic tolerance

The presence of degraded nanocarrier fragments can trigger hypersensitivity reactions, which lead to the development of allergic responses in animals. These reactions can impair systemic tolerance, where the body's immune system mistakenly targets harmless substances as threats [9]. As a result, animals may experience symptoms ranging from mild allergic responses, such as skin rashes, to severe reactions, including anaphylaxis. Hypersensitivity to nanocarrier degradation products can also affect the gut, lungs, and other organs, causing further systemic imbalance. Such immune dysfunctions not only compromise animal health but also interfere with the therapeutic potential of nanocarrier systems, limiting their use in veterinary medicine.

Oxidative and Nitrosative Stress

Overproduction of ROS damages mitochondrial function

Degradation of nanocarriers can lead to an overproduction of reactive oxygen species (ROS) within cells. ROS, such as superoxide anions and hydroxyl radicals, are highly reactive and can damage cellular structures. One of the primary targets is the mitochondria, which play a crucial role in energy production and cellular homeostasis. The accumulation of ROS within mitochondria can impair their function, leading to reduced ATP synthesis, mitochondrial membrane potential disruption, and activation of apoptotic pathways [10]. This mitochondrial dysfunction not only impacts cellular energy balance but also exacerbates cell death, tissue damage, and organ dysfunction.

Peroxynitrite formation disrupts endothelial cells

The interaction of ROS with nitrogen species, such as nitric oxide, results in the formation of peroxynitrite, a potent reactive molecule. Peroxynitrite can cause significant damage to endothelial cells, which line blood vessels and regulate vascular tone [11]. Damage to endothelial cells can result in increased vascular permeability, promoting the leakage of proteins and immune cells into tissues. This disruption impairs normal blood flow, exacerbates inflammation, and increases the risk of thrombotic events. Endothelial dysfunction caused by peroxynitrite further compromises the integrity of blood vessels and can lead to cardiovascular complications, impairing overall animal health.

Lipid peroxidation impairs cellular membranes

Lipid peroxidation occurs when ROS attack unsaturated fatty acids in cellular membranes, leading to the formation of reactive aldehydes such as malondialdehyde. These reactive products can further damage cell membranes, leading to membrane destabilization and loss of integrity [12]. The disruption of cellular membranes impairs essential processes such as nutrient transport, signal transduction, and ion homeostasis. In addition, the accumulation of lipid peroxidation products can generate secondary inflammatory responses, amplifying tissue injury. This degradation of membrane structures compromises cell function, contributing to broader organ dysfunction and affecting overall animal health and performance.

Antioxidant depletion exacerbates tissue injury

Cells utilize antioxidants such as glutathione, catalase, and superoxide dismutase to neutralize ROS and maintain redox balance. However, the excessive production of ROS due to nanocarrier degradation can deplete these antioxidant defenses, leaving cells more vulnerable to oxidative damage [13]. As antioxidants become exhausted, the ability of tissues to counteract oxidative stress diminishes, exacerbating cellular injury. Without adequate antioxidant protection, tissues experience further damage from oxidative and nitrosative stress, leading to inflammation, cellular dysfunction, and eventual organ failure. This depletion of antioxidants amplifies the severity of tissue damage and hinders recovery, impacting the overall health and welfare of animals exposed to degraded nanocarriers.

Cytotoxicity and Cellular Dysfunction

Induction of apoptosis in parenchymal cells

Degraded nanocarriers can trigger apoptosis, or programmed cell death, in parenchymal cells, which are the functional cells of organs such as the liver, kidney, and lungs [13]. When nanocarrier fragments accumulate in these cells, they may induce oxidative stress and activate pro-apoptotic signaling pathways, including the mitochondrial pathway. The release of cytochrome c from damaged mitochondria into the cytoplasm initiates a cascade of events leading to cell death. Apoptotic cell death contributes to tissue damage, functional impairment, and inflammation, ultimately compromising the organ's ability to carry out its physiological roles, thereby affecting overall animal health and productivity.

Loss of mitochondrial membrane potential impairs energy metabolism

Mitochondria are critical for cellular energy production, and the loss of mitochondrial membrane potential is a hallmark of cellular dysfunction. Nanocarrier degradation products can induce mitochondrial damage, disrupting the electrochemical gradient necessary for ATP production [14]. This loss of membrane potential reduces the efficiency of oxidative phosphorylation, leading to energy depletion within the cell. Without adequate energy, cellular processes such as protein synthesis, ion transport, and cell division are impaired. The resulting energy crisis can lead to cellular senescence, necrosis, or apoptosis, exacerbating tissue damage and contributing to dysfunction in various organ systems.

Disruption of lysosomal activity causes autophagic stress

Lysosomes play an essential role in degrading cellular waste and maintaining cellular homeostasis through autophagy. Degraded nanocarriers can accumulate in lysosomes, disrupting their normal function. The accumulation of nanoparticle debris may overload lysosomal capacity, preventing the effective breakdown of damaged proteins, lipids, and

organelles. This disruption of autophagic processes leads to the build-up of toxic cellular materials, contributing to cellular stress [15]. Autophagic dysfunction can also cause a vicious cycle of damage and inflammation, impairing tissue repair mechanisms and exacerbating the overall toxicity, which can compromise the health and performance of animals exposed to such degradation products.

Nanoparticle debris induces cell cycle arrest

Degraded nanocarrier fragments can interfere with the normal progression of the cell cycle, causing cell cycle arrest at specific checkpoints [16]. This can occur due to the accumulation of DNA damage, oxidative stress, or disturbances in cellular signaling pathways. When cell cycle progression is halted, the cell enters a state of senescence or, if the damage is irreparable, undergoes apoptosis. Cell cycle arrest impairs tissue regeneration and growth, limiting cellular repair and leading to a reduction in overall tissue function. The long-term effect of such disruption in cell cycle dynamics is a decline in organ performance, growth rate, and immune response, negatively impacting animal welfare.

Genotoxic and Epigenetic Effects

DNA strand breaks promote mutagenesis

Degraded nanocarrier products can induce DNA strand breaks, a key mechanism in genotoxicity [17]. These breaks disrupt the integrity of the genetic material, leading to chromosomal fragmentation or rearrangement. If left unrepaired, these DNA lesions can cause mutations, leading to the formation of abnormal proteins or malfunctioning genes. Mutagenesis in germline or somatic cells can result in cancerous transformations, developmental anomalies, or inherited genetic disorders. This damage to the genetic code compromises cellular function and can accumulate across generations, reducing the overall health and genetic stability of exposed animal populations.

Inhibition of DNA repair enzymes increases genomic instability

Nanocarrier degradation can interfere with the activity of DNA repair enzymes, which are responsible for detecting and repairing DNA damage [18]. The inhibition of key repair pathways, such as base excision repair and homologous recombination, results in an inability to effectively repair DNA strand breaks and other lesions. This leads to an accumulation of genomic damage, increasing genomic instability. Unrepaired DNA damage causes mutations and chromosomal aberrations, further compromising cellular integrity. Genomic instability not only contributes to cancer development but also impairs normal cell function, leading to tissue dysfunction and decreased animal health and productivity.

Altered DNA methylation disrupts gene expression

Degraded nanocarriers may alter the DNA methylation patterns within cells. DNA methylation plays a crucial role in regulating gene expression by silencing or activating specific genes. When nanocarrier degradation products induce changes in methylation patterns, they can lead to the dysregulation of gene expression [19]. This can result in the overexpression of oncogenes or the silencing of tumor suppressor genes, contributing to carcinogenesis. Additionally, disrupted gene expression can affect cellular functions such as growth, metabolism, and differentiation, leading to abnormal tissue development and reduced organismal fitness. The

long-term epigenetic effects of nanocarrier exposure could have profound implications on health, performance, and welfare.

Histone modification impairs chromatin function

Histone proteins play a crucial role in regulating chromatin structure and function. Degraded nanocarriers can influence histone modifications, such as acetylation, methylation, and phosphorylation, which are key to controlling gene expression and chromatin compaction [20]. These modifications can lead to the loosening or tightening of chromatin, affecting DNA accessibility and transcriptional regulation. Impaired histone function can disrupt normal cellular processes such as DNA replication, repair, and cell cycle progression. Furthermore, altered histone modifications can result in the misexpression of genes, contributing to cellular dysfunction, inflammation, and organ damage. In the long term, these epigenetic disruptions may lead to diseases, including cancer and metabolic disorders.

Hematological and Vascular Toxicity

Hemolysis due to membrane disruption of erythrocytes

Degraded nanocarrier particles can interact with red blood cells (erythrocytes), leading to membrane disruption and subsequent hemolysis. The physical or chemical properties of the nanocarriers, such as their size, charge, or surface reactivity, can damage the lipid bilayer of erythrocytes, causing them to rupture [21]. Hemolysis releases hemoglobin into the bloodstream, which can lead to oxidative stress and inflammation. The release of cellular contents may also trigger immune responses, contributing to further damage in blood vessels and organs. In severe cases, hemolysis can lead to anemia, reduced oxygen-carrying capacity, and impaired circulation, significantly affecting the animal's overall health and performance.

Platelet aggregation causes microthrombi

Degraded nanocarriers may activate platelets, promoting their aggregation and the formation of microthrombi [22]. These thrombi can obstruct small blood vessels, reducing blood flow and depriving tissues of oxygen and nutrients. The presence of microthrombi may trigger localized inflammation, further exacerbating tissue damage. In severe cases, the formation of thrombi can lead to ischemia and organ dysfunction. Platelet aggregation also contributes to the development of larger clots that may travel through the bloodstream, increasing the risk of deep vein thrombosis, stroke, or other cardiovascular complications. The altered hemostatic balance caused by nanocarrier degradation compromises vascular health and reduces the animal's ability to recover from injuries or infections.

Endothelial dysfunction alters vascular permeability

Nanocarrier degradation can damage endothelial cells, which line blood vessels and regulate vascular permeability. When endothelial cells are compromised by nanocarrier fragments, the blood vessel walls become more permeable, allowing proteins, immune cells, and other substances to leak into surrounding tissues [23], [24]. This increased vascular permeability can lead to edema, inflammation, and tissue swelling, further impairing organ function. Additionally, the disruption of endothelial cells can reduce the efficiency of nutrient and oxygen exchange between the bloodstream and tissues, resulting in compromised tissue regeneration and healing. The overall vascular health of animals is significantly impacted by the degradation of nanocarriers, contributing to long-term circulatory problems.

Coagulation cascade disruption affects hemostasis

Degraded nanocarriers can interfere with the coagulation cascade, a series of biochemical events responsible for blood clotting and maintaining hemostasis. Nanocarrier fragments may bind to coagulation factors or activate clotting proteins inappropriately, leading to excessive or insufficient clot formation [25]. Disruption of the coagulation cascade can result in either hemorrhage or thrombosis, both of which pose significant risks to animal health. Insufficient clotting leads to uncontrolled bleeding, while excessive clotting can block blood vessels and cause ischemia. The imbalance in the coagulation system due to nanocarrier degradation affects the animal's ability to control bleeding, repair tissues, and maintain normal vascular function, leading to severe health complications.

Hepatorenal Complications

Kupffer cell activation leads to hepatic inflammation

Degraded nanocarriers can be recognized by Kupffer cells, the macrophages of the liver, which play a central role in immune responses. The interaction between nanocarrier fragments and Kupffer cells activates these immune cells, triggering the release of pro-inflammatory cytokines and chemokines [26]. This leads to hepatic inflammation, characterized by hepatocyte damage, fibrosis, and potentially liver dysfunction. Chronic activation of Kupffer cells can result in liver injury, impairing its ability to detoxify blood and metabolize nutrients, thus affecting the overall metabolic health of the animal. This inflammatory response in the liver can lead to long-term hepatic complications, affecting the animal's well-being and performance.

Accumulation in hepatocytes impairs metabolic enzymes

Degraded nanocarriers may accumulate in hepatocytes, the liver cells responsible for detoxification and metabolic processes. The presence of these nanocarrier fragments within hepatocytes can interfere with the function of key metabolic enzymes, impairing critical liver functions such as the detoxification of waste products, synthesis of proteins, and regulation of cholesterol and glucose metabolism [27]. Disruption of these enzymatic activities leads to a decline in liver function, which can manifest as metabolic disorders, accumulation of toxins in the bloodstream, and poor nutrient utilization. Over time, this impairment can contribute to liver failure, further compromising animal health and productivity.

Renal tubular obstruction causes nephropathy

Degraded nanocarriers may accumulate in renal tubules, causing blockages that disrupt normal renal function [28]. The accumulation of nanomaterials within these structures can obstruct the filtration and reabsorption of fluids, electrolytes, and waste products, leading to nephropathy. This obstruction can result in decreased urine output, fluid retention, and the build-up of waste products in the body. Additionally, renal tubule damage may lead to inflammation, fibrosis, and progressive kidney dysfunction. Chronic nephropathy, caused by such blockages, can severely impair kidney function, leading to renal failure, which has detrimental effects on the overall health of the animal, reducing performance and welfare.

Glomerular filtration interference alters clearance rate

Nanocarrier degradation products may interfere with glomerular filtration in the kidneys, where blood is filtered to remove waste products. The presence of nanomaterials can clog the filtration slits or alter the function of podocytes and endothelial cells, which are crucial for the selective permeability of the glomerular filtration barrier [29]. This disruption can impair the kidney's ability to clear toxins, excess electrolytes, and metabolic waste from the bloodstream. As a result, the animal may experience an accumulation of waste products in the blood, leading to uremia, electrolyte imbalances, and fluid retention. Ultimately, altered renal clearance contributes to the decline in kidney function and compromises the animal's health and performance.

Endocrine and Reproductive Effects

Hormone receptor disruption alters endocrine signaling

Degraded nanocarriers can interact with hormone receptors, disrupting normal endocrine signaling pathways. These interactions may alter the binding of hormones to their respective receptors, leading to an imbalance in the regulation of various physiological processes such as growth, metabolism, and reproduction [30]. Disruption of receptor-mediated signaling can affect hormone production, release, and action, resulting in dysregulated levels of critical hormones like insulin, thyroid hormones, and sex hormones. This disturbance in endocrine signaling can lead to metabolic disorders, developmental abnormalities, and impaired reproductive function, negatively affecting animal health and overall productivity.

Impairment of gonadal tissue impacts fertility

Nanocarrier degradation products may accumulate in gonadal tissues, including the ovaries and testes, leading to impaired fertility. The accumulation of nanoparticles within these tissues can cause oxidative stress, inflammation, and cellular damage, which directly affects gamete production and function [31]. In females, this may result in irregular ovulation, reduced oocyte quality, and hormonal imbalances, while in males, sperm count, motility, and morphology may be compromised. Impairment of gonadal function leads to reduced reproductive capacity, contributing to decreased fertility rates in animals. This impact on fertility further affects livestock productivity and may have long-term consequences for breeding programs.

Placental barrier interference affects fetal development

Degraded nanocarriers can cross the placental barrier, potentially disrupting fetal development. Nanoparticles that enter the placenta may interfere with nutrient and oxygen exchange, affecting fetal growth and organogenesis [32]. The presence of nanocarrier degradation products in the placenta can also trigger inflammatory responses and oxidative stress, leading to impaired placental function. Such interference may result in fetal developmental defects, reduced birth weights, and premature birth. Long-term effects on offspring may include congenital malformations, developmental delays, or compromised immune function. The disruption of fetal development can significantly impact the productivity and welfare of future generations.

Adrenal gland dysfunction disturbs stress hormone regulation

The adrenal glands are responsible for producing stress hormones like cortisol and adrenaline. Nanocarrier degradation products can accumulate in the adrenal glands, disrupting their normal function and leading to an imbalance in the secretion of these hormones [33]. Altered stress

hormone regulation can result in exaggerated or insufficient stress responses, affecting an animal's ability to cope with environmental stressors such as heat, transportation, or disease. Chronic disruption of adrenal function can lead to conditions such as adrenal insufficiency, impaired stress resilience, and altered metabolic responses. This dysfunction not only affects animal health and welfare but can also negatively impact overall productivity and performance.

Neurological and Behavioral Impacts

Neuroinflammation compromises brain function

Degraded nanocarriers can induce neuroinflammation by activating glial cells, such as microglia and astrocytes, in the brain [34]. This activation triggers the release of pro-inflammatory cytokines, chemokines, and other inflammatory mediators that can disrupt normal brain function. Chronic neuroinflammation leads to neuronal damage, synaptic dysfunction, and impaired neuroplasticity. As inflammation persists, it may contribute to neurodegenerative diseases, cognitive decline, and altered behavior. The resulting inflammatory environment in the brain affects processes such as learning, memory, and emotional regulation, reducing overall cognitive function and animal well-being.

Blood-brain barrier penetration induces neurotoxicity

Nanocarriers, once degraded, may penetrate the blood-brain barrier (BBB), which normally protects the brain from harmful substances [35]. The degradation products of nanocarriers can compromise the integrity of the BBB, making it more permeable to potentially toxic substances. This allows the entry of nanomaterials and their fragments into the central nervous system, where they can directly cause neurotoxicity. Nanomaterials may induce oxidative stress, inflammation, and cellular damage in neurons and glial cells, resulting in brain tissue injury. Over time, this neurotoxicity can lead to neurological disorders, impaired motor function, and long-term cognitive dysfunction in animals.

Altered neurotransmitter levels affect behavior

Nanocarrier degradation can influence neurotransmitter systems in the brain, which are essential for regulating mood, cognition, and behavior [36]. Changes in the composition or function of neurotransmitters, such as serotonin, dopamine, and norepinephrine, can result from the direct interaction of nanocarrier degradation products with the brain's signaling pathways. Altered neurotransmitter levels can lead to behavioral changes, such as increased anxiety, depression, aggression, or lethargy. These changes can negatively impact animal welfare, reduce performance in tasks that require focus and coordination, and even disrupt social behavior. Long-term alterations in neurotransmitter signaling may contribute to the development of psychiatric disorders or chronic behavioral disturbances.

Disruption of synaptic signaling leads to cognitive decline

Degraded nanocarriers can interfere with synaptic signaling, which is crucial for communication between neurons. Nanomaterials may affect synaptic vesicle release, receptor function, or ion channel activity, leading to disruptions in neurotransmission [37]. This can impair processes such as learning, memory, and decision-making, ultimately contributing to cognitive decline. Long-term exposure to nanocarrier degradation products may lead to neurodegenerative conditions, where synaptic plasticity is significantly compromised. The resulting deficits in cognitive abilities can reduce an animal's ability to adapt to environmental

changes, perform complex tasks, or exhibit normal behavioral responses, negatively affecting both welfare and productivity.

Animal Performance and Welfare

Reduced feed intake due to systemic toxicity

Nanocarrier degradation products may lead to systemic toxicity, which can negatively affect an animal's appetite and feeding behavior. Toxicity-related disruptions in the gastrointestinal system, liver, or brain can impair the animal's ability to process and digest food, resulting in reduced feed intake [38]. The presence of inflammatory cytokines, oxidative stress, or gut barrier dysfunction can contribute to a decreased desire to eat, leading to malnutrition and energy depletion. Reduced feed intake further hampers growth and performance, impairing productivity and overall health. This diminished food consumption can result in weight loss, stunted growth, and poor reproductive outcomes, all of which affect animal welfare and economic viability.

Weight loss and decreased productivity from metabolic impairment

Degradation of nanocarriers can lead to metabolic impairment, disrupting essential biochemical pathways within the body. Nanoparticle-induced inflammation, oxidative stress, and cellular dysfunction may affect organs such as the liver, kidneys, and muscles, impairing metabolic processes like nutrient utilization, energy production, and waste elimination [39]. This results in weight loss, poor body condition, and decreased productivity in terms of milk yield, egg production, or meat growth. The metabolic disturbances caused by nanocarrier degradation can lead to overall decreased efficiency in food conversion, further reducing the economic value of livestock production. These impairments also compromise the animal's ability to thrive and adapt to environmental changes.

Behavioral changes indicating pain or distress

Nanocarrier degradation can lead to a variety of physiological and psychological stressors that result in behavioral changes indicative of pain or distress. Animals may exhibit signs of discomfort, such as reduced activity, increased vocalizations, restlessness, or abnormal posture. The presence of nanomaterials can cause systemic inflammation, oxidative damage, and nervous system dysfunction, all of which can contribute to heightened sensitivity to pain and stress [40]. Long-term exposure to degraded nanocarriers may lead to chronic distress, further compromising animal welfare and quality of life. Pain and distress may result in poor behavioral outcomes, reduced social interaction, and an overall decline in the animal's mental well-being.

Compromised immune competence reduces disease resistance

The degradation of nanocarriers may also compromise the immune system, leading to reduced immune competence and a decreased ability to resist infections or diseases [41]. Nanomaterials can trigger immune responses, leading to chronic inflammation, immune exhaustion, or immune suppression. The toxic effects on immune cells, such as T lymphocytes, macrophages, and dendritic cells, can impair the animal's ability to recognize and fight pathogens effectively. Weakened immune defenses result in increased susceptibility to infections, longer recovery times from illnesses, and increased use of antibiotics or other treatments. This compromised

immune function ultimately affects the overall health, welfare, and productivity of the animal, reducing its resilience in stressful or disease-prone environments.

Future directions

Future research should prioritize the development of nanocarriers with tunable degradation profiles and materials engineered for complete biocompatibility across diverse animal species. Investigations should integrate advanced toxicokinetic and toxicodynamic modeling to predict tissue-specific responses to degradation by-products. Long-term, multi-organ studies are needed to understand cumulative and chronic effects, particularly on the immune, endocrine, and nervous systems. The application of omics-based technologies may reveal molecular and epigenetic alterations induced by nanocarrier residues. Furthermore, comparative studies across age groups, physiological states, and production systems will enhance the relevance of safety assessments. Standardized evaluation protocols and regulatory benchmarks must be established to harmonize safety testing and risk assessment frameworks. Collaboration between material scientists, veterinarians, and toxicologists is essential to design safer nanotechnologies that support both therapeutic efficacy and animal welfare. These directions will ensure a balanced advancement of nanocarrier applications in livestock and companion animal management.

Conclusion

This study highlights the critical biocompatibility challenges arising from nanocarrier degradation in animal tissues, emphasizing the toxicodynamic implications for health, performance, and welfare. Degradation by-products may induce oxidative stress, immune activation, genotoxicity, and systemic organ dysfunction, ultimately compromising animal productivity and well-being. The findings underscore the need for comprehensive in vivo evaluations and predictive toxicological models to assess the safety of nanocarrier-based interventions. Incorporating controlled degradation profiles, biocompatible materials, and regulatory safeguards is essential for the responsible integration of nanotechnology in animal systems. This study provides a foundational framework to guide future research and formulation design, ensuring that the benefits of nanocarriers do not come at the expense of animal health and sustainable production.

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