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# Nanotoxicology: Balancing Risks and Opportunities in Nanotechnology

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ABSTRACT

**Background:** Nanotechnology is making remarkable strides in medicine, industry, and environmental applications, thanks to the unique behaviors of materials at the nanoscale. However, as these applications expand, so do concerns about how nanoparticles might affect human health and the environment are of great interest. The growing interest to understand the pharmaceutical benefits of nanoparticles and potential health risks necessitates the current review.

**Materials and methods**: This review brings together recent findings on nanoparticle behavior and toxicity, and explores how risk can be reduced through improved testing methods, material engineering, and stronger collaboration between researchers, policy makers, and industry stakeholders.

**Discussion:** Studies have shown that prolonged uptake of nanoparticles could bioaccumulates overtime which can trigger harmful effects like oxidative stress, inflammation, as well as genotoxic effect, which may contribute to lung, kidney, liver, cardiovascular and neurological disorders. Interestingly, deeper insight into the toxic pathways could help in the discovery and development of a safer material design and smarter applications, such as precision drug delivery with fewer side effects.

**Conclusion:** This narrative review provide rationales toxic effects of nanoparticles as well as interactions of nanomaterials with biological systems, while providing perspective on the long-term implications of nanoparticles uptakes. Thus, striking the right balance between the duration, concentration and route of exposures could reduce the toxic effect of nanoparticles. These basic studies will provide a solid foundation for engineering the next generation of nanoscale devices and materials, thus, reducing their toxic effects.

## 1.0 INTRODUCTION

Several nanoparticulate matters have attractive and very novel properties in contrast to their bulky counterparts, hence, used in various consumer products. Nanoparticles (NPs) are defined as materials with at least one dimension smaller than 100 nm, while nanotechnology is defined as the understanding and manipulation of matter at dimensions in the range of 1 to 100 nm in size with a surrounding interfacial layer, where unique phenomena enable novel applications. The interfacial layer is an integral part of nanoscale matter, fundamentally affecting all of its properties[1]. Nanotechnology introduces many potential health, environmental, and industrial benefits and its applications are widespread in daily life, transforming society[2]. NPs are employed in a various applications and professions, including industry, electronics, pharmacy, science, medical, and communication products.[3] The most prevalent and rapidly expanding type of NPs, is metallic nanoparticle; specifically carbon and silver NPs[4]. Conversely, both accidental and intentional exposures to NPs have been recorded owing to the growing use of nanotechnology. There are concerns about the potential adverse environmental impacts of this advancement.

Various in vivo and in vitro methods including

computational techniques are currently being used to assess the toxic effects of nanoparticles[5]. The in vitro models allow rapid testing of NP toxicity. The advantages include lower cost, faster and of minimum ethical concerns. Several in vivo studies have been performed to assess the distribution of NPs after inhalation, oral and parenteral exposures[5]. Interestingly, various studies have shown that NPs can cross the lung, skin, gut and brain barrier depending on the exposure route, time, concentration and its distinct characteristics.

## 2.0 Toxicity of nanoparticles

Nanotoxicology was developed to fill knowledge gaps and tackle the unique challenges of NPs, especially it's inherent toxic effect to our health and the environmt[6]. The toxicity and fate of NPs, as well as their uptake by organisms, are all dependent on numerous conditions such as size, shape, etc. The size, shape, and coatings of nanomaterials will have a significant impact on how long they will either accumulate or adsorb to suspended materials, partition to dissolved organic carbon in an aqueous column, or stay in suspension[3]. Hence, toxicity of nanomaterial depends on their physicochemical properties. These properties result in higher chemical reactivity and increased reactive oxygen (ROS) production[7].

### 2.1 Influence of physicochemical properties of nanoparticles on their toxicity

The physicochemical properties of NPs such as size, shape, surface chemistry, porosity, and others could affect their biological identity, however, in the presence of *in vivo* biological barriers, physicochemical changes could significantly modulate the therapeutic index of its cargo and alter the desired outcome.

#### 2.1.1 Size

The size of NPs plays an important role in both their cellular uptake and cytotoxicity. Thus, it is considered a key factor when designing NPs for biomedical application. It is worthy to mention that the original (primary) size of NPs differs from their hydrodynamic size in biological media. This is mainly because of the formation of a biomolecular corona and the aggregation of the NPs. In this case, the aggregation of NPs can be prevented by manipulating the balance of attractive and repulsive forces. Wei *et al*[9], performed a cytotoxicity study on the different sizes of $TiO_2$ (5 and 200 nm) and $Al_2O_3$ (10 and 50 nm) NPs, they observed the formation of aggregates in solution form when the NPs were suspended in cell medium without serum, where the sizes of all the NPs became 8–388-fold larger than their original sizes due to the higher ionic strength of the medium compared to water. Upon the addition of serum, the hydrodynamic sizes of the NPs decreased to only 1.6–10 folds larger than their original sizes[10]. This is because the formation of the protein corona around the NPs prevented them from aggregating due to steric repulsion. The findings indicate that smaller nanoparticles (in terms of primary size, rather than hydrodynamic size) of $TiO_2$ and $Al_2O_3$ show significantly higher cytotoxicity, as well as a much greater reduction in cell metabolic activity, likely due to enhanced cellular uptake[11]. For instance, systematic review of 76 articles by Dong et al.,[12] including *in vitro* studies of the size-dependent cytotoxicity of amorphous silica NPs (aSiO2; NPs), found that smaller-sized $SiO_2$-NPs exhibited greater cytotoxicity. However, it is important to consider the cell types, which plays a significant role in this process given that it depends on the predominant pathway of cellular uptake in each different cell[13].

#### 2.1.2 Shape

The shape of NPs can be controlled by manipulating the experimental conditions during their synthesis, such as super-saturation, reducing agents, temperature, surfactants, and secondary nucleation[14]. NPs have different shapes and geometries such as; spherical, rod, flower, star, disc, cubic, prismatic, and needle-like structures. The aspect ratio (AR), which is the proportion between width and height of NPs, is used to compare different shapes of NPs[14]. For example, spherical AuNPs have an AR of 1, while Au nanorods (AuNRs) have a higher AR[14]. It was proven that the cellular uptake and cytotoxicity of NPs are affected by the AR of NPs[14]. Given that AuNPs are common in many biomedical applications, many studies investigated their shape-dependent cellular uptake and cytotoxicity. For instance, Wo´zniak *et al.,*[15] compared the in vitro cytotoxicity profiles of different shapes and sizes of bare (non-coated) AuNPs in cancer (HeLa) and normal (HEK293T) cell lines. They found that Au nanospheres (AuNS) and AuNRs had higher cytotoxicity than star-, flower- and prism-shaped AuNPs. However, the sizes of these different AuNPs shapes also differed and this may explain the difference in cytotoxicity. Specifically, the AuNSs and AuNRs had smaller sizes (10 nm and 38 × 16 nm, respectively), while the flower-, prism-, and star-shaped AuNPs had larger sizes (~370 nm, ~160 nm, and ~240 nm, respec- tively).

#### 2.1.3 Surface Charge on Intra-cellular Trafficking

NPs can have negative, positive, or neutral surface charge

depending on their surface functional groups[16]. The surface charge can affect the NP–cell membrane interactions, protein corona, and consequently the cellular uptake of NPs[17]. Therefore, it is one of the most important physicochemical properties to control when designing NPs for biomedical applications. Generally, reports have shown that charged NPs have higher cellular uptake than neutral NPs. The cell membrane is negatively charged due to the anionic head group of phospholipids and the existence of some carbohydrates, such as sialic acid[18]. Considering this, cationic NPs are taken up by most non-phagocytic cells to a greater extent than anionic NPs. However, in some cases, anionic NPs have greater cellular uptake in phagocytic cells[19]. The surface charge of NPs can also tune their cellular uptake pathway. For instance, Untener *et al.,* (2013)[20] reported that positively charged AuNRs had a higher extent of internalization compared to their negatively charged counterparts. It was found that cationic AuNRs were taken up through macropinocytosis and clathrin-mediated endocytosis, while anionic AuNRs were internalized through macro- pinocytosis and caveolae-related mechanisms[20]. The cytotoxicity of NPs are affected by their surface charge. In line with the established influence of surface charge on cellular uptake, recent findings reveal that in nonphagocytic cells, charged nanoparticles exhibit greater cytotoxicity than neutral ones particularly positively charged nanoparticles tend to induce significantly higher toxicity compared to their negatively charged counterparts. This suggests that surface charge not only modulates uptake efficiency but also plays a critical role in determining the biological response and potential adverse effects of nanomaterials[20].

#### 2.1.4 Surface Functionalization

Changing the ligands on the surface of NPs will mostly tune the previous parameter (surface charge), which affects the protein corona, cellular uptake, and cytotoxicity of the NPs[21]. However, the specific functionalities on the surface of NPs can be useful for targeting purposes. Here, overexpressed or unique receptors on the cell membrane are targeted by functionalizing the NPs with a complementary aptamer, protein, or antibody, which can specifically bind to the cell receptors. Tao *et al.*[22] targeted cervical cancer cells through folic acid (FA)-poly (ethylene glycol)-b-poly (lactidecoglycolide) blended NPs, which enhanced the efficacy of cancer chemotherapy through the targeted delivery of anticancer drugs. Lund et al.[23] showed that AuNPs functionalized with 50% PEG–$NH_2$/50% glucose had an eighteen-fold higher internalization rate than NPs functionalized with either PEG–$NH_2$ or glucose alone due to their different organization patterns. Interestingly, Yeh et al.[24] studied the role of ligand coordination of two quantum dots (QDs) on their cytotoxicity. It was observed that monothiol-functionalized QDs had greater levels of cytotoxicity compared to dithiol-functionalized QDs in HeLa cell lines. However, the monothiol-functionalized QDs had a higher charge density, and thus it is difficult to tell if this tendency is solely related to the ligand coordination or charge density.

Moreover, surface functionalization plays a critical role in membrane trafficking by modulating how nanoparticles interact with the cell membrane. Functional groups and targeting ligands can influence endocytic pathways, facilitating receptor-mediated uptake and enhancing internalization efficiency. These tailored surface modifications not only support cell-specific targeting but also help direct intracellular trafficking, potentially improving therapeutic delivery while minimizing off-target effects.

### 2.2 Mechanisms of Nanoparticles Toxicity

Nanotoxicology, a critical subdiscipline of toxicology aims to understand and mitigate the adverse biological effects associated with the increasing use of nanoparticles (NPs) across various fields. Central to this field is the evaluation of nanoparticle-induced toxicity, which has largely been explored through in vitro studies.[25] These studies demonstrate that NPs can trigger a range of deleterious effects across different levels of cellular structure, including cell death and sublethal outcomes such as altered gene expression, oxidative stress, growth inhibition, malformation and impaired respiration. Among the major mechanisms implicated, the generation of reactive oxygen species (ROS) is a key factor, leading to DNA damage, lipid peroxidation, and disruption of antioxidant defense systems. To better understand these toxicological outcomes, especially oxidative stress, genotoxicity, inflammatory responses, and cytotoxicity, reliable and accessible testing methods are essential. In biological systems, the primary routes of nanoparticle exposure include adsorption onto epithelial surfaces such as gill tissues and ingestion[25]. The subsequent sections will provide further detail on the mechanisms of NP toxicity, focusing on oxidative stress, cytotoxicity, and genotoxicity.

#### 2.2.1 Oxidative Stress

Nanoparticles can generate reactive oxygen species (ROS), leading to cellular damage and inflammation[26]. ROS

production has been found in a diverse range of nanomaterials including carbon fullerenes, carbon nanotube and nanoparticle metal oxides. ROS and free radical production is one of the primary mechanisms of nanoparticle toxicity; it may result in oxidative stress, inflammation, and consequent damage to proteins, membranes and DNA[27]. For example, the application of nanoparticle metal oxide with magnetic fields that modulate ROS leads to enhanced tumor growth[28].

### 2.2.2 Cytotoxicity

Some nanoparticles have been shown to be toxic to cells, potentially causing cell death or dysfunction[26]. A primary marker for the damaging effects of NPs has been cell viability as determined by state and exposed surface area of the cell membrane. Cells exposed to metallic NPs have, in the case of copper oxide, had up to 60% of their cells rendered unviable. When diluted, the positively charged metal ions often experience an electrostatic attraction to the cell membrane of nearby cells, covering the membrane and preventing it from permeating the necessary fuels and wastes[29]. With less exposed membrane for transportation and communication, the cells are often rendered inactive. NPs have been found to induce apoptosis in certain cells primarily due to the mitochondrial damage and oxidative stress brought on by the foreign NPs electrostatic reactions[29].

### 2.2.3 Genotoxicity

Certain nanoparticles can interact with DNA, leading to genetic damage and potentially increasing the risk of cancer[26]. Metal and metal oxide NPs such as silver, zinc, copper oxide, uraninite, and cobalt oxide have also been found to cause DNA damage[29]. The damage done to the DNA will often result in mutated cells and colonies as found with the HPRT gene test [29].

### 2.3 Diseases Associated with Nanoparticle Exposure

Human skin, lungs, and the gastrointestinal tract are in constant contact with the environment. While the skin is generally an effective barrier to foreign substances, the lungs and gastrointestinal tract are more vulnerable. These three ways are the most likely points of entry for natural or anthropogenic nanoparticles. Injections and implants are other possible routes of exposure, primarily limited to engineered materials[30].

Nanoparticles, due to their nanoscale dimensions, can move from entry points into the circulatory and lymphatic systems, eventually reaching body tissues and organs. Certain nanoparticles, depending on their size and composition, may cause permanent cellular damage through mechanisms like oxidative stress or organelle injury. Figure 5 compares the relative sizes of a typical cell and its organelles to nanoparticles, helping to explain how nanoparticles can penetrate cells and interact with components such as the nucleus and mitochondria[30]. The genetic makeup of an organism also influences its susceptibility to nanoparticle toxicity, as it determines the biochemical mechanisms available to adapt to or counteract toxic substances[31].

Inhaled nanoparticles have been associated with a range of respiratory conditions, including asthma, bronchitis, emphysema, and lung cancer, and have also been implicated in the progression of neurodegenerative disorders such as Parkinson's and Alzheimer's disease[32]. In the gastrointestinal tract, exposure to nanoparticles has been linked to inflammatory bowel conditions like Crohn's disease, as well as malignancies such as colon cancer[33]. Once nanoparticles enter the circulatory system, they can contribute to arteriosclerosis, thrombus formation, arrhythmias and broader cardiovascular complications including cardiac arrest[34]. Moreover, their accumulation in filtration organs such as the liver and spleen has been connected to organ-specific pathologies[35]. Certain nanoparticles have also been implicated in the development or exacerbation of autoimmune diseases, including systemic lupus erythematosus, scleroderma, and rheumatoid arthritis[36].

### 2.4 Nanotoxicology Opportunities

The nanotoxicology presents several opportunities across the following domains.

### 2.4.1 Safety Assessment and Regulation

Developing standardized methods and protocols for assessing the toxicity of nanomaterials can help in creating regulatory frameworks, ensuring the safe use of nanotechnology in consumer products, pharmaceuticals, and industrial applications[1]. Research in nanotoxicology can provide insights into the environmental impact of nanomaterials, leading to the development of eco-friendly nanomaterials and strategies for mitigating potential environmental hazards[38]. By understanding the toxicity profiles of different nanomaterials, industries can innovate and use nanotechnology more responsibly in electronics, cosmetics, textiles, and food packaging, enhancing product safety and consumer trust[39].

### 2.4.2 Interdisciplinary Collaboration and Public Health

The field encourages collaboration between toxicologists, materials scientists, biologists, and regulatory bodies, fostering interdisciplinary research and the development of comprehensive safety guidelines for nanotechnology[40]. Advances in nanotoxicology can improve public health by identifying and mitigating risks associated with exposure to nanomaterials in everyday life, leading to better health outcomes and increased public awareness of nanotechnology's benefits and risks[41-42].

## 2.5 Conclusion

Nanotoxicology plays a crucial role in bridging the gap between the innovative potential of nanotechnology and the imperative need for safety and sustainability. The unique physico-chemical properties of nanoparticles, while offering unprecedented opportunities, also present significant challenges that must be addressed through rigorous scientific investigation and interdisciplinary collaboration. Understanding the mechanisms of nanoparticle toxicity and their association with various diseases is essential for developing safer nanomaterials and effective regulatory policies. By implementing the recommended strategies, it is possible to harness the benefits of nanotechnology responsibly, ensuring that its applications contribute positively to public health and environmental sustainability. Through continued research and collaboration, nanotoxicology will guide the responsible advancement of nanotechnology, balancing its risks and opportunities for a safer future.

## 2.6 Recommendations

I. **Enhanced Safety Assessments:** Develop and standardize comprehensive protocols for evaluating the toxicity of nanoparticles, considering their unique physico-chemical properties. These protocols should be integrated into regulatory frameworks to ensure the safe application of nanotechnology across various industries.

II. **Regulatory Frameworks:** Establish and enforce stringent regulatory frameworks that govern the production, use, and disposal of nanoparticles, minimizing potential health and environmental risks.

III. **Targeted Research Funding:** Allocate funding for research focused on the mechanisms of nanoparticle toxicity and the development of safer nanomaterials. Priority should be given to studies that investigate the long-term health effects of nanoparticle exposure.

IV. **Environmental Monitoring:** Implement monitoring systems to track the environmental distribution and impact of nanoparticles, ensuring that any adverse effects are identified and mitigated promptly.

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**Conflict of Interest**

We do not have any material or financial conflict of interest to disclose

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