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TOXICITY OF NANOPARTICLES ON ANIMAL AND HUMAN ORGANISM: CELL RESPONSE

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Review

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ABSTRACT

The review focuses on research related to the effect of nanoparticles on cells in the animal and human body and on the analysis of potential biological effects that may be caused by exposure to these materials. This review deals with the mechanisms through which nanoparticles interact with cells and analyses their potential consequences for an individual's health. The main mechanisms of toxicity are oxidative stress, inflammatory responses, cell damage, and genetic changes that can lead to apoptosis or other cellular responses. These effects are often modified by various factors, including the size and shape of the nanoparticles, their surface treatment and chemical composition. The work highlights significant differences in the responses of cells of different organ systems to nanoparticles, thereby pointing the need for a more precise examination of toxic effects depending on the biological context. This review also discusses important methods for assessing nanoparticle toxicity, including *in vitro* experiments, *in vivo* animal studies, and various clinical studies. The aim of this review was to provide a comprehensive overview of this important issue, which has significant implications for public health and the environment. Research into nanoparticles and their interaction with cells is crucial for a better understanding the risks associated with their exposure and for the development of safe technologies and applications that use these materials.

Keywords: nanoparticles, toxicity, cells, *in vitro, in vivo*

NANOPARTICLES AND THEIR CHARACTERISTICS

Nanoparticles are structures that have dimensions in nanometers (10^{-9} meters), which ranges from 1 to 100 nanometers (nm) (***AlMasoud et al.*, 2020; *Dianová et al., 2023)***. This definition considers the fact that nanoparticles are in the same size range as some molecules and biomolecules ***(Khan et al., 2020; Xuan et al., 2023)***. Nanoparticles consist of various materials, including metals, polymers, oxides, and other nanomaterials. These microscopic particles have unique physical and chemical properties that are fundamental determinants of their scientific and technological importance ***(Jalbani et al., 2014; Bahadar et al., 2016; Halo Jr et al., 2021; Kumah et al., 2023)***.
Physical properties include:

- large surface ratio: nanoparticles have a high surface-to-volume ratio, which means that they have more active surface sites for interaction with other substances ***(Khan et al., 2020; Yang et al., 2021);***
- quantum effects: in the nanometer or subnanometer range, nanoparticles can exhibit quantum effects that affect their electronic structure and optical properties ***(Yang et al., 2021);***
- change in optical properties: nanoparticles have unique optical properties that include changes in absorption and emission of light based on their size and shape. These properties are used in various optical applications. Also, some nanoparticles, such as quantum liquid dots, change colour based on their size, which is called the quantum dot phenomenon ***(Xuan et al., 2023)***.

The chemical properties of nanoparticles are often different from larger molecules due to their larger surface area ratio. This has a significant impact on their reactivity and interactions with other substances ***(Xuan et al., 2023)***.
Chemical properties include:

- increased reactivity: the high surface ratio of nanoparticles allows greater reactivity and interaction with different substances, which can cause different chemical reactions ***(Khan et al., 2019);***
- modifiability: nanoparticles are able to be surface modified with different functional groups, which enables the adaptation of their chemical properties for specific applications ***(Huang et al., 2017);***
- stability: the small size of nanoparticles can lead to their greater sensitivity to internal and external influences, such as changes in temperature and pH ***(Huang et al., 2017)***.

There are variety of different types of nanoparticles that are toxic to the cells of the animal and human body. These nanoparticles differ in their physical and chemical properties and mechanisms of toxicity ***(Halo Jr et al., 2021; Xuan et al., 2023)***. Below are some of the main types of toxic nanoparticles and their effect on the cells of the animal and human body:

- metal nanoparticles such as silver, zinc, copper, and titanium are often used in various applications, such as antibacterial agents or UV filters. Some of these metal nanoparticles can be toxic to cells by causing oxidative damage to cells, inhibiting cell metabolism, and inducing inflammatory responses ***(Bahadar et al., 2016);***
- carbonate nanoparticles including carbon nanoparticles (C60 fullerenes) are used in various nanotechnological applications. These nanoparticles may have genotoxic potential and affect cell viability ***(Joudeh & Linke, 2022);***
- quantum dots are nanostructures that are capable of generating reactive oxygen species (ROS), responsible for oxidative damage to cells and DNA ***(Lyberopoulou et al., 2016);***
- nanotubes are long, thin nanoparticles that may have potential for biocompatibility and use in areas such as cancer treatment. However, their long fibers can induce mechanical damage to cell membranes and lead to toxicity ***(Bahadar et al., 2016);***
- nanocrystalline titanium dioxide is commonly used in sun creams and cosmetic products. Studies have shown that with long-term exposure, these nanoparticles likely to initiate oxidative cell damage and genotoxicity over time ***(Lyberopoulou et al., 2016);***
- carbon nanotubes have unique properties, but some of them may have the potential to damage cells by causing mechanical damage to membranes or becoming the seeds of inflammatory reactions ***(Joudeh & Linke, 2022);***
- nanomaterials based on metal oxides such as titanium dioxide, zinc oxide and silicon dioxide are commonly used in industry and products. Some of these nanoparticles can produce inflammatory reactions and oxidative damage to cells ***(Bahadar et al., 2016)***.

MECHANISMS OF INTERACTION OF NANOPARTICLES WITH CELLS

The mechanism of interaction between nanoparticles and cells is complex and important for understanding the toxic effect of these particles on the cells of the organism ***(Awashra & Młynarz, 2023).***
The entry of nanoparticles into cells is a complex process that depends on the size, shape and surface properties of these particles. There are several mechanisms through which nanoparticles have the ability to enter the cells of the human body ***(Behzadi et al., 2017; Maciejewski et al., 2022).*** These mechanisms include the following categories:

- endocytosis – a process in which the cell surrounds the particle with its membrane and pulls it inside the cell. There are different types of endocytosis, such as phagocytosis (in which the cell "swallows" large particles) and pinocytosis (in which the cell takes in small particles or liquid droplets). These mechanisms have the ability to capture nanoparticles based on their size and surface characteristics ***(Foroozandeh & Aziz, 2018);***
- adhesion and penetration. Nanoparticles have the ability to bind to the surface of cells through interactions between their surface structures and structures on the cell surface. This process makes it more likely that the nanoparticles will enter the cell through the cell membrane. Interactions between nanoparticles and cells are influenced by the surface chemistry and size of the nanoparticles ***(Sabourian et al., 2020);***
- biointeraction with biomolecules. Biomolecules such as proteins and lipids are able to be adsorbed on the surface of nanoparticles during their passage through the body. These biomolecules may have an impact on the existence and capacity of nanoparticles to interact with cells within the organism. For example, proteins form a protein shell around nanoparticles, which has the ability to affect their dissolution and dispersion in the biological environment ***(Awashra & Młynarz, 2023);***
- transport of nanoparticles in the cell. After absorption of nanoparticles into the cell, they can be transported by various cellular structures. For example, mitochondria, lysosomes and endoplasmic reticulum may be involved in the transport and distribution of nanoparticles in cells ***(Foroozandeh & Aziz, 2018);***
- active transport. Some nanoparticles enter cells through specific transport proteins in the cell membrane. This process is called active transport because it requires energy. An example is the entry of iron into cells via the transferrin receptor ***(Foroozandeh & Aziz, 2018);***
- passive transport allows nanoparticles to penetrate the cell membrane without using energy. This happens when the nanoparticle is small enough and has certain chemical properties that make it soluble in membrane lipids. This process may involve diffusion or facilitated diffusion ***(Sabourian et al., 2020);***
- entry through ion channels. Some nanoparticles enter cells through existing ion channels in the cell membrane. This mechanism is specific to certain types of nanoparticles that have similar properties to endogenous substances that normally enter cells through these channels ***(Awashra & Młynarz, 2023).***

MECHANISMS OF TOXICITY AND SIGNS OF NANOPARTICLES TOXICITY

Nanoparticles represent a complex environment in which, due to their properties and interactions with body cells, they trigger various mechanisms of toxicity. Oxidative stress and inflammatory processes are two of the key mechanisms that are associated with the toxic effect of nanoparticles on animal and/or human cells ***(Aloisi et al., 2022; Yang et al., 2021).***

Oxidative stress

Oxidative stress is a condition that occurs when the production of reactive oxygen species (ROS) in cells and tissues exceeds the ability of the body to neutralize them with the help of antioxidants. Nanoparticles represent a source of ROS due to their large surface area ratio and ability to interact with biological molecules. ROS is able to damage cellular structures, including lipids, proteins and DNA. The result is damage to cell membranes, changes in cell metabolism, and activation of cell defense mechanisms to remove ROS ***(Awashra & Młynarz, 2023; Deepa et al., 2023; Yang et al., 2021).*** The main aspects of oxidative stress associated with nanoparticles include:

- ROS production: nanoparticles generate ROS, such as superoxide radicals and peroxides, which leads to damage cellular components such as lipid membranes and DNA ***(Elsaesser & Howard, 2012);***
- activation of oxidative pathways: nanoparticles activate oxidative pathways in cells, including the Nrf2-ARE pathway, which increases production of antioxidants ***(Awashra & Mlynarz, 2023);***
- changes in mitochondria: oxidative stress affects the function of mitochondria, which has consequences for the energy metabolism of cells ***(Awashra & Mlynarz, 2023);***

Inflammatory reactions and immune response

Inflammation is a complex immune process that the body uses to protect itself from infections and tissue damage. Exposure to nanoparticles is able to trigger inflammatory reactions in the body. Key aspects of inflammation associated with nanoparticles include:

- activation of inflammatory mediators: nanoparticles are able to activate cells of the immune system, including macrophages and neutrophils, which leads to the release of inflammatory cytokines and chemokines ***(Yang et al., 2021);***
- activation of inflammatory pathways: inflammatory pathways such as NF-κB is activated by nanoparticles, which leads to increased expression of inflammatory genes ***(Yang et al., 2021);***
- the potential role of chronic inflammation: repeated exposure to nanoparticles may contribute to the development of chronic inflammation and inflammatory diseases ***(Awashra & Młynarz, 2023);***

Cell damage and genetic changes

Nanoparticles generate cell damage by interacting with cell membranes, organelles and biomolecules such as proteins and DNA. This damage leads to cell death, such as apoptosis, or induce genetic changes in the cells ***(Kumah et al., 2023).*** We divide genetic changes into the following categories:

- mutations: nanoparticles are capable of producing genetic mutations in cells. These mutations are able to have consequences for the cell cycle and induce to the development of cancer or other diseases ***(Egbuna et al., 2021);***
- epigenetic changes: exposure to nanoparticles affects epigenetic changes in cells. These changes modify gene expression and affect cell differentiation and function ***(Egbuna et al., 2021);***
- genotoxicity: there are nanoparticles that are genotoxic, meaning they can directly damage cellular DNA. This is the reason for defects in DNA repair and stabilization, which increases the risk of mutations and cancer development ***(Shukla et al., 2021).***

Exposure to nanoparticles also have various health risks ***(Egbuna et al., 2021).*** These risks affect different systems and organs in the body and include:

Respiratory risks:

- respiratory diseases: nanoparticles penetrate deep into the airways and cause or worsen diseases such as asthma, bronchitis and chronic obstructive pulmonary disease (COPD) ***(Lu et al., 2014);***
- increased risk of infections: exposure to nanoparticles leads to weaken the immune system of the airways, which increases the risk for respiratory infections ***(Lu et al., 2014).***

Cardiovascular risks:

- atherosclerosis: nanoparticles contribute to the formation of plaques in blood vessels (atherosclerosis), which increases the risk for heart diseases, including myocardial infarction and stroke ***(Omidian et al., 2023);***
- increased blood pressure: exposure to nanoparticles increase blood pressure and contribute to hypertension ***(Omidian et al., 2023).***

Eye risks:

- nanoparticles in the air contribute to eye problems, which include inflammation of the eye tissues, eye irritation, which is manifested by redness, itching and tearing. In case nanoparticles get into the inner parts of the eye, they produce vision problems ***(Scheive et al., 2021).***

Neurological risks:

- problems with penetration into the central nervous system (CNS): the presence of nanoparticles in the brain or in the spinal cord produces various neurological effects ***(Khan et al., 2018);***
- inflammation and immune response: nanoparticles have the ability to generate inflammation in nervous tissue and trigger immune responses that affect the normal functioning of the nervous system ***(Sawicki et al., 2019);***
- oxidative stress: some nanoparticles produce increased oxidative stress in nerve tissue cells. Oxidative stress damages cells and causes neurological problems ***(Vinod & Jena, 2021);***
- changes in neurotransmitters: nanoparticles affect the levels of neurotransmitters in the nervous system, which influence behaviour and brain function ***(Zia et al., 2023);***
- changes in cognitive functions: long-term exposure to nanoparticles can affect cognitive functions, including memory and learning ***(Teleanu et al., 2018).***

Reproductive and developmental risks:

- exposure to nanoparticles affects the reproductive system and fetal development, including deformities, changes in growth parameters, and developmental problems. Nanoparticles affect changes in hormonal balance in pregnant women, which affects the normal course of pregnancy, increases the risk of miscarriage, affects fertility and the ability to conceive ***(Samrot & Noel Richard Prakash, 2023).***

Risk for tumors:

- genotoxicity: in case nanoparticles are genotoxic, they have the ability to induce damage to the genetic material in cells, increasing the risk of tumours. Genotoxicity leads to uncontrolled cell division and mutations ***(Egbuna et al., 2021);***
- oxidative stress: nanoparticles are able to generate oxidative stress in cells, which can promote processes that contribute to the development of tumours ***(Awashra & Mlynarz, 2023);***
- inflammation and immune response: some nanoparticles induce inflammation and an immune response in the body, which may be associated with the development of tumours ***(Yang et al., 2021);***
- interactions with biological structures: nanoparticles have the ability to interact with biological structures and proteins in cells, affecting their function and causing erratic cell behaviour ***(Damasco et al., 2020);***
- transfer through biological barriers: the ability of some nanoparticles to penetrate biological barriers can increase the risk that they reach critical tissues and organs and trigger tumour processes ***(Damasco et al., 2020).***

Systemic effects:

- exposure to nanoparticles can have a variety of systemic effects, meaning that nanoparticles are capable of affecting different organs and systems in the body ***(AlMasoud et al., 2020; Jalbani & Soylak, 2014).*** These effects include the consequences of absorption of nanoparticles into the blood, distribution through the body and their interaction with various cellular and tissue structures, for example:
- inflammation and immune response: nanoparticles are able to induce inflammation in the body and activate the immune system. Chronic inflammation can be linked to many diseases, including heart disease, *diabetes* and other inflammatory diseases ***(Yang et al., 2021);***
- oxidative stress: nanoparticles are able to contribute to increased oxidative stress in cells. Oxidative stress is associated with aging and may be a factor in the development of various diseases, including neurodegenerative diseases and cancer ***(Awashra & Młynarz, 2023);***
- effect on respiratory systems: when inhaled, nanoparticles can affect the respiratory system and cause problems such as pneumonia and asthma ***(Lu et al., 2014);***
- effect on the cardiovascular system: it is suspected that nanoparticles may have a negative effect on the cardiovascular system and are associated with an increased risk of heart disease ***(Omidian et al., 2023);***
- accumulation in organs: some nanoparticles may have a tendency to accumulate in certain organs, which may lead to long-term effects ***(Yang et al., 2021);***
- genetic and epigenetic changes: nanoparticles have the ability to affect the genetic material of cells and cause genetic or epigenetic changes that can affect normal cell functions and growth ***(Egbuna et al., 2021);***
- effect on the reproductive system: exposure to nanoparticles may affect the reproductive system and may be associated with reduced fertility and problems during pregnancy ***(Samrot & Noel Richard Prakash, 2023).***

Allergies and sensitivities:

Allergies are usually produced by the body's immune response to foreign substances that the body considers potentially dangerous. Allergic effects of exposure to nanoparticles include:

- allergic contact dermatitis: nanoparticles that come into contact with the skin have the ability to induce an allergic reaction in the form of skin problems such as itching, redness or rash ***(Yoshioka et al., 2017);***
- respiratory problems: nanoparticles that are inhaled can potentially induce allergic reactions in the airways, which could lead to asthma symptoms or other respiratory problems ***(Lu et al., 2014);***
- allergic conjunctivitis: exposure to some nanoparticles can trigger an allergic reaction in the eyes, causing allergic conjunctivitis, which means red, itchy, and watery eyes ***(Yoshioka et al., 2017).***

Factors influencing the toxicity of nanoparticles

The toxicity of nanoparticles is not uniform and depends on many factors that affect their ability to interact with cells and tissues of the organism ***(Huang et al., 2017).***

Size and shape of nanoparticles

The size and shape of nanoparticles have a key influence on their toxicity. Smaller nanoparticles have a larger surface area relative to their volume, which increases their reactivity and ability to interact with cells. The shape of nanoparticles affects their ability to attach to cell membranes or penetrate cells ***(Huang et al., 2017; Odaudu & Akinsiku, 2022).***

Surface treatment and chemical composition

The surface treatment of nanoparticles significantly influences their interactions with cells. Nanoparticles are functionalized with various substances, such as polymers or biomolecules, which could affect their solubility, stability and affinity to biological molecules. In addition, the chemical composition of nanoparticles plays an important role in their toxicity ***(Awashra & Mlynarz, 2023; Odaudu & Akinsiku, 2022).***

Dose and concentration of nanoparticles

The amount of nanoparticles to which the organism is exposed is a key factor affecting toxicity. A higher concentration may increase exposure and potential effect on cells. Dose per unit weight or volume can be critical in determining toxicity ***(Odaudu & Akinsiku, 2022).***

Length of exposure and cell type

The length of exposure to nanoparticles could also have a significant effect on their toxicity. Short exposure may have a different effect than long-term exposure. Different types of cells in the organism may have different sensitivities to nanoparticles. For example, cells of the immune system may respond differently than cells of epithelial tissue ***(Odaudu & Akinsiku, 2022).***

Toxicity of nanoparticles on cells of the respiratory system

The respiratory system is in direct contact with the external environment and is exposed to various pollutants, including nanoparticles. The process by which these extremely small particles enter the lungs is called respiratory exposure. This process affects various aspects of lung biology and health, and could have serious consequences for the human respiratory system ***(Lu et al., 2014; Nasirzadeh et al., 2022).***

Nanoparticles come from a variety of sources, including industrial emissions, transportation, environmental processes, and medical applications. Exposure to nanoparticles can be unintentional, as in the inhalation of polluted air, but can also be purposefully controlled, for example in the inhalation of drugs ***(Karlsson & Hartwig, 2022).***

Effect on lung cells

The effect of nanoparticles on lung cells is an important aspect when evaluating their potential toxic effect on the respiratory system. These nanoparticles are able to have various effects on lung cells, including inflammatory responses, oxidative stress, and damage to cellular structures ***(Zhou et al., 2023).*** Below are some of the main ways nanoparticles affect lung cells:

- inflammatory responses: nanoparticles have the ability to induce inflammatory responses in the lungs by activating cells of the immune system such as macrophages and neutrophils. These cells produce inflammatory cytokines such as TNF-α and IL-6, which may generate inflammation in the lung tissues. Acute or chronic inflammation may produce tissue damage and increased risk for various lung diseases ***(Bobyk et al., 2021);***
- oxidative stress: nanoparticles may cause the formation of ROS in lung cells through various mechanisms, such as interaction with cell membranes or activation of redox reactions. Excessive ROS production has the ability to damage cellular structures and trigger chain reactions that lead to oxidative stress ***(Zhou et al., 2023).***

One of the most important aspects of the impact of nanoparticles on the respiratory system is respiratory problems. Short and long-term exposure to nanoparticles may produce increased breathing difficulties, worsening of respiratory tract function, increased risk for asthma, and exacerbation of chronic obstructive pulmonary disease (COPD) ***(Lu et al., 2014).***

Table 1 General toxic effect of nanoparticles on body cells

Toxic effect	Characteristics of influence	Nanoparticles
Oxidative stress	Oxidative stress disrupts cell homeostasis, causes cell damage, leads to cell apoptosis (programmed cell death) and inflammatory reactions	Metal nanoparticles: silver Silicon nanoparticles Quantum dots Multilayer carbon nanoparticles
Inflammatory reaction	Inflammation give rise to tissue damage and an increased risk of various diseases.	Metal nanoparticles: silver, titanium Silicon nanoparticles Quantum dots Multilayer carbon nanoparticles
Toxic effect on organs	Nanoparticles have a toxic effect on various organs, such as the lungs when inhaled, the liver when taken orally, or the central nervous system when directly exposed to the nervous system.	Metal nanoparticles: gold, silver, copper, zinc, titanium Carbon nanoparticles Liquid nanoparticles Oxidized nanoparticles: titanium oxide (TiO_2) Nanotubes
Accumulation and biodistribution	Nanoparticles accumulate in certain tissues and organs, which have long-term health effects.	Multilayer carbon nanoparticles Metal nanoparticles: silver Oxidized nanoparticles: titanium oxide (TiO_2) Asbestos fibers Quantum dots
DNA damage	Nanoparticles interact with cellular DNA and cause genotoxic damage. This damage give rise to mutations and the subsequent development of cancer.	Multilayer carbon nanoparticles Quantum dots Metal nanoparticles: silver, zinc Oxidized nanoparticles: titanium oxide (TiO_2) Silicon nanoparticles
Mitochondrial damage	Nanoparticles interfere with mitochondrial function and cause an energy deficit in cells.	Quantum dots Multilayer carbon nanoparticles Oxidized nanoparticles: titanium oxide (TiO_2) Metal nanoparticles: silver, copper Nanotubes
Immunomodulating effect	Nanoparticles influence the body's immune response by modulating the activities of immune cells. This affects the body's ability to fight off infections and diseases.	Metal nanoparticles: silver, copper, zinc Oxidized nanoparticles: titanium oxide (TiO_2) Lipid nanoparticles Quantum dots
Damage to cell membranes	Nanoparticles have direct contact with cell membranes and cause their damage. This affects cellular integrity and function.	Quantum dots Multilayer carbon nanoparticles Metal nanoparticles: silver Oxidized nanoparticles: titanium oxide (TiO_2) Nanotubes
Interaction with proteins	Nanoparticles bind to cellular proteins and affect their function. This causes toxic effects and changes in cellular processes such as signaling, transport and metabolism.	Metal nanoparticles: silver, copper Oxidized nanoparticles: titanium oxide (TiO_2) Multilayer carbon nanoparticles Nanotubes Quantum dots

(Source: Adapted from ***(Jiang et al., 2019; Odaudu & Akinsiku, 2022; Teleanu et al., 2018; Xuan et al., 2023)****.*

Toxicity of nanoparticles on cells of the cardiovascular system

Exposure to nanoparticles is able to affect the endothelial cells that make up the inner lining of blood vessels. These cells have a key role in regulating blood circulation and maintaining healthy blood vessels. The effect of nanoparticles on endothelial cells might have serious consequences for the cardiovascular system ***(Pretorius et al., 2021; Smith & Edelman, 2023).*** Here are some aspects of the effect of nanoparticles on endothelial cells:

- inflammation and dysfunction of endothelial cells: exposure to nanoparticles is able to induce inflammatory reactions in endothelial cells. This can lead to the dysfunction of these cells and the deterioration of their ability to control the expansion and contraction of blood vessels ***(Omidian et al., 2023);***
- oxidative stress: nanoparticles have the ability to produce reactive oxygen species (ROS), which generates oxidative stress in endothelial cells. Oxidative stress can damage cellular structures and produce inflammation ***(Pretorius et al., 2021);***
- endothelial dysfunction and atherosclerosis: damage to endothelial cells and inflammation may contribute to the development of atherosclerosis (a disease characterized by the deposition of plaques in blood vessels, which may affect stenosis (narrowing) of blood vessels) ***(Smith & Edelman, 2023);***
- vasoconstriction: some nanoparticles are capable of generating vasoconstriction (narrowing of blood vessels), which give rise to blood pressure and increase the risk of hypertension ***(Pretorius et al., 2021);***
- activation of the coagulation system: nanoparticles are capable of affecting the coagulation system, which increases the risk for blood clots and thrombosis ***(Smith & Edelman, 2023);***
- risk for heart disease and stroke: all these effects on endothelial cells may contribute to an increased risk for heart disease, including myocardial infarction and stroke ***(Omidian et al., 2023).***

Nanoparticle exposure to the cardiovascular system can also have significant health consequences and risks. Nanoparticles are able to enter the bloodstream and circulate in the body, which can have several harmful effects on the cardiovascular system, such as:

- changes in blood components: nanoparticles are capable of affecting blood composition and increase the risk of blood clots. This may be associated with an increased risk for ischemic heart and brain diseases ***(Smith & Edelman, 2023);***
- impact on heart rate and rhythm: nanoparticles are capable of affecting heart rate and rhythm, which can be dangerous for individuals with heart disease ***(Smith & Edelman, 2023).***

Toxicity of nanoparticles on cells of the gastrointestinal system

Gastrointestinal exposure to nanoparticles is able to occur when nanoparticles enter the body orally, such as through food or water, or through inhalation, when particles are transferred to the digestive tract from the respiratory tract. This exposure can have various consequences and health risks ***(Kose et al., 2023; Vitulo et al., 2022).*** Here are some of the main aspects of the impact of nanoparticles on the human gastrointestinal system:

- absorption capacity: some nanoparticles may be absorbed by the wall of the gastrointestinal tract and enter the bloodstream. In this way, they can be spread to different tissues and organs in the body ***(Vitulo et al., 2022);***
- inflammation and tissue damage: nanoparticles are able to trigger inflammatory reactions in the walls of the digestive tract and produce mucosal damage. This give rise to various gastrointestinal diseases, for example, stomach ulcers ***(Bergin & Witzmann, 2013);***
- toxic effects: some nanoparticles may be toxic to cells in the gastrointestinal tract, which can affect their function and integrity ***(Bergin & Witzmann, 2013);***
- distribution to internal organs: nanoparticles that enter the bloodstream after absorption from the digestive tract may be distributed to internal organs, which can have serious consequences for health ***(Vitulo et al., 2022);***

- potential risks for chronic diseases: there is a connection between exposure to nanoparticles through the digestive tract and the development of chronic gastrointestinal diseases, such as Crohn's disease, irritable bowel syndrome, including metabolic diseases ***(Bergin & Witzmann, 2013; Vitulo et al., 2022).***

Effect on the intestinal barrier

Exposure to nanoparticles is able to affect the intestinal barrier, which forms an important protection between the internal environment of the body and the external environment of the digestive tract. This impact may have various consequences and health risks ***(Vitulo et al., 2022).*** Here are some of the main aspects of the impact of nanoparticles on the gut barrier and the associated health implications:

- changing the permeability of the intestinal wall: nanoparticles are capable of affecting the permeability of the intestinal wall by increasing it. This can allow unwanted substances and pathogens that would not normally penetrate the barrier to enter the bloodstream and give rise to inflammatory reactions or other problems ***(Sousa et al., 2022);***
- inflammation and intestinal damage: exposure to nanoparticles can induce inflammation in the intestinal wall, which give rise to tissue damage and cause gastrointestinal diseases such as colitis ***(Kose et al., 2023);***
- immune response: exposure to nanoparticles may affect the immune response in the intestinal wall and may have consequences for the immune system ***(Sousa et al., 2022).***

Impact on the gut microbiome

Exposure to nanoparticles is capable of affecting the gut microbiome, the complex ecosystem of microorganisms that live in the human digestive tract and play an important role in digestion, the immune system, and overall health. The effect of nanoparticles on the intestinal microbiome may have various consequences and health risks ***(Bergin & Witzmann, 2013).*** Here are some key aspects of this impact:

- change in microbial diversity: exposure to nanoparticles may produce a change in microbial diversity in the gut. This may have implications for the balance between "good" and "bad" bacteria in the microbiome ***(Kose et al., 2023);***
- inflammation and dysbiosis: nanoparticles have the ability to induce inflammatory reactions in intestinal tissues, which may affect the microbial ecology. This give rise to dysbiosis, which is associated with various gastrointestinal diseases ***(Kose et al., 2023);***
- changes in metabolism: exposure to nanoparticles is capable of affecting the metabolism of microbial populations, which may have consequences for the production of metabolites that affect the health of the host ***(Sousa et al., 2022).***

Toxicity of nanoparticles on nervous system cells

Exposure of nanoparticles to the nervous system have the ability to have potentially serious consequences for the function and health of the brain and central nervous system. This exposure can occur in a variety of ways, including inhalation, consumption of contaminated food, or entry through the blood-brain barrier ***(Teleanu et al., 2018).*** Here are some main aspects of the effect of nanoparticles on the nervous system:

- increased oxidative stress: nanoparticles have the ability to induce oxidative stress in nerve tissues, which leads to damage brain cells and cause inflammatory reactions ***(Zia et al., 2023);***
- damage to the blood-brain barrier: nanoparticles may have the potential to cross the blood-brain barrier, which protects the brain from unwanted substances. Their penetration give rise to an increased risk of inflammation and damage to brain tissues ***(Vinod & Jena, 2021);***
- increased risk of neurodegenerative diseases: there is a link between exposure to nanoparticles and an increased risk of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease ***(Sawicki et al., 2019);***
- potential effects on brain development and growth: in children and infants, exposure to nanoparticles may affect brain development and growth and may be associated with an increased risk of neurocognitive problems ***(Zia et al., 2023);***
- impaired neurovascular functions: nanoparticles are capable of affecting blood circulation in the brain and cause impaired neurovascular functions, which can be associated with health problems ***(Vinod & Jena, 2021);***
- effect on neurons: inflammation in the CNS may affect the normal function of neurons and synapses, which can have consequences for cognitive functions and behaviour ***(Sawicki et al., 2019);***
- impact on mental health: exposure to nanoparticles may have an impact on mental health and be associated with a higher frequency of depression and anxiety ***(Khan et al., 2018).***

Toxicity of nanoparticles on immune system cells

The immune system is the body's key defense mechanism and plays a key role in protecting the body against infections and other pathogens. Exposure of nanoparticles to cells of the immune system is an important aspect in the context of evaluating their safety and possible effects on the immune system. Nanoparticles have the ability to enter the body in various ways, including inhalation, food consumption, through the skin, etc. ***(Liu et al., 2022).*** Here are some of the main aspects regarding nanoparticle exposure to immune system cells:

- phagocytosis: the immune system contains cells called phagocytes, which have the ability to engulf and remove foreign substances, including nanoparticles. Macrophages and neutrophils are the two main types of phagocytes that remove nanoparticles from the body ***(Aljabali et al., 2023);***
- activation of immune responses: some nanoparticles are able to activate the immune system by acting as antigens and triggering immune responses. This may include the production of compounds such as cytokines that regulate inflammatory responses ***(Ray et al., 2021);***
- immunomodulating effects: nanoparticles are characterized by different effects on the function of the immune system. Some nanoparticles may have immunomodulatory properties, meaning they have the ability to influence the activity of immune cells and the immune system's response to infections and other external factors ***(Aljabali et al., 2023);***
- inflammatory reactions: exposure to nanoparticles is able to trigger inflammatory reactions in immune system cells and tissues. These responses are beneficial in defense against infections, but give rise to tissue damage when over-inflamed ***(Aljabali et al., 2023; Ray et al., 2021).***

METHODS OF EVALUATING THE TOXICITY OF NANOPARTICLES

Assessing the toxicity of nanoparticles is a key step in determining their potential impact on human health and the environment. There are several methods to assess the toxicity of nanoparticles, including *in vitro* methods, in vivo animal studies, and human clinical studies ***(González-Muñoz et al., 2015).***
In vitro methods are often the first step in assessing the toxicity of nanoparticles. These experiments are performed under controlled laboratory conditions and involve the use of isolated cells, cell cultures or tissues. *In vitro* studies make it possible to precisely control the exposure of nanoparticles and monitor their effect on cells or tissues ***(Kumar et al., 2017; Roberto et al., 2019).*** Below are some examples of different types of in vitro tests that are used to assess the toxicity of nanoparticles.

- cell viability studies: MTT test (methylthiazolyldiphenyl-tetrazolium bromide). This method measures the ability of living cells to metabolize MTT to purple formazan. More formazan means more cellular vitality and agility. Low MTT uptake may indicate nanoparticle-induced cell damage ***(Zhang et al., 2022);***
- cytotoxicity studies: the rate of lactate dehydrogenase (LDH) release from damaged cells serves as an indicator of membrane damage and cytotoxicity ***(González-Muñoz et al., 2015);***
- oxidative stress: measuring the level of reactive oxygen species (ROS) in cells is important to assess the oxidative stress induced by nanoparticles ***(Awashra & Mlynarz, 2023);***
- gene expression change studies: using polymerase chain reaction (PCR) and quantitative PCR (qPCR), it is possible to monitor changes in gene expression, which provides information on the toxicity of nanoparticles at the molecular level ***(González-Muñoz et al., 2015);***
- intracellular localization studies: fluorescence microscopy and electron microscopy make it possible to observe the intracellular localization of nanoparticles and their interaction with cells ***(González-Muñoz et al., 2015);***
- studies with 3D cell cultures: the use of 3D cell cultures provides a better simulation of tissues and organs and allows a better evaluation of the toxicity of nanoparticles ***(Zhang et al., 2022);***
- studies in biofluids: simulations of interactions of nanoparticles with biological fluids, such as blood plasma or the mucous layer, allow to assess their impact on the environment in the body ***(Awashra & Mlynarz, 2023);***
- studies on cell cultures of different cell types: different cell lines and cell types are beneficial to identify specific more toxic effects of nanoparticles depending on the target tissues ***(Zhang et al., 2022);***
- proteome and metabolome analysis: these analyses make it possible to assess changes in the proteome and metabolome of cells after exposure to nanoparticles and reveal potential toxic mechanisms ***(González-Muñoz et al., 2015; Zhang et al., 2022).***

In vitro methods have the advantage of speed, control over experimental conditions and lower costs compared to *in vivo* studies.
However, they have their limitations because they do not take into account complex interactions in the organism and do not allow predicting effects in the real world ***(Roberto et al., 2019; Xuan et al., 2023).***

In vivo animal studies are the next step in evaluating the toxicity of nanoparticles. These studies are performed on laboratory animals such as mice or rats. Animals are exposed to nanoparticles either by inhalation, intravenous injection or oral administration ***(Kumar et al., 2017).***
In vivo studies make it possible to obtain information about the effects of nanoparticles in a living organism ***(Xuan et al., 2023).*** *In vivo* tests include:

- acute toxicity tests: these tests focus on the short-term effects of a single exposure to nanoparticles. Animals are exposed to different doses of nanoparticles and various parameters such as behaviour, survival rate, body weight and histological changes in tissues are monitored ***(Kumar et al., 2017);***
- subchronic and chronic toxicity tests: these tests monitor the long-term effects of repeated exposures to nanoparticles. The animals are exposed to the nanoparticles for a period of time, and this can last for several weeks or months. The development of health problems and biochemical parameters is monitored ***(Kumar et al., 2017);***
- histopathological analysis: this method involves a detailed study of tissues and organs to determine possible pathological changes in response to exposure to nanoparticles. Histological analyses may reveal inflammatory reactions, fibrosis or other tissue changes ***(González-Muñoz et al., 2015);***
- hematological and biochemical blood tests: these tests monitor changes in hematological parameters (for example, white and red blood cell counts) and biochemical parameters (for example, enzyme and protein levels) in the blood of animals after exposure to nanoparticles ***(Kumar et al., 2017);***
- immunotoxicity: immunological tests evaluate the effects of nanoparticles on the immune system of animals. It might be changes in the levels of pro-inflammatory and anti-inflammatory cytokines, macrophage activity and lymphocyte function ***(González-Muñoz et al., 2015);***
- inhalation and injection: the method of application of nanoparticles depends on the expected exposure in humans. Inhalation studies are able to simulate respiratory exposure, while intravenous or other types of injection are used to simulate systemic exposure to nanoparticles ***(Kumar et al., 2017);***
- genetic and cytogenetic analyses: these tests are performed to detect possible damage to the genome of animals after exposure to nanoparticles ***(González-Muñoz et al., 2015);***
- biodistribution and bioaccumulation: biodistribution and bioaccumulation studies are carried out to determine how nanoparticles spread in the animal body and accumulate in different tissues and organs ***(González-Muñoz et al., 2015; Kumar et al., 2017).***

In vivo studies have the advantage of including complex interactions between different tissues and organs in an organism. However, they are more expensive, time-consuming, and may raise ethical questions regarding the use of animals in experimental studies ***(Xuan et al., 2023).***

Clinical studies on humans

Human clinical studies are the final step in evaluating the toxicity of nanoparticles. These studies are performed on voluntary participants exposed to nanoparticles in a real-life environment ***(Baetke et al., 2015; Xuan et al., 2023).***
Clinical studies allow direct insight into the impact of nanoparticles on humans. Clinical trials include:

- clinical observations and symptom monitoring: researchers are able to monitor volunteers who have been exposed to nanoparticles for any physical, clinical or biochemical signs of toxicity. For example, changes in health status, body temperature and basic life functions are monitored ***(Xuan et al., 2023);***
- blood tests and biopsies: in clinical trials, blood and tissue samples may be collected from participants to analyse changes in hematological and biochemical parameters. This may include measuring biomarker levels and identifying potential tissue damage ***(Han et al., 2019);***
- imaging diagnostic methods: methods such as X-ray, magnetic resonance or computed tomography are advantageous to visualize possible changes in tissues due to exposure to nanoparticles ***(Baetke et al., 2015);***
- functional tests: various functional tests can be performed to assess changes in the function of organs or systems. For example, pulmonary function, cardiovascular function or neurological function tests ***(Xuan et al., 2023);***
- biodistribution and elimination: studies include monitoring how nanoparticles are distributed in the body and how they are later eliminated, which can be monitored using bioimaging and analysis of biological fluid samples ***(Baetke et al., 2015);***
- evaluation of the immune system: studies are able to evaluate the impact of nanoparticles on the immune system and its ability to fight infections and diseases ***(Baetke et al., 2015; Han et al., 2019).***

Clinical studies have the advantage of providing real-world data on the impact of nanoparticles on human health. However, they are expensive, require long-term follow-up and must be ethically approved. The combination of these methods enables a holistic view of the toxicity of nanoparticles and their potential impact on the health of the organism ***(Xuan et al., 2023).*** The advantages and disadvantages of the presented methods are shown in Figure 1.

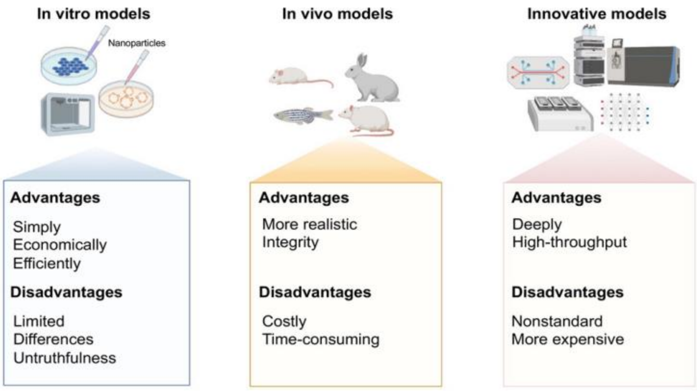

Figure 1 Evaluation of nanoparticle methods
Source: ***Xuan et al., 2023***

THE FUTURE OF RESEARCH AND APPLICATIONS OF NANOPARTICLES

Nanoparticles have broad potential in many fields of research and applications due to their unique properties and ability to influence materials and processes at the nanometer level ***(Dianová et al., 2022; Karunakaran et al., 2023).*** Below are some potential applications of nanoparticles:

Biomedicine:

- nanomedicine: nanoparticles are effective for targeted delivery of drugs and therapeutic molecules directly to affected tissues and cells, they may help in tissue regeneration and organ restoration ***(Altammar, 2023; Halo et al., 2022);***
- nanodiagnostics: nanomaterials are suitable for the development of highly sensitive diagnostic tools for disease identification ***(Altammar, 2023).***

Electronics and optics:

- nanoelectronics: nanoparticles are helpful in microprocessors, memory chips and sensors to increase the performance and reduce the dimensions of electronic devices ***(Malik et al., 2023);***
- plasmonics: the use of nanoparticles to control light and create various optical effects ***(Malik et al., 2023);***

Energy:

- lithium-ion batteries: nanoparticles are beneficial to improve battery performance and lifetime ***(Pomerantseva et al., 2019).***

Material Design:

- superhydrophobic surfaces: nanoparticles are convenient to create surfaces with high resistance to water and other liquid substances ***(Pomerantseva et al., 2019).***

Environment:

- water and air purification: nanoparticles are useful to remove harmful substances from water and air ***(Pomerantseva et al., 2019);***
- environmental monitoring: nanosensors are advantageous to monitor pollution and air and water quality ***(Moeinzadeh & Jabbari, 2017).***

Food industry and cosmetics:

- improved absorption of nutrients: nanoparticles are practical in cosmetics and food industry to improve the absorption of nutrients through the skin and the digestive tract ***(Malik et al., 2023);***
- dyes and preservatives: nanoparticles are expedient to improve the colour and preservation of food ***(Malik et al., 2023).***

Textile industry:

- self-cleaning textiles: nanoparticles are used to create textiles that are stain-resistant and self-cleaning ***(Malik et al., 2023).***

CONCLUSIONS

The study of the toxic effect of nanoparticles on the cells of the animal and human body is a complex and demanding issue that receives constant attention in the field of nanotechnology and biomedicine research. Based on the analysis and evaluation of the available information, several important conclusions can be drawn that:

1. Diversity of nanoparticles and their interaction with cells: nanoparticles are characterized by different sizes, shapes, and surface properties, which affect their ability to interact with cells. The mechanisms by which nanoparticles penetrate the cell membrane and affect cellular processes are complex and depend on the specific properties of the nanoparticles.
2. *In vitro* studies make it possible to control the conditions and examine the direct interaction of nanoparticles with cells. *In vivo* animal studies provide us with a better understanding of the impact of nanoparticles on the living organism. The combination of these two approaches enables a more comprehensive assessment of the toxicity of nanoparticles.
3. Various factors influence the risk of nanoparticle toxicity in humans, including dose, exposure, type of nanoparticle, and individual genetic predispositions. Understanding these factors is essential to determining for whom nanoparticles may be at risk.
4. Potential applications and future research: despite concerns about toxicity, nanoparticles have the potential to create revolutionary applications in medical diagnostics, therapy, and many other industries. Research should focus not only on identifying risks, but also on developing safe nanomaterials and technologies.

In conclusion, we can state that research into the toxicity of nanoparticles and their impact on the cells of the human body is a continuous process. The knowledge gained helps us better understand this phenomenon and develop safer applications of nanotechnology. Future research should be aimed at a deeper understanding of the mechanisms of nanoparticle interaction with cells and at identifying critical dose limits and factors influencing effects. It is also necessary to pay attention to the safety of nanoparticles and the development of regulations to minimize potential risks ***(González-Muñoz et al., 2015; Samrot & Noel Richard Prakash, 2023; Thwala et al., 2023).***

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