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BIOLOGICAL PROPERTIES OF NANOMATERIALS (LITERATURE REVIEW)

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Summary. In the article reviewed and discussed literature data on biological properties of nanomaterials. The biosafety of nanomaterials is a complex and multifaceted issue that demands a comprehensive, science-based approach. Modern environmental and economic factors should be considered in this regard. The EU's nanotechnology policy is based on 'an integrated, safe and responsible approach' (Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee. Regulatory aspects of nanomaterials. SEC(2008) 2036 / COM(2008) 366 final). Based on the findings of toxicity and antimicrobial activity studies, metal nanoparticles appear to be a favorable choice as antibacterial agents in developing new disinfectants. However, further measures must be taken to ensure the safe and environmentally friendly use of metal nanoparticles (MeNPs). To achieve this, it is crucial to establish toxicity parameters for MeNPs of various compositions, sizes, and concentrations. These parameters must be compared and evaluated alongside the potential effects of MeNPs on laboratory and target animals (*in vivo*), as well as their antibacterial performance against microorganisms of different strains (*in vitro*). Thus, the investigation of possible hazards associated with the use of metal nanoparticles can be effectively achieved by analyzing the fundamental systemic characteristics of biological systems under both *in vivo* and *in vitro* conditions, taking into account various aspects such as physiological, biochemical, immunological, genetic and cytological responses that may be affected by toxic effects. The literary sources analysis and article publication were conducted under the National Research Foundation of Ukraine project No. 2021.01/0076 'Development of a novel, nanoparticle-based disinfectant for deactivation of pathogens causing emergent infectious diseases'

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Introduction. The control of bacterial bacterial diseases in agriculture and livestock requires the development of new antimicrobial drugs and/or disinfectants to prevent infectious diseases in animals and increase their overall productivity (Landers et al., 2012; Manyi-Loh et al., 2018; Paliy et al., 2020). Several approaches have been proposed to overcome or at least reduce the pressure of bacterial infections caused by resistant strains, including antimicrobial peptides, bacteriophages, targeting quorum sensing and biofilm formation, etc. (Lei et al., 2019; Romero-Calle et al., 2019; Piewngam et al., 2020; Rodionova et al., 2021). All of the above strategies have their advantages and disadvantages. However, despite the obvious progress in the development of biocidal prophylactic and therapeutic agents as alternatives to antibiotics, and even promising results of clinical trials, their implementation in clinical medicine is still of limited importance.

The aim of the study was to review and to discuss literature data on biological properties of nanomaterials.

Results and discussion. Nanoparticles (NPs), materials with sizes ranging from 1–100 nm, are particularly effective in destroying microorganisms. Metal nanoparticles (MeNPs) have gained attention as potential biocides due to their unique features, making them promising candidates for high antimicrobial capacity. Their small size and distinctive properties enable nanomaterials to penetrate prokaryotic cells, allowing for toxicity. For instance, the large surface-to-volume ratio of NPs increases their interaction area with bacteria, and they can be functionalized with ligands that facilitate contact with microorganisms. However, accumulating evidence suggests that MeNPs exhibit considerable potential as antimicrobial agents. They can either amplify the effects of antibiotics or provide bactericidal effects on their own (Gao and Zhang, 2021). It is worth noting that bacteria have a limited capacity to develop resistance to nanomaterials because of the diverse mechanisms of their antibacterial activity. These include the formation of reactive oxygen species (ROS), release of metal ions, damage to bacterial membranes and cell walls, and intracellular macromolecules like proteins and DNA (Niño-Martínez et al., 2019).

In most cases, the toxicity of MeNPs is attributed to the metal ions released; the antimicrobial activity is highly dependent on their physicochemical properties, such as surface, size, and charge. Furthermore, these features can be engineered to maximize the contacts between microorganisms and MeNPs, biofilm penetration, and antimicrobial efficacy of the latter. The size of MeNPs is a significant factor, as it determines whether nanoparticles penetrate microbial cells and biofilms, thus increasing their toxicity (Amaro et al., 2021). Considering the mechanisms of antimicrobial

activity typical of MeNPs (induction of oxidative stress, release of metal ions, DNA damage, ATP depletion, non-oxidative pathways such as changes at the transcriptional and proteomic levels), bacteria may acquire resistance to such agents to a lesser extent compared to conventional antibiotics (Slavin et al., 2017; Lee et al., 2019). The use of disinfectant nanopreparations is one of the strategies to combat antibiotic resistance. However, MeNPs have been shown to be toxic to eukaryotic cells (Vimbela et al., 2017). Because of this fact, it is crucial to develop nanoparticles that are selectively toxic to prokaryotic cells while maintaining a dose-response compromise between efficacy and toxicity.

A growing number of publications indicate that bacteria develop certain mechanisms to counteract silver nanoparticles, including the production of flagellin, which causes agglomeration of MeNPs, the synthesis of pigment to bind them, or the formation of efflux pumps to remove nanoparticles (Panácek et al., 2018; Niño-Martínez et al., 2019; McNeilly et al., 2021). This indicates the relevance of developing alternatives to silver (gold, silver, copper, their oxides, etc.) that have a strong bactericidal effect (Wang et al., 2017; Sánchez-Lopez et al., 2020). Some studies have shown that cerium oxide (CeO_2) NPs have antimicrobial effects (Farias et al., 2018; Pop et al., 2020). The antimicrobial activity, the effect of medium-sized (1–2 nm) and (10–12 nm) CeO_2 NPs on DNA cleavage, microbial cell viability, and biofilm formation inhibition have been proven, and their low cytotoxicity to eukaryotic cells has been demonstrated (Yefimova et al., 2023). Thus, CeO_2 NPs demonstrate DNA cleavage activity when using plasmid DNA as a target DNA molecule, significantly inhibit the viability of microbial cells against *E. coli*; the maximum biofilm inhibition ability of 61.06% for *P. aeruginosa* and 83.86 % for *S. aureus* was achieved using smaller CeO_2 nanoparticles (1–2 nm) at a concentration of 500 mg/L.

Vanadate compounds have been shown to exhibit antiradical and antioxidant properties (Francik et al., 2011). At the same time, there are reports on the toxicity of some vanadium oxides and salts and their pro-oxidant effects, which indicates that vanadate compounds are unsuitable for use in the pharmaceutical industry due to significant side effects (Hosseini et al., 2013). Nevertheless, recent studies have shown that the biological effects of vanadium-containing nanoparticles can be completely different from those of vanadium compounds. For example, V_2O_3 nanowires have been shown to have strong antioxidant properties (enzyme-mimetic properties) in contrast to the prooxidant properties of V_2O_3 NPs (Vernekar et al., 2014; Ghosh et al., 2018). In this context, these compounds are an example of multifunctional nanomaterials with variable redox activity. VO_4:Eu_3+ NPs exhibit strong ROS scavenging ability against X-ray-induced ROS, anticancer activity, and anti-inflammatory properties (Bishayee et al., 2000; Harati and Ani, 2006; Maksimchuk et al., 2020). In addition, it is worth noting that these nanomaterials have low toxicity against eukaryotic cells. However, it is known that the antimicrobial effects of metal-containing nanoparticles depend on their shape and size (Dong et al., 2019). Larger CeO_2 NPs (10–12 nm) have been shown to be less toxic to eukaryotic cells (red blood cells) compared to smaller ones (1–2 nm) (Yefimova et al., 2023).

The cytotoxicity in a fibroblast cell model and the antimicrobial activity of $LaVO_4$:Eu_3+ NPs and $GdVO_4$:Eu_3+ NPs were analyzed (Gonca et al., 2022). The effect of the nanomaterials was evaluated using MTT assay, neutral red absorbance, and scratch assays. It turned out that $GdVO_4$:Eu_3+ NPs are less toxic to eukaryotic cells compared to $LaVO_4$:Eu_3+ NPs. Both types of nanoparticles exhibited antimicrobial activity, and the highest MIC values were shown by NPs $GdVO_4$:Eu_3+ and amounted to 64 mg/L for *E. hirae, E. faecalis* and *S. aureus*, respectively. However, GdYVO$_4$:Eu3þ NPs promoted depolarization of mitochondrial membrane (DWM) of host immune cells and leukocyte apoptosis at high concentrations (Gonca et al., 2022).

In vitro studies have shown that in determining the cytotoxic effect of nanomaterials, dose-dependent prooxidant effects have been identified (Meng et al., 2007; Jia et al., 2009; Li et al., 2009; Colon et al., 2009).

The investigation of the cytotoxicity of 71 nm NPOZn on human bronchoalveolar carcinoma cell culture showed a dose-dependent decrease in cell viability at a concentration of 10–14 μg/mL for 24 hours (Sahoo et al., 2007). Increased levels of malondialdehyde (MDA) and lactate dehydrogenase (LDH) activity were observed, indicating signs of oxidative stress and cytolysis, respectively. Furthermore, DNA damage was visible in the gel electrophoresis conducted on isolated cells. Similar results were obtained by the authors when exposing human bronchoalveolar carcinoma cells to 15 and 46 nm $NPSiO_2$ in culture.

Cultivation of BRL 3A rat liver cells for 24 hours with the presence of 10 nm and 15 nm NPAg at concentrations of 5–50 μg/mL caused a significant shift in the functional state of mitochondria (Hussain et al., 2005; Lok et al, 2007). In the presence of MeNPs such as $NPFe_3O_4$ (30–47 nm), NPAl (30–103 nm), $NPMgO_3$ (30–150 nm), and $NPTiO_2$ (40 nm) at a concentration of 10–50 μg/ml, cell state was not affected. However, at a concentration of 10–250 μg/ml, these particles contributed to decreased viability and LDHase release in the culture medium. NPAg induced ROM (reactive oxygen metabolites) generation, reduction of glutathione content and mitochondrial membrane potential. The authors suggest that oxidative stress mediates the cytotoxic effects of these MeNPs.

The pronounced cytotoxicity of NPAg was determined in a model of mammalian stem cells —

sperm progenitors and stem cells in hair follicles (Braydich-Stolle et al., 2005). Comparative evaluation of NPAg, NPMo, NPAl and NPSd in the exposure with testicular stem cells of 6-day-old mice for 48 hours revealed higher toxicity of NPAg and NPCd on spermatogenesis in experimental animals (Braydich-Stolle et al., 2005).

The toxic effects of NPAg require special attention of researchers since these NPs have been used in medicine for more than 10 years for bactericidal purposes in bone implants, dressings, and other materials (Alt et al., 2004).

It is believed that the toxicity of Ag itself to mammals is relatively low, but, especially in its ionic water-soluble form, it is toxic to aquaculture (Kim et al., 2007; Scheringer, 2008). It is important that information on the mutagenic and carcinogenic activity of this bimetal compounds is limited.

When studying the cytotoxicity of Cobalt, Nickel, Titanium, and Silicium nanoparticles on human endothelial cells *in vitro*, a dose-dependent decrease in their viability was found to be greater under the influence of NPCo and NPNi, accompanied by the expression of proinflammatory cytokines (interleukin-8, E-selectin, and ICAM-1) (Peters et al., 2004).

Cultivation of cardiovascular endothelial cells in the presence of nanoparticles at a concentration of 0.05 and 0.20 mg/l caused an increase in the expression of mRNA interleukin-4 and ecstaxin, which have an anti-inflammatory effect (Yacobi et al., 2007).

It was found that dust storm nanoparticles of 2.5 nm in size for 2 hours in experiments on isolated alveolar macrophages inhibit the activity of Na, K- and Ca, Mg-ATPases of the plasma membrane, affecting its fluidity, stimulate the release of LDHase from cells, reduce the intracellular content of glutathione and lead to the accumulation of LPO products (Meng et al., 2007).

When carbon nanotubes interacted with rat macrophages and human lung cells for 24 hours at a concentration of 10–100 μg/mL, the nanoparticles entered the cell cytoplasm, resulting in decreased cell viability as recorded by the tetrazolium test (Zhu et al., 2007). Incubating cells with carbon nanotubes led to an intracellular accumulation of ROM and a subsequent reduction in mitochondrial membrane potential. The presence of DNA damage induced by nanotubes in mouse embryonic stem cells necessitates a principled approach to utilizing such nanomaterials in biotechnology.

Studies have shown that single-walled nanotubes possess more toxicity than multi-walled tubes and fullerenes (Donaldson et al., 2006). Additionally, their cytotoxicity is high, even at lower concentrations of 0.38 μg/ml, leading to the disruption of cell morphology as well as mitochondrial and phagocytic functions.

The formation of oxidative stress and the accumulation of toxic lipid peroxidation (LPO) products are commonly associated with the mechanisms of toxic effects of carbon and other nanoparticles, as reported by most authors (Li et al., 2003).

The LC_{10} and LC_{50} values of cytotoxicity for the fraction of Fe, Al, Ca, Na, K, Mg, Pb particles in the nanophase present in the cultivation of human lung epithelial cells of the L_{132} line are 18.8 and 75.4 μg/mL, respectively. This fraction induced concentration- and time-dependent alterations in LPO and superoxide dismutase (SOD) activity, the formation of 8-hydroxy-2-deoxyguanine, poly(ADP)-ribosylation, secretion of tumor necrosis factor and NO, as well as activation of inducible NO synthase (Garcon et al., 2006).

Oberdorster et al. (2001, 2005) believe that the mechanisms of cytotoxicity and genotoxicity of carbon nanoparticles occur via pathogenetic pathways: (a) the reactive surface of nanoparticles in interaction with the cell receptor causes oxidation of proteins and lipids of the cell membrane, accumulation of toxic LPO products against the background of antioxidant depletion, which leads to an increase in the intracellular calcium content and gene activation; (b) as a result of oxidative stress, transition-valence metals are released; (c) cell membrane receptors activate transition-valence metals; (d) intracellular transcytosis of nanoparticles in mitochondria induces intracellular oxidative stress and gene expression.

If at low concentrations nanoparticles cause a moderate prooxidant effect against the background of activation of antioxidant system factors: catalase, oxidized and reduced glutathione, SOD and active induction of the antioxidant metallothionein (Oberdörster, 2001; Garcon et al, 2006; Brunner et al., 2006), while high levels of oxidative stress and inhibition of most of the AOS factors, with high levels of metallothionein.

In vivo and *in vitro* experiments have hown that the cytotoxicity of MeNPs and other nanoparticles is caused by genetic and mutagenic effects and the formation of oxidative stress with the formation of ROM in the processes of lipid peroxidation and oxidative modification of proteins (Zhang et al., 2003; Yamakoshi et al., 2003; Jia et al., 2005; Brunner et al., 2006).

When examining the molecular mechanisms behind the adverse impact of stressors on living organisms, it is important to note that the free radical theory of stress has been the most extensively researched in recent times (Pomatto and Davies, 2018; Di Meo and Venditti, 2020; Hitchler and Domann, 2021). The development of stress can be classified into three stages: mobilization (anxiety), resistance, and exhaustion. During the anxiety stage, the body undergoes catabolism, which results in accelerated breakdown of organic substances in tissues, negative nitrogen balance, and increased permeability of blood vessel walls. This phase typically lasts between 4 to 48 hours. If the stress factor is excessively intense, the animal may die.

If the body's defenses fail to overcome the stress, it enters the stage of resistance. During this stage, the metabolism returns to normal, anabolic processes occur, and the white blood cell count, corticosteroid hormone levels, and body weight increase. The resistance stage can last from several hours to several days, and sometimes even weeks. The development of stress ends at the stage of resistance when the stressor stops and the body's metabolism returns to normal. If stressors persist, they can deplete an organism's adaptive capabilities, halt development, and initiate the stage of exhaustion. During this phase, dystrophic changes can occur in organs and tissues while catabolism becomes the dominant metabolic process. Extended periods of exposure to stressors can result in altered metabolism and even animal death (Fan et al., 2002; Donaldson et al., 2003; Dahiya et al., 2007). This indicates the occurrence of destructive processes linked to the denaturation of antioxidant enzymes caused by toxic products of lipoperoxidation, the oxidative alteration of proteins, and other metabolites (Guéraud et al., 2010; Sharifi-Rad et al., 2020; Dimova et al., 2022).

The increase in the intensity of destructive processes in the liver of animals due to the development of oxidative stress under the influence of metal nanoparticles against the background of feed stress is also indicated by the dynamics of enzymes in the blood plasma of rats (Li et al., 2015; Samrot et al., 2022).

As described by Gharbi et al. (2005), after 3 weeks of intraperitoneal administration of an aqueous suspension of fullerenes C_{60} at a concentration of 0.5–2.0 g/kg body weight, no acute or subacute toxicity was detected in the histopathological data of the parenchymal structure of the liver without signs of inflammation or fibrosis. At the same time, the concentration of accumulated fullerene C_{60} in hepatocytes decreased over time, indicating their ability to be excreted from the rat liver. On the contrary, administration of an aqueous suspension of fullerenes C_{60} at a dose of 2.0 mg/kg body weight to rats for 3, 7, and 14 days before SSl4 poisoning caused a hepatoprotective effect. It is assumed that this effect of fullerenes C_{60} is associated with the prevention of oxidative stress due to their elimination of free radicals and intensification of oxidative modification of proteins against the background of ultra-high values of primary lipoperoxidation products — diene conjugates (DC) and physiological end product — malonic dialdehyde MDA, which is destructive (Jia et al., 2009).

The release of intracellular Ca^{2+}, the activation of Src-kinases, and the phosphorylation of intracellular proteins are thought to be the molecular mechanisms responsible for enhancing blood cell reactivity when influenced by metal nanoparticles. Thus, graphene's high hemocompatibility results from the interplay between its hydrophilic properties and the protection of negative charges provided by hydroxyl and carboxyl groups. This hydrophilic interaction increases under cytotoxic conditions, leading to a concentration of nanoparticles on the cell membrane and subsequent disruption of its integrity.

The LD_{50} of rare earth element (REE) compounds for laboratory animals under single oral administration ranges from 2,000.0 to > 10,000.0 mg/kg body weight, according to literature analysis conducted by Tommasi et al. (2021). These substances can be classified as low-toxic and practically non-toxic substances, falling into Class IV–V in terms of toxicity, and moderately and slightly hazardous substances, falling into Class III–IV in terms of safety, as stated by Klingelhöfer et al. (2020). Therefore, the use of organic nanoforms of REEs is considered an efficient approach due to their low toxicity (Abdelnour et al., 2019) (Cai et al., 2015; Tariq et al., 2020).

Thus, Ou et al. (2000) proposed four possible mechanisms of REE growth-stimulating effects: enhancing enzymatic activity, improving protein metabolism, inhibiting the growth of pathogenic bacteria, and promoting the secretion of digestive fluids into the digestive tract. A little later, the anti-inflammatory and immunostimulatory effects of REE were added to these (Flachowski, 2003), and in 2010, their effect on hormonal activity and increased cell proliferation were identified as possible mechanisms for enhancing the effects of REE (He et al., 2010; Xu et al., 2020). In *in vitro* experiments, $GdVO_4$:Eu^{3+} NPs showed enzyme-like properties: in aqueous solutions, inhibition of superoxide anion formation (similar to the action of superoxide dismutase) and acceleration of hydrogen peroxide decomposition (similar to the action of catalase) were observed (Maksimchuk et al., 2021).

To date, research has found that the colloidal solution of NPs $LaVO_4$: Eu^{3+} displays hydrophobic properties, indicating its aggregation stability in biological fluids, and the potential for it to interact with biomolecules containing a positive charge. Consequently, it can be utilized in both *in vitro* and *in vivo* experiments. *In vivo* experiments showed that $LaVO_4$: Eu^{3+} NPs had no significant impact on erythrocyte hemolysis curves, indicating that they did not affect the adaptation of erythrocytes to osmotic damage, regardless of the medium composition. Furthermore, these nanoparticles had no significant effect on erythrocyte osmotic hemolysis (Pakulova et al., 2017). $LaVO_4$: Eu^{3+} nanoparticles did not show any genotoxicity in the *in vitro* system. The number of micronucleated cells did not differ significantly between native cell cultures (without nanoparticles) and those treated with nanoparticles at concentrations of 30, 65 and 130 μg/cm3. However, the exposure to concentrations of 260.0–520.0 μg/cm^3 led to detachment of cells from the surface, rendering it impossible to count the number of cells with micronuclei (Prokopiuk et al., 2023).

Experiments have shown positive effects of gadolinium orthovanadate nanoparticles in the reproductology (Koshevoy et al., 2021).

To date, there is a scarcity of research on the toxicological and biochemical effects of rare earth metal nanoparticles in *in vivo* experiments. It is suggested by some scientists that the primary characteristic of metals in the nanoscale state is their reduced toxicity in contrast to the traditionally used salts of the corresponding metals. Due to their small size, nanoparticles are capable of directly penetrating and distributing throughout the body through the skin, respiratory and digestive organs, cell membrane openings, or cellular transport mechanisms (Raju et al., 2018; Friedman et al., 2021). Currently, some experimental data has been gathered on the toxicological properties of particular MeNPs through inhalation and oral routes of entry into the macroorganism and, to a lesser extent, through intramuscular, intravenous, and subcutaneous administration.

When studying the adverse effects of inhalation of some nanoparticles into the human body, it was found that inflammatory lung tissue damage is mainly caused by their prooxidant and genotoxic effects (Lam et al., 2004; El-Ansary and Al-Daihan, 2009).

Most of the very small nanoparticles (1 nm), when inhaled, penetrate through the mucosa or paroxysmally through nerve fibers to tissues, are absorbed into the bloodstream, and within 2–4 hours are found in the liver, kidneys, brain, and bone marrow. As a result of transcytosis, nanoparticles enter the blood and lymph through respiratory epithelial cells and sensory nerve endings (Lu et al., 2014; Szewczyk et al., 2022).

It has been shown that polymeric composites of Fluorine nanoparticles used to deliver hormones and bronchodilators circulate in the circulatory system, internal organs and bones, especially in the area of their growth, after 2–6 hours due to the element's tropism to osteoblasts. Additionally, their impact on the hemostatic system, including the development of coagulopathies and thrombosis, has been observed (Nemmar et al., 2002).

The studies described the results of investigating the inhalation toxicity of various nanoparticles including Argentum, Ferrum, Cadmium, Zinc, Titanium, Vanadium, Copper, and Silicon. The studied focused on determining the toxicity of NPAg, with particles ranging from 19.8 to 64.9 nm, in rats exposed to inhalation for a period of 28 days. Three different concentrations were used, with particle/ml concentrations of 1.73×10^4, 1.27×10^5, and 1.32×10^6 (Sahoo et al., 2007). A noteworthy escalation in the activity level of γ-glutamyl transpeptidase (GGT), along with an increase in neutrophils, eosinophils, and hemoglobin levels infemale rats , as well as calcium and total protein levels in the blood serum of male and female rats at a concentration of 1.27×10^5 particles/ml, was identified. There was also an observation of NPAg accumulation in the lungs, liver, and kidneys, and their penetration into the brain via axonal transport. The high stability of NPAg in the environment in terms of retention of toxic properties for several years was proved.

Inhalation of $NPTiO_2$ sized between 80 and 100 nm has been shown to increase the distribution of $NPTiO_2$ in the lungs, elevate the count of neutrophils and phagocytes, and stimulate the formation of proinflammatory cytokines (interleukin 1 (IL-1) and tumor necrosis factor alpha (TNF)) in bronchoalveolar lavage (Ferin and Oberdörster, 1985; Driscoll et al., 1990; Bermudez et al., 2004), which indicates a pronounced prooxidant effect, inflammation and leads to lung fibrosis (Bermudez et al., 2002).

Single oral administration of 25 and 80 nm $NPTiO_2$ to mice at a dose of 5,000 mg/kg body weight resulted in greater toxicity as characterized by intensified penetration into the lungs, liver, spleen, and kidneys, as well as pronounced hepatotoxicity and nephrotoxicity when compared to larger nanoparticles (155 nm) (Warheit et al., 2005; Wang et al., 2007). For instance, the blood serum of animals showed increased activity of lactate dehydrogenase (LDH) and α-hydroxybutyrate dehydrogenase (25 nm), and the animals had liver enlargement and hepatocyte necrosis (80 nm). $NPTiO_2$ has a long half-life (over 500 days) whether inhaled or orally ingested, and is not eliminated through the kidneys.

A comparative study of acute pulmonary toxicity induced by 3 and 20 nm $NPTiO_2$ revealed early biochemical changes in the bronchoalveolar fluid of mice (Bermudez et al., 2002, 2004). After just three days of inhalation, an increase in the content of total protein and alkaline phosphatase (ALP) activity was detected at high concentrations of nanoparticles (40 mg/kg body weight), and at low concentrations (4 mg/kg body weight) — only an increase in ALP, indicating less severe inflammation and no signs of cytolysis and acute pulmonary toxicity.

The impact of subcutaneous administration of 50–60 nm sized NPCu at a 0.05 mg/kg body weight dose on white mice for 3 days has also been described (Strode, 2012). It was found that, in the absence of statistically significant changes in alanine aminotransferase (ALT) activity, there was an elevation in the activity of other enzymes with intracellular localization, including aspartate aminotransferase (AST) and creatine phosphokinase, compared to their control values.

It has been established that the toxicity of MeNPs in the calculation of the maximum biocompatible dose, LD_{50} and LD_{100} depends on their size and concentration, but differs in the mechanism of development from that of metals in macrodispersed form (metal salts).

Water-insoluble nanoparticles with a size less than 20 nm are considered toxic (Hoet et al., 2004; Kagan et al., 2005; El-Ansary and Al-Daihan, 2009), as they can penetrate the body by inhalation, *per os*, through damaged skin, and during injections of drugs with nanocarriers.

Inflammatory reactions, enhanced blood clotting, and the development of coagulopathies all contribute to the detrimental impact of atmospheric nanoparticles smaller than 2.5 nm on the cardiovascular system (Yacobi et al., 2007). Nanoparticles can undergo transcytosis through epithelial and endothelial cells, spread along dendrites and axons of nerve cells, circulate in blood and lymphatic vessels, and exhibit tropism for certain tissues (Moghimi et al., 2001; Müller and Keck, 2004).

In a few studies, it was proved (Abraham and Himmel, 1997) that NPAu with a size of 0.5 to 100 nm are non-toxic, since Aurum is an inert metal in biological systems. In most cases, the formulation of colloidal Aurum is a sol (suspension or dispersion in a liquid phase), and researchers prefer ultracolloidal systems in the form of metal nanoparticles up to 30 nm.

There are data on the size-dependent distribution of NPAu in many organs and tissues of the body, such as the liver, spleen, kidneys, heart, lungs, thymus, genitals, soft tissues, and even the brain and skeleton, when administered intravenously, intratracheally, or orally (Hussain et al., 2001).

The implementation of NPAu research for biomedical purposes faces several challenges despite its prospectivity. The reproducibility of NPAu poses a significant issue (Thaxton et al., 2006), along with the need to comply with GMP requirements for their production (Smith and Korgel, 2008). Additionally, the toxicological aspect of NPAu introduction into clinical practice remains poorly understood. There is a lack of *in vivo* studies, and the mechanism of cell entry and accumulation of MeNPs in the body has not been definitively established (Banerji and Hayes, 2007).

When determining the acute toxicity of AMI-25drug containing NPFe, it was found that the LD_{50} exceeded a dose of 3,000 μmol Fe/kg. Subacute and chronic toxic effects of NPFe were manifested by hemochromatosis if the total amount of metal in the body exceeded 15 g. Since the amount of metal in the dose of the drug is much lower compared to its content in the liver in normal conditions, no significant effect on the total liver Fe concentration was observed (Li et al., 2009).

NPOFe has been found to be a safe treatment option for iron deficiency anemia and as a contrast agent (CA) for magnetic resonance imaging (MRI), with low toxicity to humans except in cases of overdose (Landry et al., 2005; Anzai et al., 2003).

Zhu et al. (2008) investigated the impact of 22 and 280 nm NPOFe on rats, administering inhalation doses of 0.8 and 20.0 mg/kg body weight. The findings revealed the emergence of inflammatory reactions in the lungs, along with ROM induction in cells and disruptions to the blood coagulation system.

In clinical practice, the side effects attributed to NPOFe usage are typically categorized as minor and short-lived. Ferumoxytol and CA AMI-121 administered orally produced hypotension, peripheral edema, and short-term watery diarrhea. Dextran-coated NPOFe preparations were responsible for headache, back pain, vasodilation, and urticaria, which lasted for only one day (Anzai et al., 2003). At the same time, the observed rise in serum iron levels was evidently short-lived, suggesting its absorption.

Inhalation and oral exposure to NPCu in determining acute toxicity revealed a pronounced dependence of the toxic effect on particle size. It was found that low concentrations of NPCu potentiate the toxicity of other elemental substances when exposed to human lung cells (Meng et al., 2007). When ingested, NPCu shifts the acid-base balance of the blood, which leads to the development of metabolic alkalosis (Galla, 2000; Williams, 1998), degenerative changes in the liver, brain tissue, and kidneys (signs of glomerulonephritis).

It is also believed that the water solubility of nanoparticles has a significant impact on cytotoxicity. It has been noted that water-soluble NPCu are toxic (Meng et al., 2007), causing genetic and morphological changes characteristic of Wilson's disease (Tao et al., 2003).

Other authors argue that non-water-soluble nanoparticles (especially those smaller than 25 nm) are more likely to be toxic (Zhu et al., 2007).

However, it is known that the toxicity of NPCu is 2.5–6.0 times lower than that of metal salts. Cu nanoparticles and ionic particles in a suspension of hydroxypolymethyl cellulose are more toxic than microparticles. Toxicity parameters for rats with oral administration of the metal in various forms have been established: LD_{50} for NPCu is 413 mg/kg; for Cu ionic particles — 110 mg/kg; for Cu microparticles — 5,000 mg/kg body weight, respectively. Biochemical changes in animals administered NPCu K4M orally at a dose of 1,080 mg/kg body weight were characterized by an increase in blood levels of urea, creatinine, total bile acids and alkaline phosphatase (ALP) activity, indicating renal and hepatic dysfunction (Chen et al., 2006).

It has been shown that nanoparticles are able to penetrate cells, bypassing any barriers (including blood-brain and placental barriers), and selectively accumulate in different cell types and cellular structures (Chen et al., 2006; Lam et al., 2004; El-Ansary and Al-Daihan, 2009; Colon et al., 2009). There are many experimental studies on the penetration of micro- and nanosized particles into cells. This phenomenon is associated with the cytotoxic effect of nanoparticles on various cell lines and has been shown for endothelial cells, lung epithelium, gastric epithelium, macrophages, nerve cells, and a number of other cells (Hoet et al., 2004).

It has been determined that the cytotoxic effect of NPs is underpinned by oxidative stress and inflammatory reactions (Kipen and Laskin, 2005; Li et al., 2009; Jia et al., 2009), resulting in the development of hepato- and pulmonary toxicity with signs of cytolytic (necrotic)

reactions. Moreover, accumulation of NPs in the liver, lungs, spleen and kidneys is dose-dependent (Lynchet et al., 2007; Bawa, 2008). The absorption of nanoparticles onto the surface of cell membranes, their interference with cell metabolism, and subsequent degradation produce cytotoxic effects. Therefore, studying the biochemical mechanisms of these processes is necessary to assess the potential hazard and biocompatibility of nanoparticles (Weyermann et al., 2005; Jurišić and Bumbaširević, 2008).

To date, our understanding of the toxicodynamics and toxicokinetics of nanoparticles in the body, as well as their impact on the environment, remains limited. Firstly, it is imperative to gather data on the correlation between the toxicity of nanoparticles and their quantity (dose and concentration) and physicochemical characteristics (size, shape, composition, reactivity, etc.) (Donaldson et al., 2004; Santamaria, 2012). Additionally, exploring the molecular mechanisms of their impact on the body, organs, tissues, cells, and identifying the mechanisms that contribute to the development of long-term toxic effects, as well as determining methods to alleviate their adverse effects, are necessary (Zhu et al., 2008; Romanko et al., 2023).

Conclusions. The biosafety of nanomaterials is a complex and multifaceted issue that demands a comprehensive, science-based approach. Modern environmental and economic factors should be considered in this regard. The EU's nanotechnology policy is based on 'an integrated, safe and responsible approach' (CEC, 2008).

Based on the findings of toxicity and antimicrobial activity studies, metal nanoparticles appear to be a favorable choice as antibacterial agents in developing new disinfectants. However, further measures must be taken to ensure the safe and environmentally friendly use of metal nanoparticles (MeNPs). To achieve this, it is crucial to establish toxicity parameters for MeNPs of various compositions, sizes, and concentrations. These parameters must be compared and evaluated alongside the potential effects of MeNPs on laboratory and target animals (*in vivo*), as well as their antibacterial performance against microorganisms of different strains *(in vitro*).

Further investigation on the impact of NPMe, whether in solid or liquid form, on cells of different organizational levels will contribute to a deeper understanding of their biocompatibility or potential toxic effects. Thus, the investigation of possible hazards associated with the use of metal nanoparticles can be effectively achieved by analyzing the fundamental systemic characteristics of biological systems under both in vivo and in vitro conditions, taking into account various aspects such as physiological, biochemical, immunological, genetic and cytological responses that may be affected by toxic effects.

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