ISSN 2223-6775, Ukrainian Journal of Occupational Health, 2022, 18 (3), 224–236

REVIEWS, LECTURES

UDC 539.51-022.513.2:615.9 https://doi.org/10.33573/ujoh2022.03.224

TO THE QUESTION OF INTENSIFICATION OF FREE RADICAL OXIDATION OF BIOSUBSTRATES UNDER ACTION OF NANOSIZED MATERIALS

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Introduction. Transformations in the structure and physicochemical properties of modern nanosized materials, in comparison with analogues in macroforms, lead to changes in their biological activity, including free radical oxidation of biosubstrates as one of the most important mechanisms for the toxicity of these products. Oxidative stress induced by engineered nanoparticles is determined by their size, surface area, composition and is manifested by peroxide damage to proteins, lipids, and nucleic acids. Nanoparticles induce oxidative stress and further pathophysiological effects including inflammation, fibrosis, genotoxicity.

The aim of the study – substantiation of the significance of changes in the intensity of free radical oxidation of biosubstrates in the mechanism of the damaging effect of nanosized materials as the main indicators of their toxicity.

Materials and methods of the study. Selective analysis of the research databases: domestic and foreign scientific materials, information materials (Medline, Pubmed, Medscape, Elsevier, Scopus, Web of Science) for systematization and generalization of data related to the research problem.

Results. The damaging effect of nanoparticles on the human body can be carried out by several mechanisms. The main and most important of them are the intensification of free radical oxidation of biosubstrates with the destruction of macromolecules (proteins, phospholipids, nucleic acids), disruption of cellular processes due to the surface power of nanoparticles (photochemical, electric field, charge density and electronic conductivity). The presence of other mechanisms of nanomaterials toxicity, caused, in particular, by their action on cell membranes and organelles, increased transport of potentially toxic components through the body's barriers, as well as possible genotoxicity and allergenic effects, cannot be ruled out. The manifestation of the damaging effects of nanoparticles depends on the size, chemical nature, physical state, and, to a large extent, on stabilization.

Conclusions. The intensification of free radical oxidation of biosubstrates is one of the main indicators of the damaging effect of nanoscale products. It has been established that nanoparticles enhance the formation of reactive oxygen species, disrupt membrane structures, enter cells and interact with cellular components as a result of their high penetrating ability and the induction of oxygen free radicals. Free radical oxidation of biosubstrates, as the main mechanism of the damaging effect of nanoparticles, is determined by their size, surface area, and composition. The properties and toxicity of nanomaterials can be modified in the course of laboratory and technological manipulations due to changes in their structure, size, and sorption of other molecules by them.

Key words: nanomaterials; nanoparticles; interaction mechanism; oxidation; danger

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Introduction

The newest branches of nanotechnology contribute to the steady growth trends in the production of nanoscale materials and their use in various fields (from medical to military industry, IT industry). However, today there are significant discrepancies in the information on the toxic effects of nanomaterials [1]. It is established that the peculiarities in the structure and physicochemical properties of modern nanoscale materials, in comparison with analogues in macroforms, lead to modifications of their biological activity, including free radical oxidation of biosubstrates as one of the most important mechanisms of toxicity of these products. Oxidative stress under the action of nanoparticles is determined by their size, surface area and is manifested by peroxidative damage to biological substrates with the subsequent development of inflammation, fibrosis, genotoxicity, etc.

Toxic effects of xenobiotics are usually the result of their interaction with cellular targets. For metals, these can be specific biochemical processes and cellular, subcellular membranes, cell organelles. Many metals have significant affinity for sulfhydryl groups of proteins, as well as competition and replacement of vital cations (iron, zinc, copper, manganese, molybdenum, cobalt, chromium, selenium, iodine). When biosubstrates react with these metals, the activity of enzymes is inhibited, and the integrity of cellular and subcellular membranes is disturbed. The latter is confirmed by signs of destabilization of lipoprotein complexes, which occurs due to the conformational rearrangement of their apoprotein part due to the blocking of SH-groups [2]. The features that cause the toxicity of nanoparticles (NPs), first of all, is the chemical and catalytic activity of their surface, which is absent in similar substances of greater dispersion. In experiments on laboratory animals, an inverse dependence of damage on the size of the NPs they were exposed to, was found. Moreover, in the consequences of the action of nano-objects there was a certain specificity of changes depending on their structure and size. Thus, aggregates of single-walled carbon nanotubes in the lung tissue of mice induced the development of granules of epithelial cells. And the same tubes, but in a dispersed state, caused diffuse interstitial fibrosis with thickening of the alveolar walls [3], that is, the toxicity and hazard of nanoscale products depended not only on their chemical composition and size, but also on the environment, in particular stabilizers.

The aim of the study – substantiation of the significance of changes in the intensity of free radical oxidation of biosubstrates in the mechanism of the damaging effect of nanosized materials as the main indicators of their toxicity.

Materials and methods of the study

Selective analysis of the source base of the study: domestic and foreign scientific materials, information databases (Medline, Pubmed, Medscape, Elsevier, Scopus, Web of Science, etc.) to systematize and summarize the data related to the research problem.

Results of the study and their discussion

NPs with small sizes and various shapes have a large specific surface area, high adsorption capacity and the ability to accumulate [4], penetrate the body by skin contact, inhalation, oral ingestion [5] and through the circulatory system are distributed and accumulate in organs and tissues, including the liver, heart, kidneys, spleen, nervous and lymphatic systems, disrupting their functioning and causing negative changes, the intensity of which

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depends not only on the concentration of nanobodies, but also on their size and stabilization methods. Metal nanoparticles form functional groups with biomolecules, changing their configuration [6], and contact with cells leads to disorders in tissues and organs. The most important factors of the damaging effect of metal nanoparticles include their ability to enhance the production of reactive oxygen species (ROS) and nitrogen species (NOS), which can cause damage to cells and tissues of the body [6–8].

Depending on the size, NPs penetrate into various biostructures and biosubstrates: 70 nm – into lungs, 50 nm – into cells, 30 nm – into blood and brain cells. Small NPs (< 20 nm) easily cross the alveolar epithelium and continue intratissue movement [6]. NPs as adsorbents can be carriers of toxins, and the body's defenses do not recognize them due to their nanometer size [9, 10]. Thus, fluorine NPs in polymer composites, which are widely used for the delivery of hormones and bronchodilators to the bronchopulmonary system, were detected in 2–6 hours in the circulatory system, internal organs and bones of laboratory animals after inhalation [11]. Penetration of NPs into cells is determined by their size, duration of contact with cells and functional state, cell type (e.g. macrophages, endothelial cells or tumor cells), exposure conditions (*in vitro* or *in vivo*). Positively charged particles enter cells more easily than negatively charged ones. The relocation of NPs along the olfactory, trigeminal, tracheobronchial nerves and neuromuscular junctions has been established [12]. The penetration of NPs between cells, mechanical damage to cell membranes, as well as phagocytosis of NPs by cells with their subsequent transfer to the external environment have been experimentally confirmed [13, 14].

Mechanisms of hazardous effects of NPs on living organisms. The main and most significant mechanism of the hazardous effects of NPs on living organisms is the formation of reactive oxygen species (O, OH^-, NO_2, H_2O_2, O_3) with subsequent destruction of macromolecules (phospholipids, nucleic acids and proteins) [15, 16], disruption of cellular structures and processes (mitochondrial, microsomal oxidation), which depend on the size of NPs, their chemical structure, surface properties.

At the same time, due to the different chemical basis of nanoparticles, for example, carbon and metal, their damaging effect is different. An important damaging mechanism of NPs action is the release of heavy metal impurities from nanomaterials. For example, cadmium ions are released from CdTe quantum dots when they get into the body [17, 18], and iron is released from carbon nanotubes that are not purified from impurities in the process of obtaining them [19]. The increase in heavy metals in the human body leads to functional disorders of the nervous system (Mn, Pb), liver and kidney dysfunction (Pb, Cu, Cd), ulcers and perforation of the nasal septum (Mn, Pb, Fe, Cu), anemia, osteoporosis (Pb, Cu, Cd), cancer (Cu, Ni, As, Cd), and high blood pressure (Cd). Heavy metal ions are deposited on the walls of blood vessels, liver tubules, kidneys, reducing the functional activity of these organs.

NPs that enter the body can destroy the barrier systems of cells and cell membranes, which was found under the influence of various NPs (Ag, fullerenes, SiO_2, TiO_2, ZnO, CuO, carbon nanotubes) [20, 21]. The toxic effect of NPs is due to their catalytic activating or inhibitory effect on biochemical processes, cell metabolism. Thus, the penetration of gold NPs into cells through the plasma membrane promoted their interaction with cell organelles [22]. It is known that in biochemical

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reactions, due to the large surface area of NPs, their reactivity increases in comparison with analogues of macro compounds.

According to current data, the mechanisms of nanoparticle-induced toxicity are mainly oxidative stress with subsequent provocation of cell death and genotoxicity. Oxidative stress is an important, key mechanism of xenobiotic toxicity as a result of the imbalance between the production of active free radicals and antioxidants in the body [23–25]. The main factors leading to oxidative stress are reactive oxygen species and nitric oxide. The former include free radicals formed during the reduction of oxygen and their secondary reactive products (superoxide radical, singlet oxygen, hydroxyl and peroxyl radicals, hydrogen peroxide, peroxide ion), hypohalides (HOCl, HOBr, NOI, NOSCN). Active forms of nitrogen are nitrogen oxides, higher nitrogen oxides, nitrites, peroxynitrite [26–28]. NO (nitric monoxide, nitric oxide) is a molecule-regulator of apoptosis, necrosis and cell survival and is able to move freely from one cell to another. NO can be involved in numerous physiopathological functions, such as cytotoxicity, cell death, and has a high reactivity. NO is produced in the body by enzymatic and non-enzymatic pathways.

After a complex cascade of transformations, endogenous nitric oxide is converted into stable compounds – nitrates, nitrites, nitrosothiols and nitrotyrosine. Nitric oxide, being a small paramagnetic radical that has no electric charge, easily passes through cell membranes, is well soluble in water and lipids, reacts with other molecules at a considerable distance from the place of its formation and can affect metabolic processes both in synthesis cells and in nearby cells [7]. Nitric oxide is an active, short-lived radical (existence period from 3 to 50 days). The biological effect of this molecule depends on the interaction with a particular chemical group. When interacting with ROS, nitric oxide is converted into reactive nitrogen species (RNS). And in the reaction with superoxide anion (O_2^-), peroxynitrite ($ONOO^-$) is formed, which reacts with many biomolecules, thereby mediating the toxic effect of NO. The effects of RNS, detected in *in vivo* experiments in tissues, cells and biomolecules, are different. RNS are able to oxidize SH-groups of cysteine amino acid in the primary structure of proteins, break the covalent bond of sulfhydryl (S–S) groups, change the tertiary structure of proteins and their functional properties [11]. In addition to modifying proteins, RNS, as well as ROS, damage lipids and nucleic acids.

Under the action of metal nanoparticles in *in vitro* experiments on eukaryotic cells, reactions associated with oxidative stress are manifested [27, 28]. The cause of the latter may be ROS and RNS, the formation of which leads to oxidative damage to cellular components and ultimately to cell death [29], which can be caused either by necrosis or apoptosis, where the first is characterized as random and pathological, and the second is considered a programmed and physiological mechanism and can be controlled. Currently, there are 34 different types of regulated cell death, which differ by different mechanisms and indicate the complexity of this process [30].

In eukaryotic organisms (protozoa, fungi, plants and animals), there is a significant range of antioxidants for detoxification of ROS and repair of proteins, lipids and DNA damaged by oxidation. These antioxidants include enzymes (superoxide dismutase, catalase, glutathione peroxidase, glutathione S-transferase and peroxiredoxins) and non-enzymatic factors – glutathione and vitamins. Evidence of the damaging effect of metal NPs (e.g., silver) in *in vivo* experiments is also a decrease in the antioxidant activity of blood serum. Glutathione,

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as the main endogenous antioxidant acceptor, protects cells from oxidative stress due to its ability to bind to ROS and reduce them. However, the literature data on changes in the antioxidant activity of biosubstrates under the influence of NPs are not unambiguous. For example, under the action of silver NPs increased the level of glutathione, which could be a cellular protection against oxidative damage. But in other studies, a decrease in glutathione levels was found, which correlated with the amount of ROS, meaning either blocking of glutathione-synthesizing enzymes or glutathione depletion. Oxidative carbonylation of proteins is considered to be an informative marker of oxidative stress detected in response to exposure to silver NPs [31–33].

Thus, the induced oxidative stress as a result of exposure to NPs of various metals is primarily due to increased free radical oxidation of lipids, proteins and a decrease in the content of antioxidants. The ambiguity of the results between studies can be explained by different ways of induction of oxidative stress and possible changes in the NPs dimension during laboratory manipulations and within biological test systems [34, 35].

In a number of studies it was found that NPs of noble metals (gold, silver) cause DNA breaks, disruption of micronuclear processes and chromosomal aberrations in human and mammalian cells [36]. The main reason for the above-mentioned genotoxic effects of silver NPs is considered to be their ability to generate ROS, which damage proteins, lipids and DNA. However, other studies have not found genotoxic effects of silver nanoparticles.

Upon penetration into the body, nanoparticles can be captured by phagocytosing cells of the immune system, resulting in the risk of inflammatory or autoimmune reactions [37]. But the immunotoxicity of NPs (in particular, silver) is not always revealed. Once in the body, NPs can bind to proteins: immunoglobulins and components of the complement system, as well as serum proteins (albumin and fibrinogen). After that, neutrophils and macrophages are able to recognize NPs as foreign and phagocytose them. The severity of immune responses to NPs exposure is determined by their physicochemical properties and surface coating. For example, the coating of silver NPs with polyethylene glycol, polyvinylpyrrolidone significantly reduced the immune system response. The possible role of silver as an immunomodulator is discussed in scientific publications. Depending on the dose, this metal can both stimulate and inhibit phagocytosis.

According to a number of studies, the leading mechanism of cytotoxicity of silver NPs, as well as other metals, is the induction of oxygen free radicals [15, 16, 38]. The severity of oxidative processes disturbances by nanoparticles depends on their size, chemical nature, physical state, and largely on their stabilization. Thus, stabilized silver NPs by polyvinylpyrrolidone did not increase the formation of reactive oxygen species, and therefore did not cause oxidative stress in cells and did not reduce the bactericidal ability of neutrophils, and unstabilized silver NPs increased the production of ROS, which indicated the development of oxidative stress in cells. Therefore, the high reactive activity of NPs requires their coating with stabilizers to maintain dimensionality. At the same time, in the body, NPs can be modified by reactions primarily with proteins, lose atoms, which can lead to changes in their reactivity. In the condensation methods of obtaining NPs (in reactions of reduction, substitution, oxidation, hydrolysis) their concentrations are insignificant from μg/ml to mg/ml. In such conditions, the

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values of lethal doses of NPs are not determined, most likely due to the limited possible volume of administration to animals, and in case of their repeated intake into the body, the damaging effect is detected in the delayed periods of experiments, and not after the first few injections. This may be the reason for a longer stay of NPs in the body and the possibility of their entry into cell organelles, including the nucleus.

The information that NPs are more toxic in comparison with their analogues in macroforms is probably justified under certain conditions. But it has been repeatedly proved by specific examples that ionic forms of metals can be more toxic than their nanoscale counterparts. Thus, biogenic metals zinc, copper and iron in the form of NPs were less toxic than in macroforms. Similarly, nanosilver, copper NPs are less toxic in some respects than their ions in $AgSO_4$ and $CuCl_2$ [39].

Physicochemical features of substances in the nanoscale state and the effects caused by them [40, 41]:

- *small size and variety of forms of nanoparticles*. Due to their small size, NPs can combine with proteins, nucleic acids, penetrate into cell organelles and, as a result, change the functions of biostructures;
- *increased specific surface of nanomaterials*. The large specific surface area of NPs enhances their catalytic properties, adsorption capacity and chemical reactivity. This can lead to an increase in the production and content of reactive oxygen species and free radicals and further damage to biological structures (nucleic acids, lipids, proteins);
- *increase of chemical potential at the interfacial boundary of high curvature*. NPs is characterized by a large surface curvature, which is the reason for the modification of their chemical potentials. Because of this, the reactivity and catalytic ability of NPs changes significantly;
- *significant adsorption activity*. Due to the highly developed surface, NPs are able to adsorb many times more substances per unit mass than macroscopic dispersions. It is possible to adsorb various contaminants on NPs and facilitate their entry into cells, which increases the toxicity of xenobiotics. Many NPs exhibit hydrophobic properties, which enhances their interaction with various toxicants and avoid contact with the protective barriers of the body;
- *high ability to accumulate*. Due to their small size, NPs are not recognized by the protective barriers of a living organism, do not undergo biotransformation and are not excreted, but accumulate in plant and animal organisms.

All these facts confirm that nanomaterials have completely different chemical and physical characteristics and biological effects than substances in conventional micro and macro states. The negative effect of metals is usually due to their connection with cellular targets [39], which are specific biochemical processes and cellular, subcellular membranes, cell organelles. And the main mechanisms of the damaging effect of NPs are oxidative stress, inflammation, DNA damage, necrosis, apoptosis.

Oxidative stress is an imbalance between the production of free radicals and antioxidant control mechanisms, accompanied by an increased rate of free radical formation and a decrease in the activity of antioxidant systems, followed by an increase in the level of radical compounds and possible cell death [41–43]. Molecular targets for free radicals are lipids, proteins and DNA. According to numerous literature data, the damaging effect of nanoscale particles is accompanied by oxidative stress, dysfunction of intracellular structures and increased

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membrane permeability. Small size and variety of forms of nanoparticles facilitate their interaction with proteins and nucleic acids; incorporation into cell membranes with subsequent change in the functions of biostructures. The presence of hydrophobic properties and electric charge in many nanomaterials enhances both the processes of adsorption of various substances on them and their penetration through the body barriers. An important feature of the properties of NPs is the increased ability to accumulate, since due to their small size these objects may not be recognized by the body's defense systems, and, consequently, may not undergo biotransformation. Manifestation of NPs toxicity is the result of multifactorial causes and mechanisms of their harmful effects, including: penetration into cell organelles, binding to DNA, accumulation in organs, changes in the functions of biostructures. The manifestations of NPs action are also influenced by the individual characteristics of biological objects, the state of metabolic systems, detoxification of warm-blooded organisms. NPs emit metal ions, which, when in contact with air, turn into oxides. A significant problem is to obtain absolutely the same size of NPs and to preserve this size and their properties when they enter the body.

Depending on the size of NPs and the environment, their physical and chemical properties (agglomeration, degradation and adsorption) change. The toxic effect of NPs differs from the effect of bulk materials due to the variety of their forms, modification of materials (carbon nanotubes, nanofibers, fullerenes), changes in the properties of NPs depending on the size and stabilization surface.

NPs are considered as a factor that has features of transformations in the cell, conjugation, transport, mechanisms of regulation of these processes (influence on gene structures, protein synthesis, immunotoxic, allergenic effects, long-term and environmental effects). In real conditions, the combined effect of several nanoscale metals is also possible. Thus, during prolonged oral exposure to a mixture of Ag, Cu, Fe and Mn dioxide (metal nanocomposition) in different doses, prooxidant effects were detected in terms of intensification of lipid and protein peroxidation in the blood plasma of white rats, which were irreversible and persisted after the cessation of toxicants administration [44].

Thus, despite the great interest in nanotechnology, information about the mechanisms of interaction of NPs with biological objects and the possible negative impact on living organisms is rather ambiguous. It is established that the surface charge and dispersibility of NPs can change during laboratory manipulations and in culture media. A molecular layer («crown») is formed on the surface of NPs, which affects the reactions in biosubstrates and cells as a result of the transformation of the dimension and properties of nanoparticles.

Significant in the manifestation of the harmful effects of NPs are many factors and processes occurring at the interface of «nano-» and «bio-»: mechanisms of penetration of nanoparticles, their accumulation, distribution and, in general, their «fate» in cells. The introduction of nanoscale products (e.g. nanospheres ~ 14 nm and gold nanorods ~ 54 × 20 nm, as well as palladium nanorods ~ 6 nm) into the culture medium was accompanied by changes in their surface charge, hydrodynamic size and dispersed state compared to suspensions in distilled water. And the surface charge of nanoparticles played a crucial role in their binding to the cell membrane [45].

The mechanisms of cell penetration and damaging effects of NPs of different metals are

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different. In epithelial cells (MDCK cultures – Madin-Darby kidneys of dogs) palladium NPs got into epithelial cells crossing the plasma membrane, caused a pronounced effect and accumulated in the nuclei of cells and cytoplasmic organelles, while the effects of gold nanospheres were realized by caveolin-dependent endocytosis and macropinocytosis without cell damage. In peritoneal macrophages, both palladium nanoparticles and gold nanospheres were delivered by phagocytosis and microendocytosis (clathrin-, caveolin- and raft-dependent endocytosis) without damaging cell structures [45]. And nanospheres and nanorods of gold coated with linear polyethyleneimine penetrated into the kidney culture cells of Syrian hamster BNK-21 by caveolin- and raft-dependent endocytosis; in melanoma cells B16, respectively, by raft-dependent endocytosis. Gold nanorods modified with linear polyethyleneimine or bovine serum albumin induced endocytosis of circular dorsal folds in these cells.

The mechanisms and dynamics of damage by nanoparticles described earlier [46, 47] are different. Changes in the intensity of free radical oxidation of biosubstrates (lipids, proteins, nucleic acids) are considered to be the most informative markers of NPs toxicity. Despite the availability of a large number of publications on the damaging effects of nanoscale structures, there are still no necessary approaches, methods and evaluation criteria that could be used to quickly judge the toxicity and hazard of NPs to humans and the environment. Very often, the authors refer to the impossibility of predicting the consequences of exposure of a living organism to technical NPs and justification of their safe levels. This may be primarily due to the peculiarities of changes in the structure of the studied nanocompositions, depending on many factors, including technical and laboratory manipulations. Therefore, it is necessary to develop methods and approaches for predicting the negative effects of nanoscale particles under different exposure conditions, which will allow to detect and predict their toxic (damaging) manifestations in acute and chronic intoxication.

The severity of toxicity of nanoscale objects when entering the body is largely determined by the mechanism of their action [48]. At the same time, the rates of NPs entry into the blood, their metabolic transformations in the blood and tissues of internal organs, the rate of penetration through histohematological barriers and interaction with biotargets, as well as some other factors determined by the magnitude of toxic doses and the peculiarities of the mechanisms of damaging effects on the body are of great importance. The greatest difficulty in the assessment of NPs is the unpredictability of changes in their states and properties from the influence of environmental factors arising in the processes of laboratory manipulations and technological operations.

The damaging effect of NPs can be carried out by several mechanisms. The main and the most significant of them is the formation of free oxygen radicals with the destruction of macromolecules (phospholipids, nucleic acids and proteins), disruption of cellular processes caused by the surface properties of nanoparticles. Other mechanisms of toxicity of nanomaterials cannot be excluded, in particular, related to their effect on cell membranes and organelles, enhanced transport of potentially toxic components across body barriers, as well as possible genotoxicity and allergic effects. The damaging effects of NPs depend on their size, chemical nature, physical state, and largely on their stabilization.

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Conclusions

The intensification of free radical oxidation of biosubstrates is one of the main indicators of the damaging effect of nanoscale products and a priority area of research on the dangerous effects of it on the human body.

It is established that nanoparticles enhance the formation of reactive oxygen and nitrogen species, disrupt membrane structures, enter cells and interact with cellular components as a result of their high penetrating ability.

Free radical oxidation of biosubstrates, as the main mechanism of damaging effect of nanoparticles, is determined by the size, surface area and composition.

Properties and toxicity of nanomaterials can be modified in the process of laboratory and technological manipulations due to changes in their structure, size, sorption of other molecules.

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ISSN 2223-6775, Ukrainian Journal of Occupational Health, 2022, 18 (3), 224–236

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Information on sources of research funding: applied research topic «Development of predictors of potential hazard of industrial aerosols of different dispersion», state registration number 0122U000674 (2022-2024).

Received: August 29, 2022
Accepted for publication: September 15, 2022

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