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Review

UPDATE ON PULMONO-, HEPATO-, AND CARDIOTOXICITY OF NANOPARTICLES *IN VIVO:* A LITERATURE REVIEW

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A wide use of nanoparticles (NPs) in various industries, agriculture, science, medicine and cosmetology, as well as their omnipresence in the environment necessitate a comprehensive study of their effects on living systems to predict health risks and develop preventive measures. In this study, we aimed to study and systematize available scientific evidence of toxic effects of nanoparticles on the lungs, liver, and heart.

The search for publications issued in 2022–2024 was carried out in Russian (eLIBRARY.RU) and foreign (PubMed, Google Scholar) databases and electronic libraries. Articles containing information on health effects of particles in the 1–100 nanometer range were eligible for inclusion in the review while descriptions of in vitro, in silico, and epidemiological studies were excluded. Of more than 150 articles screened, we selected 31 full-text in vivo study publications (including one preprint) and 18 articles describing the identified effects.

Toxic effects of nanoparticles are attributed to their unique properties and depend on numerous factors, including chemical composition, size, and shape of nanoparticles, their concentration, exposure duration, and ability to cross internal barriers of the body. Adverse effects of nanoparticles are observed at all structural levels of the organism. Nanoparticles mainly induce inflammatory, dystrophic and necrotic changes. Closely interrelated inflammation and oxidative stress are the main mechanisms of toxicity.

Assessment and analysis of an array of experimental studies on potential risks of nanoparticle exposure at various structural levels make it possible to identify minute changes in organs for further development of a system of preventive measures aimed at increasing resistance to such NP-mediated pathological effects.

Keywords: *nanotoxicity, nanoparticles, intoxication, review, in vivo studies, lung, liver, heart.*

Nanoparticles (NPs) generated in the course of natural and, to a greater extent, anthropogenic processes enter the body through various environmental media and objects, including air, water, soil, food, and cosmetics, or directly by medical manipulations (diagnostics, nanoparticle-based drug delivery), all representing inhalation, oral, percutaneous or parenteral routes of exposure. This leads to structural and functional disorders in the human body, thereby increasing the risks to human health and necessitating measures to prevent negative effects. The risk of nanoparticle-related diseases and their severity depend on many factors, including particle size and migration

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potential [1–3], cumulative properties [4–6], chemical composition [7], method of synthesis (chemical or biological) [8, 9], and exposure type (isolated or combined) [3, 10], level and duration [4, 11].

The ubiquity of NPs and their high biological activity accounting for their serious toxic effects on the body make it relevant to analyze and systematize recent data on toxicity of NPs and specifics of their pathogenesis at different levels of organization, which is also necessary for predicting health risks and further development of preventive measures. We have focused on the lungs, liver, and heart as the most studied of the main target organs for NP exposure; in addition, the NP-mediated disruption of their functioning poses a serious health threat.

We **aimed** to study and systematize available scientific evidence of toxic effects of nanoparticles on the lungs, liver, and heart.

Materials and methods. We applied information analysis techniques to systematize and summarize relevant findings. The bibliographic search was conducted in Russian and English in the databases and scientific electronic libraries (eLIBRARY.RU, PubMed, and Google Scholar) using the following keywords: toxicity, nanoparticles, size, pulmonary toxicity, cardiotoxicity, hepatotoxicity, *in vivo*. References contained in selected publications were screened for additional works to be included in the review. The inclusion criteria were the study of particles of various chemical compositions sized 1–100 nm, the presence or absence of a toxic effect of NPs on organs, and a publication date no earlier than 2022. The exclusion criteria were *in vitro, in silico* and epidemiological studies since their results are difficult to extrapolate to the organismal level. We selected five of 392 articles found on eLIBRARY.RU, one of nine found in PubMed, and 25 (including one preprint) of more than 17,000 search results on Google Scholar. Most of the studies reviewed were conducted in Russia, Egypt, China, and Iran, one each in Mexico, the United Kingdom, the UAE, Pakistan, Denmark, Türkiye, Japan, the United States, and the Republic of Korea. The review included studies of the following NPs: Ag – 11/43 (26 %), Si – 5/43 (12 %), Zn, Ti, and Al – 4/43 each (9 %), Cu – 3/43 (7 %), Pb, Fe, and Sn – 2/43 each (5 %), Ni, Au, Mo, Se, In, and Co – 1/43 each (2 %).

Results and discussion. Recent publications disclose various pathological manifestations of the toxic effect of NPs by various routes of entry, including inhalation, intratracheal, intranasal, intraperitoneal, oral, intravenous, and whole-body ones. Toxic effects were divided by selected organs and described from the molecular genetic to the organismal levels. Warm-blooded animals (rats and mice) and fish served as objects for *in vivo* studies.

Pulmonotoxic effects of nanoparticles. Starting from the molecular genetic level, changes in the bronchoalveolar lavage fluid (BALF) and blood were noticeable. An increase in the levels of malonic dialdehyde (MDA) and superoxide dismutase (SOD) in the BALF was noted after exposure to In/Sn NPs at 1.2, 3, 6 mg/kg b.w. [12], while $CoFe_2O_4$ NPs (5 mg/kg body weight (b.w.)), in addition to an increase in the MDA level, caused a decrease in that of reduced glutathione in the lung homogenate [13]. Such changes indicated the development of oxidative stress, which was closely associated with inflammation [14] induced by NPs. Thus, NPs (Al 20 and 40 mg/kg b.w. and In/Sn 1.2, 3, 6 mg/kg b.w.) caused a significant increase in the level of inflammatory cytokines (IL-1β, IL-4, IL-5, IL-6, IL-10, IL-13, and tumor necrosis factor-α (TNF-α)) in the BALF [12, 15]. Changes were also observed at the genetic level – the exposure to cobalt ferrite NPs ($CoFe_2O_4$) at the doses of 0.5 and 5 mg/kg b.w. increased the expression of *TNF-α* and *IL-1β* genes and decreased that of *IL-10* and the transforming growth factor beta-1 (*TGFβ-1*) [13], an important fibrogenic cytokine [16].

Exposures to nanoparticles of Al (1.70 mg/m^3) and In/Sn (1.2, 3, 6 mg/kg b.w.) induced an increase in the activity of lactate dehydrogenase (LDH) [17], aspartate aminotransferase (AST), and hydroxyproline [12] in blood. As for the BALF, the exposure to NPs of Sn (162 μg/mouse), Ti (162 μg/mouse), and In/Sn (1.2, 3, 6 mg/kg b.w.) induced a significant increase in the levels of total protein [18] and LDH [12], while that to Pb NPs (0.215 mg/m^3) in one of our previous studies accounted for an insignificant tendency towards an increase in alanine aminotransferase (ALT), AST, gamma-glutamyl transpeptidase (GGTP), and LDH [19]. LDH and total protein are known to be associated with pulmonary injury, inflammation, and permeability of the blood–air barrier [1, 12, 20]; GGT, being a membrane-bound enzyme, is involved in oxidative processes, and changes in AST and ALT in the BALF may indicate cellular injury [19]. Direct pulmonary damage and inflammation often develop into fibrotic changes, signs of which can be detected already at the molecular genetic level. An increase in hydroxyproline levels following the exposure to Si NPs (6.0 mg/kg b.w.) indicated collagen deposition and the development of fibrosis [21]. In addition, the relationship between oxidative stress and fibrosis was observed, as shown by the established positive correlation between hydroxyproline and MDA and nitric oxide (NO) and the negative one between that and glutathione, SOD, and catalase [22, 23]. It is important to note that fibrosis progression also correlated with the levels of interleukins IL-1β [24], IL-4 [25], and IL-13 [26] affected by NP exposures.

Changes at the molecular genetic level inevitably lead to changes at the cellular and tissue levels. When studying the cellular phagocytic activity of the respiratory tract after exposure to NPs of Pb (0.215 mg/m^3), Cu (4 mg/m^3, 2.6 and 12 μg/mouse), Al (54 μg/mouse, 20 and 40 mg/kg b.w.), Sn (162 μg/mouse), Zn (0.7 μg/mouse), Ti (162 μg/mouse), and In/Sn (1.2, 3, 6 mg/kg b.w.), an increase in the counts of neutrophils [2, 15, 18, 19], eosinophils [15], and alveolar macrophages [2, 12, 15] and a decrease in those of monocytes and lymphocytes [2, 19], alveolar macrophages in the BALF [19] were established. The study of Si NPs (3 and 6 mg/kg b.w.) found an increase in the proportion of alveolar and interstitial macrophages, while those of natural killers (NK cells), neutrophils, and monocytes were decreased [21]. Fluctuations in counts of phagocytic cells can be explained by their redistribution in tissues, increased activity followed by exhaustion, and different experimental conditions. Changes in cellular phagocytic activity and a decrease in the ratio of segmented neutrophils to alveolar macrophages observed in the studies indicate cytotoxic and inflammatory effects of NPs and activation of the immune response [2, 19]. In addition, a dose-dependent increase in inducible nitric oxide synthetase (iNOS) and Cox-2 ($CoFe_2O_4$ 0.5 and 5 mg/kg b.w.) [13], which are markers of modulation of the anti-inflammatory response [16, 27], was observed, also confirming activation of immune protection in response to toxic damage. Thus, activation of immune response can be added to the mechanisms of NP toxicity.

At the tissue and organ levels, post-exposure histological preparations of the rat lung showed epithelialization and proliferation of type 2 pneumocytes, hyperemia (Si 900 mg/kg b.w./day) [28] and pulmonary edema (Mo 1.84 mg/m^3, Cu 1.2–1.4 mg/m^3) [1, 2], brown pigmentation of macrophages, foci of emphysema and exudation of erythrocytes into the lumen of the alveoli, hemorrhagic infarction (Cu 1.2–1.4 mg/m^3, Al 1.70 mg/m^3) [2, 17], foci of interstitial inflammation (Mo 1.84 mg/m^3, Cu 1.2–1.4 mg/m^3, Al 20, 40, 100 mg/kg b.w., $CoFe_2O_4$ 0.5 mg/kg b.w.) [1, 2, 12, 13, 15, 29]. Besides, NP exposure induced collagen deposition in the lungs and alveolar wall thickening (Si 3 mg/kg

b.w. and 6 mg/kg b.w. and In/Sn 1.2, 3, 6 mg/kg b.w.) [12, 21], which, together with changes in the levels of MDA and inflammatory cytokines, confirms the effect of NPs on the development of fibrotic changes in the lungs through inflammatory and oxidative damage.

No reported changes at the organismal level were found in the reviewed articles; some studies demonstrated no significant damage either (Si 0.125 mg/kg b.w., Ag 200 μg/kg b.w.)[1] [30]. Yet, the evidence of disturbances at other levels significantly increases the likelihood of pulmonary and other respiratory diseases. Differences in the findings may be attributed to a number of factors, such as physicochemical properties of nanoparticles, the administered dose, the route and duration of exposure, methods of detection, and the types of experimental animals.

Hepatotoxic effects of nanoparticles. Liver is an important target organ for many toxicants. It performs barrier and storage functions, which makes it more vulnerable to the damaging effects of NPs [4]. At the molecular genetic level, exposures to nanoparticles of Al (100 mg/kg b.w.), Si (500 μg/kg b.w. and 1.5, 3.0, and 6.0 mg/kg b.w.), Ni (1, 20, 150 mg/kg b.w.), Ag (50 mg/kg b.w., 200 ppb, and 5 μg/kg b.w.), Ag + Zn (50 + 30 mg/kg b.w.), and Fe (100 mg/kg b.w.) were found to increase the levels of reactive oxygen species (ROS) [7, 31–33], 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-OHdG) – the main product of DNA oxidation [34], substances that react with thiobarbituric acid [31], nitric oxide (NO) [35], MDA [7, 29, 32, 35–37], and oxidized glutathione [32], and to decrease those of reduced glutathione [32, 37], catalase [29, 31, 35–37], peroxidase [29, 31, 35, 36], and SOD [29, 31, 35, 36] in the liver. Another study, on the contrary, showed an increase in SOD and catalase levels attributed by the authors to the activation of a protective feedback mechanism [34]. An imbalance between pro-oxidants and antioxidants causing disruption of cell membrane integrity and DNA damage was clearly registered [38]. In addition to oxidative stress, endoplasmic reticulum (ER) stress was induced in liver tissues. Elevated levels of immunoglobulin heavy chain binding protein were observed in the liver following exposure to Si NPs at 1.5, 3.0, and 6.0 mg/kg b.w. The same study revealed ER abnormalities, such as expansion of the ER space, detachment of ribosomes, disruption of ER integrity and structure [32].

The inflammatory response to nanoparticle exposures (Ti 50 mg/kg b.w., Ag 50 mg/kg b.w. and 200 ppb, Ag+Zn 50 + 30 mg/kg b.w., Ni 1, 20, 150 mg/kg b.w.) was accompanied by changes in the levels of inflammatory cytokines as follows: TNF-α [7, 35, 37], IL1β [7, 36, 37], IL-6 [7, 37] increased while IL-10 [37] decreased. In addition, exposures to nanoparticles of Al (1.70 mg/m^3, 100 mg/kg b.w.), Se (0.2 mg/kg b.w.), Si (250 mg/kg b.w., 500 μg/kg b.w.), Ti (50 mg/kg b.w.), Ag (10% b.w.), Ni (1, 20, 150 mg/kg b.w.) and Fe (100 mg/kg b.w.) induced an increase in the activity of ALT [4, 7, 8, 17, 29, 31, 35–37], AST[2] [4, 7, 17, 29, 31, 35–37] and LDH [36], in the level of lysophosphatidylinositols [4] and direct bilirubin [17, 29], but a decrease in the concentrations of alkaline phosphatase (ALP) [4], succinate dehydrogenase [4], levels of bile and glycocholic acids [4], albumin [31, 35, 36], total protein [36], and creatinine [6] in the blood serum. According to other data, concentrations of ALP [17, 29, 31, 36] and albumin [11] increased. Similar changes

[1] Cao X., Xie B., Xu M., Li J., Dai X., Tian Y., Zhang J., Chen Y. [et al.]. Toxicity study of silica nanoparticles following 94-day repeated oral administration in Sprague Dawley rats: preprint (Version 1). *Research Square*, 2024. DOI: 10.21203/rs.3.rs-4531919/v1

[2] Ibid.

were observed in liver homogenates, e.g. a significant dose-dependent increase in the activity of hepatic LDH, ALT, and AST (due to Si NP exposures at 1.5, 3.0, and 6.0 mg/kg b.w.) [32]. Increased values of transaminases and alkaline phosphatase in the liver indicated inflammation, dysfunction of hepatocyte mitochondria, and oxidative or nitrosative stress [31].

Changes in lipid metabolism were found to be characteristic of toxic damage to the liver. Si NPs at the doses of 1.5, 3.0, and 6.0 mg/kg b.w. caused an increase in the expression of mRNA levels of the *Fasn*, *Elovl6*, and *Scd1* genes associated with fatty acid synthesis [32, 39, 40], a decrease in the expression of the *Cpt1a*, *Acox1*, and *Ppara* genes involved in beta-oxidation of fatty acids [32, 41], and *Scarb1*, *Abca1*, *Abcg1*, and *Lxra* genes involved in reverse cholesterol transport [32, 42]. Lipid metabolism disorders were also established after exposure to nanoparticles of Al (100 mg/kg b.w.), Ti (50 mg/kg b.w.), Si (1.5, 3.0, and 6.0 mg/kg b.w. and 1,000 mg/kg b.w.), Ag (5, 10, and 15 ml/L), and Ni (1, 20, 150 mg/kg b.w.). The lipid spectrum showed an increase in the levels of triglycerides [6, 11, 29, 32, 35], cholesterol [11, 32, 35, 36], and low- and very low-density lipoproteins [29, 35] with a decrease in those of high-density lipoproteins [29, 35]. Changes in beta-oxidation of fatty acids were noted after the exposure to Se NPs at doses of 0.2, 1, and 2 mg/kg b.w. as assessed by altered blood levels of acylcarnitines and their derivatives in rats [4]. Ag NPs (200 ppb) increased the production of angiotensin-converting enzyme (ACE) in the liver [34]. The accumulation of ACE and fatty acid esters in the blood, an increased level of lysophosphatidylethanolamines, and decreased levels of bile and glycocholic acids indicated suppression of the secretory function of the liver and its damage [4, 34].

Apoptosis is yet another mechanism of the toxic effect of NPs. Animal experiments demonstrated that the exposures to Si, Ni, Ag, and Zn NPs increased the expression of the *Bax* (Si 900 mg/kg b.w., Ni 1, 20, 150 mg/kg b.w.), *Bcl-2* (Si 600 mg/kg b.w.), *Caspase3* (Cas-3) (Si 900 mg/kg b.w., Ni 1, 20, 150 mg/kg b.w., Ag 50 mg/kg b.w., Ag+Zn 50 + 30 mg/kg b.w.), and *p53* (Ni 1, 20, 150 mg/kg b.w.) genes in rats [28, 36, 37]. The level of *Bcl-2* decreased following the exposure to Ni NPs [36] due to the suppression of the anti-apoptotic system. Changes in the expression of these genes confirmed the development of apoptosis [43, 44].

Oxidative stress, inflammation, and apoptosis cause changes at other levels of the body. Thus, at the cellular level, degenerative dystrophic changes in the nucleus (karyorrhexis, karyopiconosis, karyolysis) and cytoplasm (vacuolization), as well as aniokaryolysis and cytoplasmic hypertrophy were observed in rat hepatocytes after exposure to NPs of Si (500 μg/kg b.w.) and Ag (10 % b.w., 50 mg/kg b.w., 5 μg/kg b.w., 0.04 mg/L^{-1}), [8, 10, 31, 33, 37]. NP exposure also induces mitochondrial disorders. Nanoparticles of Se (2 mg/kg b.w.) and Si (1.5, 3.0, and 6.0 mg/kg b.w.), for instance, caused a decrease in the ratio of normal mitochondria [4], their deformation, rupture, and disappearance of cristae [32]. In addition, NPs of Se (1 mg/kg b.w., 2 mg/kg b.w.), Al (100 mg/kg b.w.), Si (500 μg/kg b.w.), and Ag (0.04 mg/L^{-1}) increased the proportion of degenerated hepatocytes, as well as the number of aneuploid hepatocytes and Kupffer cells [4, 10, 29, 31]. Pathological changes were manifested by hepatocyte disorganization (Al 100 mg/kg b.w., Si 500 μg/kg b.w.) [29, 31], infiltration with inflammatory cells (Si 500 mg/kg b.w., 1.5, 3.0, and 6.0 mg/kg b.w., Al 100 mg/kg b.w., 18 and 54 μg/mouse)[3] [18, 29, 32], macrophage aggregates (Sn 54 and 162 μg/mouse, Ti 162 μg/mouse, Ag 5, 10, 15 ml/L)

[3] Cao X., Xie B., Xu M., Li J., Dai X., Tian Y., Zhang J., Chen Y. [et al.]. Toxicity study of silica nanoparticles following 94-day repeated oral administration in Sprague Dawley rats: preprint (Version 1). *Research Square*, 2024. DOI: 10.21203/rs.3.rs-4531919/v1

[11, 18], lymphocytes, and foreign materials (Sn 54 and 162 μg/mouse, Ti 162 μg/mouse) [18].

Inflammation-induced dystrophies were noted at the tissue and organ levels. Thus, NP exposures (Mo 1.84 mg/m^3, Ag 5, 10, 15 ml/L) caused widespread hydropic [1], hyaline-droplet [1] and fatty dystrophies of the liver [1, 11]. Necrotic changes were registered in some cases with necrotic zones observed in the liver parenchyma (Al 100 mg/kg b.w., Si 500 μg/kg b.w., Si 900 mg/kg b.w./day and Ag 5, 10, 15 ml/L) [11, 28, 29, 31], including the bile ducts (Al 100 mg/kg b.w., Ti 50 mg/kg b.w.) [29, 35]. As in the lungs, fibrotic changes were expressed including deposition of collagen fibers in the pericentral and periportal areas (Al 100 mg/kg b.w., Ti 50 mg/kg b.w.) [29, 35], increased deposition of lipids and collagen in the liver tissue (Si 1.5, 3.0, and 6.0 mg/kg b.w.) [32]. One of the studies of liver histomorphology also showed that the degree of damage depended on the route of administration: oral administration of Ni NPs (150 mg/kg b.w.) induced congestion, cellular degeneration, and infiltration of mononuclear cells in the liver; intraperitoneal administration (20 mg/kg b.w.), in addition to infiltration of mononuclear cells, caused hemorrhage, proliferation of Kupffer cells, sinusoidal expansion, and necrosis, while intravenous administration at 1 mg/kg b.w. induced similar disorders, except for necrosis [36].

Liver toxicity of NPs is mainly manifested by inflammatory, dystrophic, fibrotic, and necrotic changes. We did not evaluate disorders at the organismal level but the suppression of liver functioning increases the risks of developing many diseases, including those of other organs and systems, owing to the great importance of the functions it performs. Only one study (Ag 200 μg/kg b.w.) [30] found no toxic effect on the liver, which might be associated with both the properties of the substance itself and the experimental conditions.

Cardiotoxic effects of nanoparticles. A number of studies, including one of ours [45], revealed cardiac toxicity of nanoparticles. At the molecular genetic level, an increase in oxidative and nitrosative stress was observed under effect of NPs (Ag 0.5 mg/kg b.w., Cu 400 mg/kg b.w., and Fe 100 mg/kg b.w.), including a significant increase in the levels of ROS, MDA [7], lipid peroxidation, reduced glutathione, oxidized glutathione [46], total NO concentration [46, 47], total thiol, thiobarbituric acid reactive substances, with decreased levels of SOD, catalase and reduced glutathione [47] in cardiac homogenates. Signs of inflammation and apoptosis were registered. In the study of Ag NP exposure (0.5 mg/kg b.w.), a significant increase in IL-6 concentrations was observed [46], while the study with Ti and Zn NPs (10 mg/kg b.w.) showed a trend towards an increase in TNF-α production. Changes in the production of apoptotic and autophagy-related proteins, i.e. a decrease in Cyt-C and Bcl-2 and an increase in LC3B, Beclin-1, Cas-3 and Cas-9, as well as an increase in calcium levels, were also detected and likely associated with mitochondrial damage [48].

Oxidative stress caused myocardial tissue damage and inflammation, which in turn led to tissue damage and aggravated oxidative stress [46]. This forms a vicious circle that begins at the cellular level – most often with mitochondrial structure disorders – and ends with histomorphological changes in the organ, which subsequently leads to cardiac dysfunction.

Under exposure to nanoparticles of Al (1.70 mg/m^3), Si (250 mg/kg b.w., 500 μg/kg b.w.), Ag (0.5 mg/kg b.w.), Pb (2.32 mg/kg b.w.), Cd (0.22 mg/kg b.w.), and Cu (400 mg/kg b.w.), a decrease in troponin [17] and AST[4] [17, 45] and an increase in LDH [17, 46, 47], myoglobin [47] and creatine kinase MB [46, 47] were observed in rats and mice. In some studies,

[4] Cao X., Xie B., Xu M., Li J., Dai X., Tian Y., Zhang J., Chen Y. [et al.]. Toxicity study of silica nanoparticles following 94-day repeated oral administration in Sprague Dawley rats: preprint (Version 1). *Research Square*, 2024. DOI: 10.21203/rs.3.rs-4531919/v1

on the contrary, NPs of Pb (2.5 mg/kg b.w.) and Cu (400 mg/kg b.w.) decreased the activity of creatine kinase and LDH [45] and increased AST [47]. Such changes indicate cellular damage to the heart induced by nanoparticles, and the fluctuations in the indicators can be explained by different phases of the response to damage and dissimilar experimental conditions.

At the cellular level, the exposure to Pb NPs at 2.5 mg/kg b.w. resulted in some loss of myofibrils, destruction of the internal space of mitochondria and, as a consequence, a decrease in the strength of isometric contractions of isolated myocardial preparations [45]. This is consistent with the results of assessing mitochondrial function in rats – Ti and Zn NPs at doses of 10 mg/kg b.w. accelerated oxygen consumption by cardiac mitochondria, disuniting them. In addition, areas of sarcomere disorganization with a loss of ultrastructural alignment, small disorganized mitochondria, elementary particles and lysosomes inside, as well as signs of apoptosis were observed [48].

At the tissue and organ levels, the development of dystrophy was characteristic of both the heart and the liver: initial signs of myocardial dystrophy were noted following the exposure to Pb NPs at 2.5 mg/kg b.w. In the study of Cu NPs (100 mg/kg b.w.), pronounced myocardial hypertrophy, moderate congestion and severe focal necrosis of cardiomyocytes with inflammatory cellular infiltration were observed [47]. Fibrotic changes in the form of collagen accumulations were registered in one study (Zn and Ti NPs 10 mg/kg b.w.) [48], while another found no morphological changes in the heart structures after exposure to Ag NPs (0.5 mg/kg b.w.) [46]. This can be explained by the use of a polyethyleneglycol coating of Ag NPs, which mitigates the toxic effect of the latter on the organism. Yet, the rat exposure to Si NPs (without coating) at the dose of 500 mg/kg b.w. induced no significant changes,[5] possibly due to the experimental conditions.

Even small changes in the heart can provoke its functional disorders. Thus, at the organismal level, a tendency towards an increase in the QT interval, T wave amplitude, and QRS duration was observed in rats following the exposure to Pb NPs at the dose of 2.5 mg/kg b.w. [45]. Thus, NPs contribute to the development of cardiovascular diseases, thereby increasing the risks to population health.

Conclusions. The presented review of scientific literature systematizes and summarizes data on pulmonary, hepato- and cardiotoxic effects of nanoparticles at different levels of organization revealing nanoparticle exposure as a significant risk factor for population health. The review also highlights toxic effects of NPs by routes and levels of exposure and chemical nature of the toxicant determining the degree of risk of development and severity of induced pathological conditions.

The main mechanisms of toxicity include closely related direct damage, genotoxicity, mitochondrial damage, apoptosis, inflammation and oxidative stress: as a rule, nanoparticle exposure induces changes in the levels of damage biomarkers, geno- and cytotoxic phenomena, excessive ROS production, an increase in the levels of inflammation mediators and tissue damage, which can cause diseases not only of the organs under study, but also of some body systems. Assessment and analysis of the array of experimental studies on the potential risks of NPs at various structural levels can be used to identify patterns of such exposure and develop criteria and methods for hygienic assessment of risks to public health, as well as for further development of a system of preventive measures aimed at increasing the body resistance to toxic effects of nanoparticles on the lungs, liver, and heart.

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[5] Cao X., Xie B., Xu M., Li J., Dai X., Tian Y., Zhang J., Chen Y. [et al.]. Toxicity study of silica nanoparticles following 94-day repeated oral administration in Sprague Dawley rats: preprint (Version 1). *Research Square*, 2024. DOI: 10.21203/rs.3.rs-4531919/v1

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