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Research article

ASSESSMENT OF BIOACCUMULATION AND TOXIC EFFECTS OF COBALT (II) ALUMINATE NANOPARTICLES FOR HYGIENIC SAFETY PURPOSES

M.A. Zemlyanova[1,2], M.S. Stepankov[1], O.V. Pustovalova[1], A.V. Nedoshitova[1]

[1]Federal Scientific Center for Medical and Preventive Health Risk Management Technologies, 82 Monastyrskaya St., Perm, 614045, Russian Federation
[2]Perm State University, 15 Bukireva St., Perm, 614068, Russian Federation

Hygienic safety plays an important role in preventing health harm under chemical exposures. Hygienic regulation of levels of existing and new substances in environmental objects is the core element here carried out within experimental research aimed at establishing their toxic properties. Cobalt (II) aluminate nanoparticles ($CoAl_2O_4$ NPs) are a typical example of a new material with presumably higher toxic potential upon oral exposure as opposed to micro-sized particles (MPs). Given that, the development of safety standards requires identifying features of the negative impact of $CoAl_2O_4$ NPs, which are different from MPs upon oral exposure.

The study was performed on Wistar rats orally exposed to NPs and MPs for 20 days at the total dose of 10,550 mg/kg of body weight.

NPs have chemical composition similar to MPs, smaller size (87.11 times) and larger specific surface area (1.74 times). NPs have a more pronounced ability to bioaccumulate in the heart, lungs, liver and kidneys as compared to MPs (up to 7.54 times). Exposure to NPs resulted in more pronounced (up to 3.60 times) changes in blood indicators associated with developing redox imbalance, cytotoxic effect, liver, pancreas and kidney dysfunction, inflammatory process, and thrombocytopenia. NPs caused hemorrhagic infarcts and pulmonary edema not established upon MPs exposures. The calculated value of the tentatively permissible exposure level (TPEL) was 0.02 mg/dm^3 for these NPs content in drinking water, which is 10 times lower than the same value for MPs.

Thus, $CoAl_2O_4$ NPs upon oral exposure for 20 days at the total dose of 10,550 mg/kg of body weight have more marked bioaccumulation relative to MPs, which causes more pronounced negative effects identified by changes in blood indicators and developing pathomorphological changes. The study findings allow increasing accuracy and objectivity when developing safety standards for $CoAl_2O_4$ levels in food products and drinking water to ensure greater hygienic safety of the population.

Keywords: *hygienic safety, cobalt (II) aluminate, nanoparticles, microparticles, oral exposure, bioaccumulation, morphofunctional impairments, rats.*

New materials are being implemented in various economic activities everywhere. Given that, it is becoming especially relevant to develop essentials of hygienic safety to prevent health disorders among exposed population. Hygienic regulation of chemical levels in environmental objects is the core element; it should be based on results of experimental research aimed at investigating and estimating peculiarities of bioaccumulation and toxic effects of these new materials.

Nano-sized oxides with a spinel-like structure are a typical example of a new material, such as Al_2O_3 and CoO alloy as cobalt (II) aluminate nanoparticles ($CoAl_2O_4$ NPs). $CoAl_2O_4$ NPs are used as a pigment in various productions; as a catalyzer in chemical industry; as a component in microelectronics or

Marina A. Zemlyanova – Doctor of Medical Sciences, Chief Researcher with the duties of the Head of the Department of Biochemical and Cytogenetic Methods of Diagnostics; Associate Professor at the Department of Microbiology and Virology (e-mail: zem@fcrisk.ru; tel.: +7 (342) 236-39-30; ORCID: http://orcid.org/0000-0002-8013-9613).

Mark S. Stepankov – Junior Researcher at the Laboratory of Biochemical and Nanosensor Diagnostics (e-mail: stepankov@fcrisk.ru; tel.: +7 (342) 237-18-15; ORCID: https://orcid.org/0000-0002-7226-7682).

Olga V. Pustovalova – Senior Researcher at the Laboratory of Biochemical and Nanosensor Diagnostics (e-mail: pustovalova@fcrisk.ru; tel.: +7 (342) 237-18-15; ORCID: https://orcid.org/0000-0002-8050-7674).

Anna V. Nedoshitova – Senior Researcher at the Laboratory of Elemental Analysis Methods (e-mail: nedoshitova@fcrisk.ru; tel.: +7 (342) 237-10-37; ORCID: https://orcid.org/0000-0001-6514-7239).

production of construction materials; in casting processes in metallurgy[1] [1, 2]. At present, a possibility to use $CoAl_2O_4$ NPs in food industry is being investigating quite actively where the material can serve as supports for inulinase immobilization in sugar production by inulin hydrolysis [3] as well as a catalyzer in biofuel synthesis [4].

A wide range of possible applications in various industries and prospects of use in food industry create elevated risks of exposure to $CoAl_2O_4$ NPs for population including intake with foods. According to the data available in research literature and results obtained by our own experimental research, isolated $CoAl_2O_4$ NPs were established to mostly be able to penetrate through the gut-vascular barrier upon oral exposure and accumulate in target organs due to their smaller size against micro-sized particles (MPs) of chemical analogues [5, 6]. These NPs produce more substantial negative effects due to greater bioaccumulation and high reactivity. The results reported in these studies allow assuming that an alloy represented by $CoAl_2O_4$ NPs can be more toxic in comparison with its micro-sized chemical analogue. All this confirms the necessity to conduct experimental research aimed at establishing key peculiarities of toxicokinetics and toxicodynamics of $CoAl_2O_4$ NPs, which are different from those of MPs. The ultimate aim is to develop more precise and objective regulations of levels of the analyzed chemical in environmental objects.

In this study, our aim was to estimate peculiarities of bioaccumulation and toxic effects produced by $CoAl_2O_4$ NPs upon multiple oral exposures.

Materials and methods. $CoAl_2O_4$ NPs powder was used as a nanomaterial in experiments; it was synthesized by Giredmet JSC (Russia) by request from the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies. NPs were synthesized by the sol-gel process from nitro-acid 6-water cobalt (II) ($Co(NO_3)_2 \cdot 6H_2O$) and nitro-acid 9-water aluminum ($Al(NO_3)_3 \cdot 9H_2O$). A commercial MP powder produced by Khimkraft LLC (Russia) was used as a micro-sized chemical analogue.

Physiochemical properties of both materials (MPs and NPs) were compared to confirm the alleged chemical structure of the synthesized material and possibility to consider it a nano-material. The chemical structure of the alloy component was identified by x-ray spectral microprobe analysis; particle sizes were determined by analyzing images made with scanning electron microscopy; specific surface areas were identified in accordance with the Brunauer–Emmett–Teller methodology.

Experiments were conducted on female Wistar rats with average bodyweight of 244.4 ± 7.6. All experiments on animals were performed in conformity with the requirements fixed in the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (ETS № 123). The research was approved by the Ethics Committee of the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies. Prior to the experiments, all rats were acclimatized to keeping conditions for 14 days.

A median lethal dose (LD_{50}) upon single administration was established to determine an initial dose of the analyzed materials upon multiple oral exposures. To do that, an experiment was conducted to simulate an acute oral exposure in accordance with the State Standard GOST 32644-2014[2]. Three groups

[1] NN1948 Cobalt Aluminum Oxide Nano Powder. *Stanford Advanced Materials*. Available at: https://www.samaterials.com/micro-nano-materials/1948-cobalt-aluminum-oxide-nano-powder.html (November 06, 2023); Cobalt Aluminate Blue Spinel Nanopowder CoAl2O4 Size: 300-500 nm. *Nanografi*. Available at: https://nanografi.com/nanoparticles/cobalt-aluminate-blue-spinel-nanopowder-coal2o4-size-300-500-nm/ (December 06, 2023).

[2] GOST 32644-2014. OECD guidelines for the testing of chemicals. Acute oral toxicity – acute toxic class method: interstate standard, approved by the Interstate Council on Standardization, Metrology and Certification (the meeting report issued on March 28, 2014 No. 65-P). *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200115815 (March 18, 2024) (in Russian).

were made, 6 rats in each (exposure to NPs, exposure to MPs and controls). $CoAl_2O_4$ NPs and MPs were administered in a dose of 2000 mg/kg of body weight in a suspension based on bi-distilled water. The suspension was administered one time in a volume of 1 cm^3 through a probe made of stainless steel. The experimental animals were observed for 14 days after the exposure to estimate death rates in dynamics. According to survival rates, the LD_{50} value was > 2000 mg/kg of body weight.

Three groups, 10 animals in each, were created in the same manner to conduct experiments aimed at examining multiple oral exposures. Exposures were performed daily in accordance with the Methodical guidelines MU 1.2.2520-09[3] and the methodology developed by Lim with colleagues. Exposure duration was 20 days and the initial dose was 1/10 (200 mg/kg of body weight) of the established LD_{50}. The dose was increased by 1.5 times against the pervious one every 4 days. Therefore, the total NP and MP doses received by the experimental animals reached 10,550 mg/kg of body weight.

Blood samples were taken from the rats 24 hours after the last administration of the tested materials to examine their biochemical and hematological indicators. Organs were taken out to determine aluminum and cobalt levels and to identify pathomorphological changes in tissues.

Significant differences in biodistribution, bioaccumulation, biochemical and hematological blood indicators were established by the Mann – Whitney method using the U-test in STATISTICA 10. The results were considered significant at $p \leq 0.05$.

Tentative Allowable Levels (TALs) for $CoAl_2O_4$ NPs and MPs in drinking water were calculated using their toxicological hazard as a basic criterion in accordance with the Methodical guidelines MU 2.1.5.720-98[4].

Results and discussion. Comparative analysis of the chemical structure of the tested materials confirmed that they contained cobalt, aluminum and oxygen without any admixtures. This corresponds to the chemical formula stated by the manufacturers (Figure 1).

Examination of physical properties established that the nanopowder contained nano-sized particles (1–100 nanometers, 78.25 % of the total particle number), which were not found in the micropowder. NPs, as opposed to MPs, had 87.11 times smaller average size (52.12 / 4540 nanometers) and 1.74 times greater specific surface area (14.51 / 8.33 m^2/g). NP and MP images obtained with SEM are shown in Figure 2.

Upon multiple oral exposures, $CoAl_2O_4$ NPs were established to be distributed in the heart, lungs, liver, kidneys, brain and blood of the exposed rats. The total aluminum and cobalt levels were 1.57–242.69 times higher ($p = 0.002$) against the controls. Upon exposure to MPs, the total levels of the analyzed chemicals were 1.94–32.20 times higher ($p = 0.002$) in the foregoing organs and blood against the controls.

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[3] MU 1.2.2520-09. Toksikologo-gigienicheskaya otsenka bezopasnosti nanomaterialov: metodicheskie ukazaniya, utv. Rukovoditelem Federal'noi sluzhby po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka, Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii G.G. Onishchenko 05 iyunya 2009 g., vved. v deistvie s 05 iyunya 2009 g. [Toxicological and hygienic assessment of nanomaterial safety: Methodical guidelines, approved by G.G. Onishchenko, Head of the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing and RF Chief Sanitary Inspector on June 05, 2009, became valid on June 05, 2009]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200074057 (March 18, 2024) (in Russian).

[4] MU 2.1.5.720-98. Obosnovanie gigienicheskikh normativov khimicheskikh veshchestv v vode vodnykh ob"ektov khozyaistvenno-pit'evogo i kul'turno-bytovogo vodopol'zovaniya: metodicheskie ukazaniya, utv. i vved. v deistvie Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii 15 oktyabrya 1998 goda [Substantiation of safe standards for chemical levels in water supplied from water objects used for drinking and household purposes: Methodical guidelines, approved and enacted by the RF Chief Sanitary Inspector on October 15, 1998]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200006903 (March 18, 2024) (in Russian).

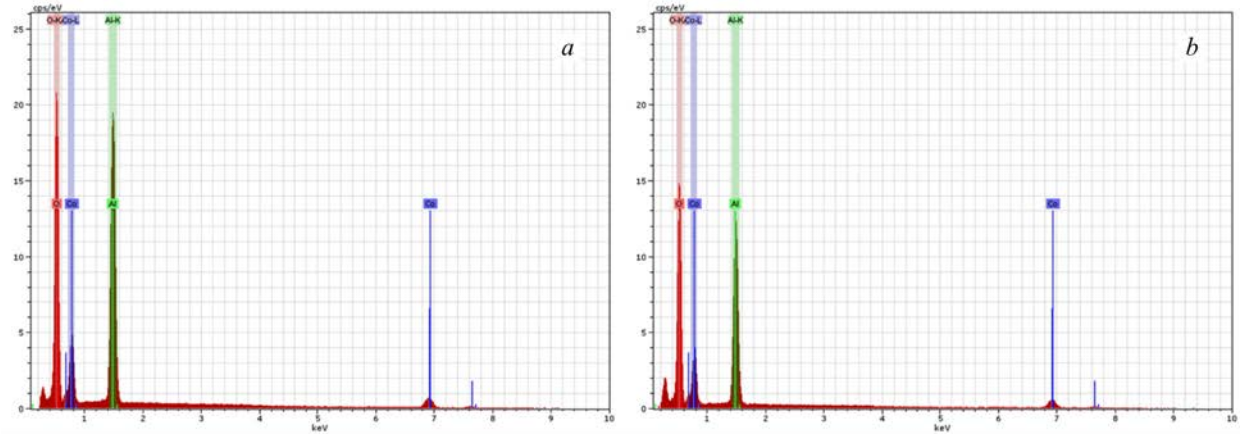

Figure 1. X-ray images of $CoAl_2O_4$ alloy samples: *a*, nano-sized; *b*, micro-sized

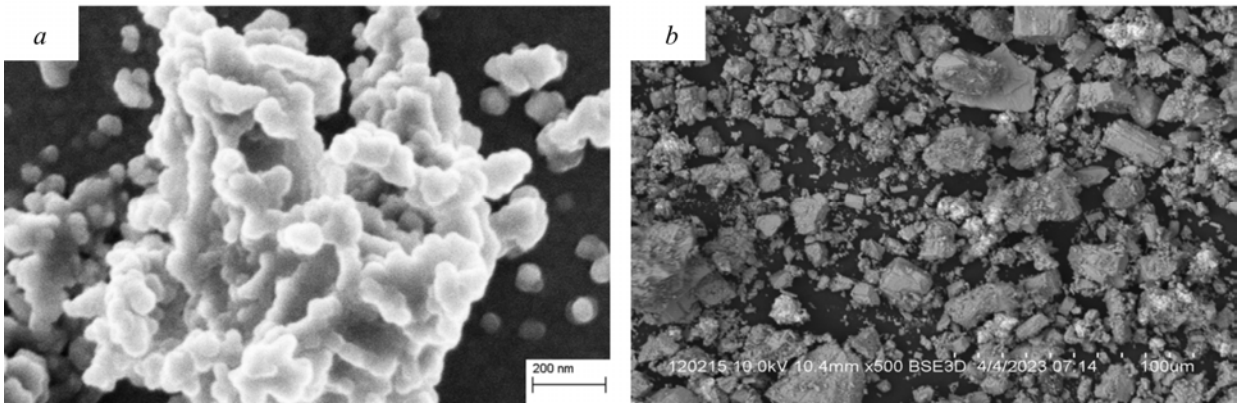

Figure 2. Images of $CoAl_2O_4$ alloy particles obtained by SEM: *a* is nanopowder; *b* is micropowder

Comparison of the obtained results established more marked bioaccumulation of $CoAl_2O_4$ NPs against their micro-sized chemical analogue judging from higher levels of aluminum and cobalt in the heart, lungs, liver and kidneys, 2.66 (p = 0.014), 7.54 (p = 0.001), 1.29 (p = 0.001) and 2.06 times (p = 0.001) respectively. The results of examining biodistribution and bioaccumulation are shown in Figure 3.

We established changes in biochemical blood indicators in the rats exposed to $CoAl_2O_4$ NPs, namely, 1.30–6.23 times higher activity of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), amylase, lactate dehydrogenase (LDH) and levels of creatinine, C-reactive protein (CRP) and malonic dialdehyde (MDA) (p = 0.002) as well as 1.99 times lower total antioxidant activity (AOA) (p = 0.005) against the controls. Exposure to the micro-sized chemical analogue led to 1.24–6.30 times higher activity of ALT, AST, GGT, amylase, and LDH and creatinine level (p = 0.002–0.012) as well as 2.31 times lower AOA (p = 0.002) against the same biochemical indicators in the control group. Comparative analysis of biochemical indicators established 1.37–2.25 times higher activity of ALT, AST, amylase, LDH and higher MDA levels (p = 0.001–0.014) upon exposure to NPs against MPs. The results of biochemical blood tests obtained for the experimental rats are shown in Figure 4.

Several changes were observed in hematological indicators in the rats exposed to NPs including 3.57–5.98 times lower platelet count (PLT), plateletcrit (PCT), and platelet large cell count (P-LCC) (p = 0.002) against the controls. These indicators were 1.66–1.79

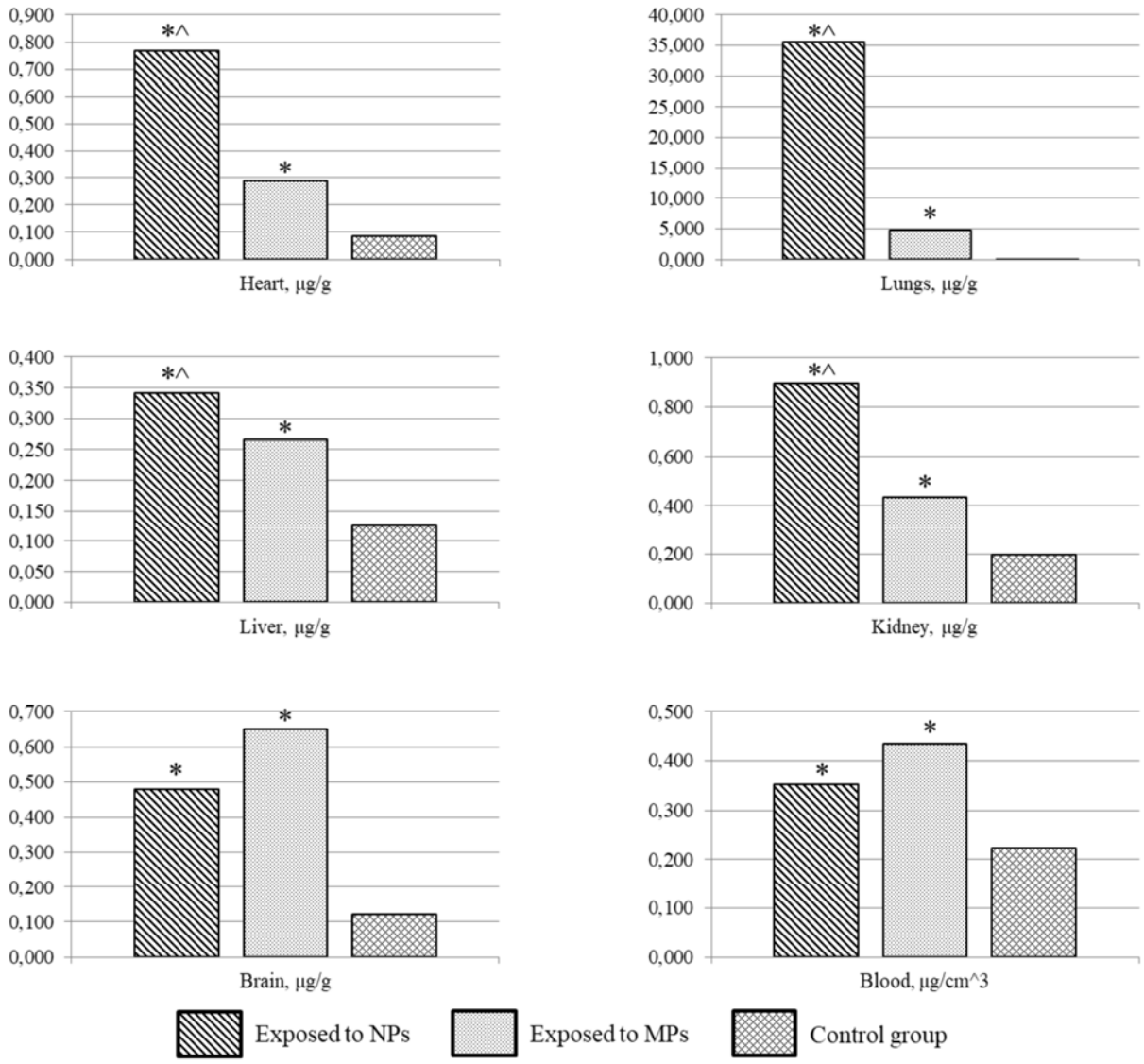

Figure 3. Total aluminum and cobalt levels in organs and tissues ($p \leq 0.05$): * means significant difference from the controls, ^ means significant difference from exposed to MPs

times lower in the rats exposed to MPs ($p = 0.045$). PLT, PCT, and P-LCC that were 2.00–3.60 times lower were a distinctive feature of effects produced by NPs on hematological blood indicators ($p = 0.001$–0.014). Figure 5 provides the results obtained by hematological blood tests.

We performed histological examination of organ tissues taken out of the rats exposed to NPs and MPs. As a result, pathomorphological changes were detected in the lungs, namely, focal interstitial pneumonia, bronchitis, vasculitis, and hyperemia; acute venous hyperemia was identified in the liver. Hemorrhagic infarctions and lung edemas were a distinctive feature upon exposure to NPs since they were not detected upon exposure to the micro-sized chemical analogue (Figure 6). We did not establish any pathomorphological changes in heart, kidney or brain tissues.

According to our calculations, TPEL of $CoAl_2O_4$ NPs amounted to 0.02 mg/md^3 and MPs 0.2 mg/dm^3 in drinking water per toxicological hazard they posed.

Analytical generalization of the results obtained by the experimental research established

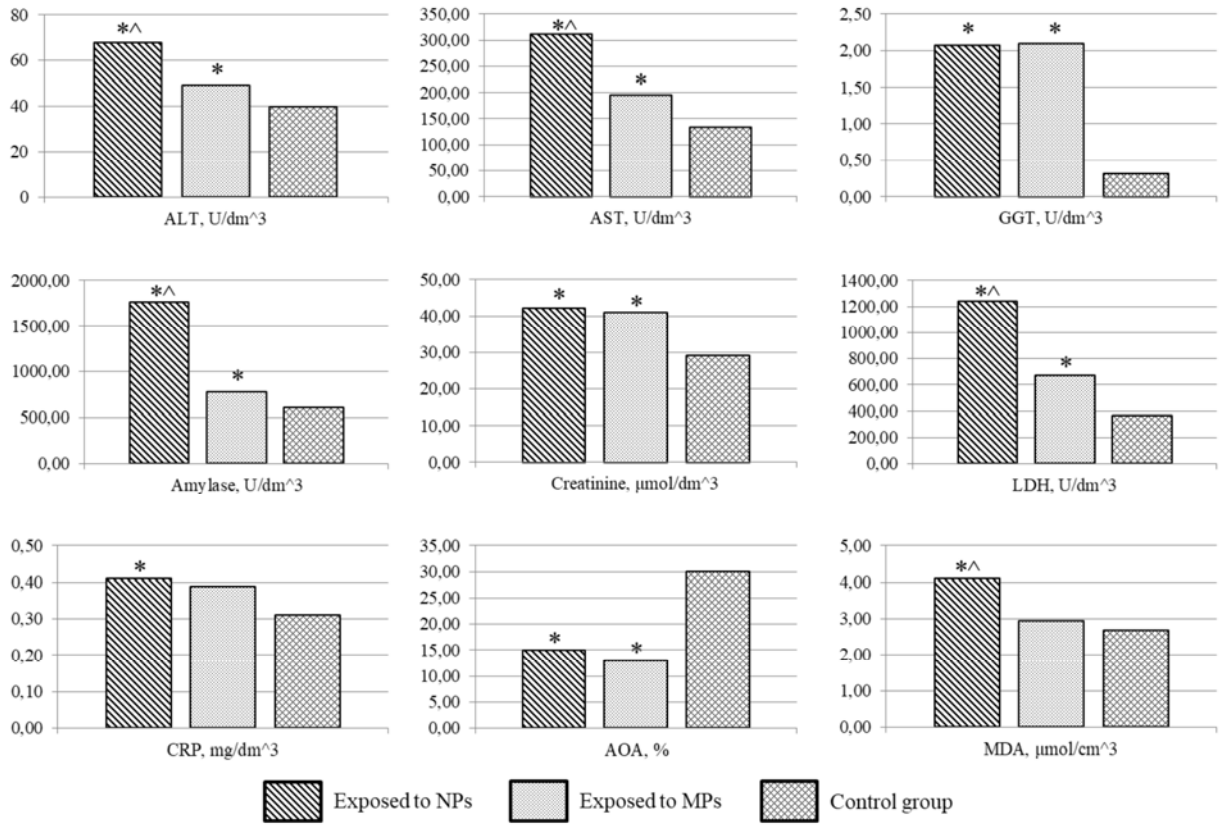

Figure 4. Biochemical indicators of rats' blood ($p \leq 0.05$): * means significant difference from the controls, ^ means significant difference from exposed to MPs

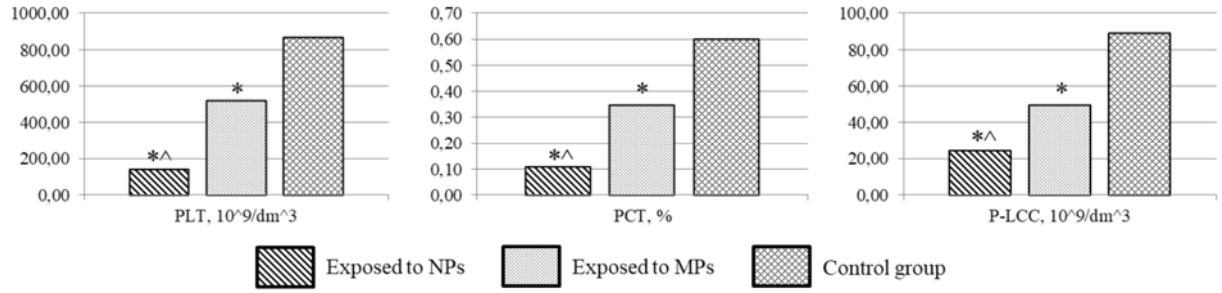

Figure 5. Hematological indicators of rats' blood ($p \leq 0.05$): * means significant difference from the controls, ^ means significant difference from exposed to MPs

that NPs of the tested $CoAl_2O_4$ powder had considerably different physical properties (up to 87.11 times) against their micro-sized chemical analogue as regards their size and specific surface area. This allows concluding that the tested nanomaterial is able to accumulate in target organs in larger quantities and induce more pronounced morphofucntional disorders [7, 8].

When considering a mechanism of $CoAl_2O_4$ NPs biodistribution and bioaccumulation upon oral administration, attention should be paid to solubility of the nanomaterial in the stomach, intestines, and blood. A study with its focus on examining cobalt bioavailability reported that levels of Co^{2+} ions did not exceed 0.1 % in artificial fluids that imitated gastric, intestine, and serum media after the tested alloy had been administered [9]. Low levels of Co^{2+} ions indicate that $CoAl_2O_4$ NPs are not soluble in the gastrointestinal tract or blood. Given that, increased aluminum and cobalt levels in organs

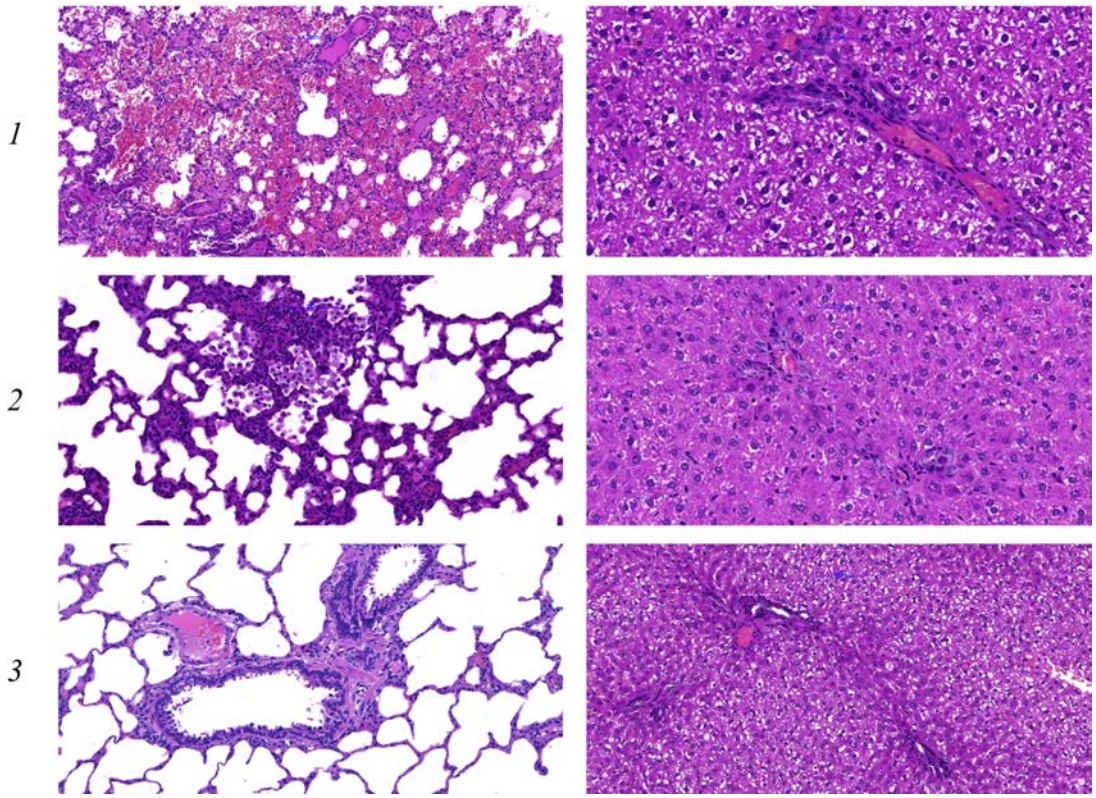

Figure 6. Microimages of tissue specimens of rats' lungs (*a*) and liver (*b*), hematoxylin and eosin stains, magnification 200x: 1 is exposed to NPs; 2 is exposed to MPs; 3 is the controls

are likely to be due to solid NPs without active participation of Al^{3+} and Co^{2+} ions in bioaccumulation.

Both $CoAl_2O_4$ NPs and MPs can penetrate through the gut-vascular barrier. This fact was evidenced by an increase in the combined aluminum and cobalt levels in the exposed rats' blood (~2 times against the controls). Blood flow carries NPs and MPs over the whole body where they are predominantly distributed in the heart, lungs, liver, kidneys, and brain (the total NP levels are up to 242.69 times higher and MP level up to 32.2 times higher against the control). NPs have a more pronounced ability to bioaccumulate (up to 7.54 times higher) in the heart, lungs, liver, and kidneys against their micro-sized analogue.

Scientific literature hardly contains any data on negative effects associated with exposure to $CoAl_2O_4$ NPs and mechanisms of their development. However, both in vitro and in vivo studies established that isolated Al_2O_3 and CoO NPs were able to stimulate generation of free radicals thereby inducing oxidative stress development [10–14]. Results reported in a study [15] also confirm this mechanism under exposure to an alloy of these two chemicals. Exposure to $CoAl_2O_4$ NPs reinforces oxidative reactions and inhibits recovery processes as evidenced by greater MDA activity and weaker AOA (~ up to 2 times against the control). Imbalance between oxidative reactions and recovery processes is more pronounced upon exposure to a nanomaterial against its micro-sized analogue (~ by 1.4 times), which may result in more marked cytotoxicity.

Greater cytolytic activity evidenced by more active LDH, ALT, and AST (up to 3.38 times against the control) indicates that cytotoxic effects develop under exposure to NPs and MPs. Changes induced by NPs are more pronounced (up to 1.85 times), which confirms their greater cytotoxicity against micro-sized materials. Changes in cell membrane per-

meability are a typical manifestation of cytotoxic effects produced by various nano-sized metal oxides [16]. An established increase in activity of such enzymes as ALT, AST and GGT in blood, which are normally localized in liver cells, can indicate increased permeability of hepatocyte membrane and, consequently, liver dysfunction [17–20]. Changes in indicators associated with hepatotoxic effects of $CoAl_2O_4$ NPs are more marked (up to 1.58 times) against influence exerted by MPs. Liver dysfunction may lead to weaker synthesis of thrombopoietin, which regulates platelet production [21]. This assumption is supported by thrombocytopenia that was established in exposed rats' blood and evidenced by lower PLT, PCT, and P-LCC (upon exposure to NPs, ~ up to 6 times against the control: upon exposure to MPs, ~ up to 2 times). Platelet indicators decreased more markedly upon exposure to NPs (up to 3.60 times against exposure to MPs). A reduction in PLT in blood can have negative effects on angiotropic, adhesive-aggregation, and fibrinolytic processes as well as immunity[5].

Cytotoxic effects caused by redox imbalance can manifest themselves as an inflammation, which is induced by pro-inflammatory cytokines released from cells due to oxidative damage done by free radicals [22]. In this study, developing inflammation was identified per growing CRP levels in blood of the rats exposed to NPs (1.3 times higher against the control) whereas exposure to MPs did not cause any significant changes in the indicator. Studies [23–25] highlight the role of inflammatory changes associated with oxidative stress in impaired functioning of the pancreas and kidneys. This is consistent with established growing activity of amylase and creatinine upon exposure to NPs and MPs (up to 2.91 and 1.41 times respectively against the controls). Effects produced by the analyzed nanomaterial on the pancreas functioning were more marked relative to effects of MPs (by 2.25 times).

$CoAl_2O_4$ NPs and MPs produce negative effects at the tissue-organ level manifested as inflammation and disrupted circulation. Exposure to NPs induces more marked disruptions of circulation in the lungs, which was evidenced by hemorrhagic infarctions and edemas. No such effects were observed in the rats exposed to MPs. This may be associated with greater NP cytotoxicity. Pro-inflammatory cytokines released from cells under exposure to NPs can increase permeability of vascular endothelium, which results in blood exudation into an organ [26, 27]. Therefore, processes that make for circulation disruptions become more pronounced as cytotoxic effects are aggravated.

The valid sanitary rules and norms[6] do not stipulate maximum permissible levels or TPEL in drinking water either for NPs or MPs of $CoAl_2O_4$ alloy. Calculated TPEL amounted to 0.2 mg/dm^3 for micro-sized particles. Considering unique physical property and more pronounced toxicity of NPs against MPs, it is advisable to reduce this calculated value by 10 times (0.02 mg/dm^3).

Conclusion. According to the results of the present study, $CoAl_2O_4$ NPs have smaller sizes (87.11 times) and greater specific surface area (1.74 times) against their micro-sized chemical analogue. Due to these properties, they have greater ability to bioaccumulate in the heart, lungs, liver and kidneys (up to 7.54 times) upon oral administration into the body during 20 days in the total dose of 10,550 mg/kg. Greater NPs bioaccumulation creates more pronounced negative effects

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[6] SanPiN 1.2.3685-21. Gigienicheskie normativy i trebovaniya k obespecheniyu bezopasnosti i (ili) bezvrednosti dlya cheloveka faktorov sredy obitaniya (s izmeneniyami na 30 dekabrya 2022 goda), utv. postanovleniem Glavnogo gosudarstvennogo sanitarnogo vracha Rossiiskoi Federatsii ot 28 yanvarya 2021 goda № 2 [Hygienic standards and requirements to providing safety and (or) harmlessness of environmental factors for people (as of December 30, 2022), approved by the Order of the RF Chief Sanitary Inspector on January 28, 2021 No. 2]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/573500115 (March 19, 2024) (in Russian).

such as intensified oxidation (~ 1.4 times higher), cytotoxicity (up to 1.85 times higher), liver (up to 1.58 times higher) and pancreas dysfunction (2.25 times higher), thrombocytopenia (up to 3.60 times higher), and inflammation (1.30 times higher). NPs induce more marked disruptions of circulation in the lungs manifested as hemorrhagic infarctions and edema. TPEL for the analyzed nanomaterial calculated relying on its toxicological hazard is equal to 0.02 mg/dm^3 in drinking water, which is tenfold lower than this value calculated for MPs.

The study findings allow increasing accuracy and objectivity when developing safety standards for $CoAl_2O_4$ NPs levels in food products and drinking water to ensure greater hygienic safety of the population.

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Competing interests. The authors declare no competing interests.

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