

Ecological and toxicological characteristics of selenium nanocompounds

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The toxicity of selenium and probiotic preparations by intragastric administration to laboratory animals (white rats), weight coefficients of their internal organs, hematological parameters of blood were determined. The studies were performed on three groups of white rats, which for thirty days received sodium selenite with probiotics and bionanoselenium at doses of fed drugs 1000, 3000, and 5000 mg/kg. We considered physiological parameters, namely, appearance, condition of fur and visible mucous membranes, behavior, rhythm, respiratory rate, attitude to food, time of onset and nature of intoxication, severity, course time of death, or recovery. Studies have shown the absence of death of animals or diseases with intragastric use of the studied drugs, which allows them to be classified as toxicity class 4 – low-toxic substances. At autopsy of the internal organs of the thoracic and abdominal cavities, no pathological changes were detected, and no significant changes in the weight of the liver, heart, lungs, and kidneys, compared with the control group, for 30 days of study supplemented with a simultaneous increase in spleen weight. No signs of inflammation, circulatory disorders, and trophies were found in the parenchymal organs. Long-term admission of the studied drugs caused a probable increase in hematological parameters (hemoglobin concentration, number of erythrocytes and leukocytes, hematocrit) in the experimental animals. 30-day application of nanoselenium caused an increase in total protein content in animals of the experimental groups by 7.9–11.5% ($p < 0.05$) compared with the control group. There was a probable increase ($p < 0.01$) in urea levels. The use of therapeutic, 5-fold and 10-fold therapeutic doses caused an increase in the content of total cholesterol and medium-weight molecules compared to the control group. The use of nanoselen did not cause significant changes in transaminase activity and glucose levels. The conducted primary toxicological study is the basis for developing and using low-toxic, effective, and environmentally friendly drugs for industrial poultry and livestock that do not cause side effects.

Keywords: nanopreparations, nanoselenium, sodium selenite, white rats, hematological parameters, blood biochemical parameters

Introduction

In recent years, researchers have shown considerable interest in obtaining and using in medicine and agriculture nanosized particles of several elements of both metallic and nonmetallic nature, particularly selenium. A promising direction is the development of a methodology for obtaining nanosized selenium-containing drugs and establishing the possibility of their use due to the presence of unique and specific therapeutic properties in medicine, biology, and animal husbandry. Vast new possibilities for the use of selenium have been reported, including the development of new types of bioadditives for animals and poultry (Yang et al., 2021). Selenium nanoparticles have advantages over other used forms of selenium because several properties characterize them due to the ability to diffuse solubility, immunogenicity, and less toxicity. They have different biological effects than traditional selenium preparations due to their high surface area to volume ratio, have a more comprehensive range of nontoxic doses, and can affect metabolic processes at a new angle according to the characteristics of the nanoparticles used. This allows us to significantly optimize selenium therapy and make it more effective due to the inclusion of selenium in the composition of selenoproteins, which are involved in some biochemical processes in the body. Selenium nanoparticles can also be used in new diagnostic methods and techniques for the early diagnosis of diseases. Today, the

auspicious synthesis of nanosized selenium particles is "green synthesis," which is the most variable among the existing physical and chemical synthesis methods. There are ample opportunities to control the formation of nanosized selenium particles according to selenium therapy needs.

Industrial poultry farming of meat and productive egg areas is characterized by a high growth rate and a significant need for a balance of feed components. Such features cause the high sensitivity of the bird to the action of stress factors, especially during the formation of adaptation mechanisms. Traditional food antioxidants can intensify metabolic processes, promoting the growth and preservation of poultry. However, their use is limited due to the individual characteristics of the drugs (narrow range of nontoxic doses, difficult assimilation of inorganic forms of drugs, and difficulty regulating the biological effect of organic forms). Substantiation of the use of a new generation of antioxidant drugs in poultry feeding, in particular, requires the study of synthesized drugs in laboratory animals to establish safe, nontoxic doses of drugs.

Nanotechnology is an interdisciplinary field that includes the synthesis, characterization, and application of nanomaterials – nanoobjects with a size range from 1 to 100 nm, in at least one dimension, which have specific properties in terms of size, shape, porosity (Israel et al., 2019; Tsekhmistrenko et al., 2020a).

The metalloids selenium (Se) plays a significant role in the regulation of redox processes in the cell and, according to modern ideas, taking into account the achievements of "omics" technologies (Misra et al., 2019), is a component of the redox interface through which the body interacts with environmental signals (exposome) and responds accordingly, maintaining homeostasis at the level of epigenome, genome, metabolite, and exposome. Selenium is present in two forms in eukaryotic proteins in the rare amino acids selenocysteine (SeCys) and selenomethionine (SeMet). The number of selenoproteins (selenoproteomes) may differ in different species of living organisms, among which the most studied are selenoproteins, glutathione peroxidase and thioredoxin reductase (Tsekhmistrenko et al., 2020c).

The addition of nano-Se is used in poultry diets to monitor the intensity of growth, redox, and immune processes (Alagawany et al., 2021; Tsekhmistrenko et al., 2020b). The addition of nanoselenium improves the reproductive performance of poultry (Elkazaz et al., 2020;). Nano-Se showed better results in terms of weight gain compared to sodium selenite in the diets of broilers. Similar results were also observed when 0.3 mg/kg Se in the form of nanoelement Se, sodium selenite, or selenium-containing yeast were added to the main diet (Boostani et al., 2015; Tymoshok et al., 2019). The combination of probiotics and Se nanoparticles has also been shown to improve growth, skeletal muscle fatty acid profile, and serum α -tocopherol content in broilers (Dalia et al., 2020).

Se and nano-Se Organic compounds showed similar improvements in growth rate, post-mortem meat, and carcass performance in broilers, but more intensely than inorganic compounds of selenium. Surai et al. (2017) found a significant increase in weight gain, preservation, and improvement of feed conversion rate by supplementation with various sources of Se compared to controls. The effect of nano-Se supplementation on growth, carcass color, and index of immune organs (thymus, spleen, and bursa) in broilers has been established.

There is current information about metalloids selenium's unique properties, particularly its antioxidant, antiapoptical, antigenotoxic, anti-inflammatory, antitumor, and immunomodulatory activities. Selenium is needed to maintain homeostasis, and deficiency provokes many diseases (Arnaut et al., 2021). The participation of the element in the formation of hormones and nucleic acid metabolism has been established.

Recently, it has been reported that biogenic selenium nanoparticles obtained by "green" chemistry with lactobacilli affect the redox-sensitive transcription factor Nrf2, which activates the transcription and synthesis of some antioxidant and detoxifying enzymes (Tu et al., 2019; Staurengo-Ferrari, 2019; Bityutsky et al., 2020; Panieri et al., 2020).

The biosafety of nanomaterials is multifaceted and ambiguous, requiring a comprehensive, safe, responsible, and scientifically sound approach (Kaphle et al., 2018). The application of new drugs in industrial poultry farming, especially of nanobiotechnological origin, requires detailed control, which is carried out according to the GLP system and the standard developed by the State Research Control Institute of Veterinary Drugs and Feed Additives. According to these documents, the main provisions on the state of biosafety of the drugs used, in particular the establishment of their toxicity, are regulated. Implementing primary toxicological studies is crucial because it determines both the successful development of clinical and experimental studies and affects the possibility of the synthesis of a modern, high-intensity, environmentally friendly, nontoxic drug that does not cause side effects.

The study aimed to investigate the toxicity of selenium and probiotic drugs by intragastric administration to laboratory animals. The task of the study was to study the acute and subacute toxicity of intragastric administration of selenium compounds to laboratory animals (rats); to determine the weight coefficients of the internal organs of white rats at the introduction of different doses of nanoselenium; to analyze the hematological and biochemical parameters of the blood of white rats on the 30th day of the experiment.

Methods

Research to develop a technology for obtaining and studying the effects of biologically active substances in poultry was conducted in the Research Institute of Ecology and Biotechnology of Bila Tserkva National Agrarian University. One of the areas is the research in nanotechnology, which is conducted in conjunction with the Institute of Microbiology and Virology named by D.K. Zabolotny National Academy of Sciences of Ukraine, where the Department of Interferon and Immunomodulators developed a technology for obtaining a new multifunctional antioxidant – nanoselenium "Nano", obtained by the method of "green" synthesis using *B. subtilis* IMV B-7392.

The parameters of acute toxicity of sodium selenite with probiotic and bionanoselenium were studied on white rats aged 2–3 months, weighing 180–200 g. The studied feed additives were administered intragastrically once.

To determine the toxicity of the feed additive "Nano" for white rats, doses of 1000, 3000, and 5000 mg/kg of animal body weight were taken. 6 laboratory animals were used for each dose. A dose of 5000 mg/kg body weight of the animal was readministered to twice the number of animals.

After introducing the studied feed additive "Nano", observations of laboratory animals were carried out for 14 days. The following indicators were taken into account: appearance, behavior of animals, condition of fur, visible mucous membranes, attitude to food, rhythm, respiratory rate, time of occurrence and nature of intoxication, its severity, course, time of death of animals or their recovery.

In the study of subacute toxicity, there were guided by the results obtained during acute toxicity. The studied feed additive "Nano" was administered intragastrically daily for 30 days. The clinical condition and behavior of the animals were observed during the experiment. Subacute toxicity was studied in 24 white rats weighing 200–220 g. For this purpose, a control and three experimental groups of animals, six rats in each, were formed according to the principle of analogs. Animals in the control group were injected with drinking water. Animals of the 1st experimental group were fed a bionanoselenium feed additive at a therapeutic dose of 0.05 g/kg body weight, the 2nd experimental group was given a five-fold therapeutic dose of 0.25 g/kg, and the 3rd experimental group was given a ten-fold therapeutic dose of 0.5 g/kg body weight. In a subacute experiment, the drug was administered to rats for 30 days. The next day after administration, laboratory animals under light ether anesthesia were decapitated, blood samples were taken, hematological studies were performed according to generally accepted methods, and dissected, and organ mass ratios were determined.

For hematological studies, we used blood-stabilized EDTA. In stabilized blood, hemoglobin content, number of erythrocytes, hematocrit, number of leukocytes, mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration (MCHC) were determined by hematology analyser Mythic-18.

Statistical processing of the obtained results was performed by method of variable statistics using Student's t-test.

Toxicological studies of drugs were performed on the scientific basis of the vivarium of the certified Laboratory of pharmacology and toxicology, entered in the Register of the certification system of the State Scientific-Research Control Institute of Veterinary Medicinal Products and Feed Additives (SCIVP), Lviv.

Results and Discussion

The introduction of new drugs into agricultural production, particularly of biotechnological origin, requires strict control, which must be carried out according to the GLP system and the standard. The current standard developed by SRCI for veterinary drugs and feed additives regulates the introductory provisions on the safety of the drugs used and the determination of their toxicity (acute and subacute).

Their administration determined the acute toxicity of selenium nanocompounds to white rats. Intragastric administration of feed additives of sodium selenite with probiotics and nanoselenium was found that their use in doses of 1000, 3000, and 5000 mg/kg did not cause death and disease of laboratory animals. During the 14-day observation, laboratory animals were active, had a satisfactory appetite, and no changes in animal behavior were detected.

Intragastric use of sodium selenite with probiotics and bionanoselenium in the above doses did not cause the death of animals or diseases, according to the classification of substances by toxicity (SOU 85.2-37-736: 2011), allowed to classify the studied drugs to toxicity class 4 - low toxicity.

In a subacute toxicity experiment, white rats were injected intragastrically into white rats for 30 days daily. The clinical condition and behavior of the animals were monitored. During the experiment, the death of laboratory rats was not established.

An essential role in studying the toxicity of drugs is to determine the coefficients of the mass of internal organs (Fig. 1). As it can be seen from the data, 30-day-long use of the studied feed additives did not cause significant changes in the weights of the liver, heart, lungs, and kidneys. The animals of the experimental groups showed an increase in the weight coefficient of the spleen, respectively, by 8.4%, 17.2 (p < 0.05), and 26.5% (p < 0.05), compared with the control group.

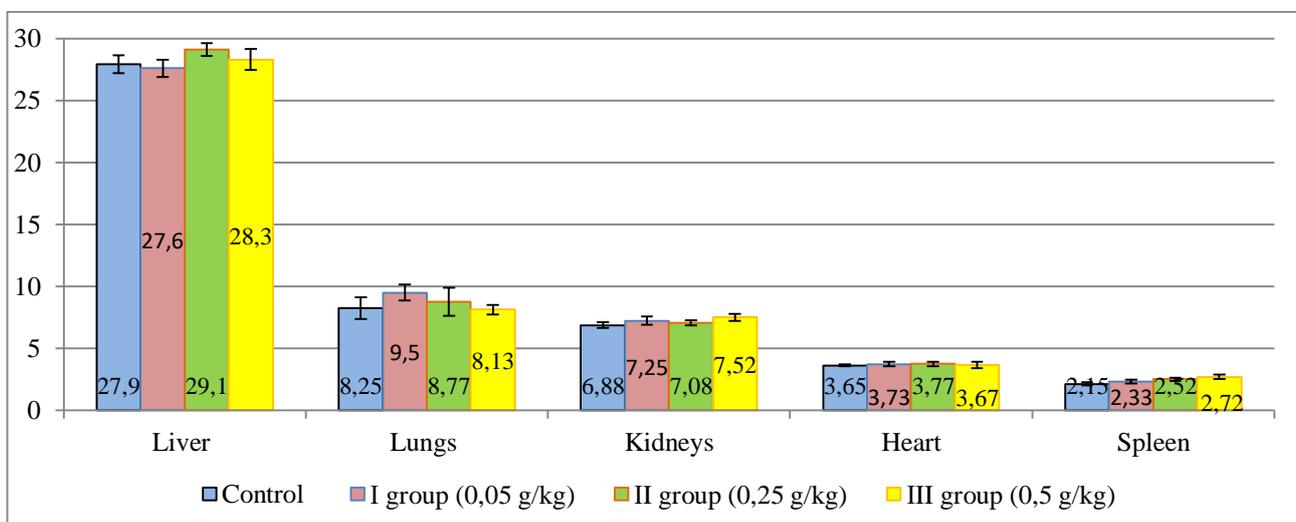


Fig. 1. Weight coefficients of the internal organs of white rats on the 30th day of the experiment, $M \pm m$, $n=6$

At autopsy, no pathological changes in the internal organs of the thoracic and abdominal cavities were detected. All organs had the correct anatomical location, standard color, and consistency. No signs of inflammation, circulatory disorders, and tropism were found in the parenchymal organs. The mucous membrane of the stomach and intestines at the time of examination was of standard color with a characteristic relief without signs of edema, erosion, and inflammation.

Long-term admission of the study agent caused in animals of the first experimental group a probable increase in hemoglobin concentration by 10.7%, erythrocyte count by 12.8%, leukocyte count by 55.2%, hematocrit by 9.4% ($p < 0.05$), compared to the indicators of the control group (Table 1). There was a slight decrease in the average content of hemoglobin in the erythrocyte (MCH), the average concentration of hemoglobin in the erythrocyte (MCHC) and the number of platelets.

Table 1. Hematological parameters of the blood of white rats on the 30th day of the experiment, $M \pm m$, $n=6$

Indexes	Groups of animals, the dose of nanoselenium			
	Control	1 st group 0.05 g/kg body weight	2 nd group 0.25 g/kg body weight	3 rd group 0.5 g/kg body weight
Hemoglobin, g/l	158.6±2.98	175.5±7.5*	167.7±0.88	172.7±5.36
Erythrocytes, T/l	7.68±0.23	8.66±0.03*	8.03±0.1	8.65±0.23*
Leukocytes, g/l	7.54±0.15	11.7±1.50**	12.1±0.98***	10.8±1.92
Hematocrit, %	39.4±0.66	43.1±0.97*	41.7±0.38	43.1±0.97*
MCH, pg	20.7±0.26	20.3±0.8	20.9±0.23	19.9±0.38
MCHC, g/dl	40.2±0.19	39.9±0.4	40.2±0.19	40.0±0.44
MCV, μm^3	51.4±0.86	50.8±1.55	51.9±0.44	49.9±1.04
Platelets	799.2±18.1	619.0±120	490.7±52.6***	578.7±148.2

In addition, animals of the 2nd and 3rd experimental groups showed an increase in the concentration of hemoglobin, respectively, by 5.74 and 8.9%, the number of erythrocytes – by 4.56 and 12.6%, leukocytes – by 60.5 and 43.2%, hematocrit values – by 5.8 and 9.4%, compared with the control group. There was also a slight decrease in the average hemoglobin content in the erythrocyte (MCH), the average concentration of hemoglobin in the erythrocyte (MCHC) and the number of platelets. However, these changes were unlikely. No significant changes were found in the leucoform of white rat blood on the 30th day of the experiment (Fig. 2). Eosinophils were not detected in animals of the 1st and 3rd groups.

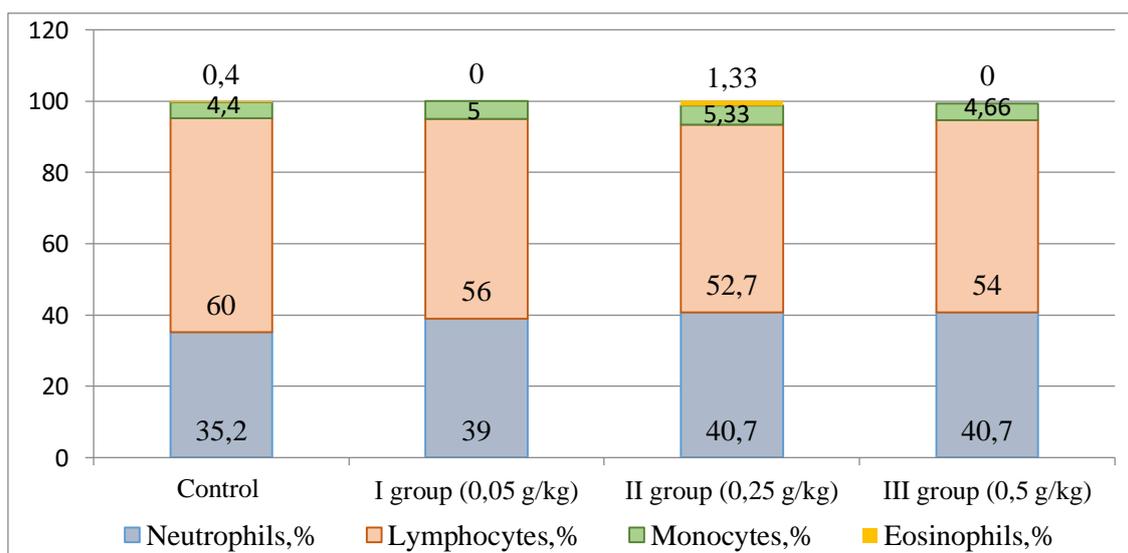


Fig. 2. Leukoformula of white rat blood on the 30th day of the experiment, $M \pm m$, $n=6$

Data from the biochemical study of blood serum of white rats are shown in Table 2. As it can be seen from the presented data, that 30-day-long use of nanoselenium caused an increase in total protein in animals of the 1st, 2nd, and 3rd experimental groups by 7.9%, 9.6 and 11, 5% ($p < 0.05$) compared with the control group. There was a significant increase ($p < 0.01$) in urea levels by 58.8%, 69.1, and 84.7%.

Table 2. Biochemical parameters of the blood of white rats on the 30th day of the experiment, M±m, n=6

Indexes	Groups of animals, the dose of nanoselenium			
	Control	I st group 0.05 g/kg body weight	II st group 0.25 g/kg body weight	III st group 0.5 g/kg body weight
Total protein, g/l	69.5±2.7	75.03±2.34	76.2±0.3	80.0±0.2*
Urea, mmol/l	3.86±0.46	6.13±0.41***	6.53±0.24**	7.13±0.14***
Creatinine, µmol/l	69.4±2.11	67.1±0.79	60.9±3.11	71.7±5.22
AST, U/l	185.2±3.27	167.5±20.5	181.9±3.95	186.3±41.1
ALT, U/l	51.3±2.63	67.3±6.31*	56.5±5.06	72.1±6.88*
Alkaline phosphatase, U/l	206.7±17.8	384.3±12.3***	342.5±29.4**	328.9±28.9**
Total cholesterol, mmol/l	1.18±0.06	1.41±0.11	1.99±0.39*	2.01±0.49
MMM, g/l	0.59±0.06	2.17±0.71*	2.46±0.15***	2.27±0.27***
Glucose, mmol/l	5.18±0.25	4.83±0.48	5.57±0.29	5.53±0.15

In the case of determining the enzymatic activity of serum in animals of the experimental groups, it was noted an increase in ALT activity by 31.2% ($p < 0.05$), 10.1 and 40.5% ($p < 0.05$) and alkaline phosphatase activity by 85, 9% ($p < 0.001$), 65.7 ($p < 0.01$) and 59.1% ($p < 0.01$), respectively to the groups.

In addition, it was noted that the use of therapeutic, 5-fold and 10-fold therapeutic doses caused an increase in total cholesterol by 19.5%, 68.6 ($p < 0.05$) and 70.3% and middle mass molecules (MMM) – by 21.8% ($p < 0.05$), 23.9 and 25.9% ($p < 0.001$) compared with the control group. It was found that the use of the study drug did not cause significant changes in the activity of AST and glucose levels.

Thus, the conduct of primary toxicological studies is a crucial link that determines the possibility of creating and using competitive, low-toxic, highly effective, environmentally friendly drugs that do not cause side effects.

Conclusion

The low-toxic effect (toxicity class 4 - low-toxic substances) of selenium preparations on experimental rats was experimentally established. It is proved that the introduction of the studied supplements for 30 days provides a significant increase in the specific hematological parameters of the blood of experimental animals and the absence of significant changes in the weights of their internal organs. Significant differences in the mass of internal organs: liver, lungs, heart, and kidneys were not detected, indicating the absence of toxic effects of nonoselenium in different doses on these organs.

Strict EU requirements prohibit the use of antibiotics and antioxidants in industrial poultry farming, so new nanoscale selenium preparations and probiotics may be an alternative. In further research, it is appropriate to study the effect of nanopopulation additives on the quality of poultry products.

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