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Ecotoxicological assessment of nanocrystalline cerium dioxide preparations

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Cerium is the most common rare earth metal and an element of industrial importance. Cerium dioxide (CeO2) is the best-known cerium compound, due to its unsurpassed redox properties and ability to guarantee excellent oxygen mobility. Upon conversion to a nanocrystalline state, the compound significantly alters its physicochemical properties, which determine the material's unique biological activity.

Recent literature reports the use of metal nanoparticles, especially cerium, as new natural feed additives in animal husbandry to increase productivity. However, there are still insufficient reports on the toxicodynamics and toxicokinetics of nanoparticles in humans and animals, as well as their environmental impact. Nanoparticles may have toxic effects because they can penetrate cells, bypass barriers such as the respiratory, dermal, gastrointestinal, blood-brain, and placental barriers, and selectively accumulate in cells and subcellular structures.

The aim of the research was to determine the acute and chronic toxicity of nanodispersed cerium dioxide obtained by the employees of the Nanomedtech laboratory (Kyiv, Ukraine) and the Department of Interferon and Immunomodulators of the D.K. Zabolotny Institute of Microbiology and Virology.

The results of the study of biochemical blood parameters showed that the research compound, after 10 days of daily administration, affected the functional state of the liver, as evidenced by impaired hepatocytes and a significant increase in transaminase activity and the mass coefficient of this organ. Hypertriacylglycerolemia, which is observed in organ lesions, also indicates impaired liver function.

As a result of studying the toxic effects of NDC, administered daily to white rats for 10 days, it was found that the compound suppressed erythro- and leukocytopoietic functions of the hematopoietic organs, regardless of dose. It caused depletion, especially in the bone marrow, and reduced body reactivity, affecting the liver and spleen. Inflammatory processes, both acute and chronic, occurred under the compound's influence. These compounds also affected some aspects of lipid metabolism and the liver's functional state, possibly increasing the liver's mass coefficient and the activities of ALT and AST.

Keywords: nanocompounds, cerium dioxide, toxicity, rats, blood, internal organs, biochemical parameters.

Problem statement and analysis of recent research. Nanodispersed cerium dioxide is currently included in the top ten priority nanomaterials by experts from the Interagency Programme on the Sound Management of Chemicals (IOMC) and the Organization for Economic Co-operation and Development (OECD) [13]. Cerium is the most common rare earth metal and an element of industrial importance. Cerium dioxide (CeO2) is the best-known cerium compound, due to its unsurpassed redox properties and ability to guarantee excellent oxygen mobility [24]. It is a powerful oxidant used in catalysis and medicine.

The interest in studying cerium dioxide stems from the fact that, upon transitioning to the nanocrystalline state, its physicochemical properties change significantly [1; 23]. In particular, as particle size decreases, the unit cell parameter of CeO2 increases. At the same time, a change in the oxygen non-stoichiometry of cerium dioxide is observed, due to an increase in the fraction of atoms at the particle surface, which alters its electronic and electrophysical properties [28].

The pronounced influence of size on the physicochemical properties of nanodispersed cerium dioxide determines its unique biological activity [21]. Low toxicity and high oxygen non-stoichiometry define the prospects and features of its application [2; 9; 15; 29]. Low toxicity ensures the comparative safety of cerium dioxide nanoparticles *in vivo*. High oxygen non-stoichiometry drives the activity of nanodispersed CeO2 in cellular redox processes, especially in the inactivation of active oxygen species [15; 21; 28]. CeO2 can regenerate its oxygen non-stoichiometry [3; 6; 15], returning to its original state shortly after redox participation. This enables repeated use of cerium dioxide nanoparticles [13; 28; 30].

Because of their small size, nanoparticles easily enter the body through the respiratory, digestive, and skin systems. Their large surface area per unit mass causes more pronounced biological activity [21; 28].

Despite the risks, nanotechnologies are widely used in all branches of industry and agriculture [4; 7; 12; 14; 19]. Once inside a biological system, nanoparticles face various physical and chemical features of the organism. These features affect nanoparticle properties and can change the organism's response [15; 20]. The ability to undergo a redox cycle between two natural oxidation states (Ce3+ and Ce4+) [30] is a key factor. However, it was previously believed that CeO2 nanoparticles are stable [23] and only poorly soluble [20] or insoluble under environmental conditions. Solubility depends on the carrier, pH, and particle size. The dissolution of nanoparticles depends on the ratio of Ce3+ to Ce4+ on their surface [20]. As nanoparticle size decreases, they become less oxygen-vacancy-rich in their lattice, locally reducing the amount of Ce4+.

In recent years, the literature has reported the use of metal nanoparticles, particularly cerium, in animal husbandry as new natural additives to feed to increase animal productivity [4; 8; 12; 14].

The effect of nanocrystalline cerium dioxide has been studied, and the lethal and semi-lethal compound doses have been established. The LD50 of nanocrystalline cerium dioxide exceeds 2000 mg/kg, confirming that this compound belongs to toxicity class V and indicating very low toxicity [9; 29]. The positive antibacterial potential of CeO2 nanoparticles against poultry pathogens has been revealed [17].

The high biocompatibility, low toxicity, and catalytic activity of nanodispersed cerium dioxide make it a promising nanobiomaterial for use in biology, medicine, and agriculture [6; 11]. However, the mechanisms underlying its biological activity are currently poorly understood and require further research.

Widespread use of metal nanoparticles and their oxides is impossible without assessing their potential impact on end consumers [10; 25]. The biosafety of nanomaterials is multifaceted and ambiguous, requiring a comprehensive, safe, responsible and scientifically sound approach. Currently, there are insufficient reports on the toxicodynamics and toxicokinetics of nanoparticles in humans and animals, as well as their impact on the environment [10; 22]. For this purpose, it is necessary to systematize information on the relationships between nanoparticle toxicity and their composition, concentration, size, shape, reactivity, etc. [16]. It is important to investigate the molecular mechanisms underlying the impact of nanoparticles on the body, organs, tissues, and cells, the mechanisms underlying the development of remote toxic effects, and ways to eliminate or reduce their undesirable effects. Such studies are possible when using key systemic characteristics of biological systems under *in vivo* and *in vitro* conditions (physiological, biochemical, immunological, genetic, cytological, etc.) sensitive to toxic effects [18]. The toxic effects of nanoparticles may be due to their ability to penetrate cells, bypassing respiratory, dermal, gastrointestinal, blood-brain, placental, and other barriers, and selectively accumulate in cells and subcellular structures [5].

The aim of the research was to determine the acute and chronic toxicity of nanodispersed cerium dioxide.

Material and methods of research. Nanocrystalline cerium dioxide (NCD) is a representative of a new class of inorganic antioxidants that can inactivate active forms of Oxygen, but does not exhibit photocatalytic activity. NCD 1 is a light yellow powder with a particle size of 4–11 nm, obtained by employees of the Nanomedtech laboratory (Kyiv, Ukraine) and excipients to create the optimal composition of the base. Cerium dioxide nanoparticles (NCD 2) were created and provided for testing by the Department of Interferon and Immunomodulators of the D.K. Zabolotny Institute of Microbiology and Virology (Head of the Department, Doctor of Biological Sciences, Corresponding Member of the NAS of Ukraine, M.Ya. Spivak) for the purpose of preventing antioxidant stress. The authors express their sincere gratitude to colleagues for providing consulting assistance and support.

The purpose of determining the acute toxicity of NDC compounds was to establish the degree of toxicity (the limits of fluctuation of toxic action) and their lethal doses.

Studying chronic toxicity is relevant for two reasons. First, it allows the study of toxic effects during long-term tests. Second, it helps identify dose levels at which no toxic effects are observed under the given experimental conditions.

To determine the toxicity of the studied feed additives in rats, doses of 1000, 3000, and 5000 mg/kg body weight were administered. 6 laboratory animals were used for each dose. The 5000 mg/kg dose was administered to twice as many animals.

After the administration of the studied feed additives, laboratory animals were observed for 14 days. The following indicators were taken into account: appearance, behaviour of animals, condition of fur, visible mucous membranes, attitude to food, rhythm, respiratory rate, time of onset and nature of intoxication, its severity, course, time of death of animals or their recovery.

When studying subacute toxicity, the results from acute toxicity were used to guide the study. Supplements were administered intragastrically, daily for 30 days. During the experiment, the animals' clinical condition and behaviour were observed. Subacute toxicity was studied in 24 white rats weighing 200–220 g. For this purpose, a control group and three experimental groups of 6 rats each were formed. The animals of the control group were given drinking water. Animals of the first experimental group were administered the feed additive in a therapeutic dose of 0.05 g/kg of body weight, those of the second experimental group were administered five times the therapeutic dose of 0.25 g/kg, and those of the third experimental group were administered ten times the therapeutic dose of 0.5 g/kg of body weight. In the subacute experiment, the compound was administered to rats for 30 days. The next day after the end of the administration, laboratory animals were decapitated under light ether anesthesia, blood samples were taken, hematological and biochemical studies were performed according to generally accepted methods, and organs were dissected, and organ mass coefficients were determined, compared with the control group.

For hematological studies, blood stabilized with EDTA was used; for biochemical studies, serum was used. In stabilized blood, the following were determined: hemoglobin content, erythrocyte count, hematocrit, leukocyte count, MCH, MCV, and MCNS - using a Mythic-18 hematological analyzer. In blood serum, the following were determined: total protein, enzyme activities (ALT, AST, LDH), total bilirubin, creatinine, urea, and total cholesterol using a semi-automatic biochemical analyzer HumaLyzer 3000 with standard kits from Human.

During the research, the general principles of bioethics, legislative norms and requirements were adhered to in accordance with the provisions of the “European Convention for the Protection of Vertebrate Animals Used for Research and Scientific Purposes” (Strasbourg, 1986), “General Ethical Principles of Experiments on Animals” (Ukraine, 2001) and the “Ethical Committee of the Bila Tserkva National Agrarian University on the Treatment of Animals in Scientific Research and the Scientific Process” (No. 6 dated 05.22.2018).

The experimental part, approbation and production checks of the research results were performed in the laboratories of the Research Institute of Ecology and Biotechnology in Animal Husbandry and the Laboratory of Bio- and Histochemical Research Methods of the Bila Tserkva National Agrarian University (BNAU). Toxicological studies of the compounds were performed on the scientific basis of the vivarium of a certified laboratory of pharmacology and toxicology, included in the Register of the UkrSEPRO certification system of the State Scientific Research Control Institute of Veterinary Drugs and Feed Additives (DNDKIVPKD) in Lviv. Chromatographic studies were performed in accordance with the Kyiv Regional Scientific and Production Center for Standardization, Metrology and Certification.

Variational and statistical data processing was carried out in Microsoft Excel using the formulas we created. We determined indicators such as the arithmetic mean (M), standard error (m), and mean square deviation (s

Variational and statistical data processing was carried out in Microsoft Excel using the formulas we created. We determined indicators such as the arithmetic mean (M), standard error (m), and mean square deviation (σ). The reliability of the changes was assessed using the Student's t-test. The critical reliability levels for testing statistical hypotheses in the studies were set at 0.95, 0.99, and 0.999. The number of experiments (n) corresponds to the number of people studied in each case.

Research results and discussion. Under conditions of acute toxicity, it was found that white rats died from the use of the studied NDCs, mainly on the first day after intramuscular administration. The mortality rates of laboratory animals and their clinical symptoms at the corresponding doses of the two compounds were identical; therefore, the study data for determining acute toxicity are presented as a single set for both NDC 1 and NDC 2. The identity of the studies was also established in the case of repeated administrations.

In previous stages of the research, the lethal (DL100) and maximally tolerated (DL0) doses of the NDC compounds, both in the dosage form and in their active substance, were identified. As a result of the research, 100% mortality of white rats (DL100) was observed at a dose of 32 ml/kg of the compounds, and no mortality of laboratory animals (DL0) at a dose of 24 ml/kg of the compounds (Table 1).

In rats, when large doses of the studied compounds were administered, the same symptoms were observed, including impaired coordination of movements, head tremor, and, later, whole-body tremor, leading to death.

The data obtained on the death of white rats, depending on the administered doses of NDC compounds, are shown in Table 2.

After the results were obtained, calculations of the average lethal doses of cerium dioxide preparations were carried out using the methods of G. Kerber, G. Pershin, B.M. Shtabsky, V.B. Prozorovsky, J. Litchfield and F. Wilcoxon. To improve understanding of the material and facilitate calculations, the administered doses of the preparations were reported in ml/kg and then converted to mg/kg.

In the final table 3, for the study of acute toxicity, the median lethal doses (LD50) of the NDC for laboratory animals were determined and calculated at the expanded stage in terms of the finished dosage form and the active substance, trivalent cerium (Ce3+), are presented. It should be noted that if, during the study of the toxicity of newly developed drugs, the median lethal doses calculated by different methods coincide, then the experiment was conducted correctly and the drug belongs to the corresponding toxicity class. The median lethal doses of the studied drugs in white rats, regardless of the calculation method, were similar and exceeded 4500 mg/kg body weight. The DL50 indicators for the active substance ranged from 2286 to 2618 mg/kg, which do not exceed the parameters of class V (1501-4500 mg/kg).

Table 1 – **Lethal (DL100) and maximum tolerated dose (DL0) values of NDC doses for white rats after intramuscular administration**, n = 9

The name of the compound	By compound	By compound	Based on active substance, mg/kg	Based on active substance, mg/kg
The name of the compound	DL100	LD0	DL100	LD0
NDC ml/kg (mg/kg)	32 (32000)	24 (24000)	2720	2040
NDC 2 (mg/kg)	32 (32640)	24 (24480)	2720	2040

Table 2 – **Survival and mortality rates of white rats during the determination of acute toxicity of nanocrystalline cerium dioxide following intramuscular administration,** n=60

Doses by compound, ml/kg (by active ingredient, mg/kg)	24 (2040)	26 (2210)	28 (2380)	30 (2550)	32 (2720)
Survival rats	6	5	4	2	0
Died rats	0	1	2	4	6

Table 3 – **Values of median lethal doses of NDC for white rats after intramuscular administration**

Calculation methods by:	Median Lethal Dose (DL50)	Median Lethal Dose (DL50)
	NDC preparation (ml/kg)	NDC preparation (ml/kg)
G. Kerber	28,7	28,7
G. Pershin	28,7	28,7
J. Litchfield and F. Wilcoxon	28,8 (27,2 ÷ 30,4)	28,8 (27,2 ÷ 30,4)
V.B. Prozorovsky	28,7 (26,9 ÷ 30,4)	28,7 (26,9 ÷ 30,4)
B.M. Shtabsky	28,9 (27,0 ÷ 30,8)	28,9 (27,0 ÷ 30,8)
	Per compound	Per active ingredient
	NDC preparation (mg/kg)	NDC preparation (mg/kg)
G. Kerber	28667	2436,695
G. Pershin	28670	2436,950
J. Litchfield and F. Wilcoxon	28750 (27200 ÷ 30389)	2444 (2312 ÷ 2583)
V.B. Prozorovsky	28659 (26898 ÷ 30420)	2436 (2286 ÷ 2586)
B.M. Shtabsky	28889 (26975 ÷ 30803)	2456 (2293 ÷ 2618)
	NDC-citrate preparation (mg/kg)	NDC-citrate preparation (mg/kg)
G. Kerber	29240	2436,695
G. Pershin	29243	2436,950
J. Litchfield and F. Wilcoxon	29325 (27744 ÷ 30997)	2444 (2312 ÷ 2583)
V.B. Prozorovsky	29232 (27436 ÷ 31028)	2436 (2286 ÷ 2586)
B.M. Shtabsky	29467 (27515 ÷ 31419)	2456 (2293 ÷ 2618)

Therefore, the conducted studies have established that the NDC data, according to the classification of toxicity of substances when administered intramuscularly by degree of danger [26] belong to toxicity class VI (relatively harmless substances), and in terms of the main active ingredient, trivalent cerium (Ce3+), which is in this dosage form, to toxicity class V (practically non-toxic substances).

Summarizing the results, it can be concluded that the toxicity of the studied compounds when administered intramuscularly belongs to the VI toxicity class (relatively harmless substances) for white rats, and their active substance, trivalent cerium (Ce3+), which is in this form, belongs to the V toxicity class (practically non-toxic substances). The median lethal dose of the NDC drug for white rats when administered intramuscularly is 28889 (26975 ÷ 30803) mg/kg.

Under the conditions of intramuscular administration of the NDC drug to white rats during the study of chronic toxicity, no deaths of laboratory animals were detected.

In rats of the experimental groups, which were administered the drug NDC for a long time, a trend was found, correspondingly with a decrease in body weight, compared to the control group, a decrease in total and average daily gains, which were characterized even by negative indicators compared to the weight of the animals at the beginning of the experiment, especially in the third group of animals, which were administered the drug in the highest dose (Table 4).

Under the conditions of long-term daily administration of the NDC compound to rats in the doses studied to determine the toxic effect of the dosage form on the body, on the 10th day, compared to the control, a significant increase in the coefficients of liver mass by 36 and 80% ($p<0.001$) was found when the drug was administered in therapeutic and 5-fold higher than therapeutic doses, respectively, and spleen by 33% ($p<0.05$) when administered in a dose 5-fold higher than therapeutic (Table 5).

So, in our opinion, under prolonged administration of the drug NDC, its toxic effect was manifested, especially at the highest dose, which caused a decrease in the body weight of laboratory animals with a simultaneous increase in the weight of the liver and spleen.

According to blood tests, the severity of the course is determined, and the body's complications from the drug's toxic effects are detected. The waste products of various organs are excreted into the blood. The amount of waste products excreted can indicate the functional state of the internal organs and the immune defence system.

Table 4 – **Dynamics of changes in body weight and growth in white rats during the determination of chronic toxicity of the drug nanocrystalline cerium dioxide, g**, M±m, n=6

animal group	Body weight	Body weight	Body weight	Body weight	Body weight gain	Body weight gain	Body weight gain
animal group	at the beginning of the experiment	at the beginning of the experiment	on the 10th day of administration	on the 10th day of administration	Total for the month by group	average daily calculated:	average daily calculated:
animal group	Total for group	Average of one animal	Total for group	Total for group	Total for the month by group	average daily calculated:	average daily calculated:
animal group	Total for group	Average of one animal	Total for group	Total for group	Total for the month by group	for all rats in the group	per rat in the group
1	835	139,2±5,23	930	155,3±9,04	95	9,5	1,6
2	831	138,5±4,86	799	133,2±4,87	–32	–3,2	–0,5
3	835	139,2±7,79	765	127,5±11,31	–70	–7,0	–1,2

Table 5 – **Weight coefficients of white rats' internal organs on the 10th day for the study of NDC compound chronic toxicity,** %, M±m, n=6

Organs examined	Group of animals	Group of animals	Group of animals
Organs examined	1	2	3
Heart	3,9±0,13	4,0±0,24	4,8±0,23
Spleen	5,2±0,25	5,7±0,44	6,9±0,64*
Kidneys (both)	8,4±0,47	8,1±0,37	9,4±0,45
Right kidney	4,3±0,22	4,1±0,24	4,8±0,34
Left kidney	4,1±0,25	4,0±0,24	4,6±0,33
Liver	38,7±1,73	52,6±2,34***	69,7±4,13***
Lungs	11,1±1,14	11,9±1,32	11,7±0,91

Note: here and further the difference is significant at: * – p<0,05; ** – p<0,01; *** – p<0,001, compared to group 1.

Analysis of the morphological picture of the rats' blood on the 10th day of NDC administration showed that the compound significantly affected hematopoietic processes in the rats' bodies. We found that with prolonged administration of the drug in therapeutic doses and in doses 5 times higher than therapeutic, a significant decrease in the number of erythrocytes, respectively, by 48% (p<0.001) and 40% (p<0.01) and leukocytes by 43% and 50% (p<0.01) (Table 6).

Table 6 – **Hematological parameters in white rats for determining the toxicity of the nanocrystalline cerium dioxide preparation,** M±m, n=6

Indicators	Group of animals	Group of animals	Group of animals
Indicators	1	2	3
Hemoglobin, g/l	101,3±5,74	96,0±8,93	97,2±7,73
Erythrocytes, T/l	9,0±0,44	4,7±0,33***	5,4±1,03**
Hematocrit value, l/l	0,36±0,02	0,38±0,02	0,38±0,02
Color index	0,35±0,02	0,60±0,06**	0,63±0,02***
Average hemoglobin content in erythrocytes, pg	11,3±0,64	20,6±2,23**	20,8±0,92**
Average erythrocyte volume, μm3	40,9±2,93	73,6±8,42**	81,9±5,03**
Leukocytes, G/l	16,6±2,03	9,5±0,72**	8,3±0,74**

Hematocrit is used to determine the average erythrocyte volume and to characterize certain types of anemia. In our experiment, prolonged administration of the compound at therapeutic and 5-fold higher than therapeutic doses resulted in a significant increase in the average erythrocyte volume by 80% and 100%, respectively ($p<0,01$).

Hemoglobin is a respiratory iron-containing blood protein contained in erythrocytes and provides transport of Oxygen from the lungs to the tissues and carbon dioxide to the lungs. In the experiment, prolonged administration of the two studied doses showed a general tendency to increase hematocrit and decrease hemoglobin. A probable decrease in the number of erythrocytes, as already indicated, contributed to a probable increase in the levels of red blood indices, namely: color index – by 71% ($p<0.01$) and by 80% ($p<0.001$) and the average hemoglobin content in erythrocytes - by 82.3% ($p<0.01$) and by 84.0% ($p<0.001$) upon administration of NDC, respectively, in therapeutic and 1/3 LD50 doses. It should be noted that erythrocytopenia exceeded the physiological norm.

Hematological indicators after long-term compound administration to rats indicate the intoxication effect of NDC regardless of the dose, which led to anemia, and this, in turn, is confirmed by pronounced hyperchromia. The determined erythrocytopenia and leukocytopenia indicate the inhibitory effect of the drug on the hematopoietic organs, the suppression of the organs of erythro- and leukocytopoietic function (bone marrow, spleen, lymph nodes), that is, the effect of NDC on erythro- and leukocytopoiesis, their depletion and a decrease in the reactivity of the organism. In addition, there was damage to the spleen, leading to an increase in its mass coefficient. In addition, a decrease in erythrocyte count and an increase in red blood indices indicate macrocytic anemia. A higher average erythrocyte volume, in turn, may indicate liver damage, and leukocytopenia - a decrease in the reactivity of the organism [27]. Determining the total number of leukocytes does not indicate the number of individual leukocyte types. Such data can be obtained by deriving a leukogram - the percentage ratio between individual types of leukocytes.

Analysis of the morphological picture of the blood of rats showed (Table 7) that with prolonged administration of NDC, regardless of the dose, a significant increase in segmented neutrophils was noted in the leukogram, compared with the control, by 2.3 ($p<0.001$) and 2.7 ($p<0.01$) times and a decrease of 13.6 and 22.0% ($p<0.01$) of lymphocytes during administration of the drug, respectively, in therapeutic and 1/3 LD50 doses.

A tendency to increase monocyte levels by 8% and 67% was observed with compound administration at therapeutic and 5-fold higher than therapeutic doses, respectively. As for eosinophils, for the administration of NDC at a therapeutic dose, a tendency to decrease their level compared to the control by 21.4% was observed, and for a dose of 1/3 LD50, their level increased by 7.1%.

The significant increase in segmented neutrophils, combined with pronounced leukocytopenia, indicates chronic processes and suggests bone marrow depletion. At the same time, the detected lymphocytopenia against the background of neutrophilia indicates acute septic processes. Lymphocytopenia, in combination with leukocytopenia, also indicates depletion of the body's defences. A tendency to increase monocyte counts, in combination with drug administration at a 5-fold higher dose than the therapeutic dose, may also indicate a chronic process [27].

The compound has been shown to affect protein and lipid metabolism, as well as the activity of intracellular enzymes (Table 8).

In the animal body, the concentration of total protein in blood serum is within a narrow range and changes significantly with significant metabolic pathology, liver disease, and other organ diseases. Our studies did not reveal significant changes in the protein content with prolonged administration of NDC in a therapeutic dose.

Table 7 – **Blood leukogram of white rats on the 10th day of a long-term experiment to study the toxic properties of the NDC compound,** %, M±m, n=6

Group	Eosinophils	Neutrophils	Neutrophils	Lymphocytes	Monocyte
Group	Eosinophils	rod-nucleated	segment-nucleated	Lymphocytes	Monocyte
1	2,8±0,75	–	9,5±2,23	86,5±2,53	1,2±0,43
2	2,2±0,81	–	21,8±1,24***	74,7±2,13**	1,3±0,74
3	3,0±1,02	–	27,2±3,74**	67,5±3,63**	2,0±0,74

Table 8 – **Biochemical blood parameters of white rats on the 10th day of a long-term experiment to study the toxic properties of the NDC compound,** M±m, n=6

Indicators	Group of animals	Group of animals
Indicators	control	Therapeutic
ALT, μkat/l	0,36±0,011	0,77±0,061***
AST, μkat/l	0,67±0,039	0,94±0,031***
LF, μkat/l	1,4±0,06	1,3±0,04
Total protein, g/l	87,9±3,03	88,3±3,23
Total lipids, g/l	2,4±0,24	2,3±0,12
Triacylglycerols, mmol/l	0,34±0,033	0,63±0,034***
Total cholesterol, mol/l	4,5±0,09	4,2±0,22
Free cholesterol, mol/l	1,5±0,04	1,6±0,13
Bound cholesterol, mol/l	3,0±0,09	2,6±0,34
Glucose, mmol/l	4,1±0,35	3,5±0,25

As for lipid metabolism, which depends on the functions of intestines, pancreas and thyroid glands, liver and other organs, a significant increase in the blood serum of the studied rats, compared with the control rats, which were administered NDC for a long time in a therapeutic dose, was found, a significant increase by 85% ($p<0.001$) in the content of triacylglycerols and a tendency to decrease by 13% in the content of bound cholesterol.

The glucose content of the blood is relatively constant. Blood glucose is constantly replenished by the tissues, liver, and intestines. In our studies, no significant changes in glucose levels were observed with prolonged administration of NDC at a therapeutic dose; only a tendency to reduce glucose concentration by 15% was observed compared with the control.

The study of enzyme activity in the blood serum in the diagnosis of liver diseases is gaining increasing importance. Enzyme diagnostics help recognize the disease at an early stage and detect minor changes in liver function and structure. Our experiments revealed a significant 2-fold increase in ALT activity and a 40% increase in AST activity ($p<0.001$) compared with the control, following long-term administration of NDC at a therapeutic dose.

Thus, biochemical blood parameters showed that the compound, after 10 days of daily administration, affected the liver's functional state due to hepatocyte dysfunction, as evidenced by a significant increase in transaminase activity and the mass coefficient of this organ. Hypertriacylglycerolemia, which is observed in organ lesions, also indicates impaired liver function [27].

As a result of studying the toxic effect of NDC, under the conditions of its daily administration to white rats for 10 days, it was established that the compound, regardless of the dose, suppressed the erythropoietic and leukocytopoietic functions of the hematopoietic organs (bone marrow, spleen, lymph nodes), caused their depletion, especially the bone marrow, and reduced the reactivity of the body, affecting the functional state of the liver and spleen. Under the influence of the compound, inflammatory processes of both acute and chronic nature took place.

As a result of studying the toxic effect of NDC, under the conditions of its daily administration to white rats for 10 days, it was found that the compound affected the hematopoietic organs and the immune system regardless of the dose (a probable decrease in the number of erythrocytes, leukocytes and lymphocytes and an increase in segmented neutrophils, red blood indices, mean erythrocyte volume and spleen mass coefficient) and this, in our opinion, indicates the transition of the acute process into a chronic one and depletion of the bone marrow. In addition, this drug affected some aspects of lipid metabolism (a probable increase in triacylglycerol content) and the functional state of the liver (a probable increase in the mass coefficient of this organ and the activity of ALT and AST).

However, it should be noted that when NDC was administered at the doses studied, no decrease in the AST-to-ALT ratio below 1 or a significant increase above 1.33 (De Ritis coefficient) was detected in the blood serum of rats, indicating minimal liver damage [27]. No significant changes were found in the content of total protein and total lipids, and cholesterol, as well as in the level of glucose. In addition, increased morphological and biochemical blood parameters in experimental animals compared with controls may indicate compensatory processes in response to the drug.

Conclusions. Summarizing the results of the conducted studies, it can be concluded that prolonged intramuscular administration of NDC, especially at a dose 5 times the therapeutic dose, resulted in a toxic effect on the mass of laboratory animals. The compound, when administered daily for prolonged periods to white rats, affected the functional state of the liver and spleen, as well as lipid metabolism. Administration of NDC to white rats for 10 days suppressed the erythropoietic and leukocytopoietic functions of the hematopoietic organs and reduced the protective functions of the body.

СПИСОК ЛІТЕРАТУРИ

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Екотоксикологічна оцінка препаратів нанокристалічного церію діоксиду

Цехмістренко О.С., Цехмістренко С.І., Бітюцький В.С.

Церій є найпоширенішим рідкоземельним металом та елементом промислового значення. Церію діоксид (CeO_2) є найвідомішою сполукою церію, завдяки його неперевершеним окисно-відновним властивостям і здатності гарантувати чудову рухливість Оксигену. При переході в нанокристалічний стан сполука значно змінює свої фізико-хімічні властивості, що обумовлює унікальну біологічну активність матеріалу.

В останні роки у літературі зустрічаються повідомлення щодо застосування наночастинок металів, зокрема церію, у тваринництві в якості нових природних добавок до корму з метою підвищення продуктивності тварин. На сьогодні недостатньо є повідомлень щодо токсикодинаміки та токсикокінетики наночастинок у організмі людей та тварин, а також їх вплив на довкілля. Токсична дія наночастинок може бути обумовлена їх здатністю проникати в клітину, оминаючи

дихальний, дермальний, шлунково-кишковий, гематоенцефалічний, плацентарний та інші бар'єри та вибірково акумулюватися у клітинах та субклітинних структурах.

Метою досліджень було визначення гострої та хронічної токсичності нанодисперсного церію діоксиду, отриманого співробітниками лабораторії «Наномедтех» (Київ, Україна) та відділом проблем інтерферону та імуномодуляторів Інституту мікробіології та вірусології ім. Д.К. Заболотного.

Результати дослідження біохімічних показників крові показали, що препарат за 10-добового щоденного введення впливав на функціональний стан печінки, внаслідок порушення гепатоцитів, про що свідчить вірогідне підвищення активності трансаміназ та коефіцієнту маси даного органу. Про порушення функції печінки вказує і гіпертриацилгліцеролемія, яка відмічається при ураженнях органу.

У результаті вивчення токсичної дії НДЦ, за умов щодобового введення його білим щурам впродовж 10 діб встановлено, що препарат не залежно від дози пригнічував еритро- та лейкоцитопоетичну функції кровотворних органів, спричиняв їх виснаженню, особливо кісткового мозку та понижував реактивність організму, впливав на функціональний стан печінки і селезінки. Під дією препарату проходили запальні процеси як гострого, так і хронічного характеру. Крім того даний препарат впливав на деякі сторони обміну ліпідів та на функціональний стан печінки (вірогідне підвищення коефіцієнту маси даного органу та активності АлАТ і АсАТ).

Ключові слова: нанопрепарати, церію діоксид, токсичність, щурі, кров, внутрішні органи, біохімічні показники.

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