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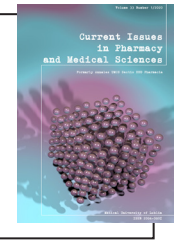

# Correction with thiocetam of lead nanoparticles influence on morpho-functional status of rat liver

Sergii Omelchuk[1], Vasyl Aleksiichuk[1], Yuri Chaikovsky[2], Liudmyla Sokurenko[2,3]*

[1] Department of Hygiene and Ecology No. 4, O.O. Bogomolets National Medical University Kyiv, Ukraine
[2] Department of Histology and Embryology, O.O. Bogomolets National Medical University, Kyiv, Ukraine
[3] Educational and Scientific Center "Institute of Biology and Medicine" Taras Shevchenko National University of Kyiv, Ukraine

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**ABSTRACT**

The aim of this paper is to investigate the influence of Thiocetam on morphological changes in the liver of rats and on biochemical changes in their blood after exposure to lead nanoparticles and compounds. The liver is an organ that performs a number of functions, such as the synthesis of enzymes, hormones, plasma components and the neutralization of toxins. It is involved in many metabolic processes in the body.

In undertaking this, colloidal solutions of lead sulphide nanoparticles at dosages 10 nm and 30 nm were injected into two groups of rats, $PbS_{nano1}$ and $PbS_{nano2}$, respectively, while group $Pb(NO_3)$ received subcutaneously a solution of lead nitrate in ion form in a dose of 1.5 mg/kg (0.94 mg/kg lead, in lead equivalent). After 60 administrations (12 weeks) of the studied substances, the exposure was discontinued and the animals were observed for 18 weeks. Subsequently, half of each group received Thiocetam by injection (for 6 weeks at a dose of 250 mg/kg) while the other half did not. We then assessed the mean body weight, absolute and relative liver weight, blood biochemistry values (total protein, albumin, glucose, total lipids, cholesterol, triglycerides levels in blood serum) and morphological changes in hepatocytes (morphological slides, nuclei cross-sectional area and cytoplasm cross-sectional area).

The outcome of this work showed that the mean body weight of animals exposed to nanoparticles with Tiocetam did not differ from that of animals exposed to nanoparticles without pharmacological correction, but relative liver weight was statistically significantly higher than the corresponding values in rats without pharmacological correction. The morphological picture in all study group animals was characterized by the normalization of microvessel blood filling, structure of hepatic plates, disappearance of infiltration with lymphocytes and histiocytes. No dystrophic changes in hepatocytes were found. All this indicates the feasibility of preventive measures during exposure to lead nanoparticles, by administering Thiocetam.

In both series of animals exposed to lead nanoparticles ($PbS_{nano1}$ and $PbS_{nano2}$), the cross-sectional area of the hepatocytes cytoplasm and the cross-sectional area of the hepatocytes nuclei were smaller than just after exposure, but in the series with Thiocetam adminstration, all the values did not differ from those in the control.

## INTRODUCTION

The liver is an organ that performs a number of functions, such as the synthesis of enzymes, hormones, plasma components and the neutralization of toxins. Moreover, it is involved in most metabolic processes in the body. At the same time, the liver is extremely susceptible to a variety of impacts, including drug-induced liver damage [1], toxins [2], alcohol [3], viruses [4-6], cancers and other types of damage [7-9].

Heavy metals like lead and mercury, which are characterized by negative effects on the liver, play a significant role among the toxic factors [10,11]. Of even more concern is the situation regarding metal nanoparticles [12].

* **Corresponding author**
e-mail: l-sokurenko@i.ua

Lead nanoparticles deserve special attention. Lead compound nanoparticles and nanocrystals of 4-10 nm in size are found in semiconductors, solar batteries, and polymer composites [13]. Lead nanoparticles smaller than 100 nm are can be encountered in welding and cutting lead-containing structures, smelting, the recovery of lead batteries and batteries [14,15].

Physical properties, such as nano-size, shape, charge, structure and large surface area determine the features of their biological action [15]. As reported in the literature, the small size of nanoparticles facilitates their free penetration into cells, binding to proteins, insertion into membranes, and penetration into organelles [15,16].

Lead is a slow acting poison and this quality is enhanced by the high ability of nanoparticles to cumulate, with their small size preventing their recognition by various structures. That is the reason for nanoparticle accumulation and slow excretion from the body [16,17]. Lead, for example, is known to form a stable deposition in the liver and bones [18].

The destructive changes in the cell due to lead ingestion are associated with the universal mechanism of lipid peroxidation activation (LPA) and the simultaneous suppression of antioxidant protection (AOP), as well as the development of oxidative stress [19-21]. That is why the drug Thiocetam, which contains both Thiotriazoline and Piracetam, has attracted our attention. Thiotriazoline blocks oxidative stress both at the initial and at the advanced stages.

The membrane stabilizing effect is also due to the antioxidant effect. Thiocetam improves microcirculation, affects the rheological characteristics of blood, and has protective and restorative effect in case of impairment of brain function due to intoxication, thus causing a positive effect on other systems that are damaged by lead.

It is known that toxic effects of lead and its compounds on the organism are manifested by damage to the nervous and cardiovascular systems, the kidneys, disorders of porphyrin metabolism, blood system, organs of hematopoiesis and immune protection [21]. Drugs promoting the elimination of metals from the body and preventing their accumulation are the classical means of preventing the toxic effect of lead.

## AIM

The study aims at assessing the influence of Thiocetam on morphological changes in the liver of rats and on biochemical changes in their blood after exposure to nanoparticles of lead compounds.

## MATERIALS AND METHODS

The studies were carried out on 120 male Wistar rats weighing 160-180 g. They were kept in vivarium conditions on a standardized water-food ration in the form of a balanced meal according to established standards and free access to drinking water and food.

The experiments were carried out in accordance with the Law of Ukraine "On protection of animals from cruelty" (2006), "General ethical principles of animal experiments", adopted by the First National Congress on Bioethics (Kiev, 2001) and with the Council of Europe Convention on the protection of vertebrates, which are used for scientific purposes and were approved by the O.O. Bogomolets National Medical University bioethics committee.

The animals were divided into 2 series, with 4 and 5 groups in them (15 animals per group). The study design is given in Table 2. In the first series, the exposure was discontinued after 60 administrations of the studied substances within 12 weeks and the animals were observed during the overall post-exposure period lasting 18 weeks. In the second series (for a total of 18 weeks), the studied substances were administered 60 times within 12 weeks and the Thiocetam drug manufactured by JSC "Halychfarm" was added to their meal for six weeks in a dose of 250 mg/kg.

In $PbS_{nano1}$ (size 10 nm) and $PbS_{nano2}$ groups (30 nm) colloidal solutions of lead sulphide nanoparticles were injected (intraperitoneally daily 5 times a week) at a dose of 1.08 mg/kg (in lead equivalent to 0.94 mg/kg lead), the nano particles of lead being of the stated size. Group $Pb(NO_3)$ was injected (intraperitoneally daily 5 times a week) with a solution of lead nitrate in ion form in a dose of 1.5 mg/kg (0.94 mg/kg lead in lead equivalent). The fourth group of animals (control) was administered 1 ml of normal saline. All the animals were sacrificed under mild ether anesthesia (in accordance with "http://web.jhu.edu/animalcare/policies/ether.html"\t "_blank").

***Table 1.*** Design groups of experimental animals

| Groups | No | 18 weeks (1nd series) = 12 weeks exposures + 6 weeks without Thiocetam | No | 18 weeks (2nd series) = 12 weeks exposures + 6 weeks with Thiocetam |
|---|---|---|---|---|
| Control | 1 | 1 ml of normal saline (daily 5 times a week = 60 injections ) | 5 | 1 ml of normal saline (daily 5 times a week = 60 injections) + 250 mg/kg Thiocetam (42 introductions) |
| $PbS_{nano1}$ | 2 | 1.08 mg/kg (daily 5 times a week = 60 injections) | 6 | 1.08 mg/kg (daily 5 times a week = 60 injections) + 250 mg/kg Thiocetam (42 injections) |
| $PbS_{nano2}$ | 3 | 1.08 mg/kg (daily 5 times a week = 60 injections) | 7 | 1.08 mg/kg (daily 5 times a week = 60 injections) + 250 mg/kg Thiocetam (42 injections) |
| $Pb(NO_3)_2$ | 4 | 1.5 mg/kg (daily 5 times a week 60 injections) | 8 | 1.5 mg/kg (daily 5 times a week = 60 injections) + 250 mg/kg Thiocetam (42 injections) |
| Thiocetam | | | 9 | 1 ml of normal saline (daily 5 times a week = 60 injections) + 250 mg/kg Thiocetam (42 injections) |

General status, behavior, and mean body weight were estimated during an 18 week period. Blood and liver of the experimental animals, as well as their absolute and relative liver weights were studied after withdrawing the animals from the experiment [22].

Total protein, albumin, glucose, total lipids, cholesterol, triglycerides levels were determined in blood serum by Vitros-250, according to the International System of Units recommended for use in clinical laboratory practice.

Histological examination was performed on sections of liver preparations fixed in 12% formalin solution on phosphate buffer (pH=7.0-7.2). Dehydration was carried out according to the traditional scheme of an alcohol battery usage of ascending concentration from 30° up to the absolute. Paraffin-celloidin sections were obtained by using a microtome. The sections were stained depending

on the needs of the study with further examination at the optical level.

General morphology of the experimental animals' livers was studied by azure II and hematoxilin-eosin staining of the nuclei, for the determination of acidic and neutral muco-polysaccharides – PAS reaction; Van Gieson's staining was used to identify the presence of connective tissue.

Morphometric studies were carried out using an image analyzer: an Olympus BX51 microscope with a C-4040zoom digital camera and a personal computer. An E. LEITZ WETZIAR micrometer was employed to calibrate the image analysis.

The following morphometric data of hepatocytes in the liver of experimental animals were studied: nuclei cross-sectional area ($\mu m^2$) and cytoplasm cross-sectional area ($\mu m^2$).

Statistical processing of measurement results was carried out with a package of statistical programs Statistica 4.0 (Statistica Inc. USA), Biostat i MS Excel. All morphometric, body and liver weights and biochemical parameters were evaluated by variational statistics using t-Student and Fisher test, after confirming the normality of distribution. The average value (M) and the standard deviation (m) were determined.

## RESULTS

In the course of the experiment we saw that the condition of rats whose meal was supplemented with Thiocetam in the post-exposure period, was satisfactory, with motor and behavioral activity being within the normal range, and food and water intake normalized. Body and liver weights of experimental animals are given in Table 2.

***Table 2.*** Body and liver weight of experimental animals (M±m), p ≤0.05

| Values | Control (n=15) | $PbS_{nano1}$ (n=15) | $PbS_{nano2}$ (n=15) | $Pb(NO_3)_2$ (n=15) | |
|---|---|---|---|---|---|
| 18 weeks (1nd series) = 12 weeks exposures + 6 weeks without Thiocetam | | | | | |
| Mean body weight, g | 343.0 ±4.1 | 249.5 ±5.5[1,2,3] | 347.8 ±1.9[2,3] | 284.5 ±14.4[1] | |
| Absolute liver weight, g | 9.15 ±0.23 | 8.46 ±0.17[1,2,3] | 9.97 ±0.34[1,2,3] | 7.78 ±0.46[1] | |
| Relative liver weight, % | 2.67 ±0.07 | 3.40 ±0.04[1,2,3] | 2.86 ±0.04[2] | 2.72 ±0.04 | |
| 18 weeks (1nd series) = 12 weeks exposures + 6 weeks with Thiocetam | | | | | Thiocetam |
| Average body weight, g | 339.5 ±4.1 | 253.5 ±8.6[1,3] | 347.5 ±5,7[3] | 296.8 ±8,9[1,4] | 337.4 ±3.6 |
| Absolute liver weight, g | 9.25 ±0.15 | 9.07 ±0.24[1,2,3] | 9.40 ±0.10[2,4] | 9.20 ±0,24[4] | 9.34 ±0.31 |
| Relative liver weight, % | 2.70 ±0.051 | 2.80 ±0.04[2,3,4] | 3.06 ±0.07[1,2,4] | 3.10 ±0,05[1,4] | 2.61 ±0.04[1] |

Notes: [1] – statistically significant differences compared with the control group (p≤0.05), [2] – statistically significant differences compared with the group of animals exposed to nanoparticles of another size (p≤0.05), [3] – statistically significant differences compared with the group of animals exposed to Lead Nitrate (p≤0.05), [4] – statistically significant differences between groups of animals of other series (p≤0.05)

When Thiocetam was used, the mean body weight of rats exposed to $Pb(NO_3)_2$ and $PbS_{nano1}$ (296.8±8.9 g, 253.5±8.9 g, respectively) remained statistically significantly lower (p≤0,05) than that in control group animals (339.5±4.1 g), however, the weight of animals of $Pb(NO_3)_2$ was statistically significantly higher (p≤0.05) than the weight of groups without pharmacological correction in the post-exposure period (284.5±14.4 g). When Thiocetam was used in the experimental animals exposed to $PbS_{nano2}$, their body weight reached the control value. Values of group with Thiocetam did not show any significant differences in comparison with the control group.

The relative liver weight of animals exposed as $PbS_{nano2}$ and $PbS_{nano1}$ groups (3.06±0.07%, 3.10±0.0%, respectively) demonstrated statistically significant (P ≤0.05) increases as compared to weights found in the animals without correction in the post-exposure period (2.86±0.04%, 2.72±0.04%, respectively).

### Changes in blood biochemical parameters

We found that when Thiocetam was used in the post-exposure period, serum concentration of total protein in the blood of rats from $Pb(NO_3)_2$ (76.6±1.3 g/L) and $PbS_{nano1}$ (80.6±1.8 g/L) groups did not statistically significantly differ from the control group (80.7+3.5 g/L). However, the $PbS_{nano2}$ group (73.7±2.5 g/L) results were statistically significantly lower than the respective value of the animals from the $PbS_{nano2}$ group (88.7±1.7 g/L) (Table 3). Moreover, concentration of albumin in animals of $PbS_{nano1}$ and $PbS_{nano2}$ groups (37.5±0.2 g/L, 37.4±0.2 g/L, respectively) was found significantly lower, and in animals of the $Pb(NO_3)_2$ group (42.9±1.2 g/L), it was close to control values (42.9±1.2 g/L) and lower than in the group without Thiocetam (45.6±1.2 g/L) (Table 3). Furthermore, level of total lipids in blood serum was statistically significantly higher (p≤0.05) in animals of $PbS_{nano1}$ and $PbS_{nano2}$ groups (4.8±0.2 g/L, 4.8±0.2 g/L, respectively) in comparison with the control value (4.3±0.2 g/L) and Pb(NO3)2 groups (4.0±0.5 g/L) (Table 3). Level of cholesterol in animals of $PbS_{nano1}$, $PbS_{nano2}$ groups and $Pb(NO_3)_2$ groups (1.7±0.2 mmol/L, 1.3±0.2 mmol/L, 1.1±0.1 mmol/L respectively) was also statistically significantly lower (p ≤0.05) in respect to control (2.0±0.2 mmol/L), and to the animals of $PbS_{nano1}$ group without Thiocetam (1.8±0.2 mmol/L) (Table 3). In addition, serum concentration of glucose was statistically significantly higher (p≤0.05) in animals of $PbS_{nano2}$ group (5.9±0.3 mmol/L) and $Pb(NO_3)_2$ groups (5.3±0.3 mmol/L) as compared to control (4.6±0.41 mmol/L), and in animals of $PbS_{nano1}$ (4.6±0.3 mmol/L), it was close to the control group values (Table 3). Triglycerides concentrations did not differ from that of the control, but $Pb(NO_3)_2$ groups (1.3±0.1 mmol/L) were statistically significantly lower than that of the group without Thiocetam (1.9±0.2 mmol/L) (Table 3). Finally, biochemical values of the blood in laboratory rats not exposed to lead, but with only Thiocetam influence did not show any significant differences in comparison with indexes in control animals (Table 3).

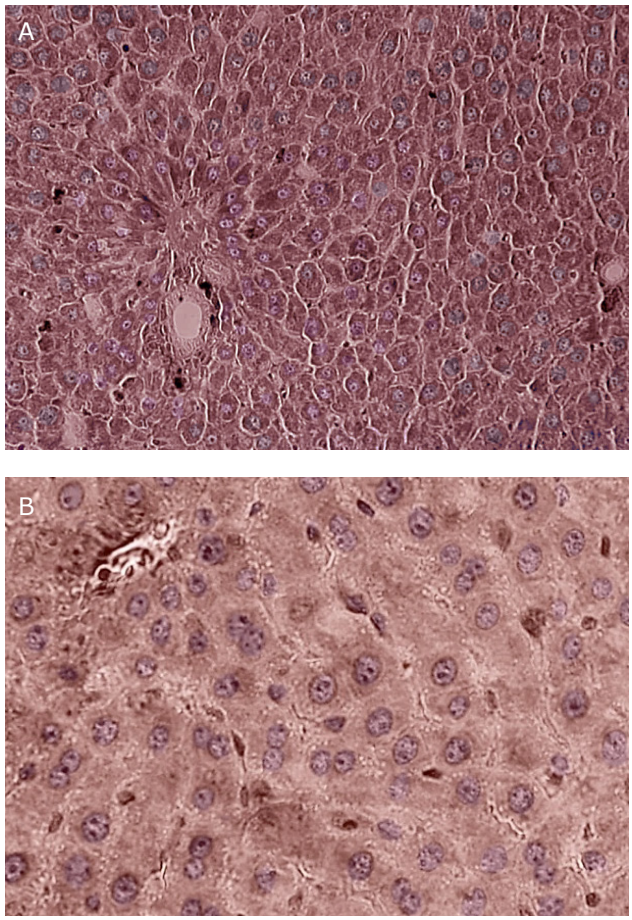
### Liver morphology

Microscopic examination of the liver at week 12 revealed dystrophic changes in the hepatocytes of the liver parenchyma of all experimental groups. These are manifested by hepatocytes losing their polygonal shape and by polymorphism of hepatocytes nuclei, vacuolization and swelling of cytoplasm, significant reduction of glycogen granules number and indistinct hepatocytes contours. Interlobular edema and infiltration by lymphocytes and histiocytes were the signs of inflammation, which is the evidence of increasing capillary permeability and also demonstrates the activation of cellular protection.

***Table 3.*** Changes in protein and carbohydrate metabolism in the blood serum of experimental animals (M±m), p≤0.05

| Values | Control | $PbS_{nano1}$ (n=15) | $PbS_{nano2}$ (n=15) | $Pb(NO_3)_2$ (n=15) |
|---|---|---|---|---|
| 18 weeks (1nd series) = 12 weeks exposures + 6 weeks without Thiocetam | | | | |
| Total protein concentration, g/L | 76.9±0.9 | 81.7±2.3[1,2,3,4] | 88.7±1.7[1,2,3,4] | 78.70±0.6[1,4] |
| Albumin concentration, g/L | 36.8±1.3 | 37.04±0.7 | 38.3±1.2 | 36.0±1.0[4] |
| Albumin content,% | 47.8±1.4 | 41.7±5.8[1,3] | 43.2±1.3[1] | 45.6±1.2 |
| Glucose concentration, mmol/L | 4.53±0.3 | 5.96±0.36[1] | 6.17±0.37[1] | 6.09±0.19[1] |
| Total lipids concentration, g/L | 3.9±0.3 | 4.6±0.1[1] | 4.8±0.1[1,3] | 4.1±0.3 |
| Cholesterol concentration, mmol/L | 2.2±0.09 | 1.8±0.2[1,3] | 1.4±0.2[1] | 1.2±0.1[1] |
| Triglycerides concentration, mmol/L | 1.5±0.1 | 1.9±0.3 | 2.0±0.3[1] | 1.9±0.2[1] |
| 18 weeks (2nd series) = 12 weeks exposures + 6 weeks with Thiocetam | | | | |
| Total protein concentration, g/L | 80.7+3.5 | 80.6±1.8[2] | 73.7±2.5[1,4] | 76.6±1.3 |
| Albumin concentration, g/L | 42.9±1.2 | 37.5±2.0[1] | 37.4±1.3[1,4] | 42.9±1.2[4] |
| Albumin content,% | 54.1±2.9 | 46.9±3.1[1] | 51.1±2.5[3,4] | 47.3±1.3[1] |
| Glucose concentration, mmol/L | 4.6±0.4 | 4.6±0.3[2] | 5.9±0.3[1,2] | 5.3±0.3[4] |
| Total lipids concentration, g/L | 4.3±0.2 | 4.8±0.2[1,3] | 4.8±0.2[1,3] | 4.0±0.5[1] |
| Cholesterol concentration, mmol/L | 2.0±0.2 | 1.7±0.2[3] | 1.3±0.2[1] | 1.1±0.1[1] |
| Triglycerides concentration, mmol/L | 1.4±0.1 | 1.5±0.2 | 1.5±0.2 | 1.3±0.1[4] |

Notes: [1] – statistically significant differences compared with the control group (p≤0.05), [2] – statistically significant differences compared with the group of animals exposed to nanoparticles of another size (p≤0.05), [3] – statistically significant differences compared with the group of animals exposed to Lead Nitrate (p≤0.05), [4] – statistically significant differences between groups of animals of another series (p≤0.05)




A – 1st series (18 weeks), and B – 2nd series (18 weeks with Thiocetam). Particles size – 30 nm. PAS-reaction and azur II (× 400)

***Figure 1.*** The structure of the liver in experimental groups after exposure to nanoparticles of lead sulfide

At week 18 without Thiocetam, destructive changes in the liver were preserved: with interlobular edema and infiltration by lymphocytes and histiocytes found less often. However, in the post-exposure period, capillary functions are restored and protective cellular responses to inflammation fade out. Euchromatin content in the rounded nuclei also did not prevail, which indicates the low synthetic activity of hepatocytes. However, at this stage, the degenerative changes in the hepatocytes are not fully restored, as evidenced by the number of glycogen granules being low and hepatocytes contours being distinct.

The liver morphology of all experimental animal groups to whom toxic substances were administered 60 times with Thiocetam added in the post-exposure period was characterized with recovery of microvascular permeability, blood filling of capillaries and structure of the hepatic plates restored (Fig. 1). There were no signs of inflammation. The observed dystrophic changes of hepatocytes were poorly discernable, and we observed rounded nuclei containing euchromatin. This indicates their synthetic activity and, respectively, restoration of the number of glycogen granules.

Without Thiocetam, the cross-sectional area of the hepatocytes nuclei in animals exposed to both $PbS_{nano1}$ (61.71±1.37 μm$^2$) and $PbS_{nano2}$ (66.32±2.34 μm$^2$) was statistical significantly larger as compared with control group (55.97±1.63 μm$^2$) and $Pb(NO_3)_2$ (58.32±1.29 μm2) (Table 4).

With Thiocetam, the cross-sectional area of the hepatocytes nuclei in animals exposed to $Pb(NO_3)_2$ (54.72±3.00 μm$^2$), $PbS_{nano1}$ (54.91±1.15 μm$^2$) and $PbS_{nano2}$ (57.01±2.72 μm$^2$) was not different to the control group index (56.45±2.72 μm$^2$) (Table 4).

Without Thiocetam, the cross-sectional area of the hepatocytes cytoplasm of rats exposed to both $PbS_{nano1}$ (156.17±7.17 μm$^2$) and $PbS_{nano2}$ (178.46±10.82 μm$^2$) was significantly smaller than in the control (200.01±5.56 μm$^2$) and in the group $Pb(NO_3)_2$ (224.93±10.71 μm$^2$) (Table 4). At the same time, indicators in the nanoparticle groups increased, unlike those in the groups without Tiocetam, possibly due to decreasing of intercellular edema. With Thiocetam, the cross-sectional area of the hepatocytes cytoplasm of rats $PbS_{nano1}$ (215.54±9.85 μm$^2$) and $PbS_{nano2}$ (216.95±11.08 μm$^2$), $Pb(NO_3)_2$ (201.34±9.01 μm$^2$) was not statistically significant different compared to control (199.20±6.66 μm$^2$) group (Table 4).

Morphometric data of laboratory rats' hepatocytes not exposed to lead, but with only Thiocetam influence did not show any significant differences in comparison with control animal values (Table 4).

***Table 4.*** Morphometric data of hepatocytes in the liver of experimental animals

| Groups | Nuclei cross-sectional area μm² (n=15) | Cytoplasm cross-sectional area μm² (n=15) |
|---|---|---|
| 18 weeks (1nd series) = 12 weeks exposures + 6 weeks without Thiocetam | | |
| Control | 55.97±1.63 | 200.01±5.56 |
| $PbS_{nano1}$ | 61.71±1.37[1,2,4] | 156.17±7.17[1,2,3] |
| $PbS_{nano2}$ | 66.32±2.34[1,2,4] | 178.46±10.82[1,2,3] |
| $Pb(NO_3)_2$ | 58.32±1.29 | 224.93±10.71[1] |
| 18 weeks (1nd series) = 12 weeks exposures + 6 weeks with Thiocetam | | |
| Control | 56.45±2.72 | 199.20±6.66 |
| $PbS_{nano1}$ | 54.91±1.15[4] | 215.54±9.85[4] |
| $PbS_{nano2}$ | 57.01±2.72[4] | 216.95±11.08[4] |
| $Pb(NO_3)_2$ | 54.72±3.00 | 201.34±9.01[4] |
| Thiocetam | 55.54±2.41 | 200.32±6.45 |

Notes: [1] – statistically significant differences compared with the control group (p≤0.05), [2] – statistically significant differences compared with the group of animals exposed to nanoparticles of another size (p≤0.05), [3] – statistically significant differences compared with the group of animals exposed to Lead Nitrate (p≤0.05), [4] – statistically significant differences between groups of animals of another series (p≤0.05)

## DISCUSSION

Thiocetam, which consists of thiotriazoline and piracetam, demonstrates a broad spectrum of antioxidative, antiischemic, nootropic, membrane stimulating and cerebroprotective effects [23-25]. As the pharmacological effect of Thiocetam is conditioned by the mutually potentiating activity of thiotriazoline [26,27] and piracetam [28], the drug has positive effects in cases of heavy metal poisoning.

Hence, the use of Thiocetam as an antioxidant statistically significantly increases the mean body weight of animals as compared to the groups without prevention. Furthermore, when the drug was used, significant increase of the relative weight of liver of the experimental groups animals was observed, which may be interpreted as restoration of regenerative processes in these rats.

It is known that blood test reflects the morphofunctional status of the liver [29,30]. We have found that when Thiocetam was used in the post-exposure period in animals from the $PbS_{nano2}$ group, concentration of the total protein in blood serum, concentration of albumin, and level of cholesterol were statistically significantly lower. Moreover, serum levels of total lipids and concentration of glucose were statistically significantly higher in animals from $PbS_{nano1}$ and $PbS_{nano2}$ groups, as compared to the control value.

This confirms that the drug has positive impact on metabolic processes by stimulating the exchange of high-energy compounds, it can accelerate oxidation of glucose in the reactions of aerobic and anaerobic oxidation, elevate ATP level and stabilize the metabolism. The drug normalizes ATP/ADP ratio, increases the activity of phospholipase A, stimulates plastic and high-energy processes, increases the resilience of cerebral tissues to hypoxia and toxic impact, optimizes oxygen and glucose consumption in the presence of inadequate blood supply or the presence of acute cerebral ischemia [31].

In our study, thiocetam administration led to decrease of AST and ALT enzymes activity in the blood of the laboratory animals, as compared to the previous periods of the study and of de Ritis ratio recovery in all study groups, which may indicate the hepatoprotective effect of the drug in case of exposure to lead sulphide nanoparticles and ionic forms of Pb nitrate [32].

In [22] and in this work, dystrophic changes of hepatocytes, impairement of vascular permeability and inflammation were observed in the liver parenchyma after exposure of animals to lead compounds. Liver damage and inflammation were also observed in rats and mice exposed to lead acetate [33,34]. The liver morphology of all experimental groups of animals to whom toxic substances have been administered with Thiocetam correction, however, was characterized by normalization of microvessels permeability and their blood filling, the restoration of hepatic plates and hepatocytes structure, and absence of inflammation.

In both series of animals exposed to lead nanoparticles ($PbS_{nano1}$ and $PbS_{nano2}$), the cross-sectional area of the hepatocytes cytoplasm and the cross-sectional area of the hepatocytes nuclei were less, but in the series treated with Thiocetam, all values did not differ as compared to control.

There are reports that using of Thiocetam in clinic also produces positive effects. Here, intraperitoneal injection of 250 mg/kg of Thiocetam for 14 days after cranial trauma essentially lowers the manifestations of liver dysfunction: the normalization of the general biliary acids content and of the conjugated bilirubin content and the biliary excretion speed occur on day 14th and day 28, respectively [35].

## CONCLUSION

The obtained results allow to conclude that Thiocetam administration shows preventive purpose in the postexposure period, and promotes restoration of biochemical and morphological indicators. This points to the feasibility of implementing preventive measures in case of exposure to lead nanoparticles.

## ORCID iDs

Sergii Omelchuk http://orcid.org/0000-0003-3678-4241
Vasyl Aleksiichuk http://orcid.org/ 0000-0002-1700-6391
Yuri Chaikovsky http://orcid.org/0000-0002-8821-8930
Liudmyla Sokurenko http://orcid.org/0000-0002-6870-2290

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