UDC 57.014:504.75.06

R.M. Tazitdinova[1], R.R. Beisenova[2], I.B. Fakhrudenova[1]

[1]Sh. Ualikhanov Kokshetau State University, Kazakhstan;
[2]L.N. Gumilyov Eurasian National University, Astana, Kazakhstan
(E-mail: irm85@mail.ru)

Change of hematological blood indicators with acute combined intoxication with zinc, copper and arsenic salts

This article indicated the investigation results on the morphofunctional blood changes of experimental animals with acute combined intoxication with heavy metal salts (zinc, copper, arsenic) carried out on 40 white outbred pubescent rats that were divided into four groups. It is noteworthy that heavy metals can accumulate in the animal and human organism. As the result, disturbed the functions of the different organs and systems and changed of hematological blood indicators. Biochemistry of blood can diagnose the pathology of the organism. There were used such solutions as copper sulfate, zinc sulphate and sodium arsenite as toxicants, which were intragastrically injected once. Blood sampling was conducted the next day after the injection. The results of our investigation showed that acute combined intoxication with zinc, copper and arsenic salts leads to the development of inflammatory processes in the body, which can be indicated by an increase of such blood indicators as leukocytes, erythrocytes, hemoglobin, hematocrit, mean hemoglobin in erythrocyte (MCH) and speed erythrocyte sedimentation (ESR). It was found that the combined effect of zinc and arsenic has the greatest toxic effect.

Keywords: heavy metals, zinc, copper, arsenic, combined intoxication, hematological blood parameters.

Introduction

One of the most important anthropogenic factors in the biosphere is pollution of the environment, and as a result, the accumulation of toxic substances in nature, which adversely affects the soil, plants, animals and humans. The intensification of industrial production and chemicalization of agriculture leads to the appearance of chemical compounds in the ecosystem, which are toxic to the people [1].

Annually, there is an increase in the amount of emissions of contaminators, which contain heavy metals, into the environment. Toxicants are able to accumulate in nature and move from plants to living organisms, having a negative impact on the health of animals and humans.

Heavy metals are dangerous substances that pose a serious risk to ecosystems and the health of organisms because of their high toxicity and stability in nature. Accumulating in the environment, heavy metals can be transported to crops and negatively affect human health through the food chain [2, 3].

In some works devoted to the problems of environmental pollution and environmental monitoring, list of heavy metals includes more than 40 metals from D.I. Mendeleev periodic table with the atomic mass of more than 50 atomic units: V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Mo, Cd, Sn, Hg, Pb, Bi, etc. [4]. For many industrially developed cities, the presence of a separate pollutant in the environment is not typical, but there is always a complex of heavy metals capable of having a combined effect on the body, in which both the summation of effects and their potentiation can be observed [5]. Therefore, the study of the technogenic accumulation consequences of heavy metals and anthropogenic natural environment pollution has now become important for the health and safety of the population [6].

In Kazakhstan, soils pollution with heavy metals is one of the relevant problems, especially in the vicinity of large industrial cities. The main environmental contaminants are represented by industrial enterprises, mining, energy, household waste, motor transport, etc [7]. The active use of natural resources, the development of the extractive industry led to the accumulation of harmful substances in the biosphere, as a result of which hundreds of land hectares became unsuitable for agricultural purposes [8].

For example, in the Akmola region, the mining, chemical, light and food industries are well developed. There are at about 20 mining and processing enterprises in the region, which use such minerals as gold, uranium-bearing, iron-containing ores and building materials. The ores in the fields contain also toxic substances, such as radioactive isotopes of uranium, thorium, potassium-40, arsenic, beryllium, selenium, phosphorus, etc. [9].

These substances, after getting into the human body, can disrupt the functions of some organs, cause morphofunctional changes in the blood, as it is indicated by hematological and biochemical blood indicators.

Hematologic parameters such as hemoglobin, red blood cells (erythrocytes), mean hemoglobin in erythrocyte (MCH) and mean hemoglobin concentration in erythrocyte (MCHC) are constantly used to assess blood capacity as an indicator of environmental pollution [10].

Blood is an important physiological system, which plays a huge role in the functioning of the whole organism, therefore hematological studies are of great value [11].

As it is known, blood is the internal environment of the body, which ensures the vital activity of cells, being an intermediary between them and the external environment. Therefore, according to the morphological and biochemical changes in blood, one can judge about certain pathological processes occurring in the body. Toxic poisoning from the hematological indicators can cause a change in the concentration of hemoglobin, erythrocytes. The eosinophilia occurs and the resistance of erythrocytes decreases [12].

The most detailed study of the changes in morphofunctional erythrocyte indicators during chemicals intoxication of different nature, which a person faces each day, allows determining the consequences of their effects properly and also selecting the most effective adjustments under the existing environmental conditions. The toxic effect of various heavy metal compounds is mainly due to the interaction with the proteins of the body, so they are called protein poisons [13].

G.R. Khanturina on the basis of E.A. Buketov Karaganda State University, studied the effect of heavy metals (zinc sulphates, copper, iron and cobalt sulfates) on the morphophysiological changes in rat blood. She revealed that as a result of acute intoxication salts of zinc, copper and iron there was leucocytosis developing, the number of red blood cells decreasing, and also the fall in the erythrocyte concentration [14].

Similar studies were carried out by authors M.R. Khanturin, R.R. Beisenova, S.S. Taikina, and A. Asankhan. They studied the effect of acute intoxication with zinc salts and copper on the cytological parameters of rat blood. Their research results showed an increase in the number of leukocytes, a decrease in the concentratin of red blood cells and a decrease in the concentration of hemoglobin in the blood of experimental animals [15].

However, the combined effect of heavy metals (zinc, copper, arsenic) has not been studied yet. Since the composition of contaminants includes several substances, the great interest is paid to the combined effect on the body. In connection with this, the goal of the study was to study the combined effects of zinc, copper and arsenic salts on hematologic indicators of blood in acute intoxication of laboratory animals.

Methodology

Experimental work was carried out on 40 white outbred pubescent rats, which were divided into four groups. The first group (n = 10) consisted of control animals, which were kept under standard conditions on the usual diet and water diet. The second group (n = 10) of laboratory animals was once intragastrically injected with solutions of zinc and copper salts, the dose of copper sulfate II was 130 mg/kg, zinc sulfate was 175 mg/kg. The third group (n = 10) was made up of animals, which were once intra-gastrointestinal injected with the solutions of copper and arsenic salts, the dose of copper sulfate II was 130 mg/kg, sodium arsenite was 10 mg/kg. The fourth group (n = 10), was also once intragastrically injected with solutions salts of zinc and arsenic, the dose of zinc sulfate was 175 mg/kg, sodium arsenite was 10 mg/kg.

Blood was collected the next day after the injection, from the carotid artery of experimental animals. Hematologic blood indicators were determined on a modern automatic hematological analyzer called Nihon Kohden Celltac E (Japan). The following methods were used during the investigation: the white blood cell was determined with the help of the unified counting method in Goryaev's counting chamber, the number of erythrocytes with the help of the unified counting with 0.9 % sodium chloride solution and the hemoglobin concentration were determined by hemoglobin cyanide method, the hematocrit was determined by a calculation, based on the number of erythrocytes in a certain volume of blood and the average volume of one erythrocyte. Average concentration of hemoglobin in the erythrocyte (MCH) was calculated by the formula:

$$\text{MCH} = \frac{\text{Hemoglobin in g/l}}{\text{First three numerals of erythrocytes concentration in 1l}}(\text{pg}).$$

ESR was determined with the help of PR-3 (ESR meter, Panchenkov's apparatus), which is a plastic tripod with nests for the installation of 20 capillaries. The Panchenkov capillary is a standard glass capillary for the determination of ESR: its length is 172 mm, outer diameter is 5 mm and the hole diameter is 1.0 mm. There is also a clear brown graduation from 0 to 10 cm, scale step of 1.0 mm high the upper division of the

scale is marked «0» and the letter «B» (blood), in front of the 50's division there is the letter «R» (reagent). The measurement time was 1 hour [16].

The results were processed using *Microsoft Office Excel* software, *Statistica* for Windows. The arithmetical mean (M), the standard error of the arithmetic mean (m) were calculated. The significance of differences in the arithmetic mean was estimated using Student's t-test (t) and significance level (p).

Results and discussion

It was found that in acute combination toxicity with copper sulfate, zinc sulfate and sodium arsenite salts, the number of leukocytes in all experimental groups increased. In the second group this index increased by 80 % ($p < 0.05$), in the third group by 29.15 % ($p < 0.05$), in the fourth group by 22.35 % ($p < 0.05$) in comparison with the control group (Table). A pronounced leucocytosis (an increase in the number of leukocytes per unit blood volume) is probably caused by hyperplasia of the myeloid or lymphatic tissue caused by the toxic effect of salts of heavy metals. As a result, myelopoiesis is activated and the output of leukocytes from the bone marrow is increased in the systemic circulation.

Table

Hematologic indicators of rats blood with acute intoxication with zinc, copper and arsenic salts

Blood indicators	Groups of experimental animals			
	1st group (control group)	2nd group (intoxication with zinc and copper salts)	3rd group (intoxication with copper and arsenic salts)	4th group (intoxication with zinc and arsenic salts)
Leucocytes, $\times 10^9$/L	6.82±0.18	11.96±0.44*	8.55±0.44*	8.1±0.08*
Erythrocytes, $\times 10^{12}$/L	7.8±0.18	8.77±0.23**	9.19±0.09*	8.9±0.16*
Hemoglobin, g/L	127±2.33	141±2.09*	158±0.53*	166±0.2*
Hematocrit, %	33.16±1.32	35.11±0.75*	38.48±0.28**	40.22±0.48*
MCH, pg	15.09±0.73	16.21±0.36*	17.27±0.13*	18.71±0.3*
ESR, mm/h	4.8±0.17	4.3±0.11**	5.6±0.12*	7.3±0.11*

Note. * — the differences are significant compared to the control group, with $p < 0.05$; ** — the differences are significant in comparison with the control group, with $p < 0.01$; *n* — the number of animals in the groups.

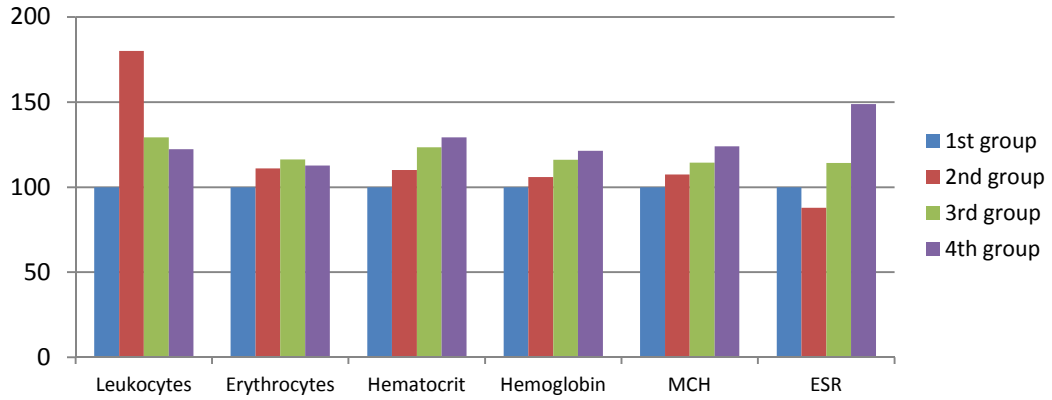

Figure. Dynamics of hematologic blood indicators in acute combined intoxication with zinc, copper and arsenic salts

It can be seen from Figure that the number of erythrocytes in the groups increased: in the second group it increased by 11.01 % ($p < 0.01$), in the third group by 16.33 % ($p < 0.05$), in the fourth by 12.66 % ($p < 0.05$) in comparison with the control group. This is probably due to an increase in the production of red blood cells in the red bone marrow, the lack of oxygen in the tissues of the body, the violation of the liver, the development of renal pathology, and as a consequence the release of erythropoietin.

The hemoglobin concentration increased in the second group by 10.15 % ($p < 0.05$), in the third group by 23.44 % ($p < 0.05$), in the fourth group by 29.69 % ($p < 0.05$). An increase in hemoglobin is associated with the increase in the number of erythrocytes, which is proved by our experiment data. An increase in the number of erythrocytes indicates the excessive formation of red blood cells in the bone marrow during poi-

soning. Perhaps, erythrocytosis is associated with an increase in the viscosity of blood in the vessels, and also with the lack of oxygen.

In the course of the experiment it was found that the hematocrit increased in the second group by 5.88 % ($p < 0.05$), in the third group by 16.04 % ($p < 0.05$), in the fourth group 21.29 % ($p < 0,05$), in comparison with the control group. Perhaps this is due to the development of pathological processes in the body, increased blood density, which may indicate leukemia or tumor processes in the kidneys, and may also indicate an oxygen deficiency, along with hemoglobin and the number of erythrocytes increase.

The mean hemoglobin content in the erythrocyte (MCH) in all groups increased, in comparison with the control group indicators: in the second group by 7.42 % ($p < 0.05$), in the third group by 14.47 % ($p < 0.05$), The increase in the mean hemoglobin content in erythrocyte can be caused by liver disease, which is called hypothyroidism.

ESR (sedimentation rate of erythrocytes) in the second group decreased by 12.2 % ($p < 0.05$), in the third and fourth groups increased by 14.28 % ($p < 0.05$) and 48.9 % ($p < 0.05$) consequently. Decrease in ESR can be caused by a violation of water-salt metabolism in the body (hyperhydration) or progressive dystrophy of the muscles (myodystrophy). Increase in the rate of erythrocyte sedimentation is probably due to a change in the protein composition of the blood, i.e. increase in fibrinogen, alpha and gamma globulins, and decrease in albumins. When developing pathological processes on the surface of the erythrocyte, molecules of fibrinogen, gamma globulin, paraprotein and other proteins are deposited, which promotes the adhesion of red blood cells to each other, and as a result, the rate of erythrocyte sedimentation increases.

Conclusion

Thus, acute combined intoxication in the group injected with zinc and copper, there was a significant increase in the number of leukocytes in the blood, i.e. leucocytosis, in comparison with the third and fourth group, an increase in the erythrocyte content, an increase in the hemoglobin level, an increase in the hematocrit, an increase in MCH, a decrease in ESR.

In the group of combined action of copper and arsenic, an increase in the content of leukocytes, erythrocytes, a greater increase in the hemoglobin content than in the second group, an increase in hematocrit, MCH, and ESR was observed.

In the group of combined effects of zinc and arsenic, an increase in the content of leukocytes, erythrocytes, a more pronounced increase in hemoglobin concentration was observed in comparison with the second and third group, i.e. erythrocytosis, increased hematocrit, a significant increase in MCH and ESR comparing with the second and third group.

All of the above can prove that the group of combined action of zinc and arsenic had the greatest toxic effect on the change in morphofunctional blood indicators.

References

1 Jong W.C. Heavy metal contamination of soils and waters in and around the Imcheon Au-Ag mine, Korea / W.C. Jong, J.Y. Eun, K.Y. Jee, Y.H. Jong, L. Khanghyun, S.L. Won et al. // Journal of Agricultural Chemistry and Environment. — 2013. — Vol. 2, No. 4. — P. 1369–1375.

2 Chen A.L. Correlation of the Taq1 dopamine D2 receptor gene and percent body fat in obese and screened control subjects: A preliminary report / A.L. Chen, K. Blum, T.J. Chen, J. Giordano, B.W. Downs, D. Han et al. // Food & Function. — 2012. — No. 3. — P. 40–48.

3 Adriano D.C. Trace Elements in Terrestrial Environments Biogeochemistry Bioavailability and Risk of Metals [Electronic resource] / D.C. Adriano // New-York: Springer-Verlag, 2001. — Access mode: https://books.google.kz/books?id=H17Tw8NujfYC&printsec=frontcover&hl=ru&source=gbs_atb#v=onepage&q&f=false

4 Зайцева О.Е. Особенности накопления микроэлементов в плаценте и пуповине при нормальной и осложненной гестозом беременности: автореф. дис. … канд. мед. наук: 14.00.01 — «Акушерство и гинекология» / О.Е. Зайцева. — М., 2006. — 157 с.

5 Ревич Б.А. «Горячие точки» химического загрязнения окружающей среды и здоровье населения России / А.Б. Ревич; под ред. В.М. Захарова. — М.: Акрополь, 2007 — 192 с.

6 Чикенева И.В. Эколого-биогеохимическая оценка растительного покрова зоны влияния Орско-Новотроицкого промышленного узла: автореф. дис. … канд. биол. наук: 03.00.16 — «Экология» / И.В. Чикенева. — Оренбург, 2009. — 27 с.

7 Национальный доклад о состоянии окружающей среды и об использовании природных ресурсов Республики Казахстан за 2017 год. [Электронный ресурс]. — Режим доступа: http://ecogosfond.kz/.

8 Нефедова Т.Г. Современные критерии рационального использования земель Казахстана [Электронный ресурс] / Т.Г. Нефедова // Ізденістер, нәтижелер. Исследования, результаты. — 2011. — № 2. — С. 231–235. — Режим доступа: http://izdenister.kaznau.kz/files/full/2013_2.pdf

9 Сыздыкова Г.Т. Воздействие состояния окружающей среды Акмолинской области на здоровье человека / Г.Т. Сыздыкова, И.Б. Фахруденова, Д.А. Сулейменова, А.Б. Билялова // Кокшетауский гос. ун-т им. Ш. Уалиханова. — 2012. — С. 135–138.

10 Shah S.L. Hematological parameters on tench (*Tinca tinca* L.) afteracute and chronic exposure to lethal and sublthal mercury treatments / S.L. Shah, A. Altindag // Bull. Environ. Contam. Toxicol. — 2004. — № 73. — P. 911–918.

11 Симонян Г.А. Ветеринарная гематология / Г.А. Симонян, Ф.Ф. Хисамутдинов. — М.: Колос, 1995. — 256 с.

12 Блинов В.А. Основы клинической биохимии человека и животных / В.А. Блинов. — Саратов: Приволж. кн. изд-во, 1996. — 248 с.

13 Кочарли Н.К. Влияние ионов тяжелых металлов на мембранную устойчивость эритроцитов в норме и при различной патологии организма. / Н.К. Кочарли, С.Т. Гумматова, Х.Д. Абдуллаев, Н.М. Зейналова // Фундаментальные исследования. — 2012. — № 11–2. — С. 299–303.

14 Хантурина Г.Р. Функциональные нарушения организма при отравлении солями тяжелых металлов и их коррекция: автореф. дис. … д-ра биол. наук: 03.03.01 — «Физиология» / Г.Р. Хантурина. — Бишкек, 2012. — 37 с.

15 Хантурин М.Р. Изменения цитологических показателей крови при острой интоксикации цинком и медью и на фоне кровохлебки лекарственной / М.Р. Хантурин, Р.Р. Бейсенова, С.С. Тайкина, А. Асанхан // Вестн. Караганд. ун-та. Сер. Биология. Медицина. География. — 2013. — Вып. 2. — С. 22–27.

16 Абрашова Т.В. Физиологические, биохимические и биометрические показатели нормы экспериментальных животных: справочник / Т.В. Абрашова, Я.А. Гущин, М.А. Ковалева, А.В. Рыбакова, А.И. Селезнева, А.П. Соколова и др. — СПб.: ЛЕМА, 2013. — 116 с.

Р.М. Тазитдинова, Р.Р. Бейсенова, И.Б. Фахруденова

Мырыш, мыс және күшәла тұздарымен жедел аралас улану кезінде қанның гематологиялық көрсеткіштерінің өзгерістері

Мақалада төрт топқа бөлінген 40 ақ тексіз жетілген егеуқұйрықтарға ауыр металдар (мырыш, мыс, күшәла) тұздарын қолдана отырып жасалған зерттеу жұмысының нәтижесі бойынша эксперименттік жануарлардың қан морфофункционалдық өзгерістері көрсетілген. Ауыр металдар жануарлар мен адам ағзасында жиналып, әртүрлі органдар мен жүйелердің жұмысын бұзады. Осыған байланысты қанның биохимиялық құрамы өзгереді. Қан биохимиясы ағзаның патологиясын анықтауға көмектеседі. Экотоксиканттардың қолданылған ерітінділері, мыс сульфаты, мырыш сульфаты және натрий арсениті, жануарларға асқазан ішек жолы арқылы бір рет енгізілген. Біздің зерттеу нәтижесі көрсеткендей, жедел мырыш, мыс және күшәла тұздарымен қосарласа уыттануы қабыну дамуына соқтырды. Ағзадағы қабыну процестерін лейкоциттер, эритроциттер, гемоглобин, гематокрит, эритроциттегі гемоглобиннің орташа құрамы ұлғаюы көрсеткіштері дәлелденді. Ең улы әсері бар топ мырыш және күшәла қосарласа әрекет еткенде анықталды.

Кілт сөздер: ауыр металдар, мырыш, мыс, күшәла, аралас улану, қанның гематологиялық көрсеткіштері.

Р.М. Тазитдинова, Р.Р. Бейсенова, И.Б. Фахруденова

Изменение гематологических показателей крови при острой сочетанной интоксикации солями цинка, меди и мышьяка

В статье приведены результаты исследовательской работы по изучению морфофункциональных изменений крови экспериментальных животных при острой сочетанной интоксикации солями тяжелых металлов (цинка, меди, мышьяка), выполненной на 40 белых беспородных половозрелых крысах, которые были разделены на четыре группы. Известно, что тяжелые металлы способны накапливаться в организме животных и человека, приводя к нарушению работы различных органов и систем, вследствие чего происходят изменения в биохимическом составе крови. Биохимия крови позволяет диагностировать патологии организма. В качестве токсикантов были использованы растворы сульфата меди, сульфата цинка и арсенита натрия, которые вводились животным внутрижелудочно однократно. Забор крови осуществляли на следующий день. Результаты исследований показали, что острая сочетанная интоксикация солями цинка, меди и мышьяка приводит к развитию воспалительных процессов в организме. На это указывает увеличение таких показателей крови, как лейкоциты, эритроциты, гемоглобин, гематокрит, среднее содержание гемоглобина в эритроците (МСН) и скорость оседания эритроцитов (СОЭ). Было выявлено, что наибольшим токсическим эффектом обладает группа сочетанного действия цинка и мышьяка.

Ключевые слова: тяжелые металлы, цинк, медь, мышьяк, сочетанная интоксикация, гематологические показатели крови.

References

1 Jong, W.C., Eun, J.Y., Jee Y.K., Jong, Y.H., Khanghyun, L., & Won, S.L., et al. (2013). Heavy metal contamination of soils and waters in and around the Imcheon Au-Ag mine, Korea, *Journal of Agricultural Chemistry and Environment*, *2, 4,* 1369–1375.

2 Chen, A.L., Blum, K., Chen, T.J., Giordano, J., Downs, B.W., & Han, D. et al. (2012). Correlation of the Taq1 dopamine D2 receptor gene and percent body fat in obese and screened control subjects: A preliminary report. *Food & Function*, *3,* 40–48.

3 Adriano, D.C. (2001). Trace Elements in Terrestrial Environments Biogeochemistry Bioavailability and Risk of Metals. New-York: Springer-Verlag. *books.google.kz.* Retrieved from https://books.google.kz/books? id=H17Tw8NujfYC& printsec=frontcover&hl=ru&source=gbs_atb#v=onepage&q&f=false

4 Zaitseva, O.E. (2006). Osobennosti nakopleniia mikroelementov v platsente i pupovine pri normalnoi i oslozhnennoi hestozom beremennosti [Peculiar properties of accumulation of trace elements in the placenta and umbilical cord with normal and complicated pregnancy gestosis]. *Extended abstract of candidate's thesis.* Moscow [in Russian].

5 Revich, B.A. (2007). *«Horiachie tochki» khimicheskoho zahriazneniia okruzhaiushchei sredy i zdorove naseleniia Rossii [«Hot points « of chemical pollution of the environment and health of the population of Russia]*. Moscow: Akropol [in Russian].

6 Chikeneva, I. V. (2009). Ekoloho-bioheokhimicheskaia otsenka rastitelnoho pokrova zony vliianiia Orsko-Novotroitskoho promyshlennoho uzla [Ecological and biogeochemical assessment of the vegetation cover of the zone of influence of the Orsk-Novotroitsky industrial site]. *Extended abstract of candidate's thesis.* Orenburg [in Russian].

7 Natsionalnyi doklad o sostoianii okruzhaiushchei sredy i ob ispolzovanii prirodnykh resursov Respubliki Kazakhstan za 2017 hod. [National report on the state of the environment and on the use of natural resources of the Republic of Kazakhstan for 2017]. (n.d.). *ecogosfond.kz.* Retrieved from. http://ecogosfond.kz/ [in Russian].

8 Nefedova, T.G. (2011). Sovremennye kriterii ratsionalnoho ispolzovaniia zemel Kazakhstana [Modern criteria of the rational use of earth of Kazakhstan]. *Izdenister, natizheler. Issledovaniia, rezultaty — Research, results, 2,* 231–235. Retrieved from: http://izdenister.kaznau.kz/files/full/2013_2.pdf [in Russian].

9 Syzdykova, G.T., Fakhrudenova, I.B., Suleimenova, D.A., & Bilialova, A.B. (2012). Vozdeistvie sostoianiia okruzhaiushchei sredy Akmolinskoi oblasti na zdorove cheloveka [The impact of the the environment of the Akmola region on human health]. *Kokshetauskii hosudarstvennyi universitet im. Sh. Ualikhanova — Sh. Ualikhanov Kokshetau State University,* 135–138 [in Russian].

10 Shah, S.L. (2004). Hematological parameters on tench (*Tinca tinca* L.) afteracute and chronic exposure to lethal and sublthal mercury treatments. *Bull. Environ. Contam. Toxicol, 73,* 911–918.

11 Simonian, G.A. (1995). *Veterinarnaia hematolohiia [Veterinary Hematology]*. Moscow: Kolos [in Russian].

12 Blinov, V.A. (1996). *Osnovy klinicheskoi biokhimii cheloveka i zhivotnykh [Fundamentals of clinical biochemistry of humans and animals]*. Saratov: Privolzhskoe knizhnoe izdatelstvo [in Russian].

13 Kocharli, N.K., Gummatova, S.T., Abdullaev, Kh.D., & Zeinalova, N.M. (2012). Vliianie ionov tiazhelykh metallov na membrannuiu ustoichivost eritrotsitov v norme i pri razlichnoi patolohii orhanizma [Heavy metal ions effect on the membrane resistance of erythrocytes in normal and with various pathologies of the body]. *Fundamentalnye issledovaniia — Basic research, 11, 2,* 299–303 [in Russian].

14 Khanturina, G.R. (2012). Funktsionalnye narusheniia orhanizma pri otravlenii soliami tiazhelykh metallov i ikh korrektsiia [Functional disorders of the body in cases of poisoning by salts of heavy metals and their correction]. *Extended abstract of Doctor's thesis.* Bishkek [in Russian].

15 Khanturin, M.R., Beisenova, R.R., Taikina, S.S., & Asankhan, A. (2013). Izmeneniia tsitolohicheskikh pokazatelei krovi pri ostroi intoksikatsii tsinkom i mediu i na fone krovokhlebki lekarstvennoi [Cytological changes of blood parameters in acute intoxication with zinc and copper amid burnet drug]. *Vestnik Karagandinskoho Universiteta. Seriia Biolohiia. Meditsina. Heohrafiia — Bulletin of Karaganda University. Series Biology. Medicine. Geography, 2,* 22–27 [in Russian].

16 Abrashova, T.V., Gushchin, Ya.A., Kovaleva, M.A., Rybakova, A.V., Selezneva, A.I., & Sokolova, A.P. et al. (2013). *Fiziolohicheskie, biokhimicheskie i biometricheskie pokazateli normy eksperimentalnykh zhivotnykh [Physiological, biochemical and biometric indicators of the norm of experimental animals]*. Saint Petersburg: LEMA [in Russian].