

# NEW METHODS FOR DETOXIFICATION OF HEAVY METALS AND MYCOTOXINS IN DAIRY COWS

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↳Supporting Information

**ABSTRACT:** Among the many environmental and industrial factors that adversely affect the soil, the pollution with heavy metals and mycotoxins occupies a special place in livestock breeding. This study aimed to demonstrate methods of treating and pharmacological correction of a toxic state intensified by heavy metals and mycotoxins in cattle using native drug as mycotoxin-deactivating feed additive. A total of 20 highly productive Holstein cows aged 3-4 years were divided into 2 groups, based on clinical and biochemical parameters. The experimental group (n=10) fed a diet supplemented with 4% sorption complex and a drug based on *Silybum marianum* and ursodeoxycholic acid as a hepatoprotector named "Hepaton-vet". The control group (n=10) was injected with a complex of sorbents (consisting of perlite, vermiculite, and polyphedan in equal proportions) at a dose of 4% of the daily intake of food, and the rest of the treatment was carried out with the help of daily infusion therapy. So in the feed samples, only the T-2 and Deoxynivalenol (DON) indicators exceeded the normal value by 1.66% and, 3%, respectively. Thus, the practical efficiency concerning T-2, aflatoxin and Deoxynivalenol were to 100%, 86%, 18%, respectively. Cadmium in compound feed was lower by 44%, in comparison with the maximum permissible concentration, followed by 53.3% in hay and 78% in silage. The amount of lead in compound feed and silage was 78%, and it was 35% in the hay. In conclusion, the use of a complex of sorbents, together with newly developed component "Hepaton-vet", led to positive results, allowing for the identification of several effects that influenced the metabolic processes in the liver, which was confirmed by the results of morpho-biochemical blood tests and clinical diagnostics of the animals' condition.

**Keywords:** Cattle, Heavy metals, Mycotoxins, Silage, Sorption complex.

## INTRODUCTION

The co-occurrence of organic pollutants and heavy metals in soil is of great concern to scientists around the world (Ye et al., 2017), but the versatility of this problem and the lack of knowledge about the relationship between soil ecology and the fate of pollutants limits the development of a specific control strategy (Yang et al., 2015). Despite this, various committees and funds have already been created around the world to monitor, assess the state, and forecast changes in the state of the environment, created to highlight the anthropogenic component of these changes against the background of natural processes (Vorotnikov et al., 2020).

Among the many techno-genic factors that adversely affect the soil cover, soil pollution with heavy metals (HMs), such as zinc, lead, and cadmium, occupies a special place. In addition, mycotoxins also cause great damage to the entire agro-industrial complex (Gallo et al., 2015) Mycotoxins can cause many adverse health effects and pose serious health risks to both humans and livestock (Haque et al., 2020). Thus, the Codex Alimentarius Commission (a joint intergovernmental body of FAO and WHO, based on the recommendations of JECFA, develops and adjusts international standards and codes of practice to limit the content of mycotoxins in certain foods (Cozma et al., 2017). The chemical composition of feed and food can be considered a reflection of the chemical pollution of the environment in general and the soil in particular (Rodrigues and Römken, 2018). Control of toxic elements is necessary to block them in any part of this ecological chain before entering to agricultural cycles (Rigby and Smith, 2020).

The maximum level of concentration of a particularly toxic element in animal feeds and diets must be considered taking into account the duration of use of contaminated feed products, methods of their processing, and storage. Prolonged exposure to heavy carcinogenic elements in small amounts, imbalance of diets in essential nutrients, keeping animals in poor conditions can also have a devastating effect on the body (EFSA's Panel on Additives and Products or Substances used in Animal Feed, FEEDAP, 2016).

At the same time, it should be taken into account that agriculture is a rapidly developing industry, and by increasing the concentration of livestock, it is difficult to provide all the necessary parameters for raising animals. And by creating

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natural conditions of detention, it is impossible to ensure the pace of production. Thus, to obtain high results, it is necessary to strike a balance between the desired profit and the physiological capabilities of animals. Particularly in cattle rearing, mismanagement of feeding program and dietary contaminations with heavy metals and mycotoxin often leads to metabolic disorders of the liver (Kan and Meijer, 2007; Semenenko et al., 2017). Degenerative obesity of the liver, leading to necrosis of hepatocytes and their disintegration with subsequent autolysis, can occur with chronic intoxication with spoiled silage with a high content of butyric acid, vegetable and mineral poisons such as alkaloids, lupine, phosphorus, arsenic, mercury, as well as feeding animals with residues technical feed processing (Dhama et al., 2015).

In the case of oral poisoning, the absorption of heavy metals occurs in an ionized form in the duodenum and the initial section of the jejunum (Foulkes, 2000). In the blood, metals circulate in the form of ions in combination with amino acids, forming a strong bond with blood proteins, therefore, within several months, metals are distributed and deposited in all organs (Elder et al., 2015; Oymak et al., 2017). Especially in large quantities, metals and arsenic accumulate in the kidney and liver tissues, because. They have an increased content of metallothionein protein, rich in thiol groups (Blanco-Penedo et al., 2006). The excretion of metals occurs through the kidneys, liver, sweat, and salivary glands, which is accompanied by damage to these organs and tissues (Lehman-McKeeman, 2008).

There is a natural relationship between the toxicity of a metal and its physicochemical properties (Jaishankar et al., 2014), such as: the higher the atomic weight of the metal, the more toxic its preparations; the stronger the association with proteins, the higher the toxicity; organic metal compounds are more toxic than inorganic ones; as the valency of a metal decreases, its toxicity increases; with an increase in the degree of dissociation of the metal salt, toxicity increases.

When animals fed by diets contaminated with toxicogenic fungi, mycotoxins can be detected in meat and dairy products (Yang et al., 2020). The mechanism of their action is due to the blocking of vital amino acids - alanine, tyrosine, tryptophan and the formation of amines, which, even in small quantities, can adversely affect blood vessels. In acute poisoning, for example, with aflatoxin, the target organ is the liver, in which necrosis and fatty degeneration develop, and in chronic poisoning, cirrhosis, and primary cancer (Burcham, 2014).

Detoxification of mycotoxins and heavy metal in feed is a new challenge of feed producing companies (Elliott et al., 2020; Neculai-Valeanu et al., 2020). Thus, present study offers a treatment regimen with native drugs (plant-based medicines) that will reduce overall intoxication and obtain high-quality environmentally friendly products. The purpose of this study is to demonstrate new ways of treating and pharmacological correction of a toxic state intensified by heavy metals and mycotoxins in cattle using native drugs.

## MATERIALS AND METHODS

In present experiment, the content of mycotoxins was determined by enzyme-linked immunosorbent assay (ELISA) on Agra Quant kits (Agra Quant® Deoxynivalenol ELISA test, Australia). To quantitatively characterize the sorption capacity of the sorption complex (perlite, vermiculite, and polyphedan), the indicator "Practical efficiency factor - PKPD" was adopted. The sorbent capacity is determined as a percentage, by the difference between adsorption and desorption. Sorption of mycotoxins was determined quantitatively at different pH, simulating the change in the acidity of the environment in the digestive tract of animals. The percentage of adsorption and desorption was measured during the in vitro test. Heavy metals in feed and milk samples were determined by the atomic absorption spectrometry according to Smirnov et al. (2008).

Production experiments were carried out at the Agricultural Production Cooperative (APC) "Kolkhoz Leninsky Put", Vasilievskoye village, Pushkinogorsk district, Pskov region, on highly productive Holstein cows aged 3-4 years. The cows participating in the experiment were housed. Feeding was carried out 2 times a day using a typical diet: corn silage, alfalfa haylage, bagasse, alfalfa hay, molasses, and compound feed. Access to water is free, *ad libitum*.

The animals were divided into 2 groups. The diagnosis was made based on clinical and biochemical parameters. The first group (n=10) was administered a sorption complex with food at a dose of 4% of the daily norm, and a drug based on *Silybummarianum* and ursodeoxycholic acid - "Hepaton-vet" (experimental prototype in the form of an emulsion, developed by the Department of Pharmacology and Toxicology of the Federal State Budgetary Educational Institution of Higher Education "SPbGUVU") was used as a hepatoprotector, which described by Kalyuzhny et al. (2021). The second group (n=10) also a tea complex of sorbents at a dose of 4% of the daily intake of food, and the rest of the treatment was carried out with the help of daily infusion therapy.

The criteria for the therapeutic efficacy of the sorption complex (based on perlite, vermiculite, and polyphedan, in equal proportions) and the drug "Hepaton-vet" were positive changes in the clinical condition of cows, the dynamics of blood homeostasis (Stepanov et al., 2021). The assessment of the clinical condition of the experimental animals was carried out daily, biochemical studies of blood serum - in the middle of the experiment and at the end of the experiment, morphological studies of blood - at the end of the course of drug therapy.

### Statistical analysis

Statistical processing of the obtained data was carried out using Microsoft Excel and Statistica 6.0 programs using Student's t-test. The results are considered statistically significant at  $p < 0.05$ .

## Ethical regulation

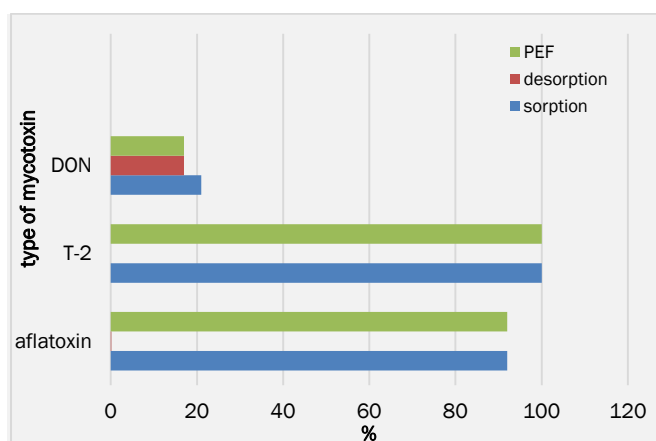
The procedure of the experiment fully complied with the Directive of the European Parliament and the Council of the European Union 2010/63/EU of September 22, 2010 on the protection of animals used for scientific purposes, and was also approved by the Bioethics Committee of the Federal State Budgetary Educational Institution of Higher Education "Saint-Petersburg State University of Veterinary Medicine".

## RESULTS AND DISCUSSION

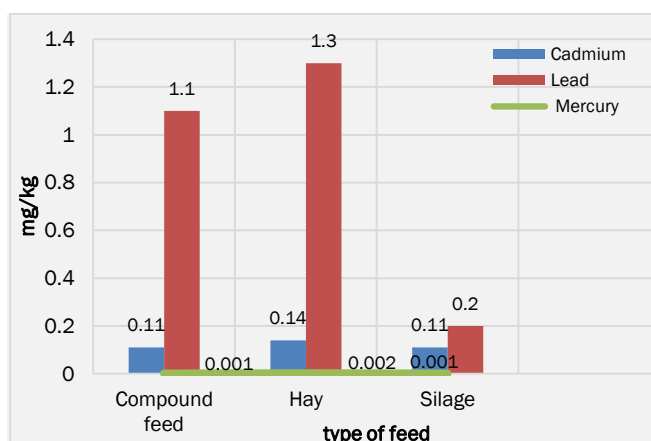
The toxicological evaluations of the feed showed that both feed and silage on the farm contain mycotoxins, which is reflected in Table 1. Table 1 shows an assessment of the content of mycotoxins in feed in the agro-industrial complex "Kolkhoz Leninsky Put", for the complex selection of sorbents in phytobiotics, when analyzing the quantitative characteristics of the sorption capacity (indicator of the practical efficiency of the sorbent in percent). Thus, the content of T-2 toxin in the silage was 25%, higher than those in compound feed and silage, zearalenone was 10% higher, also. The content of aflatoxin exceeded was 60% higher than the than in compound feed and silage. So in the feed samples, only the T-2 indicator exceeded the normal value by 1.66%, Deoxynivalenol (DON) by 3%. To quantitatively characterize the sorption capacity, the Practical Efficiency Factor (PEF) of the sorbent was determined as a percentage, by the difference between adsorption and desorption. The data is shown in Figure 1. Figure 2 shows the content of cadmium, lead and mercury in different types of feed of the APC "Kolkhoz Leninsky Put".

**Table 1** - Evaluation of the content of mycotoxins in feed in the agricultural cooperative "Kolkhoz Leninsky Put"

Mycotoxins	Content in feed, mg/kg	Compound (concentrate) feed; KK-60-1-3	Hay	Silage
T-2 mycotoxin		0.061±0.01	0.071±0.01	0.075±0.012
Zearalenone		0.067±0.01	0.082±0.008	0.11±0.03
Aflatoxin		0.0038±0.005	0.066±0.015	0.064±0.017
Deoxynivalenol (DON)		1.03±0.2	2.52±0.4	1.0±0.3
Ochratoxin		0.0001±0.00015	0.0032±0.0016	0.004±0.001



**Figure 1**- Sorption capacity of the sorption complex, % (DON= Deoxynivalenol; PEF= Practical Efficiency Factor),



**Figure 2** - The ratio of heavy metals in feed of different types at the Agricultural Production Cooperative (APC) in Pskov region (measures presented in %)

Thus, the studied feeds also turned out to be safe concerning heavy metals. Thus, cadmium in feed, in comparison with the maximum permissible concentration (MPC), was lower by 44%, in the hay by 53.3%, in silage by 78%. The largest amount of cadmium was found in hay 0.14 mg/kg, 27% more than in compound feed and silage. The amount of lead in compound feed was below the limit values by 78%, in the hay by 35%, in silage by 78%. The content of mercury, as well as in the soil, was the lowest and amounted to 0.001 mg/kg in mixed fodder and silage, 0.002 mg/kg in the hay.

The state of intoxication and pathology of the liver was diagnosed based on anamnesis, clinical examination, palpation, percussion, auscultation, and the results of morphological and biochemical blood tests. Clinical examination of cows with signs of hepatosis was characterized by symptoms, manifested by general depression, muscle weakness, progressive emaciation against the background of a decrease in appetite. On the part of the gastrointestinal tract, disorders of the proventriculus (hypotension and atony), stagnation of food masses in the book, slowing down of intestinal peristalsis, as well as diarrhea, followed by constipation, were noted. The body temperature was normal or decreased to the minimum limits of the norm.

In some cases, in animals on the mucous membranes of the eyes and eyelids, anemia, icterus, as well as hemorrhages of various scales, from pinpoint to diffuse, were recorded. Peeling of the epidermis was observed on the surface of the skin. With jerky palpation of the abdominal wall, the liver area was painful, and in most cases, there was a displacement of the percussion border of the liver. The boundaries of the area of hepatic blunting were localized in the range from the 13<sup>th</sup> to the 9<sup>th</sup> rib, while the shape of the percussion border was palpable in the form of a half-lobe or an elongated rhombus. To clarify the diagnosis, blood was taken from the animals for laboratory tests. A general blood test of cows found that the most significant differences between sick cows (with toxicity) and clinically healthy animals were revealed in the level of erythrocytes and hemoglobin, the values of which were lower than in healthy cows by 21.3% and 25.2%, respectively.

It was found that during the experimental period in the experimental groups, the hemoglobin content increased by 3.9% and 3.6%. According to the level of erythrocytes, there was a tendency to increase their number by 12.1% (experimental group 1) and 10.2% (experimental group 2). Color index values increased by 10.6% and 11.3%, respectively. Such a picture may be the result of regenerative processes in the hematopoietic system and positive changes in the work of the blood depositing organ - the liver. Whereas in animals that did not receive the drug, the number of red blood cells decreased by 14.2% compared with the background values of the group (Table 2).

Under the influence of drugs (complex of sorbents and "Hepaton-vet") in cows of both experimental groups, there was a decrease in the level of leukocytes by 23.2% and 21.4% relative to the background (Table 2). In control animals, on the contrary, signs of leukocytosis were noted in the blood. In cows with clinical signs of general intoxication, deviations were observed in several biochemical parameters of blood serum, manifested by hypoproteinemia and hypoalbuminemia against the background of a decrease in the protein-synthesizing function of the liver (the concentration of total protein and albumin fraction was 74% and 82% of the corresponding indicators of healthy cows). The level of urea was reduced in 61% of the samples, low glucose content was noted (Table 3).

**Table 2 -Hematological indices of cows after the application of a complex of sorbents and the drug "Hepaton-vet" (M±m; n=10)**

Indicator	Experimental group	Control group	P Value
Leukocytes (10 <sup>9</sup> /l)	7.4±0.17 <sup>b</sup>	10.5±0.26 <sup>a</sup>	P ≤ 0.05
Eosinophils (10 <sup>9</sup> /l)	0.4±0.02	0.5±0.02	-
Neutrophils (10 <sup>9</sup> /l)	2.1±0.09	1.9±0.19	-
Lymphocytes (10 <sup>9</sup> /l)	4.6±0.23	7.6±0.18	-
Monocytes (10 <sup>9</sup> /l)	0.3±0.03	0.3±0.02	-
Eosinophils (%)	4.0±0.07 <sup>b</sup>	4.5±0.06 <sup>a</sup>	P ≤ 0.05
Stab neutrophils (%)	2.2±0.16	2.4±0.18	-
Segmented neutrophils (%)	24.3±1.93	15.9±1.77	-
Lymphocytes, %	64.9±4.28	74.3±4.62	-
Monocytes, %	3.7±0.29 <sup>a</sup>	2.9±0.32 <sup>b</sup>	P ≤ 0.05
Erythrocytes (10 <sup>12</sup> /l)	7.44±0.38	5.21±0.4	-
Hemoglobin (g/l)	109.4±5.19 <sup>a</sup>	93.6±4.35 <sup>b</sup>	P ≤ 0.05
Hematocrit (%)	28.4±1.46	21.4±2.13	-
Average erythrocyte volume (fL)	49.7±2.5	43.5±1.6	-
Average content of hemoglobin in an erythrocyte (pg)	17.4±0.67	17.4±0.43	-
Color indicator (units)	0.96±0.06	0.83±0.04	-
Platelets (10 <sup>9</sup> /l)	316.4±26.2	232.8±34.6	-
Average platelet volume (fL)	7.0±0.51	5.1±0.34	-
Thrombocrit (%)	0.5±0.04	0.3±0.03	-
erythrocyte sedimentation rate (ESR)	1.2 ±0.06	1.4±0.03	-

Control group: ate a complex of sorbents (consisting of perlite, vermiculite, and polyphapanin equal proportions) at a dose of 4% of the daily intake of food; Experimental group: fed a diet supplemented with 4% sorption complex and a drug based on *Silybum marianum* and ursodeoxycholic acid as a hepatoprotector named Hepaton-vet.

**Table 3 - Serum biochemical parameters of cows with hepatitis when using the "Hepaton-vet" (M±m; n=10)**

Indicator	Experimental group		Control group	
	10 <sup>th</sup> day	21 <sup>st</sup> day	10 <sup>th</sup> day	21 <sup>st</sup> day
Glucose.mM/l	2.09±0.12	2.76±0.21	2.32±0.14	1.84±0.11
Cholesterol.mM/l	3.94±0.3	5.82±0.6*	3.2±0.3	3.6±0.2
Triglycerides.mM/l	0.15±0.04	0.18±0.03	0.16±0.04	0.13±0.04
Total bilirubin. μM/l	11.8±0.6	6.13±0.3**	13.1±0.7	11.2±0.5
Ca.mM/l	2.22±0.06	2.61±0.07	2.11±0.11	2.18±0.13
P.mM/l	1.4±0.1	2.4±0.5	1.4±0.1	1.7±0.2
Carotene. mg %	0.43±0.03	0.61±0.02	0.26±0.02	0.22±0.01

\* p ≤ 0.05; \*\*p ≤ 0.01

**Table 4 - Content of heavy metals in milk of cows for 21 days. (M±m. n=10)**

Indicator	Experimental group		Control group	
	10 <sup>th</sup> day	21 <sup>st</sup> day	10 <sup>th</sup> day	21 <sup>st</sup> day
Cadmium (Cd)mg/l	0.006±0.001	0.003±0.0013	0.004± 0.0016	0.0046±0.0012
Lead (Pb)mg/l	0.034±0.004	0.0113±0.005	0.0175± 0.005	0.0206±0.003
Mercury (Hg) mg/l	-	-	-	-

\* p ≤ 0.05; \*\*p ≤ 0.01

Against the background of increased destructive processes in liver cells, lipid peroxidation is activated, leading to the destruction of hepatocyte membranes, which causes the release of transamination enzymes - transaminases into the bloodstream. At the same time, there is a more pronounced increase in aspartate aminotransferase, on average, 1.61 times compared with the same indicator in the blood of healthy cows, which is a diagnostic criterion for the chronic course of the pathological process in liver cells, since Aspartate transaminase (AST) belongs to mitochondrial enzymes, the concentration of which increases sharply with destruction and necrosis of hepatocytes. The decrease in alanine aminotransferase was less pronounced - by 21.3-23.9% of the species norm.

An increase in the activity of alkaline phosphatase (by 2.02 times) may indicate the presence of cholestasis accompanying hepatitis provoked by toxins. The activation of this process can also explain the increase in the level of bilirubin in the blood (by 2.1-3.6 times) as a result of damage and compression of the bile capillaries. In all samples, a decrease in the level of triglycerides was recorded (Table 3), which indicates hypolipoproteinemia observed in parenchymal liver diseases. The values of carotene were low (the decrease was 1.57-4.12 times from the average limits of the species norm), which could be caused by general metabolic disorders in the body of cows, as well as deterioration in the functioning of the carotene-depositing system of the liver (Kalugniy II et al, 2021).

Thus, under the influence of complex treatment with the use of sorbents and the drug "Hepaton-vet", significant changes occurred in the biochemical homeostasis of cows. So, at the beginning of the experimental period, relative hypoproteinemia was observed in both experimental groups. At the same time, the type of proteinograms was characterized by a significant decrease in the content of albumin due to deep dystrophic changes in hepatocytes, leading to disruption in the biosynthesis of proteins of this fraction with a tendency to increase in  $\gamma$ -globulins (as a result of compensatory redistribution of the protein spectrum of blood serum). But already by the 12th day of therapy, there was a gradual normalization of the fractional composition of blood serum, due to an increase in the level of albumin against the background of a decrease in the level of gamma globulin fraction. At the same time, the concentration of albumins in the first group, with the use of "Hepaton-vet", by the end of the experiment increased relative to the indicators of control animals by 21.2% and 17.3%, respectively, and the concentration of the gamma globulin fraction decreased by 37.3% and 40%.

An important factor in the study of sorption medicines is their ability to absorb the main toxicants, in particular heavy metals. Heavy metals in milk samples were determined by atomic absorption spectrometry. Samples were taken from animals of the first and second groups.

At the beginning of the study, the presence of heavy metals in the experimental and control groups was significantly below the maximum allowable values. Mercury was not detected in any of the samples. The amount of cadmium in the control group by the end of the experiment increased by 15%, lead by 17%. In the experimental group, where the sorption complex and "Hepaton-vet" were used, we observed the reverse dynamics, the amount of cadmium decreased by 50%, lead by 66%. However, it should be noted that the level of heavy metals in milk in both the experimental and control groups by the end of the experiment remained within the acceptable range.

It was established that therapy with an integrated approach aimed at reducing general intoxication and maintaining the liver function, using a sorption complex based on perlite, vermiculite, and polyphapan, and the drug "Hepaton-vet", had a positive effect on the clinical and metabolic status of cows. Clinically, this was manifested by an improvement in appetite, activation of digestion processes, and normalization of the motor function of the scar. The number of ruminant periods increased on average up to 5 times per day. Starting from the third week of therapy, the condition of the skin and mucous membranes of the body improved in cows. Against this background, in animals of the control group, the clinical picture of fatty degeneration of the liver persisted.

Phytobiotics (phytosorption) are natural medicines or feed additives of plant origin, and there is numerous published studies related to potential of these components for detoxification of mycotoxins and heavy metals in farm animals (Holanda and Kim, 2020; Holanda et al., 2021a, 2021b). Essential oils that are part of phytobiotic complexes, unlike antibiotics, have a selective antimicrobial effect, inhibiting the growth of pathogenic microflora in the gastrointestinal tract, and at the same time creating conditions for the growth of "useful" probiotic microflora (Abd El-Hack et al., 2021; Krivonogova et al., 2021). The development of green technologies that make it possible to economically and effectively clean the gastrointestinal tract of animals, along with the expansion of the range of sorption preparations, is currently



promising. One of such technologies can be the addition of phytosorption complexes (FSK) to the feed (Awad et al., 2010; Nadziakiewicz et al., 2019). Known effective sorption preparations based on minerals and mineral phytosorbents are given in the following articles (Yakovleva et al., 2016; Daulet et al., 2019). However, phytosorption complexes are more promising due to the clinical efficacy comparable to sorbents of another origin (Tiwari et al., 2006; Torok et al., 2017), while they practically do not affect livestock products, are safer in pharmaco-toxicological respect, their registration is greatly simplified by the bio waiver procedure. The joint use of phytosorption complexes together with hepatoprotectors is, in many respects, an innovative idea (Ponamarev and Popova, 2020), but is one of the most effective methods of pharmacological correction of such pathologies, taking into account their pathogenesis (Patent No. 2742414 C1).

## CONCLUSION

In conclusion, based on findings of present study, it is possible to evaluate the targeted treatment of animals, and we can no longer talk about the group, but the individual treatment of productive animals based on the geographical location of the enterprise, and, consequently, cost reduction and, as a result, obtaining high-quality and safe products. Thus, the study of feed for mycotoxins showed a high degree of contamination. And although the data of the study of mixed feed show the level of mycotoxins, on the verge of acceptable values, nevertheless, such feed can subsequently harm the body. The level of productivity was lower by 11.42% in cows of the control group, which received a normal diet. During the 21 days of the experiment, dietary treatment of Sorption complex - 60 grams per animal with food, "Hepaton-vet" - orally at a dose of 100 ml 1 time per day was efficient for detoxification of mycotoxin and heavy metals in cows. The proposed method, the use of a complex of sorbents, together with "Hepaton-vet", led to positive results, identifying several effects that influenced the metabolic processes in the liver, which was confirmed by the results of morpho-biochemical blood tests and clinical diagnostics of the animals' condition. Therefore, the use of complex sorption materials and hepatoprotectors, which allow leveling the negative impact of environmental factors, is very promising. The use of sorption complexes with newly developed component "Hepaton-vet" in veterinary medicine, as part of the transition to a highly productive and environmentally friendly agricultural economy, will make it possible to carry out a pharmacological correction of the toxic state intensified by heavy metals and mycotoxins in cattle using native preparations, as well as to create pure products.

## DECLARATIONS

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### Authors' contribution

All authors have equal contribution in research and writing of the article.

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The research has no founding resources.

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The authors have not declared any conflict of interests.

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