

EXPERIMENTS TO DETERMINE THE ACTIVITY OF A CHEMICAL PREPARATION AGAINST BRUCELLOSIS

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Annotation. The article discusses the possibilities of using the preparation creolin, which is used in veterinary practice for insecto-acaricidal and disinfectant purposes, for sanitation of animals with brucellosis.

The results of studies showed that in *in vitro* experiments using *B. melitensis* 16M strain, creolin without phenol in concentration of 0.125 - 1.0% has bactericidal effect. In experiments on white mice with oral and subcutaneous administration of 1-2% suspension of phenol-free creolin in volumes of 1.0 and 0.3 ml, respectively, harmlessness and safety of the drug was established. Similar results were obtained on sheep.

The efficacy of the drug in guinea pigs pre-infected with *B. melitensis* 16M strain, when administered orally three times, amounted to -66%, and when administered subcutaneously did not exceed -33%. In animals of other groups, to which the drug was administered 4 times, the efficacy of the drug was 100% regardless of the route of administration.

Sheep, which gave positive result for brucellosis in agglutination reaction with titers 1:100-1:400, were completely cured by three times treatment with 2% creolin suspension, regardless of the method of administration. At the same time, antibody titers in animals treated 3 times, although halved from the initial level, but did not completely disappear.

Key words: creolin, phenol, brucellosis, preparation safety, sanitation efficacy.

Introduction. Creolin is a dark brown liquid with the odor of cresol. Creolin is widely used in veterinary practice as an insecto-acaricidal and disinfectant. Creolin is widely used in veterinary practice as an insecto-acaricidal and disinfectant. Coal creolin was first obtained by James in 1857 as an antiseptic. Coal creolin was introduced into veterinary practice in 1875 by Pearson and Frehner, who studied its "parasitocidal" properties [1].

As early as 1892, heavy emulsions of coal oil began to be used for winter spraying against plant pests. In 1900 coal oil began to be used as insecticides in Germany, Holland and Denmark. Since 1921, preparations based on coal oil began to be used in England, and then in the USA [2]. The main active substances of creolin are phenols (26%), neutral coal oils (51%), soaps (13%) and water (10%). The main toxicity of this product is due to phenols, which damage the gastrointestinal tract, liver, kidneys and nervous system [3].

Historically, veterinary medicine did attempt to use creolin not only as a disinfectant but also as an adjuvant in the treatment of some infections, including brucellosis, especially in the mid-twentieth century. Some old manuals mention the use of creolin in weak solutions (0.1-0.5%) for oral administration or injection into animals to stimulate the immune system and nonspecific reactions. Such methods were used as part of complex therapy along with vaccination and

antibiotics [4-6].

However, in modern veterinary practice such methods are considered outdated and ineffective. Creolin has a toxic effect when administered orally and parenterally and can cause poisoning of animals, liver and kidney damage. Today creolin is not known as a cure for brucellosis, but only as a disinfectant and antiseptic agent.

At present, phenol-free creolin is produced, containing as an active ingredient: naphthalene - 11.5% (in terms of coal tar) and as auxiliaries: rosin, sodium ichthyol, sodium hydroxide, neonol and water. In appearance, the preparation is a dark brown, transparent, homogeneous oily liquid, applied in a thin layer. With water it forms a stable emulsion of milky white or milky gray color. Phenol-free creoline is an insectocidal agent.

It is also effective against Gram-positive and Gram-negative bacteria, including the causative agent of brucellosis, when used as a disinfectant for the treatment of rooms, equipment and tools rather than for the treatment of infectious diseases [7]. According to the degree of impact on the body creolin phenol-free belongs to moderately hazardous substances (hazard class 3). Slaughter of sheep for meat is allowed 15 days after treatment. Due to the absence of phenols the action of phenol-free creolin is non-aggressive, which allows to use it for treatment of equipment and premises where contact with animals is possible. Taking into account the above-mentioned data, the purpose of our research was an attempt to use phenol-free creolin for sanitation of animals with brucellosis.

Materials and methods. Study Setting and Design

These studies were conducted on the basis of the laboratory of the brucellosis of "Kazakh Scientific Research Veterinary Institute" LLP.

Studies involving animals were approved by the Ethical Commission of "Kazakh Scientific Research Veterinary Institute" LLP.

The objects of the study were: 1. phenol-free creolin, produced by PJSC Plant "Veterinary preparations", Russia, 500 ml each in dark plastic bottles; 2. *B. melitensis* strain 16M; 3. laboratory animals - white mice (n=20), weighing 18-20 g, guinea pigs (n=12), weighing 800-900 g, and sheep (n=18), weighing 40 kg.

Serologic and bacteriologic studies for brucellosis were performed according to generally accepted methods [8].

Determination of the bacteriocidal effect of phenol-free creolin

The bacteriocidal effect of the preparation was studied in laboratory conditions in in vitro experiments. For this purpose, equal amounts of different concentrations of phenol-free creolin were added to 1 ml of meat-peptone broth (MPB) containing 1 billion CFU of *B. melitensis* 16M strain and incubated at 37°C for 48 hours. Then the bacteriocidal effect of the preparation was determined by the presence or absence of growth on MPB.

Determination of the safety of phenol-free creolin on white mice

To determine the safety of the drug, 5 white mice of the first group were orally administered 1% creolin suspension to 5 mice of the second group - 2% creolin suspension in the volume of 1.0 ml. Then the drug in these concentrations was administered subcutaneously in the volume of 0.3 ml to mice of the third and fourth groups. Then the clinical condition of white mice was monitored for 10 days.

Determination of the effectiveness of creolin sanitation of guinea pigs with brucellosis

To determine the effectiveness of sanitation with creolin, 12 guinea pigs weighing 800-900 g were pre-infected with *B. mellitensis* 16M strain at a dose of 1 billion CFU.

The experiment was conducted on 4 groups of laboratory animals, 3 animals in each group; animals of the 1st and 3rd groups were administered 3 times orally or subcutaneously. Animals of the 2nd and 4th groups were injected 4 times.

In 15 days after infection, all guinea pigs were tested for antibody titers and on the same day were treated with 1-treatment with finol-free creolin according to the above scheme, then 2-treatment was carried out 7 days after 1-treatment, 3-treatment - 7 days after 2-treatment, 4-treatment - 7 days after 3-treatment.

At the end of the experiment, the laboratory animals were slaughtered, samples were taken from different organs and bacteriological studies were performed.

Determination of the safety and dosage of the preparation on sheep

Before conducting experiments to determine the effectiveness of phenol-free creolin in sheep with brucellosis, experiments were conducted in laboratory conditions to determine the safety and dosage of the drug administered to experimental sheep.

In the brucellosis laboratory of the Institute three sheep of the first group were administered alimentary 1 ml of 1% creolin suspension per kg of body weight, based on the average sheep weight of 40 kg, each of them was administered 40 ml of the drug, and the other three sheep of the second group - 1 ml of 2% creolin suspension per kg of body weight, each of the sheep was administered alimentary 40 ml of phenol-free creolin.

In the above order, sheep of the second and third groups were administered 1 and 2% of the drug subcutaneously at a dose of 0.1 ml per kg, i.e. 4 ml per sheep.

The animals were monitored for 10 days.

Determination of the effectiveness of creolin treatment of sheep with positive serological reaction to brucellosis

The experiment to determine the effectiveness of animal organism sanitation with creolin was conducted in brucellosis-unfavorable sheep flock in rural district Kainar of Narynkol district of Almaty region. As a result of planned serologic research in 2024, brucellosis was detected in 27 heads out of a flock of 320 heads (incidence of 8.4%). At the owner's request, a decision was made to slaughter all animals in the herd. Taking advantage of this period, with his consent, we isolated 6 sheep that tested positive for brucellosis in different titers and conducted experiments until they were slaughtered. When the animals were taken to the sanitary slaughterhouse and slaughtered, pathologic material was taken from them and serologic and bacteriologic tests were performed.

Statistical Analysis. Statistical analysis of the data was processed mathematically on a personal computer using standard Microsoft Office 2016 package.

Results and analyzes. Determination of the bacteriocidal action of phenol-free creolin

The results of studies to determine the bactericidal effect of phenol-free creolin on *B. melitensis* strain 16M are shown in Table 1.

Table 1 – Investigation of bactericidal effect of creolin in in vitro experiments

№ of tube	Concentration of the preparation (%)	Presence or absence of growth on the MPB	Bacteriocidal effect of the drug
1	1,0	-	+
2	0,5	-	+
3	0,25	-	+
4	0,125	-	+
5	0,062	+	-
6	0,03	+	-
7	0,015	+	-

Table 1 shows that the drug had a bactericidal effect within the range of 0.125-1.0%, i.e. the ratio of the minimum and maximum doses of the drug causing bactericidal effect was 1:10. Taking this into account, in the following experiments to determine the effectiveness of the drug, we set the maximum dose of the drug at oral administration (10.0), and at subcutaneous administration - the minimum dose (1.0).

Determination of the safety of phenol-free creolin on white mice

The results of experiments to determine the safety of phenol-free creoline are shown in Table 2.

As shown in Table 2, no additional changes or abnormalities were observed in the mice during the 10-day observation period. A small reddening occurred at the site of subcutaneous injection of the drug, which subsequently transformed into a sterile abscess that resolved after 7-8

days. This experiment shows that the used concentration of the drug is safe for laboratory animals.

Table 2 – Harmlessness of phenol-free creoline in experiments on mice

Group number	Number of white mice, goals	Method and volume of drug administration	Clinical signs observed in white mice within 10 days
1	5	orally, 1.0 ml of 1% suspension	decreased appetite during the first two days, increase in body temperature by 0.2°C on average
2	5	orally, 1.0 ml of 2% suspension	decreased appetite during the first two days, increase in body temperature by 0.2°C on average
3	5	subcutaneously, 0.3 ml of 1% suspension	a small redness that later transformed into a sterile abscess that resolved in 7-8 days
4	5	subcutaneously, 0.3 ml of 2% suspension	a small redness that later transformed into a sterile abscess that resolved in 7-8 days

According to the data of Ilyin V.V., who conducted toxico-pharmacological evaluation of Biorex-GX, Creolin-X and Creostom-T preparations, these preparations do not inhibit antitoxic liver function, do not have allergic properties, do not cause embryotoxic and teratogenic effects in experimental pregnant rats, in therapeutic concentrations do not inhibit bactericidal and lysozyme activity of blood serum of calves [9].

According to Maltseva M.A., the preparations Creolin-X 2.5% and Biorex 2.5%, according to the current hygienic classification No. 01-19/126-17 of 15.08.96, in case of single oral exposure belong to the 3rd class of danger (moderately dangerous) and 4th class of danger (low dangerous), respectively, and in case of single dermal exposure - to the 3rd class of danger (moderately dangerous) [10].

Kukushkina T.R., Saitkhanov E.O., Novokov N.M. conducted a comparative study of insecto-acaricidal efficacy of "Delcid" and "Creolin" preparations at sheep melophagosis at their complex application in the form of treatment of animals by aerosol method, in combination with veterinary and sanitary treatment of housing places by irrigation method. On the basis of the conducted studies, the authors concluded that at clinical application of both means there is no negative effect on the main physiological parameters, as well as on the general clinical and biochemical blood parameters of sheep [11].

The scientific data obtained by the above authors agree with the results of our experiments and confirm the safety of coal phenol-free creoline in the recommended doses.

Determination of the effectiveness of creolin sanitation of guinea pigs with brucellosis

The results of experiments to determine the effectiveness of creolin sanitation of guinea pigs with brucellosis are shown in Table 3.

Table 3 – Effectiveness of sanitation with creolin for guinea pigs with brucellosis

Group no.	No. guinea pig	Results of serological tests (15 days after infection)	Method and volume of drug administration	1-treatment (15 days after infection)	2-treatment (7 days after 1-treatment)	3-treatment (7 days after 2-treatment)		4-treatment (7 days after 3-treatment)		Effectiveness of sanitation of identified in the course of bacteriological investigations
						serological results	bacteriological results	serological results	bacteriological results	
1	2	3	4	5	6	7	8	9	10	11
1	1	1:160	orally, 3.0 ml	ue	ue	1:80	-	ue	ue	66%
	2	1:160		ue	ue	1:80	-	ue	ue	
	3	1:80		ue	ue	1:40	+	ue	ue	

1	2	3		5	6	7	8	9	10	11
2	4	1:160		ue	ue	1:80	ue	1:40	-	100%
	5	1:160		ue	ue	1:80	ue	1:40	-	
	6	1:80		ue	ue	1:80	ue	1:40	-	
3	1	1:160	subcuta	ue	ue	1:40	+	ue	ue	33%
	2	1:160	-	ue	ue	1:40	+	ue	ue	
	3	1:80	neously	ue	ue	1:80	-	ue	ue	
4	4	1:80	, 0.3 ml	ue	ue	1:40	ue	1:40	-	100%
	5	1:160		ue	ue	1:80	ue	1:80	-	
	6	1:160		ue	ue	1:80	ue	1:80	-	

Footnote: ue - unexplored.

As can be seen from Table 2, in the experiment conducted on 4 groups of laboratory animals of 3 animals each, the drug was administered 3 times orally or subcutaneously to animals of the 1st and 3rd groups. Animals of the 2nd and 4th groups were administered the drug 4 times. The efficacy of the drug in guinea pigs with brucellosis at three times oral administration amounted to - 66%, and at subcutaneous administration did not exceed -33%. In animals of groups 2 and 4, to which the drug was administered 4 times, the effectiveness of the drug amounted to 100% regardless of the method of administration. In the course of the experiment it was found that 3 treatments are not enough to completely rid the organism of guinea pigs with brucellosis from the causative agent of brucellosis, 4 treatments are necessary. It should be noted that the titer of antibodies to brucellosis in the blood serum of guinea pigs before treatment with the drug was about 1:160-1:80, but after the 3rd and 4th treatments its level decreased by 2 times. However, even in animals showing 100% efficacy, the antibody titer did not completely disappear.

Determination of the safety and dosage of the preparation on sheep

The results of experiments to determine the safety of phenol-free creoline on sheep are shown in Table 4.

Table 4 – Harmlessness of phenol-free creoline in experiments on sheep

Group number	Number of sheep, head	Method and volume of drug administration	Clinical signs observed in sheep within 10 days
1	2	3	4
1	3	orally, 1.0 ml/kg of 1% suspension	no visible changes or abnormalities were observed
2	3	orally, 1.0 ml/kg of 2% suspension	no visible changes or abnormalities were observed
3	3	subcutaneously, 0.1 ml/kg of 1% suspension	no visible changes or abnormalities were observed
4	3	subcutaneously, 0.1 ml/kg of 2% suspension	no visible changes or abnormalities were observed

In the course of observation in animals treated with 1% and 2% creolin suspensions in the experiment, no visible changes and disorders were observed. On the basis of the conducted experiment in further experiments on therapy of sheep brucellosis patients, 2% suspension of finole-free creoline was used.

Russian scientists conducted an experiment to study the state of the detoxification system of the liver of calves when using the combined insectoacaricidal preparation Creolin-X. The results of the research showed that after a single spraying of calves with Creolin-X emulsion of 1- and 0.2% concentrations the general condition and behavior of experimental animals did not change, signs of oppression, toxicosis, as well as death of calves were not observed. After spraying of calves with

Creolin-X of 1% concentration there are insignificant fluctuations of bilirubin, urea and total protein ($P \geq 0,05$).

Creolin-X in 0.2% concentration does not cause changes in biochemical indices of calf blood and does not disturb metabolism and activity of calf blood enzymes. The results of the study indicate that Creolin-X at the recommended method of application does not lead to the development of pathological reactions, as well as does not have a toxic effect on the liver and on the body of calves, as evidenced by the dynamics of changes in biochemical indicators of experimental calves. The dynamics of biochemical parameters indicates the active participation of the liver in the metabolism of Creolin-X, and the acaricidal preparation does not have hepatotoxic effect [12].

Other Russian scientists Gilmudinov, R.Ya., Rakhmatullin, E.K., Kadikov, I.R., Vasilevsky, N.M. to study the carcinogenicity of phenol-free coal-bearing creoline (CBC) used 4 groups of Wistar rats and BOR mice, breeding vivarium of the N.N. Blokhin RONC of the Russian Academy of Medical Sciences. Based on the conducted experiments it was established that the acute oral toxicity of CBC (LDM) is 6200 mg/kg for rats and 2009 mg/kg for mice, which allows to attribute it to the IV class of danger.

Thus, the analysis of the results of the conducted chronic experiments on rats and mice allowed the authors to conclude that in these experiments the veterinary preparation CBC did not show carcinogenic activity. According to the totality of biological properties it should be referred to the III class of hazard. The amount of benzapyrene (BP) in the studied creoline sample is 0.018 1 0.002 g/kg (KBK contains 60% coal oil, in which benzapyrene is about 0.03 g/kg), which is quite a lot, as it could be assumed.

Thus, in chronic experiments on rats and mice, KBK, despite a rather high content of BP, did not show carcinogenic properties [13].

The data obtained by us are in agreement with the data of the above authors, who experimentally proved the absence of harmfulness and carcinogenic properties of phenol-free coal creoline when used in the recommended doses.

Effectiveness of Creolin treatment of sheep with positive serological reaction to brucellosis

The results of the experiment to determine the effectiveness of creolin treatment of sheep with positive serological reaction to brucellosis are presented in Table 5.

Table 5 – Effectiveness of creolin treatment of sheep with positive serological reaction to brucellosis

Group number	No. of sheep	Results of serologic tests (RA titers)	1-treatment (after positive brucellosis result)	2-treatment (on day 7 after 1-treatment)	3-treatment (on day 7 after 2-treatment)	Collection of pathologic material on day 7 after 3-treatment		Effectiveness of sanitation
						serological results	bacteriological results	
1	1	1:100	orally, 1.0 ml/kg	orally, 1.0 ml/kg	orally, 1.0 ml/kg	1:50	-	100%
	2	1:200				1:100	-	
	3	1:400				1:200	-	
2	4	1:100	subcutaneously, 0.1 ml/kg	subcutaneously, 0.1 ml/kg	subcutaneously, 0.1 ml/kg	-	-	100%
	5	1:200				1:100	-	
	6	1:400				1:200	-	

Table 5 shows that animals treated 3 times with both methods were cleared from the brucellosis pathogen. Antibody titer in animals treated 3 times, although decreased twice from the initial level, but did not completely disappear. This situation indicates that the level of antibodies in blood serum is not an indicator of the presence of the pathogen in the organism, but only to some extent characterizes the protective forces of the organism. For example, in sheep No. 3 and No. 6 the antibody titer is 1:200, but the brucellosis pathogen has not been isolated in them.

Many scientists of the world inform about the danger of uncontrolled use of insecticides [14-18]. The use of coal coal phenol-free creolin, which is an insecticidal preparation, although it showed a significant therapeutic effect in experimental brucellosis, requires experiments on large animals, because of the possible distant negative effect on the organism of animals and the environment [19-20].

As a result of this experiment it was found that after three times treatment with 2% suspension of the preparation "Creolin" sheep sick with brucellosis were completely cured. However, given the small number of animals involved in the experiment and the limited time, we consider it advisable to conduct further research on a larger scale to develop specific recommendations on this issue.

Conclusion. Phenol-free creolin preparation at a concentration of 0.125-1.0% had a bactericidal effect on *B. melitensis* strain 16M in vitro.

No additional changes or abnormalities were observed during oral and subcutaneous administration of 1-2% suspension of phenol-free creoline to 10-white mice during the 10-day observation period. When the drug was administered orally, decreased appetite and a slight increase in body temperature were observed during the first two days; when administered subcutaneously, a slight redness was observed, which subsequently transformed into a sterile abscess that resolved after 7-8 days.

The same signs were observed in sheep.

Thus, at oral and subcutaneous administration in recommended doses of phenol-free creolin to experimental white mice and sheep, harmlessness and safety of the drug was confirmed.

Four-fold treatment of guinea pigs infected with *B. melitensis* strain 16M with creolin showed 100% efficacy regardless of the route of administration. Sheep that tested positive for brucellosis in the agglutination reaction with a titer of 1:100-1:400 were completely cured when treated three times with a 2% suspension of creolin.

Administration of the drug orally or subcutaneously gave the same results. Experiments to determine the effectiveness of creolin treatment of sheep with positive serologic reaction to brucellosis showed that animals treated 3 times by both methods were cleared of the brucellosis pathogen. The antibody titer in animals treated 3 times, although halved from the initial level, did not completely disappear.

This preliminary experiment did not study the effect of the drug on the internal organs of the animals, its elimination period, or the safety of processed animal products for food purposes. However, since the experiments yielded encouraging results, we believe that these efforts should be repeated on a larger scale in the future, including studies of the drug's effects on the body and its food safety.

Conflict of interest statement. The authors declare that they have no conflict of interest.

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БРУЦЕЛЛЕЗГЕ ҚАРСЫ ХИМИЯЛЫҚ ПРЕПАРАТТЫҢ БЕЛСЕНДІЛІГІН АНЫҚТАУҒА АРНАЛҒАН ТӘЖІРИБЕЛЕР

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Аңдатпа. Мақалада ветеринариялық тәжірибеде инсектоакарицидтік және дезинфекциялық мақсатта қолданылатын креолин препаратын бруцеллезбен ауырған жануарларды емдеу үшін қолдану мүмкіндіктері қарастырылған.

Зерттеу нәтижелері *B. melitensis* 16М штаммын, фенолсыз креолинді 0,125-1,0% концентрацияда қолданылған *in vitro* тәжірибелерінде бактерицидтік әсер көрсеткенін анықтады. Фенолсыз креолиннің 1-2% суспензиясын тиісінше 1,0 және 0,3 мл көлемінде ауызша және тері астына енгізу арқылы ақ тышқандарға жүргізілген тәжірибелер препараттың зиянсыздығы мен қауіпсіздігін көрсетті. Қойларға фенолсыз креолиннің 1-2% суспензиясын ауыз қуысына және тері астына енгізу арқылы жүргізілген ұқсас тәжірибеде зертханалық жануарлардың жалпы жағдайы мен мінез-құлқы өзгермеді, депрессия, токсикоз, қойдың өлу белгілері байқалмады.

B. melitensis 16М штаммымен алдын ала жұқтырылған теңіз шошқаларында препараттың тиімділігі үш рет ауыз қуысына құйғаннан кейін -66%, тері астына енгізгеннен кейін -33% құрады. Препаратты төрт рет қолданылған басқа топтағы жануарларда препараттың тиімділігі енгізу жолына қарамастан 100% құрады.

Агглютинация сынамасы 1:100–1:400 титрімен бруцеллезге оң нәтиже берген қойлар енгізу жолына қарамастан 2% креолин суспензиясымен үш рет емдеуден кейін толық сауығып кетті. Алайда үш рет емделген жануарлардағы антидене титрлері бастапқы деңгейден екі есе азайғанымен, толығымен жойылған жоқ.

Тірек сөздер: креолин, фенол, бруцеллез, препараттың қауіпсіздігі, санация тиімділігі.

ЭКСПЕРИМЕНТЫ ПО ОПРЕДЕЛЕНИЮ АКТИВНОСТИ ХИМИЧЕСКОГО ПРЕПАРАТА ПРОТИВ БРУЦЕЛЛЕЗА

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Аннотация. В статье рассматриваются возможности использования препарата креолин, который применяется в ветеринарной практике в инсектоакарицидных и дезинфицирующих целях, для санации животных, больных бруцеллезом.

Результаты исследований показали, что в опытах *in vitro* с использованием штамма *B. melitensis* 16М, креолин без фенола в концентрации 0,125 – 1,0% оказывает бактерицидное действие. В опытах на белых мышах с пероральным и подкожным введением 1-2% суспензии безфенольного креолина, в объемах 1,0 и 0,3 мл, соответственно, установлена безвредность и безопасность препарата.

При проведении аналогичного опыта на овцах с пероральным и подкожным введением 1-2% суспензии безфенольного креолина общее состояние и поведение подопытных животных не менялись, признаки угнетения, токсикоза, а также гибель овец не наблюдались. Эффективность препарата у

морских свинок, предварительно инфицированных штаммом *B.melitensis* 16М, при трехкратном пероральном введении составила – 66%, а при подкожном введении не превысила – 33%. У животных других групп, которым препарат вводился 4 раза, эффективность препарата составила 100% независимо от способа введения.

Овцы, давшие положительный результат на бруцеллез в реакции агглютинации с титром 1:100–1:400, полностью излечились при трехкратной обработке 2%-ной суспензией креолина, независимо от способа введения. При этом титры антител у животных, обработанных 3 раза, хотя и снижается вдвое от исходного уровня, но полностью не исчезает.

Ключевые слова: креолин, фенол, бруцеллез, безопасность препарата, эффективность санации.