

DOI: 10.31073/onehealthjournal2024-III-02

UDK: 619:615.015.35-285:615.454.15

**EXPERIMENTAL ASSESSMENT OF THE ACUTE TOXICITY OF "KUBAZOL" –
SOLUTION FOR EXTERNAL APPLICATION BASED ON BIRCH TAR**

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Abstract. *Laboratory studies were conducted to determine the acute toxicity of the veterinary drug "Kubazol" on white rats.*

The drug "Kubazol" - a veterinary drug (spray for external use, solution) contains birch tar in its composition. Intended for the treatment and prevention of lesions of the skin (wounds, dermatitis, eczema), claws (injuries, superficial panaritium), hooves and hooves (foot rot, etc.) in dogs, wild pigs, wild birds and sports horses.

According to the results of determining the parameters of the acute toxicity of the drug "Kubazol" (spray for external use, solution), in the case of a single intragastric administration, the LD₅₀ for male rats is 7328.87±878.80 mg/kg of body weight, which allows us to classify it as toxic up to V class - practically non-toxic substances (LD₅₀ 5001-15000 mg/kg), and according to the degree of danger - up to IV class - low-hazard substances (LD₅₀ > 5000 mg/kg).

According to the results of toxicological studies of the veterinary drug "Kubazol" (spray for external use, solution), the LD₅₀ indicator could not be calculated, since the death of laboratory animals was not detected within 14 days after application to the skin of rats. At the same time, the maximum dose of the drug "Kubazol (spray for external use, solution) applied to the skin of rats (based on the absolute weight of the drug) was 15,000.0 mg/kg of body weight, which allows the drug to be classified according to the degree of danger to the IV class - low-hazardous substances (LD₅₀Cut>2500.0 mg/kg of body weight).

Further studies will be the next stage of pre-registration tests aimed at studying the chronic toxicity of "Kubazol", which is mandatory material in the section "Studies on safety and residues" of the dossier for this drug.

Key words: "Kubazol", rats, acute toxicity, dose, lethality, toxicity.

Effective treatment and prevention of lesions of the skin (wounds, dermatitis, eczema), claws and hooves (injuries, superficial panaritium) in Ukraine are possible only with the use of highly effective and affordable medicines. Therefore, the development of drugs with significant effectiveness and environmental safety does not lose its relevance today. Thus, "DEVIE" LLC was offered a new veterinary drug - "Kubazol" (spray for external use, solution). One milliliter of the drug contains: birch tar – 45 mg, auxiliary substances: ethyl acetate, polybutyl methacrylate – up to one milliliter. Birch tar has strong antiseptic, local irritant, anti-inflammatory, insecticidal, antiparasitic and disinfectant effects, improves blood circulation, stimulates the regeneration of the epidermis of damaged tissues, enhances the process of keratinization, dries wounds and accelerates their healing. In small concentrations (3-5%) it activates the growth of granulation, in large ones (above 10%) it sharply weakens it (Kaliuzhna & Bardova, 2011; Orlovetska & Lukianchuk, 2018; Kychan & al., 2024).

The drug "Kubazol" (spray for external use, solution) is used for the treatment of hoof and claw diseases in cattle, horses, sheep, goats, pigs, European fallow deer, deer, wild pigs, dogs

and poultry, in which the use of tar is recommended (rotting of the horn arrow); postoperative intervention on hooves and claws; for the treatment of superficial scratches and skin and claw defects; for nail care after cosmetic procedures; to stabilize bandages on hooves; treatment of dermatomycoses of domestic animals, especially in the initial stage or during recovery, when the drying effect of tar is manifested; for the treatment of wounds caused by cannibalism of poultry and pigs.

Therefore, the purpose of the research was to provide a toxicological (preclinical) assessment of the veterinary medicinal product "Kubazol" (spray for external use, solution) by determining its acute toxicity on white rats.

The purpose of the study is to carry out a toxicological assessment of the veterinary drug "Kubazol" (spray for external use, solution), under the conditions of an acute toxicological experiment on a model of white rats.

Materials and methods. An experiment to determine the parameters of the acute toxicity of the drug "Kubazol" (spray for external use, solution), with a single intragastric administration to laboratory animals, was conducted on 58 male non-linear white rats (3-4) months old and weighing (180-200) g, which were kept under optimal vivarium conditions (Zapadniuk, 1983; Kotsiumbas & al., 2006; Karkyshchenko & Hrachev, 2010): the temperature in the room was $(18\pm 2)^{\circ}\text{C}$, the relative humidity was (60-70)%, the day-night lighting cycle, during the experiment, was (10-14) hour, and the air volume in the vivarium room was changed 10 times per hour.

Rats were fed complete rodent feed. Animals had free access to water and feed.

Each animal was weighed before the start of the research. The administered doses were calculated individually according to the weight of each rat, while the volume of the drug administered intragastrically at one time did not exceed 2,5 cm³. Determination of the dose range for the main experiment was carried out in a previous experiment.

For this purpose, a control and 3 experimental groups of 4 animals each (n=4) were formed in the previous experiment based on the principle of analogues. The drug was administered in doses of 2000,0; 6000,0 and 12000,0 mg/kg of body weight, based on the absolute weight of the drug, once orally using an esophageal-gastric probe. Animals of the control group were injected with distilled water.

After taking into account the results of the previous experiment, 6 experimental groups were formed in the main experiment, whose rats were administered the drug in doses of 2000,0; 4000,0; 6000,0; 8000,0; 10,000,0 and 12,000,0 mg/kg of body weight, as well as a control group, the animals of which were injected with distilled water in a volume of 2,0 cm³ according to a similar protocol. There were 6 animals in each group (n=6).

It should be noted that the manipulations on rats were carried out in accordance with the existing regulatory documents, which regulate the organization of work using experimental animals and compliance with the principles of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986).

The clinical condition of the experimental animals was observed for 14 days, noting the appearance and development of clinical signs of poisoning, the time of death or recovery to the physiological norm. During the clinical examination of rats, attention was paid to behavior, reaction to external stimuli, presence of appetite, skin condition, color of mucous membranes, frequency of breathing and defecation, changes in color and consistency of feces, etc (Zapadniuk, 1983; Kotsiumbas & al., 2006; Karkyshchenko & Hrachev, 2010).

After the death of the animals, a pathological autopsy was performed. The macroscopic method of research was used to establish patho-anatomical changes (Zharov & al., 2003). Pathological autopsy was performed according to the following scheme:

- at the first stage, an external examination was performed, noting the condition of the wool coat and mucous membranes;

- on the second - an autopsy and examination of body cavities and internal organs, such as: pharynx, trachea, larynx, heart, lungs, liver, spleen, kidneys, stomach, intestines, was performed, noting changes in color, consistency, pattern and shape of organs.

Based on the results of death, LD₁₀, LD₁₆, LD₅₀, LD₈₄, LD₉₀, LD₁₀₀ and the error of LD₅₀ were calculated using the method of probit analysis in the modification of V. B. Prozorovsky.

The parameters of acute dermal toxicity of the drug "Kubazol" (spray for external use, solution) were studied on 36 white male rats, aged (4-5) months, weighing (250-260) g. The animals were kept in standard vivarium conditions at a temperature of (18- 21)°C, humidity (55- 65)%, on a standard diet that meets the standards.

Experiments on animals were carried out in compliance with the rules of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Scientific Purposes".

One control and 5 experimental groups, 6 rats in each, were formed for the research. A day before the beginning of the experiment, wool was removed at the intended place of application, and it was carefully cut with scissors.

Observation of experimental animals lasted 14 days, taking into account the general condition of animals, the nature of skin lesions at the application site, as well as the time of death or recovery of animals. The application of the drug "Kubazol" (spray for external use, solution) was carried out in the morning before feeding the animals.

The drug "Kubazol" (spray for external use, solution) was evenly applied to a 4×4 cm area of the skin of rats.

The animals of the experimental groups were given the drug "Kubazol" (spray for external use, solution) on the skin in doses (by absolute weight): 5000.0; 7500.0; 10000.0; 12500.0; 15000.0 mg/kg of body weight, respectively. Animals of the control group, under similar conditions, were given distilled water.

The experimental animals were observed for 14 days, taking into account the general condition of the experimental rats, the amount of feed and water consumed, the depth and nature of the skin lesions at the application site, as well as the time of death or recovery of the animals.

The obtained results were processed by methods of variational statistics using the StatPlus 7.6.5.0 software package. Data were presented as mean values with standard deviation at the 95% confidence level.

Results. In the experiment, the drug Kubazol (spray for external use, solution) was administered to rats in doses of 2000.0; 6000.0 and 12000.0 mg/kg body weight. Clinical observations showed that the intragastric administration of the drug in a dose of 2000.0 mg/kg of body weight to rats of the 1st experimental group after (5-10) minutes caused slight depression and impaired coordination of movements, which disappeared within 2 days after administration. At the same time, a decrease in appetite and thirst was registered. Starting from the 3rd day after administration, the animals were active, responded adequately to external stimuli, consumed food and water. Until the end of the experiment, the parameters of the physiological state and behavior of the rats did not differ from those of the animals of the control group. Death of rats in this group was not observed.

The pattern of poisoning by the drug was more pronounced in rats of the II experimental group (dose 6000.0 mg/kg of body weight). After 5-10 minutes, after the introduction of the drug, pronounced depression, impaired coordination of movements and heavy breathing, refusal of feed and water were observed. On the 2nd and 3rd day, the rats did not move much, they breathed hard. A decrease in feed intake and thirst was also observed. Starting from the 4th day of the experiment, the clinical condition of the 2 rats gradually recovered and on the 10-11th day of the experiment did not differ from that of the control, along with this, a comatose state and death were observed in the 2 animals on the 3rd day of the experiment.

SECTION 1

In the rats of the III experimental group (dose 12000,0 mg/kg of body weight), 5-10 minutes after administration, pronounced increasing depression was observed. Along with this, impaired coordination of movements and heavy breathing were recorded. After 3-4 hours, after the administration of the drug, the rats sat in one place, some lay on their stomachs with their pelvic limbs stretched back and practically did not react to external stimuli, their breathing was shallow and heavy. The death of all animals occurred within the first day after administration of the drug (Table 1).

Table 1

The dynamics of the death of rats in the previous experiment, to determine the acute toxicity of the drug "Kubazol" (n=16)

Terms of death rats, through	Groups of rats and doses, mg/kg body weight			
	Control	Experiment		
		I (2000,0)	II (6000,0)	III (12000,0)
1	–	–	–	4
2	–	–	–	–
3	–	–	2	–
4 – 14 days	–	–	–	–
All died	–	–	2	4

In the main experiment, the drug Kubazol (spray for external use, solution) was administered to rats in doses of 2000,0; 4000,0; 6000,0; 8000,0; 10000,0 and 12000,0 mg/kg body weight. Intragastric administration of the drug in a dose of 2000.0 mg/kg of body weight to rats of the 1st experimental group, 5-10 minutes after administration, caused slight depression and impaired coordination of movements, which disappeared within 2 days after administration. At the same time, a decrease in appetite and thirst was registered. Starting from the 3rd day after administration, the animals were active, responded adequately to external stimuli, consumed food and water. Until the end of the experiment, the parameters of the physiological state and behavior of the rats did not differ from those of the animals of the control group. The deaths of rats in this group were not observed (Table 2).

Table 2

The dynamics of the death of rats in the main experiment, to determine the acute toxicity of the drug Kubazol (n=42)

Groups of rats and doses, mg/kg body weight		Terms of death rats, through				
		1 day	2 day	3 day	4 – 14 day	Everything died
Control		–	–	–	–	–
Experiment	I (2000,0)	–	–	–	–	–
	II (4000,0)	–	–	1	–	1
	III (6000,0)	–	–	2	–	2
	IV (8000,0)	–	2	1	–	3
	V (10000,0)	4	1	–	–	5
	VI (12000,0)	6	–	–	–	6

The pattern of poisoning by the drug in rats of II-IV experimental groups (doses of 4000,0-8000,0 mg/kg of body weight) was more pronounced and dose-dependent. After 5-10 minutes, after the introduction of the drug, pronounced depression, impaired coordination of movements and heavy breathing, refusal of feed and water were observed. On the 2nd and 3rd day, the rats did not move much, they breathed hard. A decrease in feed intake and thirst was also observed. Starting from the 4th day of the experiment, the clinical condition of 5 rats from the II, 4 from the III, and 3 from the IV experimental groups gradually recovered and on the 10-14th day of the experiment did not differ from that of the control, along with this in one rat from the II, 2 from the III and 3 from the IV experimental groups was observed to be in a comatose state and died on the 2nd-3rd day of the experiment (Table 2).

A severe course of poisoning was observed in rats of V-VI experimental groups (doses of 10000,0-12000,0 mg/kg of body weight). After 5-10 minutes after the introduction, pronounced increasing depression was observed. Along with this, impaired coordination of movements and heavy breathing were recorded. After 3-4 hours, after the administration of the drug, the rats sat in one place, some lay on their stomachs with their pelvic limbs stretched back and practically did not react to external stimuli, their breathing was shallow and heavy. The death of all animals from the VI experimental group occurred within the first day after the administration of the drug, and in the V experimental group, 5 animals died within 2 days after the administration. The animal from V experimental group, which remained alive, recovered by the end of the experiment.

After the death of the rats, a pathological autopsy was performed. During the external examination, discharge from the nasal and oral cavity was noted, the wool was disheveled and dirty-white in color. The specific smell of the drug came from the rats that died on the first day. Paleness of visible mucous membranes was also observed.

At the autopsy, the animals were registered:

- blood filling of the heart, an increase in the volume of the atria, the blood was not coagulated;
- the lungs and spleen were slightly congested without visible changes;
- the stomach is very swollen with the remains of the drug;
- liver - light brown in color, not increased in volume, flabby consistency;
- kidneys slightly increased in volume, light brown in color, elastic consistency;
- in the small and large intestines, swelling and inflammation of varying degrees of severity, from serous to catarrhal-hemorrhagic, were detected.

The next stage of studying the toxicological characteristics of the drug "Kubazol" (spray for external use, solution) was the determination of the average lethal dose and its standard error (LD_{50} , LD_{10} , LD_{16} , LD_{84} , LD_{90} , LD_{100}).

The average lethal dose LD_{50} was calculated using the method of probit analysis according to V. B. Prozorovsky. The toxicometric parameters of the drug were calculated using the method of least squares, for probit analysis - lethality curves. The percentage of lethality, probits (Y), weighting coefficients of probits (Z) are established.

To construct the graph, the values of drug doses (mg/kg) were plotted on the abscissa axis, and the effect values (%) were plotted on the ordinate axis.

A graphic representation of the curve showing the dose-effect relationship for rats is presented in Fig. 1.

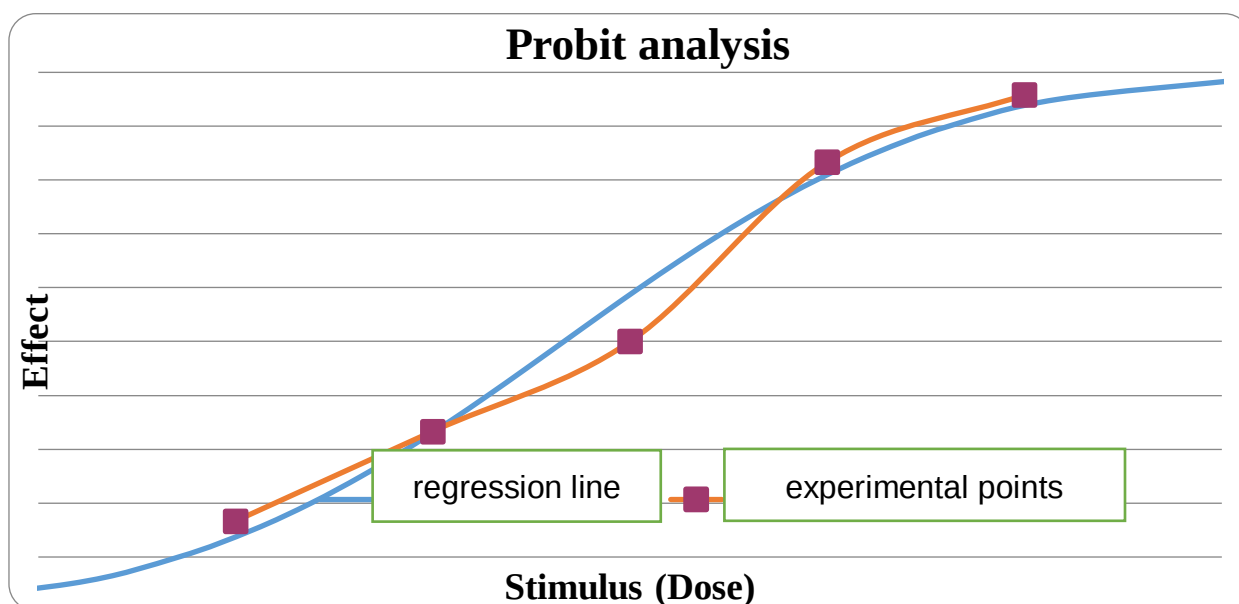


Fig. 1. The curve of lethality of male rats, under the conditions of a single oral administration of the drug "Kubazol"

The results of calculating the average lethal dose of the drug for rats, under the conditions of oral administration, are given in table. 3.

Based on the results of research, it was established that the LD_{50} of the drug "Kubazol" (spray for external use, solution) under the conditions of its single oral administration to male rats was $7328,87 \pm 878,80$ mg/kg, LD_{10} – 3426,94 mg/kg, LD_{16} – 4284,60 mg/kg, LD_{84} – 10373,13 mg/kg, LD_{90} – 11230,79 mg/kg, LD_{100} – 11895,27 mg/kg body weight, respectively.

Table 3

Results of calculation of lethal doses of the drug "Kubazol" under the conditions of a single oral administration to male rats

Stimulus (Dose)	Percentage (%)	N	Probit (Y)	Weighting factor (Z)
2000	4,1667	6	3,2680	1,5359
4000	16,6667	6	4,0326	3,5653
6000	33,3333	6	4,5697	4,5697
8000	50,0000	6	5,0000	5,0000
10000	83,3333	6	5,9674	3,5653
12000	95,8333	6	6,7320	1,5359
Regression statistics				
LD_{50}	7328,87	LD_{50} standard error		878,80
LD_{10}	3426,94	LD_{16}	4284,60	
LD_{84}	10373,13	LD_{90}	11230,79	
LD_{100}	11895,27			

Therefore, the drug "Kubazol" (spray for external use, solution) can be classified in terms of toxicity to class V – practically non-toxic substances (LD_{50} 5001-15000 mg/kg), and in terms of the degree of danger to class IV – low-hazard substances ($LD_{50} > 5000$ mg/kg) (Kotsyumbas, 2006).

It was established that after a single application of the drug "Kubazol" (spray for external use, solution) to the skin of rats in doses (5000,0-15000,0) mg/kg of body weight, no changes in the general condition and appetite of the animals were observed, which indicates absence of toxic effects of the drug. It should also be noted that none of the experimental animals died during the experiment.

Therefore, according to the results of toxicological studies of the drug "Kubazol" (spray for external use, solution), the LD₅₀ indicator could not be calculated, since the death of laboratory animals was not detected within 14 days after application to the skin of rats.

At the same time, the maximum dose applied to the skin of rats (based on the absolute weight of the drug) was 15000,0 mg/kg of body weight, which allows the drug to be classified according to the degree of danger to Class IV – low-hazardous substances (LD₅₀>2500,0 mg/kg of body weight bodies) (Kotsyumbas, 2006).

Conclusions. According to the results of determining the parameters of the acute toxicity of the drug "Kubazol" (spray for external use, solution), in the case of a single intragastric administration, the LD₅₀ for male rats is 7328,87±878,80 mg/kg of body weight, which allows it to be classified as toxic up to V class – practically non-toxic substances (LD₅₀ 5001-15000 mg/kg), and according to the degree of danger – up to IV class – low-hazard substances (LD₅₀ > 5000 mg/kg).

According to the results of toxicological studies of the veterinary drug Kubazol (aerosol), the LD₅₀ indicator could not be calculated, since the death of laboratory animals was not detected within 14 days after application to the skin of rats. At the same time, the maximum dose of the drug Kubazol (aerosol) applied to the skin of rats (based on the absolute weight of the drug) was 15000,0 mg/kg of body weight, which makes it possible to classify the drug according to the degree of danger to class IV – low-hazard substances (LD_{50Cut}>2500,0 mg/kg of body weight).

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ЕКСПЕРИМЕНТАЛЬНА ОЦІНКА ГОСТРОЇ ТОКСИЧНОСТІ “КУБАЗОЛУ” – РОЗЧИНУ ДЛЯ ЗОВНІШНЬОГО ЗАСТОСУВАННЯ НА ОСНОВІ ДЬОГТЮ БЕРЕЗОВОГО

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Резюме. Проведені лабораторні дослідження з визначення гострої токсичності ветеринарного препарату “Кубазол” на білих щурах.

Препарат “Кубазол” – ветеринарний препарат (спрей для зовнішнього застосування, розчин) у своєму складі містить дьоготь березовий. Призначений для лікування та профілактики уражень шкіряного покриву (рани, дерматити, екземи), кігтів (травми, поверхневий панарицій), копит та ратиць (гниття копитної стрілки, тощо) у собак, диких свиней, диких птахів і спортивних коней.

За результатами визначення параметрів гострої токсичності препарату “Кубазол” (спрей для зовнішнього застосування, розчин), у разі одноразового внутрішньошлункового введення LD₅₀ для щурів-самців, складає 7328,87±878,80 мг/кг маси тіла, що дозволяє за токсичністю віднести його до V класу – практично не токсичні речовин (LD₅₀ 5001-15000 мг/кг), а за ступенем небезпечності – до IV класу – малонебезпечних речовин (LD₅₀ > 5000 мг/кг).

За результатами токсикологічних досліджень ветеринарного препарату “Кубазол” (спрей для зовнішнього застосування, розчин), показник LD₅₀ розрахувати не вдалося, оскільки загибелі лабораторних тварин не було виявлено протягом 14-ти діб після нанесення на шкіру щурів. При цьому максимальна, нанесена на шкіру щурів доза препарату “Кубазол (спрей для зовнішнього застосування, розчин) (за абсолютною масою препарату), становила 15000,0 мг/кг маси тіла, що дозволяє віднести препарат за ступенем небезпечності до IV класу – малонебезпечних речовин (LD_{50cut}>2500,0 мг/кг маси тіла).

Подальші дослідження будуть черговим етапом передреєстраційних випробувань, спрямованих на вивчення хронічної токсичності “Кубазол”, що є обов’язковим матеріалом розділу “Дослідження щодо безпеки і залишків” досьє на даний лікарський засіб.

Ключові слова: “Кубазол”, щури, гостра токсичність, доза, летальність, токсичність.