



The acute toxicity assesment of Mospilan RP and Actara 25 WG for White Mice

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ABSTRACT

In this article an attempt was made to present the results of toxicity assessment of insecticides from the group of neonicotinoids, Mospilan RP (active substance acetamiprid) and Actara 25 WG (active substance thiamethoxam) in white mice. The aim was to investigate the acute toxicity of Mospilan RP and Actara 25 WG in white mice. The half-lethal dose (LD50) of Mospilan RP was found to be 131.25 ± 34.12 mg/kg Body Weight (BW) per active substance and 656.25 ± 170.6 mg/kg BW per drug, and the Lethal Dose (LD100) was 200 mg/kg BW by the active ingredient (1000 mg/kg BW by drug). The half-life dose (DL50) of Actara 25 WG for white mice was 907.81 ± 24.03 mg/kg BW for the active substance, and 3631.24 ± 96.12 mg/kg BW for the drug; The lethal dose (LD100) was also 1200 mg/kg BW per active ingredient (4800 mg/kg BW per drug). The acute course of poisoning by Mospilan RP and Actara 25 WG in mice was characterized mainly by nervous disorders (lesions of the central and peripheral nervous systems), which is evidenced by the clinical features of poisoning including depression, convulsions, ataxia (impaired movement coordination), tremor and impaired breathing. It has been established that Mospilan RP belongs to the third toxicity class according to the Hygienic classification of substances by skin-resorptive toxicity (DL50 > 2000 mg/kg).

Key words: Actara 25 WG insecticides, Acute toxicity, Insecticides toxicity, Mospilan PP, Neonicotinoids, White mice

INTRODUCTION

In Ukraine, Imidacloprid (included in the drug Confidor, 20% bp), Thiacloprid (Calypso drug, 48% bp), Acetamiprid (Mospilan drug, 20% pp), Thiamethoxam (Actor 25 WG preparation for the cultivation of vegetative crops), and neo-nicotinic insecticides are used as seed dressing agents for protecting of orchards (apple, plum), vineyards and field crops (corn, potatoes, tomatoes, cucumbers, hops, sugar beets, cereals, rapeseed, sunflower) (Bazaka et al., 2018).

In recent years, there has been an increasing amount of using anti-ectoparasite agents for dogs and cats in the veterinary practice which are based on two active substances; neonicotinoids -Nitenpyram (tablets Capstar, by Novartis Switzerland) and Imidacloprid, manufactured by the German company, Bayer Krop Sayens AG. The agents containing active substances, Imidacloprid or Thiamethoxam have been registered for home usage, public health or veterinary practice for the purposes of

disinfestation. Granular baits such as Kvik Byte VG 10 (10% imidacloprid, Kvizda Agro GmbH, Austria), Agita (10% thiamethoxam, Novartis, Switzerland), and Adamant bait for flies (1% thiamethoxam, Russia) are allowed to be used for fly control in the livestock (Smith et al., 2016).

It is believed that Neonicotinoids act selectively on the target sites, and its toxicity to animals and humans is not much significant (Ford and Casida, 2008). According to the chemical structures, Neonicotinoids are characterized to the class of nitromethylene heterocyclic compounds. They are suggested to be highly efficient at low cost rates, and relatively harmless to non-target organisms and the environment (Abrieux et al., 2016). Despite its safety and efficacy, there is evidence of Neonicotinoid toxicity to bees and other pollinator insects. Consequently, there are some restrictions imposed on the use of Imidacloprid, Thiamethoxam and Clothianidin in several European countries. What is not yet clear is the untraceable side effects of Neonicotinoids

on the animals' body, due to their vast usage in the agriculture. Previous studies in Japan have demonstrated a high sensitivity of rats' brain receptors to the effects of Imidacloprid and Acetamiprid in low doses (Kimura-Kuroda *et al.*, 2012).

In addition, a group of Turkish scientists have found the effects of Imidacloprid at doses (0.5; 2 and 8 mg/kg Body Weight (BW) for three months) on the reproduction system of male rats, indicating impaired mobility and morphological structure of sperms, as well as a significant decrease in the level of blood testosterone, activation of germ cell apoptosis, DNA fragmentation, and changes in the composition of fatty acids (Bal *et al.*, 2012a).

Clothianidin at a dose of 32 mg/kg/day has been also found to have negative effects on the reproductive functions of male rats, as a result of a significant decrease in the absolute weight of the right testicle appendage and the seminal vesicles, a decrease in the concentration of sperms, testosterone and glutathione, as well as a decrease in the number of abnormal germ cell forms, and DNA fragmentation (Bal *et al.*, 2012b). However, the same authors indicated that Clothianidin has a slight effect on the reproductive capacity of male rats in later publications (Bal *et al.*, 2013).

Imidacloprid and Thiacloprid have been discussed to have embryotoxic effects. While the authors do not describe the type of changes in the reproductive organs of males and females, it is only mentioned that pesticides provoke abortions in the pregnant females (Basaka *et al.*, 2018). Neonicotinoids are not believed to be absorbed by the skin due to their poor solubility in lipids, so acute toxicity is more evident when they are taken orally. Inacute cases of toxicity, neonicotinoids are considered mild and hazardous compounds. The prolonged exposure of the active substances in this group to laboratory animals is characterized by a general effect on the body with a predominant hepatotoxic effect (Felsot, 2001).

Acute oral toxicity of Acetamiprid (DL50) (active ingredient in the commercial drug Mopilan) for rats is 146–217 mg/kg BW, and for mice is 184–198 mg/kg BW. Acute dermal toxicity of > 2000 mg/kg BW to rats does not irritate rabbits' skin and their mucous membranes. Acute oral toxicity for quails is 180 mg/kg BW, and Lethal Concentration 50% (CL50) (24–96 years) is more than 100 mg/l, CL50 (3–6 h) for crabs, and more than 1000 mg/l for Daphnias (Basaka *et al.*, 2018).

The clinical features of intoxication are characterized by decreased activity, salivation, tremor, convulsions, ataxia, lateral recumbency, and in severe cases, hemorrhages in the lungs may cause death.

Acetamiprid is low toxic on the skin of rats for 24 hours. No clinical signs of intoxication and no irritant effects were found in DL50 in males and females at the doses greater than 2000 mg/kg BW. Additionally, no macroscopic changes have been observed in the internal organs (Basaka *et al.*, 2018). Oral toxic dose of Thiamethoxam (DL50) (active ingredient of the commercial preparation of Actara) is 1563 mg/kg BW in rats, and 871 mg/kg BW in mice. Its acute dermal toxicity (DL50 24 hours) is more than 2000 mg/kg parts per million (ppm) in rats. However, recent studies about to determine the toxicity of Neonicotinoids to bees by A.I. Illarionov (Illarionov, 2012) indicates a relationship between the death of bees and contacting to the plants treated with Thiamethoxam or Imidacloprid on the day of drugs use. Moreover, several studies have been made to show the potential danger of neonicotinoids for bees (Decourtye *et al.*, 2003; Decourtye and Devillers, 2010).

Overall, these studies provide important insights into the toxicological characteristics of Neonicotinoids. They will allow to expand and supplement the information on the potential danger of Neonicotinoids and will promote their safe usage in the agriculture and veterinary medicine.

MATERIALS AND METHODS

Experimental studies on white mice were prepared according to the procedure of Toxicological Control of New Animal Protection guidelines (Denisenko, 2013), existing documents organizing the work with laboratory animals, and the principles of the European Convention on the Protection of Vertebrate Animals for experimental and scientific purposes (Strasbourg, 1986) and Art. 26 of the Law of Ukraine No. 5456-VI of 16.10.2012. "On the Protection of Animals from Cruelty". Afterward, 104 nonlinear white mice weighing 18–20 gram were examined for acute toxicity of Mospilan RP and Actara 25 WG.

Previous study based its criteria on the method established by G. Kerber to measure the half-life dose. The direct results of the study were used to calculate the LD50. The mice were divided into equivalent groups (at least 6 mice in each one). Regarding the doses, they included LD50 and LD100 taken in different intervals for 4-5 times which were believed to be sufficient. The study was conducted in the vivarium of the Veterinary Medicine Faculty of the National University of Life and Environmental Sciences of Ukraine. Before starting the study, the mice were kept for 7 days during the adaptation period, in which a daily close observation of their clinical

condition was done. They have been hungry for 3–4 hours before the experiment started. The drug solutions were administered orally using a calculated probe, so that the solution volume did not exceed 0.4 milliliter (ml). The dose was calculated in milligram (mg) of active substance (AS) per 1 kg body weight (BW).

Twelve groups (6 groups of mice to determine the acute toxicity of Mospilan RP and 6 groups of mice to determine the acute toxicity of Actara 25 WG), and one control group (in each group $n = 8$) were set to conduct the studies on the determination of acute toxicity parameters. The mice of the experimental groups for Mospilan RP acute toxicity took 400; 200; 150; 100; 50 and 25 mg/kg body weight of the drug orally including the active substance.

the mice grouped for parameter determination of Actara 25 WG acute toxicity also took the drug orally at a rate of 1200.0; 1000.0; 875.0; 600.0; 437.5 and 218.8 mg/kg ppm in terms of AS. Mice in the control group were administered distilled water in a volume of 0.4 ml.

During the study, the clinical condition of the animals were carefully monitored for 14 days. The animals were constantly monitored on the first day. The appearance, reaction to stimuli, changes in body position, behavior, food and water intakes, the intensity and type of locomotor activity, the condition of the skin and mucous membranes were taken into account, and the development of intoxication and their death were recorded.

As a result of the studies in mice, lethal (DL100) and semi-lethal (DL50) doses of the studied drugs were used.

RESULTS AND DISCUSSION

One of the first and most important steps for determining the toxicological characteristics of a substance is to study its acute toxicity. The purpose of studying acute toxicity is to find out the toxic effects of the drug with a single injection, and to determine lethal, toxic and non-toxic doses. Acute toxicity studies include the recording of specific and nonspecific symptoms of intoxication, the general pattern of poisoning, its onset, course and consequences. The main parameter of acute toxicity is the DL50 (which leads to the death of 50% of animals after single or multiple administration over a short period of time). The average lethal (semi-lethal) dose (DL50) of the toxic substance is determined in mg/kg BW, and administered orally (or subcutaneously, intravenously, intraperitoneally, subcutaneously) in weeks.

The available literature indicated that Acetamiprid and Thiamethoxam are low-toxic substances. The half-life

of Acetamiprid (DL50) is 213 mg/kg BW for white rats, and 98 mg/kg BW for poultry. The DL50 of Thiamethoxam is 1563 mg/kg BW for white rats, and 576 mg/kg BW for poultry.

In order to find the lethal dose of Mospilan RP, the mice were separated to six experimental groups and a control one ($n=8$). The mice in the experimental groups were orally administered an aqueous solution of 0.4 ml of Mospilan RP at doses of 2000, 1000, 750, 500, 250, 125 mg/kg BW (which for DR was 400; 200; 150; 100; 50 and 25 mg/kg BW), and the control group took distilled water in a volume of 0.4 ml.

The response of the experimental groups to the drug was as same as the control one's, while the mice had a reaction to the stress caused by manipulation, There was a slight increase in locomotor activity in the first few seconds, followed by sedation of the animals. Thirst was not noticed. Changes in the general condition of mice were found in 1–5 min in animals in groups 1, 2 and 3 after they took the drug (Mospilan RP at the dose of 2000, 1000, 750 mg/kg BW). the development of signs such as depression, rapid breathing, clonic-tonic convulsions, tremor, and bouncing were exactly observed. The mice moved individually in the cage, 5 to 8 minutes after drug administration. clinical signs of inhibition increased, and the animals were supine. The average time of death for animals in the 1st and 2nd experimental groups (all were killed) was 6.5 minutes. In the group 3, 5 out of 8 animals were killed within 5 hours. No further death was observed. Relating to the mice in the group 4, the signs described were less pronounced and longer, and 2 animals were killed within 12 hours. The animals in the experimental group 5 showed mild signs of impaired locomotor activity during the first 1.5 to 2 hours, which then disappeared. The condition of animals in the experimental group 6 did not differ from the animals in the group 7 (control group).

The results of the determination of the acute toxicity of Mospilan RP are given in table 1. The data in the table show a strong evidence of Mospilan RP toxicity to white mice on oral administration at the doses of 100 mg/ kg or more. From the data, it can be seen that the deaths of mice in the experimental groups range from two to eight mice.

$$DL_{50} = DL_{100} - \frac{\sum zd}{m}$$

DL₁₀₀: the dose of the substance investigated that caused the death of all animals in the group.

d : the interval between two adjacent doses; z : = arithmetic mean of animals killed by two adjacent doses; m : the number of animals in each group.

The results of these calculations are shown in table 2.

Table 1. Protocol and the results of the acute experiment with oral administration of Mospilan RP to white mice in 2016, based on the Department of Pharmacology and Toxicology of the National University of Life and Environmental Sciences of Ukraine.

Dose, mg/kg		Number of animals in a group	The number of animals dead					The average time of death (h)
By acceptable level (active substance)	By the 3a drug		In days			all	in%	
			1	2	15			
400	2000	8	8	-	-	8	100	0.1
200	1000	8	8	-	-	8	100	0.1
150	750	8	5	-	-	5	62.5	3
100	500	8	2	-	-	2	25	12
50	250	8	0	-	-	0	0	-
25	125	8	0	-	-	0	0	-

This data is sufficient to calculate the DL50.

Table 2. Toxicity assessment of Mospilan RP according to G. Kerber method on white mice weighing 18–20 grams in 2016, based on the Department of Pharmacology and Toxicology of the National University of Life and Environmental Sciences of Ukraine.

Dose, mg/kg (by active substance)	25	50	100	150	200
Survived	8	8	6	3	0
Dead	0	0	2	5	8
Z	0	1	3.5	6.5	
d	25	50	50	50	
Zd	0	50	175	325	
Σzd			550		

d: = the interval between two adjacent doses; z: arithmetic mean of animals killed by two adjacent doses

In the present study, $m = 8$; $DL_{100} = 200$ mg/kg of body weigh by Acceptable Level (AL);

$DL_{50} = 200 - (550/8) = 200 - 68.75 = 131.25$ mg/kg of BW by AL; DL_{84} and DL_{16} were calculated using the two-point method, which examined two doses of substances selected in such a way that the frequency of the alternative effect was less than 50% in one case and higher in the other. The equation of a line passing through two points was used:

$$\frac{Y - Y_1}{Y_2 - Y_1} = \frac{X - X_1}{X_2 - X_1}$$

X_1 and X_2 are the values of the two doses tested;

Y_1 and Y_2 are the respective mortality rates.

$$\frac{84 - 25}{62.5 - 25} = \frac{X - 100}{150 - 100}, \text{ thus we get } X = DL_{84} =$$

178,67 mg/kg BW by active substance.

Similarly, DL_{16} is calculated.

$$\frac{16 - 25}{62.5 - 25} = \frac{X - 100}{150 - 100}, \text{ thus we get } X = DL_{16} = 88,0$$

mg/kg of boy weight by active substance .

The confidence limits of the DL_{50} are found by the method of K. Miller and M. Tainter by the formula $DL_{50} \pm mt$. In this case, $2\sigma = DL_{84} - DL_{16}$, and the mean error (m) of the half-lethal dose is

$$m = \frac{2\sigma}{\sqrt{N' \times 2}},$$

N' is the total number of animals in groups in which at least one animal died or survived.

According to our data, $2\sigma = 90.7$;

$$m = \frac{90,7}{\sqrt{16 \times 2}} = \frac{90,7}{5,66} = 16,02$$

The value of t is found from the Student's table, guided by a given value of $P = 0.05$, for the number of degrees of freedom $f = N' - 1$.

$$t = 2.13$$

Confidence limits DL_{50}

$$mt = 16.02 \times 2.13 = 34.12$$

$DL_{50} \pm mt = 131.25 \pm 34.12$ mg/kg BW by active substance.

As a result of the experiment, it was found that the half-lethal dose of Mospilan RP insecticide preparation is $DL_{50} \pm mt = 131.25 \pm 34.12$ mg/kg BW for active substance (656.25 ± 170.6 mg/kg for the preparation).

Lethal dose, $DL_{100} = 200$ mg/kg ppm for active substance (1000 mg/kg for drug). Due to the certain acute toxicity indicators according to the toxicity classification of substances, the investigated insecticidal drug Mospilan RP belongs to class IV – low toxic ($DL_{50} = 501-5000$ mg/kg BW), according to the classification of chemicals in

accordance with the degree of danger (GOST 12.1.007-76) it belongs up to the third class (DL50 = 151–5000 mg/kg BW).

Six experimental groups of mice and one control group (n = 8) were formed to determine the acute toxicity parameters of Actara 25 WG preparation. The experimental drug was administered orally to the animals at a rate of 4800.0 mg/kg BW in the first group, 4000.0 mg/kg BW in the second, 3500.0 mg/kg BW in the third, 2400.0 mg/kg BW in the fourth; 1750 mg/kg BW in the fifth, and 875.2 mg/kg BW in the sixth experimental group, which for DR was 1200.0, 1000.0, 875.0, 600.0, 437.5 and 218.8 mg/kg BW, respectively. For the control group, distilled water in a volume of 0.4 ml was administered to the mice. The animals were monitored for 14 days, and their dynamics of changes in their clinical conditions were observed. On the first day, the animals were under constant surveillance.

According to the results of the experiment, a lethal (DL100) and a half-lethal (DL50) dose of the study drug was set up. The animals' response in the experimental groups to the drug introduction was as same as that of the animals of the control group when the placebo was taken, while the mice had a stressful reaction to manipulation.. Although there was a slight arousal for the first few seconds, the mice settled down after a while. After the

drug was administered, changing in their general conditions were observed for 5 to 10 minutes in the mice of groups 1 and 2 (at doses of 4800, 4000 mg/kg BW). Frequent breathing, convulsions, and muscle tremors were noticed, and the mice bounced and moved individually in the cage. Over time, in 10–20 minutes after the drug used, signs of depression increased and the mice took a supine position.

The average death time of the animals in group 1 (all killed) was 15 minutes. In group 2, 7 out of 8 mice were killed within an hour. In group 3, 2 out of 8 mice were killed in 2 hours. No further death was observed. In the group 4, the signs described were less pronounced and prolonged, and no death was observed. In the mice of group 5, there was a mild inhibition during the first 1.5–2 hours. There were no significant differences in the condition of the mice in group 5 and group 7.

Table 3 indicates the toxic effects of Actaras 25 WG when administered orally to white mice in doses of 875 mg/kg BW in DR. As a result, the deaths of mice in the experimental groups ranges from two to eight mice. This data is sufficient to enable the DL50 to be calculated.

The results of calculations of the half-life dose of Actara 25 WG in accordance with the results obtained from the experiment (Table 3) using the Kerber method are shown in table 4.

Table 3. A protocol of the results of the oral administration of Actara 25 WG to white mice in 2016, basis on the Department of Pharmacology and Toxicology of the National University of Life and Environmental Sciences of Ukraine.

Dose, mg/kg		Number of animals in a group	The number of animals dead					The average term of death (h)
By active substance	By the drug		In days			all	in%	
			1	2	15			
1200	4800	8	8	-	-	8	100	0.25
1000	4000	8	7	-	-	7	87.5	1
875	3500	8	2	-	-	2	25	2
600	2400	8	0	-	-	0	0	-
437.5	1750	8	0	-	-	0	0	-
218.8	875.2	8	0	-	-	0	0	-

This data is sufficient to calculate the DL50.

Table 4. Toxicity determination of Actara 25 WG by G. Kerber method

Dose, mg/kg (by AL)	600	875	1000	1200
Survived	8	6	1	0
Dead	0	2	7	8
Z	1	4.5	7.5	
d	275	125	200	
Zd		275562	1500	
Σzd		2337.5		

d = the interval between two adjacent doses; *z* = arithmetic mean of animals killed by two adjacent doses; AL: Acceptable Level

$m = 8$; $DL_{100} = 1200$ mg/kg BW by active substance;
 $DL_{50} = 1200 - (2337,5/8) = 1200 - 292.19 = 907.81$
 MG/KG MT.

The average error (m) of the half-lethal dose is equal:

$$m = \frac{2\sigma}{\sqrt{N' \times 2}},$$

N' is the total number of animals in the groups in which at least one animal has died or survived.

In the present case (by the method of K. Miller and M. Tainter) $2\sigma = DL_{84} - DL_{16}$. The indicators DL_{84} and DL_{16} are calculated using the two-point method, in which substances were studied in two doses selected in such a way that the frequency of the alternative effect was less than 50% in one case and greater in the other. the equation of a line passing through two points is used:

$$\frac{Y - Y_1}{Y_2 - Y_1} = \frac{X - X_1}{X_2 - X_1},$$

X_1 and X_2 are the values of the two doses tested;

Y_1 and Y_2 are the respective mortality rates.

After calculations on the respective parameters of the mice in the experimental groups 2 and 3, it was found that $DL_{84} = 993$ mg/kg for active substance, and $DL_{16} = 857.0$ mg/kg of metric tons for AS. So if $2\sigma = 993 - 857 =$

136, then: $m = \frac{136}{\sqrt{16 \times 2}} = \frac{136}{5.66} = 24.03$

$DL_{50} = 907.81 \pm 24.03$ mg/kg BW by active substance.

$DL_{50} = 3631.24 \pm 96.12$ mg/kg of BW.

The half-lethal dose of the Actara 25 WG insecticide drug for white mice was $DL_{50 \pm mt} = 907.81 \pm 24.03$ mg/kg BW (3631.24 ± 96.12 mg / kg BW); lethal dose $DL_{100} = 1200$ mg/kg BW for active substance and 4800 mg/kg BW for drug.

On the basis of certain indicators of acute toxicity according to the classification of toxic substances, the investigated insecticidal drug Aktara 25 WG belongs to the class IV – low toxic ($DL_{50} = 501 - 5000$ mg/kg m.); according to the classification of chemicals about the degree of its danger (GOST 12.1.007-76), it belongs to up to the third class ($DL_{50} = 151 - 5000$ mg/kg BW).

According to the toxicity classification of substances, the results of half-lethal dose determination of Mospilan RP and Actara 25 WG when they are administered orally once to white mice indicate that the investigated insecticides are low-toxic. The DL_{50} values of the investigated preparations for white mice were 656.25 ± 170.6 mg/kg BW for Mospilan RP (131.25 ± 34.12 mg/kg BW for DR), and 3631.24 ± 96.12 mg/kg

BW for Actara 25 WG (907.81 ± 24.03 mg/kg BW for DR), which was somewhat dissimilar from the DL_{50} of active substances for white mice determined by another author (Tomlin, 2009).

The physicochemical properties of the auxiliaries and formants included in the preparations could be the reason of differences in the results.

The acute course of poisoning by Mospilan RP and Actara 25 WG in mice was characterized mainly by nervous disorders (lesions of the central and peripheral nervous systems), as evidenced by the clinical features of poisoning, including depression, convulsions, ataxia (impaired movement coordination), tremor and impaired breathing. Ataxia could be a consequence of impulse transmission inhibition in the neuromuscular synapses (curative action), and interneuronal impulse transmission in the central nervous system. It is found that, at high concentrations of Acetylcholine in the blood and the effector organs, the inhibitory reaction developing as a result of the mediator's action at the central synapses is determined by the nervous system. Then, the inhibition extends to every part of the central nervous system, which is evidenced by the disorder of movement coordination in animals. The onset of tremor, and also convulsive syndrome in more severe cases result from central nervous system over-excitation. The leading role in this case was the development of tissue hypoxia to which brain cells are most sensitive (Lavryshyn et al., 2016).

Respiratory disorders associated with the development of toxic encephalopathy and disorders of the regulatory function of the central nervous system are a pathogenetic basis for the development of hypoxia, which leads to a dysfunction of all vital organs and systems (Livanov, 2008).

Considering the mechanism of action of Neonicotinoids on insects, specifically their interaction with H-cholinoreceptors (Matsuda et al., 2001; Jones and Sattelle, 2010), it was assumed that the consequence of the excessive intake of nicotinic receptor agonists in animals was a violation of the efferent impulse transmissions in vegetative ganglia, cerebral ganglia, cerebral ganglion of synapses, in chemoreceptors and generation of afferent impulses in the carotid glomerulus, as well as in the interneuron transmission of excitation in the central nervous system. In this case, there was a two-phase effect on H-cholinoreceptors. the excitation stage was changed by the inhibition effect.

Overall, the pattern of acute toxicity of Mospilan RP and Actaraa 25 WG in this study was shown to have the

same results as the other reaserch (Mohamed et al., 2009; See et al., 2009; Kammon et al., 2010; Iyadurai et al., 2010; Mossa et al., 2018).

CONCLUSION

According to the classification of substances by toxicity, the studied drugs Mospilan RP and Actara 25 WG are found to be in class IV – low toxic. Furthermore, according to the classification of chemicals in accordance with the degree of danger, they belong to up to class III, because the half-lethal dose of Mospilan RP for white mice was $DL_{50} \pm mt = 656.25 \pm 170.6$ mg/kg BW, and for Actors 25 WG was $DL_{50} \pm mt = 3631.24 \pm 96.12$ mg/kg BW. It has been established that Mospilan RP belongs to the third toxicity class according to the Hygienic classification of substances by skin-resorptive toxicity ($DL_{50} > 2000$ mg/kg).

DECLARATIONS

Author's contribution

Volodymyr Dukhnytskyi conducted the research, collected data and performed the statistical analysis. Vasily Sokolyuk, Petro Boiko, Irina Ligomina and Vladimir Goncharenko wrote the manuscript. All authors have read and approved the final manuscript.

Competing interests

The authors have declared that no competing interest exists.

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