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Influence of preparative form on the target efficiency and toxicity of the solid insecticide based on pyrethroid and neonicatinoid

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Abstract

The influence of solid preparative form was studied on the «GET Dry» insecticide based on alpha-cypermethrin and imidacloprid. The target efficiency as acute and residual impact was studied when agent was applied against the bedbugs (*Cimex hemipterus*), German cockroach (*Blatella germanica*), common house flies (*Musca domestica*) and larvae of the leather beetles (*Attagenus smirnovi*). The agent demonstrated strong acute effect (about 100%) when applied against the cockroaches, bugs, and flies. Moreover, the agent demonstrates the residual impact on the cockroaches, flies, fleas for 45 days, and on the bugs for 30 days. The slight insecticidal activity was observed when the agent was applied against the larvae. We studied toxicity of the agent, LD_{50}, when swallowed (moderately hazardous substances, class III) and when applied to the skin (low-hazard substance, class IV) as well as studied its inhalation hazard according to its volatility $C^{20\,°C}$, irritant action when applied to the skin (slight) and eye irritation (moderate). Sensibilizing action was not observed.

Keywords

solid form
insecticide
pyrethroid
neonicatinoid
target efficacy
toxicity

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1. Introduction

In the world practice of disinsection, there is a shortage of effective and at the same time ready-to-use formulations. In the control of household crawling pests, the priority is given to the contact type of agents, which are blockers or inhibitors of acetylcholinesterase. If the formulation of the insecticide is ready for use, there is a possibility of low efficacy or high toxicity of the drug. Existing ready-made insecticides often have an intestinal (calcium, magnesium, barium arsenates, etc.) or fumigation (katfos, dichlorvos, etc.) principle of action; as a result, the disinsector is exposed to an additional risk of drug poisoning. In the case of domestic use, when the products are used by non-professionals, insecticides of these types of action can cause undesirable consequences due to the poisoning.

Taking this into account, specialists of "GET Biotechnology" Ltd (Yekaterinburg, Russia) have developed a ready-made insecticide with a contact type of action for use in everyday life [1]. The agent contains the active ingredients alpha-cypermethrin with a mass fraction of 3% and imidacloprid with a mass fraction of 0.4%. These active ingredients have relatively low toxicity and resistance in most insects [2–4].

Alpha-cypermethrin (concord, renegade, fastak, fendon) – is an (S)-α-cyano-3-phenoxybenzyl ester of (1R, 1S)-cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid (Fig. 1).

A similar solid insecticidal agent with contact action principle is known [5]. The use of an insecticide based on pyrethroids for the control of household pests was described in the patents [6–7]. Toxicological tests and monitoring of insecticide degradation were discussed in the article [8].

Alpha-cypermethrin is a contact-intestinal pyrethroid with repellent properties, effective in combating all stages of insect development.

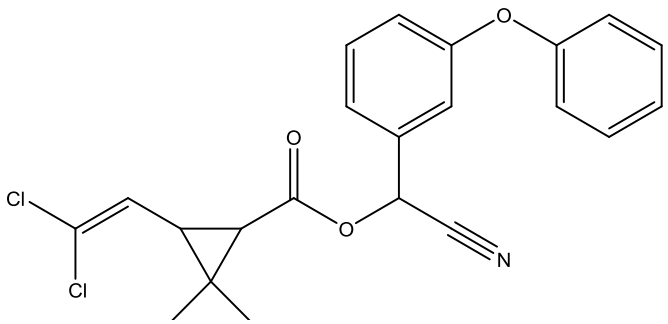

Fig. 1 Structural formula of alpha-cypermethrin

For a long time, it retains its insecticidal and acaricidal properties, and it is resistant to being washed out by rain. It is safe for bees, as it has a repellent effect on them – bees leave the site immediately after processing. Alpha-cypermethrin does not pose danger to mammals and birds [9].

Resistance to alpha-cypermethrin may be due to mutations in voltage-sensitive sodium channels (VSSCs) and enhanced detoxification by P450 monooxygenase. The authors of [10] included both components in insects to determine the effects of pyrethroids. Pyrethroid hydrolase in bacteria and P450 in insects are potential targets. Pyrethroid hydrolase was aimed at increasing the biodegradation of bacteria, and P450 was aimed at increasing insect sensitivity/resistance. Similarly, the chimeric P450 enzyme has been reported to be involved in pyrethroid resistance in Helicoverpa armigera (Hubner).

A study [11] reports on the effect of the presence of pyrethortroids in combination with other environmental pollutants (microplastics) on the vital activity of Chironomus riparius. Combined and single exposure to pyrethroids and microplastics affects vital traits and microbiomes, therefore, it is necessary to focus on effects at limited food levels because they can simulate realistic nutritional conditions in nature and indicate competition for food in the host microbiota.

The results of a study [12] show that ecologically significant concentrations of pyrethroids can disrupt the behavior of delta smelt larvae even at the lowest concentrations (<1 ng/L) and that salinity can alter the dynamics of pyrethroid toxicity in terms of behavioral effects, especially for bifenthrin, where salinity was positively correlated with antithigmotaxis at each concentration.

The aim of the study [13] was to investigate the enantiomerically specific acute toxicity for the earthworm Eisenia fetida and a potential mechanism through a multilevel response. Gut damage, changes in body weight, and DNA damage caused by oxidative stress may be the main mechanisms of tefluthrin toxicity to earthworms.

The authors of [14] report a strong correlation between surface area/volume and toxicokinetic (TK) parameters (rate constants of sorption and absorption and the resulting bioconcentration factors (BCF)), but none of the TK parameters correlated with sensitivity. The only parameter consistently correlating with sensitivity for all species was the death rate constant of the GUTS-RED-SD model (models with a reduced overall unified survival threshold, suggesting stochastic death), indicating that sensitivity to cypermethrin is more related to toxicodynamic (TD) parameters than the parameters of the TK.

Research [15] reports that due to its regulatory role at the initial stage of hydrolysis of the ester bond, esterase acts as a regulatory enzyme in all organisms in the case of pyrethroid metabolism. This family of enzymes exists in almost all life forms (bacteria, fungi, plants, animals), and pyrethroid degradation functions have been reported in all organisms. In insects, these enzymes play a role in pest resistance and have also been reported to have a detoxifying role in animals. Pesticides are not toxic to animals in low doses due to the presence of pyrethroid hydrolase isoenzymes. Bacteria and fungi produce pyrethroid hydrolase to degrade pyrethroid insecticides.

Based on the evidence that dopamine regulates behavior and studies showing that other pyrethroids affect the dopamine system, transcripts involved in dopaminergic signaling were measured. Researchers [16] found that the active dopamine transporter was inhibited with 0.2 mg/L of a similar pyrethroid insecticide, esfenvalerate.

The results of the study [17] showed that the administration of deltamethrin is associated with a significant decrease in reproductive hormones, especially FSH, LH, and a significant increase in the levels of interleukin 2 (IL2), interleukin 6 (IL6), histamine and cortisol. They also noted the importance of suppressing sperm motility and viability, reducing testicular weight, sperm count and fructose in sperm. These results clarify the deleterious effects of deltamethrin on the male reproductive system, causing significant changes in reproductive hormones, markers of inflammation, and testicular function.

The structure-activity relationships showed that substituents at the position of the chiral atom in the oxadiazine ring are very important for the biological activity of the oxadiazine insecticide. Zhang et al. [18] synthesized a series of derivatives of tricyclic oxadiazine 4a-methyl ester.

The authors of [19] created a NavMs-based cockroach sodium channel model in which pyrethrin II docked with the pyrethroid receptor 1 (PyR1) site and proposed a rationale for the observed structure-activity relationship of six pyrethrins. Our study shed light on the molecular mechanism of action of pyrethrum on sodium channels and revealed differences in the modes of action of the six biologically active components of pyrethrum.

LD_{50} of pyrethrum when introduced into the stomach, depending on the solvent and the species of animals, varies for mice 762.0 mg/kg (in corn oil), 35 mg/kg – in DMSO and 168 mg/kg – in 2% starch gel; for rats in the range of 80–368 mg/kg in corn oil, 75 mg/kg – in ethyl

alcohol, 208 mg/kg – in 2% starch gel and according to State All-Union standard 12.1.007-76 it belongs to 2–3 hazard classes. LD_{50} when applied to the skin of rats is 500 mg/kg, on the skin of rabbits >2000 mg/kg. CL_{50} for rats with 4-hour inhalation exposure in the form of dust >1300 mg/m^3 (according to the active substance >400 mg/m^3). The clinical picture of acute poisoning is characterized by a neurotoxic type of action with impaired coordination of movements and the appearance of seizures, tremors, salivation, etc. The most affected organs are the nervous system, liver, and kidneys. In case of contact with eyes, it causes moderate irritation of the mucous membranes. Has a mild irritant effect on the skin of rabbits.

Cumulative activity of alpha-cypermethrin using the method of Yu.S. Kagan et al. is moderate (C_{cum} = 4.6). The skin-resorptive effect is poorly expressed. A weak sensitizing effect of the substance was established (the Magnusson-Kligman method on guinea pigs). Mutagenic activity, studied in various test systems in vivo and in vitro, has not been identified. Carcinogenic, embryotoxic and teratogenic effects have not been established. SRLI (safe reference level of impact) of alpha-cypermethrin in the air of the working area – 0.1 mg/m^3; SRLI in atmospheric air 0.002 mg/m^3.

Imidacloprid (admir, gauchko, copfidor, prime) is a 4,5-dihydro-N-nitro-1-[(6-[chloro-3-pyridyl)-methyl]-imidazolidin-2-ylen-amine (Fig. 2).

Imidacloprid is a synthetic insecticide from the group of neonicatinoids, which, when ingested by an insect, suppresses the activity of acetylcholinesterase. This leads to prolonged opening of sodium channels, because of which the nervous system is overexcited, and the insect is paralyzed for a long time, which leads to death. Low concentrations of imidacloprid can lead to reversibility of paralyzed insects.

The authors of [20] report the zero efficacy of Confidor with the active ingredient Imidacloprid against female N. Californicus ticks.

According to the LD_{50} value, the substance for rats belongs to the 3rd class of moderately hazardous substances (LD_{50} 410–475 mg/kg), for mice – to the 2nd class of highly hazardous substances (LD_{50} 98 mg/kg) according to State All-Union standard 12.1.007-76.

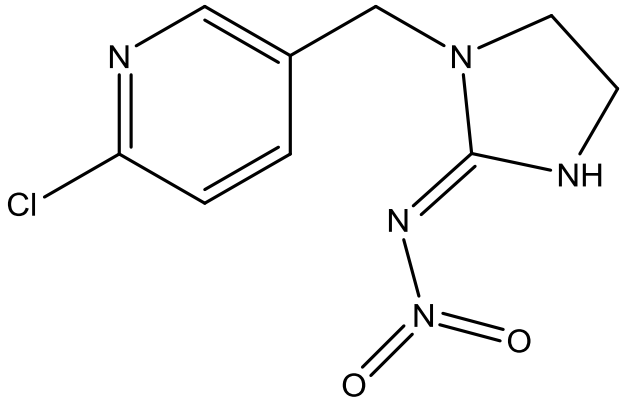

Fig. 2 Structural formula of imidacloprid

Clinical signs of poisoning: tremor, staggering gait, narrowing of the eye slits, apathy, shortness of breath, inhibited movements.

With a single application to the skin, imidacloprid is classified as low-hazard – LD_{50} for rabbits is more than 5000 mg/kg. The irritant effect on the skin of rabbits at a dose of 5000 mg/kg (exposure 4 hours) has not been established. No irritating effect was found on the mucous membranes of the eyes of rabbits, which were injected into the conjunctival sac of the eye with a substance in the form of a 20% aqueous solution. The sensitizing effect has also not been identified [21].

As a result of numerous studies, the following long-term effects of imidacloprid have not been identified: embryotoxic, teratogenic, gonadotoxic, mutagenic, carcinogenic.

MCL (maximum concentration limit) in the air of the working area is 0.5 mg·m^3 (aerosol), SRLI in the atmospheric air of populated areas is 0.002 mg/m^3.

Synthetic pyrethroids in composition with neonicatinoids enhance each other's action, creating a synergistic effect. Such compositions make it possible to control populations resistant to pyrethroids.

In connection with the above, the aim of the work was to study the effectiveness against cockroaches, bedbugs, house flies, and leather beetle, as well as the toxicity of a solid insecticidal agent based on alpha-cypermethrin and imidacloprid.

2. Experimental

2.1. Target effectiveness of the product

2.1.1. Characteristics of test conditions

Target effectiveness tests were carried out according to the methods described in guidelines P 4.2.2643-10 issued by the Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing (Rospotrebnadzor) of the Russian Federation. The results were evaluated in accordance with the criteria set out in P 4.2.2643-10 "Methods of laboratory research and testing of disinfectants to assess their effectiveness and safety".

2.1.2. Applicable test objects

German cockroaches (*Blatella germanica* L.), bedbugs (*Cimex hemipterus*), house flies (*Musca domestica*), and larvae of leather beetle (*Attagenus smirnovi*) of a sensitive laboratory race were used as test objects for testing the agent.

To determine the acute action of the agent, the experiment was carried out according to the standard technique adopted for testing agents in the form of insecticidal crayons and bars against flightless insects and imago of houseflies. The study of the acute action of the agent was carried out at a temperature of 22–24 °C and a relative humidity of 60–70%. Plywood plates 10×10 cm in size, which were previously weighed, were used as test surfaces. The

consumption rate for the test agent is calculated for an area of 100 cm². The optimal consumption rate was chosen to be 0.4 g per 100 cm². The agent was applied to the entire area of the test surface; after application, the weight of the plate was fixed to control the consumption rate. When determining the acute effect, insect replanting was carried out immediately after the application of the agent, the experiment time was 30 s (for larvae of leather beetle the exposure was 15 min), then the insects were transferred to clean glasses. The deaths were recorded for 24 hours.

To determine the residual effect, the treated surfaces were stored upright at room temperature. To determine the duration of the insecticidal action, insects were planted on previously treated surfaces (on days 7, 30, 45 and 60), the exposure time was 30 s (for larvae of leather beetle the exposure was 15 min). After contact with the treated plates, the insects were transferred to clean vessels and their condition was recorded 24 hours later. The residual action was considered complete when the insect mortality was less than 50%.

When determining the acute and residual effects, each experiment was performed 3 times, using 10 insects for each iteration.

2.1.3. Criteria for evaluating results

In accordance with the manual, “Methods of laboratory research and testing of disinfectants to assess their effectiveness and safety. 2011" P 4.2.2643-10, the criteria for evaluating insecticidal agents are:

1. Acute effect on flightless insects: death in 24 hours – not less than 100%;

2. Residual action – 7–60 days.

2.2. Assessment of toxicity and hazard of the agent

Studies to assess the toxicity and hazard of the product were carried out in accordance with the manual "Methods of laboratory research and testing of disinfectants to assess their effectiveness and safety 2011" P 4.2.2643-10, Methodical Guidelines "Requirements for experimental studies to justify the MPC of industrial allergens in the air zones and atmosphere”, as well as measures for the protection of animals used for scientific and educational purposes in Ltd GET Biotechnology.

The studies were carried out on white outbred mice weighing 18–27 g and rabbits of the "Soviet Chinchilla" breed weighing 2.5–3.5 kg. Groups of animals were formed according to their weight and age. The animals were kept in the vivarium, their food ration included all the necessary components for their normal life in the form of briquetted feed and vegetables.

Average lethal doses were determined by intragastric administration and application to the skin in white mice. The duration of observation after exposure was 14 days.

The local irritant effect was assessed with a single application of 500 mg of the substance on a cut-out area of the skin of the lateral surface of the back of rabbits with an area of 56 cm, followed by removal of the substance after 4 hours. Also, to determine the local irritant effect, 50 mg of the substance was added once to the conjunctival sac of the rabbit's eye and the condition of the animals was monitored for 2 weeks.

The sensitizing effect of the substance was studied in accordance with the Methodological Guidelines in mice (delayed-type hypersensitivity reaction – DTHR).

Sensitization of mice was carried out by intradermal injection into the base of the tail of 60 μl of a mixture of the test drug (100 μg) with complete Freund's adjuvant in a ratio of 1:1. The degree of sensitization was assessed after 5 days by introducing a substance in a dose of 100 μg in Hanks solution into the hind paw pad of mice, followed by measuring the thickness of the hind paws after 24 hours. The DTHR indicator was assessed by the amount of edema measured by the difference between the experimental and control groups.

Methods for studying the functions of organs and systems in experimental animals were chosen considering the data on the biological effect of the studied drug. To register the manifestations of intoxication, both integral indicators and indicators of the functional state of organs and systems were used.

The integral indicators of the organism's vital activity were the survival rate of animals and the clinical picture of poisoning.

The function of the respiratory system was studied by recording the respiratory rate using a complex for assessing the cardiorespiratory system of small laboratory animals.

The state of the nervous system was assessed by changes in behavioral reactions in the open field test.

Statistical processing of the data obtained was carried out using the Student-Fisher test. The level of reliability was taken as statistically significant changes at $P \leq 0.05$.

3. Results and discussion

3.1. Target effectiveness of the product

The results of the acute and residual insecticidal action of the agent against insects are listed in Tables 1–4.

From the data presented, a solid insecticidal agent has maximum acute efficacy as well as a long residual effect (up to 30 days) against red cockroaches, bedbugs, and house flies. However, the agent showed low efficacy both in the acute and in the residual phase against the larvae of leather beetle.

The low insecticidal effect on larvae of leather beetle may be due to the phase of insect development. So, the presence of villi in the larvae of the leather beetle can prevent the insecticide from getting on the chitinous cover of the insect, resulting in a low penetration of the active substance into the insect's body.

Table 1 Efficiency of the agent applied against the cockroaches *Blatella germanica*

Identifiable indicators	Amount of the agent per 100 cm²	Test results, units: Death of insects 24 hours later	Norm, units	Regulatory documents for the test methods
Acute impact	0.4 g	100%	100%	P 4.2.2643-10 Sec. 6.3.1
Residual impact as on the 7th day	0.4 g	100%	7–90 days, minimum 50% of insects died	
Residual impact as on the 30th day	0.4 g	100%		
Residual impact as on the 45th day	0.4 g	60%		
Residual impact as on the 60th day	0.4 g	6%		

Table 2 Efficiency of the agent applied against the bedbugs *Cimex hemipterus*

Identifiable indicators	Amount of the agent per 100 cm²	Test results, units: Death of insects 24 hours later	Norm, units	Regulatory documents for the test methods
Acute impact	0.4 g	100%	100%	P 4.2.2643-10 Sec. 6.3.1
Residual impact as on the 7th day	0.4 g	93%	7–90 days, minimum 50% of insects died	
Residual impact as on the 30th day	0.4 g	85%		

Table 3 Efficiency of the agent applied against the false stable flies *Musca domestica*

Identifiable indicators	Amount of the agent per 100 cm²	Test results, units: Death of insects 24 hours later	Norm, units	Regulatory documents for the test methods
Acute impact	0.4 g	100%	100%	P 4.2.2643-10 Sec. 6.3.1
Residual impact as on the 7th day	0.4 g	100%	7–90 days, minimum 50% of insects died	
Residual impact as on the 30th day	0.4 g	100%		

Table 4 Efficiency of the agent applied against the beetle larvae *Attagenus smirnovi*

Identifiable indicators	Amount of the agent per 100 cm²	Test results, units: Death of insects 24, 48 and 72 hours later			Norm, units	Regulatory documents for the test methods
		24 hours	48 hours	72 hours		
Acute impact	0.4 g	16%	27%	47%	100% after 72 hours	P 4.2.2643-10 Sec. 6.3.1
Residual impact as on the 7th day	0.4 g	10%	30%	43%	7–90 days, minimum 50% of insects died	

3.2. Assessment of toxicity and hazard of the agent

3.2.1. Determination of acute toxicity when administered to the stomach and applied to the skin

To determine the LD_{50} when administered to the stomach of white rats, the agent was administered in doses ranging from 500 to 5000 mg/kg. The LD_{50} value was 2000±450 mg/kg.

The clinical picture of acute poisoning in animals was characterized by excitement, lethargy, adynamy, refusal to feed, as well as the presence of tremors and tail rigidity. The death of animals occurred in 1–2 days after exposure.

With a single application of the test agent to the skin of sexually mature rats at a dose of 2500 mg/kg, no clinical manifestations of poisoning and death of animals were observed during the next 14 days. LD_{50}>2500 mg/kg.

Thus, when injected into the stomach, the agent belongs to the 3rd class of moderately hazardous substances, when applied to the skin, it belongs to the 4th class of low-hazard substances according to the classification of State All-Union standard 12.1.007-76.

3.2.2. Inhalation hazard according to the degree of volatility

The inhalation hazard of the volatile components of the agent was determined by preliminary saturation of the desiccator for 24 hours at room temperature (21 °C), followed by placing the experimental animals (white mice) in the desiccator. The exposition time was 2 hours.

During the observation of the animals exposed to the vapors of the agent, the animals showed no clinical signs of poisoning. In appearance, and in response to painf and sound stimuli, the animals belonging to the experimental group did not differ from those in the control one.

After the termination of the exposure, the animals were examined according to a number of indicators reflecting the functional state of the respiratory and nervous systems. The results of the experiment are presented in Table 5.

As follows from the data presented, when exposed to vapors of the agent in animals, no changes were revealed in the recorded indicators of intoxication.

Table 5 Indicators of the functional state of the mice after the impact of the agent

Parameters	Control	Test
Respiration rate per min	212.0±2.9	215.5±3.5
Horizontal activity	97.2±6.7	91.8±10.5
Vertical activity	5.8±1.7	10.3±2.7
Hole exploratory behavior	3.7±0.4	4.3±0.3

Thus, with inhalation exposure to a vapor, agents in saturating concentrations belong to the 4th class of low-hazard substances according to the Criteria for the selection of insecticidal preparations.

3.2.3. Local irritant effect on mucous membranes of eyes and skin

With a single contact of the composition with the mucous membranes of eyes of rabbit, signs of moderate irritant action were observed: hyperemia (2 points); edema (1 point), discharge (1 point), total points – 4. The revealed changes disappeared on their own after 3–4 days.

With a single contact of the agent with the skin in rabbits, no changes were detected at the application site: there was no erythema (0 points), the thickness of the skin fold of the experimental animals did not differ from that of the control group of animals (control: 3.0±0.3; experiment: 3.1±0.2 mm, P>0.005). On visual examination, the experimental animals' skin was clean, without features.

Thus, the agent has a moderate irritant effect on the mucous membranes of the eyes and a weak irritant effect on the skin with repeated applications.

3.2.4. Sensitizing effect of the agent

The sensitizing effect of the investigated substances was studied in accordance with the Methodological Guidelines on white mice (DTHR).

The effect on mice of the agent did not lead to statistically significant differences in the response between the experimental and control groups of animals. The data obtained indicate the absence of sensitizing activity in the agent. The data are presented in Table 6.

Table 6 The results of the delayed hypersensitivity reaction of mice

Parameters	Difference between the thickness of paws of the test group and control group (mm)	
	Variation range	Average within the group
Test	0.05–0.15	0.070±0.008
Hole exploratory behavior	0.05–0.10	0.080±0.008

4. Conclusions

The solid insecticidal agent containing the active substances alpha-cypermethrin 3% and imidacloprid 0.4% has insecticidal activity against cockroaches, bedbugs, flies, fleas. The agent also has a residual effect: against cockroaches, flies, fleas for 45 days , and towardsbedbugs within 30 days. The recommended application rate is 0.4 g of the product per 1 dm² of the treated surface. According to the parameters of acute toxicity when administered into the stomach, the agent belongs to the 3rd class of moderately hazardous substances, when applied to the skin – to the 4th class of low-hazard substances in accordance with State All-Union standard GOST 12.1.007-76 "Occupational safety standards system. Noxious substances. Classification and general safety requirements". Vapors of the agent in saturating concentrations belong to the 4th hazard class according to the Criteria for the selection of insecticidal preparations. The irritating effect of the agent after a single contact with the skin was not revealed. When the agent comes into contact with the mucous membranes of the eyes, a moderate irritant effect was found. The product does not have a sensitizing effect.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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