Efficacy of Chlorfenapyr against *Musca domestica* (Diptera: Muscidae): A Laboratory Study[1]

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Abstract The housefly, *Musca domestica* L. (Diptera: Muscidae), is a globally distributed synanthropic insect that must be controlled to maintain appropriate sanitary conditions for livestock and poultry. The efficacy of chlorfenapyr, a broad-spectrum insecticide, was tested against houseflies under laboratory conditions. In bioassays with a forced contact of adult flies with insecticide residues on the bottom of a glass cup, the chlorfenapyr contact toxicity was compatible to that of permethrin toxicity. When applied to surfaces, the chlorfenapyr contact toxicity was lower than that of pyrethroids and similar to neonicotinoids. In nonchoice feeding bioassays, chlorfenapyr demonstrated high intestinal toxicity to *M. domestica*: median lethal dose (LD_{50}) was 4.18 μg of active ingredient per gram of sugar. As a fly bait (3% and 6% wet powder), chlorfenapyr insecticidal efficacy was not less than 98% and 100% after 24 and 48 h of the exposure, respectively. The results indicate that chlorfenapyr, especially in the form of baits, may be recommended for fly control in livestock farms, and it may be useful for the development of insecticide resistance management strategies.

Key Words chlorfenapyr, contact activity, intestinal activity, housefly, fly bait

The housefly, *Musca domestica* L. (Diptera: Muscidae), is a synanthropic insect of medical and veterinary importance (World Health Organization 1997) because of its ability to transmit pathogens (Förster et al. 2007; Scott et al. 2014; Wang et al. 2011). Controlling the numbers of *M. domestica* in livestock and poultry farms is necessary to ensure appropriate sanitary conditions. The use of insecticides still remains an important part of integrated pest management programs (Zhu et al. 2016). Chemistries used in insect control are constantly being improved, new compounds with insecticidal activity are being synthesized (Jeanguenat 2013; Rueda et al. 2017), and new methods and approaches are proposed to protect animals while controlling harmful insects (Maia et al. 2010). Preference is given to

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highly effective compounds that have selective toxicity to insects and minimal risks to humans and the environment.

At the end of the 20th Century, a novel group of insecticides, pyrroles, namely chlorfenapyr, was described (Black et al. 1994). According to the Insecticide Resistance Action Committee mode of action classification (Sparks and Nauen 2015), it is an oxidative phosphorylation uncoupler. Chlorfenapyr [4-bromo-2-(4-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile] is a proinsecticide whose biological activity depends on its activation by mixed-function oxidases in insect cells. Chlorfenapyr is converted into a chemical compound that dissociates oxidative phosphorylation in the mitochondria. As a result, the synthesis of ATP decreases, which leads first to cell death and then the death of the entire organism (Black et al. 1994; US Environmental Protection Agency 2001).

Chlorfenapyr is a broad-spectrum insecticide with contact and intestinal action. It is used to protect plants (Abdel Ghani and Abdallah 2016; Leonard 2000), combat termites (Rust and Saran 2006), and has promise for the malaria vector control (Ngufor et al. 2016; Raghavendra et al. 2011). The use of chlorfenapyr to protect animals from zoophilic flies was also described (Guglielmone et al. 2000). The aim of this work was to study the contact and intestinal toxicity of chlorfenapyr against adults and larvae of *M. domestica* under laboratory conditions. The insecticidal efficacy of a fly bait (wet powder) containing chlorfenapyr against *M. domestica* was assessed as well.

Materials and Methods

Insects. Adults and larvae of *M. domestica* of a laboratory strain were used to estimate the toxicity of chlorfenapyr under laboratory conditions. The laboratory strain of *M. domestica* was obtained from Novosibirsk Agrarian University (Novosibirsk, Russia) in 2009 and was reared at 26–28°C, at 50–60% relative humidity, and at a 12:12 h light:dark period in the insectarium without contact with insecticides for more than 50 generations. The adult flies were kept in metal cages, $25 \times 25 \times 25$ cm, covered with a fine mesh. Rearing cages were supplied with water (cotton wicks lowered in cups filled with water) and glucose and milk powder (1:1 by weight). The breeding medium for rearing larvae consisted of 200 g wheat bran, 400 ml water, and 10 g Baker's yeast. Larvae were kept in glass containers with the breeding medium. The containers were covered with gauze; as the larvae developed, the medium was added and periodically mixed for aeration. Second- to third-instar larvae and 3–5 day-old adult flies were used in tests.

Chemicals. We used industrial chlorfenapyr (99%, Chengdu Newsun Biochemistry Co. Ltd., Chengdu, Sichuan, China) as an active ingredient and acetone (Sibtechnology Co., Russia) as a solvent. We used cis-9-tricosene (97%, Zhangzhou Enjoy Agriculture Technology Co., Ltd., China), sucrose (Sibtechnology Co., Russia), and cold water swelling starch (Sibtechnology Co) to prepare the stock solution. The following components were included in the formulation (wet powder): active ingredient, chlorfenapyr (6%); auxiliary agent, cold water swelling starch (18%); sex attractant, tricosene (0.15%); food attractant, sucrose (the rest of the powder). A commercial neonicotinoid bait with thiamethoxam ("Agita 10% WG,"

Novartis Animal Health Inc., Switzerland) was used as the reference due to lack of commercial baits containing chlorfenapyr.

Evaluation of the contact toxicity for adults. To determine the contact toxicity of chlorfenapyr to flies, a method of dosed contact for insects was used (Pavlov and Pavlova 2005). A group of insects was exposed to chlorfenapyr without anesthetic by forced contact with insecticide residues on the bottom of a glass cup for 30 min. Acetone solutions of chlorfenapyr were prepared in 6–8 different concentrations (from 0.00007% to 0.01%). Then, 1 ml of each solution was added to a glass cup of 35–40 mm diameter and 40–45 mm height. After evaporation of the acetone, a certain amount of the active substance—the dose—was left in each cup. Then 10 flies were placed into each cup by a plunger consisting of a mesh cloth and a spring spacer ring, achieving close contact of the insects with the insecticide residues on the bottom of the cup. After a 30-min exposure, plungers in the cups were raised and insects were given a 5% glucose solution. The death of the insects was recorded after 24 h.

To determine the insecticidal effect of chlorfenapyr when applied to surfaces, the method of forced contact of insects with insecticide residues was used. Glass and wood test objects of 100 cm^2 were used; they were sprayed with the aqueous suspension of the insecticide in the volume of 0.5 ml and 1 ml, respectively. Chlorfenapyr was tested at concentrations of 0.001–0.1% on glass and 0.1–1% on wood. After the application of chlorfenapyr solutions, the test objects were allowed to air dry at room temperature. Then, 10 flies were placed on each test object using Nabokov-Laryukhin exposimeters that are glass cylinders 6–8 cm in height, 3.5–4.0 cm in diameter, with mesh plungers on top sides. By lowering the plunger, insects were forced to contact the treated surfaces. After 30 min, flies in the exposimeters were removed from the test objects and supplied with 5% glucose solution. The insect mortality was recorded after 24 h.

The residual insecticidal effect of chlorfenapyr on the surfaces was assessed in doses of 0.25 and 0.5 mg of active ingredient (a.i.)/100 cm^2 on glass and 2.5 and 5.0 mg of a.i./100 cm^2 on wood surfaces. As a reference, thiamethoxam (Agita 10% WG) was used in doses 0.275 and 0.55 mg of a.i./100 cm^2 on glass and 5.5 and 11 mg of a.i./100 cm^2 on wood. These doses of chlorfenapyr and thiamethoxam were chosen because they produced a highly lethal effect with 70% and more mortality. After chlorfenapyr or thiamethoxam treatments, test objects were stored at room temperature in the dark and were used for forced contact of insects with insecticide residues in 6–7 d.

Evaluation of the intestinal toxicity for adults. The intestinal insecticidal effect of chlorfenapyr was evaluated by a no-choice feeding test. Flies were starved for 12 h prior to the experiment. Sugar cubes (5.5 g) were treated with 0.3-ml acetone solutions of chlorfenapyr in concentrations of 0.0001% to 0.1%. The dose of chlorfenapyr was calculated in micrograms of a.i./g of sugar. In the control experiment, the sugar was treated with pure acetone. After the acetone evaporated, the sugar was placed in glass cups with 20 starved flies. The cups were sealed with mesh plungers from the top and supplied with water. Mortality of the flies was recorded after 24 h.

Evaluation of insecticidal baits. The insecticidal action of chlorfenapyr was tested by a method of evaluating the effectiveness of food insecticide baits for fly control (Federal Center of Hygiene and Epidemiology 2011). We prepared

insecticidal powders with a chlorfenapyr content of 3% and 6%, then these mixtures were diluted with water in a ratio of 1:3 (for example, 10 g of powder and 30 g of cold water) under constant stirring. The resulting mass was again diluted with water; 2 ml of this mixture then was applied by brushing onto glass test objects of 100 cm^2. Chlorfenapyr rates were 0.0002, 0.0004, 0.002, 0.004, 0.02, and 0.04 g a.i/100 cm^2. After drying, the test objects were placed in a cage of 25 × 25 × 25 cm; as an alternative, the conventional food was placed in the cage (glucose mixed with dry milk). Then, more than 100 flies were released into the cage. The insect mortality was recorded after 24 and 48 h. The commercial Agita 10% WG was diluted with water according to the manufacturer's recommendations as follows: 100 g of the product in 80 ml of water to treat 2,400 cm^2 of a surface, which corresponds to 0.417 g of a.i./100 cm^2. Two water solutions of Agita 10% WG with concentrations of a.i. at 20.85% and 2.085% were prepared and applied to test objects in the volume of 2 ml.

Evaluation of the larvicidal toxicity. To determine the larvicidal effect of chlorfenapyr, a substrate (the breeding media) containing larvae was treated. A breeding medium (wheat bran, 50 g; water, 100 ml) was placed in 0.5-L glass containers and mixed, and then 20 larvae were introduced in each container. The surface of the substrate was sprayed with a chlorfenapyr suspension in concentrations from 0.01% to 0.5% at a rate of 2 L/m^2 of the surface. The water in the same rate was used in the control. Larval mortality was recorded after 24 and 48 h. Nonmoving, elongated larvae were considered dead.

Data analysis. Experiments with each dose of chlorfenapyr in determining the adulticidal and larvicidal effect were performed at least three times. Insect mortality due to the pesticide dose was corrected for control mortality by Abbott's (1925) formula and was analyzed by a probit analysis using Free LD50/LC50 Calculator (July 7, 2016, posting Dr. M. Alpha Raj by calculating LD50/LC50 using probit analysis in Excel blog) for calculating LD_{50} and LD_{95} for 95% confidence intervals (CI), slopes, and standard errors. The LD was expressed in micrograms of a.i./g of insect weight (dosed contact), milligrams of a.i./100 cm^2 of the surface (forced contact), micrograms of a.i./g of sugar (feeding), and grams of a.i./m^2 (larvicidal effect).

Results

Adulticidal toxicity. In dosed and forced contact bioassays, chlorfenapyr had an irreversible insecticidal effect. The onset of an insecticidal effect was observed 3 h after the contact. Having studied the contact effect of chlorfenapyr on two types of surfaces, we established that there was no insecticidal activity at the dosage of 0.005 mg/100 cm^2 on glass and at 0.5 mg/100 cm^2 on wood test objects. Absolute mortality occurred when applying 0.5 mg of a.i./100 cm^2 on glass and 5.0 mg a.i./100 cm^2 on wood test objects. Calculated values of the median LD of chlorfenapyr on glass and wood surfaces differed by a factor of 10 and LD_{95} only by a factor of 3.2 (Table 1). The slope is steeper when applying chlorfenapyr on wood test objects; that is, the rate of increase in toxicity is greater when increasing the dose than in the case of glass surfaces. The duration of the residual toxicity of chlorfenapyr (>70% mortality) was 2 weeks on glass surfaces in the dose of 0.5 mg

Table 1. Contact and intestinal toxicity of chlorfenapyr to adult and larvae of *Musca domestica* under laboratory conditions.*

M. domestica	Number of Adult Flies/ Larvae	Units	LD_{50} (95% CI)	LD_{95} (95% CI)	Slope (±SE)	χ^2	df
Adult			Contact toxicity (dosed contact)				
	440	μg of a.i./g of weight	28.29 (17.42–45.96)	324.96 (200.11–527.79)	1.565 (0.107)	0.112	4
		μg of a.i./10 flies	5.204 (3.204–8.452)	59.76 (36.80–97.06)			
			Contact toxicity (contact with residues on surfaces)				
	240	mg of a.i./100 cm^2	glass surface 0.132 (0.086–0.203)	0.726 (0.473–1.115)	2.227 (0.095)	0.743	2
	300		wood surface 1.323 (1.077–1.626)	2.310 (1.880–2.839)	6.802 (0.046)	0.713	1
			Intestinal toxicity (feeding)				
	985	μg of a.i./g of sugar	4.18 (2.11–8.27)	93.53 (47.24–185.18)	1.27 (0.151)	0.081	3
Larvae			Contact–intestinal toxicity (substrate treatment)				
	300	g of a.i./m^2	1.772 (1.193–2.633)	6.428 (4.326–9.552)	2.941 (0.088)	0.600	1

* LD = lethal dose; CI = confidence interval; χ^2 = chi-squared.

of a.i./100 cm^2 and no less than 11 weeks on wood surfaces in doses of 2.5 and 5.0 mg of a.i./100 cm^2. The duration of residual toxicity of thiamethoxam was no less than 14 weeks on both glass and wood (Table 2).

Evaluation of the intestinal toxicity of chlorfenapyr by the no-choice feeding test showed that after 24 h, 1.7% of flies died when the chlorfenapyr concentration was 0.055 μg of a.i./g of sugar, and 100% of insects died when the chlorfenapyr concentration was 27–55 μg of a.i./g of sugar.

Larvicidal toxicity. To determine the larvicidal effect, the 0.001–1% concentrations of aqueous suspensions of chlorfenapyr were tested. The onset of the toxicity manifestation (death of 5% of larvae) was observed with 0.025% chlorfenapyr concentration. The maximum larvicidal effect (death of 100% of larvae) was achieved when the substrate was treated with chlorfenapyr at the concentration of 0.5–1%.

Toxicity of the chlorfenapyr bait to adults. After 24 h of exposure, the insecticidal effect for chlorfenapyr bait (0.002–0.004 g of a.i./100 cm^2) was 99.2–99.3% and, after 48 h, 100% of insects died (Table 3). For comparison, the commercially available Agita 10% WG (a.i.; thiamethoxam) showed 100% insecticidal efficacy after 24 and 48 h of exposure in the recommended mode of application. A 10-fold reduced dose of Agita 10% WG (0.0417 g of a.i./100cm^2) also caused 100% death of flies in 24 h.

Discussion

Insecticides on livestock and poultry farms for insect control can be used in various ways; powders, granules, solutions, emulsions, poisoned baits, etc. Depending on the formulation and the method of application, a contact, intestinal, or contact-intestinal toxicity of insecticides route of exposure may occur.

Assessment of the contact insecticidal activity of chlorfenapyr against the adult laboratory strain of *M. domestica* by the method of dosed contact showed that its toxicity (for LD_{50}) to a housefly is comparable to the toxicity of permethrin from the group of pyrethroids (Levchenko et al. 2017). This is consistent with the data by Scott et al. (2004) in that the toxicity of chlorfenapyr to two strains of *M. domestica* (LD_{50} 70 and 99 ng/fly in topical application bioassay) was comparable to pyrethroids such as permethrin, fenvalerate, and bifenthrin. While studying the contact toxicity of other insecticides to laboratory strains of *M. domestica* by the method of topical application, the following LD_{50} values (micrograms of a.i./fly) were established: fipronil, 0.0025 (Ibragimkhalilova and Eremina 2007) and 0.6 μg of a.i./g of insect's weight (Kristensen et al. 2004); permethrin, 0.012–0.014 (Acevedo et al. 2009, Ibragimkhalilova and Eremina 2007); and thiamethoxam, 0.13 (Ibragimkhalilova and Eremina 2007). According to our results, chlorfenapyr is a medium-effective insecticide (LD_{50} in the range of 5–50 μg/g of insect weight) with a delayed effect. Moore and Miller (2006) reported that the formulation containing chlorfenapyr had a slower effect on the common bed bug, *Cimex lectularius* L. (Hemiptera: Cimicidae) as compared to conventional neurotoxicants such as pyrethroids. In Romero et al. (2010), the slow action of chlorfenapyr on bed bugs was explained by the mode of action. Chlorfenapyr is a proinsecticide, and its transformation into a toxic metabolite in the insect body requires time (Romero et al. 2010).

Table 2. Mortality (%) of adults of *Musca domestica* exposed to insecticide residues in different periods after treatment on glass (G) and wooden (W) surfaces.*

	Dose, mg of a.i./100 cm^2		Week after Treatment of Surfaces													
			Initial		1		2		4		5		11		14	
Insecticide	G	W	G	W	G	W	G	W	G	W	G	W	G	W	G	W
Chlorfenapyr	0.5	5.0	100	100	80	100	80	100	nd	nd	nd	nd	nd	100	60	nd
	0.25	2.5	70	97	15	100	30	100	nd	nd	nd	nd	nd	100	0	nd
Control	0	0	0	0	0	0	0	0	nd	nd	nd	nd	nd	15	10	nd
Thiamethoxam	0.55	11	96.7	93.3	nd	100	85	100	60	nd	nd	80	nd	nd	96.7	93.3
	0.275	5.50	70	83.3	nd	90	85	83.3	90	nd	nd	90	nd	nd	96.7	80
Control	0	0	0	0	nd	10	0	0	0	nd	nd	0	nd	nd	0	0

* nd = not determined.

Table 3. Toxicity of chlorfenapyr bait to adults of *Musca domestica* under laboratory conditions.[a]

Concentration of a.i. in the Preparative Formulation, %	Concentration of a.i. in Final Solution, %	Dose, g of a.i./100 cm^2	Number of Flies	Fly Mortality, %	
				24 h	48 h
Chlorfenapyr					
6	2	0.04	200	98.5	100
	0.2	0.004	789	99.2	100
	0.02	0.0004	570	52.5	89.2
3	1	0.02	200	98.0	100
	0.1	0.002	412	99.3	100
	0.01	0.0002	408	36.3	83.2
Thiamethoxam					
10	20.85	0.417	200	100	100
	2.085	0.0417	200	100	100
0 (Control)			609	14.4	15.3

[a] a.i. = active ingredient.

The contact toxicity of chlorfenapyr, when applied on surfaces, was lower compared to pyrethroids. For example, Kaufman et al. (2010) obtained LD_{50} of permethrin at 0.13 μg/cm^2 after contacting flies with insecticide residues on the glass surface. This is a 10-fold lower dose compared to the $LD_{50\ of}$ chlorfenapyr we obtained on glass surfaces (Table 1). We previously found (Levchenko et al. 2016) that LD_{50} for pyrethroids such as deltamethrin and cypermethrin as a component of conventional formulations, by forced contact of insects with insecticide residues, may reach 0.01–0.032 and 0.26–0.46 mg of a.i./100 cm^2 on the glass and wood surfaces, respectively. At the same time, the contact toxicity of chlorfenapyr on surfaces is the same or exceeding that of neonicotinoids; for example, thiamethoxam. Ong et al. (2016) found that the LC_{50} for thiamethoxam (Agita 10% WG), when applied to the plywood surfaces for adults of *M. domestica*, was 1.099 g/L. In terms of the volume of application and the area treated by the researchers, this corresponds to 54.95 mg of a.i./100 cm^2. This is much more than the LD_{50} of chlorfenapyr obtained in our experiments when applied to wood surfaces (Table 1). For the duration of the contact toxicity to flies on the surfaces, chlorfenapyr was similar to thiamethoxam (Agita 10% WG) when applied to wood surfaces (Table 2). However, the duration of the chlorfenapyr contact toxicity on glass lasted less time compared to thiamethoxam (Table 2) or pyrethroids whose residual toxicity to flies on glass surfaces can reach 60 d under laboratory conditions (Araya et al. 2011).

The results of the no-choice feeding test demonstrate that chlorfenapyr has a rather high intestinal toxicity to *M. domestica*. The intestinal toxicity (LD_{50}) of

chlorfenapyr (Table 1) and of other insecticides is similar. Based on previous experiments, LD_{50} values (micrograms of a.i./g of sugar) of insecticides in feeding bioassays with laboratory strains of *M. domestica* were as follows: fipronil, 1.0–3.5 (Ibragimkhalilova and Eremina 2007; Kristensen et al. 2004; Roslavtseva et al. 2007); permethrin, 1 (Ibragimkhalilova and Eremina 2007); thiamethoxam, 1.1–2.2 (Kristensen and Jespersen 2008) and 11–36 (Ibragimkhalilova and Eremina 2007; Roslavtseva al. 2007); and imidacloprid, 18 (Kaufman et al. 2010). Li et al. (2012) reported the toxicity of chlorfenapyr to *M. domestica* in a no-choice feeding bioassay as LC_{50} of chlorfenapyr at 13.6 μg of a.i./ml, which was less than the same dose of imidacloprid, acetamiprid, and chlorpyrifos (Li et al. 2012).

The toxicity of chlorfenapyr to other insect species has been studied as well, in particular the toxicity of chlorfenapyr to mosquitoes. For example, Yuan et al. (2015) showed that for adults of *Culex pipiens pallens* Coq (Diptera: Culicidae) LD_{50} of chlorfenapyr was 13.15 ng/adult by topical application, LC_{50} was 0.82–1.26% when exposed to insecticide-soaked paper, and for the larvae LC_{50} was 12.69–27.76 ng/ml. For mosquitoes *Anopheles stephensi* Liston (Diptera: Culicidae) of sensitive and multiresistant lines, an LD_{50} of chlorfenapyr was 0.616–0.827 μg of a.i./g weight of insects by topical application (Verma et al. 2015). Paul et al. (2006) found that the LC_{50} of chlorfenapyr for adult *Aedes aegypti* L. (Diptera: Culicidae), contacted with insecticide residues on a glass surface, was 16 ng/ml (this corresponds to 0.009 μg of a.i./100 cm^2). For the toxicity to field populations of *Culex quinquefasciatus* Say (Diptera: Culicidae), chlorfenapyr surpassed pyrethroids, neonicotinoids, and organophosphates and was the most toxic adulticide with an LC_{50} 0.024 μg/L determined by feeding bioassay (Shah et al. 2016). For the susceptible line of horn flies, *Haematobia irritans* L. (Diptera: Muscidae), contacted with chlorfenapyr residues on filter paper, the LC_{50} was 1.43 μg of a.i./cm^2 (Sheppard and Joyce 1998). This is similar to our results for houseflies on glass surfaces.

The low solubility of chlorfenapyr in water (0.12–0.14 mg/L) (U.S. Environmental Protection Agency 2001) creates difficulties in the use of aqueous suspensions for treating surfaces against adults and substrate against larvae of flies. Obviously, it might be more efficient to use this insecticide in another formulation and in a different way; for example, in the form of a powder, gel, or granules in baits. Our experiments of the use of chlorfenapyr in insecticide baits showed that under the laboratory conditions its efficacy against houseflies does not exceed that of a conventional insecticide containing neonicotinoid thiamethoxam (Agita 10% WG).

Previously, Guglielmone et al. (2000) demonstrated the successful use of cattle ear tags containing 30% of chlorfenapyr (weight of tag being 13 g) against zoophilic flies, *H. irritans*. The protective effect of chlorfenapyr at 90% level in the group of heifers with tags lasted 9 weeks compared to the control group situated near the experimental one and 12 weeks compared to the control group distanced from the experimental group by 700 m (Guglielmone et al. 2000). Results reported by Guglielmone et al. (2000) and our results on the insecticidal efficacy of chlorfenapyr against the housefly in the laboratory suggest that chlorfenapyr (compared to pyrethroids and neonicotinoids) may be an appropriate part of integrated pest management programs for fly control in livestock farms. Formulations containing chlorfenapyr also may be useful for the development of insecticide resistance

management strategies. There is a need for future field studies to estimate the efficacy of chlorfenapyr baits to housefly control in poultry and livestock farms.

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