

RESISTANCE IN GERMAN HOUSEFLY POPULATIONS (*MUSCA DOMESTICA* L., DIPTERA) –SUMMARY OF RECENT STUDIES

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Abstract—The housefly *Musca domestica* L. belongs to the most important hygiene pests world-wide – especially in livestock. Due to its fast development and high reproductive rate the housefly has developed severe resistance against commonly used insecticides. Sometimes resistance problems against new active ingredients occur even after the first treatment because of cross resistance to previously used insecticides.

Populations of the housefly *Musca domestica* L. were collected from farms in different German districts with severe resistance problems and compared to laboratory populations with different resistance spectra. Their resistance, in comparison to a susceptible housefly strain (origin WHO), against pyrethroids, organophosphates and carbamates was determined using impregnated filter papers and by topical application. Different groups of insect growth regulators (juvenile hormone analogues, chitin synthesis inhibitors and triazine derivatives) were tested in a special larvicidal test. Additionally, the insecticides were combined with different synergists (e.g. piperonyl butoxide, a mixed function oxidase inhibitor and S,S,S-tributyl phosphorotrithioate (DEF), an esterase inhibitor) in order to evaluate relevant detoxification mechanisms. The results were incorporated into fly control programmes, taking into account the different resistance spectra and existing fly control strategies, especially for animal production. Increasing resistance to insect growth regulators indicates that not only adulticides but also larvicides should be utilised in a rotation programme.

INTRODUCTION

The house fly *Musca domestica* (Linnaeus) is one of the most important hygiene pests world-wide. At first glance, flies seem to be only a nuisance, but their ability to carry diseases indicates that house flies are serious pests (Kettle, 1984). Effective insecticides were first introduced against flies in the 1940's, however, their effectiveness became unsatisfactory within a few years as fly populations developed resistance to these insecticides. Since then many insecticides have been introduced but they all failed within a few years due to resistance problems (Pospischil and Hanke, 1994; Jespersen, 1992; and Keiding and Jespersen, 1986). Resistance to insecticides has been found in at least 400 arthropod species (Pospischil and Hanke, 1994). Some important pest species include populations which are resistant against nearly all common insecticides (e.g. *Musca domestica*). Insecticidal resistance has a genetic base and is therefore found in larvae as well as in adults and is transferred to the following generations. Resistance in other insect species has a similar genetic base (e.g. *Lucilia cuprina* and *Drosophila melanogaster*) (Hughes *et al.*, 1984). There are limited number of genetic factors involved in the development of resistance which are not strictly confined to specific insecticide molecules (Oppenoorth, 1982; Plapp, 1986; Scott, 1990; and Ahmad and Mc Caffery, 1991). This is one important reason for the occurrence of cross resistance to novel insecticidal groups. The use of synergists gives some indications for the mechanism of resistance. The dominance to resistance genes and the speed of introduction into susceptible fly populations is another important factor for the understanding of resistance development in *M. domestica* under practical conditions.

Characterisation of resistance mechanisms is an important means of devising solutions for multiple resistance and to develop effective fly control programmes. This article shall help to identify the resistance spectrum of house fly populations in Germany and to develop effective fly control programmes which include adulticides and larvicides.

MATERIAL AND METHODS

Insecticides

The active ingredients mentioned in this paper belong to the chemical groups of the carbamates, organophosphates, pyrethroids, benzoylphenyl ureas, triazine derivatives and juvenile hormone

analogues and are used for fly control under practical conditions. These compounds are summarised in Table 1.

Fly strains

The tests were conducted with 3 laboratory populations of *M. domestica* with different resistance spectra and 23 populations collected from 1987 to 1995 from livestock farms with significant fly problems in the Lower Rhine District, Wuppertal and Upper Franconia.

Laboratory strains: WHO-N – This strain was isolated by the WHO in the 1950's and cultured at the university of Padua (Italy). From 1987 to 1995 this strain WHO-N was the susceptible reference in tests with resistant flies. During this period, the pattern of susceptibility to the tested active ingredients did not change. Since 1963 this strain has also been cultured in our laboratories in Monheim. The strain WHO-N was compared to the susceptible strain 'Leiden' from the UBA (Institute for water, soil and air hygiene of the Federal Environmental Agency) in Berlin (Germany) in 1990 and 1994. There were no differences between these two strains concerning carbamates, organophosphates and pyrethroids.

Weymann – This strain was collected in the Lower Rhine District in 1969 and is strongly resistant to organophosphates and carbamates. The organophosphate resistance is selected every six months.

Hans – The *M. domestica* strain 'Hans' was taken from a farm situated in the Lower Rhine District in 1980 when pyrethroid resistance was first detected. The flies were selected with the pyrethroid cyfluthrin once every six months.

Field strains: Small fly populations were isolated, preferably as larvae or adults, from 23 farms with severe fly problems and a hint of strong resistance. The adults (100 to 1000 individuals) were captured with a net, narcotised with carbon dioxide and put into a cage with a water source and some food (sugar/milk powder). The resistance tests were carried out mainly with the first and second laboratory generations. Special consideration is given to the strain 'Grimm' from the Lower Rhine District with extreme resistance, even against specific larvicides. This strain was isolated in 1994.

Table 1. Insecticides tested against susceptible and resistant housefly strains

Common Name	Chemical Group	Cas-No.	Type of Action
propoxur	carbamates	114-26-1	adulticide (contact)
methomyl	carbamates	16752-77-5	adulticide (bait)
dichlorvos	organophosphate	62-73-7	adulticide (contact)
trichlorfon	organophosphate	52-68-6	adulticide (contact)
fenthion	organophosphate	55-38-9	adulticide (contact)
azamethiphos	organophosphate	35575-96-3	adulticide (contact/bait)
ethylchlorpyrifos	organophosphate	2921-88-2	adulticide (contact)
propramphos	organophosphate	31218-83-4	adulticide (contact)
fenitrothion	organophosphate	122-14-5	adulticide (contact)
phoxim	organophosphate	14816-18-3	adulticide (contact)
dimethoate	organophosphate	60-51-5	adulticide (contact)
cyfluthrin	pyrethroid	68359-37-5	adulticide (contact)
deltamethrin	pyrethroid	52918-63-5	adulticide (contact)
fenvalerate	pyrethroid	51630-58-1	adulticide (contact)
d-phenothrin	pyrethroid	26002-80-2	adulticide (contact)
pyriproxyfen	diphenylether	95737-68-1	larvicide* ¹
methoprene	terpenoid	40596-69-8	larvicide* ¹
cyromazine	triazine-derivate	66215-27-8	larvicide
diflubenzuron	benzoylphenyl-urea	35367-38-5	larvicide* ²
triflumuron	benzoylphenyl-urea	64628-44-0	larvicide* ²
Piperonyl butoxide	benzodiazole	51-03-6	synergist
DEF	organophosphate	78-48-8	synergist
Cibacron blue	anthracenesulfonic acid derivate	12236-82-7	synergist

*¹ = juvenile hormone mimic

*² = chitin synthesis inhibitor

Breeding procedure: The cultures of *M. domestica* were reared under constant temperature of 25°C. Egg laying is directly onto dog food. The larvae are fed on curd and Altromin in plastic scales. Development from egg to adult fly takes about 6 days. The puparia are put in cages (50×50×40 cm) for emergence and further egg laying. For the test procedure only 3 day old flies were used.

Biological tests

Filter test (adult flies): Round filter paper discs (diameter=9,5 cm) were treated with the abovementioned insecticides dissolved in acetone and were put into glass jars (diameter=10cm, height=6cm). The test concentrations ranged from 1% to 0.0000128%, or 1.1 to 3500 mg active ingredient per m², with two replicates. The biological test was conducted the following day. 10 flies narcotised with carbon dioxide, were placed in each jar. Mortality of the flies was assessed at defined time intervals until 24 hours after the start of exposure. The criterion for the limiting dose was 100% mortality after four hours contact on the treated filter paper.

Topical application: Adults of *M. domestica* were anaesthetised with carbon dioxide and each of them was treated topically with an electronic micro applicator (Microlab P, Hamilton). Each insecticide was dissolved in acetone and 1.0 µl of each concentration was applied to the mesonotum of the flies. The control flies were treated with the solvent only. Mortality was assessed at defined time intervals up to 24 hours post treatment. Because of the better comparability of the filter test method with the practical situation in the field, the topical application method was only used to evaluate the amount of insecticide needed per fly to get 50% (=LC 50) and 95% (=LC 95) mortality and to estimate the effect of the active ingredient during application.

Larvicidal test: Cattle manure was put into plastic jars and was sprayed with larvicides suspended in water (rate: ml/m² manure surface). Fifty 2nd instar larvae were placed onto the manure in plastic jars. Three to four weeks later the tests were terminated by counting dead larvae, puparia and adult flies.

Crossing experiments: Crossing experiments were carried out with a multi-resistant strain from the Lower Rhine District ('Schneider') and the susceptible strain 'WHO-N' selected with the organophosphate phoxim. For each crossing experiment 500 males from one strain were coupled with 500 females from the other strain. To avoid copulation before the test, only flies less than 12 hours old were used.

RESULTS

The results of the resistance tests with the *M. domestica* strains isolated from different areas in Germany (Lower Rhine District, Wuppertal and Upper Franconia) from 1987 to 1995 are given in Table 2.

Carbamates

The carbamate propoxur was used in the 1950's and 1960's for the control of flies until the development of resistance against carbamates. 100% mortality against the susceptible strain WHO-N is achieved at 50 mg a.i./m². For the resistant laboratory strains and the field strains tested, 100% mortality was not achieved at 3500 mg a.i./m² (table 2). Even the LC50 is above 3500 mg a.i./m² (Pospischil *et al.*, 1996; and Szomm, 1996). Methomyl also has only poor efficacy as a contact insecticide.

Organophosphates

Most of the tested organophosphates achieve 100% mortality against the susceptible fly strain WHO-N at 28 mg a.i./m². Dichlorvos and ethylchlorpyrifos are effective at even lower application rates (1.1–5.6 mg a.i./m²). Dimethoate is less effective than the other organophosphates.

Against the multi-resistant fly strains the organophosphates tested have only poor effect and the limit of efficacy is generally between 700–3500 mg a.i./m² or even above 3500 mg a.i./m². The

Table 2. Toxicity of commonly used insecticides against *M. domestica* strains with different resistance level (Adulticides: 100% mortality after 4 hours; larvicides: 100% suppression of emergence)

Active ingredient	<i>M. domestica</i> Field Strains* mg a.i./m ²	<i>M. domestica</i> Strain Weymann mg a.i./m ²	<i>M. domestica</i> Strain Hans mg a.i./m ²	<i>M. domestica</i> Susceptible Strain Who-N mg a.i./m ²
Carbamates*³				
propoxur	>3500	>3500	>3500	50
methomyl	>3500	n.d.	n.d.	140
Organophosphates*³				
dichlorvos	140	28–140	140	1.5
trichlorfon	>3500	>3500	>3500	28
fenthion	3500	<u>700–3500</u> * ⁵	700	5.6–28
azamethiphos	>3500	n.d.	n.d.	28–140
ethylchlorpyrifos	700	>3500	700	1.1–5.6
propetamphos	700–3500	>3500	3500	28
fenitrothion	>3500	>3500	>3500	28
phoxim	<u>700–3500</u>	>3500	>3500	28
dimethoate	>3500	700	>3500	94
Pyrethroids*³				
cyfluthrin	>3500	5.6–28	>3500	1.1–5.6
deltamethrin	>3500	n.d.	n.d.	5.6
fenvalerate	>3500	700	>3500	28
d-phenothrin	>3500	140	>3500	55
Larvicides*⁴				
pyriproxyfen	≥1000	100–1000	≥1000	10–100
methoprene	>1000	n.d.	n.d.	100–300
cyromazine	<u>10–30</u>	<u>10–30</u>	<u>10–30</u>	<u>10–30</u>
diflubenzuron	<u>50–100</u> * ²	10–100	10–100	10–50
triflumuron	<u>50–100</u> * ²	10–100	10–100	10–50

* mean resistance level of 23 *M. domestica* strains isolated from 1987 to 1995

*² Strain 'Grimm' (Lower Rhine District) = >10.000 mg a.i./m²

n.d. not tested

*³ tests on impregnated filter papers

*⁴ tests in impregnated manure

*⁵ underlined value is closest to correct value

toxicity to the multiresistant laboratory strain 'Hans' is similar to that of the field strains. Only dichlorvos showed good efficacy against the multi-resistant fly strains probably due to its fast evaporation (vapour pressure = 2.9×10^{-3} hPa 20°C).

Pyrethroids

All pyrethroids tested demonstrated good efficacy against the susceptible strain WHO-N and the organophosphate resistant strain 'Weymann'; but the efficacy against the multi-resistant strain 'Hans' and the field strains was poor. More than 3500 mg a.i./m² are required to obtain 100% mortality. Cyfluthrin was also tested using topical application (Table 3). The LC 95 of cyfluthrin against the susceptible strain WHO-N is 0.0028 µg a.i./fly. For the resistant strain 'Grimm' the LC95 is 0.076 µg a.i./fly; a resistance factor of 27. This is nowhere near as large as the results obtained by the impregnated filter paper method.

The synergistic effect of piperonyl butoxide, DEF and cibacron blue to cyfluthrin is demonstrated in Table 5. Even in high doses these synergistes have nearly no efficacy to the fly strain 'Grimm'. In combination with piperonyl butoxide the LC 95 of cyfluthrin declines from 1750 mg a.i./m² to 30.5 mg a.i./m² (ratio=57 fold). With cibacron blue and DEF the efficacy of cyfluthrin rises 22 fold to 80.5 mg a.i./m² and 14 fold to 120 mg a.i./m² respectively.

Table 3. Toxicity of topically applied cyfluthrin to two fly strains

Compound	Fly-strain ^a	LC 95 ^b	Factor LC 95 ^c	Slope ^d	±SE
Cyfluthrin	WHO-N	0.0028	–	2.97	0.20
Cyfluthrin	Grimm	0.076	27	4.31	0.59

^aWHO-N = susceptible fly strain, 'Grimm' = multiresistant strain from the Lower Rhine district.

^bµg insecticide per fly

^cresistance factor of the strain 'Grimm' in comparison to the susceptible fly-strain WHO-N

^dSlope = calculated from least square fitted straight lines of the probit log transformation (sigma plot, Jandel Scientific)

Larvicides

There was interest in the efficacy of the insect growth regulators against the field strains, in view of their marked resistance against other insecticides (Tables 2, 4).

The benzoylphenyl ureas triflumuron and diflubenzuron act as chitin synthesis inhibitors and they are effective against the larvae of the susceptible *M. domestica* strain WHO-N at low doses (10–50mg a.i./m²). Against the multi-resistant field-strains 100% mortality is generally achieved at 50 to 100 mg a.i./m². However one strain ('Grimm') was found to be extremely resistant to benzoylphenyl ureas (>10.000mg a.i./m²).

The triazine derivative cyromazine revealed a good efficacy against all tested fly strains between 10 and 30 mg a.i./m².

The insecticide-susceptible and multi-resistant strains of *M. domestica* differed at least 100 fold in their sensitivity to juvenoids. Pyriproxyfen also has a low toxicity to the susceptible WHO-N strain with 10–100mg a.i./m² being required (Table 2). With an increase of resistance, the amount of active ingredient per m² manure surface for 100% mortality rises rapidly (Table 4). In combination to the synergists piperonyl butoxide and cibacron blue the efficacy of pyriproxyfen to the fly strain 'Grimm' increases 2.4 fold and 4.8 fold respectively (Table 5). DEF has no synergistic effect to pyriproxyfen.

Transmission of resistance factors: Resistance is manifested genetically. The period of time which is needed to introduce resistance alleles from a resistant fly strain to a susceptible strain might also be a criterion for the understanding of resistance development. The results of this crossing experiment indicate that resistance alleles against new compounds may rapidly become established fast in a susceptible strain after being introduced (Table 6).

DISCUSSION

From 1987 to 1995 more than 20 *M. domestica* strains from livestock farms from the lower Rhine district were tested for their resistance level in comparison to field strains from the area around Wuppertal and Upper Franconia (Bavaria) with similar results. Marked resistance to carbamates, organophosphates and pyrethroids, was a consistent finding.

Table 4. Response of fly-strains with different resistance levels to the juvenile hormone mimic pyriproxyfen

Fly Strain	% Larval Development in Treated Manure* ²			
	1.0* ¹	10* ¹	100* ¹	1000* ¹
WHO-N	20.1	12.0	1.6	0.5
Weymann	27.7	35.1	14.8	1.8
Hans	64.1	73.5	65.8	16.2
Multiresist. field strain	92.1	81.6	78.1	32.5

*¹mg pyriproxyfen/m² manure surface

*²expressed as a % of the development in the untreated control.

Table 5. Response of two fly-strains to cyfluthrin and pyriproxyfen resp. combined with synergists (11)

Compound	Synergist	Fly-strain ^a	LC 95 ^b	Slope ^c	SE
Contact-test on impregnated filter paper					
Cyfluthrin	–	WHO-N	2.3	1.74	±0.55
Cyfluthrin	–	Grimm	1750	2.22	±0.41
Cyfluthrin	PBO	Grimm	30.5	3.29	±0.81
Cyfluthrin	DEF	Grimm	126	2.66	±0.52
Cyfluthrin	Cibacron blue	Grimm	80.5	3.07	±0.79
–	PBO	Grimm	22085	3.03	±0.84
–	DEF	Grimm	>35000	–	–
–	Cibacron blue	Grimm	>1400	–	–
Larvicidal test on treated manure					
Pyriproxyfen	–	WHO-N	4.78	1.33	±0.23
Pyriproxyfen	–	Grimm	1380.38	0.93	±0.19
Pyriproxyfen	PBO	Grimm	575.43	2.14	±0.16
Pyriproxyfen	DEF	Grimm	>1000	2.53	±0.26
Pyriproxyfen	Cibacron blue	Grimm	288.4	1.66	±0.22
–	PBO	Grimm	>3000	3.93	±0.22
–	DEF	Grimm	>3000	0.81	±2.51
–	Cibacron blue	Grimm	>3000	1.31	0

^aSee text for description of the strains

^bmg insecticide per m²; ratio insecticide : synergist = 1 : 10

^cSlope = calculated from least square fitted straight lines of the probit log transformation (sigma plot, Jandel Scientific)

Table 6. Toxicity of the organophosphate phoxim to the F1 generation after crossing the parental generation of a susceptible and a multiresistant fly strain

Susceptible Strain	X	Multiresistant Strain 'SCHNEIDER'	100% in 4 hours (mg a.i./m ²) F1-Generation	
			males	females
WHO-N				
males/females		–	≈5.6	≈28
males	X	females	≈700	≈700
females	X	males	≈700	>700
–		males/females	>700	>700

Organophosphate resistance in the house fly has been known since the early 1970's. To a considerable degree, but not exclusively it is caused by an altered acetyl cholinesterase which is less sensitive to organophosphates and carbamates. Additionally caused by glutathione-s-transferase, oxidases and in some cases by increased hydrolysis (Oppenoorth, 1982).

Resistance to pyrethroids has also been known for a long time and is mainly referred to as the *kdr*-factor (Oppenoorth, 1982 and Plapp, 1986). In the field tests in the Lower Rhine District pyrethroids have been applied since 1978 and resistance was first observed in 1979. For the past 10 years the efficacy of pyrethroids is restricted to the knock-down effect at the time of application; residual efficacy is no longer observed. These results correspond with the laboratory tests on impregnated filter papers shown in table 2 and with the literature data (Jespersen, 1992; Keiding and Jespersen, 1986; Georghiou and Mellon, 1983; Oppenoorth, 1982; Plapp, 1986 and Scott, 1990). According to our results the extreme level of pyrethroid resistance seems to be spread evenly over Germany. Fly populations susceptible to pyrethroids were not found. The knock-down effect of pyrethroids observed during application is ascribed to the fact that the flies are wet by the spray. According to table 3 relatively small amounts of the active ingredient cause knock-down followed by mortality when applied topically.

In order to gain information about the resistance mechanisms of pyrethroids cyfluthrin was tested in an assay combined with synergists (piperonyl butoxide, DEF and cibacron blue resp.) According to the literature the mixed function oxidase inhibitor piperonyl butoxide increases the efficacy of cyfluthrin against multi-resistant *M. domestica* strains. The esterase inhibitor DEF and the glutathion-s-transferase inhibitor cibacron blue had only small effects on pyrethroid resistance in *M. domestica* (Pospischil *et al.*, 1996, Thomas and Boethel, 1994, Jao and Casida, 1974 and Cochran, 1994).

Due to the resistance problems with commonly used adulticides, insect growth regulators proved to be good alternatives as larvicides. Numerous field tests performed on livestock farms from 1987 to 1995, demonstrated that benzoylphenyl ureas (e.g. triflumuron) have a good and long lasting efficacy against fly larvae. Cross resistance of benzoylphenyl ureas to other compounds in flies has been described in literature, but under practical conditions cross-resistance seem to occur at a low level (Retnakaran *et al.*, 1982; Maas *et al.*, 1981; and Shen and Plapp, 1990). Only a slight difference in efficacy between the susceptible and multi-resistant fly strains was found which might be caused by reduced penetration and a higher metabolism rate in the resistant strains (table 2) (Pimpricar and Georghiou, 1979). There are only a few cases of house fly resistance to benzoylphenyl ureas mentioned in literature and in Germany resistance of *M. domestica* to these compounds is not known (Pimpricar and Georghiou, 1979; and Pospischil and Hanke, 1996). However, there was one case in the Lower Rhine District, where benzoylphenyl ureas failed under field conditions in a piggery with severe fly problems. This strain 'Grimm' was cultured and tested against a range of benzoylphenyl ureas in the laboratory. Triflumuron, diflubenzuron, flufenoxuron and lufenuron could not achieve 100% mortality of the larvae at concentrations up to 10.000 mg a.i./m² manure surface (Pospischil *et al.*, 1996). On this farm triflumuron has often been applied since 1988, but because of the severe fly problems which were caused by the type of construction, it was nearly impossible to get 100% fly control on this farm.

Cyromazine was never used on the farms which were chosen for the field tests, and the strains tested did not show resistance to cyromazine. However, cyromazine resistance is mentioned in the literature (Furlong and Wright, 1994; Adcock *et al.*, 1993 and others).

The development of juvenile hormone substances against insect pests (e.g. *M. domestica*) was connected with the hope that insects would be unable to develop resistance against these compounds which are similar to the natural insect hormones (Retnakaran *et al.*, 1982; and Williams, 1967). The multi-resistant strains of *M. domestica* mentioned above were shown to display a cross-resistance to different juvenile hormone analogues based on an increased oxidative metabolism, resistance to penetration and increased excretion (Plapp and Vinson, 1973; Hammock *et al.*, 1977; and Londershausen *et al.*, 1996). The combination of pyriproxyfen with the synergists piperonyl butoxide and cibacron blue respectively was found to give a significant increase of efficacy. DEF did not show any synergistic effect. This result indicates that oxidative metabolism and glutathion transferase resistance might be responsible for the resistance of the tested *M. domestica* strains tested to pyriproxyfen.

The results indicate that multi-resistance against commonly used insecticides is wide-spread in German fly populations. Due to this resistance situation fly control is only effective with special application programmes based on adulticides and larvicides with a special view to the resistance spectrum of the respective fly population. Adulticides should be alternated to delay further increase of resistance in house flies. Some active ingredients displaying high resistance factors when used as contact insecticides, can still be given as baits which are ingested by the flies (Pospischil and Hanke, 1996). Resistance against larvicides (triacine deriyates and benzoylphenyl ureas) has a scattered distribution. In cases of emerging resistance, the larvicide has to be alternated, and where possible, the fly population of the farm has to be eradicated to avoid further distribution of this resistance factor.

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