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MONITORING OF RESISTANCE TO SEVERAL PYRETHROID AND NEONICOTINOID INSECTICIDES IN *Aphis gossypii* (GLOVER) FROM EGYPT

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ABSTRACT

The resistance of cotton aphid, *Aphis gossypii* Glover to six pyrethroid and four neonicotinoid insecticides was investigated using slide-dip technique in two field strains collected from Fayoum and Gharbia Governorates representing Upper and Lower Egypt during the cotton seasons 2005- 2007.

In the case of pyrethroids, low levels of resistance were detected for deltamethrin, lambda-cyhalothrin, esfenvalerate, alpha-cypermethrin and fenvalerate, fluctuated between 1.0-7.4-fold during 2005-2007 in both strains, while fenpropathrin showed high level of resistance recording a maximum value of 31.3-fold.

In the case of neonicotinoids, low to moderate levels of resistance was observed in 2005-2007 where resistance ratios ranged between 1.2 and 7.0-fold. However, the low resistance level (1.6-fold) to imidacloprid, recorded in 2005, increased gradually to reach a maximum level of 5.3-fold in season 2007. On the other hand, the resistance levels to insecticides tested was not extremely variable between two different regions (Upper and Lower Egypt).

The toxicity results of insecticides tested against the two field strains indicated that, with regard to pyrethroid, deltamethrin was the most toxic followed by esfenvalerate and lambda-cyhalothrin while fenpropathrin was the least toxic followed by fenvalerate and alpha-cypermethrin. On the other hand, the neonicotinoid, dinotefuran was the most toxic followed by acetamiprid, imidacloprid and thiamethoxam.

INTRODUCTION

Pyrethroid insecticides are characterized by high knockdown and lethal activity, efficiency against wide spectrum of insect pests which permit them to be widely used for plant protection. Their major use in Egypt has been for the control of cotton leafworm and bollworms but have also achieved widespread use for controlling various species of lepidopterous pests, aphids and many other minor outlets (Hirano, 1989).

Neonicotinoids, as a novel class of potent insecticides, such as imidacloprid, acetamiprid, thiamethoxam and dinotefuran are compounds acting agonistically on insect nicotine acetylcholine receptors. They are active against numerous sucking and biting insects, including aphids, whiteflies, thrips, leaf miners, beetles and some lepidopterous species as well (Elbert *et al.*, 1998; Nauen *et al.*, 2003). Neonicotinoids show good activity against pest insects resistant to other classes of insecticides such as organophosphates, carbamates, pyrethroids and chlorinated hydrocarbons (Denholm *et al.*, 2002). The neonicotinoid imidacloprid has been used on cotton for control cotton aphid in Egypt since 1997, while the neonicotinoid acetamiprid , thiamethoxam and diotefuran have has been used for controlling aphid pests in vegetable since 2002,2003 and 2004, respectively. Resistance in various species of aphids became a serious problem. Such resistance in the cotton aphid, *Aphis gossypii* Glover has been reported to different insecticides in many countries.

In Egypt, no report on monitoring of resistance to pyrethroid and neonicotinoid insecticides in the cotton aphid, *A. gossypii* had yet been done. Annual evaluation of resistance monitoring data on field population is needed to provide an adequate data base that would allow more flexibility in choosing an appropriate insecticide for control of pests. Thus the present study was conducted to determine resistance of several pyrethroid and neonicotinoid insecticides in the two field populations of the cotton aphid, *Aphis gossypii* Glover collected form Fayoum and Gharbia Governorates during the cotton seasons 2005 - 2007 to investigate how far resistance is likely to occur.

MATERIALS AND METHODS

Samples of cotton leaves infested with *Aphis gossypii* Glover were collected from cotton fields of Fayoum and Gharbia Governorates representing Upper and Lower Egypt during early seasons of 2005- 2007. Slide-dipping technique was used to evaluate the toxicity of the tested insecticides against the adult stage. Serial concentrations of each insecticide were prepared by dilution in water. By means of fine brush, ten adults were fixed to double face scotch tap and stuck tightly to slide on the dorsal part. The slides were then dipped in the prepared insecticide aqueous solutions for ten seconds. Each insecticide was tested at five different concentrations. Three replicates of ten adults each were used for each concentration. Mortality was recorded two hours after treatment and all insects responded to touching with the fine brush were considered alive.

Abbott formula (Abbott, 1925) was adopted and data were then subjected to statistical analysis by the method of Busvine (1957). The rates of resistance were expressed as resistance ratio (RR) at the LC_{50} level of the field strains as compared with the laboratory strain which has been reared in condition laboratory for more than 15 generations without exposed to any insecticides.

$$\text{Resistance ratio (RR))} = \frac{LC_{50} \text{ of the field strains}}{LC_{50} \text{ of laboratory strain}}$$

The toxicity index of each insecticide was determined according to Sun (1950) as follow:

$$\text{Toxicity index (TI)} = \frac{LC_{50} \text{ of the most effective insecticide X 100}}{LC_{50} \text{ of the least effective insecticide}}$$

Pesticides used:

I-Pyrethroid insecticides: deltamethrin, Decis 2.5% EC (Bayer Crop Science); lambda-cyhalothrin, Karate 20% EC, (Syngenta); fenvalerate, Sumicidin 20% EC (Sumitomo); esfenvalerate, Sumi-alpha 5% EC

(Sumitomo); fenpropathrin, Meothrin 20% EC (Sumitomo); alpha-cypermethrin, Fastac 15% EC, (BASF).

II- Neonicotinoid insecticides: imidacloprid, Confidor 20% SL (Bayer CropScience); acetamiprid, Mospilan 20% SP (Nippon Soda); thiamethoxam, Actara 25% WG (Syngenta); dinotefuran, MTI 446 4% SG (Mitsui chemicals).

RESULTS AND DISCUSSION

Resistance for pyrethroids: Data in Table (1) showed very low levels of resistance were observed for deltamethrin and lambda-cyhalothrin in both two strains with insignificant changes between their levels during 2005-2007, where resistance ratios ranged between 1.0-2.8-fold. On the other hand Fayoum samples showed slightly higher resistance for deltamethrin than Gharbia (max. 2.7 and 1.7-fold, respectively), but it showed slightly lower resistance for lambda-cyhalothrin than Gharbia samples (max. 1.7 and 2.8-fold, respectively). Resistance to esfenvalerate and alpha-cypermethrin was relatively low in 2005 growing season which ranged between 3.1-4.4-fold. During the next two seasons, no significant changes in resistance to α-cypermethrin was observed in Gharbia samples (4.4 and 4.1-fold in 2005 and 2007, respectively), while Fayoum showed slight increase in resistance (3.7 and 5.2-fold in 2005 and 2007, respectively), but esfenvalerate resistance reverted to susceptibility in both Fayoum and Gharbia, where resistance level reached 2.1 and 1.1-fold, respectively in 2007 season. In contrast, fenvalerate resistance was very low in 2005 season in both Fayoum and Gharbia, but it increased to reach 7.4 and 5.3-fold, respectively in 2007 season. High levels of resistance was detected with fenpropathrin but was more higher in Gharbia than Fayoum samples, where the maximum level of resistance was 31.3 and 24.9-fold, respectively.

It should be pointed out that pyrethroid insecticides have only been used to control both cotton leafworm and bollworm in the cotton during mid growing seasons for over a period of 30 years in Egypt. With continued their use, cotton leafworm acquired high levels of resistance to these compounds (El-Gunidy *et. al.*, 2002) as well as pink bollworm (Abd El-Haleem, *et. al.*, 2007 in press). Fortunately, the cotton aphid, *A. gossypii* showed very low levels of resistance for most of pyrethroids tested in the present study here although coincidental cotton aphid in cotton was being exposed to these insecticides when used against cotton leafworm and bollworm. Exception of fenpropathrin which recorded high levels of resistance, low levels of resistance were observed in all other pyrethroids in both strains during 2002-2007 (Table 1). In 2007, the resistance levels ranged from 1.1-2.7-fold for deltamethrin, labda-cyhalthrin and esfenvalerate and ranged between 4.1-7.4-fold for alpha-cyhalthrin and fenvalerate. These results are in agreement with results obtained by Jiang *et al.*, (1994) who studied the changes in resistance to deltamethrin and cyfluthrin in *A. gossypii* on cotton in China in 1980-1993.

Table (1): Toxicity index and resistance to some pyrethroid insecticides in the cotton aphid, *Aphis gossypii* Glover collected from Fayoum and Gharbia Governorates during 2005 - 2007 growing seasons

Insecticide	season	Fayoum				Gharbia			
		Slope ± EC	LC_{50} ppm (95 % FL.)	RR*	TI**	Slope ± EC	LC_{50} ppm (95 % FL.)	RR*	TI**
Deltamethrin Decis 2.5% EC	Lab. strain	0.93 ± 0.26	1.5 0 (0.54 - 2.7)	--------	--------	0.93 ± 0.26	1.50 (0.54 - 2.7)	--------	--------
	2005	1.36± 0.28	3.3 (1.8 - 4.9)	2.2	100 %	1.12 ± 0.27	2.2 (0.9 - 3.6	1.5	100 %
	2006	1.51± 0.27	3.8 (2.6 - 5.9)	2.5	100 %	1.05 ± 0.36	2.4 (1.3 - 6.7	1.6	100 %
	2007	1.51± 0.29	4.2 (3.1 -5.3)	2.7	100 %	1.06 ± 0.26	2.5 (1.49 - 4.2	1.7	100 %
Lambda-cyhalothrin Karate 20 % EC	Lab. strain	2.89 ± 0.69	5.7 (3.6 - 7.3)	--------	--------	2.89 ± 0.69	5.7 (3.6 - 7.3)	--------	--------
	2005	1.19 ± 0.84	9.5 (----------)	1.7	35 %	1.59 ± 0.36	15.7 (10.6 - 20.2)	2.8	14 %
	2006	2.89± 0.69	5.6 (3.5- 7.2)	1.0	67 %	2.62 ± 0.49	7.5 (5.4 - 9.6)	1.3	32 %
	2007	0.90 ± 0.28	8.6 (1.9 -5.5)	1.5	48 %	1.48 ± 0.27	13.8 (9 - 19.3)	2.4	18 %
Fenvalerate Sumicidin 20%EC	Lab. strain	1.63 ± 0.34	10.6 (5.7 - 15.21)	--------	--------	1.63 ± 0.34	10.6 (5.7 - 15.21)	--------	--------
	2005	1.24 ± 0.27	26.9 (14.5 - 40.2)	2.5	12 %	1.17 ± 0.26	19.3 (11.4 - 29.5)	1.8	11 %
	2006	1.19 ± 0.27	47.9 (28.6 - 72.9)	4.5	8 %	1.69 ± 0.32	39.0 (29.7 - 53.7)	3.7	6 %
	2007	1.15 ± 0.27	78.8 (32.6 - 124.7)	7.4	5 %	2.31 ± 0.35	56.4 (40.2 - 71.8)	5.3	4 %
Esfenvalerate Sumi-alpha 5%EC	Lab. strain	0.66 ± 0.25	3.8 (1.80 - 21.04)	--------	--------	0.66 ± 0.25	3.8 (1.80 - 21.04)	--------	--------
	2005	1.23 ± 0.27	11.7 (6.7-17.5)	3.1	28 %	1.48 ± 0.37	15.8 (8.3 - 23)	4.2	14 %
	2006	1.38 ± 0.29	4.8 (2.4 -7.1)	1.3	79 %	1.03 ± 0.35	3.9 (2.1 - 8.4)	1.0	62 %
	2007	1.51 ± 0.29	8.0 (5.1 - 11.1)	2.1	51 %	1.28 ± 0.26	4.0 (2.4 - 5.8)	1.1	63 %
Fenpropathrin Meothrin 20% EC	Lab. strain	2.18 ± 0.41	5.3 (3.83 - 6.9)	--------	--------	2.18 ± 0.41	5.3 (3.83 - 6.9)	--------	--------
	2005	2.30 ± 0.42	83.5 (64.4 - 115.8 0	15.8	4 %	2.65 ± 0.70	115.1(82.9 - 197.0)	21.7	2 %
	2006	1.52 ± 0.38	132.4 (91.3 - 266.2)	24.9	3 %	1.58 ± 0.37	166.1(123.4 - 254.4)	31.3	2 %
	2007	1.69 ± 0.52	116.5 (85.8 - 162.2)	22	4 %	1.71± 0.28	143.8(89.9 - 221.2)	27.1	3 %
Alpha-cypermethrin Fastac 15 % EC	Lab. strain	0.94 ± 0.22	10.7 (2.4 - 20.8)	--------	--------	0.94 ± 0.22	10.7 (2.4 - 20.8)	--------	--------
	2005	0.90 ± 0.22	39.7 (2.3 -20.8)	3.7	8 %	2.21 ± 0.35	47.2 (32.9 - 61.9)	4.4	5 %
	2006	2.4 ± 0.40	127.9 (95.8 - 180.0)	2.6	14 %	1.73 ± 0.29	33.1(19.5 - 51.6)	3.1	7 %
	2007	1.18 ± 0.26	55.5 (32.7 - 84.2)	5.2	7 %	1.41 ±0.27	44.0 (30.7 - 65.7)	4.1	6 %

RR * (Resistance ratio) = LC_{50} of the field strain / LC_{50} of the laboratory strain

TI** (Toxicity index) = (LC_{50} of the most effective insecticide / LC_{50} of the least effective insecticide) x 100

They found that reduced usage of these insecticides after 1985 led to increase their efficacy in 1993. In contrast, Gubran *et. al*., (1992) found that three strains of *A. gossypii* collected from cotton fields in Sudan over 3 years (from 1988 to 1990) were highly resistance to fenvalerate and deltamethrin in laboratory. Ahmed *et. al*., (2003) found that field populations of *A. gossypii* collected from cotton field from 1997 to 2000 in Pakistan showed very high levels of resistance to seven pyrethroids, namely cypermethrin, α-cypermethrin, zeta-cypermethrin, cyfluthrin, fenpropathrin, bifenthrin and lambda-cyhalothrin. They also found that resistance to deltamethrin was lower than to other pyrethroids. Subbaratinam and Radhika (2005) reported that *A. gossypii* has acquired a high level of resistance to deltamethrin and fenvalerate in China, bifenthrin in Israel and fenvalerate in France.

Resistance for neonicotinoid: Results obtained in Table (2) indicated that in 2005 both strains had developed resistance to neonicotinoid insecticides despite their use in control of cotton aphid on cotton for only the recent three years, but resistance to imidacloprid during (2005) was lower than thiamethoxam and dinotefuran and acetamiprid although imidacloprid has been used for control cotton aphids on cotton while the other neonicotinoids have been used for control of aphid pests on vegetable. On the other hand, Gharbia strain had higher resistance to dinotefuran, acetamiprid and imidacloprid than Fayoum strain. The resistance ratios were 7.0 and 4.9-fold for thiamethoxam, 3.7 and 6.1-flod for diotefuran, 2.2 and 3.9- fold for acetamiprid, 1.6 and 2.9-flod for imidacloprid in Fayoum and Gharbia strains respectively. However, the low resistance level to imidacloprid was acquired in 2005, increased gradually with continuance of its use to reach 5.3 and 3.9-fold in season 2007 in Fayoum and Gharbia strains, respectively, while acetamiprid resistance declined with continuous of its used recording a level of 1.4 and 2.5-fold in 2007 in Fayoum and Gharbia strains, respectively. These results indicated that cotton aphid developed resistance to imidacloprid but not to acetamiprid. On the other hand, resistance to dinotefuran and thiamethoxam which was moderate in 2005 reverted to susceptibility during the next two seasons which might be due to discontinuation of their application in the late year 2004. From these results, it is suggested no or little cross-resistance between imidacloprid and the other neonicotinoid dinotefuran, thiamethoxam and acetamiprid.

The evolution of resistance in *A. gossypii* to the neonicotinoid imidacloprid has been reported in recent years (wang *et. al*., 2001 and 2002, Yu *et.al*., 2004). They examined the development of resistance in *A. gossypii* that had exposed for several generations of selection with imidacloprid in laboratory. They found that the colony selected with this insecticide developed only 4.7-fold after 13 generations, 8.1-fold after 12 generations 10.1-fold after 18 generations, respectively.

By comparing the levels of resistance to neonicotinoids with pyrethroids, the results in Tables (1, 2) indicated that resistance to the Pyrethroid fenvalerate increased with the increase in resistance to the neoniotinoid imidacloprid.

Table (2): Toxicity index and resistance to some neonicotinoid insecticides in the cotton aphid , *Aphis gossypii* Glover collected from Fayoum and Gharbia Governorates during 2005 - 2007 growing season

Insecticide	season	Fayoum				Gharbia			
		Slope ± EC	LC_{50} ppm (95 % FL.)	RR*	TI**	Slope ± EC	LC_{50} ppm (95 % FL.)	RR*	TI**
Dinotefuran MTI446 4 %SG	Lab. strain	1.84 ± 0.29	3.2 (2.3 - 4.22)	--------	--------	1.84 ± 0.29	3.2 (2.3 - 4.22)	--------	--------
	2005	1.41 ± 0.27	11.7 (8.2 - 7.5)	3.7	100 %	1.53 ± 0.42	19.4 (12.8 - 38.9)	6.1	100 %
	2006	1.47 ± 0.27	4.1 (2.8 - 5.81)	1.3	100 %	1.99 ± 0.31	3.9 (2.8 - 5.2)	1.2	100 %
	2007	1.71 ± .30	4.8 (3.1 - 6.6)	1.5	100 %	2.36 ± 0.34	6.7 (5.1 - 8.4)	2.1	100 %
Imidacloprid Confidor 20 % SL	Lab. strain	0.97 ± 0.25	7.4 (3.7 - 2.2)	--------	--------	0.97 ± 0.25	7.4 (3.7 -12.2)	--------	--------
	2005	2.68 ±0.44	11.6 (9.1 - 14.5)	1.6	100 %	1.56 ± 0.28	21.1 (15.6 - 29.2)	2.9	91 %
	2006	1.77 ± 0.48	17.2 (1.4 - 49.9)	2.3	24 %	0.97 ± 0.25	14.4 (5.7 - 28.0)	2.0	27 %
	2007	1.28 ± 0.26	39.1(24.5 - 57.7)	5.3	12 %	2.34 ± 0.33	29.1(21.7 - 38.5)	3.9	23 %
Acetamiprid Mospilan 20 % SP	Lab. strain	1.77 ± 0.34	9.2 (5.3 - 13.1)	--------	--------	1.77 ± 0.34	9.2 (5.3 - 13.1)	--------	--------
	2005	3.79 ± 0.63	20.6 (16.7 - 24.8)	2.2	57 %	1.21 ± 0.26	36.3 (22.5 - 54.5)	3.9	53 %
	2006	1.37 ± 0.27	13.2 (7.6 -19.1)	1.4	31 %	2.77 ± 0.50	18.4 (13.3 - 21.8)	2.0	21 %
	2007	2.29 ± 0.35	13.1(9.7 - 16.7)	1.4	37 %	1.64 ± 0.29	22.5 (13.8 - 31.3)	2.5	30 %
Thiamethoxam Actara 25 % WG	Lab. strain	1.59 ± 0.32	14.7 (7.6 - 22.1)	--------	--------	1.59 ± 0.32	14.7 (7.6 - 22.1)	--------	--------
	2005	1.57 ± 0.37	102.7 (69.5 - 159.3)	7.0	11 %	1.06 ± 0.36	72.4 (11.8 - 130.7)	4.9	27 %
	2006	2.32 ± 0.33	33.9 (18.5 - 30.3)	2.3	17 %	1.41 ± 0.29	21.0 (11.3 - 30.6)	1.4	19 %
	2007	1.89 ± 0.30	41.1 (29.5 - 54.2)	2.8	12 %	2.16 ± 0.33	20.6 (5 - 26.5)	1.4	33 %

RR * (Resistance ratio) = LC_{50} of the field strain / LC_{50} of the laboratory strain

TI (Toxicity index) = (LC_{50} of the most effective insecticide / LC_{50} of the least effective insecticide) x 100**

This phenomenon agree with results obtained by wang *et al*., (2001) who found that the R-imidacloprid strain of *A. gossypii* (4.7-fold) became highly cross-resistance to fenvalerate, while the R-fenvalerate strain (29.0-fold) did not show any cross-resistance to imidacloprid. On the other hand, this phenomenon had not been detected for the other pyrethroids especially deltamethrin, lambda-cyhalothrin and esfenvalerate, where no change in resistance ratios was observed for deltamethrin and lambda-cyhalothrin, while esfenvalerate resistance declined with further increase in resistance to imidacloprid Table (1). These results are in agreement with the results obtained by Denholm *et. al*., (2002).

The toxicity of pyrethroid and neonicotinoid insecticides tested against two field strains of *A. gossypii* collected from Fayoum and Gharbia Governorates during 2005-2007cotton growing seasons were shown in Tables (1, 2). With regard to pyrethroid compounds, deltamethrin was the most toxic followed by esfenvalerate and lambda-cyhalothrin, while the other Pyrethroid compounds were least toxic in both strains during 2005-2007. In general, the relative toxicity factors ranged between 14-79% for esfenvalerate, 14-67% for lambda-cyhalothrin, while the other pyrethroids were less toxic which ranged between 2-14% during 2005-2007, but in 2007 became far less toxic (relative toxicity ranged between 3-7%) as compared with the toxicity of deltamethrin. Similar results were also reported by Ayad *et al.* (1991-1992) who found that among the pyrethroid insecticides, deltamethrin showed the most toxic effect on field population of cotton aphid, *A. gossypii* followed by lambda-cyhalothrin and cypermethrin.

Regarding of neonicotinoid compounds, dinotefuran was the most toxic followed by acetamiprid, imidacloprid and thiamethoxam. The relative toxicity factor ranged between 21-57% for acetamiprid, 12-100 % for imidacloprid and 11-33% for thiamethoxam as compared with the toxicity of dinotefuran. However, Chalam *et al.* (2003) found that among the new insecticides (neonicotinoids), acetamiprid recorded the highest toxicity followed by diafenthiuron and thiamethoxam to the cotton aphid *A. gossypii.* In contrast, Praveen and Regupathy (2003) reported that the acute toxicity was highest for thiamethoxam and lowest for imidacloprid in all cotton aphid populations studied.

From these results it is suggested that pyrethroids such as deltamethrin, lambda-cyhalothrin and esfenvalerate could be used with neonicontinoid insecticides in rotation in resistance management programs in order to preservate of both insecticides efficacy.

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تقصى مستويات المقاومة للعديد من مبيدات البيرثرويد والنيونيكوتينويد فى" من القطن" فى مصر

محمد سنجاب

المعمل المركزى للمبيدات – مركز البحوث الزراعية – الدقى – مصر

تم دراسة مقاومة حشرة المن "من القطن" لعدد ستة مركبات بيرثرويد واربعة مركبات نيونيكوتينويد باستخدام طريقة غمر الشرائح على سلالتين حقليتين لحشرة من القطن والتى جمعت من حقول القطن فى محافظتى الفيوم والغربية واللتان تمثلا الوجة القبلى والوجة البحرى خلال مواسم زراعة القطن فى الفترة من 2005 الى 2007.

فى حالة مركبات البيرثرويد لوحظت مستويات مقاومة صغيرة لكلا من دلتامثرين – لمبادا ثيهالوثرين – ايسى اس فنفليريت – الفا ثيبرمثرين وفنفليريت مع وجود اختلافات بينها وانحصرت بين 1.2 – 7.4 ضعف خلال الفترة من 2005 الى 2007 فى كلا السلالتين ، بينما أظهر مركب الفنبروباثرين مستويات مقاومة مرتفعة وكانت أعلى قيمه له هى 31.3 ضعف.

وفى حالة مركبات النيونيكوتينويد لوحظت مستويات مقاومة متوسطة فى اعوام 2005 – 2007 ، وانحصرت مستويات المقاومة بين 1.2 – 7 ضعف ، ومن ناحية أخرى فان مستوى المقاومة وصل الى 1.6 ضعف لمركب اميداكلوبريد فى عام 2005 وازداد تدريجيا ليصل الى أعلى قيمة له وهى 5.3 ضعف فى موسم 2007 ، ومن جهه اخرى كانت مستويات المقاومة للمبيدات الأخرى المختبرة متغيرة الى أبعد الحدود بين الأقليمين (الوجه القبلى والوجة البحرى).

أظهرت نتائج معامل السمية لهذه المركبات على حشرة "من القطن" أنه فى مركبات البيرثرويد كان مركب دلتامثرين هو الأكثر سمية يلية اي اس فنفليريت ثم لمبادا ثيهالوثرين ، بينما كان مركب فنبروباثرين هو الأقل سمية يليه – فنفليريت ثم الفا ثيبرمثرين. وفى مركبات النيونيكوتينويد كان مركب داينوتيفيوران هو الأكثرسمية يلية اسيتامبريد ثم اميداكلوبريد وثياميثوكسام.