Pestic. Phytomed. (Belgrade), 26(3), 2011, 185–195
Pestic. fitomed. (Beograd), 26(3), 2011, 185–195

UDC: 632.934:632.95.02:632.951
Review paper * Pregledni rad
DOI: 10.2298/PIF1103185M

# Cyclic Ketoenols – Acaricides and Insecticides with a Novel Mode of Action

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*Received: August 5, 2011*
*Accepted: August 29, 2011*

**SUMMARY**

Modern crop protection industry puts great efforts into the investigation and development of pesticides (insecticides, acaricides) with a novel mode of action, primarily because of increasingly important problem of resistance of pest organisms to pesticides. Resistance of many pest arthropod species (insects and mites) to insecticides and/or acaricides became a global phenomenon in the last decades. Therefore, pest management heavily relies on constant introduction of novel active ingredients in use, i.e. on the alternative use of a number of compounds with different modes of action in order to save the longevity of newly developed products. Among pest arthropods, according to the potential for resistance development and a number of documented cases, spider mites (Acari: Tetranychidae), especially species *Tetranychus urticae* and *Panonychus ulmi*, as well as certain species of whiteflies and leaf aphids (Homoptra: Aleyrodidae, Aphididae) stand out.

In 2002, the company Bayer CropScience introduced spirodiclofen, a tetronic acid derivative and the first cyclic ketoenol, acaricide with a wide spectrum and a novel mode of action – inhibition of acetyl-CoA-carboxylase. Soon after, spiromesifen was introduced, also a derivative of tetronic acid, acaricide and insecticide intended for control of phytophagus mites and whiteflies. Spirotetramat, a tetramic acid derivative, and the third member of the ketoenol group, was recently commercialised as an insecticide efficient against whiteflies, leaf aphids and other harmful Homoptera. In this paper are presented the most significant properties of cyclic ketoenols, aiming at pointing to the possibilities and prospects of their use, but also to potential problems and limitations.

**Keywords:** Cyclic ketoenols; Spirodiclofen; Spiromesifen; Spirotetramat

## INTRODUCTION

Modern crop protection industry puts great efforts into the search for new pesticides (insecticides, acaricides) acting on novel biochemical and physiological target sites, primarily because of a seriously increasing problem of pest resistance to pesticides. The resistance of many important arthropod pest species to insecticides and/or acaricides has become a global phenomenon in the past decades (Whalon et al., 2008, 2011). Therefore, crop protection practice has relied upon continual introduction of new active ingredients, with emphasis on alternation of compounds with different modes of action in order to prolong the lifespan of a newly introduced products. On the other hand, increasing regulatory restrictions are affecting a number of old but still effective and commercially important pesticides (Dekeyser and Downer, 1994; Casida and Quistad, 1998; Dekeyser, 2005; Elbert et al., 2007).

Among arthropod pests, spider mites (Acari: Tetranychidae) are known for their remarkable intrinsic potential for rapid development of acaricide resistance (Cranham and Helle, 1985; Knowles, 1997; van Leeuwen et al., 2009). Nearly 80% of cases of spider mite resistance reported until now deals with the resistance of two-spotted spider mite (*Tetranychus urticae*) and European red mite (*Panonychus ulmi*). In the list of „top 10" resistant arthropods in the world, based on the number of compounds for which resistance has been reported, *T. urticae* and *P. ulmi* rank first and sixth, respectively. Several generations of acaricides – acting on targets in nervous system (organophosphates, pyrethroids, formamidines, avermectins), growth and development targets (clofentezine, hexythiazox, benzoylureas), respiration targets (organotins, propargite, METI acaricides), as well as compounds of unknown or uncertain mode of action (dicofol, brompropylate, chinomethionat) – had been commercialized until the end of 20$^{th}$ and the beginning of 21$^{st}$ century (Dekeyser and Downer, 1994; Dekeyser, 2005). For both *T. urticae* and *P. ulmi*, the most of reports are related to resistance to organophosphates and pyrethroids, acaricides that have been used for a long time, and still account for a considerable part of global market. Nevertheless, there have also been an increasing number of cases of resistance to METI and some other acaricides introduced in the last 10-15 years (Whalon et al., 2008; van Leeuwen et al., 2009; Whalon et al., 2011). There are few data on spider mite resistance in Serbia (Marčić, 1997), but reports on considerably reduced efficacy of some acaricides and field experiences point to possible presence of resistant populations of tetranychids at several localities (Marčić, 2003; Petanović et al., 2010).

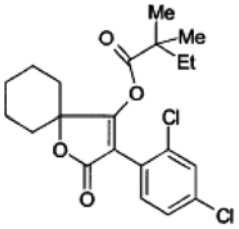


**Figure 1.** Spirodiklofen

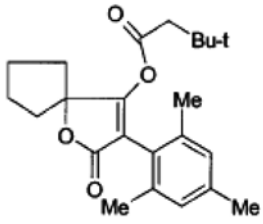


**Figure 2.** Spiromesifen

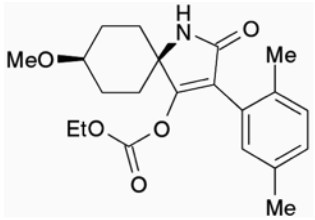


**Figure 3.** Spirotetramat

In 2002, Bayer CropScience launched ***spirodiclofen*** (Figure 1), the first member of the ketoenol group, a new acaricide with unique symptomology of poisoning, indicating a totally novel biochemical mode of action (Wachendorff et al., 2002; Nauen, 2005). Soon after, the second ketoenol was introduced, ***spiromesifen*** (Figure 2), acaricide and insecticide active against spider mites and whiteflies (Nauen et al., 2002, 2005; Kontsedalov et al., 2009). Recently introduced the third cyclic ketoenol, ***spirotetramat***, (Figure 3) is an insecticide proved as effective against whiteflies, aphids and other homopteran pests (Nauen et al., 2008). Expansion of the ketoenol activity spectrum to the above mentioned insect pests is very important for crop protection practice, having in mind that among „top 10" resistant arthropods are also some species of whiteflies and aphids.

## BIOLOGICAL ACTIVITY AND MODE OF ACTION

The basic characteristic of biological profile of spirodiclofen**,** a tetronic acid derivative, is activity on all developmental stages of spider mites. In baseline susceptibility studies (Wachendorff et al., 2002), it showed excellent action on eggs and immatures of two-spotted spider mite. After treatment with relatively low concentrations, the immature stages (larva, protonymph, deutonymph) usually die after reaching the next quiescent stage i.e. proto-, deuto-, or teleiochrysalis. In contrast to high susceptibility of *T. urticae* pre-adult stages, female adults were less susceptible and responded

slower to spirodiclofen treatment. Their fecundity was affected in that the produced eggs could not be deposited, and most females died after several days probably due to inability to lay eggs. Some of the females had an unusual big size, as a consequence of the high number of eggs accumulated in their body.

Marčić (2007) and Marčić et al. (2009) reported significant decrease in fecundity and fertility, and reduced viability of *T. urticae* females treated by spirodiclofen, resulting in significantly reduced intrinsic rate of increase in a concentration-dependent manner. The authors noted that the effects on reproduction were the most evident on the first day after treatment, when both fecundity and fertility were strongly reduced, as well as that from the second day a gradual recovery of females begins, especially of those treated with lower concentrations. The symptoms of poisoning described by Wachendorff et al. (2002) were also observed. Additionally, van Pottelberge et al. (2009a) observed in the females treated with higher concentrations of the acaricide sticky egg remnants on their ovipositors, as a symptom of intoxication more striking than a bigger size.

The unique symptomology of poisoning observed in immatures and female adults of *T. urticae*, not yet described for any other commercially available acaricide, indicates a totally new mode of action of spirodiclofen. It is obviously not a neurotoxic compound, but its mode of action is similar to growth-regulating insecticides, with considerably faster the onset of the activity. Based on a significant decrease in lipid content found in treated *T. urticae* females (Wachendorff et al., 2002) and some other results (Nauen, 2005) indicating an interference with lipid biosynthesis, it is concluded that acetyl-CoA-carboxylase, a key enzyme in fatty acid biosynthesis, is likely to be the biochemical target responsible for spider mite intoxication. Moreover, spirodiclofen was synthetized in the optimization and development process that had started after unexpected discovery of acaricidal properties in the acylated derivative of a herbicidal compound acting on acetyl-CoA-carboxylase (Bretschneider et al., 2007).

Another tetronic acid derivative, spiromesifen, shows acaricidal profile and symptomology clearly comparable with that previously described for spirodiclofen. In baseline susceptibility studies (Nauen et al., 2002, 2005), spiromesifen was highly toxic to eggs and immatures. Female adults were also quite susceptible, due to the accumulation of eggs which cannot be deposited, and their fecundity was strongly affected. These results suggested the same mode of action of these two tetronic acid derivatives. Additionally, comparative trials against larvae of both *T. urticae* and *P. ulmi*, showed that spiromesifen efficacy is similar or even higher than the efficacy of other commercial acaricides (Nauen et al., 2005).

Marčić et al. (2010a) further investigated the effects of spiromesifen on *T. urticae* females. The authors demonstrated significant reduction in a concentration-dependent manner of fecundity, fertility, and the instantaneous rate of increase after treatments of female teleiochrysalises, and pre-ovipositional females, and noted that the effects were stronger after the treatment of latter.

Besides effects on spider mites, baseline studies with spiromesifen (Nauen et al., 2002, 2005) revealed its considerable activity against sweet potato whitefly, *Bemisia tabaci*. The authors observed high mortality rates after treatments of eggs and nymphs of 1$^{st}$ and 3$^{rd}$ instar, moderate to high mortality in pupae, low mortality and strong reduction of fecundity and fertility in female adults. Contrary to effects on *T. urticae* eggs, the authors noted that the compound is not particularly ovicidal, but ovo-larvicidal against whiteflies. Similar pattern of spiromesifen activity against sweet potato whitefly was reported by Liu (2004) who found high toxicity to 2$^{nd}$ instar nymphs, moderate toxicity to 3$^{rd}$ and 4$^{th}$ instar nymphs, and low toxicity to adults and eggs. Spiromesifen was also highly toxic to the early first instars or crawlers that hatched from treated eggs. On the other hand, Kontsedalov et al. (2009) found considerably greater susceptibility in *B. tabaci* eggs and adults to spiromesifen, than it was recorded in the two previous papers. Additionally, Kontsedalov et al. (2009) observed some morphological effects on the eggs laid by the treated females (smaller size, an abnormally perforated chorion, abnormally formed and improperly localized bacteriomes), as well as reduced number of ovarioles in the treated females and an abnormal egg stuck in their ovipositors.

Spirotetramat, a tetramic acid derivative and the third member of ketoenol family, exhibits biological activity against sucking insect pests. In baseline studies, spirotetramat showed excellent activity against nymphs of *Myzus persicae*, *Aphis gossypii, Phorodon humuli*, and *B. tabaci*: the nymphs were very susceptible, they could not moult properly and died within few days. The adult females were much less susceptible, but their reproduction was strongly affected. In both *B. tabaci* and *M. persicae* females, the number of deposited eggs/nymphs decreased and the viability of eggs/nymphs was reduced in a concentration-dependent manner. One of the most prominent effects in aphid females was the cumulation of nymphs in their body, followed by weight gain,

which caused death several days after treatment (Nauen et al., 2008; Brück et al., 2009).

Few data are available concerning acaricidal effects of spirotetramat. Brück et al. (2009) only noted its suppressive side effects on spider mites and rust mites in some field trials targeted against insect pests. Recently, Marčić et al. (2010c) tested toxicity of spirotetramat to developmental stages of *T. urticae*, while Marčić et al. (2011) investigated its effects on fertility, viability, and the instantaneous rate of increase, after treatments of female teleiochrysalises, and pre-ovipositional females. The authors found the profile of biological activity and symptomology of poisoning of this compound similar to those previously described for spirodiclofen and spiromesifen. On the other hand, in two recent studies dealing with spirodiclofen resistance, the data on toxicity of spirotetramat to larvae of susceptible and resistant strains of *Panonychus citri* (Hu et al., 2010) and *P. ulmi* (Kramer and Nauen, 2011) were presented.

Both spirodiclofen and spiromesifen act as contact acaricides. As highly lipophilic compounds (logP* = 5.83 and 4.55, respectively), they tend to stick to the waxy leaf surface. Although some amounts of spiromesifen also penetrate into the leaf tissue, it is probably not enough to achieve any significant action against spider mites, while for intoxication of whiteflies translaminar activity is important to a certain degree (Nauen et al., 2005; Kontsedalov et al., 2009).

Unlike the former two compounds, spirotetramat is a two-way systemic compound, unique among recently developed insecticides. It also shows excellent translaminar action, whereas its contact activity is rather limited. Spirotetramat is able to penetrate into the leaf, due to its reduced lipophilicity (logP = 2.51). After penetration into the plant tissue it is hydrolysed to spirotetramat-enol, which has physicochemical properties (a weak acid, logP = 0.3) that allow its ambimobility i.e. translocation in both long distance transport systems, phloem and xylem. Owing to this unique ambimobile activity, spirotetramat can protect new leaves appearing after foliar application, as well as roots (Fisher and Weiss, 2008; Nauen et al., 2008; Brück et al., 2009).

## SPECTRUM OF ACTIVITY AND FIELD PERFORMANCE

Spirodiclofen is a broad spectrum acaricide, effective against spider mites, false spider mites (Tenuipalpidae), gall and rust mites (Eriophyoidea), with performance at least equal or superior to other available acaricides (Elbert et al., 2002; Bretschneider et al., 2007). In field trials carried out iu European Union, USA, Japan and Brazil spirodiclofen showed high and long lasting efficacy against *P. ulmi* and *T. urticae* on pome fruit, stone fruit, and grapes, *Eotetranychus carpini* and *Calepitrimerus vitis* on grapes, *P. citri*, *Phyllocoptruta oleivora* and *Brevipalpus phoenicis* on citrus, *Aculus schlechtendali* on apple, *Bryobia rubrioculus* on almonds (Elbert et al., 2002), *T. urticae* on black currant (Labanowska, 2002) and strawberry (Raudonis, 2006), *Phyllocoptes gracilis* on raspberries (Linder et al., 2008). In Serbia, spirodiclofen achieved high efficacy against both overwintering eggs and summer populations of *P. ulmi* on apple, and *T. urticae* on greenhouse cucumber (Marčić et al., 2007, 2010b). Although at relatively high population densities good results are achieved in mite control, the best solution is to apply spirodiclofen at the beginning of the infestations, before mite populations reach economic threshold (Elbert et al., 2002).

In addition to acaricidal action, spirodiclofen showed considerable insecticidal activity against eggs and larvae of pear sucker (*Cacopsylla pyri*) and mobile stages of scales *Lepidosaphes ulmi* and *Quadraspidiotus perniciosus* (De Maeyer et al., 2002a). In field trials carried out in Serbia (Marčić et al., 2007, 2008), this compound achieved good efficacy against *C. pyri*, applied before or at the very beginning of hatching of the first generation larvae. The results reported by Saour et al. (2010) showed that pear sucker population could be effectively suppressed over the entire season by three spirodiclofen treatments.

Spiromesifen is an acaricide and insecticide that can compete with the best standard compounds, effective against phytophagous mites and whiteflies (Elbert et al., 2005; Bretschneider et al., 2007). In field and greenhouse trials conducted in European countries, USA, Central and South America and Japan, spiromesifen achieved high efficacy against *T. urticae* on vegetables, strawberry, corn, apple and ornamentals, *T. cinnabarinus* on ornamentals, *P. ulmi* on apple, *Aculops lycopersici* on tomato, as well as *Trialeurodes vaporariorum* and *B. tabaci* on vegetables, strawberry and cotton. Spiromesifen was also effective against psyllid *Paratrioza cockerelli*, an important pest of vegetables in North and Central America. Due to its mode of action, best results are obtained when the product is applied at the beginning of the infestation (Elbert et al., 2005).

Spirotetramat is primarily an insecticide effective against a wide spectrum of homopteran insect pests, such as aphids (Aphididae), whiteflies (Aleyrodidae),

* n-octanol/water partition coefficient, the log value

psyllids (Psyllidae), soft scales (Coccidae), armoured scales (Diaspididae) and mealybugs (Pseudococcidae). The trials conducted in European countries, Brazil and USA (Bell et al., 2008; Cantoni et la., 2008; Kühnhold et al., 2008; Brück et al., 2009) proved spirotetramat as highly effective against aphids *Nasonovia ribisnigri* on lettuce, *Brevicoryne brassicae* and *M. persicae* on cabbage, *A. gossypii* on melon, *Dysaphis plantaginea*, *Aphis pomi* and *Eriosoma lanigerum* on apple, *Hyalopterus pruni* on stone fruits; whiteflies *B. tabaci* and *T. vaporariorum* on vegetables; psyllids *C. pyri* and *C. pyricola* on pome fruits; scales *Aonidiella aurantii* on citrus, *Pseudaulacaspis pentegona* on peach, *Q. perniciosus* on pome fruits and stone fruits, and citrus; mealybugs *Planococcus ficus*, *Pseudococcus maritimus*, *P. longispinus* and *P. viburni* on grapes. In addition to its activity against hemipteran pests, field trails in Australia showed that spirotetramat could be a very useful against larvae of western flower thrips, *Frankliniella occidentalis* (Kay and Herron, 2010).

Although in some field trials suppressive side-effects of spirotetramat on phytophagous mites were observed (Brück et al., 2009) currently there are no data on trials aiming at testing acaricidal effects of this compound under field and/or greenhouse conditions.

The recommended application rates for ketoenols range between 48-144 mg a.i./l (spirodiclofen), 72-180 mg a.i./l or 50-280 g a.i./ha (spiromesifen), and 45-288 g a.i./ha or 75-96 g a.i./ha × m CH (spirotetramat), depending on crop and pest species, and formulation type (Bretschneider et al., 2007; Kühnhold et al., 2008). The following formulation types were developed: SC (=suspension concentrate), all three compounds; WG (=water dispersible granules) and WP (=wettable powder), only spirodiclofen; OD (=oil dispersion), only spirotetramat (Tomlin, 2009). In order to optimise the penetration of spirotetramat through the leaf cuticle, it is recommended to tank-mix SC formulations with a suitable adjuvant (e.g. rape seed oil methyl ester), or use the adjuvanted formulation (Bretschneider et al., 2007; Brück et al., 2009).

## RESISTANCE AND CROSS-RESISTANCE

Because of the novel mode of action, no obvious cross-resistance could be expected between cyclic ketoenols and any other commercial acaricide and/or insecticide. Spirodiclofen and spiromesifen showed high activity against various *T. urticae* and *P. ulmi* strains resistant to dicofol, organophosphates, mite growth inhibitors, abamectin, METI acaricides, (Wachendorff et al., 2002; Nauen and Konanz, 2005; Pree et al., 2005; van Pottelberge et al., 2009b). Similarly, none of *B. tabaci* strains resistant to endosulfan, organophosphates, carbamates, pyrethroids, neonicotinoids, pyriproxyfen, diafenthiuron, showed any cross-resistance to spiromesifen (Nauen and Konanz, 2005; Prabhaker et al., 2008; Kontsedalov et al., 2009). Also, spirotetramat showed excellent efficacy against *M. persicae* strains resistant to organophosphates, carbamates and pyrethroids, and *B. tabaci* strains resistant to endosulfan, organophosphates, pyrethroids, neonicotinoids, pymetrozine and buprofezin (Elbert et al., 2008).

Since the ketoenols have been recently introduced, there are few reports on field resistance. Hu et al. (2010) investigated spirodiclofen susceptibility in *P. citri* populations collected from citrus orchards at six locations in China and found high resistance ratios (RR) in two populations (RR=50 and 90.8). These two populations also showed various levels of resistance to other acaricides used in *P. citri* control, as well as moderate cross-resistance to spirotetramat (RR=16.9 and 22.4), which was not present on Chinese market at the time. However, mortality was assessed after 24 h, which may be too short for reliable assessment of effects, having on mind that spirodiclofen acts rather slow. Kramer and Nauen (2011) tested European populations of *P. ulmi* for their susceptibility to spirodiclofen. In four populations collected in south-western Germany age-specific expression of resistance was found: larvae exhibited resistance (RR=12-59) whereas eggs were susceptible to spirodiclofen (RR=1.1-2.9). The population with the highest RR was further artificialy selected with spirodiclofen until strong resistance (RR>7000, larvae) developed. However, resistance in eggs was much lower (RR=56). Additionally, the selection provided only moderate to low cross-resistance to spiromesifen in larvae and eggs (RR=30.4 and 4, respectively), as well as low cross-resistance to spirotetramat in larvae (RR=3). Age-specific expression of resistance to spirodiclofen in larvae and eggs (RR=274 and 2, respectively) and moderate level of cross-resistance between this acaricide and spiromesifen (RR=18, larvae), was previously shown in SR-VP strain, a laboratory-selected resistant strain of *T. urticae* (van Pottelberge et al., 2009b). Spirodiclofen resistance in another strain selected in laboratory, SR-FZ strain of *P. citri*, was age-specific as well (RR=51.2-157, juvenile stages; RR=4.6, eggs), and the strain was moderate cross-resistant to spirotetramat (Yu et al., 2011). In these two strains, the fertility of female adults was not affected after the treatment with spirodiclofen, in contrast to that of females from corresponding susceptible strains (van Pottelberge et al., 2009a, Yu et al., 2011).

Genetic analysis of resistance in SR-VP strain of *T. urticae* showed the intermediate and polygenic inheritance of the resistance to spirodiclofen. Biochemical analysis of this strain suggested that P450 monooxygenases might be the most important enzyme system in the metabolic detoxification, but esterases and glutathion-S-transferases could be involved as well (van Pottelberge et al., 2009b). In SR-FZ strain of *P. citri*, synergism tests also indicated involvement of these three enzyme systems in an enhanced metabolism of spirodiclofen (Yu et al., 2011).

In order to save the longevity of the ketoenol products, resistance management guidelines (Elbert et al., 2002; Nauen and Konanz, 2005; Elbert et al., 2008) recommended only one application per cropping cycle for spirodiclofen, up to four applications for spiromesifen, and up to three applications for spirotetramat.

## THE EFFECTS ON BENEFICIAL ARTHROPODS

### Predatory mites

The baseline laboratory studies with $LR_{50}$ (= application rate at which 50% mortality occurs) as the endpoint indicated considerable acute toxicity of ketoenols to *Typhlodromus pyri*, an indicator species and the key natural predatory mite in apple orchards and vineyards in North America and Europe (Table 1). The $LR_{50}$ data obtained in these studies, however, can not be directly compared to the recommended application rates, nor can the impact of pesticides on predator populations under natural field conditions be reliably predicted using these data.

**Table 1.** $LR_{50}$ data for *Typhlodromus pyri* obtained in the baseline studies

| Compound | Formulation | $LR_{50}$ (g a.i./ha) | Test regime | Reference |
|---|---|---|---|---|
| Spirodiclofen | SC | 2.3 | apple leaves | Wolf and Schnorbach, 2002 |
| Spiromesifen | SC | 68.4 | glass plates | Nicolaus et al. 2005 |
| Spirotetramat | OD | 0.33 | glass plates | Maus, 2008 |
| | OD | 1.59 | bean leaves | |
| | SC | 40.5 | bean leaves | |
| | SC | 38.9 | apple leaves | |

$LR_{50}$ = application rate at which 50% mortality occurs
SC = suspension concentrate
OD = oil dispersion

Further field trials conducted in apple orchards revealed adverse side effects of ketoenols on *T. pyri* populations, but the effects were considered acceptable and the ketoenols compatible with the predatory mite in the IPM (=integrated pest management) systems. Applied at 144 g a.i./ha, spirodiclofen decreased population density by 35-55%, but the population fully recovered before the next season started, while no significant reduction was observed at the application rate of 96 g a.i./ha. This result showed that population of *T. pyri* would be maintained sustainable in the orchards receiving one spray treatment within the season (Wolf and Schnorbach, 2002). In a starting IPM system, spirodiclofen (48-96 mg a.i./l) strongly reduced the number of *T. pyri* (up to 93%); however, the prey/predator-ratio dropped to favorable low values (as *P. ulmi* and *A. schlechtendali* were effectively controlled as well), and by the end of the season the population of *T. pyri* reached the same level as in untreated plots. Application in a stable IPM system caused reduction of 27.1% 28 DAT (=days after treatment), which was considered to be slightly harmful, according to the IOBC scale (De Maeyer et al., 2002b). The authors concluded that spirodiclofen in starting systems would regulate the start of IPM by lowering the prey/predator-ratio, while in stable systems could be applied as a correction measure against occasional outbursts of spider mites and rust mites. Spirotetramat applied at 75 g a.i./ha × m CH reduced *T. pyri* population by around 80% 31 DAT, but the populations had recovered at the last assessment, 47 DAT. The prey/predator-ratio was lower than in untreated plots, which indicated that the prey was more sensitive than the predator (Schnorbach et al., 2008; Brück et al., 2009).

Testing of spiromesifen effects on *T. pyri* under field conditions was not conducted, probably because this product was developed primarily for the use in vegetables and field crops, not in tree fruit crops.

As for the other predatory mites, the most data are available on effects of ketoenols on the western orchard predatory mite *Galendromus occidentalis*, under laboratory conditions. Sáenz-de-Cabezón-Irigaray and Zalom

(2006, 2007) investigated sublethal effects of spiromesifen, applied at label rate, on newly emerged adult females of *G. occidentalis* and found that the effects varied by the methods of exposure. In the treatment described as „worst case exposure" (i.e. direct treatment, treated prey, treated leaf surface) female longevity and fecundity were reduced by 36% and 89%, respectively, and the eggs laid did not hatch. In the females treated directly (and transferred to untreated leaf surface) fecundity was reduced by 31%, while the exposure to leaf surface residues reduced fecundity by 55%; neither of two methods of exposure significantly reduced fertility. The authors concluded that spiromesifen, despite observed adverse effects, may be compatible with the predator under field conditions. Levebvre et al. (2011) tested toxicity of the label concentration of spirotetramat (228 mg a.i./l) to developmental stages of *G. occidentalis* and observed mortality of 90.4%, 100%, and 72.4% in eggs, larvae, and female adults, respectively, while the number of laid eggs was reduced to almost zero. The label concentration was 7.7-fold the $LC_{50}$ obtained in „worst case exposure". Based on these results, the authors recommended further field evaluations of spiromesifen only if alternatives are unavailable. In contrast to other two compounds, the recommended rate of spirodiclofen was non-toxic to *G. occidentalis* females in „worst case exposure", while their fecundity was slightly but not significantly reduced (Bostanian et al., 2009).

There are also few data obtained in field trials. Raudonis (2006) rated spirodiclofen, applied at 48-96 g a.i./ha in strawberry fields, as non-toxic to *Amblyseius andersoni*, while spirotetramat at 75 g a.i./ha was moderately harmfull to *Kampimodromus aberans* in the trials conducted in grapevines (Schnorbach et al., 2008).

## Other predators and parasitoids

Spirodiclofen is selective and safe for predatory insects, such as the common green lacewing, *Chrysoperla carnea*, the ladybirds *Coccinella septempunctata* and *Stethorus punctillum,* the earwig *Forficula auricularia*, and the bug *Anthocoris nemoralis*, as well as for parasitoid wasps *Aphidius rhopalosiphi* and *Trichogramma cacoeciae*, as the results from the baseline laboratory, semi-field and field trials indicated (De Maeyer et al., 2002b; Wolf and Schnorbach, 2002).

In the baseline laboratory studies (Nicolaus et al., 2005), the wasp *A. rhopalosiphi* and the larvae of the ladybird *C. septempunctata* were rather sensitive to spiromesifen on glass plates ($LR_{50}$ = 9.8 and 41.7 g a.i./ha, respectively), but no adverse effects on mortality and fecundity of the wasp were observed on detached leaves up to 864 g a.i./ha, the maximum predicted foliar residue level. Mortality and fecundity of *C. carnea* were not significantly affected up to the same level as well, but under the exposure on glass plates.

Bielza et al. (2009) evaluated side effects of spiromesifen, applied at full label rate, on the parasitoid wasp *Eretmocerus mundus*, and the predatory bug *Orius laevigatus*, the key natural enemies of *B. tabaci*, and *F. occidentalis*, respectively, on vegetable crops in Spain. No significant reduction in both the percentage of parasitism of *E. mundus* and the number of *O. laevigatus* adults and larvae was observed in the trials carried out in commercial greenhouses, which indicates favorable selectivity of spiromesifen to these two biological control agents.

Spirotetramat showed low toxicity to the parasitoid *A. rhopalosiphi*, and the predators *C. carnea* and *C. septempunctata*: $LR_{50}$ values obtained in the baseline laboratory tests on leaf surface were above 288 g a.i./ha, with no significant effects on reproduction (Maus, 2008). The baseline semi-field and field trials on various crop plants showed that this compound can be considered as harmless to moderately harmful to the predators *Macrolophus caliginosus*, *Orius* spp, *A. nemoralis*, *Chilocorus nigritus*, *C. septempunctata*, *F. auricularia*, *Episyrphus balteatus*, and parasitoids *Aphelinus mali*, *Encarsia formosa*, *Aphytis lingnanensis* (Schnorbach et al., 2008).

## Honeybees

Cyclic ketoenols have no acute toxicity to honeybee (*Apis mellifera*). In the baseline studies (Wolf and Schnorbach, 2002; Nicolaus et al., 2005; Maus, 2008), the following $LD_{50}$ values (µg a.i./bee; 48 h) were obtained: for spirodiclofen, spiromesifen, and spirotetramat: ≥100, 60.2, and 91.7, respectively (oral), and ≥100, ≥200, and 162, respectively (contact). In a semi-field study carried out under realistic conditions, however, an adverse impact of spirodiclofen on the development of honeybee brood was recorded, which does not allow its use during the blossom period (Wolf and Schnorbach, 2002). The adverse effects of spirotetramat on the brood were observed in a test which strongly overemphasized the exposure, but further field studies carried out under realistic use conditions (application to bee-attracting crops according to the recommended use patterns) supported the conclusion that spirotetramat is safe for the brood (Maus et al., 2008).

## USES AND STATUS

Currently, almost a decade after spirodiclofen had been introduced on the market, cyclic ketoenols are registered or are in registration process in many countries worldwide. Spirodiclofen products are registered for uses in perennials e.g. pome and stone fruit, citrus, grapes, strawberries, hops, nuts, while spiromesifen products are primarily used in vegetables and field crops (cotton, maize, potatoes). In Japan, however, there is a product that has been developed for mite control in pome fruit. The intended use of spirotetramat products is both in vegetables and field crops (cotton, soybean), and perennials e.g. pome and stone fruit, grapes, hops, citrus, nuts, bananas (Nauen et al., 2002; Elbert et al., 2005; Tomlin, 2009).

In European Union, spirodiclofen has been approved under Regulative (EC) No. 1107/2009 (repealing Directive 91/414/EEC), and authorised in 17 member states. Spiromesifen and spirotetramat have been authorised in six EU member states, while their evaluation under the Regulative is in progress (EU, 2011).

Spirodiclofen has been available on the Serbian market since 2005, and its intended use is in control of *P. ulmi*, *T. urticae* and *A. schlechtendali* in apple, *P. gracilis* in raspberry and *C. pyri* in pear. Spirotetramat also became available on the Serbian market from this year, and it is registered for control of *C. pyri* in pear, *E. lanigerum* in apple, *Diaspis pentagona* in peach and *T. vaporariorum* in tomato.

The new mode of action and long-lasting efficacy of the ketoenols, as well as the unique ambimobile properties of spirotetramat, are the basic advantages of ketoenols. Besides this, ketoenols have favorable toxicological and ecotoxicological profiles, and show a great potential for implementation in IPM programs. From the perspectives of the applied acarology/entomology, there is plenty of space for further investigations of this new group of acaricides and insecticides, especially for the more comprehensive and detailed study of their effects on various biological agents, as well as for testing the acaricidal properties of spirotetramat.

## ACKNOWLEDGMENTS

This work was carried out as a part of the Project TR 34043 which is financially supported by the Ministry of Education and Science of the Republic of Serbia.

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# Ciklični ketoenoli – akaricidi i insekticidi novog mehanizma delovanja

**REZIME**

Moderna hemijska industrija u oblasti zaštite bilja ulaže velike napore u istraživanje i razvoj pesticida (insekticida, akaricida) novih mehanizama delovanja, pre svega zbog sve ozbiljnijeg problema rezistentnosti štetnih organizama na pesticide. Rezistentnost mnogih štetnih vrsta artropoda (insekata i grinja) na insekticide i/ili akaricide postala je poslednjih decenija globalni fenomen. Otuda se praksa zaštite bilja u velikoj meri oslanja na stalno uvođenje u primenu novih aktivnih materija, odnosno na alternativnu primenu što većeg broja jedinjenja različitih mehanizama delovanja radi produžavanja vremena upotrebe novouvedenih proizvoda. Među štetnim artropodama, po svom prirodnom potencijalu za razvoj rezistentnosti i broju dokumentovanih slučajeva izdvajaju se grinje paučinari (Acari: Tetranychidae) – posebno vrste *Tetranychus urticae* i *Panonychus ulmi* – kao i pojedine vrste leptirastih (Aleyrodidae) i lusnih vaši (Aphididae).

Godine 2002, kompanija Bayer CropScience uvela je u primenu spirodiklofen, derivat tetronske kiseline i prvi ciklični ketoenol, akaricid širokog spektra i novog mehanizma delovanja – inhibicije acetil-koenzim A-karboksilaze. Ubrzo je u primenu uveden spiromesifen, takođe derivat tetronske kiseline, akaricid i insekticid namenjen suzbijanju fitofagnih grinja i leptirastih vaši. Nedavno je komercijalizovan i treći ketoenol, spirotetramat, derivat tetramske kiseline, insekticid efikasan protiv leptirastih vaši, lisnih vaši i drugih štetnih hemiptera. U ovom radu su predstavljene najznačajnije osobine cikličnih ketoenola, sa ciljem da se ukaže na mogućnosti i perspektive njihove primene, ali i na potencijalne probleme i ograničenja.

**Ključne reči**: Ciklični ketoenoli; spirodiklofen; spiromesifen; spirotetramat