A review of sulfoxaflor, a derivative of biological acting substances as a class of insecticides with a broad range of action against many insect pests

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Abstract

Sulfoxaflor is an insecticide used against sap-feeding insects (Aphididae, Aleyrodidae) belonging to the family of sulfoximine; sulfoximine is a chiral nitrogen-containing sulphur (VI) molecule; it is a sub-group of insecticides that act as nicotinic acetylcholine receptor (nAChR) competitive modulators. Sulfoxaflor binds to nAChR in place of acetylcholine and acts as an allosteric activator of nAChR. Thanks to its mode of action resistance phenomena are uncommon, even few cases of resistance were reported. It binds to receptors determining uncontrolled nerve impulses followed by muscle tremors to which paralysis and death follows. Sulfoxaflor acts on the same receptors of neonicotinoids as nicotine and butenolides, but it binds differently. It binds to insects nAChRs more strongly than to mammals' ones, so it is much less toxic for mammals and man. Sulfoxaflor is supposed to have a low environmental impact and is not much aggressive against non-target species. Unfortunately, it is toxic to impollinator insects, so it must be used only in compliance with a series of legislative norms. At present sulfoxaflor can be considered one of the most interesting products to be used in fighting against agriculture insect pests.

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Introduction

Insecticides are important tools in the control of insect pests. An unexpected unfavourable consequence of the increased use of insecticides was the reduction of pollinator species and the subsequent declines in crop yields. Multiple factors in various combinations as modified crops, habitat fragmentation, introduced diseases and parasites, including mites, fungi, virus, reduction in forage, poor nutrition, and queen failure were other probable contributory causes of elevated colony loss of pollinator species, but the reduction of pollinator species was often attributed to some classes of insecticides.

In an effort to reduce the unfavourable consequences of an indiscriminate use of insecticides, their usage is actually regulated by a detailed complex of norms to avoid an unreasonable environmental risk. In any case the economic, social, and environmental costs and benefits connected with their use should be taken into account. For this reason, beyond the research efforts in discovering new formulas and new mechanisms of actions, there is the actual tendency to introduce mitigation measures following a series of legislative norms. Insecticide Resistance Management (IRM) programs have the aim to promote research to manufacture products that exhibit high potency and lack insecticidal cross-resistance (Babcock *et al*., 2011). The aim is to reduce the adverse effects of their unregulated use, avoiding the insurgence of resistance phenomena, considering that a total banning of insecticides is at present impossible and unrealistic and the present situation is not expected to change in the immediate or less immediate future.

Neonicotinoids (neonics) act as plant systemic, especially suited in control of sucking insects, they are effective also in flea control on dogs and cats. They are a new generation of insecticides that has its historical basis on the use of tobacco nicotine to control pest plants since fifteen centuries. Seven groups of neonics are actually known (Figure 1, Table 1): Butenolide, Cyanoimines (NCN), Mesoionic, nitroimines (NNO_2), nitromethylene ($CHNO_2$), Nicotinoids and Sulfoximine. Imidacloprid, clothianidin, thiamethoxam, and dinotefuran are the most known compounds among nitroimines group, cycloxaprid, nitenpyram among nitromethylene compounds, acetamiprid and thiacloprid among the cyanoimines, the old nicotine among nicotinoids and sulfoxaflor among sulfoximine.

Neonicotinoids were developed to control species detrimental to agriculture, but they were also used to control insects of sanitary interest. They were tested on many pest species, the most investigated are summarized in Table 2, together some predators and parasitoids.

The efficacy of an insecticide was traditionally measured as LC_{50} or LD_{50} that is the concentration or the amount of a substance

respectively determining 50% mortality of insect pest. At present the toxic action of neonicotinoids is supposed to be related to their capacity to bind to the nAChR receptors. So, beyond LC_{50} measure, their toxicity can be measured with electrophysiological tests, as IC_{50}, where IC_{50} is the ligand Insecticide Concentration that reduces the acetylcholine (Ach) induced current by 50%. The technique used to measure the induced Ach current is based on the patch clamp technique that studies ionic currents in individual isolated cells or patches of cell membrane. The technique is especially useful in the study of excitable cells such as neurons to study ion channels performance. Borosilicate glass electrodes filled with a solution of known osmolarity are connected to a patch-clamp amplifier and acetylcholine (Ach) induced currents measured (Oliveira *et al*., 2011).

The research around neoticotinoids (shortened to "neonics"), in an attempt to discover products able to bypass the insecticide-resistance phenomena, put on the market new products. Among them the novel sulfoximine insecticide sulfoxaflor (isoclast active™, Closer®) was proposed as a potent and more effective insecticide than the neonicotinoids thanks to toxicity to many insect pests as green peach aphids (GPA, *M. persicae,* Table 2).

All neonics are nicotinic acetylcholine receptor (nAChR) agonists with a similar mode of action and target-site cross-resistance, despite some important differences in their formula, and are much more effective on insect than on mammalian nAChRs at defined binding sites (Tomizawa & Casida, 2003).

The neonics, in comparison with the old nicotine, have the advantage to be readily metabolized and have favourable toxicological profiles, unfortunately they are very toxic to impollinators (Casida, 2018; Siviter *et al*., 2018). Honey bees are highly sensitive to nicotinoids indeed, even if some toxicity differences between the different groups are apparent, the nitroimines and nitromethylenes appearing as the most toxic and with high photolability, while the cyanoimines should be the less toxic to bees according to experimental evidences (Table 3) (Iwasa *et al*., 2004).

The sulfoximines, as exemplified by sulfoxaflor ([N-Imethyloxido[1-[6-(trifluoromethyl)-3-pyridinyl]ethyl]-lambda(4)-sulfanylidene]cyanamide] represent a new class of insecticides. Sulfoxaflor is a chiral (that is a compound that can be distinguished by its mirror image) nitrogen-containing sulphur (VI) molecule, it exhibits a high degree of efficacy against a wide range of sap-feeding insects, including those resistant to neonicotinoids and other insecticides. Sulfoxaflor is an agonist at insect nicotinic acetylcholine receptors (nAChR) and seems to function in a manner distinct from other insecticides acting at nAChRs, because the sulfoximines exhibit Structure Activity Relationships (SAR) that are different from other nAChR neonicotinoids agonists. The sulfoximine SAR mode of action and the biochemistry underlying the observed efficacy on resistant insect pests, with a particular focus on sulfoxaflor reserves attention. Butenolide flupyradifurone is structurally related and shows a similar action.

Sulfoxaflor, as a new alternative sucking pest insecticide used in Integrated Pest Management (IPM) programs; was developed by Dow AgroSciences and it is supposed to have a new mode of action so sulfoxaflor is not considered a neonicotinoid, even if there is no agreement in this point, because some authors suggest that sulfoxaflor should be considered a neonicotinoid because a point mutation in *M. persicae* determines a cross-resistance to all exprimented neonicotinoids including sulfoxaflor (Cutler *et al*., 2013).

Insecticide Resistant Action Committee (IRAC) has classified its unique mode of action in the new subgroup 4C of Sulfoximines. Sulfoxaflor is extremely effective against many sap-feeding insects, including scales, aphids, leafhoppers and whiteflies (Bedford *et al.,* 1994) in all major crops, such as pome fruits, stone fruits, citrus, vegetables and ornamentals.

The registration of Closer®, 120 SC formulation of sulfoxaflor on solanaceae, cucurbits and lettuce in the open field and greenhouse, as well as on legumes, brassicas, potato, ornamentals, pome, stone, citrus fruit has been requested. Label extensions are planned for vine, strawberry and artichoke. (Tescari *et al*., 2016)

For its new mode of action and its favourable toxicological and eco-toxicological profile, sulfoxaflor is an ideal tool for IPM programs**;** the contact and anti-feeding activity ensure a high knock-down effect against adults of whiteflies and a prolonged efficacy on neanids**.**

The aim of the present review is to summarize the most recent progress in clarifying the mechanism of action, toxicity and efficacy of the sulfoxaflor and to present some experimental evidence of their effects.

Toxicity on target organisms

In 2010, Dow AgroSciences LLC applied to the US Environmental Protection Agency (EPA) for the registration of sulfoxaflor, as a new systemic insecticide (EPA (US Environmental Protection Agency), 2010). This insecticide was thereafter available for use in the European Union (EC, 2015, 2017) (Centner *et al*., 2018).

Sulfoxaflor exhibits high potency and lacks insecticidal cross-resistance, so it is particularly useful in insecticide resistance management (IRM) programs; it is the first compound under development from the novel sulfoxamine class of insecticides. In the laboratory, sulfoxaflor demonstrated high levels of insecticidal activity against many sap-feeding insects species. The efficacy of sulfoxaflor was comparable with that of other neonicotinoids, for the control of a wide range of aphids, whiteflies (Sternorrhyncha) and true bugs (Heteroptera).

In the following table (Table 2) the species that are target of sulfoxaflor, their parasitoids and predators are given together some impollinator species; some congeneric species present in Italy are also reported.

Sulfoxaflor was successfully used against the following species (Table 2): *A. aurantii*, *P. citri* on citrus, *P. comstocki* and *P. pentagona* on Drupaceae, *P. ficus*, *T. vitis* and *P. corni* on vine (Convertini *et al*., 2018a), *D. plantaginea* on apple (Boselli *et al*., 2018), *A. gossypii* on horticultural crops (Convertini *et al*., 2018b), *V. vitifoliae* on vine (Bacci *et al*., 2018a).

Sulfoxaflor performed well in the laboratory against both insecticide-susceptible and insecticide-resistant populations of sweetpotato whitefly, *B. tabaci*, (Table 2) and brown plant-hopper, *N. lugens* (Table 2), including populations resistant to the neonicotinoid imidacloprid. These trends were confirmed in the field from different area and for different crops, and in populations of insects with repeated exposure to insecticides. In particular, a sulfoxaflor use rate of 25 g ha^{-1} against cotton aphid (*A. gossypii,* Table 2) outperformed acetamiprid (25 g ha^{-1}) and dicrotophos (560 g ha^{-1}). Sulfoxaflor (50 g ha^{-1}) provided also a control of sweetpotato whitefly similar to acetamiprid (75 g ha^{-1}) and imidacloprid (50 g ha^{-1}) and performed better than thiamethoxam (50 g ha^{-1}). The novel chemistry of sulfoxaflor, its unique biological spectrum of activity and lack of cross-resistance highlight the potential of sulfoxaflor as an important new tool for the control of sap-feeding insect pests (Babcock *et al*., 2011).

B. tabaci and *T. vaporariorum* (Table 2) are two of the most polyphagus, problematic and persistent greenhouse pests. They are

phloem sap feeding pests, but indirect damages are often more serious than direct damages; indirect effects are caused by sooty mold fungus and by virus transmission, especially *Geminivirus* (De Barro *et al.,* 2011). Pest insects determine damage to Cucurbitaceae, Leguminosae, Euphorbiaceae, Malvaceae and Solanaceae (Bedford *et al.,* 1994)). These two-whitefly species are often a considerable problem under glass, especially in more temperate areas.

T. vaporariorum is a very polyphagous pest, more dangerous in protected crops and transmits a limited number of viruses, all within the genera *Crinivirus* and *Torradovirus* (Wisler *et al.,* 1998; Brown, 2007; Navas-Castillo *et al.,* 2011).

B. tabaci is a serious pest of both open-air and protected cropping (e.g. Spain, Israel and Europe-Mediterranean area). It includes a complex mix or genetically but not morphologically distinguishable populations, which have been referred as biotypes. Recently, it has been proposed that *B. tabaci* is a complex of different species (Dinsdale *et al.,* 2010; De Barro *et al.,* 2011, see also Table 2).

Middle East-Asia minor 1 (MEAM1, formerly biotype B) (Demichelis *et al.,* 2000) and Mediterranean (MED, formerly biotype Q) are the most common and polyphagous species of the *B. tabaci* complex found in Italy (Demichelis *et al.,* 2000; Bosco *et al.,* 2001) and worldwide; they are both responsible for the transmission and appearance of *Begomoviruses* and some *Criniviruses* worldwide.

These two biotypes (B and Q) differ in a range of biological characteristics, including host plant range and adaptability, ability to transmit plant virus, copulation efficiency, composition of harboured symbionts, and expression of resistance to heat shock and insecticides (Iida *et al*., 2009; Ahmad *et al*., 2009; Horowitz *et al*., 2005; Elbaz *et al*., 2011; Liu *et al.*, 2012; Fang *et al.*, 2013). These differences contribute to the competitive outcomes between the two biotypes in various habitats. The biotype B is more adapted to open fields, whereas the biotype Q is more competitive in protected agricultural facilities (Kontsedalov *et al.*, 2012; Hsieh *et al.*, 2012). Whiteflies, especially *Bemisia* complex, have been reported to develop resistance to a wide range of insecticides, including conventional ones such as organo-phosphates, carbamates, pyrethroids, and novel ones, such as neonicotinoids and insect growth regulators (Kontsedalov *et al.*, 2012; Luo *et al.*, 2010; Wang *et al*., 2010; Ahmad *et al*., 2010). Their control depends heavily on insecticides because of their easy application, quick action, and high efficacy. The prolonged presence in the greenhouse of both crop and pests at high temperature causes a large number of whiteflies generations and a consequent high number of treatments. However, repeated spray applications with the same insecticide induce various issues e.g. impact on non-target organisms (Guedes *et al*., 2016; Desneux *et al*., 2007) and the selection of resistant pest populations (Roditakis *et al*., 2015; Campos *et al*., 2015; Liang *et al*., 2012). For these reasons it becomes necessary the rotation of different active ingredients with different mode of action (Integrated Pest Management, or IPM strategy).

Greenhouse studies were carried out using a randomized complete block design in evaluating the action of six insecticides on transmission of virus. The virus was Tomato yellow leaf curl virus (TYLCV) transmitted by *B. tabaci* biotype B Gennadius to tomato, *Lycopersicon esculentum* (Miller) (Solanales: Solanaceae). The tomato seedlings were inoculated with whiteflies from a TYLCV colony in cages 3, 7, or 14 d after treatment with insecticide. The research had the aim to reveal differences in residual efficacy of six insecticides. Four insecticides were near registration for use on tomato: they were cyazypyr, flupyradifurone, pyrafluquinazon, and sulfoxaflor and two were just authorised: pymetrozine and a zeta-cypermethrin/bifenthrin combination. Differences in efficacy were expected because these six materials represent distinct modes of action and both contact and systemic materials. Percentage of tomato seedlings expressing virus symptoms tended to be lowest in seedlings treated with flupyradifurone. The zeta-cypermethrin/bifenthrin insecticide demonstrated comparable efficacy to flupyradifurone in some trials at 3 and 7 d after treatment inoculations, but not the 14 d after treatment inoculation. Pyrafluquinazon was not statistically different from cyazypyr or sulfoxaflor in percentage of plants with virus symptoms in any trial. Percentage virus in the cyazypyr and sulfoxaflor treatments was not statistically different in the 3 and 7 days after treatment inoculations. Among seedlings treated with insecticide, percentage with virus symptoms tended to be highest in the seedlings treated with pymetrozine; in conclusion sulfoxaflor had an efficacy similar to the other five insecticides used (Smith & Giurcanu, 2014).

The Asian citrus psyllid, *D. citri* is the most important international pest of citrus because it transmits the bacteria that cause huanglongbing (HLB). HLB limits citrus production globally. The toxicity of sulfoxalor against *D. citri* was evaluated. Sulfoxaflor was as toxic as imidacloprid to adult *D. citri*. The LC_{50} values for sulfoxaflor and imidacloprid were 8.17 and 5.7 mg ai L^{-1}, respectively. Treatment with sulfoxaflor resulted in reduced oviposition, development of nymphs, and emergence of adult *D. citri* on plants, as compared with controls. The lowest concentration that reduced adult emergence was 0.6 mg ai L^{-1}. There was reduced feeding by *D. citri* adults on leaves treated with sulfoxaflor. The residual toxicity of sulfoxaflor was equivalent to imidacloprid. Under field conditions, formulated sulfoxaflor reduced populations of *D. citri* compared with untreated controls. Sulfoxaflor is a novel mode of action and is an effective tool for *D. citri* management; in this context its action seems similar to the one of imidacloprid (Brar *et al* 2017). Vial assay (Dow AgroSciences , 2017) carried out on *M. persicae* gave an LC_{50} of 0.11 µg/vial for sulfoxaflor, 0.23 µg/vial for imidacloprid and 0.81 µg/vial for acetamiprid, indicating that sulfoxaflor is ~ 2× more active than imidacloprid and ~7× more active than acetamiprid. In comparison with spirotetramat and flonicamid it reduces the production of honeydew in *M. persicae* (Dow AgroSciences, 2017).

The results of toxicity tests on different target species are summarized in Tables 4-7. In these Tables the LC_{50} (LC_{95}) and their fiducial limits of different neonicotinoids on different target species are given.

Toxicity on insect predators or parasitoids of useful species

Integrated Pest Management (IPM) strategies against crop pests must consider the side effects of insecticides on species that act as biological control agents. The toxicity and sublethal effects (fecundity and fertility) of the following neonicotinoids flonicamid, flubendiamide, metaflumizone, spirotetramat, sulfoxaflor and deltamethrin were tested on the predators *C. carnea* and *A. bipunctata* (Table 2), natural enemies of insect pests. The side effects of the active ingredients were evaluated utilizing residual contact tests for the larvae and adults of these predators; the test were carried out in laboratory. Flonicamid, flubendiamide, metaflumizone and spirotetramat appeared not toxic to last instar larvae and adults of *C. carnea* and *A. bipunctata,* whereas sulfoxaflor resulted slightly toxic to adults of *C carnea* and was highly toxic to the L-4 larvae of *A. bipunctata*. For *A. bipunctata* sulfoxaflor and deltamethrin were the most toxic determining a 100% larval mortality. Deltamethrin was also very toxic to larvae and adults of

C. carnea. In accordance with the results obtained, the compounds flonicamid, flubendiamide, metaflumizone and spirotetramat should be incorporated into IPM programs in combination with these natural enemies for the control of particular greenhouse pests. The use of sulfoxaflor and deltamethrin in IPM strategies should be considered when either of these biological control agents is released, because of the toxic behaviour observed under laboratory conditions. It is need to develop a sustainable approach combining the use of insecticides in ecosystems in which these natural enemies are present is recommended to obey to the directives of the IPM (Garzon *et al*., 2015)

Toxicity on beneficial and non-target organisms

Toxicity to impollinators

The efficacy of an insecticide on target species is of primary importance to select it among other products, but its effects on beneficial and not target species and on human health must also be taken into account.

In this context the registration of sulfoxaflor in the United States was accompanied by four mitigation measures, that were recommended to reduce the risk of harm to pollinator species (Table 8). Another mitigation measure is avoiding its use when air humidity is high (Bottacini, 2012).

The need to take additional steps and to adopt a greater variety of measures was in any case recommended, given the importance of pollination to food crops. It is necessary to take adequate measures to mitigate harm to pollinators; this aim could be reached through a comparison of different regulatory options for use of insecticides.

Rather than advocating that harmful insecticides be banned, as the European Union has done on a temporary basis for neonicotinoids [EC (European Commission), 2013], it is proposed to facilitate agricultural production with accompanying mitigation measures to reduce adverse effects on pollinator species. The measures would need to prevent unacceptable levels of pollinator declines in areas where they are used.

Honey bee populations began to drastically decline in 2006 in USA determining the so-called Colony Collapse Disorder. Pesticides belonging to the class of neonicotinoids quickly emerged as identifiable responsibles with an LC_{50} of 0.81 ng a.i. diet μL^{-1} (or 0.81 µg a.i. diet mL^{-1}, or 0.81 mg a.i. diet L^{-1} or 0.81 ppm a.i. diet) (Tables 9-12). In response the Environmental Protection Agency (EPA) developed an ecological risk assessment framework at different levels to better analyse the risk that pesticides caused to honey bees and other insect pollinators. In 2012, the EPA applied guidelines to the application for registration of a new type of neonicotinoid, sulfoxaflor. Sulfoxaflor registration was approved despite its high risks to honey bees (Table 12), but led also to the creation of the Pollinator Risk Assessment guidelines. These new guidelines included set standards that allowed the use of sulfoxaflor with a reduced risk, but pollinator advocates had an instrument from then on to successfully challenge a registration whenever an environmental risk is threatened (Vanegas, 2017).

Transform (sulfoxaflor) alone had 71% and 88% bee mortality, respectively, significantly higher than that of Advise (imidacloprid) alone and the mixtures of Advise with Transform (Zhu *et al*, 2017).

Different neonicotinoids have different mechanism of action on impollinators. Interestingly, the less toxic neonicotinoids or neonics ("bee safe") have a cyanoimine substituent (THIA and ACET) ("magic cyano" for safety), while the more toxic ones ("bee tox") have a nitroimine or nitromethylene substituent ("magic nitro" for toxicity) (Tables 1 and 3).

Cytochrome P450 (CYP6G1) monooxygenases play a major role in neonic resistance and they are probably involved in toxicity mechanism to bees. These monooxygenases are very effective in degrading many insecticides, and the ability of sulfoxaflor to escape the degradation by Cytochrome P450 monooxygenase CYP6G1 (Sparks *et al*., 2012) makes sulfoxaflor very effective against insect pests avoiding the mechanism of resistance, but also harmful to non-target species as bees.

Differences between cyanoimines and nitroimines toxicity are not due to the sensitivity of the bee to nAChR binding sites or formation of bioactivated metabolites, but instead to an efficient CYP450 oxidative detoxification mechanism for the cyanoimine compounds; in this respect sulfoxaflor is more similar to nitroimines than to cyanoimines (Watson *et al*., 2011).

Toxicity to other beneficial arthropods

Sulfoxaflor has low impact on other benefical arthropods (Dow AgroSciences, 2017), as:

Coleoptera: Coccinellidae, Nitidulidae, Staphylinidae
Neuroptera: Chrysopidae
Hemiptera: Anthocoridae, Miridae
Hymenoptera: Aphelinidae, Encyrtidae, Braconidae
Predatory mites (Phytoseiidae) and spiders

Results of test of toxicity on beneficial arthropods are summarized in Table 13.

Toxicity to parasitoids

Little information is available about the effects of sulfoxaflor on parasitoids. Only the toxicity of sulfoxaflor against *T. radiata* a parasitoid of *D. citri* was evaluated. Sulfoxaflor was almost as toxic as imidacloprid for adults of *D.citri* with an LC_{50} of 8.17 µg ai mL^{-1}.for sulfoxaflor and 5.7 µg ai $mL^{-1}$for imidacloprid. The LC_{50} of sulfoxaflor for adults of *T. radiata* was 3.3 times greater than for *D. citri* adults, this result allows to state that sulfoxaflor is less toxic to parasitoid than to target species (Brar *et al*., 2017).

Toxicity to plants

Stress tolerance in plants is induced by some neonicotinoids via salicylate-associated systems, but this mechanism of action is not demonstrated for sulfoxaflor (Casida, 2018), so at present there is no evidence for a direct effect of sulfoxaflor on plants.

Sulfoxaflor shows a translaminar activity and is able to protect plant canopy and undersides leaves. The acute toxicity to the aquatic plant *Lemna gibba* (duckweed) is very low with a 7 days EC50 >99 mgL^{-1} (Dow AgroSciences, 2017)

Toxicity to mammals

Registration of new plant protection products (e.g., herbicide, insecticide, or fungicide) requires comprehensive mammalian toxicity evaluation including carcinogenicity studies in rodents, rats, mice and man. Carcinogenicity tests results influence the process of authorization of insecticide in agriculture also. Regulatory agencies expectation, in order to understand the relevance of a specific tumor finding to human health, is that a systematic, transparent, and hypothesis-driven mode of action (MoA) investigation be carried out. A novel approach of generating MoA data was implementing additional end points to the standard guideline toxicity studies with sulfoxaflor. This MoA approach resulted in a more robust integration of molecular with apical end points while minimizing animal use. Sulfoxaflor induced liver effects (increased liver weight due to hepatocellular hypertrophy) in an initial palatability probe study for

selecting doses for subsequent repeat-dose dietary studies and induced liver tumors in rats and mice in the bioassays. The MoA data available by the time of the carcinogenicity finding supported the conclusion that the carcinogenic potential of sulfoxaflor was due to two nuclear receptors (NR) activation (CAR and PXR) with subsequent hepatocellular proliferation. NR mechanism is explained in the section "Action at cellular level" (see below). This MoA was not considered to be relevant to humans as sulfoxaflor is unlikely to induce hepatocellular proliferation in humans and therefore would not be a human liver carcinogen (LeBaron *et al*., 2013).

Results of some toxicity tests on mammals are summarized in Table 14 (Dow AgroSciences, 2017)

Action at cellular level

Sulfoxaflor belongs to sulfoximines and, as other neo-nicotinoids as nitroimines (imidacloprid), butenolides and mesoionic triflumezopyrim (TRIF), block insect nicotinic acetylcholine receptors (nAChR). Sulfoxaflor has a unique Mechanism of Action (MOA) involving the disruption of nAChR. It acts as activator of nAChR (Figures 2 and 3), through a site that is supposed to be distinct from other neo-nicotinoids or nicotinic active sites.

The mesoionic TRIF acts as a nAChR competitive modulator with little or no target-site cross-resistance. Butenolides and mesoionic TRIF act as competitive modulators of imidacloprid binding to nAChR in the same manner of the radioisotope [^{3}H]imidacloprid ([^{3}H]IMI) (tritiated radiolabelled imidacloprid) (Casida, 2018) allowing radioligand binding studies.

The action of sulfoxaflor was characterized using electrophysiological and radioligand binding techniques (Watson *et al*., 2011) and thanks to these studies it was discovered that it acts at nAChR sites (Figure 4). When tested for agonist properties on *Drosophila melanogaster* Da2nAChR subunit, sulfoxaflor elicited very high amplitude currents. Sulfoximine analogs of sulfoxaflor were also agonists on Da2/b2nAChR, but did not produce high currents equivalent to sulfoxaflor and were not toxic to green peach aphid (GPA). Only clothianidin, among the neonicotinoids produced maximal currents as large as those produced by sulfoxaflor. It can be concluded that the potent insecticidal activity of sulfoxaflor is probably bound to its very high efficacy at nAChR. In contrast, sulfoxaflor displaced [(3)H]IMI from green peach aphid nAChR membrane preparations with weak affinity compared to most of the neonicotinoids examined. The nature of the interaction of sulfoxaflor with nAChR apparently differs from that of IMI and other neonicotinoids, and when coupled with other known characteristics (novel chemical structure, lack of cross-resistance, and metabolic stability), indicate that sulfoxaflor represents a significant new insecticide option for the control of sap-feeding insects. The maximal currents induced by sulfoxaflor were significantly larger than those induced by imidacloprid (Zhu *et al*., 2011).

The average number of ligand molecules bound per binding partner [LP] is a function of ligand concentration [L], its binding affinity K and number of binding sites N:

$$[LP] = \frac{NK[L]}{1 + K[L]}$$

The binding affinity *K* is the association constant defined as:

$$K = \frac{[LP]}{[L][P]}$$

where [LP] and [L] are as above and [P] is the ligand protein concentration.

The above equation may be linearized (Scatchard equation) rewriting it as:

$$[LP] = (N - [LP])K[L]$$

dividing both members by [L] we obtain:

$$\frac{[LP]}{[L]} = NK - K[LP]$$

allowing to plot a graph with [LP] as abscissa and [LP]/[L] as ordinate, in this manner a straight line is obtained with a slope equal to -K and an origin intercept equal to NK (Figure 5); the steepest the line, the highest the K; it is evident that a higher number of free sites gives lower ordinate values (Figure 5), meaning lower affinity of the compound for the receptor protein. In other words, if a compound has a low affinity for a binding site it is less able to compete with [^{3}H]IMI in occupying the binding sites; and a steeper line is observed (K larger), meaning that in correspondence of the same number of sites bound (same abscissa values [LP]) a higher number of free sites [L] is observed (lower ordinate value [LP]/[L]) (Figure 5).

Sulfoxaflor shows higher association constant, (that in the present case has the meaning of an Inhibition Constant) (K=265±49) respect to imidacloprid (K=5.1±0.7) meaning lower affinity for [^{3}H]IMI binding site (Watson *et al*., 2011). This evidence is used to support the hypothesis that sulfoxaflor is not a true neonicotinoid.

Some structural differences in nAChR binding sites explaining the different sensitivity of different species to acetylcholine, nicotine and different groups of neonicotinoids including sulfoxaflor are not well known. A substantial difference is only known between mammalians and insects, and is bound to the presence of an anionic subsite in mammalian nAChR and a cationic subsite in insects nAChR (Tomizawa & Casida, 2003). Different binding sites present in nAChRs of insects are supposed to bind acetylcholine, neonicotinoids and sulfoxaflor differently (Figure 4), but at present only indirect evidence based on different signals and different toxicity of the various molecules is available.

The mechanism of synthesis suppression of the so-called Nuclear Receptors (NR) through small or short interfering RNA (siRNA) is here summarized to clarify the experiment exposed in the following section. When long double-stranded RNA (dsRNA) molecules are given to a cell, an enzyme cleaves dsRNA into short double-stranded fragments called siRNA. Each siRNA is thereafter unwound into two single-stranded RNAs (ssRNAs), the passenger strand and the guide strand. The passenger strand is degraded and the guide strand is incorporated into the RNA-induced silencing complex (RISC). In RISC the guide strand pairs with a complementary sequence of a messenger mRNA molecule and induces the cleavage of this mRNA determining its consequent silencing (Figure 6). In this manner the mRNA implied in the production of NR is silenced and NR production is suppressed.

Different responses caused by different insecticides, including insecticide mechanism of resistance, can be explained by the ability of different molecules to silence the NR. It is known that nuclear receptors activating metabolism of xenobiotic compounds occurs in insects. These NR are implied in detoxification mechanism and their production is stimulated in insects resistant to insecticides and is probably at the basis insecticide resistance. Sulfoxaflor induces the expression of a family of NR in an attempt of the insect to degrade the insecticide. Sulfoxoflor induces expression of different NR with a different time table and some are expressed after 24 h others after 48 h. Different organs can accumulate different concentrations of NR.

The employment of gene silencing RNAi (interference RNA) confirmed the mechanism of action of sulfoxaflor. The synthesis

suppression of NR determined by RNAi caused the death of *N.lugens*, confirming that sulfoxaflor acts promoting synthesis of NR. dsRNA (double filament RNA) feeding, significantly silenced NR receptors compared with the control. The notable and specific knockdown of above NR genes resulted in a higher nymph mortality, suggesting that the RNAi-mediated silencing of above NR genes increased the susceptibility of *N. lugens* to sulfoxaflor (Xu *et al*, 2017).

Resistance and cross-resistance

The emergence of resistant insects is a common situation when an insecticide is spread for long time (Roush & Tabashnik, 1991; Lawrence & Sarjeet, 2010), thus the potential development of a resistance in an insect should be evaluated.

A problem connected with resistance is also the cross-resistance, which is observed when the same mechanism of resistance allows the insect to resist to different insecticides.

Compounds that are effective against pests such as the whiteflies *B. tabaci* and *T. vaporariorum*, which show resistance to a range of insecticidal modes of action (MOA), have particular value as components of resistance management programmes. The sulfoximine insecticides are chemically unique as they are the first compound in this category of insecticides that incorporate a sulfoximine functional group. Sulfoxaflor is the first sulfoximine compound under commercial development for the control of sap-feeding insects. Its cross-resistance relationships were investigated by comparing the responses of field-collected strains with those of insecticide-susceptible laboratory strains of *B. tabaci* and *T. vaporariorum*.

Resistance ratios (RR) are calculated to monitor the evolution of insecticide resistance in a field population. RR is calculated dividing the LC_{50} of the field population by the LC_{50} of a susceptible strain. When RR is ³ 10 the target field population is considered highly resistant.

Sulfoxaflor tested against strains of *B. tabaci* exhibited an RR of about 3, while imidacloprid tested against the same strains of *B. tabaci* produced an RR of up to 1000-fold RR. Imidacloprid emphasized cross-resistance to other neonicotinoid insecticides, while sulfoxaflor was not cross-resistant; similarly a strain of *B. tabaci* exhibiting resistance to a pyrethroid (deltamethrin) and to an organophosphate (profenophos) did not exhibit cross-resistance to sulfoxaflor. No cross-resistance was also observed between sulfoxaflor and imidacloprid in *T. vaporariorum*. Three field strains of *T. vaporariorum* showed only slightly reduced susceptibility to sufloxaflor with an RR of 4.17 expressed by only one strain of three. On the contrary, the same population of *T. vaporariorum* exhibited an RR of more than 23.8-fold for imidacloprid relative to the susceptible population. Sulfoxaflor shares a target site with neonicotinoids (the nicotinic acetylcholine receptor), but it is largely unaffected by existing cases of neonicotinoid resistance in *B. tabaci* and *T. vaporariorum*. Neonicotinoid resistance mechanisms in *B. tabaci* and *T. vaporariorum* are known to be primarily based on enhanced detoxification of insecticide. This detoxification mechanism is inactive with sulfoxaflor, determining lack of cross-resistance of this insecticide, so here again it can be stated that sulfoxaflor is a valuable tool for the management of sap-feeding insect pests, which are resistant to other neonicotinoids (Longhurst *et al.*, 2013).

A resistance mechanism to insecticides is differently expressed in response to different products by different strains of insect pests. The cotton aphid *A. gossypii* (ThR) developed a strain displaying a thiamethoxam-resistance 13.79-fold greater than a susceptible cotton aphid (SS) strain. The toxicity of thiamethoxam in the resistant strain was synergistically increased by Piperonyl butoxide (PBO) and triphenyl phosphate (TPP), whereas significant synergistic effects were not exhibited by diethyl maleate (DEM). The ThR strain developed increased levels of cross-resistance to bifenthrin (11.71 fold), cyfluthrin (17.90 fold), esfenvalerate (6.85 fold), clothianidin (6.56 fold), methidathion (5.34 fold) and a-cypermethrin (4.53 fold), whereas cross-resistance to malathion, omethoate, acephate, chlorpyrifos, methomyl, sulfoxaflor or imidacloprid was not expressed. Bifenthrin toxicity in the resistant strain increased in presence of PBO and TPP by 2.38 and 4.55 fold, respectively. The mRNA expression levels of the a1, a4-1, a4-2, a5 and a7 subunits of nAChR receptors decreased significantly by 332, 1.60, 2.05, 5.41 and 1.48 fold, respectively, in the resistant strain compared with those in the susceptible strain, as demonstrated by quantitative real-time PCR, but the expression levels of the a2, a3 and b1 subunits were not significantly modified. The ThR strain did not express any target-site mutation within the a1, a2 and b1 subunit of nAChR. Some other mechanism, not attributable to structural modifications of subunits receptors in absence of target-site mutations, should explain the resistance mechanism. The overexpression of detoxification-related mechanisms including both monooxygenase (cytochrome P450) and esterase could alternatively explain and regulate the levels of thiamethoxam resistance and cross-resistance observed in the ThR strain. The understanding of thiamethoxam resistance mechanism could aid in the management of insecticide-resistant cotton aphids (Wei *et al* 2017).

A major pest of citrus crops worldwide is the Asian citrus psyllid, *D. citri*. To manage *D. citri* a large number of insecticides were tested. These practices determined the insurgence of insecticide resistance phenomena. An early warning system is suggested to monitor insecticide susceptibility in populations of *D. citri,* allowing citrus producers to modify chemical control strategies with the aim to reduce the use of chemicals in controlling this pest. Is here described a simple and fast tool to determine insecticide resistance in *D. citri* and apply it to commercial citrus production. LC_{50} and LC_{95} estimates were determined for 8 commonly used insecticides on a susceptible laboratory population of *D. citri* 24 h after treatment in a residual contact bottle assay. A test was carried out using 5 to 7 concentrations of each insecticide. The LC_{50} values (and 95% fiducial limits) ranged from 0.06 (0.02-0.26) to 0.80 (0.26-2.46) ng μL^{-1} for each insecticide tested. Exposure time-mortality indices were determined for 0, 10, 100, 1,000, and 10,000 ng μL^{-1} concentrations of each insecticide in a laboratory susceptible strain. Knockdown was observed after 15, 30, 45, 60, 75, 90, 105, and 120 min. A 100% knockdown occurred within 60 min using dimethoate, fenpropathrin, imidacloprid, bifenthrin, and flupyradifurone at the 10,000 ng μL^{-1} concentration. Spinetoram determined 86.7% knockdown within 120 min at 10,000 ng μL^{-1}. Sulfoxaflor and cyantraniliprole were responsible of 44.0 and 42.6% knockdown, respectively within 120 min at 1,000 ng μL^{-1}. A bottle bioassay was proposed to survey field populations of *D. citri* for insecticide resistance. Exposure time-mortality indices developed in the laboratory were used to assess susceptibility of 1 laboratory and 4 field populations of *D. citri* after 15, 30, 50, 75, 90, 105, and 120 min of exposure at the 10,000 ng μL^{-1} concentration of various insecticides. Bifenthrin, dimethoate, imidacloprid, and fenpropathrin did not emphasize any evidence of resistance. A bottle bioassay appeared suitable for assaying insecticide resistance in *D. citri* adults under laboratory and field conditions. The bottle bioassay is suggested as a flexible tool for rapid tests of insecticide resistance in possible cases of insecticide failure. It is simple to carry out, allowing trained professionals to a quick monitoring for insecticide resistance of *D. citri* populations (Chen & Stelinski, 2017).

Experimental work

Trials with sulfoxaflor (isoclast active™, Closer®) were carried out in Italy (Center, South and Sicily) in the last three years under greenhouse condition on tomato crops, to have the opportunity to evaluate different control strategies by alternating sulfoxaflor with various standard reference products against *B. tabaci* and *T. vaporariorum.* Samples from the greenhouses were slide mounted to identify the target species (Bacci *et al*., 2018b).

The studies reported (Tables 15 and 16) were designed as randomized complete block design with four replications and were conducted in compliance with the principles of Good Experimental Practice (GEP) as defined by 91/414/EEC Directive and according to the EPPO guidelines PP 1/135(3), 1/152(4), 1/181(4), 1/225(2), 1/239(2), 1/36(3).

Each product was applied in all trials using a backpack engine pump precision sprayer, calibrated to apply different spray volumes per hectare according to the protocols. This equipment mounted hollow cone nozzles Albuz ATR80 Yellow @ 300 kPa.

Adults were assessed in the greenhouse on 20 leaves/plot, while eggs, neanids and pupae were assessed in laboratory on 1 cm^2 of leaf surface. All the trials started when the infestation was very low, about 1-2 neanids/leaf. The treatment effect was reported in terms of percentage of efficacy respect to the untreated control by using Abbott formula:

$$p_{corr} = \frac{p_{exp} - p_{cont}}{1 - p_{cont}}$$

where p_{corr} is the mean experimental treatment response corrected for control response, p_{exp} is the experimental treatment response and p_{cont} is the mean control response

Statistical computations were performed by using ARM 2017 software (Gylling Data Management). The data were also processed all together using meta-analysis, obtaining a percentage of overall average effectiveness. Sulfoxaflor and other products were applied at different rates.

Experimental results

The control of whiteflies in protected crops with a single active substance is always difficult and many times failed the long-lasting protection of the crop. The level of infestation, the timing of application (growth stage of pest) and the capability of the pest to develop resistance are critical to deliver a good control.

Sulfoxaflor gave an excellent knockdown effect on adult stage (Figure 7) combined with high efficacy against neanids after 7 days from application (Figure 8) of both *B. tabaci* and *T.vaporariorum*. Knockdown effect in insects following application of an insecticide may be defined as the state of intoxication and partial paralysis which usually precedes death.

Exploiting the combined action on the two whitefly stages and considering that at the beginning of the infestation there are mainly adults and neanids, it is useful to optimize the positioning of sulfoxaflor, often at the beginning of spray program exploiting the knockdown effect on the adult stage and the consequent reduction of the oviposition activity.

To evaluate the control strategies, it was combined with products with different mode of action, in particular flonicamid (strategy with a low impact on useful organism) and spirotetramat (exploiting persistence and control on neanids) (Table 17).

Flipper (Potassium salts of fatty acids 47.8 g [479.8 g/L], was applied at the end of all the strategies, it maintained a good control of the populations, suggesting its use near the harvest thanks to its favourable toxicological and ecotoxicological profile and the different mode of action. All the tested strategies gave on neanids a control over 85% without statistically differences (Figures 9 and 10).

The effectiveness of sulfoxaflor and Flipper, combined with the favourable toxicological and ecotoxicological profile, and their different mode of action make them extremely interesting tools in the management of resistance and in Integrated Pest Management strategies. In addition, IsoclastTM has proved to have good selectivity towards B. terrestris (Table 2) and predators of mites, whiteflies and trips that allows its use in integrated strategies control (Cocuzza *et al.,* 2018a). Sulfoxaflor, flonicamid and imidacloprid were compared to test the response of *B. terrestis;* an overall survival rate was calculated on the basis of multiple responses (flight, feeding activity etc.) and emphasized the better performance of sulfoxaflor respect to the other two insecticides (Cocuzza *et al.,* 2018b).

Conclusions

Sulfoxaflor and its commercial products (isoclast™ Closer®) are an ideal tool for managing the launches of predatory and parassitoid arthropod species; in fact, integrating the chemical control and the use of useful insects optimizes the whiteflies control as well (Figure 11).

Because certain subpopulations of insects could be controlled by sulfoxaflor that were not controllable with neonicotinoids, the pesticide is especially useful in these situations (Longhurst *et al*., 2013; Centner *et al*., 2018).

Small modification in the molecule in sulfoxaflor increased its activity. The observed absence of cross-resistance with other products as imidacloprid further supports its utility. The product is also more stable to UV maintaining its activity above 50% 10 days after its application and maintains its activity after rain, manifesting an excellent “rainfastness”.

Some monooxygenase as Cytochrome P450 are able to degrade some neonicotinoids, it was observed that monooxygenase CYP6G1 is able to degrade also DDT and imidacloprid, but it is incapable of metabolizing sulfoxaflor; this can explain the ability of sulfoxaflor to by-pass cross-resistance of many pest species (Zhu *et al*., 2011).

In addition, can be of utility to improve the efficacy of spray programs including predatory arthropods species in the rotation for its safe profile against beneficial, pollinators and predatory arthropods (Anh *et al*., 2016; Serdar Satar *et al*., 2018).

Unfortunately, the property of sulfoxaflor to by-pass monooxygenase degradation, useful to avoid the insurgence of resistant population, makes the product harmful to useful insects as impollinators.

For this reason, the recommendation is to use the product in a well-integrated managing policy, including a careful management of the landscape, where agroecosystems are planned to be integrated into larger landscapes which include natural ecosystems (Zasada *et al*., 2017), allowing the development of metacommunities where both specialist and omnivorous natural enemies of pest species are present (Chailleux *et al*., 2017).

Table 1. Physical properties and toxicological profiles of neonics and other nAChR agonists and competitive modulators (Casida, 2018). IC_{50}: ligand concentration that reduces the ACh induced current by 50%, LD_{50}: concentration of ligand that causes the death of 50%.

Name	Abbreviation	Molecular weight	nAChR IC_{50} (nM) Insect Pest	LD_{50} (mg kg^{-1}) 48 h Mammals	Ratio Mammals/ insects	Honey beeμg/ bee	Mammal	Bird	Fish
Neonics									
Imidacloprid	IMI	255.7	4.3	2,600	605.0	18.0	450	31	211
Clothianidin	CLO	249.7	2.2	3,500	1,591.0	3.8	>5,000	>2,000	>100
Thimethoxam	TMX	291.7	5,000	>100,000	>20.0	5.0	1,563	1,552	>100
Dinotefuran	DIN	202.2	900	>100,000	>111.0	23.0	2,400	>2,000	>100
Nithiazine	-	160.1	4,800	26,000	5.4	-	300	2,290	117
Nitromethylene-IMI	CH-IMI	253.7	0.24	210	875.0	-	-	-	-
Cycloxaprid	CYC	308.7	43	302	7.0	140.0	1,260	-	-
Nitenpyram	NIT	270.7	14	49,000	3,500.0	140.0	1,628	>2,250	>1,000
Thiacloprid	THIA	252.7	2.7	860	319.0	39.0	640	49	31
Acetamiprid	ACET	222.7	8.3	700	84.0	8.1	182	180	>100
Other nAChR competitive modulators									
Sulfoxaflor	SULF	277.3	265	-	-	150.0	1,000	676	>387
Flupyradifurone	FPF	288.7	2.4	-	-	1.2	>300	232	>74
Nicotinoids									
(−)-Nicotine	NIC	162.2	4,000	7	0.00200	toxic	50-60	toxic	4
Epibatidine	EPI	208.7	430	0.04	0.00009	-	0.08	-	-
Desnitro-IMI	DN-IMI	210.7	1,530	8.2	0.00500	-	8.0	-	-
Mesoionic									
Triflumezopyrim	TRIF	398.3	43	-	-	0.39	-	2,109	>100

Table 2. Species of interest in this review, with notes on distribution, common name, infested plant.

Hemiptera (Heteroptera) Cimicomorpha
- Miroidea Miridae
- Mirinae Mirini
  - *Lygus hesperus* (Knight, 1917), not present in Europe, Western tarnished plant bug
  - *Lygus italicus* Wagner, 1950, present in Italy
- Deraeocorinae
  - *Deraeocoris spp.*
- Orthotylinae
  - *Heterotoma spp.*
  - *Malacocoris spp.*
- Phylinae
  - *Pilophorus spp.*
- Bryocorinae
  - *Macrolophus caliginosus* Wagner, 1951
- Cimicoidea Anthocoridae
  - *Anthocoris nemoralis* (Fabricius, 1794)
  - *Orius laevigatus* (Fieber, 1860)

Hemiptera (Homoptera) Sternorryncha
- Aleyrodoidea Aleyrodidae
  - *Bemisia tabaci* (Gennadius, 1889), not present in Italy, sweetpotato whitefly or tobacco whitefly
  - *Bemisia afer* (Priesner & Hosny, 1934), present in Italy
  - *Trialeurodes vaporariorum* (Westwood, 1856), not present in Italy, Glasshouse whitefly
  - *Trialeurodes sardiniae* Rapisarda, 1986, present in Sardinia
  - *Trialeurodes ericae* Bink-Moenen, 1976, present in Italy
  - *Trialeurodes lauri* (Signoret, 1882), present in Italy
- Aphidoidea Aphididae
  - *Aphis (Aphis) gossypii* Glover, 1877, present in Italy, cotton aphid
  - *Dysaphis (Pomaphis) plantaginea* (Passerini, 1860), present in Italy,apple
  - *Myzus (Nectarosiphon) persicae* Sulzer, 1776, present in Italy, green peach aphid

To be continued on next page

Table 2. Continued from previous page.

Hemiptera (Homoptera) Sternorryncha
- Coccoidea Coccidae
  - *Parthenolecanium corni* (Bouché, 1844), present in Italy,,vine
- Diaspididae Aspidiotini
  - *Aonidiella aurantii* (Maskell, 1879), present in Italy, citrus
  - *Diaspidiotus perniciosus* (Comstock, 1881), present in Italy, San José scale
  - *Pseudaulacaspis pentagona* (Targioni Tozzetti, 1886), present in Italy, Drupaceae
  - *Targionia vitis* (Signoret, 1876) present in Italy,,vine
- Pseudococcidae
  - *Planococcus citri* (Risso, 1813), present in Italy,,citrus,
  - *Planococcus ficus* (Signoret, 1875), present in Italy,,vine
  - *Pseudococcus comstocki* (Kuwana, 1902), present in Ukraina, in Italy (?), Drupaceae
- Phylloxeroidea Phylloxeridae
  - *Viteus vitifoliae* (Fitch, 1855), [=*Daktulosphaira vitifoliae* (Fitch, 1856)], present in Italy,,vine
- Psylloidea Psyllidae
  - *Diaphorina citri,* Kuwayama, 1908, not present in Europe, Asian citrus psyllid
  - *Diaphorina chobauti* Puton, 1898, present in Italy
  - *Diaphorina continua* Loginova, 1976, present in Sardinia
  - *Diaphorina lycii* Loginova, 1978, present in Italy
  - *Diaphorina putonii* Low, 1879, present in Sardinia, Sicily
- Auchenorryncha Delphacidae
  - *Nilaparvata lugens* (Stål, 1854), not present in Europe, brown planthopper

Hymenoptera Apocrita
Chalcidoidea
- Eulophidae Tetrastichinae
  - *Tamarixia radiata* (Waterstone, 1922), not present in Europe
  - *Tamarixia leptothrix* Graham, 1991, present in Italy
  - *Tamarixia monesus* (Walker, 1839), present in Italy
  - *Tamarixia tremblayi* (Domenichini, 1965), present in Italy
- Aphelinidae
  - *Aphytis melinus* (DeBach, 1959)
- Encyrtidae
  - *Anagyrus pseudococci* (Girault, 1915)

Apoidea
- Apidae
  - *Apis mellifera* Linnaeus, 1758,present in Italy
  - *Bombus terrestris* (Linnaeus, 1758), present in Italy
  - *Melipona scutellaris* Latreille, 1811, not present in Europe, present in Brasil
- Ichneumonoidea Braconidae
  - *Aphidius rhopalosiphi* de Stefani-Perez, 1902

Neuroptera Hemerobiiformia
- Chrysopidae Chysopinae
  - *Chrysoperla carnea* (Stephens, 1836), present in Italy

Coleoptera Polyphaga Cucujimorphia Cucujoidea Coccinellidae
- Coccinellinae
  - *Adalia (Adalia) bipunctata* (Linnaeus, 1758), present in Italy
- Chilocorinae
  - *Chilocorus bipustulatus* (Linnaeus, 1758)
  - *Harmonia axyridis* Pallas, 1773
- Scymninae
  - *Scymnus spp.*

Chelicerata Arachnida Micrura
Megoperculata Araneae
- Labidognatha Theridiidae
  - *Latrodectus tredecimguttatus* (Rossi, 1790), present in Italy
  - *Latrodectus hesperus* Chamberlin & Ivie, 1935, present in North America

Acari Anactinotrichida
- Mesostigmata Dermanissina Ascoidea Phytoseiidae
  - *Amblyseius andersoni* (Chant, 1957)
  - *Amblyseius cucumeris* (Oudemans, 1930)
  - *Amblyseius swirskii* Athias-Henriot, 1962
  - *Phytoseiulus persimilis* Athias-Henriot, 1957
  - *Typhlodromus pyri* Scheuten, 1857

Table 3. Mortality 24 h after the topical application of neonicotinoid insecticides metabolites to the dorsum of the honey bee thorax (Iwasa *et al.*, 2004).

Insecticide metabolites	LD50 (ng/bee)	LD50 (µg/bee)	95% CI
Acetamiprid	7070.0	7.0700	4.57-11.2
Imidacloprid	17.9	0.0179	0.0092-0.0315
Thiacloprid	14600.0	14.6000	9.53-25.4
Nitenpyram	138.0	0.1380	0.0717-0.259
Clothianidin	21.8	0.0218	0.0102-0.0465
Dinotefuran	75.0	0.0750	0.0628-0.0896
Thiamethoxam	29.9	0.0299	0.0208-0.0429

Table 4. Laboratory Efficacies of Sulfoxaflor and Imidacloprid on different strains of Sap-Feeding Insects: LC_{50} in ppm (mgL^{-1}) with fiducial limits in different susceptible and resistant strains; RR: resistance ratio = LC_{50} resistant strain/LC_{50} of susceptible strain (Zhu *et al.*, 2011).

Insecticide	Susceptible strain	Resistant strain	RR
M. persicae			
sulfoxaflor	0.074 (0.049-0.101)		
sulfoximine **2**	0.374 (0.199-0.484)		
imidacloprid	0.090 (0.07-0.13)		
Sulfoxaflor	4.13 (2.25-6.82)	1.52 (0.644-2.65)	0.37
sulfoximine **2**	62.3 (14.5-186.1)	12.5 (3.44-23.4)	0.20
Imidacloprid	0.896 (0.620-1.15)	15.3 (10.62-21.40)	17.1
Aphis gossypii			
sulfoxaflor	0.20 (0.015-1.1)		
sulfoximine **2**	3.0 (0.6-7.0)		
imidacloprid	7.8 (2.4-15.6)		
L. hesperus			
sulfoxaflor	2.78 (1.41-4.95)		
sulfoximine **2**	1.69 (0.42-3.82)		
imidacloprid	1.32 (0.48-2.61)		
B. tabaci			
sulfoxaflor	0.85 (0.40-1.5)		
sulfoximine **2**	0.29 (0.083-0.66)		
imidacloprid	0.37 (0.18-0.63)		
sulfoxaflor	2.8 (1.2-5.5)	6.4 (2.6-13.1)	2.3
imidacloprid	0.20 (0.05-0.55)	174 (24.6->2000)	870
sulfoxaflor	18 (13-24)	28 (25-55)	1.6
imidacloprid	4.4 (2.8-6.1)	>1000 (-)	>230
sulfoxaflor	18 (13-24)	39 (25-55)	2.2
imidacloprid	4.4 (2.8-6.1)	4500 (1900-29000)	1022
sulfoxaflor	1.80 (0.84-3.13)	5.0 (3.13-7.76)	2.8
sulfoximine **2**	4.48 (2.01-8.16)	13.2 (7.25-23.2)	2.9
imidacloprid	1.23 (0.203-4.17)	>1000	>833

Table 5. Insecticidal activity of neonicotinoids on major pests, LC_{50} and LC_{95} in ppm or mgL^{-1}

Scientific name	Growth stage	Crop	References	Hours	LC50 (LC95)	Range
A. gossypii	3rd instar larva	Cotton	Gore *et al.* 2013	48	1.01	-
				48	5.85	-
				72	0.92	-
				72	4.13	-
D. perniciosus	Crawler	Deciduous fruit tree	Buzzetti *et al.* 2015	48	2.90	(2.59-3.23)
				48	3.10	(2.79-3.44)
				48	3.24	(2.92-3.57)
				48	3.50	(3.17-3.85)
				48	3.56	(3.23-3.91)
				48	(44.27)	(31.20-73.12)
				48	(40.91)	(29.60-64.13)
				48	(38.82)	(28.70-58.36)
				48	(39.03)	(29.19-57.54)
				48	(35.56)	(27.22-50.21)
M. persicae	Adult	Many crops	Tang *et al.* 2015	48	0.059	-
D. citri	Adult	Citrus	Brar *et al.* 2017	48	8.17	-
D. citri	Adult	Citrus	Chen & Stelinski 2017	24	(797.77)	(130.13-16,474.00)
				24	0.80	(0.26-2.46)
N. lugens	3rd instar	Rice	Liao *et al.* 2017	96	1.63	-
				96	13.2	-

Table 6. Activity of sulfoxaflor compared with commercial sap-feeding insecticides for the control of green peach aphid and cotton aphid in laboratory bioassays, LC^{50} in ppm or mgL^{-1}.

	M. persicae LC_{50} (95% CI)	*A.gossypii* LC_{50} (95% CI)
Sulfoxaflor	0.05 (0.02-0.09)	0.2 (0.015-1.1)
Imidacloprid	0.09 (0.07-0.13)	7.8 (2.4-15.6)
Acetamiprid	0.07 (0.03-0.12)	5.8 (1.1-12.3)
Thiamethoxam	0.05 (0.03-0.08)	0.6 (0.09-2.0)
Dinotefuran	1.76 (0.87-4.48)	40 (30-60)
Flonicamid	0.76 (0.26-7.16)	80 (50-140)
Spirotetramat	0.26 (0.14-0.52)	770 (280-5110)

Table 7. Activity of sulfoxaflor compared with commercial sap-feeding insecticides for the control of sweetpotato whitefly and western tarnished plant bug in laboratory bioassays LC_{50} in ppm or mgL^{-1}.

	B. tabaci LC_{50} (95% CI)	*Lygus hesperus* LC_{50} (95% CI)
Sulfoxaflor	1.29 (0.76-2.08)	2.78 (1.41-4.95)
Imidacloprid	0.64 (0.32-1.11)	1.23 (0.48-2.61)
Acetamiprid	0.04 (0.02-0.08)	7.42 (2.73-30.47)
Thiamethoxam	0.20 (0.11-0.34)	0.09 (0.002-0.36)
Dinotefuran	0.13 (0.07-0.23)	4.95 (2.66-8.90)
Flonicamid	>200	>200
Spirotetramat	1.47 (0.28-4.24)	>200

Table 8. Risk mitigation measures incorporated in the registration of sulfoxaflor to minimize damages to bees (Centner *et al.*, 2018).

Measure	Benefit	Limitation	Potential for harm
No application until after petal fall	Pollinators gone before applications	Doesn't cover situations with blooming weeds	Pollinator Stewardship Council (2015); Center for Biological Diversity (2016)
12-foot buffer	Keeps spray drift away from pollinators	Offers little protection against chronic risks	Center for Biological Diversity (2016)
Permissible tank mixes	Prevents unknown detrimental effects	Insufficient information on synergistic effects	Center for Biological Diversity (2016)
Nozzle size and height of sprayer	Reduces drift from harming off property pollinators	No consideration of other drift reduction technologies	Palardy and Centner (2017)

Table 9. Acute toxicity values of imidacloprid for *M. scutellaris* (Table 2, Costa *et al.*, 2015).

Exposure mode	Time (hours)	LD^{50}	LC^{50}	C.I.95%	χ^2	D.F.
Topicng a.i/bee	24	2.41	-	1.630 3.270	0.753	4
	48	1.29	-	0.813-1.903	2.642	4
Ingestionng a.i. diet μL^{-1}	24	-	2.01	1.551-2.618	2.534	4
	48	-	0.81	0.264-1.538	4.001	4

(LD^{50}) mean lethal dose; (LC^{50}) mean lethal concentration; (C.I. 95%) confidence interval 95%; (χ^2) chi-square, and (D.F.) degree of freedom.

Table 10. Clothianidin, Imidacloprid and Thiamethoxam: acute oral toxicity LD_{50} expressed as ng/bee at 24, 48, and 72 hours for different subspecies species of A. mellifera (Table 2; Laurino *et al.*, 2013).

Hive	Subspecies	Geographic origin	Strain	Clothianidin			Imidacloprid			Thiamethoxam		
				24h	48h	72h	24h	48h	72h	24h	48h	72h
lig1	*A.m. ligustica*	Piedmont (Italy)	A	1.24	1.11	1.25				4.32	3.90	3.59
lig2	*A.m. ligustica*	Piedmont (Italy)	A	2.75	2.82	2.79	99.82	34.37	29.70	2.26	2.31	2.15
lig3	*A.m. ligustica*	Piedmont (Italy)	A	5.37	5.07	4.83	170.52	85.47	65.14	5.01	5.06	4.52
lig4	*A.m. ligustica*	Piedmont (Italy)	A							4.13	3.68	4.27
lig5	*A.m. ligustica*	Piedmont (Italy)	B	2.85	2.61	2.50	83.97	28.81	24.96	2.48	2.44	2.44
lig6	*A.m. ligustica*	Piedmont (Italy)	C	2.20	2.19	2.16	120.65	59.36	34.96	1.99	1.65	1.64
mel1	*A. m. mellifera*	South-East France	D	6.76	6.27	6.13		242.45	193.59	3.40	3.40	3.36
car1a	*A. m. carnica*	Croatia	E							9.00	9.07	8.86
car1b	*A. m. carnica*	Croatia	E							5.73	5.56	5.46
car2	*A. m. carnica*	Croatia	E							5.71	5.64	5.36

Table 11. LD_{50} values (ng/bee) at the different times for the three active ingredients (Laurino *et al.*, 2010).

	Beeehive 1	Beeehive 2	Beeehive 3
Clothianidin			
24 h	4.930	3.885	4.627
48 h	4.671	3.789	4.507
72 h	4.514	3.747	4.369
Imidacloprid			
24 h	191.044	173.088	187.208
48 h	99.063	103.705	109.579
72 h	74.631	46.763	97.425
Thiametoxam			
24 h	2.761	3.336	4.546
48 h	2.644	3.018	4.383
72 h	2.556	2.936	3.151

Table 12. Acute toxicity of sulfoxaflor (IsoclastTM) for bees (Dow AgroSciences, 2017).

Isoclast Active	Acute oral toxicity	Acute toxicity by contact exposure
Honeybee (*Apis mellifera*)		
Technical (95.6% a.i.)	LD_{50}(48 h) = 146 ng a.i./bee	LD_{50}(72 h) = 379 ng a.i./bee
Formulation SC	LD_{50}(48 h) = 65 ng a.i./bee	LD_{50}(48 h) = 283 ng a.i./bee
Bumble bee (*Bombus terrestris*)		
Formulation SC	LD_{50}(72 h) = 27 ng a.i./bee	LD_{50}(72 h) = 7554 ng a.i./bee

Table 13. Effect of sulfoxaflor on beneficial arthropods (Dow Agro Sciences, 2017).

Family	IOBC*	Beneficial arthropod	Assays number	Type	Exposure	Rate (gai/ha)	Notes
Phytoseiidae	1-2	*Amblyseius andersoni*	3	F		Topical	24-48
	1	*Amblyseius cucumeris*	1	Lab	Fresh residue	24-48	Adults
	1	*Amblyseiusswirskii*	5	G	Topical	24	LAB (48 gai/ha)-IOBC Class: 1
	1	*Phytoseiulus persimilis*	2	Lab	Freshr esidue	24-48	
	1	*Typhlodromus pyri*	5	F	Topical	24-48	LAB (48 gai/ha)-IOBC Class: 1
Coccinellidae	2-3	*Chilocorusbipustulatus*	1	F	Topical	36-48	
	2	*Harmonia axyridis*	1	F	Topical	24	
	2	*Scymnus* spp.	1	F	Topical	24	
Chrysopidae	1	*Chrisoperlacarnea*	3	Lab	Fresh residue	24-48	Larvae
Miridae	2	*Deraeocoris* spp.	1	F	Topical	24	
	2	*Heterotoma* spp.	1	F	Topical	24	
	2	*Malacoris* spp.	1	F	Topical	24	
	2	*Pilophorus* spp.	1	F	Topical	24	
	1	*Macrolophus caliginosus*	1	Lab	Fresh residue	24-48	Adults
	2	*Macrolophus caliginosus*	1	F	Topical	24	
Anthocoridae	1-2	*Anthocoris nemoralis*	1	F	Topical	24-48	Adults
	2-3	*Anthocoris nemoralis*	1	F	Topical	24-36	Larvae
	1	*Orius laevigatus*	2	Lab	Fresh residue	24-48	
	1	*Orius laevigatus*	1	G	Dry residue	24	Release 3 days after applic.
Aphelinidae	2	*Aphytis melinus*	1	Lab Ext.	Dry residue	24-48	Adults
Encyrtidae	1	*Anagyruspseudococci*	1	F	Topical	48	Parasitism >20%
Braconidae	2	Aphidiusrhopalosiphi	1	Lab	Dry residue	24-48	Release 14 days after applic.

*IOBC (International Organization Biological Control) classification as follows. Harmless = 1 (Labtest <30%; Semi-field and field test <25%); Slightly harmful = 2 (Labtest 30-75%; Semi-field and field test 25-50%); Moderately harmful = 3 (Labtest 76-99%; Semi-field and field test 51-75%); Harmful = 4 (Labtest >99%; Semi-field and field test >75%). F: Field; Lab: Laboratory; G.: Greenhouse. Assessment: Field and greenhouse, 2-7 days after treatment; Lab, 1-7 days of exposure; LAB Ext. 7 days after treatment.

Table 14. Toxicological profile in mammals (Dow AgroSciences, 2017).

Study	Results
Acute oral LD_{50} (rat)	1,000 mg/kg
Acute dermal LD_{50} (rat)	>5,000 mg/kg
Acute inhalation LC_{50} (rat)	>2.09 mg/L
Dermal irritation (rabbit)	Minimal
Eye irritation (rabbit)	Slight
Skin sensitization (mouse)	None
4 weeks dietary exposure (rat)	NOAEL = 24.8 mg/kg bw/d
13weeks dietary exposure (rat)	NOAEL = 6.36 mg/kg bw/d
4 weeks dermal exposure (rat)	NOAEL = 1,000 mg/kg bw/d
Developmentaltoxicity(rat)	NOAEL = 11,5 mg/kg bw/d
Acute neurotoxicity	NOAEL = 25 mg/kg bw/d
Genotoxicty	
Ames test	Negative
Chromosomal aberration	Negative
Mouse micronucleus(in vivo)	Negative

Table 15. Details of the trials carried out between 2015-2017.

Trials	Year	Region	Species
1	2015	Lazio	*T. vaporariorum*
2	2015	Lazio	*T. vaporariorum*
3	2015	Sicilia	*B. tabaci*
4	2016	Lazio	*T. vaporariorum*
5	2017	Sicilia	*B. tabaci*
6	2017	Sicilia	*B. tabaci*
7	2017	Lazio	*T. vaporariorum*

Table 16. Characteristics of the formulations used in the trials.

Treatment name	Active substance	Conc. of active subs % g/L g/Kg	Formulation type	Treatment rate
Closer	Isoclast™	120	SC	200/400 mL/ha
Teppeki	Flonicamid	500	WG	0.1-0.12 Kg/ha
Movento	Spirotetramat	48	SC	1.5/2.0 L/ha
Flipper	Fatty acid	73	EC	1% V/V
Codacide	Rapeseed oil		L	2.5 L/ha

Table 17. Description of the two strategies experimented between 2015 and 2017 for *T. vaporariorum* and *B. tabaci*.

Treatment number	Treatment name	Application timing	Treatment rate (mL or Kg/ha)
1	Isoclast™	A	200
1	Colza oil	A	2500
1	Flonicamid	B	0.1
1	Isoclast™	C	200
1	Colza oil	C	2500
1	Flonicamid	D	0.1
1	Flipper	E	1% v/v
2	Isoclast™	A	200
2	Codacide oil	A	2500
2	Spirotetramat	B	2000
2	Isoclast™	C	200
2	Colza oil	C	2500
2	Spirotetramat	D	2000
2	Flipper	E	1% v/v
3	Untreated		

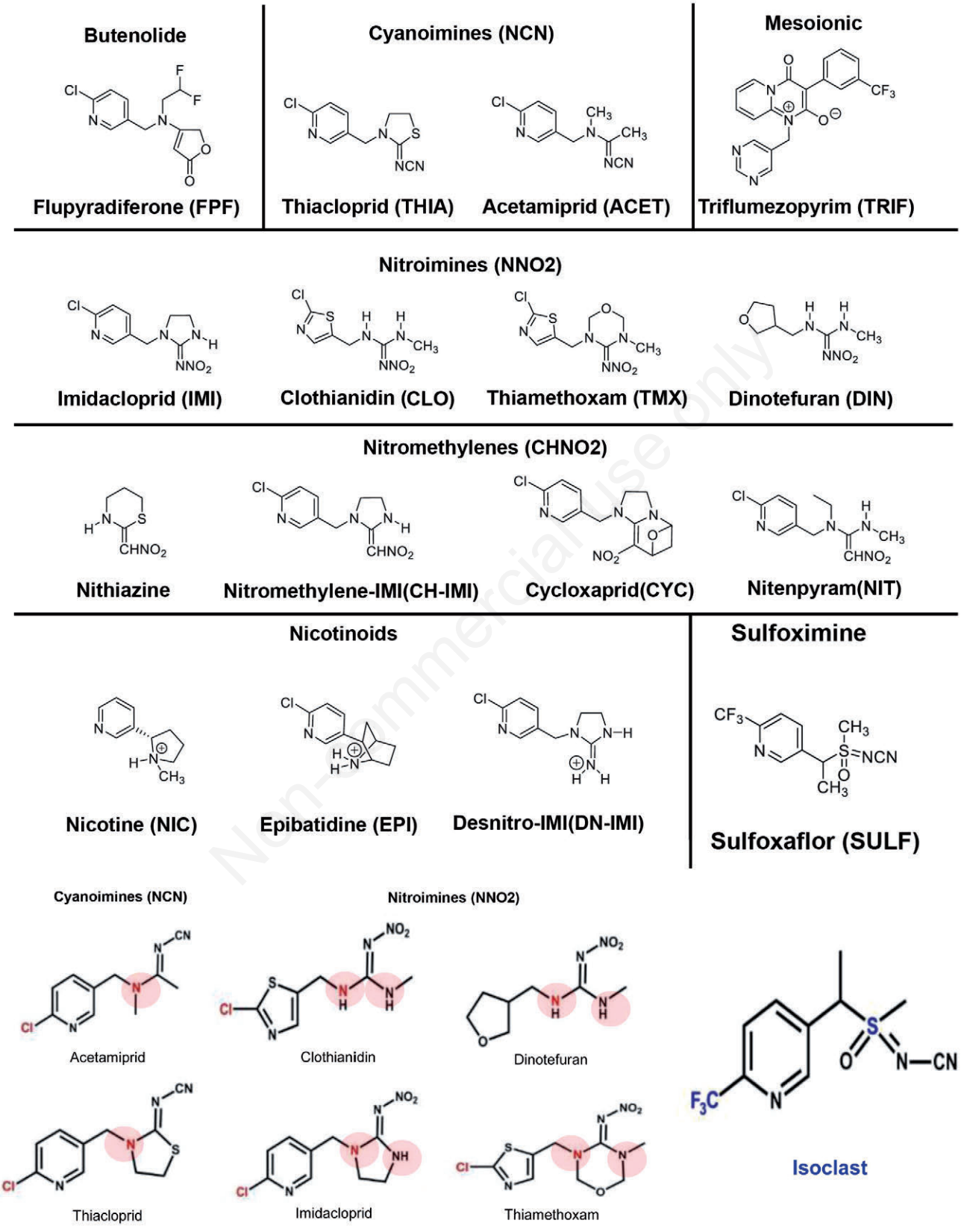

Figure 1. Chemical formula of sulfoxaflor and some neonicotinoids.

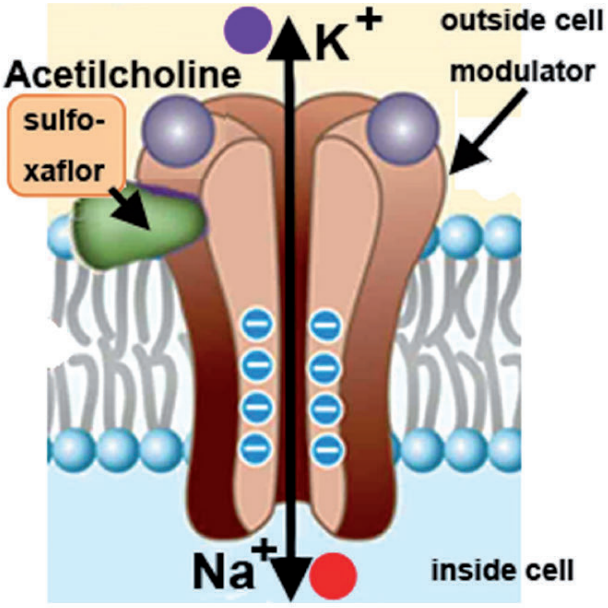

Figure 2. Action of sulfoxoflor on nicotinic receptors Nicotinic acetylcholine receptor (nAChR) agonist insecticide target in insect cation channel excitatory synapse.

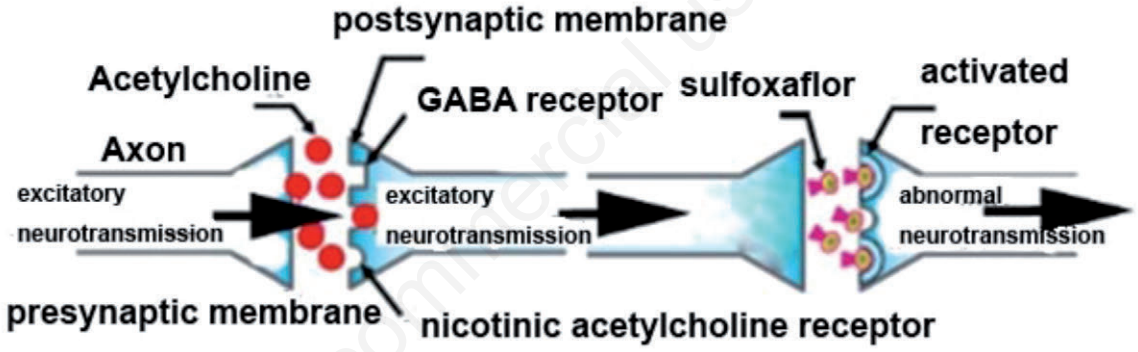

Figure 3. Mechanism of transmission along the synapsis.

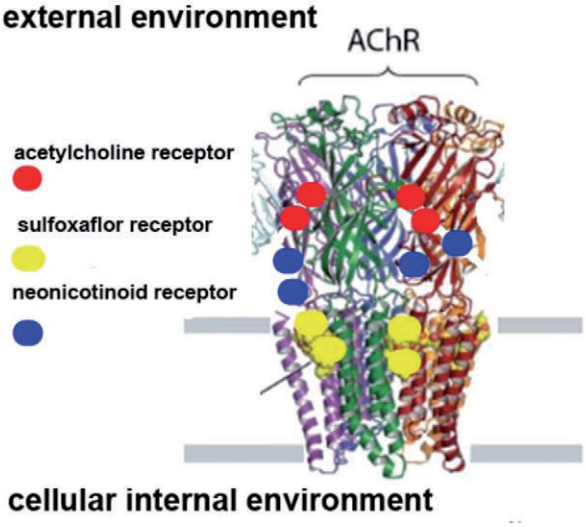

Figure 4. Hypothetic structure of AChR receptor ligating acetylcholine, neonicotinoids, sulfoxaflor.

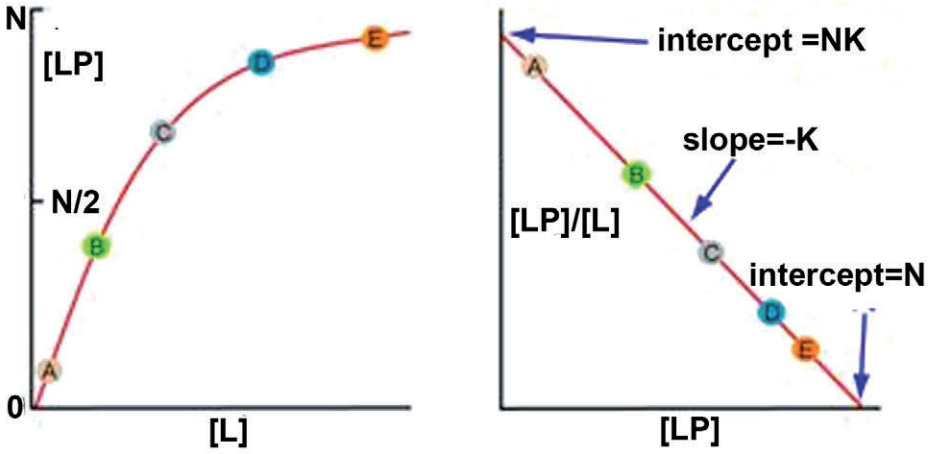

Figure 5. On the left relation between unbound insecticide concentration [L] and number of bound sites [LP], on the right the linearization of the equation called Scatchard equation.

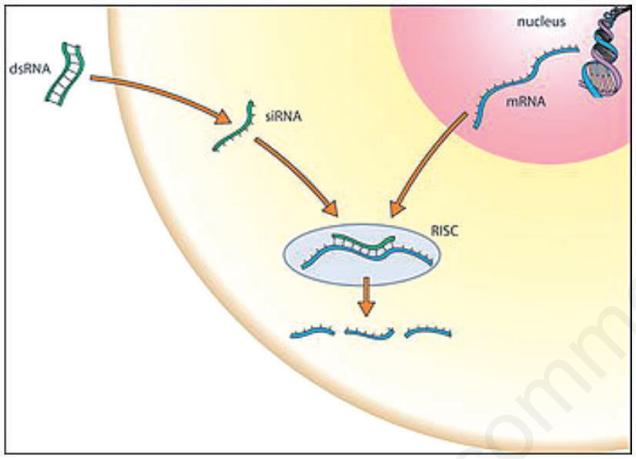

Figure 6. dsRNA action on nuclear receptors NR.

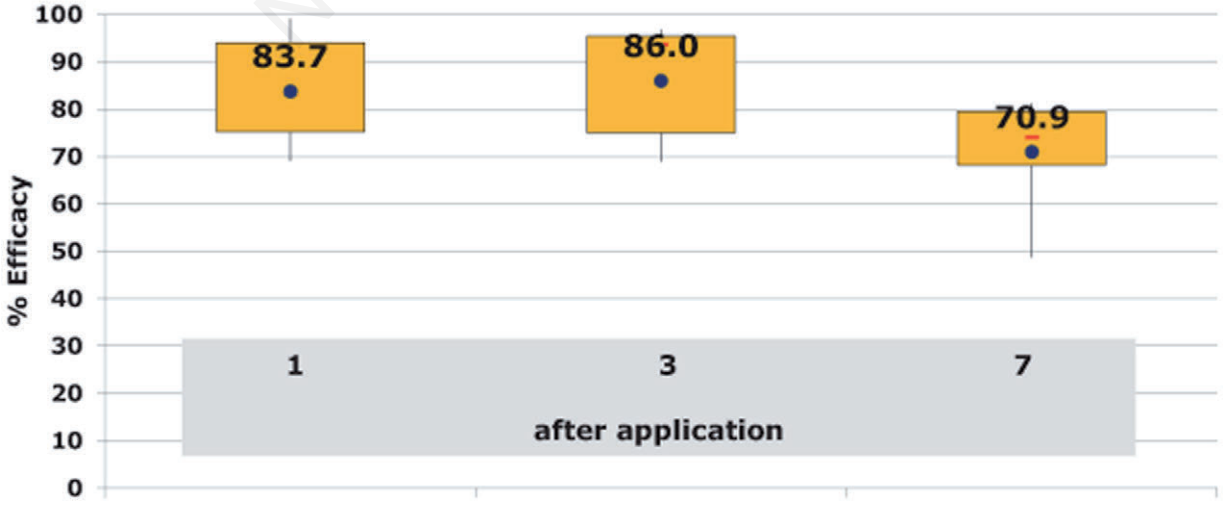

Figure 7. Isoclast™ 24 g ai/ha: efficacy % on adults of *B. tabaci* and *T. vaporariorum* after 1,3,7 day of application.

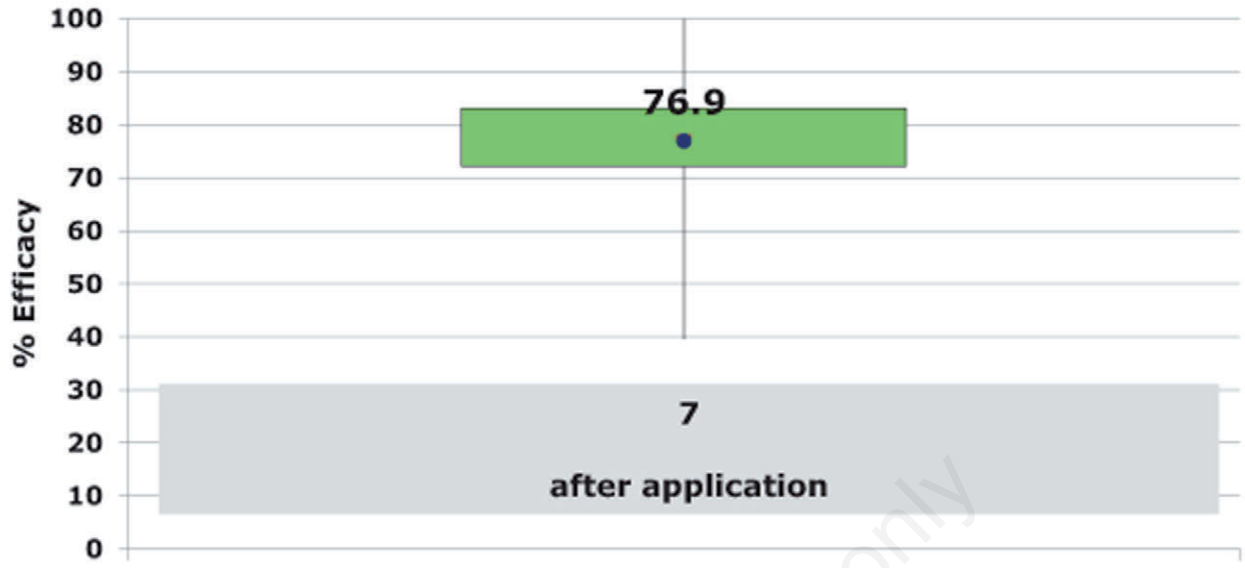

Figure 8. Isoclast™ 24 g ai/ha: efficacy % on neanids of *B. tabaci* and T. *vaporariorum* after 7 day of application.

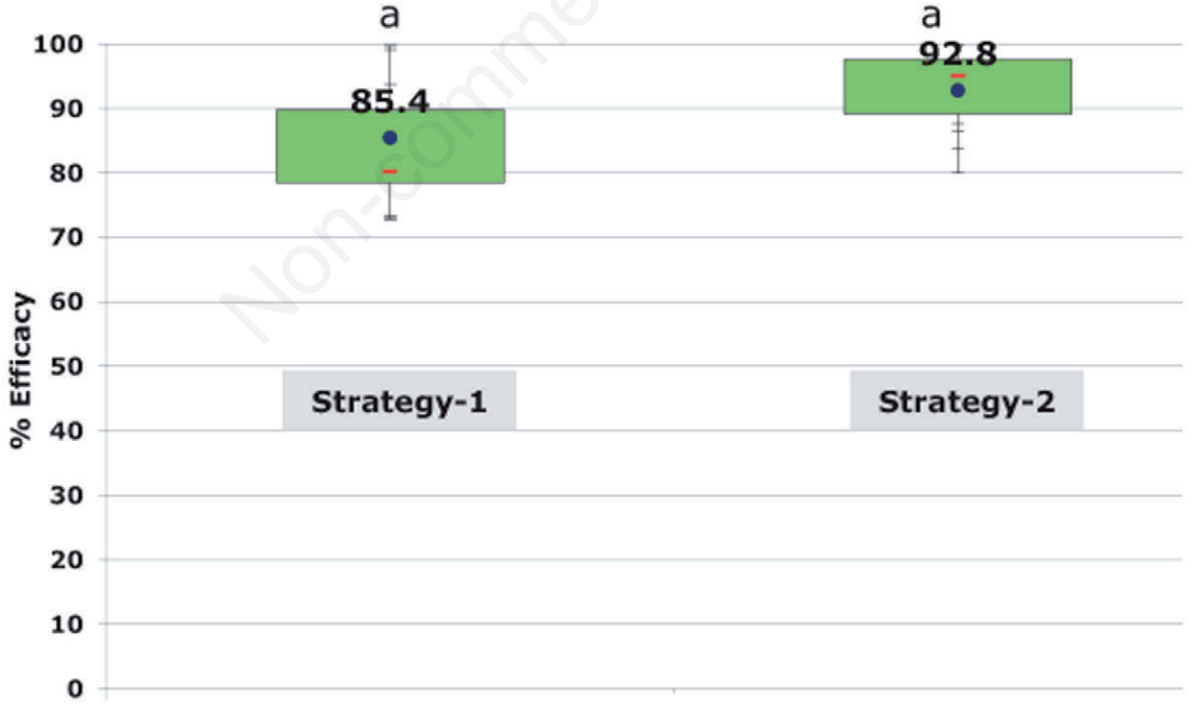

Figure 9. Isoclast™ 24 g ai/ha: efficacy % on adults of *B. tabaci* and *T. vaporariorum* after 7 day of application.

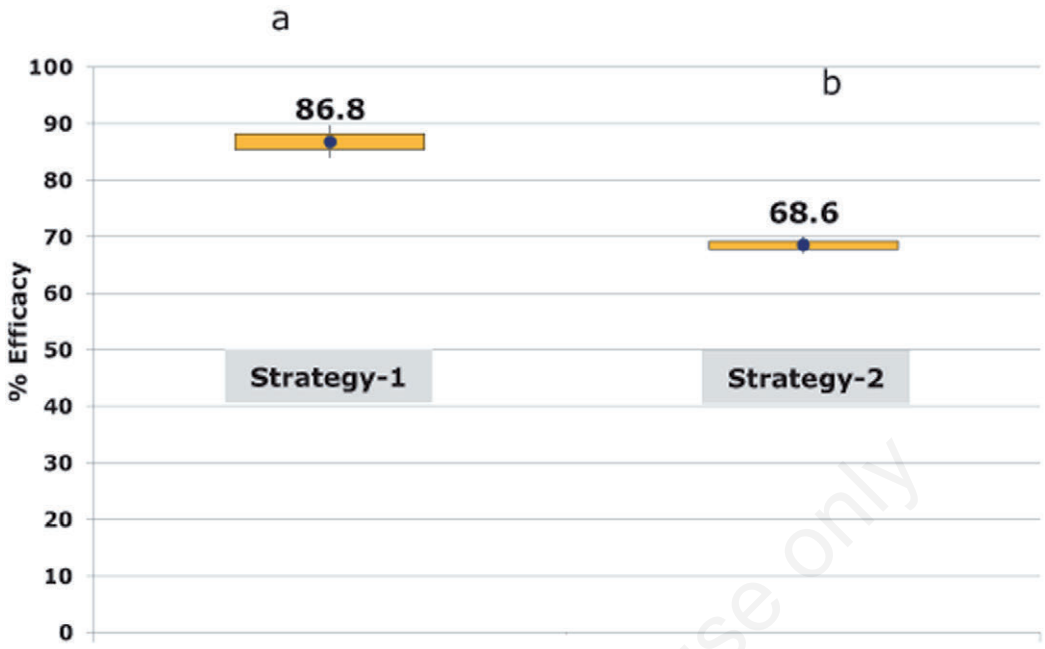

Figure 10. Isoclast™ 24 g ai/ha: efficacy % on neanids of *B. tabaci* and *T. vaporariorum* after 7 day of application.

Figure 11. Isoclast™: Knockdown effect on *T. vaporariorum*, adults (A) before the treatments (B) sulfoxaflor (48 g ai/ha) after 24 hours.

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