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Mini Review

Sulfoxaflor and the sulfoximine insecticides: Chemistry, mode of action and basis for efficacy on resistant insects

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ABSTRACT

The sulfoximines, as exemplified by sulfoxaflor ([*N*-[methyloxido[1-[6-(trifluoromethyl)-3-pyridinyl]ethyl]-λ^4-sulfanylidene] cyanamide] represent a new class of insecticides. Sulfoxaflor 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 (nAChRs) and functions in a manner distinct from other insecticides acting at nAChRs. The sulfoximines also exhibit structure activity relationships (SAR) that are different from other nAChR agonists such as the neonicotinoids. This review summarizes the sulfoximine SAR, mode of action and the biochemistry underlying the observed efficacy on resistant insect pests, with a particular focus on sulfoxaflor.

1. Introduction

Resistance to existing insecticides is an on-going problem [1] that requires the development of new insect control tools. A number of sap-feeding insects including *Myzus persicae* (green peach aphid; GPA), *Aphis gossypii* (cotton aphid), *Bemisia tabaci* (sweet potato whitefly) and *Nilaparvata lugens* (brown plant hopper), have a history of developing resistance to available insecticides [1]. Although initially slow to develop, many of these same sap-feeding insect pests have now developed resistance to the neonicotinoid insecticides [2–4] that are currently the mainstay for their control in a wide range of crops [2,3].

The sulfoximines are a new class of insecticides targeting sap-feeding insects [5–7]. Sulfoxaflor (Fig. 1) is the initial compound in this new sulfoximine insecticide class to be selected for commercial development. The sulfoximines, as exemplified by sulfoxaflor, exhibit several unique characteristics. The members of this class contain a unique chemical moiety, a sulfoximine, the first for a commercial agrochemical, and one which confers a unique set of structure activity relationships (SAR) compared to other insecticides. Like several chemically diverse classes of insecticides (spinosyns, neonicotinoids, nereistoxin analogs), sulfoxaflor acts on insect nicotinic receptors (nAChRs). However, as discussed below, there are aspects of the sulfoxaflor – nAChR interaction that distinguish it from the other nAChR acting insecticides. The sulfoximines are also effective against a wide range of sap-feeding insect pests that are resistant to other classes of insecticides, including many that are resistant to the neonicotinoids. Associated with this lack of cross-resistance, the sulfoximines such as sulfoxaflor are poor substrates for the metabolic enzymes involved in resistance to other classes of insecticides. This review examines each of these aspects and how it applies to insecticide resistance management (IRM) for this novel class of chemistry.

2. Chemistry

2.1. Discovery

The sulfoximine insecticides (SFI), including sulfoxaflor, emerged from exploration of unusual and underrepresented chemical moieties for pesticidal activity an example of which is the sulfoximine moiety (Fig. 1) [6]. Early sulfoximine analogs (Fig. 1, strucuture A) exhibited weak fungicidal activity [6]. Continued exploration led to *N*-nitro substituted sulfoximines (Fig. 1, structure B), which evolved to a chloropyridine analog (SFI-1 Fig. 1) that

Abbreviations: GPA, green peach aphid (*Myzus persicae*); IRM, insecticide resistance management; IRAC, Insecticide Resistance Action Committee; MTH, 2-CH_3-thiazole; nAChR, nicotinic acetylcholine receptors; SAR, structure activity relationships; SFI, sulfoximine insecticide; SFX, sulfoxaflor; TFT, tertrahydrofuran.

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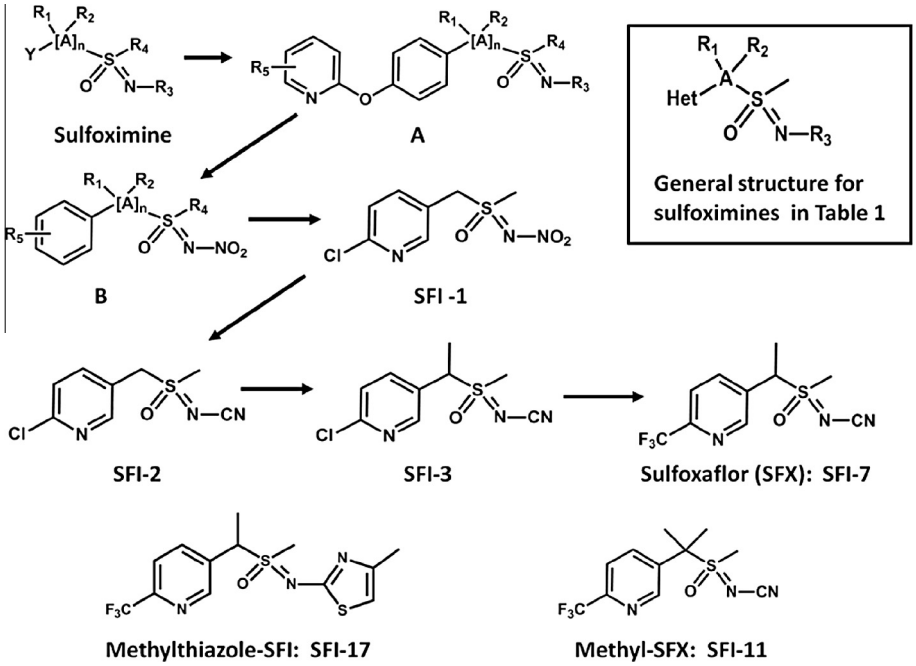

Fig. 1. Evolution of sulfoximine analogs leading to sulfoxaflor, structures of selected sulfoximines and general structure for the sulfoximines in Table 1. Structures A and B represent generalized motifs for early sulfoximine analogs, where R_1-R_5 are substituents and $[A]_n$ = 0-2 atoms.

exhibited a shift in biological activity towards sap-feeding insects [6,8]. Replacement of the nitro substituent on the imine nitrogen with a cyano group improved insecticidal activity (SFI-2; Fig. 1, Table 1), while addition of a methyl group on the methylene bridge between the sulfoximine and the chloropyridine provided a further boost in insecticidal potency (SFI-3, Fig. 1, Table 1). Finally, replacement of the chlorine on the pyridine with a CF_3 resulted in an additional improvement in activity (SF-7; sulfoxaflor, Fig. 1, Table 1).

Table 1
Insecticidal activity of sulfoximine analogs against *Myzus persicae*.

						M. persicae	
SFI[a]	Het	R1	R2	R3	A	LC90[b]	LC50[c]
1	6-Cl-3-pyridyl	H	H	NO2	C	239	–
2	6-Cl-3-pyridyl	H	H	CN	C	11.3	–
3	6-Cl-3-pyridyl	H	CH3	CN	C	1.1	1.4
4	6-Cl-3-pyridyl	H	CH3	NO2	C	12.0	–
5	6-CF3-3-pyridyl	H	H	CN	C	5.0	–
6	6-CF3-3-pyridyl	H	CH3	NO2	C	4.6	>100
7[d]	6-CF3-3-pyridyl	H	CH3	CN	C	0.19	0.08
8	2-Cl-5-thiazoyl	H	H	CN	C	>200	14.4
9	2-CF3-5-thiazoyl	H	H	CN	C	>200	–
10	THF[e]	H	CH3	CN	C	>200	–
11	6-CF3-3-pyridyl	CH3	CH3	CN	C	1.4	0.45
12	6-CF3-3-pyridyl	F	CH3	CN	C	–	4.64
13	6-CF2Cl-3-pyridyl	H	H	CN	C	–	9.6
14	6-Cl-3-pyridyl	H	H	CN	N	>200	–
15	6-Cl-3-pyridyl	H	CH3	CN	N	22.3	–
16	6-CF3-3-pyridyl	H	CH3	CN	N	7.1	–
17	6-CF3-3-pyridyl	H	CH3	MTH[6]	C	3.8	–
Imidacloprid	–	–	–	–	–	0.24	0.1

[a] SFI – sulfoximine insecticide: see Fig. 1 for generic structure of the sulfoximine insecticides.
[b] Watson et al. [23] & unpublished Dow AgroSciences data, LC_{90}, ppm.
[c] [24], ppm.
[d] Sulfoxalfor.
[e] THF = tetrahydrofuran.
[f] MTH = 2-CH_3-thiazole.

The CF_3 analog (sulfoxaflor) was selected for commercial development (Fig. 1).

2.2. Sulfoximines: distinct from the neonicotinoids

Because the sulfoximines and neonicotinoids both function as nAChR agonists, it might be assumed that the SARs and interactions with the insect nAChR of the two chemistries are quite similar. However, the sulfoximines and neonicotinoids are distinct just as other classes of structurally similar insecticides are distinct. For example, the organophosphorus and carbamate insecticides, both of which inhibit acetylcholinesterase, can possess very similar structural elements (Fig. 2), and yet are widely viewed as different classes of insecticides each possessing very individual SARs. These chemistries are defined by the organophosphorus and carbamate functional groups [9–12], not by the presence of a particular aryl or heterocyclic ring system. For instance, methiocarb, MTMC and fenthion, all possess very similar aryl ring systems (Fig. 2), and yet are clearly defined

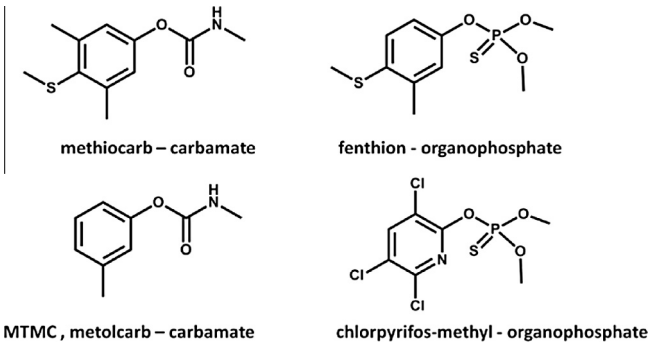

Fig. 2. Structures for selected organophosphorus and carbamates possessing similar aryl moieties or a halopyridine.

by their carbamate and organophosphate moieties. Likewise the presence of a halopyridine on the organophosphate chlorpyrifos-methyl (Fig. 2) does not define it as a neonicotinoid. In a similar manner, the SAR of the sulfoximines is highly contrasted when compared to the neonicotinoids. For example, a defining characteristic of all commercial neonicotinoids is the presence of at least one sp^3 nitrogen, either as part of a heterocyclic or an acyclic moiety (Fig. 3). It is the presence of this sp^3 nitrogen in association with a conjugated electron withdrawing group that led to the definition of "neonicotinoid" [13–14] and remains central to the neonicotinoid pharmacophore [2,15,16]. Importantly, the absence of a sp^3 nitrogen in a neonicotinoid is associated with a loss of insecticidal activity [17,18]. In marked contrast to the neonicotinoids, the sulfoximines lack any sp^3 nitrogen [19] (Fig. 3) and yet are highly insecticidal [5,6]. Moreover, incorporation of a sp^3- nitrogen into the sulfoximine structure results in a marked reduction in insecticidal activity (Table 1), further illustrating differences in the SARs of the sulfoximines and neonicotinoids.

In addition to lacking a sp^3 nitrogen in a conjugated system, other contrasts in the sulfoximine SAR include the marked improvement in insecticidal activity associated with the presence of a 6-CF_3 substituent on the pyridine ring (Table 1). Replacement of the chlorine with a CF_3 group on the pyridine of a nitromethylene neonicotinoid results in a large decrease in activity [20]. A similar reduction in activity is also associated with replacement of the chlorine with a CF_3 on the thiazole ring of clothianidin [21]. Additionally, substitution of the 6-chloropyridine moiety with a 5-chlorothiazole can have little effect on the activity of neonicotinoids [22] and in some cases provides an improvement in insecticidal efficacy [21]. However for the sulfoximines, replacement of the 6-chloropyridine with a 5-chlorothiazole, results in a dramatic decline in insecticidal activity [23,24] (Table 1). Further, replacement of the 6-chloropyridine moiety of sulfoxaflor with a tetrahydrofuran, like that of dinotefuran (Fig. 3), results in a total loss of insecticidal activity (Table 1). Thus, based on the numerous contrasts in the SARs, the sulfoximines, and especially sulfoxaflor, are clearly distinct from the neonicotinoids. This differentiation was recently recognized by the Insecticide Resistance Action Committee (IRAC) classifying sulfoxaflor (Group 4C) as separate from the neonicotinoids (Group 4A) [25].

2.3. Sulfoximine analogs

In light of the excellent insecticidal efficacy of the sulfoximines and following the publication of the first Dow AgroSciences sulfoximine insecticide patent [8], an expanding range of insecticidal sulfoximines has been described in the literature [6,7,23,24,26] (Figs. 1 and 4), and in numerous patents and patent applications [27–36] (Figs. 4 and 5). Following up on sulfoximines described by Zhu et al. [8] and Loso et al. [29], a small set of these sulfoximines with a mono- or di-substituted-thiazole in place of the 6-chloropyridine (Fig. 4) were investigated for insecticidal activity [37], as were other 5-chlorothiazole sulfoximines with an extended bridge containing a substituted benzylamine [38] or benzamides [39] (Fig. 4). Based on insecticidal activity, the motif of these particular sulfoximines appears to be far less efficacious than that of the sulfoximines closely related to sulfoxaflor.

Recently, a number of other insecticidal sulfoximines related to sulfoxaflor (e.g. two methyl groups on the methylene bridge; e.g. SFI-11, Fig. 1) have been described [24]. However, the added methyl group on the methylene bridge is clearly detrimental since none of these analogs were as active as sulfoxaflor [24] (Table 1). Likewise, the insecticidal activity of sulfonimidamides (a nitrogen in the methylene bridge) related to sulfoxaflor [36] (Fig. 5); lags behind those of sulfoximines and sulfoxaflor [40] (Table 1). Thus, the configuration of sulfoxaflor is highly optimized for a sulfoximine-based insecticide targeting sap-feeding insect pests. Deviation from this particular configuration quickly leads to a reduction in insecticidal activity. Also, as noted below, even among the sulfoximine insecticides, sulfoxaflor is a more potent insecticide than might otherwise be expected based on the target-site binding affinity.

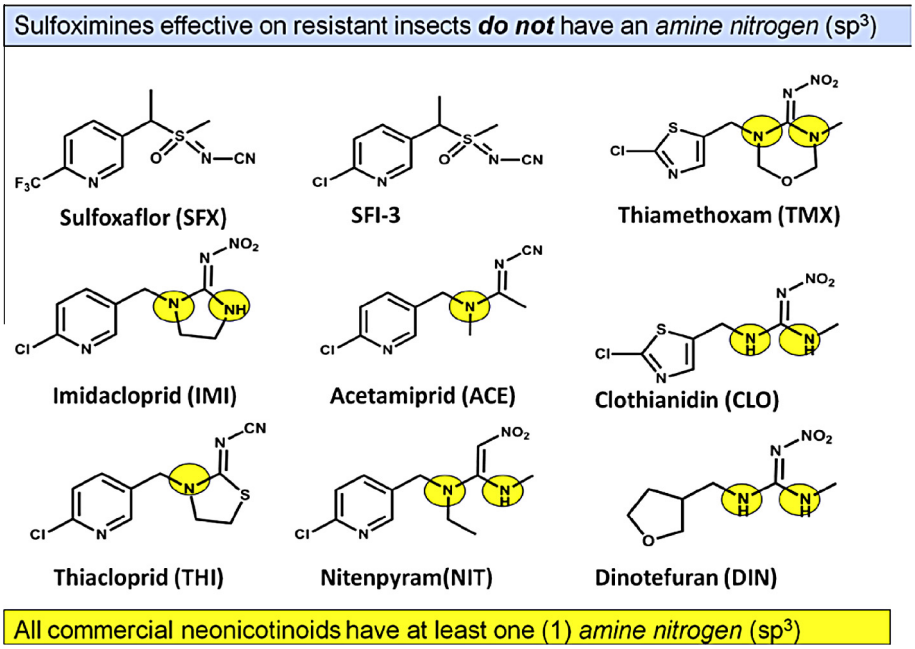

Fig. 3. Structures of sulfoximines compared to commercial neonicotinoids highlighting the presence of one or more sp^3 nitrogens in the neonicotinoids.

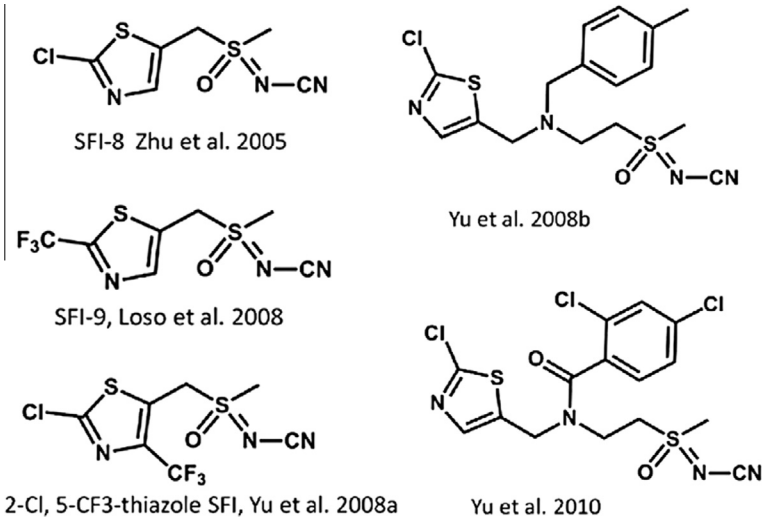

Fig. 4. Examples of sulfoximines with a thiazole in place of a pyridine.

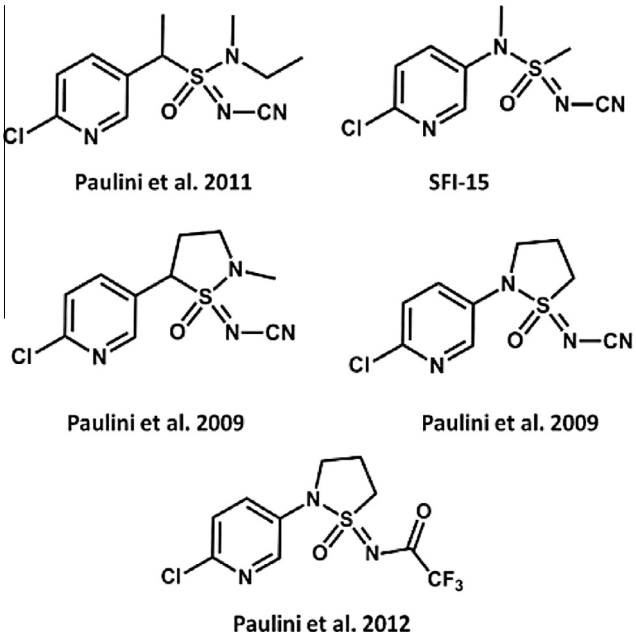

Fig. 5. Examples of sulfoximines containing an sp^3 nitrogen.

3. Mode of action

It was initially demonstrated that the affinity for a set of sulfoximines for the low affinity [^{3}H] IMI binding site was significantly correlated with GPA toxicity (r^2 = 0.68 with sulfoxaflor, 0.85 without sulfoxaflor [23]). However, sulfoxaflor has relatively weak affinity for the low affinity GPA nAChR binding site compared to most neonicotinoid insecticides such as imidacloprid [6,23,24,40]. As implied from the higher correlation coefficient with the omission of sulfoxaflor from the binding/toxicity correlation, even when compared to other sulfoximines, sulfoxaflor may be distinct. For example, the 6-Br-3-pyridyl sulfoximine analog exhibits affinity for the low affinity GPA nAChR binding site that is nearly identical to imidacloprid and is >30× higher affinity than sulfoxaflor [23]. Nonetheless, the 6-Br-3-pyridiyl analog is substantially less insecticidal (5-fold) than sulfoxaflor [23], suggesting that in addition to nAChR affinity, other factors must contribute to the potent insecticidal activity of sulfoxaflor.

Additionally, Cutler et al. [24] also detailed the binding and pharmacology of a sulfoxaflor analog, [^{3}H]-methyl-sulfoxaflor ([^{3}H]Me-SFX), concluding that [^{3}H]Me-SFX is a selective radioligand for a high affinity nAChR binding site and suggest, by inference, that the binding of sulfoxaflor at this site constitutes an important nAChR interaction for toxicity. However, the affinity of sulfoxaflor for the site identified by [^{3}H]Me-SFX, while significantly higher than that for the low affinity nAChR binding site, it is nonetheless significantly weaker relative to equally toxic neonicotinoid insecticides. Therefore, the affinity at neither the low nor the high affinity nAChR binding sites fully account for the potent insecticidal actions of sulfoxaflor. Perhaps additional studies using radiolabeled sulfoxaflor will more clearly demonstrate whether binding of sulfoxaflor to the high or low affinity nAChR binding site, or perhaps both, is most relevant to insect toxicity.

The symptoms of GPA intoxicated by sulfoxaflor are initially excitatory and include tremors, antennal waving, and leg extension or curling, followed by partial or complete paralysis and death [23]. Consistent with the early symptoms, sulfoxaflor was found to be an agonist at the insect nAChR [23]. Using cloned and expressed nAChRs from *Drosophila melanogaster*, the nAChR-mediated currents induced by sulfoxaflor (I_{max} = 348%) were determined to be significantly larger than those for other nAChR-acting insecticides (the neonicotinoids; I_{max} = 12.2–47.2%) except clothianidin (I_{max} = 273%) [23]. Further, sulfoxaflor also produced larger amplitude currents than all the tested sulfoximines, including SFI-3 (compound Cl-SFI, I_{max} = 94%), which has a Cl-pyridine replacement of the CF_3-pyridine moiety of sulfoxaflor [23]. However, other sulfoxaflor-sensitive nAChRs may not share the high efficacy observed in these initial studies. For example, a study on neurons from the stick insect, *Carausius morosus*, found that sulfoxaflor may act as a desensitizing partial agonist on nAChRs from this model organism [26]. The symptoms of sulfoxaflor intoxication for this species were predominantly inhibitory, and clearly different from those of the neonicotinoid imidacloprid [26]. The lack of excitatory symptoms is consistent with desensitization of nAChRs as well as with a partial agonist action of sulfoxaflor. The authors further demonstrated that, when pharmacologically isolated by desensitization, there are distinctions between the nAChR subtype selectivity and affinity of sulfoxaflor and imidacloprid [26].

Further evidence of nAChR subtype selectivity between sulfoxaflor and imidacloprid comes from studies on mutagenized *D. mel-*

Table 2
Resistance ratios for sulfoximines, neonicotinoids and other insecticides in insecticide resistant strains.

Compound	*M.p* R[a]	*M.p* FRC-P[b]	*B.t* 499[c]	*B.t* Chk[d]	*B.t* 497[e]	*N.l.* Ogori[f]	*A.g.* Belz[g]	*A.g.* Gre[h]	*D.m* Dα1[i]	*D.m.* Dβ2[i]	*D.m.* 4A4D[i]
Sulfoximines											
Sulfoxaflor	0.4	43	1.6	2.8	2.2	1.5	0.9	2.5	1.5	2.8	2.6
SFI-2	0.7	–	–	5.2	–	–	–	–	–	–	–
SFI-3	0.2	–	–	2.9	–	–	–	–	–	–	–
Neonicotinoids											
Imidacloprid	17	2350	>225	>800	1020	438	–	–	20.6	28.7	26.8
Thiacloprid	–	>2500	–	–	–	–	–	–	–	–	–
Clothianidin	–	3013	–	–	–	–	–	–	16.1	34.6	12.4
Thiamethoxam	–	270	132	–	–	–	29.1	550	–	–	–
Acetamiprid	–	82	13.4	–	–	–	–	–	23.3	27.3	27.3
Dinotefuran	–	54	20.1	–	–	–	–	–	2.1	24.9	20.3
Nitenpyram	–	–	–	–	–	–	–	–	13.2	70.3	35.2
Pyrethroids											
Deltamethrin	60	–	–	835	–	–	–	–	–	–	–
lambda-Cyhalothrin	–	>5000	–	–	–	–	–	–	–	–	–
Other insecticides											
Profenofos	–	–	–	189	–	–	–	–	–	–	–
Pirimicarb	–	11	–	–	–	–	–	–	–	–	–
Pymetrozine	–	6	–	–	–	–	–	–	–	–	–
Flonicamid	–	2	–	–	–	–	1.1	–	–	–	–

[a] *M. persicae* – R-4013A: [6,56,57].
[b] *M. persicae* – FRC-P: [24,58].
[c] *B. tabaci* – 4991BT1: [42,56].
[d] *B. tabaci* – Chloraka: [42,56].
[e] *B. tabaci* – 4971BT9: [42,56].
[f] *N. lugens* – Ogori-R: [5].
[g] *A. gossypii* – Belzoni 2011 (72 h) [43].
[h] *A. gossypii* – Grenada MS (A) 2009 (48 h) [43].
[i] *D. melanogaster*[41].

anogaster. Here, insects with altered Dα1 and Dβ2 nAChR subunits were resistant to imidacloprid and other neonicotinoids, but showed very limited or no resistance to sulfoxaflor, suggesting a differential interaction with nAChRs between the neonicotinoids and sulfoxaflor [41]. One potential explanation for the differences between sulfoxaflor and the neonicotinoids in this study is that sulfoxaflor may act on different *D. melanogaster* nAChR subunit combinations than the neonicotinoids.

4. Cross-resistance and differential metabolism

A notable feature of sulfoxaflor is the high level of efficacy against a range of sap-feeding insects that are resistant to a variety of insecticides, including the neonicotinoid imidacloprid [5–7,42,43] (Table 2). Resistance to the neonicotinoid insecticides is most commonly associated with enhanced metabolism [2,44–50]. Thus, one hypothesis for the lack of cross-resistance to sulfoxaflor in imidacloprid resistant strains would be that sulfoxaflor is not metabolized by the enzymes involved in imidacloprid metabolism. Recent studies support this hypothesis in that sulfoxaflor and the chloro-SFI analog (SFI-3) are not metabolized *in vitro* by the monooxygenase CYP6G1 [19], an enzyme associated with resistance to a range of insecticides including pyrethroids, organophosphates and neonicotinoids in *D. melanogaster* [51]. Molecular modeling studies rationalize that the lack of metabolism is a function of the structure in that the three-dimensional shape of sulfoxaflor prevents it from getting close enough to the heme-oxo active site for metabolism to occur [19]. Interestingly, the number of sp^3 nitrogens and their associated Hückle charges is correlated with susceptibility of the neonicotinoids and sulfoximines to metabolism by the monooxygenase CYP6G1 [19]. This rationale is supported by studies where the introduction of a sp^3 nitrogen into the sulfoximine structure resulted in increased susceptibility to metabolism by the CYP6G1 [19]. Perhaps surprisingly, the monooxygenase associated with neonicotinoid resistance in the whitefly *B. tabaci* (CYP6CM1vQ; [50]) is able to metabolize imidacloprid, thiacloprid and clothianidin, but not acetamiprid or thiamethoxam [50]. In contrast, CYP6G1 is able to metabolize a wide range of insecticides including organophosphorus, pyrethroid, organochlorine and neonicotinoid insecticides [51], suggesting that CYP6G1 has a much broader substrate range than CYP6CM1vQ. Thus, the inability of CYP6G1 to metabolize sulfoxaflor is all the more remarkable and further supports the importance and uniqueness of the sulfoximine structure in the overall insecticidal efficacy of the sulfoximines.

5. Cross-resistance and insecticide resistance management

The efficacy of sulfoxaflor against pest insect strains resistant to neonicotinoids and other insecticides has been examined in a variety of studies [5–7,41–43]. In general, these studies show a broad lack of cross-resistance to sulfoxaflor across a range of species (Table 2). As noted above, virtually all cases of resistance to the neonicotinoids are associated with enhanced levels of metabolism [2,44–49], and available data [7,19] suggest that the sulfoximines are likely to be unaffected by the monooxygenases involved in these neonicotinoid-resistant strains. Thus, the broad lack of cross-resistance towards sulfoxaflor in neonicotinoid and other resistant strains is consistent with the unique chemistry and biochemistry of the sulfoximines.

There is now a single example where a modest level of cross-resistance to sulfoxaflor was observed in a strain resistant to the neonicotinoids and other insecticides (e.g. *lambda*-cyhalothrin) (Table 2). In this particular instance, a strain (FRC-R) of GPA only found on peaches in a few regions of France, Spain and Italy, possesses both enhanced metabolism and a mutation in the nAChR target site [24,52]. This FRC-R strain exhibits more than 2300-fold

resistance to imidacloprid, but only a 43-fold resistance to sulfoxaflor [24] (Table 2). Although significant, the level of cross-resistance observed for sulfoxaflor, and other non-neonicotinoid insecticides (e.g. pirimicarb, pymetrozine), is lower than that for any of the neonicotinoid insecticides examined [24] (Table 2). Furthermore, field trials on GPA populations confirmed to possess the mutation have demonstrated good efficacy for sulfoxaflor at anticipated label rates (unpublished data). The limited degree of cross-resistance observed to sulfoxaflor may be due to its inherent metabolic stability [19,24] minimizing the effects of the enhanced metabolism that also exists in the FRC-P strain. Additionally, the distinct action of sulfoxaflor at nAChRs relative to the neonicotinoids may also render this specific target site mutation (R81T) less significant for sulfoxaflor than for neonicotinoids such as imidacloprid. Interestingly, this same point mutation has also been recently found associated with imidacloprid resistance in strains of the cotton aphid, *A. gossypii* [53,54]. The specific impact of R81T on the action of sulfoxaflor remains an area for further study. Other recent studies with neonicotinoid resistant *D. melanogaster* possessing target site-based resistance involving two nAChR subunits (Dα1 and Dβ2) showed very limited or no cross-resistance to sulfoxaflor and another sulfoximine insecticide while displaying resistance to a wide range of neonicotinoids [41] (Table 2). Thus, sulfoxaflor should be broadly active on a wide range of resistant sap-feeding insect pests including those resistant to the neonicotinoids, whether by metabolic or in some instances target site-based mechanisms.

In spite of a broad lack of cross-resistance between sulfoxaflor and the neonicotinoids, Dow AgroSciences supports and follows guidelines from the IRAC that recommend that compounds in different subgroups should not be rotated unless there are no other options [25]. However, available data indicate that sulfoxaflor is an excellent potential replacement for neonicotinoid insecticides, and would make an excellent foundation insecticide in an IRM rotation scheme with other classes of aphid insecticides (e.g. pymetrozine, flonicamid), where resistance to the neonicotinoids is a potential concern.

6. Conclusions

The sulfoximines, especially sulfoxaflor, are chemically and biochemically distinct from other insecticides acting on nAChRs including the neonicotinoids, spinosyns and nereistoxin analogs. Perhaps not surprisingly, the sulfoximines possess SARs that are highly divergent from other nicotinic agonists such as the neonicotinoids. Sulfoxaflor is active against a wide range of sap-feeding insect pests [5,7,55], including those that are resistant to neonicotinoids and other insecticides [5–7,42,43]. In recognition of these facts, the IRAC has placed sulfoxaflor in a mode of action subgroup (Group 4C) [25] that is separate from the neonicotinoids (Group 4A). Thus, sulfoxaflor provides growers with new options in pest insect control and IPM programs.

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