Pesticide Action Network Europe

Brussels, September 2016

Sulfoxaflor and flupyradifurone: Neonicotinoids or not ?

Summary

The pesticide industry is trying to hide the reality behind two new chemicals that are similar to the notorious group of neonicotinoids linked to massive bee death all over the world.

Their properties clearly show that they should be classified as neonicotinoids (see Table):

Characteristics	Sulfoxaflor	Flupyradifurone	Other neonicotinoids
Capable of binding insect nicotinic acetylcholine receptors?	Yes	Yes	Yes
Do they function in a systemic way?	Yes	Yes	Yes
Toxic to bees?	Yes	Yes	Yes

The pesticide companies have managed to classify sulfoxaflor and flupyradifurone insecticides as different to neonicotinoids by hiding the great similarities in their biochemical properties. They even suceeded to deceive regulators by artificially designing new insecticide categories. The problem here is that the pesticide companies themselves decide what category a pesticide belongs to (see below). These active substances are now approved.

Introduction

Two controversial active substances of insecticides have received an EU authorisation in 2015: sulfoxaflor and flupyradifurone. These insecticides have been presented by their producers as belonging to new chemical groups, namely sulfoximines and butenolides as to avoid classification as neonicotinoids. This assumption is not validated by facts and science, as detailed in this factsheet.
Neonicotinoids currently have a bad reputation worldwide, due to their toxicity to pollinators. Four substances (3 neonicotinoids and one phenylpyrazole) have been partially banned in 2013 due to this toxicity. This might be the reason why sulfoxaflor and flupyradifurone producers created new classes of insecticides…

I. IRAC classification

Companies producing sulfoxaflor (Dow Agrochemicals) and flupyradifurone (Bayer CropScience) insecticides have each published a scientific article[1] aiming at explaining that these two substances are not neonicotinoids. Their main argument is that there is a difference in chemical structure compared to the insecticides classified as neonicotinoids. Consequently, two new insecticide categories were created by the IRAC (Insecticide Resistance Action Committee): sulfoximine for sulfoxaflor and butenolide for flupyradifurone.
The distinction between sulfoximines, butenolides and neonicotinoids originates from a 2012 classification from the IRAC. This classification is detailed in a publication from Sparks and Nauen 2015[2]. Sparks *et al.* (2013)[1] refers to this IRAC classification concerning sulfoxaflor (Sparks is a Dow Agrochemical employee) just as Nauen *et al.* (2014)[1] does about flupyradifurone (Nauen is a Bayer Cropscience employee).

Table 1
Modes of action (based on IRAC MoA classification) for current insecticide groups.

IRAC group	Primary site of action/MoA[a]	Chemical subgroup/exemplifying active	1st year[b]	No. of products[c]	Market[d] value
Nerve and Muscle Targets					
1	AChE inhibitor	1A carbamates	1950	30	$667
		1B organophosphates	1944	90	$1794
2	GGCC antagonist	2A cyclodienes	1950	7	$7
		2B fiproles	1990	3	$801
3	VGSC modulator	3A pyrethroids and pyrethrins	1977	30	$2777
		3B DDT and analogs	1944	7	$<1
4	nAChR agonist	4A neonicotinoids	1990	8	$4650
		4B nicotine	1763	1	–
		4C sulfoximines	2013	1	$8
		4D butenolides	2014	1	–

Source: T.C. Sparks, R. Nauen/Pesticide Biochemistry and Physiology 121 (2015) 122–128

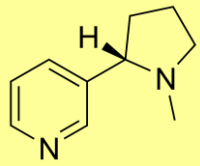
The IRAC insecticides classification[2] (see table above) indicates that the fourth group of insecticides corresponds to the nicotinic acetylcholine receptor agonist substances, divided into 4 families: nicotine, néonicotinoïdes, sulfoximines and butenolides.

[1] Flupyradifurone: a brief profile of a new butenolide insecticide. Nauen R, Jeschke P, Velten R, Beck ME, Ebbinghaus-Kintscher U, Thielert W, Wölfel K, Haas M, Kunz K, Raupach G. Pest Manag Sci. 2015 Jun;71(6):850-62. doi: 10.1002/ps.3932. Epub 2014 Nov 27.
Sulfoxaflor and the sulfoximine insecticides: chemistry, mode of action and basis for efficacy on resistant insects. Sparks TC, Watson GB, Loso MR, Geng C, Babcock JM, Thomas JD. Pestic Biochem Physiol. 2013 Sep;107(1):1-7. doi: 10.1016/j.pestbp.2013.05.014. Epub 2013 Jun 13. Review.
[2] IRAC: Mode of action classification and insecticide resistance management. Sparks TC, Nauen R. Pestic Biochem Physiol. 2015 Jun;121:122-8. doi: 10.1016/j.pestbp.2014.11.014. Epub 2014 Dec 4.

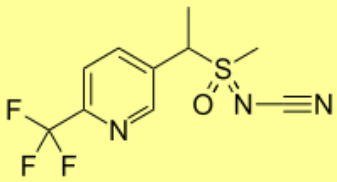
IRAC itself indicates that it is the mode of action (as well as its resistance pattern) that defines the category an insecticide belongs to, not the structure[3]. The IRAC was created by CropLife international (the "voice and leading advocates for the plant science industry »[4]), Dow, and Bayer, all of whom are also active members of the classification committee (named "Mode of action committee")[5]. IRAC members thus seem not to be respecting the rules they created. According to the mode of classification from IRAC[3], nitroguanidine, cyanoamidines, sulfoximines and butenolides should be "subgroups" of the neonicotinoid insecticides class.

In our view, these two publications, that strongly rely on the work from the IRAC do not aim at increasing scientific knowledge but are communication tools used by companies in order to avoid the "bad reputation" that neonicotinoids currently have. The arguments developed by Dow and Bayer to exclude sulfoximines and butenolides from neonicotinoids are not scientifically relevant as we further detail in this document. These substances are neonicotinoids and must be treated accordingly by risk managers. The risk that those systemic insecticides pose to pollinators and the environment must be recognised and prevented.

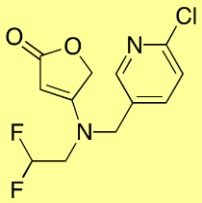
<u>In conclusion:</u> the pesticides industry defines itself what category their own insecticide is part of.



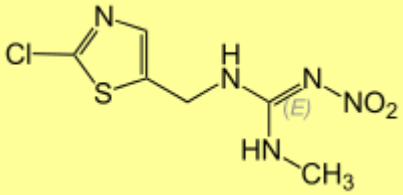
Nicotine



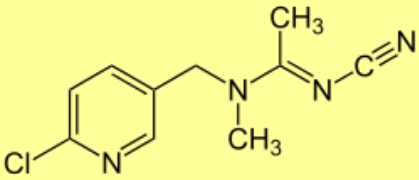
Sulfoxaflor



Flupyradifurone



Clothianidin (N-nitroguanidine)



Acetamiprid (N-cyanoamidines)

[3] http://www.irac-online.org/documents/new-actives-for-moa-classification-procedure/?ext=pdf
[4] http://croplife.org/about/ Consultation on 24 February 2016
[5] http://www.irac-online.org/documents/moa-team-update-2014/?ext=pdf

II. What is a neonicotinoid ?

Neonicotinoid: literally, « new nicotine-like substance ». Nicotine has a long history of use in agriculture while imidacloprid (the first industrial neonicotinoid) was developed in Japan in 1985[6].

Despite of its frequent use in scientific literature, in the press or in politics, there is no clear scientific definition of the term "neonicotinoid".

Yamamoto and Casida (1999)[7] wrote "*« Nicotinoid insecticides » is the terminology used (…) to include nicotine and the synthetic analogs of discernable structural and conformational similarities and the same mode of action in insects". The authors then explain that "subsequent chemical structures become increasingly dissimilar from the nicotine and imidacloprid prototypes. "Neonicotinoids" as a term emphasized the relationship to nicotine and implied their improved properties (...)."*
According to the authors, it is thus not surprising that neonicotinoids become more and more dissimilar to nicotine with the creation of new molecules. Indeed, 17 years after Yamamoto and Casida's publication, the examination of the chemical structure of all official neonicotinoids[8] confirms their assertion.

Structurally, nicotine is composed of two rings: a hexagonal pyridine and a pentagonal pyrrolidine. None of these rings can be considered a characteristic of neonicotinoids as the previously existing neonicotinoids do not always present them. Neonicotinoids differ in their molecular structure among themselves as well as with nicotin. What makes neonicotinoids different from nicotin, is their selective toxicity to insects, due to their different binding mode with the acetylcholine receptor. This selectivity can be obtained with different molecular structures and chemical compositions. Neonicotinoids' insecticidal properties thus do not rely on a conserved structure.
Furthermore, among official neonicotinoids, there are already 2 different families based on their structure: the N-nitroguanidines (imidacloprid, clothianidin and thiamethoxam) and the N-cyanoamidines (acetamiprid and thiacloprid)[9].

The link between neonicotinoids is their mode of action (agonists of nicotinic acetylcholine receptors) and their systemicity, not their structure. The definition of a neonicotinoid could thus be: "Synthetic and systemic molecule with a mode of action comparable to that of nicotine (agonist of nicotinic acetylcholine receptors)". Thus, "neonicotinoid" does not refer to a specific chemical family but rather to a superfamily of nicotine-like insecticides.

<u>In conclusion:</u> neonicotinoid is a superfamily that comprises several chemical families such as nitroguanidines and cyanoamidines, sulfoximines and butenolides.

[6] Source : Bayer website : http://www.seedgrowth.bayer.com/explore/100%20years%20of%20innovation/imidacloprid
[7] Nicotinoid Insecticides and the Nicotinic Acetylcholine Receptor, Yamamoto and Casida, 1999
[8] « Official neonicotinoids » refers to the active substances classified as such.
[9] Molecular features of neonicotinoid pharmacophore variants interacting with the insect nicotinic receptor. Ohno I, Tomizawa M, Durkin KA, Naruse Y, Casida JE, Kagabu S. Chem Res Toxicol. 2009 Mar 16;22(3):476-82. doi: 10.1021/tx800430e.

III. Sulfoxaflor and neonicotinoids

Sparks *et al.* (2013)[1] explain in detail why sulfoxaflor cannot be categorised a neonicotinoid (§2.2). However, none of their arguments are coherent:

1. Following the authors, chemicals presenting the same mode of action can belong to different chemical families (e.g. carbamates, organophosphates). It is actually the same for the subdivision of neonicotinoids in 2 structure-based families: N-cyanoamidines and N-nitroguanidines. But these 2 subgroups are still bound by a similar mode of action and are classified as neonicotinoids, following the IRAC rules of classification. Sulfoximine and butenolides should thus be classified as neonicotinoids as well.

2. The authors state that "It is the presence of this sp3 nitrogen in association with a conjugated electron withdrawing group that led to the definition of ''neonicotinoid'' [13-14]". In the references provided for this assertion[10], it is not written anywhere that a neonicotinoid is defined by the sp3 nitrogen. The authors of these publications explain the characteristics of neonicotinoids: high affinity for acetylcholine receptors and they explain the molecular features that lead to this affinity. They do not provide a definition of what a neonicotinoid is and what it should be as Sparks *et al.* imply. Thus Sparks et al. provided misleading information by referencing publications that do not support their premise.
3. Basing their findings on IRAC classification is also irrelevant, as explained before: it is unacceptable for the industry to design its own classification rules. Further, the authors refer to themselves to justify the classification. This is not scientifically acceptable.

4. The authors indicate that sulfoxaflor currently does not present cross resistance with other neonicotinoids. However, among official neonicotinoids, cross resistance is not a criterion for classification. For example, Roditakis *et al.* (2011) discovered a neonicotinoid resistance pathway in silverleaf whitefly (*Bemisia tabaci*). It resisted to imidacloprid (N-nitroguanidine) as well as to clothianidin (N-nitroguanidine) and thiacloprid (N-cyanoamidine) but not acetamiprid (N-cyanoamidine) or thiamethoxam (N-nitroguanidine).

5. Dow competitor Syngenta published an article indicating that sulfoxaflor is a neonicotinoid (Cutler *et al.* 2013)[11].

6. Finally, in the conclusions of a court case opposing environmental NGOs and the US Environmental Protection Agency, the US Court of Appeal for the Ninth Circuit states: "Sulfoxaflor (…)is currently the only member of a subclass of neonicotinoids called sulfoximines"[12].

<u>In conclusion:</u> sulfoxaflor has the same mode of action as nicotine, it is systemic, it is thus a neonicotinoid.

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[10] Structure-Activity Relationships of Nicotinoids and Imidacloprid Analogs. Tomizawa M. and Yamamoto I. J. Pesticide Sci. 18, 91-98 (1993)
Nicotine to nicotinoids: 1962–1997, in: I. Yamamoto, J.E. Casida (Eds.), Nicotinoid Insecticides and the Nicotinic Acetylcholine Receptor, Springer, New York, 1999, pp. 3–27.

[11] Investigating the mode of action of sulfoxaflor: a fourth-generation neonicotinoid. Cutler P, Slater R, Edmunds AJ, Maienfisch P, Hall RG, Earley FG, Pitterna T, Pal S, Paul VL, Goodchild J, Blacker M, Hagmann L, Crossthwaite AJ. Pest Manag Sci. 2013 May;69(5):607-19. doi: 10.1002/ps.3413. Epub 2012 Oct 30.

[12] http://cdn.ca9.uscourts.gov/datastore/opinions/2015/09/10/13-72346.pdf

IV. Flupyradifurone and neonicotinoids

The same reasoning prevails for flupyradifurone (butenolide). Being an agonist to nicotinic acetylcholine receptor, flupyradifurone is structurally close to imidacloprid (N-nitroguanidine) with whom it also shares a common metabolite (6-chloro-nicotine[13]). The arguments developed by Bayer (Jeschke 2015)[14] to not classify flupyradifurone as a neonicotinoid are comparable to the ones from Dow: distinct structure and no cross-resistance with imidacloprid. Further, another Bayer sponsored publication (Nauen *et al.* 2015)[15] refers to the Tanimoto index to justify a difference in chemical structure between neonicotinoids and flupyradifurone. As explained previously, the mode of action and not the structure is the correct way to characterize neonicotinoids.

In conclusion: flupyradifurone is an agonist of the nicotinic acetylcholine receptors, it is systemic, it thus belongs to the neonicotinoids superfamily.

V. General conclusion

This factsheet has demonstrated how pesticide companies make use of pseudo-science to give their new pesticides a more positive image. In the frame of the ever greater interest of the general public in the relation between pesticide use and health damage, including bee health, the fact that pesticide companies themselves decide what category a pesticide belongs to, for mere regulatory or marketing purposes should not be authorised.

Sulfoxaflor and flupyradifurone are neonicotinoid insecticides. They should be treated accordingly by regulator, taking into account their systemicity and the harm they could cause to non-target organisms such as bees.

[13] Source : Draft Assessment Report, Flupyradifurone, European Commission, janvier 2014

[14] Flupyradifurone (Sivanto™) and its novel butenolide pharmacophore: Structural considerations. Jeschke P, Nauen R, Gutbrod O, Beck ME, Matthiesen S, Haas M, Velten R. Pestic Biochem Physiol. 2015 Jun;121:31-8. doi: 10.1016/j.pestbp.2014.10.011. Epub 2014 Oct 24. Review.

[15] Flupyradifurone: a brief profile of a new butenolide insecticide. Nauen R, Jeschke P, Velten R, Beck ME, Ebbinghaus-Kintscher U, Thielert W, Wölfel K, Haas M, Kunz K, Raupach G. Pest Manag Sci. 2015 Jun;71(6):850-62. doi: 10.1002/ps.3932. Epub 2014 Nov 27.