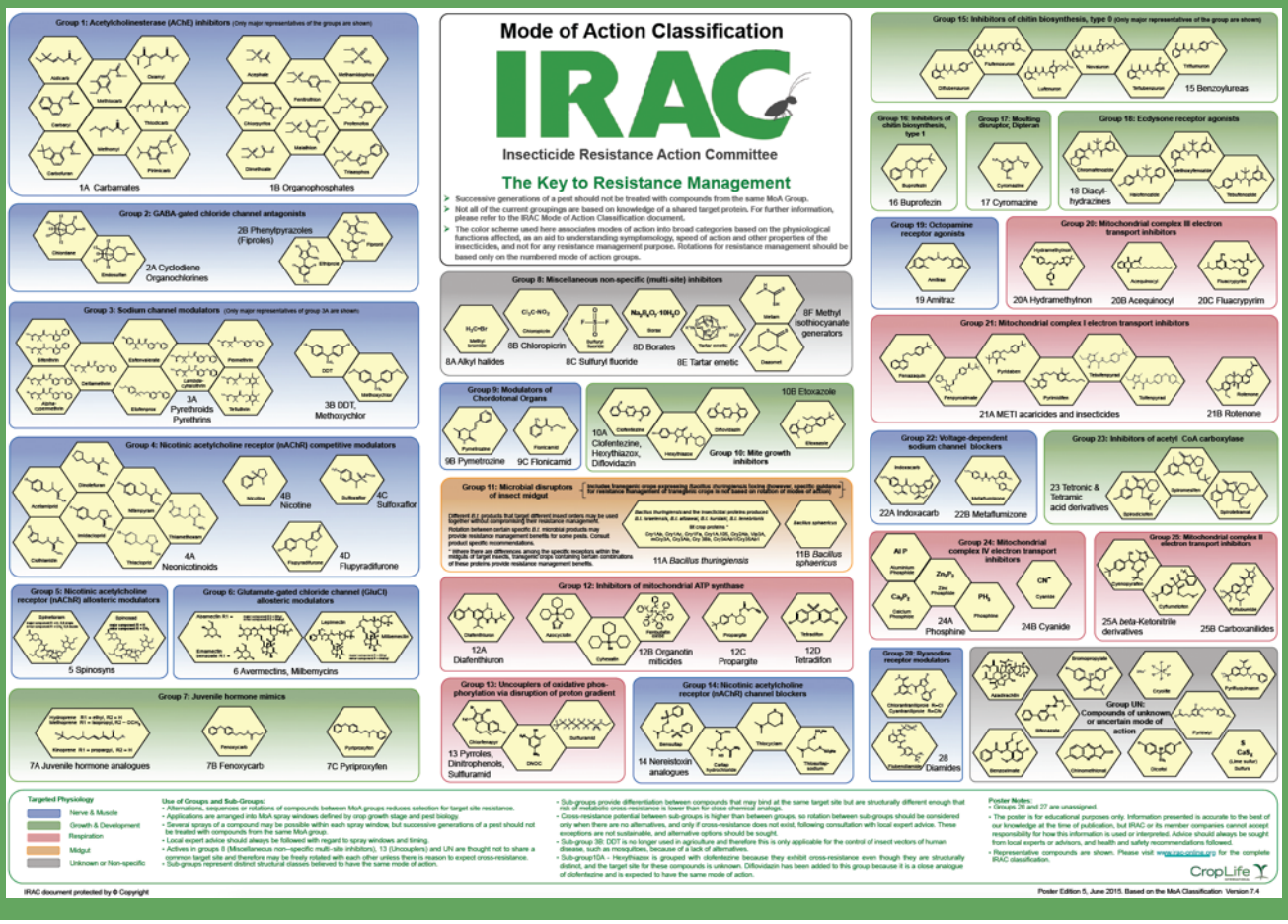
IRAC
Insecticide Resistance Action Committee
eConnection

About This Issue

This edition of the eConnection Newsletter is focused on the important area of Mode of Action (MoA). The IRAC MoA Classification Scheme in its simplest form has been around almost as long as the IRAC organisation. As more active ingredients have been developed and more information discovered about their different modes of action, the classification scheme has evolved with now more than 25 main groups, many of which are divided into sub-groups. IRAC promotes the Classification Scheme as a key tool and the basis for effective and sustainable insecticide and acaricide resistance management. The latest edition of the IRAC MoA Classification Scheme (version 7.4) has just been published on the IRAC website (www.irac-online.org) and hence we have devoted this edition of eConnection to update you on some of the MoA resources available from IRAC along with a brief review of the importance of MoA in resistance management and finishing up with a summary of the changes in the latest version of the Classification Scheme

The best source for MoA information is the IRAC website (www.irac-online.org). The 26-page IRAC MoA Classification Scheme (v. 7.4) is available in full with a group-by-group listing as well as a list of the active ingredients in alphabetical order. Lots of other resources are also available via the IRAC website including the MoA Mobile App, the MoA Mini-booklet and various MoA pest-specific posters as well as the MoA poster showing the chemical structures available in six different languages (Fig. 1). Printed copies of the booklet and the English version of the structures poster are available from the IRAC Coordinator via the website. (Note: some of the resources are in the process of being updated to reflect the changes in the Classification Scheme version 7.4).

Figure 1. IRAC MoA Structure poster showing the different Groups and subgroups. Colors represent the targeted physiology. Blue – nerve & muscle, green – growth & development, red – respiration, brown – midgut, grey – unknown / nonspecific.



Insecticide Resistance Management & MoA Classification - A review

Since the first paper documenting insecticide resistance was published a little more than 100 years ago[1] and the subsequent rapid introduction of the synthetic organic insecticides starting in the 1940s, the number of cases of insecticide resistance has expanded rapidly in the 1960s-1980s and continues to climb, albeit at a lesser rate since 1990 (Fig. 2).

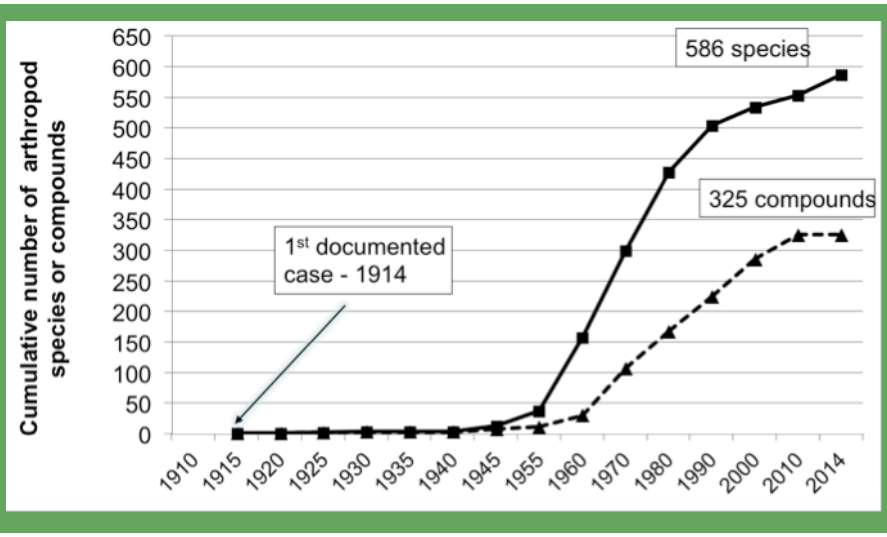


Figure 2. Cumulative increase in the number of species resistant to one or more insecticides or acaricides, and the number of insecticides and acaricides for which one or more species has shown resistance.

Data adapted from [2,17,18] and David Mota-Sanchez, Michigan State University, personal communication, 2014.

In the past two decades, there has been a dramatic consolidation in the agrochemical industry resulting in far fewer companies able or willing to undertake the discovery and development of new insect control options[2], potentially limiting the number of new insecticidal tools with new modes of action. As such, insecticide resistance management (IRM) has become a critical consideration in seeking to preserve the future efficacy of existing and new insecticides.

Agrochemical companies have long recognized the importance of, and need for effective, proactive resistance management[3-10] which, in part, gave rise to IRAC 30 years ago (1984). IRAC has a two-fold mission:

1) Facilitate communication and education on insecticide and trait resistance
2) Promote the development and facilitate the implementation of insecticide resistance management strategies to maintain efficacy and support sustainable agriculture and improved public health.

Among the insecticide-based IRM approaches, alternation/rotation/sequences of insecticides are one of the more direct / simplest to execute having the fewest assumptions regarding the implementation[11,12]. A rotation approach uses a "window" or block strategy[10] that is frequently defined by the length of a pest generation or crop growth stage[13-15], and ideally involves the rotation of insecticides with different MoAs to minimize selection of cross-resistance[15]. The IRAC MoA Classification Scheme (Table 1) provides a means to select insecticide options for these types of rotation schemes by providing up-to-date information on the MoA of existing and newly registered insecticides and acaricides.

Among the more than 25 MoAs (main groups) currently in the IRAC classification (Table 2), 85% of the end-user market value of these MoAs is derived from insecticides that act on the insect nerve - muscle system (Fig. 3). In contrast, insecticides altering growth and development account for only 9% of the total insecticides sales, while those disrupting energy production (respiration targets) account for only 4% (Fig. 3).

In addition to the current groups and subgroups listed in the MoA Classification Scheme, there are a number of insecticides in development targeting new / undetermined target sites in development[16,17]. However, the ongoing expansion of insecticide resistance and regulatory requirements can limit any new and existing insect and mite control options in IPM and IRM programs. Thus, it is vitally important that any new insecticide / miticide / MoA option(s), be viewed as a limited resource that needs to be used with care, to minimize the chances for resistance development and ensure utility far into the future.

Some of the insect and mite pests have a long history of developing resistance to nearly any insecticide or acaricide used for their control (Table 1). Perhaps not surprisingly, nearly all members of this set of high-risk pest arthropods have hundreds of cases of resistance documented (Table 1). A common set of characteristics for these pests includes high mobility, a short generation time, high fecundity, and being pests of crops where there may be few other control options or where little damage can be tolerated. In light of their history, IRM and IPM programs targeting these high-risk species may require special attention when a new insecticide or acaricide tool is introduced.

The increasingly complex and expensive process of discovering and developing new insect and mite control products requires that the current and new insecticide and acaricide tools be used wisely to safeguard their long-term efficacy and utility. The IRAC MoA Classification Scheme, the associated MoA labeling, and IRM recommendations are tangible evidence of the agrochemical industry's commitment to providing sustainable, long-term pest arthropod control options. IRM is of vital importance and is key to ensuring that current and future arthropod control tools are not mis-used or over-used and continue to be available to address the expanding global need for the production of food and fiber as well as for improved public health.

This IRAC eConnection article is a brief summary of a recently published paper on the IRAC MoA classification scheme and its implications for IRM (*T.C. Sparks & R. Nauen (2015) Pesticide Biochemistry and Physiology;* http://dx.doi.org/10.1016/j.pestbp.2014.11.014)

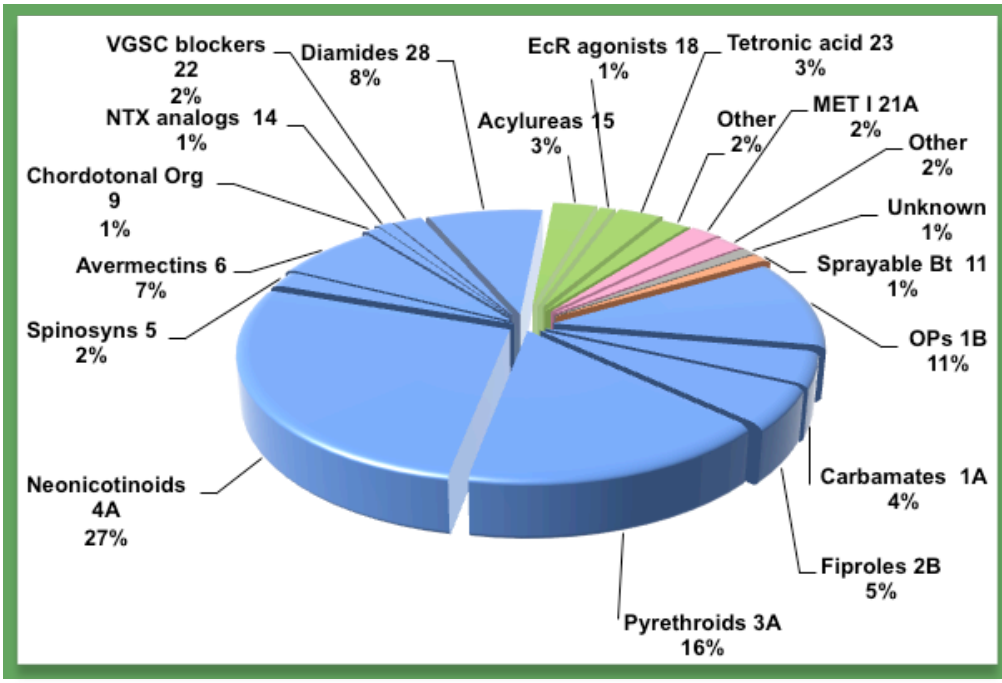


Figure 3. Distribution of total insecticide sales (percent of total value) by IRAC MoA Group or Subgroup.

Colors correspond to the targeted physiology shown in Table 2.

Total value = $17 billion, excludes fumigants. Based on 2013 End-user sales data from Agranova July 2014.

Table 1. Top 10 Arthropod Species at High Risk for Resistance[1]

# Cpds[1]	# Cases[2]	Species	Common Name	Order
93	414	*Tetranychus urticae*	two-spotted spider mite	Acari
91	576	*Plutella xylostella*	diamondback moth	Lepidoptera
75	402	*Myzus persicae*	green peach aphid	Hemiptera
58	303	*Musca domestica*	house fly	Diptera
54	555	*Bemisia tabaci*	sweetpotato whitefly	Hemiptera
54	279	*Leptinotarsa decemlineata*	Colorado potato beetle	Coleoptera
48	231	*Aphis gossypii*	cotton aphid	Hemiptera
48	197	*Panonychus ulmi*	European red mite	Acari
47	692	*Helicoverpa armigera*	cotton bollworm	Lepidoptera
44	167	*Boophilus* microplus*	southern cattle tick	Ixodida

[1] Based on the number of different compounds for which resistance has been reported. Data from the Arthropod Resistance Database, July 2014.
[2] Number of unique instances of resistance reported for each species Arthropod Resistance Database in the July 2014.
* *Rhipicephalus*

Table 2. IRAC Mode of Action Classification. The colour scheme associates mode of action into broad categories based on the physiological functions affected, as an aid to understanding symptomology, speed of action and other properties of the insecticides, and not for any resistance management purpose. Rotations for resistance management should be based only on the numbered mode of action groups. (Table taken from the MoA page on the IRAC website: www.irc-online.org)

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IRAC Insecticide Mode of Action Classification (Version 7.4) - Summary of updates

Version 7.4 of the IRAC MoA Classification includes a number of new active ingredients and the renaming of some groups.

Triflumezopyrim, a new insecticide currently in development at DuPont was added to the classification well in advance of expected registration. As the classification is intended to include materials currently on the market we have created Appendix 6, which lists classified compounds pending registration. Triflumezopyrim acts at the agonist binding site of the nicotinic acetylcholine receptor, where group 4 compounds act, but it is not an agonist, necessitating the renaming of Group 4 from nicotinic acetylcholine agonists to nicotinic acetylcholine receptor competitive modulators. For consistency, we also renamed Group 5 from nicotinic acetylcholine receptor allosteric activators to nicotinic acetylcholine receptor allosteric modulators and Group 6 from glutamate-gated chloride channel allosteric activators to glutamate-gated chloride channel allosteric modulators.

The new Nihon Nohyaku acaricide pyflubumide received registration and was launched in Japan earlier this year. It inhibits mitochondrial electron transport complex II and appears to act at the same site as the current Group 25 *beta*-ketonitrile derivatives, cyenopyrafen and cyflumetofen. Available data indicate that spider mites with metabolic resistance to *beta*-ketonitrile derivatives are not cross-resistant to the carboxanilide pyflubumide. Accordingly, Group 25 was divided into two sub-groups, 25A, the *beta*-ketonitrile derivatives and 25B, carboxanilides.

IRAC MoA Classification version 7.4, May 2015

See section 7.4 for further information on sub-groups.
See section 7.3 for criteria for descriptors of the quality of MoA information.

Main Group and Primary Site of Action	Chemical Sub-group or exemplifying Active Ingredient	Active Ingredients
25 **Mitochondrial complex II electron transport inhibitors** Energy metabolism {Good evidence that action at this protein complex is responsible for insecticidal effects}	**25A** *Beta*-ketonitrile derivatives	Cyenopyrafen, Cyflumetofen
	25B Carboxanilides	Pyflubumide

Other additions to the classification document included insecticides already on the market. A new sub-group 8F was added to Group 8, miscellaneous non-specific (multi-site) inhibitors. 8F – methyl isothiocyanate generators includes dazomet and metam. Also, sulfur and lime sulfur were added to Group UN. Appendix 5 of the classification is intended to be a comprehensive listing of IRAC-classified insecticides. Accordingly, calcium cyanide, potassium cyanide, sodium cyanide, boric acid, disodium octaborate, sodium borate and sodium metaborate were added to the list.

Furthermore, a number of changes in the introductory text and appendices were made to clarify the scope of the classification and procedures for getting new active ingredients classified by IRAC and labeled correctly with the IRAC classification.

The first addition was a scope statement to clarify what types of insect control agents are included in the classification. “The IRAC classification is intended to cover insecticides and acaricides acting at specific target sites where mutations could confer cross-resistance to all compounds acting at the same site. Some insecticides and acaricides also control nematodes, but selective nematicides are not included in the classification. Insecticidal oils, soaps, living organisms and viruses that are not known to act at specific target sites are currently not included. Uncouplers and non-specific (multi-site) inhibitors also do not act at specific target sites but are included.”

Additional text was added to make very clear that inclusion of the IRAC group on a product label is a warrant from the manufacturer that the insecticide has been classified by IRAC itself and is listed in Appendix 5 of the classification document, which is intended to be comprehensive. Only IRAC may confer an IRAC classification to a product. If an insecticide is not listed in Appendix 5 and falls within the stated scope of the IRAC classification, the manufacturer is given explicit instructions as to how to petition IRAC for classification of the product before drafting a label. It is further stated that insecticidal materials falling outside the scope of the classification, including insecticidal oils, soaps, living organisms and viruses, may be labeled as “Exempt from IRAC Classification”. Text, links and an online form are provided on the website to facilitate this process. The MoA Working Group wishes to make the process transparent and discourage manufacturers from classifying their own products, which is invalid.

Disclaimer

This eConnection Newsletter was prepared by the IRAC MoA Working Group supported by the 13 member companies of the IRAC Executive. If you have information for inclusion in the eConnection or feedback on this issue please email aporter@intraspin.com.

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