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Insecticides, biologics and nematicides: Updates to IRAC's mode of action classification - a tool for resistance management

Thomas C. Sparks[a,1], Andrew J. Crossthwaite[b,*], Ralf Nauen[c], Shinichi Banba[d], Daniel Cordova[e], Fergus Earley[b], Ulrich Ebbinghaus-Kintscher[c], Shinsuke Fujioka[f], Ayako Hirao[g], Danny Karmon[h], Robert Kennedy[i], Toshifumi Nakao[d], Holly J.R. Popham[j], Vincent Salgado[k], Gerald B. Watson[a], Barbara J. Wedel[k], Frank J. Wessels[a]

[a] Corteva Agriscience, Discovery Research, 9330 Zionsville Road, Indianapolis, IN 46268, USA
[b] Syngenta Crop Protection, Jealott's Hill International Research Centre, Bracknell Berkshire RG42 6EY, UK
[c] Bayer AG, Crop Science Division, R&D, Alfred-Nobel Str. 50, 40789 Monheim am Rhein, Germany
[d] Mitsui Chemicals Agro Inc., Agrochemical Research Center, Mobara, Chiba 297-0017, Japan
[e] FMC Agricultural Solutions, Stine Research Center, 1090 Elkton Rd., Newark, DE 19711, USA
[f] Nihon Nohyaku Co. Ltd., Research Center, Research Division, 345 Oyamada-cho, Kawachinagano, Osaka 586-0094, Japan
[g] Sumitomo Chemical Company, Ltd., AgroSolutions Division-International, Tokyo Sumitomo Twin Bldg., East 27-1 Shinkawa 2- Chome, Tokyo, Japan
[h] Adama Agricultural Solutions, Airport City, Golan Street, 7015103, Israel
[i] Vestaron, 4717 Campus Dr, Suite 1200, Kalamazoo, MI 49008, USA
[j] AgBiTech, 14401 Soverign Rd, Fort Worth, TX 76155, USA
[k] BASF Corporation, Agricultural Solutions, 26 Davis Drive, Research Triangle Park, Raleigh, NC, 27709, USA

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ABSTRACT

Insecticide resistance has been and continues to be a significant problem for invertebrate pest control. As such, effective insecticide resistance management (IRM) is critical to maintain the efficacy of current and future insecticides. A technical group within CropLife International, the Insecticide Resistance Action Committee (IRAC) was established 35 years ago (1984) as an international association of crop protection companies that today spans the globe. IRAC's focus is on preserving the long-term utility of insect, mite, and most recently nematode control products through effective resistance management to promote sustainable agriculture and improved public health. A central task of IRAC has been the continual development and documentation of the Mode of Action (MoA) Classification scheme, which serves as an important tool for implementing IRM strategies focused on compound rotation / alternations. Updates to the IRAC MoA Classification scheme provide the latest information on the MoA of current and new insecticides and acaricides, and now includes information on biologics and nematicides. Details for these new changes and additions are reviewed herein.

1. Introduction

Insect resistance to insecticides has been and continues to be a critical concern impacting pest insect control globally. At present, there are more than 16,000 documented cases of insecticide resistance involving more than 600 insect and mite species that have developed

Abbreviations: ACCase, acetyl CoA carboxylase; AChE, acetylcholinesterase; AI, active ingredient; APRD, Arthropod Pest Resistance Database; Bt, *Bacillus thuringiensis*; CC, chloride channel; CSI, chitin synthase inhibitor; EC-R, ecdysone receptor; FRAC, Fungicide Resistance Action Committee; GGCC, GABA-gated chloride channel; Glu-Cl, Glutamate gated chloride channel; GMO, genetically modified organism; GV, granuloviruses; IRAC, Insecticide Resistance Action Committee; IPM, Integrated Pest Management; IRM, Insecticide Resistance Management; JH-R, juvenile hormone receptor; MET, mitochondrial electron transport; MoA, Mode of Action; nAChR, nicotinic acetylcholine receptor; Nema, nematicide; nc, not yet classified; NP, natural product; NPV, Nucleopolyhedrovirus; N-UN, nematicide: unknown or uncertain MoA; OA-R, octopamine receptor; Ox-Ph, oxidative phosphorylation; PIF, per os infectivity factor; RNAi, RNA interference; Ry-R, ryanodine receptor; TRPV, transient receptor potential cation channel vanilloid subtype; VGSC, voltage gated sodium channel; WG, working group; UN, unknown or uncertain mode of action

* Corresponding author at: Syngenta Crop Protection, Jealott's Hill International Research Centre, Bracknell Berkshire RG42 6EY, UK.
E-mail address: andrew.crossthwaite@syngenta.com (A.J. Crossthwaite).
[1] Retired, Present address, Agrilucent LLC, Greenfield IN 46140, USA.

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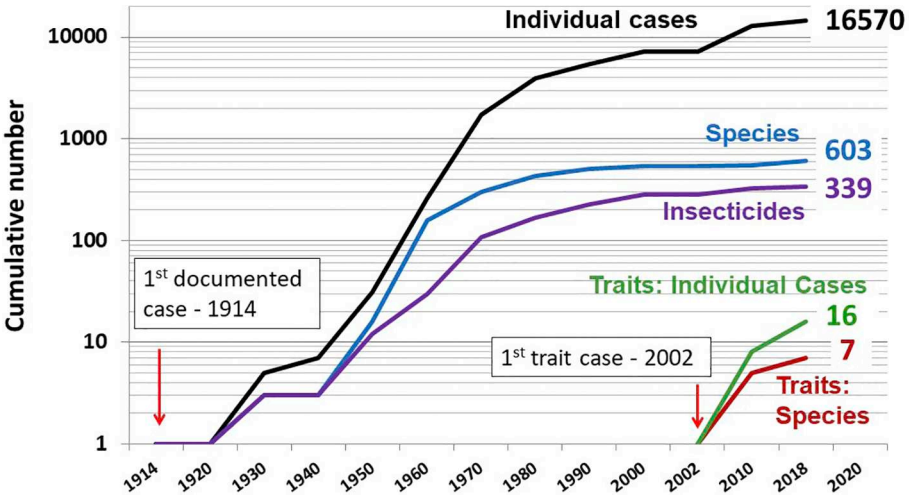

Fig. 1. Cumulative increase in a) the number of species resistant to one or more insecticides (blue line), b) number of insecticides for which one or more species has shown resistance (purple line), and c) number of GMO traits for which resistance has been reported (red line). Data adapted from (Whalon et al., 2008; Sparks and Nauen, 2015; Tabashnik and Carriére, 2017; Nauen et al., 2019), and David Mota-Sanchez, Michigan State University, personal communication, 2019. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Top 15 Resistant Insect Species[a].

Rank[a] - species	Common name	Order	AI–cases[b]	AI-cases	AI-cases
			2002[c]	2019[d]	Change since 2002
1 *Tetranychus urticae*	Two-spotted spider mite	Acari	69–232	96–517	27–285
2 *Plutella xylostella*	Diamondback moth	Lepidoptera	69–168	96–866	26–698
3 *Myzus persicae*	Green peach aphid	Homoptera	68–247	80–469	12–222
4 *Bemisia tabaci*	Sweetpotato whitefly	Homoptera	32–50	64–631	32–581
5 *Musca domestica*	House fly	Diptera	26–58	64–398	38–340
6 *Leptinotarsa decemlineata*	Colorado potato beetle	Coleoptera	38–124	56–300	18–176
7 *Boophilus** *microplus*	Southern cattle tick	Ixodida	40–87	50–562	10–475
8 *Aphis gossypii*	Cotton aphid	Homoptera	27–37	50–281	23–244
9 *Helicoverpa armigera*	Cotton bollworm	Lepidoptera	25–74	48–856	23–782
10 *Panonychus ulmi*	European red mite	Acari	38–172	48–196	10–24
11 *Blattella germanica*	German cockroach	Blattodea	40–162	43–279	3–117
12 *Culex quinquefasciatus*	Southern house mosquito	Diptera	28–173	41–298	13–125
13 *Spodoptera frugiperda*	Fall armyworm	Lepidoptera	–[e]	41–143	–
14 *Spodoptera litura*	Mediterranean climbing cutworm	Lepidoptera	–	40–667	–
15 *Spodoptera exigua*	Beet armyworm	Lepidoptera	–	40–576	–

[a] Ranking based on the number of different active ingredients (AI) for which resistance has been reported.
[b] Number of unique active ingredients (AI) – cases of resistance reported for each species.
[c] Data adapted from Mota-Sanchez et al. (2002); number of references = cases (D. Mota-Sanchez, personal communication, 12-9-2019).
[d] Data from APRD (Mota-Sanchez and Wise, 2019).
[e] not among the Top 20 resistant insect species in 2002.
* *Rhipicephalus.*

resistance to at least one insecticide (Fig. 1). In addition, seven insect species have developed resistance to one or more insecticidal traits, and there are more than 335 insecticides/acaricides for which there is at least one documented case of resistance (Fig. 1). Most of the primary pest species impacting the major crops and human health have developed resistance to many of the available insecticides since the introduction of synthetic organic insecticides some 75 years ago (Georghiou and Mellon, 1983, Whalon et al., 2008, Sparks and Nauen, 2015, Mota-Sanchez and Wise, 2019). Due to agronomic practices, pest biology and genetics, global crop range and potential for crop damage, some of these key insect and mite pests (Table 1) are associated with resistance to 40 or more different insecticides or acaricides, with the top pests exhibiting resistance to nearly 100 different insecticides (Table 1). As might be expected, cases of resistance for these top pests continue to increase, in some cases substantially. Since 2002 some of the most important insect and mite pest species exhibit new examples of more than 200 to 690 new cases of resistance involving more than 20 to 35 additional insecticides (Table 1), further emphasizing the continued impact of insecticide resistance, and the need for effective insecticide resistance management (IRM) (Borel, 2017; Tabashnik and Carriére, 2017).

Although insecticides are just one component of most current integrated pest management (IPM; integration of multiple practices for the economic control of pests while minimizing risks to human health and the environment) and vector control programs, they remain important tools. Resistance to current and newly developed insecticides and acaricides continues to be a concern, impacting insect and mite control options and decisions for growers around the world. Importantly, insecticide resistance has been and remains one of the key considerations and drivers in the discovery and development of new insect and mite control compounds (Lamberth et al., 2013; Maienfisch and Stevenson, 2015; Sparks and Lorsbach, 2017a). Likewise, given the ever-increasing costs, regulatory hurdles, time, complexities and uncertainties involved in insecticide discovery (Lamberth et al., 2013; Maienfisch and Stevenson, 2015; Sparks and Lorsbach, 2017a), effective insecticide resistance management (IRM) is also critical to preserving the utility and investment related to current as well as future insect and mite control options.

In addition to conventional insecticides and acaricides, interest in natural products (NPs) and biologics as insect and mite control options has been increasing. In part, this interest in biologics and NPs is in response to consumer concerns with conventional insect control

products and the comparatively simpler regulatory requirements involved in their registration, which reduces the time and cost of development (Marrone, 2014, 2019). Biologics are thus an increasingly attractive option for research and development by a number of crop protection companies (Phillips McDougall, 2019). As such it is also important to address their potential as tools in IRM programs as well as their potential for resistance.

2. IRAC - industry responding to insecticide resistance

The crop protection industry has long recognized the importance of, and need for effective, proactive resistance management (Jackson, 1986; Voss, 1988; McCaffery and Nauen, 2006). Thirty-five years ago (1984) the crop protection industry came together to address insecticide resistance through the formation of the Insecticide Resistance Action Committee (IRAC) (Voss, 1988; Ruscoe, 1987; Nauen et al., 2012). Now part of CropLife International, IRAC is an industry-based, technical working group made up of scientific experts from the member companies from across the globe (Nauen et al., 2012; Sparks and Nauen, 2015). Presently there are 11 member companies that make up IRAC; Adama, AgBiTech, BASF, Bayer AG, Corteva Agriscience, FMC, Mitsui Chemicals Agro, Nihon Nohyaku, Syngenta, Sumitomo, and United Phosphorus Limited (UPL) representing crop protection and vector control companies located in a range of countries around the globe including Australia, Germany, India, Israel, Japan, Switzerland and the US. A few companies such as Vestaron are solely members of individual Working Groups (WG), an option offered by IRAC to those companies interested to contribute in certain fields of interest. Additionally, there are also local IRAC regions / country teams located in Argentina, Asia, Australia, Brazil, Europe, India, Israel, Japan, Philippines, South Africa, Spain and the United States.

As outlined on the IRAC website (IRAC, 2019) and in several publications (Nauen et al., 2012, 2019; Sparks and Nauen, 2015), the goal of IRAC is to aid in preventing or delaying the development of resistance in insect and mite pests (Sparks and Nauen, 2015; IRAC, 2019) and part of its mission includes facilitating communication and education on insecticide and trait resistance. In addition, as outlined previously (Nauen et al., 2012; Sparks and Nauen, 2015), IRAC's mission also includes encouraging the development and implementation of IRM strategies to maintain efficacy of current and future insect control compounds to support sustainable agriculture and improved public health (IRAC, 2019). As part of IRAC's IRM programs, IRAC and its member companies, strongly support the mandatory or voluntary adoption of mode of action icons on pesticidal product labels. Resistance management depends on the alternation of different modes of action throughout and between growing seasons (Fig. 2) and therefore the clear and pronounced acknowledgement of the mode of action of the active ingredients contained in a pesticidal product is critical for implementing resistance management.

Among the numerous IRAC WGs, the Mode of Action (MoA) WG is charged with maintaining and updating the MoA Classification scheme, an important tool to facilitate IRM programs around the globe, and currently recognized as a key global authority on MoAs for insecticides and acaricides. The MoA WG is presently composed of representatives from member companies including Adama, AgBiTech, Bayer AG, BASF, Corteva Agriscience, FMC, Mitsui Chemicals Agro, Nihon Nohyaku, Sumitomo, Syngenta, and Vestaron.

3. IRAC mode of action Classification

The IRAC MoA Classification scheme categorizes insecticides based on their MoA, using the best information available from experts in industry, universities, research institutes, etc., and affords local, regional and global government agencies, growers, advisors, consultants, universities and extension staff with guidelines for the selection of insecticides and acaricides. References for MoA and target site- based resistance are available on the IRAC website (http://www.irac-online.org). The IRAC MoA Classification supports and facilitates IRM programs especially those focused on alternation or rotation-based programs (Roush, 1989; IRAC, 2019).

Because compounds can disrupt some of the more complex target sites in insects through effects at multiple binding sites, there can be multiple IRAC groups acting at same target proteins. Ligand-gated ion channels, for example, are large transmembrane proteins containing multiple domains forming an ion channel controlled by a receptor for an endogenous ligand. They can be disrupted by insecticides binding at the receptor site, within the ion channel itself, or at any of several potential modulatory sites that interfere with ion channel gating (Fig. 3). Incidentally, ligand-gated ion channels are often called receptors for the particular endogenous ligand that they respond to; nicotinic acetylcholine receptors (nAchR), GABA-gated chloride channels (GGCC) and glutamate-gated chloride channels (Glu-Cl) are all members of the Cys-loop ligand-gated ion channels or receptor superfamily.

Insecticides that bind at the receptor site compete with the endogenous ligand and are therefore called competitive modulators of that receptor. Group 4 insecticides, for example, are nicotinic acetylcholine receptor competitive modulators, and they may be agonists, which activate the receptor to open the ion channel, or antagonists, which occupy the receptor site without opening the channel, thereby preventing the endogenous ligand from doing its job. Agonists and antagonists are given the same IRAC mode of action group classification because they bind at the same site and could therefore be affected by the same target site mutations.

Insecticides that bind within the pore of the ion channel inhibit ion

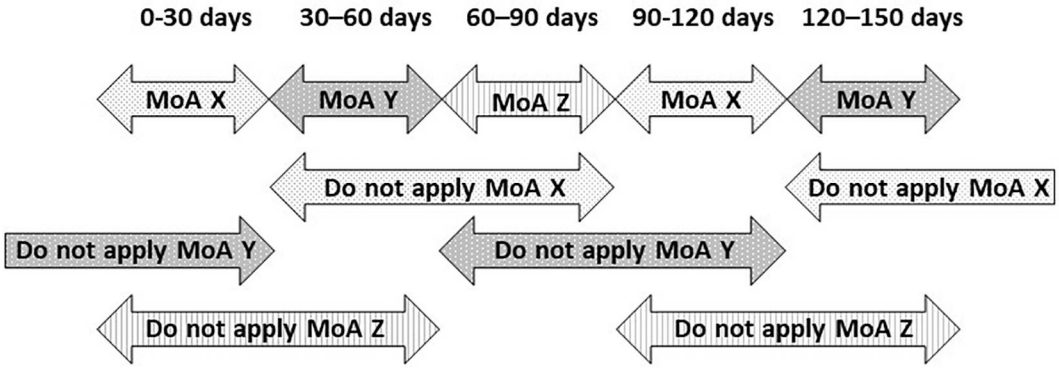

Fig. 2. Cartoon depicting an optimal MoA window scheme involving the rotation of three different insecticidal MoA groups through a growing season that avoids treating consecutive generations with the same MoA. See text for details.

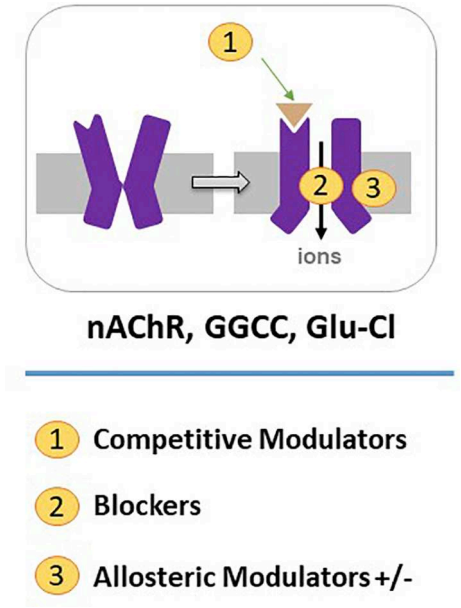

Fig. 3. Cartoon depicting possible interactions of compounds with ligand-gated ion channel targets.

flux, which is a potential mode of action at any ion channel, are called blockers,. Group 14 insecticides are nAChR channel blockers, Group 2 insecticides are GG-CC blockers, but for historical reasons are called antagonists, and Group 22 insecticides are voltage-dependent sodium channel blockers.

Insecticides that bind to ligand-gated ion channels at a site that is not the receptor site or the ion channel pore are called allosteric modulators, There are two IRAC groups for nAChR modulators: Group 5, acting at site I and Group 32, acting at site II (Table 2). While this classification does not specify whether these two sites are on the same target protein, unpublished results indicate that they are on two distinct nicotinic receptor subtypes. Group 6 insecticides are allosteric modulators of Glu-Cl and group 30 insecticides are allosteric modulators of GG-CC.

Compounds in the same MoA Group are all thought to act on the same target site. For example, carbamate (Group 1A) and organophosphorus (OP) (Group 1B) insecticides both act by inhibiting acetylcholinesterase (AChE); as such they are both placed in Group 1, AChE inhibitors (Table 2). Thus, it is the Group number that is associated with a specific MoA as shown in Table 2. Compounds in sub-groups within a particular MoA Group still share the same MoA, as illustrated by the OPs and carbamates, even though they represent different classes of chemistry. Since the goal of the MoA Classification scheme is to reduce the likelihood of selecting for resistance, compounds sharing the same Group number should not be rotated since the chances of selecting for a target site-based resistance that could confer resistance to all compounds within that Group may be higher than for compounds in different Groups (IRAC, 2019; Nauen et al., 2019). While there may be instances where rotation of compounds in different sub-groups within a particular Group might be considered, IRAC guidelines emphasize this option is the least desirable option, only to be considered in circumstances where no other effective options are available (IRAC, 2019, Nauen et al., 2019).

The IRAC MoA Classification scheme is constantly updated as new information becomes available (Wege and Leonard, 1994; McCaffery and Nauen, 2006; Elbert et al., 2007; Nauen et al., 2012, 2019; Sparks and Nauen, 2015), and the present update reflects IRAC's long standing commitment to widely share this information (see Table 2). As part of the present update, a section on biologics has been added (Table 2) reflecting the increasing interest in biologics as tools for the control of pest insects and mites, as well as options for IRM programs.

3.1. New insecticide MoA Groups added

The present update reflects several changes and additions of particular note, with several new Groups having been added (Table 2). As reported recently (Nauen et al., 2019), the mode of action of pymetrozine (Group 9B) has been found to be modulation of transient receptor potential cation vanilloid subtype (TRPV) channels in chordotonal organs (Nesterov et al., 2015). Likewise, the MoA of flonicamid (formerly 9C) has been shown to be distinct from pymetrozine (Kandasamy et al., 2017) and it has consequently been placed in a new Group (Group 29, Table 2). Additionally, a new sap-feeding insecticide, afidopyropen, was recently added to the MoA Classification scheme and has been shown to share the MoA of pymetrozine (Kandasamy et al., 2017), but as per IRAC guidelines (IRAC, 2019), afidopyropen's very different chemical structure and differential metabolism relative to other Group 9 insecticides, IRAC has placed it in a different subgroup, Group 9D (Table 2).

Three other new MoA Groups have also been recently added to the MoA Classification scheme. The first is Group 30, the meta-diamides / isoxazolines, as exemplified by broflanilide and isoxazoline insecticides (e.g. fluxametamide, isocycloseram), currently in commercialization or in late development. These insecticides act at an allosteric site in the GABA-gated chloride channel (Nakao and Banba, 2016; Asahi et al., 2018) (Table 2), representing a new MoA, and thus represent a new Group.

Another new Group addition to the IRAC MoA Classification scheme is Group 31 (baculoviruses) (Table 2). The baculovirus MoA is composed of at least nine proteins called per os infectivity factors (PIFs) found on the membrane of virus derived from occlusion bodies. Together these nine proteins form a complex capable of entering host midgut cells (Boogaard et al., 2018; Wang et al., 2019).

A third new addition, Group 32, encompasses a peptide-based insecticide (GS-omega/kappa HXTX-HV1A peptide) (Fanning et al., 2018) (Table 2), which acts as a positive modulator at an allosteric site in the insect nAChR that is distinct from that of the spinosyns (Group 5) or any other nAChR-acting insecticide (Chambers et al., 2019). This is the first example of a peptide-based insecticide to be included in the IRAC MoA Classification scheme and provides additional IRM options.

3.2. Biologics (new)

There has been an expanding interest in biologics as insect control tools (Copping and Menn, 2000, Glare et al., 2012, Gross et al., 2014, Marrone, 2014, Phillips McDougall, 2019). Reflecting this interest, and as noted above, IRAC has added biologics to the MoA Classification (Table 2). The IRAC Classification scheme is based on MoA and the specific MoAs of most biologics have not been identified. As such biologics have been arranged into four broad Groups in the section on unknown or undefined MoA that includes UNB - unknown non-*Bt* bacterial agents e.g. *Burkolderia* spp., UNE - botanical essence including synthetic extracts and undefined oils such as neem oil, UNF - fungal agents such as *Beauveria bassiana* strains, and UNM - non-specific mechanical agents such as diatomaceous earth (Table 2). These new groupings allow companies and other organizations to provide a MoA classification for biologics to fulfill the needs for regulatory agencies and IRM guidelines. As more information regarding the MoA of specific biologics becomes available, the classification will be revised.

4. Nematicide MoA Classification (new)

IRAC has recently added an entirely new MoA classification specifically addressing nematicides (Table 3, Fig. 4b). Although no

Table 2
IRAC Modes of action for current insecticides, acaricides and biologics.

IRAC group	Chemical subgroup / exemplifying active	Primary site of action / MoA[a]	Representative[b]	# AIs[c]	Market[d] value 2018
			AI / biologic		
Nerve & muscle targets					
1	1A Carbamates	AChE Inhibitors	Carbofuran	43	$ 550
	1B Organophosphates		Chlorpyrifos	165	$1467
2	2A Cyclodienes	GGCC antagonist	Endosulfan	7	$ <1
	2B Fiproles		Fipronil	3	$ 466
3	3A Pyrethroids & pyrethrins	VGSC modulators	*lambda*-cyhalothrin	81	$ 2978
	3B DDT & analogs		Methoxychlor	7	$ <1
4	4A Neonicotinoids	nAChR competitive modulators	Thiamethoxam	8	$ 4752
	4B Nicotine		Nicotine	1	–
	4C Sulfoximines		Sulfoxalfor	1	$ 110
	4D Butenolides		Flupyridifurone	1	$ 28
	4E Mesoionics		Triflumezopyrim	1	New
5	Spinosyns	nAChR allosteric modulators–Site 1	Spinosad	2	$ 590
6	Avermectins & milbemycins	Glu-Cl allosteric modulators	Abamectin	4	$ 1597
9	9B pyridine azomethine derv.	Chordotonal organ	Pymetrozine	2	$ 70
	9D Pyropropenes		Afidopyropen	1	New
14	Nereistoxin analogs	nAChR channel blockers	Cartap	5	$ 144
19	Formamidines	OA-R agonist	Amitraz	6	$ 7
22	22A Oxadiazines	VGSC blocker	Indoxacarb	1	$ 277
	22B Semicarbazones		Metaflumizone	1	$ 101
28	Diamides	Ry-R	Chlorantraniliprole	7	$ 2336
29	flonicamid	Chordotonal org. Mod. Undefined target site	Flonicamid	1	$ 55
30	Meta-diamides & isoxazolines	GGCC allosteric modulators	Broflanilide	7	New
32	GS-omega/kappa HXTX-HV1A peptide	nAChR allosteric modulators – Site II	GS-omega/kappa HXTX-HV1A peptide	1	New
Growth & development targets					
7	7A Juvenoids	JH-R agonists	Methoprene	5	$ 6
	7B fenoxycarb		Fenoxycarb	1	$ 7
	7C pyriproxyfen		Pyriproxyfen	1	$ 74
10	10A hexathiazox	MGI	Hexathiazox	3	$ 46
	10B Oxazoles		Etoxazole	1	$ 68
15	Benzoylureas	CSI	Lufenuron	14	$ 426
16	Buprofezin	CSI	Buprofezin	1	$ 130
17	Cyromazone	Moulting disruptors, dipteran	Cyromazone	1	$ 12
18	Diacylhydrazines	EC-R agonist	Methoxyfenozide	6	$ 201
23	Tetronic / tetramic acids	Inhibitors of ACCase	Spirotetramat	4	$ 652
Respiration targets					
12	12A diafenthiuron	Inhibitors of ATP synthase	Diafenthiuron	1	$ 44
	12B Organotin miticides		Fenbutatin oxide	3	$ 23
	12C propargite		Propargite	1	$ 40
	12D tetradifon		Tetradifon	1	$ 1
13	Pyrroles, dinitrophenols, sulfuramid	Ox-phos uncouplers	Chlorfenapyr	3	$ 93
20	20A hydramethylnon	MET III inhibitors	Hydramethylnon	1	$ <2-3[e]
	20B acequinocyl		Acequinocyl	1	$ 20
	20C fluacrypyrim		Fluacrypyrim	3	$ 24
	20D bifenazate		Bifenazate	1	$ 37
21	21A MET I inhibitors	MET I inhibitors	Fenproximate	6	$ 255
	21B rotenone		Rotenone	1	$ <2-3[e]
24	24A Phosphine	MET IV inhibitor	Al phosphide	4	$ 125
	24B cyanide		Calcium cyanide	3	–
25	25A β-Ketonitrile derivatives	MET II inhibitors	Cyflumetofen	2	$ 91
	25B Carboxanilides		Pyflubumide	1	$ 20
Midgut targets					
11	*11A Bacillus thuringiensis (Bt)*	Midgut membrane	*B. thuringiensis*	14	$ 320
	11B Bacillus sphaericus		*B. sphaericus*	1	–
31	Granuloviruses (GVs) / Nucelopolyhedroviruses (NPVs)	Midgut membrane	*Cydia pomonella* GV	3	–
Miscellaneous non-specific (multi-site) inhibitors					
8	8A Alkyl halides	Multi-site	1,3-dichloropropene	Many	$ 357
	8B chloropicrin	Multi-site	Chloropicrin	1	$ 287
	8C Fluorides	Multi-site	Sulfuryl fluoride	2	$ 43
	8D Borates	Multi-site	Boric acid	4	–
	8E tartar emetic	Multi-site	Tartar emetic	2	–
	8F Methyl isothiocyanate generators	Multi-site	Dazomet	1	$ 313

(*continued on next page*)

Table 2 (*continued*)

IRAC group	Chemical subgroup / exemplifying active	Primary site of action / MoA[a]	Representative[b]	# AIs[c]	Market[d] value 2018
			AI / biologic		
Unknown or uncertain MoA – includes biologics					
UN	Azadirachtin	Unknown	Azadirachtin	1	$ ~5–7
	Benzoximate	Unknown	Benzoximate	1	$ <1
	Bromopropylate	Unknown	Bromopropylate	1	$ <1
	Chinomethionat	Unknown	Chinomethionat	1	$ <1
	Dicofol	Unknown	Dicofol	1	$ <1
	Lime sulfur	Unknown	Lime sulfur	1	–
	Pyridalyl	Unknown	Pyridalyl	1	$ 108
	Sulfur	Unknown	Sulfur	1	$ 400
UNB	Unknown bacterial agents (non-*Bt*)	Unknown	*Burkolderia* spp.	–	–
UNE	Botanical essence including Synthetic extracts and unrefined oils	Unknown	Neem oil	–	–
UNF	Fungal agents	Unknown	*Beauveria bassiana* strains	–	–
UNM	Non-specific mechanical disruptors	Unknown	Diatomaceous earth	–	–

[a] – references for the different MoAs can be found on the IRAC website; http://www.irac-online.org,
[b] – representative active ingredient / compound within an IRAC grouping, typically (where it can be determined) with highest sales in 2018 based on data from (Agranova, 2019).
[c] – Approximate number of products / molecules (past, present and/or in development) in each class. Based, in part, on data from Alan Wood Compendium of Pesticide Common Names (Compendium of Pesticide Common Names, 2019), Cropnosis (Cropnosis Agrochemical Service, 2014) and Agranova (Agranova, 2019).
[d] – 2018 sales (end user, millions USD) for the different IRAC classes of insecticides – data from (Agranova, 2019).
[e] – Sales estimate – information from Agranova (Agranova, 2019).

substantiated examples of nematicide resistance resulting in failure of commercial nematicides in agriculture have been documented in the past 100 years, under intense laboratory selection reduced susceptibility to nematicides has been demonstrated (Meher et al., 2009). Thus, as a proactive informational measure, the nematicide MoA Classification has been developed to provide manufactures, regulatory agencies, and other organizations with a MoA reference point for nematicides. As with the updated Insecticide MoA Classification (Table 2), the Nematicide MoA Classification incorporates a wide range of active ingredients including conventional nematicides, fumigants and biologics (Table 3). Conventional nematicides include a number of carbamate (Group N-1A) and organophosphate (Group N−1B) compounds, along with avermectins (abamectin, Group N-2), pyridinylmethyl benzamides (fluopyram, Group N-3), tetramic acids (spirotetramat, Group N-4), a group of compounds (Group N-UN) with unknown MoAs, and a group of fumigants (Group N-UNX) (Table 3). Among these recent nematicides with as yet unidentified MoAs are tioxazafen (South et al., 2019), fluazaindolizine (Lahm et al., 2019) and fluensulfone (Maienfisch et al., 2019). Details regarding the conventional nematicides and fumigants can be found in recent reviews (Loisleur et al., 2012; Maienfisch et al., 2019). The recent development of biologics for plant parasitic nematode control (Maienfisch et al., 2019) provides added options for growers. The biologics for nematode control have been divided into three Groups; bacteria (N-UNB), fungi (N-UNF), and botanical / animal

Table 3
IRAC Mode of action classification for nematicides.

Nema Group	Chemical subgroup / exemplifying active	Primary site of action / MoA	Representative[a]	IRAC/FRAC Group[b]
			AI / biologic	
N-1	N-1A Carbamates	AChE inhibitors	Oxamyl	IRAC 1A
	N-1B Organophosphates	AChE inhibitors	Fosthiazate	IRAC 1B
N-2	Avermectins	Glu-Cl allosteric modulators	Abamectin	IRAC 6
N-3	Pyridinylmethyl-benzamides	MET II inhibitors	Fluopyram	FRAC 22
N-4	Tetramic acids	Inhibitors of ACCase	Spirotetramat	IRAC 23
N-UN	imidazopyridine	Unknown	Fluazaindolizine	–
	Heterocyclic fluoroalkenyl sulfone	Unknown	Fluensulfone	–
	Cyclic aldehyde	Unknown	Furfural	–
	Dicarboximide	Unknown	Ipodione	–
	Disubstituted oxadiazole	Unknown	Tioxazafen	–
N-UNX	Volatile sulfur generator	Unknown, multi-site	Carbon disulfide	–
	Carbon disulfide liberator	Unknown, multi-site	Sodium tetrathiocarbonate	–
	Alkyl halides	Unknown, multi-site	Methyl bromide	IRAC 8A
	Halogenated hydrocarbon	Unknown, multi-site	1,3-dichlorpropene	IRAC 8A
	chloropicrin	Unknown, multi-site	Chloropicrin	IRAC 8B
	Methyl isothiocyanate generator	Unknown, multi-site	Diazomet	IRAC 8F
N-UNB	Biological – bacterium	Unknown, bacterial action	*Bacillus firmus* I-1582	
N-UNF	Biological – fungus	Unknown, fungus	*Purpureocillium lilacinum*	
N-UNE	Biological	Unknown, botanical / plant origin	Pongamia oil	–
	Biological – tetranortriterpines	Unknown, botanical / plant origin	Azadiractin	IRAC UN
	Biological – saponins from *Quillaja saponaria* tree	Unknown, botanical / plant origin	*Quillaja saponaria* extract	–
	Biological – essential oil	Unknown, botanical / plant origin	Carvacrol	IRAC UNE

[a] Representative compound / active within an IRAC grouping.
[b] Equivalent IRAC or FRAC grouping.

derivatives, and extracts (N-UNE) (Table 3). As with the insecticide MoA Classification, as new information becomes available, the nematicide MoA Classification scheme will be revised as necessary to incorporate new information.

5. Options for access to IRAC MoA Classification information

IRAC provides a wide range of options regarding its activities and the current MoA Classification scheme through its website, which is open access. IRAC periodically (several times per year) provides information on activities and notifications through its free e-Connection newsletter – which can be accessed via sign-up through the IRAC website. In addition, information on the MoA Classification scheme is available in several formats including the recently updated MoA Structures poster (Fig. 4a), a mini-booklet an on-line searchable web-based tool, a smartphone app, and a white paper pdf document that contains more detailed and up-to-date information. The MoA Structure poster is available in several languages including Chinese, English, French, Japanese, Portuguese and Spanish. A related MoA Structure poster has also been developed for the nematicides (Fig. 4b). Additionally, videos providing information on IRM implementation and understanding insecticide MoA are available on YouTube and via the IRAC web-site, as is a slide set on insecticide MoA. Also available on the website, and as part of the MoA WG documents (https://www.irac-online.org/teams/mode-of-action/) and the Classification scheme pdf document is information on the classification process and procedures for submitting compounds to IRAC for classification (IRAC, 2019).

As part of the present update, Table 2 summarizes the current version of the MoA Classification scheme including recent updates. Additionally, Table 2 provides updated information on the number of active ingredients in each Group or Sub-group, as well as corresponding global end-user sales data for 2018 (Table 2). As noted previously (Sparks and Nauen, 2015; Nauen et al., 2019), IRAC employs the best information available from technical experts within the crop protection industry and external internationally recognized technical experts in the fields of insecticide biochemistry, toxicology, MoA and resistance.

6. IRAC MoA Classification and Insecticide Resistance Management

Growers have long employed a range of crop protection approaches and tools to control pest insects (National Academy of Sciences, 1969). This toolbox has been expanding to include biologics / biopesticides, genetically modified plants incorporating traits conferring resistance to pest insects, and perhaps in the future sprayable RNAi (Borel, 2017). These newer additions provide options that can further support more traditional techniques including autocidal control, biological control, crop rotation, cultural control, host-plant resistance, semiochemicals, as well as conventional insecticides (Sparks and Lorsbach, 2017b). However, in many instance's insecticides remain the cornerstone of many IPM programs and maintaining insecticide efficacy and availability will be essential to global food production. As outlined in previous IRAC publications (Nauen et al., 2012, 2019; Sparks and Nauen, 2015), the overall goal of IRM programs is to reduce pest pressure on the crops while simultaneously minimizing selection pressure towards any one specific group of insecticides, biologics or transgenic insect resistance traits. Maintaining the efficacy of the available insecticides is critical as in some pest-crop-geography situations the insect pest control options

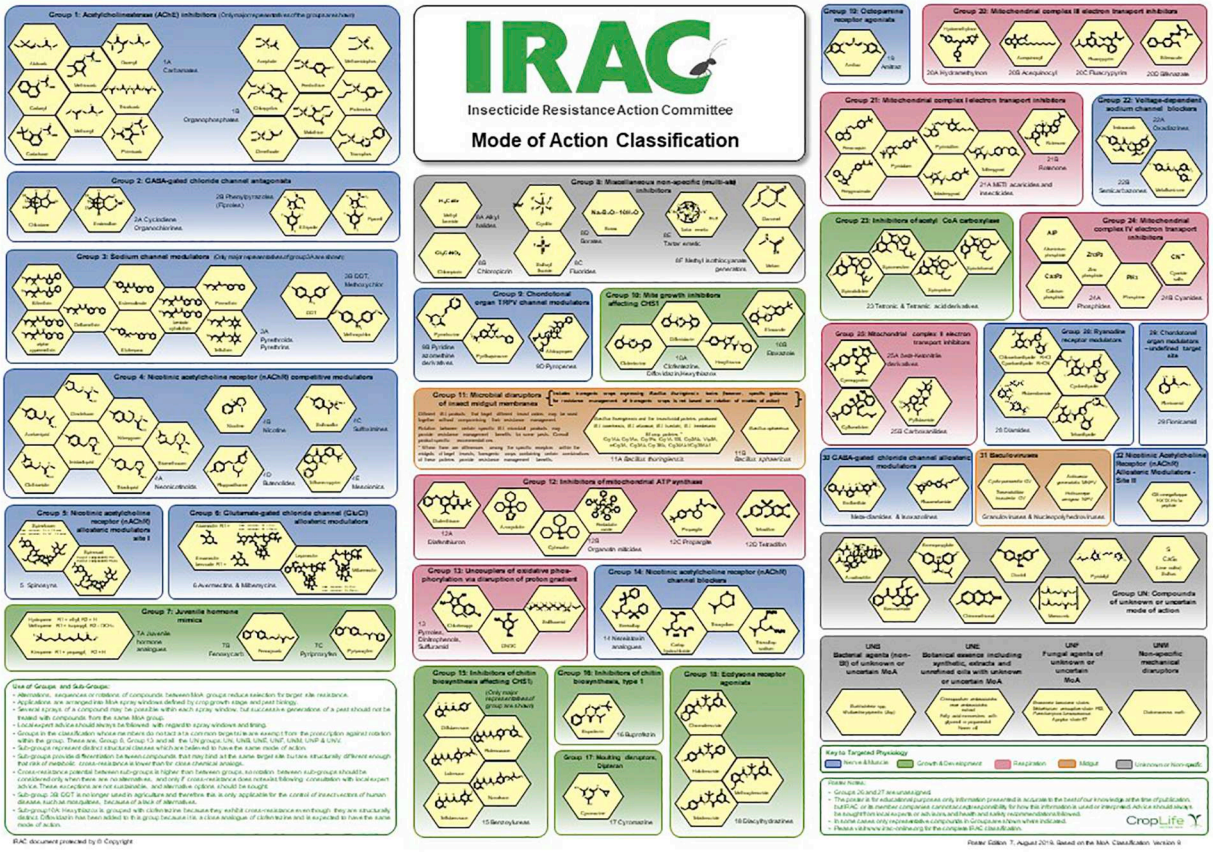

Fig. 4. Examples if the new updated Insecticide MoA Structure poster (**A**) (available in several languages), and the new nematicide MoA poster (**B**) – available on the IRAC website. http://www.irac-online.org Colour code for nematicide poster; blue – nerve and muscle (i.e. carbamates, OPs and avermectins), magenta – pyridinylmethyl benzamides, green – tetronic and tetramic acid derivatives, gray – Unknown, aqua – biologicals. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

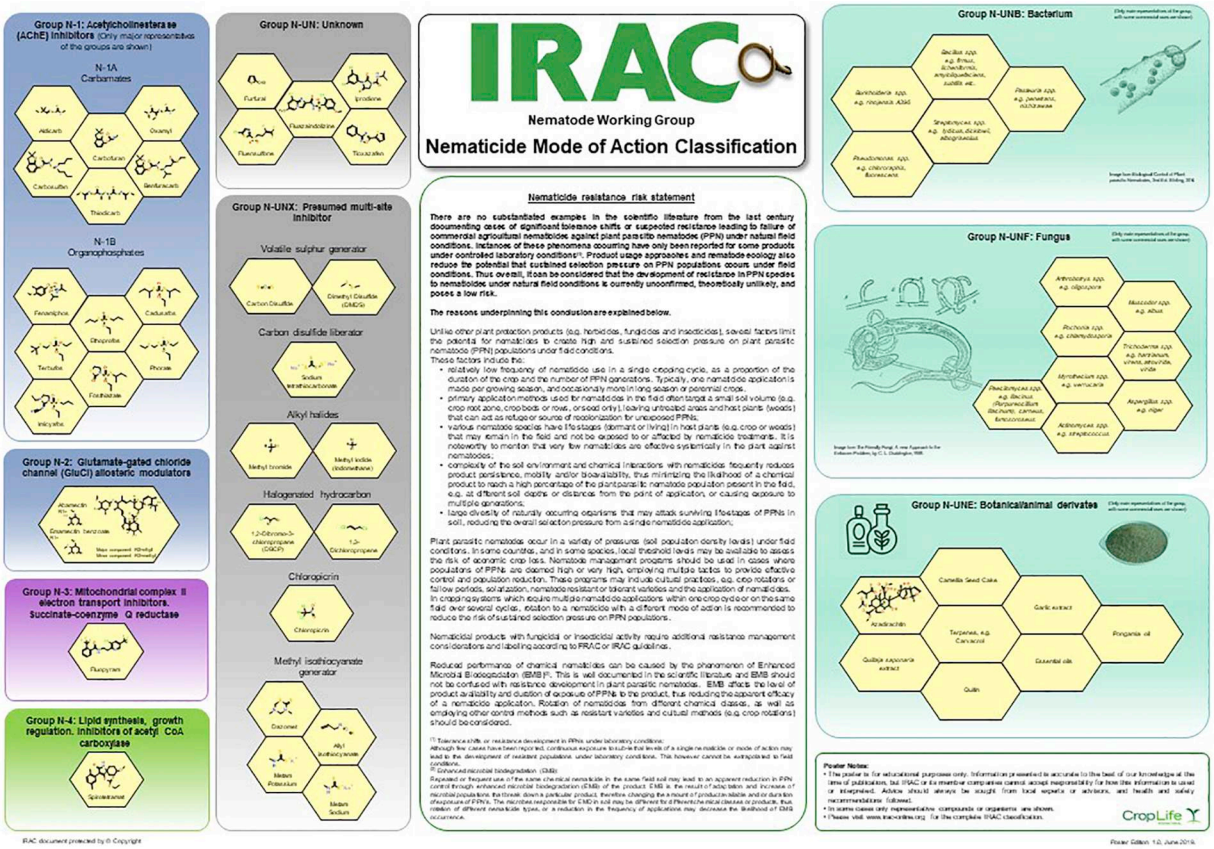

Fig. 4. (*continued*)

are limited. IRM can take many forms, including the use of insecticide mixtures, mosaics or alternations / rotations (National Research Council, 1986; Roush, 1989; Zhao et al., 2010; IRAC International Mixture Statement, 2012). In the majority of settings, the rotation of insecticide modes of action (Fig. 2) is considered the most effective IRM approach (National Research Council, 1986, Roush, 1989, IRAC International Mixture Statement, 2012). Insecticide mixtures may offer benefits for IRM when appropriately incorporated into rotation strategies with additional mode(s) of action, but generally a single mixture should not be relied upon alone (IRAC International Mixture Statement, 2012; https://www.irac-online.org/?s=mixtures).

1) The basic rule for adequate rotation of insecticides by mode of action (MoA) is to avoid treating consecutive generations of the target pest with insecticides in the same MoA group, by using a scheme of" MoA treatment windows" (Fig. 2).
2) A treatment window typically encompasses a full life-cycle of the targeted pest (max. 30 days).
3) Multiple applications of the same MoA group may be possible within a particular window (follow label for maximum number of applications within a window and per crop cycle).
4) After a first MoA window of max. 30 days is completed and if additional insecticide applications are needed, a different and effective MoA should be selected for use in the next 30 days (second MoA window) etc.

The proposed "MoA treatment windows" scheme seeks to minimize the selection of resistance to any given MoA group and usually requires a minimum of three effective insecticide MoA groups (Fig. 2).

While IRAC supports the use of insecticide mixtures (IRAC International Mixture Statement, 2012), they are most commonly used to improve pest insect control and/or spectrum, and less frequently used for IRM.

7. Perspective

The IRAC MoA Classification scheme currently encompasses more than 29 specific MoAs, along with a range of nonspecific or unknown / uncertain MoAs (Table 2). Most of the well characterized MoAs act on the insect nerve–muscle systems and account for the largest share (79%) of the global insecticide market ($19.8 billion USD in 2018; Fig. 5). Compounds acting against growth & development targets, and respiration-based targets account for 8.2% and 3.9%, respectively. *Bacillus thuringienis* and related *Bacillus* species used in sprayable formulations account for 1.6% of the total market, leaving multisite inhibitors and those compounds with unknown or uncertain MoAs to make up the remaining 7.6%. The nerve-muscle systems have the largest market share and perhaps not surprisingly, the largest number of AIs (356; Table 2) accounting for 76% of all AIs listed in Table 2 (470), with the bulk of these being OPs and carbamates. The largest market share for the insecticides is presently derived from the neonicotinoids (Group 4A) accounting for 24% of the global market, followed by the synthetic pyrethroids (Group 3A; 15%) and diamides (Group 28; 12%) (Fig. 5). This is in stark contrast with sales in the US in the 1970s where 70% of sales was due to just the OPs and carbamates (Sparks et al., 2019). Today (2018 values) the OPs and carbamates together account for only 11% (Fig. 5). Such changes highlight the continued evolution of the global insecticide portfolio with many older chemistries being replaced due to increasingly stringent regulatory requirements relative to human and environmental safety (Sparks and Lorsbach, 2017a, Phillips McDougall, 2019). One outcome of this continued evolution in insecticidal chemistries is an increasing diversity of insecticide classes (Sparks et al., 2019) and MoA Groups (Table 2), which can facilitate in IRM. In 2007, there were 21 specific MoAs in the IRAC MoA Classification scheme (Elbert et al., 2007). Today there are 29 specific MoA Groups, with more potentially on the horizon (Table 4), and the addition of biologics further expands options for possible MoA rotations.

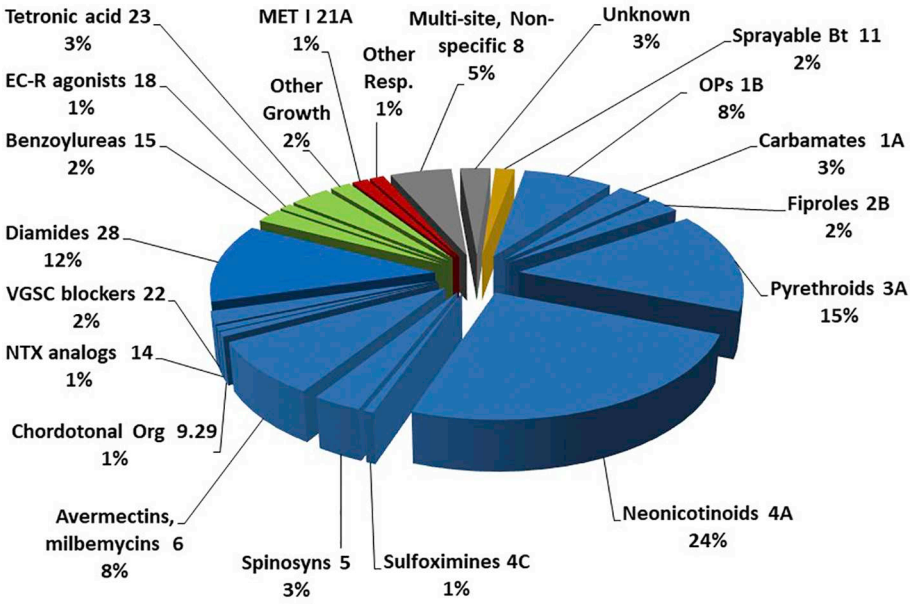

Fig. 5. Distribution of insecticide sales by IRAC MoA Groups. Colors correspond to broad IRAC MoA groupings. Blue = nerve-muscle, green = growth & development, red = respiration, yellow = midgut, gray = unknown or non-specific. Based on 2018 End-user sales data (total = $19.8 billion USD) (Agranova, 2019). The chordotonal org. Grouping includes combined sales of Groups 9 and 29. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 4
Modes of action for future chemistries currently in development and/or not yet classified.

Primary site of action / MoA	Compound	1st year[a]	Commercalized[b]
nAChR competitive modulators	Cycloxaprid	2011	2015 – China
nc[c]	Flometoquin	2011	2019 – Japan
Ry-R modulators	Cyhalodiamide	2015	
Ry-R modulators	Tetrachlorantraniliprole	2016	2013 - China
nc	Acynonapyr	2017	2019 - Japan
nc	Benzpyrimoxan	2017	
nAChR competitive modulators	Flupyrimin	2017	
nc	Oxazosulfyl	2017	
GGCC allosteric modulators	Isocycloseram	2018	
nc	Dimpropydriaz	2018	

[a] – First year of appearance of the compound name in the Alan Wood database (Compendium of Pesticide Common Names, 2019) or literature.
[b] – Year commercialized and country (Agranova, 2019).
[c] nc – Not yet classified; MoA currently not known, not yet reported and/or not yet classified.

Although biologics, biopesticides or microbial insecticides, especially *Bacillus thuringiensis,* have been used for decades (Ignoffo, 1975), interest in biologics by crop protection companies of all sizes, including the global multi-nationals, has increased in recent years (Marrone, 2019). Sales of biologics of all kinds has grown from approximately 0.4% of the global crop protection market in 1993 to 5.6% in 2016 (Phillips McDougall, 2019). Thus, given the increasing interest and impact of biologics in all sectors of crop protection, including pest insect control and as potential options for IRM, IRAC has added biologics to the Mode of Action Classification scheme (Table 2). Since approximately 2003, the numbers of new biologic active ingredients (AIs) introduced each year has matched or exceeded the numbers of new conventional synthetic organic pesticide AIs (Phillips McDougall, 2019). However, because the exact MoA of the majority of biologics is not known, relatively broad groupings are used for the current IRAC classification of insect active biologics (see also Section 3.2). As noted above, these grouping will be refined as more information about their MoAs become available.

7.1. IRM for biologics

Just as IRM is critical for conventional insecticides, IRM will become equally important for biologics. With increasing use of biologics, effective IRM will be needed to safeguard their continued efficacy. Insect resistance to *B. thuringiensis* and other Group 11 members is well documented with more than 300 individual cases of resistance across 20 different pest insect species (Mota-Sanchez and Wise, 2019). Laboratory induced resistance and field resistance to a nuclear polyhedrosis virus (NPV) and granulovirus (GV) have also been demonstrated, respectively (Abot et al., 1996; Sauer et al., 2017). Thus, it is reasonable to expect that resistance can be selected for a range of biologics, including bacterial-based AIs, NPVs, GVs, botanicals, and fungi, if sufficient selection pressure is applied. As such it will be critical to incorporate IRM measures into any pest insect/mite control program that relies on biologics, just as it is important for conventional insecticides. Here again the use of the IRAC MoA Classification scheme can be an important aid, especially as new information regarding the MoA of biologics becomes available.

8. Conclusions

As noted above and in numerous recent reviews (e.g. Marrone, 2014; Sparks and Lorsbach, 2017b; Maienfisch et al., 2019; Sparks et al., 2019) the types and numbers of insecticides, acaricides, nematicides and biologics continue to evolve, and so have IRAC and its MoA Classification scheme. The present update reflects recent additions of new classes of crop protection compounds, and the increasing importance and impact of biologics. The new addition of a Nematicide MoA Classification also recognizes the growing interest and focus on new compounds for nematode control, and as tools for integrated nematode management. Thus, IRAC continues its longstanding goal of promoting and enabling effective IRM. Importantly, effective IRM benefits everyone - growers, crop protection and extension specialists, universities and the crop protection industry. IRM has been and remains essential to enable the long-term utility of the insecticide, acaricide, nematicide and biological tools needed for food production and vector control for public health.

Declaration of Competing Interest

None.

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