

Using "Mode of Action" to Manage Insecticide Resistance

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The <u>Insecticide</u> <u>Resistance</u> <u>Action</u> <u>Committee</u> (IRAC) is a coordinated industry response to resistance management

What is Insecticide Resistance?

- Insecticide resistance is the <u>decreased susceptibility</u> of a pest population to an insecticide that was previously effective at controlling that pest.
- Insecticide resistance typically evolves through <u>genetic</u> <u>selection</u> by excessive exposure of insecticides with the same mode of action (MOA) to the same pest population. Resistant individuals survive and <u>transfer their genetic</u> <u>traits</u> to their offspring.
- Overdependence on the same insecticide MOA leads to greater potential for resistance in a pest population.





RED FLAG • Field failure • Lab verfication

YELLOW FLAG

- Observation
- Not verified
 or
- Low "R" level

GREEN FLAG

 Green Markets have mainly susceptible populations

BASIC GENETICS TRAINING REQUIRED

....all about the individual

Genetic Nomenclature	Individual Insect "R" Status	# "R" Genes (alleles)
RR	High	2
RS	Moderate	1
SS	Susceptible	0
Assume co-domi RS x SS = ½ RS -	nance: • Typically high % of point of the second s	opulation is Ra population genes

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What is an Insecticide's 'Mode of Action'? The Mode of action defines the process of how an insecticide works on an insect at the molecular level



The Key To Managing Resistance (target site)

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IRAC INSECTICIDE MODE OF ACTION (MOA) CLASSIFICATION PER TARGET SITE

Nerve & muscle targets

Group 1 Acetylcholinesterase (AChE) inhibitors Group 2 GABA-gated chloride channel blockers

Group 3 Sodium channel modulators

Group 4 Nicotinio acetylcholine receptor (nAChR) competitive modulators

Group 5 Nicotinic acetylcholine receptor (nAChR) allosteric modulators

Group 6 Glutamate-gated chloride channel (GluCl) allosteric modulators

Group 9 Chordotonal organ TRPV channel modulators

Group 14 Nicotinic acetylcholine receptor (nAChR) channel blockers

Group 19 Octopamine receptor agonists

Group 22 Voltage dependent sodium channel blockers

Group 28 Ryanodine receptor modulators

Group 29 Chordotonal organ modulators

Group 30 GABA-gated chloride channel allosteric modulators/Broflanamide

Nerve & muscle targets

Group 11 Microbial disruptors of insect midgut membranes Group 31 Granuloviruses, Nucleopolyhedroviruses

Nerve & muscle targets

Group 8 Miscellaneous non-specific (multi-site) inhibitors

Respiration targets

Group 12 Inhibitors of mitochondrial ATP synthesis **Group 13** Uncouplers of oxidative phosphorylation via disru

Group 13 Uncouplers of oxidative phosphorylation via disruption of the proton gradient
 Group 20 Mitochondrial complex III electron transport inhibitors

Group 21 Mitochondrial complex I electron transport inhibitorsGroup 24 Mitochondrial complex IV electron transport inhibitorsGroup 25 Mitochondrial complex II electron transport inhibitors

Growth & Development targets

Group 7 Juvenile hormone mimics
Group 10 Mite growth inhibitors,
Group 15 Inhibitors of chitin biosynthesis, Type 0, Benzoylureas
Group 16 Inhibitors of chitin biosynthesis, type 1,
Group 17 Moulting disruptors
Group 18 Ecdysone receptor agonists
Group 23 Inhibitors of acetyl CoA carboxylase

For a full and up to date list of insecticide target site classification please visit the IRAC website at http://www.irac-online.org/modes-of-action

IRAC INSECTICIDE MODE OF ACTION (MOA) CLASSIFICATION PER TARGET SITE



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Major Mechanisms of Insecticide Resistance



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Biochemical Targets Differ in Their Propensity to Develop Resistance

Metabolic Resistance is More Common

Target Site Resistance is More Common



<u>Rotate insecticides</u> with different modes of action to reduce selection pressure for resistance

Two successive insect generations shouldn't be treated with the same MoA insecticides.

Repeated exposure of pest populations to insecticides with the same Mode of Action will select for resistant insects.





There are currently 27 insecticide modes of action identified, but not all are active against all insect pests

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TANK MIXING VS MOA ROTATION:

GENERAL GUIDANCE FOR PESTICIDE RESISTANCE MANAGEMENT

	FUNGICIDES	HERBICIDES	Insecticides
Much Preferred	Mixes	Mixes	Rotation
Acceptable	Rotation	Rotation	Mixes

Mixes = tank mix or premixed active ingredients

TANK MIXING VS MOA ROTATION:

GENERAL GUIDANCE FOR PESTICIDE RESISTANCE MANAGEMENT

	FUNGICIDES	HERBICIDES	Insecticides		
Much Preferred	Mixes	Mixes	Rotation		
Acceptable	Potation	Rotation	Mixes		
Mixes = tank mix Both Rotation and Mixing RM Strategies Require					
Knowledge of Product Modes of Action					



Insecticidal Mode of Action

Growers/Customers need to understand:

- What is the MoA # for each product
- Where to find it
- What to do with it.

Labels That Display IRAC Mode of Action Number for Quick Identification



Where to find it

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A Tool to Help You Identify Different Product Chemistries and Mode of Action #'s

Mode of Action Classification: Phone/Tablet App (Its Free!!)

Search for: IRAC moa



T inhibitors GABA-gated chloride receptor agonists receptor allosteric



Search for active ingredient

What to do with it.

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IRM RECOMMENDED LANGUAGE IN LABEL TEXT

2

Contains at least three 'REQUIRED' components:

1 State the IRAC <u>MoA Group Number (in addition to the icon shown elsewhere)</u>

2 Provide guidance to <u>avoid treating consecutive generations</u> with the same MoA.

3 <u>Rotate</u> products with different Modes of Action using MoA treatment windows.

[Product] is a Group N insecticide

Do not exclusively use *[Product]* or other Group *N* insecticides to control the same pest throughout the season. Avoid exposing consecutive generations of a pest to the same mode of action by using the "application window" approach which rotates products with different MoA chemistries.

An "application window" is the period of residual activity that a single application or sequential applications of a MoA provide. It can also be defined as the duration of an insect generation or if unknown, then use an approximate 30 day period. Rotate windows of treatments of *[Product]* and other Group *N* products followed by blocks of treatments with other effective products from different modes of action before returning to Group *N* products.

- Implement Integrated Pest Management (IPM) practices to control pest populations and reduce the development of insect resistance.
- Use recommended label rates, timings, and spray intervals with maintained application equipment to reduce insect resistance risk.
- For additional information on insect resistance, visit the Insecticide Resistance Action Committee (IRAC) website at http://www.irac-online.org

What to do with it.

IRM rotation strategy developed for brassica crops in **Philippines**





Insecticidal Mode of Action

Growers/Customers need to understand:

Same MoA: Product Characteristics are sometimes Similar

- Product attributes:
 - contact (KD), ingestion, adulticide, ovicidal, pest spectrum, beneficial safety, systemic ____
- Spray timing and number of apps:
 - treatment thresholds differ by product
 - adult flight, egg laying, first larvae, sight of damage, (rescue?)

IMPACTS RM

Max population control in a generation. Remove multiple pest stages.

> Conserve beneficials

Poor timing – Poor control! Leaves RS insects

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MoA: Understanding How Insecticides Bind to Target Sites at the Molecular Level.....is Complicated Detailed IRAC tutorial available at

http://www.irac-online.org/modes-of-action



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Nerve & Muscle Targets

- 1. Acetylcholinesterase (AChE) inhibitors
 - 1A: Carbamates
 - 1B: Organophosphates
- 2. GABA-gated chloride channel blockers

2A: Cyclodiene Organochlorines 2B: Phenylpyrazoles

- 3. Sodium channel modulators *3A: Pyrethrins, Pyrethroids*
- 4. Nicotinic acetylcholine receptor (nAChR) competitive modulators *4A: Neonicotinoids*
- 5. Nicotinic acetylcholine receptor (nAChR) allosteric modulators Site I 5 Spinosyns
- 6. Glutamate-gated chloride channel (GluCl) allosteric modulators 6: Avermectins, Milbemycins
- 14. Nicotinic acetylcholine receptor (nAChR) channel blockers 14: Nereistoxin analogues
- 22. Voltage-dependent sodium channel blockers

22A: Oxadiazines

22B: Semicarbazones

- 28. Ryanodine receptor modulators *28: Diamides*
- 30. GABA-gated chloride channel allosteric modulators *30: Meta-diamides, Isoxazolines*
- 32. Nicotinic acetylcholine receptor (nAChR) allosteric modulators Site II 32: GS-omega/kappa HXTX-HV1a Peptide

Lepidoptera - Mode of Action Classification by Target Site



Unknown or uncertain MoA

Azadirachtin, Pyridalyl, Beauveria bassiana, Burkholderia spp, Paecilomyces fumosoroseus

Respiration Targets

13. Uncouplers of oxidative phosphorylation via disruption of the proton gradient

13: Chlorfenapyr

21. Mitochondrial complex I electron transport inhibitors 21A: METI acaracides and insecticides (Tolfenpyrad)

Midgut Targets

11. Microbial disruptors of insect midgut membranes

11A: Bacillus thuringiensis,

- 11B: Bacillus sphaericus
- 31. Baculoviruses 31: Host-specific occluded pathogenic viruses Granuloviruses, Nucleopolyhedroviruses

Growth & Development Targets

- 7. Juvenile hormone mimics
 7A: Juvenile hormone analogues
 (Hydroprene)
 7B: Fenoxycarb
- 15. Inhibitors of chitin biosynthesis affecting CHS1 15: Benzoylureas
- 18. Ecdysone receptor agonists 18: Diacylhydrazines

Nerve & Muscle Targets

- Acetylcholinesterase (AChE) inhibitors
 1A: Carbamates
 - 1B: Organophosphates
- 2. GABA-gated chloride channel blockers 2A: Cyclodiene Organochlorines 2B: Phenylpyrazoles
- Sodium channel modulators 3A: Pyrethrins, Pyrethroids
- 4. Nicotinic acetylcholine receptor (nAChR) competitive modulators 4A: Neonicotinoids 4C: Sulfoximines 4D: Butenolides
 - 4E: Mesoionics
- 9. Chordotonal organ TRPV channel modulators 9B: Pyridine azomethine derivatives
 - 9D: Pyropenes
- 22. Voltage-dependent sodium channel blockers 22A: Oxadiazines
- 28. Ryanodine receptor modulators 28: Diamides (Cyantraniliprole)
- 29. Chordotonal organ modulators undefined target site 29: *Flonicamid*
- 32. Nicotinic acetylcholine receptor (nAChR) allosteric modulators Site II 32: GS-omega/kappa HXTX-HV1a Peptide

Aphids, Whiteflies, Planthoppers and Leafhoppers - Mode of Action Classification by Target Site



3Z



MoA Group	Aphids	Whiteflie s	Planthoppers Leafhoppers
1A	Х	Х	Х
1B	Х	Х	Х
2A	Х	Х	Х
2B			Х
3A	Х	Х	Х
4A	Х	Х	Х
4C	Х	Х	Х
4D	Х	Х	Х
4E			Х
7A	Х	Х	
7C		Х	
9B	Х	Х	Х
9D	Х	Х	Х
12A	Х	Х	
15		Х	
16		Х	Х
21A		Х	
22A			Х
23	Х	Х	
28	Х	Х	Х
29	Х	Х	Х
00	V	V	

Respiration Targets

- 12. Inhibitors of mitochondrial ATP synthesis 12A: Difenthiuron
- 21. Mitochondrial complex I electron transport inhibitors 21A: METI acaracides and insecticides (Pyridaben, Tolfenpyrad)

Growth & Development Targets

- 7. Juvenile hormone mimics 7A: Kinoprene 7C: Pyriproxyfen
- 15. Inhibitors of chitin biosynthesis, affecting CHS1 15: Benzoylureas
- 16. Inhibitors of chitin biosynthesis, type 1

16: Buprofezin

- 23. Inhibitors of acetyl CoA carboxylase
 - 23: Tetronic & Tetramic acid derivatives

The table lists the main mode of action groups for the control of aphids, whiteflies and hoppers. However, the availability may differ regionally due to registration status.



Insecticide Mode of Action Major Classes



Nerve and Muscle Targets for Insecticidal Control



Mode of Action (Nerve and Muscle Target)		Chemical Group	Active ingredients	MoA #
Sodium channel modulators (OPENS)	<u>Prolong</u> influx of sodium ions into the nerve cells leading to an over stimulated nervous system; <mark>paralysis</mark> and rapid knockdown	Pyrethroids	Betacyfluthrin Bifenthrin Cypermethrin Deltamethrin Lambda cyhalothrin Permethrin	3A
Voltage dependent sodium channel (BLOCKER)	Block sodium channels resulting to nervous system shutdown and paralysis	Oxadiazines	Indoxacarb Metaflumizone	22 A



Mod	e of Action (N	erve and Muscle Target)	Chemical Group	Active ingredients	MoA #
Acetylchol inhibitors	inesterase	Cause unregulated neuro transmission in the neuro muscular system resulting in disruption of insect locomotion and eventual paralysis	Organophosphates Carbamates	Profenophos, Chlorpyrifos Malathion Phenthoate Carbofuran Carbaryl Thiodicarb	1A 1B
	Central/P Ne	Peripheral rve Sodium hannels AChE Acetylcholine receptors Motor Nerve	GABA receptors GABA	uscle iber	
					IRA

Mode of Action (Nerve Target) Chemical Groups: Neonicotinoids, Nereistoxin analogues, Spinosyns



Mode of Action (Ne	rve and Muscle Target)	Chemical Group	Active ingredients	MoA #
nAChr Nicotinic acetylcholine receptor competitive modulators	oline tive cline tive tive cline cline tive cline tive cline tive cline tive cline tive cline tive cline tive cline tive cline tive cline tive cline tive cline tive cline tive cline tive cline tive cline tive cline tive cline tive cline tive		Acetamiprid Clothianidin Dinotefuran Imidacloprid Thiametoxam Thiacloprid Nitempyram	4A
nAChr Nicotinic acetylcholine receptor channel blockers	Block the nAChR ion channel, resulting to nervous system block and paralysis	Nereistoxin analogues	Cartap	14
nAChr Nicotinic acetylcholine receptor allosteric modulators	KersSpinosyns primarily target the binding sites on nicotinic acetylcholine receptors (nAChRs) of the insect nervous system that are distinct from those at which other insecticides have their activity. This leads to disruption of acetylcholine neurotransmission and hyperexitation.Spinosyns system the insect nervous system that are distinct from those at which other insecticides have their activity.		Spinosad Spinetoram	5

Mode of Action		Chemical	Active	MoA #
(Nerve and Muscle Target)		Group	ingredients	
GABA –gated chloride channel blockers	Cause hyper excitation of nerves and muscles	Phenylpyrazoles	Ethiprole Fipronil	2B



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	Mode of Action (Nerve Target)	Chemical Group	Active ingredients	MoA #
Ryanodine receptor modulators	Ryanodine receptors control the release of stored calcium ions inside muscle tissue. Diamides affect the receptor, open the ion channels, and release calcium ions leading to paralysis and death	Diamides	Chlorantraniliprole Cyantraniliprole Cyclaniliprole Flubendiamide Tetraniliprole	28
	Central/Peripheral Nerve Diamides Sodium channels AChE Acetylcholine Construction of the optimised of the op	ABA ptors Co R	Muscle Fiber	

Mode of Action (Nerve Target)		Chemical Group	Active ingredients	MoA #
Glutamate-gated chloride channel allosteric modulators	Stimulates the uncontrolled influx of chloride ions in post synaptic nerve cells de-regulatng the nervous system leading to paralysis and death	Avermectins	Abamectin Emamectin	6



- Inhibitory Glutamate-gated chloride channels (GluCl) are widespread on insect nerve and muscle cells and likely function in inhibitory neurotransmission
- GluCl modulators activate chloride influx, causing flaccid paralysis

Mode of Action (Nerve Target)		Chemical Group	Active ingredients	MoA #
Chordotonal organ TRPV channel modulators	Prevent target insects from feeding and reproducing due to malfunction of hind legs, fail to attach to the plant and mate	Pyridine azomethine derivatives	Pymetrozine Afidopyropen	9

Insect stretch receptor signaling (Chordotonal Organ)

The detection of the relative position and motion of body parts



Insecticide Mode of Action Major classes Nerve & Muscle Growth Respiration Midgut **Unknown or Non-Specific**



Growth & Development Disruptors

The insect's skeleton is external (**exoskeleton**) and contains **Chitin.** Since the exoskeleton cannot expand, it must be replaced with a larger one by the process of molting as the insect grows, requiring **chitin synthesis**. Molting is under strict hormonal control:

Ecdysone is released to induce molting

EcR agonists persistently activates Ecdysone receptors causing the insect to go into an early incomplete molt, leading to death



JH prevents molting to a more mature stage

JH production stops during metamorphosis

JH mimics suppress the development of adult characteristics keeping the insect in an 'immature' state

Insect Growth Regulator Effects















Mode of Action (Growth and Development Target)		Chemical Group	Active ingredients	MoA #
Moulting disruptors (dipterans)	Interfere with the production of insect cuticle. Insect fails to grow and dies	Cyromazine	Cyromazine	17
Inhibitors of chitin biosynthesis, type 1	Interfere in the chitin formation process (homopterans)	Buprofesin	Buprofesin	16
Inhibitors of chitin biosynthesis,type O	Interfere in the chitin formation process (lepidopterans)	Benzoylureas	Lufenuron Chlorfuazuron	15
Inhibitors of acetyl CoA carboxylase	Prevent the process of lipid biosynthesis . Affect insect development at the egg and nymphal stages	Tetronic and Tetramic acid derivataves	Spirotetramat	23
Juvenile hormone mimics	Target protein responsible for biological activity is unknown, or uncharacterized}	Pyriproxyfen	Pyriproxyfen	7C

Insecticide Mode of Action Major Classes



Inhibitor of Mitochondrial ATP synthaseCarbodiamide binds to mitochondrial ATPase and inhibits its function resulting in shutdown of insect respiration system leading to paralysis and mortalityDiMitochondrial complex I electron transport inhibitorsEnergy metabolismMage action inCentral/Peripheral NerveMarket MerveMage Market			
Mitochondrial complex M I electron transport Energy metabolism ac inhibitors in Central/Peripheral Nerve	Diafenthiuron	Diafenthiuron	12 A
Central/Peripheral Nerve	METI acaricides & nsecticides	Fenazaquin, Pyridaben, Tolfenpyrad	21 A
Sodium channels AChE Acetylcholine receptors Motor Nerve 37	Muscle Fiber	Cells get energy such as fat and s carbon dioxide a	by "oxidizing" food sugars to produce and water

38

Insecticide Mode of Action Major Classes

Nerve & Mi	ıscle
Growth	
Respiratior	
Midgut	
Unknown o	r Non-Specific



Using "Mode of Action" to Manage Insecticide Resistance	Nerve & Muscle Growth Respiration	1
CONCLUSION	Midgut Unknown or Non-Specific	
Must specific MoA products within the "Nerve and Muscle" classes be rotated with each other?	NO	
Must specific "Nerve and Muscle" class products be rotated with specific "Respiration" or "Growth" class products?	NO	
Rotate all different MoA products within and across the major classes using the 30 day window rotation strategy. Ideally do not treat successive generations with the products from the same MoA.	YES	



<u>Rotate insecticides</u> with different modes of action to reduce selection pressure for resistance

Two successive insect generations shouldn't be treated with the same MoA insecticides.

Repeated exposure of pest populations to insecticides with the same Mode of Action will select for resistant insects.





There are currently 27 insecticide modes of action identified, but not all are active against all insect pests

Managing Resistance Is Much More Difficult Than..... **Preventing Resistance**

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