

IRAC Mode of Action Classification

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Prepared by: IRAC Mode of Action Working Group

The IRAC Mode of Action (MoA) classification provides farmers, growers, advisors, extension staff, consultants and crop protection professionals with a guide to the selection of insecticides or acaricides for use in an effective and sustainable insecticide or acaricide resistance management (IRM) strategy. In addition to presenting the MoA classification, this document outlines the background to, and purposes of, the classification list and provides guidance on how it is used for IRM purposes. The list is reviewed and re-issued at intervals as required.

What is resistance?

Resistance to insecticides may be defined as *'a heritable change in the sensitivity of a pest population that is reflected in the repeated failure of a product to achieve the expected level of control when used according to the label recommendation for that pest species'* (IRAC). This definition differs slightly from others in the literature, but IRAC believes it represents the most accurate, practical definition of relevance to farmers and growers. Resistance arises through the over-use or miss-use of an insecticide or acaricide against a pest species and results in the selection of resistant forms of the pest and the consequent evolution of populations that are resistant to that insecticide or acaricide.

MoA, Target-site resistance and Cross-resistance

In the majority of cases, not only does resistance render the selecting compound ineffective but it often also confers cross-resistance to other chemically related compounds. This is because compounds within a specific chemical group usually share a common target site within the pest, and thus share a common mode of action (MoA). It is common for resistance to develop that is based on a genetic modification of this target site. When this happens, the interaction of the selecting compound with its target site is impaired and the compound loses its pesticidal efficacy. Because all compounds within the chemical sub-group share a common MoA, there is a high risk that the resistance that has developed will automatically confer cross-resistance to all the compounds in the same sub-group. It is this concept of cross-resistance within chemically related insecticides or acaricides that is the basis of the IRAC mode of action classification.

Effective IRM strategies use alternations or sequences of different modes of action (MoA)

The objective of successful Insecticide Resistance Management (IRM) is to prevent or delay the evolution of resistance to insecticides, or to help regain susceptibility in insect pest populations in which resistance has already arisen. Effective IRM is thus an important element in maintaining the efficacy of valuable insecticides. It is important to recognize that it is usually easier to proactively prevent resistance occurring than it is to reactively regain susceptibility. Nevertheless, the IRAC MoA classification will always provide valuable guidance to the design of effective IRM strategies.

Experience has shown that all effective insecticide or acaricide resistance management strategies seek to minimise the selection for resistance from any one type of insecticide or acaricide. In practice, alternations, sequences or rotations of compounds from different MoA groups provide a sustainable and effective approach to IRM. This ensures that selection from compounds in any one MoA group is minimised. The IRAC classification in this document is provided as an aid to insecticide selection for these types of IRM strategies.

Applications are often arranged into MoA spray windows or blocks that are defined by the stage of crop development and the biology of the pest(s) of concern. Local expert advice should always be followed with regard to spray windows and timings. Several sprays of a compound may be possible within each spray window but it is generally essential to ensure that successive generations of the pest are not treated with compounds from the same MoA group.

Non-target site resistance mechanisms

It is fully recognized that resistance of insects and mites to insecticides and acaricides can, and frequently does, result from enhanced metabolism by enzymes within the pest. Such metabolic resistance mechanisms are not linked to any specific site of action classification and therefore they may confer resistance to insecticides in more than one IRAC MoA group. Where such metabolic resistance has been characterized and the cross-resistance spectrum is known, it is possible that certain alternations, sequences or rotations of MoA groups cannot be used. Similarly, mechanisms of reduced penetration of the pesticide into the pest, or behavioural changes of the pest may also confer resistance to multiple MoA groups. Where such mechanisms are known to give cross-resistance between MoA groups, the use of insecticides should be modified appropriately.

Where the resistance mechanism(s) is unknown, the intelligent use of alternations, sequences or rotations of compounds from different MoA classes remains an entirely viable resistance management technique since such a practice will always minimise selection pressures.

The Mode of Action (MoA) classification

The following classification scheme developed and endorsed by IRAC is based on the best available evidence of the mode of action of available insecticides. Details of the listing have been agreed by IRAC companies and approved by internationally recognized industrial and academic insect toxicologists and biochemists.

It is our aim to ensure that insecticide and acaricide users are aware of mode of action groups and that they have a sound basis on which to implement season-long, sustainable resistance management through the effective use of alternations, sequences or rotations of insecticides with different modes of action. To help delay resistance it is strongly recommended that growers also integrate other control methods into insect or mite control programmes. Further advice is given in Appendix 2.

Note: Inclusion of a compound in the MoA list does not necessarily signify regulatory approval.

Rules for inclusion of a compound in the MoA list:

- Chemical nomenclature is based on that appearing in *The Pesticide Manual*, 14th edition, 2006, Ed. C.D.S. Tomlin, published by The British Crop Protection Council. 3500pp., ISBN-10: 1901396142
- To be included in the active list, compounds must have, or be very close to having, a minimum of one registered use in at least one country.
- In any one MoA classification sub-group, where more than one active ingredient in that chemical sub-group is registered for use, the chemical sub-group name is used.
- In any one MoA classification sub-group, where only one active ingredient is registered for use, the name of that exemplifying active ingredient is used
- Where more than one chemical sub-group or exemplifying active ingredient appears in a single mode of action group, each is named according to the above rules; chemical sub-groups having precedence over single active ingredients

IRAC Mode of Action Classification v 6.1, August 2008 ¹		
Main Group and Primary Site of Action	Chemical Sub-group or exemplifying Active Ingredient	Active Ingredients
1* Acetylcholinesterase inhibitors Nerve action {Strong evidence that action at this protein is responsible for insecticidal effects} <i>* Please see footnotes for further information on the use of compounds between sub-groups</i>	1A Carbamates	Alanycarb, Aldicarb, Bendiocarb, Benfuracarb, Butocarboxim, Butoxycarboxim, Carbaryl, Carbofuran, Carbosulfan, Ethiofencarb, Fenobucarb, Formetanate, Furathiocarb, Isoprocarb, Methiocarb, Methomyl, Metolcarb, Oxamyl, Pirimicarb, Propoxur, Thiodicarb, Thiofanox, Triazamate, Trimethacarb, XMC, Xylylcarb
	1B Organophosphates	Acephate, Azamethiphos, Azinphos-ethyl, Azinphos-methyl, Cadusafos, Chlorethoxyfos, Chlorfenvinphos, Chlormephos, Chlorpyrifos, Chlorpyrifos-methyl, Coumaphos, Cyanophos, Demeton-S-methyl, Diazinon, Dichlorvos/ DDVP, Dicrotophos, Dimethoate, Dimethylvinphos, Disulfoton, EPN, Ethion, Ethoprophos, Famphur, Fenamiphos, Fenitrothion, Fenthion, Fosthiazate, Heptenophos, Isofenphos, Isopropyl O-(methoxyaminothio-phosphoryl) salicylate, Isoxathion, Malathion, Mecarbam, Methamidophos, Methidathion, Mevinphos, Monocrotophos, Naled, Omethoate, Oxydemeton-methyl, Parathion, Parathion-methyl, Phenthoate, Phorate, Phosalone, Phosmet, Phosphamidon, Phoxim, Pirimiphos-methyl, Profenofos, Propetamphos, Prothiofos, Pyraclofos, Pyridaphenthion, Quinalphos, Sulfotep, Tebupirimfos, Temephos, Terbufos, Tetrachlorvinphos, Thiometon, Triazophos, Trichlorfon, Vamidothion
2 GABA-gated chloride channel antagonists Nerve action {Strong evidence that action at this protein is responsible for insecticidal effects}	2A Cyclodiene organochlorines	Chlordane, Endosulfan
	2B Phenylpyrazoles (Fiproles)	Ethiprole, Fipronil
3 Sodium channel modulators Nerve action {Strong evidence that action at this protein is responsible for insecticidal effects} <i>* Please see footnotes for further information on the use of compounds between sub-groups</i>	3A Pyrethroids Pyrethrins	Acrinathrin, Allethrin, d-cis-trans Allethrin, d-trans Allethrin, Bifenthrin, Bioallethrin, Bioallethrin S-cyclopentenyl, Bioresmethrin, Cycloprothrin, Cyfluthrin, beta-Cyfluthrin, Cyhalothrin, lambda-Cyhalothrin, gamma-Cyhalothrin, Cypermethrin, alpha-Cypermethrin, beta-Cypermethrin, theta-Cypermethrin, zeta-Cypermethrin, Cyphenothrin, (1 <i>R</i>)- <i>trans</i> -isomers], Deltamethrin, Empenthrin, (E <i>Z</i>)- (1 <i>R</i>)- isomers], Esfenvalerate, Etofenprox, Fenpropathrin, Fenvalerate, Flucythrinate, Flumethrin, tau-Fluvalinate, Halfenprox, Imiprothrin, Permethrin, Phenothrin [(1 <i>R</i>)- <i>trans</i> - isomer], Prallethrin, Pyrethrins (pyrethrum) Resmethrin, RU 15525, Silafluofen, Tefluthrin, Tetramethrin, Tetramethrin [(1 <i>R</i>)-isomers], Tralomethrin, Transfluthrin, ZXI 8901,
	3B DDT Methoxychlor	DDT Methoxychlor

IRAC Mode of Action Classification v 6.1, August 2008 ¹		
Main Group and Primary Site of Action	Chemical Sub-group or exemplifying Active Ingredient	Active Ingredients
4 Nicotinic acetylcholine receptor agonists Nerve action {Strong evidence that action at one or more of this class of protein is responsible for insecticidal effects}	4A Neonicotinoids	Acetamiprid, Clothianidin, Dinotefuran, Imidacloprid, Nitenpyram, Thiacloprid, Thiamethoxam,
	4B Nicotine	Nicotine
5 Nicotinic acetylcholine receptor allosteric activators Nerve action {Strong evidence that action at one or more of this class of protein is responsible for insecticidal effects}	Spinosyns	Spinetoram, Spinosad
6 Chloride channel activators Nerve and muscle action {Strong evidence that action at one or more of this class of protein is responsible for insecticidal effects}	Avermectins, Milbemycins	Abamectin, Emamectin benzoate, Milbemectin
7 Juvenile hormone mimics Growth regulation {Target protein responsible for biological activity is unknown, or uncharacterized}	7A Juvenile hormone analogues	Hydroprene, Kinoprene, Methoprene
	7B Fenoxycarb	Fenoxycarb
	7C Pyriproxyfen	Pyriproxyfen
8 Miscellaneous non-specific (multi-site) inhibitors	8A Alkyl halides	Methyl bromide and other alkyl halides
	8B Chloropicrin	Chloropicrin
	8C Sulfuryl fluoride	Sulfuryl fluoride
	8D Borax	Borax
	8E Tartar emetic	Tartar emetic

IRAC Mode of Action Classification v 6.1, August 2008 ¹		
Main Group and Primary Site of Action	Chemical Sub-group or exemplifying Active Ingredient	Active Ingredients
9 Selective homopteran feeding blockers {Target protein responsible for biological activity is unknown, or uncharacterized}	9B Pymetrozine	Pymetrozine
	9C Flonicamid	Flonicamid
10 Mite growth inhibitors Growth regulation {Target protein responsible for biological activity is unknown, or uncharacterized}	10A* Clofentezine Hexythiazox <i>* Please see footnotes for further information on this sub-grouping</i>	Clofentezine, Hexythiazox
	10B Etoxazole	Etoxazole
11 Microbial disruptors of insect midgut membranes (includes transgenic crops expressing <i>Bacillus thuringiensis</i> toxins, however specific guidance for resistance management of transgenic crops is not based on rotation of modes of action)	<i>Bacillus thuringiensis</i> or <i>Bacillus sphaericus</i> and the insecticidal proteins they produce	<i>Bacillus thuringiensis</i> subsp. <i>israelensis</i> <i>Bacillus sphaericus</i> <i>Bacillus thuringiensis</i> subsp. <i>aizawai</i> <i>Bacillus thuringiensis</i> subsp. <i>kurstaki</i> <i>Bacillus thuringiensis</i> subsp. <i>tenebrionis</i> Bt crop proteins: Cry1Ab, Cry1Ac, Cry1Fa, Cry2Ab, mCry3A, Cry3Ab, Cry3Bb, Cry34/35Ab1
12 Inhibitors of mitochondrial ATP synthase Energy metabolism {Compounds affect the function of this protein, but it is not clear that this is what leads to biological activity}	12A Diafenthuron	Diafenthuron
	12B Organotin miticides	Azocyclotin, Cyhexatin, Fenbutatin oxide
	12C Propargite	Propargite
	12D Tetradifon	Tetradifon
13 Uncouplers of oxidative phosphorylation via disruption of the proton gradient Energy metabolism	Chlorfenapyr	Chlorfenapyr
	DNOC	DNOC

IRAC Mode of Action Classification v 6.1, August 2008 ¹		
Main Group and Primary Site of Action	Chemical Sub-group or exemplifying Active Ingredient	Active Ingredients
<p>14 Nicotinic acetylcholine receptor channel blockers</p> <p>Nerve action</p> <p>{Compounds affect the function of this protein, but it is not clear that this is what leads to biological activity}</p>	Nereistoxin analogues	Bensultap, Cartap hydrochloride, Thiocyclam, Thiosultap-sodium
<p>15 Inhibitors of chitin biosynthesis, type 0, Lepidopteran</p> <p>Growth regulation</p> <p>{Target protein responsible for biological activity is unknown, or uncharacterized}</p>	Benzoylureas	Bistrifluron, Chlorfluazuron, Diflubenzuron, Flucycloxuron, Flufenoxuron, Hexaflumuron, Lufenuron, Novaluron, Noviflumuron, Teflubenzuron, Triflumuron
<p>16 Inhibitors of chitin biosynthesis, type 1, Homopteran</p> <p>Growth regulation</p> <p>{Target protein responsible for biological activity is unknown, or uncharacterized}</p>	Buprofezin	Buprofezin
<p>17 Moulting disruptor, Dipteran</p> <p>Growth regulation</p> <p>{Target protein responsible for biological activity is unknown, or uncharacterized}</p>	Cyromazine	Cyromazine
<p>18 Ecdysone receptor agonists</p> <p>Growth regulation</p> <p>{Strong evidence that action at this protein is responsible for insecticidal effects}</p>	Diacylhydrazines	Chromafenozide, Halofenozide, Methoxyfenozide, Tebufenozide

IRAC Mode of Action Classification v 6.1, August 2008 ¹		
<i>Main Group and Primary Site of Action</i>	Chemical Sub-group or exemplifying Active Ingredient	Active Ingredients
19 Octopamine receptor agonists Nerve action {Good evidence that action at one or more of this class of protein is responsible for insecticidal effects}	Amitraz	Amitraz
20 Mitochondrial complex III electron transport inhibitors (Coupling site II) Energy metabolism {Good evidence that action at this protein complex is responsible for insecticidal effects}	20A Hydramethylnon	Hydramethylnon
	20B Acequinocyl	Acequinocyl
	20C Fluacrypyrim	Fluacrypyrim
21 Mitochondrial complex I electron transport inhibitors Energy metabolism {Good evidence that action at this protein complex is responsible for insecticidal effects}	21A METI acaricides	Fenazaquin, Fenpyroximate, Pyrimidifen, Pyridaben, Tebufenpyrad, Tolfenpyrad
	21B Rotenone	Rotenone (Derris)

IRAC Mode of Action Classification v 6.1, August 2008 ¹		
Main Group and Primary Site of Action	Chemical Sub-group or exemplifying Active Ingredient	Active Ingredients
22* Voltage-dependent sodium channel blockers Nerve action {Good evidence that action at this protein complex is responsible for insecticidal effects} <i>* Please see footnotes for further information on sub-grouping</i>	22A Indoxacarb	Indoxacarb
	22B Metaflumizone	Metaflumizone
23 Inhibitors of acetyl CoA carboxylase. Lipid synthesis, growth regulation {Good evidence that action at this protein is responsible for insecticidal effects}	Tetronic and Tetramic acid derivatives	Spirodiclofen, Spiromesifen, Spirotetramat
24 Mitochondrial complex IV electron transport inhibitors Energy metabolism {Good evidence that action at this protein complex is responsible for insecticidal effects}	24A Phosphine	Aluminium phosphide, Calcium phosphide, Phosphine, Zinc phosphide
	24B Cyanide	Cyanide
25 Vacant		
26 Vacant		
27 Vacant		
28 Ryanodine receptor modulators Nerve and muscle action {Good evidence that action at this protein complex is responsible for insecticidal effects}	Diamides	Chlorantraniliprole, Flubendiamide

IRAC Mode of Action Classification v 6.0, June2008 ¹		
Main Group and Primary Site of Action	Chemical Sub-group or exemplifying Active Ingredient	Active Ingredients
un Compounds of unknown or uncertain mode of action² {Target protein responsible for biological activity is unknown, or uncharacterized}	Azadirachtin	Azadirachtin
	Benzoximate	Benzoximate
	Bifenazate	Bifenazate
	Chinomethionat	Chinomethionat
	Cryolite	Cryolite
	Dicofol	Dicofol
	Pyridalyl	Pyridalyl

Notes to be read in association with the above classification:

Mode of action assignments will usually involve identification of the target protein responsible for the biological effect, although groupings can be made where compounds share distinctive physiological effects and have related chemical structures.

¹ Inclusion of a compound in the list above does not necessarily signify regulatory approval

² A compound with an unknown or controversial mode of action or an unknown mode of toxicity will be held in category 'un' until evidence becomes available to enable that compound to be assigned to a more appropriate mode of action class

Criteria for descriptors of the quality of mode of action information

{Strong evidence that action at this protein (or protein complex) is responsible for insecticidal effects}	Potent effects on the function of the target protein <u>and</u> either resistance due to mutation / overexpression / removal of this protein <u>or</u> correlation of potency between effects on the protein and biological activity for a set of analogues.
{Good evidence that action at this protein (or protein complex) is responsible for insecticidal effects}	Highly potent effects on the function of the protein combined with clearly consistent physiological effects
{Compounds affect the function of this protein, but it is not clear that this is what leads to biological activity}	Compounds (or their metabolites) have moderate or low potency on the function of the protein, and there is little or no evidence associating this effect with biological activity. Compounds may be grouped because of similarity of structure and distinctive physiological effect.
{Target protein responsible for biological activity is unknown, or uncharacterized}	Compounds may be grouped because of similarity of structure and distinctive physiological effect.

Sub-groups

Sub-groups represent distinct structural classes believed to have the same mode of action. In principle, they provide a useful level of differentiation between compounds that may bind at the same target site but are nevertheless structurally different enough that the risk of metabolic cross-resistance is lower than for close chemical analogs. Subgroups are likely to be metabolized by different enzymes and may bind differently enough within the target site that the chance of selection for either metabolic or target-site resistance is reduced compared to close analogs. In the absence of other alternatives, it may be possible to rotate compounds between sub-groups if it is clear that cross resistance mechanisms do not exist in the target populations. By definition, subgroups are established to represent distinct chemical classes with a common mode of action. Whether they should be rotated or not will depend on knowledge and experience of cross-resistance patterns, resistance mechanisms, and furthermore on the pest, crop and region considered.

Sub-group number	Notes
1A & B	If there are no other alternatives, compounds from groups 1A and 1B may be rotated in situations where cross-resistance mechanisms are known to be absent in the insect populations to be treated.
3A & B	If there are no other alternatives, compounds from groups 3A and 3B may be rotated in situations where cross-resistance mechanisms (e.g., kdr) are known to be absent in the insect populations to be treated. Because DDT is no longer used in agriculture, this is only applicable for the control of human disease vectors such as mosquitoes, because of a lack of alternatives.
10A	Clofentezine and Hexythiazox have been grouped because they commonly exhibit cross-resistance even though they are structurally distinct, and the target site for neither compound is known.
22A & B	Although these compounds are believed to have the same target site, they have been sub-grouped because they are chemically distinct, and current evidence indicates that the risk of metabolic cross-resistance is low..

General notes

This document has been prepared using the most up-to-date information available to IRAC. It is provided to user groups, grower organisations, extension personnel, regulatory authorities such as the US EPA and all those involved in resistance management, as an agreed definitive statement by the agrochemical industry on the mode of action of insecticides currently in use. Given the broad nature of this user community and the many uses that are demanded of this document, readers should be aware that IRAC has sought to provide a workable listing that serves the needs of as many of these users as possible.

In a continued effort to refine the list, readers are kindly asked to inform IRAC of factual errors or omissions, citing definitive evidence wherever possible. Such submissions should be directed to IRAC via the website at: www.ircac-online.org. Suggestions for improvements are likewise welcome.

Updates

The IRAC MoA classification is reviewed and reissued at intervals as required. The latest version is always available for reference via IRAC's website www.irc-online.org

Submissions for new active ingredients together with recommendations for their inclusion in specific new or existing MoA classes, together with citations or evidence for classification should be made to IRAC through the website. IRAC member companies review draft versions before an agreed final version of any update is published. In addition, a number of internationally well-known insect toxicologists and biochemists are also consulted regarding additions, deletions or other changes to the list.

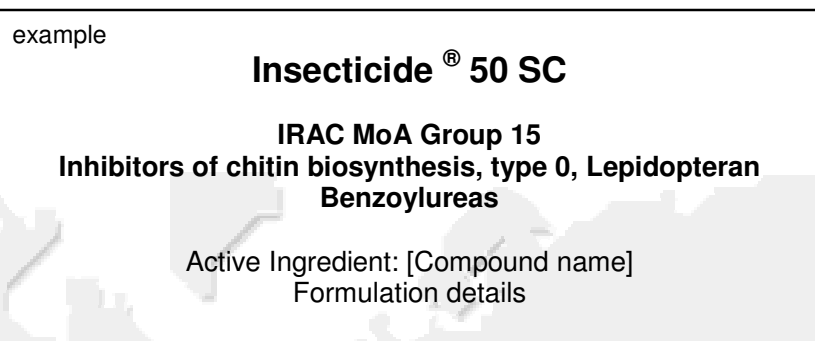
Changes to the listing may have serious consequences. In those countries where insecticide labels display the IRAC MoA number or class name as an aid to good IRM (see Appendix 1), changes may be especially costly to implement. In general, changes are therefore only endorsed when the scientific evidence supporting the change is compelling.

Superseded, obsolete or withdrawn compounds for which no current registration exists, and that are no longer in common usage, are not listed.



Appendix 1**Product labels: Indication of MoA of active ingredient and accompanying IRM advice**

To assist users in the selection of insecticides for use in IRM strategies employing sequences, rotations or alternations of MoA groups, IRAC is encouraging producers to clearly indicate the IRAC MoA group number and description on the product label, and to accompany this with appropriate advice of the type indicated below. Thus, in addition to the detailed product information, handling, and safety information required by local regulations, a typical title label should clearly indicate the IRAC MoA Group number & description, and minimal, brief advice on IRM as indicated in the example below.



“For resistance management purposes, Insecticide 50SC is an IRAC Mode of Action Group 15 insecticide. Any insect population may contain individuals naturally resistant to Insecticide 50SC and other Group 15 insecticides. If these insecticides are used repeatedly, the resistant individuals may eventually dominate the pest insect population. These resistant insects may not be controlled by Insecticide 50SC or by other Group 15 insecticides. To delay the development of resistance:

- Avoid exclusive repeated use insecticides from the same chemical subgroup, (indicated by the IRAC Mode of Action Group number).
- Alternate with products from other IRAC Mode of Action Groups
- Integrate other control methods (chemical, cultural, biological) into insect control programs.

For further information on resistance management and advice on IRM programmes contact your local distributor.”

Appendix 2

The following IRM principles are recommended and endorsed by IRAC:

- a. Consult a local agricultural advisor or extension services in the area for up-to-date recommendations and advice on IPM and IRM programmes
- b. Consider options for minimizing insecticide use by selecting early-maturing or pest-tolerant varieties of crop plants
- c. Include effective cultural and biological control practices that work in harmony with effective IRM programmes. Adopt all non-chemical techniques known to control or suppress pest populations, including biological sprays such as Bt's, resistant varieties, within-field refugia (untreated areas) and crop rotation
- d. Where possible select insecticides and other pest management tools which preserve beneficial insects
- e. Use products at their full, recommended doses. Reduced (sub-lethal) doses quickly select populations with average levels of tolerance, whilst doses that are too high may impose excessive selection pressures
- f. Appropriate, well-maintained equipment should be used to apply insecticides. Recommended water volumes, spray pressures and optimal temperatures should be used to obtain optimal coverage
- g. Where larval stages are being controlled, target younger larval instars where possible because these are usually much more susceptible and therefore much more effectively controlled by insecticides than older stages
- h. Use appropriate local economic thresholds and spray intervals
- i. Follow label recommendations or local expert advice for use of alternations or sequences of different classes of insecticide with differing modes of action as part of an IRM strategy
- j. Where there are multiple applications per year or growing season, alternate products of different MoA classes
- k. In the event of a control failure, do not reapply the same insecticide but change the class of insecticides to one having a different mode of action and to which there is no [locally] known cross-resistance
- l. Mixtures may offer a short-term solution to resistance problems, but it is essential to ensure that each component of a mixture belongs to a different insecticide mode of action class, and that each component is used at its full rate
- m. Consideration should be given to monitoring for the incidence of resistance in the most commercially important situations and gauge levels of control obtained
- n. Withholding use of a product to which resistance has developed until susceptibility returns may be a valid tactic if sufficient alternative chemical classes remain to provide effective control.