IRAC MoA Classification for Mosquito Vectors of Disease

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(Based on the IRAC MoA Classification Scheme - Version 7.4)

1. Mode of Action Classification

The IRAC mode of action classification scheme is an up-to-date and accurate guide which may be used in formulating resistance management strategies. IRAC has worked with several government agencies to develop this comprehensive scheme with the eventual goal of including such information on all product labels. The system lists all of the current known insecticide modes of action (designated by a unique number) along with the chemical classes in use, and examples of the active ingredients that belong to each class. By searching on the chemical name of the compound it is therefore possible to determine its mode of action (this can easily be done on the IRAC web site by using a tool called eClassification).

Insecticides are assigned to groups (designated by number) based on the primary target site of action. There may be chemical subgroups (designated by letter) that have the same mode of action but are chemically different and so are less likely to lead to cross-resistance. For example, the organophosphate (1A) and the carbamates (1B) have the same mode of action, but there is not always cross-resistance to the two groups, especially when metabolic resistance is involved. In certain circumstances class 1A and 1B products could be rotated (as opposed to products in the same subclass which shouldn't). If rotation of insecticides from different classes is not possible, then rotation between subclasses is preferred to the use of the same insecticide.

2. The IRAC Scheme

The MOA Classification Scheme developed and endorsed by IRAC is based on the best available evidence of the MoA 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 users are aware of MoA groups and that they have a sound basis on which to implement sustainable resistance management through the effective use of alternations, sequences or rotations of insecticides with different modes of action

2.1. Rules for inclusion of a compound in the MoA list and MoA Classification for Vectors

- Only those insecticides approved through the WHO Pesticide Evaluation Scheme (WHOPES) are included in the MoA Classification for Vectors.
- Chemical nomenclature is generally based on that appearing in *The Pesticide Manual*, 16th edition, November 2012, Ed. Colin MacBean, published by The British Crop Protection Council. ISBN 9781901396867
- 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 MoA group, each is named according to the above rules, with chemical sub-groups having precedence over single active ingredients.

2.2. Classification Table - Larvicides

Based on IRAC MoA Classification v 7.4, May 2015		
Main Group and Primary Site of Action	**Chemical Sub-group or exemplifying Active Ingredient**	**Active Ingredients**
1* **Acetylcholinesterase (AChE) inhibitors** Nerve action {Strong evidence that action at this protein is responsible for insecticidal effects} **Please see footnotes for further information on the use of compounds between sub-groups*	**1B** Organophosphates	Fenthion, Pirimiphos-methyl, Temephos
5 **Nicotinic acetylcholine receptor (nAChR) allosteric modulators** Nerve action {Strong evidence that action at one or more of this class of protein is responsible for insecticidal effects}	**5** Spinosyns	Spinosad
7 **Juvenile hormone mimics** Growth regulation {Target protein responsible for biological activity is unknown, or uncharacterized}	**7A** Juvenile hormone analogues	Hydroprene, Methoprene
	7C Pyriproxyfen	Pyriproxyfen
11 **Microbial disruptors of insect midgut membranes**	**11A** *Bacillus thuringiensis* and the insecticidal proteins they produce	*Bacillus thuringiensis* subsp. *Israelensis* strain AM65-52
15 **Inhibitors of chitin biosynthesis, type 0** Growth regulation {Target protein responsible for biological activity is unknown, or uncharacterized}	**15** Benzoylureas	Diflubenzuron, Novaluron

2.3. Classification Table - Adulticides

Based on IRAC MoA Classification v 7.4, May 2015			
Main Group and Primary Site of Action	***Chemical Sub-group or exemplifying Active Ingredient***	***Active Ingredients***	***Uses recommended by WHO***
1* **Acetylcholinesterase (AChE) inhibitors** Nerve action {Strong evidence that action at this protein is responsible for insecticidal effects} **Please see footnotes for further information on the use of compounds between sub-groups*	**1A** Carbamates	Bendiocarb	IRS
		Propoxur	IRS
	1B Organo-phosphates	Fenitrothion	IRS
		Malathion	IRS, SS
		Pirimiphos-methyl	IRS
3* **Sodium channel modulators** Nerve action {Strong evidence that action at this protein is responsible for insecticidal effects} **Please see footnotes for further information on the use of compounds between sub-groups*	**3A** Pyrethroids Pyrethrins	Bifenthrin	IRS
		Cyfluthrin	IRS, ITN
		lambda-Cyhalothrin	IRS, ITN, SS, LN**+**
		alpha-Cypermethrin	IRS, ITN, LN*****
		Deltamethrin	IRS, ITN, LN, SS
		Etofenprox	IRS, ITN
		Permethrin	ITN, LN, SS
		d-d, trans-cyphenothrin	SS
	3B DDT	DDT	IRS

Table Notes:

- IRS = Insecticide Residual Spray, SS = Space Spray, ITN = Insecticide Treated Nets, LN = Long Lasting Insecticidal Nets, LN***** = Long Lasting Insecticidal Nets with interim WHOPES approval and LN**+** = Long Lasting Net Treatment with interim WHOPES approval.
- Inclusion of a compound in the classification above does not necessarily signify regulatory approval.
- MoA 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.
- Please refer to the WHOPES website for full details, specifications and manufacturers of WHOPES approved insecticides.

2.4. Criteria for descriptors of the quality of MoA 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 and either resistance due to mutation / overexpression / removal of this protein or correlation of potency between effects on the protein and biological activity for a set of analogues.
{Target protein responsible for biological activity is unknown, or uncharacterized}	Compounds may be grouped because of similarity of structure and distinctive physiological effect.

2.5. Notes regarding sub-groups

Sub-groups represent distinct chemical classes that are believed to have the same MoA but are different enough in chemical structure or mode of interaction with the target protein that the chance of selection for either metabolic or target-site cross-resistance is reduced compared to close analogs. Sub-groups may also distinguish compounds that are chemically similar but known to bind differently within the target or to have differential selectivity among multiple targets.

The cross-resistance potential between sub-groups is higher than that between different groups, so rotation between sub-groups should be avoided. In exceptional circumstances (i.e. where effective registered insecticides from other mode of action groups are unavailable) rotation may be considered following consultation with local expert advice and where cross-resistance does not exist. These exceptions should not be considered sustainable resistance management strategies, and alternative options should be sought to maintain pest susceptibility.

Sub-groups	Notes
1A & 1B	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. Different resistance mechanisms that are not linked to target site of action, such as enhanced metabolism, are common for the OPs. Some of these metabolic resistance mechanisms may be specific to a particular subgroup or particular compounds within the OPs. As a result, there are proven examples of the successful management of resistance to a particular compound or subgroup of compounds within the OPs using OP compounds from a different subgroup.
3A & 3B	If there are no other alternatives, compounds from groups 3A and 3B may be rotated in situations where cross-resistance mechanisms (e.g., *kdr* mutations) are known to be absent in the insect populations to be treated.

2.6. General notes & MoA Classification Scheme Updates

- Further details on the MoA Group Descriptors are given in the Appendix.
- The Classification Scheme 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 MoA of insecticides currently in use.
- The IRAC MoA classification is reviewed and reissued at intervals as required. The latest version is always available for reference via the IRAC website (www.irac-online.org).
  - Proposals for new compounds or for changes to the current IRAC MoA scheme should be submitted to the IRAC MoA Team via the IRAC International Coordinator. A link to the coordinator is provided on the IRAC website (www.irac-online.org) at the bottom of each page under 'Contact'. Alternatively, the online request can be completed at
  - http://www.irac-online.org/submit-an-active/
- 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 can be 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 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.
- 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. Suggestions for improvements are likewise welcome.

3. Further Information

Further information is available on the IRAC website at www.irac-online.org. This includes the publications:

- IRAC MoA Classification
- Prevention and Management of Insecticide Resistance in Vectors of Public Health Importance.

Further information on the WHO Pesticide Evaluation Scheme (WHOPES) is available on the website - http://www.who.int/whopes/en/

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.

Inclusion of the IRAC group on the label is a warrant from the manufacturer that the insecticide has been classified by IRAC, the only authoritative and comprehensive list of IRAC-classified insecticides. If an insecticide is not listed and falls within the scope of the IRAC classification as stated at the beginning of this document, please petition IRAC for classification of the product, before drafting a label. Insecticidal materials falling outside the scope of the classification, including insecticidal oils, soaps, living organisms and viruses, may be labeled as "Exempt from IRAC Classification".

Example

Insecticide ® 50 SC

IRAC MoA Group 15
Inhibitors of chitin biosynthesis, type 0
Benzoylureas

Active Ingredient: [Compound name]
Formulation details

For resistance management purposes, Insecticide 50SC is an IRAC MoA 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 of insecticides from the same chemical subgroup, (indicated by the IRAC MoA Group number).
- Alternate with products from other IRAC MoA Groups
- Integrate other control methods (chemical, biological) into vector control programs.

For further information and advice on resistance management strategies contact your local distributor.

Appendix 2

MoA Group Descriptors

Nerve and Muscle Targets

Most current insecticides act on nerve and muscle targets. Insecticides that act on these targets are generally fast acting.

Group 1 Acetylcholinesterase (AChE) inhibitors

Inhibit AChE, causing hyperexcitation. AChE is the enzyme that terminates the action of the excitatory neurotransmitter acetylcholine at nerve synapses.

Group 3 Sodium channel modulators

Keep sodium channels open, causing hyperexcitation and, in some cases, nerve block. Sodium channels are involved in the propagation of action potentials along nerve axons.

Group 5 Nicotinic acetylcholine receptor (nAChR) allosteric modulators

Allosterically activate nAChRs, causing hyperexcitation of the nervous system. Acetylcholine is the major excitatory neurotransmitter in the insect central nervous system.

Growth and Development Targets

Insect development is controlled by the balance of two principal hormones: juvenile hormone and ecdysone. Insect growth regulators act by mimicking one of these hormones or directly perturbing cuticle formation/deposition or lipid biosynthesis. Insecticides that act on individual targets in this system are generally slow to moderately slow acting.

Group 7 Juvenile hormone mimics

Applied in the pre-metamorphic instar, these compounds disrupt and prevent metamorphosis.

Group 15 Inhibitors of chitin biosynthesis, type 0

Incompletely defined MoA leading to inhibition of chitin biosynthesis.

Midgut Targets

Group 11 Microbial disruptors of insect midgut membranes

Protein toxins that bind to receptors on the midgut membrane and induce pore formation, resulting in ionic imbalance and septicemia.

Appendix 3

Key Considerations in Vector Resistance Management

- Prevention of resistance is much better than trying to resolve the problem once resistance has developed. Insect susceptibility and effective products are both non-renewable valuable economic resources that should be preserved.
- Resistance management strategies are most effective when developed before control programmes are started.
- It is essential that the delivery of insecticide to the target insect is correct. This includes dose, application timing and technique.
- Insecticidal interventions should be part of a wider integrated vector management programme.
- If resistance occurs take immediate steps to contain it and reduce the selection pressure produced by the insecticide.
- Failure to successfully manage resistance has well documented financial implications and failure to implement an Insecticide Resistance Management programme on financial grounds is a false economy that will lead to increased costs in the future. For more information see the IRAC publication “Prevention and Management of Insecticide Resistance in Vectors of Public Health Importance” available from the IRAC website (www.irac-online.org).