Insecticide Resistance Management
Global Guidelines for
IRAC Group 28 (Diamide) Insecticides

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Prepared by: IRAC Group 28 (Diamide) Working Group

Contents

Summary

IRAC International "Group 28 Working Group" supports the IRAC General Principles of Insecticide Resistance Management (see Appendix III). The Resistance Management Guidelines contained in this document complement the IRAC General Principles, and are specifically aimed at properly managing the susceptibility of target insect pest populations to Group 28 Insecticides (see reference table of IRAC Mode of Action Classification, Appendix IV). These general guidelines are a reference document for the IRAC Country Groups and other regional IRM groups as they develop language for their local labels, rotational strategies, product positioning, and portfolio integration. Local guidelines should not be less restrictive but may be more restrictive than the Guidelines in this document.

To prevent the development and spread of insecticide resistance, Group 28 Insecticides should not be used exclusively in one crop season to numerous generations of the same target pest. It is fundamentally important that applications of Group 28 Insecticides are alternated with non-Group 28 insecticides that are effective against the target species and control the insect pest by a different mode of action (MOA). Always follow label recommendations on dose, water volumes, spray timing, and additional locally specific IRM guidelines.

Risk of Resistance Development

There are currently no recorded cases of insect resistance to IRAC Group 28 insecticides. However, as of time of writing, the number of granted registrations for these products is limited. As registrations and product use increases, so will the risk of resistance development.

Factors that may contribute to the development of resistance to Group 28 Insecticides:

- **Long residual activity: Group 28 insecticides are highly effective and can provide long residual activity depending on method of application and rate used. While these characteristics are desirable, if not properly managed, they can impose significant selection pressure on a target pest population. This can decrease the susceptibility of selected pest populations in a relatively short period of time.**

- **Risk for cross-resistance: Group 28 Insecticides have a unique mode of action and novel chemical structure types and thus, *"target site cross-resistance"* (see Appendix II) is most-likely a lower risk than resistance resulting from enhanced enzymatic metabolism by individuals within the pest population. Such metabolic resistance mechanisms may confer *"metabolic cross-resistance"* to unique and novel insecticides such as those in Group 28.**

- **Multiple Group 28 products commercially available: At the time of writing there are four companies (Bayer CropScience, DuPont, Nihon Nohyaku, and Syngenta) that have developed and registered products containing a Group 28 Insecticide. This increases the challenge of maintaining susceptible populations and requires discipline in implementing coordinated IRM programs through inter-company cooperative efforts.**

- **Wide natural variation in susceptibility: Baseline susceptibility monitoring studies have highlighted the existence of natural variability in the susceptibility of some target pest species among tested populations worldwide. This highlights the need for end users to follow local recommended application guidelines and follow recommended resistance management programs to ensure long term effective control.**

Global IRM Principles for IRAC Group 28 Insecticides

◆ USE THESE GUIDELINES FOR LABEL DEVELOPMENT, PRODUCT POSITIONING, AND DEVELOPMENT OF LOCAL IRM PROGRAMS.

Group 28 Insecticides control insect pests by affecting ryanodine receptors in muscle cells. The risk for resistance development exists and can occur rapidly. Therefore, it is critical that preventive measures are taken, with the objective of minimizing selection for resistance development. Rotation of *effective* compounds with *different* modes of action minimizes the potential for resistance development to any given MOA.

1. **Position Group 28 Insecticides in Integrated Pest Management and Insecticide Resistance Management Programs** (see IRAC General Guidelines, Appendix III).

2. **Ensure correct use of the Group 28 Insecticide Label which include:**

   a. Where possible according to local regulatory guidelines, include the Group 28 MOA Classification (designation as shown below) on the label (preferably placed by the list of ingredients on the label or within the IRM statement).

GROUP	28	INSECTICIDE

   b. Where possible a comprehensive IRM statement (reference example below).

   c. Where possible, the maximum number of applications per crop cycle

   d. Where possible, the maximum seasonal use rate per crop cycle

Example 1: Comprehensive Version – Preferred

Insecticide Resistance Management (IRM)

General Recommendations: Repeated and exclusive use of ____ (product name) or other Group 28 Insecticides may lead to the development of insect resistant populations in some crops. Maintaining the longevity of ____ (product name) as an effective pest control tool for growers is critical, thus an insecticide resistance management (IRM) strategy should be established in the area of use. ____ (product name) should wherever possible be incorporated into an Integrated Pest Management program that includes cultural and biological control practices in association with the IRM guidelines detailed below. Consult your local agricultural authorities or company representative for more details.

Unless directed otherwise in the specific crop/insect sections of the label, the following practices are recommended to prevent or delay the development of insecticide resistance to ____ (product name):

- Apply ____ (product name) or other Group 28 insecticides using a "window" approach to avoid exposure of consecutive insect pest generations to the same mode of action. Multiple successive applications of ____ (product name) are acceptable if they are used to treat a single insect generation.
- Following a "window" of ____ (product name) or other Group 28 insecticide, rotate to a "window" of applications of effective insecticides with a different mode of action.
- The total exposure period of all "Group 28-active windows" applied throughout the crop cycle (from seedling to harvest) should not exceed 50% of the crop cycle.
- Avoid using less than labeled rates when applied alone or in tank mixtures.
- Target most susceptible insect life stages, whenever possible.
- Monitor insect populations for product effectiveness. If poor performance cannot be attributed to improper application or extreme weather conditions, a resistant strain of insect may be present. In this situation, ____ (product name) or other products with a similar mode of action may not provide adequate control. If insect resistance is a reasonable possibility, immediately consult with your local company representative or agricultural advisor for the best alternative method of control.

For additional information on insect resistance, modes of action and monitoring visit the Insecticide Resistance Action Committee (IRAC) on the web at http://www.irac-online.org.

Example 2: Short Version

Insecticide Resistance Management (IRM)

General Recommendations:

____ (product name) contains _____ (active ingredient name), a Group 28 Insecticide.

Unless directed otherwise in the specific crop/insect sections of the label, the following practices are recommended to prevent or delay the development of insecticide resistance to ____ (product name) and to Group 28 insecticides:

- Apply ____ (product name) or other Group 28 insecticides using a "window" approach to avoid exposure of consecutive insect pest generations to the same mode of action. Multiple successive applications of ____ (product name) are acceptable if they are used to treat a single insect generation.
- Following a "window" of ____ (product name) or other Group 28 insecticide, rotate to a "window" of applications of effective insecticides with a different mode of action.
- The total exposure period of all "Group 28-active windows" applied throughout the crop cycle (from seedling to harvest) should not exceed 50% of the crop cycle.
- Incorporate IPM techniques into the overall [pest management program.
- Monitor insect populations for loss of field efficacy.

For additional information on insect resistance, modes of action and monitoring visit the Insecticide Resistance Action Committee (IRAC) on the web at http://www.irac-online.org.

Example 3: Shortest Version – Minimal Text Required on Label

Insecticide Resistance Management (IRM)

General Recommendations:
In order to avoid fast resistance development, avoid treating consecutive generations of the target pest with the same product or products with the same mode of action. Apply ____ (product name) using a "window" approach, alternating blocks of treatments with ____ (product name) followed by blocks of treatments with other effective products with different modes of action. The total exposure period of all "Group 28 active windows" applied throughout the crop cycle cannot exceed 50% of the crop cycle.

For additional information on insect resistance, modes of action and monitoring visit the Insecticide Resistance Action Committee (IRAC) on the web at http://www.irac-online.org.

3. Apply Group 28 Insecticides using a 'window' approach to avoid exposure of consecutive pest generations to the same mode of action.

- A Group 28-Active window is defined as the period of residual activity provided by a single or sequential application(s) of a Group 28 Insecticide.
- A Group 28-Free window is the period between Group 28-Active windows, where target pests are controlled with other effective non-Group *28* insecticides.
- The total exposure period of all Group 28-Active windows applied throughout the crop cycle (from seeding to harvest) should not exceed more than 50% of the crop cycle. The maximum number of applications of Group 28 insecticides per crop cycle is calculated as the maximum seasonal rate allowed to be applied onto the crop in a single cropping cycle**,** divided by the max use rate per application. Note that this exercise must consider not simply single products, but rather a cross-analysis of all Group 28 insecticide products (i.e. chlorantraniliprole- and flubendiamide-containing products) registered for use in a given country and crop, their respective maximum seasonal rates and single use rates per application.

Note. Local deviations of the above guidelines should be brought to the attention of the manufacturers of these products as well as the regional and global IRAC committees for adjustments as needed to ensure sustainable use of Group 28 Insecticides.

3.1 Annual Crops: The duration of a Group 28-Active Window can be defined in one of two ways: (i) The duration of one generation of the targeted pest. Sequential applications may be possible for pests with longer generation cycles; (ii) The duration of the residual activity provided by a single application (alternative definition for cases where a single application exceeds the duration of one generation of the target pest).

- ❖ Limit the number of applications within a Group 28-Active window, based on known residual control provided. If additional control is needed, targeting a second generation of the same pest species, subsequent applications should be made with effective non-Group *2*8 insecticides (see diagram 1).
- ❖ Depending on the duration of the crop cycle and particular pest infestation periods, two or three Group 28-Active windows may be included against the very same pest species. In addition, effective insecticides belonging to a different mode of action (non-Group 28) must be alternated with each Group 28-Active window (see diagram 1).

See below, examples of recommended rotational programs, including Group 28-Active Windows alternated with Group 28-Free Windows:

- ◆ Residual activity provided by each Group 28-Active Window should not exceed one generation of the target pest. In cases where this may not be technically possible (i.e. period of residual activity provided by a single application is greater than the period of one generation of the target pest), limit the number of applications within the active window to a single application.
- ◆ Each Group 28-Active window should be followed by a Group 28-Free Window in which effective insecticides with different modes of action (non-Group 28) should be used.
- ◆ A new Group 28-Active window cannot be initiated *unless* at least one other effective non-Group 28 insecticide has been used in that field to control the following target pest generation.

Diagram 1 (Annual Crops):

← Crop Cycle Period →			
Group 28 Active Window	**Alternative MoA Window**	**Group 28 Active Window**	**Alternative MoA Window**
Single or Sequential application(s) depending on residual activity of treatment **but covering only one generation of the target pest** ***Note***. *If residual activity provided by a single application is longer than a single generation of the target pest, restrict use to a single application.*	Single or Sequential application(s) with alternative MoA insecticide class(es), **covering AT LEAST one generation of the target pest.** ***Note.*** *If residual activity provided by a single application is longer than a single generation of the target pest, restrict use to a single application.*	Single or Sequential application(s) depending on residual activity of treatment **but covering only one generation of the target pest.** ***Note.*** *If residual activity provided by a single application is longer than a single generation of the target pest, restrict use to a single application.*	Single or Sequential application(s) with alternative MoA insecticide class(es), **covering AT LEAST one generation of the target pest.** ***Note.*** *If residual activity provided by a single application is longer than a single generation of the target pest, restrict use to a single application.*

3.2 Perennial Crops: In perennial crops, generation time of lepidopteran pests is more predictable (e.g. codling moth in apples). In such cases, ensure that the period of insecticidal activity provided by a Group 28-Active window does not exceed the duration of one generation of the target pest (see diagram 2).

- For instance, use a Group 28 Insecticide to control the first generation and switch to a different and effective MOA to control the second generation.
- Or, Use non-Group 28 Insecticides to control the first generation, and reserve the Group 28 Insecticide for the control of the second generation. Do not apply the same MOA to consecutive generations of the same target pest.

Diagram 2 (Perennial Crops):

Group 28 Active Window	Alternative MoA Window
Single or Sequential application(s) depending on residual activity of treatment **but covering only one generation of the target pest.** ***Note***. *If residual activity provided by a single application is longer than a single generation of the target pest, restrict use to a single application.*	Single or Sequential application(s) with alternative MoA insecticide class(es). ***Note.*** *If residual activity provided by a single application is longer than a single generation of the target pest, restrict use to a single application.*

OR

Alternative MoA Window	Group 28 Active Window
Single or Sequential application(s) depending on residual activity of treatment **but covering only one generation of the target pest.** ***Note***. *If residual activity provided by a single application is longer than a single generation of the target pest, restrict use to a single application.*	Single or Sequential application(s) with alternative MoA insecticide class(es). ***Note.*** *If residual activity provided by a single application is longer than a single generation of the target pest, restrict use to a single application.*

4. IRM recommendations for multiple cropping scenarios (short cycle crops)
In case of repeated cultivation of short cycle crops (less than 50 days) do not treat consecutive crops, but alternate with different mode of actions. The residual control by group 28 compounds in multi cropping situations has to be less than 50% of the cropping time per year irrespective of the application method.

5. **Use of Group 28 Insecticides in insecticide mixtures:** Tank mixtures or pre-mixtures should not be applied where resistance* to either one or both of the components is known to be present in the target pest population. Any insecticide not belonging to Group 28 can be used as a rotation or mixture partner with Group 28 insecticides in accordance with label recommendations (i.e. no cross-resistance known to be present in the target pest population). However this may change as products are used and new knowledge is gathered, so please ask your local experts for advice.

   * *Resistance* to insecticides is 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 label recommendation for that pest species (IRAC definition).

APPENDIX I

New Mode of Action

Group 28 Insecticides have a novel mode of action which means that they DO NOT interact with the target sites affected by insecticides in IRAC MOA groups 1-27.

Mode of Action and Symptomology: Group 28 Insecticides control insect pests by activation of insect ryanodine receptors (RyRs). These receptors play a critical role in muscle function, modulating the release of calcium from internal stores. Group 28 Insecticides bind to these receptors, causing uncontrolled release and depletion of internal calcium, preventing further muscle contraction. Insects treated with Group 28 Insecticides exhibit rapid cessation of feeding, lethargy, regurgitation, muscle paralysis, and ultimately death.

APPENDIX II

What is Resistance and Cross-resistance (IRAC definitions)

Resistance to insecticides is 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 label recommendations for that pest species (IRAC). Resistance arises through the over-use or misuse of an insecticide 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.

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).

Because all compounds within a chemical sub-group share a common MOA, there is a high risk that the resistance mechanism that has developed will automatically confer cross-resistance to all compounds within the same sub-group. This concept is the basis of the IRAC Mode of Action Classification (see Appendix IV). And it is also the reason why it is essential for Group 28 Insecticides resistance management programs to consider and include as one group, all insecticides within Group 28 (Ryanodine Receptor Activators). Metabolic cross-resistance is unpredictable and it may not be managed by alternation of MOA's. The most appropriate but also resource intensive way of accessing the risk for metabolic cross-resistance is to conduct dose-response bioassays using samples of the target species collected at the specific locations of interest, since the metabolic profiles may vary widely from insect population to insect population.

Definition of Cross-resistance: abusive use of insecticide "A" causes high selection pressure upon the pest population, resulting in broad spectrum resistance not only to insecticide "A", but to one or several other insecticides. (a) *Target site cross-resistance*: abusive use of insecticide "A" within MOA group "X" selects for *mutant forms that have an altered target site*, resulting in broad spectrum resistance not only to insecticide "A", but to all insecticides that interfere with that particular

target site or, in other words, all insecticides with the same mode of action. (b) *Metabolic cross-resistance*: abusive use of insecticide "A" selects for mutant *forms that have increased or novel metabolic enzyme activity*, resulting in broad spectrum resistance not only to insecticide "A", but to one or more insecticides that share a chemical bond that can be broken and de-activated enzymatically. It is very difficult to predict which classes of chemistry or which MOA groups could be affected by metabolic cross-resistance. This phenomenon highlights the importance of extensive baseline testing prior to launch, which is the only way to identify metabolic cross-resistance such that it can be properly managed.

APPENDIX III

IRAC General Principles of Insecticide Resistance Management

Further information can be obtained from the Insecticide Resistance Action Committee or from their website at http://www.irac-online.org

Definitions of Resistance and Resistance Management: Resistance to insecticides is 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). The key to managing resistance is to reduce selection pressure caused by the over-use or misuse, because this could result in the selection of resistant forms of the pest and the consequent evolution of populations that are resistant to that insecticide or miticide.

Practical Principles of Insecticide Resistance Management (IRM): Consistent with IPM and IRM principles, IRAC recommends the following resistance management guidelines to keep valuable protection tools working effectively and minimize user costs.

1. Consult an advisor for insecticide resistance management and IPM strategies. Consider the pest management options available and map out a season-long plan to avoid unnecessary applications of insecticides. The best plans are those developed by local experts and farmers and adopted on a regional basis.
2. Before planting, consider the options for minimizing insecticide use by selecting early maturing varieties or varieties that are resistant to insect attack. Manage the crop for "earliness".
3. Consider an integrated approach incorporating as many different control mechanisms as possible. IPM-based programs will include the use of synthetic insecticides, biological insecticides, beneficial insects (predator/parasites), cultural practices, transgenic plants, crop rotation, pest-resistant crop varieties and chemical attractants or deterrents.
4. Select insecticides with care and consider the impact on future pest populations. Avoid broad-spectrum insecticides when a narrow or specific insecticide will suffice. A wide range of parameters should be considered beyond simply cost and effectiveness. These should include:
   Beneficial arthropods: Maintenance of beneficial arthropods can keep pest populations below economic thresholds, thereby reducing the need for treatments or the number of applications.

Product class: Follow label recommendations for rotating or mixing products from different classes based on modes of action, not just different brands (see IRAC Mode of Action Classification). When there are multiple applications per season, use alternate products from different mode of action classes so that only one generation per season is exposed to a class. If feasible, rotate products from different classes from year to year to reduce selection pressure when only one application is being made.

Rates and spray intervals: Use insecticides and miticides at labeled rates and spray intervals. Do not reduce or increase rates from manufacturer recommendations as this can hasten resistance development. Monitor subsequent pest levels to gauge control and the success of IRM programs.

Application of products: If resistance develops, the margin for error in terms of insecticide dose, timing, coverage, etc., assumes even greater importance. In the case of aerial application, the swath widths should be marked, preferably by permanent markers. Sprayer nozzles should be checked for blockage and wear, and be able to handle pressure adequate for good coverage. Spray equipment should be properly calibrated and checked on a regular basis. Also, in tree fruits, proper and intense pruning will allow better canopy penetration and tree coverage. Use application volumes and techniques recommended by the manufacturers and local advisors.

Tank Mixes: It is often considered necessary to tank mix different chemicals for improved or broader spectrum pest control. If this is to be successful it is important to mix compounds which have different modes of action to maximize pest control and reduce the potential for development of resistance. Where possible compounds should also persist on the crop or surface for similar periods in order to expose insects to both modes of action for the same length of time. Use of multiple products of the same mode of action in the spray tank will do little more than using an increased rate of a single compound of the same chemical class.

Timing of applications: Applications of insecticide and acaricides should be made against the most vulnerable life stage of the insect pest. Care should be taken to follow the recommendations of the manufacturer and local advisors.

5. Watch the pest population during the growing season. Regularly monitor fields to identify pests and natural enemies, estimate insect populations and track stage of development. Insecticides and miticides generally should be used only if insect counts exceed the local economic threshold or the point where economic losses exceed the costs of insecticide plus application. Time applications against the most susceptible life stages to gain maximum benefit from the product.
6. At the end of the season remove crop residues, as appropriate, to eliminate food sources and over wintering habitats for pests. Consider next year's IPM/ Insecticide Resistance Management plans while planning and preparing for next year's crops.
7. Prevention is the best strategy, but if you suspect resistance, first consider and eliminate other possible causes. In many instances, lack of control can be attributed to application error, equipment failure, or less-than-optimal environmental conditions. If these possibilities have been ruled out, work with local agricultural advisors and the manufacturer to confirm actual resistance to the compound applied. In the event of a control failure due to resistance, do not repeat the application with an insecticide of the same chemical class.

APPENDIX IV - Group 28 Diamide Products: Action Plan To Address Insect Resistance

Guideline for High Risk Insect Pests in Targeted Markets

Time ↓

Guidelines: PROCESS – PROCEDURES - ACTIONS	RESPONSIBILITY
INITIAL STEPS: (PRE-LAUNCH AND EARLY POST-LAUNCH)	
1. Establish standard diamide insecticide bioassays to test targeted insects **2. Develop baseline data on feral populations in targeted markets with diamide products** **3. Establish "Diagnostic Doses" for diamide products and targeted insect pests.**	**1. Company, GDWG*, IRAC Int'l** **2. Company (option-with GDWG)** **3. Company (option-with GDWG)**
IDENTIFICATION, CONFIRMATION, AND COMMUNICATION OF SUSCEPTIBILITY SHIFT IN INSECT PEST POPULATION	
4. Conduct susceptibility testing in targeted markets- monitoring for lower than expected mortality at diagnostic doses: **4.1 proactive monitoring program – optional** **4.2 testing in reaction to field performance issue** **5. Determine reduced susceptibility in insect population:** **5.1. replicate diagnostic dose bioassay (comparison with baseline)** **5.2 conduct full dose-response bioassay (comparison with baseline) - optional** **5.3 determine LC_{50} for susceptible population (calculate RR) - optional** **5.4 assess extent of susceptibility by regional monitoring (ID field failures, grower practices)** **6. If reduced susceptibility <u>is confirmed</u> by testing above:** **6.1 GDWG develops a message, approved by the affected company, that explains the status of confirmed insect resistance and communicates it to all appropriate entities.** **6.2 check for cross-resistance to other Group 28 products (including selected other products)** **6.3 identify resistance mechanisms**	**4.Company or Local DWG* or Contractor** **5. Company or Local DWG or contractor** **6.1 Affected Company + GDWG** **6.2 Company option** **6.3 Company option**
MITIGATION ACTIONS	
7. Country Diamide WG (if established) develops a case-adjusted IRM mitigation plan in conjunction with Global Diamide WG and local technical experts **8. Local Diamide WG aggressively implements the mitigation plan (training, monitoring, adjusts use recommendations) with assistance from academic and industry influencers** **9. Further restrictions of product use** **10. Continue susceptibility monitoring** * DWG – Diamide Working Group, GDWG - Global Diamide Working Group	**7 .Country and Global Diamide WG's and local influencers** **8. GDWG, local DWG, influencers** **9. Manufacturer option** **10. Company, Local DWG or Contractor**

APPENDIX V

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} *Please see footnotes for further information on the use of compounds between sub-groups	**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} *Please see footnotes for further information on the use of compounds between sub-groups	**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*R*)-*trans*-isomers], Deltamethrin, Empenthrin , (*EZ*)- (1*R*)- isomers], Esfenvalerate, Etofenprox, Fenpropathrin, Fenvalerate, Flucythrinate, Flumethrin, tau-Fluvalinate, Halfenprox, Imiprothrin, Permethrin, Phenothrin [(1*R*)-trans- isomer], Prallethrin, Pyrethrins (pyrethrum)Resmethrin, RU 15525, Silafluofen, Tefluthrin, Tetramethrin, Tetramethrin [(1*R*)-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 **Please see footnotes for further information on this sub-grouping*	Clofentezine, Hexythiazox
	10B Etoxazole	Etoxazole
11 **Microbial disruptors of insect midgut membranes** (includes transgenic crops expressing *Bacillus thuringiensis* toxins, however specific guidance for resistance management of transgenic crops is not based on rotation of modes of action)	*Bacillus thuringiensis* or *Bacillus sphaericus* and the insecticidal proteins they produce	*Bacillus thuringiensis* subsp. *israelensis* *Bacillus sphaericus* *Bacillus thuringiensis* subsp. *aizawai* *Bacillus thuringiensis* subsp. *kurstaki* *Bacillus thuringiensis* subsp. *tenebrionis* 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** Diafenthiuron	Diafenthiuron
	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 DNOC	Chlorfenapyr 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**
14 **Nicotinic acetylcholine receptor channel blockers** Nerve action {Compounds affect the function of this protein, but it is not clear that this is what leads to biological activity}	Nereistoxin analogues	Bensultap, Cartap hydrochloride, Thiocyclam, Thiosultap-sodium
15 **Inhibitors of chitin biosynthesis, type 0, Lepidopteran** Growth regulation {Target protein responsible for biological activity is unknown, or uncharacterized}	Benzoylureas	Bistrifluron, Chlorfluazuron, Diflubenzuron, Flucycloxuron, Flufenoxuron, Hexaflumuron, Lufenuron, Novaluron, Noviflumuron, Teflubenzuron, Triflumuron
16 **Inhibitors of chitin biosynthesis, type 1, Homopteran** Growth regulation {Target protein responsible for biological activity is unknown, or uncharacterized}	Buprofezin	Buprofezin
17 **Moulting disruptor, Dipteran** Growth regulation {Target protein responsible for biological activity is unknown, or uncharacterized}	Cyromazine	Cyromazine
18 **Ecdysone receptor agonists** Growth regulation {Strong evidence that action at this protein is responsible for insecticidal effects}	Diacylhydrazines	Chromafenozide, Halofenozide, Methoxyfenozide, Tebufenozide

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**
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)
22* **Voltage-dependent sodium channel blockers** Nerve action {Good evidence that action at this protein complex is responsible for insecticidal effects} **Please see footnotes for further information on sub-grouping*	**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

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Main Group and Primary Site of Action	**Chemical Sub-group or exemplifying Active Ingredient**	**Active Ingredients**
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
un **Compounds of unknown or uncertain mode of action[2]** {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 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.
{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.irac-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.irac-online.org

Submissions for new active ingredients together with recommendations for their inclusion in specific new or existing MoA classes, togther 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, 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.