The Mode Of Action of Diamides and Other Lepidopteran Insecticides and General Rotation Recommendations

6th International DBM Conference
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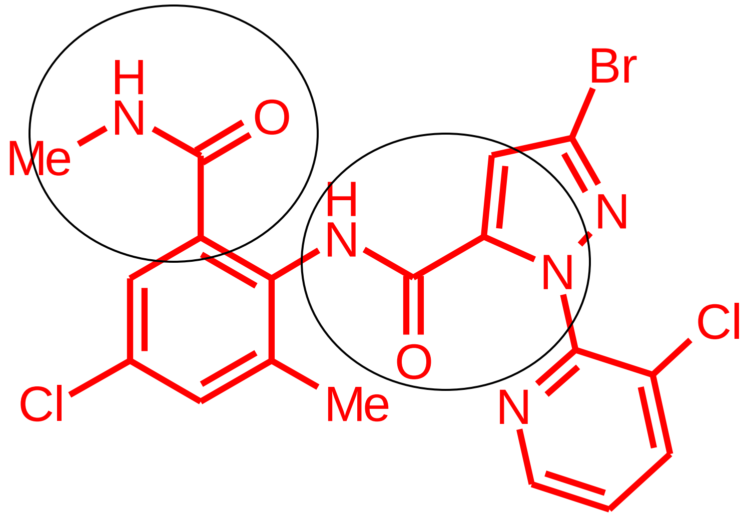
What's a diamide?

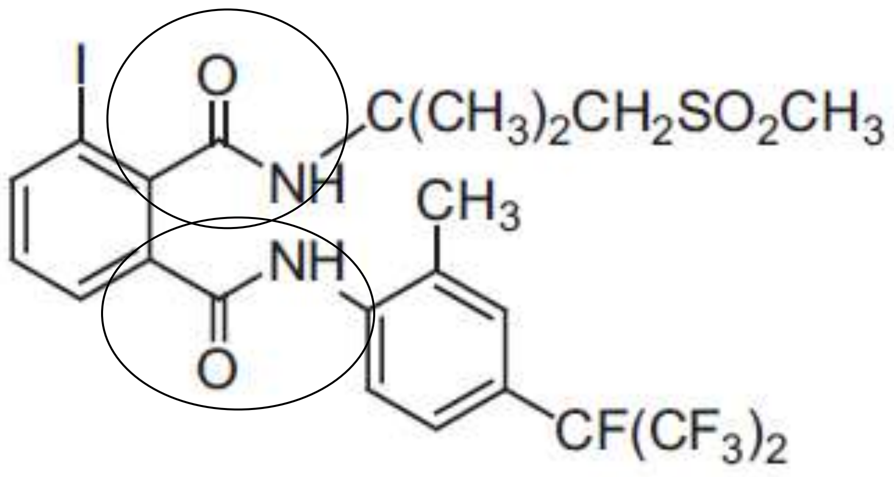
Diamide Chemistry:
Two Different Molecules



Anthranilic Diamide

Chlorantraniliprole

Ryaxypry®



Phthalic Diamide

Flubendiamide

Insecticides That Are "Diamides"

There are different products available in the market that represent two different, but related, chemical classes of insecticides

Product Trade Name Examples	Insecticide Chemistries	Company
Prevathon®	Anthranilic Diamide	DuPont
Voliam Flexi®	Anthranilic Diamide + Neonicotinoid (thiamethoxam)	Syngenta
Fenos®	Phthalic Diamide	Bayer
Tourismo®	Phthalic Diamide + IGR (buprofezin)	Nihon Nohyaku

Based on their common chemistry these products are generally referred to as "Diamides" and Diamide Premixes

Label Examples:
Reference to Diamide Class of Chemistry

RESISTANCE MANAGEMENT

Some insect pests are known to develop resistance to products after repeated use. Because resistance development cannot be predicted, the use of this product should conform to sound resistance management strategies established for the crop and use area. Syngenta encourages responsible product stewardship to ensure effective long-term control of the insects on this label.

Voliam Flexi contains a Group 4A insecticide (thiamethoxam, belonging to the neonicotinoid class of chemistry) and a Group 28 insecticide (chlorantraniliprole, belonging to the diamide class of chemistry).

Syngenta
Voliam Flexi®

RESISTANCE MANAGEMENT

For resistance management, CORAGEN® is a Group 28 Insecticide. Repeated and exclusive use of CORAGEN® (chlorantraniliprole) or other Group 28 insecticide belonging to the anthanilic diamide class of chemistry may lead to the buildup of resistant strains of insects in some crops.

DuPont
Coragen®

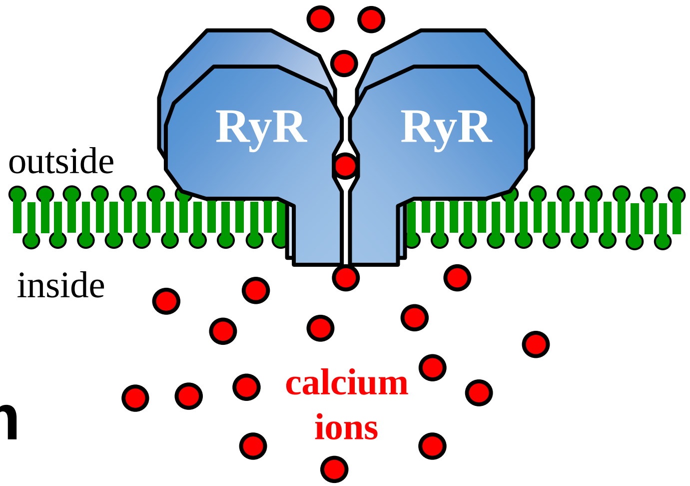
Why are diamides in the IRAC Group 28 MOA??

28 **Ryanodine receptor modulators** Nerve and muscle action {Good evidence that action at this protein complex is responsible for insecticidal effects}	Diamides	Chlorantraniliprole, Flubendiamide

From the IRAC MOA publication, 2008

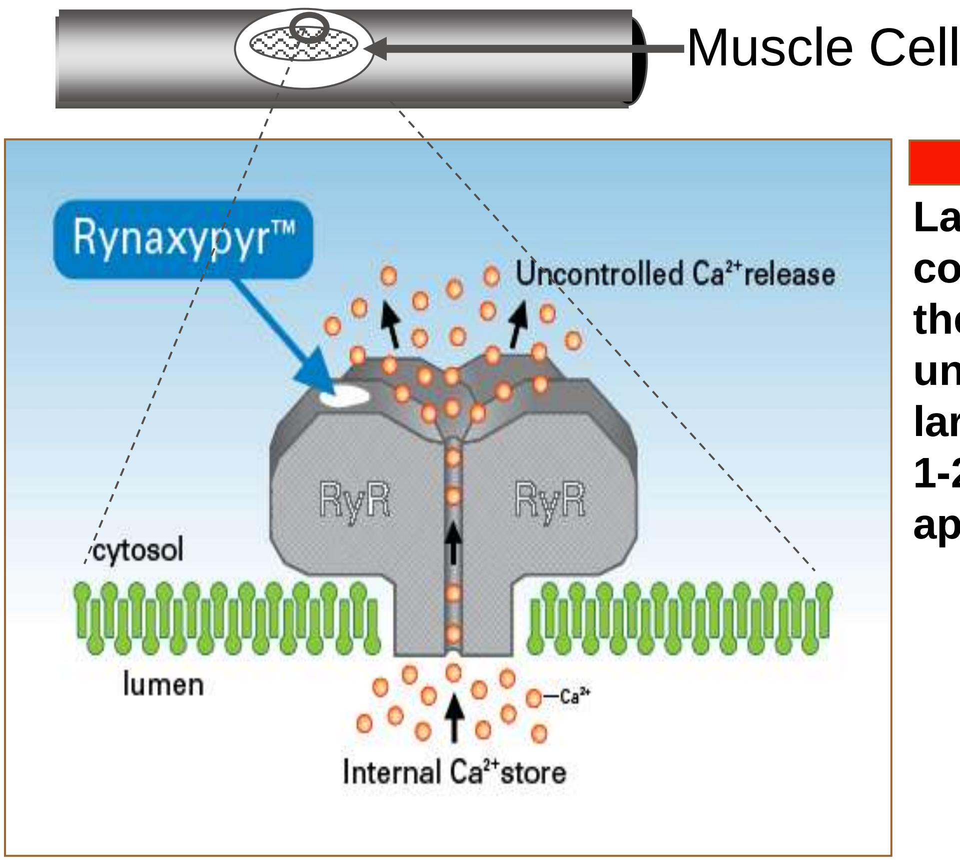
A Novel Insecticidal Target: Acts At The Ryanodine Receptor…Group 28 MOA

- ***Commercial insect control products with phthalic & anthranilic diamide chemistry***

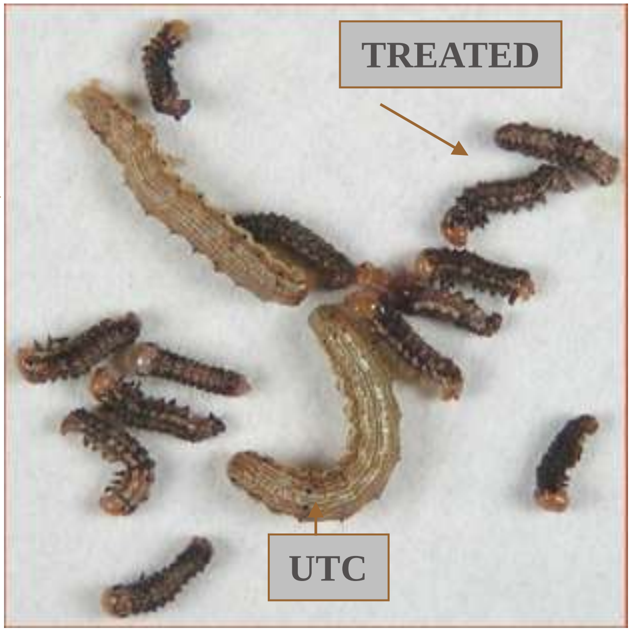


- **Calcium channel**
- **Regulates release of stored calcium**
- **Ryanodine locks the RyR partially open (like a doorstop)**
- **Critical for muscle contraction**
- **Diamides are inactive against cells that don’t express RyRs**

Group 28 MOA Insecticides: From The Insect's Point of View

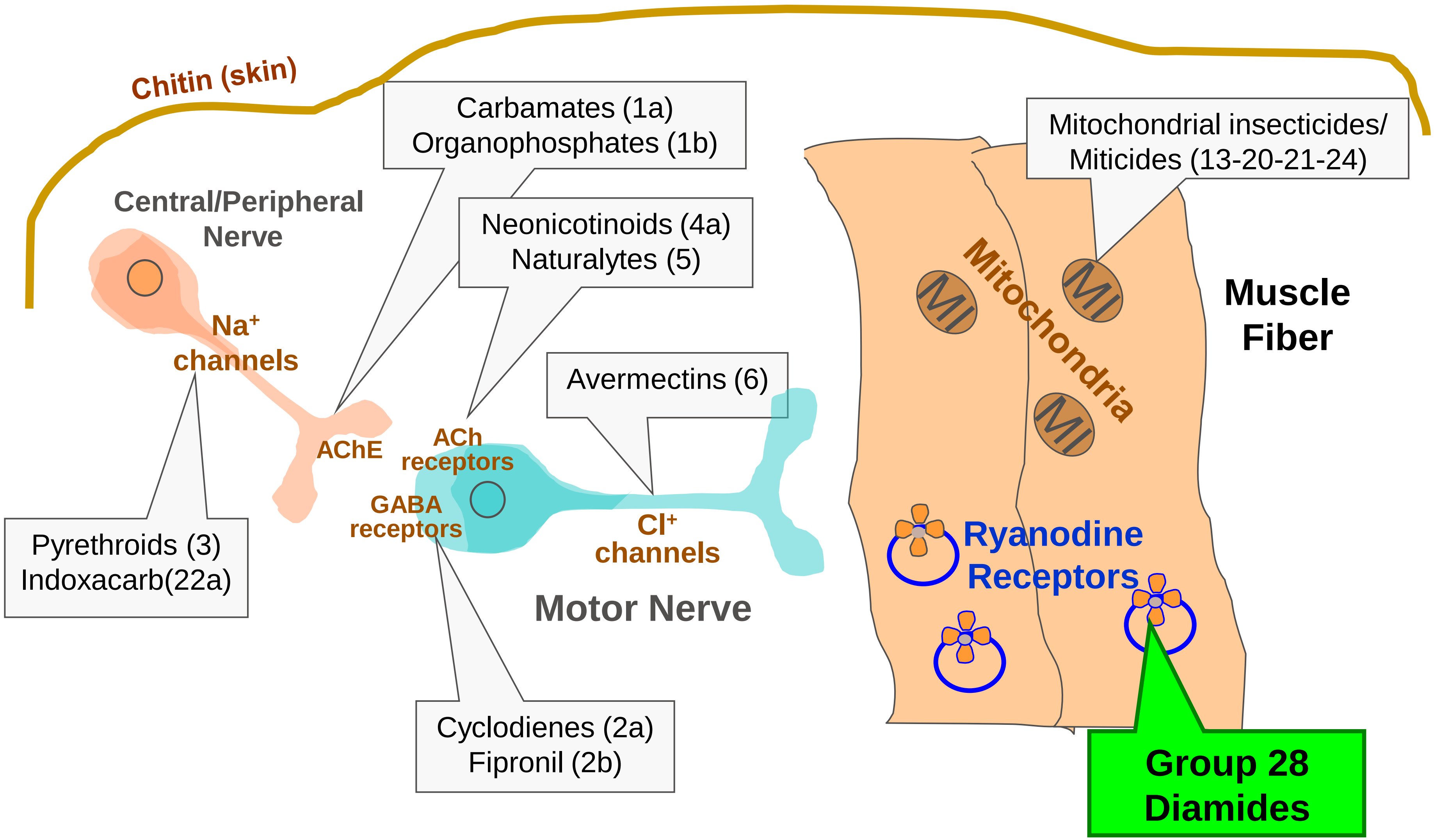


Larvae contract to half the size of untreated larvae within 1-2 hours post application.



- **Regurgitation**
- **General Lethargy**
- **Muscle paralysis**
- **Rapid feeding cessation**
- **Death within ~ 72 hours**

Group 28 Products Paralyze Insect Muscle: An Alternate MoA for IRM



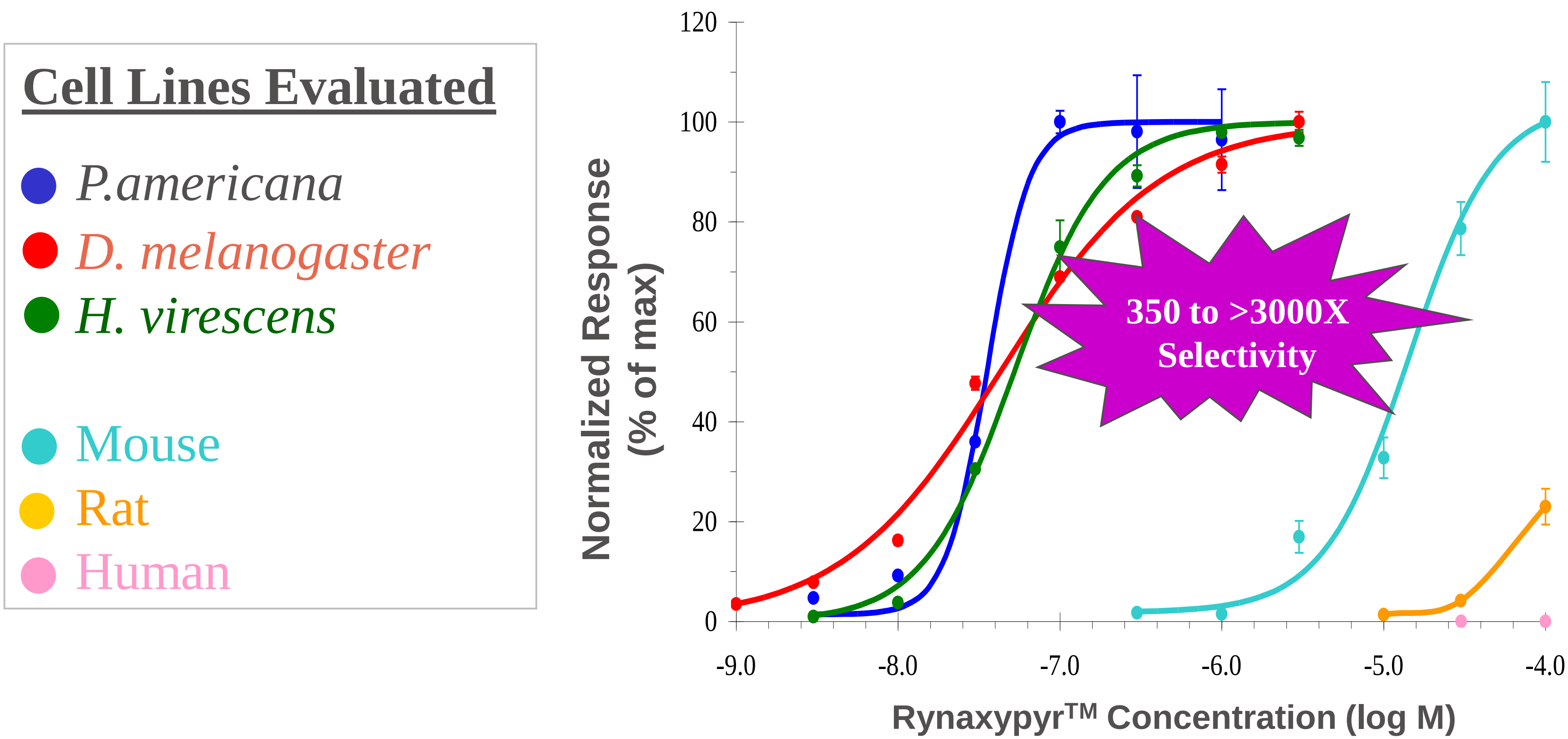
Why is the Ag Industry interested in preserving diamide chemistry???

Diamide products:

- ✓ **remarkably potent vs insect pests**
- ✓ **work on insects “R” to other chemistries**
- ✓ **great rotational partners with other products**

Diamide products:

- ✓ **excellent selectivity that favors beneficial insects**
- ✓ **excellent safety selectivity to mammals**



Cordova et al. 2006. Pesticide Biochemistry and Physiology 84: 196-214

Insecticide Resistance Action Committee

Many Global Formulations Contain Diamide Chemistry: Increasing and Not Obvious to Growers

Examples of Products in Group 28 Diamide Chemical Class

DuPont
Chlorantraniliprole

- Coragen® 200 SC
- Prevathon® 50 SC
- Altacor® 35 WDG
- Ferterra® 0.4G
- Dermacor® 60FS

2012-2020
2+ Potential New Diamide Products

Syngenta
Chlorantraniliprole + 6 partners

- Durivo® 40WG
- Voliam Flexi® 300SC
- Voliam Flexi® 40 WG
- Voliam Targo® 063SC
- Voliam Targo® 22.5SC
- Voliam Xpress® 150ZC
- Ampligo® 150ZC
- Soros ® 2.7SC

Nihon Nohyaku
Flubendiamide + premix products

- Phoenix ® 20WG
- Vetica® 32%SC
- Tourismo® 38%SC

Bayer
Flubendiamide + premix products

- Takumi 20%WG
- Belt® 480SC
- Fame/Fenos® 480SC
- Synapse® 24WG
- Lineout®
- Tihan®

Diamide products:

✓ great opportunity for overuse and insect resistance

Insect Control Eras

1940s - 1950	1970s	1990s	2010s
Organochlorines Organophosphates Carbamates	Pyrethroids	Neonicotinoids	Diamides

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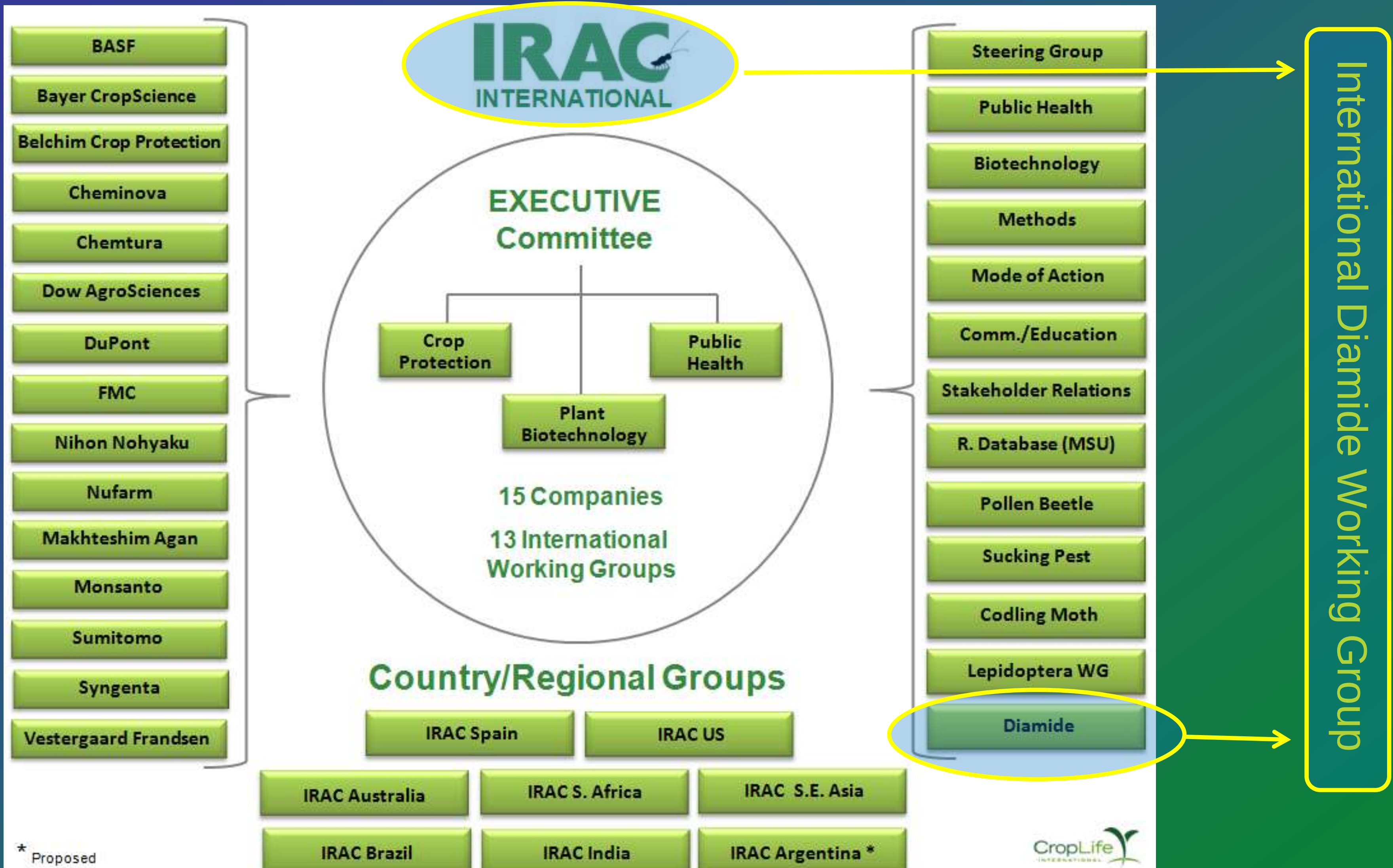
What is the industry doing to preserve diamide chemistry???

The miracles of science™

International Diamide Working Group

Insecticide Resistance Action Committee



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- MONSANTO — imagine
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- BELCHIM — Crop Protection
- CHEMINOVA
- VESTERGAARD FRANDSEN — DISEASE CONTROL TEXTILES

✔ Company members of Global Diamide Working Group

Global IRAC Diamide Working Group Developed Guidelines for Group 28 Insecticides (2009)

- ❑ **Applies to <u>all</u> Modes of Action for Lepidoptera**
- ❑ **Developed by Chemical Industry members**
- ❑ **Being adapted by country diamide teams to local situation**

IRAC

Insecticide Resistance Action Committee
www.irac-online.org

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

Issued: March 2010

Version: 2.1

Prepared by: IRAC Group 28 (Diamide) Working Group

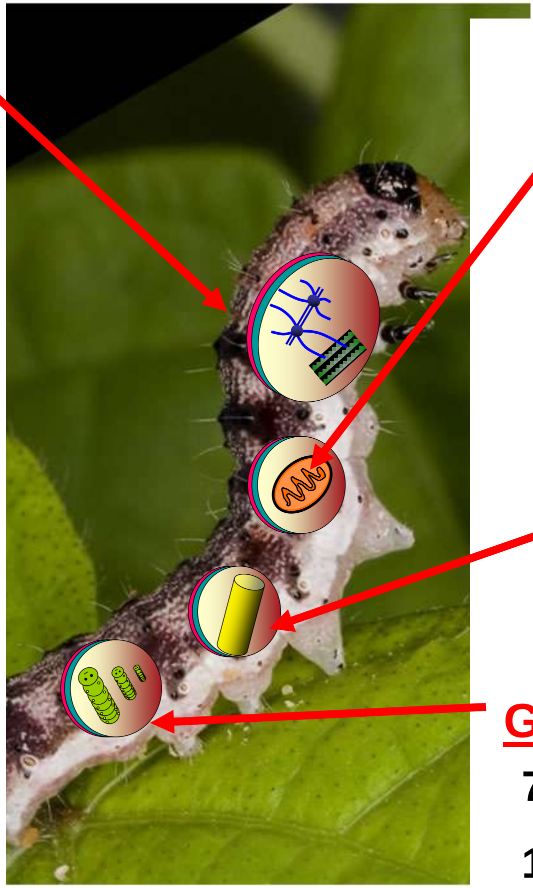
Contains IRM guidelines, and examples of rotation schedules.

Rotation MoA Alternatives:
Lepidoptera Mode of Action Classification by Target Site

Nerve & Muscle Targets

1. Acetylcholinesterase inhibitors
2. GABA-gated chloride channel antagonists
3. Sodium channel modulators
4. Nicotinic acetylcholine receptor agonists
5. Nicotinic acetylcholine receptor allosteric activators
6. Chloride channel activators

14. Nicotinic acetylcholine receptor channel blockers.
19. Octopamine receptor agonists
22. Sodium channel blockers
28. Ryanodine receptor modulators



IRAC Publication
Lep MoA Poster

Respiration Targets

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

Midgut Targets

21. Mitochondrial complex I electron transport inhibitors
11. Microbial disruptors of insect midgut membranes

Growth/Development Targets

7. Juvenile hormone mimics
15. Inhibitors of chitin biosynthesis, Type 0
18. Ecdysone receptor agonists

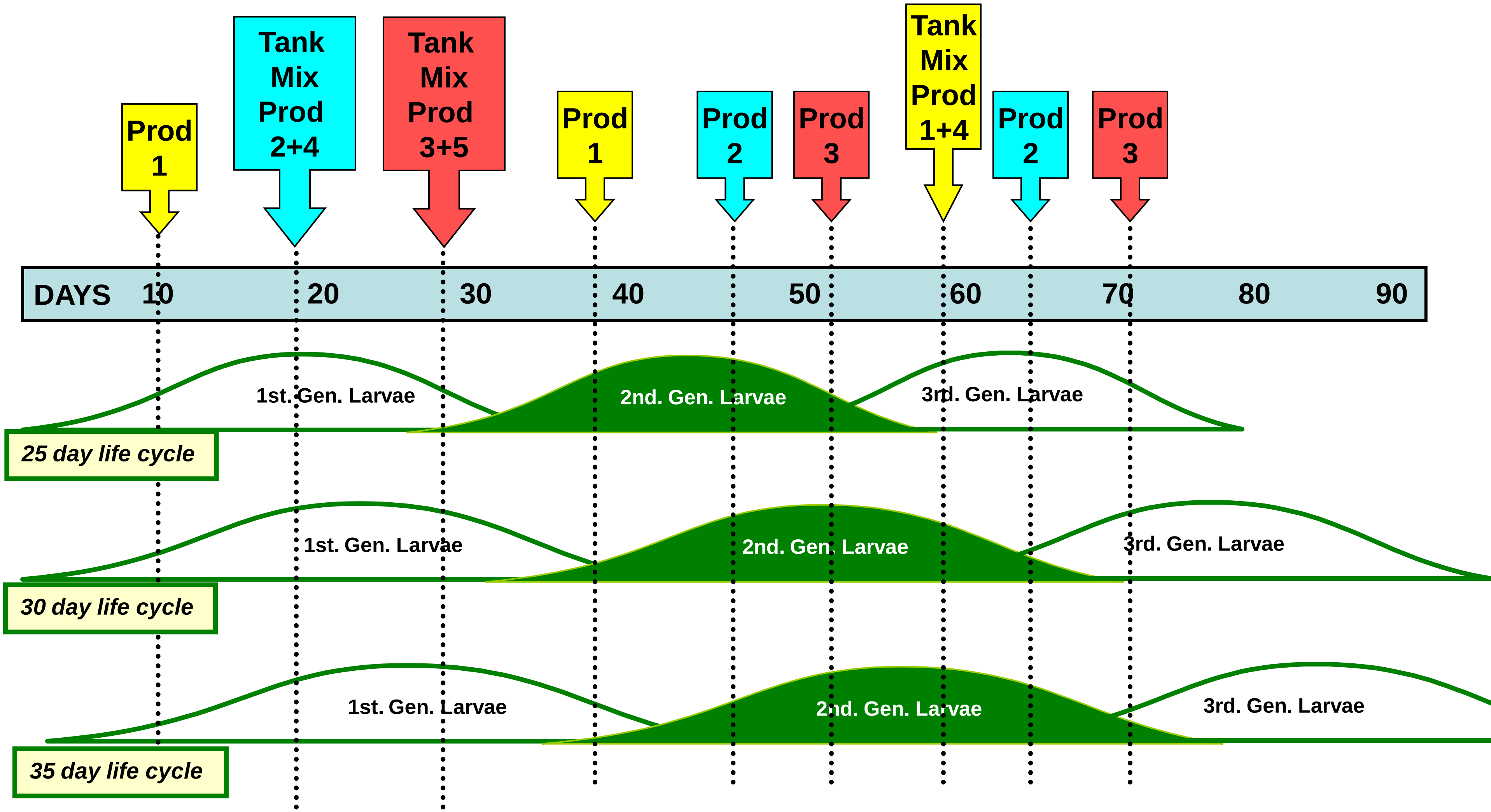
Rotation Strategy: Assumptions

- No cross resistance among rotated insecticides
- Rotation across generations
- High rate
- Refugia
- R alleles carry significant fitness cost
- Low initial frequency of R genes
- *No movement of pest between locations in different phases of the rotation*

Approximate Example of Typical Spray Schedule:

Application every 7-10 days using multiple products against multiple insect pests.

Result: Greater chance of successive insect generations being exposed to the same mode of action and increasing risk of resistance



Effective IRM strategies: Sequences or Alternations of MoA: IRAC IRM Recommends

- Effective (IRM) strategies seek to minimise the selection of resistance to any one type of insecticide.
- In practice, alternations, sequences or rotations of compounds from different MoA groups provide sustainable and effective IRM.
- Applications are often arranged into MoA spray windows or blocks that are defined by the stage of crop development and the biology of the Lepidopteran species of concern.
- **Several sprays may be possible within each spray window, but it is generally essential that successive generations of the pest are not treated with compounds from the same MoA group.**
- Metabolic resistance mechanisms may give cross-resistance between MoA groups; where this is known to occur, the above advice should be modified accordingly.

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Insecticide Resistance Action Committee

General Positioning Guidelines

IRM guidelines below show least to best product rotaton recommendations

Maintaining insect susceptibility greatly depends on rotation of Diamide insecticides with effective products with a different MOA that eliminate Diamide-resistant individuals. Rotation with products that provide poor control of the target pest increases the risk of developing Diamide resistance.

Year 1		Year 2		Year 3		Year 4	
1st Gen	2nd Gen	1st Gen	2nd Gen	1st Gen	2nd Gen	1st Gen	2nd Gen

No alternation/rotation

High selection pressure

No recovery of sensitive population.

Year 1		Year 2		Year 3		Year 4	
1st Gen	2nd Gen	1st Gen	2nd Gen	1st Gen	2nd Gen	1st Gen	2nd Gen

Rotation within generation

Consecutive generations exposed to same MoA. Selection pressure doesn't change between generations. Risk of resistance development for both ai's

Year 1		Year 2		Year 3		Year 4	
1st Gen	2nd Gen	1st Gen	2nd Gen	1st Gen	2nd Gen	1st Gen	2nd Gen

Rotation among generations

Following generations are not exposed to same MoA. Selection pressure doesn't increase within the generation. Recovery of susceptible population.

Year 1		Year 2		Year 3		Year 4	
1st Gen	2nd Gen	1st Gen	2nd Gen	1st Gen	2nd Gen	1st Gen	2nd Gen

Rotation within and between

Ideal situation (very low risk) Not alway applicable with good efficacy.

MoA 1 MoA 3

MoA 2 MoA 4

Insecticide Rotation Strategy

- Alternate different insecticide modes of action across pest generations
- Basic principle
  - frequency of alleles for Resistance to an insecticide will decline during application of alternative insecticide
    - resistant alleles removed by effective products (SS, RS)
    - fitness costs associated with resistance
    - mating with SS genotypes from refugia

George Kennedy, NC State Univ; 2010 IRM Conference, San diego

Insecticidal Chemistries Must Be Rotated by MOA Group

Syngenta's Voliam Flexi®

Use Restrictions:

- **Maximum Voliam Flexi Allowed per Growing Season:** Do not exceed a total of 14.0 oz. of Voliam Flexi or 0.172 lb. a.i. of thiamethoxam containing products or 0.2 lb a.i. of chlorantraniliprole containing products per acre per growing season.

DuPont's Coragen®

Do not apply more than 15.4 fl oz CORAGEN® or 0.2 lbs a.i. of chlorantraniliprole-containing products per acre per crop

Develop IRM Guidelines by Crop: Transition From Diamide IRM to Insecticide IRM

Insecticide Resistance Action Committee

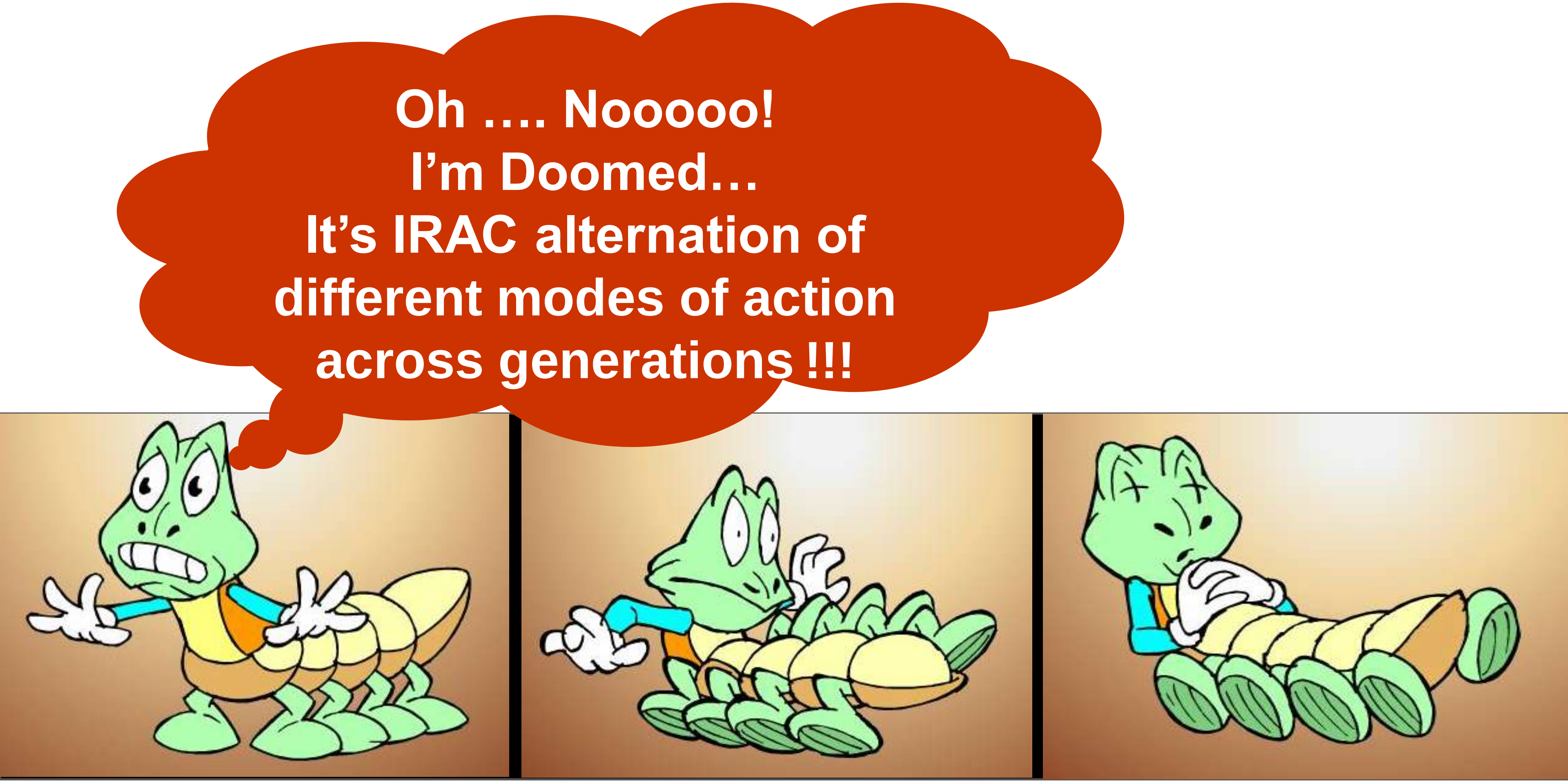
- **IRAC agrees on IRM rotation scheme & guidelines.**
- **Demonstrate the concepts visually: "not treating successive generations" and the "Treatment Window" concept.**
- **Example below" Spain – Tuta absoluta (tomato pinworm)**

<u>Example:</u> Insecticide Mode of Action (MoA)
"Window" Approach – 150 day cropping cycle

0-30 days	30-60 days	60-90 days	90-120 days	120-150 days
Insecticide MOA x	Do not apply MoA x		Insecticide MOA x	Do not apply MoA x
Do not apply MoA y	Insecticide MOA y	Do not apply MoA y		Insecticide MOA y
Do not apply MoA z		Insecticide MOA z	Do not apply MoA z	

Sequence of Mode of Action (MoA) Windows throughout the season

QUESTIONS???


Oh …. Noooooo!
I'm Doomed…
It's IRAC alternation of
different modes of action
across generations !!!

EXTRA SLIDES

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MOA Group 28 Insecticides
Affect Muscle Contraction

Impairs function of the insect heart muscle!

<u>Experiment with Manduca sexta larvae</u>

- Electrodes inserted into cardiac muscle
- Treated with chlorantraniliprole
- Heart beat frequency drastically reduced

heart4.mpg

INSECT RESISTANCE STATEMENT

BELT SC Insecticide contains an active ingredient with a mode of action classified as a Group 28 insecticide – ryanodine receptor modulators. Studies to determine cross-resistance of Group 28 insecticides with other chemical classes have demonstrated no cross-resistance. However, repeated use of any crop protection product may increase the development of resistant strains of insects. Rotation to another product with a different mode of action is recommended. Contact your local extension specialist, certified crop advisor and/or Bayer CropScience representative for additional resistance management or IPM recommendations. Also, for more information on Insect Resistance Management (IRM), visit the Insecticide Resistance Action Committee (IRAC) on the web at http://www.irac-online.org.

A new mode of action gives Flubendiamide and Chlorantraniliprole solo and pre-mixture products an excellent fit as rotational partners to control lepidopteran pests.

Lepidoptera Insecticide Mode of Action Classification:

A key to effective insecticide resistance management

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Insecticide Resistance Action Committee

www.irac-online.org

Introduction and background

The agrochemical industry has developed a broad range of very effective insecticides for the control of lepidopteran pests. Unfortunately, as a consequence of the misuse or overuse of these insecticides, many species have developed resistance. Populations of *Plutella xylostella*, for example, have developed resistance to virtually every insecticide used against them. Additionally, there are numerous other species prone to resistance development. In recent years the industry has worked especially hard to develop new types of insecticides with novel modes of action, but this process is becoming ever harder and more costly. It is therefore vital that effective insecticide resistance management (IRM) strategies are implemented, to ensure that resistance does not develop to these new compounds, or to older chemistries that are still effective.

In order to help prevent or delay the incidence of resistance, IRAC promotes the use of a Mode of Action (MoA) classification of insecticides in effective and sustainable IRM strategies. Available insecticides are allocated to specific groups, based on their target site, as described below. By using sequences or alternations of insecticides from different MoA classes, resistance is less likely to occur. Available at the IRAC website www.irac-online.org, this IRAC MoA classification list provides farmers, growers, advisors, extension staff, consultants and crop protection professionals with a guide to the selection of insecticides in IRM programs.

Effective IRM strategies: Sequences or alternations of MoA

Effective insecticide resistance management (IRM) strategies seek to minimise the selection of resistance to any one type of insecticide. In practice, alternations, sequences or rotations of compounds from different MoA groups provide sustainable and effective IRM.

Example:

MoA w | MoA x | MoA y | MoA z | MoA w | MoA x

Sequence of insecticides through season

Applications are often arranged into MoA spray windows or blocks that are defined by the stage of crop development and the biology of the Lepidopteran species of concern. Local expert advice should always be followed with regard to spray windows and timing. Several sprays may be possible within each spray window, but it is generally essential that successive generations of the pest are not treated with compounds from the same MoA group. Metabolic resistance mechanisms may give cross-resistance between MoA groups; where this is known to occur, the above advice should be modified accordingly.

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.

1A Carbamates (e.g. Methomyl, Thiodicarb) **1B** Organophosphates (e.g. Chlorpyrifos)

Group 2 GABA-gated chloride channel antagonists

Block the GABA-activated chloride channel, causing hyperexcitation and convulsions. GABA is the major inhibitory neurotransmitter in insects.

2A Cyclodiene Organochlorines (e.g. Endosulfan) **2B** Phenylpyrazoles (e.g. Fipronil)

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.

3A Pyrethrins, Pyrethroids (e.g. Cypermethrin, λ-Cyhalothrin)

Group 4 Nicotinic acetylcholine receptor (nAChR) agonists

Mimic the agonist action of acetylcholine at nAChRs, causing hyperexcitation. Acetylcholine is the major excitatory neurotransmitter in the insect central nervous system.

4A Neonicotinoids (e.g. Acetamiprid, Thiacloprid, Thiamethoxam)

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.

Spinosyns (e.g. Spinosad, Spinetoram)

Group 6 Chloride channel activators

Allosterically activate glutamate-gated chloride channels (GluCls), causing paralysis. Glutamate is an important inhibitory neurotransmitter in insects.

Avermectins, Milbemycins (e.g. Abamectin, Emamectin Benzoate)

Group 14 Nicotinic acetylcholine receptor (nAChR) blockers

Block the nAChR ion channel, resulting in nervous system block and paralysis. Acetylcholine is the major excitatory neurotransmitter in the insect central nervous system.

Bensultap, Cartap

Group 22 Voltage dependent sodium channel blockers

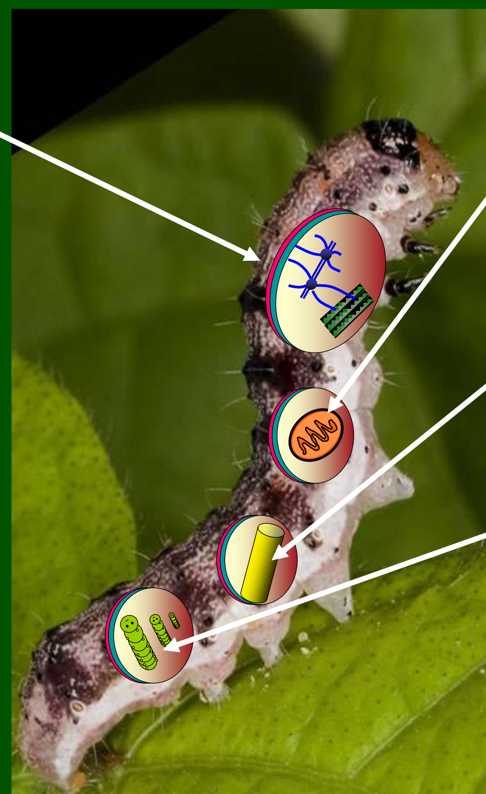
Block sodium channels, causing nervous system shutdown and paralysis. Sodium channels are involved in the propagation of action potentials along nerve axons.

22A Indoxacarb 22B Metaflumizone

Group 28 Ryanodine receptor modulators

Activate muscle ryanodine receptors, leading to contraction and paralysis. Ryanodine receptors mediate calcium release into the cytoplasm from intracellular stores.

Diamides (e.g. Chlorantraniliprole, Flubendiamide)



Respiration Targets

Mitochondrial respiration produces ATP, the molecule that energizes all vital cellular processes. In mitochondria, an electron transport chain uses the energy released by oxidation to charge a proton gradient battery that drives ATP synthesis. Several insecticides are known to interfere with mitochondrial respiration by the inhibition of electron transport and/or oxidative phosphorylation. Insecticides that act on individual targets in this system are generally fast to moderately fast acting.

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

Protonophores that short-circuit the mitochondrial proton gradient so that ATP can not be synthesized.

Chlorfenapyr

Group 21 Mitochondrial complex I electron transport inhibitors

Inhibit electron transport complex I, preventing the utilization of energy by cells.

Midgut Targets

Lepidopteran-specific microbial toxins that are sprayed or expressed in transgenic crops.

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.

Bacillus thuringiensis, Bacillus sphaericus

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 by directly affecting cuticle formation/deposition or lipid biosynthesis. Insecticides that act on individual targets in this system are generally slowly to moderately slowly acting.

Group 7 Juvenile hormone mimics

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

7B Juvenile hormone analogues (e.g. Fenoxycarb)

Group 15 Inhibitors of chitin biosynthesis, Type 0

Incompletely defined mode of action leading to inhibition of chitin biosynthesis.

Benzoylureas (eg. Flufenoxuron, Lufenuron, Novaluron)

Group 18 Ecdysone receptor agonists

Mimic the moulting hormone, ecdysone, inducing a precocious molt.

Diacylhydrazines (e.g. Methoxyfenozide, Tebufenozide)

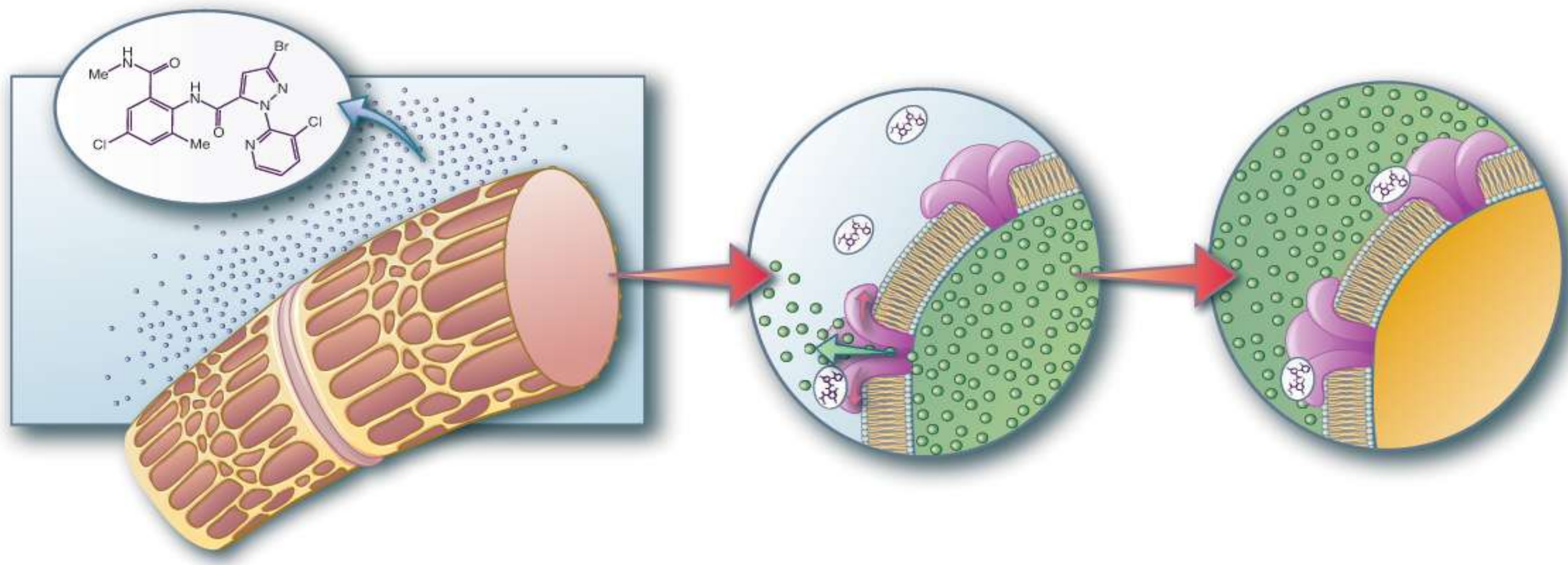
Unknown Several insecticides are known to affect less well-described target-sites or functions, or to act non-specifically on multiple targets.

Azadirachtin, Pyridalyl

Designed & produced by IRAC MOA Working Group, September 2009, Poster Ver. 3.3 Based on MoA Classification Ver. 6.3

For further information visit the IRAC website: www.irac-online.org Photograph courtesy of Nigel

How does Rynaxypyr® Work?



Phase 1 →	Phase 2 →	Phase 3
Exposure:	**Binding**	**Calcium Depletion & Paralysis**
Insect comes in contact or ingests Rynaxypyr®.	Rynaxypyr® binds to the ryanodine receptors located in the insect's muscle, and activates them.	Calcium floods out of the open receptors. As stored calcium is needed for contraction, muscles become paralyzed.

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Selected slides from Dec 2010 presentation at IRM Conference
San Diego, CA

Insecticide Resistance Primer

George G. Kennedy

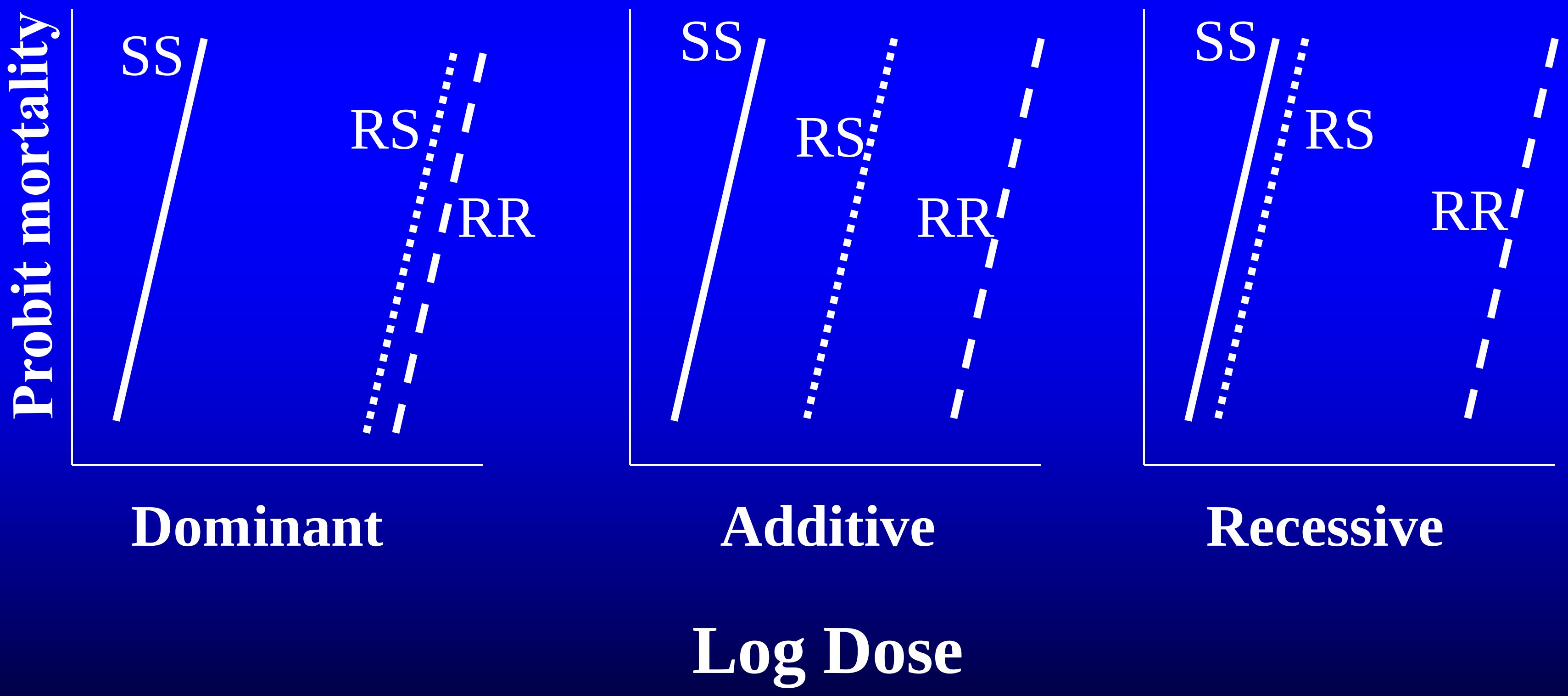
Department of Entomology

North Carolina State University

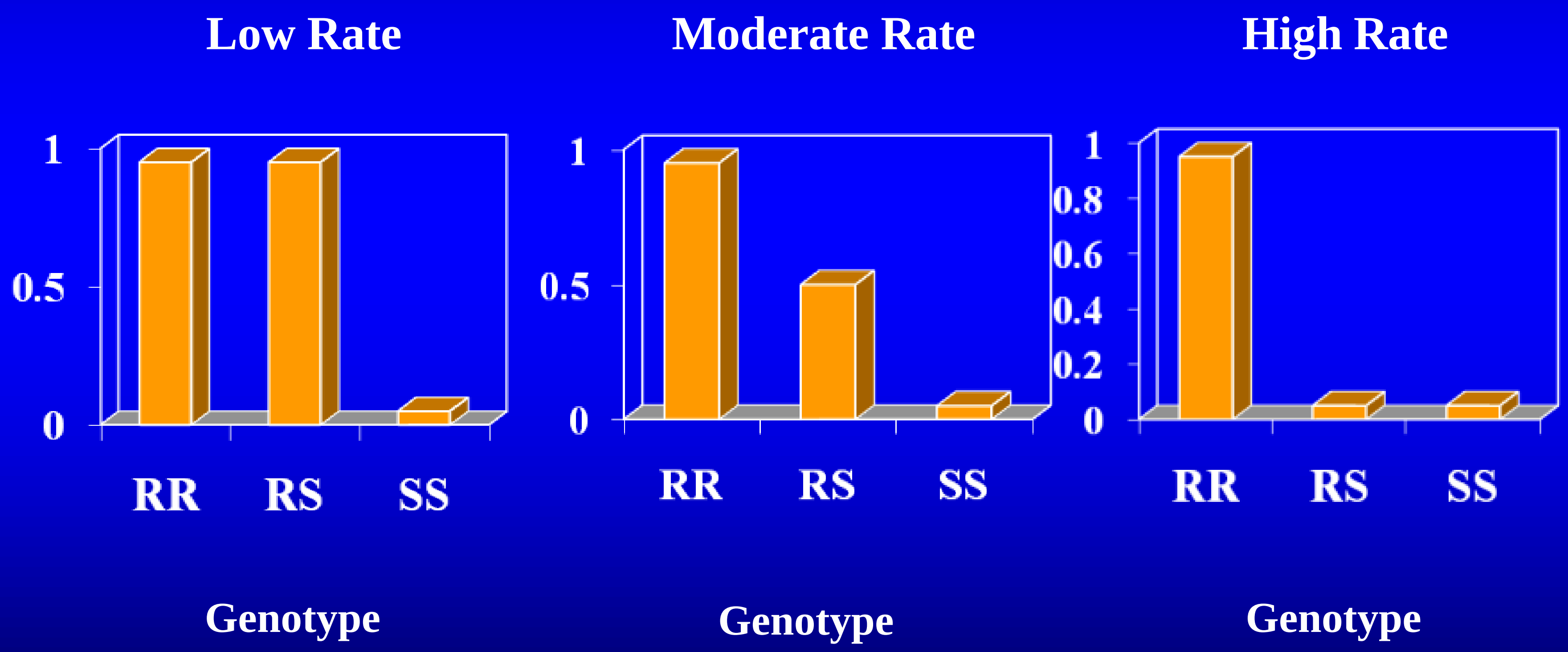
Raleigh, NC

Mendelian Inheritance of Resistance

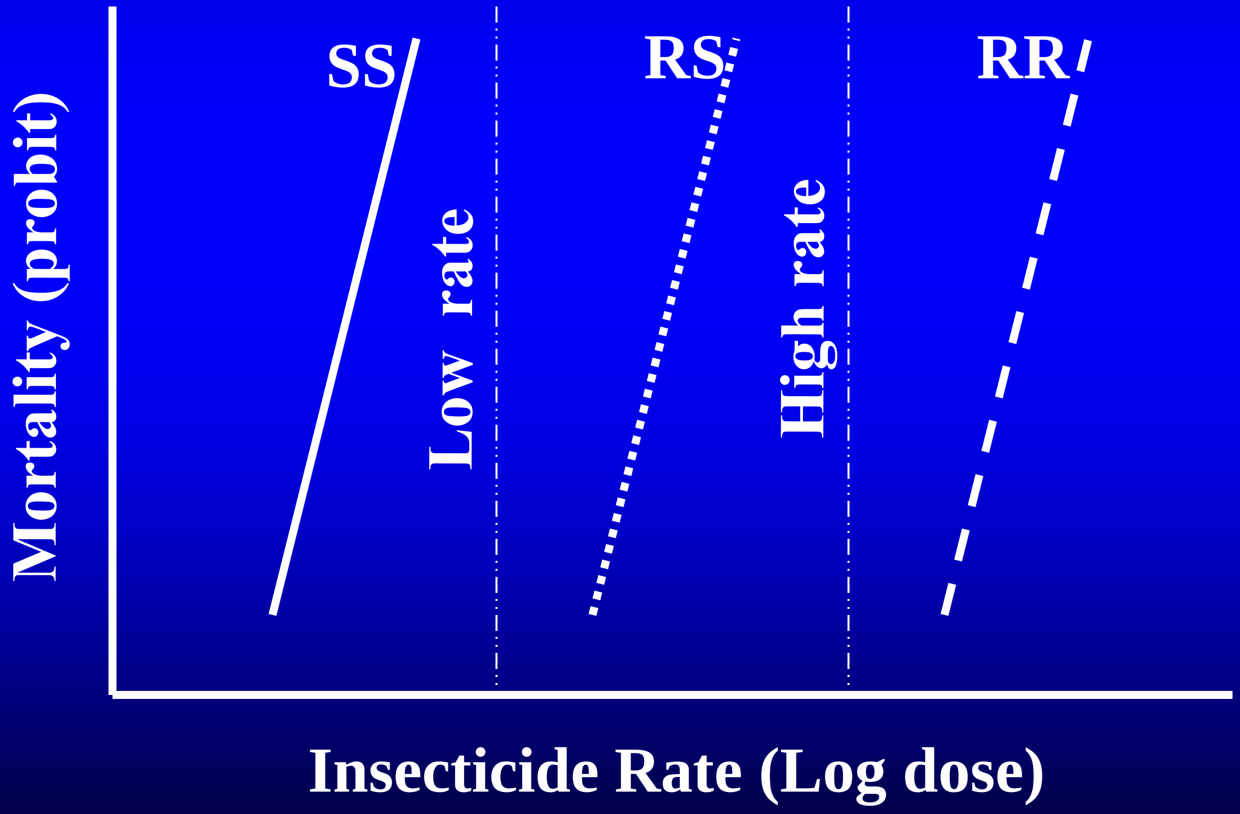
Genotypes: Susceptible = SS; Resistant = RR; F_1 heterozygote = RS



Effect of Insecticide Rate on Fitness of Heterozygote: Inheritance Truly Additive



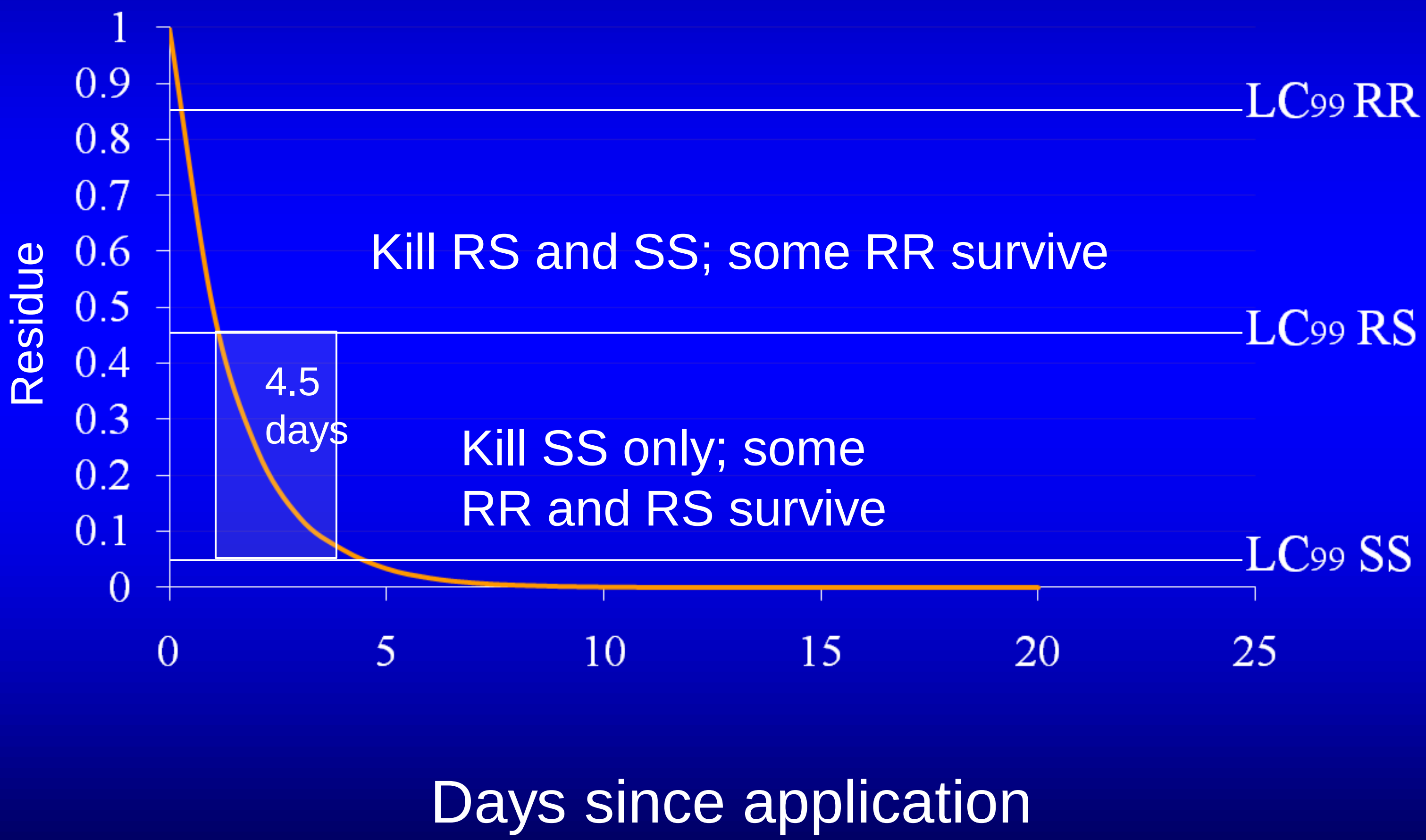
Functional Dominance:
R alleles inherited as either dominant or recessive depending on insecticide rate



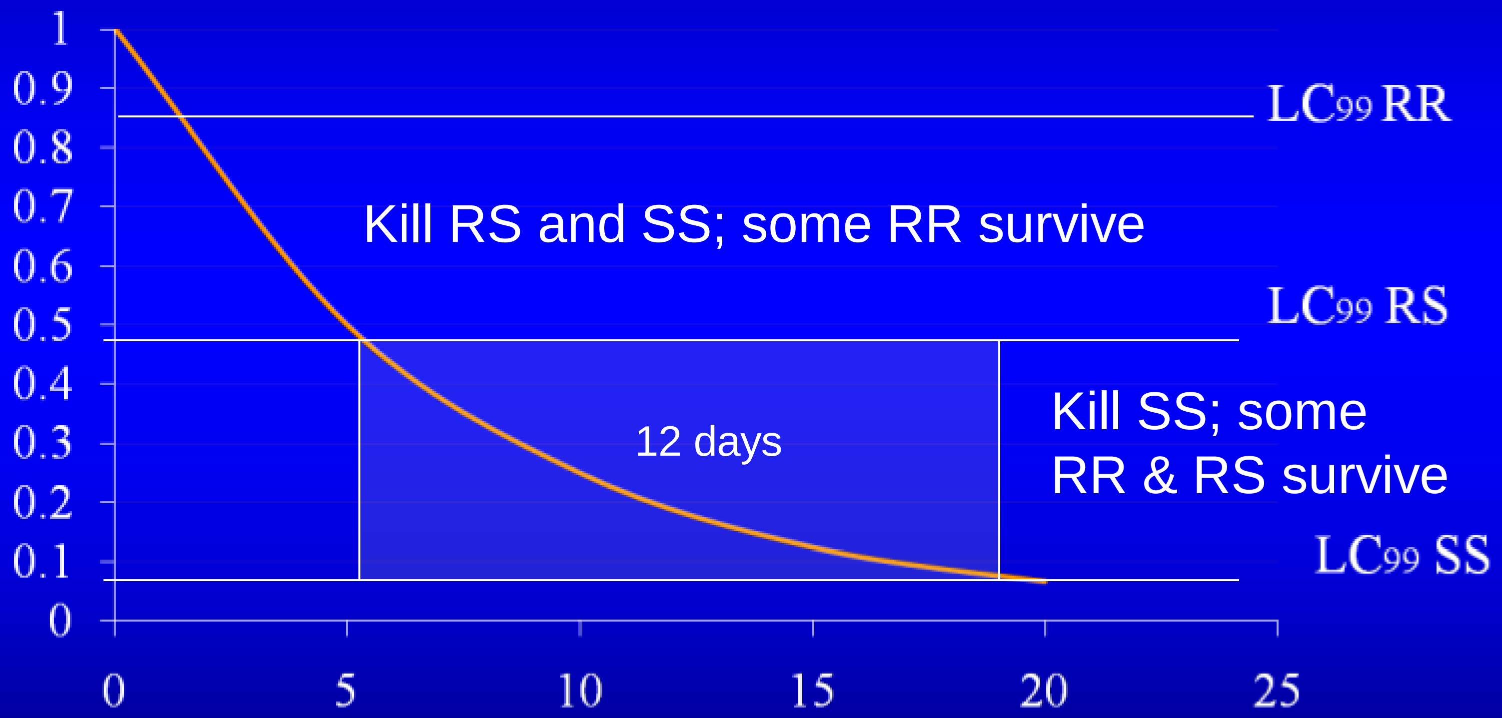
Heterozygotes are the most common carriers of R alleles in the population

- Development of resistance is most rapid when control measure discriminates between heterozygotes and susceptible homozygotes
  - i.e., when R is functionally dominant

Residue half life 1 days: inheritance additive

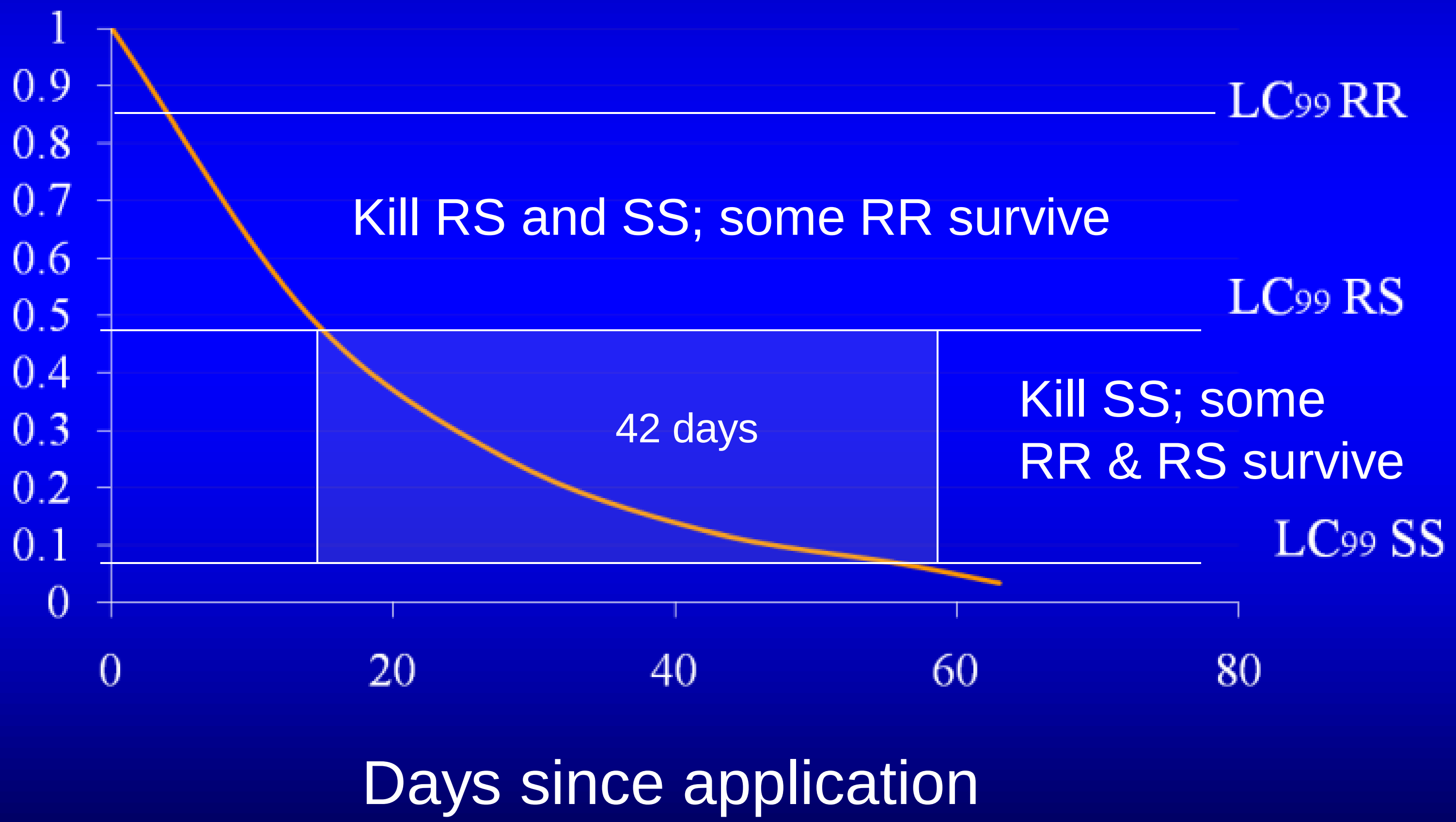


Residue half life 5 days: inheritance additive



Days since application

Residue half life 14 days: inheritance additive



Residue half life 14 days: inheritance largely recessive