Insecticidal Modes of Action

Implications for application, beneficials, and the applicator

The miracles of science™

Topics

1. Commonly used modes of action
2. Basis for Selectivity
3. Ingestion versus contact
4. Systemic versus non-systemic
5. Delivery methods

Lepidoptera - Mode of Action Classification by Target Site

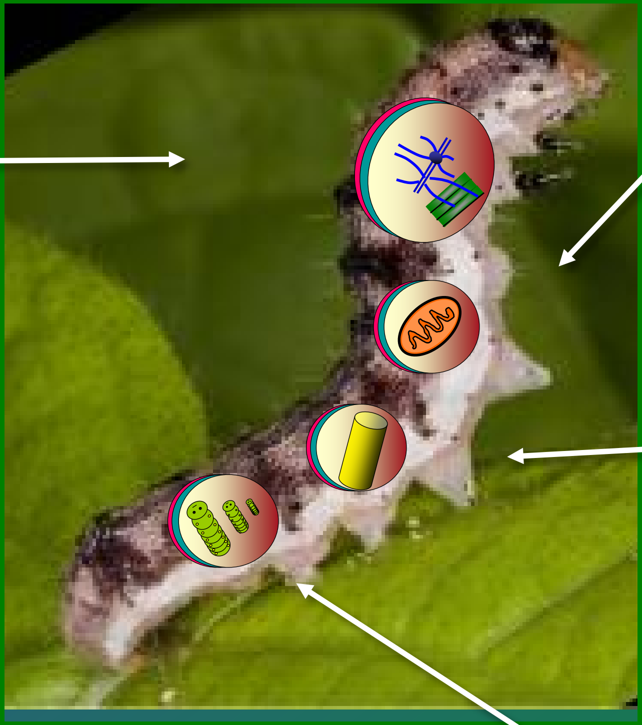
Nerve & Muscle Targets

1. **Acetylcholinesterase (AChE) inhibitors**
   1A Carbamates, 1B Organophosphates
2. **GABA-gated chloride channel antagonists**
   2A Cyclodiene Organochlorines
   2B Phenylpyrazoles
3. **Sodium channel modulators**
   3A Pyrethrins, Pyrethroids
4. **Nicotinic acetylcholine receptor (nAChR) agonists**
   4A Neonicotinoids
5. **Nicotinic acetylcholine receptor (nAChR) allosteric activators**
   5 Spinosyns
6. **Chloride channel activators**
   6 Avermectins, Milbemycins

14. **Nicotinic acetylcholine receptor (nAChR) channel blockers**
   14 Nereistoxin analogues

22. **Voltage-dependent sodium channel blockers**
   22A Indoxacarb, 22B Metaflumizone

28. **Ryanodine receptor modulators**
   28 Diamides



Respiration Targets

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

21. **Mitochondrial complex I electron transport inhibitors**
   21A Tolfenpyrad

Midgut Targets

11. **Microbial disruptors of insect midgut membranes**
   11A Bacillus thuringiensis,
   11B Bacillus sphaericus

Growth & Development Targets

7. **Juvenile hormone mimics**
   7B Juvenile hormone analogues

15. **Inhibitors of chitin biosynthesis, Type 0**
   15 Benzoylureas

18. **Ecdysone receptor agonists**
   18 Diacylhydrazines

Unknown or uncertain MoA
Azadirachtin, Pyridalyl

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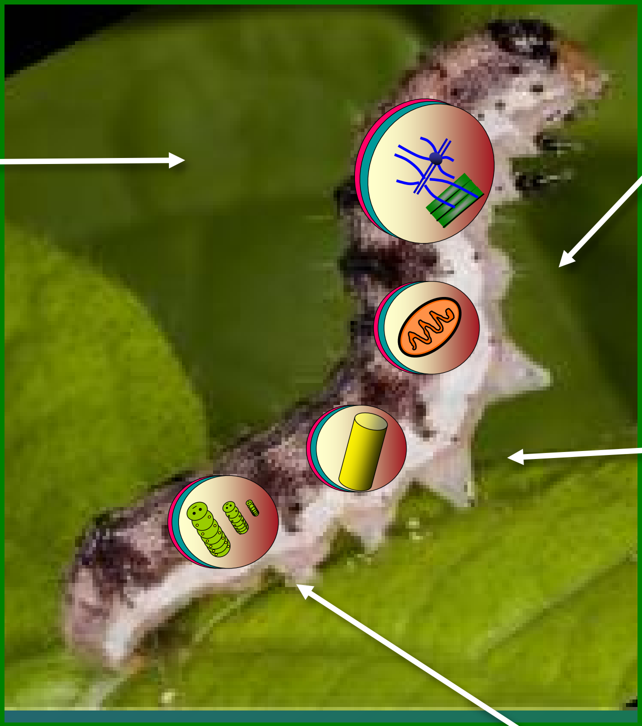

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Aphids, Whiteflies & Hoppers - Mode of Action Classification by Target Site

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   4A Neonicotinoids, 4C Sulfoxaflor, 4D Flupyradifurone
9. **Modulators of Chordotonal Organs**
   9B Pymetrozine 9C Flonicamid
22. **Voltage-dependent sodium channel blockers**
   22A Indoxacarb
28. **Ryanodine receptor modulators**
   28 Cyantraniliprole

MoA Group	Aphids	Whiteflies	Hoppers
1A	X	X	X
1B	X	X	X
2A	X	X	X
2B			X
3A	X	X	X
4A	X	X	X
4C	X	X	X
4D	X	X	X
7A	X	X	
7C		X	
9B	X	X	X
9C	X	X	X
12A	X	X	
15		X	
16		X	X
21A		X	
22A			X
23	X	X	
28	X	X	X
UN *	X	X	

Respiration Targets

12. **Inhibitors of mitochondrial ATP synthase**
    12A Diafenthiuron
21. **Mitochondrial complex I electron transport inhibitors**
    21A Tolfenpyrad, Pyridaben

Growth and Development Targets

7. **Juvenile hormone mimics**
   7A Kinoprene, 7C Pyriproxyfen
15. **Inhibitors of chitin biosynthesis, Type 0**
    15 Benzoylureas
16. **Inhibitors of chitin biosynthesis, Type 1**
    16 Buprofezin
23. **Inhibitors of lipid synthesis**
    23 Tetronic & Tetramic acid derivatives

Unknown or uncertain MoA

*UN Pyrifluquinazon **

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

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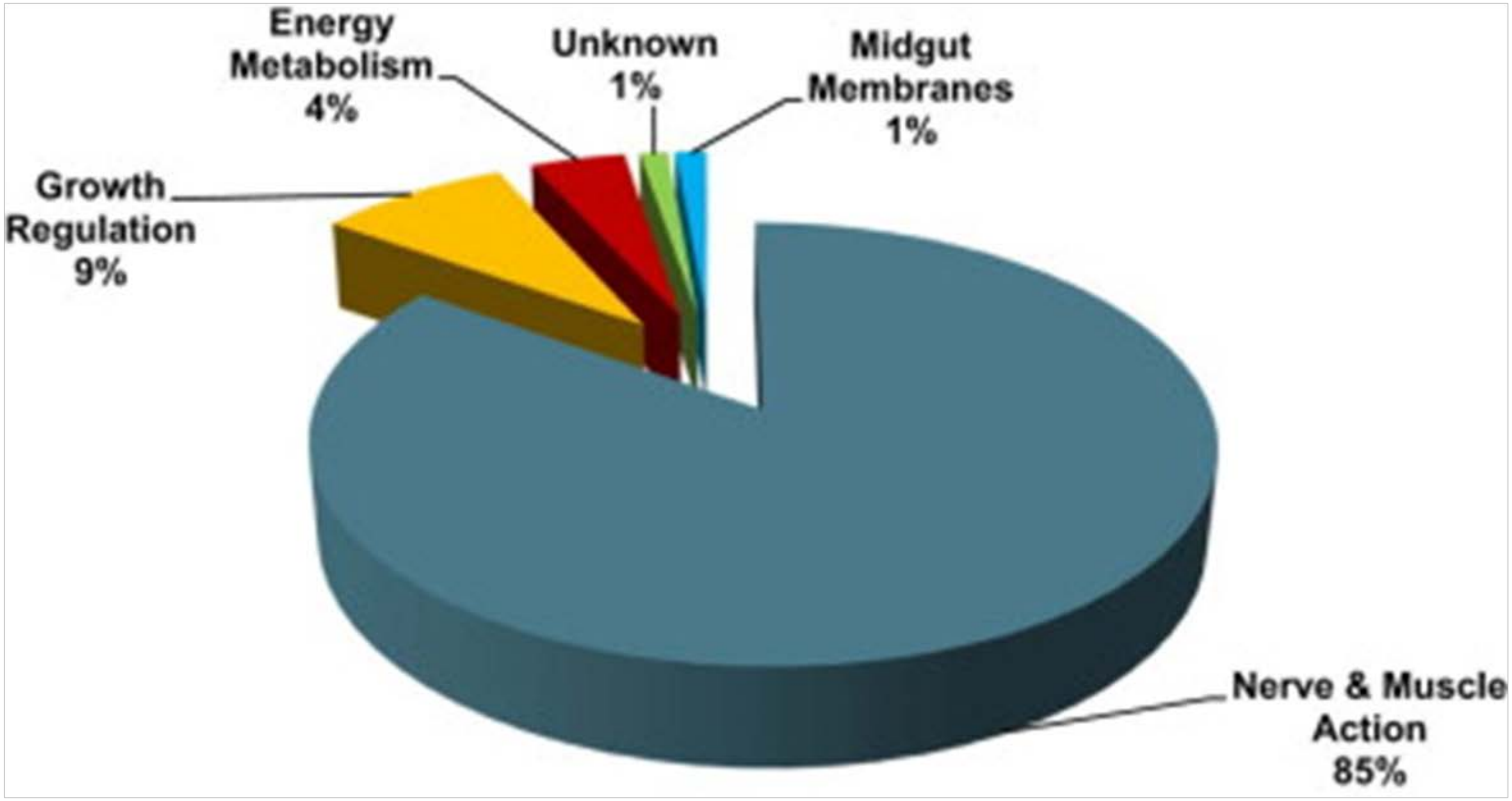
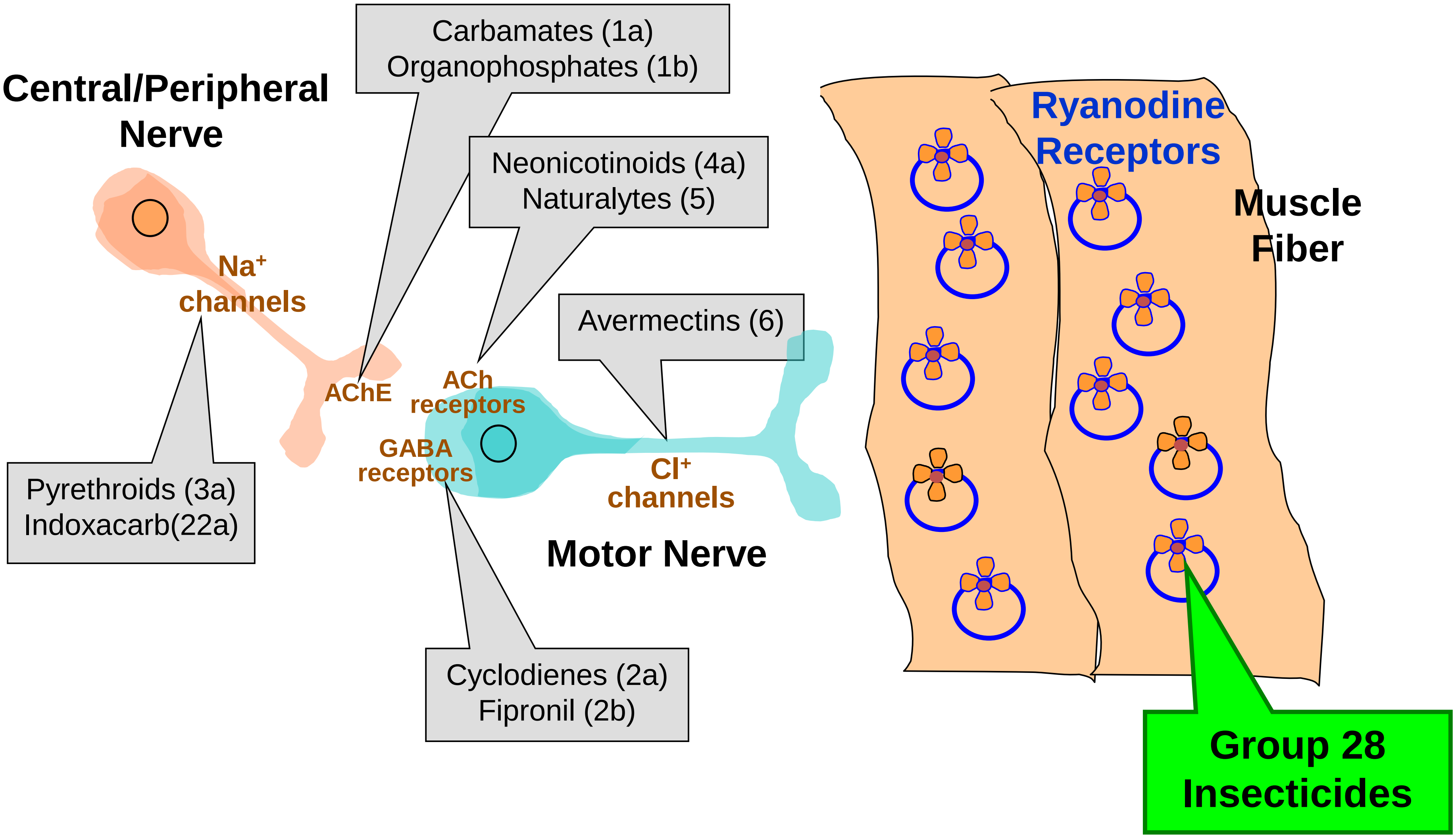
Distribution of total insecticide sales (percent of total value) by broad mode of action (2103)



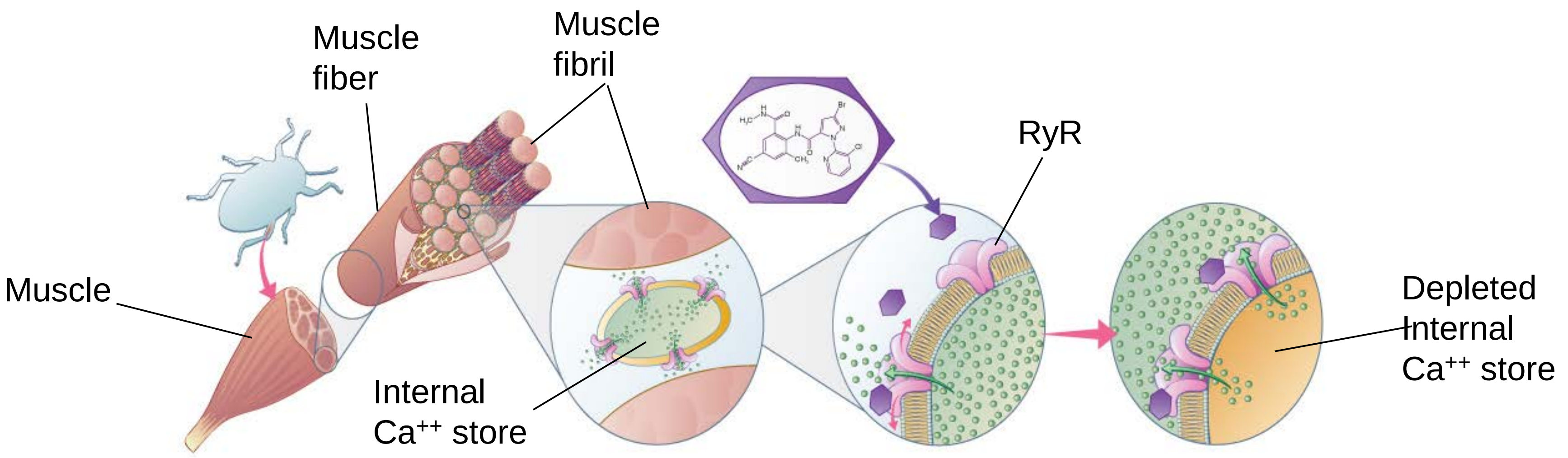
Thomas C. Sparks, Ralf Nauen. **IRAC: Mode of action classification and insecticide resistance management.** Pesticide Biochemistry and Physiology, Volume 121, 2015, 122–128

Group 28 Insecticides - Unique Biochemical Target



Mode of Action of Diamides (GR 28):

The basis for rapid feeding cessation and plant protection



Impacts insect behavior by impairing muscle function (release of Ca++), which causes muscle paralysis & death

Basis for Selectivity

- In order to have a toxic effect, the product must:
  - Reach the insect
  - Be absorbed into the insect (contact or gut)
  - Reach the target site in sufficient concentrations
    - Not detoxified/metabolized/excreted
    - Be in its active form, e.g. conversion from pro-insecticide
  - Be able to bind to the target site (receptor)

Basis for Pyrethroid Selectivity Between Insects and Mammals

Table 1

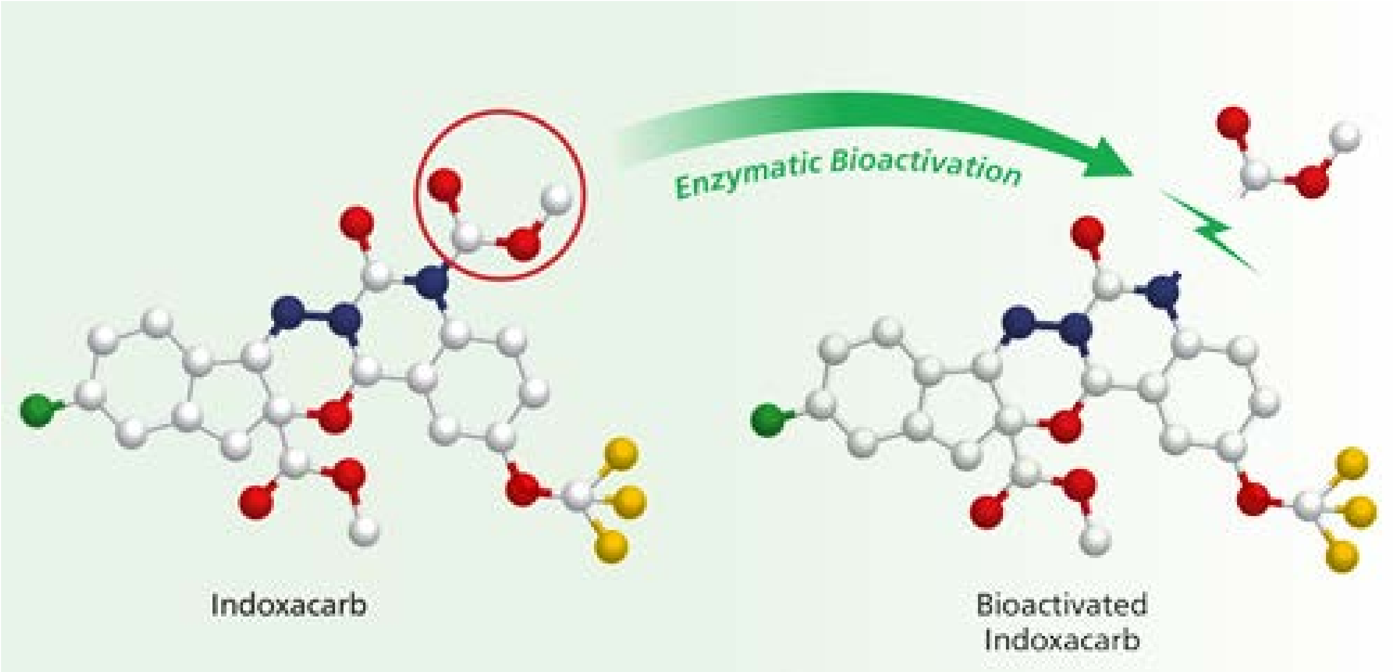
Mechanism of selective toxicity of pyrethroids

Selectivity factors	Mammals	Insects	Estimated differences
Potency on nerve Na^{+} channels			
Due to temperature dependence	Low (37°C)	High (25°C)	5
Due to intrinsic sensitivity	Low	High	1000
Detoxication rate	High	Low	3
Overall difference = 15 000			

T Narahashi,* X Zhao, T Ikeda, K Nagata, and JZ Yeh. Differential actions of insecticides on target sites: basis for selective toxicity. Hum Exp Toxicol. 2007 Apr; 26(4): 361–366.

Example of a Pro-Insecticide

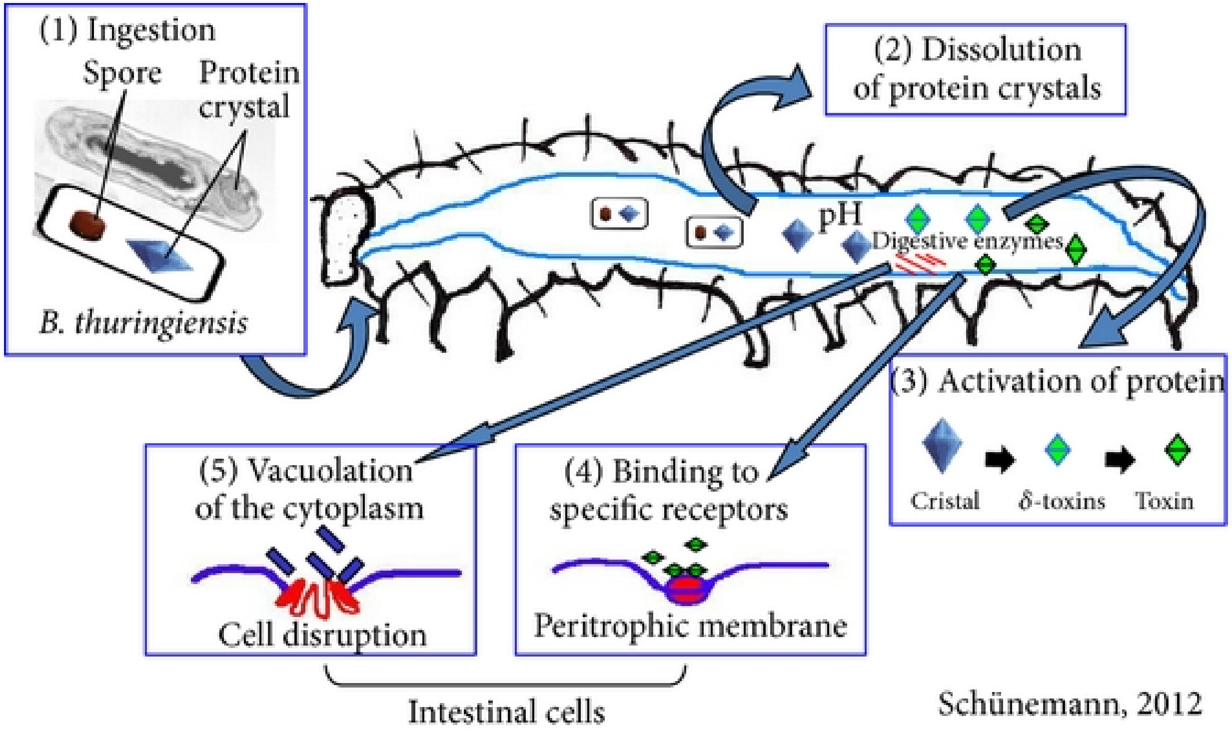
- Insect specific enzymes/conditions activate the insecticide



http://www.merck-animal-health-usa.com/

Bt Activation in the Midgut is highly pH Dependent

Bacillus thuringiensis (*Bt*) is a natural bacteria that produces insect control proteins called "Cry".



Proteins specific to lepidoptera are solubilized a pH >9.5.

Rogério Schünemann, Neiva Knaak, and Lidia Mariana Fiuza, "Mode of Action and Specificity of *Bacillus thuringiensis* Toxins in the Control of Caterpillars and Stink Bugs in Soybean Culture," *ISRN Microbiology*, vol. 2014, Article ID 135675, 12 pages, 2014. doi:10.1155/2014/135675

Bt Plant Protection Mechanisms

Toxicity ⟷ **Non-preference**

Cry1Ab
European corn borer

Cry1F
Black cutworm

Growers can realize tremendous value
without a product being highly toxic or providing a "High Dose"

Basis for Diamide Selectivity to Beneficials

1. Potent via ingestion
   a) Effective on chewing pests that consume treated foliage
   b) Most beneficials are carnivores

2. Moderately soluble, xylem systemic

3. Differences in susceptibility?

Little to no exposure at the target site.

Rynaxypyr® selectivity to Beneficial Arthropods

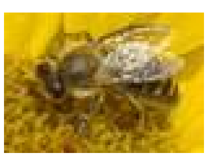
Evaluation of Rynaxypyr® on Key Predators

GROUP	ORDER	FAMILY	SPECIES	RESULT
Predators 	**Neuroptera**	**Chrysopidae**	*Chrysoperla carnea*	●
	Lacewings		*Mallada signatus*	●
	**Coleoptera**	**Coccinellidae**	*Hippodamia convergens*	●
	Ladybird beetles		*Hippodamia variegatta*	●
			Harmonia axyridis	●
	**Hemiptera**	**Nabidae**	*Nabis kinbergii*	●
	Predatory bugs	**Anthrocoridae**	*Orius insidiosus*	●
			Anthocoris nemoralis	●
		Miridae	*Deraeocoris brevis*	●
		Lygaeidae	*Geocoris punctipes*	●
	**Acari**	**Phytoseiidae**	*Amblyseius herbicolus*	●
	Predatory mites		*Amblyseius andersoni*	●
			Kampimodromus aberrans	●
			Euseius citrifolius	●
			Iphiseiodes zulugai	●
			Typhlodromus occidentalis	●
			Typhlodromus pyri	●

● **no impact, (0-30% mortality).**
Rating according to IOBC/ WPRS Working Group, Hassan et al. 1988.

Rynaxypyr® has excellent selectivity to Beneficial Arthropods & Pollinators

Evaluation of Rynaxypyr® on Key Parasitoids and Pollinators

GROUP	ORDER	FAMILY	SPECIES	RESULT
Parasitoids	**Hymenoptera**	**Trichogrammatidae**	*Trichogramma pretiosum*	●
	Parasitic wasps		*Trichogramma chilonis*	●
		Braconidae	*Aphidius rhopalosiphi*	●
			Bracon hebetor	●
			Dolichogenidea tasmanica	●
		Encyrtidae	*Ageniaspis citricola*	●
		Aphelinidae	*Aphelinus mali*	●
Pollinators	**Hymenoptera**	**Apidae**	*Apis mellifera*	●
	Honey bees			

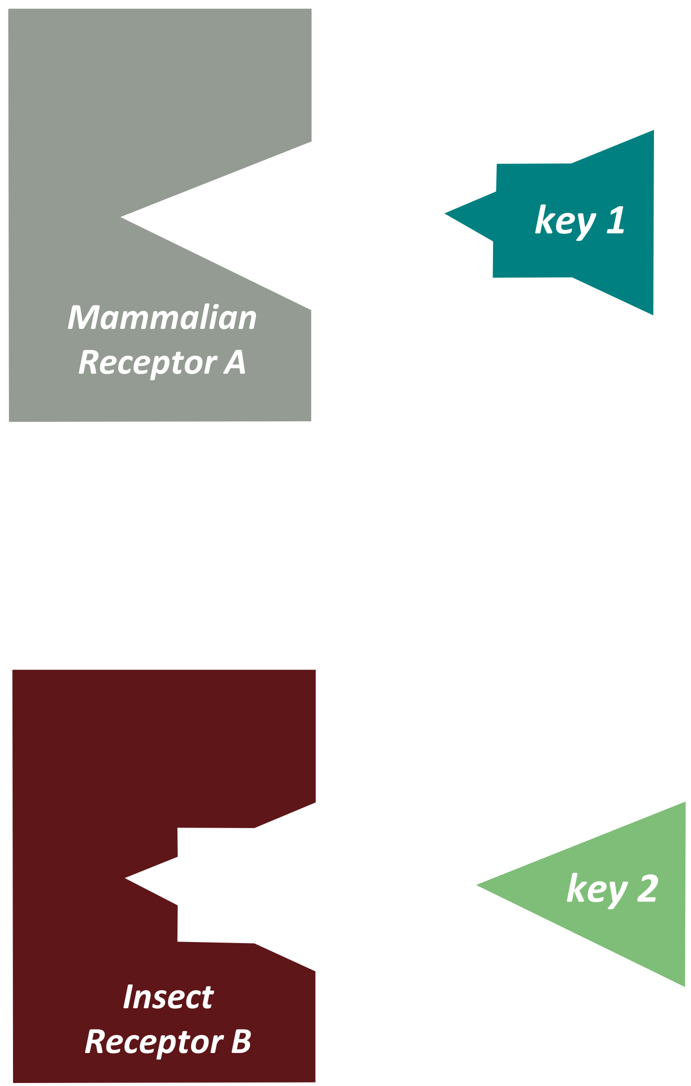
● **no impact,** (0-30% mortality). Rating according to IOBC/ WPRS Working Group, Hassan et al. 1988.

Basis for Diamide Selectivity to Mammals

1. Target site differences at the Ryanodine receptor
   a) The basis for the remarkable mammalian selectivity is a structural difference between insect and mammalian ryanodine receptors (RyRs).
   b) Homology of nucleic sequence is < 40%, coding for distinct proteins, with distinct tri-dimensional shape
   c) Rynaxypyr® is 400-3000 times more effective in activating RyRs from insects than from mammals.

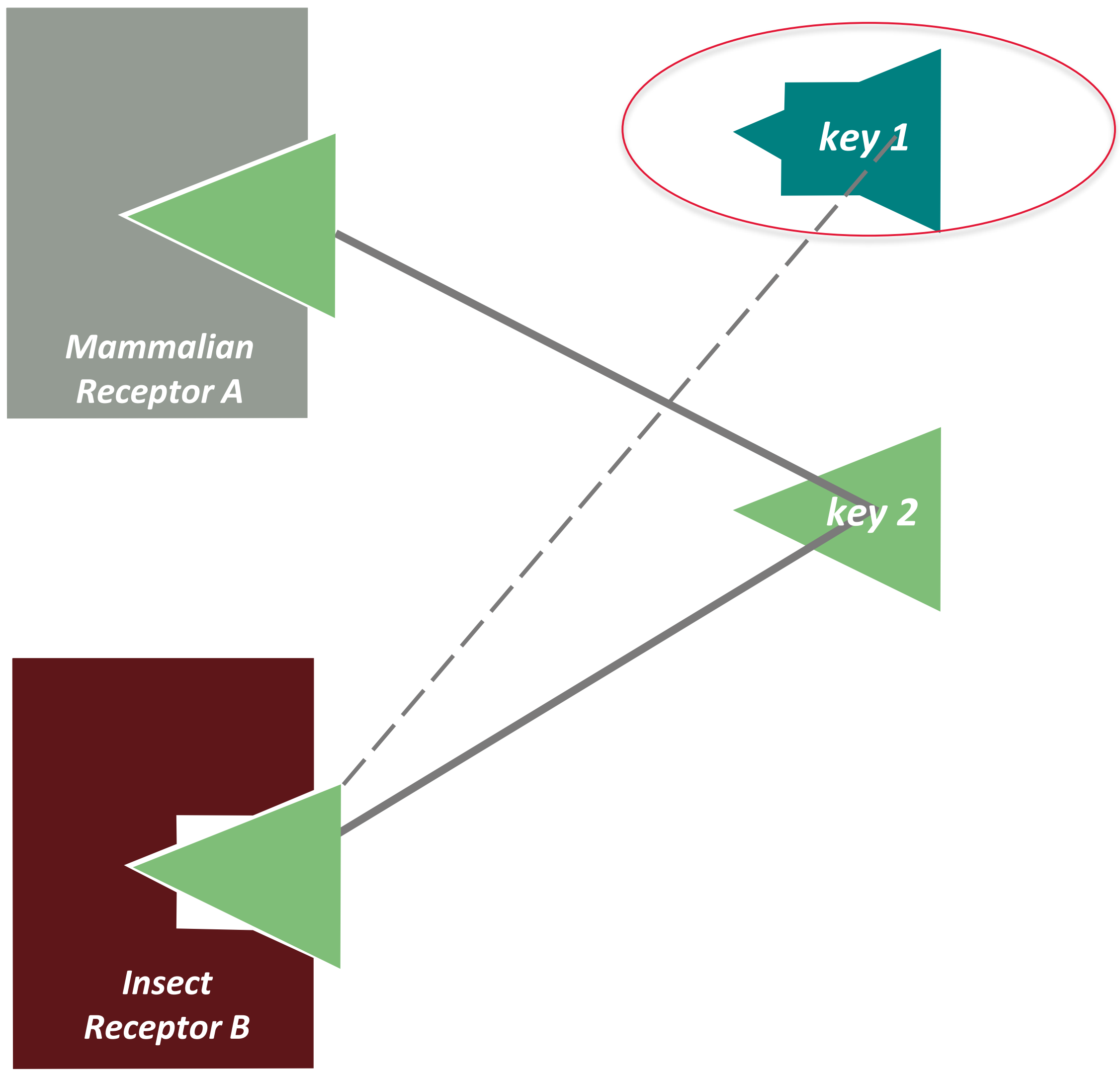
Rynaxypyr® fits into insect but not mammalian ryanodine receptors.

Selectivity at the Receptor



Which active is selective between Receptor A and B?

Selectivity at the Receptor

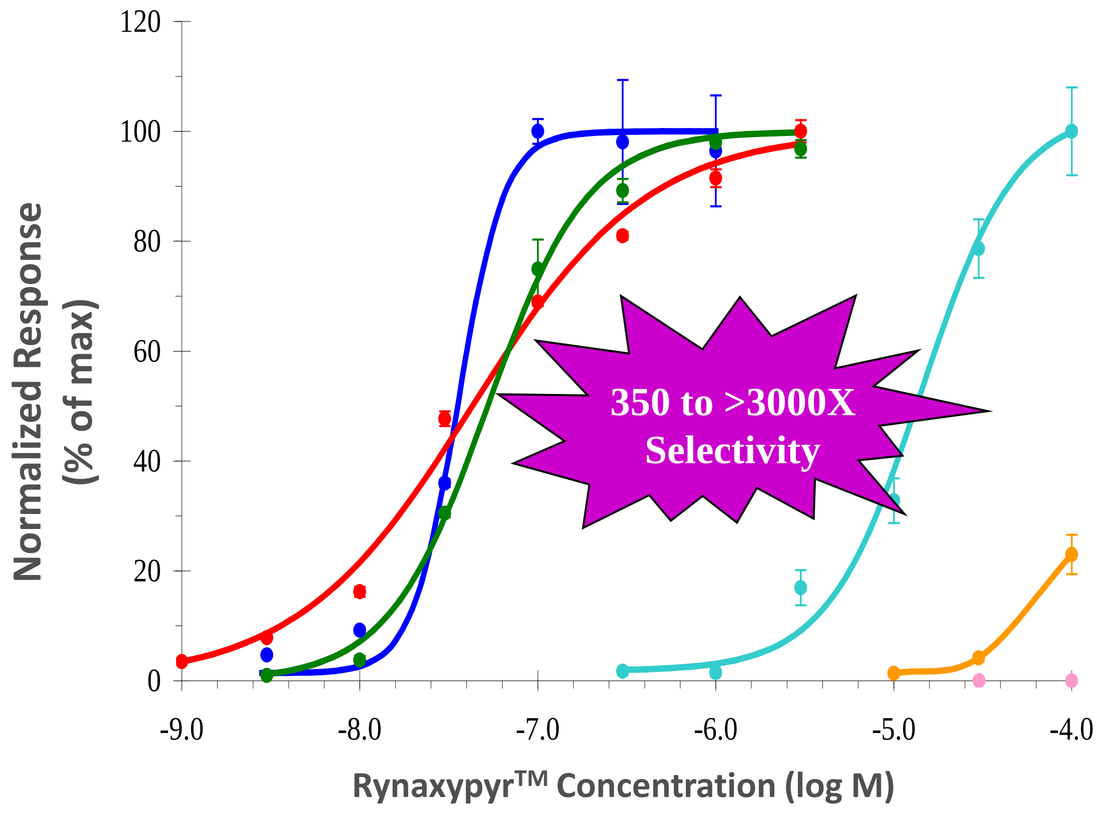


DuPont Rynaxypyr® Selectivity to Mammals

Cell Lines Evaluated

- *P.americana*
- *D. melanogaster*
- *H. virescens*

- Mouse
- Rat
- Human



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

Mammalian Toxicology – Rynaxypyr®

REPRESENTATIVE TEST	RESULT
Acute oral toxicity, rat LC_{50}: …………..........................	> 5,000 mg/ kg
Acute dermal toxicity, rat LD_{50}: …………………………..	> 5,000 mg/ kg
Sub-acute and subchronic toxicity (mouse, rat, dog):	No adverse effects
Inhalation, rat LC_{50}: ………....………………………………	> 5.1 mg/ L
Dermal irritation: …..………….....................….....	Not irritant
Eye irritation:	Slight, clearing in 72 hours
Dermal sensitization: …………………………………………	Not a sensitizer
Mutagenicity: ………………………………………………..	Not mutagenic
Carcinogenicity: …………………………………………….	Not carcinogenic
Neurotoxicity: ……………………………………………….	Not neurotoxic
Immunotoxicity: ……………………………………………	Not immunotoxic
Developmental toxicity: ……………………………………	No adverse effects
Reproductive toxicity: ……………………………………...	No adverse effects

Selectivity Allows for Greater Flexibility

- Broad crop labels
- Multiple applications
- Short PHIs
- Short re-entry intervals

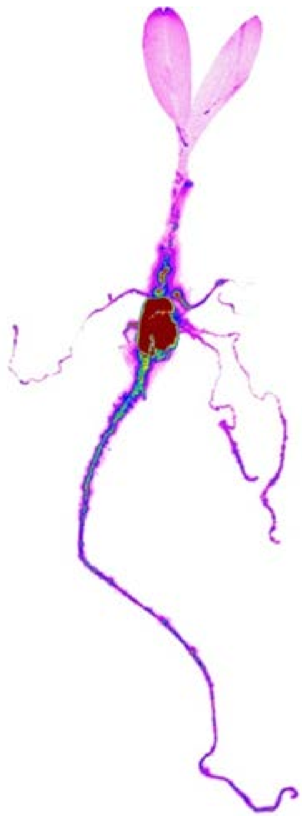
Ingestion and/or Contact Activity?

	Ingestion	Contact
Life stage controlled	Actively feeding life stages	Life stages present at application
Length of control	Longer, dependent on breakdown	Short
Pest spectrum	Limited to pests feeding on foliage	Broad
Insect selectivity	More selective	Less selective
Timing	More flexibility	Pest must be present

In reality, most products act in some combination of ingestion and contact, but usually one is predominant

Systemic Movement – Factors to Consider

1. Xylem only, xylem and phloem
2. Uptake from soil
3. Translocation after foliar application
4. Protection of existing growth vs. new growth
5. Movement to reproductive parts of the plant, which are fed via phloem



Delivery Methods

The site and method of delivery significantly affects potential for applicator and non-target exposure, e.g.

- Foliar
- Seed
- Soil drench, in-furrow
- Transplant
- Genetics
- Bait

What Does The Future of Insecticides Look Like?

- Highly selective, conserving beneficials
- Ingestion
- Plant protection vs. “knock-down”
- Low use rate
- Not highly soluble
- Chemical + Genetic + Biological

The Future of Insect Trait Development

Novel mode of action

- Broad spectrum on targets
- No toxicity to non-targets

Durability

- Activity (dose) against targets
    - Pest susceptibility (toxicity)
    - Plant expression (exposure)

Conclusions

When we understand a product's:

- Mode of action
- Behavior in plants and insects
- The basis for its selectivity

Then we can make better and more informed decisions, to ensure we get the right product on the right acre, at the right timing.