New Insecticide Modes of Action: Whence Selectivity?

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Outline

- Selectivity
- New Insecticide Classes
  - Neonicotinoids
  - Fipronil
  - Chlorphenapyr
  - Sulfuramid
  - Spinosads
  - Buprofezin
  - Diafenthiuron
  - Indoxacarb
  - Metaflumazine
  - Pymetrozine
Where have we been?

DDT
dieldrin

lindane
Where are we now, and where are we headed?

Neonicotinoids
Imidacloprid

Mode of Action

• Binds irreversibly to postsynaptic nicotinic acetylcholine receptors.
Neonicotinoids: Acetylcholine Agonist

Neonicotinoids Thiamethoxam

Control wide range of sucking / chewing pests like aphids, thrips, termites, weevils, beetles, wireworms, fire ants
Neonicotinoids--Thiamethoxam

Toxicity to non-targets
- Rat oral LD$_{50}$ a.i. = 1,563 mg/kg
- Rat dermal LD$_{50}$ a.i. >2,000 mg/kg

Water solubility = 4,100 mg/L

Fipronil
fipronil - Regent

- Phenyl-pyrazole family
- fipronil - primary family member in production

Fipronil Mode of Action

- Acts as an inhibitor at the γ-aminobutyric acid (GABA) receptor as a noncompetitive blocker of the GABA-gated chloride channel (similar to lindane and cyclodienes)
- Chemical and biological activation producing equally toxic and sometime more persistent metabolites with same mode of action
Nerve Axon

GABA-gated Chloride Channel

Fipronil Mode of Action

Antagonist at GABA-gated Chloride Channel
Selective Toxicity of Fipronil

Vertebrate

Acute Mouse Oral LD$_{50}$
$= 41 \text{ mg/kg}$

Insect

Acute Housefly Contact
LD$_{50}$ $= 0.13 \text{ mg/kg}$

Chlorfenapyr
Chlorfenapyr

- American Cyanamid product, now BASF
- Registered outside U.S. for cotton
- Broad-spectrum insecticidal action

Chlorfenapyr, AC-303,630

Chlorfenapyr

Oxidative Phosphorylation

Chemiosmotic theory

Electron flow through the electron transport chain is accompanied by a transfer of protons

ATP synthesis driven by proton-motive force

Electron transport train uses O₂ as final electron receptor
Sulfluramid

CH$_3$CH$_2$N$\text{S}$C$\text{C}$C$\text{C}$C$\text{C}$C$\text{C}$C$\text{C}$CF$_3$

sulfluramid
Spinosads

New class of potent natural insecticides
Spinosads

- Mode of action – acts on the acetylcholine receptor to make it more excitable.
- Overstimulation of the nerve results.
- Hypothesis currently considered most plausible, although not really accepted as the last word.
Buprofezin

Inhibits chitin synthesis/deposition
Effect similar to benzoyl phenylureas
Insects die when newly molted
IGR
Diafenthiuron

Diafenthiuron- Mode of Action

- Inhibits ATPase in mitochondria
- Blocks utilization of energy (ATP)
- Thiourea compound
Indoxacarb

Indoxacarb – Mode of Action

- Blocks sodium channel in nerve axon
- Inhibits propagation of nerve potential
- Oxadiazine compound
Indoxacarb effect on nerve axon

Nerve Potential Propagation

Metaflumizone
**Metaflumizone**

- Putative mode of action – blocks sodium channel in nerves
- Log P 4.7-5.4

**Pymetrozine**

[pymetrozine structure]
Pymetrozine – Mode of Action

- Inhibits feeding of sucking insects
- Especially active on aphids
- Pyridine azomethine compound

Conclusions

- A number of very new classes of insecticides have been developed, with new modes of action.
- Availability of products is changing, toward newer classes of insecticides.
- Selectivity is ever more important:
  - to applicators, to livestock, pets, wildlife, environment, residues in food.
Conclusions

- Some of the new chemistry perpetuates non-selective insecticide toxicity.
- Some of it allows opportunities for safer, more selective insecticides.

Questions

- How many and which modes of action should be screened for in non-target bioassays? High throughput assays?
- Can we predict which species will be most vulnerable and under what exposure (conc., timing)?
The First McKim Conference: Some Important Questions

- Best bioassays?
- Specificity and selectivity?
- Extrapolation?
- Metabolic detoxification or activation?

“*If you’re not part of the solution... you’re part of the precipitate.*”

- Anon (C&EN)
Getting answers depends on the quality of “the hired help.”

Steve Bradbury, circa 1984
Part of Jim McKim’s rich legacy