Modes of Action and Target Pests for Insecticides

- Insecticides are chemicals that kill insects … they may also kill other organisms at commonly used rates.
- Their “safe” but effective use depends on
  - (1) target insects’ greater exposure than nontarget organisms;
  - (2) their breakdown over time;
  - (3) differences in toxicity of the active ingredient to different species;
  - (4) differences in rates of detoxification among target and nontarget organisms.
- Many insecticides are registered for use in the U.S., and they differ widely in effectiveness to different insects, nontarget toxicity, and persistence

Overview

- Insecticides … by chemical structure and modes of action
- Why structures and modes of action matter
- What’s effective against what?
- Alternative insecticides
- Available references

Chemical names, common names, and trade names …

- Chemical name: 2-Methyl-3-phenylphenyl)methyl (1S,3S)-3-[(Z)-2-chloro-3,3,3-trifluoroprop-1-enyl]-2,2-dimethylcyclopropane-1-carboxylate
- Common name: bifenthrin
- Trade name (original) Capture
- Generic products (and “re-names”): Talstar, Brigade, Bifenthrin, Discipline, Sniper, Ortho Home Defense Max, Scotts LawnPro Step 3, and others.

Insecticides

- Organochlorines
  - DDT and others long-since banned) plus endosulfan (Thiodan, Endosulfan, Thionex) (Group 2A)
- Organophosphates (Group 1B)
  - clorethoxyfos (Fortress)
  - chlorpyrifos (Lorsban, Dursban, many more)
  - diazinon (Diazinon)
  - dimethoate (Cygon, Dimate, Dimethoate)
  - malathion
  - methyl parathion (Penncap-M)
  - terbufos (Counter)
- Carbamates (Group 1A)
  - acephate (Orthene)
  - carbaryl (Sevin)
  - carbofuran (Furadan)
  - methomyl (Lannate)
  - thiodicarb (Larvin)

Organochlorines were the first synthetic organic insecticides. Many were very persistent in the environmnent. Almost none are currently labeled for use in the US. Organophosphates and carbamates were developed in the 1950s through 1980s … they are less persistent, but several were more acutely toxic to mammals, posing greater risks to applicators.

Insecticides

Pyrethroids came to market primarily in the 1980s and 1990s. Their mode of action is similar to that of DDT, but they are much less persistent and effective at greatly lower doses.

- Pyrethroids (Group 3)
  - bifenthrin (Capture, Brigade, Bifenthrin, Bifenture, Discipline, Fanfare, Sniper, Tundra, more)
  - cyfluthrin (Baythroid, Renounce, Tombstone, more)
  - cypermethrin (Ammo)
  - esfenvalerate (Asana, Adjourn)
  - fenpropathrin (Danitol)
  - lambda-cyhalothrin (Warrior, Silencer, more) (related, gamma cyhalothrin = Pro-axis)
  - permethrin (Ambush, Pounce, Arctic, Permethrin, Perm-UP, and more)
  - tefluthrin (Force)
  - zeta-cypermethrin (Mustang Max)

Neonics were first marketed in the late 1980s, and many new products came to market during the last 20 years.

Insecticides

- Neonicotinoids (Group 4A)
  - acetamiprid (Assail)
  - clothianidin (Poncho, Belay)
  - imidacloprid (Admire, Provado, Couraze, Imida, Macho, Malice, Montana, Nuprid, Torrent, Widow, more)
  - dinotefuran (Venom)
  - thiamethoxam (Actara, Platinum, Cruiser)
- Spinosyns (Group 5)
  - spinosad (Tracer, Success, Entrust)
  - spinetoram (Radiant)

Additional insecticide structures

- Avermectins and similar compounds (Group 6)
  - abamectin (Agri-Mek, Abba, Epi-Mek, Zoro)
  - emamectin benzoate (Proclaim)
- Juvenile hormone analogs (Group 7)
  - pyriproxyfen (Esteem)
- Benzoylureas (Group 15)
  - Diflubenzuron (Dimilin)
  - Novaluron (Rimon)
- Indoxacarb (Group 22)
  - Indoxacarb (Avaunt)
- Tetronic acid derivatives (Group 23)
  - Spirotetramat (Movento)
- Anthranilic diamides (Group 28)
  - chlorantraniliprole (Altacor, Coragen)
  - flubendiamide (Belt/Synapse)
- Diacyl hydrazines (Group 18)
  - methoxyfenozide (Intrepid)
  - tebufenozide (Confirm)
  - azadirachtin (neem)
- Phenylpyrazoles (Group 2)
  - fipronil (Regent)

Many other chemical structures have been identified as insecticidal and “satisfactorily” low in nontarget toxicity, persistence, etc.

Miticides

Other types of chemical structures are used as miticides … a pesticide that is widely effective against a range of insects usually is NOT effective against mites.

- Organochlorines
  - dicofol (Kelthane, Dicofol) (Group un)
- Avermectins (Group 6)
  - abamectin (Agri-Mek, Abba, Epi-Mek, Zoro)
- Tetronic acid derivatives (Group 23)
  - spiromesifen (Oberon)
- Neuronal inhibitors
  - bifenazate (Acramite) (Group 25)

Understanding insecticides

- ***An Introduction to Insecticides***, by George Ware, at
  - http://ipmworld.umn.edu/ware-intro-insecticides
- ***Insecticides: Chemistries and Characteristics***, by Jeffrey Bloomquist, at
  - http://ipmworld.umn.edu/bloomquist-insecticides

Insecticide Modes of Action

- IRAC Mode of Action Classification
  - Insecticide Resistance Action Committee
  - 28+ modes of action and insecticide groups

http://www.irac-online.org/documents/moa-classification/?ext=pdf

http://pested.okstate.edu/pdf/insecticide%20moa.pdf

http://www.irac-online.org/content/uploads/IRAC-general-MoA-Poster-v2-2_Mar2012.pdf

Insecticide Modes of Action

- Group 1: **Acetylcholinesterase inhibitors**
  - 1A: carbamates: Sevin, Furadan, Orthene, Lannate, Vydate
  - 1B: organophosphates: Counter, Fortress, Lorsban, Diazinon, Dimethoate, Malathion, Penncap-M
- Group 2: GABA-gated chloride channel antagonists
  - 2A: Endosulfan (an organochlorine); 2B: Regent
- Group 3: **Sodium channel modulators**
  - (DDT, methoxychlor) all pyrethroids, and natural pyrethrins
- Group 4: **Nicotinic acetylcholine receptor promoters and antagonists (acetylcholine mimics)**
  - 4A: neonicotinoids: Assail, Admire/Provado, Actara/Platinum, Poncho, Cruiser, Venom

Insecticide Modes of Action

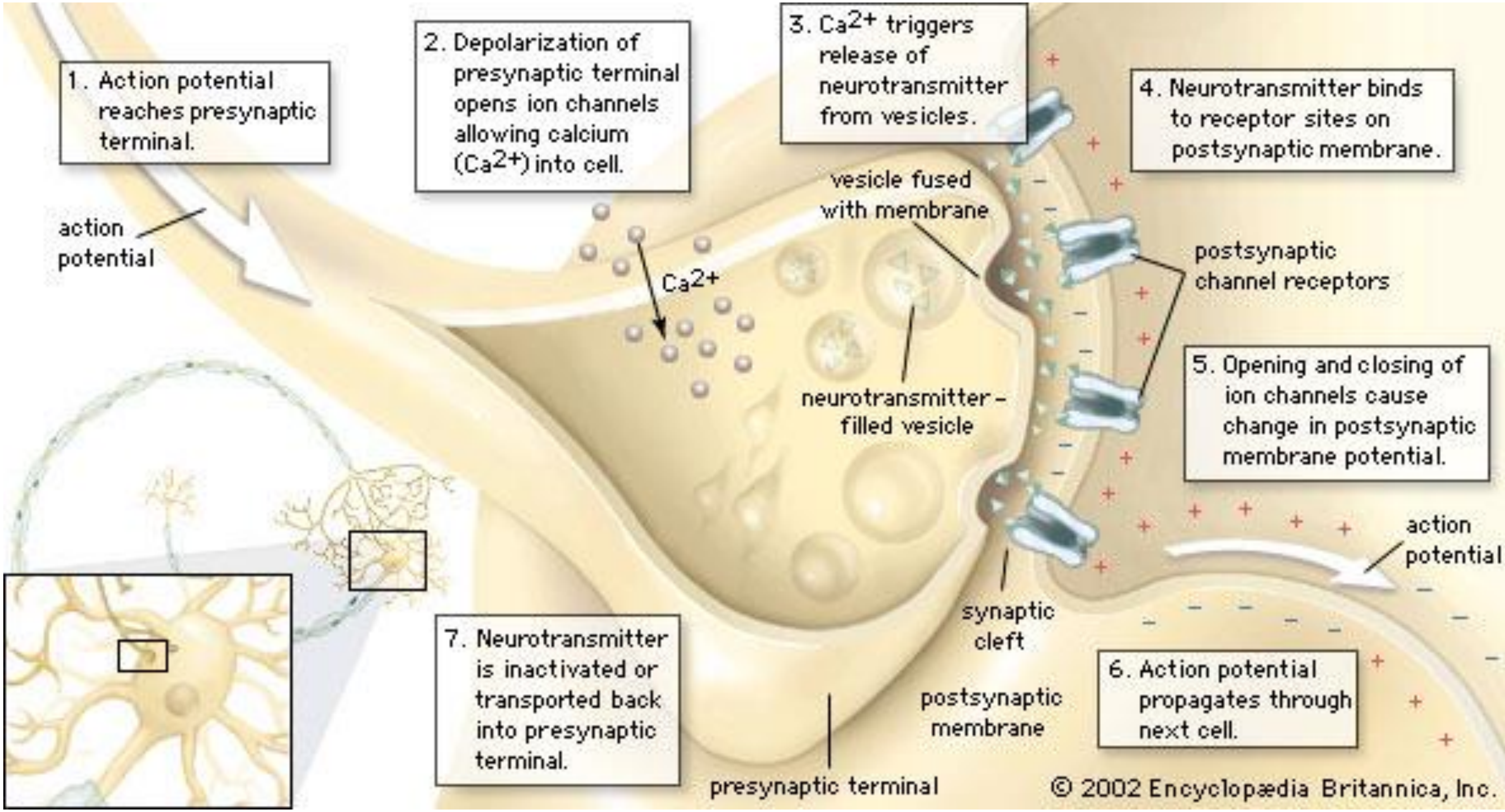
- Group 5: Nicotinic acetylcholine receptor promoters (different from Group 4)
  - spinosad (SpinTor, Entrust)
  - spinetoram (Delegate, Radiant)
- Group 6: Chloride channel activators
  - abamectin (Agri-Mek)
  - emamectin benzoate (Proclaim)
- Group 7: Juvenile hormone mimics
  - pyriproxyfen (Esteem); others include hydroprene, kinoprene, methoprene, and fenoxycarb)
- Group 11: Microbial disruptors of insect midgut membranes:
  - *Bacillus thuringiensis* (with multiple subspecies) (and multiple trade names)
  - These include the toxins that make up GMO Bt corn and cotton
- Group 15: Chitin inhibitors
  - Diflubenzuron (Dimilin)
  - novaluron (Rimon)
- Group 18: Ecdysone (molting hormone) promoters / mimics & molting disruptors
  - tebufenozide (Confirm), methoxyfenozide (Intrepid)

Insecticide Modes of Action

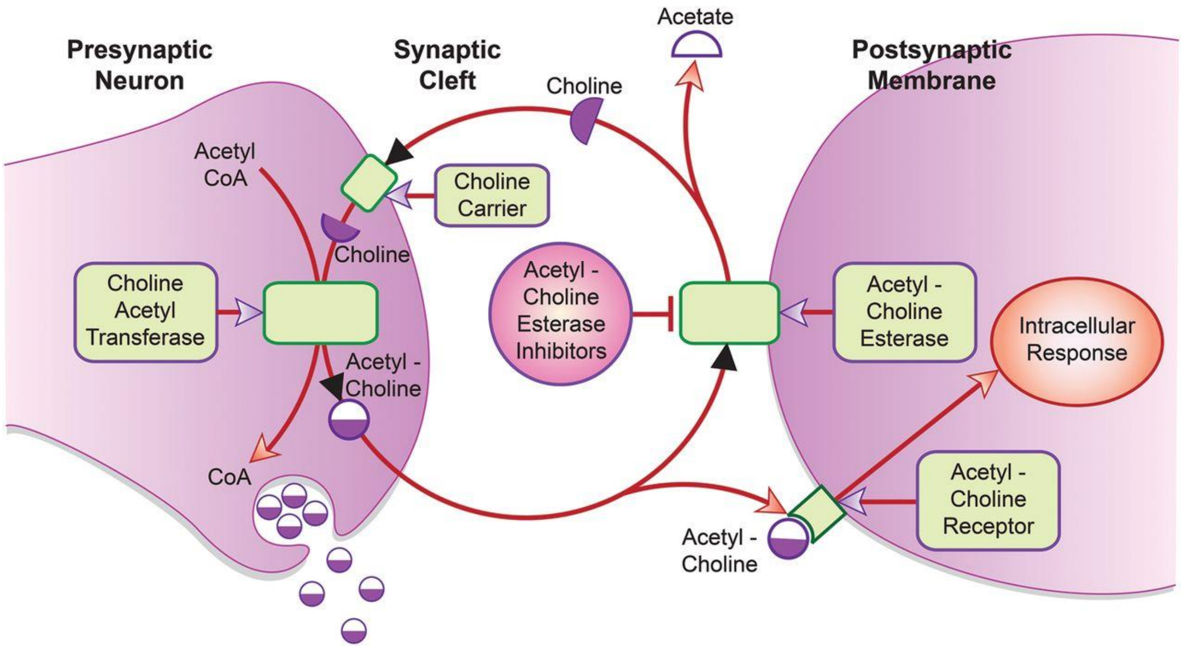
- Group 21: Mitochondrial electron transport inhibitors
  - rotenone
- Group 22: Voltage-dependent sodium channel blockers
  - indoxacarb (Avaunt)
- Group 23: Lipid synthesis inhibitors
  - spiromesifen (Oberon)
  - Spirotetramat (Movento)
- Group 28: Ryanodine receptor modulators
  - chlorantraniliprole (Altacor, Coragen)
  - flubendiamide (Belt/Synapse)
- Group un: Unknown mode of action
  - dicofol (Kelthane), [azadirachtin (neem)]

It is not necessary to know/remember any of these … do know that there are modes of action and registered insecticides that work differently than the primary groups described above.

Nerve impulse transmission … axonic and synaptic. (Most insecticides are nerve poisons.)

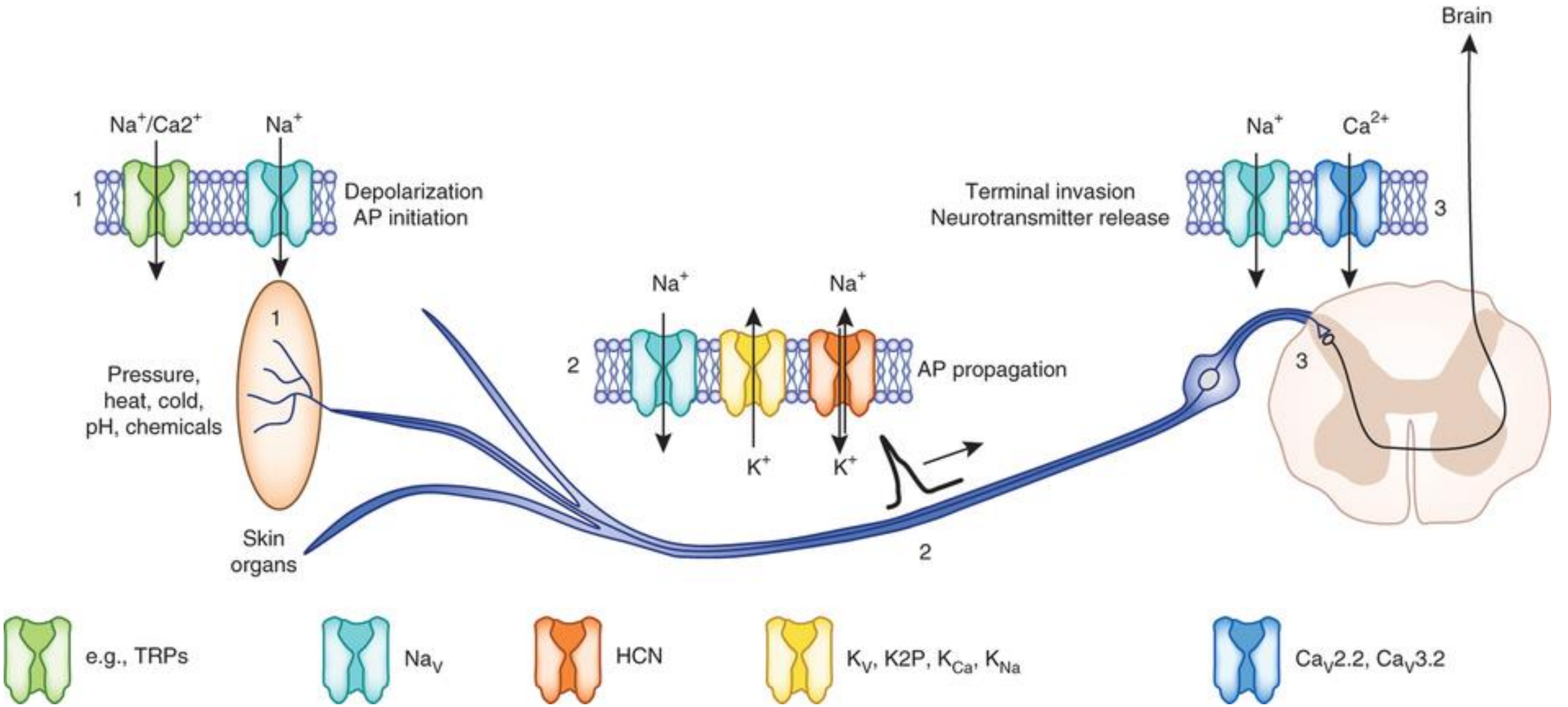


Group 1, acetylcholinesterase inhibitors



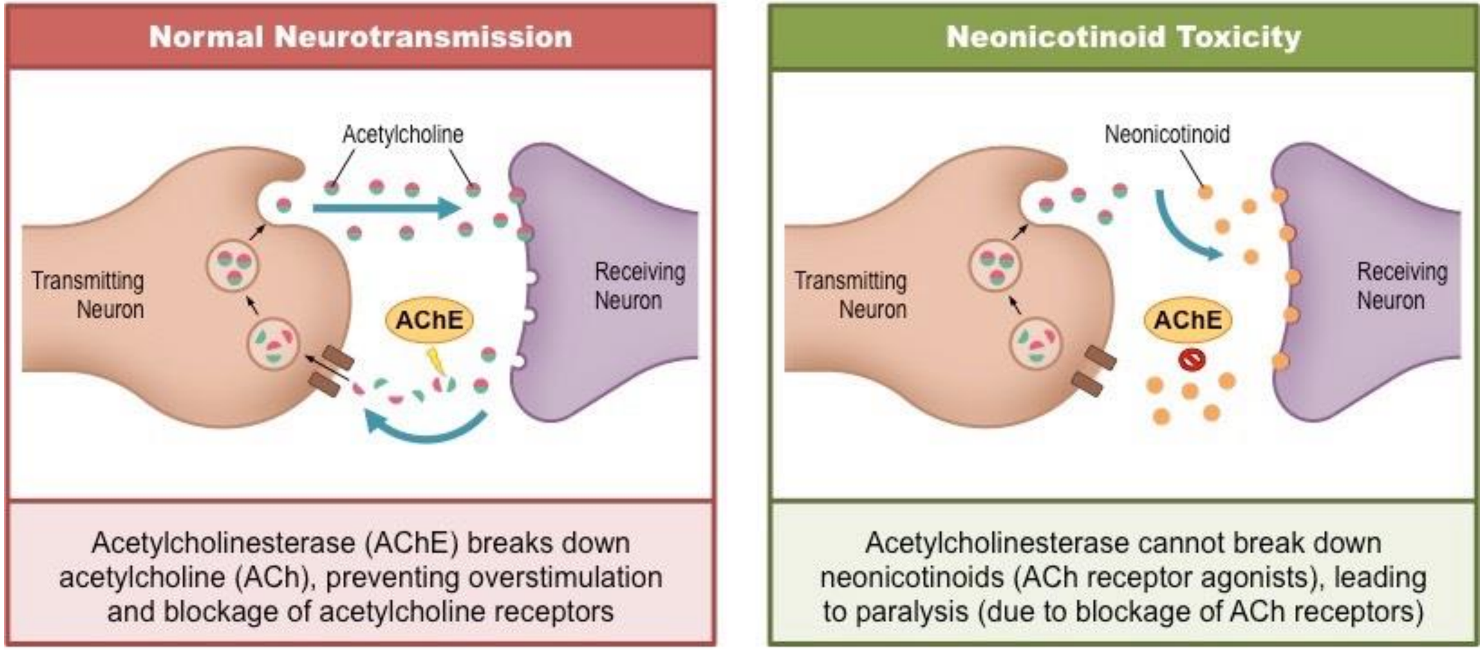
- When a nerve impulse reaches the end of an axon, it must be transmitted across a synapse to a receptor. Acetylcholine is one of the common neurotransmitters that does this. It is then broken down by acetylcholinesterase.
- Organophosphates and carbamates “tie up” acetylcholinesterase and prevent it from breaking down acetylcholine, causing repeated “firing” of the nerve receptor … poisoned insects often exhibit tremors because of this.

Group 3, sodium channel modulators (axonic poisons) DDT, pyrethroids, and natural pyrethrins



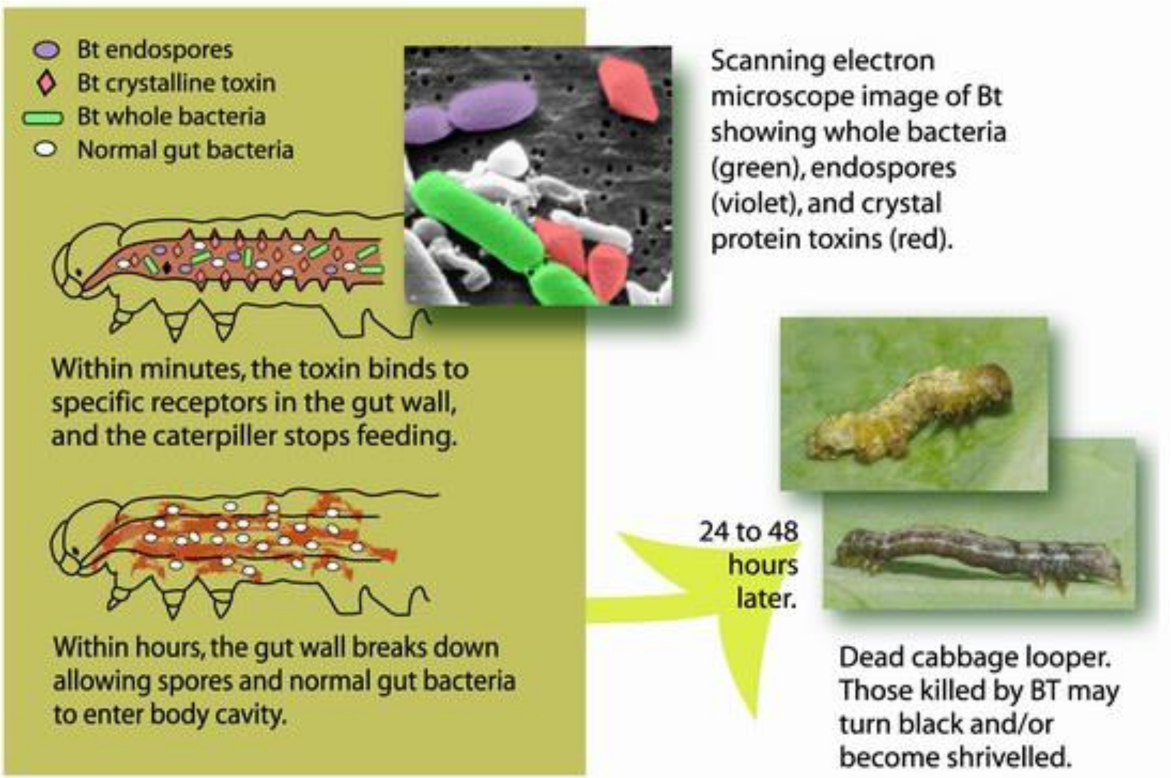
- Nerve impulse transmission along an axon depends on movement of sodium and potassium ions into and out of the axon.
- Sodium channel modulators (Group 3 mode of action) interfere with this by blocking sodium channels.

Group 4, acetylcholine mimics (neonicotinoids)



- When a nerve impulse reaches the end of an axon, it must be transmitted across a synapse to a receptor. Acetylcholine is the neurotransmitter that does this. It is then broken down by acetylcholinesterase.
- Neonicotinoids mimic acetylcholine but are not broken down by acetylcholinesterase. They attach to acetylcholine receptors in the receiving neuron or muscle cell, causing repeated “firing” of the receptor or blockage of the receptor.

Group 11: Microbial disruptors of insect midgut membranes



- *Bacillus thuringiensis* is a bacterium, and it is used in sprayable insecticides and as a source of genes for transgenic crops. Its toxins do not act as nerve poisons. Instead it causes the gut wall to break down, and gut bacteria enter the insect's body cavity. In Bt crops, only the crystalline toxin is produced, not whole bacteria or spores. Different strains and different crystalline toxins are specific to certain insect groups. None have been shown to be toxic to vertebrate animals.

So why are chemical structures and modes of action important?

- Insecticides work if (1) they remain intact within an insect to reach a target site and (2) the target site is susceptible to their attachment and interference.
- Differences among species in natural susceptibility to an insecticide and evolution of resistance in populations of a given species result primarily from (1) increased metabolism or breakdown of insecticide molecules – related to their structure – and from (2) receptor sites that are not susceptible to insecticide attachment and interference.
- Repeated use of insecticides within the same structural family or mode of action group result in more rapid development of resistance
- Rotating among structural families and modes of action – assuming there are alternatives that are effective – is recommended to maximize long-term effectiveness of insecticides and miticides.

So what is the range of target pests for the different groups / modes of action?

- Group 1A, carbamates, acetylcholinesterase inhibitors
  - Furadan: few remaining labeled uses.
  - Orthene: effective against aphids and certain Leps.
  - Sevin: effective against many beetles; not great against most Leps; kills natural enemies of aphids and mites and triggers their outbreaks in susceptible crops.
  - Larvin and Lannate … some Lep activity (generally not as effective as pyrethroids), some aphid activity. Lannate's residual activity is very short.

Of these, only Sevin (carbaryl) is used widely. It remains a common garden and small farm insecticide.

- Group 1B, organophosphates, acetylcholinesterase inhibitors
  - Counter and Fortress: soil-applied for corn rootworm control
  - Lorsban: Soil and seed treatment uses against root and seed maggots, corn rootworm larvae, wireworms, and white grubs; foliar uses against miscellaneous, Leps, beetles, aphids
  - Diazinon: Seed treatment uses against seed maggots, wireworms, white grubs … homeowner formulations have been "un-registered"
  - Dimethoate: Moderately effective against aphids and leafhoppers, some miticidal action.
  - Malathion: Most often used against aphids

- Group 3, DDT, pyrethroids and natural pyrethrins; sodium channel modulators
  - Pyrethroid products include permethrin, Asana, Capture/Brigade/Talstar, Baythroid, Danitol, Force, Warrior/Proaxis, Mustang Max. OMRI-approved Natural pyrethrins include Pyganic, Pyrenone, etc.
  - In general, pyrethroids are good against a range Leps and beetles, as well as grasshoppers, stink bugs, plant bugs, and some thrips.
  - Most compounds in this group are ineffective against most aphids and mites and trigger more severe infestations of these pests by killing their natural enemies.
  - Force is labeled for soil use against corn rootworm larvae.
  - Natural pyrethrins are effective against several beetles but break down **<u>very</u>** rapidly. Using synergists (not OMRI-approved) and spraying at night increases effectiveness.

- Group 4A, neonicotinoids; nicotinic acetylcholine receptor promoters and antagonists
  - Products that are active primarily against aphids, leafhoppers, etc. (plus systemically against corn flea beetle and cucumber beetles) include Gaucho, Cruiser, and Poncho, Admire, Provado, Venom, etc. Assail is used against a broader range of orchard pests.
- Group 5, spinosyns, nicotinic acetylcholine receptor promoters that differ from group 4A
  - Tracer/Success/SpinTor, Entrust, Delegate and Radiant … effective primarily against Lep larvae

Effective primarily against Lepidopteran larvae…

- Group 6: Chloride channel activators
  - emamectin benzoate (Proclaim)
- Group 11: Microbial disruptors of insect midgut membranes:
  - *Bacillus thuringiensis* (with multiple subspecies) (and multiple trade names) (Transgenic corn used for corn rootworm control contains toxins from unique Bt isolates that effective against rootworms)
- Group 15: Chitin inhibitors
  - Novaluron (Rimon) (also effective against Colorado potato beetle)
- Group 18: Ecdysone (molting hormone) promoters / mimics & molting disruptors
  - 18A: tebufenozide (Confirm), methoxyfenozide (Intrepid)
- Group 22: Voltage-dependent sodium channel blockers
  - indoxacarb (Avaunt)
- Group 28: Ryanodine receptor modulators
  - chlorantraniliprole (Altacor/Coragen)
  - flubendiamide (Belt/Synapse)

Specific miticides …

- Group 6: Chloride channel activators
  - abamectin (Agri-Mek)
- Group 23: Lipid synthesis inhibitors
  - spiromesifen (Oberon) (also effective against whiteflies)
- Group 25: Neuronal inhibitors (unknown mode of action)
  - bifenazate (Acramite)
- Group un: Unknown mode of action
  - dicofol (Kelthane)

Pyrethroids that have some miticidal action include Capture and Danitol, but these are not usually the best choices for mite control.

Resistance Management

- Simple rules:
  - Do not use insecticides in the same MOA group repeatedly in the same crop/field/season
  - Rotate among MOAs at least across generations
  - Where an insect pest is not controlled by application(s) of an insecticide in a given MOA group, do NOT switch to another insecticide within the same MOA group
  - If the target pest migrates into the region from an area with known resistance to a particular MOA, do not rely on an insecticide from that MOA group for control at your site

Alternative insecticides

- Benefits:
  - Less persistent in the environment
  - Most are less toxic to nontarget organisms
    - More specific modes of action
- Examples include
  - Botanical insecticides
    - Synergists may be beneficial
  - Soaps and oils
  - Microbial insecticides
  - Growth regulators
  - Pheromones

Botanicals

- Prepared from plants
  - Crude dusts or powders (pyrethrum)
  - Extracts or resins (pyrethrins, neem seed oils)
  - Isolated, refined components (d-limonene, linalool)

  Always -- minimal alteration of naturally occurring compounds
- Strengths and weaknesses
  - Rapid action
  - Rapid degradation
  - Low toxicity to mammals (in general, not always)
  - Minimal technology required for preparation

Older botanicals and their origins

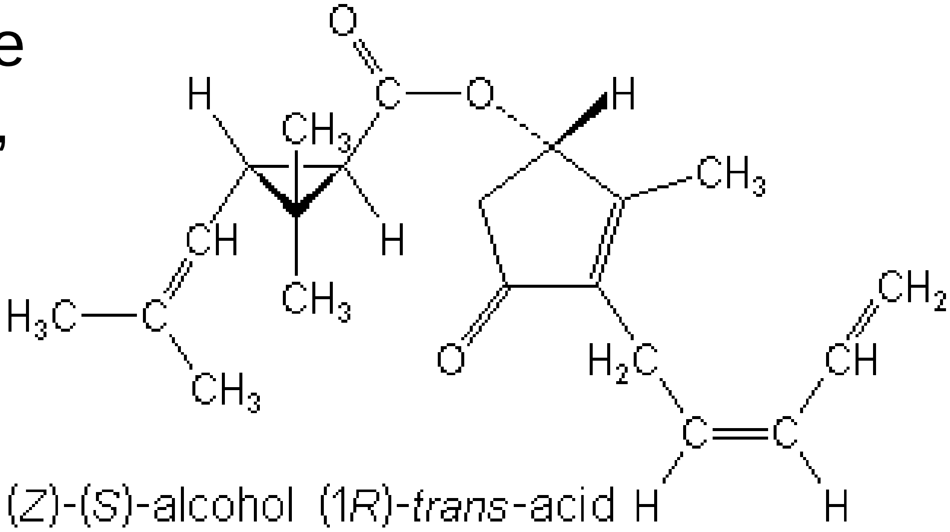
- Nicotine – *Nicotiana* spp.
- Pyrethrins – *Chrysanthemum cinerariaefolium*
- Rotenone – *Derris, Lonchocarpus* and other legumes
- ~~Sabadilla – *Schoenocaulon officinale* (a tropical lily)~~
  - ~~Similar veratrine alkaloids in white hellebore, *Veratrum album*~~
- ~~Ryania – *Ryania speciosa*~~
- Others
  - Soaps, horticultural oils, essential oils, diatomaceous earth

Modes of action, toxicity, and uses of “old” organic insecticides derived from plants

Nicotine	Acetylcholine mimic	Toxicity: Mod-High (dermal and oral)	Greenhouse / Homoptera
Pyrethrins	Na+ / K- ion trans in axons	Toxicity: Low	Animals, humans, organic crops
Rotenone	Electron transfer in cellular respiration	Toxicity: Moderate (implicated in Parkinson’s disease)	Beetles in organic crops
~~**Sabadilla**~~	~~Nerve membrane function~~	~~Toxicity: Low (but mucous membrane irritant)~~	~~Squash bug~~
~~**Ryania**~~	~~Calcium channel disruptors (axonic)~~	~~Toxicity: Low~~	~~Beetles, caterpillars in organic crops~~

Regulatory and marketing status in the United States

- Only pyrethrins are widely available with labels covering a range of crop, animal, indoor, and human uses



More recent botanicals (and similar ingredients) and their origins

- Linalool and d-limonene – citrus oil derivatives
- Neem – *Azadirachta* spp. and *Melia* spp.
- Garlic oils
- Hot pepper oils
- Microbials
  - Toxins from *Bacillus thuringiensis* and other soil micro-organisms (avermectins, spinosyns)

Azadirachta windbreak.
(E. Fernandez, http://www.css.cornell.edu/ecf3/Web/new/AF/arid.html)

Modes of action, toxicity, and uses

Citrus derivatives	Nerve cell stimulants	Toxicity: Low	On pets, indoor plants
Neem	Multiple actions, ecdysone agonist	Toxicity: Very Low (medicinal uses)	Many crop pests
Garlic oil	?	Toxicity: Low	Many labeled uses, limited positive data on effectiveness
Hot pepper extracts	?	Toxicity: Low	
Microbials	Multiple	Toxicity:Low	Many for *Bt* and other products

Effectiveness of currently available botanicals

- Older botanicals
  - Generally well understood based on field trials and small plot trials from 1920s through 1950s
- More recent products
  - More unsupported label claims

Insecticidal soaps

- Salts of fatty acids
- Kill insects by disrupting membranes (including tracheal linings)
- Work only against those insects that are wetted by the spray ... no residual action
- Effective against aphids, whiteflies, mites, and other soft-bodied, not-too-mobile pests
- Best-known brand names are Safer’s and M-Pede

Oils … may be vegetable oils or highly refined petroleum oils

- Dormant oils for fruit and landscape trees
  - Against overwintering aphid eggs, mite eggs, scales
- Stylet oils
  - reduce virus transmission, may suppress powdery mildew
- Summer oils
  - Against mites, aphids, other soft-bodied pests
- Coverage is essential (upper and lower leaf surfaces); oils kill by suffocating pests that are sprayed directly

Absorbents & abrasives

- Clays, diatomaceous earth, silica aerogels
  - disrupt the insect's cuticle and kill by dehydration
- Kaolin clay ... "Surround"

Microbials … will cover these under biological control

- Bacteria
- Viruses
- Fungi
- Microsporidia (Protozoans)
- Nematodes

Insect growth regulators

- Because they are enclosed in an exoskeleton, insects must "shed their skins", or molt, to grow larger. The molting process in immatures and the transformation from larva to pupa to adult is regulated by hormones.
- One is **ecdysone (molting hormone)** secreted by the prothoracic gland; it stimulates shedding of the cuticle.
- Another is **juvenile hormone (JH)**. JH is secreted from the corpora allata; it suppresses adult characteristics. As growth during each stage triggers secretion of ecdysone, if juvenile hormone is present, the cuticle is shed and replaced, and the insect reaches its next juvenile stage.
- As the immature insect grows and eventually discontinues production of juvenile hormone, secretion of ecdysone in the absence of JH triggers pupation and subsequent development of adult form.
- Synthetic hormones that mimic JH and ecdysone have been developed for use as insecticides that disrupt insect development and cause death.

- Juvenile hormone mimics
  - methoprene
  - hydroprene
  - kinoprene
  - pyriproxyfen
  - diflubenzuron (Dimilin)
  - buprofezin
  - hexaflumuron (Sentricon termite control)
  - novaluron (Rimon)
- Ecdysone agonists (= promoters) Existing compounds target Lepidoptera
  - tebufenozide (Confirm)
  - methoxyfenozide (Intrepid)
  - halofenozide (Mach 2, against cutworms in turf)

Useful References

- Pest Management in Wisconsin Field Crops
  - https://learningstore.uwex.edu/Pest-Management-in-Wisconsin-Field-Crops2016-P155.aspx
- Pest Management in Indiana Field Crops
  - https://mdc.itap.purdue.edu/item.asp?Item_Number=ID-179
- Midwest Vegetable Production Guide
  - http://btny.purdue.edu/Pubs/ID/ID-56/
- Midwest Fruit Pest Management Guide
  - https://ag.purdue.edu/hla/Hort/Documents/ID-465.pdf

What you should really know … what does all this nerve impulse transmission and mechanism of poisoning really mean?

- Explain axonic inhibition.
- Explain ACH inhibition.
- Explain AC mimicry.
- How does Bt kill insects?
- For the organophosphates, carbamates, pyrethroids, neonicotinoids, and Bt toxins … how do they kill insects (MOA) and what insects – in general – do they work effectively against?