

Insecticide acaricides & nematicides: 1. neuroactive

Biological and Chemical Control Methods 2005: L2

Principal insect-toxic modes of action

Neuroactive Insecticides

- Axonal: sodium channel of nerve membrane
- GABA chloride channel inhibitors
- Synaptic

Non-neuroactive Insecticides

- insect growth regulators
- juvenile hormone analogues
- ecdysone agonists
- biological (~ly derived) agents
- *etc ...*

Tend to be more specific

1. Axonal action

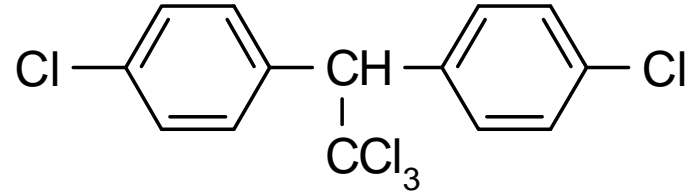
DDT and analogues [sodium channel]

Pyrethrins & pyrethroids [sodium channel]



Natural pyrethrum
Photolabile pyrethroids
Agricultural pyrethroids

DDT



- Introduced in 1944
- Persistent, non-systemic with contact and stomach action
- Original attraction: relatively low mammalian toxicity
- High environmental impact (e.g. on raptors) led to discontinued use in agriculture in the 1980s
- High persistence, low cost: still considered useful for public health in a few countries

First generation synthetic pyrethroids: pyrethrin I analogues

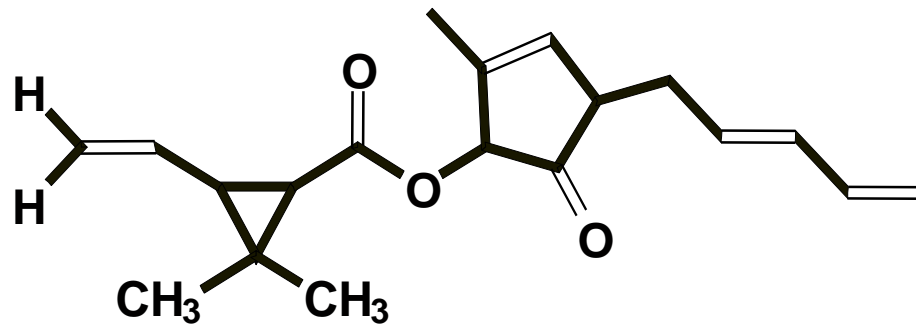
e.g. bioallethrin
tetramethrin
resmethrin

- ❑ all photolabile, short persistence
- ❑ formulations combine KD and kill agents + synergist
- ❑ household, hygiene, food storage and preparation,

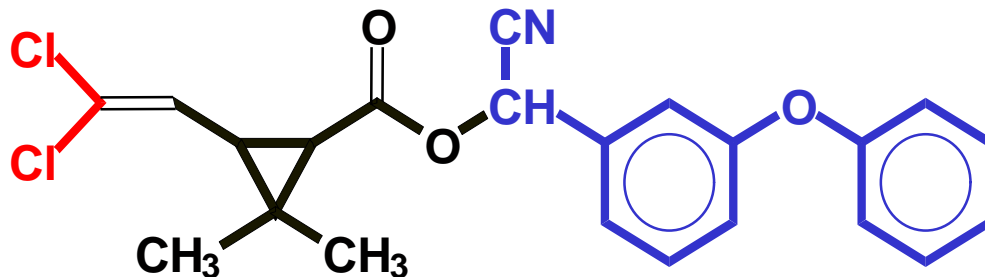


Photostable pyrethroids

Synthetic analogues of pyrethrins



pyrethrin I



cypermethrin

- Residual / contact / stomach acting
- None systemic or translaminar
- Some have acaricidal as well as insecticidal activity

Characteristics of agricultural (photostable) pyrethroids

- rapid insect kill - typical symptoms
- high toxicity group (lambda-cyhalothrin, beta-cyfluthrin, alpha-cypermethrin, deltamethrin)
 - contact action against hemiptera
 - aduIticidal and ovicidal action
- sub-lethal effects
 - irritancy/activation/avoidance behaviour
 - (walk-off, spin-down, “repellency”)
 - paralysis with recovery

Characteristics of agricultural (photostable) pyrethroids

- low water solubility
- photostable - 10-20 days residuality on foliage at typical application rates
- typical rates - 20-200 g.a.i./ha
- no systemic activity - good coverage required
- strongly adsorbed to soil
- broad-spectrum (little selectivity)

2. Insecticides acting at GABA-gated Cl⁻ channels

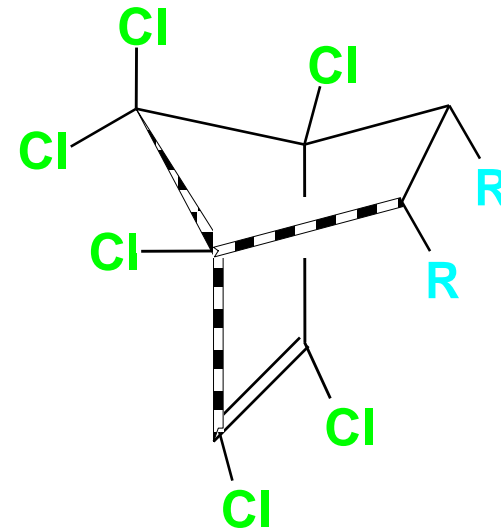
- Cyclodienes (e.g. dieldrin, endosulfan)
- Lindane (gamma-HCH)
- Phenylpyrazoles (e.g. fipronil)

GABA = gamma amino butyric acid:

Important for nerve transmission in both invertebrates and vertebrates - but binds less strongly to latter

Cyclodienes

- ❑ Highly toxic GABA-antagonists: produced from cheap by-products of synthetic rubber industry
- ❑ Many now banned in most countries

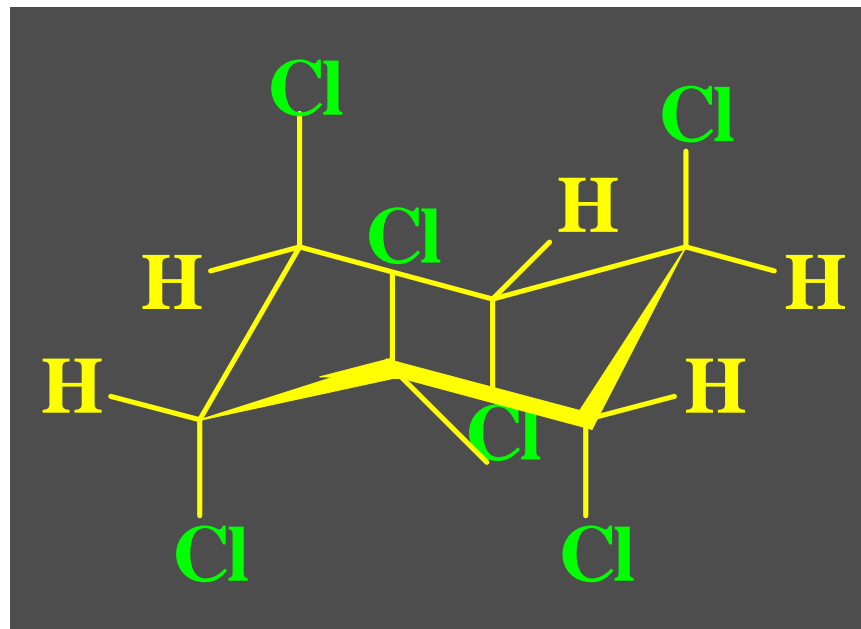


CYCLODIENES

- ALDRIN
- DIELDRIN
- ENDRIN
- HEPTACHLOR
- MIREX
- TOXAPHENE
- CHLORDANE
- ENDOSULFAN

Lindane (gamma-hexachlorocyclohexane = gamma-HCH)

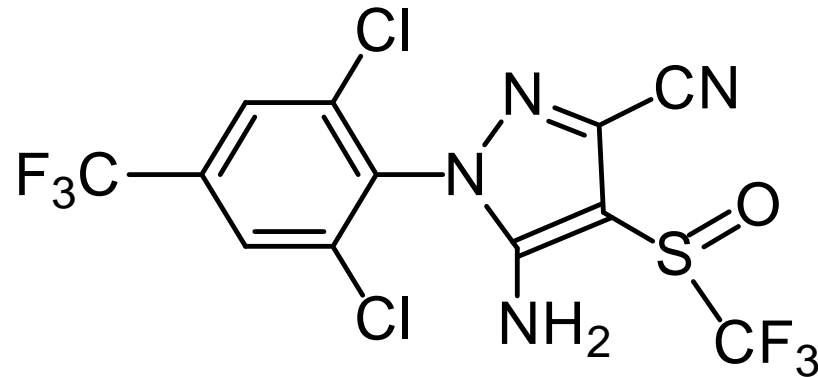
- Broad-spectrum soil insecticide - seed dressing
- Now withdrawn in most countries
- Contact, stomach, some vapour action
- Approved chemical was >99% gamma-isomer
- Accumulation of beta-isomer in animal tissues from impure preparations (BHC - the impure form)



Phenylpyrazoles

- ❑ Most recent class of GABA-R agonists
- ❑ Residual/persistent on surfaces
- ❑ No cross-resistance to cyclodienes (different binding site?)
- ❑ Higher affinity for insect GABA-R (relatively low mammalian toxicity)
- ❑ Broad spectrum activity (similar to pyrethroids) vs agricultural pests, termites, cockroaches, fleas, ticks, mites
- ❑ But chronic toxicity and side effects risks?

Fipronil (Regent®)



Other insecticides acting at Cl⁻ channels

Avermectins

□ Abamectin (Agrimec®)

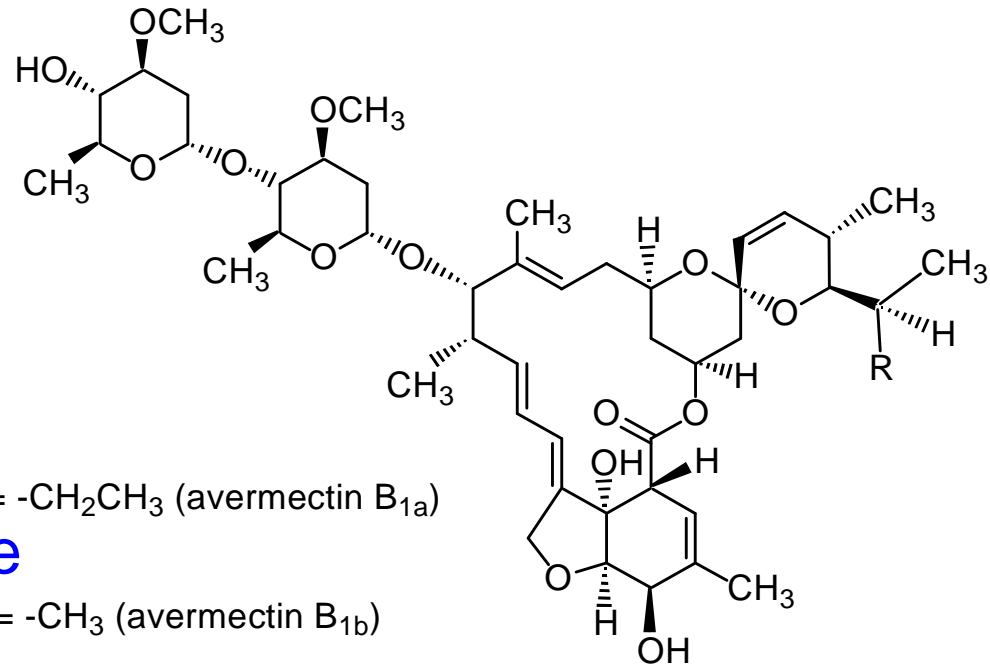
Excellent activity against
mites some lepidoptera
and diptera

□ Emamectin benzoate (Proclaim®)

Broader-spectrum activity
against lepidoptera

(i) R = -CH₂CH₃ (avermectin B_{1a})

(ii) R = -CH₃ (avermectin B_{1b})



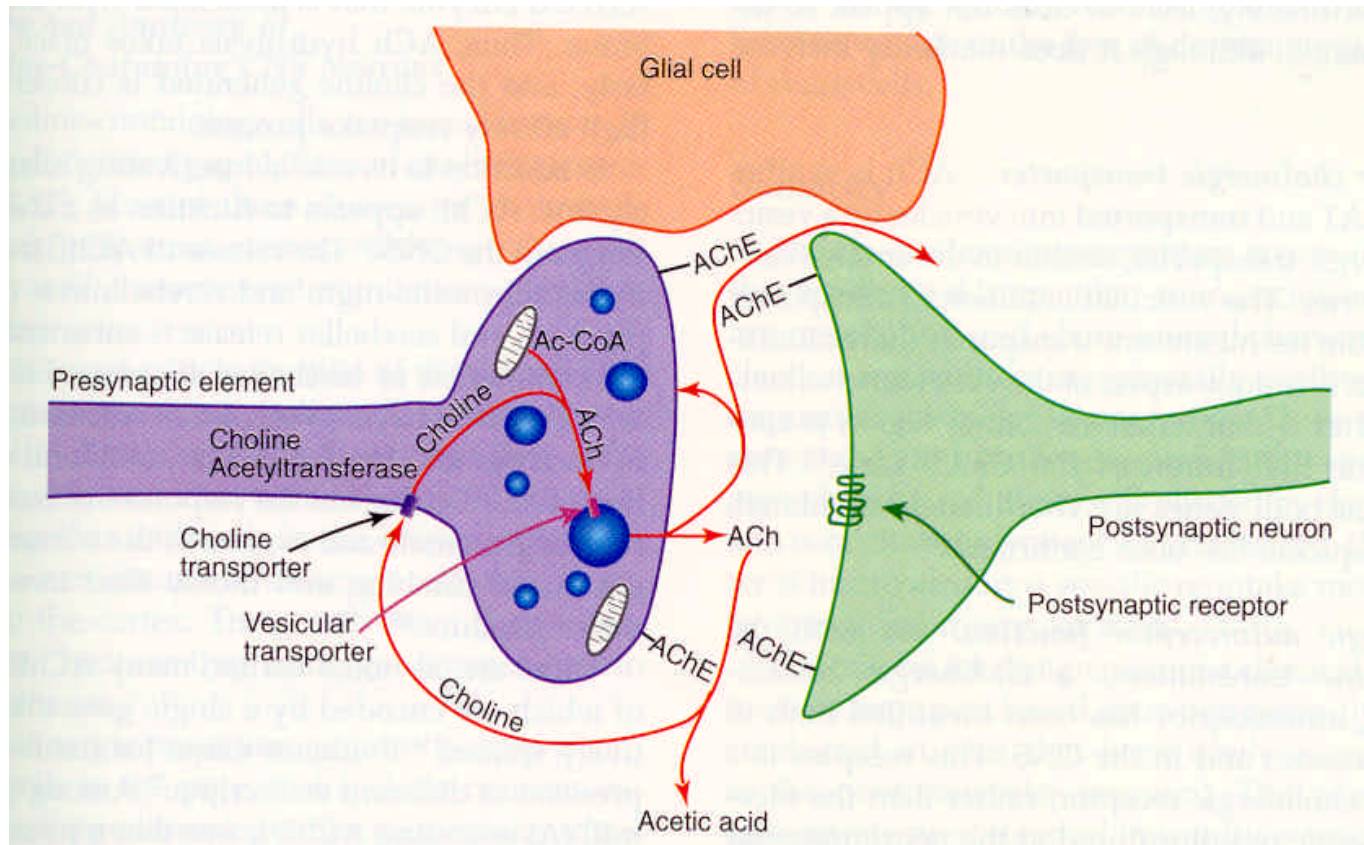
Macrocyclic lactones from
Streptomyces avermitilis

Evidence that avermectins impair function of
glutamate-gated and GABA-gated Cl⁻ channels

3. Synaptic action

acetylcholinesterase inhibitors

Organophosphates & Carbamates



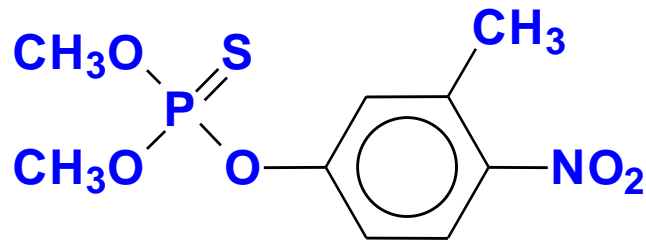
Acetylcholinesterase

- membrane-bound enzyme in synaptic cleft
- found in insect CNS (not neuromuscular junction and CNS as in mammals)
- enzyme inhibited by OP's and carbamates
- difficult to reactivate OP inhibited enzyme - essentially irreversible inhibition
- carbamate inhibition relatively reversible

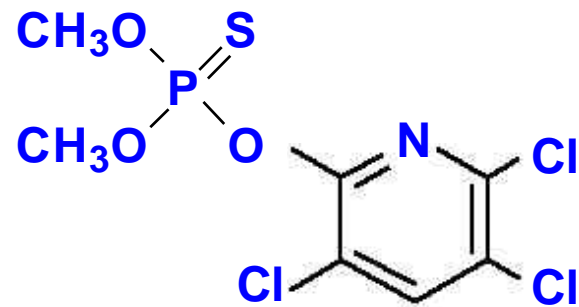
Organophosphates: structure



e.g. fenitrothion



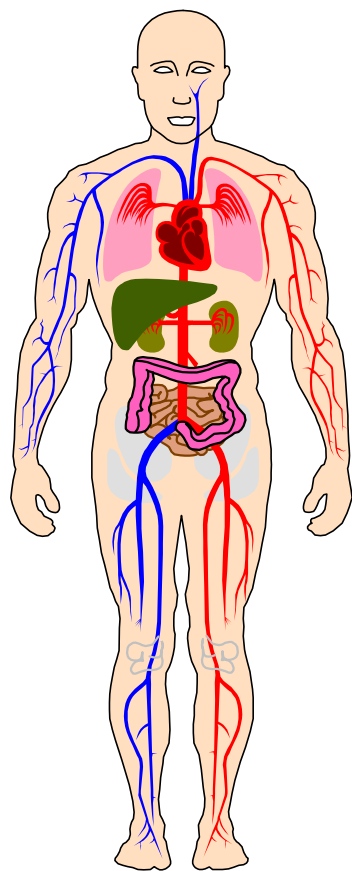
chlorpyrifos



OP's - effects on insects

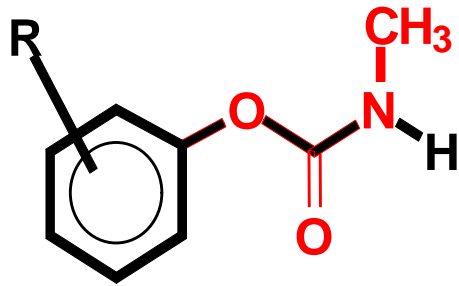
- rapid action (stomach, contact, vapour)
- 5 min. - 2 hours depending on dose - uncoordinated movement = “knockdown”
- phytophagous insects stop feeding
- 24-48 hours - insects have either survived or succumbed - “end point mortality”
- cause of death unclear and variable (loss of homeostasis - massive release of neurohormones?)

Would we be better off without OPs?



- Agricultural, veterinary & public health uses
- generally high operator hazard (with exceptions, e.g. temephos, malathion)
- concerns about effects of long-term exposure (known effects of nerve gases)
- generally high acute toxic hazard to wild-life (aquatic, terrestrial, avian)
- resistance problems
- but no environmental build-up

Carbamates

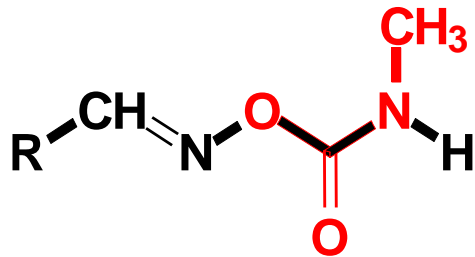


aryl N-methyl carbamates

carbofuran
carbaryl
propoxur

- based on plant toxin physostigmine (from beans of *Physostigma venenosum* used as fish poison)

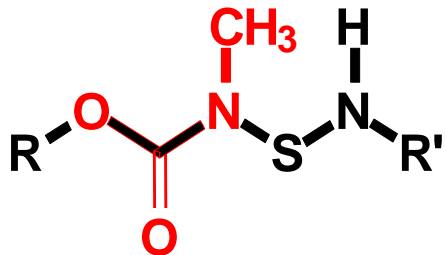
oxime carbamates



aldicarb
methomyl
thiodicarb

- mostly introduced 1950 - 1975
- broad-spectrum, relatively low-activity insecticides with action on insects as for OPs

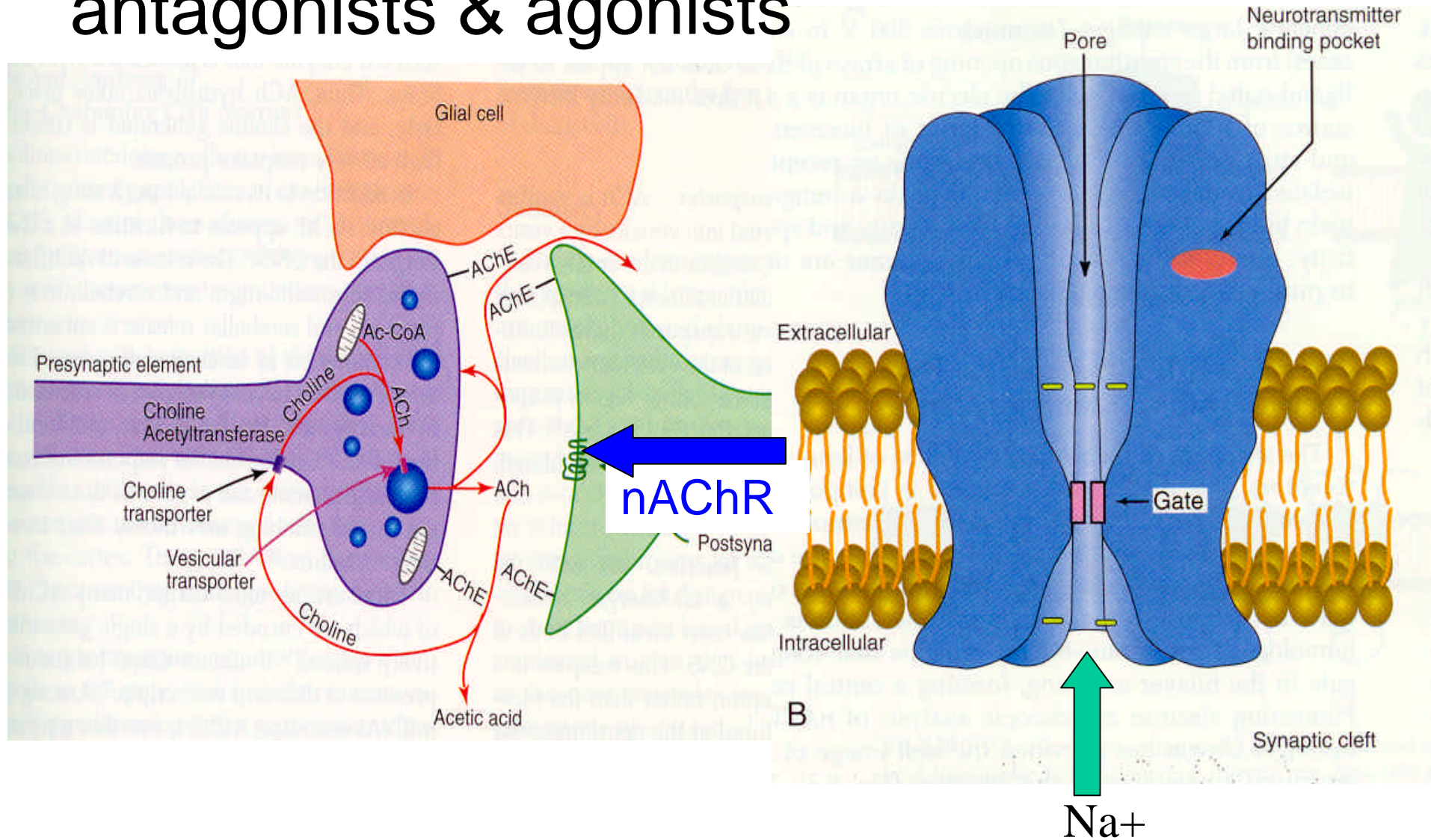
N-sulfenylated carbamates



carbosulfan
benfuracarb
furathiocarb

- systemic and/or residual

Nicotinic acetylcholine receptor (nAChR) antagonists & agonists



Insecticides acting at nAChR

Agonists (= acetylcholine mimics)

- **NICOTINE**

Alkaloid from *Nicotina spp.* - no commercial analogues

- **NEONICOTINOIDS**

A number of different chemistries have high activity

- **SPINOSYNS**

Macrocyclic lactones from soil actinomycete

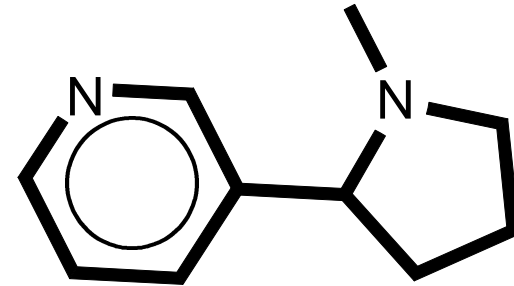
Antagonists

- **NEREISTOXIN GENERATORS**

Small group of commercial pro-insecticides generating nereistoxin, alkaloid from marine worm

Nicotine

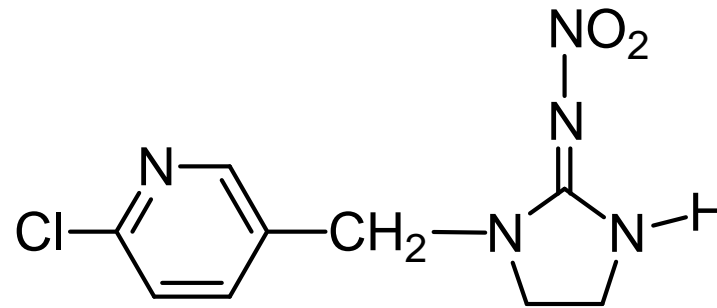
- Aphids, thrips, some mites in protected crops; non-residual, suitable as pre-biological control disinfestation treatment
- No cross-resistance to OP or pyrethroid R strains
- High mammalian toxicity
- Formulated in soaps (slow release of free base) and “shreds” - impregnated paper - smoulders to release nicotine



Neonictinoids

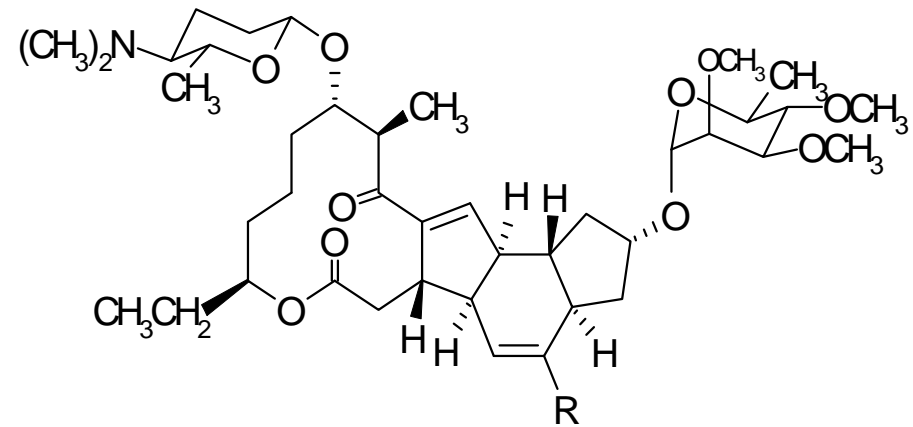
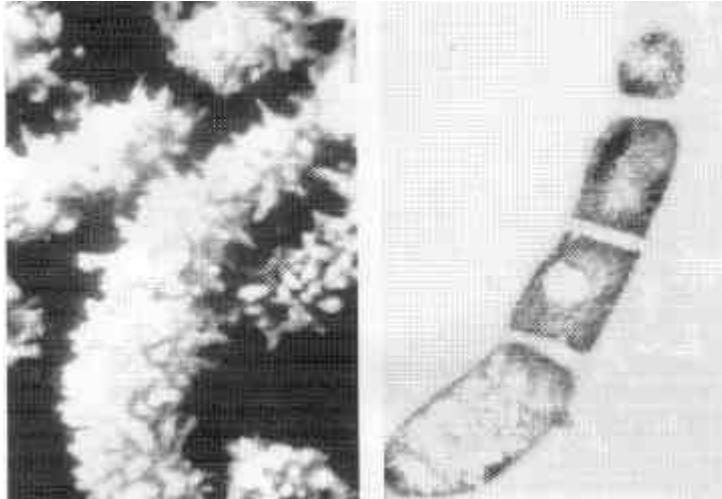
- Broad-spectrum – systemic -
- No site-specific cross-resistance
- Seed and soil treatment
- Cause leg tremors, rapid wing motion, stylet withdrawal (aphids), disorientated movement, paralysis
- Rapid action (minutes-hours)
- Little or no recovery

Imidacloprid (Goucho®)



Thiamethoxam (Actara®)

Spinosyns



spinosyn A, R = H-

spinosyn D, R = CH

- ❑ Macrocyclic lactones in actinomycete *Saccharopolyspora spinosa* - mixture of spinosyns a and d
- ❑ Spinosad (Success®)
 - Broad spectrum: adults/larvae of thrips/coleoptera/lepidoptera
 - Fast action via ingestion/contact - leading to progressive paralysis
 - Photolysis major route of degradation on leaf surfaces

Toxicity of neuroactive insecticides

Axonal action

- **DDT** and analogues [sodium channel] (EPA Class II)
- **Pyrethrins & Pyrethroids** [sodium channel] (II)

Synaptic action

- **Organophosphates & Carbamates** [acetylcholinesterase] (I-II)
- **Neonicotinoids & Spinosyns** [acetylcholine receptors] (II-III)
- **Avermectins, Cyclodienes, Gamma-HCH** [glutamate/GABA chloride ion channels] (I-II)
- **Phenylpyrazoles** [GABA chloride channels] (II)

Summary

- ❖ Neuroactive Insecticides can be classified by action at 3 major sites
 - Axonal: sodium channel of nerve membrane
 - GABA chloride channel inhibitors
 - Synapses