

Synthetic Pyrethroids & other Agrochemicals in the Environment

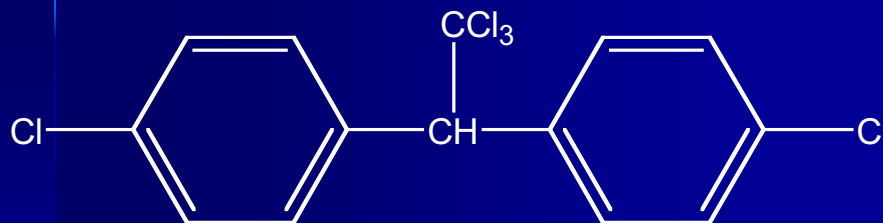
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Outline

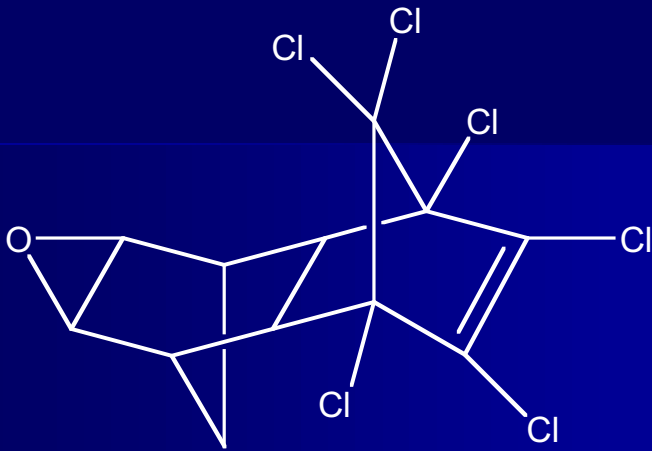
- EPA (1970) & regulatory attitudes
- Natural pyrethrins to synthetic pyrethroids
- Mechanism of action
- Other agrochemicals:
 - Other insecticides
 - Veterinary antibiotics
 - *B.t.* protein toxins

Chlorinated Hydrocarbons

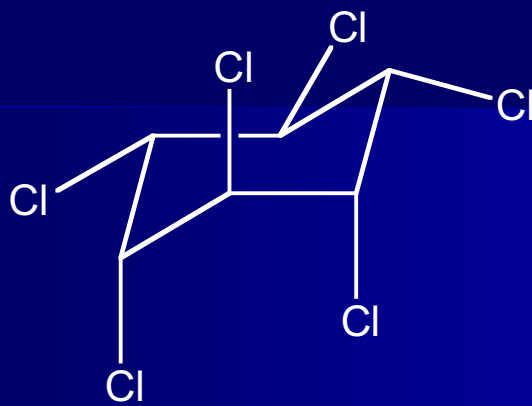
- Old-fashioned insecticides
- Highly persistent, heavily chlorinated
- Very lipophilic, accumulating in fats
- Very toxic to aquatic species
- Chronic toxicity problems, especially in birds, mammals



DDT



dieldrin



lindane

U.S. EPA (1970-2005) Philosophies & Strategies

- Agrochemicals development and registration responded to EPA attitudes, as well as:
 - FIFRA
 - Public opinion
 - Scientific data
 - Lobbying

- Priorities focused, sequentially, on:
 - Biodegradability/lower persistence
 - Lower lipophilicity/bioaccumulation
 - Carcinogenicity
 - Groundwater contamination
 - Acute toxicity
 - Endocrine disruptors
- Has resulted in a cycle, with improvements

Synthetic Pyrethroid Insecticides

a natural pyrethrin



pyrethrin I
from flowers of a chrysanthemum

Natural Pyrethrins

The extract is called “pyrethrum”

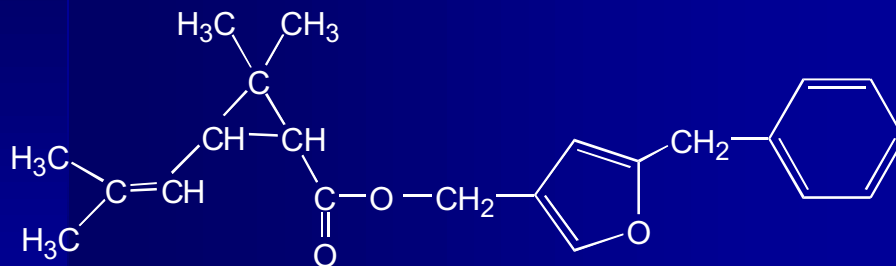
Mammalian LD₅₀

1000 - 2370 mg/kg (rats)

273 – 800 mg/kg (mice)

resmethrin

synthetic pyrethroid (1st gen.)



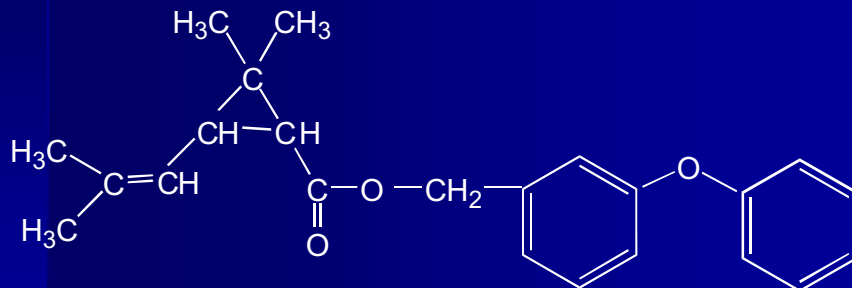
Resmethrin

Mammalian LD₅₀

>2,500 mg/kg

d-phenothrin

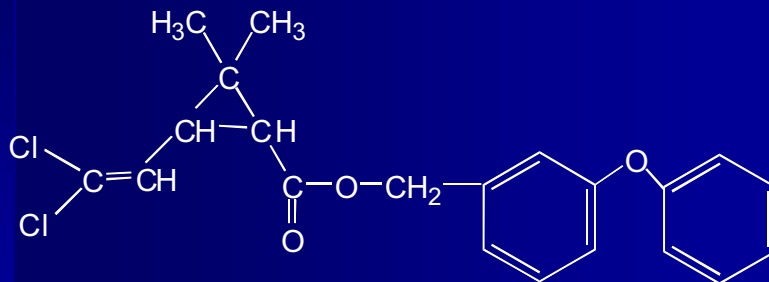
synthetic pyrethroid (1st gen.)



d-phenothrin
mammalian toxicity
LD₅₀ >5000 mg/kg

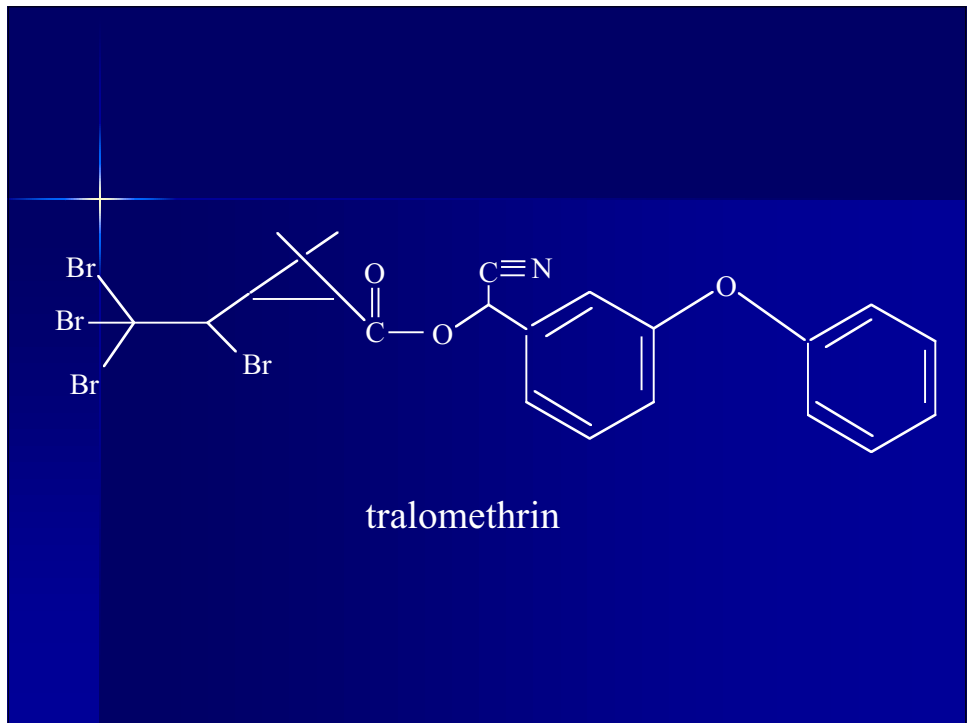
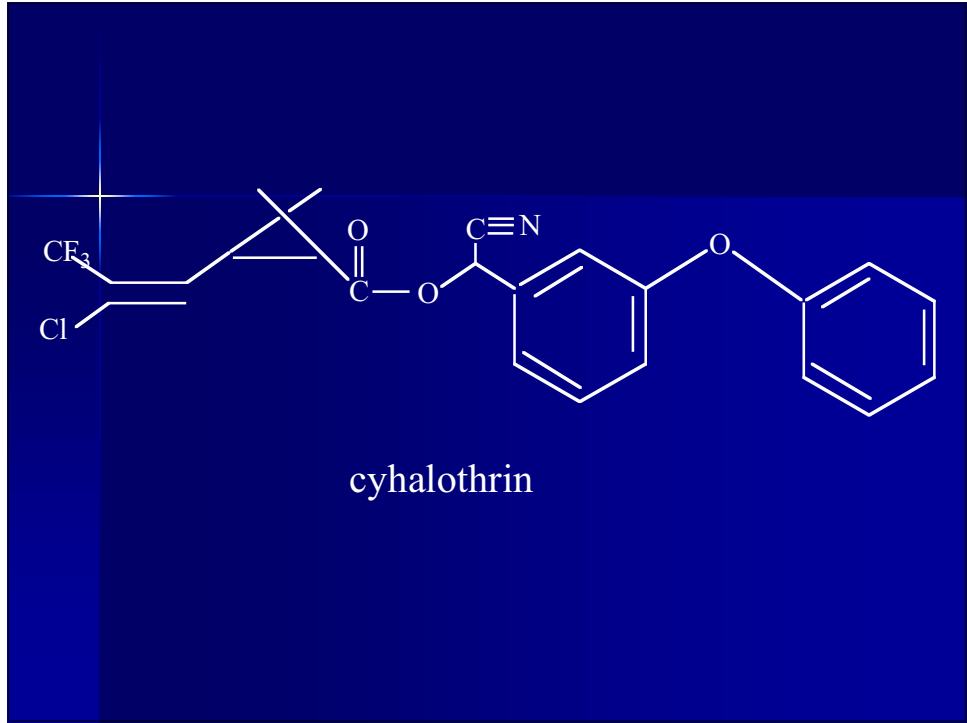
permethrin

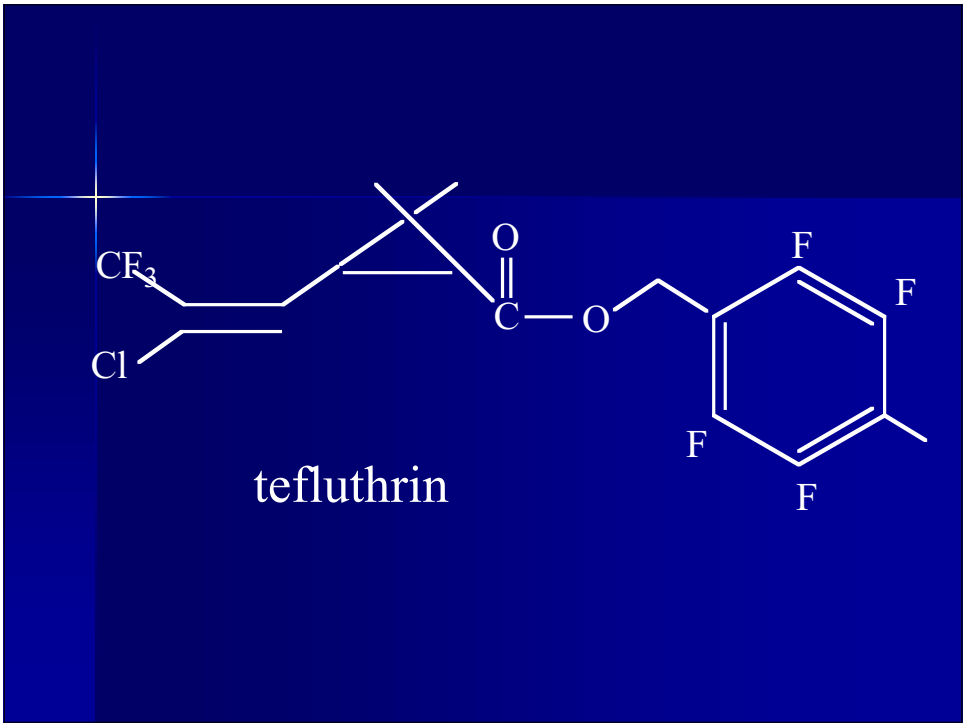
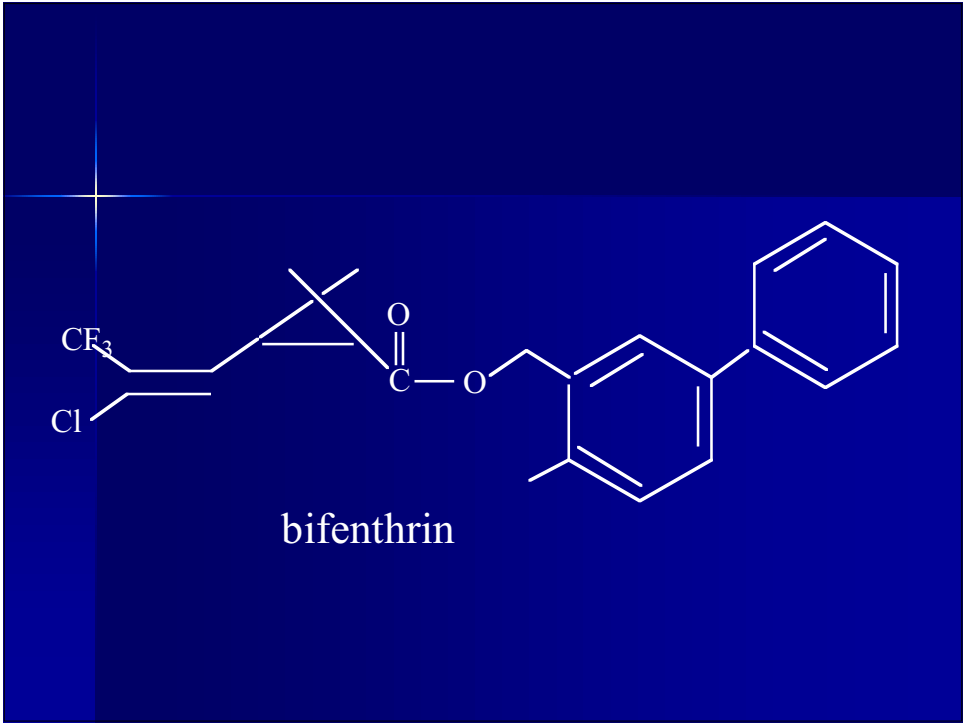
synthetic pyrethroid (photostable)

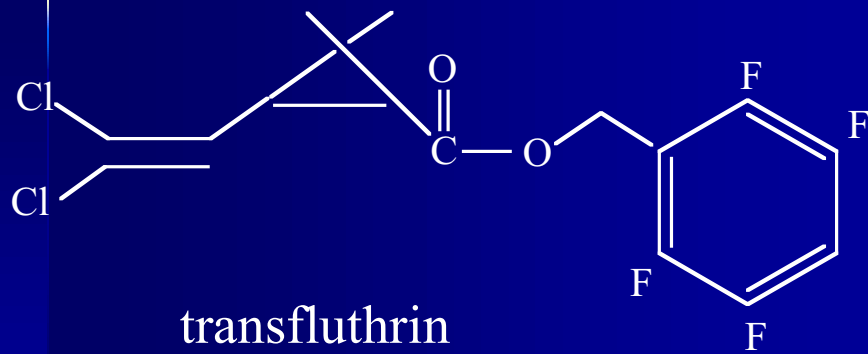


Permethrin
mammalian toxicity
LD₅₀ 400-4,000 mg/kg









Properties:

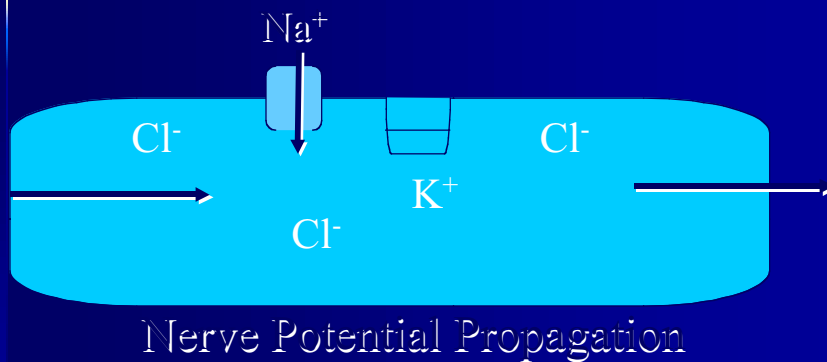
- Increased persistence
- Increased mammalian toxicity

Pyrethroids

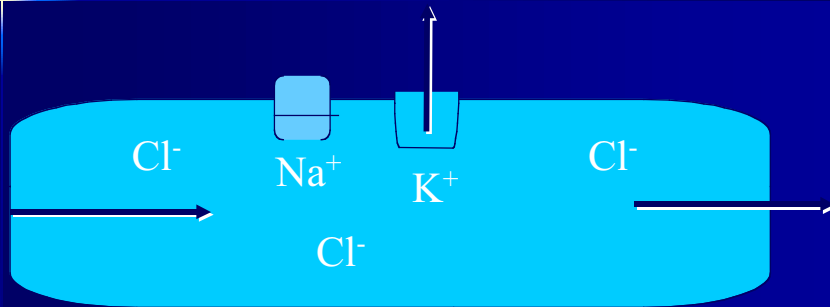
Mode of action

- Prevents sodium gates from closing in nerves of insects (also mammals, birds, fish, etc.)

Nerve Axon

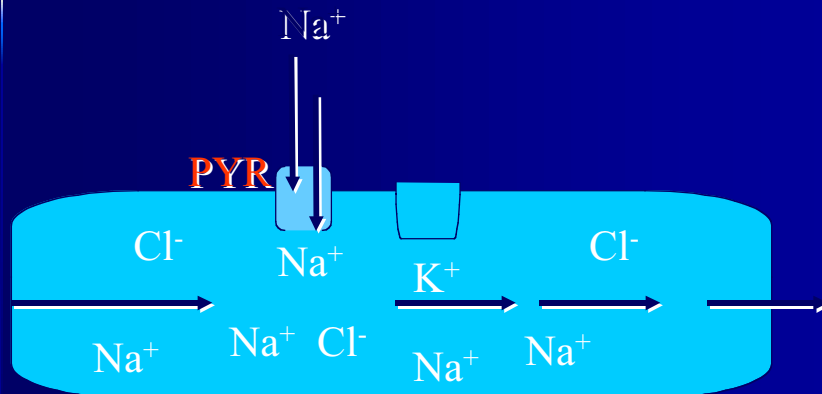


Nerve Axon



Nerve Potential Propagation

Nerve Axon With Pyrethroid Present



Repeated Nerve Impulses

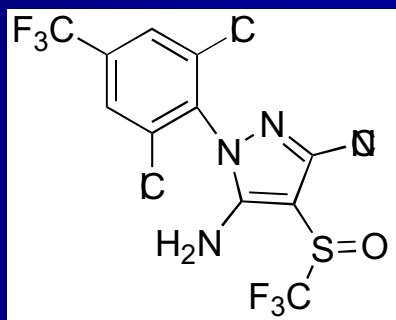
Synthetic Pyrethroids

- Photostable
- Persistent
- Lipophilic
- Toxic to many aquatic species
- More toxic to mammals & birds
 - some LD₅₀'s of 35-100 mg/kg

Fipronil

fipronil

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



Fipronil

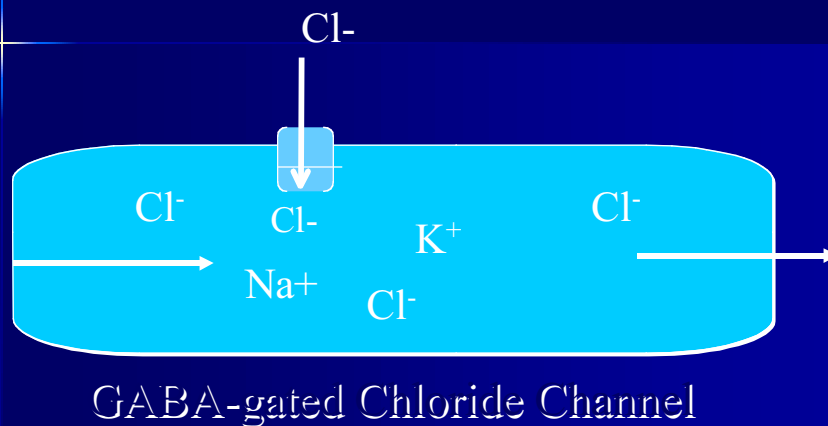
Current Labels for U.S. Markets

<u>Target Pest</u>	<u>Trade Name</u>
Mole Crickets (Turf)	Chipco Choice
Ants and Roaches	Combat; Maxforce
Ticks and Fleas (pets, domestic animals)	(baits) Frontline; Topspot
Lepidoptera and Orthoptera in crops; Coleoptera in Soil	Regent
Termites	Termidor

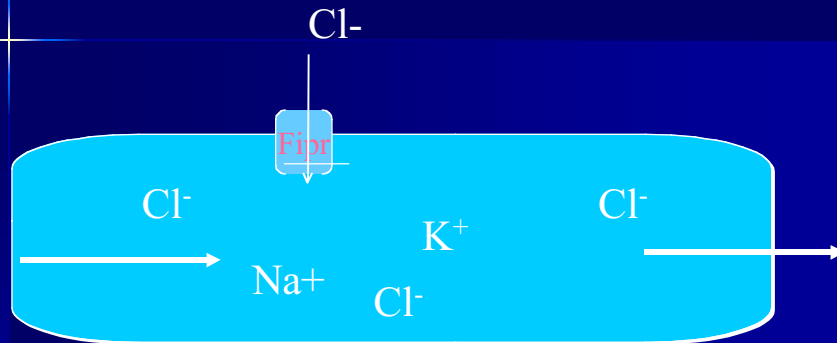
Fipronil Mode of Action

- 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 chlorinated cyclodienes
- Chemical and biological activation producing equally toxic, more persistent metabolite with same mode of action

Nerve Axon



Fipronil Mode of Action



Antagonist at GABA-gated Chloride Channel

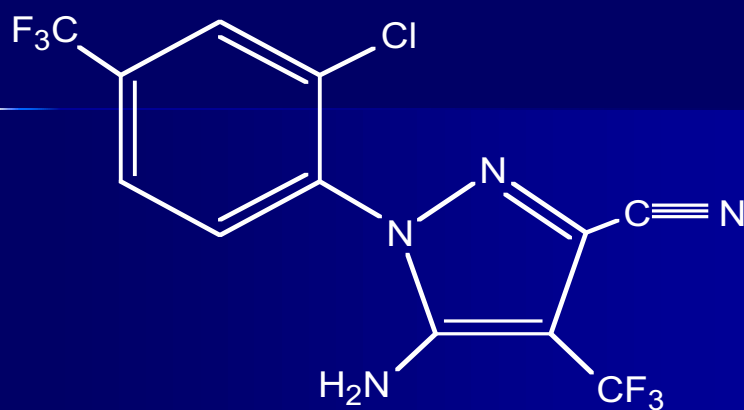
Environmental Toxicity Data

- Acute Rat LD₅₀ = 97 mg/kg
- Dog LOEL for neurotoxicity = 2 mg/kg (0.2 NOEL)
- Highly toxic to upland birds (pheasant 31 mg/kg)
- Highly toxic to blue-gill sunfish (Acute LC₅₀ = 0.083 mg/L)
- Highly toxic to Daphnia (Acute LC₅₀ = 0.190 mg/L)
- Toxic to green algae (EC₅₀ = 0.14 mg/L)

***Note: Fipronil-desulfinyl (metabolite) is more toxic to fish, birds, and invertebrates**

Environmental Fate of Fipronil

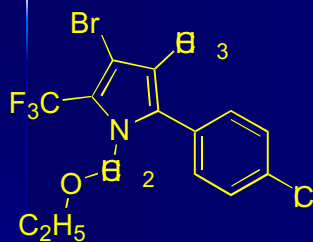
- Half-life of fipronil for photodegradation is 4 hours in water and 34 days in soil with fipronil-desulfinyl as primary metabolite
- Half-life for fipronil in aerobic (dark) soil is 125 days and 116 days in anaerobic sediment
- Fipronil binds tightly to soil and is not expected to leach
- Field dissipation has been shown to occur with a half-life of 45 days in unvegetated and 15 days in turfed soil.
- Bioconcentration factors in fish of 200 to 500 have been shown for fipronil and fipronil-desulfinyl.



fipronil desulfinyl

Chlorfenapyr

Chlorfenapyr

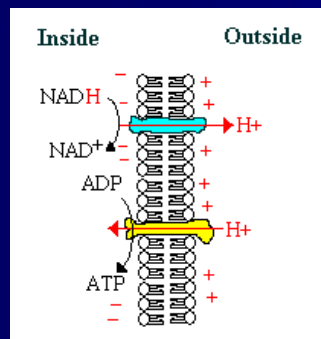


- Registered outside U.S. for cotton, in U.S. for termites & other pests
- Broad-spectrum insecticidal action

Chlorfenapyr

Chlorfenapyr

Oxidative Phosphorylation



Chemiosmotic theory

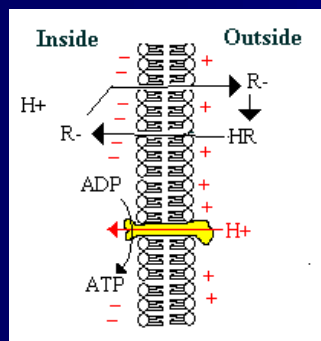
Electron flow through the electron transport chain is accompanied by a transfer of protons.

ATP synthesis driven by proton-motive force.

Electron transport train uses O₂ as final electron receptor.

Chlorfenapyr

Uncouplers



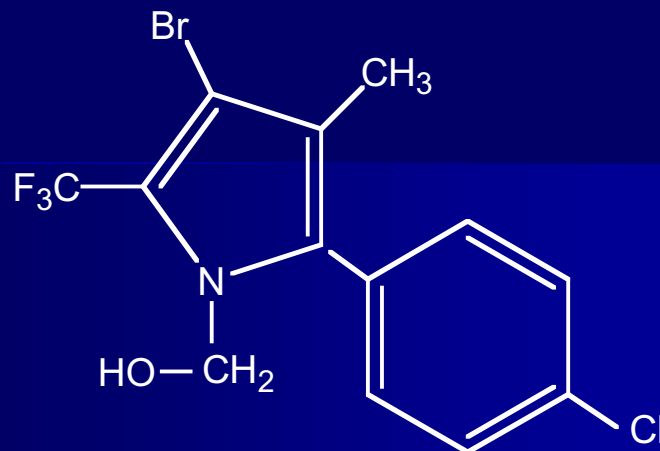
Hydrophobic weak acids can “short circuit” oxidative phosphorylation by transferring protons across the membrane

Increased respiration is then necessary to maintain ATP production

No ATP = no energy

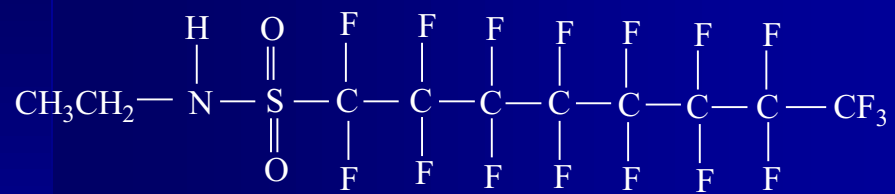
Chlorfenapyr

- Acute Insect LD₅₀ = 1-6 mg/kg;
- Acute duck LD₅₀ = 10 mg/kg; quail 34 mg/kg
- **Toxic metabolite found in both vertebrate and invertebrate species
- Potent uncoupler of oxidative phosphorylation in both vertebrates and invertebrates



desethyl chlorfenapyr

Sulfluramid



sulfluramid

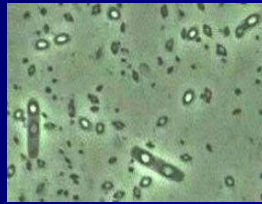
Conclusions

- Several newer classes of insecticides have been developed.
- Some are very biodegradable and have selective mechanisms of action.
- Some are persistent.
- Some have non-selective mechanisms of action.

Transgenic Proteins

- Insecticidal proteins
- Herbicide tolerance proteins
- Biopharming proteins

Bacillus thuringiensis... otherwise known as Bt



Background

■ *Bacillus thuringiensis* (Bt)

- Spore-forming soil bacterium
- Produces insecticidal δ -endotoxins
- Bacterial formulation used for over 40 years

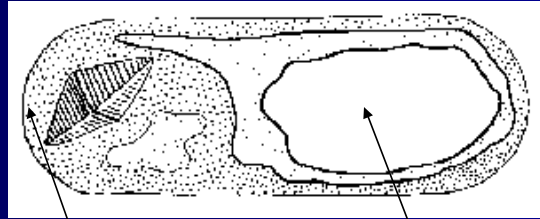


■ Rapid increase in use of transgenic Bt crops

- In the US: 2.8 million ha in 1998, ~12 million ha in 2002
- Worldwide: 9.8 million ha in 2001, 15.5 million ha in 2003

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Anatomy of Bt Bacterium



Bacterium
(University of
Edinburgh
website)

Crystalline
Protein

Endospore

Domain Structures

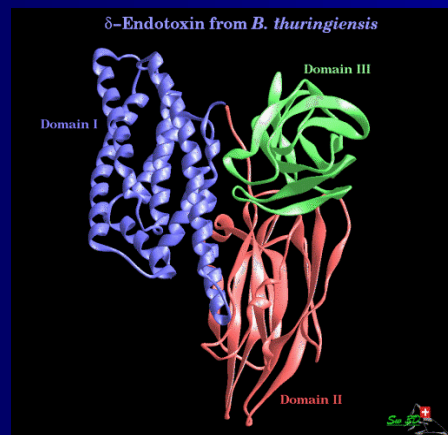


Diagram based
on: Li et al. 1991

Protein Toxins

- Insecticidal protein toxins in transgenic plants
- Responsible for reduced insecticide usage
- Usually quite selective

Exposure from Transgenic Crops

- Degradation of Bt toxin in plant material and soil is poorly understood
- Bt protein retained in soil on clays
- Dissipation of Bt proteins in soil is generally biphasic
- Wide variation in persistence data

Protein Toxins

- Some persistence in soil
- Occasional nontarget effects
- Massive quantities produced
 - Ten of thousands of plants/acre
 - Whole plant, whole growing season
 - Residue analysis nightmare
 - Bioavailability?

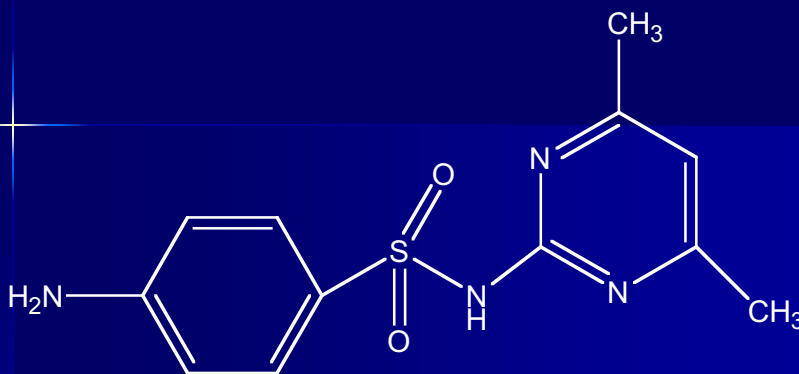
Veterinary Pharmaceuticals

Veterinary Antibiotics & other pharmaceuticals

- Presence confirmed in many waters, but at very low concentrations
- Persistent?
- Contribute to drug-resistant microbes?
- Affect microbial communities
 - in environment?
 - in gut flora of animals?

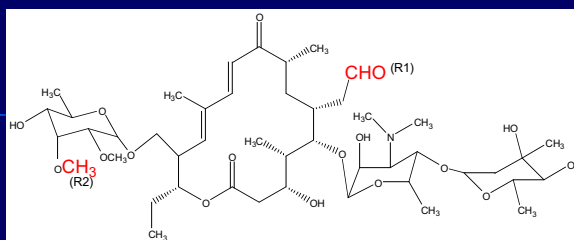
Veterinary antibiotics

- Mostly the same or in the same classes as human antibiotics
 - Sulfonamides
 - Tetracyclines
 - Macrolides
 - Penicillins



sulfamethazine

Molecular structures of tylosin and its related compounds

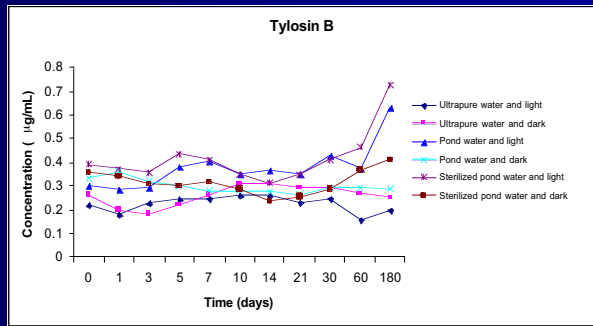
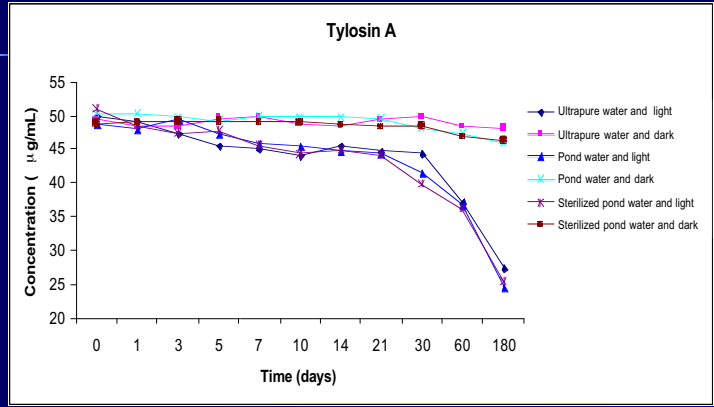


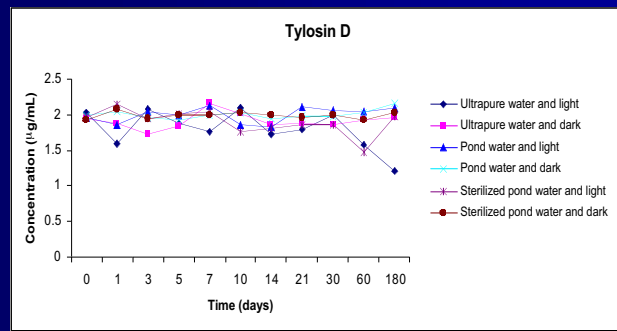
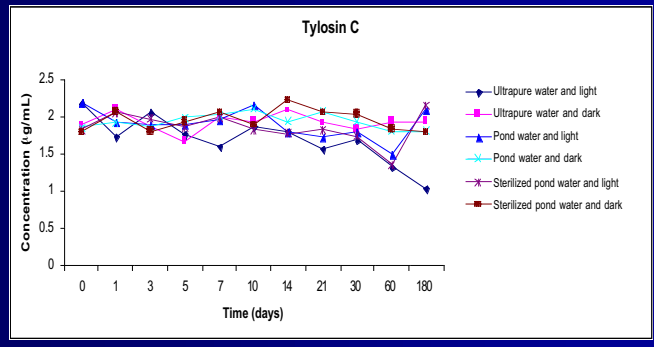
Mycinose Tylonolide Mycarose Mycinose

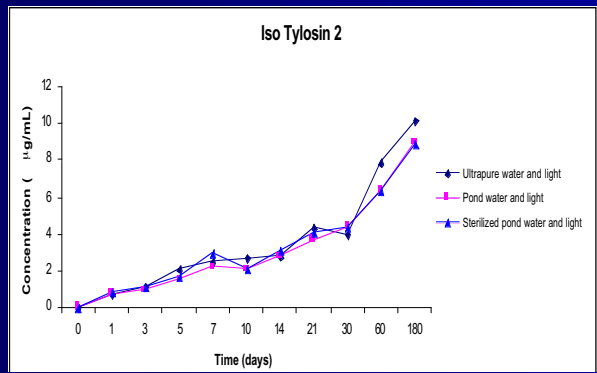
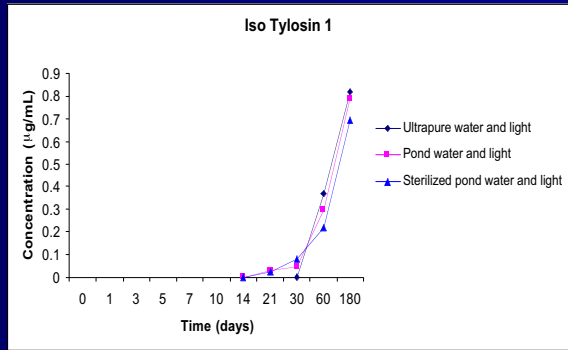
	R1	R2	Mycarose	Mycinose
Tylosin A	CHO	CH ₃	+	+
Tylosin B	CHO	CH ₃	-	+
Tylosin C	CHO	H	+	+
Tylosin D	CH ₂ OH	CH ₃	+	+
Lactenocin	CHO	H	-	+
OMT	CHO		-	-
DMT	CHO		+	-

Water dissipation study

Water dissipation study







Areas of Uncertainty

- Persistence
- Toxic transformation products
- Bioavailability
- Non-selective mechanisms of action
- Potential nontarget impacts
 - Human
 - Wildlife
 - Aquatic and marine fishes
 - Invertebrates
 - Microbial communities

