

UNIVERSITY OF MINNESOTA



AN INTRODUCTION TO INSECTICIDES (3rd edition)

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Apunte aquí para versión en Español [X]

Some 10,000 species of the more than 1 million species of insects are crop-eating, and of these, approximately 700 species worldwide cause most of the insect damage to man's crops, in the field and in storage.

Humanoids have been on earth for more than 3 million years, while insects have existed for at least 250 million years. We can only guess, but the first materials likely used by our primitive ancestors to reduce insect annoyance were mud and dust spread over their skin to repel biting and tickling insects, a practice resembling the habits of elephants, swine, and water buffalo. Under these circumstances, mud and dust would be classed as *repellents*, a category of *insecticides*.

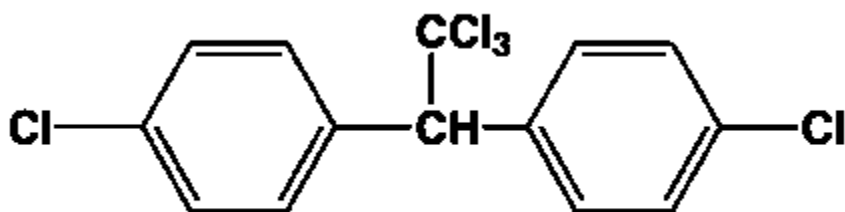
Historians have traced the use of pesticides to the time of Homer around 1000 B.C., but the earliest records of insecticides pertain to the burning of "brimstone" (sulfur) as a fumigant. Pliny the Elder (A.D. 23-79) recorded most of the earlier insecticide uses in his *Natural History*. Included among these were the use of gall from a green lizard to protect apples from worms and rot. Later, we find a variety of materials used with questionable results: extracts of pepper and tobacco, soapy water, whitewash, vinegar, turpentine, fish oil, brine, lye and many others.

At the beginning of World War II (1940), our insecticide selection was limited to several arsenicals, petroleum oils, nicotine, pyrethrum, rotenone, sulfur, hydrogen cyanide gas, and cryolite. And it was World War II that opened the *Chemical Era* with the introduction of a totally new concept of insect control chemicals--synthetic organic insecticides, the first of which was DDT.

ORGANOCHLORINES

The organochlorines are insecticides that contain carbon (thus *organo-*), hydrogen, and chlorine. They are also known by other names: *chlorinated hydrocarbons*, *chlorinated organics*, *chlorinated insecticides*, and *chlorinated synthetics*. The organochlorines are mostly of historic interest, since only a few survive in today's arsenal.

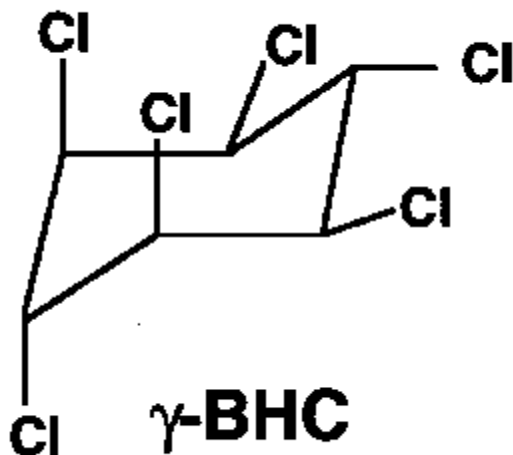
Diphenyl Aliphatics--The oldest group of the organochlorines is the *diphenyl aliphatics*, which included DDT, DDD, dicofol, ethylan, chlorobenzilate, and methoxychlor. DDT (Figure 1) is probably the best known and most notorious chemical of the 20th century. It is also fascinating, and remains to be acknowledged as the most useful insecticide developed. More than 4 billion pounds of DDT were used throughout the world, beginning in 1940, and ending essentially in 1973, when the U.S. Environmental Protection Agency canceled all uses. The remaining First World countries rapidly followed suit. In 1948, Dr. Paul Muller, a Swiss entomologist, was awarded the Nobel Prize in Medicine for his lifesaving discovery of DDT (1939) as an insecticide useful in the control of malaria, yellow fever and many other insect-vector diseases.



DDT

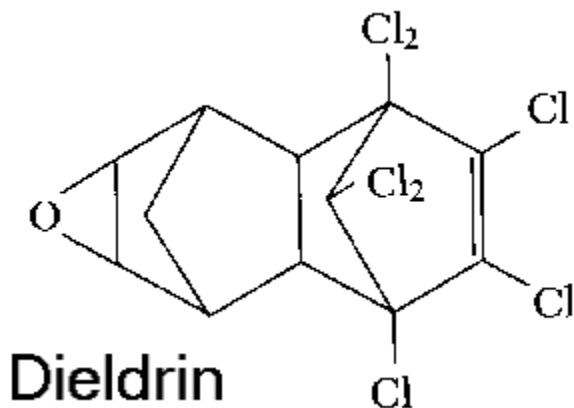
Mode of action--The mode of action for DDT has never been clearly established, but in some complex manner it destroys the delicate balance of sodium and potassium ions within the axons of the neuron in a way that prevents normal transmission of nerve impulses, both in insects and mammals. It apparently acts on the sodium channel to cause "leakage" of sodium ions. Eventually the neurons fire impulses spontaneously, causing the muscles to twitch-- "DDT jitters"-- followed by convulsions and death. DDT has a negative temperature correlation--the lower the surrounding temperature the more toxic it becomes to insects..

Hexachlorocyclohexane (HCH)--Also known as benzenehexachloride (BHC) (Figure 2), the insecticidal properties of HCH were discovered in 1940 by French and British entomologists. In its technical grade, there are five isomers, *alpha*, *beta*, *gamma*, *delta* and *epsilon*. Surprisingly, only the *gamma* isomer has insecticidal properties. Consequently, the *gamma* isomer was isolated in manufacture and sold as the odorless insecticide *lindane*. In contrast, technical grade HCH has a strong musty odor and flavor, which can be imparted to treated crops and animal products. Because of its very low cost, HCH is still used in many developing countries.



Mode of action--The effects of HCH superficially resemble those of DDT, but occur much more rapidly, and result in a much higher rate of respiration in insects. The *gamma* isomer is a neurotoxicant whose effects are normally seen within hours as increased activity, tremors, and convulsions leading to prostration. It too, exhibits a negative temperature correlation, but not as pronounced as that of DDT.

Cyclodienes--The cyclodienes appeared after World War II: chlordane, 1945 (Figure 3) ; aldrin and dieldrin, 1948; heptachlor, 1949; endrin, 1951; mirex, 1954; endosulfan, 1956; and chlordecone (Kepone(r)), 1958. There were other cyclodienes of minor importance developed in the U.S. and Germany. Most of the cyclodienes are persistent insecticides and are stable in soil and relatively stable to the ultraviolet of sunlight. As a result, they were used in greatest quantity as soil insecticides (especially chlordane, heptachlor, aldrin, and dieldrin) for the control of termites and soil-borne insects whose larval stages feed on the roots of plants.

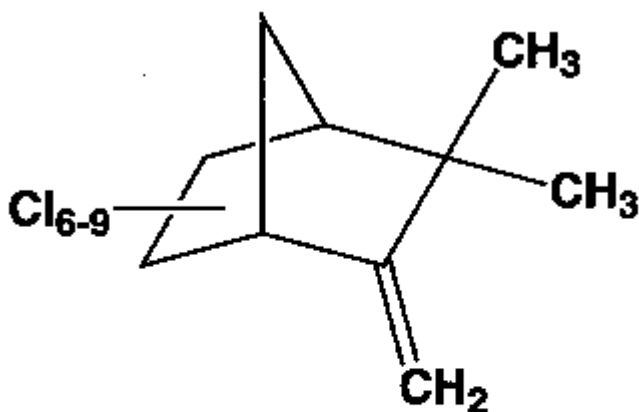


To appreciate the effectiveness of these materials as termiticides, consider that wood and wooden structures treated with chlordane, aldrin, and dieldrin in the year of their development are still protected from damage--more than 55 years! The cyclodienes were the most effective, long-lasting and economical termiticides ever developed. Because of their persistence in the environment, resistance that developed in several soil insects, and in some instances *biomagnification* in wildlife food chains, most agricultural uses of

cyclodienes were canceled by the EPA between 1975 and 1980, and their use as termiticides canceled in 1984-88.

Mode of action--Unlike DDT and HCH, the cyclodienes have a positive temperature correlation--their toxicity increases with increases in the surrounding temperature. Their modes of action are also not clearly understood. However, it is known that this group acts on the inhibitory mechanism called the GABA (gamma-aminobutyric acid) receptor. This receptor operates by increasing chloride ion permeability of neurons. Cyclodienes prevent chloride ions from entering the neurons, and thereby antagonize the "calming" effects of GABA. Cyclodienes appear to affect all animals in generally the same way, first with the nervous activity followed by tremors, convulsions and prostration.

Polychloroterpenes--Only two polychloroterpenes were developed--toxaphene in 1947 (Figure 4), and strobane in 1951. Toxaphene had by far the greatest use of any single insecticide in agriculture, while strobane was relatively insignificant. Toxaphene was used on cotton, first in combination with DDT, for alone it had minimal insecticidal qualities. Then, in 1965, after several major cotton insects became resistant to DDT, toxaphene was formulated with methyl parathion, an organophosphate insecticide mentioned later.



Toxaphene: A Mixture of Chlorinated Camphene

Toxaphene is a mixture of more than 177 10-carbon polychlorinated derivatives. These materials persist in the soil, though not as long as the cyclodienes, and disappear from the surfaces of plants in 3-4 weeks. This disappearance is attributed more to volatility than to photolysis or plant metabolism. Toxaphene is rather easily metabolized by mammals and birds, and is not stored in body fat nearly to the extent of DDT, HCH and the cyclodienes. Despite its low toxicity to insects, mammals and birds, fish are highly susceptible to toxaphene poisoning, in the same order of magnitude as to the cyclodienes. Toxaphene's registrations were canceled by EPA in 1983.

Mode of action--Toxaphene and strobane act on the neurons, causing an imbalance in sodium and potassium ions, similar to that of the cyclodiene insecticides.

ORGANOPHOSPHATES

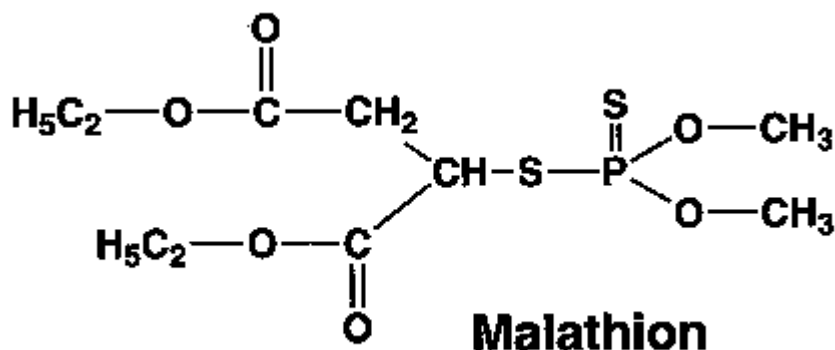
Organophosphates (OPs) is the currently used generic term that includes all insecticides containing phosphorus. Other names used, but no longer in vogue, are *organic phosphates*, *phosphorus insecticides*, *nerve gas relatives*, and *phosphoric acid esters*. All organophosphates are derived from one of the phosphorus acids, and as a class are generally the most toxic of all pesticides to vertebrates. Because of the similarity of OP chemical structures to the "nerve gases", their modes of action are also similar. Their insecticidal qualities were observed in Germany during World War II in the study of the extremely toxic OP nerve gases *sarin*, *soman*, and *tabun*. Initially, the discovery was made in search of substitutes for nicotine, which was heavily used as an insecticide but in short supply in Germany.

The OPs have two distinctive features: they are generally much more toxic to vertebrates than other classes of insecticides, and most are chemically unstable or nonpersistent. It is this latter characteristic that brought them into agricultural use as substitutes for the persistent *organochlorines*.

Mode of action--The OPs work by tying up or inhibiting certain important enzymes of the nervous system, namely *cholinesterase* (ChE). The enzyme is said to be *phosphorylated* when it becomes attached to the phosphorous moiety of the insecticide, a binding that is irreversible. This inhibition results in the accumulation of acetylcholine (ACh) at the neuron/neuron and neuron/muscle (neuromuscular) junctions or synapses, causing rapid twitching of voluntary muscles and finally paralysis.

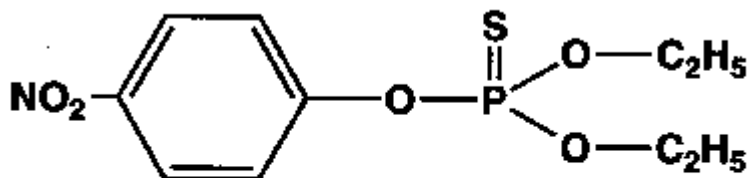
Classification--All OPs are esters of phosphorus having varying combinations of oxygen, carbon, sulfur and nitrogen attached, resulting in six different subclasses: phosphates, phospho-nates, phosphorothioates, phosphorodithioates, phosphorothiolates and phosphoramidates. These subclasses are easily identified by their chemical names. The OPs are generally divided into three groups--*aliphatic*, *phenyl*, and *heterocyclic* derivatives.

Aliphatics--The aliphatic OPs are carbon chain-like in structure. The first OP brought to agriculture, TEPP (1946) belonged to this group. Other examples are malathion (Figure 5), trichlorfon (Dylox(r)), monocrotophos (Azodrin(r)), dimethoate (Cygon(r)), oxydemetonmethyl (Meta Systox(r)), dimethoate (Cygon(r)), dicrotophos (Bidrin(r)), disulfoton (Di-Syston(r)), dichlorvos (Vapona(r)), mevinphos (Phosdrin(r)), methamidophos (Monitor(r)), and acephate (Orthene(r)).



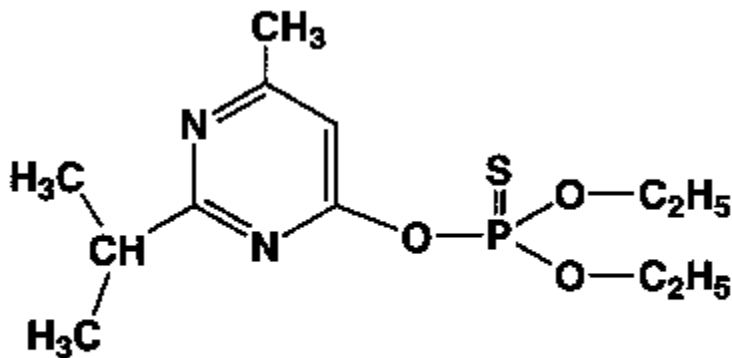
Phenyl derivatives--The phenyl OPs contain a phenyl ring with one of the ring hydrogens displaced by attachment to the phosphorus moiety and other hydrogens frequently displaced by Cl, NO₂, CH₃, CN, or S. The phenyl OPs are generally more stable than the

aliphatics, thus their residues are longer lasting. The first phenyl OP brought into agriculture was parathion (ethyl parathion) (Figure 6) in 1947. Examples of other phenyl OPs are methyl parathion, profenofos (Curacron(r)), sulprofos (Bolstar(r)), isofenphos (Oftanol(r), Pryfon(r)), fenitrothion (Sumithion(r)), fenthion (Dasanit(r)), and famphur (Cyflee(r), Warbex(r)).



Ethyl-Parathion

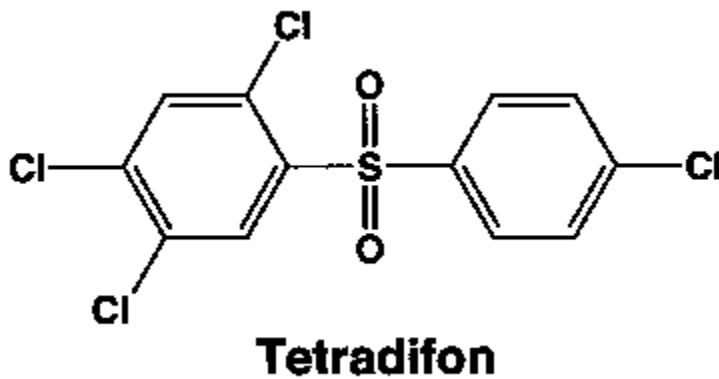
Heterocyclic derivatives--The term *heterocyclic* means that the ring structures are composed of different or unlike atoms, e.g. oxygen, nitrogen or sulfur. The first of this group was diazinon (Figure 7) introduced in 1952. Other examples in this group are azinphos-methyl (Guthion(r)), azinphos-ethyl (Acifon(r), Gusathion(r)), chlorpyrifos (Dursban(r), Lorsban(r), Lock-On(r)), methidathion (Supracide(r)), phosmet (Imidan(r)), isazophos (Brace(r), Triumph(r)), and chlorpyrifos-methyl (Reldan(r)).



Diazinon

ORGANOSULFURS

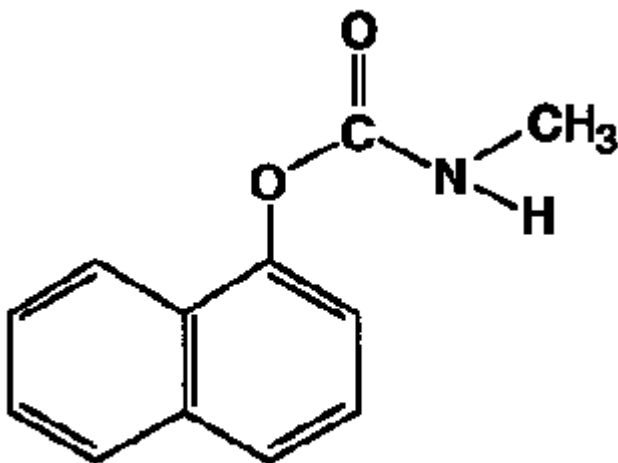
These few materials have very low toxicity to insects and are used only as acaricides (miticides). They contain two phenyl rings, resembling DDT, with sulfur in place of carbon as the central atom. These include tetradifon (Tedion(r)) (Figure 8), propargite (Omite(r), Comite(r)), and ovex (Ovotran(r)).



CARBAMATES

The carbamate insecticides are derivatives of carbamic acid (as the OPs are derivatives of phosphoric acid). And like the OPs, their mode of action is that of inhibiting the vital enzyme *cholinesterase* (ChE).

The first successful carbamate insecticide, carbaryl (Sevin(r)) (Figure 9), was introduced in 1956. More of it has been used worldwide than all the remaining carbamates combined. Two distinct qualities have made it the most popular carbamate: its very low mammalian oral and dermal toxicity and an exceptionally broad spectrum of insect control. Other carbamates are methomyl (Lannate(r)), carbofuran (Furadan(r)), aldicarb (Temik(r)), oxamyl (Vydate(r)), thiodicarb (Larvin(r)), methiocarb (Mesurol(r)), propoxur (Baygon(r)), bendiocarb (Ficam(r)), carbosulfan (Advantage(r)), aldoxycarb (Standak(r)), promecarb (Carbamult(r)), and fenoxycarb (Logic(r), Torus(r)).



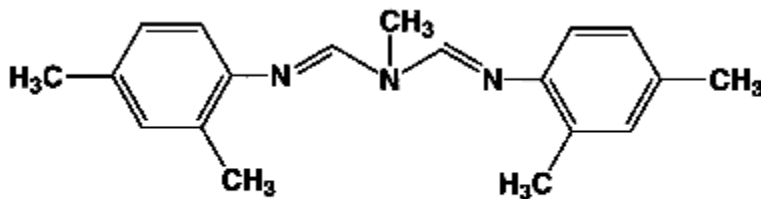
Carbaryl

Mode of action--Carbamates inhibit cholinesterase (ChE) as OPs do, and they behave in almost identical manner in biological systems, but with two main differences. Some carbamates are potent inhibitors of aliesterase (miscellaneous aliphatic esterase whose exact functions are not known), and their selectivity is sometimes more pronounced against the ChE of different species. Second, ChE inhibition by carbmates is reversible.

When ChE is inhibited by a carbamate, it is said to be *carbamylated*, as when an OP results in the enzyme being *phosphorylated*. In insects, the effects of OPs and carbamates are primarily those of poisoning of the central nervous system, since the insect neuromuscular junction is not cholinergic, as in mammals. The only cholinergic synapses known in insects are in the central nervous system. (The chemical neuromuscular junction transmitter in insects is thought to be glutamic acid, but that has not been proved.)

FORMAMIDINES

The formamidines comprise a small group of insecticides. Three examples are chlordimeform (Galecron(r), Fundal(r)), which is no longer registered in the U.S., formetanate (Carzol(r)), and amitraz (Mitac(r), Ovasyn(r)) (Figure 10). Their current value lies in the control of OP- and carbamate-resistant pests.

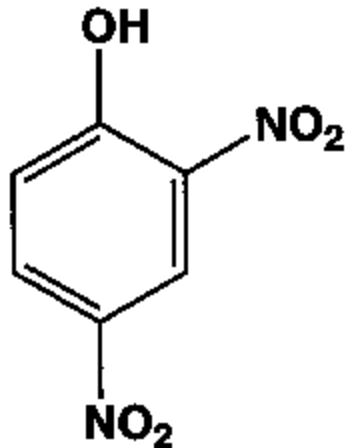


Amitraz

Mode of action--Formamidine poisoning symptoms are distinctly different from other insecticides. Their proposed action is the inhibition of the enzyme monoamine oxidase, which is responsible for degrading the neurotransmitters norepinephrine and serotonin. This results in the accumulation of these compounds, which are known as *biogenic amines*. Affected insects become quiescent and die.

DINITROPHENOLS

The basic dinitrophenol molecule (Figure 11) has a broad range of toxicities--as herbicides, insecticides, ovicides, and fungicides. Of the insecticides, binapacryl (Morocide(r)) and dinocap (Karathane(r)) were the most recently used. Dinocap is an effective miticide and was very heavily used as a fungicide for the control of powdery mildew fungi. Because of the inherent toxicity of the dinitrophenols, they have all been withdrawn..

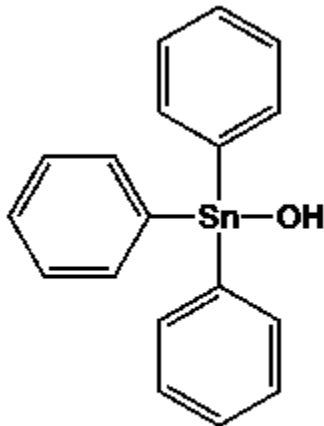


2,4-Dinitrophenol

Mode of action--Dinitrophenols act by uncoupling or inhibiting oxidative phosphorylation, which basically prevents the formation of the high-energy phosphate molecule, adenosine triphosphate (ATP).

ORGANOTINS

The organotins are a group of acaricides that double as fungicides. Of particular interest is cyhexatin (Plictran(r)) (Figure 12), one of the most selective acaricides known, introduced in 1967. Fenbutatin-oxide (Vendex(r)) has been used extensively against mites on deciduous fruits, citrus, greenhouse crops, and ornamentals.



Cyhexatin

Mode of action--These tin compounds inhibit oxidative phosphorylation at the site of dinitrophenol uncoupling, preventing the formation of the high-energy phosphate molecule adenosine triphosphate (ATP). These trialkyl tins also inhibit photophosphorylation in chloroplasts, the chlorophyll-bearing subcellular units) and could therefore serve as algicides.

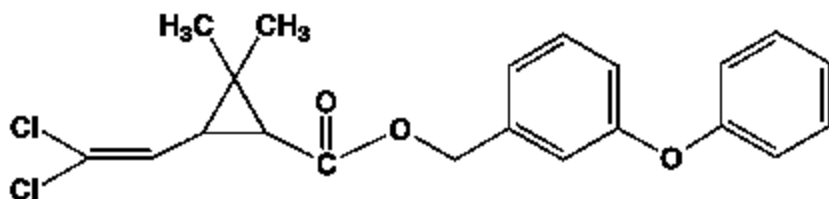
PYRETHROIDS

Natural pyrethrum has seldom been used for agricultural purposes because of its cost and instability in sunlight. Over the past two decades many synthetic pyrethrin-like materials have become available. They were originally referred to as *synthetic pyrethroids*. Currently, the better nomenclature is simply *pyrethroids*. These are very stable in sunlight and are generally effective against most agricultural insect pests when used at the very low rates of 0.01 to 0.1 pound per acre.

The pyrethroids have an interesting evolution, which is conveniently divided into four generations. The **first** generation contains only one pyrethroid, allethrin (Pynamin(r)), which appeared in 1949. Its synthesis was very complex, involving 22 chemical reactions to reach the final product.

The **second** generation includes tetramethrin (Neo-Pynamin(r)) (1965), followed by resmethrin (Synthrin(r)) in 1967 (20X as effective as pyrethrum), then bioresmethrin (50X as effective as pyrethrum) (1967), then Bioallethrin(r) (1969), and finally phonothrin (Sumithrin(r)) (1973).

The **third** generation includes fenvalerate (Pydrin(r) [discontinued], Tribute(r), & Bellmark(r)), and permethrin (Ambush(r), Astro(r), Dragnet(r), Flee(r), Pounce(r), Prelude(r), Talcord(r) & Torpedo(r)) (Figure 13) which appeared in 1972-73. These became the first agricultural pyrethroids because of their exceptional insecticidal activity (0.1 lb ai/A) and their photostability. They were virtually unaffected by ultraviolet in sunlight, lasting 4-7 days as efficacious residues on crop foliage.



Permethrin

The **fourth** and current generation, is truly exciting because of their effectiveness in the range of 0.01 to 0.05 lb ai/A. These include bifenthrin (Capture(r), Talstar(r)), *lambda*-cyhalothrin (Demand(r), Karate(r), Scimitar(r) & Warrior(r)), cypermethrin (Ammo(r), Barricade(r), Cymbush(r), Cynoff(r) & Ripcord(r)), cyfluthrin (Baythroid(r), Countdown(r), Cylense(r), Laser(r) & Tempo(r)), deltamethrin (Decis(r)) esfenvalerate (Asana(r), Hallmark(r)), fenpropathrin (Danitol(r)), flucythrinate (Cybolt(r), Payoff(r)), fluvalinate (Mavrik(r), Spur (r), discontinued), prallethrin (Etoc(r)), *tau*-fluvalinate (Mavrik(r)) tefluthrin (Evict(r), Fireban(r), Force(r) & Raze(r)), tralomethrin (Scout X-TRA(r), Tralex(r)), and *zeta*-cypermethrin (Mustang(r) & Fury(r)). All of these are photostable, that is, they do not undergo photolysis (splitting) in sunlight. And because they have minimal volatility they provide extended residual effectiveness, up to 10 days under optimum conditions.

Recent additions to the **fourth** generation pyrethroids are acrinathrin (Rufast(r)), and the still experimental imiprothrin (Pralle(r)).

Mode of action--The pyrethroids share similar modes of action, resembling that of DDT, and are considered axonic poisons. They apparently work by keeping open the sodium channels in neuronal membranes. There are two types of pyrethroids. Type I, among

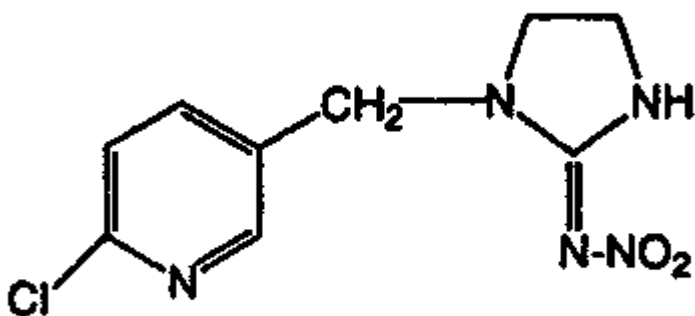
other physiological responses, have a negative temperature coefficient, resembling that of DDT. Type II, in contrast have a positive temperature coefficient, showing increased kill with increase in ambient temperature. Pyrethroids affect both the peripheral and central nervous system of the insect. They initially stimulate nerve cells to produce repetitive discharges and eventually cause paralysis. Such effects are caused by their action on the sodium channel, a tiny hole through which sodium ions are permitted to enter the axon to cause excitation. The stimulating effect of pyrethroids is much more pronounced than that of DDT.

NICOTINOIDS

The nicotinoids are a new class of insecticides with a new mode of action. They have been previously referred to as *nitro-quanidines*, *neonicotinyls*, *neonicotinoids*, *chloronicotines*, and more recently as the *chloronicotinyls*. Just as the synthetic pyrethroids are similar to and modeled after the natural pyrethrins, so too, are the nicotinoids similar to and modeled after the natural nicotine. Imidacloprid was introduced in Europe and Japan in 1990 and first registered in the U.S. in 1992. It is currently marketed as several proprietary products worldwide, e.g., Admire(r), Confidor(r), Gaucho(r), Merit(r), Premier(r), Premise(r) and Provado(r). Very possibly it is used in the greatest volume globally of all insecticides.

Imidacloprid (Figure 14) is a systemic insecticide, having good root-systemic characteristics and notable contact and stomach action. It is used as a soil, seed or foliar treatment in cotton, rice cereals, peanuts, potatoes, vegetables, pome fruits, pecans and turf, for the control of sucking insects, soil insects, whiteflies, termites, turf insects and the Colorado potato beetle, with long residual control. Imidacloprid has no effect on mites or nematodes.

IMIDACLOPRID (Gaucho[®], Provado[®])



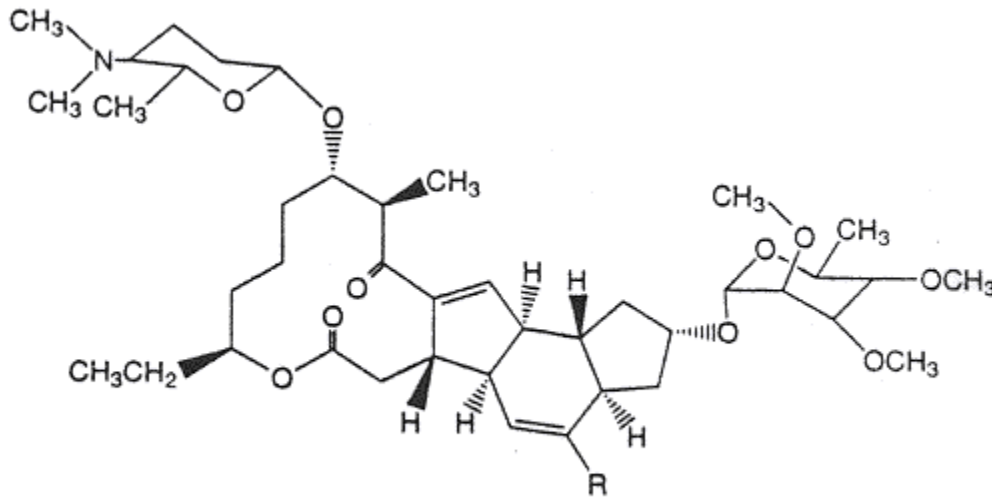
1-(6-chloro-3-pyridin-3-ylmethyl)-N-nitroimidazolidin-2-ylideneamine

Other nicotinoids include acetamiprid (Mospilan(r)), thiamethoxam (Actara(r), Platinum(r)), and nitenpyram (Bestguard(r)). All are pursuing U.S. registration.

Mode of action--The nicotinoids act on the central nervous system of insects, causing irreversible blockage of postsynaptic nicotinic acetylcholine receptors (See also *Nicotine* under the Botanicals).

SPINOSYNS

Spinosyns are perhaps the newest class of insecticides, represented by spinosad (Figure 15) (Success(r), Tracer Naturalyte(r)). Spinosad is a fermentation metabolite of the actinomycete *Saccharopolyspora spinosa*, a soil-inhabiting microorganism. It has a novel molecular structure and mode of action that provide excellent crop protection typically associated with synthetic insecticides, first registered for use on cotton in 1997. Spinosad is a mixture of spinosyns A and D (thus its name, spinosAD). It is particularly effective as a broad-spectrum material for most caterpillar pests at the astonishing rates of 0.04 to 0.09 pound of active ingredient (18 to 40 grams) per acre. It has both contact and stomach activity against lepidopteran larvae, leaf miners, thrips, and termites, with long residual activity. Crops registered include cotton, vegetables, tree fruits, ornamentals and others.



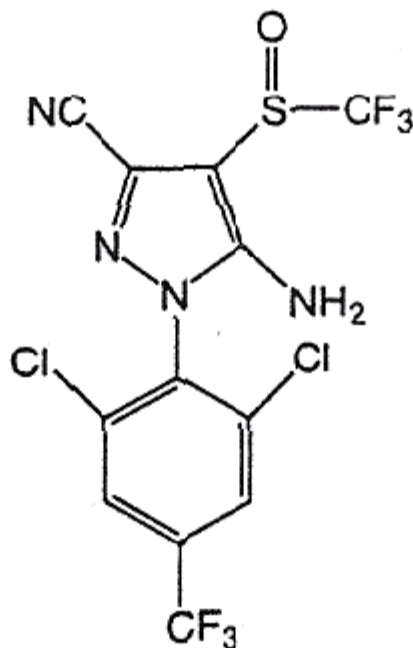
spinosyn A: R = H, MW = 731.98
 spinosyn D: R = CH₃, MW = 746.00

Mode of action--Spinosad acts by disrupting binding of acetylcholine in nicotinic acetylcholine receptors at the postsynaptic cell (Salgado VL 1997) (See also *Nicotine* under the Botanicals).

FIPROLES (or Phenylpyrazoles)

Fipronil (Figure 16) (Regent(r), Icon(r), Frontline(r)) is the only insecticide in this new class, introduced in 1990 and registered in the U.S. in 1996. It is a systemic material with contact and stomach activity. Fipronil is used for the control of many soil and foliar insects, (e.g., corn rootworm, Colorado potato beetle, and rice water weevil) on a variety of crops, primarily corn, turf, and for public health insect control. It is also used for seed treatment and formulated as baits for cockroaches, ants and termites. Fipronil is effective against insects resistant or tolerant to pyrethroid, organophosphate and carbamate insecticides.

FIPRONIL (Frontline[®], Icon[®], Regent[®])



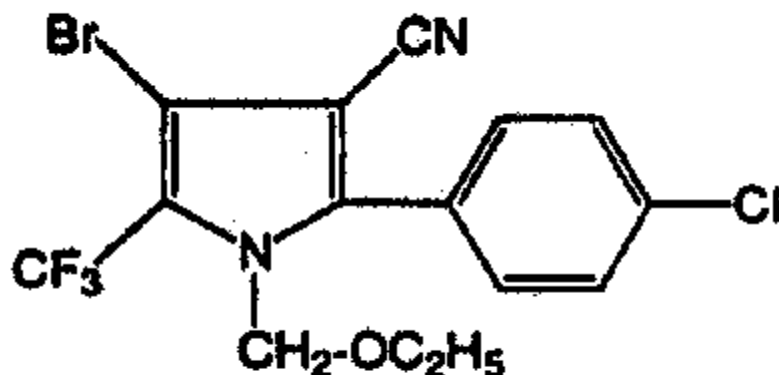
5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-3,4-cyano-4-trifluoromethylsulphonylpyrazole

Mode of action--Fipronil blocks the gamma-aminobutyric acid- (GABA) regulated chloride channel in neurons, thus antagonizing the "calming" effects of GABA, similar to the action of the Cyclodienes (see page 3).

PYRROLES

Chlorfenapyr (Figure 17) (Alert(r), Pirate(r)) is the first and only member of this unique chemical group, as both a contact and stomach insecticide-miticide. It is used on cotton and experimentally on corn, soybeans, vegetables, tree and vine crops, and ornamentals to control whitefly, thrips, caterpillars, mites, leafminers, aphids, and Colorado potato beetle. It has ovicidal activity on some species.

CHLORFENAPYR (Pirate[®], Alert[®])



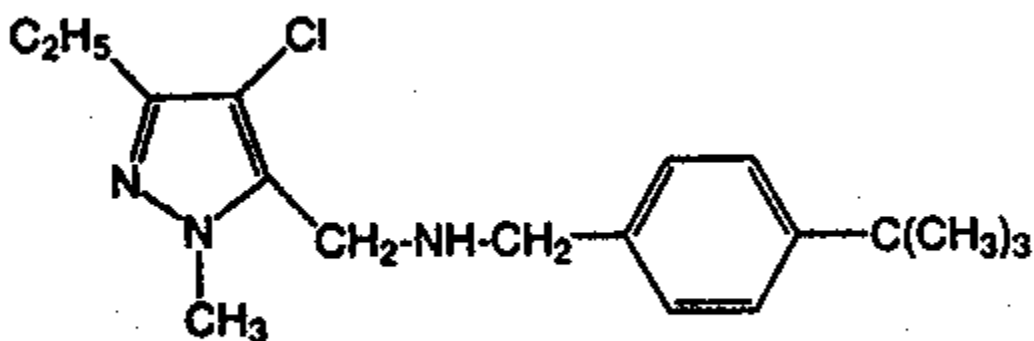
4-bromo-2-(4-chlorophenyl)-1-ethoxymethyl-5-trifluoromethylpyrrole-3-carbonitrile

Mode of action--Chlorfenapyr is an "uncoupler" or inhibitor oxidative phosphorylation, preventing the formation of the crucial energy molecule adenosine triphosphate (ATP) (See also Dinitrophenols, page 6).

PYRAZOLES

The pyrazoles consist of tebufenpyrad (Figure 18) and fenpyroximate (not illustrated). These were designed primarily as non-systemic contact and stomach miticides, but do have limited effectiveness on psylla, aphids, whitefly, and thrips. Tebufenpyrad (Pyranica(r), Masai(r)) is used experimentally on cotton, soybeans, vegetables, pome fruits, grapes and citrus. Fenpyroximate (Acaban(r), Dynamite(r)) controls all stages of mites, gives fast knockdown, inhibits molting of immature stages of mites, and has long residual activity.

TEBUFENPYRAD (Pyranica[®], Masai[®])



4-chloro-N[[4-(1,1-dimethylethyl)phenyl]methyl]-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide

Mode of action--Their mode of action is that of inhibiting mitochondrial electron

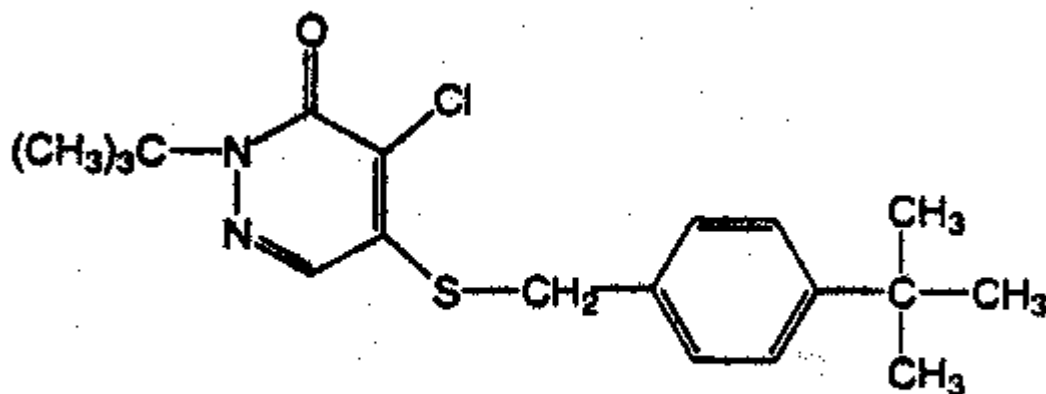
transport at the NADH-CoQ reductase site, leading to the disruption of adenosine triphosphate (ATP) formation, the crucial energy molecule.

PYRIDAZINONES

Pyridaben (Figure 19) (Nexter(r), Sanmite(r)) is the only member of this class. It is a selective contact insecticide and miticide, also effective against thrips, aphids, whiteflies and leafhoppers. Registrations are for pome fruits, almonds, citrus, ornamentals and greenhouse ornamentals. Pyridaben provides exceptionally long residual control, and rapid knockdown at a broad range of temperatures.

Mode of action--Pyridaben is a metabolic inhibitor that interrupts mitochondrial electron transport at Site 1, similar to the Quinazolines, below.

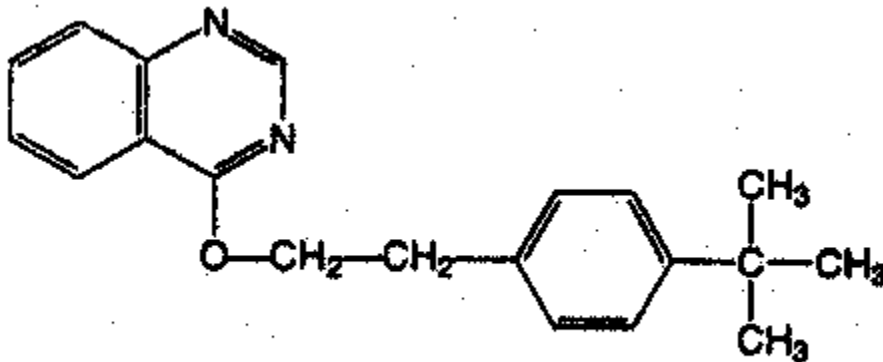
PYRIDABEN (Nexter[®], Sanmite[®])



2-tert-butyl-5-(4-tert-butylbenzylthio)-4-chloropyridazin-3(2H)-one

QUINAZOLINES

The quinazolines offer a unique chemical configuration, consisting only of one insecticide, fenazaquin (Figure 20) (Matador(r)). Fenazaquin is a contact and stomach miticide. It has ovicidal activity, gives rapid knockdown, and controls all stages of mites. Not yet registered in the U.S., it is used on cotton, stone and pome fruits, citrus, grapes and ornamentals.



4-[[4-(1,1-dimethylethyl)phenyl]ethoxy]quinazoline

Mode of action--Fenazaquin inhibits mitochondrial electron transport at Site 1, similar to the Pyridazinones, above.

BENZOYLUREAS

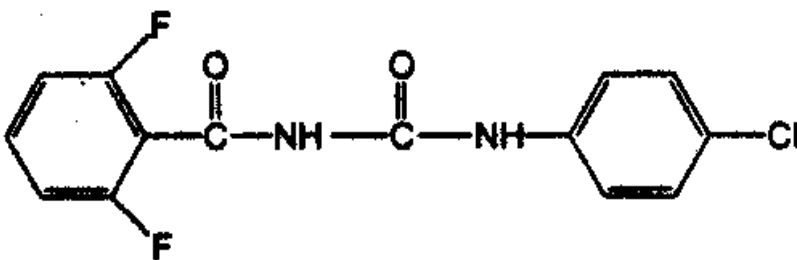
Benzoylureas are an entirely different class of insecticides that act as insect growth regulators (IGRs). Rather than being the typical poisons that attack the insect nervous system, they interfere with chitin synthesis and are taken up more by ingestion than by contact. Their greatest value is in the control of caterpillars and beetle larvae.

Benzoylureas were first used in Central America in 1985, to control a severe, resistant leafworm complex (*Spodoptera spp.*, *Trichoplusia spp.*) outbreak in cotton. The withdrawal of the ovicide chlordimeform made their control quite difficult due to their high resistance to almost all insecticide classes, including the pyrethroids.

The first benzoylureas were introduced in 1978 by Bayer of Germany, triflumuron (Alsystin(r)) being the first. Others appearing since then are chlorfluazuron (Atabron(r), Helix(r)), followed by teflubenzuron (Nomolt(r), Dart(r)), hexaflumuron (Trueno(r), Consult(r)), flufenoxuron (Cascade(r)), and flucyclozuron (Andalin(r)). Others are flurazuron, novaluron, and diafenthiuron. Lufenuron (Axor(r)) is the newest addition to this group, appearing in 1990. Surprisingly, none of these are registered in the U.S.

The only benzoylurea registered in the U.S. is diflubenzuron (Figure 21) (Dimilin(r), Adept(r), Micromite(r)). It was first registered in 1982 for gypsy moth, cotton boll weevil, most forest caterpillars, soybean caterpillars, and mushroom flies, but now with a much broader range of registrations.

DIFLUBENZURON (Dimilin®)



1-(4-chlorophenyl) 3-(2,6-difluorobenzoyl)urea

Though not a benzoylurea, cyromazine (Larvadex(r), Trigard(r)), a triazine, is also a potent chitin synthesis inhibitor. It is selective toward Dipterous species and used for the control of leafminers in vegetable crops and ornamentals, and fed to poultry or sprayed to control flies in manure of broiler and egg producing operations, and incorporated into compost of mushroom houses for fungus gnats.

Mode of action--The benzoylureas act on the larval stages of most insects by inhibiting or blocking the synthesis of chitin, a vital and almost indestructible part of the insect exoskeleton. Typical effects on developing larvae are the rupture of malformed cuticle or death by starvation. Adult female boll weevils exposed to diflubenzuron lay eggs that do not hatch. And, mosquito larvae control can be achieved with as little as 1.0 gram of diflubenzuron per acre of surface water.

BOTANICALS

Botanical insecticides are of great interest to many, for they are *natural* insecticides, toxicants derived from plants. Historically, the plant materials have been in use longer

than any other group, with the possible exception of sulfur. Tobacco, pyrethrum, derris, hellebore, quassia, camphor, and turpentine were some of the more important plant products in use before the organized search for insecticides began in the early 1940s. Botanical insecticide use in the U.S. peaked in 1966, and has declined steadily since. Pyrethrum is now the only botanical of significance in use. We will mention briefly the others.

Pyrethrum is extracted from the flowers of a chrysanthemum grown in Kenya and Ecuador. It is one of the oldest and safest insecticides available. The ground, dried flowers were used in the early 19th century as the original louse powder to control body lice in the Napoleonic Wars. Pyrethrum acts on insects with phenomenal speed causing immediate paralysis, thus its popularity in fast knockdown household aerosols. However, unless it is formulated with one of the *synergists*, most of the paralyzed insects recover to once again become pests. Pyrethrum is a mixture of four compounds: pyrethrins I and II and cinerins I and II.

Mode of action--Pyrethrum is an axonic poison, as are the synthetic pyrethroids and DDT. Axonic poisons are those that in some way affect the electrical impulse transmission along the axons, the elongated extensions of the neuron cell body. Pyrethrum and some pyrethroids have a greater insecticidal effect when the temperature is lowered, a negative temperature coefficient, as does DDT. They affect both the peripheral and central nervous system of the insect. Pyrethrum initially stimulates nerve cells to produce repetitive discharges, leading eventually to paralysis. Such effects are caused by their action on the sodium channel, a tiny hole through which sodium ions are permitted to enter the axon to cause excitation. These effects are produced in insect nerve cord, which contains ganglia and synapses, as well as in giant nerve fiber axons.

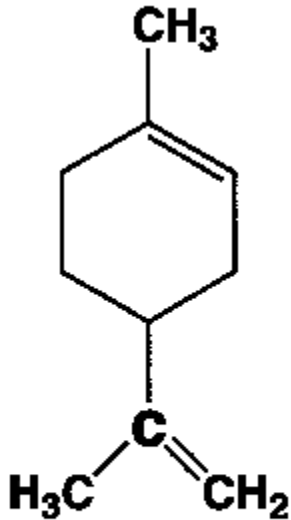
Nicotine is extracted by several methods from tobacco, and is effective against most all types of insect pests, but is used particularly for aphids and caterpillars--soft bodied insects. Nicotine is an alkaloid, a chemical class of heterocyclic compounds containing nitrogen and having prominent physiological properties. Other well-known alkaloids that are not insecticides are caffeine (coffee, tea), quinine (cinchona bark), morphine (opium poppy), cocaine (coca leaves), ricinine (a poison in castor oil beans), strychnine (*Strychnos nux vomica*), coniine (spotted hemlock, the poison used by Socrates), and, finally LSD (a hallucigen from the ergot fungus attacking grain).

Mode of action--Nicotine action is one of the first, classic modes of action identified by pharmacologists. Drugs that act similarly to nicotine are said to have a nicotinic response. Nicotine mimics acetylcholine (ACh) at the neuromuscular (nerve/muscle) junction in mammals, and results in twitching, convulsions, and death, all in rapid order. In insects the same action is observed, but only in the central nervous system ganglia.

Rotenone or rotenoids are produced in the roots of two genera of the legume family: *Derris* and *Lonchocarpus* (also called cubé) grown in South America. It is both a stomach and contact insecticide and used for the last century and a half to control leaf-eating caterpillars, and three centuries prior to that in South America to paralyze fish, causing them to surface and be easily captured. Today, rotenone is used in the same way to reclaim lakes for game fishing. Used on a prescribed basis, it eliminates all fish, closing the lake to reintroduction of rough species. It is a selective piscicide in that it kills all fish at dosages that are relatively nontoxic to fish food organisms, and is degraded rapidly.

Mode of action--Rotenone is a respiratory enzyme inhibitor, acting between NAD⁺ (a coenzyme involved in oxidation and reduction in metabolic pathways) and coenzyme Q (a respiratory enzyme responsible for carrying electrons in some electron transport chains), resulting in failure of the respiratory functions.

Limonene or *d*-Limonene (Figure 22) is the latest addition to the botanicals. Extracted from citrus peel, it is effective against all external pests of pets, including fleas, lice, mites, and ticks, and is virtually nontoxic to warm-blooded animals. Several insecticidal substances occur in citrus oil, but the most important is limonene, which constitutes about 98% of the orange peel oil by weight.



Limonene

Mode of action--Its mode of action is similar to that of pyrethrum. It affects the sensory nerves of the peripheral nervous system, but it is not a ChE inhibitor.

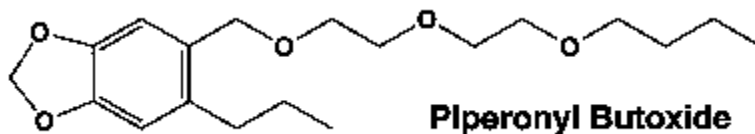
Neem oil extracts are squeezed from the seeds of the neem tree and contain the active ingredient *azadirachtin*, a nortriterpenoid belonging to the limonoids. Azadirachtin has shown some rather sensational insecticidal, fungicidal and bactericidal properties, including insect growth regulating qualities. Azatin(r) is marketed as an insect growth regulator, and Align(r) and Nemix(r) as a stomach/contact insecticide for greenhouse and ornamentals.

Mode of action--Azadirachtin disrupts molting by inhibiting biosynthesis or metabolism of ecdysone, the juvenile molting hormone.

SYNERGISTS OR ACTIVATORS

Synergists are not in themselves considered toxic or insecticidal, but are materials used with insecticides to synergize or enhance the activity of the insecticides. The first was introduced in 1940 to increase the effectiveness of pyrethrum. Since then many materials have appeared, but only a few are still marketed. Synergists are found in most all household, livestock and pet aerosols to enhance the action of the fast knockdown insecticides pyrethrum, allethrin, and resmethrin, against flying insects. Current synergists, such as piperonyl butoxide (Figure 23), contain the methylenedioxyphenyl

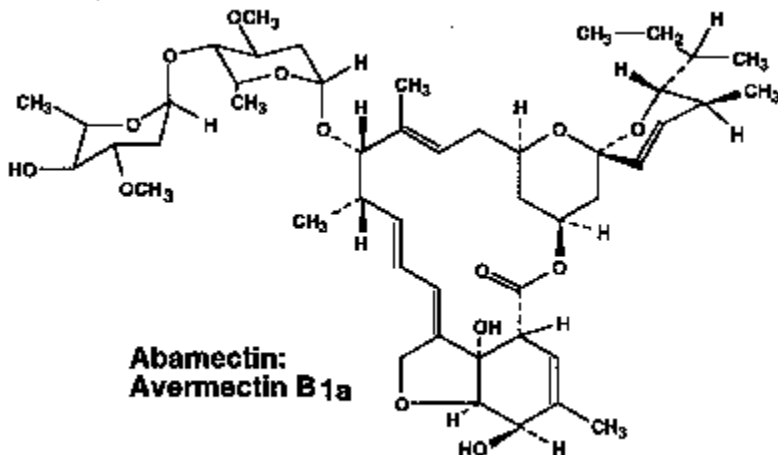
moiety, a molecule found in sesame oil and later named *sesamin*.



Mode of action--The synergists inhibit cytochrome P-450 dependent polysubstrate monooxygenases (PSMOs), enzymes produced by microsomes, the subcellular units found in the liver of mammals and in some insect tissues (e.g., fat bodies). The earlier name for these enzymes was mixed-function oxidases (MFOs). These PSMOs bind the enzymes that degrade selected foreign substances, such as pyrethrum, allethrin, resmethrin or any other synergized compound. Synergists simply bind the oxidative enzymes and prevent them from degrading the toxicant.

ANTIBIOTICS

In this category belong the *avermectins*, which are insecticidal, acaricidal, and antihelminthic agents that have been isolated from the fermentation products of *Streptomyces avermitilis*, a member of the actinomycete family. *Abamectin* (Figure 24) is the common name assigned to the avermectins, a mixture of containing 80% avermectin B1a and 20% B1b, homologs that have about equal biological activity. Clinch(r) is a fire ant bait, and Avid(r) is applied as a miticide/insecticide. Abamectin has certain local systemic qualities, permitting it to kill mites on a leaf's underside when only the upper surface is treated. The most promising uses for these materials are the control of spider mites, leafminers and other difficult-to-control greenhouse pests, and internal parasites of domestic animals.



Emamectin benzoate (Proclaim(r), Denim(r)) is an analog of abamectin, produced by the same fermentation system as abamectin. It is both a stomach and contact insecticide used primarily for control of caterpillars at the rate of 0.0075 to 0.015 lb (3.5 to 7.0 grams) a.i. per acre. Shortly after exposure, larvae stop feeding and become irreversibly paralyzed, dying in 3-4 days. Rapid photodegradation of both abamectin and emamectin occurs on the leaf surface.

Mode of action--Avermectins block the neurotransmitter gamma aminobutyric acid (GABA) at the neuromuscular junction in insects and mites. Visible activity, such as

feeding and egg laying, stops shortly after exposure, though death may not occur for several days.

FUMIGANTS

The fumigants are small, volatile, organic molecules that become gases at temperatures above 40°F. They are usually heavier than air and commonly contain one or more of the halogens (Cl, Br, or F). Most are highly penetrating, reaching through large masses of material. They are used to kill insects, insect eggs, nematodes, and certain microorganisms in buildings, warehouses, grain elevators, soils, and greenhouses and in packaged products such as dried fruits, beans, grain, and breakfast cereals.

Methyl bromide is the most heavily used of the fumigants, 68,424 metric tons worldwide in 1996, almost half of which is used in the U.S. (Aspelin & Grube 1998). The dominant use is for preplanting soil treatments, which accounted for 70% of that global total.

Quarantine uses account for 5-8%, while 8% is used to treat perishable products, such as flowers and fruits, and 12% for nonperishable products, like nuts and timber.

Approximately 6% is used for structural applications, as in drywood termite fumigation of infested buildings (C&E News, Nov. 9, 1998).

With the recently passed change to the Clean Air Act amendments of 1990, U.S. production and importation must be reduced 25% from 1991 levels by 1999. A 50% reduction must be achieved by 2001, followed by a 70% reduction in 2003, and a full ban of the product in 2005. Under the Montreal Protocol, developing countries have until 2015 to phase out methyl bromide production (C&E News, Nov. 9, 1998).

Some of the other common fumigants are ethylene dichloride, hydrogen cyanide, sulfuryl fluoride (Vikane(r)), Vapam(r), Telone(r) II, D-D(r), chlorothene, ethylene oxide, and the familiar home-use moth repellents naphthalene crystals and paradichlorobenzene crystals. Phosphine gas (PH₃) has also replaced methyl bromide in a few applications, primarily for insect pests of grain and food commodities. Treatment requires the use of aluminum or magnesium phosphide pellets, which react with atmospheric moisture to produce the gas. Phosphine, however, is very damaging to fresh commodities and is highly adsorbed onto oil, thus does not perform as a soil fumigant.

As to a replacement for methyl bromide, the search for alternatives, chemical and other, will continue for an additional four years, however, during this extension it is unlikely that a good substitute can be found.

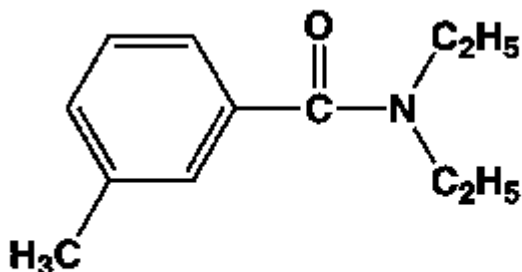
Mode of action--Fumigants, as a group, are narcotics. That is, they are more physical than physiological. The fumigants are liposoluble (fat soluble); they have common symptomology; their effects are reversible; and their activity is altered very little by structural changes in their molecules. As narcotics, they induce narcosis, sleep, or unconsciousness, which in effect is their action on insects. Liposolubility appears to be an important factor in their action, since these narcotics lodge in lipid-containing tissues found throughout the insect body, including their nervous system.

INSECT REPELLENTS

Historically, repellents have included smoke, plants hung in dwellings or rubbed on the skin as the fresh plant or its brews, oils, pitches, tars, and various earths applied to the body. Before a more edified approach to insect olfaction and behavior was developed, it was assumed that if a substance was repugnant to humans it would likewise be repellent to annoying insects.

In recent history, the repellents have been dimethyl phthalate, Indalone(r), Rutgers

612(r), dibutyl phthalate, various MGK(r) repellents, benzyl benzoate, the military clothing repellent (N-butyl acetanilide), dimethyl carbate (Dimelone(r)) and diethyl toluamide (DEET, Delphene(r)) (Figure 25). Of these, only DEET has survived, and is used worldwide for biting flies and mosquitos. Most of the others have lost their registrations and are no longer available.



DEET-*N,N*-diethyl-*m*-toluamide

INORGANICS

Inorganic insecticides are those that do not contain carbon. Usually they are white crystals in their natural state, resembling the salts. They are stable chemicals, do not evaporate, and are usually water soluble.

Sulfur, mentioned in the introduction, is very likely the oldest known, effective insecticide. Sulfur and sulfur candles were burned by our greatgrandparents for every conceivable purpose, from bedbug fumigation to the cleansing of a house just removed from quarantine of smallpox. Today, sulfur is a highly useful material in integrated pest management programs where target pests specificity is important. Sulfur dusts are especially toxic to mites of every variety, such as chiggers and spider mites, and to thrips and newly-hatched scale insects. Sulfur dusts and sprays are also fungicidal, particularly against powdery mildews.

Several other inorganic compounds have been used as insecticides: mercury, boron, thallium, arsenic, antimony, selenium, and fluoride. Arsenicals have included the copper arsenate, Paris green, lead arsenate, and calcium arsenate. The arsenicals uncouple oxidative phosphorylation, inhibit certain enzymes that contain sulfhydryl (-SH) groups, and coagulate protein by causing the shape or configuration of proteins to change.

The inorganic fluorides were sodium fluoride, barium fluosilicate, sodium silicofluoride, and cryolite (Kryocide(r)). Cryolite has returned in recent years as a relatively safe fruit and vegetable insecticide, used in integrated pest management programs. The fluoride ion inhibits many enzymes that contain iron, calcium, and magnesium. Several of these enzymes are involved in energy production in cells, as in the case of phosphatases and phosphorylases.

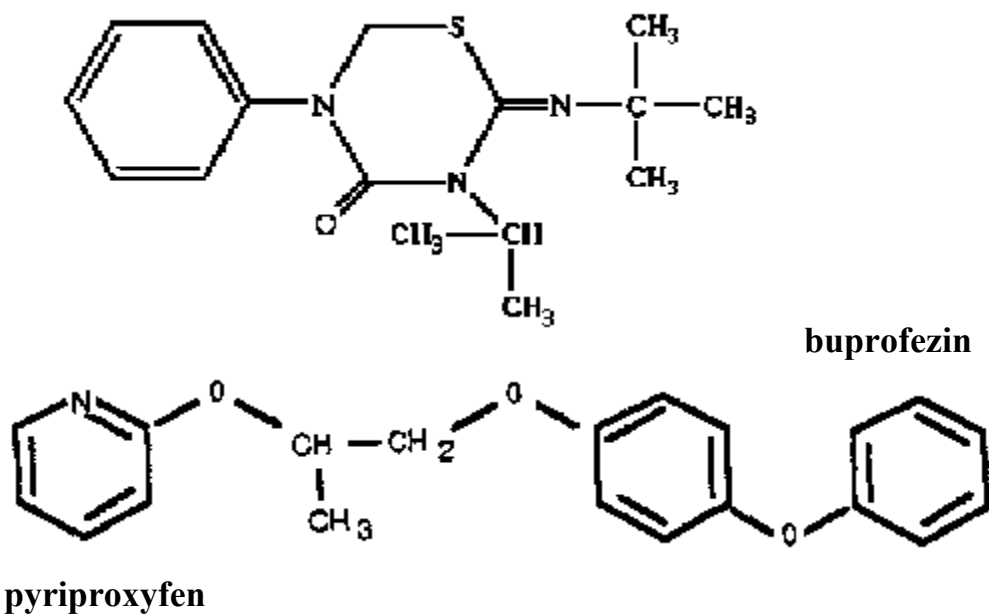
Boric acid, used against cockroaches and other crawling household pests in the 1930's and '40's, has also returned. As a salt, it is non-volatile and will remain effective so long as it is kept dry and in adequate concentration. Consequently, it has the longest residual activity of any insecticide used for crawling household insects, and is quite useful in the control of all cockroach species when placed in wall voids and other protected, difficult-to-reach sites. It acts as a stomach poison and insect cuticle wax absorber.

Sodium borate (disodium octaborate tetrahydrate) (Tim-Bor(r), Bora-Care(r)) resembles boric acid in its action. This water-soluble salt is used to treat lumber and other wood products to control decay fungi, termites, and other wood infesting pests.

The last group of inorganics is the silica gels or silica aerogels--light, white, fluffy, silicate dusts used for household insect control. The silica aerogels kill insects by absorbing waxes from the insect cuticle, permitting the continuous loss of water from the insect body, causing the insects to become desiccated and die from dehydration. These include Dri-Die(r), Drianone(r), and Silikil Microcel(r). Drianone(r) is fortified with pyrethrum and synergists to enhance its effectiveness.

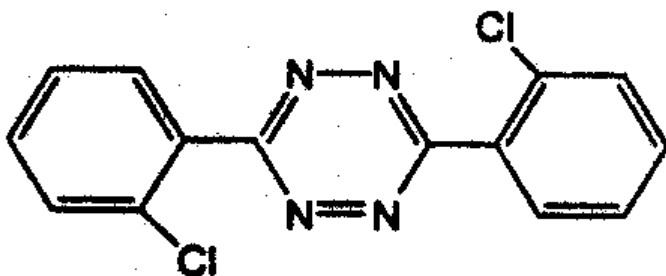
MISCELLANEOUS COMPOUNDS

New molecular structures are being synthesized routinely by basic manufacturers in search of new insecticides with new modes of action. Two recent examples introduced in 1996, are pyriproxyfen (Knack(r), Esteem(r), Archer(r))(Figure 26), classed as a pyridine IGR, and buprofezin (Applaud(R)) (Figure 27), classed as a thiadiazine IGR. Both have given excellent results in controlling the whitefly complex, now a universal problem in U. S. cotton production.



Clofentezine (Figure 28) (Apollo(r), Acaristop(r)), belongs to the unique group, the tetrazines, used as an acaricide/ovicide for deciduous fruits, citrus, cotton, cucurbits, vines and ornamentals. It inhibits mite growth, but the mode of action is not known.

CLOFENTEZINE (Apollo[®], Acaristop[®])



3,6-bis(2-chlorophenyl)-1,2,4,5-tetrazine

Enzone(r), sodium tetrathiocarbonate, is used only on grapes and citrus applied as a water application and irrigated into the soil. It breaks down in the soil to form carbon disulfide, which acts rapidly, decomposes quickly, and is effective against nematodes, soil insects, and soil borne diseases.

Clandosan(r) is a naturally occurring product derived from crab and shrimp shells and used as a nematicide. It is a dried, powdered, chitin protein isolated from crustacean exoskeletons and blended with urea. It stimulates growth of beneficial soil microorganisms that control nematodes, but does not have a direct adverse effect on nematodes as such.

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